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LARGE ANIMAL INTERNAL MEDICINE

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LARGE ANIMAL INTERNAL MEDICINE

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Preface

CONTENT

Large Animal Internal Medicine is an encyclopedic volume for the large-animal veterinarian working with horses, cattle, sheep, or goats. Using the same popular format as the third edition, this edition provides the most current information available by utilizing over 190 experts as authors. This edition contains five entirely new chapters and more than 450 illustrations. Many sections have been strengthened by the addition of outstanding new authors, and chapters have been revised and improved with new references added.

PROBLEM-ORIENTED APPROACH TO DISEASE DIAGNOSIS

The catch-22 of most textbooks is that the clinician must know the diagnosis to locate and read about a specific disease. *Large Animal Internal Medicine* is a multiauthored text that allows the clinician to use the problem-oriented approach to the diagnosis of diseases of horses, cattle, sheep, and goats. Over 130 clinical signs or manifestations of disease are discussed. They are listed alphabetically on pp. 21 and 22; this list can be used to locate a particular manifestation of disease. These same manifestations are listed by organ system at the beginning of Chapter 3 to Chapter14 (Part Two of the book). A favorite feature of the previous editions is the differential diagnosis boxes. We have retained these invaluable diagnostic tools in this edition. Throughout Part Two, complete lists of common, less common, and uncommon diseases associated with manifestations or signs of disease are given in these easy-to-find boxes (see pp. xx to xxi for examples). The clinician is given an approach to each manifestation of disease and a method to work toward a diagnosis. The pathophysiology of a particular manifestation of disease is concisely summarized. Even if a final diagnosis is not reached, the animal with diarrhea, cough, or other problem can be treated symptomatically, a practice that is commonly used in the everyday world.

Similarly, abnormalities in laboratory test results are discussed in Part Four, and complete lists of diseases associated with a given laboratory abnormality are found in easy-to-read boxes (see p. xxi for an example). Interpretation of abnormalities in clinical chemistry, hematology, blood proteins, and clotting tests is made easy. For example, if the problem is elevated serum calcium, the causes of hypercalcemia are discussed concisely, and lists of diseases are given. The clinician can then proceed to a rational approach to the particular laboratory

abnormality. Many readers have found the table for conversion from “American” units to SI units extremely useful.

ORGANIZATION

The basic organization has not changed from the third edition. The book is divided into seven parts:

PART ONE: History, Physical Examination, and Medical Records

PART TWO: Manifestations of Disease

PART THREE: Disorders and Management of the Neonate

PART FOUR: Collection of Samples and Interpretation of Laboratory Tests

PART FIVE: Disorders of the Organ Systems

PART SIX: Preventive and Therapeutic Strategies

PART SEVEN: Congenital, Hereditary, Immunologic, and Toxic Disorders

A detailed discussion of each disease is contained in Parts Five, Six, and Seven of *Large Animal Internal Medicine*. Once the reader has a list of diseases that fit the current problem, specific diseases can be found in these final sections of the book. The organization is that of a traditional disease-oriented text:

Definition and Etiology

Clinical Signs and Differential Diagnosis

Clinical Pathology

Pathophysiology

Epidemiology

Necropsy Findings

Treatment and Prognosis

Prevention and Control

Part Five is organized according to body system and includes internal medicine approaches. Diagnostic tests used in that system are delineated, including ultrasound, endoscopy, radiography, thermography, computed tomography, magnetic resonance imaging, sample collection techniques, electrocardiography, cerebrospinal fluid collection, and biopsy of organs. Numerous illustrations include photographs, ultrasound images, radiographs, electrocardiogram tracings, and endoscopic views. These chapters are written by experts in the field of large animal internal medicine and give details of the most up-to-date treatments available. *Large Animal Internal Medicine* complements existing texts dealing with current therapy.

A neonatal disease section (Part Three), organized by presenting problem, discusses everything from diarrhea to septicemia of foals, calves, lambs, and kids. To aid the clinician in arriving at the proper diagnosis, lists of diseases are given for each manifestation of neonatal disease and are presented in Chapter 19 and Chapter 20, Chapter 51 and Chapter 52 deal with genetic disorders and genetic tests, most of which have only recently been developed. Differences in approach to diagnosis or treatment of neonates and adult animals are cross-referenced throughout the text.

Preventive and Therapeutic Strategies, Part Six, includes chapters with practical information on critical care and fluid therapy, antimicrobial therapy, infection control, prevention and detection of foreign animal diseases, vaccines and vaccination programs, and parasite control programs. Chapter 50 addresses nutrition of the sick animal and gives formulas for both enteral and parenteral support.

POPULAR FEATURES RETAINED

COLOR INSERTS

Chapter 32, Diseases of the Alimentary Tract, has color plates that give endoscopic views of equine alimentary tract disorders. Chapter 39, Diseases of the Eye, contains color plates of ophthalmologic conditions that are best seen in full color.

PRINTED ENDPAPERS

The printed endpapers found in the front and back of the text provide information that is referred to frequently:

Manifestations of Disease

Manifestations of Disease in the Neonate

Clinical Chemistry: Normal Ranges for Large Animals

Normal Values for Erythron Data in Ruminants and the Horse

Normal Values for Leukogram Data (Adult Animals)

Normal Values for Hemostatic Data in Ruminants and the Horse

NEW TO THIS EDITION

NEW TOPICS

The range of new topics is extraordinary. Every chapter has been thoroughly updated. A sampling of new topics includes collection and evaluation of bone marrow, antigen detection tests and PCR, new aspects of critical care, infection control methods for a large animal hospital, prevention, detection, and response to foreign animal diseases, new genetic tests, new tests for *Clostridium difficile,* and new findings on bovine viral diarrhea infection. New ultrasound images are widely used, National Research Council tables have been updated, the neonatal sections are extensively revised, new findings in the etiologies of pinkeye are described, legal requirements for use of pharmaceuticals in food animals, and vaccine advances, advances in treating headshaking in horses, and advances in endocrine and muscle disorders have been added.

INDEX

As a reference, a book is only as good as its index. The index of *Large Animal Internal Medicine* is thorough and extensive, making it an easy-to-use reference to find the answer to any question you may have. The initial page number given is the primary listing.

ACKNOWLEDGMENTS

Many people worked hard to make *Large Animal Internal Medicine* the quality text that it is. More than 190 authors contributed in their area of expertise. Special thanks to Teri Merchant, Shelly Stringer, Sarah Wunderly, Gretchen Van Houten, and all the others at Elsevier who worked so hard on this project. Diana Gomez helped greatly with typing and manuscript preparation, and I am indebted to her.

The motivation for undertaking *Large Animal Internal Medicine* came, in large part, from having been influenced in my professional career by many teachers and colleagues with high standards. In particular I would like to acknowledge Alex Ardans, Humphrey Knight, Martin Drost, and Dick Mansmann. My gratitude to them and respect for them run deep. During my 35 years as a teacher, I had the good fortune of working with many talented, inquisitive, and dedicated colleagues, including Gary Carlson, Ian Mayhew, Lisle George, Sharon Spier, John Madigan, and Bob BonDurant, as well as countless others who helped me. Perhaps the individuals who have the greatest influence on a teacher are the students and residents who through their inquisitiveness keep us interested. Thanks to John House, Gilles Fecteau, Dave Van Metre, John Angelos, Mike McCloskey and all the other great veterinarians I got to work with.

Finally, I would like to acknowledge the love, support, and encouragement of my terrific family: Yibi, Chris, Alex, Bonnie, Kate, and Everett. Family keeps you grounded in reality and tells you when to shut up and sit down!

Bradford P. Smith

Davis California

Causes of Icterus in Horses

LIVER

Common Causes

- Pyrrolizidine alkaloid toxicity
- Serum-associated hepatitis
- Acute hepatitis
- Chronic active hepatitis
- Cholangitis or cholangiohepatitis
- Bile stones, other biliary obstruction
- Fasting hyperbilirubinemia

Less Common Causes

- Aflatoxicosis with liver failure
- Tyzzer's disease (foals)
- Hepatic lipidosis
- Hepatic abscess

Uncommon Causes

- Black disease (infectious necrotic hepatitis)
- Hemangioma, hemangiosarcoma, angiosarcoma

Cardiac neoplasm

Viral arteritis

Gastric or duodenal ulcers

Severe ascarid infection

Lymphosarcoma

HEMOLYTIC ANEMIA

Common Causes

Immune-mediated hemolytic anemia

Ehrlichiosis *(Ehrlichia equi)*

Neonatal isoerythrolysis

Less Common Causes

Piroplasmosis (babesiosis)

Snake bite

Blood transfusion

Erythrocytosis

Uncommon Causes

Equine viral arteritis

Leptospirosis

Bee or wasp sting

Sulfur toxicity

Trichloroethylene-extracted feed

Iron toxicity

Phosphorus toxicity

Herbicide toxicity

Phenothiazine toxicity

White snakeroot poisoning (tremetol)

Onions

Red maple *(Acer rubrum)*

Pentachlorophenol toxicity

Oak toxicity

Mycotoxicosis

Surra, *Trypanosoma evansi* (exotic)

Mal de caderas, *Trypanosoma equinum* (exotic)

Murrina de caderas, *Trypanosoma hippicum* (exotic)

Causes of Icterus in Ruminants

LIVER

Common Causes

Pyrrolizidine alkaloid toxicity

Aflatoxicosis

Fat cow syndrome (fatty liver)

Less Common Causes

Acute hepatitis

Liver flukes

Infectious necrotic hepatitis (black disease)

Liver abscess

Cholangiohepatitis

Uncommon Causes

Sarcocystosis

Hepatic neoplasia

Ruptured gallbladder

Cholelithiasis

Biliary obstruction

Nolina (beargrass) toxicity

Lantana toxicity

Agave toxicity

Wesselsbron disease (exotic) (B, O)

HEMOLYTIC ANEMIA

Common Causes

Leptospirosis

Anaplasmosis

Bacillary hemoglobinuria *(Clostridium hemolyticum)*

Piroplasmosis, babesiosis (exotic)

Less Common Causes

Snake bite

Immune-mediated hemolytic anemia

Transfusion reaction

Postparturient hemolytic anemia

Copper toxicity (especially sheep)

Neonatal isoerythrolysis

Yellow lamb disease (*Clostridium perfringens* type A) (O)

Uncommon Causes

Anaplasma ovis

Eperythrozoonosis

Bee or wasp sting

Brassica species toxicity

Trichloroethylene-extracted feed toxicity

Iron toxicity

Onion poisoning

Zinc poisoning

Phosphorus poisoning

Mercury poisoning

Fireweed *(Kochia scoparia)* poisoning

Mycotic lupinosis

Mycosporum poisoning

Theileriosis (East Coast fever) (exotic)

B, Bovine; *O,* ovine.

Causes of Elevations in Serum Enzymes

ELEVATION OF SDH

Common Causes

Acute liver failure

Liver abscess

Secondary to damaged bowel

Strangulating intestinal lesion

Acute toxic enteritis

Chronic liver failure

Less Common Causes

Acute and severe anemia

General anesthesia

Anoxia

ELEVATION OF GGT

Common Causes

Acute liver failure

Chronic liver failure

Pyrrolizidine alkaloid toxicity

Aflatoxicosis

Cholangiohepatitis

Cholelithiasis

Liver flukes

Uncommon Causes

Higher normal range in young animals

Fatty liver

ELEVATION OF AP

Common Causes

Acute liver failure

Chronic liver failure

Pyrrolizidine alkaloid toxicity

Cholangiohepatitis

Cholelithiasis

Liver flukes

Uncommon Causes

Higher normal range in young animals

Fatty liver

ELEVATION OF CPK

Common Causes

Exertional rhabdomyolysis (azoturia, myositis, tying-up)

Nutritional myodegeneration (selenium, vitamin E deficiency)

Postendurance ride multisystemic disorder

Alert downer cow syndrome (muscle crush syndrome)

Malignant hyperthermia

Malignant edema

Prolonged recumbency with inability to rise

Uncommon Causes

Normal postexercise or postshipping modest increase

Acute cardiomyopathy

Purpura hemorrhagica

Equine influenza

Sarcosporidiosis

Local irritation from intramuscular injections

ELEVATION OF LDH

Common Causes

Muscle Disease

Exertional rhabdomyolysis (azoturia, myositis, tying-up)

Nutritional myodegeneration (selenium, vitamin E deficiency)

Postendurance ride multisystemic disorder

Alert downer cow syndrome (muscle crush syndrome)

Malignant hyperthermia

Malignant edema

Liver Disease

Acute liver failure

Chronic liver failure

Cholangiohepatitis

Cholelithiasis

In Vitro Hemolysis

Uncommon Causes

Hemolytic anemia

Acute cardiomyopathy

Purpura hemorrhagica

Equine influenza

Sarcosporidiosis

Local irritation from intramuscular injections

Fatty liver

Use of the *Consultant* Diagnostic Database for Development of This Textbook

MAURICE E. WHITE

The writing of each edition of *Large Animal Internal Medicine* has been facilitated by the online diagnostic system *Consultant*.[1] *Consultant* contains information on diseases described in the veterinary literature: 1183 diseases of cattle; 1165 of horses; 808 of sheep; 662 of goats; 606 of pigs; 1491 of dogs; 1046 of cats; and 395 of birds at the time this is being written. For each disease there is a brief description, references, links to the ever-expanding number of online journal articles, and clinical signs that might be seen. Information in *Consultant* is updated daily based on review of periodical literature available online and on paper through the Flower-Sprecher Veterinary Library at Cornell University. *Consultant* is on the Web at http://www.vet.cornell.edu/consultant/consult.asp; in 2006 it received about 1.3 million page views from 380,000 visits.

Two characteristics of *Consultant* are the keys to its use for this textbook. Online editing is rapid, and information from the literature appears in the database quickly; this rapid updating combined with the large number of information sources allows *Consultant* to contain a breadth of up-to-date material that is difficult to find elsewhere, including information on poisonings, rare diseases, or diseases exotic to North America. The second important

factor is the ability of the user to enter a clinical sign or signs (e.g., cough, colic, abortion) for a given species and be presented with a list of diseases for which that sign or signs have been reported.

How was *Consultant* used for development of *Large Animal Internal Medicine?* Much of this textbook is organized by clinical signs. *Consultant* provided a broad overview of possible causes for clinical problems that authors were encouraged to incorporate into their lists of differential diagnoses. Contributors were encouraged to compress, rank, and add to *Consultant*-generated lists on the basis of clinical experience. The use of the database in this fashion facilitated the organization of sign-based chapters.

Consultant and this textbook are symbiotic. The database can be thought of as a generalist that "knows" some up-to-date information on almost every disease in veterinary medicine. Despite that, it remains merely a tool for the clinician who uses it. For example, there are dozens of causes of epistaxis in the horse and it is simple to get a complete list of them and other information from *Consultant*. The clinician must take that list and decide which causes to pursue in an individual patient, in what order, by what means, at what cost, and to what treatment or prognostic end. When tough decisions must be made, expert opinions such as those found in this book are of great help.

We are in the nascent stages of new ways of accessing veterinary information—online journal articles; online textbooks; "distributed" textbooks with reviews by experts on servers throughout the world. As I write this, the website "Veterinary Wiki" has no content and coverage of veterinary topics in Wikipedia is spotty, but growth of the Wiki mode of handling information seems inexorable.[2] In spite of these trends the printed word remains a popular and effective way to capture knowledge. Cooperation such as that between *Consultant* and *Large Animal Internal Medicine* allows practitioners and students to benefit from the linkage between the tireless memory and ease of retrieval of the computer and the convenience of expert knowledge in book form.

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1 Chapter 1 Ruminant History, Physical Examination, and Records

Ronald L. Terra

1.1 OBTAINING THE HISTORY

The initial and often the most important step in the diagnostic approach to the sick ruminant is the physical examination. Throughout this process an anamnesis is obtained by asking questions of the owner or manager during the examination of the animal. The examiner should obtain the signalment either by observation or by questioning the owner. The information that one wishes to obtain while taking the history is that related to the chief, or presenting, complaint—that is, the complaint, the duration, whether the onset was gradual or sudden, and any associated signs that have been noted. For females, one must know when the last parturition occurred, and for dairy cows, what the production parameters were in the previous lactation as well as in the current lactation. With dairy cows a drop in milk production is often the only sign noted by the owner. Weight can be either approximated, via heart-girth measurements, or determined exactly if facilities exist to do so. What and how the animal is fed are questions to be asked. Does the animal refuse any or all of the feed offered? Is there more than one ration or feeding regimen for this particular operation? If so, are these same signs noted in animals exposed to different feeding practices? The examiner also obtains vaccination and worming history and inquires about pasture or housing practices to determine the influence that management factors have on the incidence of the disease. Previous diseases noted in the herd, therapeutic regimens used, and resolutions of previous problems are pertinent aspects. Finally, the examiner should note the treatment history of the patient. An example of a history questionnaire that can be used for ruminants is included (Fig. 1-1). Specific problems that are noted in the history or physical examination can be looked up on pp. 21 and 22, and lists of differential diagnoses considered.

1.2 EXAMINATION

A complete examination should always be performed even if the presenting complaint is easily recognizable. The physical examination provides the veterinarian with information that is used to assess the health status of the patient. This information, combined with that obtained while taking the history, enables the practitioner to determine which specific signs of disease are present and often to localize the disease process to specific organ systems. The physical examination also helps to determine which ancillary diagnostic tests must be performed. Additional information gathered during the examination may reveal disorders other than the presenting complaint that warrant further attention and may have a profound influence on the prognosis of the case. Realistically, economic and temporal constraints preclude full examinations in some cases. In these situations the veterinarian must be familiar enough with the complete physical examination to know which aspects can be excluded and which should be performed.

A systematic approach to the animal must be developed and used in every physical examination. The first step is to form an initial overall impression by observing the animal from a distance. The animal is then restrained and examined topographically, beginning on one side, moving to the other, then evaluating the rear and finally the head and neck. Thus individual organs and systems are examined completely, although disjointedly, and the information gained is correlated to form the complete diagnosis.

1.2.1 Visual Examination

As observations are made and a physical examination performed, it is important to follow a systematic approach and to record findings. A checklist has been found to be extremely useful (Fig. 1-2). While observing the animal

from a distance, the examiner should assess its posture, gait, behavior, and physical condition. Observation of the other members of the flock or herd helps to differentiate normal from abnormal characteristics under each particular management system because normal may vary from farm to farm and because what is considered "normal" for a farm by the owner or herdsman might actually be abnormal; this information is valuable for assessing the incidence of a disease or disorder that is caused by management. As more animals in more herds are observed, a background of knowledge is gained that allows the practitioner to assess these management deficiencies more reliably.

The general appearance and conformation of the animal are included in determining posture. These are assessed in light of the age and breed of the patient. Determining abnormalities in posture can be difficult; however, noting these subtle changes can contribute greatly to the diagnosis of a disease process. Conformation is recognized by looking at the overall size and shape with particular regard to height, width, and relationship of the head, neck, and legs to the trunk. The general appearance of the patient in light of overall conformation can then be assessed. Determining a body condition score and correlating it with stage of lactation can offer insight into the course of the presenting complaint. Is the young, growing animal within breed standards for size and weight? (See Chapters 9 and Chapter 13), The condition of the hair coat and presence of external parasites can be noted during the physical examination (e.g., frank hair loss, as seen in louse infestation, or dander and scruffiness of the hair coat, as seen in chronic debilitating diseases).

Fig. 1-1 Example of an initial encounter history form for use in ruminants.

VETERINARY MEDICAL TEACHING HOSPITAL
FOOD ANIMAL
INITIAL ENCOUNTER HISTORY

Observe the animal for signs of abdominal splinting or arching of the back, as can be seen with peritonitis. This posture can also be noted with other disease processes when these produce pain in the ventral abdomen. Lateral curvature of the spine could indicate a congenital defect or a chronic spinal lesion. Carrying the tail up away from the body is seen with conditions resulting in pain or irritation in the perineal region, vagina, or rectum. Standing with all four legs in the classic "saw-horse" stance with the neck and tail held erect is typical of tetanus. Abduction of the elbows is seen in disorders that cause thoracic pain. Lameness can be noted by observing unwillingness to bear weight fully on the affected limb, while either standing or walking. Loss of extensor or flexor capabilities of the joints is seen in nerve paralysis or paresis; it can also be caused by tendon and/or joint contractures, in which case joints are rigid. Walking as if all four feet are sore may indicate laminitis. With bright and alert recumbent animals, a thorough examination to rule out fractures or severe joint trauma is essential. Once these have been ruled out, inability to stand may be indicative of generalized muscular paresis or paralysis. These can be of a primary nature, as with lesions within the spinal column causing cord compression, or secondary to mineral or electrolyte deficiencies (e.g., hypocalcemia, hypomagnesemia, or hypokalemia).

Fig. 1-2 Example of a data sheet for the recording of the pertinent findings from the physical examination.

VETERINARY MEDICAL TEACHING HOSPITAL

FOOD ANIMAL

PHYSICAL EXAM DATA

To be able to judge the behavior of the animal as being normal or abnormal, the observer must call on a large amount of experience. Observing the animal from a distance allows assessment of eating and drinking behavior, as well as assessment of the subject as it is ruminating, urinating, and defecating. How the animal gets up or lies down and how it ambulates are important. Signs indicative of estrus or signs commonly seen with calving might be considered normal or abnormal, given the history and behavior of the animal during these events. Observing the patient during the milking process may also be beneficial. The influence of the manager on animal behavior is very important, as is the overall temperament of the particular breed or herd in question. Normal animals react to the approach of a human being by moving away; however, those that have had extensive contact with people may be more inquisitive. Within a herd one can note animals that are more tolerant than others, more stubborn, more restless, and more anxious. These traits are not necessarily abnormal and need to be differentiated from behavior that would be considered secondary to disease. In general, one must determine whether the behavior is one of a depressed or apathetic animal or of a hyperexcitable or frenzied animal.

Nutritional status and physical condition are assessed by means of observation and palpation. Special attention is paid to the dewlap, the spinous processes of the thoracic and lumbar vertebrae, the shoulder area, and the area around the tailhead. Determination of body condition will then result in a classification of the animal as being anywhere from severely emaciated or cachectic to extremely overconditioned or fat (see Chapter 9 andChapter 13 for body scores). Next it must be determined whether the condition is of a primary or nutritional nature or the result of disease. Disease processes can influence or be influenced by the animal's body condition. Extremely thin animals are seen in primary undernutrition and also with chronic disease. Females carrying multiple fetuses and lactating animals with metabolic abnormalities secondary to abomasal displacements would also show signs of weight loss. Overconditioned animals are at greater risk for a wide variety of disorders primarily related to the accumulation of fat in the liver and excessive fat storage in the omentum.

1.2.2 Physical Examination

With the animal properly restrained, the physical examination can now progress to specific palpation, auscultation, and percussion. Obtaining a sample of urine for urinalysis is of great value if incorporated into the physical examination; it is easy to perform with the use of dipsticks such as N-Multistix. Stroking the perineal region can aid in eliciting urination in the bovine; however, even this is futile if the animal is apprehensive. Consequently, it is recommended that this be done first, while the patient is still fairly relaxed. In the male, elicitation of urination is slightly more difficult and requires massaging of the preputial orifice. Another method is to wash the outside of the prepuce with warm water, but this is less successful. In the female sheep and goat, stroking the perineal area can be attempted, but positive results are rarely achieved. A method that is more reliable but that causes the animal much greater stress is to prevent it from breathing until urination is stimulated. In male or castrated male sheep and goats, gentle massage of the prepuce sometimes results in urination. If that fails, the breath-holding technique can be used. It is recommended that this not be attempted on patients that are severely compromised because of any disease process. (See Chapter 22 for further information on interpretation of the urinalysis.)

Body temperature is then measured with a rectal thermometer. Normal values for each species are given in Table 1-1. There are no absolute values, and the upper and lower limits should be adjusted as necessary to account for ambient temperature and housing. For example, if the ambient temperature is greater than 37.5° C (100° F), a body temperature of 39.5° C (103° F) may still be considered normal for the adult bovine, especially if the animal is not allowed access to shade. When body temperatures approach 41° C (106° F), as a result of very high ambient temperatures, heat stroke may occur. Keep in mind that the animal tries to maintain its body temperature within these normal limits, and marked deviation from the norm would be indicative of a disease process. A markedly

elevated temperature is seen in acute, severe inflammatory processes. Pathologic lowering of the body temperature is seen in disorders that cause an inhibition of metabolism such as postparturient paresis, neonatal hypoglycemia, the end stages of a chronic disease, or severe septicemia resulting from gram-negative bacteria. There is a normal diurnal variation in body temperature of as much as 0.5° to 1° C. In the female there can also be a slight increase in temperature in the days preceding estrus. Neonates are poor thermoregulators and often have a normal body temperature that is 0.5° to 1° C higher than that of adults.

In the evaluation of the thoracic and abdominal cavities, the initial step is the ballottement of the abdomen on the right side. An increase in fluid being sequestered intraabdominally could be related to some degree of intestinal or ruminal stasis or associated with an increase in peritoneal fluid, as with peritonitis or ruptured bladder. Ballottement can also reveal whether any firm mass such as a fetus, impacted abomasum, abscess, or tumor is located in the abdomen. In goats the abdominal fat pad is quite prominent and tends to obscure any significant finding on ballottement. Deep palpation of the paralumbar fossa can sometimes reveal masses in this region, including lymphomas, fat necrosis, or abscesses. In goats, lambs, and calves, two hands are used to deeply palpate the abdomen; the normal freely movable left kidney is usually readily palpable. On the right side an enlarged or painful liver or kidney can be noted. Palpation of an abnormal swelling or firmness, especially with the elicitation of pain, indicates a problem that must be further evaluated.

Table 1-1 Normal Values for Temperature in the Ruminant[1–3]

Animal	Degrees Celsius	Degrees Fahrenheit
CATTLE		
Adult	38–39	100.5–102.5
Calf	39–40.5	101.5–103
SHEEP		
Adult	39–40	102–103.5
Lamb	39.5–40.5	102.5–104
GOAT		
Adult	38.5–39.5	101.5–103.5
Kid	39–40.5	102–104

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The spinal column and ribcage are then palpated; the presence of fractures, enlargement of the costochondral junctions, or the elicitation of pain is noted. Enlargement or fractures of the costochondral junctions are commonly seen in young animals with deficiencies of calcium, copper, or vitamin D.

Auscultation with concurrent percussion by snapping the finger against the thoracic and abdominal walls is the next procedure. Gas trapped within abdominal viscera elicits a “pinging” sound that can be heard with the stethoscope. Localization of these gas pings to certain areas within the abdomen is helpful in determining which alimentary structure is involved (Figs. 1-3 to 1-5). If the cecum is enlarged and gas filled, an abdominal ping can be heard. This can extend caudally to the tuber coxae and cranially through the paralumbar fossa and under the ribcage on the right side (see Fig. 1-3). The diameter of this area can be variable and range from 6 inches (15 cm) in a cecal displacement to 3 feet (1 m) horizontally in cecal torsions. Spiral colon pings are generally localized to the right dorsocranial paralumbar fossa and rarely extend farther forward than the tenth intercostal space. They tend to be round areas 10 inches (25 cm) or less in diameter centered high under the last rib (see Fig. 1-3) and are

commonly found in sick cattle that are anorectic. These pings have no specific diagnostic significance. Gas pings associated with a right-sided displacement or torsion of the abomasum can extend as far cranially as the ninth intercostal space and caudally into the paralumbar fossa (see Fig. 1-4). The diameter of displacements is usually 18 inches (45 cm), whereas that of torsions can be up to 3 feet (1 m). In cases of abomasal volvulus, the animal is usually exhibiting other systemic signs such as increased heart rate, dehydration, depression, scleral injection, and mild colic. In simple right-sided displacements or dilations of the abomasum, the only significant finding may be the small gas ping localized to the abomasum in a cow with depressed appetite and decreased milk production.

Fig. 1-3 Schematic representation of areas of gas pings elicited by percussion of the cecum and spiral colon.

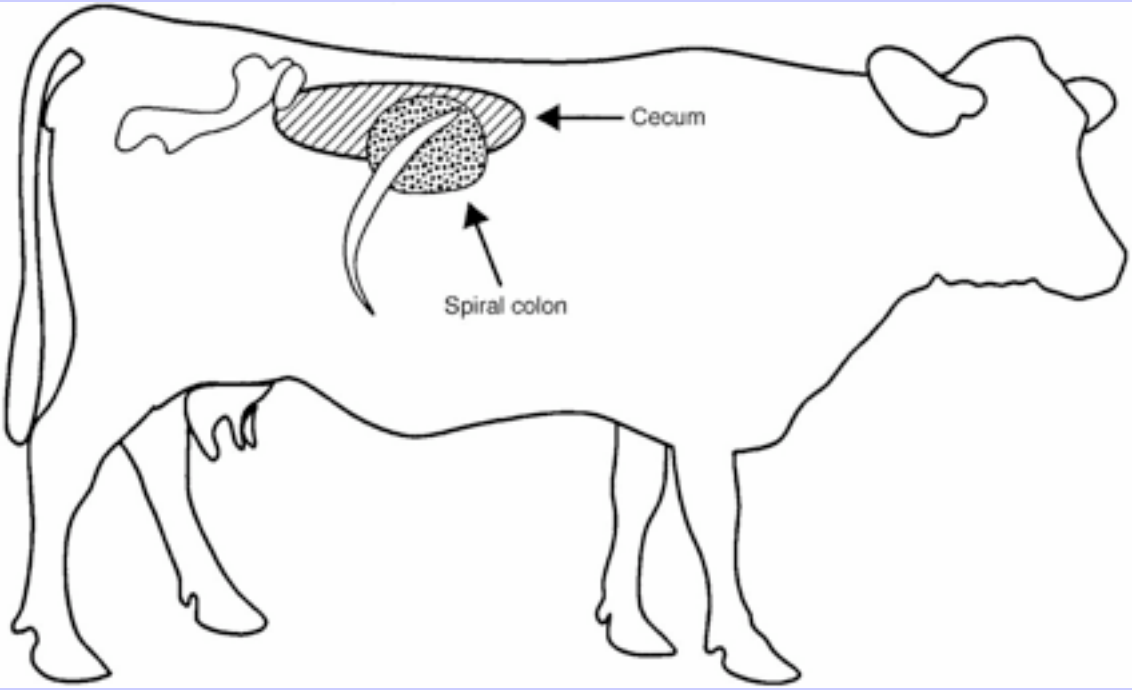


Fig. 1-4 Schematic representation of the area of the gas ping percussed in association with a right displaced abomasum (RDA) or abomasal torsion.

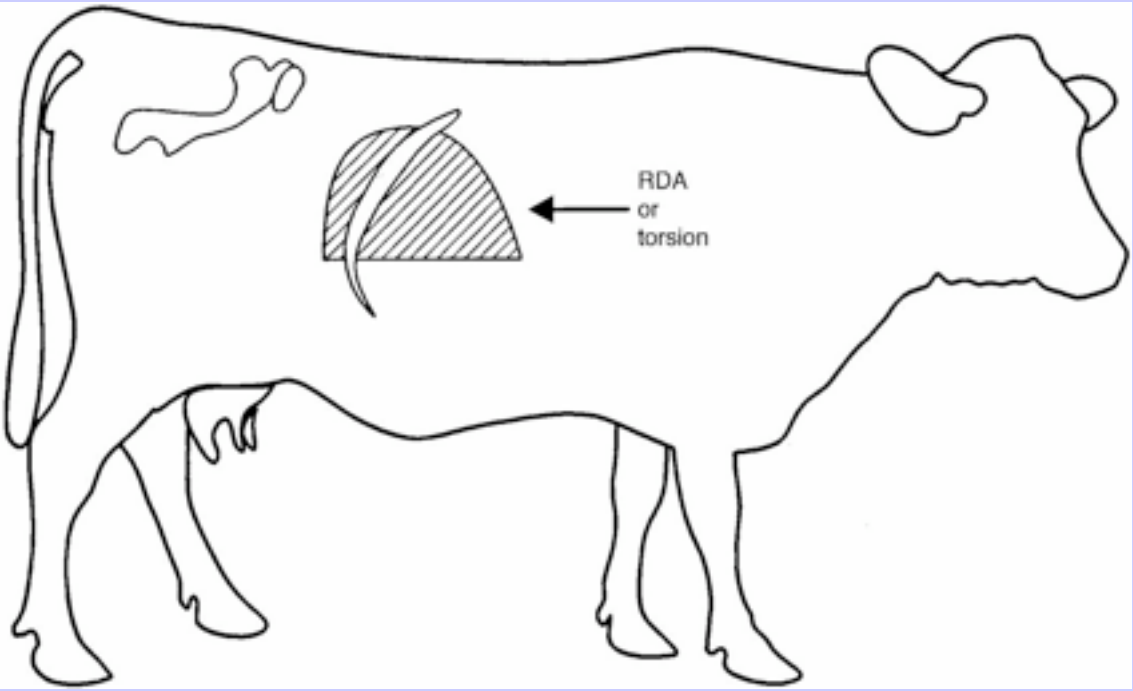
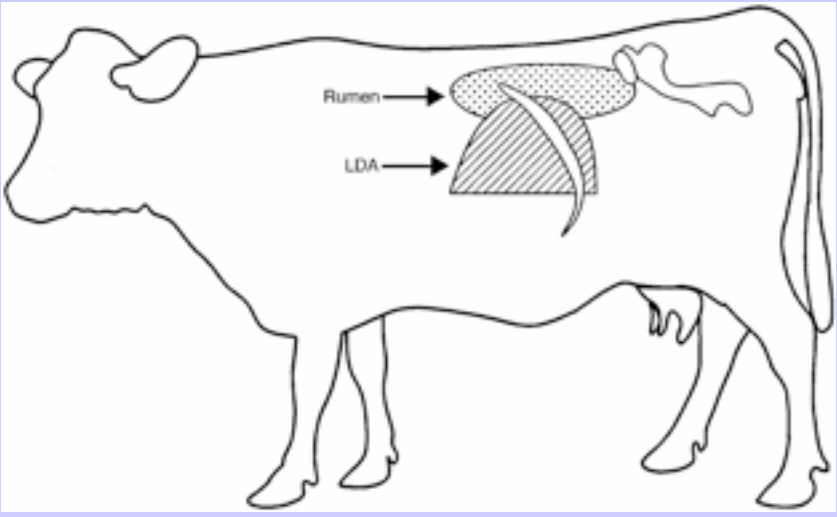


Fig. 1-5 Schematic representation of the area of the gas ping percussed in association with a left displaced abomasum (LDA) or gas ping in the rumen.



On the left side, gas pings can be noted as originating from the rumen, the peritoneum, or a left displaced abomasum (LDA). The auscultation of a gas ping that is primarily localized to the dorsal aspect of the paralumbar fossa and auscultable on both sides of the spinal column would be indicative of a pneumoperitoneum. The extent of these pings can be from the thoracolumbar junction caudally to the retroperitoneal space. Pings associated with ruminal tympany occupy the whole of the paralumbar fossa and can extend dorsally to the spinal column but generally do not extend over to the right side (see Fig. 1-5). LDA results in a gas ping that is localized, easily outlined, and approximately 12 to 18 inches (30 to 45 cm) in diameter. Caudal extent of the displacement is generally the thirteenth rib; however, it can extend into the paralumbar fossa, in which case the outline of the abomasum can be easily palpated. The LDA should ping over the eleventh rib on a line from the hip to the elbow (see Fig. 1-5). Rumen gas associated with a left-sided ping will rarely ping at this location. Identification of a fluid line within the displacement can aid in diagnosis and is accomplished by ballotting the left paralumbar fossa while auscultating the area of the gas ping concurrently, a process known as *succussion*. LDA often gives a pitch that changes in tone as it is percussed, as a result of movement of the rumen behind the abomasum. Often with LDA, intermittent gas bubbling or "sloshing fluid" sounds are heard. Rumen gas can be further differentiated from gas trapped in an LDA by rectal palpation of the rumen. One can also differentiate rumen gas from that trapped in an LDA by passage of a stomach tube into the rumen. Blowing into the rumen yields obviously auscultable sounds unless an LDA is present, in which case the sounds are muffled as the practitioner listens over the area of the ping. Performing a rumen or abomasal tap, the Liptac test, can further differentiate whether the ping originates from an LDA or the rumen. Fluid collected from an LDA would have a pH of less than 4, whereas that of the rumen should be 6 or higher.

The rumen is examined by both auscultation and palpation. It should have a doughy texture with a small gas cap in its dorsal regions and usually is not distended above a plane formed by the coxofemoral joints. Increased accumulation of gas within the rumen would be seen with acute primary frothy bloat and also with free gas bloat. The rumen contractions should be counted, observed, and auscultated. Normally, primary ruminal contractions occur one and one-half to three times per minute, and the force of the contraction should displace the lateral body wall at least ½ to 1 inch (1 to 2 cm). When auscultated, the ruminal contraction sounds like a dull roar that starts quietly, rises to a peak, and dies away. Hypocalcemia and peritonitis are examples of disorders that result in weak or absent ruminal contractions. Hypermotility is rarely seen but can occur and has been described in association with vagal indigestion.

The cardiac region of the thorax is auscultated next. Heart rate and rhythm are determined at this time. Rate varies among species, and age differences within species are noted. In general, older or larger animals have a slower heart rate. Table 1-2 lists the ranges of heart rate that are considered normal for the ruminant species, depending on age. Tachycardia can be seen in animals that have been stressed or excited, as in the process of restraint. However, with time the rate should return to within a more normal range. Any deviation from the normal heart rate in a quiet, relaxed animal implies a general disturbance of the normal health of the animal. Increased heart rate can be seen with fever, inflammation, pain, hypocalcemia, or metabolic disturbances that result in hypovolemia. Bradycardia is seen with conduction disorders within the heart muscle and with some metabolic disorders (uremia, hypokalemia). The most common causes of arrhythmias are atrial fibrillation in adult cattle and hyperkalemia in diarrhetic neonates. Location and intensity of the heart sounds are also important to note, because muffling or displacement of the sounds can indicate space-occupying lesions within the thorax, pericardium, or mediastinum. With pericardial effusion the heart sounds are initially dull but develop splashy washing machine sounds as a gas-fluid interface develops. This often takes weeks. Normally the heart occupies a space on the ventral thorax between the third and sixth ribs. Most of the heart mass is located on the left side of the chest; thus the heart sounds should be louder on that side. However, if the heart is muffled on the left side and louder than normal on the right, one should consider the possibility of inflammation of the pericardium or lung lobes on the

left side of the chest. Displacements of the heart sounds caudally are an indication of a space-occupying lesion in the anterior thorax or mediastinum, such as an abscess or neoplasm. Cranial displacements of the heart sounds would be noted with distention of the ruminoreticulum, eventration of abdominal viscera into the thorax through a diaphragmatic hernia, or other space-occupying lesions as noted previously. If any murmurs are noted on auscultation, an attempt should be made to localize the murmur to a specific heart valve. While the heart is auscultated, the pulse should also be palpated. The easiest point to fine a pulse while the heart is being auscultated is at the vascular notch of the mandible where the facial artery is easily palpated. Pulse deficits in conjunction with an increase in heart rate are seen in arterial fibrillation and premature ventricular contractions. The heart rhythm is also noted. Dropped beats, gallop rhythm, and sinus arrhythmias should be compared with other clinical signs to determine importance.

Table 1-2 Normal Resting Heart Rates (Beats/Min) for Adult and Young (<30 Days of Age) Ruminants[1–3]

Animal	Average	Range
CATTLE		
Adult	60	40–80
Calf	120	100–140
SHEEP		
Adult	75	60–120
Lamb	140	120–160
GOAT		
Adult	85	70–110
Kid	140	120–160

The prefemoral and prescapular lymph nodes are palpated. Enlargements would be seen with inflammatory processes occurring in the regions that they drain. The skin is then palpated, starting along the top line and moving down over the abdominal and chest walls to the ventral midline. The presence of subcutaneous gas or edema is noted, as is any elicitation of pain. Emphysema can have iatrogenic causes (e.g., be secondary to abdominal surgery) or result from pulmonary alveolar rupture, gas gangrene, or puncture wounds. Edema, if noted, is usually ventral and is the result of lowered plasma oncotic pressure or increased venous pressure. Right-sided heart failure, as seen in traumatic retic-ulopericarditis, pericarditis, mediastinal masses, or severe pulmonary disease, results in increased venous pressure. If this is the case, a distention of the jugular veins with jugular pulse should also be evident. Protein-losing enteropathies or nephropathies are causes of lowered oncotic pressure, as is liver failure, which results in a lack of synthesis of plasma proteins. Fluid and gas from subcutaneous injection of large volumes of medications such as calcium gluconate can sometimes be confusing.

The thorax is then auscultated and percussed. Respiratory rate (Table 1-3) and pattern are determined at this time, and the lungs are auscultated. If increased inspiratory or expiratory effort is noted, it should be correlated with auscultatory and percussive findings in an effort to determine lung pathology. Normal ruminant lung sounds vary greatly among species. In calves, sheep, and goats the relatively thin chest wall allows one to hear inspiratory sounds ventrally and over the large airways, whereas expiratory sounds are minimal (except in sheep, where they are frequently audible because of the large amount of mucus in sheep airways). In larger cattle, only very faint

inspiratory sounds are normally heard. Lung sounds can be classified as normal or harsh (tubular) or as wheezes or crackles. These sounds can vary over the different areas of the thorax or can be found singularly over the entire lung field. Significant pulmonary pathology may be present in ruminants *without* any auscultable abnormalities. Total absence of lung sounds ventrally indicates pleural effusion or pulmonary abscessation with loss of airways. When ventral consolidation of the lung occurs, airway sounds are transmitted well and easily heard ventrally as pipestem sounds similar to those heard over the trachea, whereas percussion reveals a marked increase in ventral lung density. The trachea should also be auscultated. Inspiratory dyspnea and stridor are usually the result of extrathoracic obstructions to airflow (nose, pharynx, larynx, extrathorac-ic trachea). Pneumothorax can also result in loss of auscult-able airway sounds, which may be absent dorsally or entirely over the entire side if the lung has collapsed completely.

Table 1-3 Normal Resting Respiratory Rates (Breaths/Min) for Adult and Young Ruminants[1–3]

Animal	Average	Range
CATTLE		
Adult	24	12–36
Calf	48	30–60
SHEEP		
Adult	36	12–72
Lamb	50	30–70
GOAT		
Adult	28	15–40
Kid	50	40–65

Place the middle finger in the intercostal space and slap the finger with the opposite hand or use a tablespoon and rubber hammer to accomplish percussion of the chest wall to determine the ventral lung border. Percussion is most useful in goats and calves. In sheep the wool precludes effective use of the technique, and in adult cattle the chest wall is often too thick to effectively evaluate changes in percussion tones. The chest is percussed in a dorsal-to-ventral direction, moving caudal to cranial on the chest wall. A change in resonance is noted when the ventral border is reached; a line demarcating this change in resonance is the junction of the diaphragm to the thoracic wall. In the ruminant this line should be described by joining a point at the junction of the eleventh rib and the epaxial musculature dorsally to a point at the middle of the ninth rib, then cranially to the point of the olecranon. The cranioventral portion of the percussed thorax is dull because of the heart field (approximately 3 inches [7.5 cm] above the olecranon in adult cattle; 1 to 2 inches [2.5 to 5 cm] in calves, sheep, and goats). Finding an increased area of dullness in the cranioventral lung field associated with harsh lung sounds would be an indication of lung consolidation as seen in *Pasteurella* pneumonia. Pulmonary emphysema (atypical interstitial pneumonia) should be considered when the lung field is larger than expected, the animal is dyspneic, and airway sounds are minimal. A ventral border that is markedly elevated and in a straight line could be an indication of pleural effusion. In this case auscultation would reveal decreased lung sounds ventrally and possibly the presence of pleural friction rubs. Acoustic percussion of the lung field can extend into the chest only to a depth of 2 to 2½ inches (5 to 6 cm). Lesions within the thoracic cavity that lie deep-er than this cannot be percussed.

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The next step in the physical examination is to assess for evidence of pain in the ventral portion of the abdomen and thorax. This can be accomplished through the use of the withers pinch test or by ballottement of the xiphoid region. The withers pinch test involves auscultating the trachea while the withers are simultaneously squeezed and pushed ventrally. Painful lesions result in the ruminant resisting normal ventral movement of the spine and/or emitting a grunt or holding its breath when this test is performed. Ballottement of the xiphoid is also done while the trachea is auscultated. The xiphoid region is pushed with a knee or struck with a closed fist, and an elicitation of a grunt would indicate pain in this region. The examiner can then ballotte the remainder of the ventral abdomen and thorax to classify the lesion as localized or diffuse. If localized, the region affected should be identified. It should be noted that the animal may kick the examiner during the xiphoid ballottement test; thus proper precautions should be taken.

The subcutaneous abdominal veins are assessed next and palpated along their length for the presence of thickened walls, distention, or pulses. Distention and pulses may be abnormal if they correlate with other clinical evidence of right-sided heart failure. Thickening of the wall or evidence of thrombosis is often a consequence of faulty intravenous injection of irritating substances or of injuries that result in hematomas or abscesses.

If the animal is lame or has postural abnormalities, the feet and legs are palpated next. If the animal is uncooperative, it may be necessary to sedate and/or cast it. If sedation is necessary, it should be performed at the end of the physical examination. Care should be exercised for obvious reasons. The examination consists of comparing one foreleg with the other then comparing both with the expected norm. The same procedure is followed for the hind legs. Abnormalities in the shape of the claw may be hereditary or may be caused by nutritional deficiencies, poor leg conformation, poor housing, or as a sequela to laminitis. The coronary bands should be palpated for evidence of pain or increased heat. An attempt should be made to pick up all four feet individually and observe the soles and interdigital regions for necrotic areas, areas of bruising or swelling, draining tracts, or presence of foreign bodies. The fetlock, carpal and tarsal, stifle, and elbow joints are all easily accessible and should be examined for swelling, tenderness, edema, heat, instability, and crepitation. Each joint should be tested over its full range of motion, and any elicitation of pain should be noted. Physical findings should be consolidated into a decision as to whether the joint problems are infectious or traumatic. Sheep or goats with acute polyarthritis most commonly have mycoplasma or chlamydial infection. Chronic joint pain in goats (often with soft-tissue thickening and enlargement caused by synovitis) is frequently attributable to caprine arthritis encephalomyelitis. Conformation of the legs should be analyzed because this could contribute to a joint or foot problem. The pelvic girdle does not lend itself to extensive examination; however, one can note symmetry or asymmetry and further evaluate during the rectal examination. Fractures of the tuber coxae, subluxation of the sacroiliac junction, acetabular fractures, fractures of the head or neck of the femur, and dislocation of the coxofemoral joint may all be diagnosed by evidence gained during palpation and observation of the pelvic area. The dislocated or fractured limb is frequently shorter than the normal opposite limb. The tail can also be examined for evidence of fractures, paresis, or paralysis.

The perineal region is examined by noting the external condition of the genitals and rectum. Anal sphincter tone can be assessed, and the presence of vaginal discharge can be noted. In males the testicles, spermatic cord, and epididymis should be palpated for the presence of nodules or areas of fibrosis. The testicular circumference can be measured and compared with what is expected for age and breed. These measurements are noted in Tables 1-4 and 1-5. The perineal part of the penis can be palpated for the presence of hematoma or swelling and pain (cellulitis or abscess). In the female the supramammary lymph nodes can be felt at the attachment of the udder to the perineum. Enlargement of these nodes occurs with mastitis or lymphosarcoma. The udder is palpated for the presence of fibrotic areas, commonly seen secondary to staphylococcal mastitis or associated with *Arcanobacterium (Actinomyces) pyogenes* abscesses. The presence of a swollen quarter or quarters with pain and

heat may be associated with mastitis caused by gram-negative bacteria. Cold damp areas of skin on the udder that are discolored, necrotic, and possibly sloughing are evidence of gangrenous mastitis. In lactating animals, milk should be present in each quarter, and some of this milk should be expressed for examination. The milk should be of normal color and consistency and should not have any appreciable smell. The presence of leukocytic flakes or clots (garget) is an indication that the udder is mounting an inflammatory response. This response can be measured qualitatively by using the California Mastitis Test (CMT). One should also collect individual quarter samples from those quarters showing garget or those that test positive on the CMT for bacterial culture and sensitivity.

The next step is to evaluate the head and neck regions. The head should be symmetric in appearance, and any asymmetry should be evaluated to determine whether the deviation is caused by a neuromuscular or a skeletal defect. Facial nerve paralysis results in one type of asymmetry, whereas a frontal sinusitis with concurrent displacement of the frontal bone appears differently. Discharges from the eyes, ears, nose, or mouth are noted and correlated with other physical findings. The oral cavity is examined by grasping the tongue with the hand and extending it out through the interdental space. Muscular tone of the tongue is evaluated at this time. The normal animal will resist extraction of the tongue and will quickly retract the tongue into the oral cavity when released. Increased ease of extraction and delayed retraction are indicative of diseases resulting in flaccid paralysis or paresis of skeletal muscle, such as seen in botulism, for example. The tongue and oral mucosa are examined for the presence of erosions, ulcerations, foreign bodies, or areas of necrosis. The dental arcade is evaluated for age of animal, absence of teeth, loose teeth, or necrotizing gingivitis. The color of the mucous membranes is noted. Icterus, pallor, hyperemia, cyanosis, excessive reddening, or brown “mud-colored” mucous membranes can all be noted, depending on the underlying disorder. Mucous membrane color is best evaluated in the eyes and/or vulva because of the presence of pigments in the oral mucosa of many ruminants. The smell of the breath is noted and, if fetid, might be an indication of a retropharyngeal abscess caused by trauma, lung abscess, or gangrenous pneumonia. If the breath is foul, deep palpation within the oral cavity for an abscess or necrotic area is indicated.

Table 1-4 Expected Values for the Scrotal Circumference of the Bull at Different Ages[4]

Age (Months)	Scrotal Circumference (cm)
12–14	30–34
15–20	31–36
21–30	32–38
31	34–39

Table 1-5 Expected Values for the Scrotal Circumference of the Ram at Different Body Weights[5]

Body Weight (kg)	Scrotal Circumference (cm)
<45	23–27
45–70	27–33
70–90	30–36
90–115	31–37
115–135	33–38
135–160	36–40

The mucous membranes of the nares are examined, and erosions and ulcerations are noted. Nasal discharges can be an indication of a pulmonic problem but can also be seen with sinusitis. Bilateral discharge is most commonly associated with pneumonia, and unilateral discharge is more often an indication of a sinus problem. However, percussion of the sinuses is necessary to fully evaluate the presence of a discharge. Normal sinuses percuss with a hollow sound, much like that of a hollow tree, and dullness on percussion might indicate sinusitis, sinus cyst, or other fluid or mass in the sinus.

The eyes are examined next. The sclera and mucous membranes are evaluated in much the same manner as the oral and nasal mucous membranes. The corneas are examined for the presence of opacities, discolorations, ulcerations, and lacerations. The position and size of the corneal opacities or ulcerations can be helpful in determining the cause. Foreign bodies such as plant awns and seeds beneath the third eyelid often cause opacity of the medial aspect of the cornea. Infectious bovine keratoconjunctivitis (pinkeye) is usually localized to the central cornea and causes severe corneal ulceration. When the mucosal diseases cause corneal opacities, they generally do so at the junction of the cornea and sclera and usually do not ulcerate the cornea. The anterior chamber should be examined for the presence of hyphema or hypopyon. These can sometimes be seen in animals with severe bacteremia, especially in neonates with failure of passive transfer. The animal should be evaluated for the presence of a menace reflex (absent in normal neonates for up to 2 weeks), and the pupillary light responses should be observed. Nystagmus and strabismus should be characterized, if present, because the direction is important in localizing the lesion. Nystagmus or strabismus or a deficit noted in the pupillary light reflex or menace reflex is indicative of underlying neurologic or ophthalmologic disease.

The ears should be palpated and evaluated as to their temperature and the presence of skin lesions. They should be warm to the touch. Ears that are cold are an indication that there is decreased blood flow to the periphery, as seen in hypocalcemic states, with decreased cardiac output, or in severe toxic states caused by peripheral vasoconstriction. The presence of small crusty areas or erosions of the skin of the pinna is seen in some of the mucosal diseases such as bluetongue or bovine virus diarrhea. In sheep with acute bluetongue, edema of the face and ears sometimes occurs. If aural discharge or head tilt is present, the ear canal should be examined grossly and with the use of an otoscope for the presence of foreign body or parasites. Purulent discharge can be noted and is an indication of otitis externa. Noting that the eardrum has ruptured along with the purulent discharge is diagnostic of otitis media (and possibly otitis interna). Animals that have suffered trauma to the laryngeal or throat latch region and have a basisphenoid fracture can have bloody discharge from the aural canal. Correlation of the otoscopic findings with other clinical findings is necessary to arrive at a definitive diagnosis.

The palpable lymph nodes of the head and neck include the parotid, the submandibular, and the deep retropharyngeal. The deep retropharyngeals can be palpated externally, if enlarged, in the sheep, goat, and calf. They can be examined in the adult bovine by extending the hand through the mouth and palpating the pharynx. By keeping the animal's mouth open with one hand and guiding the other hand along the dorsum of the tongue to its base, the examiner can then extend the hand aborally into the pharynx. Enlargements of the deep retropharyngeals, abscesses, or other masses can then be palpated. The most common causes of masses or abscesses in the pharyngeal region are infectious or iatrogenic (e.g., secondary to trauma from a balling gun, paste wormer gun, or other instrument). The submandibular nodes are located in the intermandibular space and are identified by slipping the skin and underlying tissue through the fingers. These nodes are oval and about the size of a walnut, or 1 to 2 inches in diameter (2.5 to 5 cm). The parotid lymph nodes are almond shaped and are located just caudal to the ramus of the mandible and about 4 inches (10 cm) ventral to the ear.

The skin of the neck is palpated, with attention paid to the presence of abscesses, lacerations, or other lesions. Skin turgor can be assessed by tenting the skin and measuring the time it takes for the skin to return to normal shape. This is used to determine the state of hydration. In normal, hydrated animals the skin returns to normal position within 1 second. Using other factors such as sunken eyes, dryness of mucous membranes, abnormal heart rate, and degree of illness, an estimation of percent dehydration is made. Dehydration is first noted clinically when the animal is approximately 5% dehydrated, and death occurs at 12% to 15% dehydration.

The larynx should be palpated for enlargement and the presence of pain. The trachea should also be palpated for the presence of fractured tracheal rings, collapsed areas, and pain on palpation. The jugular veins are examined for the presence of distention and pulses. Thrombosed veins should also be noted because this condition may alter the desired course of therapy and often prevents placement of a catheter. The venous stasis test is performed on the jugular by holding off the vein in the midcervical region. Normally the vessel fills above the point of occlusion and remains collapsed below. With restricted venous blood flow, as seen in cases of right-sided heart failure, a positive stasis test can result. In these cases the vessel below the occluded point fails to collapse or takes a prolonged time to do so, and a jugular pulse is frequently present.

The final step in the physical examination is rectal palpation. This cannot be accomplished in small ruminants, so this section is directed primarily toward the bovine. The pelvic area is evaluated for the presence of retroperitoneal abscesses or fractures of the pelvic bones. The left kidney can be palpated for overall size and shape, which is normally lobulated in cattle, and the kidney can be gently squeezed to determine if pain is evident. The rumen should be palpated and the findings compared with those noted on percussion and auscultation. If there is any evidence of intraabdominal gas pings, an attempt should be made to palpate the suspected organ. This can provide information that may be helpful in determining therapeutic or diagnostic directions. The rectal palpation can reveal the presence of masses that were not palpable externally, such as fat necrosis or tumors. Adhesions and evidence of peritonitis can also be palpated rectally, and attempts should be made to localize them to a specific area of the abdomen to establish potential cause. The preiliac (or internal iliac) lymph nodes are located by sweeping the hand along the craniodorsal face of the ilium. These nodes normally have the size and shape of a walnut. Enlargements are noted with lymphosarcoma, peritonitis, and severe limb inflammation. The lymph nodes of the aortic bifurcation are very small and not easily palpated. Their ability to be palpated would be evidence of abnormal enlargement. Palpation of the genital tract is directed toward establishing size, shape, and presence of abnormalities. These contents could be normal, as with a pregnant animal bearing a fetus, or abnormal, as seen with a pyometra. If it is determined that a cow is not pregnant, the ovaries and oviducts should be palpated for structures and abnormalities. In the bull, particular attention should be paid to the prostate, seminal vesicles, and bulbourethral gland.

Diagnostic imaging using an ultrasound probe in conjunction with rectal palpation can add to the information already gathered during the physical examination to further refine the problem and aid in prognostication and development of the therapeutic plan. Proper manipulation of the probe can allow for imaging the kidney, the uterus, the bladder, and the rumen wall. Abnormal structures noted on palpation of the abdominal cavity can also be imaged. The accessory sex glands in the male can be visualized also.

1.3 MEDICAL RECORD

The information gathered by means of the physical examination (see Fig. 1-2) is compiled and correlated with the data obtained during the history (see Fig. 1-1). A problem list should be formulated through the physical examination and anamnesis, leading to the development of a specific diagnostic plan, diagnostic ruleouts, and a proposed course of therapy (Fig. 1-6). Prognosis can also be assessed with the information now in the examiner's hands. Accurate recording of the abnormalities noted during the examination should become part of the medical record and can prove valuable in following the course of the case. In addition, with each complete and accurate physical examination performed, the practitioner becomes more skilled in the procedure, adapting it to fit his or her needs, and using his or her time more efficiently. With the number of diagnostic tests available to the profession today, the information gained from the physical examination will allow the examiner to pick the tests that are specific for those disorders suspected, which saves the practitioner time and the client money.

1.4 DIAGNOSTIC TESTS THAT CAN BE APPLIED IN THE FIELD

There are laboratory procedures that can be performed in the field, the results of which would prove beneficial in the development of a diagnostic plan. These include the CMT, partial urinalysis (dipsticks), ruminal pH determination, and milk or blood progesterone tests. In addition, some serum chemistries can be performed cowside with the use of the i-Stat.*

The CMT is a simple procedure that aids in the detection of clinical or subclinical mastitis (see Chapter 36). This procedure is done routinely during all physical examinations of lactating cows. Partial urinalysis is accomplished by collecting the urine and using any one of a number of urine dipsticks that can be commercially obtained. With a suspected case of lactic acidosis, a rumen sample can be collected through the stomach tube or via percutaneous needle puncture, and rumen pH can be determined. Most drugstores carry pH paper that can be used for this procedure. Be certain that the paper has a standard range, because there are papers that are specific for the acidic or the alkaline range. A rumen pH below 4.5 would be indicative of lactic acidosis. Numerous cowside progesterone assays that use either milk or blood as substrate have recently been developed. These can be relatively easy to use and interpret or they can be difficult, so discretion should be used when making initial purchases. These ancillary diagnostic procedures are explained in greater detail later in this text.

* i-Stat Serum Chemistry Analyzer, i-Stat Corp., Princeton, NJ; distributed by Heska Corp., Waukesha, WI.

1.5 INSURANCE, INTERSTATE, AND PREPURCHASE HEALTH EXAMINATIONS

The complete physical examination as described in the preceding sections is necessary for a proper prepurchase or insurance examination. For insurance purposes a more complete accounting of the examination must be done. This means that all findings, whether normal or abnormal, have to be recorded. A specific form is generally provided by the insuring agent, and this should be used. Potential for future legal action also exists whenever an animal is insured; therefore it is in the practitioner's best interest to complete the insurance form accurately.

The prepurchase examination is similar to the insurance examination. The physical examination form (see Fig. 1-2) can be used to record findings. The prepurchase examination could be performed on the highly pedigreed female that is being consigned to sale, but it is more often performed on the male scheduled for use as an artificial insemination stud. Occasionally one could be asked to examine an animal under consideration for purchase. Experience indicates that the veterinarian should be employed by the potential buyer in these cases. This arrangement avoids any potential accusations of conflict of interest on the part of the examining veterinarian. A complete blood count and a chemistry panel should be run. Generally it is prudent to certify that the animal is healthy and to test for tuberculosis, brucellosis, and bovine leukosis (using agar gel immunodiffusion). Additional laboratory tests for anaplasmosis and bluetongue may be indicated. Often an animal being consigned to sale or one going into artificial insemination service is required to meet federal regulations for interstate shipment. This information can be obtained from the federal veterinarian in charge in your area or from the office of the state veterinarian in the state of destination.

A problem arises when the number of animals submitted for interstate health examination is large. Economic and temporal constraints usually preclude complete examination of all the animals presented. At such times the visual examination described earlier can prove helpful in determining which animals are to be singled out for the more complete physical examination. The examination of individuals is less complete than for prepurchase or insurance examinations, because such factors as fertility are not at issue when filling out an interstate health certificate. Choosing animals with abnormalities in behavior, physical condition, gait, or posture allows the practitioner to concentrate on those that have the most potential to be diseased. Also, one can be fairly confident that if all the animals appear normal on the general examination, they are healthy and would be suitable for interstate shipment as long as the results of the intradermal tuberculosis test and required serologic tests prove negative. To sign an interstate health certificate, a veterinarian must be accredited and licensed in a state. It is essential that a veterinarian signing an interstate health certificate have examined the livestock sufficiently and diligently enough to be confident that no infectious or contagious diseases are present in the consigned group. A call should be placed to the office of the state veterinarian in the state of destination to be sure that all current requirements are fulfilled before shipment is scheduled.

Fig. 1-6 Example of a diagnostic and treatment sheet. (Courtesy Lander Veterinary Clinic, Turlock, Calif.)

LANDER VETERINARY CLINIC, INC

2930 Lander Avenue
Turlock, California 95830

Telephone (209) 634-5801
Fax (209) 634-2228

DIAGNOSTIC AND TREATMENT SHEET

FARM OWNER _____ **DATE** _____

ANIMAL ID NUMBER _____ **PRODUCTION CLASS** _____
LACTATING COW/DRY COW/HEIFER/CALF/BULL

PHYSICAL EXAM

TEMPERATURE	NORMAL	FEVER	HYPOTHERMIA		
RUMEN MOTILITY	NORMAL	WEAK	ABSENT	BLOAT	COLLAPSED
ABDOMINAL PINGS/SPLASHES/PAIN	NORMAL	ABNORMAL	LDA/RDA/RTA	GRUNT	DIARRHEA
RECTAL PALPATION FINDINGS	NORMAL	ABNORMAL	DISTENDED BOWEL	KIDNEY	OTHER
MANURE	NORMAL	DIARRHEA	SCANT/NEG	FIRM	BLOOD/FIBRIN
URINE	NORMAL	KETONES	+ ++ +++	BLOOD/PUS	
REPRODUCTIVE TRACT	NORMAL	PREGNANT	METRITIS	PERIMETRITIS	ADHESIONS
LUNGS	NORMAL	PNEUMONIA	EMPHYSEMA	PLEURITIS	CHRONIC
HEART SOUNDS/RHYTHM	NORMAL	MURMUR	ARRHYTHMIA	SPLASHING	MUFFLED
LYMPH NODES/CNS	NORMAL	ENLARGED	DOWN COW	CNS SIGNS	
MAMMARY GLANDS	NORMAL	MASTITIS	TEAT ABNORMALITY		
EYES/MOUTH/MUCOUS MEMBRANES	NORMAL	ABNORMAL	PALE/JAUNDICE	SQUAMOUS CELL	LUMPY JAW
LIMBS/BODY EXTERIOR	NORMAL	ABNORMAL	SKIN LESIONS	LAMENESS	INJURY

Diagnosis 1. _____ 2. _____ 3. _____

TREATMENT

IV FLUIDS	CALCIUM	DEXTROSE	7.2% NA CL	K CL	ELECTROLYTES	PHOSPHATE
ANTIINFLAMMATORY	DEXAMETHASONE	PREDEF 2X	BANAMINE	PHENYLBUT	ASPIRIN	SOLUDELTA
ANTIBIOTICS	OXYTETRACYCLINE	ALBON	PENICILLIN G	POLYFLEX	NAXCEL	TRIBRISSEN
RUMENATORICS	LAXATIVE BOLUS	EPSOM SALTS	CHARCOAL	MINERAL OIL	NUTRADRENCH	NA HCO3
VITAMINS/MINERALS	MULTI B	B 12	D PANTHENOL	VIT E/SE	ORAL KCL	ORAL PO4
ANALGESICS	TORBUGESIC	VALIUM	EPIDURAL	SEDATION		
LONG ACTING ANTIBIOTICS	LA 200	MICOTIL	NUFLOR	LS 50	ERYTHROMYCIN	LA SULFA
HORMONES	OXYTOCIN	GNRH	LUTALYSE	ECP		
OTHER	EQUIPOISE	NA IODIDE	IU OXYTET BOL			

SURGERY LDA ☐ RDA ☐ **EXPLORATORY** ☐ **C-SECTION** ☐ **OTHER** ☐ _____

FOLLOW-UP THERAPY **PROGNOSIS** EXC☐ GOOD☐ FAIR☐ POOR☐

1. _____
2. _____
3. _____
4. _____

WITHDRAWAL INFORMATION

DRUG _____ **MILK** _____ **SLAUGHTER** _____

DOCTOR: _____

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2 Chapter 2 Equine History, Physical Examination, and Records

Kathleen Casey Gonda

T. Douglas Byars

The ideal purpose of the physical examination is to determine what or if a problem exists. The results should be used to establish a diagnostic plan, prepare a therapeutic approach, and develop a prognosis.

The nature of an internal medicine problem does not always allow for each objective of the physical examination to spontaneously or quickly generate either a diagnosis or a prognosis. More realistically, the examination process dictates the specific laboratory tests or procedures to be performed that support the diagnostic or therapeutic effort. The clinician's self-discipline regarding the extent of the physical examination should be guided by experience, efficiency of time, and the ancillary diagnostic aids that are available. A complete and extensive examination of each patient may not always be practical, especially in busy private or academic practice situations. In these cases the clinician should provide for the client's concerns with an expedient history and a pertinent physical examination process that addresses the client's complaint (e.g., a rectal examination is not required for an evaluation of a pneumonia patient).

2.1 PHYSICAL EXAMINATION RECORD

Preparation for the initial contact time with the client and patient should begin with a system of record keeping. Ambulatory records are usually more flexible than “in-house” hospital admission forms. Both field and clinic forms should include designated spaces for the client or agent's address and phone number. An area for the complete signalment (name, sex, breed, color, age), including an estimated weight, should be provided. If the patient is unnamed, as with foals, it should be listed in the dam's name with the year of birth (e.g., Curious' 06). The sire's name should not be used because more than one foal per year would be expected from a stallion's crop. Whenever surrogate mares produce multiple foals from a single embryo transfer dam, a new system of naming and identification will have to be incorporated. Additional identification of the patient may include a lip tattoo, freeze brand, or microchip number and if available should be noted in the horse's record. By 2009 the federal government will have in place a system that uses microchip technology to permanently identify and track the movement of all species of livestock, including Equidae. In the event of a disease outbreak, rapid identification and surveillance of affected or exposed individuals will be possible. The National Animal Identification System (NAIS) will allow all livestock owners, including hobbyists, to enroll and participate in this program.[1]

2.2 EQUINE INSURANCE

If the animal is insured, this should be documented, preferably with the insurer's telephone number. In addition, the type of insurance should be noted (e.g., mortality and/or surgical and medical). It is the client's or his or her agent's responsibility to notify the insurance company representative whenever an animal insured for full mortality contracts an illness or sustains an insult, life-threatening or not, that requires a veterinary examination. If the patient is insured, it is considered a professional courtesy for the veterinarian to also communicate directly with the insurance company, especially with a life-threatening illness. Also, permission from the insurance company is required whenever a general anesthetic, surgical procedure, or euthanasia is to be performed. Whenever euthanasia is requested, the insurance company may require a second opinion from an adjusting veterinarian. If a direct representative from the insurance company cannot be contacted immediately, the clinician must exercise professional judgment in assuming the responsibility for a humane or critical decision. The client or agent should be

in agreement with the decision, and all communications and pertinent data should be documented in the medical record. If a necropsy is to be performed, it should preferably be in the presence of another veterinarian from a different practice. The American Association of Equine Practitioners (AAEP) provides an insurance pamphlet as a guide to veterinarians.[2] Table 2-1 is an abbreviated list of the types of equine insurance offered.[3]

2.3 HISTORY

The medical history should be directed to the clinical problem. The "herd health" of the stable or farm is briefly depicted by the vaccination and parasite control program. The diet should be determined, including supplements, the grazing environment, stall or housing schedule, and the medical problems concerning other animals on the premises that may coincide with a group incidence of the client's complaint.

When a veterinarian is dealing with neonates, the reproductive and foaling history of the mare is important in establishing an early diagnosis. Any compromise to the mare's gestation (e.g., systemic disease, general anesthesia, or administration of certain medications), foaling, or lactation; placental abnormalities; and any problems that occurred during previous pregnancies should be questioned and considered to be important, pertinent historical data.

A description of the types of medication used before hospitalization may aid in determining if "masking" agents have inadvertently been used. Tranquilizers or sedatives are frequently used for vanning and shipping purposes, and in many instances a van driver or hauler is unaware of medications used or the patient's medical condition. Analgesics such as flunixin meglumine, which are often inappropriately administered by owners or farm staff, may mask signs of pain or colic and alter interpretation of the severity of the horse's condition on arrival. These drugs can cause confounding clinical signs of hypotension, bradycardia, lethargy, weakness, and ataxia. Failure of such an analgesic to abolish clinical signs may necessitate hospital or clinic admission for further evaluation or surgical consultation. Conversely, the failure of other previous medical treatments can aid in the initial selection of more appropriate therapeutic planning.

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Table 2-1 Equine Insurance

Type of Insurance*	Coverage	Role of Attending Veterinarian
Perils	Covers mortality claims for shipping accidents, fire, and natural disasters such as lightning	Inform clients of responsibility to inform insurance company
Mortality†	Covers mortality claims for all life-threatening conditions (e.g., colics)	Inform clients of responsibility to inform insurance company of any anesthetic, surgical needs, or euthanasia
Use	Covers a loss in intended use (e.g., racing, fertility)	Inform clients of responsibility to inform insurance company of any anesthetic, surgical needs, or euthanasia
Major medical or surgical	Covers payment of medical or surgical costs with set limits based on policy	Inform clients of responsibility to inform insurance company before procedures Supply estimate of cost to client Policy is in addition to mortality coverage

* The client is responsible for the costs of veterinary care and treatment unless a medical and surgical policy exists.

† Fetal mortality insurance covers unborn foals, usually until 24 hours after birth.

The patient's individual problems should be determined according to such factors as clinical history of onset, feed and water consumption, fevers, and decrease in performance. In essence, the clinician must effectively “zero in” on the problems at hand.

2.4 PHYSICAL EXAMINATION

The extent of the physical examination will be subject to the environment where the examination is conducted (field vs. hospital), the equipment at hand, and the ancillary personnel available for restraint and procedural purposes. In a hospital setting the clinician should have immediate access to most of the equipment and diagnostic instrumentation listed in Box 2-1. The physical examination sheet should provide a systematic list of the organ systems being evaluated. Vital signs (temperature, pulse, and respiratory rate) should be documented in the “calm” animal, if possible. Abnormal findings are described in an appropriate space provided, usually below the body systems checklist. Using the same numeral for each body system throughout the examination process and in problem identification is useful for future caseload recall, especially if a computer is used and codes can be applied to clinical findings and diagnosis. At the completion of the physical examination, the major problems identified are listed, and appropriate laboratory tests can be requested. The final diagnosis is seldom determined at the time of the initial examination. The final diagnosis represents the final assessment and should be filled in at the appropriate time (e.g., hospital discharge).

A general evaluation of the equine patient should be made from afar. This is particularly important for neonates at the side of their dams. The initial observations of body condition, posture, weakness, lethargy, incoordination, lameness, and musculoskeletal asymmetry are more easily observed a slight distance away from the patient.

2.4.1 Box 2-1 Recommended Examination Room Equipment and Ancillary Services

2.4.1.1 EXAMINATION ROOM EQUIPMENT

Records (examination sheet and request forms)

Thermometer

Clock with second hand

Stethoscope

Twitch

Rectal sleeves, sterile examination gloves, and lubricants

Nasogastric tube

Hoof knife and testers

Ophthalmoscope

Otoscope

Endoscope

Electrocardiogram (ECG) machine

Ultrasound (linear or sector scanner)*

Sphygmomanometer and Doppler ultrasound scanner (tail or limb)

2.4.1.2

ANCILLARY SERVICES

Radiology and imaging services

Ultrasound consultation

Laboratory services including point-of-care diagnostics

* The ultrasound service is more appropriately located in the examination room rather than as a consultation service.

The integumentary system can usually be quickly evaluated as to the type, distribution, and number of lesions and site and layer of involvement—for example, 3 × 6 × 2 cm raised, nodular, nonpainful mass involving the cutis and subcutis. Such a lesion would be readily available for superficial evaluation. However, subtle lesions of petechia and ecchymosis cannot be visualized in the integument because the hair coat and pigment hide lesions that are obvious in other species, such as purpura of nonpigmented humans and pigs. In these instances the mucous membranes must be examined as an extension of the integumentary system. If obvious multiple lesions of the skin are present, documentation is usually expedited by drawing a picture of a horse and indicating the distribution in the drawing, including both sides of the horse (see Skin Disease Examination, Chapter 11). Gross generalized distortions (e.g., anasarca) may be viewed as lesions of possibly more than one body system (integumentary and circulatory).

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For the internist, evaluation of the musculoskeletal system usually involves a rudimentary examination of the site and appearance of the disease processes. Primary lameness is more commonly evaluated by clinicians familiar with diagnostic nerve blocks, arthrocentesis methods (e.g., septic arthritis in foals), and radiographic findings. It should be noted, however, that acute (caused by fracture) or chronic lameness can coexist with primary neurologic disorders (e.g., equine protozoal myeloencephalitis). Therefore, when warranted, the patient should receive a cursory neurologic evaluation (see Chapter 8) in conjunction with the musculoskeletal examination. Conversely, all horses presented with systemic illness (pneumonia, colitis) should also be evaluated for the presence of laminitis, as this complication is often the limiting factor for the horse's survival. Careful palpation of the lower limbs may indicate increased intensity of digital pulses or changes in the coronary band that may be related to the “sinker” syndrome (distal phalangeal displacement).[4] If laminitis is present as a complicating factor, the clinician should be able to add to the clinical prognosis by using Obel grading (1 to 4).

Evaluation of the circulatory system starts with assessment of heart rate, rhythm, and any presence of murmurs. Mucous membrane color, capillary refill time, scleral injection, palpable changes in the temperature of the ears and extremities, jugular pulsation, and pitting subcutaneous edema are the most common obvious circulatory physical examination parameters. The heart should be auscultated bilaterally, and murmurs graded according to intensity (I to VI or I to V), character, the valvular site, and phase of the cardiac cycle. Arrhythmias usually involve a request for an electrocardiogram (ECG), except with the common findings such as type II heart blocks in clinically asymptomatic horses. Type II heart block in normal horses can usually be obliterated by exciting the horse with a threatening gesture. In addition to electrocardiography, transcutaneous ultrasound examination of the heart and pericardium and transrectal evaluation of the caudal aorta and iliacs for intraabdominal thrombotic lesions can be

used.[5,6] If procedural assessments of blood pressure are needed, a manometer for central venous pressure or a sphygmomanometer with Doppler ultrasound is used on the base of the tail in adults and the tail or inside radius (forearm) in foals.[7]

The respiratory system is similar to the circulatory system in that the breathing rate and mucous membrane color are important assessments. Respiratory effort and the phase of increased work should be assessed (e.g., heaves). Auscultation should be of both the upper (larynx and trachea) and lower airways. Nasal airflow can be determined by wetting the hands and holding them gently over the nostrils so that both intensity and equality of air movement can be assessed. Smelling the breath for fetid or necrotic odors (ozena) is similarly important, and endoscopic evaluation of the upper airways should be an adjunct to abnormal clinical findings. A penlight can be used to visualize the internal nares (septal mucosa). Percussion of the sinuses should be performed for detection of dullness, suggesting sinusitis or the presence of fluid within the sinus cavity. In addition, the head should be carefully examined ventrally and caudally for the presence of lymphadenopathy.

The interpretation of lung sounds has been described elsewhere,[8] and the clinician should make an effort to auscultate dorsal and ventral regions of the thorax bilaterally and document findings as to the location or absence of sounds and the phase of respirations involved.

Percussion is a reliable clinical tool and should be performed in cases of suspected abscess, tumor, or pleural effusion. A pleximeter and tablespoon are the only tools required, although some clinicians are adept at direct finger percussion of the chest. In foals, percussion can be performed by placing a stethoscope on one side of the chest and reaching over the back of the foal to manually percuss the opposite side. Fractured ribs may be recognized in the neonatal foal as palpable asymmetry or a bony crepitus (“clicks”), often with edema of the sternum or elbow coinciding with the fractured side.

Ultrasound has revolutionized the clinical evaluation of the thoracic cavity. Unfortunately, the familiarity of clinicians in thoracic interpretation is directly related to access and frequency of ultrasound use. However, subtle pneumonia, abscess, and pleural effusion represent rapid and definitive objective findings.[5] Because radiographic changes often lag behind clinical disease, serial examinations via ultrasound may be a more accurate way of monitoring response to treatment. Ultrasound may, in fact, eliminate the need for chest radiographs in numerous cases, thereby increasing efficiency and decreasing client costs.

A systematic approach should always be used when examining the horse for gastrointestinal disease. Although the majority of emergencies and referrals are related to colic or acute intestinal disease, the clinician should resist the temptation to focus only on the abdomen, so that important clinical signs relating to other problems are not missed (e.g., gastric ulceration, botulism). If a clinical complaint involving the abdomen is present or in suspected cases of intestinal displacement, obstruction, or volvulus, the gastrointestinal system is initially examined by bilateral auscultation of intestinal sounds. In addition, the abdomen should be auscultated ventrally for sounds similar to “ocean waves” or sand pouring on itself, indicative of the presence of sand within the gastrointestinal tract.[9] In cases in which the gastrointestinal tract is the site of the primary lesion, checking for gastric reflux and performing a rectal examination[10] may become a necessity. Clinicians should strive to become adept at rectal palpation and regard the procedure as a premier diagnostic skill while respecting the risks involved for the patient and veterinarian.

The patient should be observed for the presence of normal prehension, eating, and drinking whenever dysphagia is present or neurologic dysfunction is suspected. The evaluation of the gastrointestinal system should also include a dental examination for the presence of malocclusion and dental abnormalities (e.g., missing or damaged teeth) that can affect prehension or mastication. Accurate notation of affected teeth should be made in the medical record using a universally accepted identification system, such as a numeric system in which the horse's head is divided into four

quadrants, with each tooth described by its own number (e.g., two central upper incisors on horse's right and left would be 101 and 201, respectively). Clinicians should also become adept at dental age determinations, albeit with an awareness of its limitations and subjectivity.[11] Nasogastric intubation is useful in evaluating dysphagia and esophageal blockage (choke) and determining the presence or absence of gastric reflux. In addition, the volume and character (e.g., color, pH, presence of blood or toxic plant material) of reflux obtained can be rapidly evaluated and may aid in the diagnosis.

The use of long endoscopes (e.g., 2 to 3 m) is valuable in the visual assessment of the esophagus and stomach with lesions such as esophageal stricture and gastric ulceration. For a diagnostic endoscopic examination of the stomach, it is recommended that the patient be muzzled or held off feed for at least 10 hours to allow complete visualization of the stomach.[12]

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Ultrasound evaluation of the abdomen in conjunction with aspiration and analysis of fluid visualized may quickly reveal peritonitis, uroperitoneum, hemorrhage, ascites, visceral rupture, or abdominal masses. In adults, palpable abdominal masses and enlarged lymph nodes usually can be scanned transrectally.

The urogenital system can be examined by manual palpation, rectal palpation, vaginoscopic (speculum examination) viewing, endoscopic viewing, and ultrasound. The caudal portion of the left kidney is easily palpated in most horses. Catheterized samples should be obtained (e.g., cultures, urinalysis) before any contaminating invasive procedures (e.g., rectal palpation) are performed and before fluid therapy is initiated. Sphincter tone may be subjectively or objectively (urethral pressure profile) assessed in horses with urinary incontinence or stranguria. Horses with incontinence often demonstrate “scalding” of the perineum and hind legs.

The eyes can be examined by a rapid visual assessment using a penlight. The cornea and cranial and caudal lens capsules can be evaluated by horizontally moving the penlight and noting the crossing light reflexes. Pupillary constriction to light and the “menace” response should be observed, although these reflexes may be significantly slower or absent in the neonate. An ophthalmoscopic retinal examination should be performed whenever the eyes represent the primary complaint, and fluorescein dye strips should be used for the detection of corneal ulcers. Blindfolding of one eye at a time may aid in the assessment of unilateral blindness and should be conducted in a safe area with “blunt” devices contrived as an obstacle course.

The neurologic system examination should involve a consistent procedure for all patients with nervous system disorders (see Nervous System Examination, Chapter 8 and Chapter 35). The patient's attitude, posture, and head carriage should be assessed from afar. The cranial nerves should be evaluated, followed by examination of the spinal reflexes and tail tone. Sensory deficits should be noted at this time. Conscious proprioception and postural responses (e.g., placement, hemihopping, sway) can then be assessed before observing the patient in locomotion. Notes regarding symmetry, asymmetry, ambulation, paresis, muscle atrophy, and upper and lower motor neuron deficits should be documented to aid in determining the sites for any additional ancillary tests such as radiographs or cerebral spinal fluid collection. Blindfolding should be conducted in a safe area, especially for patients with vestibular disease. An area of incline is useful for evaluating the locomotor deficits, especially when the horse is led with the head elevated.

The lymphatic system is usually evaluated merely by recording any obvious lymphadenopathy. This can be regional or local (as in strangles) or generalized (cutaneous lymphosarcoma) and may be appreciated on rectal examination. Lymphangitis or the presence of edema should also be noted.

Once a patient has been admitted to the clinic or hospital, well-organized flow charts should be used for monitoring and assessing the patient.

2.4.2 Use of Ancillary Equipment in the Examination Procedure

Advancing technologies are allowing the practitioner or clinician to add to or replace many physical examination procedures with techniques capable of providing diagnostic information or direct therapeutic intervention. Ultrasound of the chest for the definitive diagnosis of a pleural effusion is an example of an objective procedure that may obviate much of the traditional physical examination procedures used for the clinical diagnosis of pleuropneumonia (e.g., auscultation, percussion, ballottement). For diagnostic equipment to be used in this capacity, it should be available in the physical examination area.

The size of equipment is a determining factor in whether or not a diagnostic tool is suitable for the examination area. For example, equipment such as computerized axial tomography scanners, magnetic resonance imaging (MRI) units, and nuclear scintigraphy units do not currently fit into the space available in most hospital physical plants. Large, modular ultrasound machines can be cumbersome in small areas, although units available for field reproductive use (linear or sector scanners) are appropriate for any area, including vehicle transport. The choice of ultrasound equipment is an individual decision based on need, budget, and available units. Security should also be a consideration in stocking an examination area with equipment and medications. The clinical examination areas of most facilities tend to be high-traffic regions; this may be a primary reason for not stocking certain pieces of equipment in both university practices and private facilities.

2.5 MEDICAL RECORD

In 1968 Lawrence Weed[13] published on the use of the problem-oriented medical record. This system of recordkeeping emphasizes the justifications for daily decision making during hospitalization. Problems are defined by the history, physical examination, and laboratory findings. Daily (and more frequently for intensive care unit patients) *s*ubjective findings (e.g., appetite, attitude) are documented, and *o*bjective data (e.g., heart rate, temperature) are recorded. This information (e.g., patient is febrile) is then *a*ssessed by the clinician, and a *p*lan (e.g., resubmit laboratory tests, change antibiotic medications) is derived based on the assessment. The abbreviated form of this type of medical record is SOAP, and this method is applied to each problem identified. Although the system encourages medical judgment and accountability, it more directly serves as a teaching tool within institutions by which the student's clinical thinking can be evaluated by the in-charge clinician. In private practices the method of record keeping is more flexible and tends to document vital information that primarily serves as an accounting of services and provides a medicolegal record. Unfortunately, many medical records function only as invoices and do not record medical information regarding the patient. This is more often true of ambulatory records but can be found in certain hospital practices. Whichever system is used, the responsibly prepared medical record should provide medical information, justification for charges, and a protection from liability. A thorough medical record further allows for the retrieval of retrospective information. The accumulation of data is beneficial to the communication of clinical caseload experiences to other clinicians for the benefit of their patients.

2.5.1 Medical Record Filing

Two major systems of medical record filing exist: numeric and name filing. Numeric systems offer consistency of the record and avoid the confusion of patients with similar names. The problem of name similarity is primarily confined to the nonregistered breeds of horses. Breed registration requires name approval to avoid duplication, among other undesirable designations. Again, for record-keeping purposes, clinic or ambulatory records for unnamed young horses are best designated by the dam's name and the foal's year of birth (e.g., Curious' 06) and filed by month and year of examination. A “master” admission log should be maintained for record retrieval

purposes, especially when a patient has been seen on multiple occasions. Color coding, along with numbering of the file folders, may be helpful in record retrieval. Computers offer the advantage that records can be retrieved through any one of a number of recall parameters (e.g., problem, client).

2.5.2 Computer-Generated Medical Records

Traditionally, patient medical records (PMRs) are maintained via a manual, paper-based, on-site system of data storage and retrieval as described previously. Before computerization and its acceptance by the medical community, all information regarding patient history, diagnostic testing, and treatment notes was handwritten and filed. Unfortunately, a number of problems coexist with a paper-based system, including illegible handwriting by practitioners or staff, poor integration of patient information (e.g., diagnostic test results and imaging studies filed separately from PMR), and loss of or damage to files.[14] In addition, state veterinary boards require that all patient records and imaging studies be retained by a practice for minimum period of time before they can legally be disposed of. Storage issues can be a particular problem for equine practices that do many prepurchase examinations, in which radiographs may be retained for 10 to 20 years. Although many veterinary facilities currently use computers for various tasks, such as accounting and inventory, few have eliminated the paper-based PMR completely.

Computers offer the advantages of legibility, quick data retrieval, and immense archiving capacity. The need for rapid transfer of medical information from doctor to doctor or doctor to referral facility is being met by advances in computer software and Internet access. Thus, the current trend in human and veterinary medicine is the development and implementation of an electronic medical record (EMR) that is entirely computer generated. An EMR permits one or more individuals, simultaneously, to access laboratory results, imaging studies, and other pertinent patient information.[15] For the equine practitioner, the availability of real-time ultrasound imaging and digital radiography has revolutionized the production and transmission of high-quality diagnostic images, via computer, within moments after they have been taken. This has greatly increased the quality of medicine and efficiency of patient care, allowing general practitioners rapid access to the opinions of specialists at sites distant from the patient. Over time, acceptance of the EMR may result in the complete dissolution of the paper-based medical record.

At this time, several software systems are available to veterinarians that are designed specifically for equine hospitals and include adaptations for ambulatory “off-site” data entry and retrieval.[*][†][‡] In addition to patient information, other applications, such as client invoicing, inventory management, payroll, and so on, are included in these software packages.

Three basic types of systems are currently available to the equine practitioner: standalone and multiuser on-site systems; on-site systems with external synchronization; and Internet-based multiuser systems. The first and second types of systems are similar, but with the addition of external synchronization, patient information can be collected on hand-held devices or laptop computers away from the main hospital (e.g., by ambulatory staff) and downloaded directly to an in-house computer. The third system is the most technologically advanced and offers not only greater efficiency, but the ability to continuously upgrade software. This system offers access to the Internet through either a hospital Web page or a client Internet server and allows practitioners in the field the ability to transmit information, such as digital radiographs, immediately to other doctors, referral hospitals, or specialists throughout the world. These connections can be made via wireless (e.g., cell phone) or direct Internet access (e.g., phone line, cable). Currently, certain veterinary laboratories are capable of sending test results directly to the PMR as soon as they are available.[‡][§] Another advantage to this system is that all information

contained in the EMR can be stored on an off-site server and downloaded to the hard drives of in-house computers.

This technology can be a cost-effective, important tool in modern practice management that increases efficiency and quality of patient care and dramatically reduces storage requirements.

* Mobile Data Software, Inc., 5654 E. Grandview St., Mesa, AZ 85205.

† Elinc Corporation, 5068 W. Plano, Pkwy. Suite 300, Plano, TX 75093.

† Idexx Laboratories, One Idexx Dr., Westbrook, ME 04092.

‡ Idexx Laboratories, One Idexx Dr., Westbrook, ME 04092.

§ VCA Antech, Inc., 12401 West Olympic Blvd., Los Angeles, CA 90064.

2.5.3 Record Keeping for Special Purposes

The Drug Enforcement Administration (DEA) requires veterinary practices to maintain detailed inventory records for scheduled drugs. Drug inventory and use must be documented in a record book kept accessible to the area contained behind two locks where the scheduled drugs are stored. Records must be documented to either a clinic area where a minimal volume of drug can be kept (e.g., a single vial of diazepam), or for patient use. Use should identify the patient, volume used, date, and authorized person who obtained the drug. The drug use should be further documented in the PMR so as to account for the volume having been depleted from the inventory. A monthly or bimonthly accounting suitable for inspection should be conducted from the storage inventory and patient files to accurately account for scheduled drug use. This same accounting and inventory system applies to ambulatory vehicles.

Occupational Safety and Health Administration (OSHA) records are comparable to the DEA ongoing inventory and use records and are stringent in terms of compliance with OSHA regulations.[16] Documentation regarding safety procedures (e.g., fire safety inspections) is required after an initial inspection for labeling and safety protocol. Upgrading of Material Safety Data Sheets (MSDSs) is a further requirement and should comply with current standard.

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3 Chapter 3 Pain

Consulting Editors

James N. Moore

3.1 ANATOMIC AND PHYSIOLOGIC BASIS OF PAIN

3.1.1 What Is Pain?

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James N. Moore

The International Association for the Study of Pain describes pain as an unpleasant sensory and emotional experience associated with actual or imminent tissue damage.[1] However, this definition continues to be debated. Although most agree that pain is “perceived” by organisms that have a nervous system, the degree of “suffering” experienced by various animals is controversial. In human medicine many believe that pain must be defined in the context of intelligence, consciousness, and the memory of painful experiences. However, pain reactions are readily recognizable in large animals and are clearly “remembered” by animals that have experienced them. Perhaps what differentiates humans and other animals is the complexity and manner in which pain is expressed. In verbally competent humans, linguistically reported pain is the gold standard. In human neonates and animals, recognition of pain reactions or behaviors becomes of paramount importance. Despite phylogenetic differences among members of the animal kingdom, it is incumbent on the veterinary practitioner to presume that large animals perceive, react to, and suffer from painful stimuli and experiences.

3.1.2 Nociceptors and Nociception

The International Association for the Study of Pain's definition of pain highlights two important aspects of pain, namely a sensory discriminative component and an emotional, or affective, component. The sensory component of pain is often referred to as *nociception,* or the sensory reception of noxious or injurious stimuli by nociceptors. Nociceptors are sensory neurons having free, unmyelinated nerve endings. These nociceptors respond selectively to noxious stimuli but cannot be characterized based purely on histology. The three main functional types of nociceptors are mechanical, thermal, and chemical. Anatomically they are classified as A-delta or C-polymodal. A-delta nociceptors are unimodal, high-threshold, small-diameter, myelinated fibers that respond to deforming mechanical stimuli such as tissue compression. They typically do not respond to excessive temperatures or chemicals unless sensitized. C-polymodal nociceptors are small-diameter, unmyelinated, slowly conducting fibers that respond to chemical, thermal, and mechanical extremes. Thermal nociceptors, typically present in skin, respond to temperatures exceeding 45° C. For example, radiant heat sufficient to raise the temperature of the skin over the withers (44° to 50° C) elicits the protective twitch reflex within 5 seconds. Chemical nociceptors respond to noxious chemicals (e.g., caustics, acids, bases, hypertonic solutions) or inflammatory mediators (e.g., prostaglandins, bradykinin). Nociceptors exist in muscles, the skin, the periosteum, most internal organs, the tooth pulp, the cornea, and the meninges. With the exception of pain in the meninges (i.e., headache), “pain” in these tissues can be readily recognized.

Nociceptors serve to warn an animal of imminent or ongoing tissue injury. This warning typically elicits protective reflexes, such as the skin twitch reflex described previously, that attempt to separate the animal from the noxious stimulus. The limb withdrawal reflex after the application of a hoof tester can be used as a measure of pain threshold in horses.[2] Pain threshold can be defined as the stimulus intensity (e.g., temperature, pressure) that is sufficient to elicit a behavioral pain response. Nonsteroidal antiinflammatory analgesics increase the amount of hoof compression tolerated by laminitic horses,[3] and opioid analgesics lengthen the time required to produce the limb withdrawal and skin twitch reflexes in horses exposed to noxious heat.[4] Because these analgesics act preferentially on nociceptors and their peripheral and central pathways, these reflexes represent true "pain responses" by the horse. Clearly, such reflexes are critical in protecting horses from hostile environmental insults.

3.1.3 Inflammatory Pain and Hyperalgesia

The reflexes discussed previously signal imminent tissue injury; but what happens when tissues actually are damaged? The sensitivity of damaged tissues (especially the skin) to pain and other stimuli differs from that of normal intact tissue. The first phenomenon observed in injured tissues is allodynia, the production of pain by a stimulus that previously was nonpainful. For example, lightly probing the withers of a horse does not usually elicit a response. However, gently stroking the same site in horses with severe dermatophylosis can elicit a vigorous, attention-getting twitch response. This is an example of allodynia. The second phenomenon is hyperalgesia, which occurs when previously painful stimuli produce pain of greater magnitude, duration, or area. Osteoarthritis is a condition associated with inflammatory hyperalgesia, in which weight bearing on already painful joints results in a greater degree of pain. Nonsteroidal antiinflammatory drugs are particularly effective in reducing hyperalgesia but have little effect on pain sensitivity in healthy tissues.

The phenomenon of hyperalgesia is a subject of considerable research. Current theories suggest that persistent tissue injury is mediated by numerous endogenous chemicals, which alter both the peripheral and the central nervous systems. Peripheral hyperalgesia occurs at the site of injury and is mediated by the release and conversion of arachidonic acid into prostaglandins (mainly PGE_2) and leukotrienes (mainly LTB_4 products). Together with bradykinin and histamine, these mediators render nociceptors hyperresponsive to noxious stimuli. Serotonin from platelets and mast cells, interleukins 1 and 8, and tumor necrosis factor from immune cells contribute to hyperalgesia. Retrograde release of substance P and calcitonin gene-related peptide from neighboring nociceptors amplifies the hyperalgesia. The sympathetic nervous system appears to be involved in hyperalgesia, as norepinephrine, released from sympathetic efferents, provides additional amplification. In fact, sympathectomies have been used to minimize certain types of intractable pain.

More recently adenosine (and other products of adenosine triphosphate [ATP] metabolism) and the excitatory amino acid glutamate have been implicated in the pain amplification cascade. The short-lived gaseous neurotransmitter nitric oxide is produced at inflammatory sites and by pain neurons in the central nervous system. Nitric oxide is formed by the action of nitric oxide synthase, an enzyme, on L-arginine. In fact, nitric oxide synthase inhibitors (e.g., L-NAME) reduce inflammatory pain in several laboratory animal species. Nerve growth factor has also been recognized as contributing to hyperalgesia. A number of these mediators appear to exist in horses and other species. Currently they are targets for pharmacologic intervention in the pain process.[5]

Hyperalgesia also appears to occur centrally within the spinal cord, mirroring the peripheral event. Many of the same transmitter substances released peripherally by nociceptors are released in the spinal cord. Persistent tissue damage triggers the release of substance P, and glutamate/aspartate from the intraspinal terminals of the nociceptors, activating NK-1 and NMDA/AMPA receptors, respectively. These powerful excitatory transmitters

appear to lower the response thresholds of second-order dorsal horn neurons. This process appears to mediate both allodynia and hyperalgesia and is often referred to as *secondary* or *central hyperalgesia*. Recent evidence suggests that prostaglandins are also released into the spinal cord from peripherally activated nociceptors. Therefore nonsteroidal antiinflammatory drugs that inhibit prostaglandin synthesis may act at the site of injury and centrally to relieve inflammatory pain. Lastly, persistent tissue inflammation may recruit previously inactive neurons or silent nociceptors, which are quiescent in normal tissue. These nociceptors may further enhance the excitability of the spinal cord to peripheral pain.

The prevention of secondary hyperalgesia is of great interest in human and veterinary medicine. It has been proposed that if the barrage of sensory impulses from damaged tissue can be prevented from influencing the spinal cord, less central hyperalgesia should occur. This has been supported by the results of several studies. For example, intra-spinal administration of local anesthetics and opiates to animals before surgery results in less postoperative pain than if the same drugs are administered postoperatively. Thus, the preemptive use of analgesics and anesthetics may reduce postoperative pain and improve recovery from surgery. The relatively common procedure of lumbar puncture should lend itself well to preemptive analgesic therapy in horses and other large animals. From these approaches, it has been suggested that the developing nervous system remembers pain. Stated another way, pain changes the nervous system. Consequently, the long-term impact of surgery-induced pain should perhaps be reexamined.

3.1.4 Pain Transmission Within the Central Nervous System

The simplest pain responses are unconscious motor reflexes. These reflexes are segmentally controlled within the spinal cord and do not require conscious intervention. Animals whose spinal cords have been severed can still demonstrate withdrawal reflexes below the level of transection. Such reflexes normally serve to protect animals from injury.

Noxious stimuli are initially transduced by A-delta and C nociceptors, which then synapse with spinal cord dorsal horn neurons in several of the layers or laminae. Lamina I (i.e., the marginal zone), the most superficially located layer, receives A-delta and C fibers that carry pain and temperature information. Lamina II (i.e., the substantia gelatinosa) consists mostly of interneurons that integrate information from A-delta and C fibers from Lissauer's tract. Warmth, cold, and pain are integrated and modulated in laminae III and IV. Lamina V and VI neurons are critical in pain processing and modulation. They receive information primarily from thermosensitive and mechanosensitive nociceptors and may project directly to the thalamus and brain. These neurons also receive input from descending brainstem pathways capable of modulating pain signals.[6] The relatively superficial location of the pain pathways in the spinal cord helps explain the rapid and selective analgesia achieved after intrathecal administration of local anesthetics in horses.

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The dorsal column pathway and spinothalamic tract are involved in conveying pain signals from the spinal cord to the brainstem or brain. There are species differences in the roles of each of these pathways. For example, the spinothalamic tract is more important in pain transmission in primates than in nonprimates. The dorsal column-medial lemniscus pathway carries information about pain, touch, and pressure. It is unique in that some nociceptors travel directly to the brainstem via this pathway, resulting in rapid contact between periphery and brain. The brainstem plays a key role in the autonomic responses to pain (see later). Cells from the medial lemniscus synapse with the intralaminar nuclei of the thalamus. The spinothalamic tract carries information about pain, temperature, and to some extent touch. However, spinothalamic tract cells originate mainly in lamina V and do not synapse with the brainstem. Instead they innervate the ventral posterior and other nuclei of the thalamus. The trigeminal nerve contains nociceptors that convey temperature and pain information from the face, jaw, teeth, tongue, and lips. These trigeminal nociceptors synapse with the nucleus of the spinal tract (similar to the

spinothalamic tract) and go on to form the trigeminothalamic tract. This is a particularly important pathway in horses, considering that orofacial pain, applied through a bit, is used to command attention and control motor behavior. The spinothalamic tract pathways appear to play an important, albeit not exclusive, role in chronic burning pain states especially involving the polymodal nociceptors. Overall, it is generally believed that the lateral thalamus is involved in the discriminative sensory component of pain, whereas the medial thalamus mediates the emotional and motivational aspects of pain.[7]

Processing of pain in cortical sites may to some extent underlie species differences in the experience and expression of pain. Clearly the relative size and complexity of the cerebral cortex differs among animals. Modern functional imaging studies show that painful stimuli activate subcortical regions such as the periaqueductal gray, the hypothalamus, the amygdala, and the cerebellum. However, painful stimuli selectively activate cortical sites such as the insular and cingulate cortices, which receive input from the thalamus. It is interesting to note that the frontal and cingulate cortices of the cerebrum seem to be necessary for experiencing suffering. Early human studies have indicated that patients receiving frontal lobotomies were able to describe a painful stimulus but not to be concerned about it.[7,8]

3.1.5 Types of Physical Pain

Pain has often been categorized as superficial, deep somatic, and visceral. Cutaneous or superficial pain tends to be definitive, well localized, and constant and may follow the distribution of somatic nerves. Deep somatic and visceral pain tends to be diffuse, dull, poorly localized, and periodic and elicits more pronounced autonomic changes. Visceral pain may also be referred to other deep or cutaneous sites.

It may be more relevant for the practitioner to identify pain in terms of its site of origin. Visceral, musculoskeletal, and cutaneous areas are perhaps the most recognizable sites for pain in large animals. Rapid distention, ischemia, pulling on the root of the mesentery, or high luminal pressure in any portion of the hollow viscus elicits pain behavior in horses and cattle. This is most rapidly characterized by biting, looking at, or kicking at the abdomen or thorax and probably reflects an attempt to remove the painful stimulus from the referred site. Dorsolateral rolling, whole body hyperextension, and groaning can be observed in horses with severe intestinal colic. Muscle pain can be induced by strenuous exercise, trauma, or sustained contraction. Alterations in weight bearing, abnormal body postures, and lameness and tenderness on palpation are the most recognizable signs. Severe rhabdomyolysis (“tying up”) certainly initiates dramatic changes in muscle tension. Joint pain accompanies acute traumatic, infectious, and degenerative arthritis and is associated with decreased range of motion, hypoactivity, and lameness. Cutaneous pain usually results from traumatic skin injury, bite wounds, or infections. Typically these sites of injury may be guarded, scratched, or licked. Exaggerated withdrawal or evasive reflexes may occur in an attempt to remove the noxious stimulus. Corneal pain can be elicited by chemical, thermal, or mechanical stimuli and is often accompanied by increased tear production and blinking. Dental pain, perhaps the only sensation in teeth, is difficult to detect in large animals but has been associated with head tossing, jaw opening, or mandibular activation. Whereas headache pain is of considerable concern in human medicine, there have been no systematic attempts to identify or characterize this phenomenon in large animals.

3.1.6 Autonomic and Emotional (Affective) Components of Pain

Affective, or emotional, responses to painful stimuli appear to vary widely in the animal kingdom and within a species. The neuroanatomic correlates of emotional pain involve higher brain functions and add another dimension to simple reflex responses. Humans experiencing pain often use terms such as *exhausting, terrifying, sickening, cruel,* and *vicious*. Changes in facial expression, body posture, and gestures signaling disgust, fear, and

anger have also been described.[9] These expressions serve to alert others to an individual's condition of pain. Some of these human “emotions” may have large-animal counterparts. In addition to site-related motor responses, changes in temperament have been described.[10] Animals showing aggression in the form of kicking, biting, striking, head butting, teeth grinding, fighting, and escaping may be in pain. Grunting, moaning, or squealing may be heard. On the other hand, some individuals may appear docile and defeated. Changes in facial expression such as dull eyes; drooping eyelids, ears, and head; excessive tears; and hyperresponsiveness to light or sound may be observed. Thus, animals and humans may share the fear-, anxiety-, and anger-associated expressions of pain.

Along with the expression of pain behaviors, autonomic disturbances in homeostasis occur. It is worth noting that some nociceptive dorsal horn neurons synapse with the pontine and midbrain reticular formation, the lateral periaqueductal gray, the ventral medulla, and the hypothalamus. Nociceptive activation of the ventral medulla results in increases in heart rate, respiratory rate, and blood pressure. Activation of the hypothalamus results in the release of vasopressin and adrenocorticotropic hormone (ACTH), which affect hemodynamics and blood glucose concentration. Stimulation of the reticular formation results in enhanced vigilance and attention. Activation of the periaqueductal gray results in recruitment of an endogenous, descending pain suppression system (see endogenous pain suppression later), which “attempts” to modulate the intensity of painful stimuli at the level of the spinal cord. These gross autonomic and metabolic responses contribute to the aversive and arousal nature of the painful experience.

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In addition to its aversive quality, pain can motivate and be learned and avoided by animals. The application of acute pain is used universally to control equine behavior. Common examples include the use of a bit to coerce movement, the application of a whip to increase racing performance, the application of a twitch for restraint, and sole “soring” to increase gait animation. There is little doubt that the average horse learns and remembers the aversiveness of these stimuli and “works” to avoid them. However, acute pain (e.g., kicking, biting) is inflicted conspecifically to establish social and reproductive dominance within a herd. Pain can also be used to subdue adversarial predators. Past experiences can profoundly influence the affective response to pain. Factors such as anticipation, anxiety, and fear can negatively influence future pain response. Horses that appear “head shy” after years of abuse have learned, all too well, how to detect and avoid imminent tissue injury.

3.2 PATHOPHYSIOLOGIC EFFECTS OF PAIN

3.2.1 Acute Pain

Pain of short duration alerts animals to potential injury and is adaptive for survival. It is also a signal to stop using injured tissues, to promote healing. Acute pain usually elicits quick behavioral action and resolves without a significant disruption in homeostasis. Acute pain may be caused by environmental stimuli, trauma, surgery, acute medical conditions, or normal physiologic processes (e.g., parturition). A common constellation of signs may be seen in large animals. Neurologic signs include behavioral excitement, confusion, tremors, rigidity, twitching, hyperreflexia, and ataxia or immobility, paralysis, and inertia. Cardiorespiratory signs include hypertension, tachycardia, vasospasm, venous stasis, and tachypnea. Gastrointestinal hypomotility or hypermotility, urinary retention, sweating, and hyperthermia may also occur. Acute pain of a more debilitating nature may produce more profound changes in posture, temperament, and locomotion. Head and neck ptosis, rolling on the ground, hyperextension or hyperflexion of the body and neck, widened stance, and prolonged sternal or lateral recumbency may be observed. A spectrum of emotional reactions from aggressiveness, anxiety, self-mutilation, and vocalization (moaning, grunting) to marked depression may occur. Specific lamenesses and weight-bearing deficits may accompany more specific musculoskeletal insults.[10]

3.2.2 Chronic Pain

Fortunately, most acute pain resolves and homeostasis is restored. However, extensive tissue injury or disease may result in pain that persists for days or weeks. Such pain is often associated with inflammation and accompanying allodynia and hyperalgesia. Pain states that persist for months, even after healing has occurred, are classified as chronic. Chronic pain often includes a continuation of the acute manifestations described previously. However, more global, systemic changes emerge as unabated pain continues.

Chronic pain can be best assessed by noting changes in eating, sleeping, social behavior, reproductive activity, personality, growth and performance, body position, and activity level and certain physiologic signs. Chronic unrelieved pain may result in depression, inappetence, weight loss, and reduced growth or milk production (e.g., in cows or goats). Musculoskeletal pain may actually impair mobility and prevent normal social competition for food, contributing to further weight loss. Disruption in sleep-wake cycles may add to the overall debility. Psychologic alterations expressed as personality changes toward an owner or cohort may emerge, along with a positional change in the herd hierarchy. Conspecific grooming and other social interactions may decline as well. Signs of psychomotor stress may develop including trembling and rigidity, as well as stereotypies such as pacing, head shaking, pawing, scratching, and stall walking.

The persistent disruption in homeostasis may have serious long-term consequences. Increased release of cortisol, catecholamines, and renin is associated with pain and other forms of distress. These hormonal responses can impair normal cardiovascular function and may contribute to hypertension. In fact, acute changes in plasma concentrations of cortisol, catecholamines, glucagon, blood glucose, insulin, β-endorphin, lactate, and growth hormone have been used as indirect measures of pain. Depending on the site of pain or injury, prolonged recumbency in large animals can result in pulmonary congestion, hypoxemia, pneumonia, and altered thermoregulation. Data also suggest that chronic pain may be immunosuppressive.

Although the use of analgesics for pain relief is not discussed in this chapter, it is worth noting that analgesics can be used to diagnose pain. Opiates elevate the nociceptive threshold by preferentially inhibiting dorsal horn neurons in pain reflex pathways. This in part explains their ability to dull pain sensations. This occurs without altering other sensory modalities (e.g., touch, pressure). Opiates also activate (1) descending brainstem inhibitory pathways, which alter spinal pain transmission, and (2) ascending pathways to the nucleus accumbens, amygdala, frontal cortex, striatum, thalamus, hypothalamus, and ventral hippocampus.[11] These latter sites are intimately associated with emotionality and the affective and autonomic responses to pain. Therefore, relief of the aforementioned behavioral signs and symptoms by opioids is indirect evidence that pain contributed to their expression.

3.2.3 Are Animal and Human Pain Equivalent?

Whether nonhuman animals feel pain the way humans do continues to be debated, along with the need for analgesics. Arguments favoring a difference include the following:

- The relative speed with which animals recover from major surgery
- Stoicism in the face of severe injury
- Anatomic differences in pain pathways

- Lesser-developed cortices in nonhuman animals
- Unusual responses to some analgesic drugs

Arguments favoring a similarity include the following:

- The hypothesis that stoicism is adaptive and reflects a difference in pain expression rather than perception.
- Acute and chronic pain symptoms and sequelae are similar.
- Autonomic and endocrine responses to pain are similar.
- The same chemical, thermal, and mechanical stimuli elicit pain in humans and animals.
- The same pain-mediating neurotransmitters and modulators are present in humans and animals.
- There are qualitative similarities in the neuroanatomic pain pathways.
- Surgical procedures (e.g., auricular, thoracotomy) and diseases (e.g., arthritis, pancreatitis, colic) that are painful to humans are also painful to animals.
- Opioids are universally analgesic.

Although these arguments persist, many large animal practitioners avoid using analgesics because they mask symptoms and impair the diagnosis of underlying disease. Drugs such as nonsteroidal antiinflammatory drugs may also produce serious side effects such as gastric and abomasal ulcers. On the other hand, public and regulatory agencies insist that animal pain be recognized, avoided, and treated whenever possible.

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3.2.4 Endogenous Pain Suppression

The expression of pain seems to differ widely across and within animal species. Some animals (and humans) cry out at the slightest provocation, whereas others seem to endure traumatic insults interminably. Most veterinary practitioners have had the misfortune of observing a horse finish or perhaps win a race, undeterred, with a fractured cannon bone. One may ask how this occurs. There is growing neurochemical and neuroanatomic evidence for the existence of an endogenous pain suppression system with segmental and suprasegmental components.

The segmental component is thought to exist within the dorsal horn of the spinal cord. It is probably this system that we activate when we lightly but vigorously rub a recently acquired bruise for pain relief. The licking or light rubbing of a fresh wound by an animal would represent the corollary process. The light touch or vibration stimulates larger-diameter, A-beta mechanoceptive afferents at or near the site of injury. At the same time, A-delta and C fibers are transmitting nociceptive signals from the injured site. These fibers somatotopically converge on a common spinothalamic tract cell. However, the A-beta fiber is thought to activate an inhibitory interneuron en route to the spinothalamic tract cell. Thus, the large fiber damps down or closes the gate to pain signals delivered by the neighboring nociceptor. This formed the basis of the Gate Control Theory of Pain by Melzack and Wall.[12] This theory has also been advocated to explain the operation of transcutaneous electrical nerve stimulation devices. These devices deliver nonnoxious electrical stimuli to the skin via electrodes placed at or near injured or inflamed sites. The direct current (DC) electrical current activates mainly large-diameter, cutaneous, low-threshold mechanoceptors, which damp down nociceptor input from converging dermatomes.

Variations in impulse magnitude, shape, frequency, and duration are selected to maximize this effect. Transcutaneous electrical nerve stimulation devices are used routinely in human medicine and by racetrack practitioners to reduce inflammatory pain.

For function in the face of severe pain and distress, certain endogenous coping mechanisms exist that modulate the intensity and quality of pain. The best understood of these is the descending pain suppression system. This system consists of a family of descending neurons from the hypothalamus, midbrain periaqueductal gray, rostral ventromedial medulla, and dorsolateral pontine tegmentum. These pathways form a cascading neuronal circuit that ultimately influences activity in pain-sensitive spinothalamic tract cells in the spinal cord dorsal horn. The neuronal components of this descending system are activated by pain and other stressful stimuli.[11]

The command center of the system is the periaqueductal gray. The periaqueductal gray contains both opiate receptors and enkephalins. Enkephalins are small, short-acting peptides that bind to opiate receptors and mimic the actions of morphine. In fact, the name is derived from the term *en*dogenous *cephalic* peptide. Activation of or application of morphine or enkephalin into the periaqueductal gray activates the rostral ventromedial medulla. The rostral ventromedial medulla then releases serotonin from its terminals in the spinal cord dorsal horn. Serotonin is an indoleamine neurotransmitter involved in the control of mood, vigilance, sleep, and pain threshold. Once released into the spinal cord, serotonin activates specific dorsal horn interneurons that contain enkephalin. The enkephalins then act on opioid receptors located on pain-responsive neurons in the spinal cord. Stimulation of these opioid receptors inhibits the pain-responsive cells, rendering them less excitable by nociceptive signals from the periphery. The periaqueductal gray also activates the dorsolateral pontine tegmentum, which sends its norepinephrine-releasing neurons to the dorsal horn as well. The norepinephrine acts on α_2-receptors also located on pain-sensitive neurons, inhibiting them. Thus, three separate neurotransmitter systems play a role in endogenous pain modulation-serotonin, enkephalin, and norepinephrine. Activation of these systems ultimately results in inhibition of pain reflexes and pain sensations (i.e., analgesia).[11] This mechanism not only explains how pain can induce endogenous analgesia, but also how intrathecal and systemically administered morphine and xylazine relieve pain.

Another important morphine-like peptide involved in the production of endogenous analgesia is β-endorphin. Pain, parturition, exercise-stress, acupuncture, and surgery increase circulating levels of this pituitary hormone along with ACTH. β-Endorphin, which can be detected in plasma and cerebrospinal fluid, is larger and longer-acting than enkephalin and also binds to opioid receptors. It produces analgesia when administered, and its effects can be blocked by the opioid antagonist naloxone. Endorphins are involved in regulating pain threshold in horses, as they follow the same diurnal rhythm.[13] Plasma concentrations of endorphins and pain threshold also appear to increase after strenuous exercise in thoroughbred horses.[14] Endogenous opioids are also present in the gastrointestinal tract and are thought to modulate muscle tone and possibly sensation. We believe that this system is operative in the horse, as we have observed colic pain and diarrhea in horses receiving the opioid antagonist naloxone.[15]

3.2.5 Approach to Diagnosis of Abdominal Pain

Diseases characterized by abdominal pain occur commonly in horses and ruminants. In most instances the painful stimuli originate secondary to an intestinal obstruction or malposition (Boxes 3-1 and 3-2). In male or castrated male sheep and goats, the most common cause of abdominal pain is urolithiasis. When the pain is intestinal in origin, there may be distention of the intestinal wall with gas or ingesta, increased tension on the mesentery, or ischemia of the intestine. The clinical signs exhibited by the animal depend on the species, the age of the particular animal, and the severity of the underlying cause. The presence of abdominal pain may be characterized

by outward clinical signs ranging from mild depression to repeated pawing or stamping of the feet to violent behavior. For example, in the horse many problems can cause abdominal pain, ranging from distention of the cecum with gas to simple obstruction of the intestinal lumen with ingesta to strangulation obstruction of the intestine (see Colic, Chapter 7). Consequently the clinical signs exhibited by the horse may range from repeated pawing with a front foot and turning around to look at the abdominal region to uncontrollable rolling and thrashing. Although the severity of the clinical signs exhibited by the horse tends to correlate with the severity of the underlying problem, exceptions to this rule occur commonly. Thus, the importance of performing a thorough physical examination in these instances cannot be overstated. Finally, the age of the animal must be considered in light of the clinical signs manifested. For example, the foal frequently swishes its tail from side to side and rolls up onto its back as part of its characteristic response to the presence of abdominal pain. In addition, bruxism is not an uncommon manifestation of pain in foals. Abdominal pain caused by liver disease is uncommon; however, it can occur in cases of severe hepatic lipidosis (especially in ponies and miniature horses). In horses with cholelithiasis, intermittent abdominal pain is the most common clinical sign, presumably resulting from bile duct distention.[16]

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3.2.5.1

Box 3-1 Causes of Abdominal Pain in the Horse

3.2.5.1.1

Common Causes

- Accumulation of gas
- Intestinal obstruction
- Intestinal muscle spasm (cramps)
- Gastric ulcers (foal)
- Meconium impaction (neonate)
- Parturition

3.2.5.1.2

Less Common Causes

- Colitis or enteritis
- Colonic displacements
- Colonic volvulus
- Ileal impaction

Ileus

Intestinal foreign body (sand, enterolith, phytobezoar)

Irritant cathartics

Parasympathomimetic drugs

Peritonitis

Proximal enteritis (duodenitis-jejunitis)

Small intestinal strangulation obstructions

Thromboembolism

Uroperitoneum (ruptured bladder in newborn)

Uterine torsion

3.2.5.1.3

Uncommon Causes

Acute hepatitis

Acute toxic enteritis

Ascarid impaction

Botulism

Cantharidin toxicity

Cholelithiasis

Rhodococcus (Corynebacterium) equi mesenteric abscess

Equine viral arteritis

Gastric dilation (cribbing, wind sucking)

Hernias (diaphragmatic, umbilical, other)

Intraabdominal adhesions

Intussusception

Malignant mesothelioma

Mesenteric abscess *(Streptococcus equi, Streptococcus zooepidemicus)*

Necrotizing enterocolitis (foals)

Neoplasia

Pedunculated lipoma

Plant poisonings

Potomac horse fever

Psychogenic colic

Rectal tear

Stenosis or stricture of bowel

Tetanus

Urolithiasis

3.2.6

Approach to Diagnosis of Chest Pain

Generally pain associated with conditions involving the pleural cavity is severe. The painful stimuli usually originate from the inflamed parietal pleura because few nociceptors are present in the visceral pleura. Because of the primary involvement of the parietal pleura, the pain is referred to a site directly overlying the thoracic wall. Consequently, if the focus of inflammation is relatively well localized, as occurs with traumatic

reticuloperitonitis-pericarditis, sensitivity to externally applied pressure may be restricted to one area of the chest wall (Box 3-3). If, however, the inflammation is generalized, as in equine pleuropneumonia, pain may be elicited by applying digital pressure over several sites. Similarly, because movement of the inflamed tissue accentuates the production of painful impulses, the animal remains stationary and is reluctant to lie down; the elbows are abducted; the chest wall is splinted; and the respiratory excursions are shallow, rapid, and accompanied by grunting. It is common that the severity of pain is reduced as the volume of pleural effusion increases.

3.2.6.1

Box 3-2 Causes of Abdominal Pain in Ruminants

3.2.6.1.1

Common Causes

- Abomasal gas (calf)
- Abomasal volvulus
- Abomasal ulcer
- Accumulation of gas (bloat)
- Cecal displacement or torsion
- Intestinal torsion or volvulus
- Intussusception
- Peritonitis
- Traumatic reticuloperitonitis
- Urolithiasis
- Uterine tear with peritonitis or adhesions
- Vagus indigestion

3.2.6.1.2

Less Common Causes

- Abomasal displacement

Abomasal impaction

Atresia coli (neonate)

Cholelithiasis

Cystitis or pyelonephritis

Enterotoxemia

Enterotoxigenic colibacillosis (neonate)

Fat necrosis with intestinal obstruction

Ileus

Intestinal adhesions

Rumenitis

Thrombophlebitis

Uterine torsion

3.2.6.1.3 Uncommon Causes

Hepatitis or liver abscess

Intestinal neoplasia

Plant poisonings

3.2.6.2 Box 3-3 Causes of Chest Pain in the Horse

3.2.6.2.1 Common Causes

Lung abscess

Pleuritis

Pleuropneumonia

Pneumonia

3.2.6.2.2 Less Common Causes

Choke

Fractured ribs

Mediastinal masses (abscess, tumor)

Neoplasia

Osteomyelitis

Ruptured esophagus

White muscle disease (rhabdomyolysis, tying up)

3.2.6.3 Box 3-4 Causes of Chest Pain in Ruminants

3.2.6.3.1 Common Causes

Pleuropneumonia

Pneumonia

Shipping fever complex

Thrombosis of the caudal vena cava

Traumatic reticuloperitonitis-pericarditis

3.2.6.3.2

Less Common Causes

Acute bovine emphysema (atypical interstitial pneumonia)

Choke

Fractured ribs

Mediastinal masses (abscess, tumor)

Osteomyelitis

Pleuritis

Ruptured esophagus

Chest pain may also develop acutely as a result of pulmonary arterial thromboembolism in cattle (Box 3-4). Presumably the acute development of pulmonic ischemia in such instances causes the local generation and release of several proinflammatory substances. Most of these problems occur secondary to thrombosis of the caudal vena cava.

Although less dramatic than that accompanying either pleuropneumonia or thromboembolism, pain also accompanies pneumonia and pulmonary contusions. The pain associated with pneumonia occurs secondary to pleural irritation and is well localized only if the parietal pleura is involved. Because the pain appears to be most evident during forced respiratory excursions, splinting of the thorax is common. Chest pain may also occur secondary to traumatic incidents. Although rib fractures occur rarely in horses and ruminants, they must be given some consideration in an animal exhibiting clinical signs of chest pain. Rib fractures occur more commonly in neonatal foals during birth and may result in respiratory distress. Obviously the force required to fracture a rib will cause severe bruising and inflammation of the underlying pleura.

3.2.7

Approach to Diagnosis of Pain in the Extremities

Although the reflex contraction of flexor muscles occurs with all types of pain, this reflex is most evident with pain in the extremities. Thus, as a result of a painful stimulus and to minimize the continued stimulation of the nociceptors in the affected area, the animal alters its stance or gait to protect the source of pain. Therefore, it is vital that the animal be inspected initially from a distance to determine which limb is involved. It may be necessary to move the animal at either a walk or a faster gait to identify the affected limb. It is important for the clinician to recognize that (1) the painful impulses may originate from several tissues in the extremity, including the skin, joint, periosteum, muscle, and the sensitive laminae of the distal phalanx; and (2) several factors may be contributing to the source of the pain. These factors may represent a particular conformational, breed, or familial predisposition toward development of the condition, the effects of nutritional imbalances on the development or stability of either bone or soft tissue, the effects of the use or performance of the animal, the possible involvement of infectious agents, and the effects of trauma (Boxes 3-5 and 3-6).

Careful palpation of both the soft tissues and the bones of the limbs must be performed to identify sources of inflammation or pain. Furthermore, the responses, if any, to flexion and extension of the joints must be evaluated, and the examination performed in a systematic manner. It may be necessary to inject a local anesthetic over a sensory nerve or into a synovial structure (joint, tendon sheath, bursa) to prevent the conduction of pain impulses to the central nervous system. The judicious use of local anesthesia combined with a careful physical examination should allow the affected site to be identified. On the basis of this information, the clinician can then make efficient use of other diagnostic aids (radiography, synovial fluid analysis, scintigraphy, ultrasonography) to determine the underlying cause of the pain and direct therapy accordingly.

3.2.8

Approach to Diagnosis of Back and Neck Pain

The association between pain arising from either the back or the neck and irritation of spinal nerve roots has not been as well established in large animal species as it has in small animals and people. However, there is considerable evidence that muscle damage, ligamentous strain, sacroiliac strain, and either fracture or overriding of the dorsal spinous processes of the thoracic vertebrae cause varying degrees of back pain in horses.[17,18] Attention must be given to the detection and treatment of exertional rhabdomyolysis in horses and postanesthetic myopathy in horses and cattle (Boxes 3-7 and 3-8). Each of these conditions is characterized by painful impulses originating from ischemic or damaged muscles. Similarly, the development of nutritional myopathy associated with selenium deficiency must be considered in horses and ruminants in certain areas of the country. All large animals are susceptible to traumatic incidents that may result in fracture of either cervical or sacral vertebrae. Horses occasionally rear up and fall over backward, fracturing the sacrum or dorsal processes of the thoracic vertebrae. Cattle fracture the pelvis or develop sacroiliac luxations when they slip on concrete floors, often when mounting is occurring during estrus.

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3.2.8.1

Box 3-5 Causes of Pain in Extremities of the Horse

3.2.8.1.1

Common Causes

Degenerative joint disease

Hoof wall defects

Improper trimming or shoeing

Lacerations

Ligamentous strain (sprain)

Navicular disease

Sole abscesses and bruises

Synovitis

3.2.8.1.2

Less Common Causes

Bucked shins

Cellulitis or abscess

Epiphysitis

Flexural deformities (contracted tendons)

Fractures

Desmitis

Laminitis

Osteomyelitis

Osteochondrosis

Septic arthritis or physitis

Tenosynovitis

3.2.8.1.3

Uncommon Causes

Keratoma

Neoplasia

Purpura hemorrhagica

Toxins

Ulcerative lymphangitis

Upward fixation of the patella

White muscle disease (rhabdomyolysis, tying up)

3.2.8.2

Box 3-6 Causes of Pain in Extremities of Ruminants

3.2.8.2.1

Common Causes

Degenerative arthritis

Foot rot

Interdigital fibroma

Lacerations and foreign bodies

Laminitis (horizontal fissures of hoof wall)

Sole abscess

Sole bruise; puncture wounds

Sole ulcers

Traumatic gonitis

Vertical fissure of hoof wall (sand crack)

3.2.8.2.2

Less Common Causes

Caprine arthritis encephalomyelitis (C)

Chlamydial polyarthritis (O, C)

Coxofemoral luxation

Digital tenosynovitis

Mycoplasma polyarthritis (O, C)

Rupture of cranial cruciate ligament

Septic arthritis

Septic navicular bursitis

Upward fixation of the patella

3.2.8.2.3 Uncommon Causes

Bone or physeal abscess

Bicipital bursitis

Fescue foot

Fractures

Neoplasia

Peripheral nerve paralyses

Sacroiliac luxation

Toxins and plant poisonings

C, Caprine; *O,* ovine.

3.2.8.3 Box 3-7 Causes of Neck and Back Pain in the Horse

3.2.8.3.1 Common Causes

Exertional rhabdomyolysis

Fractures of dorsal spinous processes

Ligamentous strain

Muscular damage

Overriding dorsal spinous processes

Thrombophlebitis

3.2.8.3.2 Less Common Causes

Fracture of the cervical vertebrae

Meningitis

Ossifying spondylosis

Postanesthetic myopathy

Tetanus

3.2.8.3.3 Uncommon Causes

Clostridial myopathy

Congenital defects

Renal pain (acute pyelonephritis, renal calculus)

White muscle disease

3.2.8.4 Box 3-8 Causes of Pain in the Neck and Back in Ruminants

3.2.8.4.1 Common Causes

Meningitis

Muscle injury

Tuber coxae fractures

Urolithiasis

Vertebral and sacral fractures

White muscle disease

Vertebral and spinal abscess

3.2.8.4.2

Less Common Causes

Bladder calculus

Clostridial myopathy

Pharyngeal abscess

Renal pain (acute pyelonephritis or renal calculus)

Ruptured or ulcerated esophagus

Sacroiliac subluxation

Tetanus

Thrombophlebitis

Vertebral neoplasia

Neck pain is frequently manifested by splinting and unwillingness to eat from the ground or assume any but the most benign neck position. Trauma is the most common cause, but meningitis may also cause severe neck pain.

3.2.9

Approach to Diagnosis of Pain on Urination

Although the term *dysuria* means difficult urination, its use has become synonymous with pain on urination. The painful impulses may arise from distention of the wall of the urethra, bladder, or pelvis of the kidney or irritation or spasm of the urethra. The most common causes of dysuria are inflammatory or obstructive conditions involving the urethra (Boxes 3-9 and 3-10). Thus, care must be exercised to identify uroliths, strictures, urethritis, vaginitis,

neoplasia, or fractures involving the pelvic bones. Because urethritis may coexist with other inflammatory conditions involving the urinary tract (e.g., cystitis, pyelonephritis), the diagnostic plan should include physical and laboratory assessments of the kidneys, ureters, and bladder. Urine should be collected for urinalysis, culture, and sensitivity testing. A rectal examination should be performed to detect vesical calculi, tumors, and alterations in the architecture of the kidneys or the size of the ureters. In many cases ultrasonography will be used to evaluate the kidney. Because the severity of pain can resemble that associated with acute abdominal obstruction, the physical examination must be thorough.

3.2.9.1 Box 3-9 Causes of Pain on Urination in the Horse

3.2.9.1.1 Common Causes

- Bladder calculus
- Ruptured bladder

3.2.9.1.2 Less Common Causes

- Cystitis
- Neoplasia
- Urethritis
- Urethral calculi
- Vaginitis

3.2.9.1.3 Uncommon Causes

- Pelvic fracture
- Urethral strictures

3.2.9.2 Box 3-10 Causes of Pain on Urination in Ruminants

3.2.9.2.1 Common Cause

- Urolithiasis

3.2.9.2.2

Less Common Causes

Cystitis

Prolapsed prepuce

Pyelonephritis

Preputial injury or infection

Vaginitis

Urolithiasis occurs more commonly in ruminants than in horses. Of the ruminants, young feedlot steers less than 18 months of age and male sheep and goats (intact or castrated) appear to be at the highest risk. There is an association among sorghum feeds, diets high in magnesium, and the development of the condition. In horses, urinary calculi occur most commonly in geldings, and straining to urinate is the most common clinical sign. Rectal examination of the bladder, endoscopic examination of the urethra, and urinalysis are important aspects of the diagnostic plan. Most calculi in horses are rough, calcium carbonate stones, whereas most calculi in ruminants are magnesium ammonium phosphate, calcium phosphate, carbonate, or silicate in composition (see Chapter 32). Rupture of the bladder, the urethra, or occasionally the ureter may occur secondary to the obstruction.

Straining to urinate is a common clinical sign in newborn foals with a ruptured bladder. This condition generally occurs after the first 24 hours of life, occurs most commonly in males, and involves the dorsal aspect of the bladder. Presumably the rupture occurs during parturition. The diagnosis is facilitated by comparison of creatinine concentration in the blood and peritoneal fluid and by determination of serum electrolyte status. Most foals with the condition are hyperkalemic, hyponatremic, and hypochloremic.

3.3

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4 Chapter 4 Alterations in Body Temperature

Susan L. White

4.1 CONTROL OF BODY TEMPERATURE

Mammalian species maintain core body temperature within a narrow range despite extremes in environmental conditions. Core body temperature is not constant but exhibits diurnal variation. The normal range of temperature for individuals within a species may vary by as much as 1° C (2° F).

Maintenance of body temperature is under neuronal control in a negative feedback system. Warm- and cold-sensitive neurons within the hypothalamus sense existing core body temperature via peripheral nerve receptors and blood bathing the hypothalamus. Integrative structures located in the preoptic region of the anterior hypothalamus (POAH) that act similarly to a thermostat with a desired "set point" recognize temperatures as either too low or too high and activate both behavioral and autonomic effector responses to either lose or gain heat (Fig. 4-1).[1]

Heat production occurs primarily from muscle activity, which can vary according to need. Muscle activity may range from inapparent contractions to generalized shivering. Digestion of food also contributes significantly to total body heat and may be clinically important as a means of heat production in ruminants both in low environmental temperatures and in high temperatures when the threshold for heat stroke may be lowered. Heat conservation occurs from adrenergic autonomic stimuli to decrease peripheral circulation and cause piloerection. Behavioral means of heat conservation include adopting a "huddled" posture, group aggregation, and seeking a sheltered environment.

Heat loss occurs from conduction, convection, and radiation from body surfaces and by evaporation. Sympathetic vasodilation of cutaneous vessels contributes to surface cooling. As ambient temperature rises, evaporative heat loss becomes more important. In ruminants evaporative heat loss is confined to the respiratory system; respiratory rate increases concurrently with temperature. In horses, sweating aids evaporative heat loss. Behavioral responses that contribute to heat loss include seeking shade and wind currents and wading into water.

4.2 CONDITIONS OF INCREASED BODY TEMPERATURE

Body temperature disorders in which the core body temperature set point is unaltered can occur from increased heat production, absorption of heat, or impairment of heat loss. Central nervous system disorders that disturb the hypothalamic regulatory center, certain drugs, and metabolic disorders may also cause temperature changes. Phenothiazine tranquilizers are a recognized cause of loss of ability to control body temperature.[2] Erythromycin may induce hyperthermia during hot weather, particularly in foals.[3] Hyperkalemic periodic paralysis of horses has also been associated with episodes of hyperthermia.[4]

4.2.1 Exercise

During sustained exercise, heat production may exceed the ability of heat loss mechanisms, leading to a stable increase in core body temperature proportional to the intensity and duration of exercise. The elevation in temperature often persists for several hours after exercise, but temperature returns to normal with rest as heat loss mechanisms remain activated. Body temperatures during exercise greater than 2° C (4° F) above normal, especially if reached early in exercise, are usually the result of severe environmental conditions and/or failure in

heat loss mechanisms. Peripheral cooling to augment heat loss should be used to lower body temperature, as increases in temperature caused by exercise are unaffected by antipyretic drugs.[2,5,6]

The intense muscular activity associated with generalized tonic clonic seizures may, like vigorous exercise, cause a rise in body temperature. If central heat regulatory systems are unaffected by the disease process, body temperatures return to normal no longer than 48 hours after the last seizure.[7] Elevated temperatures that persist for longer periods should prompt investigation into other causes for the increased temperature.

4.2.2 Malignant Hyperthermia

Malignant hyperthermia consists of a group of inherited skeletal muscle calcium metabolism disorders in which a hypermetabolic state of muscle is induced by the administration of halogenated inhalation anesthetics, depolarizing skeletal muscle relaxants, or, occasionally, local anesthetics. Although malignant hyperthermia is most common in humans and pigs, it has been reported in horses.[8–11] Mutation of the ryanodine receptor 1 gene, which is essential in skeletal muscle excitation-contraction coupling, is the basis of malignant hyperthermia in humans, pigs, and dogs. Mutation of this gene has been documented in two horses with malignant hyperthermia.[12] Rapid increase in core body temperature (39° C to 42° C), skeletal muscle rigidity, tachycardia, metabolic acidosis, and muscle necrosis may lead to death.

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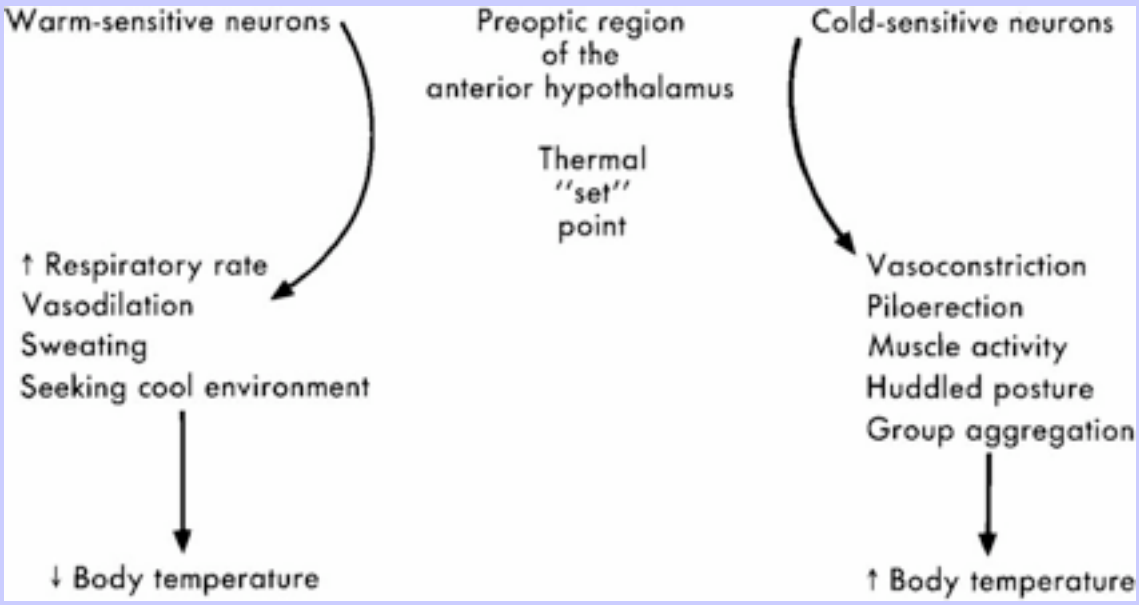
Fig. 4-1 Regulation of body temperature.



4.2.3 Ergopeptine Alkaloid Toxicosis

Tall fescue infected with the endophyte *Neotyphodium coenophialum* contains vasoactive ergopeptine alkaloids that cause vasoconstriction and reduced blood flow to the skin of ruminants. These alkaloids also induce bronchoconstriction and pulmonary vasoconstriction, which further compromise ruminants' ability to lose heat, especially during hot environmental conditions. Affected animals have a poor appetite and other indications of

poor performance recognized as part of the syndrome of fescue toxicosis or "summer slump."[13] A related endophyte infesting perennial ryegrass has been found to produce a similar hyperthermic condition in the western United States.[14] *Claviceps purpurea* infestations of annual or perennial ryegrass and of cereal grain heads have also been reported to produce a similar hyperthermic syndrome, which may lead to heat prostration and death when ambient temperatures are high.[15–17]

Cattle affected by any of these ergopeptine alkaloids have few to no clinical signs when environmental conditions are cool and heat loss mechanisms are not challenged. It is not yet known, however, if all of the effects of the alkaloids are peripheral or if they may also act within the central nervous system.[13]

4.2.4 Heat Stroke

When animals are exposed to high ambient temperatures, intense solar radiation, and/or high humidity so that heat load increases at a rate faster than heat can be dissipated, heat stroke may develop. Heat stroke is more common in ruminants because of their inability to sweat and thus their diminished evaporative ability for heat loss. Sheep with fleece and large dense cattle are especially prone to heat stroke when denied access to shade or adequate water and/or when physical activity is imposed on them. Rectal temperature will often exceed 41.5° C (107° F), and central body temperature may exceed 44.5° C (112° F). Horses continuously exercised in high heat and humidity may also develop heat stroke. Evaporative heat loss from sweating is the most important means of heat loss as metabolic heat production increases during exercise, especially as ambient temperature and humidity increase.[18] Efficiency of evaporative heat loss diminishes when temperature and humidity are high and there is a significant radiation component resulting from strong sunshine.[19] Horses' susceptibility to heat stroke is enhanced if dehydration and electrolyte imbalances occur because of large losses of sweat (see Exhaustion in Endurance Horses, Chapter 42).

As rectal temperature increases above 41.5° C (107° F), the homeostatic mechanisms of temperature regulation fail; peripheral vasoconstriction, decreased blood pressure, and decreased cardiac output occur. The animals are lethargic and have weak, flaccid muscles; prostration and shock occur rapidly. Disseminated intravascular coagulation, liver damage, renal failure, and myocardial necrosis are frequent complications.

4.2.5 Anhidrosis

As many as 25% of horses in hot, humid environments lose their ability to sweat and subsequently suffer from hyperthermia as a result of impairment of heat loss.[20] Horses in training have been reported to have a higher frequency of anhidrosis, as are horses shipped to hot environments from more temperate regions; however, horses indigenous to hot, humid areas that perform less rigorously or not at all may also develop anhidrosis.[21,22] In addition to hyperthermia, clinical signs are poor performance, total or partial loss of ability to sweat, increased respiratory rates (three to five times normal), and dry, thin hair coats with areas of alopecia (see also Anhidrosis, Chapter 41).

4.2.6 Diseases of the Nervous System

Central nervous system disorders that damage areas of the hypothalamus associated with temperature regulation may lead to either decreases or increases in body temperature, although hypothermia is most common. Hemorrhage, space-occupying masses (abscesses, tumors), infectious or inflammatory diseases, and degenerative disorders have all been implicated in hyperthermia. Central hyperthermia is usually characterized by lack of

diurnal variation, absence of sweating, resistance to antipyretic drugs, and excessive response to external cooling.[1,2]

Certain toxins and drugs may act to increase body temperature by causing an increase in metabolic work (Boxes 4-1 to 4-3). Chlorophenols and nitrophenols, used as herbicides and wood preservatives, cause uncoupling of oxidative phosphorylation within mitochondria and lead to rapid extreme rises in body temperature.[23] Chronic and/or low-level exposure to these compounds may manifest clinically as hyperthermia.

4.3 FEVER

True fever differs from other hyperthermic states in that the desired core body temperature or set point is elevated. This new, higher set point is vigorously defended by the same mechanisms that maintain body temperature in health. Initiation of the febrile state can occur by a variety of infectious, inflammatory, immunologic, neoplastic, or injurious conditions. In the classic model of fever these stimuli cause the production of multifunctional pyrogenic cytokines by a wide variety of cells, but primarily by fixed or circulating monocytes and macrophages (Fig. 4-2). Currently at least 11 cytokines have been shown to induce the febrile response in humans and animals. Of these cytokines, interleukin 1 (IL-1α, IL-1β) and tumor necrosis factor alpha (TNF-α) are the most potent. Each of these cytokines induces others and stimulates the production of other pyrogenic cytokines (IL-6, interferon [IFN-α, IFN-β, IFN-γ], ciliary neurotropic factor [CNF], and IL-11) that signal cells through a common receptor (glycoprotein 130). Pyrogenic cytokines reach the POAH via the circulation and attach to receptors on the endothelium of the capillaries of the circumventricular vascular organs (CVVOs), which induce the production of arachidonic acid and its metabolism to prostaglandin E_2 (PGE_2), by the cyclooxygenase (COX)-2 pathway. PGE_2, produced on the brain side of the CVVOs, binds to PGE_2 type 3 receptors of glial cells and possibly neuronal cells to initiate neuronal signaling by producing a cascade of changes in cyclic nucleotides, calcium, and neurotransmitters that result in a higher "set point" within the hypothalamic thermoregulatory center[24,25] (see Fig. 4-2). COX inhibitors, and specifically COX-2 inhibitors, effectively reduce the febrile temperature to normal but have no effect on normal body temperature.[2,25]

Box 4-1 Drugs Associated with Fever

FREQUENTLY

Penicillins

Sulfonamides

Erythromycin

Antihistamines

Procainamide

Quinidine

Amphotericin B

4.3.1.2 OCCASIONALLY

Cephalosporins

Cimetidine

Ranitidine

Iodides

Rifampin

Ranitidine

Levamisole

Furazolidone

4.3.1.3 RARELY

Chloramphenicol

Tetracyclines

Phenothiazines

Salicylates

Herbal remedies

Others

4.3.2 Box 4-2 Toxins Associated with Fever in the Horse

Blister beetle (cantharidin)

Selenium

Arsenic

Mercury

Chlorinated hydrocarbons

Dinitrophenol

Propylene glycol

Trichloroethylene extracted feed

4.3.2.1 PLANT TOXINS

Pyrrolizidine alkaloid—containing plants

Algae

Castor bean (*Ricinus* species)

Water hemlock (*Cicuta* species)

Jimson weed *(Datura stramonium)*

Mycotoxicosis

4.3.3 Box 4-3 Toxins Associated with Fever in Ruminants

Arsenic

Selenium

Mercury

Zinc

Crude oil, kerosine, coal oil

Organochlorine, chlorinated hydrocarbons

Iodine

Paraquat

Dinitrophenol

Propylene glycol

Trichloroethylene-extracted feeds

Halothane toxicity (C)

4.3.3.1 PLANT TOXINS

Fescue toxicosis (B)

Ergot *(Claviceps)* (B)

Pyrrolizidine alkaloid—containing plants, algae

Brassica species (mustards, crucifers, cress)

Bracken fern

Castor bean

Water hemlock

Milkweed *(Asclepias* species) (B, O)

Buttercup *(Caltha palustris* and *Ranunculus* species) (O)

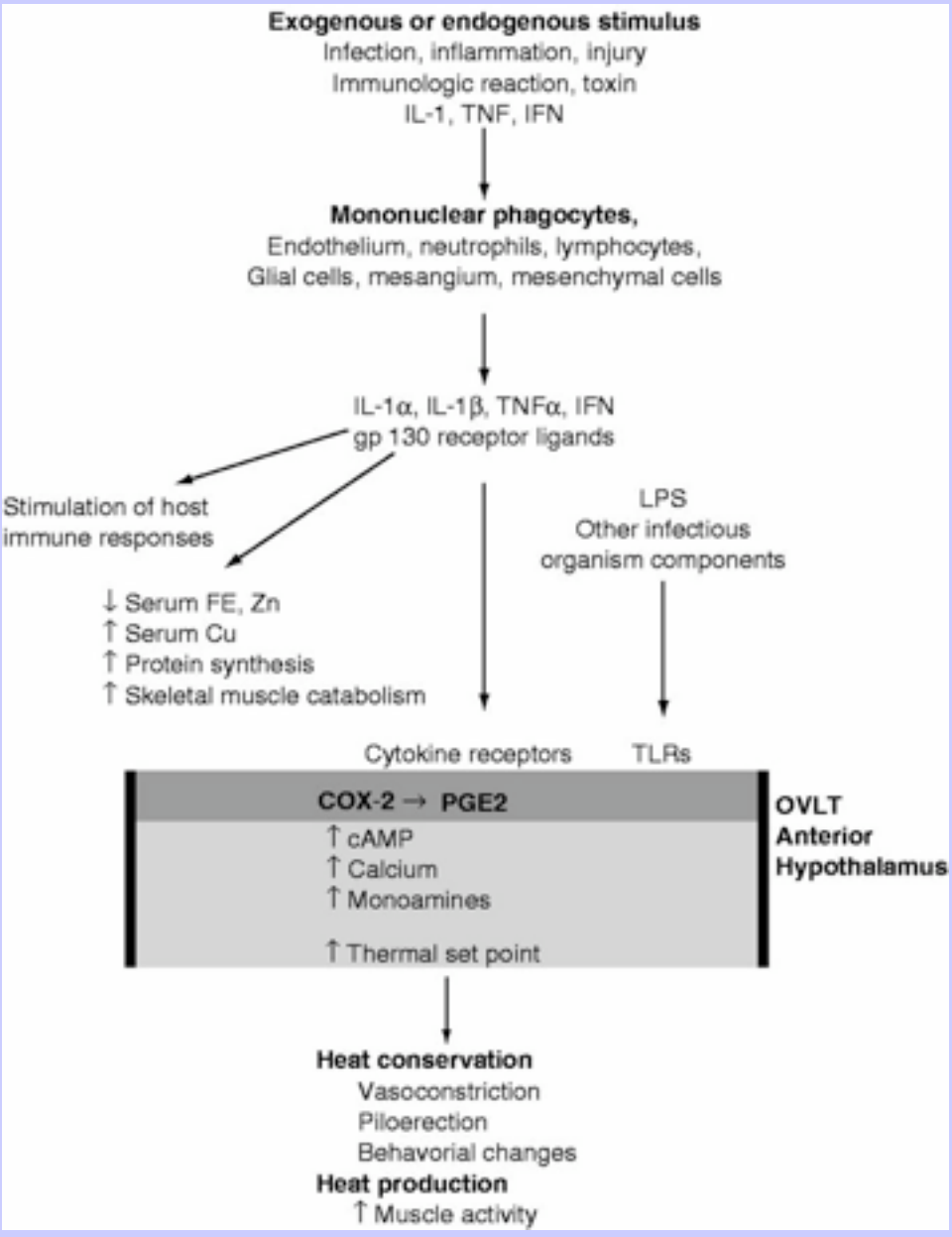
Rhododendron (C, O)

Gossypol toxicity (B)

Jimson weed *(Datura stramonium)*

B, Bovine; *C,* caprine; *O,* ovine.

Fig. 4-2 Pathogenesis of fever. *OVLT,* Organum vasculosum laminae terminalis endothelium; *TLRs,* toll-like receptors.



This model, however, does not fully explain the presence of fever, because specific blockade of IL-1 or TNF-α activity does not diminish the febrile response to lipopolysaccharide (LPS) or other microbial products in experimental studies or in patients with natural infections. Microbial products from a variety of agents bind to toll-like receptors (TLRs) on the surface of cells. Toll-like receptors and IL-1 receptors share the same signaling areas and, along with other pyrogenic cytokines, a common pathway to activate nuclear factor (NF)–κB. Activated NF-κB in turn results in expression of COX-2 or COX-3 and PGE_2 synthesis. Mice deficient in COX-2 and injected with LPS, IL-1, TNF-α, or IL-6 either intravenously or within the central nervous system do not develop a fever.[25] Thus the induction of COX-2 and the subsequent production of PGE_2 provide a common pathway for divergent pyrogens to produce the febrile response (see Fig. 4-2).

There is an apparent role for the vagal nerve in the production of the febrile response. Studies in laboratory animals in which the hepatic branch of the vagus nerve is severed have shown diminution of the febrile response to a relatively low dose of intraperitoneally injected LPS but not intramuscularly administered LPS or high-dose intraperitoneally injected LPS. Local production of cytokines may stimulate primary hepatic vagal receptors that, via vagal afferent fibers and A1/A2 noradrenergic cell groups in the brainstem, release noradrenaline, which subsequently induces the production of PGE_2 and fever.[26]

In addition to a rise in body temperature, the febrile state is accompanied by a variety of metabolic, hematologic, and immunologic changes. IL-6 and IL-11, induced by IL-1α, IL-1β, and TNF-α, induce the synthesis of fibrinogen, C-reactive protein, haptoglobin, ceruloplasmin, and certain macroglobulins, known collectively as *acute phase proteins,* by hepatocytes. In addition, these cytokines mediate the accompanying hypoferremia, hypozincemia, and hypercupremia of the acute phase response. Pyrogenic cytokines stimulate the activation and proliferation of T-lymphocytes and of antibody-producing B lymphocytes which, in turn, produce additional cytokines that both enhance and inhibit further production of pyrogenic cytokines.[27,28] Pyrogenic cytokines, particularly IL-1 and TNF-α, cause membrane perturbation in a variety of body tissues, with a resultant increase in phospholipases and the production of arachidonic acid. Subsequent production of mediators is dependent on the metabolic pathways for arachidonic acid in the target tissue. Prostaglandins induced by pyrogenic cytokines have been shown to stimulate the muscle catabolism associated with fever and to induce collagenase synthesis from synovial cells.[29] These processes contribute to the muscle and joint pain associated with fevers that are relieved by COX inhibitors. Lymphocyte and granulocyte response to IL-1 has been shown to be blocked by inhibitors of lipoxygenase but unaffected by indomethacin.[27] Local tissue responses to IL-1β and TNF-α may stimulate afferent neural impulses that are responsible for many of the behavioral changes (increased sleep, decreased appetite, and loss of social behavior) associated with fever. Transection of the visceral vagal afferents has been shown to attenuate febrile behavioral responses, but not the associated temperature elevation, to high-dose intraperitoneal LPS injection in rats.[30]

Physiologic control of the febrile response is multifactorial and prevents extreme elevations in body temperature that are incompatible with life in most instances. TNF-α inhibits further production of itself. IL-1 and other inhibitory cytokines stimulate the production of IL-1 receptor agonist, which prevents further binding of IL-1. In addition, one of the receptors on cell surfaces for IL-1 (type II receptor) does not result in cell signaling and is thought to serve as a "decoy" receptor to decrease the concentration of IL-1.[31] IL-10, induced by pyrogenic cytokines, inhibits IL-1, TNF, and IL-6 production and suppresses the production of IL-2 and IFN-γ by T-helper cells.[31,32] Circulating pyrogenic cytokines may be bound to carrier molecules that reduce or prevent the interaction with receptors. For example, IL-1β has been shown to bind to α_2-macroglobulin, a protein increased during the acute phase response.[1] Glucocorticoids inhibit the transcription of numerous genes encoding the pyrogenic cytokines IL-1β, Il-6, and TNF-

α. Within the brain both arginine vasopressin (AVP) and alpha melanocyte stimulating hormone (αMSH) act as potent antipyretic agents. Receptors for AVP, which acts as a neurotransmitter within the brain, are found lateral to the PAOH and decrease fever in both natural and experimentally induced fever, whereas injection of AVP receptor antagonist elevates fever and delays defervescence.[33,34] αMSH binds to local melanocortin receptors within the brain and on cell receptors of immune cells to decrease fever and inflammation. When administered systemically to humans, αMSH is 20,000 times more potent on a molar basis than acetaminophen in decreasing fever from endogenous pyrogens.[34] In the brain, nitric oxide (NO), by activating soluble guanylate cyclase and increasing cyclic guanosine monophosphate (cGMP) levels, participates in regulation of body temperature. Intracerebral ventricular injection of NO donors depresses fever in rats, whereas inhibition of NO synthesis within the central nervous system enhances fever.[31]

In summary, the occurrence of fever during disease results from a complex interaction of multiple cytokines and microbial products that act locally (site of tissue injury), systemically (in the circulation) and in the POAH of the brain and affect the immune, endocrine, and nervous systems.

4.3.4 Beneficial Effects of Fever

Body temperature elevation in pyrogenic mediated fevers, in contrast to hyperthermic states, rarely exceeds 2.5° C (5° F) above normal. Although the severity of some viral infections is decreased at these temperatures, most pathogens are not affected by a modest rise in temperature. Studies on bacterial infections in fish, lizards, rabbits, and humans, however, have shown an increase in survival correlated with the presence of fever.[2,35,36] One well-studied effect of fever on bacterial proliferation is the effect of hypoferremia. Bacteria, which require iron for multiplication, are inhibited by the reduced availability of iron during the acute phase reaction. This response is augmented by the increased susceptibility of bacteria to low iron at higher temperatures.[37,38] Certain neoplastic cells are inhibited during fever, although it is likely that inhibition of neoplastic cell division results from augmentation of immune responses.

35
36

Literature on the effect of fever is conflicting owing to the multiple variables present in in vivo studies and the application of heat in temperature ranges exceeding those of natural fevers in in vitro studies. Enhancement of host defenses, however, appears to be the primary beneficial effect of fever. Fever or heat applied in in vitro studies within the physiologic range of natural fevers has a beneficial effect on multiple processes of the adaptive immune response. Neutrophils and monocytes have increased motility and emigration, enhanced phagocytosis, increased oxygen radical production, and enhanced killing of intracellular bacteria. IFN production increases, and its antiviral, antitumor, antiproliferative, and natural killer (NK) cell—stimulating properties are enhanced. Increased T-cell proliferative responses to nonspecific mitogens IL-1 and IL-2, and enhanced T-helper cell activation, expression, recruitment, and cytotoxicity have all been correlated with fever. Enhancement of B cells, with a subsequent increase in production of antibodies, and enhanced expression of Fc receptors occur during fever.[39]

Activity of pyrogenic cytokines is also influenced by temperatures achieved during fever. For example, in a mouse-endotoxin model, fever enhanced the early expression of TNF-α but limited the duration of its expression. Production of IL-1β was delayed, whereas that of IL-6 (which downregulates production of TNF-α and IL-1β) was enhanced, preventing the simultaneous expression of TNF-α and IL-1β and the potential harmful effects of their simultaneous expression.[40] Other studies have demonstrated that the effect of fever on various cytokines is specific for each cytokine and specific to body compartments. Thus fever is an important component of the coordinated and specific cytokine response of the host to various inflammatory stimuli.[1,28,39]

4.3.5

Adverse Effects of Fever

The beneficial effects of fever during bacterial infections in rabbits have been shown to reverse at temperatures greater than 3° C (5° F) above normal. Cytokine disregulation may result in prolonged or extreme fevers with adverse effects on a variety of body functions in addition to the immune response. Catabolic metabolic processes during fever are markedly different from catabolism of starvation. Protein loss occurs four times as rapidly in individuals with infectious or inflammatory diseases as compared with starvation-adapted individuals. Ketonemia is inhibited, resulting in the oxidation of large amounts of muscle-derived amino acids for energy. This cytokine-driven catabolism, combined with the decreased feeding behavior that accompanies fever, variable anorexia (even if feed is provided), and increased metabolic rate at higher temperatures, can result in rapid and severe muscle wasting, weakness, and atrophy. In humans high fevers frequently cause seizures, especially in children,[2] but this is rare in animals unless temperatures reach 42° C (108° F) in neonates. Prolonged high fevers in debilitated animals may lead to failure of the cardiovascular system.

Fever is one of the earliest and most prominent manifestations of the acute phase reaction. Veterinarians have used the clinical thermometer to aid in diagnosis and to monitor the progress of illness in animals since 1770. With the increased knowledge of the pathogenesis of fever has come a better appreciation for the diverse causes of the febrile state. In ruminants and horses, however, infectious disease remains the most common reason for development of fever (Boxes 4-4 and 4-5). Careful evaluation for the presence of infectious disease is always indicated, especially when the onset of a fever is abrupt; the temperature is >39.4° C (103° F); and the fever is accompanied by depression, variable loss of appetite, serous nasal exudate, epiphora, enlargement of lymph nodes, or diarrhea and a decreased or increased leukocyte count. Other causes of fever are neoplasia (Boxes 4-6 and 4-7), immune-mediated diseases (Boxes 4-8 and 4-9), noninfectious inflammation (Boxes 4-10 and 4-11), and certain drugs.

4.3.5.1

Box 4-4 Infectious Causes of Fever in Horses

4.3.5.1.1

COMMON CAUSES

Upper respiratory viral diseases

Strangles, *Streptococci equi*

Pneumonia, bacterial or viral

Pleuropneumonia

Gastrointestinal parasitic infections

Enteritis, *Clostridium difficile, Lawsonia,* or of unknown causes

Salmonellosis

Equine monocytic ehrlichiosis (Potomac horse fever)

Proximal duodenitis-jejunitis

Rotavirus diarrhea (foals)

Endotoxemia from gastrointestinal disorders

Septicemia, septic arthritis, osteomyelitis (foals)

Urachal abscess (foals)

Metritis (mares)

Peritonitis

Tetanus

Traumatic tenosynovitis, cellulitis

Localized occult abscesses (thorax, abdomen, upper respiratory system)

Tumors (see list in Box 4-6)

4.3.5.1.2

LESS COMMON CAUSES

Equine encephalomyelitis (EEE, WEE)

West Nile virus

Osteomyelitis (adults)

Vesicular stomatitis

Tyzzer's disease (foals)

Malignant edema

Bacterial endocarditis

Mastitis

Pyelonephritis

Equine infectious anemia

Equine viral arteritis

Otitis media and interna

4.3.5.1.3

UNCOMMON CAUSES

Pericarditis

Systemic or pneumonic aspergillosis, candidiasis

Pneumocystis carinii

Brucellosis

Tularemia

Anthrax

Rabies

Lyme disease *(Borrelia burgdorferi)*

Nocardiosis

Coccidioidomycosis

Babesiosis, piroplasmosis

Toxoplasmosis

EEE, Eastern equine encephalitis; *WEE,* western equine encephalitis.

4.4 FEVERS OF UNKNOWN ORIGIN

Most febrile illnesses encountered in large animal practice are caused by infectious diseases that are readily diagnosed by careful evaluation of history and physical examination or are of short duration, run their course, and progress to complete recovery within 2 weeks without a specific etiologic diagnosis having been made. Some febrile conditions, however, continue for weeks or months, accompanied only by nonspecific signs of depression, variable anorexia, and weight loss, while the diagnosis remains obscure. Patients with prolonged febrile episodes of 3 weeks' duration or longer in which a diagnosis has not been made after a week of routine diagnostic efforts or after 3 days of hospitalization and diagnostic tests are considered to have fever of unknown origin (FUO). The majority of cases that meet the definition of FUO have infectious causes. Neoplastic diseases, immune-mediated vasculitides, and autoimmune diseases are the next most common causes. Adverse drug reactions and other miscellaneous diagnoses are the least common documented causes of FUO. Most cases of FUO are caused by common diseases with an unusual presentation; an ordered, problem-oriented approach to diagnosis will render a diagnosis in 90% of cases.[37,41] The following steps are suggested (Fig. 4-3).

4.4.1 Box 4-5 Infectious Causes of Fever in Ruminants

4.4.1.1 COMMON CAUSES

Mastitis

Metritis

Pneumonia: viral, mycoplasma, bacterial

Traumatic reticuloperitonitis (B)

Leptospirosis

Septicemia, osteomyelitis, infectious arthritis, omphalophlebitis (neonates)

Toxemia from gastrointestinal disorders

Enteritis

Abscesses

Pharyngeal

Internal lymph nodes (C, O)

Associated with foot

Verminous pneumonia (B)

Listerosis

Bovine viral diarrhea (BVD), mucosal disease (B)

Otitis media, interna

Balanoposthitis (O)

Clostridial infections

Blackleg *(Clostridium chauvoei)*

Clostridium perfringens types D, A (C, O)

Anaplasmosis

Contagious ecthyma (C, O)

Haemophilus somnus infection (thromboembolic meningoencephalomyelitis)

Mycoplasma species arthritis, septicemia (C)

4.4.1.2 LESS COMMON CAUSES

Endocarditis

Pericarditis (B)

Bluetongue (O)

Tetanus

Vesicular stomatitis

Malignant catarrhal fever (B)

Verminous pneumonia (C, O)

Cystitis, pyelonephritis

Epididymitis (C, O)

Chlamydial abortion

Enzootic abortion (C, O)

Epizootic abortion (B)

Caprine arthritis encephalomyelitis (C)

Hoof abscess, footrot

4.4.1.3 UNCOMMON CAUSES

Neoplasms (see list in Box 4-7)

Rabies

Infectious necrotic hepatitis *(Clostridium novyi)*

Sarcocystosis (B)

Tuberculosis (B)

Systemic candidiasis, aspergillosis

Eperythrozoonosis

Brainstem, pituitary abscess

Systemic toxoplasmosis (C, O)

Tularemia

Pseudorabies

Brucellosis

Ovine progressive pneumonia

Chlamydial sporadic bovine encephalomyelitis

B, Bovine; *C,* caprine; *O,* ovine.

4.4.2

Box 4-6 Neoplastic Causes of Fever in Horses

4.4.2.1

COMMON CAUSES

Metastatic melanomas

Lymphosarcoma

Squamous cell carcinoma

Fibrosarcoma

4.4.2.2

LESS COMMON CAUSES

Granulosa cell tumors in mares

Undifferentiated reticuloendothelial cell sarcomas

Adenocarcinomas

Myeloproliferative diseases

4.4.2.3 UNCOMMON CAUSES

Hemangiosarcoma

Mesothelioma

Pheochromocytoma

Osteosarcoma

Myeloma of the gastrointestinal tract

4.4.3 Box 4-7 Neoplastic Causes of Fever in Ruminants

4.4.3.1 COMMON CAUSES

Bovine leukosis (B)

Lymphosarcoma

4.4.3.2 LESS COMMON CAUSES

Adenocarcinoma

Metastatic melanoma (C)

Liver neoplasia

Mesothelioma

4.4.3.3 UNCOMMON CAUSES

Skeletal neoplasia

Malignant neuroblastoma

B, Bovine; *C,* caprine.

4.4.4

Box 4-8 Immunologic Causes of Fever in Horses

4.4.4.1

COMMON CAUSES

Purpura hemorrhagica

Urticaria

Drug-induced fever

4.4.4.2

LESS COMMON CAUSES

Immune-mediated hemolytic anemia, thrombocytopenia

Combined immunodeficiency of foals

IgM deficiency

Pemphigus foliaceus

Chronic necrotizing vasculitis

Neonatal isoerythrolysis

4.4.4.3

UNCOMMON CAUSES

Connective tissue disorders, rheumatoid arthritis

Transient agammaglobulinemia of foals

Bullous pemphigoid

Common variable immunodeficiency

IgM, Immunoglobulin M.

4.4.5

Box 4-9 Immunologic Causes of Fever in Ruminants

4.4.5.1

COMMON CAUSES

Drug allergies

Urticaria (milk allergy in cattle)

4.4.5.2

LESS COMMON CAUSE

Neonatal isoerythrolysis (B)

4.4.5.3

UNCOMMON CAUSE

Pemphigus foliaceus (C)

B, Bovine; *C,* caprine.

4.4.6

Box 4-10 Noninfectious Inflammatory and Miscellaneous Causes of Fever in Horses

Hepatic disorders

Hyperlipidemia, equine hepatic lipidosis

Acute hepatic necrosis (Theiler's disease)

Chronic active hepatitis

Cholelithiasis

Hyperkalemic periodic paralysis

Foreign bodies

Nasal, oral, pharyngeal, tracheal, bronchial

Thrombophlebitis

Ocular trauma, recurrent uveitis

Burns, smoke inhalation

Snake bite

Acute renal failure

Idiopathic interstitial pneumonia

4.4.7

Box 4-11 Noninfectious Inflammatory and Miscellaneous Causes of Fever in the Ruminant

Phlebitis, thrombophlebitis

Salt toxicity, water deprivation

Acute bovine pulmonary emphysema

Fat necrosis (B)

Burn, smoke inhalation

Ocular trauma

Snake bite

Acute renal failure

Primary photosensitization

Cholelithiasis (B)

Postparturient hemoglobinuria (B)

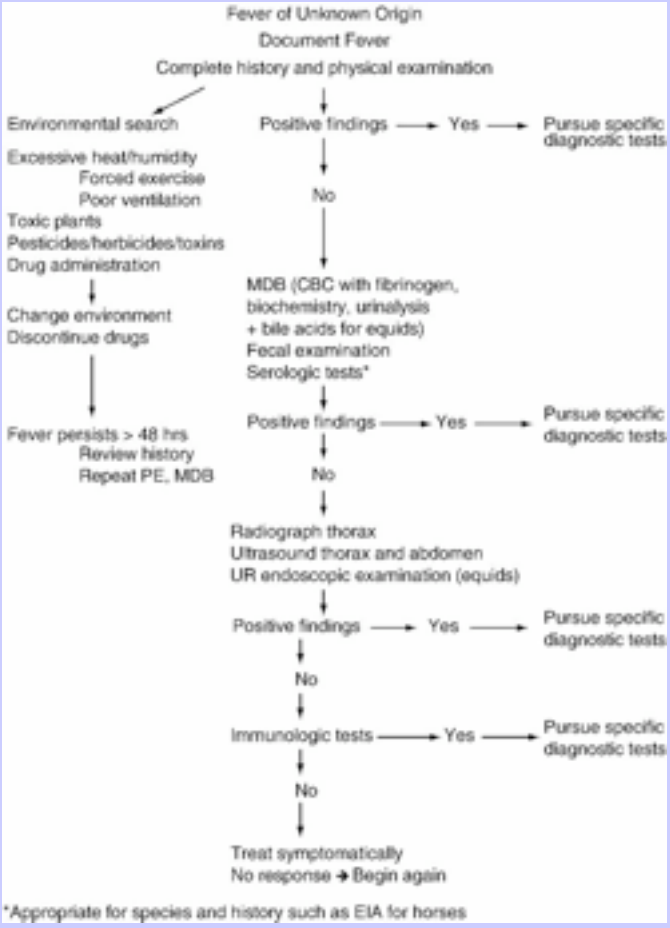
B, Bovine.

4.4.8

Document Fever

A temperature chart consisting of at least twice daily determination of rectal temperature should be completed to characterize the fever pattern. *Intermittent fevers* are characterized by diurnal variation in which a peak elevation of temperature of >0.75° C (1.5° F) occurs, followed by a decline in temperature, which in some patients falls within the normal range. Most intermittent fevers peak in late afternoon or evening, with the lowest temperatures occurring in the morning; but approximately 10% of cases will have a reverse pattern. Intermittent fever is most commonly associated with pyrogenic infections, although it may occur in neoplasia, especially if tissue necrosis and inflammation are concurrent. *Remittent fevers* are characterized by a period of days in which elevated temperatures occur, followed by several days of normal temperature, only to have the cycle repeat again. Brucellosis in ruminants, equine infectious anemia (EIA) in horses, and blood-borne protozoal diseases such as babesiosis may exhibit this type of pattern. *Sustained fevers* are characterized by a consistently raised temperature without variation and appear as a "flat line" on a temperature chart. Fevers caused by drug administration and certain toxins may be of this type, especially if the patient does not exhibit any other signs of illness.[2] Any pharmacologic agents being administered to the patient should be discontinued. Defervescence of fever from drug administration should occur in 48 hours.

Fig. 4-3 Approach to fever of unknown origin (FUO).



4.4.9 Consideration of Epidemiology

Repeated efforts to obtain a complete history in chronologic order of development of clinical signs may be necessary to extract all the information pertaining to the individual animal. A knowledge of forage available, presence of nutrient deficiencies and excesses, toxic plants, and infectious organisms indigenous to the area, as well as the threat of exotic diseases, is necessary for the present and past geographic environment of the animal.

4.4.10 Physical Examination

A physical examination (see Chapter 1 and Chapter 2) should be carefully performed to evaluate all body systems as thoroughly as possible and repeated as often as practical, because it is unusual for a disease to cause a prolonged fever without the occurrence of some physical signs. Examination should include the following:

1 Horses

- a Complete visual or manual oral examination; percussion of sinuses; endoscopic examination of upper airway structures and of the trachea and bronchi (if length of the endoscope allows)
- b Complete ophthalmic examination
- c Thorough auscultation of cardiopulmonary system at rest, with rebreathing bag, and following exercise; evaluation of peripheral perfusion before and after exercise
- d Palpation of external lymph nodes, ballottement, and deep palpation of external abdomen for pain
- e Rectal examination
- f Fecal odor, consistency, volume; frequency of defecation
- g Evaluation of external genitalia and mammary gland
- h Evaluation of musculoskeletal conformation and gait analysis for lameness

2 Ruminants

- a Complete visual or manual oral examination; percussion of sinuses
- b Complete ophthalmic examination
- c Thorough auscultation of cardiopulmonary system, evaluation of peripheral perfusion
- d Palpation of all external lymph nodes
- e Rate and quality of rumen contractions, abdominal ping, and ballottement for rumen fill and pain
- f Fecal color, consistency, volume; frequency of defecation
- g Complete udder examination and milk evaluation of lactating females
- h Testicular and penile palpation of males

i Complete rectal examination (cattle)

j Evaluation of musculoskeletal conformation and gait analysis for lameness

4.4.11 Diagnostic Aids (Table 4-1)

All cases of FUO should have a laboratory database consisting of a complete blood count (CBC), urinalysis, and biochemical profile. The CBC should include morphology of red blood cells and white blood cells (WBCs), WBC differential, and fibrinogen determination. Chronic inflammatory disease produces characteristic changes in the CBC (see Chapter 24 and Chapter 26), and morphologic evaluation of the blood smear may reveal blood-borne parasites.

Serum protein and albumin determinations characterize either hypoproteinemia or hyperproteinemia. Serum protein electrophoresis and immunoelectrophoresis further classify deficiencies or increased production of proteins. Serum enzyme determinations and bile acid concentration for liver evaluation are also warranted.

Because much of the abdomen is unavailable to rectal palpation, abdominocentesis and evaluation of peritoneal fluid for protein, cellularity, and cell morphology are justified. Peritoneal fluid is obtained more consistently in horses than in ruminants with abdominal disease because of the presence of the greater omentum and the rapid formation of fibrinous adhesions in ruminants with inflammatory abdominal disease. Peritoneal fluid evaluation is usually most helpful in inflammatory diseases, but it may be diagnostic in some cases of abdominal neoplasia. Bacterial culture and sensitivity of peritoneal fluid are indicated in inflammatory diseases when WBCs show degenerative or toxic changes but are rarely positive unless gross bowel contamination has occurred. Polymerase chain reaction (PCR) for *Streptococcus equi* and/or *Rhodococcus equi* may be warranted in horses with evidence of chronic inflammation of the abdominal cavity.

Blood cultures are best used after characterization of a remittent fever and evidence of pyogenic inflammatory disease from the laboratory database. Any antimicrobial therapy should be discontinued 48 to 72 hours before sampling. Three to five samples should be collected at least 45 minutes apart and are best taken directly into culture media. Sampling just before and during a temperature rise is more likely to yield positive results than sampling at the temperature peak and decline.

Serologic evaluation for infectious diseases common in the geographic area and/or patient population should be performed. Single serologic determinations usually are of value only in those diseases in which one positive titer is significant and when the disease is characterized by persistent infection such as EIA, brucellosis, or Johne's disease. In many instances vaccination history and/or accompanying clinical signs must be correlated with titer determinations. Paired samples for toxoplasmosis, babesiosis, and various mycotic diseases (especially coccidioidomycosis) are indicated when the diagnosis remains obscure. Serologic determination of antibody titers to the SeM protein of *S. equi* can aid in the diagnosis of internal abscessation.[42] Virus isolation and/or PCR, particularly in persistent bovine viral diarrhea (BVD)–infected cattle, may be helpful.

Evidence of gastrointestinal protein loss, chronic diarrhea, or persistent melena warrants several fecal or rectal biopsy cultures for salmonella in horses and calves, whereas such signs in adult dairy cattle warrant ruling out bovine leukosis as the cause.

Also helpful are biopsies of enlarged lymph nodes, accessible abdominal masses, and the liver and kidney when laboratory data indicate abnormalities. Liver biopsies should be cultured and evaluated histologically, because bacterial cholangiohepatitis can be a cause of FUO. Evaluation of biopsies for the presence of immunoglobulins,

particularly if skin lesions are present, may add in diagnosis of immune-mediated disorders. Antinuclear antibody determinations and a Coombs' test are also indicated in suspected immune-mediated diseases.

Radiographic evaluation, particularly of the thorax, should be performed in horses and small ruminants and is often possible in dairy cattle. Ultrasonographic examination of the heart may definitively diagnose cardiac abnormalities and may provide more complete scrutiny of other organs in the thorax and abdomen, as well as deep structures of the musculoskeletal system. Ultrasonographic examination also aids in percutaneous biopsy of internal structures and may help the practitioner make the decision for exploratory laparotomy. 39

Table 4-1 Fever of Unknown Origin: Diagnostic Procedures

Procedure	Indications
Abdominocentesis	Abdominal pain Abnormal rectal examination (e.g., mass) Fluid wave on ballottement or ultrasonography
Biopsy	Enlarged lymph nodes or other mass found Abnormal renal or liver function test results Vesicular or ulcerative skin lesions
Blood culture	Intermittent fever, especially in a neonate with failure of passive transfer Neutropenia or neutrophilia ± bands Increased fibrinogen Cardiac murmurs (bacterial endocarditis)
Radiography	Any musculoskeletal pain, heat, swelling Thorax, see transtracheal aspirate
Synovial fluid aspirate	Joint effusion, heat, pain
Thoracocentesis	Abnormal percussion of chest Fluid line thoracic radiographs Fluid found on ultrasonography
Transtracheal aspirate	Persistent cough or nasal exudate with normal upper respiratory tract Abnormal auscultation or percussion of thorax Persistent increased respiratory rate
Bronchial alveolar lavage	Exercise intolerance with normal cardiovascular system
Immunodiagnostic screening	
Serum protein electrophoresis	Abnormal serum protein
Serum protein immunoelectrophoresis	Hypergammaglobulinemia Hypogammaglobulinemia (horses)
Direct Coombs' test	Hemolytic anemia RBC autoagglutination
Skin biopsy direct immunofluorescence	Vasculitis, purpura Bullous or ulcerative skin lesions
Antinuclear antibody	Multiple noninfectious arthritis
ECG	Dysrhythmia, congestive heart failure
Bone marrow aspiration	Anemia Thrombocytopenia
Gastrointestinal absorptive tests (horse)	Hypoproteinemia with normal kidney, liver
Serology	Persistent undiagnosed disease
Exploratory laparotomy	Abnormal rectal examination, ultrasonography Chronic abdominal pain Abnormal peritoneal fluid
Ultrasonography	Cardiac murmurs, dysrhythmias Abnormal liver or kidney function tests Abdominal mass Suspect fluid in thorax, pericardium, abdomen

ECG, Electrocardiogram; *RBC,* red blood cell.

Exploratory laparotomy without direct evidence of abdominal disease should be performed only in patients that are becoming progressively debilitated and in which all other avenues of diagnosis have been exhausted. Blind exploratory laparotomies usually do not contribute to diagnosis, are costly, and are not without risk. Exploratory laparotomy is used for diagnostic purposes more routinely in ruminants than in horses.

Nuclear imaging and imaging using autologous WBCs labeled with technetium-99m or indium-111 are increasingly used in human and small animal medicine.[43] These procedures may be helpful in localizing abscesses, particularly osteoarticular infections. These modalities may prove to be of benefit for large animals as the modalities' availability increases.

The use of therapeutic trials of antimicrobials in FUO should be restricted to cases in which strong evidence of a bacterial infection exists. The therapeutic regimen should be as specific as possible and administered for a predetermined amount of time. Inappropriate use of broad-spectrum antimicrobials for all febrile diseases contributes to interference in accurate diagnosis.

4.5 HYPOTHERMIA

Decreases in body temperature may occur when environmental stresses (cold, wet, wind) overwhelm the body's capability of heat production (especially when the body is weakened from disease), when central nervous system disease has resulted in damage to the regulatory centers within the hypothalamus, or when adrenergic or sympathetic effector systems have been damaged. Newborns, cachexic, and very aged animals are most susceptible to heat loss caused by cold exposure (see neonatal sepsis and weak calf syndrome, Chapter 20). Concurrent signs of septic disease in hypothermic animals signify a guarded prognosis because the body's defense mechanisms are often overwhelmed when core body temperature declines. Severely hypothermic animals (core body temperature >30° C) 40
are profoundly depressed and have marked reduction in ventilation, absence of muscle activity, and decreased 41
reflexes. Decreased intravascular volume and depressed cardiac function lead to hypoxia, acidemia, and cardiac dysrhythmias. Newborns are often hypoglycemic and have potassium imbalances. These animals should be warmed by protecting them from wind or drafts, drying them, and providing a microenvironment of high ambient temperature. Applying thermal blankets and housing them in an insulated stall, with or without supplemental heat, are superior to direct external heat from heat lamps or other sources. Direct external heat without environmental control causes cutaneous vasodilation, often exacerbates central hypothermia, and contributes to cardiovascular compromise.

Animals with severe hypothermia should be warmed gradually over 24 hours, with careful monitoring of body temperature and the cardiovascular system. Maintenance of adequate systemic perfusion is the most important means of preventing cardiac failure.[44,45] Acidosis and potassium imbalances are common and may fluctuate rapidly. Consequently, repeated measurements, especially when a patient's clinical condition worsens in the process of warming, are often necessary. Appropriate crystalloid fluids, warmed to body temperature, are usually necessary throughout the warming process. Evaluation of blood glucose and concurrent dextrose therapy, especially in neonates, should also be performed.

Warmed humidified oxygen therapy both as an aid in treatment of hypoxia and as a means of warming is helpful. Gastric (rumen) or rectal lavage with warmed fluids may also be used. However, care should be taken in rapid rewarming, because an imbalance in the basal metabolic rate (which is temperature dependent) and systemic perfusion may result in life-threatening cardiac dysrhythmias and worsening of metabolic acidosis and hypoxia. Hypothermia attenuates the inflammatory response by a multiplicity of effects on cytokines and other key signaling mechanisms.[46] Thus the adverse metabolic effects of disease are slowed at low body temperatures, and, as body

temperature elevates, signs of systemic disease become apparent.[47] In hypothermic animals in shock, particularly neonates, severe anoxic changes in the bowel wall may result in severe diarrhea, sloughing of mucosa, or clostridial growth in the bowel.

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5 Chapter 5 Alterations in Respiratory Function

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5.1 COUGH

5.1.1 Definition

Coughing, a normal and important respiratory defense mechanism, is the sudden, forceful, noisy expulsion of air through the glottis to clear mucus, particles, and other material from the tracheobronchial tree and glottis.

5.1.2 Pathophysiology

The mucociliary escalator and the cough reflex are the major protective mechanisms that function together to remove material from the respiratory tract.[1,2] Particles trapped in mucus are carried toward the trachea by continuous waves of ciliary motion that start at the level of the terminal bronchioles. Coughing may effectively remove secretions from the tracheobronchial tree proximal to the level of the segmental bronchi.[3]

5.1.2.1 NEURAL PATHWAYS INVOLVED IN THE COUGH REFLEX

Coughing is an involuntary reflex that can also be suppressed or initiated voluntarily.[2,3] The reflex pathway involves sensory receptors of nerve fibers that extend between epithelial cells and ramify throughout the tracheobronchial tree from the level of the larynx to the respiratory bronchioles.[4,5] These receptors, many of which are irritant receptors, are particularly numerous in the trachea and bronchi, especially around the hilus of the lung and at the bifurcation of bronchi.[1,4] Other receptors that can stimulate coughing are found in the lung parenchyma, in the pleura, and in other locations. Myelinated afferent fibers from cough receptors pass predominantly in the vagal, but also in the glossopharyngeal, trigeminal, and phrenic nerves, to the cough center in the medulla oblongata.[1,3,5] Brainstem neuronal pathways for the cough reflex in the horse are not well characterized. Efferent fibers pass in the vagal, phrenic, intercostal, and lumbar nerves and motor portions of the trigeminal, facial, hypoglossal, and accessory nerves to supply the striated and smooth muscles of the larynx, tracheobronchial tree, diaphragm, intercostal muscles, abdominal muscles, and glands of the respiratory tract.[1,5–7]

Irritant receptors are stimulated by mechanical deformation such as that induced by pinching the trachea or by bronchoconstriction, by chemically inert dusts such as carbon, by pollutant gases such as ammonia, by inflammatory conditions, and by chemical mediators such as histamine (Boxes 5-1 and 5-2).[2,4] Sensitivity to mechanical stimulation varies along the airway, and in horses the upper airway cough receptors appear to be less active than in many other species.[8] For example, a stomach tube inadvertently passed into the trachea frequently does not induce coughing until it reaches the bifurcation. Similarly, endoscopic examination often reveals a large pool of exudate in the trachea of horses with little or no history of coughing.[6] Foals with

Rhodococcus equi pneumonia often have a tracheal rattle, reflecting accumulation of tenacious exudate in the trachea, but may not cough. Repeated stimulation of irritant receptors over several hours does not appear to diminish sensitivity but may lead to changes in threshold.[4]

Bronchoconstriction is a constant component of cough,[3,7,8] and stimuli of cough also may induce reflex bronchoconstriction through the parasympathetic nervous system.[4] However, cough and bronchoconstriction are separate airway reflexes.[7] Whereas stimulation of irritant receptors in large airways may induce both cough and reflex bronchoconstriction independently, stimulation of nerve endings in smaller airways does not directly initiate coughing but does cause bronchoconstriction, which may initiate coughing indirectly.[4] The role of bronchoconstriction in the induction of coughing is supported by studies showing that coughing in asthmatic people can be prevented by aerosol administration of salbutamol (a bronchodilator) or of local anesthetics or cromolyn sodium.[9,10] This suggests that mediator release (blocked by cromolyn) causes bronchoconstriction (blocked by bronchodilators), which stimulates irritant receptors (blocked by local anesthetics) and causes coughing.[4] Much of the airflow obstruction in horses with recurrent airway obstruction (RAO) appears to be mediated through these pathways and in many cases can be eliminated with atropine, a parasympatholytic bronchodilator.[4]

5.1.3

Mechanics of Coughing

The mechanical events that produce coughing occur during four phases: inspiration, compression, expression, and relaxation.[2–4] The first three phases are necessary to create the decreased airway cross-sectional area and high airflow rates needed for an effective cough. Coughing is a maximum expiratory flow maneuver that begins with deep inhalation to expand lung volume, increase elastic recoil, and dilate the airways through the tethering effect exerted by surrounding lung tissue.[11] Closure of the glottis is followed by forced expiratory efforts involving the rib cage, abdomen, and diaphragm, which increase pressure in the abdominal, pleural, and alveolar spaces to over 500mm Hg.[4] The glottis then opens suddenly, allowing the elevated alveolar pressure to rapidly accelerate gas flow from the respiratory tree.[2,4,11] This high-velocity gas stream shears exudate from the airway walls and lumen and carries it to the nasopharynx, from which point it exits the respiratory tract as nasal discharge or is swallowed.[11] Airflow stops before the animal has exhaled to residual volume because the glottis closes or the driving force provided by the muscles abates.[4] The characteristic sound of coughing is produced by vibration of laryngeal and pharyngeal tissues, narrowing and deformation of airways, vibration of surrounding lung tissues, and turbulent gas flow vibration in the airway.[4,7]

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5.1.3.1

Box 5-1 Causes of Coughing in Horses

5.1.3.1.1

COMMON CAUSES

Equine influenza A2 virus

Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)

Other viruses (rhinovirus types 1, 2, 3; reovirus)

Bacterial pneumonia

Bacterial pleuropneumonia, pleuritis

Recurrent airway obstruction (RAO or COPD)

Mechanical causes (e.g., nonspecific dust irritation)

Pharyngitis (acute; chronic pharyngeal lymphoid hyperplasia)

Postviral hyperreactive airways

5.1.3.1.2

LESS COMMON CAUSES

Strangles (*Streptococcus equi* infection)

Equine viral arteritis

Parascaris equorum migration

Pharyngeal paresis

Guttural pouch empyema

Guttural pouch mycosis

Pharyngeal, laryngeal trauma or surgery

Postsurgical aspiration (e.g., after laryngeal prosthesis surgery)

Epiglottal entrapment

Subepiglottal cyst or abscess

Chondritis, chondromas of the arytenoid cartilages

Retropharyngeal abscess

Tracheal collapse (including scabbard trachea in ponies)

Tracheal stenosis, stricture

Choke, esophageal obstruction

Aspiration pneumonia (foreign bodies, feed material)

Inhalation pneumonia (smoke, thermal injury, noxious gases)

Lungworm infection *(Dictyocaulus arnfieldi)*

Pulmonary abscessation

Exercise-induced pulmonary hemorrhage (EIPH)

Pulmonary edema (smoke inhalation, acute renal failure, overhydration, septicemia, anaphylaxis)

Summer pasture—associated obstructive airway disease (SPOAD)

Left-sided heart failure

Congestive cardiac failure

Neonatal septicemia

5.1.3.1.3

UNCOMMON CAUSES

Tuberculosis

Pneumoconiosis or silicosis; other interstitial pneumonias

Eosinophilic interstitial pneumonia

Nocardiosis

Coccidioidomycosis

Chlamydia psittaci pneumonia

Mycoplasma species pleuritis

Tularemia

Pulmonary hydatidosis

Tracheal perforation or rupture

Cryptococcosis

Dorsal displacement of the soft palate (laryngopalatal dislocation)

Rostral displacement of the palatopharyngeal arch

Idiopathic laryngeal hemiplegia

Guttural pouch neoplasia

Rectus capitis ventralis muscle rupture

Adenovirus infection

Pneumocystis carinii pneumonia

Esophageal ectasia, dysfunction, stricture, perforation; esophagitis

Megaesophagus

Progressive ethmoidal hematoma

Nasal or paranasal sinus neoplasia

Fistula (pharyngeal, esophageal, esophagobronchial, esophagotracheal, bronchobiliary)

Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)

Infarctive lobar pneumonia

Bronchopleural fistula

Pleural mesothelioma

Pneumothorax

Pulmonary tumor, primary or metastatic

Lymphosarcoma, lymphoma, leukemia

Pulmonary aspergillosis

Phycomycosis, pythiosis

Plant awn stomatitis

Anaphylaxis or acute drug reaction

Atrial fibrillation

Tetralogy of Fallot

Cor pulmonale

Endocarditis

Ruptured mitral chordae tendineae

Melioidosis, *Pseudomonas pseudomallei* (exotic)

Glanders (exotic)

African horse sickness (exotic)

5.1.3.1.4 TOXIC CAUSES

Crofton weed *(Eupatorium adenophorum)*

α-Naphthyl thiourea (ANTU)

Pentachlorophenol

Organophosphate

Carbamate

B, Bovine; *C*, caprine; *O*, ovine.

During forced expiration such as occurs with coughing, the increased pleural pressure is transmitted to the intrathoracic airways and alveoli. Intraalveolar pressure exceeds pleural pressure by an amount equal to the elastic recoil pressure of the lung.[4,11] A pressure gradient thus exists between the alveoli and atmospheric pressure at the nostrils and mouth. At a point in the airways known as the *equal pressure point* (EPP), the pressure in the airway lumen equals the pleural pressure because the elastic recoil pressure has been dissipated.[2–4,11] In the intrathoracic airways rostral to this point, the intraluminal pressure is lower than the pleural pressure; therefore a transmural pressure gradient exists, which tends to cause the airways to be dynamically compressed or collapsed.[2,4,11] The location of the EPP is determined by the elastic recoil pressure, and thus indirectly by lung volume, and by the frictional resistance to flow in the airways between the alveoli and the EPP.[4] At high lung volumes, elastic recoil pressure is high, resistance in peripheral airways is low, and the EPP is typically located in the larger intrathoracic airways, which have cartilaginous support for their walls, thereby preventing airway collapse.[4] As lung volume decreases, elastic recoil force decreases, airway resistance increases, and the EPP moves more peripherally, subjecting lower and less well-supported parts of the tracheobronchial tree to dynamic compression.[3,4,11] Dynamic compression reduces the cross-sectional area of intrathoracic airways and thus increases the velocity of airflow through the narrowed segment.[4] These spikes of accelerated airflow promote more effective shearing of mucus and debris from the airway wall and lumen during coughing.[11]

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5.1.3.2 Box 5-2 Causes of Coughing in Ruminants

5.1.3.2.1 COMMON CAUSES

*Mannheimia hemolytica** or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)

Haemophilus somnus pneumonia (B)

Lungworm infection, verminous pneumonia

Atypical interstitial pneumonia (B)

Chronic bacterial pneumonia with abscessation or consolidation (*Arcanobacterium [Actinomyces] pyogenes*[†] and other bacteria)

Infectious bovine rhinotracheitis (IBR; bovine herpesvirus type 1 [BHV-1]) (B, C)

Bovine respiratory syncytial virus (B)

Parainfluenza virus type 3

Mycoplasma species pneumonia

Caprine *Mycoplasma mycoides* subsp. *mycoides* infection (C)

Caprine arthritis-encephalomyelitis (CAE) pneumonia (C)

Necrotic laryngitis, calf diphtheria (B, O)

Abscess (oral, lingual, retropharyngeal, pharyngeal, laryngeal)

Trauma (pharyngeal, laryngeal, tracheal, bronchial, chest wall)

Esophageal obstruction, foreign body choke

Septicemia (neonates)

5.1.3.2.2

LESS COMMON CAUSES

Bovine rhinovirus (B)

Bovine adenovirus (B)

Bovine malignant catarrhal fever (B)

Bovine virus diarrhea (BVD-MD) (B)

Herpesvirus DN-599 (B)

Bovine herpesvirus type 4 (BHV-4) (B)

Bovine coronavirus (B)

Pulmonary adenomatosis (Jaagsiekte) (O)

Ovine adenovirus (O)

Caprine respiratory syncytial virus (C)

Ovine progressive pneumonia and arthritis, maedi (O)

Aspiration, foreign body pneumonia

Foreign body (pharyngeal, laryngeal, tracheal, bronchial, pulmonary)

Inhalation pneumonia (smoke, noxious gases, thermal injury)

Pulmonary embolus from posterior vena cava thrombosis (B)

Anaphylaxis or adverse drug reaction

Reaction to death of parasites after anthelmintic treatment (B)

Milk allergy in cows (B)

Farmer's lung disease (hypersensitivity to *Faenia rectivirgula* and other mold spores) (B)

Pleuritis, pleural effusion

Pneumothorax

Diffuse fibrosing alveolitis (B)

Left-sided heart failure (left atrioventricular [mitral] insufficiency, pericarditis, congenital cardiac defects, other causes)

High altitude disease (B)

Enzootic bovine leukosis (B)

Chlamydia psittaci pneumonia

5.1.3.2.3

UNCOMMON CAUSES

Diaphragmatic hernia

Pleural mesothelioma (B, C)

Sarcocystosis (B)

Sporadic bovine leukosis, thymic lymphosarcoma (B)

Tuberculosis

Tularemia (O)

Tracheal actinomycosis

Tracheal collapse, stricture, stenosis

Phycomycosis, pythiosis (B)

Pulmonary aspergillosis

Rhinosporidiosis

Zygomycosis, mucormycosis (B)

Pulmonary listeriosis (B)

Pneumocystis carinii pneumonia

Cor pulmonale (C)

Neoplasia (nasopharyngeal, oropharyngeal, pulmonary)

Postpartum hemolytic-uremic syndrome (B)

Esophageal rupture, laceration, ulceration, megaesophagus, hiatal hernia

Neoplasia, skeletal (B, O)

Buss disease, chlamydial sporadic bovine encephalomyelitis (B)

Winter dysentery (B)

Ascaris suum migration in calves (B)

Rinderpest (exotic)

Theileriosis, East Coast fever (exotic)

Melioidosis, *Pseudomonas pseudomallei* (exotic)

Contagious bovine pleuropneumonia (exotic) (B)

African bovine malignant catarrhal fever (exotic) (B)

Virulent sheep and goat pox (exotic) (O, C)

Peste des petits ruminants (exotic) (O, C)

Contagious caprine pleuropneumonia (exotic) (C)

Viral dermatitis of goats (exotic) (C)

Ibaraki disease (exotic) (B)

5.1.3.2.4

TOXIC CAUSES

Organophosphate, carbamate

Mercury (B)

Iodine (B, O)

Insect fogger (B)

Levamisole (O, C)

Nitrogen dioxide (B)

Hairy vetch *(Vicia villosa)* (B)

Sneezeweed (*Helenium* species)

Aflatoxicosis (C)

B, Bovine; *C*, caprine; *O*, ovine.

* Formerly named *Pasteurella hemolytica*.

† Formerly named *Actinomyces pyogenes*.

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Dynamic compression also increases the resistance to airflow.[4] Once dynamic compression of peripheral (smaller) airways occurs, further increases in expiratory effort cause greater narrowing of the airway; thus the flow rate that can be generated at a given lung volume does not increase beyond a certain maximum point (maximum expiratory flow).[4] Maximum expiratory flow decreases progressively as the animal exhales because lung volume declines. Thus coughing beginning at high lung volumes achieves the highest airflows.[4] However, only the larger intrathoracic airways are compressed and subjected to these spikes of higher airflow velocity.[2,4,11] As lung volume falls or if cough is initiated at lower lung volumes, smaller airways are dynamically compressed

and cleared of mucus.[2,3,11] The effectiveness of coughing can thus be improved by repeating it several times in succession, either in a progression from high to low lung volume during the same breath or by inhaling between breaths.[4]

Because maximum airflows are lower in smaller airways, coughing is probably less effective in clearing material from the smaller airways than from the larger ones.[4] In the alveolar regions of the lung, gas flow is too slow for coughing to be an effective means of clearance.[11] Because only intrathoracic airways are dynamically compressed and subjected to these spikes of higher flow velocity during forced expiration, the extrathoracic trachea should be less effectively cleared by coughing.[4] However, horses and other animals with long necks do not seem to have great difficulty in clearing their airways, although they do lower their heads and straighten their airways during coughing to assist the clearance process.

In diseases such as RAO that cause narrowing of the airway lumen, the increased resistance to airflow, especially in peripheral airways, causes the EPP to move more peripherally toward the alveoli, resulting in a reduction in the maximum expiratory flow rate.[2,4] In this situation the effectiveness of coughing in clearing the airways is reduced. Thus administration of a bronchodilator may greatly improve the effectiveness of coughing in patients with RAO.[4]

5.1.3.3

COUGH STIMULI

Cough may be stimulated by bronchoconstriction, excessive mucous production, deposition of inhaled particles in the airways, release of inflammatory mediators (infectious diseases), exposure to hot or cold air, intramural or extramural pressure or tension on the airways (tumor, granuloma, abscess, or decreased pulmonary compliance caused by restrictive disease such as interstitial fibrosis or pleural effusion), sloughing of airway epithelial cells, and enhanced epithelial permeability (pulmonary edema).[12] Epithelial sloughing and enhanced epithelial permeability theoretically increase the accessibility of cough receptors to the mechanical or chemical agents that stimulate them. Loss of integrity of the epithelial lining of the respiratory tract is a common feature in many respiratory diseases associated with cough (infectious diseases); however, a cause-and-effect relationship between alterations in pulmonary epithelium and cough has not been established.[12] Diseases of the respiratory tract may alter the sensitivity of the cough reflex.[12] For example, viral infections may increase the responsiveness of cough receptors to stimuli.[7,12] Of the many causes of coughing in large animals, viral infections such as equine influenza and infectious bovine rhinotracheitis (IBR) are particularly important, because they cause outbreaks of respiratory disease that has acute onset of coughing as a prominent feature and that is frequently associated with persistence of coughing for prolonged periods after signs of acute disease have abated. These features of viral infections reflect the decreased effectiveness of mucociliary clearance resulting from virus-induced injury to ciliated epithelial cells, together with exposure and sensitization of irritant airway receptors, which lead to persistent bronchial hyperreactivity.[4,13] Affected individuals show bronchoconstriction and coughing in response to mildly irritating stimuli such as dust, stable pollutants, cold air, dry air, and exercise that would not normally cause coughing. Coughing subsides only when the airway epithelium has healed, which takes approximately 7 weeks.[4]

The role of mucus in coughing is not clear.[4] Fluid flushed over the tracheobronchial epithelium stimulates irritant receptors, particularly if the fluid is hypertonic or hypotonic.[9,10,14] Coughing is also stimulated by fluid that lacks permeant anions (i.e., anions that have a hydrated size and membrane-penetrating characteristics similar to the chloride anion).[15] Excessive accumulation of mucus in the airways may mechanically stimulate

irritant receptors and cause coughing.[4] However, mucus may have a protective effect by coating the epithelium with a layer that separates the receptors from the irritants.[4]

Coughing is a prominent feature of cardiac disease in many species, although cardiac diseases are not often encountered in large domestic animals. Failure of the left side of the heart as a result of congenital defects, valvular stenosis or incompetence, conduction disturbances, myocardial disorders, or restrictive pericardial disease causes an increase in pressure in the pulmonary venous return from the lung. This results in transudation of fluid from the pulmonary capillaries into the pulmonary parenchyma and airspaces (cardiogenic pulmonary edema) and causes swelling of the mucosal lining of small airways.[2] These changes stimulate cough receptors and initiate the cough reflex. Coughing that occurs secondary to cardiac disease is usually chronic, although acute-onset coughing may be observed with ruptured mitral chordae tendineae and bacterial endocarditis.[16]

5.1.4 Approach to Diagnosis of Coughing

5.1.4.1 HISTORY

The history should include questioning relative to the patient, the cough, the environment, and management. The *age* of the affected animal is important because many conditions have a marked age incidence. For example, *R. equi* pneumonia occurs primarily in foals younger than 6 months of age, equine herpesvirus type 4 predominantly affects weanling and yearling horses, atypical interstitial pneumonia (fog fever) affects predominantly pastured adult cattle, and RAO affects primarily mature stabled horses. The *use of the horse;* its state of fitness; the presence of vices such as crib biting; and any *history of contact with other horses* at shows, events, sales, racetracks, or breeding farms should be determined.

Recent stressors such as transportation, surgery, strenuous activity, or weaning should be determined, because these are known risk factors for conditions such as pneumonia and pleuropneumonia. The duration of ownership of the animal, its previous health, and the geographic location of origin, if it was recently purchased, may help identify regional diseases not normally seen in the area (e.g., systemic mycosis, lungworms, or silicosis in horses) or indicate the degree of stress likely to have been recently experienced. For recently purchased feedlot cattle and sheep, it should be determined if the animals were preconditioned before sale, their place of origin, the number of sale yards through which they have passed, and the duration of transportation.

When evaluating for potentially contagious diseases or those related to common environmental conditions, the vaccination status of the affected animal and herdmates and the presence of similar clinical signs in other in-contact animals sharing common facilities or common airspaces should be determined. In nursing animals the vaccination status of the dam is important. A history of other signs such as anorexia, nasal discharge, weight loss, exercise intolerance, stridor, lymphadenopathy, facial swelling, diarrhea, colic, and edema may provide important clues to the cause of the current problem. Weight loss occurs in many acute and chronic diseases, both infectious and noninfectious. Anorexia may indicate that the animal feels too systemically sick to eat, that it has a sore throat, or that it is devoting so much effort to breathing that it will not eat.

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Environmental considerations such as the introduction of new animals into the environment or the return of animals from shows, sales, training centers, or breeding farms should increase the suspicion of infectious viral or bacterial diseases such as IBR in cattle or influenza in horses. For diseases such as *R. equi* pneumonia in foals, it is useful to know if similar cases have been seen on the premises in the past. The type of housing or pasturing facilities should be evaluated, particularly with regard to airspace, ventilation, sanitation, stocking

density, dust, shade, and shelter. Equine stabling facilities that have enclosed barns, particularly when the stalls face a central arena or are located under a hay storage loft, promote the spread of contagious agents and almost invariably increase the concentration of dust, mold spores, and noxious gases such as ammonia and tractor exhaust fumes in the environment. The type of feed and bedding, storage facilities, and feeding arrangements should be evaluated, especially in chronically coughing horses suspected of having allergic lung disease. Quantitative measures of ventilation and environmental quality can be made and can prove helpful in case management and in monitoring the effectiveness of measures to reduce environmental dust and other pollutants.[17] Similarly, the sampling of air in barns or paddocks using special devices that allow quantitation of bacterial pathogens such as *R. equi* may prove to be useful for assessing risk of infection.

A history of recent access to lush green pastures is frequently obtained in cattle with atypical interstitial pneumonia (fog fever). The quality of the feed should be evaluated visually and by smell, particularly with regard to the presence of mold spores. General management, pasture management, and parasite control measures should also be evaluated, especially if lungworm infection is suspected. Horses with lungworm infection almost invariably have a history of current or previous co-grazing with donkeys. The season and seasonal incidence of recurrence of the coughing can provide useful clues (e.g., marked seasonal worsening of signs in the late autumn when horses are stabled suggests chronic allergic respiratory disease). The history should also include the nature of previous treatments and the response.

Important historical features of the cough include the time and speed of onset; frequency; duration (chronic if longer than 1month); relation to feeding, housing, or weather; relation to exercise and timing during exercise; improvement, deterioration, or other change since onset; and the presence of and similarity to previous episodes of coughing or respiratory disease. Many coughs are exacerbated by exercise because exercise places greater stress on the respiratory tract. The resulting rapid airflow improves mobilization of secretions and irritates the airway directly. Coughs that occur during eating suggest specific or nonspecific sensitivity to molds, pollen, or other dusts in feed; inflammatory conditions of the larynx or pharyngeal region; laryngeal or pharyngeal problems, including complications of surgery, that interfere with swallowing or guarding of the lower airway; or esophageal obstruction (choke). The effort required to cough and associated pain may also give clues to the cause of the cough.

The character of the cough should be evaluated, because certain features of a cough tend to point toward its origin and possible causes but are by no means pathognomonic for either. Coughs originating in the upper airway are usually of acute onset, loud, harsh, coarse, dry, hacking, and nonproductive in character. Painful upper airway conditions such as acute pharyngitis, strangles, or necrotizing laryngitis can make the cough more muted. Lower airway coughs are usually soft, deep, and productive (mucus, pus) and tend to be more persistent than coughs originating in the upper airway. However, chest pain frequently attenuates coughing in horses with pleuropneumonia. In horses the fixed intranarial position of the larynx usually precludes expectoration of sputum into the mouth; thus the productive nature of the cough is difficult to assess. Excess mucus or exudate that is coughed up into the pharynx is usually swallowed; thus a cough can be productive without evidence of a nasal discharge. Swallowing efforts that follow a cough generally indicate that the cough is productive.

5.1.4.2

PHYSICAL EXAMINATION

The extent of the physical examination varies with the information already gained and the severity of the problem. It should include both distant and close evaluation of the patient and the environment. In addition to a detailed examination of the respiratory and cardiovascular systems, a general physical examination should be completed so that diseases in other systems can be detected and systemic manifestations of cardiopulmonary disease can be evaluated. The attitude of the animal, the respiratory rate and character, the presence of

excessive intercostal or abdominal respiratory effort or of a “heave line” or “barrel chest,” the presence and nature of respiratory distress or stridor at rest, and the presence and character of any nasal and ocular discharge should be noted before the animal is restrained. The following should then be determined: (1) rectal temperature, pulse rate, pulse rhythm and character, mucous membrane color, and capillary refill time; (2) symmetry of airflow from each nostril; (3) odor from the nostrils and mouth; (4) facial symmetry and swelling; (5) resonance or painful response on percussion of the maxillary and frontal sinuses; (6) enlargement of submandibular, parotid, retropharyngeal, and other regional lymph nodes; (7) enlargement of the parotid salivary glands or thyroid gland; (8) swelling, pain, or palpable abnormalities in the retropharyngeal region; (9) palpable swelling or flattening of the cervical trachea; and (10) masses at the thoracic inlet and palpable turbulence such as a tracheal rattle in the extrathoracic airway. The oral cavity should also be examined. If spontaneous coughing is not heard during the physical examination, a cough should be induced after auscultation of the airways by pinching the larynx or trachea, and it should be ascertained whether the induced cough sounds like the animal's spontaneous cough. Pinching of the trachea generally causes normal animals to cough once or twice, whereas it often induces paroxysmal coughing in animals with lower airway disease. The laryngeal or tracheal cough reflexes show increased sensitivity in most infective and inflammatory airway diseases.[16]

The larynx, trachea, lungs, and heart should be carefully *auscultated* on both sides of the chest in a quiet environment with the animal at rest and after the rate and depth of respiration have been increased by application of a rebreathing bag, by temporary occlusion of the nostrils, or by light exercise (see Cyanosis, p. 68). This permits detection of turbulent airflow, increased or decreased bronchovesicular sounds, wheezes, crackles, pleural friction rubs, or pleural fluid splashes, all of which indicate disease of the airways, pulmonary parenchyma, or pleura. Wheezes and crackles reflect airway narrowing and dynamic airway collapse, respectively, and are both evidence of small airway disease.[16] A small or medium-size plastic trash bag makes an adequate rebreathing bag; a plastic rectal sleeve is satisfactory for foals or calves if the opening is stretched so that it does not occlude the nostrils. The response to application of a rebreathing bag should also be noted. Most horses tolerate this procedure well and breathe more deeply, whereas animals with chest pain often do not. Normal horses do not cough when the bag is applied unless they have been eating recently, whereas horses with airway irritation caused by pneumonia or other conditions often cough paroxysmally in response to application of a rebreathing bag. The time taken to regain the normal respiratory rate and character after removal of the bag provides a reasonable crude indicator of ventilatory reserve. Normal animals recover quickly, within a few breaths, whereas respiration may be altered for several minutes in animals with significant lung disease.

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The chest wall should be *palpated* to detect pleural friction rubs or lesions such as rib fractures, and the symmetry of chest expansion should be determined. Unilateral chest pain (pleurodynia) often reduces chest excursion on the affected side. Both sides of the chest should be *percussed* systematically to detect changes in resonance and chest pain. The caudoventral percussion border in the normal horse traces from the level of the tuber coxae at the seventeenth intercostal space (the horse normally has 18 pairs of ribs) to the level of the tuber ischii at the fifteenth intercostal space to the midthorax at the thirteenth intercostal space to the level of the point of shoulder at the eleventh intercostal space; it continues as a curving line to a point 1 to 3 inches above the olecranon. The normal caudoventral percussion boundary in cattle and small ruminants traces from the eleventh intercostal space at the level of the lateral edge of the epaxial musculature to the ninth rib at a level halfway between the costochondral junction and the lateral edge of the epaxial musculature to the fifth rib at the olecranon (cattle, goats, and sheep normally have 13 pairs of ribs). Percussion is an important diagnostic tool in all large animals, but it is most useful in foals, calves, and goats. The precise percussion boundaries, degree of resonance, and auscultation findings are influenced by age, size, body condition, fitness, and hair coat, as well as by disease processes; a gas-filled abdominal viscus can also confuse interpretation.

Hyporesonance (dullness) may indicate pulmonary consolidation, large mass lesions, cardiomegaly, pleural effusion, or other pleural disease. Free pleural fluid usually causes an abrupt change from normal resonance above a horizontal fluid line to hyporesonance below this line. Hyperinflation or pneumothorax may cause hyperresonance with or without expansion of the normal percussion boundaries. A painful response to percussion may indicate pleuritis or some other inflammatory process involving the parietal pleura.

In cattle the presence of thoracic or cranial abdominal pain should be ascertained by application of upward pressure to the xiphoid area with the knee or by application of downward pressure with both hands just caudal to the withers. Animals with cranial abdominal or thoracic pain resist these maneuvers and may make an audible or auscultable grunting noise. Signs such as jugular distention or pulsation (or both) and peripheral edema, which may indicate heart failure, should be noted; and the heart should be auscultated to detect murmurs, dysrhythmias, muffling of heart sounds, or other abnormalities that would indicate the need for further cardiovascular diagnostic procedures.

5.1.4.3

COMPLETE BLOOD COUNT

A complete blood count, including fibrinogen concentration, usually reveals nonspecific findings but may be useful in the evaluation of cases in which primary or secondary inflammatory conditions are suspected and in conditions such as pulmonary thromboembolism secondary to caudal vena cava thrombosis (CVCT) in cattle and guttural pouch mycosis in horses in which blood-loss anemia is likely to be a complicating problem. Acute viral infections often induce a transient anemia and leukopenia, predominantly lymphopenia, followed by a monocytosis during recovery. Neutrophilia and hyperfibrinogenemia are features of many inflammatory conditions but are usually most marked when bacterial infection is involved. Some parasitic diseases (e.g., lungworm infection in cattle) may induce eosinophilia, as may allergic conditions, but eosinophilia is not a common feature of either lungworm infection or allergic RAO in the horse.

5.1.4.4

NASAL OR NASOPHARYNGEAL SWABBING

Nasopharyngeal swabbing and direct cytologic examination and culture are indicated for confirmation of viral or bacterial infections that involve the upper airway. Because a large number of bacteria normally inhabit the nasopharynx, only the presence of *Streptococcus equi* or some other pathogen not considered part of the resident flora can be considered significant. When clinical signs suggest a viral respiratory infection, especially when an outbreak of coughing occurs in several animals, *molecular detection by polymerase chain reaction (PCR), antigen detection by antigen-capture enzyme-linked immunosorbent assay (ELISA)*, or *virus isolation* from nasal or nasopharyngeal swabs, tracheal wash, and/or buffy coat (ethylenediaminetetraacetic acid [EDTA] blood) samples collected during the acute phase of the disease and *viral serologic tests* on acute and convalescent serum samples are indicated.[18] Under these circumstances, sampling as many of the most severely affected, often younger, animals as early as possible in the disease course maximizes the chances of establishing an etiologic diagnosis. Large absorbent Dacron or rayon swabs[*] should be used for nasopharyngeal swabbing. The swab should be placed in viral transport medium for dispatch to the diagnostic laboratory if virus isolation is desired, and the laboratory should be notified in advance that samples will be submitted. Antigen-capture ELISA[†] and PCR tests are now available for testing of nasal or nasopharyngeal swabs and other samples to confirm a diagnosis of viral infection.[18] These rapid-screening tests are sensitive, less cumbersome to perform than virus isolation, do not require such stringent conditions for handling and transporting samples, and provide results sufficiently quickly that specific control measures can be implemented. However, they do not yield an isolate that can be used to monitor genetic and antigenic evolution of the viral agent. Serologic testing often provides only retrospective information, but it can prove very helpful

in the formulation of future control measures, including vaccination. The larger the number of animals tested, the more informative are the results of serologic testing in a herd or flock. Serologic testing is also indicated when pneumonia caused by *Coccidioides immitis* or other fungal agents is suspected.

* Fox 16-inch Procto Swabs, Allegiance Healthcare, Hayward, Calif.

† For example, influenza Directigen Flu A test, Becton-Dickinson, Franklin Lakes, NJ.

5.1.4.5

ENDOSCOPIC EXAMINATION

Endoscopic examination of the nasal passages, conchae (turbinates), pharynx, larynx, and trachea allows the presence, nature, and source of exudates and the presence of anatomic or functional abnormalities or mass lesions to be noted. Endoscopic examination of the upper airway of the horse to evaluate for partial airway obstruction is best performed without the use of sedatives or tranquilizers if possible because these alter the tone and function of the muscles supporting laryngeal and pharyngeal anatomy and function and confuse interpretation of endoscopic findings. In the horse the interior of the guttural pouches may be examined by advancing the endoscope through the pharyngeal openings of each guttural pouch using a guide wire such as a closed biopsy instrument passed through the biopsy channel of the endoscope and into the pouch. Most coughing horses have lower airway disease, which may be reflected in accumulation of endoscopically visible exudate in the horizontal trachea, particularly after exercise. Lungworm larvae may be grossly visible in the trachea of horses with lungworm infection. Deeper bronchoscopic examination is necessary to determine whether exudate is a reflection of diffuse airway disease or whether it arises from a specific area of the lung, such as would occur with a pulmonary abscess or a foreign body lodged in a bronchus. Sedation may or may not be needed to permit endoscopic examination of the extrathoracic airways in the standing horse; however, sedation with xylazine, detomidine, or romifidine supplemented with butorphanol is recommended to facilitate bronchoscopy and to dampen the cough reflex, as is spraying of the carina and bronchial branches with 2% lidocaine via the biopsy channel of the endoscope to reduce coughing during the procedure. Tracheobronchial aspiration and bronchoalveolar lavage (BAL) can be performed by introduction of appropriate catheters via the biopsy channel of the endoscope.

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5.1.4.6

TRACHEAL ASPIRATION

Tracheal aspiration with cytologic studies and quantitative or semiquantitative aerobic and anaerobic culture of collected samples is indicated in the evaluation of patients suspected of having disease of the lungs or pleura, particularly if an infectious cause is likely. Tracheal wash samples collected using the percutaneous transtracheal technique are preferred for bacterial culture because they are not contaminated by oropharyngeal organisms.[19,20] Collection of samples by introduction of a sterile catheter through the biopsy channel of a presterilized endoscope inserted within a sterile sheath, or by introduction of a double-sheathed catheter via the biopsy channel, is acceptable and less subject to complications than is the transtracheal technique, but samples obtained transendoscopically may be contaminated with *Pseudomonas* species and anaerobic bacteria despite use of a guarded technique.[20] If tracheal aspiration is to be performed percutaneously, the procedure should precede endoscopic examination of the lower airways to avoid contamination. Culture may fail to reveal the primary bacterial pathogen, especially in animals that have been treated with antibiotics. The diagnostic value of tracheal wash samples can be improved by discontinuing antibiotic therapy for at least 24 hours before collecting samples, rapidly processing samples, using antibiotic removal devices and selective culture media and, if necessary, repeating sampling. Culture results should be evaluated in relation to the clinical signs, clinical experience (especially on the farm of origin of the patient), results of cytologic evaluation, and

response to treatment. The trachea is not a sterile environment; therefore, culture of small numbers of bacteria without cytologic evidence of infection is of questionable significance.

5.1.4.7

BRONCHOALVEOLAR LAVAGE

Samples collected by BAL are less useful than those collected by tracheal aspiration for evaluating infectious lower airway diseases and focal pulmonary conditions because the technique samples secretions from only a limited area of the caudodorsal lung on one side and is subject to contamination during collection. However, BAL yields better samples for cytologic assessment and is therefore preferred for evaluation of patients with generalized, noninfectious lower airway diseases such as RAO or silicosis.[18] BAL samples can be collected under endoscopic guidance by means of catheters introduced through the biopsy channel of a suitable endoscope (less than 9mm in diameter and longer than 180cm) or by using commercially available BAL tubes. The advantage of collection via endoscopy is that specific areas of the lung can be sampled, although gaining access to the cranial lung lobes is difficult with any method. Differential cell counts in BAL fluid of normal horses vary depending on age, environment, activity, and other factors. In young horses (<6 years of age), the distribution of macrophages, lymphocytes, neutrophils, mast cells, and eosinophils is on average 65%, 30%, 3%, 0.5%, and 0%, respectively.[21] In horses >6 years of age, the neutrophil population may reach 15% in normal horses, with a corresponding decrease in the proportion of lymphocytes and macrophages.[21]

Neutrophils are usually the predominant cell type in BAL fluid or tracheal washes of horses with RAO and in animals with bacterial infections. The neutrophils usually show degenerative changes when significant bacterial infection is present. Large numbers of eosinophils are a feature of parasitic infections such as lungworms, some allergic conditions, and infiltrative eosinophilic interstitial pneumonia. The presence of hemosiderin-laden macrophages is an indication of recent pulmonary hemorrhage, and finding refractile intracytoplasmic granules in macrophages or giant cells should raise the suspicion of silicosis, especially in animals showing radiographic evidence of marked pulmonary interstitial disease. Noting the presence, number, location (intracellular or extracellular), and Gram stain characteristics of bacteria permits a reasoned selection of antibiotic treatment while awaiting the results of culture and susceptibility tests.

5.1.4.8

ULTRASOUND EXAMINATION

Ultrasound examination is useful for examining externally visible lesions such as possible retropharyngeal abscesses that may be impinging on the airway and causing coughing. Ultrasound examination of the chest is indicated to determine the presence and extent of pleural effusion, pleural roughening, pleural fibrin deposits, gas echoes in pleural fluid, pleural adhesions, and pulmonary lesions such as consolidation, atelectasis, or abscessation in animals with lesions in contact with the pleural surface or in animals in which sufficient pleural fluid has accumulated to allow evaluation of the underlying lung. The tissue-to-air interface at the visceral surface of the normal lung appears as a thin, smooth, bright echogenic line on ultrasound because it reflects the ultrasound beam, precluding visualization of deeper structures. Penetration of the ultrasound beam beyond the surface of the lung occurs only in the presence of lung pathology that extends to the visceral pleural surface of the lung in the area being scanned.

5.1.4.9

BLOOD GAS ANALYSIS

Blood gas analysis on arterial blood to determine oxygen (O_2) and carbon dioxide (CO_2) tensions is indicated in the evaluation and monitoring of patients in which a history or clinical signs of coughing are accompanied by signs of respiratory distress or cyanosis (see Respiratory Distress, p. 60, and Cyanosis, p. 68).

5.1.4.10

THORACOCENTESIS

Thoracocentesis with culture and cytologic examination of collected samples is indicated in animals with clinical or ultrasonographic evidence of effusive pleural disease. Normal pleural fluid is odorless, pale yellow to straw colored, and transparent and has a total nucleated cell count of <10,000/μL cells, most of which are mononuclear cells (macrophages and mesothelial cells), and a protein concentration of <2.5g/dL.[18] Determination of the pH and concentrations of glucose, lactate, and lactate dehydrogenase (LDH) in pleural fluid collected into a heparinized tube or syringe helps differentiate septic from nonseptic effusions while awaiting culture results.[22] Septic effusions are typically acidic (pH <7.2), have a low glucose concentration (<40mg/dL), a high LDH concentration (>1000IU/L), and a lactate concentration higher than that present in venous blood.[22–24] The best site for collecting pleural fluid can be confirmed by ultrasonography after auscultation and percussion of the chest. The sixth or seventh intercostal spaces at the level of the costochondral junction are commonly used sites in horses and cattle. The thorax should be penetrated in the part of the intercostal space immediately adjacent to the cranial border of the rib to avoid the intercostal vessels and nerves.

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5.1.4.11

PLEUROSCOPY

Pleuroscopy is a more invasive procedure with limited indications that include investigation of chronic pleural diseases such as abscesses, pleural adhesions, and possible primary or metastatic pulmonary or pleural neoplasia such as lymphosarcoma, gastric squamous cell carcinoma, or mesothelioma.

5.1.4.12

FECAL EXAMINATION

Fecal examination using the Baermann technique to detect lungworm larvae is indicated in ruminants suspected of having a lungworm infection. Because lungworm infections in the horse rarely become patent, larvae are not usually demonstrable by fecal examination. Pulmonary signs related to *Parascaris equorum* infection in foals occur during the prepatent (migratory) period; therefore the fecal flotation test for ascarid eggs often yields a negative result despite significant parasitic infection.

5.1.4.13

RADIOGRAPHIC EXAMINATION

Radiography of the chest is indicated in patients suspected of having lower airway disease to determine the presence, severity, and pattern of disease changes involving the lungs, pleura, and mediastinum. Four overlapping lateral projections usually are required to evaluate the whole lung field in an adult horse. Because ventrodorsal projections are possible only in young foals, lateral projections from each side may be necessary to lateralize lesions within the chest. Radiographs of the lungs are particularly useful for determining the prognosis and for monitoring the response to therapy of pulmonary diseases such as bacterial pneumonia and lung abscesses. The cardiac silhouette and the pattern and caliber of the aorta, vena cava, pulmonary artery,

pulmonary veins, and other vessels should be evaluated for evidence of cardiac failure and pulmonary vascular disease. Radiographs of the pharynx, retropharyngeal area (including guttural pouches in the horse), larynx, and proximal trachea are indicated in some cases to confirm problems not definitively diagnosed by clinical examination and endoscopy.

5.1.4.14

NUCLEAR SCINTIGRAPHY

Nuclear scintigraphy using aerosolized technetium-99m (^{99m}Tc)–labeled diethylenetriaminepentaacetic acid (DPTA) and intravenously injected ^{99m}Tc-labeled microaggregated albumin particles has been used to determine patterns of pulmonary ventilation, perfusion, and ventilation/perfusion ratios.[19,25] This technique requires special equipment and personnel but provides an objective assessment of pulmonary function and gas exchange capability.[25]

5.1.4.15

BIOPSY

Biopsy, with histologic evaluation of samples, is indicated to diagnose certain mass lesions such as neoplasms, cysts, polyps, fungal granulomas, or foreign body granulomas in or surrounding the airway. Masses in the airway can be biopsied through the biopsy channel of an endoscope, but these samples inevitably are small. Biopsies can also be collected at the time of exploratory or corrective surgery from lesions in the upper airway. Lung biopsies can be collected blindly, using Tru-Cut, Biopty, or similar instruments, preferably from the peripheral areas of the lung to reduce the likelihood of serious hemorrhage (see Chapter 31). Focal lesions should be visualized ultrasonographically or radiographically before or during the biopsy procedure. Lung biopsy is most useful for diagnosing diffuse nonseptic conditions such as pneumoconiosis. The inherent risks associated with the procedure indicate that percutaneous lung biopsy should be reserved for circumstances in which the animal is not showing signs of marked respiratory distress, uncontrollable coughing, or bleeding disorders and a high likelihood exists that the procedure will yield significant diagnostic information. Open lung biopsy is rarely indicated.

5.1.4.16

IMMUNOGLOBULIN DETERMINATIONS

Quantitative immunoglobulin determinations and possibly other *immune function tests* may be indicated in animals, especially young ones, with chronic or recurrent respiratory tract infections or other indications of immune compromise.

5.1.4.17

ALLERGEN TESTING

Intradermal allergen testing (IDT), a radioallergosorbent test (RAST), ELISA tests for immunoglobulin E (IgE) on serum, and *inhaled challenge* have been advocated for the evaluation of horses suspected of having allergic respiratory disease based on exacerbation of signs in certain environments or with certain feeding practices. Whereas there are anecdotal reports that horses with RAO have been hyposensitized successfully using allergens selected on the basis of these allergen tests, we are unaware of documentation in well-controlled studies. In addition, a recent study showed that compared with normal nonatopic horses, RAO-affected horses did not have a significantly greater number of positive reactions in intradermal skin tests (IDT) against any allergen group (molds, grasses, weeds, trees, and insects), leading the authors to conclude that reactions to individual allergens in IDTs should not be used to determine that horses have clinically relevant hypersensitivity.[26] Many normal horses show sensitivity to individual mold spores and other allergens, and

there is poor correlation between the dermal and pulmonary reactivities to mold antigens.[13] Furthermore, when compared with the results of IDT, RAST and ELISA serum allergy tests have been shown to have low sensitivity in detecting allergen sensitivity.[27] Whereas the use of recombinant allergens rather than crude mold extracts in ELISA tests substantially improves sensitivity in detecting levels of allergen-specific IgE,[28] and significantly more RAO-affected horses than normal horses have high allergen-specific IgE levels, the degree of overlap of results precludes use for diagnostic purposes.[29] The crude trial-and-error approach of adding or removing potential allergens from the environment is sometimes very helpful diagnostically and therapeutically in RAO cases in which an allergic cause is suspected. Feeding of pellets instead of hay and using shredded paper, peat moss, or wood shavings instead of straw bedding are common examples of this approach (see the section on RAO in Chapter 31).

5.1.4.18

PULMONARY FUNCTION TESTING

With the exception of measurement of pleural pressure using an esophageal balloon catheter attached to a pneumotachograph, pulmonary function testing and evaluation of airway dynamics during exercise have until recently been largely research techniques that were not readily applicable to clinical patients. Recent development of the minimally invasive techniques of oscillometry (forced oscillatory mechanics [FOM]), forced expiratory maneuvers, and flowmetrics now permits physiologic assessment of lung function in clinical patients.[30,31] When coupled with histamine provocation tests to assess airway reactivity and bronchodilator response tests, pulmonary function tests can provide a considerable amount of information to guide therapy and prognosis. Indications for pulmonary function testing might include evaluating horses with a history of poor performance or exercise intolerance but no other detectable abnormalities; assessing the degree of functional impairment in horses with known evidence of respiratory disease; assessing the efficacy of therapeutic regimens; determining if a horse has recovered from a diagnosed respiratory disorder and can be returned to training; and ruling out functional pulmonary abnormalities in horses with upper airway conditions.

5.1.4.19

BRONCHODILATOR RESPONSE TESTING

Bronchodilator response testing involves determining the response of measured pulmonary functions and pleural pressures to rapidly acting bronchodilator drugs such as albuterol (450 to 900mcg) or ipratropium bromide, administered by aerosol, or atropine administered parenterally.[30] Results are often helpful in determining the pathogenesis of RAO and the likely response to bronchodilator therapy. In the field setting, useful information can be gained by assessing the response of respiratory rate, respiratory character, and lung sounds to intravenous (IV) administration of a low dose of atropine (5 to 7mg/450-kg horse). This test can be made more objective by measuring pleural pressures using a Ventigraph recorder* attached to an esophageal catheter or flowmetric techniques.[13,30,32,33]

* Boehringer Ingelheim, Vet Medica, Inc., St Joseph, Mo.

5.1.4.20

DIFFERENTIAL DIAGNOSIS OF COUGHING

The differential diagnosis of coughing can be enhanced by arbitrarily categorizing it on the basis of *duration of signs* into acute or chronic (more than 1month) and by the *presence or absence of fever*.[34] It should be kept in mind that some acute coughs become chronic and that, conversely, conditions that cause chronic coughing may be seen early in the disease course. Conditions typically associated with *acute coughing* include viral, bacterial, and parasitic infections of the upper and lower respiratory tract; acute allergic reactions or acute toxic injury to

the lung such as in atypical interstitial pneumonia (fog fever) of cattle; foreign bodies; choke; injuries to the larynx, trachea, or chest; pharyngeal or laryngeal dysfunction secondary to neurologic disorders or surgery; aspiration of food material or foreign bodies; smoke inhalation; and compressive upper airway lesions such as retropharyngeal abscesses or necrotic laryngitis. In most instances, outbreaks of sudden-onset coughing in groups of animals are the result of viral infection involving the upper and lower respiratory tract.[8,16]

Conditions typically associated with *chronic coughing* include chronic bacterial pneumonia; pulmonary abscess; chronic pleuritis; chronic allergic pulmonary diseases such as RAO in horses and farmer's lung disease in cattle; postviral bronchial hyperreactivity, chronic viral respiratory disease such as ovine progressive pneumonia and caprine arthritis-encephalomyelitis pneumonia; irritant airway disease caused by environmental irritants such as dust; lungworm infections, particularly in horses and small ruminants; functional or anatomic problems in the pharynx or larynx that interfere with guarding of the airway, including postsurgical problems; heart failure resulting in pulmonary edema; tumors or polyps in the upper airway or lung; mycotic infections of the upper airway, lung, or pleura; chronic guttural pouch infections in horses; tracheal collapse, especially in ponies; chronic interstitial disease such as pneumoconiosis caused by inhalation of particulate material; and so-called “nuisance coughs.” Nuisance coughs are common in horses, especially at the beginning of exercise, which emphasizes the fact that coughing is a normal airway protective mechanism and not always evidence of disease. Nuisance coughs tend to bother the owner more than the horse and can result from habit; vices such as crib biting, wind sucking, or greedy eating; and environmental factors such as dust, ammonia, and cold air. Some of these nuisance coughs are correctable by modifying the stabling or work environment.

Cough with fever usually indicates a primary infectious cause or a secondary infection superimposed on a noninfectious cause.[34] Fever is a typical but not an invariable feature of aspiration pneumonia, bacterial pneumonia, pulmonary abscess, viral respiratory tract infection, strangles, fungal pneumonia, pleuropneumonia (bacterial, viral, or mycoplasmal), acute bronchointerstitial pneumonia, and thoracic neoplasia.[34]

Cough without fever is typically found in RAO, abnormalities of the larynx or pharynx, parasitic pneumonia, exercise-induced pulmonary hemorrhage (EIPH), tracheobronchial foreign body, tracheal collapse, and airway-oriented neoplasia (e.g., bronchial carcinoma).[34] Horses with chronic interstitial pneumonia such as silicosis or granulomatous pneumonia are usually afebrile but may have mild to moderate fever.[1]

5.2 NASAL DISCHARGE

5.2.1 Definition

Nasal discharge, which is any nongaseous material that exits the respiratory tract through the external nares, is described according to its *physical characteristics* (serous, mucoid, purulent, hemorrhagic [sanguineous], or a combination of these types or feed material); *acuteness of onset* (sudden or insidious); *origin* (unilateral or bilateral); *volume* (profuse or scant); and *association with activity* (spontaneous or intermittent).[35–37]

5.2.2 Pathophysiology

5.2.2.1 NORMAL NASAL SECRETIONS

The ciliated, pseudostratified columnar epithelium lining the respiratory tract from the nasal passages to the level of the respiratory bronchioles contains serous, mucous, and mixed tubuloalveolar glands in its lamina

propria.[35] Goblet cells are present in large numbers throughout the nasal cavity and are present in the airway mucosa to the level of secondary and tertiary bronchi.[35] The secretions of these glands and goblet cells and the fluid transudated from serum together serve to warm and humidify inspired air, trap particulate matter, protect the respiratory epithelium from desiccation and infection, and provide the serous-mucous bilayer necessary for effective ciliary function.[38,39] The tracheobronchial fluid that constitutes the mucous blanket in the lower parts of the respiratory tract contains exfoliated epithelial cells, alveolar macrophages, and other mononuclear cells, glycoproteins, bacteriostatic proteins (primarily lysozyme), lactoferrin, secretory IgA, IgG, IgM, and serum proteins (primarily albumin).[38,39] The cilia lining the pseudostratified columnar epithelium beat in coordinated waves to carry mucus, trapped particles, and cells from the lower respiratory tract to the nasopharynx. Material cleared from the tracheobronchial tree is normally swallowed on reaching the pharynx but may appear at the external nares as nasal discharge.[39]

Serous nasal secretions in normal animals are responsible for the moist appearance of the ventral portion of the external nares. In cattle normal nasal secretions are more voluminous and more mucoid compared with other large animal species. Healthy cattle keep their external nares clean through licking. Cattle that are systemically ill or otherwise debilitated often neglect to do this, and as a result mucoid secretions accumulate and crust around the external nares. On the other hand, a buildup of nasal discharge in cattle with respiratory disease can be removed by frequent nose licking, masking the presence of disease.

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Lacrimal secretions also drain into the nasal passages through the nasolacrimal ducts and may appear at the external nares as a thin, watery, clear, nonviscous discharge, particularly in animals with conjunctival irritation or ocular inflammatory diseases that stimulate excessive lacrimation.[36]

5.2.2.2

ABNORMAL NASAL SECRETIONS

Inflammatory conditions involving the nasal cavity stimulate increased production of glandular secretions.[39] These secretions initially are serous but later become mucoid and purulent as secondary bacterial invasion induces an influx of neutrophils.[35] Serous nasal discharge generally indicates disease conditions affecting the nasal passages or upper respiratory tract.

Inflammation, irritation, and other pathologic states affecting the trachea and bronchi increase the production of mucous and serous secretions in the tracheobronchial tree[39] (Boxes 5-3 and 5-4). Initially the accompanying nasal discharge is mucoid (clear, colorless, thin, and elastic in consistency), but with chronicity and secondary bacterial invasion, neutrophils and other inflammatory cells accumulate in the tracheobronchial secretions and the nasal discharge becomes purulent, progressing from cloudy to opaque and then to viscous with a whitish cream color (Boxes 5-5 and 5-6).

Conditions such as chronic bronchitis and RAO cause goblet cell hyperplasia and increased mucous production, which may be reflected as a discharge at the external nares, depending on the efficiency with which the animal swallows these secretions. In some cases nasal discharge is evident only early in the morning or after a period of recumbency because in these situations secretions accumulate in the trachea and pharynx, drain into the nasal passages, and exit from the nares.

5.2.2.2.1

Box 5-3 Causes of Serous and Mucoid Nasal Discharge in Horses

5.2.2.2.1.1

COMMON CAUSES

Influenza

Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)

Rhinovirus

Other viruses (e.g., adenovirus, reovirus, EHV-2)

Pharyngitis, chronic pharyngeal lymphoid hyperplasia

Nasal or paranasal sinus infection, cysts, polyps, tumors

Early bacterial pneumonia or pleuritis

Early strangles (*Streptococcus equi* infection)

Guttural pouch infection, mycosis

Overflow of nasolacrimal ducts

Recurrent airway obstruction (RAO or COPD)

5.2.2.2.1.2

LESS COMMON CAUSES

Equine viral arteritis

Burn (thermal, chemical)

Anaphylaxis or acute drug reaction

Aspiration or foreign body pneumonia, smoke inhalation

Foreign body (nasal, pharyngeal, guttural pouch, tracheal, or bronchial)

Summer pasture—associated obstructive airway disease (SPOAD)

5.2.2.2.1.3

UNCOMMON CAUSES

Nasal fungal infection (rhinophycomycosis), aspergillosis

Nasal amyloidosis

Coccidioidomycosis

Restrictive pulmonary disease, pneumoconiosis

Trauma to the skull or upper airway

Tuberculosis

Tularemia

Guttural pouch neoplasia

Chlamydia psittaci pneumonia

Nocardiosis

Cryptococcosis

Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma, pythiosis

Lungworm infection *(Dictyocaulus arnfieldi)*

Ascarid migration

Cyst (pharyngeal, subepiglottal)

Progressive ethmoidal hematoma

Lymphosarcoma, lymphoma, leukemia

Halicephalobus (Micronema) deletrix granuloma

Pulmonary edema

Pulmonary aspergillosis

Stachybotryotoxicosis

Trichloroethylene-extracted feed toxicity

Pentachlorophenol toxicity

Organophosphate, carbamate toxicity

Ammonia toxicity

St George disease (*Pimelea* species poisoning) (exotic)

Trypanosoma evansi, surra (exotic)

Trypanosoma equinum, mal de caderas (exotic)

Trypanosoma hippicum, murrina de caderas (exotic)

Besnoitiosis, globidiosis (exotic)

African horse sickness (exotic)

Getahvirus (exotic)

Glanders (exotic)

Louping ill (exotic)

Hemorrhagic (sanguinous) nasal discharge, or epistaxis, occurs secondary to trauma, coagulopathies, and erosive or invasive conditions that insult the richly vascular nasal mucosa or secondary to conditions that invade regional blood vessels such as occurs when the internal carotid artery is eroded by a mycotic plaque in

horses with guttural pouch mycosis. Pulmonary disorders such as infarctive pneumonia in horses and pulmonary thromboembolism secondary to posterior vena cava thrombosis in cattle may also induce epistaxis (see Epistaxis, p. 56).[35–37]

Foul odor (ozena) accompanying nasal discharge suggests an anaerobic infection, a necrotizing condition (e.g., fungal infection, neoplasia, turbinate necrosis, or necrotizing pneumonia), foreign body, or communication between the oral and nasal cavities (e.g., maxillary sinusitis secondary to a patent infundibulum in the horse).[37]

Food or water may drain from the external nares when there is communication between the oral and nasal cavities (e.g., cleft palate); in association with swallowing disorders (e.g., pharyngeal paresis secondary to botulism, cranial nerve damage secondary to guttural pouch mycosis in the horse); or in cases of obstructive dysphagia (e.g., severe pharyngitis, guttural pouch enlargement in horses, retropharyngeal abscesses, esophageal obstruction, obstructions of the gastrointestinal tract that lead to regurgitation of food from the stomach).[35–37] The respiratory position of the epiglottis dorsal to the soft palate in the horse means that except in cases of dorsal displacement of the soft palate (laryngopalatal dislocation), food regurgitated from the digestive tract enters the nasopharynx and appears at the external nares rather than at the mouth (see Regurgitation and Vomiting, Chapter 7).

5.2.2.2.2

Box 5-4 Causes of Serous of Mucoid Nasal Discharge in Ruminants

5.2.2.2.2.1

COMMON CAUSES

Debilitating illnesses that reduce lingual nose cleaning in cattle (B)

Mannheimia hemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)

Haemophilus somnus pneumonia (B)

Nose bots *(Oestrus ovis)* (O, C)

Lungworm infection, verminous pneumonia

Atypical interstitial pneumonia (B)

Infectious bovine rhinotracheitis (IBR; BHV-1) (B, C)

Bovine respiratory syncytial virus (B)

Parainfluenza virus type 3

Mycoplasma species pneumonia

Caprine *Mycoplasma mycoides* subsp. *mycoides* infection (C)

Caprine arthritis-encephalomyelitis (CAE) pneumonia (C)

Early bacterial pneumonia

Trauma (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial, chest wall)

Abscess (oral, pharyngeal, retropharyngeal)

Esophageal obstruction, foreign body, choke

Septicemia (neonates)

5.2.2.2.2.2

LESS COMMON CAUSES

Paranasal sinus infection

Foreign body (oral, pharyngeal, laryngeal, tracheal, bronchial, pulmonary)

Aspiration, foreign body pneumonia

Ovine progressive pneumonia and arthritis, maedi (O)

Bluetongue

Bovine virus diarrhea (BVD-MD) (B)

Ovine adenovirus (O)

Caprine respiratory syncytial virus (C)

Bovine rhinovirus (B)

Bovine adenovirus (B)

Bovine malignant catarrhal fever, early (B)

Herpesvirus DN-599 (B)

Bovine herpesvirus type 4 (BHV-4) (B)

Pulmonary adenomatosis (Jaagsiekte) (O)

Inhalation pneumonia, smoke, noxious gases

Anaphylaxis or adverse drug reaction

Milk allergy in cows (B)

Farmer's lung disease (hypersensitivity to *Faenia rectivirgula, Aspergillus fumigatus*, and other mold spores) (B)

Chlamydia psittaci pneumonia

Burns (thermal, chemical)

Vagal indigestion, abomasal impaction

Nasal adenoma, adenopapilloma, adenocarcinoma, polyp (O, C)

5.2.2.2.2.3

UNCOMMON CAUSES

Familial allergic rhinitis (B)

Bovine nasal granuloma, atopic rhinitis, summer snuffles (B)

Fungal granuloma, maduromycosis, mycetoma, rhinosporidiosis

Nasal actinobacillosis (B)

Sarcocystosis (B)

Tularemia (O)

Phycomycosis, pythiosis (B)

Pulmonary aspergillosis

Bronchobiliary fistula (yellow froth) (B)

Zygomycosis, mucormycosis (B)

Pneumocystis carinii pneumonia

Neoplasia (nasal, paranasal sinus, pharyngeal, pulmonary)

Buss disease, chlamydial sporadic bovine encephalomyelitis (B)

Winter dysentery (B)

Immunodeficiency states

Pregnancy toxemia (B)

Border disease (hairy shaker) (O, C)

Lymphosarcoma

Johne's disease

Listeriosis (C)

Tetanus

Rinderpest (exotic)

Theileriosis, East Coast fever (exotic)

Contagious bovine pleuropneumonia (exotic) (B)

African bovine malignant catarrhal fever, early (exotic) (B)

Virulent sheep and goat pox (exotic) (O, C)

Peste des petits ruminants (exotic) (O, C)

Contagious caprine pleuropneumonia (exotic) (C)

Rift Valley fever (exotic)

St George disease (*Pimelea* species poisoning) (exotic)

Trypanosoma evansi, surra (exotic) (B)

Trypanosomiasis, nagana (exotic)

Jembrana disease (exotic) (B)

Sweating sickness (exotic) (B, O)

Cestrum poisoning (exotic)

Stinkweed poisoning (exotic) (B)

Endemic ethmoid carcinoma (exotic) (B)

Ephemeral fever (exotic) (B)

Lumpy skin disease (exotic) (B)

Nasal schistosomiasis (exotic)

Besnoitiosis, globidiosis (exotic)

Louping ill (exotic)

Theilezia rhodensis (exotic)

Cotyledon species poisoning, Krimpsiekte (exotic) (O, C)

Gedoelstia hasleri nasal bots (exotic) (O, C)

Nairobi sheep disease (exotic) (O, C)

Schistosoma nasale (exotic) (B)

5.2.2.2.2.4

TOXIC CAUSES

Organophosphate or carbamate

Mercury (B)

Iodine (B, O)

Ammonia

Sodium hydroxide (caustic soda)

Trichloroethylene-extracted feed (B, O)

Formaldehyde irritation

Oxalate (B, O)

Thallium (O)

Furazolidone

Hairy vetch *(Vicia villosa)* (B)

Ergot *(Claviceps purpura)*

Sneezeweed (*Helenium* species)

Aflatoxicosis (C)

Rubber weed (*Hymenoxys* species)

Acorn, oak (B, O)

Perennial broomweed (*Gutierrezia* species)

Chinese tallow *(Sapium sebiferum)* (B)

Stachybotryotoxicosis

Slender ice plant *(Mesembryanthenum nodiflorum)*

5.2.2.2.3

Box 5-5 Causes of Purulent Nasal Discharge in Horses

5.2.2.2.3.1

COMMON CAUSES

Postviral bacterial infection of the respiratory tract

Strangles (*Streptococcus equi* infection)

Bacterial rhinitis

Pharyngitis

Bacterial pneumonia

Bacterial pleuritis or pleuropneumonia

Guttural pouch empyema or chondroids

Guttural pouch mycosis

Lung abscess

Pharyngeal, retropharyngeal abscess

Paranasal sinus infection, cyst, tumor (unilateral discharge)

Fungal rhinitis (rhinophycomycosis), nasal granuloma, nasal aspergillosis (unilateral discharge)

Nasal foreign body (unilateral discharge)

Conchal necrosis (unilateral discharge)

Progressive ethmoidal hematoma (unilateral discharge)

Nasal tumor, polyp, cyst (unilateral discharge)

Trauma (nasal, skull, upper airway) (unilateral or bilateral discharge)

5.2.2.2.3.2 LESS COMMON CAUSES

Burn (thermal, chemical)

Aspiration or foreign body pneumonia, smoke inhalation

Foreign body (pharyngeal, guttural pouch, tracheal, bronchial)

Esophageal obstruction, choke, stricture, ectasia, megaesophagus

Neurologic deficits affecting swallowing

5.2.2.2.3.3 UNCOMMON CAUSES

Coccidioidomycosis

Tuberculosis

Tularemia

Guttural pouch neoplasia

Chlamydia psittaci pneumonia

Nocardiosis

Cryptococcosis

Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma, pythiosis

Ascarid migration

Lymphosarcoma, lymphoma, leukemia

Halicephalobus (Micronema) deletrix granulomas

Pulmonary aspergillosis

Pneumocystis carinii pneumonia

Ammonia toxicity

Trypanosoma evansi, surra (exotic)

Besnoitiosis, globidiosis (exotic)

African horse sickness (exotic)

Glanders (exotic)

Melioidosis, *Pseudomonas pseudomallei* (exotic)

5.2.2.2.4

Box 5-6 Causes of Purulent Nasal Discharge in Ruminants

5.2.2.2.4.1

COMMON CAUSES

Debilitating illnesses that reduce lingual nose cleaning in cattle

Postviral bacterial infection of the respiratory tract

Mannheimia hemolytica or *Pasteurella multocida* pneumonia

Haemophilus somnus pneumonia (B)

Necrotic laryngitis, calf diphtheria (B)

Lungworm infection, verminous pneumonia

Mycoplasma species pneumonia

Caprine *Mycoplasma mycoides* subsp. *mycoides* infection (C)

Chronic bacterial pneumonia with consolidation or abscessation (*Arcanobacterium [Actinomyces] pyogenes* and other bacteria)

Esophageal obstruction, foreign body, choke

Nose bots *(Oestrus ovis)* (O, C)

Trauma (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial, chest wall)

Abscess (oral, pharyngeal, retropharyngeal)

Septicemia (neonates)

5.2.2.2.4.2

LESS COMMON CAUSES

Foreign body (oral, pharyngeal, laryngeal, tracheal, bronchial, pulmonary)

Aspiration, foreign body pneumonia

Paranasal sinus infection

Pulmonary embolism from posterior vena cava thrombosis (B)

Ovine progressive pneumonia and arthritis, maedi (O)

Bovine malignant catarrhal fever (B)

Bluetongue

Pulmonary adenomatosis (Jaagsiekte) (O)

Inhalation pneumonia, smoke, noxious gases

Chlamydia psittaci pneumonia

Burns (thermal, chemical)

Vagal indigestion, abomasal impaction

Nasal adenoma, adenopapilloma, adenocarcinoma, polyp (O, C)

5.2.2.2.4.3

UNCOMMON CAUSES

Ovine nasal granuloma, atopic rhinitis, summer snuffles (B)

Fungal granuloma, maduromycosis, mycetoma, rhinosporidiosis

Nasal actinobacillosis (B)

Bovine salmonellosis (B)

Sarcocystosis (B)

Tularemia (O)

Tuberculosis

Phycomycosis, pythiosis (B)

Pulmonary aspergillosis

Bronchobiliary fistula (yellow froth) (B)

Zygomycosis, mucormycosis (B)

Pneumocystis carinii pneumonia

Neoplasia (nasal, paranasal sinus, pharyngeal, pulmonary)

Immune deficiency states

Lymphosarcoma

5.2.2.2.4.4 TOXIC AND EXOTIC CAUSES

See Box 5-4, p. 52

B, Bovine; *C*, caprine; *O*, ovine.

Chronic nasal discharges often cause scalding in the area ventral to the external nares.[36] Mucoid and purulent nasal discharges tend to dry and crust as an admixture with environmental dust and dirt around the external nares. In all large animal species but particularly in sheep and goats, tenacious exudates may obstruct the nasal passages and induce a snuffling noise. Horses with profuse nasal discharge often rub the nose on the dorsum of the front fetlock and cannon regions. During the physical examination these areas should be inspected for mucoid exudate, dried crusts, or swarms of flies.

5.2.2.3 ACUTENESS OF ONSET

Sudden-onset nasal discharge usually is associated with acute infection, trauma, or esophageal obstruction, whereas nasal discharge of insidious onset generally accompanies chronic infection, progressive neurologic disease that causes dysphagia, or neoplasia.[40]

5.2.2.4 ORIGIN OF NASAL SECRETIONS

Unilateral nasal discharge generally originates from structures located rostral to the caudal end of the nasal septum. Bilateral nasal discharge results from disease processes affecting structures caudal to the caudal end of the nasal septum or from conditions involving the nasal passages or paranasal sinuses bilaterally.[36,37] A discharge that appears from one nostril on some days and from the opposite nostril on others generally indicates a lesion or disease process caudal to the nasal septum.[37] The paired guttural pouches of the horse drain separately through ostia located dorsolaterally in the wall of the nasopharynx. Exudate draining from the guttural pouches may appear unilaterally at the ipsilateral nostril if the volume of drainage is small, but moderate to profuse guttural pouch drainage appears as a bilateral nasal discharge.[37]

5.2.2.5

VOLUME OF NASAL SECRETIONS

The volume of nasal discharge frequently increases when the head is lowered, regardless of the source of the discharge, because of pooling of exudate in the trachea, pharynx, or nasal passages. However, the appearance of profuse, unilateral, purulent nasal discharge when the head is lowered generally indicates sinus empyema, and profuse bilateral nasal discharge under these circumstances suggests guttural pouch empyema.[20] This is attributed to accumulation of large volumes of exudate in the sinus cavities or guttural pouches when the head is elevated and to the fact that the ostia through which these structures drain are not located on the most dependent aspect of these cavities; thus significant drainage can occur only when the head is lowered. Nasal discharge observed only after exercise suggests an origin in the lower respiratory tract.[41]

5.2.3

Approach to Diagnosis of Nasal Discharge

Because many conditions, particularly those involving the lower respiratory tract, are associated with both nasal discharge and cough, the diagnostic approach used for large animal patients presented for evaluation of nasal discharge is similar to that used for large animals presented for evaluation of cough (see Cough, p. 42). Only those components of the history and diagnostic evaluation that differ substantially from those used in patients with cough are described in depth in this section.

5.2.3.1

HISTORY

The patient history should include information about the rapidity of onset and duration of nasal discharge; whether the discharge is consistently unilateral, consistently bilateral, or intermittently bilateral; and the volume, color, consistency, and odor of the discharge.

The association of discharge with certain activities such as initiation of exercise, when the animal is first disturbed in the morning, or when it is eating with its head lowered can provide useful clues to the origin or cause. It should be determined if the animal is showing other signs of respiratory disease (e.g., cough, respiratory distress, or exercise intolerance), dental disease (e.g., quidding or slow eating), or systemic disease (e.g., weight loss, depression, anorexia, fever, or lymphadenopathy).

It should also be determined if in-contact animals have exhibited nasal discharge or other signs of respiratory disease. The vaccination status of affected and in-contact animals should be ascertained. Recent stressors such as transportation, surgery, or weaning should be noted, and a history of contact with other animals at sales, shows, or other events should be established. Environmental quality and the overall management of the affected animal and the herd should be assessed (see Cough, p. 42). Progression or improvement in the signs, attempted therapy, and response to current or previous treatments should also be ascertained.

5.2.3.2

PHYSICAL EXAMINATION

Physical examination of an animal showing nasal discharge should include inspection from a distance and close examination using *auscultation, palpation*, and *percussion* techniques (see Physical Examination, p. 46, and Cough, p. 42). The character and volume of the nasal discharge should be noted. Particular attention should be paid to whether:

- The nasal discharge is unilateral or bilateral

- The airflow from both nostrils is symmetric
- Odor emanates from the oral or nasal cavity
- Facial asymmetry is present
- Hyporesonance (dullness) or a painful response is elicited on percussion of the maxillary and frontal sinuses
- Enlargement of submandibular, parotid, retropharyngeal, or other regional lymph nodes is present
- Palpable turbulence, such as a tracheal rattle, is present

The depth and symmetry of chest expansion should be assessed, and the rostral end of both nasal passages should be illuminated with a penlight and examined carefully.

The roots of the third through the sixth maxillary cheek teeth (108 to 111 and 208 to 211) in the horse are contained within the maxillary sinus; therefore infection of these teeth frequently leads to sinus empyema with drainage from the nasomaxillary opening into the middle nasal meatus and ultimately to a unilateral nasal discharge. Disease involving the paranasal sinuses should be considered in horses with unilateral nasal discharge, particularly when ozena is present. Under these circumstances a thorough *oral examination*, which should include probing of the occlusal surfaces of the maxillary cheek teeth with a fine dental pick, is indicated. Particular attention should be paid to detecting erosive periodontal disease, fractured maxillary cheek teeth, open pulp chambers, and patent infundibula. In cattle the oral examination should include palpation of the base of the tongue, the oropharynx, and, if possible, the larynx to detect mass lesions or swelling of the tongue.

Further diagnostic evaluation of nasal discharge may include a complete blood count with determination of the fibrinogen concentration, a serum biochemistry profile, endoscopy of the upper and lower airways and the esophagus, nasal or nasopharyngeal swabbing for molecular diagnostic testing or virus isolation, virus serologic testing, tracheal aspiration, BAL, ultrasonography, thoracocentesis, radiography, blood gas analysis, nuclear scintigraphy, fecal examination, pulmonary function testing, and lung biopsy. For further information on diagnostic procedures not discussed in the following sections, see Cough, p. 42.

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5.2.3.3

ENDOSCOPIC EXAMINATION

Endoscopic examination of the upper and lower airways is a useful ancillary diagnostic procedure in all animals with nasal discharge. The nasal passages; the conchae (turbinates), including the ethmoidal conchae; the nasal septum; and the pharynx, larynx, and trachea should be examined through both nostrils. The presence, nature, and origin of exudates and the presence of anatomic or functional abnormalities or mass lesions should be noted. Although it is not possible to introduce standard, 8- to 12-mm—diameter endoscopes into the paranasal sinuses via the nasal passages, drainage from the sinuses may be detected by examining the middle meatus.[37] Examination of the middle meatus may also reveal turbinate necrosis or mass lesions (e.g., tumors, fungal granulomas, nasal foreign bodies). Lesions such as progressive hematomas (expanding mass lesions of variable size on the ethmoid turbinates) can be visualized by advancing the endoscope slightly, after deflecting its tip dorsally through the common meatus, from a position in the caudal part of the ventral meatus just rostral to the choana. In the horse the pharyngeal openings of the guttural pouches, which are located dorsolaterally on the wall of the pharynx, should be inspected for drainage. The interior of both guttural pouches can be examined for exudate, blood, mycotic plaques, and other proliferative lesions by advancing the endoscope

through the pharyngeal openings of each guttural pouch. This procedure is facilitated by first introducing a biopsy instrument or similar guide wire into the guttural pouch via the biopsy channel of the endoscope.

Bronchoscopic examination may prove useful for identifying the bronchus of origin of pulmonary exudates and for facilitating appropriate BAL. In horses with intermittent bilateral nasal discharge, it may be helpful to repeat the endoscopic examination after exercise, which often mobilizes secretions from the lower respiratory tract and causes them to pool in the horizontal trachea. Endoscopic examination of the esophagus is indicated in patients with a history of dysphagia or return of ingesta through the nose (Boxes 5-7 and 5-8).

5.2.3.4

RADIOGRAPHY

Radiography with lateral, dorsoventral, and oblique radiographic projections of the nasal passages, paranasal sinuses, pharynx, retropharyngeal area (including guttural pouches in the horse), larynx, and proximal trachea is indicated to confirm problems identified by clinical examination and endoscopy and to identify conditions not recognized by other diagnostic techniques. The demonstration of increases in tissue density, fluid lines, bony lysis or proliferation, distortion of normal architecture, or changes around tooth roots assists in the diagnosis and localization of disorders of the nasal passages, conchae, and paranasal sinuses. Space-occupying lesions in the oropharynx, nasopharynx, or larynx may also be demonstrated by radiographic examination of these areas. The presence of fluid lines, soft-tissue densities, or thickening of the floor of the guttural pouches helps differentiate guttural pouch diseases (e.g., empyema) from other space-occupying lesions (e.g., abscesses) in the retropharyngeal region. Contrast radiographic studies such as barium swallows are indicated to evaluate aspiration during swallowing in horses suspected of having pharyngeal paresis. Carotid angiography under general anesthesia has been used to demonstrate aneurysms in the internal carotid artery of horses with guttural pouch mycosis.[42] Thoracic radiographs are indicated in patients suspected of having pulmonary, mediastinal, or pleural disease to determine the presence, pattern, and severity of radiographic changes.

5.2.3.4.1

Box 5-7 Causes of Ingesta in Nasal Discharge in Horses

5.2.3.4.1.1

COMMON CAUSES

Esophageal obstruction, choke

Cleft palate, palatal hypoplasia (neonate)

Pharyngitis

Strangles (*Streptococcus equi* infection)

Dorsal displacement of the soft palate

Guttural pouch infection, mycosis, neoplasia

Glossopharyngeal nerve damage

Botulism, shaker foal

Retropharyngeal abscess

5.2.3.4.1.2

LESS COMMON CAUSES

Complications of laryngeal surgery

Laryngeal web defect

Epiglottal entrapment, subepiglottal abscess or cyst

Tetanus

Fistula (pharyngeal, esophageal, esophagobronchial, esophagotracheal)

Esophageal stricture, ectasia, diverticulum, megaesophagus, ulcer, rupture

Gastric, duodenal ulceration (foals)

Gastric dilation, rupture

Proximal enteritis, jejunitis

Small intestinal obstruction

Rabies

Other neurologic deficits affecting swallowing

5.2.3.4.1.3

UNCOMMON CAUSES

Persistent right aortic arch, vascular ring anomaly

Gastric tumor

Gastric stenosis

Rostral displacement of the palatopharyngeal arch

Hypoplasia of the soft palate

White muscle disease, nutritional myodegeneration

Rectus capitis ventralis muscle rupture

Lymphosarcoma, lymphoma, leukemia

Oleander poisoning

White snakeroot (tremetol) poisoning

Lead toxicity

Grass sickness (exotic)

5.2.3.5

COMPUTED TOMOGRAPHY SCANNING

When a definitive diagnosis is not achieved using plain radiographs, computed tomography (CT) scanning with the horse positioned in dorsal recumbency under general anesthesia has proven valuable for more accurately defining the location, nature, and extent of lesions involving the nasal passages, paranasal sinuses, and cheek teeth.[43,44] Intracarotid or IV injection of contrast material further enhances the diagnostic utility of CT for evaluation of mass lesions.

5.2.3.6

ULTRASOUND EXAMINATION

Ultrasound examination of externally visible lesions such as possible retropharyngeal abscesses or distended guttural pouches assists in characterization of lesions and collection of samples by aspiration or biopsy. Thoracic ultrasound is indicated when lower airway, pleural, or cardiac disease is the suspected cause of nasal discharge.

5.2.3.7

PERCUTANEOUS ASPIRATION

Percutaneous aspiration, performed either blindly or with the assistance of ultrasound, followed by cytology and culture of aspirated material, is useful in the evaluation of masses such as submandibular or retropharyngeal abscesses that are also causing a nasal discharge.

5.2.3.7.1

Box 5-8 Causes of Ingesta in Nasal Discharge in Ruminants

5.2.3.7.1.1

COMMON CAUSES

Esophageal obstruction, foreign body, choke

Pharyngeal, retropharyngeal abscess

Pharyngeal trauma, foreign body

Megaesophagus (B, C)

5.2.3.7.1.2

LESS COMMON CAUSES

Rhododendron poisoning (O)

Diaphragmatic hernia

Water deprivation, salt toxicity (B, O)

Ruptured or lacerated esophagus

Tetanus

Cleft hard or soft palate

Glossopharyngeal nerve damage

5.2.3.7.1.3

UNCOMMON CAUSES

Neoplasia of the esophagus or rumen (B)

Persistent right aortic arch, vascular ring anomaly (B, O)

Listeriosis

Bronchobiliary fistula (yellow froth) (B)

Congenital defects of Kodiak Island calves (B)

Oleander poisoning

White snakeroot (tremetol) poisoning (B, O)

Crude oil toxicity (B)

Geigeria species poisoning

Sneezeweed (*Helenium* species) poisoning

Rubberweed (*Hymenoxys* species) poisoning

B, Bovine; *C*, caprine; *O*, ovine.

5.2.3.8

CENTESIS

Centesis of affected paranasal sinuses helps localize the source of exudates and provides samples for cytologic examination and culture in patients with chronic unilateral nasal discharge in which sinus percussion or radiographic examination (or both) suggests the presence of a sinus lesion. In the normal horse the rostral and caudal maxillary sinuses are separated by a thin osseous septum. This septum is often eroded in horses with septic sinusitis; therefore the caudal maxillary sinus is typically entered first. If no exudate can be aspirated, either directly or after lavaging the sinus, and if increased purulent drainage from the ipsilateral nostril is not accomplished during lavage, centesis of the rostral maxillary sinus is performed and the procedure repeated. If the aspirated material is not malodorous and if there is no evidence of dental disease, there is a reasonable likelihood that primary (nondental) sinusitis is present. In the horse the rostral maxillary sinus can be entered at a site 2.5cm dorsal and 2 to 3cm caudal to the rostral end of the facial crest. The caudal maxillary sinus is entered at a point 2.5cm dorsal to the facial crest and 2cm rostral to the medial canthus of the eye. After shaving and surgical preparation of the skin and subcutaneous placement of a small volume of local anesthetic, a stab incision is created through the skin and extended down to the periosteum. A small hole is then drilled through the bone with a Steinmann pin in a hand-held chuck or a 14-gauge needle. A 14-gauge cannula is introduced into the sinus and, if necessary, a No. 5 French catheter can be inserted through the cannula to facilitate sample collection and lavage (see Diseases of the Paranasal Sinuses, Chapter 31).

5.2.3.9

CATHETERIZATION

Catheterization of the guttural pouches via the pharyngeal orifice, either blindly or under endoscopic guidance, followed by aspiration or lavage, culture, and cytologic examination of aspirated contents is helpful in the evaluation of horses with chronic purulent nasal discharge in which guttural pouch empyema is suspected or has been confirmed by radiographic or endoscopic examination. In horses with large accumulations of fluid exudate, voluminous drainage of pus both through and around the catheter may occur when the pouch is first

catheterized. In horses with chronic guttural pouch infection accompanied by tenacious or inspissated exudate, lavage with 250 to 400ml of sterile saline or Ringer's solution facilitates sample collection.

5.3 EPISTAXIS AND HEMOPTYSIS

5.3.1 Definition

Epistaxis is defined as the presence of blood at the external nares[45]; the amount of blood at the nostrils can range from small flecks incorporated in serous nasal discharge to large volumes flowing freely from both nostrils. Hemoptysis is the coughing up of blood.[46]

5.3.2 Pathophysiology

Blood at the external nares originates from one or more of the following structures: nasal cavity, paranasal sinuses, guttural pouch (auditory tube diverticulum), oral cavity, pharynx, larynx, trachea, or lungs.[45] These respiratory structures may be affected by a primary disease process or may be one of many mucosal surfaces involved in a bleeding diathesis (Boxes 5-9 and 5-10). The actual disease condition, the affected structure, and the large animal species involved determines whether epistaxis is profuse or scant, unilateral or bilateral, induced by exercise, accompanied by hemoptysis, and/or associated with concurrent abnormal nasal discharge.

5.3.2.1 NASAL CAVITY OR PARANASAL SINUS PATHOLOGIC CONDITIONS

Epistaxis associated with diseased respiratory tract structures rostral to the caudal border of the nasal septum (e.g., nasal cavity, paranasal sinuses) usually is unilateral and appears spontaneously (i.e., occurs without exertion or lowering of the head). However, with profuse hemorrhage from these sites, blood may drain caudally, accumulate in the pharynx, and exit from both nostrils.

Nasal cavity structures are highly vascular and prone to injury. Bleeding can be caused by foreign bodies, fungal granulomas, or neoplasms that invade the nasal cavity; epistaxis associated with these lesions is commonly unilateral, scant, and evident only intermittently. Trauma induced by passage of a nasogastric tube or endoscope is the most common cause of profuse hemorrhage of nasal origin in horses.[45] Erosive diseases that affect the paranasal sinuses of horses (e.g., progressive ethmoidal hematoma)[45] or sheep (endemic nasal adenocarcinoma)[47] commonly cause a unilateral, serosanguineous nasal discharge preceded or accompanied by mucopurulent discharge. In the case of sinusitis the exudate often is malodorous, particularly when the process occurs secondary to dental disease. Epistaxis resulting from fractures of the nasal bones or skull can be scant or profuse, depending on the extent of the fracture.

5.3.2.2 PATHOLOGIC CONDITIONS OF THE GUTTURAL POUCHES OF THE HORSE

Spontaneous epistaxis that occurs at rest in a mature horse warrants consideration of the guttural pouch as the source of hemorrhage.[48] In the case of guttural pouch mycosis, epistaxis is typically caused by fungal erosion of the internal carotid artery in the roof of the medial compartment of the guttural pouch.[48–50] The horse initially experiences several episodes of minor hemorrhage characterized by a small amount of fresh blood at the external nares; this may be preceded by a unilateral catarrhal nasal discharge and followed by a seromucous nasal discharge. Ultimately, massive arterial bleeding associated with erosion of the internal carotid artery

manifests as large volumes of blood gushing from both nostrils.[49] Epistaxis caused by bleeding from the guttural pouch is typically most pronounced on the ipsilateral side, but nasal bleeding is usually bilateral in this condition, especially if hemorrhage is profuse, because the nasopharynx drains into both nasal passages.[50]

5.3.2.2.1

Box 5-9 Causes of Epistaxis in Horses

5.3.2.2.1.1

COMMON CAUSES

- Exercise-induced pulmonary hemorrhage (EIPH)
- Guttural pouch mycosis
- Progressive ethmoidal hematoma
- Nasal trauma
- Pharyngeal or retropharyngeal trauma or abscess
- Nasal polyps
- Tumors (nose, paranasal sinuses)
- Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)
- Purpura hemorrhagica

5.3.2.2.1.2

LESS COMMON CAUSES

- Pleuropneumonia
- Infarctive lobar pneumonia
- Pulmonary neoplasia
- Fungal granuloma (maduromycosis, aspergillosis, rhinosporidiosis, mycetoma)
- Cryptococcal rhinitis

Coccidioidomycosis

Guttural pouch empyema

Guttural pouch neoplasia

Guttural pouch foreign body

Vesicular stomatitis

Atrial fibrillation

Idiopathic thrombocytopenic purpura

Immune-mediated thrombocytopenia

Lymphosarcoma

Myeloproliferative disease

Disseminated intravascular coagulation (DIC)

Toxic hepatic failure

Multiple clotting defects (foals)

Equine infectious anemia (EIA)

Skull fracture

Gunshot

Pharyngeal lymphoid hyperplasia

5.3.2.2.1.3

UNCOMMON CAUSES

Nasal amyloidosis

Rectus capitis ventralis rupture

Black's disease *(Clostridium novyi)*

Snakebite

Retrobulbar neoplasia

Chronic hepatitis or cholangitis

Acute renal failure

Cardiac neoplasia

Laryngeal hemiplegia

Phycomycosis, pythiosis, zygomycosis

Thrombasthenia-like syndrome

Besnoitiosis, globidiosis (exotic)

Dacryohemorrhea (exotic)

5.3.2.2.1.4

TOXIC CAUSES

Arsenic

Warfarin or dicumarol

Stachybotryotoxicosis (*Stachybotrys* species)

Plant toxins

Moldy sweet clover *(Melilotus alba)*

Pyrrolizidine alkaloid (e.g., common groundsel *[Senecio vulgaris]*, fiddleneck [*Amsinckia* species], tansy ragwort *[Senecio jacobeae]*)

5.3.2.2.2

Box 5-10 Causes of Epistaxis in Ruminants

5.3.2.2.2.1

COMMON CAUSES

Pharyngeal or retropharyngeal trauma or abscess

Lung embolus from caudal vena cava thrombosis (CVCT) (B)

Infection of paranasal sinuses

Nasal trauma

Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)

Nasal bots *(Oestrus ovis)* (C, O)

Nasal adenoma, adenopapilloma, adenocarcinoma (C, O)

Dehorning of adult animals (B)

5.3.2.2.2.2

LESS COMMON CAUSES

Nasal granuloma, atopic rhinitis (B)

Fungal granuloma (maduromycosis, rhinosporidiosis, mycetoma) (B, C)

Neoplasia (nose, paranasal sinuses)

Skull fracture

Gunshot injury

Bluetongue (O)

Vesicular stomatitis

Bovine virus diarrhea (BVD-MD) (B)

Malignant catarrhal fever (B)

Infectious bovine rhinotracheitis (IBR; BHV-1) (B)

5.3.2.2.2.3

UNCOMMON CAUSES

Black's disease *(Clostridium novyi)* (B, O)

Acute anthrax *(Bacillus anthracis)*

Bacillary hemoglobinuria *(Clostridium hemolyticum)* (B, O)

Snakebite

Acute renal failure

Endocarditis

Liver fluke disease

Pulmonary neoplasia

Pasteurella pneumonia or septicemia (C, O)

Xylazine-induced pulmonary edema (O)

Idiopathic granulocytopenia or thrombocytopenia (B)

Hemophilia A (factor VIII deficiency) (B)

Factor XI deficiency (B)

Hereditary platelet aggregating disorder in Simmentals (B)

Cardiomyopathy in polled Hereford calves (B)

Trypanosomiasis (exotic) (B, O)

Ondiri disease (exotic) (B, O)

Besnoitiosis, globidiosis (exotic) (B, O)

Endemic ethmoid carcinoma (exotic) (B)

Gedoelstia hasleri nasal bots (exotic) (O, C)

Nairobi sheep disease (exotic) (O, C)

Leech infestation (hirudiniasis) (exotic)

5.3.2.2.2.4

TOXIC CAUSES

Mercury

Arsenic

Warfarin, diphacinone

Furazolidone

Trichloroethylene-extracted feed

Oak (acorn poisoning)

Bracken fern *(Pteridium aquilinum)*

Moldy sweet clover *(Melilotus alba)*

Phytogenous selenium poisoning (e.g., *Astragalus* species)

Oxalate poisoning (e.g., *Halogen* species, *Sarcobatus* species)

Stachybotryotoxicosis (*Stachybotrys* species)

Mycotoxicosis

B, Bovine; *C*, caprine; *O*, ovine.

5.3.2.3

PULMONARY PATHOLOGIC CONDITIONS

In horses, pulmonary hemorrhage manifests as bilateral epistaxis, most often during or immediately after strenuous exercise.[45] However, in many cases of pulmonary hemorrhage, epistaxis may not be observed because blood originating from the lungs is swallowed when it reaches the pharynx. Hemoptysis, the hallmark of pulmonary hemorrhage in cattle, is rarely observed in horses because the laryngopalatal articulation of the horse fixes the larynx in an intranarial position and generally prevents blood flow from the nasopharynx to the oropharynx and mouth. In contrast to humans and other animal species, where foaming of blood exiting the nares suggests pulmonary hemorrhage, foaming of the blood is rarely encountered in horses with pulmonary hemorrhage because the horizontal position of the major bronchi allows blood to pool and flow freely without having to be coughed up.

EIPH, a syndrome experienced by 40% to 75% of thoroughbred racehorses and by horses of other breeds engaged in strenuous activity, is characterized by hemorrhage into the tracheobronchial tree during competitive exercise.[45,51,52] Although pulmonary hemorrhage can be identified by endoscopic examination of the trachea immediately after exercise in these horses, EIPH manifests as frank epistaxis at the external nares in only a small percentage of cases.[51] Bleeding at the nares may range from a slight orange-tinged serous nasal discharge to a constant trickle of fresh blood that persists for several hours after exercise.[45,52] The exact source of hemorrhage in horses with EIPH has not been identified, but it is known that affected horses have proliferation of the bronchial arterial blood supply to the lungs.[53] Fatal massive epistaxis, an infrequent sequela to exercise, has been attributed to tearing of the lung in association with pleural adhesions or focal shear stress.[54] Other less common causes of postexercise pulmonary hemorrhage in horses include pulmonary abscesses or pleuropneumonia with pulmonary infarction; in these cases the odor of the breath may be fetid, and hemorrhage may occur spontaneously (without exercise), which aids in the differentiation of these conditions from EIPH.[45,55]

CVCT (also known as *pulmonary embolic aneurysm* or *pulmonary thromboembolism*) is the disease most likely to be associated with epistaxis and hemoptysis in cattle (Box 5-11).[56] This sporadic, fatal condition of feedlot cattle is the result of a four-step sequence of events that culminates with the rupture of a pulmonary artery aneurysm into a bronchus. Initially, affected cattle exhibit tachypnea, lethargy, painful cough, melena, and anemia. Terminally the disease is characterized by discharge of bright, foamy red blood from the nose and mouth, severe respiratory distress, and widespread pulmonary crackles.[56]

5.3.2.3.1

Box 5-11 Causes of Hemoptysis in Ruminants

Caudal vena cava thrombosis (CVCT)

Aspiration pneumonia

Pharyngeal or retropharyngeal abscess or trauma

Thoracic trauma (fractured ribs or sternum)

Foreign body (nasal, oropharyngeal, tracheal, bronchial)

Pulmonary aspergillosis

Pulmonary edema present in the terminal stages of left-sided heart failure may also be responsible for bilateral serosanguineous discharge at the external nares of large animals.[45]

5.3.2.4 PATHOLOGIC CONDITIONS OF THE ORAL CAVITY, PHARYNX, OR LARYNX

Less often, epistaxis can result from bleeding from lesions in the oral cavity, pharynx, or larynx. Examples include oral cavity erosions associated with infectious diseases (e.g., mucosal form of bovine virus diarrhea infection in cattle, or bluetongue in sheep); erosions associated with epiglottic entrapment in horses; foreign bodies wedged in the mouth or pharynx of large animals; and pharyngeal or retropharyngeal trauma caused by a “balling gun.”

5.3.2.5 BLEEDING DIATHESIS

Several inherited and acquired coagulation disorders of large animals manifest as epistaxis.[57] Inherited clotting factor deficiencies (usually deficiencies of factors VIII, IX, or XI) or acquired factor deficiencies (those caused by warfarin, sweet clover toxicosis, or advanced liver disease) cause bleeding from large vessels. In addition to epistaxis, subcutaneous hematomas, hemarthrosis, melena, and hematuria, prolonged bleeding from sites of injury may be observed. With conditions causing vasculitis (e.g., equine purpura hemorrhagica, equine viral arteritis), small vessel bleeding occurs. Vasculitis is characterized by mucous membrane petechiae and ecchymoses and demarcated areas of skin edema. Nasal mucous membrane petechiae associated with vasculitis may manifest as epistaxis. Similarly, thrombocytopenia (e.g., immune-mediated thrombocytopenia in horses, bracken fern toxicosis in cattle) is characterized by mucous membrane petechiae and occasionally epistaxis. In rare cases disseminated intravascular coagulation (DIC) in large animals manifests as a consumptive coagulopathy with bleeding from mucous membranes and blood at the external nares.

5.3.3 Approach to Diagnosis of Epistaxis and Hemoptysis

5.3.3.1 HISTORY

History taking should closely follow that described for animals with nasal discharge and should include duration of ownership, time of first appearance of blood at the nares, number of times the animal has bled, volume and color of blood, presence of blood at one or both nostrils, association of epistaxis with exercise,

swallowing motions or cough after exercise, concurrent hemoptysis, other signs of respiratory tract disease (e.g., stridor, cough, nasal discharge, respiratory distress), evidence of involvement of cranial nerves (e.g., feed particles at the nares, drooping of the lip or ear), possibility of recent trauma (e.g., nasogastric intubation or head injury), and exposure to toxic plants (e.g., bracken fern or sweet clover).

5.3.3.2

PHYSICAL EXAMINATION

A complete physical examination should be performed to detect abnormalities indicative of systemic disease or disease affecting other body systems. This examination should include assessment of the attitude of the animal; determination of rectal temperature, pulse rate, and respiratory rate and character; evaluation of mucous membranes for color and petechiae; inspection of the animal to detect hematomas or prolonged bleeding from sites of injury or venipuncture; and neurologic examination to detect neurologic dysfunction (e.g., dysphagia, Horner's syndrome, facial paralysis, head tilt, or nystagmus), which may accompany guttural pouch mycosis. 58 59

5.3.3.3

EVALUATION OF THE HEAD AND RESPIRATORY SYSTEM

A complete evaluation of the head and respiratory system should also be carried out. The nasal bones and flat bones overlying the maxillary and frontal sinuses should be examined for asymmetry or deformation; the eyes should be evaluated for exophthalmos or epiphora; the nasal mucosae should be inspected with a light source to demonstrate erosive, ulcerative, or mass lesions; and the sinuses should be percussed to detect altered resonance or pain. On continuing the examination, the following should be evaluated: symmetry and amount of airflow through the nostrils and the effect of occluding each nostril independently; odor at the nose or mouth; presence of stridor; and the effect of applying pressure to the larynx or trachea. The oral cavity should be carefully inspected in animals in which epistaxis is accompanied by a necrotic breath odor. Special attention should be paid to the maxillary cheek teeth of horses and the base of the tongue and the oropharynx of all large animals. Structures in the external pharyngeal region (mandibular lymph nodes, Viborg's triangle, retropharyngeal lymph nodes, parotid salivary gland) should be observed and palpated for swelling, heat, or pain, and the trachea should be observed and palpated where exposed to detect any abnormalities. The larynx, trachea, and lungs should be carefully auscultated at rest and after application of a rebreathing bag for abnormally loud breath sounds, crackles, or wheezes, which may implicate pulmonary disease as the cause of epistaxis. Careful cardiac auscultation should be carried out to detect murmurs or dysrhythmias, which may be associated with left-sided heart failure and pulmonary edema. The chest wall should be palpated to detect rib fractures or pleural friction rubs, and the thorax should be percussed bilaterally to demonstrate large mass lesions, pleural effusion, or pleurodynia.

5.3.3.4

COMPLETE BLOOD COUNT

A complete blood count and assessment of fibrinogen concentration can be useful in the evaluation of animals with primary or secondary inflammatory conditions or those that have developed blood loss anemia as a sequela to epistaxis (e.g., horses with guttural pouch mycosis or cattle with pulmonary thromboembolism secondary to CVCT). The degree of anemia may give an indication of the severity and chronicity of the bleeding or, in cases of bracken fern poisoning, of the degree of bone marrow suppression.

5.3.3.5

CLOTTING PROFILE

A clotting profile should be performed (platelet count, prothrombin time [PT], activated partial thromboplastin time [APTT], concentration of fibrin degradation products [FDPs], and plasma antithrombin III) if mucous

membrane petechiae or a tendency to bleed was noted on the general physical examination or if the history suggests exposure to sweet clover, warfarin, or bracken fern.

5.3.3.6

BIOCHEMISTRY PROFILE

A biochemistry profile should be performed to detect disease processes in organ systems other than the lungs (e.g., increased liver enzyme activity in cattle with hemoptysis secondary to CVCT or animals with liver failure causing secondary clotting factor deficiency).

5.3.3.7

OCCULT BLOOD

Feces should be tested for occult blood. Positive results may suggest swallowing of blood originating from the lungs or pharynx or gastrointestinal bleeding.

5.3.3.8

ENDOSCOPIC EVALUATION

Endoscopic evaluation using a fiberoptic or video endoscope is a useful diagnostic aid in cases of epistaxis. The nasal passages, nasomaxillary aperture in the middle meatus, turbinates (conchae), nasal septum, pharynx, guttural pouches, larynx, and tracheobronchial tree should be systematically evaluated through both nostrils at rest and after exercise if indicated to determine the presence, nature, and source of blood and the anatomic or mass lesion responsible for the bleeding. Care should be taken when endoscopy is performed in horses with guttural pouch mycosis, because dislodging a clot of blood in the affected guttural pouch may result in fatal hemorrhage.[58] Similarly, the stress of endoscopy may prove fatal to cattle with pulmonary thromboembolism secondary to CVCT. If EIPH is suspected, endoscopy should be performed 30 to 120 minutes after strenuous exercise to allow time for the mucociliary escalator to transport blood to where it can be visualized[51]; this blood may persist from 6 hours to 4 days after exercise, depending on the severity of pulmonary hemorrhage. It is important to remember that EIPH may not be repeatable. In one study only 33% of thoroughbred racehorses tested positive for EIPH on all subsequent endoscopic examinations after breezing.[59] Biopsy (with histologic evaluation and possibly culture of samples) is indicated when granulomas, polyps, erosions, or mass lesions are visualized through the endoscope.

5.3.3.9

TRACHEAL ASPIRATION, BRONCHOALVEOLAR LAVAGE, AND THORACOCENTESIS

Percutaneous transtracheal aspiration or endoscopic tracheal aspiration, BAL, or thoracocentesis with cytologic studies and culture of collected samples is indicated when pulmonary or pleural diseases are thought to be responsible for hemorrhage into the respiratory tract. BAL is a technique best suited to evaluation of diffuse lung disease; BAL fluid analysis can yield a normal result in horses with focal lung disease (e.g., pulmonary abscess, pneumonia, or pleuropneumonia) because lavage fluid is instilled into a limited region of the lung.[60] Quantitative culture techniques should be used for samples obtained via BAL because contamination by nasopharyngeal organisms can occur.[61] Although there is a poor correlation between cytologic findings in tracheal wash fluid and histopathologic changes in the lungs of individual horses, increased cell counts with degenerative neutrophils and large numbers of intracellular and extracellular bacteria suggest a diagnosis of bronchopneumonia.[62] Percutaneously obtained tracheal wash samples are usually not contaminated by oropharyngeal organisms and can be submitted for culture[61]; transendoscopically obtained samples may be

contaminated with *Pseudomonas* species and anaerobic bacteria despite the use of guarded tracheal swabs.[63] The presence of hemosiderophages in tracheobronchial aspirates or BAL fluid is generally considered indicative of previous pulmonary hemorrhage[51]; however, mucopolysaccharides engulfed by alveolar macrophages can bind plasma iron in the absence of pulmonary hemorrhage to form an iron pigment resembling hemosiderin.[64]

5.3.3.10

RADIOGRAPHIC EXAMINATION

Radiographic examination of the nasal passages, paranasal sinuses, pharynx, retropharyngeal region (including the guttural pouches), larynx, and trachea is indicated if the source of nasal bleeding cannot be definitively diagnosed through physical examination and endoscopy. The nasal passages, turbinates, and paranasal sinuses should be evaluated for fluid lines, cystic structures, bony lysis or proliferation, distortion of normal architecture, or changes in the tooth roots. Space-occupying lesions in the pharynx and larynx may also be demonstrated by radiographic examination. Demonstration of a fluid-air interface in the guttural pouch may indicate guttural pouch hemorrhage or guttural pouch empyema.[45] New bone formation and sclerosis around the *temporohyoid articulation* may accompany mycotic infections of the guttural pouch.[45] CT examination may be indicated if the lesion in the head or neck causing hemorrhage cannot be defined adequately with plain radiographs. Thoracic radiographs using four overlapping lateral views in adult horses and cattle and lateral and ventrodorsal views in immature animals and small ruminants aid in identification and definition of diseases affecting the lungs, pleurae, and mediastinum.[61]

59

60

5.3.3.11

ULTRASOUND EXAMINATION

Ultrasound examination is used as an adjunct to thoracic radiology in animals suspected of having pleural effusion[61]; this procedure allows the examiner to determine the extent of the effusion and the presence of fibrin deposits or pleural adhesions. Pulmonary consolidation, atelectasis, infarction, and abscessation can also be demonstrated with this technique if these lesions are contiguous with the pleural surface.[61] Ultrasound examination of externally visible swellings such as enlarged retropharyngeal lymph nodes or distended guttural pouches may provide additional diagnostic information and may assist with appropriate placement of needles or biopsy instruments for sample collection.

5.3.3.12

PARACENTESIS

Paracentesis of the maxillary sinus[61] can be performed if percussion and inspection indicate that a lesion in the maxillary sinus may be the cause of epistaxis. Using sedation and analgesia, a small hole is trephined into the maxillary sinus with a Steinmann pin or 14-gauge needle; sinus contents can then be aspirated and submitted for cytologic and bacteriologic examination (see Nasal Discharge, p. 50).

5.3.3.13

PLEUROSCOPIC EXAMINATION

Pleuroscopic examination[65] can be performed in a standing, sedated patient by using a sterile rigid or fiberoptic endoscope. This procedure is indicated for patients in which large intrathoracic masses and adhesions have been demonstrated by thoracic radiology and ultrasonography. Pleuroscopy allows direct visualization of affected structures and provides an opportunity to biopsy masses or aspirate fluid. Pleuroscopy is a procedure

fraught with complications (e.g., pneumothorax, lung lacerations, infection) and should be reserved for cases in which less invasive procedures have failed to adequately diagnose the condition.[61]

In some teaching and research institutions *ventilation/perfusion ratios* can be measured in horses using nuclear scintigraphic techniques. A study of horses with EIPH demonstrated both ventilation and perfusion deficits in the dorsocaudal lung field that corresponded to the area in which EIPH lesions were detected at postmortem examination.[66]

5.4 TACHYPNEA

5.4.1 Definition

Tachypnea is the term used to describe an increase in the respiratory rate; the term *hyperpnea* is used when both the rate and depth of respiration have increased.

The respiratory rate, which is assessed by counting rib or nostril movements or by thoracic or tracheal auscultation, is best determined before the patient is disturbed or restrained. Under average conditions of temperature and humidity, acceptable ranges for the respiratory rate in normal adult animals are as follows: cattle, 10 to 30 breaths/min; horses, 8 to 15 breaths/min; sheep and pigs, 10 to 20 breaths/min; and goats, 25 to 35 breaths/min. Resting respiratory rates in young animals are higher than those in adults. A neonatal foal has a resting respiratory rate of 60 to 80 breaths/min during the first 30 minutes of life, a rate that later falls to 20 to 40 breaths/min. A young calf has a respiratory rate of 20 to 50 breaths/min by 30 minutes of age.

5.4.2 Pathophysiology

Respiratory rate, depth, and rhythmicity are regulated by respiratory centers in the brainstem. Central chemoreceptors responding to increased levels of CO_2 (decreased cerebrospinal fluid pH) and peripheral chemoreceptors (carotid and aortic bodies) responding to hypoxemia (Pa_{O_2} below 60mm Hg), increases in Pa_{CO_2}, and decreases in pH initiate increases in the respiratory rate. Mechanoreceptors in the lungs and joints also influence ventilation. Lung inflation stimulates stretch receptors in the airways, which decreases the inspiratory effort, whereas mechanoreceptors in the joints are thought to be partly responsible for the increases in ventilation that occur during exercise. Pulmonary chemoreceptors that influence the respiratory cycle include irritant receptors in the airways, which are stimulated by dust and histamine, and J receptors, which apparently detect levels of interstitial fluid and are thought to be responsible for the respiratory pattern observed in animals with pulmonary edema.

Tachypnea is classified as physiologic when it occurs in the absence of underlying disease and as pathologic when it is a manifestation of respiratory distress. Physiologic tachypnea is associated with pain, exertion, heat, fever, anxiety, and other stresses (Boxes 5-12 and 5-13). Factors predisposing to pathologic tachypnea are the same as those that cause respiratory distress: inadequate oxygenation of the blood (i.e., a need for additional oxygen); compensation for metabolic acidosis; excessive environmental heat; disorders that damage the central nervous system respiratory centers in the medulla (e.g., head trauma, inflammation, mass lesions) if they disrupt the control of breathing; disorders that cause dysfunction of motor nerves and/or weakness of respiratory muscles (e.g., botulism, myasthenia gravis, or diaphragmatic paralysis); and painful conditions involving the respiratory sensory nerves, muscles, pleurae, and ribs (e.g., chest trauma, pleural infection, or neoplasia)[67] (see Respiratory Distress, below).

5.4.3 Approach to Diagnosis of Tachypnea

Because tachypnea is a manifestation of respiratory distress, the approach used for evaluating patients with tachypnea is the same as that used for evaluation of respiratory distress (see below).

5.5 RESPIRATORY DISTRESS (DYSPNEA)

5.5.1 Definition

Respiratory distress indicates an inappropriate degree of effort to breathe based on an assessment of respiratory rate, rhythm, and character.[68,69]

Respiratory distress is a clinical sign that implies labored breathing, whereas dyspnea is a symptom that describes the subjective feeling of difficult, uncomfortable, or unpleasant breathing (shortness of breath) in human patients.[68–70] As such the term *dyspnea* is not strictly applicable to animal patients, although it is widely used by veterinarians to describe respiratory distress.

Manifestations of respiratory distress include elevated respiratory rate (see Tachypnea, at left), extended head and neck position, mouth breathing (ruminants), nostril flaring (horses, sheep, and goats), abnormal respiratory noise (stridor or stertor), exercise intolerance, exaggerated intercostal or abdominal effort (or both), a double expiratory lift and a “heave line” (expiratory respiratory distress), abducted elbows, stridor, anxious expression, and inactivity. Animals in severe respiratory distress may show cyanosis (see p. 68) and (especially those with severe RAO) may exert so much effort to breathe that the whole body rocks, the anus pumps in and out, and the animal does not move or eat because this diverts its energies from respiration.[69]

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5.5.1.1 Box 5-12 Causes of Tachypnea in Horses*

5.5.1.1.1 COMMON RESPIRATORY CAUSES

Bacterial pneumonia

Pleuropneumonia, pleuritis

Pulmonary abscessation

Recurrent airway obstruction (RAO or COPD)

Viral pneumonia (equine influenza, adenovirus, equine viral arteritis, others)

Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)

Aspiration pneumonia

Prematurity, dysmaturity, or immaturity (foals)

5.5.1.1.2 COMMON NONRESPIRATORY CAUSES

Hyperthermia (fever, postexhaustion syndrome, heat stroke, anhidrosis, other)

Pain (abdominal crisis, laminitis, exertional myopathy, other)

Acidosis (acute enterocolitis, urinary bladder rupture, renal tubular acidosis, other)

Anaphylaxis

Blood transfusion reaction

Shock (hypovolemic, cardiac, septic)

Anemia (neonatal isoerythrolysis, blood loss, hemolytic anemia, iron deficiency, bone marrow suppression, ruptured middle uterine artery, other)

Cardiac disease (ruptured mitral chordae tendineae, ventricular septal defect, endocarditis, other)

Gastric dilation

5.5.1.1.3 LESS COMMON RESPIRATORY CAUSES

Smoke inhalation pneumonia

Parasitic pneumonia *(Dictyocaulus arnfieldi)*

Stenotic nares, choanal atresia

Nasal septum abnormalities

Neoplasia (nose, paranasal sinuses)

Fungal granuloma

Nasopharyngeal cicatrix

Paranasal sinus infection

Dorsal displacement of the soft palate

Pharyngeal or retropharyngeal abscess or trauma

Epiglottic entrapment

Chondroma of arytenoid cartilage

Guttural pouch empyema

Tracheal stenosis, collapse, stricture

Foreign body (nasal, nasopharyngeal, laryngeal, tracheal, bronchial)

Diaphragmatic hernia

Pneumothorax

Thoracic trauma

5.5.1.1.4 LESS COMMON NONRESPIRATORY CAUSES

Anaphylaxis

Air embolism

Intracarotid injections

Fluid therapy complications

Tetanus *(Clostridium tetani)*

Malignant edema *(Clostridium septicum)*

Malignant hyperthermia

Meningoencephalitis

Anemia (piroplasmosis, iron deficiency, hemolytic blood loss, other)

Cardiovascular anomalies (tetralogy of Fallot, tricuspid insufficiency, atrial septal defect, hypoplastic left heart, transposition of great vessels, persistent right aortic arch, patent ductus arteriosus)

Cor pulmonale

Pericarditis

Atrial fibrillation

Ventricular tachycardia, fibrillation, flutter

5.5.1.1.5

UNCOMMON RESPIRATORY CAUSES

Pulmonary lobar hypertrophy

Branchial or thyroglossal duct cyst

Tracheal rupture

Fracture of laryngeal cartilage

Fracture of hyoid bone

Cutaneous or nasal amyloidosis

Pulmonary tuberculosis

Pulmonary nocardiosis

Pneumocystis carinii pneumonia

5.5.1.1.6 UNCOMMON NONRESPIRATORY CAUSES

Lactation tetany

Hydroallantois or hydrops

Nutritional myodegeneration (foals)

Methemoglobin reductase deficiency

Acute hepatic insufficiency

Electrocution

Cardiac neoplasia

Embryonal mediastinal cyst

5.5.1.1.7 TOXIC CAUSES

α-Naphthyl thiourea (ANTU)

Arsenic

Bromide

Sodium fluoroacetate

Cantharidin (blister beetle)

Ammonia

Amitraz

Propylene glycol

Dioctyl sodium sulfosuccinate

Iron

Selenium

Metaldehyde

Organophosphate

Organochlorine, chlorinated hydrocarbon

Phenothiazine

Potassium

Larkspur (*Delphinium* species)

Japanese yew *(Taxus cuspidata)*

White snakeroot *(Eupatorium rugosum)*

Water hemlock (*Cicuta* species)

Jimson weed *(Datura stramonium)*

Potato *(Solanum tuberosum)*

Cyanogenic plants

Onion (*Allium* species)

Red maple *(Acer rubrum)*

* All causes of respiratory distress (p. 60) are also causes of tachypnea.

5.5.1.2

Box 5-13 Causes of Tachypnea in Ruminants

5.5.1.2.1

COMMON RESPIRATORY CAUSES

Mannheimia hemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)

Haemophilus somnus pneumonia (B)

Visceral caseous lymphadenitis *(Corynebacterium pseudotuberculosis)* (C, O)

Chronic bacterial pneumonia with consolidation or abscessation (*Arcanobacterium [Actinomyces] pyogenes* and other bacteria)

Necrotic laryngitis *(Fusobacterium necrophorum)* (B)

Pulmonary embolus from posterior vena cava thrombosis (B)

Respiratory syncytial virus

Parainfluenza type 3 virus

Adenovirus (B, O)

Infectious bovine rhinotracheitis virus (IBR; BHV-1) (B)

Ovine progressive pneumonia virus (O)

Mycoplasma species

Caprine *Mycoplasma mycoides* subsp. *mycoides* infection

Mycoplasma ovipneumoniae (O)

Parasitic pneumonia (*Dictyocaulus viviparus* [B]; *Dictyocaulus filaria* [O, C]; *Müllerius capillaris* [O, C]; *Protostrongylus rufescens* [O, C])

Bovine atypical interstitial pneumonia (B)

Acute pulmonary edema and emphysema (B)

Farmer's lung (*Faenia rectivirgula* hypersensitivity pneumonitis) (B)

Aspiration or foreign body pneumonia

5.5.1.2.2 COMMON NONRESPIRATORY CAUSES

Hyperthermia (fever, heat stroke, rapid rise in ambient temperature, other)

Pain (abdominal crisis, urethral calculi, traumatic reticuloperitonitis, musculoskeletal injury, other)

Acidosis (ruminal lactic acidosis, pregnancy toxemia, other)

Electrolyte aberrations (hypocalcemia, hypomagnesemia, other)

Shock (hypovolemic, cardiac, septic)

Anemia (iron deficiency, postparturient hemoglobinuria, blood loss, other)

Distended abdominal viscus (ruminal bloat, other)

Anaphylaxis

Blood transfusion reaction

White muscle disease

5.5.1.2.3 LESS COMMON RESPIRATORY CAUSES

Nasal trauma

Tumors of the nose and paranasal sinuses

Nasal granulomas (fungal granuloma, atopic rhinitis)

Congenital cystic nasal conchae

Laryngeal trauma, abscess

Tracheal stenosis, collapse, stricture

Bovine rhinovirus (B)

Bovine malignant catarrhal fever (B)

Ascaris suum migration (calves) (B)

Thoracic trauma, other causes of chest pain

Pneumothorax

Diaphragmatic hernia

Pleuritis or pleural effusion

Caprine arthritis-encephalitis (CAE) pneumonia (C)

Sheep pulmonary adenomatosis virus pneumonia (O)

5.5.1.2.4 LESS COMMON NONRESPIRATORY CAUSES

Cardiac anomalies (ventricular septal defect, tetralogy of Fallot, other)

Endocarditis

Pericarditis

Central nervous system disease (meningoencephalitis, polioencephalomalacia, other)

Esophageal obstruction or foreign body

Clostridial diseases (Black's disease, enterotoxemia, tetanus)

Anaphylaxis

5.5.1.2.5 UNCOMMON RESPIRATORY CAUSES

Pleural mesothelioma

Pneumocystis carinii pneumonia

Pulmonary aspergillosis

Pulmonary neoplasia

Cyst (branchial, cervical, thyroglossal duct) (B)

Bronchobiliary fistula

Contagious bovine pleuropneumonia (exotic) (B)

Endemic ethmoid carcinoma (exotic) (B)

5.5.1.2.6 UNCOMMON NONRESPIRATORY CAUSES

Bluetongue (B, O)

Thymic lymphosarcoma (B)

Retrobulbar neoplasia (B)

Calf lymphosarcoma (B)

Adult multicentric lymphosarcoma (B)

Embryonal mediastinal cyst

Dwarfism (B)

Anthrax

5.5.1.2.7

TOXIC CAUSES

Sodium fluoroacetate

Strychnine

Sulfur

Propylene glycol

Urea or nonprotein nitrogen

Water deprivation or salt toxicity

Potassium

Nitrates

Bromide

Iron

Selenium

Organophosphate

Organochlorine or chlorinated hydrocarbon

Larkspur (*Delphinium* species)

Japanese yew *(Taxus cuspidata)*

Sneezeweed *(Helenium autumnale)*

Hairy vetch *(Vicia villosa)*

Whitehead *(Sphenosciadium capitellatum)*

White snakeroot *(Eupatorium rugosum)*

B, Bovine; *C*, caprine; *O*, ovine.

Note: Tachypnea is a rather nonspecific sign and is associated with toxicity caused by a large number of plant species; only a few are listed in this box. See also Box 5-15, p. 65.

5.5.2

Pathophysiology

Normal respiratory rate and character are maintained by central and peripheral monitoring of blood gas and acid-base status, with resulting reflex adjustments that maintain carbon dioxide (CO_2), oxygen (O_2), and the blood hydrogen ion concentration (pH) within a narrow range.[71] Respiratory distress may occur for the following reasons[72]:

- Inadequate oxygenation of blood (i.e., a need for additional oxygen)
- Compensation for metabolic acidosis
- Excessive environmental heat
- Disorders that damage the central nervous system respiratory centers in the medulla (e.g., head trauma, inflammation, mass lesions) if they disrupt the control of breathing
- Disorders that cause dysfunction of motor nerves or weakness of respiratory muscles (e.g., botulism, polyradiculoneuritis, myasthenia gravis, or diaphragmatic paralysis)
- Painful conditions involving the respiratory sensory nerves, muscles, pleura, and ribs (e.g., chest trauma, pleural infection, or neoplasia)

Inadequate oxygenation of blood leads to arterial hypoxemia (low partial pressure of oxygen in arterial blood [Pa_{O_2}]). This can be caused by a low partial pressure of inspired oxygen (PI_{O_2}), such as occurs at high altitude; by disorders that interrupt the transfer of oxygen from the environment to the blood (e.g., upper and lower airway obstruction, pulmonary disease associated with alveolar flooding or collapse, and pulmonary or intracardiac right-to-left shunting of blood); or by a decrease in the oxygen-carrying capacity of the blood, such as occurs in anemia, methemoglobinemia, and carboxyhemoglobinemia.[72] Primary or secondary disease conditions that affect the respiratory and cardiovascular systems induce arterial hypoxemia by causing alveolar hypoventilation, ventilation-perfusion mismatch, diffusion limitation, right-to-left shunting of blood, or combinations of these abnormalities (see Cyanosis, p. 68).[68,72]

Compensation for metabolic acidosis involves “blowing off” carbon dioxide, which may increase both the rate and depth of respiration.[72] The resulting hyperventilation causes a decline in the partial pressure of arterial carbon dioxide (Pa_{CO_2}) in the face of clinical signs of respiratory distress.

Animals dissipate a considerable amount of heat through the respiratory tract. In ruminants, but not in horses, heat dissipation is further aided by the animals' ability to mouth breathe and pant to increase evaporative cooling of blood passing through the tongue and other structures in the oral cavity and oropharynx. The need to dissipate heat when exposed to high environmental temperatures induces labored breathing (Boxes 5-14 and 5-15).

Apparent respiratory distress also occurs when the weather is not excessively hot but the temperature has risen rapidly, such as occurs when cattle in cold climates are brought indoors in the winter. When the environmental temperature has been consistently low, cattle in feedlots may also experience respiratory distress if the temperature suddenly rises to 4.4° to 10°C (40° to 50°F).

Observation of the nature of the respiratory distress may give important clues as to the functional characterization, and perhaps cause, of the underlying disease process. Obstructive diseases involving the intrathoracic airways (e.g., RAO in horses and farmer's lung in cattle) are more likely to cause flow limitation during expiration because of dynamic airway narrowing or collapse (see Cough, p. 42).[68,73,74] This results in expiratory respiratory distress and a pattern of respiration in which the expiratory phase occupies an increased proportion of the respiratory cycle as the patient attempts to expel air from the lungs.[68] In the extrathoracic airways, dynamic collapse occurs during inspiration because intraluminal pressures are subatmospheric at this time.[68,73,74] Therefore patients with upper airway obstructions, especially of the nonfixed type (e.g., laryngeal hemiplegia), generally show inspiratory respiratory distress and may have a prolonged inspiratory phase.[68,73] Fixed airway obstructions of either the upper or lower airway (e.g., intraluminal mass, bronchoconstriction) are present during both phases of respiration and may lead to both inspiratory and expiratory distress.[68] However, the distress is likely to be accentuated during a particular phase of respiration, depending on the anatomic site of the obstruction (i.e., fixed upper airway obstructions cause more distress during inspiration, and fixed lower airway obstructions cause more distress during expiration). Restrictive diseases (e.g., pleural effusion, pneumoconiosis) inhibit expansion of the lungs and therefore generally lead to inspiratory respiratory distress.[68] Because an animal with restrictive disease has reduced compliance and must perform more respiratory work than normal to expand its lungs, a common strategy for maintaining adequate ventilation is to increase the respiratory rate and lower the tidal volume (i.e., rapid, shallow breathing).[68] Animals with obstructive diseases generally have a normal or even increased tidal volume.[68]

In many instances, respiratory distress is not apparent at rest but occurs in association with exercise. Under these circumstances the animal's capacity to exercise is impaired, and the owner may complain of exercise intolerance (see Exercise Intolerance and Poor Performance in Horses, p. 76).

5.5.3 Approach to Diagnosis of Respiratory Distress

5.5.3.1 HISTORY

After ruling out environmental causes of respiratory distress (e.g., heat stress, high humidity, moving from outside into a heated barn in the winter, handling stress, or relocation to high altitude) and attending to the immediate needs of the patient, a careful history should be taken that includes the following factors: time and speed of onset of the clinical signs of respiratory distress; progression of clinical signs; whether this is the first episode of respiratory distress or whether the animal is subject to recurrent attacks; whether signs are present at rest or only after exercise; the relationship of signs to environmental conditions and the response to environmental change; recent administration of pharmacologic or biologic agents; the presence of an audible respiratory noise; or other signs of respiratory tract, oropharyngeal, or neurologic disease (e.g., nasal discharge, cough, dysphagia, facial paralysis, or retropharyngeal swelling). A history of recent trauma or exposure to potentially toxic substances, such as lead-containing paints, nitrate-accumulating plants or urea (ruminants), or carbon monoxide, should be elicited. The animal's appetite and attitude and signs of disease in other systems (e.g., diarrhea) should be determined. In neonates the circumstances surrounding gestation and parturition should be ascertained, because prematurity, dysmaturity, congenital infection, birth trauma (e.g., rib fracture)

related to dystocia, prolonged parturition, and aspiration of amniotic fluid and meconium are all important causes of respiratory distress. However, it should be noted that tachypnea, with respiratory rates of 60 to 80 breaths/min, is normal in foals during the first 30 minutes after birth as they "blow off" carbon dioxide (see Disorders and Management of the Neonate, Chapter 15 and Chapter 19). 66

5.5.3.1.1

Box 5-14 Causes of Respiratory Distress in Horses

5.5.3.1.1.1

COMMON RESPIRATORY CAUSES

Bacterial pneumonia

Pleuropneumonia Pleuritis

Pulmonary abscessation

Recurrent airway obstruction (housing or pasture associated)

Strangles (*Streptococcus equi* infection)

Viral pneumonia (influenza, adenovirus, equine viral arteritis, others)

Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)

Aspiration pneumonia

Prematurity, dysmaturity, immaturity (foals)

Neonatal septicemia (foals)

Pharyngeal, retropharyngeal abscess or trauma

5.5.3.1.1.2

COMMON NONRESPIRATORY CAUSES

Cardiac disease (e.g., congestive cardiac failure, mitral insufficiency, other cardiac diseases)

Shock (septic, cardiogenic, hypovolemic, acute blood loss)

Endotoxemia

Anemia (e.g., neonatal isoerythrolysis, autoimmune hemolytic anemia, blood loss, other causes of acute anemia)

Pain (e.g., abdominal crisis, laminitis, myopathy, fracture, other lameness)

Hyperthermia (e.g., fever, postexhaustion syndrome, anhidrosis, heat stroke, erythromycin associated)

5.5.3.1.1.3

LESS COMMON RESPIRATORY CAUSES

Epiglottic entrapment with secondary infection or granulation

Arytenoid chondritis

Guttural pouch empyema, tympany, mycosis, neoplasia

Progressive ethmoid hematoma

Nasal polyps

Pharyngeal, subepiglottic cysts

Fungal rhinitis, cryptococcal rhinitis, equine nasal granuloma, nasal aspergillosis, rhinosporidiosis, rhinophycomycosis, maduromycosis, mycetoma

Cleft palate

Laryngeal or hyoid trauma, fractured laryngeal cartilages, laryngeal granuloma or scar

Paranasal sinus infection, cyst, trauma, tumor

Nasal trauma, nasal neoplasia

Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)

Exercise-induced pulmonary hemorrhage (EIPH)

Parasitic pneumonia *(Dictyocaulus arnfieldi)*

Coccidioidomycosis, cryptococcosis, mycotic pneumonia

Inhalation pneumonia, smoke inhalation, drowning, water inhalation

Hyaline membrane disease (foals)

Acute bronchointerstitial pneumonia

Peripartum asphyxia syndrome

Fractured ribs or sternum, thoracic trauma

Pneumothorax

Diaphragmatic hernia

Mediastinal abscess

5.5.3.1.1.4

LESS COMMON NONRESPIRATORY CAUSES

Purpura hemorrhagica

Blood or plasma transfusion reaction

Complications of fluid therapy

Anaphylaxis

Intracarotid injection

Acidosis

Gastric distention (e.g., as in small intestinal obstruction)

Pulmonary edema

Malignant hyperthermia

Cardiovascular anomalies (ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, common ventricle, other anomalies)

Endocarditis

Pericarditis

Cardiac dysrhythmias (atrial fibrillation, heart block, ventricular premature beats, ventricular tachycardia, ventricular fibrillation)

Ruptured mitral chordae tendineae

Mitral insufficiency or stenosis

Clostridial infections (e.g., tetanus, malignant edema, injection abscess)

Procaine penicillin G reaction or intravascular administration

Hyperkalemic periodic paralysis (HYPP)

5.5.3.1.1.5

UNCOMMON RESPIRATORY CAUSES

Stenotic external nares

Cutaneous, nasal amyloidosis

Cutaneous, nasal habronemiasis (summer sore)

Failure of closure of the false nostril

Abnormalities of the nasal septum

Choanal (posterior nares) atresia or stenosis (foals)

Nasopharyngeal cicatrix

Laryngopalatal dislocation (dorsal displacement of soft palate), soft palate hypoplasia

Rostral displacement of the palatopharyngeal folds

Pharyngeal hematoma

Laryngeal paralysis

Fistula (pharyngeal, esophageal, esophagobronchial, esophagotracheal)

Chondroma of the arytenoid cartilage

Laryngeal spasm

Hypertrophic ossification of the laryngeal cartilages, laryngeal chondropathy

Neoplasia of the upper airway

Tracheal stenosis, stricture, collapse, rupture

Phycomycosis, pythiosis

Pneumoconiosis (e.g., silicosis)

Interstitial pneumonia (restrictive pulmonary disease)

Pulmonary thromboembolism

Pneumocystis carinii pneumonia

Pulmonary lobar hypertrophy (foals)

Infarctive lobar pneumonia

Chlamydia psittaci pneumonia

Pulmonary nocardiosis

Pulmonary tuberculosis

Pulmonary aspergillosis

Besnoitiosis *(Besnoitia besnoiti* and *Besnoitia jellisoni)*

Pulmonary neoplasia (primary or metastatic)

Pleural neoplasia (mesothelioma, lymphosarcoma)

Embryonic cyst (mediastinal, branchial, cervical, thyroglossal duct)

Morbillivirus infection (exotic)

5.5.3.1.1.6

UNCOMMON NONRESPIRATORY CAUSES

Nutritional myodegeneration

Lactation tetany (eclampsia)

Hydroallantois or hydramnios

Methemoglobin reductase deficiency

Hemophilia A (factor VIII deficiency)

Acute hepatic insufficiency

Electrocution

Cor pulmonale

Neoplasia (all systems)

Snake or insect bite

Aortoiliofemoral thrombosis

Equine motor neuron disease

Cholesteremic granuloma

5.5.3.1.1.7 TOXIC CAUSES

Vitamin D

Lead

Organophosphate-associated laryngeal paralysis

Monensin, lasalocid, salinomycin

Propylene glycol

Iron

Dinitrophenol

Selenium

Bromide

Sodium fluoroacetate

Strychnine

Ammonia

Theobromine, chocolate

Cantharidin (blister beetle)

α-Naphthyl thiourea (ANTU)

Red maple *(Acer rubrum)*

Water hemlock (*Cicuta* species)

Oleander *(Nerium oleander)*

Japanese yew *(Taxus cuspidata)*

Larkspur (*Delphinium* species)

Ryegrass (*Lolium* species)

White snakeroot *(Eupatorium rugosum)*

Crofton weed *(Eupatorium adenophorum)*

Pyrrolizidine alkaloid

Locoweeds (*Astragalus* species, *Oxytropis* species)

Avocado *(Persea americana)*

Hoary alyssum *(Berteroa incana)*

Coffee senna seed *(Cassia occidentalis)*

Rubber vine *(Cryptostegia grandiflora)*

Birdsville disease (*Indigofera* species) (exotic)

Trachyandra paralysis (exotic)

5.5.3.1.2

Box 5-15 Causes of Respiratory Distress in Ruminants

5.5.3.1.2.1

COMMON RESPIRATORY CAUSES

Mannheimia hemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)

Bacterial pneumonia with consolidation or abscessation (*Arcanobacterium [Actinomyces]* and other bacteria)

Haemophilus somnus pneumonia (B)

Visceral caseous lymphadenitis *(Corynebacterium pseudotuberculosis)* (O, C)

Aspiration or foreign body pneumonia (especially after hypocalcemia)

Necrotic laryngitis *(Fusobacterium necrophorum)* (B, O)

Infectious bovine rhinotracheitis virus (IBR; BHV-1) (B)

Respiratory syncytial virus

Ovine progressive pneumonia virus (O)

Mycoplasma mycoides subsp. *mycoides, Mycoplasma agalactiae*, other *Mycoplasma* species (C)

Mycoplasma ovipneumoniae (O)

Parasitic pneumonia (*Dictyocaulus viviparus* [B], *Dictyocaulus filaria* [O, C], *Müllerius capillaris* [O, C], *Protostrongylus rufescens* [O, C])

Bovine atypical interstitial pneumonia (B)

Acute bovine pulmonary edema and emphysema (B)

Farmer's lung disease (*Faenia rectivirgula* hypersensitivity pneumonitis) (B)

5.5.3.1.2.2

COMMON NONRESPIRATORY CAUSES

Hyperthermia (fever, heat stroke, rapid rise in ambient temperature, other)

Pain (abdominal crisis, urethral calculi, traumatic reticuloperitonitis, other)

Distended abdominal viscus

Acidosis (ruminal lactic acidosis, pregnancy toxemia, other)

Electrolyte aberrations (hypocalcemia, hypomagnesemia, other)

Hypovolemic, cardiac, or septic shock

Fluid or electrolyte loss (acute diarrhea, gastrointestinal obstruction, other)

Endotoxemia (coliform mastitis, metritis, enteritis, salmonellosis, septicemia, other)

Neonatal septicemia

Anemia (iron deficiency, postparturient hemoglobinuria, hemolytic, anaplasmosis, eperythrozoonosis, other)

White muscle disease (nutritional myodegeneration)

Anaphylaxis or allergy, milk allergy

5.5.3.1.2.3

LESS COMMON RESPIRATORY CAUSES

Pulmonary embolus from posterior vena cava thrombosis (B)

Parainfluenza virus type 3

Adenovirus (B, O)

Nasal trauma

Tumors of the nose, paranasal sinuses, oral cavity

Nasal granulomas (fungal granuloma, atopic rhinitis)

Congenital cystic nasal conchae

Nose bots *(Oestrus ovis)*

Sinusitis (maxillary, frontal, postdehorning)

Laryngeal trauma or abscess

Trauma (oral, pharyngeal, retropharyngeal), abscess, hematoma

Tracheal stenosis, collapse, stricture

Bovine rhinovirus (B)

Bovine malignant catarrhal fever (B)

Bovine herpesvirus DN-599 (B)

Ascaris suum migration (calves) (B)

Thoracic trauma, rib fracture

Pneumothorax

Pleuritis or pleural effusion

Caprine arthritis-encephalitis (CAE) pneumonia (C)

Sheep pulmonary adenomatosis virus (Jaagsiekte) (O)

Smoke inhalation

Foreign body (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial)

Caprine herpesvirus (C)

Bluetongue

Peste des petits ruminants (C, O) (exotic)

Congenital cardiac anomalies (ventricular septal defect, tetralogy of Fallot, patent ductus arteriosus, transposition of the great vessels, other anomalies)

Acquired cardiac failure (bacterial endocarditis, valvular incompetence, valvular stenosis, cardiomyopathy, pericarditis, other causes)

Central nervous system disease (trauma, meningoencephalitis, encephalomalacia, abscess, louping ill, pseudorabies, other causes)

Esophageal obstruction, foreign body, laceration, rupture, megaesophagus

Clostridial diseases (Black's disease, enterotoxemia, tetanus, blackleg, bacillary hemoglobinuria, others)

Anthrax

Complications of fluid therapy (pulmonary edema)

Water deprivation (salt poisoning) (B)

Blood transfusion reaction

Anaphylaxis

Burn, thermal injury, electrocution

Systemic toxoplasmosis (C, O)

Tick paralysis (C, O)

Bladder rupture

Bee or wasp sting, snakebite

Photosensitization

5.5.3.1.2.4

UNCOMMON RESPIRATORY CAUSES

Actinobacillosis (wooden tongue)

Actinomycosis (lumpy jaw)

Diaphragmatic hernia

Pleural mesothelioma

Pneumocystis carinii pneumonia

Pulmonary aspergillosis

Pulmonary neoplasia

Pulmonary tuberculosis

Chlamydia psittaci pneumonia

Cyst (branchial, cervical, salivary, thyroglossal duct)

Bronchobiliary fistula

Contagious bovine pleuropneumonia (exotic) (B)

Endemic ethmoid carcinoma (exotic) (B)

Theileria annulata and *Theileria hirci* (exotic) (B)

Heartwater *(Cowdria ruminatum)* (exotic)

5.5.3.1.2.5

UNCOMMON NONRESPIRATORY CAUSES

Retrobulbar neoplasia (B)

Enzootic bovine leukosis (B)

Thymic lymphosarcoma or thymoma

Calf lymphosarcoma (B)

Adult multicentric lymphosarcoma (B)

Embryonal mediastinal cyst

Dwarfism (B)

Botulism

Vesicular stomatitis

High altitude (brisket) disease, cor pulmonale (B, C)

Procaine penicillin G reaction or intravascular administration

Liver disease (infectious, toxic, parasitic, other)

Border disease (hairy shaker) (C, O)

5.5.3.1.2.6

TOXIC CAUSES

Sodium fluoroacetate

Strychnine

Sulfur (B, O)

Propylene glycol (B)

Oxalate, ethylene glycol (B, O)

Urea or nonprotein nitrogen

Potassium (B)

Nitrates

Bromide (B, C)

Lead

Mercury (C)

Iron (B, C)

Selenium

Arsenic

Organophosphate or carbamate

Organochlorine or chlorinated hydrocarbon

Permethrin

Gossypol

Ergot *(Claviceps purpura)*

Phosphate fertilizer (B, O)

Vitamin D_3 (B)

Warfarin, dicumarol, diphacinone

Metaldehyde

Formaldehyde

Ammonia

Hydrogen sulfide

Monensin, salinomycin

Dinitrophenol (B, O)

Copper (acute oral toxicity)

Insect fogger pneumonitis (B)

Aflatoxicosis (C)

Levamisole (C, O)

Polychlorinated biphenyl (PCB) (B)

Xylazine-induced pulmonary edema (O)

Carbolic dips (O)

Cyanogenic plants (arrow grass, Johnson grass, common sorghum, Sudan grass, chokecherry, acacia, other plants)

Avocado *(Persia americana)*

Moldy sweet clover (*Melilotus* species)

Moldy sweet potato *(Ipomoea batatas)* (B)

Brassica species

Ryegrass (*Lolium* species) (B, O)

Larkspur (*Delphinium* species)

Japanese yew *(Taxus cuspidata)*

Hairy vetch *(Vicia villosa)* (B)

Whitehead *(Sphenosciadium capitellatum)* (B)

White snakeroot *(Eupatorium rugosum)* (B, O)

Chinese tallow *(Sapium sebiferum)* (B)

Purple mint *(Perilla frutescens)* (B)

Oleander *(Nerium oleander)*

Nightshade (*Solanum* species) (B)

Cocklebur (*Xanthium* species) (B, O)

Locoweeds (*Astragalus* species, *Oxytropis* species) (B, O)

Foxglove *(Digitalis purpurea)* (B)

Water hemlock (*Cicuta* species)

Milkweed (*Asclepias* species) (B, O)

Hepatotoxic plants (*Senecio* species, *Amsinckia* species, others containing pyrrolizidine alkaloid)

Fescue summer poisoning (B)

Rubberweed (*Hymenoxys* species)

Sneezeweed *(Helenium autumnale)*

False hellebore (*Veratrum* species) (B, O)

Rhododendron (*Andromeda* species) (B, O)

Algae

Lupines (*Lupinus* species) (B, O)

Prickly paddy melon *(Cucumis myriocarpus)*

B, Bovine; *C*, caprine; *O*, ovine.

Note: Respiratory distress is a sign associated with toxicity caused by a large number of plant species. Not all have been listed here.

5.5.3.2

PHYSICAL EXAMINATION

The physical examination should follow the same general approach as that described for cough. In particular, the following should be determined: rectal temperature, pulse rate, respiratory rate and character; regularity and pattern of breathing; presence of excessive intercostal or abdominal respiratory effort; synchrony and symmetry of chest excursion; presence of a “heave line”; presence of stridor at rest (the examiner listens at the nostrils); symmetry of airflow from each nostril; effect of occlusion of each nostril independently; odor from the nose or mouth (or both); presence and character of nasal discharge; swelling around the external nares, inside the nasal passages, or inside the false nostril; facial symmetry and swelling; ocular discharge; resonance or painful response on percussion of the maxillary and frontal sinuses; palpable abnormalities of the mandibles and hyoid apparatus; enlargement of submandibular, parotid, retropharyngeal, and other regional lymph nodes; enlargement of the parotid salivary glands or thyroid gland; swelling, pain, or palpable abnormalities in the retropharyngeal region; a palpable, left-sided pit on the dorsal surface of the larynx; accentuation of stridor, induction of a cough, or evidence of pain on application of pressure to the larynx and trachea; palpable swelling or flattening of the cervical trachea; masses at the thoracic inlet; and palpable turbulence in the extrathoracic airway.

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The mucous membranes should be examined carefully for cyanosis, pallor, cherry red color, hemorrhages, congestion, or injection. The capillary refill time should be determined, and the peripheral pulse rate, rhythm, and character should be assessed. Other signs of heart failure (e.g., jugular distention or pulsation and peripheral edema) and signs of dehydration (e.g., delayed jugular filling, dry mucous membranes, and altered skin turgor) should be noted. The larynx, trachea, and lungs should be carefully *auscultated* at rest and after the rate and depth of respiration have been increased, if it is safe to do so, by application of a rebreathing bag, by occlusion of the nostrils, or by exercising the animal, so that turbulent airflow and abnormal lung sounds may be detected. The heart should be auscultated to detect murmurs, cardiac dysrhythmias, muffling of heart sounds, or other abnormalities. The chest wall should be carefully *palpated* to detect rib fractures and other lesions; and both sides of the chest should be *percussed* to detect large mass lesions, lung consolidation, pleural

effusion, hyperinflation, pneumothorax, or a painful response, which may indicate pleuritis. A thorough oral examination is important, and in cattle this should include palpation of the base of the tongue, the oropharynx, and, if possible, the larynx (see Nasal Discharge, p. 50).

A general physical examination should be completed so that diseases in systems other than the cardiovascular and respiratory systems (e.g., respiratory distress in cattle secondary to ruminal bloat and respiratory distress secondary to central nervous system trauma or severe metabolic acidosis) can be detected. Attempts should also be made to identify conditions that may cause severe acid-base disturbances and hemoconcentration (e.g., diarrhea, renal disease), pain (e.g., laminitis or trauma), or hyperthermia (e.g., infectious conditions or heat stroke).

Further diagnostic evaluation of respiratory distress may include a complete blood count with fibrinogen concentration; blood gas analysis; serum biochemistry determinations; endoscopy of the upper and lower airways and esophagus; nasal or nasopharyngeal swabbing or scraping; virus identification, isolation, and serologic testing; bronchodilator response testing; tracheal aspiration; BAL; ultrasound examination of the chest and of suspected mass lesions that impinge on the upper airway; thoracocentesis; radiography of the nasal passages, paranasal sinuses, pharynx, guttural pouches, larynx, trachea, and chest; fecal examination for lungworms and other parasites; CT scanning of the upper airway; nuclear scintigraphy; pulmonary function testing; and biopsy of externally visible or palpable lesions or those identified by ultrasound, endoscopy, or radiography as described for the evaluation of cough and nasal discharge (see Cough, p. 42, and Nasal Discharge, p. 50).

5.5.3.3

COMPLETE BLOOD COUNT

A complete blood count, including fibrinogen and plasma protein concentrations, helps evaluate the role of hemoconcentration, anemia, or leukocytosis and hyperfibrinogenemia, which may accompany pneumonia and other inflammatory conditions.

5.5.3.4

ENDOSCOPIC EXAMINATION

Endoscopic examination of the upper and lower airways using fiberoptic or video endoscopes is particularly helpful in evaluating patients suspected of having obstructive disease[75] (see Cough, p. 42; Nasal Discharge, p. 50; and Stridor, p. 71). Endoscopic examination of the esophagus is indicated in patients with a history of bloat, dysphagia, or return of ingesta through the nose in addition to respiratory distress (see Nasal Discharge, p. 50, and Stridor, p. 71).

5.5.3.5

BLOOD GAS ANALYSIS

Blood gas analysis and acid-base determinations should be performed on arterial blood to determine O_2 and CO_2 tensions so that the contribution of hypoxemia or acidosis to the signs of respiratory distress can be ascertained. In foals and calves, arterial samples usually are obtained from the great metatarsal artery or the brachial artery as it crosses the medial aspect of the foreleg.[76] The auricular artery is also convenient in calves. The femoral artery can be used in neonates but is less convenient because it has a tendency to roll. The facial artery can be used in adult horses, and the auricular or coccygeal artery can be used in mature ruminants.[77] During the sampling process the patient should be quiet and not struggling, which can decrease the $PaCO_2$.[78] Local subcutaneous infiltration of 2% lidocaine without epinephrine over the artery being sampled minimizes

needless struggling and facilitates sample collection. A heparinized syringe and a 22- to 26-gauge needle can be used. Any air bubbles should be removed after sample collection and the needle properly sealed. If the sample is kept on ice, the pH will remain unchanged for 3½ hours and the blood gases for 6 hours.[79] The animal's temperature should be recorded at the time of sample collection so that it can be used in the calculation of actual blood gas concentrations.

The normal Pa_{O_2} for the horse is 83.6 ± 1.7mm Hg, and the normal Pa_{CO_2} is 42.2 ± 0.8mm Hg.[57] Hypoxemia is defined as a Pa_{O_2} below 80mm Hg.[80] Cyanosis is usually not evident until the Pa_{O_2} is much lower than this (usually below 40mm Hg).[80] Hypercarbia, or hypercapnia, is a condition of increased Pa_{CO_2} (above 44mm Hg).[80] Because CO_2 diffuses readily, considerable ventilatory dysfunction can occur before the Pa_{CO_2} rises; therefore severe hypoxemia can occur with a normal Pa_{CO_2}. An elevated Pa_{CO_2} generally indicates that hypoventilation or a severe pulmonic pathologic condition is present. Because venous blood samples reflect tissue metabolism, they are not considered adequate for evaluating pulmonary function. However, a partial pressure of carbon dioxide in venous blood (Pv_{CO_2}) above 60mm Hg usually reflects arterial hypercapnia, and a partial pressure of oxygen in venous blood (Pv_{O_2}) below 20mm Hg usually indicates arterial hypoxemia.[79]

Venous admixture is the term used to denote the ways that blood can pass from the right side to the left side of the circulation without being properly oxygenated and represents the efficiency with which the lung oxygenates blood. The magnitude of venous admixture (efficiency of oxygenation) can be assessed by calculating the Pa_{O_2}/Fi_{O_2} ratio or the alveolar-arterial P_{O_2} gradient. The Pa_{O_2}/Fi_{O_2} ratio is normally 500. Pa_{O_2}/Fi_{O_2} ratios between 300 and 400 reflect significant lung injury, values below 300 reflect profoundly inefficient lung function such as occurs with acute lung injury, and values below 200 reflect severe life-threatening lung disease typical of acute respiratory distress syndrome (ARDS). The alveolar-arterial (A-a) P_{O_2} gradient difference is the difference between calculated alveolar P_{O_2} and the measured arterial P_{O_2}. Alveolar P_{O_2} = Inspired P_{O_2} − Pa_{CO_2} (1.1), where inspired P_{O_2} = barometric pressure × 21% and 1.1 = 1/RQ, where RQ is the respiratory quotient and has an assumed value of 0.9. The A-a P_{O_2} difference is typically about 10mm Hg in a normal horse breathing 21% oxygen (room air) at sea level and about 100mm Hg when breathing 100% oxygen. The “120 rule” is a simplified version of the alveolar gas equation that can be applied to a patient breathing 21% oxygen at near sea level. The measured Pa_{O_2} and Pa_{CO_2} should add up to 140 ± 10. If the sum is less than 120, the patient has venous admixture; and the lower the value, the worse the admixture.

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5.5.3.6

INSUFFLATION OF 100% OXYGEN

Insufflation of 100% oxygen causes a significant increase in Pa_{O_2} if hypoxemia is caused by hypoventilation or ventilation-perfusion mismatch, whereas little or no improvement in Pa_{O_2} occurs if hypoxemia is caused by anatomic or physiologic right-to-left shunting.[68] Therefore measuring Pa_{O_2} 5 minutes after insufflation of 100% oxygen can help in determining the pathophysiologic processes contributing to arterial hypoxemia. In full-term neonates and adults the Pa_{O_2} should exceed 200mm Hg after 5 minutes of oxygen administration.[78] Continued cyanosis or inability to raise the Pa_{O_2} above 100mm Hg is highly suggestive of a right-to-left shunt.

5.5.3.7 DETECTION OF ABNORMAL HEMOGLOBIN

Blood samples should be evaluated for abnormal hemoglobin (e.g., methemoglobin) and also if exposure to nitrates or similar toxins is suspected (see Cyanosis, p. 68).

5.5.3.8 RADIOGRAPHIC EXAMINATION

Radiographic examination of the nasal passages, pharynx, larynx, and trachea permits detection and evaluation of obstructive lesions in the upper airway, especially if tachypnea is accompanied by inspiratory stridor, asymmetric nasal airflow, or other evidence of upper airway obstruction.

Radiographic examination of the trachea and thorax should include end-inspiratory phase radiographs to facilitate identification of pulmonary lesions and disorders such as dynamic collapse of the trachea that are visible only on inspiratory-phase radiographs. Chest radiographs help detect evidence of pneumonia, pleural effusion, pneumothorax, cardiomegaly, and mediastinal lesions. The cardiac silhouette and the pattern and caliber of the aorta, vena cava, pulmonary artery, pulmonary veins, and other vessels should also be evaluated for evidence of cardiac failure and pulmonary vascular disease. *Contrast angiography* and other diagnostic procedures, such as *echocardiography, electrocardiography*, and *hemodynamic (pressure and flow) studies*, may be indicated in patients with respiratory distress that has occurred secondary to cardiovascular disease.

5.5.3.9 ULTRASOUND EXAMINATION

Ultrasound examination of the thorax is performed to detect pleural inflammation and effusion, pulmonary consolidation, pulmonary abscessation, and cardiac anomalies if the clinical examination suggests that pulmonary, pleural, or cardiac disease is the cause of the signs of respiratory distress.

5.6 CYANOSIS

5.6.1 Definition

Cyanosis is the bluish discoloration of skin, conjunctivae, and visible mucous membranes that results from an increase in the absolute amount of reduced hemoglobin in the blood.[81]

5.6.2 Pathophysiology

Oxygen is carried in blood in two forms, dissolved and in combination with hemoglobin (Hb). The amount of dissolved oxygen present in arterial blood is relatively small and is proportional to the Pa_{O_2}. Oxygen transport to tissues is facilitated by the ability of hemoglobin in erythrocytes to combine in a reversible manner with oxygen. When erythrocytes pass through the pulmonary circulation, oxygen binds to hemoglobin, forming oxyhemoglobin (HbO_2). As oxyhemoglobin passes through systemic capillaries, oxygen diffuses into tissues, and hemoglobin is once again formed.

The Bohr effect describes the ability of hemoglobin to bind to a number of different ligands (CO_2, H^+, and 2,3-diphosphoglycerate [2,3-DPG]), which results in modification of hemoglobin's affinity for oxygen. When tissue

pH decreases, hemoglobin acts as a buffer and binds excess H^+, which decreases its affinity for oxygen. When the CO_2 concentration increases, some CO_2 is converted to bicarbonate and the remainder is bound to hemoglobin to form carbaminohemoglobin; this also decreases the affinity of hemoglobin for oxygen. Therefore the net effect of a decreased blood pH and increased blood CO_2 concentration is unloading of oxygen to the tissues. Conversely, as the CO_2 concentration in the pulmonary capillaries decreases and blood pH rises, the affinity of hemoglobin for oxygen increases; thus the net effect of elevated blood pH in pulmonary capillaries is increased uptake of oxygen by hemoglobin.

The affinity of hemoglobin for oxygen is also influenced by the concentration of 2,3-DPG, a metabolic intermediate of the Rappaport-Luebering shunt involved in erythrocyte glycolysis. An increase in the 2,3-DPG concentration may occur in association with chronic hypoxemia (high altitude, chronic lung disease), anemia, chronic alkalosis, phosphate retention, and red cell pyruvate kinase deficiency. When the 2,3-DPG concentration is increased, the affinity of hemoglobin for oxygen is decreased, resulting in improved unloading of oxygen to peripheral tissues. Conversely, a decreased 2,3-DPG level results in an increased affinity of hemoglobin for oxygen. A decrease in the 2,3-DPG concentration may occur in stored blood, in association with chronic acidosis, and with hypophosphatemia.

Cyanosis develops when the oxygen saturation of hemoglobin is below 80%. With a normal oxygen-hemoglobin dissociation curve, the Pa_{O_2} usually is below 40mm Hg before cyanosis is noted in the patient.[82] The hemoglobin concentration of blood must be near normal for cyanosis to be clinically evident[83]; therefore patients with severe anemia and concomitant marked arterial oxygen desaturation may not show cyanosis. In contrast, patients with marked polycythemia may be cyanotic at a higher arterial oxygen saturation than patients with normal hematocrit values.

5.6.3 Classification

Cyanosis can be classified as either *peripheral* or *central*.

5.6.3.1 PERIPHERAL CYANOSIS

Peripheral cyanosis is caused by slowing of blood flow to an area, resulting in abnormally increased extraction of oxygen from normally saturated arterial blood. Decreased blood flow through the peripheral capillary bed may be caused by vasoconstriction of superficial vessels, obstruction of arteries or veins, or low cardiac output. Peripheral cyanosis is observed in the extremities, nose, and ears and usually is not associated with cyanosis of mucous membranes. Peripheral cyanosis is rarely recognized in large domestic animals because of their skin pigmentation and hair cover.

5.6.3.2 CENTRAL CYANOSIS

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Central cyanosis results from either inadequate oxygenation of arterial blood or from the presence of an abnormal hemoglobin derivative and is characterized by cyanosis of mucous membranes (Table 5-1). Causes of inadequate oxygenation of arterial blood are respiratory diseases or congenital cardiac anomalies that cause right-to-left shunting (Boxes 5-16 and 5-17). Acquired abnormalities of hemoglobin function can be induced by a number of chemicals. Exposure to these chemicals results in the formation of methemoglobin or sulfhemoglobin, neither of which is capable of binding oxygen. Nitrites and nitrates are powerful reducing agents that produce methemoglobinemia by directly oxidizing hemoglobin to methemoglobin. Nitrate

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poisoning is most commonly associated with the incorporation of nitrate-accumulating plants (e.g., pigweed *[Amaranthus retroflexus]*, lamb's-quarters *[Chenopodium album]*, and mintweed *[Salvia reflexa]*) in livestock forage. Nitrate intoxication usually is seen only in ruminants because rumen microorganisms reduce nitrate to the more toxic nitrite ion. Congenital defects in hemoglobin function have been reported in humans and may occur in large domestic animals. Examples of such defects are nicotinamide adenine dinucleotide methemoglobin reductase deficiency and familial methemoglobinemia.

Table 5-1 Pathophysiologic Classification of Central Cyanosis and Examples of Associated Conditions

Classification	Associated Condition
Decreased arterial oxygen saturation	Respiratory disease Ventilation-perfusion mismatch Alveolar hypoventilation Impaired oxygen diffusion Pulmonary arteriovenous shunting Cardiac disease Cardiac anomalies that cause right-to-left shunting (e.g., tetralogy of Fallot)
Abnormal hemoglobin derivative	Methemoglobinemia Sulfhemoglobinemia

5.6.4

Conditions That Predispose to Hypoxemia and Central Cyanosis

The remainder of this section is confined to the discussion of respiratory conditions and cardiovascular anomalies that predispose to hypoxemia and central cyanosis. Impaired pulmonary function may cause hypoxemia and, in some circumstances, cyanosis. Mechanisms by which hypoxemia of pulmonary origin can arise include alveolar hypoventilation, reduced gas transfer or diffusion across the blood-gas barrier, ventilation-perfusion mismatch, pulmonary arteriovenous shunt, or a combination of these factors.[81,83] An additional cause of hypoxemia is the decrease in the partial pressure of alveolar oxygen that occurs at high altitudes.

5.6.4.1

ALVEOLAR HYPOVENTILATION

Alveolar hypoventilation is defined as a reduced volume of inspired air reaching the alveoli per unit time. Alveolar hypoventilation is always associated with an increased $PaCO_2$. Conditions associated with alveolar hypoventilation are drug-induced respiratory depression (morphine, barbiturates), brainstem disease (encephalitis, trauma, hemorrhage, neoplasia), and transection of the cervical spinal cord. All these conditions prevent proper generation and transmission of signals from the respiratory center to respiratory muscles. Other possible causes of alveolar hypoventilation are abnormal respiratory muscle function (diaphragmatic hernia, botulism), thoracic cage abnormalities (rib fracture), increased airway resistance (e.g., stenotic nares, laryngeal stricture or paresis, foreign body obstruction, bronchitis, bronchiectasis), and pleural space disease (inflammatory or neoplastic effusions, pneumothorax, hydrothorax, chylothorax, pyothorax, hemothorax).

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5.6.4.1.1

Box 5-16 Causes of Central Cyanosis in Horses

5.6.4.1.1.1

COMMON CAUSES

Bacterial pneumonia, pleuritis, pulmonary abscessation (*Rhodococcus equi, Streptococcus* species, other bacteria)

Recurrent airway obstruction (RAO or COPD)

Aspiration pneumonia

Viral pneumonia (equine influenza, adenovirus, other viruses)

Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)

Acute bronchointerstitial pneumonia

Prematurity, dysmaturity, immaturity (foals)

Ventricular septal defect with pulmonary hypertension

Tetralogy of Fallot

Toxic methemoglobinemia

Anaphylaxis

Shock (hypovolemic, cardiac, septic)

5.6.4.1.1.2

LESS COMMON CAUSES

Stenotic nares or choanal atresia

Neoplasia (nose, paranasal sinuses)

Nasal granuloma

Nasopharyngeal cicatrix

Tracheal stenosis, collapse, stricture

Tracheal rupture or perforation

Diaphragmatic hernia

Pneumothorax

Pulmonary edema

Smoke inhalation pneumonia

Pneumoconiosis interstitial pneumonia

Atrial septal defect with pulmonary hypertension

5.6.4.1.1.3

UNCOMMON CAUSES

Pulmonary lobar hypertrophy (foals)

Embryonal mediastinal cyst

Pulmonary tuberculosis, nocardiosis

Pneumocystis carinii pneumonia

Air embolism

Pulmonary neoplasia

Transposition of great vessels

Tricuspid atresia

Aortic, pulmonary artery rupture

Interruption of aortic arch

Common ventricle with separate pulmonary outflow chamber

Multiple cardiac anomalies

Methemoglobin reductase deficiency

Lactation tetany

Clostridial diseases

Malignant hyperthermia

5.6.4.1.1.4

TOXIC CAUSES

Sulfur, hydrogen sulfide

α-Naphthyl thiourea (ANTU)

Chlorinated hydrocarbon

Organophosphate, carbamate

Red maple *(Acer rubrum)*[*]

Redroot pigweed *(Amaranthus retroflexus)*[*]

Sudan grass *(Sorghum vulgare var sudanensis)*[*]

Mintweed *(Salvia reflexa)*[*]

Lamb's-quarters *(Chenopodium album)*[*]

Variegated thistle *(Silybum marianum)*[*]

Winged thistle *(Carduus tenuiflorus)*[*]

* Nitrate accumulator, which causes methemoglobinemia.

5.6.4.1.2

Box 5-17 Causes of Central Cyanosis in Ruminants

5.6.4.1.2.1

COMMON CAUSES

Bacterial pneumonia, pulmonary abscessation (*Mannheimia hemolytica, Arcanobacterium [Actinomyces] pyogenes, Pasteurella multocida, Corynebacterium pseudotuberculosis* [O, C], other bacteria)

Viral pneumonia (respiratory syncytial virus [B], ovine progressive pneumonia [O], caprine arthritis-encephalomyelitis [C], other viruses)

Parasitic pneumonia (*Dictyocaulus viviparus* [B], *Dictyocaulus filaria* [O, C])

Aspiration pneumonia

Acute bovine pulmonary edema and emphysema (B)

Pulmonary edema

Ventricular septal defect with pulmonary hypertension

Tetralogy of Fallot

Toxic methemoglobinemia

Anaphylaxis

Shock (hypovolemic, cardiac, septic)

Rumen bloat

5.6.4.1.2.2

LESS COMMON CAUSES

Obstruction of nasal passages or paranasal sinuses (neoplasm, granuloma, abscess, other)

Laryngeal abscess

Tracheal stenosis, collapse, stricture

Tracheal rupture, perforation

Diaphragmatic hernia

Prematurity, dysmaturity, immaturity

Inhalation pneumonia (smoke)

Pneumothorax

Hemothorax

Pulmonary contusion

Ventricular septal defect with pulmonic stenosis

Postparturient hemoglobinuria

Clostridial diseases (e.g., malignant edema, blackleg, tetanus)

Bluetongue (O)

Obstructive urolithiasis, ruptured urethra

5.6.4.1.2.3

UNCOMMON CAUSES

Pleural mesothelioma (B)

Water inhalation (drowning)

Pulmonary adenomatosis (O)

Transposition of great vessels

Double-outlet right ventricle

Common ventricle with separate pulmonary outflow chamber

Acute anthrax

White liver disease (exotic) (O)

Sweating sickness (exotic) (B, O)

5.6.4.1.2.4

TOXIC CAUSES

Strychnine

Arsenic

Metaldehyde

Hydrogen sulfide

Organochlorine, chlorinated hydrocarbon

Organophosphate, carbamate

Acute selenium toxicosis

Nitrate, nitrite

Perennial broomweed *(Gutierrezia microcephala)*

Oleander *(Nerium oleander)*

Whitehead *(Sphenosciadium capitellatum)*

Milkweed (*Asclepias* species) (O)

Rhododendron (*Andromeda* species)

Fireweed *(Kochia scoparia)*

Canary grass (*Phalaris* species)

Kikuyu poisoning (exotic) (B, O)

Albizia poisoning (exotic) (B, O)

Euphorbia, *Sarcostemma* poisoning (exotic) (B, O)

Acacia poisoning (exotic) (B, O)

Wild onion *(Allium validum)** [O]

Variegated thistle *(Silybum marianum)**

Redroot pigweed *(Amaranthus retroflexus)*

Sudan grass *(Sorghum vulgare var sudanensis)**

Winged thistle *(Carduus tenuiflorus)**

Mintweed *(Salvia reflexa)**

Lamb's-quarters *(Chenopodium album)**

Many pasture grasses fed during optimum growth conditions*

Locoweeds (*Astragalus* species, *Oxytropis* species)*

B, Bovine; *C*, caprine; *O*, Ovine.

* Netrate accumulator, which causes methemoglobinemia.

5.6.4.2

IMPAIRED DIFFUSION

Impaired diffusion, a second cause of hypoxemia, results from an increase in the blood-gas barrier. Equilibrium between alveolar oxygen and pulmonary blood oxygen is not reached because of the increased barriers through which oxygen must pass to reach hemoglobin. Because carbon dioxide diffuses more readily than oxygen, the $PaCO_2$ usually is not increased in conditions that cause impaired diffusion. In fact, the $PaCO_2$ may actually be reduced because of hyperventilation stimulated by hypoxemia. Conditions that may result in impaired diffusion are pneumonia, pulmonary edema, atelectasis, pulmonary contusions, and pulmonary neoplasms.

5.6.4.3 VENTILATION-PERFUSION MISMATCH

Ventilation-perfusion mismatch occurs eventually in all generalized pulmonary diseases and is the predominant mechanism by which hypoxemia develops in respiratory conditions. Overall gas exchange is impaired by uneven ventilation and blood flow. Lung areas that are overperfused in relation to ventilation (low ventilation/perfusion ratio) contribute disproportionate amounts of blood with a low Pa_{O_2} to the systemic circulation. Examples of respiratory diseases that can result in a low ventilation/perfusion ratio include bronchitis, bronchoconstriction, airway closure, pulmonary atelectasis or consolidation, and local restriction of lung movement. In the case of pulmonary embolization or decreased pulmonary arterial pressure, ventilation may exceed perfusion (high ventilation/perfusion ratio) and result in pathologic dead space. Pulmonary mechanisms can partly compensate for ventilation-perfusion inequalities. Alveolar hypoxia may lead to reflex pulmonary arterial constriction, which redirects blood flow to alveoli that are adequately ventilated. Airway hypocapnia can stimulate bronchoconstriction, resulting in redirection of airflow to better-perfused alveoli.

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5.6.4.4 SHUNTING

Shunting is defined as any mechanism by which blood that has not passed through ventilated areas of the lung is added to arteries of the systemic circulation. The term *venous admixture* is used to describe venous blood that passes through the lungs without being properly oxygenated. Animals with venous admixture often hyperventilate and thus have normocapnia or hypocapnia in association with hypoxemia. The most common cause of shunting is congenital heart disease, which allows unoxygenated blood from the right heart to pass directly into the left heart without passing through the pulmonary circulation. Intrapulmonary anatomic shunts can result from pulmonary artery to pulmonary venous fistulas or severe lung lobe consolidation, in which a large part of the lung is ventilated but not perfused. Cyanosis or hypoxemia unresponsive to oxygen therapy suggests the presence of such congenital cardiac anomalies or intrapulmonary shunts.[84] Examples of the more common cyanotic congenital cardiac defects are tetralogy of Fallot, truncus arteriosus, transposition of the great arteries, tricuspid atresia, and hypoplastic left heart syndrome.[82,84] Aside from congenital defects, reversion to fetal circulation should be considered in any critically ill neonatal animal with hypoxemia that is unresponsive to oxygen insufflation.[84]

5.6.5 Approach to Diagnosis of Cyanosis

5.6.5.1 HISTORY

The history should include questions about the duration of the cyanosis (e.g., cyanosis that has been present since birth or an early age may indicate congenital heart disease with right-to-left shunting); possible exposure to toxic plants or chemicals that may result in production of abnormal types of hemoglobin; evidence of an abnormal respiratory pattern (respiratory distress, inspiratory stridor, cough); and signs of episodic weakness or syncope that may be consistent with congenital cardiac anomalies or severe upper airway obstruction (e.g., tracheal collapse or severe laryngeal edema associated with necrotic laryngitis in calves).

5.6.5.2

PHYSICAL EXAMINATION

The physical examination should include *inspection* to detect abnormalities in the respiratory pattern (e.g., tachypnea, respiratory distress, or stridor). Careful *auscultation* of the larynx, trachea, and lungs is also imperative. A rebreathing bag (8-L capacity for adult horses and cattle, 1- to 2-L capacity for calves, foals, and small ruminants) causes a temporary buildup of CO_2, stimulates the respiratory center, and prompts deep breaths when the animal is again allowed to inspire room air. Loud breath sounds, pulmonary crackles and wheezes, or pleural friction rubs may suggest that cyanosis is associated with a pathologic respiratory condition. Loud cardiac murmurs accompanied by precordial thrills point to congenital heart disease as the cause of cyanosis.

Palpation and *percussion* of the chest are also important examination procedures in an animal with cyanosis. Chest palpation may reveal pleural friction rubs or the pain and crepitus associated with rib fractures. Increased resonance on percussion may indicate pneumothorax, whereas decreased resonance suggests pulmonary congestion or consolidation, pleural effusion, or a space-occupying lesion in the thorax.

5.6.5.3

ENDOSCOPIC EXAMINATION

An endoscopic examination should be performed if upper airway obstruction or malformation is suspected (see Cough, p. 42; Nasal Discharge, p. 50; and Respiratory Distress, p. 60).

5.6.5.4

RADIOGRAPHIC EXAMINATION

Radiographs of the upper respiratory tract and thorax can be used to further characterize a pathologic respiratory condition. Abnormalities that may be detected include space-occupying lesions in the oropharynx, nasopharynx, or larynx; tracheal compression or collapse; enlargement or distortion of the cardiac silhouette; pulmonary consolidation; pneumothorax; pleural effusion; and pulmonary abscessation.

5.6.5.5

ULTRASOUND EXAMINATION

Ultrasound examination of the chest and heart is indicated to characterize cardiac anomalies and to detect the presence and determine the extent of pleural effusion, pulmonary consolidation, and pulmonary abscessation.

5.6.5.6

ARTERIAL BLOOD GAS ANALYSIS

Arterial blood gas analysis is indicated to determine O_2 and CO_2 tension (see Respiratory Distress, p. 60).

5.6.5.7

COMPLETE BLOOD COUNT

A complete blood count should be performed to determine if polycythemia or inflammatory leukogram is present. Polycythemia may develop secondary to chronic hypoxemia associated with long-standing pulmonary disease or right-to-left shunting. An inflammatory leukogram would be consistent with a diagnosis of bacterial or aspiration pneumonia or other inflammatory respiratory condition.

5.6.5.8 HEPARINIZED BLOOD

A sample of heparinized blood should be shaken gently in the air for 15 minutes. Reduced hemoglobin (cardiovascular or respiratory disease) turns red on exposure to air, whereas methemoglobin remains chocolate brown after shaking.

5.6.5.9 SPECTROSCOPIC EXAMINATION

A spectroscopic examination should be performed to determine if methemoglobin is present. Methemoglobin is stable in refrigerated heparinized blood for only a few hours. To preserve methemoglobin, one part of blood can be mixed with 20 parts of phosphate buffer (pH 6.6) or diluted 1:20 in distilled water. These diluted samples can be refrigerated or frozen until they are analyzed.

5.7 ABNORMAL RESPIRATORY NOISE (STRIDOR)

5.7.1 Definition

Stridor is an abnormal, intense respiratory sound (wheeze) that is audible without the use of a stethoscope. The sound usually is generated in the upper airway and is most often heard during inspiration.

5.7.2 Pathophysiology

The extrathoracic airway of the horse consists of segments that are relatively rigid (e.g., the nasal fossa and extrathoracic trachea) and others (e.g., the nostrils, soft palate, and larynx) that not only are elastic but also have valvelike actions that are further capable of modifying the cross-sectional area and therefore resistance to airflow.[85,86] Pressures in the extrathoracic airways are subatmospheric during inspiration,[85–87] which causes the less rigidly supported parts of the upper airway to narrow (dynamic narrowing or collapse) during inspiration.[85–90] A major function of the upper airway muscles and other supporting structures is to prevent this dynamic collapse during periods of high inspiratory gas flow.[85] Disease in these structures or a more rostral obstructing lesion that causes a greater negative pressure during inspiration may make them incapable of resisting axial displacement.[85,87] The increased resistance to flow induced by static or dynamic obstructions increases the driving pressure and therefore the work needed to move a given volume of air.[86]

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Approximately 80% of the total airway resistance to gas flow at rest and during exercise is located in the upper airway rostral to the thoracic inlet.[87] Nasal resistance, most of which is caused by resistance just within the external nares, comprises more than 50% of the total upper airway resistance in the horse.[88,89] In most species, including ruminants, this resistance can be bypassed by mouth breathing to accommodate the high airflow rates that accompany strenuous exercise. The horse, in contrast, is limited to nasal breathing even during exercise,[87–89,91] because the larynx is firmly maintained in an intranarial position by the tight seal formed around it by the muscular palatopharyngeal ring (intrapharyngeal osteum) except during swallowing.[91,92] Therefore mechanisms other than mouth breathing are needed to reduce the energy cost of breathing in the horse.[85,88,91] These mechanisms include dilation of the distensible external nares by actively pulling the alar folds laterally,

vasoconstriction in the erectile nasal vascular tissues to reduce congestion in the nasal mucosa, straightening of the respiratory tract, and dilation of the larynx by abduction of the vocal folds.[85–88,90,91,93,94]

The horse is capable of generating very high respiratory rates during fast exercise. This is accomplished at the canter and gallop, but not at the trot, by locking respiration to locomotion so that the horse takes one breath for each stride.[92,95–97] Exhalation occurs each time the lead forelimb strikes the ground.[91,92,95] The horse can swallow during fast galloping exercise; the entire process is completed in exactly a two-stride sequence.[92,98]

At all levels of the respiratory tract, respiratory sounds are thought to result from vibrations in tissue and sudden changes in the pressure of gas moving in the airway lumen.[87,92] Airflow in the normal respiratory tract at rest occurs in a laminar fashion (i.e., the air closest to the wall of the airway is almost stationary, whereas succeeding layers toward the center of the lumen move progressively more rapidly).[92] Respiration in normal horses and in ruminants at rest does not generate easily audible sounds.

High rates of gas flow and airway narrowing increase both the tendency for dynamic collapse and the degree of turbulence and genesis of sounds. Very high peak flow rates of 125ml/sec/kg have been reported in galloping horses.[97] During exercise significant sound frequencies are generated and can be detected using sound spectrography or radiostethoscopes, although most of these sounds are of frequencies and amplitudes not detectable by the human ear.[99,100] Deformities in the wall and masses in the lumen of the airway cause airway narrowing and further disturbances in laminar flow, resulting in more severe turbulence and sudden changes in the pressure of moving gas, which may generate audible sounds.[92] High airflow rates are necessary to induce most audible stridors; therefore examination of the horse at exercise is an essential part of the physical examination.[91,92]

Stridor is best heard during inspiration in most cases because the usual source of origin, the upper airway, is subject to dynamic narrowing during the inspiratory phase of the respiratory cycle.[85,88,89] In particular, nonfixed obstructions, such as the paretic vocal folds of horses with idiopathic laryngeal hemiplegia (ILH), cause obstruction to airflow and turbulence only when dynamically drawn into the airway by the high inspiratory airflow rates that accompany fast exercise. Other obstructions such as arytenoid chondritis are fixed and obstruct airflow during both inspiration and expiration, which frequently results in audible stridor during both phases of respiration.

The pharynx is the site of greatest airway angulation as a result of flexion of the atlantooccipital joint. At rest the horse's head is usually held at about 50 degrees to the horizontal plane.[92] At the gallop the horse extends its head and neck and thus straightens the pharyngeal airway.[92] This maneuver also stretches and straightens the trachea, making it less compliant and less subject to dynamic narrowing during inspiration.[88] When ridden at a collected canter, the horse is forced to flex its poll so that its face is nearly vertical, thereby increasing the angulation of the pharyngeal airway and the obstruction to gas flow at this point.[92] Therefore abnormal respiratory sounds originating in the pharyngeal region are often more easily heard when the horse is ridden at a collected canter than when it is exercised at a full, extended gallop.[91,92]

Because food animals are not normally expected to perform fast exercise, signs of stridor are usually present at rest when the animals are presented to veterinarians for examination. Stridor in resting animals usually indicates moderate to severe upper airway obstruction of a fixed nature. In ruminants the epiglottis is relatively short and blunt, and the palatopharyngeal ring allows the laryngopalatal dislocation necessary for mouth breathing. In conditions that give rise to respiratory distress and mouth breathing, the turbulence produced is often sufficient to

induce abnormal (grunting) expiratory sounds, which may be classified as expiratory stridor. The external nares of cattle are much less compliant than those of sheep, goats, and horses, which prevents dynamic collapse during inspiration; thus conditions such as paresis of the nares that cause stridor in sheep, goats, and horses do not cause stridor in cattle (Boxes 5-18 and 5-19).

5.7.3 ## Approach to Diagnosis of Stridor

5.7.3.1 ### HISTORY

The procedure for taking a history should follow that used in the evaluation of cough and nasal discharge (see Cough, p. 42, and Nasal Discharge, p. 50). The history should also include the duration of ownership; time of onset of the clinical signs of stridor; progression of clinical signs; presence or absence of the noise at rest; relation of noise to fitness; relation of noise to speed, duration, and direction of work; relation of noise to head position during work; association of noise with poor performance or exercise intolerance; and other signs of respiratory tract, oropharyngeal, or neurologic disease (e.g., nasal discharge, cough, dysphagia, or retropharyngeal swelling).

5.7.3.2 ### PHYSICAL EXAMINATION

A physical examination of the entire respiratory tract at rest should be performed as described for cough (see p. 42) and respiratory distress (see p. 60). In addition, the presence or absence of stridor at rest should be ascertained by listening at the nostrils, and digital pressure should be applied to the retropharyngeal region and to the larynx during palpation of these areas to evaluate whether stridor or pain (or both) can be easily induced or exacerbated. The dorsal surface of the larynx should be palpated with the fingertips with the horse relaxed and its head and neck in an extended position. This permits comparison of the prominence of the muscular process of the arytenoid cartilages and the thickness of the cricoarytenoideus dorsalis (CAD) muscle, both of which are affected in horses with atrophy of the CAD in association with ILH. Air turbulence, flattening, swelling, and pain should be assessed during palpation of the extrathoracic airway. The larynx, trachea, and lungs should be carefully *auscultated*, and the chest should be *percussed*. A thorough oral examination should be completed, particularly in ruminants; in cattle this should include palpation of the base of the tongue, the oropharynx, and, if possible, the larynx through the oral cavity.

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5.7.3.2.1 #### Box 5-18 Causes of Stridor in Horses

5.7.3.2.1.1 ##### COMMON CAUSES

Idiopathic laryngeal hemiplegia (ILH, roaring)

Dorsal displacement of the soft palate (laryngopalatal dislocation)

Epiglottic entrapment

Retropharyngeal abscess

Strangles (*Streptococcus equi* infection)

Guttural pouch empyema

Chronic pharyngeal lymphoid hyperplasia

Arytenoid chondritis

Guttural pouch mycosis

Laxity of the alar cartilage

5.7.3.2.1.2

LESS COMMON CAUSES

Arytenoid chondroma, chondropathy

Pharyngeal paresis

Botulism, shaker foal

Dynamic collapse of the pharynx

Subepiglottal, pharyngeal cyst

Subepiglottal abscess

Epiglottal retroversion

Guttural pouch tympany

Guttural pouch neoplasia

Rostral displacement of the palatopharyngeal arch

Nasal fungal infection (e.g., aspergillosis, rhinophycomycosis)

Nasal polyp

Nasal foreign body

Nasal trauma

Nasal tumor

Nasopharyngeal cicatrix

Progressive ethmoidal hematoma

Sinusitis (sinus empyema)

Sinus cyst

Sinus tumor

Atheroma

Laryngeal trauma

Tracheal collapse (scabbard trachea)

Tracheal stricture, stenosis

Tracheal chondroma

Tracheal rupture, perforation

Stenotic nares

Laryngeal edema

Purpura hemorrhagica

Anaphylaxis or acute drug reaction

Chronic lead poisoning

Choanal (posterior nares) atresia, hypoplasia (foals)

Fracture of laryngeal cartilages

Laryngeal granuloma, scar tissue

Equine influenza

Exercise-induced pulmonary hemorrhage (EIPH)

Jugular thrombosis

Hyperkalemic periodic paralysis (HYPP)

5.7.3.2.1.3

UNCOMMON CAUSES

Amyloidosis (cutaneous, nasal)

Lymphosarcoma, lymphoma

Bee or wasp sting

Snakebite

Thyroid adenoma, adenocarcinoma

Vesicular stomatitis

Retrobulbar neoplasia

Dystrophic myodegeneration (white muscle disease)

Neoplasia (oral, mandibular, maxillary, laryngeal, pharyngeal, tracheal)

Coccidioidomycosis

Inhalation pneumonia, smoke inhalation

Burns (thermal, chemical)

Congestive cardiac failure

Cutaneous habronemiasis

Unilateral ventral displacement of the roof of the nasopharynx

Epiglottiditis

Hyoid bone injuries

Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma, cryptococcal rhinitis, equine nasal granuloma

Goiter

Hypertrophic ossification of the laryngeal cartilages

Abnormalities of the nasal septum

Intramural esophageal cyst

Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)

Hyperparathyroidism

Phycomycosis, pythiosis

Anaerobic abscesses (e.g., *Clostridium perfringens*)

Besnoitiosis, globidiosis (exotic)

Glanders (exotic)

5.7.3.2.1.4

TOXIC CAUSES

Organophosphate-induced laryngeal paralysis

Lead-induced laryngeal paresis

Reserpine

5.7.3.3

FIELD EXERCISE TESTING[92]

In performance horses most examinations are carried out because the horse makes a noise only when worked, because of exercise intolerance or poor performance, or as part of a prepurchase examination. Unless a high-speed treadmill is available, the exercise testing should be completed under saddle with a competent rider, preferably with an intensity of work that matches the horse's normal activity.[87,91] It is less satisfactory but often necessary to work the horse on a lunge line, in which case it should be lunged in both directions.[91]

The horse should be worked in a circle about 30 yards in diameter so that it passes close to the observer on each circuit.[92] The observer should first identify the expiratory sound by its association with locomotion and then try to fit abnormal sounds into this base rhythm. At fast speed respiration is very rapid; thus the observer should not stand too far away from the horse because the slow speed at which sound is transmitted confuses interpretation of whether the sound is inspiratory or expiratory.[92,98] In cold weather the visibility of exhaled breath aids interpretation. It is important to ride the horse in both directions because an abnormal sound is frequently heard more clearly when the horse is exercising in one direction than in the other.[91] If the presence or character of a respiratory noise remains in doubt after the horse has been exercised in a circle at a collected canter, the horse should be galloped until it is blowing hard then ridden past the observer at a fast gallop.[91]

A satisfactory exercise test should include at least 5 minutes of work at the canter, after which the horse should immediately be brought over to the observer so that the character and sequence of abnormal sounds that persist can be determined. All horses that have been worked adequately make a loud expiratory blowing sound at this time. Turbulence of airflow in the larynx may be audible with a stethoscope.[92] Inducing adduction of the vocal fold, particularly on the right side, by application of gentle pressure in a rostromedial direction to the muscular process of the arytenoid cartilage often accentuates an inspiratory noise in horses with laryngeal hemiplegia. Noises originating from unilateral lesions in the nasal passages are easily localized because the sound can be eliminated by alternately blocking off airflow through each nostril with the hand. Temporary occlusion of both nostrils simultaneously may provoke laryngopalatal dislocation and a loud gurgling sound in a susceptible horse.[91,92] The presence of nasal discharge or blood at the nostrils should be noted, and the time required for the heart and respiratory rates to return to preexercise values should be interpreted in light of the severity of the exercise test.[91]

5.7.3.3.1

Box 5-19 Causes of Stridor in Ruminants

5.7.3.3.1.1

COMMON CAUSES

Necrotic laryngitis (calf diphtheria) (B, O)

Abscess (pharyngeal, laryngeal, retropharyngeal, oral)

Nose bots *(Oestrus ovis)* (C, O)

Caseous lymphadenitis *(Corynebacterium pseudotuberculosis)* (C, O)

Actinobacillosis (wooden tongue, nasal actinobacillosis)

Nasal adenocarcinoma, adenoma, adenopapilloma, polyp (C, O)

Trauma (oral, nasal, pharyngeal, laryngeal, tracheal)

Anaphylaxis or drug reaction

Sinusitis

Foreign body (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial)

5.7.3.3.1.2

LESS COMMON CAUSES

Actinomycosis (lumpy jaw)

Tracheal stenosis, collapse, stricture

Bovine leukosis (enzootic adult lymphosarcoma) (B)

Sporadic bovine leukosis (adult multicentric lymphosarcoma) (B)

Thymic lymphosarcoma (juvenile) (B)

Mannheimia hemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)

Infectious bovine rhinotracheitis (IBR; BHV-1) (B)

Atypical interstitial pneumonia (B)

Malignant catarrhal fever (B)

Vesicular stomatitis

Clostridial infection of the head (O)

Pulmonary embolism from posterior vena cava thrombosis (B)

Snakebite

Bee or wasp sting

Bovine nasal granuloma, atopic rhinitis (summer snuffles) (B)

Honker syndrome in feedlot cattle (B)

Neoplasia (nasal, paranasal sinus, oral, pharyngeal, laryngeal, tracheal, maxillary, mandibular, retrobulbar)

Congenital abnormalities

Inhalation pneumonia, smoke inhalation

5.7.3.3.1.3

UNCOMMON CAUSES

Tuberculosis (B)

Congenital cystic nasal conchae (B)

Choanal atresia (O)

	Salivary cyst, mucocele, ranula, trauma (C)
	Photosensitization in Southdown and Corriedale sheep (O)
	Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma (B, C)
	Phycomycosis, pythiosis (B)
	Goiter, iodine deficiency
	Hyperparathyroidism (B, C)
	Enzootic ataxia, swayback (C, O)
	Besnoitiosis, globidiosis (exotic)
	Endemic ethmoid hematoma (exotic) (B)
	African bovine malignant catarrhal fever (exotic) (B)
	Lumpy skin disease (exotic) (B)
	Nasal schistosomiasis (exotic)
	Virulent sheep and goat pox (exotic) (C, O)
	Peste des petits ruminants (exotic) (C, O)
	Gedoelstia hasleri nasal bots (exotic) (C, O)

B, Bovine; *C*, caprine; *O*, ovine.

*Bergstrom biopsy needle Mortenson, Copenhagen, Copenhagen, Denmark.

5.7.3.4

INTERPRETATION OF ABNORMAL SOUNDS

A normal horse makes no audible respiratory sound at rest and when exercised at a canter or slow gallop makes only a blowing expiratory sound.[87,91,92] In unfit horses, particularly overweight ones, an inspiratory sound is

also frequently audible. This sound can be quite loud, and it may be difficult to differentiate from sounds caused by abnormalities of the respiratory tract.[90,91] Thus evaluation of the horse's “wind” is best carried out when the horse is in fit condition for its intended use. It takes at least 1month for an older horse that has been turned out to pasture to regain a satisfactory level of fitness to perform a meaningful wind examination. Many normal horses produce a harsh expiratory “high blowing sound” of variable pitch, which results from resonance in the cavity of the false nostril during expiration.[91,92,98] If the source of the stridor remains in doubt, temporary suturing of the alar fold dorsal to the nostril can help localize noises suspected of being caused by vibration of the alar fold.

Horses with ILH make a rather characteristic biphasic sound, the inspiratory sound occurring between successive expiratory sounds. The pitch of the sound can vary from a whistle to a deep roar, the lower-pitched note giving rise to the so-called “sawing wood” sounds.[92] Sonographic and spectrographic analysis of the sounds produced by “roarers” indicates that the range of sound frequencies generated by these horses is the same as that produced by normal horses.[99,100] However, horses that make an audible whistle generate an intense band of frequencies centered on 1.9kHz that are thought to result from amplification by the still-patent lateral ventricle of the frequency generated by vibration of the incompletely abducted left vocal fold.[100] In a normal horse the left vocal fold is fully abducted, and the cavity of the lateral ventricle is thus obliterated during strenuous exercise.[94]

The sounds generated by horses with laryngeal chondritis, severe proliferative pharyngeal lymphoid hyperplasia, epiglottic entrapment, and tracheal stenosis can be very similar to those caused by ILH.[91,92] Laryngopalatal dislocation (dorsal displacement of the soft palate) gives rise to a transient, vibrant, gurgling sound.[89,91,92] In many instances a severe exercise test is required to induce this condition; thus this sound may be heard only during a race.[87,91,92] It is thought that the condition may occur when pharyngeal stimulation causes swallowing during fast exercise.[92] Instead of the horse completing the process and regaining the laryngopalatal seal consistent with the respiratory position of the larynx in the nasopharynx, the tip of the epiglottis disengages from the rostroventral aspect of palatopharyngeal ring (caudal free border of the soft palate), resulting in the entire epiglottis slipping ventral to the soft palate. At the subsequent inspiration the palatopharyngeal arch tends to be drawn into the rima glottis, and at expiration it is driven toward the roof of the pharynx by the air stream. The palatopharyngeal arch acts as an airway obstruction, and the tissue vibration and resulting turbulence generate a sound of varying pitch and intensity, often described as gurgling followed by swallowing.[92] The horse often slows suddenly or stops when this event occurs, and the jockey often reports that the horse stopped after “choking” or “swallowing its tongue.” If repeated swallowing is successful in relocating the normal laryngopalatal respiratory arrangement, the horse often continues to race after slowing or stopping.[70]

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Gross obstruction of the airway by pressure from pus-filled guttural pouches, retropharyngeal abscesses, large subepiglottal cysts or abscesses, or large proliferative lesions (e.g., laryngeal tumors) produces loud, stertorous breathing (snoring) often heard at rest and readily so with exercise; both inspiratory and expiratory sounds are clearly audible.[92]

In a normal horse the pattern of respiratory sounds is regular and synchronized with the pace of the exercise. Laryngeal irritation caused by exudate from the upper or lower airway, pharyngeal lymphoid hyperplasia, or other inflammatory or space-occupying conditions causes the horse to swallow more frequently during exercise, which generates an irregular pattern of respiratory sounds characterized at the canter and gallop by a respiratory cycle of double the normal length.[92,98]

Interpretation of stridor in yearlings presented for sale is difficult because these animals are rarely fit and it is usually possible to exercise them only at a canter on a lunge line. It has been shown that resentment of restraint under such circumstances can significantly alter the linking of locomotion and respiration, which complicates recognition of the respiratory phasing of noise production.[94] In addition, there is not always a close correlation between noise production, endoscopically visible abnormalities, and signs of exercise intolerance even in fit adult horses.[87,91]

5.7.3.5

ENDOSCOPIC EXAMINATION

Endoscopic examination of the upper airway is the most useful diagnostic procedure for investigating stridor. The examination should be performed at rest before exercise and again immediately after exercise or, if possible, during exercise on a high-speed treadmill. Endoscopic examination immediately after cessation of exercise is less satisfactory than endoscopy during treadmill exercise because dynamic collapse of the rima glottis terminates rapidly on cessation of exercise. Because sedatives and tranquilizers may alter the tone and function of the muscles supporting laryngeal and pharyngeal anatomy, endoscopic examination should be performed without chemical restraint whenever possible.[87] The nasal passages, conchae (turbinates) (including the ethmoidal concha), nasal septum, pharynx, larynx, and trachea should be examined through both nostrils so that the presence, nature, and source of exudates and the presence of anatomic or functional abnormalities or mass lesions can be determined. If problems are suspected in the guttural pouches, the interior of these structures should be examined for exudate, proliferative lesions, or arterial aneurysms by advancing the endoscope through the pharyngeal openings. Because the larynx is viewed slightly obliquely when examined from the left or the right ventral meatus, an apparently asymmetric larynx should be viewed through both nostrils.[87,91]

Interpretation of the findings of the endoscopic examination of the pharynx and larynx is by no means straightforward. The results can be influenced by the day the examination was done, the use of sedation, the side through which the endoscope was passed, and the observer's interpretation.[101] The appearance of laryngeal symmetry or asymmetry in resting horses varies considerably and therefore is of limited clinical usefulness unless complete hemiparalysis is present. Many horses have asynchronous or asymmetric laryngeal movement at rest but not during exercise, whereas other horses have a normal-appearing larynx at rest but suffer dynamic collapse during exercise. Interpretation of findings is improved by use of an objective grading system, which includes assessment of the ratio of the areas of the left and right half of the rima glottis and by correlating findings at rest with those observed on video endoscopy performed during maximal exercise.[101] For evaluation of the larynx at rest, full abduction of the vocal folds should be induced by exercise or by temporary occlusion of the nostrils.[91] Contralateral adductory laryngeal move-ment should be stimulated by slapping the horse just behind the withers (slap test).[102] To induce the horse to swallow, the tip of the epiglottis should be touched with the endoscope, or water should be flushed through the endoscope. These maneuvers help to establish whether movement of the arytenoid cartilages is synchronous and symmetric and increase the predictive value of endoscopic observations, allowing laryngeal function to be graded as follows.[101]

- *Grade 1:* Synchronous, full adduction and abduction of the left and right arytenoid cartilages (considered normal).
- *Grade 2:* Asynchronous movement such as hesitation, fluttering, or adductor weakness of the left arytenoid cartilage during inspiration, expiration, or both, but full abduction of the left arytenoid

cartilage, inducible by nasal occlusion or swallowing. Grade 2 findings are considered a normal variation and are not usually associated with dynamic airway collapse during exercise.

- *Grade 3:* Asynchronous movement of the left arytenoid cartilage during inspiration, expiration, or both, but full abduction is not inducible by nasal occlusion or induction of swallowing. The true functional significance of grade 3 findings can be determined only by performing endoscopic examination during maximal exercise on a high-speed treadmill, a procedure that has led to subclassification of grade 3 findings.[103] Some grade 3 horses *(grade 3A)* are able to achieve full abduction during exercise, whereas others maintain a partly abducted position similar to the resting position *(grade 3B)* or experience dynamic collapse *(grade 3C)*.[103]

- *Grade 4:* Marked asymmetry of the larynx at rest and no substantial movement of the left arytenoid cartilage during any phase of respiration. These horses have complete left laryngeal hemiplegia, are true "roarers," and consistently experience dynamic collapse on inspiration during strenuous exercise.[101]

Performing an endoscopic examination during maximal exercise on a high-speed treadmill makes it possible for a stationary observer to gain a good dynamic appreciation of the significance of upper airway abnormalities (i.e., dynamic endoscopy)[103–107] (see Exercise Intolerance and Poor Performance in Horses, p. 76). Dynamic changes in airway lumen diameter occur quickly during treadmill endoscopy and may be difficult to visualize; therefore the endoscopic examination should be videotaped for later playback in slow motion and freeze-frame.[107] It is important to exercise horses maximally and to exhaustion (inability to keep up with the treadmill), because some abnormalities are apparent only at maximal exercise toward the end of a race when pharyngeal or laryngeal muscles become fatigued and are no longer able to resist the transmural pressure gradient, which tends to induce dynamic collapse of the upper airway during inspiration.[103–107] Endoscopic identification of an upper respiratory tract abnormality in a resting horse does not necessarily mean that it is inducing a problem during exercise, and, conversely, the absence of an upper respiratory tract abnormality at rest does not rule out the possibility of intermittent airway obstruction during strenuous exercise. For example, dorsal displacement of the soft palate, epiglottic entrapment, dorsal displacement of the epiglottis, dynamic collapse of the left arytenoid cartilage or vocal fold (or both), and unilateral or bilateral ventral displacement of the roof of the pharynx (dynamic pharyngeal collapse) have been observed during treadmill exercise in horses with an endoscopically normal upper airway at rest.[103–107]

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5.7.3.6

RADIOGRAPHIC EXAMINATION

Radiographic examination of the nasal passages, paranasal sinuses, pharynx, retropharyngeal area (including guttural pouches), larynx, and proximal trachea is indicated to confirm anatomic or functional problems or space-occupying lesions not definitively diagnosed by clinical examination and endoscopy (see Nasal Discharge, p. 50 and Respiratory Distress, p. 60). Radiography is particularly useful for visualizing subepiglottic masses such as cysts or abscesses and for evaluating the epiglottis of the horse when it is obscured from endoscopic view by dorsal displacement of the soft palate or other space-occupying lesions. An accurate assessment of epiglottic length can also be made from standardized true lateral radiographs of the larynx by measuring the distance from the body of the thyroid cartilage to the tip of the epiglottis (thyroepiglottic length).[108] The mean ± SD (standard deviation) thyroepiglottic length in normal thoroughbred horses is reported to be 8.76 ± 0.44cm.[108] Significantly shortened thyroepiglottic lengths have been recorded in thoroughbred horses with dorsal displacement of the soft palate (laryngopalatal dislocation) and in those with entrapment of the

epiglottis in the aryepiglottic folds.[108] Tracheal diseases such as chondroma or dynamic collapse may be visualized on radiographs of the trachea, particularly those made during the inspiratory phase.

5.7.3.7 ULTRASOUND EXAMINATION

Ultrasound examination of externally visible lesions such as possible retropharyngeal abscesses that may be impinging on the airway helps to characterize lesions and assist in the collection of samples by aspiration or biopsy.

5.7.3.8 BIOPSY

Biopsy and histologic evaluation of samples are indicated to diagnose certain mass lesions such as neoplasms, cysts, polyps, fungal granulomas, or foreign body granulomas in or surrounding the airway. Masses in the airway can be biopsied through the biopsy channel of fiberoptic or video endoscopes, but these samples inevitably are small. Larger samples can be collected from lesions in the nares, nasal diverticulum, and nasal passages using uterine biopsy forceps, laparoscopy forceps, or curettes. Hemorrhage usually accompanies such procedures. Biopsies can also be collected at the time of exploratory or corrective surgery from lesions in the nasal passages, pharynx, larynx, and guttural pouches. Lesions such as habronemiasis involving the external nares and lesions in other accessible areas such as the parotid salivary gland can be biopsied percutaneously using Tru-Cut or similar instruments.

5.7.3.9 ASPIRATION

Aspiration, performed either blindly or with the assistance of ultrasound, followed by cytologic examination and culture of aspirated material is useful in the evaluation of masses such as retropharyngeal abscesses that are causing stridor by impinging on the upper airway.

5.7.3.10 SWABBING OR SCRAPING

Nasal or nasopharyngeal swabbing or scraping followed by direct cytologic examination and culture is indicated for confirmation of nasal fungal infection and bacterial infections of the upper airway (e.g., strangles).

5.7.3.11 COMPLETE BLOOD COUNT

A complete blood count, including fibrinogen concentration, can be useful in evaluating patients suspected of having a primary or secondary inflammatory condition or conditions such as ethmoidal hematoma and guttural pouch mycosis in which blood-loss anemia is likely to be a complicating problem.

5.7.3.12 ASPIRATION, LAVAGE, OR THORACOCENTESIS

Transtracheal aspiration, BAL, and/or thoracocentesis with cytologic examination and culture of collected samples are indicated in the evaluation of patients suspected of having disease of the lungs or pleura.

5.8 EXERCISE INTOLERANCE AND POOR PERFORMANCE IN HORSES

Stephanie J. Valberg

W. David Wilson

The popularity of performance horses has broadened our perspective on health beyond the conventional diagnosis of health or disease in a horse at rest. Sports medicine defines equine health as the optimum function of all body systems during the expected level of performance. Because many body systems function at only a small fraction of their maximum capacity in a resting athlete, a clearer understanding of exercise responses in the horse and new methods of evaluating horses during exercise are needed.

5.8.1 Exercise Responses

As horses accelerate during exercise, motor units within active muscles fire in a coordinated fashion to produce the power necessary to drive the animal forward. Initially, slow-twitch type 1 muscle fibers are recruited, followed at increasing speed by recruitment of oxidative fast-twitch type 2A fibers and finally the fastest and most powerful muscle fibers, type 2B (also called 2X). The increased demand for adenosine triphosphate (ATP) to support muscle contractions during exercise can be met initially by small intracellular stores of creatine phosphate, but within seconds oxidative or glycolytic metabolism (or both) is activated. At submaximal speeds the major factors contributing to fatigue are total depletion of fuel reserves (glycogen), fluid and electrolyte losses, and hyperthermia.[109] Training increases the oxidative and endurance capacity of skeletal muscle by increasing the volume of mitochondria and the capillary density surrounding muscle fibers.[110] This delays the onset of fatigue by increasing the availability and metabolism of plasma free fatty acids and glucose, thus sparing muscle glycogen. Training also fine-tunes the motor unit recruitment pattern to provide the most efficient and coordinated pattern of movement.

When a horse accelerates toward a maximum speed, a peak in the total amount of oxygen consumed is realized (Vo_{2max}). Additional energy to produce speeds beyond Vo_{2max} must be supplied by anaerobic glycolysis with lactic acidosis as a consequence. The term *anaerobic threshold* has been used to describe the speed at which this exponential rise in lactate begins to occur. Fatigue with maximum (fast) exercise occurs when muscle pH falls so low that glycolysis and excitation contraction coupling are inhibited and muscle ATP concentrations fall.[111,112] Muscle glycogen stores are not a limiting factor with maximum exercise. ??????[113] Training over time increases the mitochondrial volume and the ratio of type 2A to type 2B muscle fibers.[110,114] As a result, the onset of anaerobic metabolism is delayed until a higher speed is reached, and horses are able to maintain a higher speed over a given distance.

The cardiovascular system plays a central role in the oxygenation of blood by the lungs, in the delivery of oxygen and other energy substrates to exercising muscles, and in the removal of metabolic products from those muscles. Cardiac output increases with exercise in horses, largely as a function of an increase in heart rate.[115] As exercise begins, the heart rate quickly increases then reaches a steady state within minutes at a submaximal speed. With increasing exercise intensity the heart rate shows a linear relationship with speed up to a maximum rate of 210 to 230 beats/min. The mean systemic arterial pressure does not change with submaximal exercise but rises with maximum exercise. Mean pulmonary arterial pressures increase with speed as the heart rate increases, reaching remarkably high levels that are four times resting values.[116] The oxygen-carrying capacity of the blood also rises with increasing speed through splenic contraction and a more than 50% increase in blood hemoglobin.[117] The increase in blood viscosity that occurs with splenic contraction is believed to contribute to the increase in blood pressure with exercise. Among the adaptive cardiovascular responses to training are a lowered heart rate and

blood pressure at the same exercise intensity[118]; increased red cell volume[100]; and increased capillarization of muscle.[110]

After an initial abrupt rise the respiratory rate increa-ses linearly with the speed of trotting until, at a canter or gallop, respiration is linked to stride frequency on a 1:1 basis.[119,120] This leaves less time available for completing a respiratory cycle at faster speeds. To counter this, inspiratory and expiratory airflow velocities must increase to maintain or increase minute volume. As airflow rates increase, increased turbulence and an increased tendency for dynamic narrowing of the airways causes an increased resistance to flow and increases the work (energy cost) of breathing.[121,122] A finite maximum flow rate is eventually achieved, beyond which the expiratory muscles and the physical characteristics of the respiratory tract do not permit further increases in flow rate.[121] In addition, a maximum stride frequency is reached, restricting the maximum respiratory rate to 140 to 150 breaths/min.[119,120] It has been suggested that beyond the finite maximum flow rate, the animal is forced to hypoventilate, which may result in arterial hypoxemia during fast exercise.[123] The limitation placed on oxygen diffusion by blood hyperviscosity and the short transit time of blood through the pulmonary capillary bed at rapid heart rates also likely contribute to arterial hypoxemia.[124] The arterial hypoxemia and incomplete saturation of hemoglobin that occur during strenuous exercise do not necessarily limit delivery of oxygen to the tissues, however, because the decline in blood oxygen tension is offset by the increase in the total blood hemoglobin oxygen content resulting from splenic contraction. This fact and the horse's ability to sustain at least a sixfold increase in cardiac output between rest and the point of maximum oxygen uptake ($V_{O_{2max}}$)[125] are the major factors that contribute to the enormous aerobic capacity of the horse.

In contrast to the muscular and cardiovascular systems, the respiratory system shows little adaptation to training. Whether the apparent inability of the equine respiratory system either to adjust to training[126] or to compensate fully for the increased flow demands of heavy exercise limits athletic performance remains to be proven. However, it is likely that the maximally exercising horse is operating near the upper limit of ventilation and that even slight degrees of respiratory disease profoundly affect oxygen uptake and performance.[127] Any condition that causes increased resistance to airflow, decreased minute volume, decreased diffusion of gases, ventilation-perfusion mismatch, shunt, or increased oxygen cost of breathing constitutes a respiratory cause of exercise intolerance.

5.8.2 Approach to Diagnosis of Exercise Intolerance and Poor Performance

Top athletes arise from both a genetic background that emphasizes athletic ability and environmental influences that capitalize on this inherent potential. A coordinated, energy-efficient gait, muscular power and endurance, a large capacity for oxygen transport, and several intangible factors, such as the horse's mental toughness and competitive spirit and the rider's skill, all contribute to successful performance. *Poor performance* most often results from inadequate training, a lack of genetic potential, or both or from a congenital or acquired dysfunction of the locomotor, cardiovascular, or respiratory systems. The term *exercise intolerance* is often used to describe this inability to perform up to an expected or previously attained intensity of exercise.

5.8.2.1 HISTORY

An accurate history is a fundamental part of the evaluation of exercise intolerance and should include the age, breed, and use of the horse and the training and feeding programs. The onset (time and rapidity) of the problem, previous performance history, the activity level at which signs are observed, whether the horse performs well at

first then suffers tailing off of performance (no stamina) or whether performance is poor throughout the work period should be ascertained. If performance drops off during work, it should be established whether the drop-off is associated with the onset of other signs such as stridor. The presence of coughing, respiratory distress, stridor, excessive sweating associated with stress or exercise, or muscle stiffness should be noted. It should be ascertained whether the affected horse or in-contact horses have recently shown signs of respiratory disease, especially viral infections, and whether other horses are perceived to be performing poorly. It should be determined if the horse has shown lameness, gait abnormalities, or bitting problems. Any medications or other treatments that have been used and their effects should be noted.

In particular, it is important from the history to distinguish between horses that have never been able to perform satisfactorily and horses that suddenly or gradually show a reduction in the level of performance after a background of satisfactory performance. The first scenario suggests a lack of genetic potential, congenital abnormalities, or inadequate training. Some horses do not have the genetic background to perform the expected work (e.g., racing quarter horses rarely make good endurance horses, and thoroughbreds from sprinting families rarely excel at distances of more than 1¼ miles).

5.8.2.2

CLINICAL EXAMINATION

Overt clinical diseases that cause exercise intolerance at moderate speeds usually can be diagnosed with a good history, physical examination, and selected ancillary diagnostic techniques. The diagnostic procedures and specific diseases that can be identified at rest are detailed in subsequent chapters in this book (particularly Chapters 30, 31, 37, 38, and 42). Problems that are subclinical at rest provide a greater diagnostic challenge. When testing procedures at rest fail to identify the cause of exercise intolerance, various types of ancillary diagnostic procedures including exercise tests may be used to further define the problem. Because the respiratory, cardiovascular, musculoskeletal, and hematopoietic systems are all important for competitive performance and because diseases in these systems are the most likely causes of exercise intolerance, these systems should receive particular attention in the detailed clinical examination of the horse at rest.

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5.8.2.3

HEMATOLOGIC ASSESSMENT

Hematologic tests have historically been popular in the evaluation of fitness and performance because they are easy to perform and because of the important role of hemoglobin in oxygen transport.[128,129] Routine hematologic evaluation may be useful in monitoring the general health status and perhaps fitness of horses if the conditions of collection, particularly in relation to time of day and exercise, can be carefully controlled and if attention is paid to horses that become excited before or during sample collection.

Anemia can result in a decreased oxygen-carrying capacity during exercise. Veterinarians traditionally have regarded resting hematocrits below 35% as abnormal and likely to cause suboptimal racing performance, but values lower than this have been found in normal thoroughbred racehorses.[130] Endurance horses and eventing horses usually have resting hematocrit values that are lower than those of racehorses.[130] However, the fact that a significant proportion of equine red blood cells and hemoglobin are contained in the splenic reserve makes interpretation of resting values for these parameters difficult (inaccurate). There is no correlation between the resting level of hemoglobin and the total body hemoglobin or red cell mass.[117,130] Consequently, even though total body hemoglobin does increase in response to training and may correlate with performance, this cannot be determined from a resting blood sample. Measurement of the total hemoglobin or total red cell mass requires collection of a blood sample after strenuous exercise or after administration of epinephrine to mobilize the red cell reserve and the determination of plasma volume using a technique such as Evans blue dye dilution.[117]

These techniques have been used to document red cell hypervolemia in poorly performing, overtrained standardbreds.[117]

Some veterinarians use the resting leukocyte count to monitor fitness, and particularly overtraining, in performance horses.[130] Decreases in the neutrophil/lymphocyte (N/L) ratio have been used to indicate overtraining (training off or adrenal exhaustion). However, the N/L ratio varies in individual horses, depending on when it is determined in relation to the timing and type of exercise and on factors such as age, stress, and disease. Reliable evidence indicates that the N/L ratio is not a good predictor of adrenal status.[131] Indeed, adrenal function in horses with “adrenal exhaustion syndrome” remains to be accurately characterized on the basis of reproducible function tests.

5.8.2.4

SERUM BIOCHEMICAL PROFILES

Biochemistry profiles are commonly used to monitor performance horses and to evaluate those with performance problems. These profiles are useful, but interpretation must take into account that when many measurements are performed, there is a high statistical probability that one or two results will be outside the normal range (95% confidence).[130] If only one or two results on a profile are slightly abnormal, the tests are best repeated on a second sample before the true significance of the result is ascribed. Biochemistry profiles are most useful in detecting horses with subclinical muscle problems (either primary exertional rhabdomyolysis or muscular strain secondary to skeletal problems), liver diseases, renal diseases, and gross disturbances in electrolyte and acid-base regulation. Biochemical profiles usually include aspartate aminotransferase (AST), creatine kinase (CK), LDH, alkaline phosphatase (AP), γ-glutamyltransferase (GGT), sorbitol dehydrogenase (SDH), blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), chloride (Cl), bicarbonate, phosphate, calcium (Ca), magnesium (Mg), glucose, and other parameters that are of variable clinical relevance. Studies of horses during training have failed to show any correlation between resting or exercising values for these parameters and fitness.[130] In endurance horses, evaluation of renal fractional excretions of electrolytes may provide better information regarding the horse's electrolyte balance than serum chemistry measurements alone.[132]

5.8.2.5

EVALUATION OF THE RESPIRATORY TRACT

Standard parameters of a routine examination including rectal temperature, respiratory rate, respiratory character, mucous membrane color, and capillary refill time should be carefully evaluated at rest. The presence of nasal discharge, cough, edema, jugular distention or pulsation, or other signs suggesting local or systemic disease should be noted. The larynx, muscular process of the arytenoid cartilages, retropharyngeal area, and trachea should be palpated for size and symmetry. The heart and lungs should be carefully auscultated and percussed at rest, and auscultation of the lungs should be repeated as the horse is induced to breathe more deeply by application of a rebreathing bag. When stridor is part of the history, the upper respiratory tract should receive particular attention in the diagnostic evaluation. Not only must the character of the noise be determined, but the extent of work the patient can tolerate before exhibiting diminished performance must be established, because this helps in the interpretation of abnormalities seen on the endoscopic examination (see Stridor, p. 71). Often the onset and intensity of the stridor coincides with a decrease in work capacity that is typical of certain obstructive airway diseases. Endoscopy, including treadmill endoscopy if facilities permit, and radiography form an important part of the diagnostic evaluation of horses with upper airway abnor-malities[133] (see Respiratory Distress, p. 60, and Stridor, p. 71). The most common abnormalities of the upper airway that cause poor performance include dorsal displacement of the soft palate, dynamic pharyngeal collapse, dynamic

collapse of the left arytenoid cartilage in association with ILH, epiglottic entrapment, pharyngitis, and collapse of the alar folds.[134,135] Diminished performance in horses with mild or subclinical viral infection is probably mediated at least partly by abnormalities in the respiratory tract.[136] If no abnormalities are detected at rest, functional disturbances of airflow may occur during maximum exercise, and these disorders can best be identified by examining the upper airway using video endoscopy during treadmill exercise. The use of Velcro to attach the endoscope to the halter after insertion of the tip of the endoscope to the depth of the guttural pouch openings decreases the blurring of the image that occurs during exercise. Slow-motion playback must be used because many abnormalities occur rapidly with each respiratory cycle. In particular, dorsal displacement of the soft palate and the extent of dynamic laryngeal obstruction with ILH can be more fully evaluated with treadmill exercise tests.[133–135] The presence of inspiratory or expiratory obstruction can be further evaluated during treadmill exercise by introducing transducers via the nostrils to measure airway pressures at the level of the pharynx and trachea.[133,135] During a treadmill exercise test, samples for blood gas analysis can be drawn from extension tubing connected to an 18-gauge, 2-inch catheter inserted into the transverse facial artery.

Further diagnostic evaluation of the lower airways is indicated in horses with an abnormal respiratory rate or character, cough, nasal discharge, abnormal lung sounds, prolonged recovery after application of a rebreathing bag, or a history of EIPH, cough, or respiratory distress with exercise. Horses in which excess mucus or exudate can be demonstrated in the trachea during endoscopy performed after exercise are also candidates for further evaluation. Applicable tests include a complete blood count, tracheal wash or BAL, endoscopy, radiography, and ultrasound examination (see Cough, p. 42, and Stridor, p. 71). Tracheal wash samples collected after exercise are more likely to identify lower airway disease than those collected before exercise.[137] Respiratory viral infection, EIPH, bronchiolitis, hyperreactive airways and recurrent airway obstruction (RAO), and chronic obstructive pulmonary disease (COPD) are all conditions that may not be apparent at rest but that constitute significant causes of exercise intolerance.

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5.8.2.6

EVALUATION OF THE CARDIOVASCULAR SYSTEM

A full evaluation of the mucous membranes, capillary refill time, pulse rate, pulse character and rhythm, heart rate and rhythm, and auscultatory findings is an important part of the evaluation of the performance horse. Failure to maintain cardiac output because of an inability to regulate either heart rate or stroke volume is the mechanism through which cardiac diseases induce exercise intolerance. Many cardiac dysrhythmias and valvular dysfunctions are readily apparent on auscultation of the resting horse. However, the contribution of mild abnormalities to exercise intolerance may require exercise testing. In addition, some arrhythmias and valvular or myocardial dysfunctions can be detected only during or shortly after exercise. Thus resting and exercising electrocardiography and echocardiography before and immediately after exercise are indicated.[133,135] The heart rate can be monitored during exercise using either telemetric electrocardiography or commercial heart rate monitors. Electrocardiograms (ECGs) provide the additional benefit of evaluating both heart rate and rhythm. Supraventricular tachyarrhythmias, the most important of which is atrial fibrillation (AF) in horses, can lead to heart rates exceeding 240 beats/min at submaximal exercise.[138] Under these circumstances, cardiac output may be limited by the decreased time available for diastolic perfusion of the myocardium; the absence of atrial contraction; and the reduced time for passive ventricular filling, leading to reduced stroke volume. Many horses with AF maintain efficient circulation at rest and during light exercise but are intolerant to strenuous exercise because they are unable to increase cardiac output sufficiently at rapid heart rates.[139] Some horses show transient paroxysmal AF during exercise but not at rest.[139] These are often easiest to observe in ECG tracings obtained within 60 seconds after an exercise test. Conversion to sinus rhythm, either spontaneously with quinidine sulfate, or electroconversion[140] usually leads to a return to normal performance

in horses with AF.[141,142] The ability to maintain cardiac output can be compromised by other cardiac arrhythmias such as ventricular tachycardia and ventricular premature depolarization.[135,143] The frequency of premature depolarization can increase with exercise, and the timing of resultant abnormal extra systoles can reduce cardiac output even at submaximal heart rates.[143] Intraatrial block, second-degree atrioventricular (AV) block, and intraventricular block have also been documented in exercise-intolerant, poorly performing horses.[144,145] Horses with cardiac arrhythmias may show abnormal elevations in lactate concentration in response to exercise, indicating a lowered anaerobic threshold, which contributes to exercise intolerance.[118]

Electrocardiography is believed by some veterinarians to be of value in identifying myocarditis. T wave abnormalities (positive and peaked T waves, in contrast to the normal diphasic T waves) in multiple leads on resting ECG traces have been found in a high percentage of horses with a history of fading during the final portion of a race.[144] T waves are highly labile, affected by training status, and the mechanism by which abnormal T waves are generated is uncertain. However, T wave changes have been identified in some horses with myocarditis confirmed at necropsy.[130,145,146] Myocarditis may be more definitively documented by evaluating the distribution of serum isoenzymes of LDH and CK or measurement of cardiac troponin I.[147] Although total LDH concentrations in serum are often normal, with myocarditis the percentage of the LDH_1 isoenzyme may be elevated.[148] A positive correlation has been demonstrated between heart size and racing performance.[145] Electrocardiography has been used to assess performance potential by heart score measurement. The heart score represents the mean QRS duration in leads 1, 2, and 3 expressed in milliseconds and has been strongly correlated with heart weight and prize money won by racehorses.[130,145] The physiologic basis for heart score remains in dispute, and expertise is required to standardize leads and measure QRS complexes.

An *echocardiogram* provides essential information in many cases in which clinical evidence of valvular or myocardial dysfunction is present. The pericardium, the size of the heart chambers, the presence of congenital defects, the function of valvular leaflets, and myocardial contractility all can be assessed (see Chapter 30). Decreased myocardial contractility, regurgitant leaks caused by valvular incompetence, left-to-right shunts, and increases in afterload, such as occurs in aortic stenosis, result in systolic dysfunction and a drop in cardiac output.[149] A pulsed, continuous, or color flow Doppler technique may be necessary to determine the size and significance of any disturbances to flow. Cardiac conditions such as effusive pericarditis and myocardial fibrosis and peripheral vascular conditions that inhibit venous return may interfere with ventricular filling during diastole, resulting in decreased end-diastolic volume, stroke volume, and cardiac output.[149] Measurement of fractional shortening before and immediately after treadmill exercise, when pulse rates are above 100 beats/min, permits documentation of resting and exercise-induced myocardial dysfunction.[135] Contrast angiographic studies may be indicated if congenital or acquired cardiac outflow problems are suspected. Nuclear angiocardiography is also useful for evaluating myocardial contractility, cardiac chamber enlargement, outflow problems, and other abnormalities. Hemodynamic studies, which measure pulmonary capillary wedge pressure, pulmonary driving pressure, and pressure in the right side of the heart and pulmonary artery, have proven useful in detecting early cardiac and pulmonary failure in poorly performing trotting horses. These studies involve the introduction of flow directional balloon-tipped catheters through the jugular vein into awake horses.[148]

5.8.2.7

EVALUATION OF THE SKELETAL SYSTEM

A lameness examination, including appropriate flexion tests and other stress tests, should be completed to help rule out musculoskeletal problems. If lameness is observed, appropriate diagnostic nerve blocks, radiographs, scintigraphy, rectal examination of the bony pelvis and aortoiliofemoral arterial pulses, or ultrasound examinations are indicated to help localize the lameness and determine its cause, significance, and prognosis. Some lameness problems that are evident only at high speed may best be evaluated using treadmill exercise. For example, aortoiliofemoral thrombosis reduces peripheral perfusion but often causes only progressive hindlimb lameness with exercise. Foot balance should be carefully assessed at rest and, if possible, during exercise, because gait changes and subtle lameness related to foot imbalance can adversely affect performance. Dynamic evaluation of hoof balance can be accomplished by examining videotapes recorded from behind the horse while it is exercising on a high-speed treadmill or by trotting the horse over force plates embedded in a firm level surface.[150]

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Subtle lameness can increase the metabolic cost of locomotion by inducing changes in gait and coordination, which accelerate the onset of fatigue. In the same fashion, some horses may have an inefficient gait that reduces their performance capacity. Video imaging systems and gait analysis may play an increasingly important role in identifying these individuals in the future.

5.8.2.8

EVALUATION OF THE MUSCULAR SYSTEM

Primary skeletal muscular limitations on performance may occur as the result of painful conditions such as exertional rhabdomyolysis. In resting samples high serum AST may indicate chronic rhabdomyolysis. Measurement of serum CK 4 to 6 hours after an exercise test is most useful in detecting horses with chronic or subclinical forms of exertional rhabdomyolysis. Serum muscle enzyme concentrations measured in blood samples collected immediately after exercise are often normal, but in horses with chronic exertional rhabdomyolysis significant abnormal elevations may be seen when CK peaks at 4 to 6 hours after completion of exercise. In the past it has been recommended that the exercise test be conducted at a speed and duration of exercise similar to that expected of the horse in competition. However, it has been shown that a 15- to 30-minute test at a slow trot more frequently produces abnormal elevations in serum CK (more than twofold to threefold) in susceptible horses.[151] Standardbred and thoroughbred horses with histories of recent episodes of recurrent exertional rhabdomyolysis and horses with polysaccharide storage myopathy often show a greater than twofold increase over normal resting values in response to an exercise test.[151]

Muscle biopsy is a relatively simple procedure that can prove useful for characterizing the nature of an identified exertional myopathy. However, the procedure is not widely used in the diagnostic assessment of poor performance because the evaluation of samples requires considerable histochemical expertise. Percutaneous techniques using a 6-mm—diameter needle* and local anesthetic are routinely used. The middle gluteal muscle is most often sampled because it is relatively accessible and active at all intensities of exercise.[110,114,152] In adult horses a biopsy is collected at a depth of 2½ to 3 inches from a site 8 inches from the tuber coxae along a straight line connecting the point of the tuber coxae with the base of the tail. Open surgical biopsies are most easily obtained from the semimembranosus or semitendinosus muscle at a site approximately 3 inches below the tuber ischii. After the skin has been shaved and aseptically prepared, lidocaine is injected under the skin. A 2-inch—long incision is made through the skin and fascia, and two parallel incisions, 1 inch long and ½ inch apart, are made vertically in the muscle. The muscle is grasped in one place, to prevent handling artifacts, and the biopsy is first transected proximally, freed to a depth of ¼ inch, then transected distally. The disadvantage

of open surgical biopsies is the recovery period of 1 week that is often required, whereas when the needle biopsy is used horses can immediately begin to exercise. Muscle samples should be sent to a laboratory, where they will be frozen in isopentane that has first been chilled in liquid nitrogen. Commonly used histologic and histochemical stains include adenosine triphosphatase (ATPase) after alkaline and acid preincubations, nicotinamide dinucleotide diaphorase (NADH), periodic acid—Schiff (PAS), and hematoxylin and eosin.

An estimate of the state of training can be made by determining the percentage of type 1, type 2A, and type 2B (or type 2X) muscle fibers as well as the oxidative capacity of skeletal muscle in these small muscle samples. In general, horses suited for short-distance, fast exercise have a greater proportion of fast-twitch fibers in the middle gluteal muscles than horses suited for longer distance events, which have a higher proportion of slow-twitch type 1 fibers.[152] However, there are many successful athletes that do not follow this pattern. The proportion of type 1 to type 2 fibers is thought to be genetically based and cannot be manipulated to a great extent by training, whereas age and training increase the proportion of oxidative fast-twitch type 2A fibers relative to type 2B fibers.[110,114,151] Histochemical assessment of NADH staining or quantitative measurement of enzymes such as citrate synthase in biopsy samples frozen rapidly in liquid nitrogen may provide a guide to the state of aerobic fitness.[149] The use of muscle biopsies in horses with poor performance has also aided in the identification of oxidative enzyme defects in Arabian horses and glycogen storage disorders in quarter horses that can markedly affect performance.[152,153]

* Bergstrom biopsy needle, Mortenson, Copenhagen, Denmark.

5.8.3

Standardized Exercise Testing

Exercise intolerance is ultimately a neuromuscular phenomenon resulting from extreme metabolic stress at the level of the muscle fibers.[11] Under many circumstances premature muscle fatigue occurs secondary to disorders that affect oxygen transport (cardiopulmonary systems) or mechanical efficiency (lameness) (Box 5-20). Standardized treadmill exercise tests are often required to assess the function of these systems at high speeds to determine the primary cause of poor performance and to measure the metabolic response of skeletal muscle relative to work intensity. In a substantial number of cases, poor performance results from related or unrelated disorders in more than one body system, such as dynamic airway obstruction and cardiac dysrhythmia in the same horse.[135]

5.8.3.1

TREADMILL TESTS

Horses often need to be acclimated to a treadmill before representative exercise testing can be performed. Standardbred horses are typically exercised while wearing their usual racing tack, whereas horses of other breeds are typically exercised in a halter or bridle with a lead rope attached to each side. Most horses exercise comfortably on a treadmill after two to four training sessions at speeds that include all gaits to be tested. Breaking into a canter is an important skill to train horses to perform on the treadmill. During one of the training sessions, endoscopy of the upper airway can be performed to evaluate upper airway function during maximal speeds. Two types of standardized exercise tests can be used: a high-speed test, in which horses are accelerated to maximal speed for their normal racing distance, or an incremental test, in which speed is increased every 1 or 2 minutes until fatigue is reached. The incremental exercise test is used most commonly because it includes both submaximal and maximal intensities and is readily reproducible. Many exercise tests are performed with the treadmill set at a 6% to 10% slope to minimize the possibility of injury at top speeds and to ensure that maximum exercise intensity is reached.

Several measurements are possible during treadmill exercise testing. In its simplest form, the heart rate can be monitored after 1 minute at each intensity of exercise using a heart rate monitor, although recording of an ECG during exercise provides additional information about exercise-associated dysrhythmias.[135] Blood samples can also be drawn from a jugular catheter during the final 15 seconds at each speed. A linear relationship between heart rate and speed is expected, with a plateau forming at the maximum heart rate. The maximum heart rate does not change with training, but the speed at which the maximum heart rate is reached should increase with training. As an alternative, a linear regression can be used to determine the horse's speed at a heart rate of 200 beats/min (V_{200}). V_{200} is close to the anaerobic threshold, may predict aerobic capacity, increases with increasing fitness, and has a high individual predictability that allows for early and valid detection of clinical disorders that limit performance.[118,130,154] The speed at which horses reach a maximum heart rate has been proposed as a better measure than V_{200} because it is an absolute rather than a relative measure; however, measurement of maximum heart rate requires a more strenuous exercise test. Parameters such as the velocity at which the whole blood lactate value reaches 4mmol/L (V_{LA4}) and the heart rate at which blood lactate reaches 4mmol/L (HR_{LA4}) can be calculated to evaluate the anaerobic threshold.[118,154] The rate of lactate accumulation may also provide valuable information.

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5.8.3.1.1

Box 5-20 Causes of Exercise Intolerance That Are Inapparent at Rest

5.8.3.1.1.1

RESPIRATORY CAUSES

5.8.3.1.1.1.1

Obstructive Upper Airway Diseases

5.8.3.1.1.1.1.1

Common Causes

Laryngopalatal dislocation (dorsal displacement of the soft palate)

Dynamic pharyngeal collapse

Dynamic collapse of the left arytenoid cartilage in association with idiopathic laryngeal hemiplegia

Chronic pharyngeal lymphoid hyperplasia

Epiglottic entrapment

Axial deviation of the aryepiglottic folds

Arytenoid chondritis

Paranasal sinus empyema

Paranasal sinus cysts

Guttural pouch infections

5.8.3.1.1.1.1.2 Uncommon Causes

Dynamic collapse of the alar folds

Nasal polyps

Progressive ethmoid hematoma

Subepiglottic cysts

Epiglottic retroversion

Chondroma of the arytenoid cartilages

Fractured laryngeal cartilages

Nasopharyngeal cicatrix

5.8.3.1.1.1.1.3 Congenital

Choanal (posterior nares) atresia or stenosis

Excessive alar folds

Stenotic nares

Abnormalities of the nasal septum

Rostral displacement of the palatopharyngeal arch

Tracheal stenosis, stricture, collapse

5.8.3.1.1.1.2 Lower Airway Diseases

5.8.3.1.1.1.2.1 Common Causes

- Exercise-induced pulmonary hemorrhage (EIPH)
- Recurrent airway obstruction (RAO or COPD)
- Equine herpesvirus types 1 and 4 (EHV-1 and EHV-4)
- Other viral infections (influenza, rhinovirus, adenovirus, reovirus)
- Inflammatory lower airway disease
- Bacterial pneumonia
- Pleuropneumonia, pleuritis

5.8.3.1.1.1.2.2 Uncommon Causes

- Pulmonary abscess
- Pneumoconiosis (e.g., silicosis)
- Interstitial pneumonia
- Diaphragmatic hernia

5.8.3.1.1.2 CARDIOVASCULAR CAUSES

5.8.3.1.1.2.1 Common Causes

- Atrial fibrillation
- Ventricular premature contractions
- Ventricular tachycardia

Mitral insufficiency

Aortic insufficiency

Resting or exercise-induced myocardial dysfunction and reduced fractional shortening

Pericarditis

Aortoiliofemoral arteriosclerosis or thrombosis

5.8.3.1.1.2.2 Uncommon Causes

Ventricular septal defects

Monensin toxicity

Heart block (intraatrial, second- and third-degree atrioventricular and intraventricular)

Endocarditis

Congestive cardiac failure

Ruptured chordae tendinea

Cor pulmonale

Congenital defects

5.8.3.1.1.3 MUSCULOSKELETAL CAUSES

Exertional rhabdomyolysis

Lameness involving limbs, sacroiliac joint, back

Focal muscle strain

5.8.3.1.1.4

METABOLIC AND SYSTEMIC CAUSES

- Anemia
- Fluid and electrolyte imbalances
- Anhidrosis
- Heat exhaustion
- Neoplasia
- Liver disease (pyrrolizidine alkaloid)

5.8.3.1.1.5

GENERAL CAUSES

- Obesity
- Poorly trained horse
- Poor genetic potential
- Administration of illicit medications (doping)

Lactate concentrations can be determined in either whole blood or plasma. Recent studies suggest whole blood lactate may provide a more accurate reflection of lactate accumulation than plasma lactate,[155] because red blood cells actively take up lactate and buffer it, and the type and number of red blood cell lactate transporters differ markedly among horses.

The value of V_{200}, V_{LA4}, HR_{LA4}, and other parameters is that they provide standards against which improvement or deterioration in fitness can be assessed and individual horses can be objectively compared.[118,130,154] Hematocrits can also be easily determined from blood samples obtained at each speed to provide a rough estimate of the number of circulating red blood cells. Blood samples drawn before and 4 hours after exercise for measurement of CK concentration can be used to screen for subclinical exertional rhabdomyolysis.

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Further evaluation of the oxygen transport system can be obtained in laboratories where the sophisticated open-flow gas-collection system necessary to measure oxygen consumption ($\dot{V}O_2$) is available. During the incremental exercise test, a plateau in oxygen consumption eventually is reached, representing maximum oxygen uptake. $\dot{V}O_2$ can be used at submaximal speeds to calculate the oxygen cost of locomotion, and $\dot{V}O_{2max}$, a key indicator of aerobic capacity, can be determined. The cardiopulmonary system can be further

evaluated during exercise by measuring arterial blood gases from the transverse facial artery using an 18-gauge indwelling catheter.[154] An accurate measure of the total red blood cell volume in a horse can be determined using an Evans blue dye dilution technique immediately after maximal exercise.

5.8.3.2 FIELD TESTS

Standardization of field exercise tests is very difficult because weather, track conditions, and other factors influence the amount of work performed. The simplest form of exercise test involves timing a horse exercising maximally over a fixed distance and evaluating heart rate recovery rates at specific time points after exercise. Additional information can be obtained by measuring heart rate during exercise using a cardiotachometer.[130] As fitness improves, the heart rate for a given speed of exercise should be lower. Incremental field exercise tests have been used most successfully in standardbred horses in which the heart rate and blood lactates were measured after several heats at predetermined increases in pace. At speeds above 450m/min, lactate begins to accumulate in the blood during exercise; the precise kinetics of accumulation depends on the horse's fitness and exercise capacity. Fitness responses include a lower heart rate and lactate concentration for the same exercise speed. The value of these measurements is only as good as the standardization of the testing procedures used.

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6 Chapter 6 Alterations in Cardiovascular and Hemolymphatic Systems

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6.1 PERIPHERAL EDEMA, PLEURAL EFFUSION, ASCITES

Edema is an abnormal accumulation of extracellular fluid in the interstitial spaces of the tissues or in body cavities that can be generalized or localized. If the fluid accumulation occurs in the pleural cavity, it is referred to as *pleural effusion* or *hydrothorax;* if the fluid accumulation is in the abdominal cavity, it is referred to as *peritoneal effusion* or *ascites*.

Fluid accumulates more easily in those parts of the body where the connective tissue structure is relatively loose. The accumulated fluid tends to gravitate to the dependent areas of the body. In the cow, generalized edema is detected externally by swelling of the submandibular tissue, the brisket, the ventral abdomen, and occasionally the limbs (Fig. 6-1). External manifestation of generalized edema in the horse is frequently in the pectoral region between the front limbs, along the ventral abdomen, in the prepuce in stallions and geldings (Fig. 6-2), in the limbs, and sometimes in the head. Stocking up, or limb edema restricted to the lower limbs, is commonly detected in stabled horses with no underlying disease. Large amounts of fluid may accumulate before clinical signs become evident. External evidence of pulmonary edema (i.e., a frothy, possibly blood-tinged fluid in the nares or expectorated) is rarely detected in large animals (Fig. 6-3). There are numerous causes of edema, including congestive heart failure (CHF) (Boxes 6-1 and 6-2). Edema is a late sign of CHF; other subtle signs of failure may be present before edema appears.

6.1.1 Mechanisms of Edema

Edema is caused by an alteration in the equilibrium between capillary permeability and the forces that govern fluid movements at the capillary level. These forces are as follows:

1. Intravascular hydrostatic pressure
2. Interstitial fluid hydrostatic pressure, which exerts a counterpressure to keep fluid within the capillary
3. Intravascular colloid oncotic pressure exerted by plasma proteins, which favors the resorption of interstitial fluid; the major determinant of colloid osmotic pressure in the capillary is albumin
4. Interstitial fluid colloid osmotic pressure exerted by some proteins in the interstitial fluid, which resists resorption of fluid from the interstitial space
5. Vascular surface area capable of fluid transport
6. Vascular permeability to proteins and water

Activation of complement and liberation of cytotoxic agents such as oxygen radicals, leukotrienes, hydrogen peroxide, platelet-activating factor, and lysosomal enzymes contribute to the endothelial and epithelial damage, causing permeability edema. Subsequent increase in colloid osmotic pressure causes fluid accumulation in the interstitial space. The most common causes of increased capillary permeability are trauma, infection,

endotoxemia, and hypersensitivity (allergic) vasculitis. Topical administration of counterirritants can also cause local increase in capillary permeability. Equine purpura hemorrhagica, the most common vasculitic disease in horses, may in its mildest form have symptoms of mucosal petechiae and plaques of edema or, in severe cases, serum exudation from and necrosis of skin surfaces.

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Fig. 6-1 Cow with brisket, ventral, and udder edema.

Fig. 6-2 Gelding with ventral and preputial edema.

Increased hydrostatic pressure can cause either localized or generalized edema. In horses and ruminants the most common causes of increased hydrostatic pressure are CHF, venous thrombosis, liver disease causing obstruction of the portal venous system, lymphadenopathy, a cranial mediastinal mass, compression bandages, limb immobilization, and topical administration of counterirritants. CHF occurs when there is concomitant pulmonary and systemic vascular congestion. The compensatory salt and water retention increases ventricular diastolic, venous, and capillary pressures, which can result in the formation of generalized edema. Arteriolar vasodilation, caused by release of tissue mediators of inflammation or increased venous pressure resulting from obstruction to venous outflow, can also elevate capillary hydrostatic pressure and result in edema formation.

When the plasma protein concentration decreases from normal to values less than 5 g/dL or albumin concentration is less than 1.5 g/dL, generalized edema may occur. Hypoproteinemia can result from (1) decreased production of plasma proteins with starvation, liver disease, or severe heart failure, or (2) augmented loss of plasma proteins resulting from kidney disease, protein-losing enteropathies (Johne's disease, chronic inflammatory bowel disease), peritonitis, or pleuritis. Hemodilution as a result of overzealous administration of fluids or decreased elimination of fluid can cause edema. Failure to excrete adequate water to maintain fluid balance can result from decreased glomerular filtration as a result of kidney disease or heart failure. 84 85

6.1.1.1

Box 6-1 Causes of Peripheral Edema, Pleural Effusion, and Ascites in Horses

6.1.1.1.1

COMMON CAUSES

Chronic heart failure

Mitral or tricuspid regurgitation

Aortic regurgitation

Vegetative endocarditis

Congenital heart defects

Cardiomyopathy

Vitamin E, selenium deficiency

Pericarditis

Pleuritis

Neoplasia: lymphosarcoma

Hypoproteinemia

Liver disease

Gastrointestinal malabsorption: inflammatory bowel disease, neoplasia, parasitism

Peritoneal or pleural effusion

Vasculitis

Equine infectious anemia

Purpura hemorrhagica

Equine ehrlichiosis

Equine viral arteritis

Thrombophlebitis

Lymphatic obstruction

Ulcerative lymphangitis

Lymphadenitis (*Corynebacterium pseudotuberculosis* abscesses)

Trauma

6.1.1.1.2 UNCOMMON CAUSES

Aortic cardiac fistula

Heart base tumor other than lymphosarcoma

Cranial mediastinal mass

Neoplasia: plasma cell myeloma, squamous cell carcinoma, fibrosarcoma

Starvation

Kidney disease: glomerulonephritis, amyloidosis

Ionophore toxicity

Copper deficiency

Counterirritant application

Hemodilution

Pregnancy

Ruptured bladder

Cassia occidentalis toxicity

Fig. 6-3 Gelding with acute fulminant pulmonary edema.

6.1.1.2

Box 6-2 Causes of Peripheral Edema, Pleural Effusion, and Ascites in Ruminants

6.1.1.2.1

COMMON CAUSES

Chronic heart failure

Mitral or tricuspid regurgitation

Vegetative endocarditis

High-altitude disease (brisket disease)

Congenital heart defects

Cor pulmonale

Vitamin E, selenium deficiency

Pericarditis (traumatic reticulopericarditis)

Pleuritis

Heart base tumor: lymphosarcoma

Hypoproteinemia

Liver disease

Kidney disease: amyloidosis, glomerulonephritis

Gastrointestinal malabsorption: lymphosarcoma, Johne's disease, parasitism

Peritoneal or pleural effusion

Lymphatic obstruction (*Corynebacterium pseudotuberculosis*, lymphosarcoma)

Thrombophlebitis

Urolithiasis: ruptured urethra or bladder

6.1.1.2.2

UNCOMMON CAUSES

Eperythrozoan wenyoni (B)

Idiopathic pericardial effusion

Cardiomyopathy

Starvation

Hemodilution

Ionophore toxicity

Copper deficiency

Infectious myocarditis

Vasculitis

Trauma

Pregnancy

Caudal vena caval thrombosis

Ehrlichiosis

Gossypol toxicity

Cassia occidentalis

Phalaris species toxicity

Oxytropis sericea (locoweed) toxicity

Increased tissue colloid osmotic pressure is rarely a cause of edema in horses and ruminants. Interstitial fluid has a lower plasma protein concentration than plasma. When capillary permeability is increased or when abnormal protein-like material is present in the interstitial space, edema can develop by this mechanism. The latter may occur with infection or after administration of topical counterirritants.

Lymphedema occurs when lymphatics are absent or obstructed. Congenital absence of lymphatics is extremely rare. Obstruction to lymphatic drainage can be caused by tumor, local inflammation (lymphangitis or lymphadenitis), or elevated central venous pressure as in heart failure.

6.1.2

Approach to Diagnosis of Peripheral Edema, Pleural Effusion, and Ascites

1 Take history. Note especially history of deworming program, diet, and vitamin or mineral supplements. Determine onset, progression, and duration of the problem and whether other animals are affected. Ask about history of fever, signs of respiratory disease or difficulty, appetite, consistency of feces, and previous medications. Establish the function of the animal and whether there have been changes in performance capability. Compare growth and activity level to that of peers.

2 Perform a physical examination and record vital signs. Determine whether edema is localized or generalized. Palpate external lymph nodes. Palpate edematous areas to determine whether there is heat, pain, or fluid exudation. Edema is typically cool, nonpainful, and pitting, leaving an indentation when a finger is pushed against it. Carefully auscultate heart and lungs. Note abnormalities in cardiac rhythm, murmurs, or other sounds associated with the cardiac cycle. Palpate a peripheral pulse; observe mucous membranes for color, capillary refill time, and petechiae. Observe the jugular vein for distention and pulsations. Evaluate peripheral veins, including the mammary vein, for distention and pulsations. Perform a rectal examination to determine whether internal lymph nodes are enlarged. Palpate the aorta and iliac arteries for pulse strength and fremitus.

3 Obtain blood for the following:

- a Complete blood count (CBC) (includes fibrinogen and plasma protein concentration)
- b Selenium concentrations if cardiomyopathy is suspected
- c *Ehrlichia equi* morula in granulocytes or *Ehrlichia* DNA by polymerase chain reaction if edema, petechial hemorrhages, fever, icterus, or muscle stiffness is present

4 Test serum for the following:

- a Albumin and globulin concentrations
- b Muscle enzyme (creatine kinase [CK], including creatine kinase, myocardial bound [CK-MB] [isoenzyme]; cardiac troponin I [cTnI]; and aspartate aminotransferase [AST]) concentrations
- c Liver enzyme concentrations and liver function (AST, sorbitol dehydrogenase [SDH], alkaline phosphatase, γ-glutamyltransferase [GGT], bilirubin, and bile acid concentrations); values may be elevated in CHF
- d Tests for kidney function as follows: serum urea nitrogen (SUN) and creatinine concentrations, serum electrolyte (Ca, P, Na, K, Cl) concentrations, fractional excretion of electrolytes (see Chapter

34 for method), urinalysis; serum concentrations of Na may be decreased, and SUN may also be elevated in chronic heart failure

e Check for antibodies to equine infectious anemia virus by agar gel immunodiffusion (AGID) or Coggins' test

f Determine titers to equine viral arteritis by serum neutralization if there is ocular inflammation, nasal discharge, abortion, or fever with edema

g *E. equi* antibodies as demonstrated by immunofluorescence if physical examination reveals icterus and fever with edema

h Vitamin E levels if cardiomyopathy suspected

5 Record an electrocardiogram (ECG) to rule out an arrhythmia or conduction disturbance (see Chapter 30); if abnormalities of the ECG are noted, an echocardiogram should be performed.

6 Perform two-dimensional (2-D), M-mode, and Doppler echocardiography if there is a cardiac murmur that is not localized to the left heart base, that radiates, is greater than 2/6 intensity, or is of significant duration.

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7 Analyze fluid to rule out peritonitis, pleuritis, and pericarditis; if physical examination and CBC findings are compatible, examine:

a Pleural fluid

b Pericardial fluid

c Peritoneal fluid

8 Isolate virus from nasopharyngeal swabs, buffy coat, or semen for equine viral arteritis if clinical signs are compatible.

9 Oral D-xylose or glucose absorption test should be done in horses if there is hypoproteinemia and if starvation, renal disease, hepatic disease, pleuritis, peritonitis, infectious gastrointestinal disease, and hemodilution have been ruled out; these tests are not useful in ruminants unless intraabomasal instillation of D-xylose or glucose is accomplished.

6.2 CARDIAC ARRHYTHMIAS

Cardiac arrhythmias are abnormalities in the normal heart rate, rhythm, or conduction pattern. Arrhythmias result from abnormalities of impulse generation or impulse conduction or a combination of both. In the normal heart the impulse is generated in the sinus node because it has the highest rate of spontaneous depolarization. Atrial contraction is followed shortly by ventricular contraction. There is variability in reported normal ranges for heart rate in the large adult animal species, but there is general acceptance of the following ranges:

- Horses: 26 to 50 beats/min; 60 to 80 beats/min in foals
- Cattle: 49 to 84 beats/min
- Sheep and goats: 70 to 90 beats/min

Arrhythmias are more common in horses than in other domestic animal species. As many as 25% of horses that have no other signs of heart disease have cardiac arrhythmias during routine examination or electrocardiography.[1] During continuous 24-hour electrocardiography, 44% of normal horses had second-degree atrioventricular (AV) block, 10% had sinus arrhythmia, 3% had sinoatrial (SA) block, 27% had occasional supraventricular extrasystoles, and 15% had occasional ventricular arrhythmias.[2] Cardiac arrhythmias may be present in 40% of horses that have other signs of cardiac disease.[1] Unlike other species, the horse has arrhythmias at rest that are considered benign or functional. Benign, physiologic, or functional arrhythmias are usually bradyarrhythmias and are thought to be the result of increased vagal tone. These arrhythmias disappear at high heart rates (exercise or excitement) or with the administration of atropine (0.02 to 0.05 mg/kg subcutaneously [SC] or intramuscularly [IM]) or glycopyrrolate (0.003 to 0.006 mg/kg SC or IM). Some examples of benign or functional arrhythmias are as follows:

- Second-degree AV block
- Sinus arrhythmia
- Sinus bradycardia
- SA block
- SA arrest

Other arrhythmias are usually considered to be pathologic, even if there are no other overt signs of cardiac disease. Some examples of pathologic arrhythmias are:

- Atrial fibrillation
- Atrial and ventricular premature depolarizations
- Supraventricular or ventricular tachycardia
- Advanced second-degree or third-degree (complete) AV block

The most effective method of identifying the specific arrhythmia is by performing an ECG. Arrhythmias that are transient or intermittent may not be detected with resting electrocardiography. Radiotelemetry or continuous 24-hour ECG recordings are useful to characterize the type, frequency, and severity of arrhythmias. Exercising electrocardiography may identify arrhythmias that are absent or clinically insignificant at rest but that may impair performance.

In general, cattle do not have benign arrhythmias like horses, but they are frequently found to have sinus bradycardia and sinus arrhythmia associated with lack of feed intake. These arrhythmias were previously thought to be abnormal and associated with vagal indigestion but have been shown to occur in normal cattle held off feed for 12 to 48 hours.[3] Cattle with gastrointestinal disease seem to have increased susceptibility to cardiac arrhythmias, especially atrial premature depolarizations and fibrillation. Although the reason for the susceptibility is not established, abnormal electrolyte concentrations, acid-base disturbances, and aberrations in autonomic nervous system balance have been proposed.[4,5] Sinus arrhythmia in goats is considered to be a benign arrhythmia and is present in many normal animals. Normal camelids also frequently have sinus arrhythmia.

6.2.1

Mechanisms of Cardiac Arrhythmias

Arrhythmias result from abnormalities of impulse generation or impulse conduction or a combination of both. A variety of mechanisms can cause abnormal impulse generation or conduction (Boxes 6-3 and 6-4). Abnormal impulse generation occurs because of localized changes in ionic currents that flow across the membranes of single cells or groups of cells. Abnormal impulse generation can be seen as automaticity (normal and abnormal) or triggered activity.

Automaticity, the ability to initiate action potentials spontaneously, is a property of cells in the sinus node, some parts of the atria, the AV junction, and the His-Purkinje system. Cardiac disease can be responsible for the development of automaticity in cells that normally do not have this property. Normal automaticity develops when the membrane potential slowly falls (i.e., becomes less negative) during diastole. When the membrane reaches its threshold potential, an impulse is initiated. The most common clinical arrhythmias that are thought to be caused by the automaticity mechanism are sinus tachycardia and sinus bradycardia, which are the result of alterations in autonomic nervous system tone. Enhanced automaticity in another area of the heart that is capable of automaticity (spontaneous depolarization) may be responsible for atrial or ventricular premature beats. It is not clear what clinical arrhythmias are caused by triggered activity.

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6.2.1.1

Box 6-3 Causes of Cardiac Arrhythmias in Horses

6.2.1.1.1

COMMON CAUSES

Excitement

Autonomic imbalance

Fever

Sepsis

Toxemia

Hypoxemia

Colic

Metabolic imbalance

Electrolyte abnormalities

Congenital defects

Myocarditis

Valvular disease

6.2.1.1.2 UNCOMMON CAUSES

Ionophore toxicity

Anesthesia

Other drugs

Pericarditis

Cardiomyopathy

Cardiac or heart base tumor

Aortic root rupture

6.2.1.2 Box 6-4 Causes of Cardiac Arrhythmias in Ruminants

6.2.1.2.1 COMMON CAUSES

Gastrointestinal disease

Lymphosarcoma

Valvular heart disease

Myocardial diseases

Brisket disease

Pericarditis

Cor pulmonale caused by pulmonary hypertension

Excitement

Foot rot

Fever

Sepsis

Toxemia

Metabolic imbalance

Electrolyte abnormalities

Myocarditis

6.2.1.2.2

UNCOMMON CAUSES

Ionophore toxicity

Anesthesia

Hypoxemia

Cardiomyopathy

Autonomic imbalance

Under certain circumstances, conduction abnormalities allow a propagating impulse, which has already excited the heart, to persist and reexcite the atria or ventricles after the end of the refractory period. This can occur in an ordered or random fashion. Random reentry occurs over reentrant pathways that continuously change in size and location with time, whereas ordered reentry occurs over a relatively fixed reentrant pathway. Impulse propagation may be slow enough that reentrant circuits can be established in very small areas of myocardium. In large animals the size of the myocardial circuit is large enough that relatively mild alterations in impulse propagation may make reentry feasible and may account for the relatively greater frequency of arrhythmias in these species. Although it is not possible to precisely define the mechanism of clinical arrhythmias, it is believed that atrial and ventricular fibrillation may be caused by random reentry.

Under clinical conditions, cardiac arrhythmias may be associated with disturbances in electrolyte concentrations, especially potassium and calcium, in acid-base balance, and in autonomic nervous system balance. These

conditions can precipitate cellular changes conducive to the development of arrhythmias by any of the above mechanisms.

6.2.2 Approach to Diagnosis of Cardiac Arrhythmias

It is important to distinguish between abnormal arrhythmias that are primary and those that are secondary. Most abnormal arrhythmias of horses and cattle are tachyarrhythmias. Primary arrhythmias are caused by pathologic conditions of the heart (myocarditis, valvular disease, conduction system abnormalities, and pericarditis). Secondary arrhythmias develop in the absence of heart disease and can be caused by excitement, fever, sepsis, hypoxemia, metabolic or electrolyte imbalances, gastrointestinal disturbances, anesthesia, ionophores, other drugs, or toxemia. The treatment and prognosis for the two types of arrhythmias can be very different, and examination and laboratory tests are used to assist in making the distinction.

1. Take history. Determine the diet, feed additives, or medication (including furosemide, bicarbonate, or other prerace medications); note whether there has been exercise intolerance, syncope, fever, coughing, or edema; inquire about gastrointestinal problems, diarrhea, or colic; inquire about access to cattle or chicken feed or supplements and about previous respiratory tract infections in this animal or stablemates.

2. Perform a physical examination to determine whether there is primary cardiac disease. Record the animal's vital signs. Determine whether this is a bradyarrhythmia or tachyarrhythmia. Careful auscultation should note which heart sounds are present and should characterize the arrhythmia. There may be irregularities in the basic rhythm, added sounds, or long pauses; classification of heart rate by regularity of rhythm can distinguish one arrhythmia from another (see Chapter 30). Note whether a pulse deficit is present by simultaneous auscultation and palpation of the peripheral arterial pulse; note the strength of the peripheral arterial pulse; observe the jugular vein for pulsations and distention; examine peripheral veins for distention; and examine mucous membrane color and capillary refill time. Careful auscultation of the lungs with and without a rebreathing bag should be performed.

3. Record an ECG. The base-apex lead can be used to screen for arrhythmias; it is attached using positive, negative, and ground leads as follows:

    a. Positive lead is attached to skin over the left fifth intercostal space at the point of maximal intensity (PMI) of the apex beat; using lead I, this is the left arm electrode; using lead II or lead III, it is the left leg electrode.

    b. Negative lead is attached to the skin of the right jugular furrow two thirds of the distance from the ramus of the mandible to the thoracic inlet; using lead I or lead II, this is the right arm; using lead III, it is the left arm. ECG interpretation is discussed in Chapter 30.

4. If there is a cardiac murmur, perform an echocardiogram (including 2-D, M-mode, and Doppler). Look for evidence of ventricular dysfunction, myocardial failure, chamber dilation, tumor, valvular abnormalities such as endocarditis, congenital defects, aortic cardiac fistula, and pericardial effusion.

5. Obtain feed for analysis if ionophore (monensin, lasalocid, salinomycin) exposure is suspected.

6. Obtain blood for the following:

    a. CBC

    b. Selenium concentrations if cardiomyopathy suspected

c Blood gas determinations and acid-base status

7 Test serum for the following:

a Electrolyte (Na, K, Cl, Ca, Mg, P) concentrations

b Vitamin E (α-tocopherol) concentration

c Cardiac isoenzyme determinations of CK (CK-MB) and cardiac troponin-I (cTnI)[6] if myocarditis or myocardial necrosis is suspected

8 Test urine for the following:

a Electrolyte (Na, K, Cl) concentrations

b Creatinine determination

9 Calculate fractional excretion of potassium in the urine. This will be variable, depending on the diet, but a low value indicates the need for supplementation.

10 Treat the arrhythmia if:

a Patient is hemodynamically unstable (e.g., poor cardiac output, weak peripheral pulses, cold extremities, syncopal)

b There is ventricular tachycardia with a rapid rate (heart rate >100 beats/min for horses and >120 beats/min for cows)

c There are multifocal ventricular ectopic beats

d A QRS is detected in the preceding T wave (R on T)

e There are more than 15 extra systoles per minute

f There is advanced second-degree or complete (third-degree) AV block

g The primary problem is cured or the condition is stabilized, and the patient is symptomatic with the cardiac arrhythmia

6.3 CARDIAC MURMURS

Throughout the cardiovascular system, blood has a laminar or streamlined flow, except in the heart and sometimes in the aorta. Occasionally conditions occur that cause turbulent flow that is sufficient to cause resonance in adjacent structures. This resonance may be heard as a murmur when a critical level of turbulence is reached (Boxes 6-5 and 6-6). The factors that determine whether blood flow is laminar or turbulent are related by the Reynolds number, which is the ratio of the inertial to viscous forces. When the Reynolds number exceeds a critical value (about 2000 in large vessels), turbulence occurs. Increased flow velocity or reduced blood viscosity (e.g., anemia) predisposes to murmur development. The characteristics of the murmur depend on the velocity of the blood flow and the nature of the structures that are caused to vibrate.

It is useful to characterize murmurs with regard to timing in the cardiac cycle (systolic, diastolic, or continuous), duration in the cardiac cycle (early, mid, late, holo-, pan-), intensity (loudness), shape and quality or frequency, PMI, and radiation of the murmur. Systolic murmurs occur anytime between the first and second heart sound. Diastolic murmurs occur between the second and first heart sounds. Continuous murmurs occur throughout the cardiac cycle (Fig. 6-4). The intensity of murmurs is frequently graded on a scale of 1 to 6[7]:

- *Grade 1* is a soft murmur heard only after minutes of careful listening.
- *Grade 2* is a soft murmur heard immediately on auscultation.
- *Grade 3* is a murmur of moderate intensity.
- *Grade 4* is a loud murmur associated with a palpable thrill.
- *Grade 5* is a loud murmur that is not heard when the stethoscope is removed from the chest wall.
- *Grade 6* is a loud murmur that is audible with the entire stethoscope chest piece held away from the chest wall.

6.3.1

Box 6-5 Causes of Cardiac Murmurs in Horses

6.3.1.1

COMMON CAUSES

Anemia

Excitement

Fever

Functional murmur

Exercise

Valvular disease: degenerative, infective, dilation

Congenital defects

Myocarditis

6.3.1.2

UNCOMMON CAUSE

Aortic cardiac fistula

Cardiomyopathy

Pericarditis

Cranial mediastinal abscess

6.3.2 Box 6-6 Causes of Cardiac Murmurs in Ruminants

6.3.2.1 COMMON CAUSES

Anemia

Excitement

Fever

Functional murmur

Valvular disease: infective, degenerative, dilation

Congenital defects

Lymphosarcoma

Pericarditis (usually traumatic reticulopericarditis)

6.3.2.2 UNCOMMON CAUSES

Cardiomyopathy

Myocarditis

The PMI of a murmur usually corresponds to the location of one of the heart valves. Murmurs associated with the mitral valve will frequently be heard best in the left fifth intercostal space just dorsal to the level of the elbow. These murmurs usually radiate dorsally or toward the aortic valve area. Pulmonic valve and aortic valve murmurs are best heard at the base of the heart. For this area to be accessed, the hand is moved under the left triceps muscle to the third and fourth intercostal spaces just below the level of the shoulder. Aortic valve murmurs are located just dorsal and caudal to the pulmonic valve. Murmurs associated with the tricuspid valve are frequently located in the right third or fourth intercostal space between the shoulder and elbow.

Most systolic murmurs fall into one of two categories: ejection or regurgitant (see Fig. 6-4). Systolic ejection murmurs are caused by obstructed, increased, or turbulent blood flow across normal or damaged semilunar valves. Valvular obstruction is rare in large animals, but functional ejection murmurs are commonly found in healthy horses. The PMI of the functional murmur is typically at the pulmonic or aortic valve or just dorsal to them over the great vessels. It is a crescendo-decrescendo murmur that is audible in early-to-mid systole. The diagnostic considerations for systolic ejection murmurs are given in Box 6-7. The innocent or functional murmur may be distinguished from a pathologic murmur by being of lower and variable intensity, peaking in early-to-mid systole, ending well before the second heart sound, and having no radiation. The physiologic systolic ejection murmur may disappear or become louder after exercise. Diagnostic considerations for systolic regurgitant murmurs are listed in Box 6-7.

Regurgitant murmurs typically begin with AV valve closure and end after pulmonic and aortic valve closure, making the second heart sound inaudible. They can be variable in duration, however, and occur in early, mid, or late systole or can be pansystolic or holosystolic. Location of the PMI and the direction of radiation of the systolic murmur distinguish mitral or tricuspid regurgitation from a ventricular septal defect (VSD). Systolic clicks are rare in horses and cattle but may indicate abnormalities of the chordae tendineae, AV valve prolapse, or dilation of the aorta.

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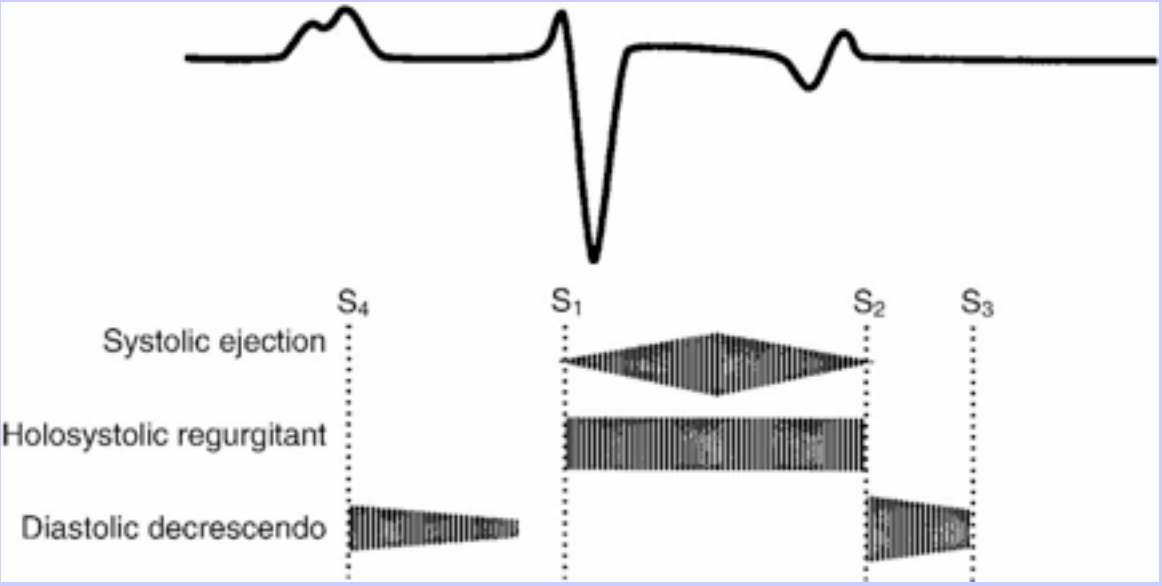
Fig. 6-4 Phonocardiographic characteristics of systolic ejection, holosystolic (pansystolic) regurgitant, and diastolic decrescendo cardiac murmurs.



6.3.3

Box 6-7 Possible Causes of Ejection and Regurgitant Systolic Cardiac Murmurs

6.3.3.1

EJECTION

Innocent murmur

Anemia

Fever

Aortic stenosis

Pulmonic stenosis

Atrial septal defect

Ventricular septal defect

Tetralogy of Fallot

6.3.3.2 REGURGITANT

Mitral regurgitation

Tricuspid regurgitation

Ventricular septal defect

Tetralogy of Fallot

Diastolic murmurs can occur between S_4 and S_1 (atrial systolic murmurs), between S_2 and S_3 (ventricular filling murmurs), or from S_2 to S_1 (aortic regurgitation or rarely, pulmonic regurgitation). Both the atrial systolic and ventricular filling murmurs are usually functional, can be heard over the left or right hemithorax, and can vary in intensity. The aortic regurgitation murmur is typically a decrescendo murmur with its PMI over the aortic valve that begins immediately after S_2 (see Fig. 6-4). Some aortic regurgitation murmurs can be harsh or musical, associated with high-frequency vibrations of an aortic valve leaflet, and they may be audible over the right thorax.

Continuous murmurs are uncommon in horses and ruminants. Patent ductus arteriosus, a finding in normal foals for a short time after delivery, can be heard in the left third intercostal space. This murmur can be continuous, but more frequently only a residual systolic murmur is audible.[8] Continuous machinery murmurs are most frequently reported in adult horses with an aortic cardiac fistula secondary to rupture of the aortic root or of a sinus of Valsalva aneurysm. A continuous “washing machine” murmur, which is most easily heard over the left cardiac area, is associated with traumatic pericarditis in cattle and is caused by the accumulation of fluid, gas, and fibrin within the pericardium. Acquired systolic and diastolic murmurs in adult horses or cattle are usually the result of separate murmurs.

6.3.4 Approach to Diagnosis of Cardiac Murmurs

1 Take a history. Note the age, onset, duration, and progression of the condition. Determine exercise capability, growth, and attitude; inquire about previous fever, illness, or medications.

2 Perform a physical examination. Record the animal's vital signs. Determine timing, duration, intensity, location of PMI, shape, and radiation of murmur. Palpate peripheral arterial pulse and observe jugular vein for distention and pulsations. Carefully auscultate the lungs at rest and during deep inspiration.

3 Obtain blood for CBC (includes fibrinogen and total plasma protein concentration).

4 Test serum for the following:

a Electrolyte concentrations

b Bovine leukosis virus (BLV), AGID status (cows)

c Cardiac isoenzyme determinations of CK (CK-MB) and cTnI[6] if myocarditis or myocardial necrosis is suspected

5 Record an ECG.

6 Perform a phonocardiogram to confirm timing and shape of murmur, if available.

7 Perform an echocardiogram to look for valve abnormalities, abnormalities of the aortic root, congenital defects, chamber enlargement and wall motion abnormalities; use pulsed wave and color flow Doppler echocardiography to localize the shunt, regurgitant blood flow, or stenosis (rare); use color flow and continuous wave Doppler echocardiography to estimate the severity of the jet associated with a shunt, valvular regurgitation, or stenosis (rare); contrast echocardiography can be used for examination of congenital defects and detection of an aortic cardiac fistula and some valvular insufficiency.

8 Take radiographs to find evidence of pulmonary edema or pleural effusion.

9 Perform thoracic and abdominal ultrasonographic examinations to find pleural effusion, peritoneal effusion, and evidence of pulmonary edema or hepatic congestion.

10 Cardiac catheterization for pressures, oximetry, or angiocardiography may complement data obtained noninvasively with Doppler echocardiography.

6.4 MUFFLED HEART SOUNDS

Auscultation of heart sounds requires that the vibrations generated by the heart be transmitted through the tissues of the thorax to the outer chest wall with sufficient amplitude to be heard. Blood transmits sound very well, whereas lung tissue strongly attenuates sound waves. The chest wall itself causes attenuation of the sound that is most significant at the interface between bone and muscle. Therefore physical factors in a normal patient, such as a large, thick chest or obesity, can cause heart sounds to be muffled. If the environment for auscultation is conducive to hearing heart sounds, other factors such as stethoscope quality may cause muffling of heart sounds in a normal patient. One should strive to have a stethoscope with comfortably fitting earpieces, thicker and shorter tubing, a rigid

diaphragm to hear S_1, S_2, and higher-frequency sounds, and a bell piece for auscultation of S_3, S_4, low-frequency sounds, and murmurs.

Heart sounds are muffled primarily because of displacement of the heart from the thoracic wall by fluid (pericardial effusion), a soft-tissue mass (abscess or tumor), or air (pneumothorax, pneumomediastinum, or emphysema) (Boxes 6-8 and 6-9). Rarely is muffling of heart sounds attributed to weak cardiac contractions alone, although this may be a finding in recumbent cows with marked hypocalcemia.

6.4.1

Approach to Diagnosis of Muffled Heart Sounds

1. Take a history. Inquire about any change in attitude, appetite, diet, or posture; determine whether a magnet has been administered to cattle; note any history of fever, weight loss, respiratory disease, colic, or diseases of other body systems and the deworming history; determine whether cattle are known to be BLV positive.

2. Perform a physical examination and determine vital signs. Carefully auscultate the lungs to establish whether there is ventral dullness or evidence of increased or added sounds from pulmonary parenchymal compression; carefully auscultate the heart for pericardial friction rubs; determine whether there are signs of CHF (jugular venous distention, peripheral edema); percuss the thorax to determine whether there is emphysema, pleural fluid, or pneumothorax; note that pleural fluid in the absence of pericardial effusion causes radiating heart sounds but absence of airway sounds; determine whether there is thoracic and/or abdominal pain; in cattle, check for presence of a reticular magnet using a compass or stud finder.

3. Obtain blood for the following:

    a. CBC

    b. Fibrinogen concentration

    c. Plasma or serum protein concentration

    d. Liver enzymes and tests for liver function (AST, SDH, alkaline phosphatase, GGT, bilirubin, and bile acid concentration)

    e. Tests for kidney function (urinalysis, creatinine, blood urea nitrogen [BUN], Na, K, Cl, P concentrations and fractional excretion of Na, Cl, P)

4. Test serum for BLV serology and for equine influenza, viral arteritis, and herpesvirus.

5. Take radiographs of the thorax to determine whether there is pulmonary parenchymal and/or pleural or pericardial disease.

6. Perform an ECG.

7. Perform a thoracic ultrasound examination to determine if there is pericardial or pleural fluid, a cardiac mass, or a mass in the cranial mediastinum compressing the heart. Determine the location and type of fluid present.

8. Analyze pericardial or pleural fluid, and perform culture and sensitivity testing if indicated.

6.4.1.1

Box 6-8 Causes of Muffled Heart Sounds in Horses

6.4.1.1.1

COMMON CAUSES

Obesity

Large or thick chest wall

Pericarditis

Neoplasia: lymphosarcoma

Abscess

Chronic heart failure

6.4.1.1.2

UNCOMMON CAUSES

Pulmonary emphysema

Pneumothorax

Neoplasia: squamous cell carcinoma, fibrosarcoma

6.4.1.2

Box 6-9 Causes of Muffled Heart Sounds in Ruminants

6.4.1.2.1

COMMON CAUSES

Obesity

Large or thick chest wall

Pericarditis (traumatic reticulopericarditis)

Neoplasia: lymphosarcoma

Abscess

Chronic heart failure

Emphysema

6.4.1.2.2 UNCOMMON CAUSE

Pneumothorax

6.5 CARDIOVASCULAR EXERCISE INTOLERANCE, WEAKNESS, AND SYNCOPE

Exercise intolerance, weakness, or syncope can be a clinical sign associated with disease in many body systems. Exercise intolerance can be manifested as sudden deceleration or stopping, failure to perform at an expected level, a sudden change in the level of performance or production, lowered enthusiasm for work, cough on exertion, evidence of respiratory distress, or excessive sweating. Weakness can be manifested as recumbency, difficulty in rising from recumbency, muscle tremors or fasciculations, reluctance to move, or toe dragging. Syncope is a sudden collapse and loss of consciousness (fainting).

6.5.1 Mechanisms of Cardiovascular Exercise Intolerance, Weakness, and Syncope

The clinical signs of exercise intolerance, syncope, or weakness can be caused by cardiovascular disease (Boxes 6-10 and 6-11). They are the result of failure to maintain cardiac output, caused by inability to regulate either heart rate or stroke volume. A normal horse increases cardiac output at submaximum heart rates (less than 210 beats/min in horses) primarily by tachycardia. At maximum heart rates (approximately 210 to 240 beats/min in horses), subsequent increments in cardiac output occur by increased stroke volume.[9] The maximum heart rate for cattle and small ruminants has not been published.

Supraventricular cardiac arrhythmias, primarily atrial fibrillation in horses, can lead to heart rates greater than 240 beats/min with submaximum exercise.[10,11] Heart rates exceeding the maximum rate may limit cardiac output by decreasing the time for diastolic perfusion of the myocardium or by limiting stroke volume because the short diastolic intervals leave inadequate time for ventricular filling. The ability to maintain cardiac output can also be compromised by other cardiac arrhythmias such as ventricular premature systoles. The frequency of extrasystoles can increase with exercise, and the timing of the abnormal beats can reduce cardiac output even at submaximum heart rates.[12] Horses with cardiac arrhythmias can have abnormal elevations in lactate concentration in response to exercise, indicating a lower anaerobic threshold and leading to exercise intolerance.[13,14]

6.5.1.1 Box 6-10 Causes of Exercise Intolerance, Weakness, and Syncope in Horses*

6.5.1.1.1 COMMON CAUSES

Myocardial disease

Cardiac arrhythmias

Aortic or pulmonary artery rupture

Aortoiliac-femoral arteriosclerosis or thrombosis

Congenital heart defects

Chronic heart failure

Pericardial disease

Hyperkalemic periodic paralysis

Central nervous system disturbances resulting in loss of consciousness

* See Chapters 8 and 13 for additional noncardiac causes.

6.5.1.2

Box 6-11 Causes of Exercise Intolerance, Weakness, and Syncope in Ruminants*

6.5.1.2.1

COMMON CAUSES

Myocardial disease

Cardiac arrhythmias

Congenital heart defects

Chronic heart failure

* See Chapters 8 and 13 for additional noncardiac causes.

Cardiac output maintenance may also be compromised in animals by diseases affecting myocardial contractility or diseases that result in increased end-systolic volume despite a submaximum heart rate.[15] Diseases that result in decreased venous return (peripheral vascular disease) can also reduce cardiac output and cause signs of exercise intolerance, weakness, or syncope.

Exercise intolerance or weakness can also be caused by painful peripheral vascular conditions or conditions causing peripheral hypoxia or lactic acid accumulation. In horses such conditions may exist with aortoiliac

thrombosis. Sudden episodes of weakness and collapse without change in consciousness are associated with hyperkalemic period paralysis in horses (see Chapter 42).

Syncope may be associated with epilepsy or other central nervous system (CNS) disturbance. If cardiovascular and pulmonary function appears normal, the nervous system should be examined in detail (see Chapter 8). Collapse during exercise is most commonly caused by cardiovascular disease, whereas collapse at rest is usually associated with neurologic disease.

6.5.2 Approach to Diagnosis of Exercise Intolerance, Weakness, and Syncope

1. Take history. Establish onset of problem, previous performance history, and activity level when clinical signs are observed. Determine whether there is coughing, dyspnea, or excessive sweating associated with stress or exercise.
2. Perform a physical examination and record vital signs to determine whether lameness or respiratory or neurologic disease is the cause of these clinical signs. Of particular importance are heart rate at rest, peripheral arterial pulse characteristics, presence of pulse deficits, mucous membrane color, and appearance of jugular venous pulses. Lungs should be auscultated for evidence of pulmonary edema or pleural effusion. The chest should be percussed. Rectal examination should be performed to evaluate aortic and iliac arterial pulses; metatarsal artery pulses and saphenous vein refill should be evaluated.
3. Perform a rectal ultrasound examination if aortoiliac thrombosis is suspected, to document the disease and assess its severity.
4. Record an ECG at rest, during exercise (preferably with radiotelemetry), and after exercise, if it is safe for the animal to exercise. Perform a continuous 24-hour ECG to evaluate frequency of arrhythmias.
5. Perform an echocardiogram (2-D, M-mode and Doppler) to evaluate size of heart chambers; to look for congenital defects, acquired valvular heart disease, and pericardial disease; and to evaluate myocardial contractility and ventricular wall motion.
6. Perform a stress echocardiogram before and after exercise to evaluate changes in myocardial contractility and ventricular wall motion with exercise.
7. Perform an exercise test to measure a parameter of lactic acid concentration (i.e., lactic acid accumulation after exercise test, lactic acid concentration at defined velocity of exercise, or velocity of exercise at a defined lactic acid concentration), arterial blood gas concentrations, preexercise and postexercise CK levels, cTnI, and exercise endoscopy to make an upper airway evaluation.

6.6 VENOUS DISTENTION AND PULSATIONS

The jugular venous pulsations observed in the neck are primarily a reflection of right atrial and right ventricular activity. There may be some small contribution from carotid arterial impact.[16] The jugular venous pulse reflects the right atrial or central venous pressure, which is influenced by blood volume, right ventricular cardiac output, and right atrial contractility (Boxes 6-12 and 6-13). Jugular venous pulsations are observed in normal animals, but the pulse seldom radiates more than one third of the distance from the thoracic inlet to the ramus of the mandible when the head is held in a normal, upright position.

6.6.1

Mechanisms of Venous Distention and Pulsations

The normal jugular venous pulse consists of three positive and two negative deflections (Fig. 6-5). The first and dominant positive wave is the A wave, produced by atrial contraction. During atrial relaxation the pressure declines until ventricular systole. The second positive deflection is the C wave, which is produced by the bulging of the tricuspid valve leaflets into the right atrium during early (isovolumetric) right ventricular systole. Carotid arterial impact on the jugular vein may also contribute to the C wave.[16] As the ventricle contracts, the plane of the tricuspid valve is pulled toward the apex of the heart and the atrial pressure declines, producing the X descent. The X descent is terminated by the V wave, which is associated with venous return, subsequent atrial filling, and a closed tricuspid valve. At the end of ventricular systole, the atrial pressure falls again as a result of tricuspid valve opening and rapid right ventricular filling. This is the Y descent. The Y descent is terminated as the pressure gradually rises with right-sided heart filling.

Abnormal pulsations occur with increased resistance to right ventricular filling, regardless of the cause. Distention and pulsations in the jugular vein are usually associated with an elevated right ventricular pressure, such as occurs in right-sided heart failure, constrictive pericarditis, or, more rarely, cardiomyopathy. Prominent jugular pulsations are noted with tricuspid regurgitation and certain cardiac arrhythmias, especially those arrhythmias associated with atrial contraction against a closed AV valve. The carotid arterial pulse can mimic jugular venous pulsations. To distinguish among the causes of jugular venous pulsations, lightly compress but do not occlude the jugular vein at the thoracic inlet. The jugular vein will distend enough to eliminate carotid arterial pulsations. If pulsations are still present, tricuspid regurgitation, atrial arrhythmias, or right-sided heart failure should be considered. If the jugular vein is compressed near the ramus of the mandible and massaged toward the thoracic inlet, refilling is indicative of tricuspid regurgitation. Jugular venous distention without pulsations can occur with compression of the cranial vena cava from a cranial thoracic or mediastinal mass or from occlusion of the jugular vein with a thrombus.

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6.6.1.1

Box 6-12 Causes of Jugular Venous Distention and Pulsation in Horses

6.6.1.1.1

COMMON CAUSES

Right-sided heart failure

Chronic heart failure

Cardiomyopathy

Atrial fibrillation

Tricuspid regurgitation

Cranial mediastinal mass

Lymphosarcoma

Abscess

Jugular venous phlebitis and thrombosis

6.6.1.1.2 UNCOMMON CAUSES

Ionophore toxicity

Pericarditis

Myocarditis

Squamous cell carcinoma

Fibrosarcoma

Cor pulmonale

Chronic obstructive pulmonary disease

Overhydration

6.6.1.2 Box 6-13 Causes of Jugular Venous Distention and Pulsation in Ruminants

6.6.1.2.1 COMMON CAUSES

Right-sided heart failure

Chronic heart failure

Vitamin E or selenium deficiency (white muscle disease)

Cardiomyopathy

Tricuspid regurgitation

Pericarditis

Jugular venous phlebitis and thrombosis

Heart base tumor: lymphosarcoma

Heart base abscess

Cor pulmonale caused by chronic pneumonia

Brisket disease

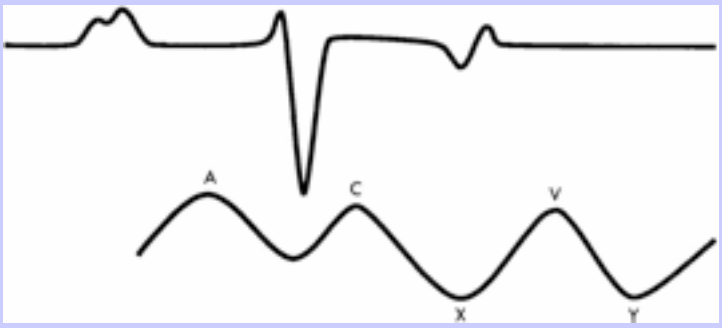
6.6.1.2.2 UNCOMMON CAUSES

Ionophore toxicity

Overhydration

Cranial mediastinal mass

Fig. 6-5 Schematic illustration of a venous (jugular or atrial) pressure curve and its relationship to events of the electrocardiogram. *A,* Positive wave produced by atrial contraction; *C,* second positive deflection caused by bulging of the tricuspid valve during isovolumetric systole; *X,* first negative wave produced by the plane of the AV valve being pulled toward the apex of the heart during systole; *V,* positive pressure wave caused by venous return; *Y,* negative wave produced by AV valve opening.



6.6.2 Approach to Diagnosis of VenousDistention and Pulsations

1 Take history. Note especially history of respiratory disease, exposure to high altitude and locoweed, or ingestion of potential cardiotoxins. Determine whether other animals have been similarly affected, whether the BLV status of affected cattle is known, and whether a magnet has been administered.

2 Perform a physical examination. Determine whether there is tachypnea or tachycardia. Carefully auscultate for abnormal heart sounds, rhythm, or intensity of sounds; note whether jugular veins are patent. Look for jugular venous pulsations as described previously.

3 Obtain blood for the following:

a CBC

b Fibrinogen concentration

c Total protein concentration

d BLV status (bovine) and serology for equine influenza, viral arteritis, and herpesvirus

e Vitamin E (serum) and selenium concentrations if cardiomyopathy suspected

4 Take radiographs of the thorax and abdomen to establish whether there is respiratory disease, a magnet, or a penetrating foreign body.

5 Record an ECG when there is an arrhythmia to look for atrial premature depolarizations.

6 Perform an echocardiogram to examine the following:

a Right ventricular size and function

b Right atrium, for abnormal size or structures

c Tricuspid valve

d Pulmonary artery diameter

e Left atrial size

f Left ventricular size and function

g Pericardium

h Interventricular septal thickness and motion

7 Perform Doppler echocardiogram to look for:

a Tricuspid regurgitation

b Pulmonic regurgitation

c If tricuspid or pulmonic regurgitation detected, check for concurrent mitral and aortic regurgitation

8 Perform ultrasound examination of the cranial thorax and cranial mediastinum.

9 Jugular venous catheterization may be useful to determine right atrial (central venous), right ventricular, and pulmonary arterial pressures.

6.7 PAINFUL PERIPHERAL SWELLINGS

Close inspection of the skin and extremities of patients can reveal evidence of peripheral vascular or lymphatic system disease. These diseases can be manifested by diffuse swelling, localized swelling (papules, nodules, macules, or wheals), or subcutaneous edema of the extremities. Frequently there is necrosis, ulceration of the skin, and exudation as the disease progresses. Animals may be lame or dyspneic, have heat in the involved area, or exhibit a painful response to palpation of the area (Boxes 6-14 and 6-15), which helps to differentiate these conditions from nonpainful peripheral edema.

6.7.1 Approach to Diagnosis of PainfulPeripheral Swellings

1 Take history. Establish whether there is a history of a wound or trauma to the area or previous drainage; inquire about previous infections, particularly those referable to the respiratory system, in this animal or others; determine vaccination, deworming, and drug administration history.

6.7.1.0.0.0.1

Box 6-14 Causes of Painful Peripheral Swellings in Horses

6.7.1.0.0.0.1.1

COMMON CAUSES

Thrombophlebitis

Abscess (*Corynebacterium pseudotuberculosis* in western United States)

Cellulitis

Hypersensitivity vasculitis (complicated by skin necrosis and secondary infection)

Equine viral arteritis

Ehrlichia equi

Equine infectious anemia

Purpura hemorrhagica

Clostridium species myositis

Insect bite

Snakebite

Application of topical counterirritants, firing, or soring

6.7.1.0.0.0.1.2

UNCOMMON CAUSES

Frostbite

Piroplasmosis

Ulcerative lymphangitis

Epizootic lymphangitis

Glanders

Sporotrichosis

Immune vasculitis

Aortoiliac thrombosis

Sporadic lymphangitis

Congenital lymph node and lymphatic dysgenesis

Hemangiosarcoma

6.7.1.0.0.0.2

Box 6-15 Causes of Painful Peripheral Swellings in Ruminants

6.7.1.0.0.0.2.1

COMMON CAUSES

Thrombophlebitis

Abscess

Clostridial myositis

Malignant edema

Blackleg

Fescue foot

Ergotism

Cellulitis (injection site or wound)

Insect bite

Snakebite

Frostbite

6.7.1.0.0.0.2.2 UNCOMMON CAUSES

Disseminated hemangiosarcoma

Ehrlichiosis

2 Perform a physical examination. Determine vital signs. Note whether animal is febrile; examine extremities for wounds, dilated lymphatic channels, ulcers, focal swellings, and edema; determine the temperature and sensitivity of the swollen area; examine mucous membranes for color and presence of hemorrhages; perform a rectal examination and palpate aortic quadrifurcation in horses for vessel size, firmness, pain, fremitus, and strength of pulse; evaluate these vessels before and after exercise, if indicated; test saphenous refill by holding off the saphenous vein distally over the hock, stripping the vein proximally and releasing the pressure over the vein at the level of the hock.

3 Obtain blood for the following:

a CBC (includes examination of red blood cells, neutrophils, and eosinophils for inclusion bodies or morula and determination of platelet count)

b Fibrinogen concentration

c Total protein concentration

d Coombs' or direct immunofluorescence test

e Appropriate tests for equine ehrlichiosis (immunofluorescence assay), piroplasmosis (complement fixation), or viral arteritis (serum neutralization), if indicated

4 Take radiographs of swollen extremities, if appropriate.

5 Perform an ultrasound examination of the swelling, if appropriate.

6 Obtain Gram stain and bacterial and fungal culture of ulcerated area or exudate.

7 Perform a biopsy of granulomas and submit for histopathology and culture and sensitivity testing, if appropriate.

8 Analyze and culture fluid obtained from dilated lymphatic channels or localized edematous areas.

9 Analyze urine to look for hemoglobinuria or hema-turia.

10 Test feces for fecal occult blood.

6.8 ENLARGED LYMPH NODES

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Diffuse or single lymph node enlargement occurs with infectious (bacterial, viral, fungal) conditions, neoplasia, and, rarely, immune-mediated causes in large animals (Boxes 6-16 and 6-17). Lymphadenopathy may cause obstruction to lymphatic drainage, leading to peripheral edema, pleural effusion, or ascites. The peripheral lymph nodes that are most readily accessible for examination are the submandibular (horses), superficial cervical (ruminants), and superficial inguinal (ruminants) lymph nodes. When there is generalized lymphadenopathy, internal lymph nodes may be enlarged, causing clinical signs such as dyspnea, esophageal obstruction, diarrhea, or other signs of organ dysfunction.

6.8.1 Box 6-16 Causes of Enlarged Lymph Nodes in Horses

6.8.1.1 COMMON CAUSES

Strangles

Lymphosarcoma

Upper respiratory infection

Corynebacterium pseudotuberculosis lymphadenitis

6.8.1.2 UNCOMMON CAUSES

- Ulcerative lymphangitis
- Epizootic lymphangitis
- Sporadic lymphangitis
- Glanders
- Granulomatous lymphadenitis
- Plasma cell myeloma
- Tuberculosis
- Hemolytic uremic-like syndrome

6.8.2 Box 6-17 Causes of Enlarged Lymph Nodes in Ruminants

6.8.2.1 COMMON CAUSES

- Caseous lymphadenitis (*Corynebacterium pseudotuberculosis*)
- Lymphosarcoma (including bovine leukosis virus)
- Abscess or cellulitis of area drained

6.8.2.2 UNCOMMON CAUSES

- Tuberculosis
- Sporadic bovine encephalomyelitis
- Malignant catarrhal fever

6.8.3 Approach to Diagnosis of Enlarged Lymph Nodes

1 Take history. Note especially history of weight loss, inappetence, depression, lethargy, or lymph node enlargement; inquire about previous illness or wounds; for cattle, determine whether there is a history of lymphosarcoma in the family or herd and whether the cow has a positive BLV test result; for sheep and goats, determine whether there is a history of *Corynebacterium pseudotuberculosis* abscesses in the flock or herd.

2 Perform physical examination. Determine vital signs. Examine peripheral lymph nodes or other swellings, perform a rectal examination to palpate accessible internal lymph nodes, and, when appropriate, examine the uterus in cattle; check mucous membranes for pallor or icterus; determine whether there is jugular venous distention or pulsations or whether there is evidence of pleural or pericardial effusion or ascites.

3 Obtain blood for the following:

a CBC to examine for anemia or leukemic changes; note inclusions, morula, or abnormal appearance of cells

b Serum chemistry profile to determine if there are signs of other organ dysfunction (e.g., gastrointestinal [hypoproteinemia], liver, or kidney)

4 Test feces for occult blood, if indicated.

5 Perform ultrasonographic examination of the lymph node or swelling.

6 Obtain lymph node or swelling aspirate and biopsy sample for culture and histopathologic examination.

7 Obtain a bone marrow sample for cytologic exam-ination.

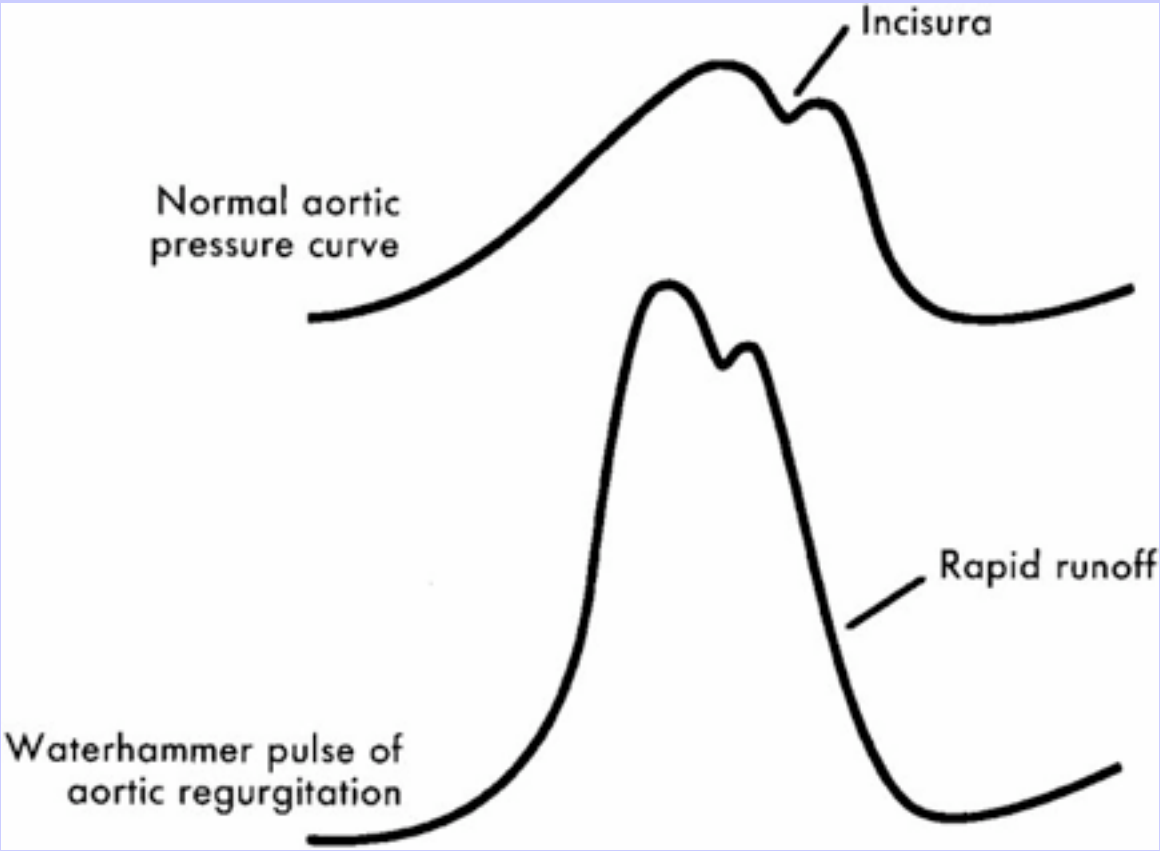
6.9 ABNORMAL PERIPHERAL PULSE

Palpation of the arterial pulse is an important aspect of the examination of the patient with cardiovascular disease. Arterial pulse strength and contour (how fast pressure rises and falls) are the objectives of the examination and are determined by the cardiac output, heart rate, and vascular impedance. The arterial pressure pulse begins with the opening of the aortic valve and ventricular ejection and rises rapidly in early systole. The pulse pressure reaches a peak then declines as ventricular ejection slows. During isovolumic relaxation (before AV valve opening), there is a transient reversal of flow in the arterial system, and an incisura or dicrotic notch (Fig. 6-6) is inscribed on the descending limb of the pressure curve. Following the incisura, there is a small positive wave that is attributed to elastic recoil of the aorta and the aortic valve and the summation of reflected waves from more distal arteries.[15] After the positive wave, the pulse pressure declines because there is peripheral runoff of blood in diastole. The incisura and secondary positive wave are not usually palpable. Palpation of peripheral arteries (facial, transverse facial, and digital arteries in the horse and median and coccygeal arteries in ruminants) normally reveals a smooth, rapid upstroke, a dome-shaped summit, and a downstroke that is slightly more prolonged than the upstroke.

Pressure values and pulse wave configurations are altered as the pressure waves are transmitted through the peripheral arterial tree. With increasing distance from the heart, the dicrotic notch and second positive wave disappear, the systolic pressure gets higher (loss of distensibility in the distal arteries and summation of reflected pulse waves from the distal vascular bed), and the diastolic pressure gets lower. The difference between the systolic

and diastolic pressure determines pulse pressure and can be evaluated by an impression of pulse strength. Pulse pressure increases as one moves to more peripheral arterial sites. The mean arterial pressure changes very little but decreases slightly as one moves downstream in the arterial system from the pressure source. Systolic blood pressure, as measured indirectly at the tail or on a limb, is higher than that measured in the ascending aorta. In smaller arterial beds (e.g., arteries of the ear), the pulse wave is gradually dampened and pulsatile characteristics are lost on the capillaries and small veins.

Fig. 6-6 Schematic illustration of the normal arterial pressure pulse. The incisura that occurs during the descending limb is caused by a transient reversal in flow during isovolumic relaxation. Compared with the normal arterial pressure pulse, the waterhammer pulse of aortic regurgitation builds rapidly and has a rapid runoff.



6.9.1 Mechanisms of Abnormal Peripheral Pulse

Hyperkinetic arterial pulses occur in patients with increased cardiac output (e.g., fever, exercise, excitement), increased stroke volume, or bradycardia (Boxes 6-18 and 6-19). It may also occur when there is rapid runoff of blood in the arterial system, as occurs with aortic valve regurgitation, patent ductus arteriosus, or aortic cardiac fistulas. In aortic valve regurgitation the rapidly rising, hyperdynamic pulse is caused by increased stroke volume

(regurgitated blood in the left ventricle), followed by a rapid runoff of pressure later in systole as a result of regurgitation (see Fig. 6-6).

Hypokinetic pulses are present in patients with diminished stroke volume caused by hypovolemia, left ventricular failure, or, rarely, in large animals, mitral or aortic valve stenosis.

Abnormal peripheral pulses are detected in patients with cardiac arrhythmias. With premature ventricular contractions (PVCs), the compensatory pause that occurs after the PVC allows a longer period of time for ventricular filling, which results in a greater end-diastolic volume, increased contractile force, and a stronger pulse in the beat that follows the PVC. The strength of the peripheral pulse is variable in arrhythmias such as atrial fibrillation because the irregular rhythm is associated with variable time for ventricular filling. Certain arrhythmias, particularly tachyarrhythmias, allow inadequate ventricular filling to generate a peripheral arterial pulse, and a pulse deficit is palpated.

6.9.2 Approach to Diagnosis of Abnormal Peripheral Pulse

1 Take history. Note changes in appetite, attitude, milk production, or ability to exercise; determine whether there have been signs of previous illness and duration and progression of the problem.

2 Perform a physical examination. Determine vital signs. Note whether there is a cardiac arrhythmia, murmur, or other evidence of heart disease (e.g., jugular venous distention or pulsation, edema). Palpate the pulse in multiple sites and bilaterally to rule out occlusive arterial disease; check patient's hydration.

3 Obtain blood for the following:

   a CBC; look for evidence of toxemia or anemia

   b Blood gases to determine acid-base balance

   c Electrolyte concentration, especially Ca and K

4 Record an ECG to characterize any arrhythmia.

5 Determine blood pressure. The site for indirect blood pressure measurement in the standing animal is the tail over the coccygeal artery; a limb can be used in a recumbent animal. Take the mean of several (minimum of three) readings in which the blood pressure cuff is gradually inflated and deflated at approximately 2 to 4 mm Hg/sec; values obtained should be corrected for the difference in height between the site measured and the heart, which is considered to be at the level of the shoulder; the difference in height (centimeters) between the heart and the site of pressure measurement is multiplied by 0.77 (constant used to convert centimeters of blood to millimeters of mercury). In standing horses, approximately 27 mm Hg is added to the indirectly measured coccygeal artery pressure to give the corrected value[17]; no correction factor is needed if the measurement is made in a recumbent animal. An appropriately sized blood pressure cuff is considered to be one fourth of the tail circumference[18]; in horses a 4.5- to 5.6-cm cuff has been recommended for electronic oscillometric devices, and a 10.6-cm cuff for ultrasonic flowmeters.[17] Values for normal horses by blood flow detection methods are 79/49 to 145/106 mm Hg (uncorrected for the height of the tail).[16]

6 Blood pressure can be evaluated by Doppler scan, or measurements can be recorded by direct cardiac catheterization (see Chapter 30).

7 Perform an echocardiogram to evaluate size of chambers, myocardial function, presence of valvular or pericardial disease, or congenital defects.

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7 Chapter 7 Alterations in Alimentary and Hepatic Function

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7.1 DIARRHEA

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Diarrhea, is defined as an increase in the frequency, fluidity, or volume of bowel movements. Diarrhea may be a sign of a primary bowel disease or a nonspecific response to sepsis, toxemia, or disease of another organ system.

Under normal circumstances a large volume of essentially isotonic fluid enters the proximal bowel daily. Most of this fluid is resorbed, and only a small percentage is passed with the feces. The fluid comes from dietary intake and from endogenous secretions of the upper digestive tract. The total daily volume exchanged exceeds that of the animal's total extracellular fluid volume. Normally absorption just exceeds secretion; therefore very small changes in rate of absorption or secretion can result in diarrhea. In the horse most water resorption occurs in the cecum and large colon, and diarrhea in the horse (other than neonates) usually involves some abnormality in the lumen or wall of the large bowel.

Normal fecal color is tan, brown, or greenish, depending on diet. The adult horse normally produces 11 to 13 kg of fecal material per day (20 to 28 g/kg of body weight per day) while on a diet of grass hay and 3 lb of oats.[1] Fecal output was as high as 20 kg/day in horses fed a mixture of alfalfa and orchard grass ad libitum.[2] Horses with chronic watery diarrhea can produce up to 214 g/kg of body weight per day,[1] which is over 90 L of diarrhea in a 450-kg horse. Cattle normally produce 15 to 28 kg of feces per day with a water content of about 75% to 85% on a diet of grass hay.[3] Fluidity of cattle feces can increase markedly in animals on lush green feed. Sheep and goat feces contain only 50% to 60% water.[3] Fluid feces in the cow and unformed feces in the horse, goat, and sheep are very nonspecific signs that often accompany sepsis or illness other than a primary gastrointestinal disease.

Animals with chronic diarrhea rarely develop severe dehydration because they compensate for increased fecal water losses by increasing water consumption by an equivalent amount. Normal water consumption in the horse on a hay diet in a mild ambient temperature environment is about 24 to 30 L/day, whereas cattle consume 30 to 60 L/day based on 10 kg of dry matter feed intake. Water and feed intake do not increase linearly with increasing body size, but by multiplying body weight in kilograms to the 0.75th power ($BW^{0.75}_{kg}$) by a base factor (about 200 mL for water). Thus a 500-kg horse requires 21 L of water. The effect of temperature on water intake is dramatic and is not linear; as ambient temperatures rise close to 37° C (98° F), water intake per kilogram of dry matter increases much more rapidly than at lower temperatures. Exercise and loss through sweat, particularly in the horse, can dramatically increase salt and water requirements.

7.1.1 Mechanisms of Diarrhea (Box 7-1)

The following six major mechanisms produce diarrhea:

- Decreased or damaged absorptive surface area (malabsorption)
- Increased numbers of osmotically active particles within the intestinal lumen
- Increased volume of secretion of solutes and water
- Abnormal intestinal motility resulting in decreased transit time, as with systemic inflammatory response syndrome (SIRS)
- Increased blood-to-lumen pressure as in heart failure or acute or chronic inflammatory bowel diseases
- Gastrointestinal inflammation, as occurs with peritonitis

The common net result is an increase in fecal water.

Decreased surface area, is mainly a result of villus blunting (atrophy) and/or microvillus damage in the small intestine, which lead to malabsorption. Both occur to some degree with most enteric diseases, and regeneration of surface area from crypt cells with healing is accompanied by a gradual decrease in volume of diarrhea. Diseases in which this is a major mechanism include neonatal diseases such as rotavirus and coronavirus enteric disease,[4] cryptosporidiosis, acute inflammatory disease such as salmonellosis, and chronic diseases such as Johne's disease and other granulomatous bowel diseases. The finding of villus atrophy is so nonspecific that it is not diagnostic in itself. It can also occur in advanced cases of secondary copper deficiency (molybdenosis) with diarrhea. Loss of villus epithelial cells can result in maldigestion because these cells produce important enzymes such as lactase. Many neonates with enteritis develop temporary lactose intolerance as a result, especially with rotaviral and clostridial infections.

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7.1.1.1

Box 7-1 Mechanisms of Diarrhea

Malabsorption (villus atrophy)

Osmotic overload

Secretory

Abnormal motility

Increased blood-to-lumen hydraulic pressure

Inflammation

Decreased transit time

Inflammation, can be accompanied by increased mucus production and increases in size of membrane pores, through which tissue fluids and serum proteins leak into the lumen. This is associated with increased capillary

and lymphatic hydraulic pressures. Whether acute *(Salmonella)*, or chronic (Johne's), inflammatory bowel diseases are protein-losing enteropathies. Low plasma protein concentrations, particularly low albumin, are often found (unless hypovolemia and hemoconcentration are present). Bowel inflammation often results in transudation and exudation of serum proteins, blood, and/or mucus, resulting in dysentery (bloody diarrhea). In addition to salmonellosis, dysentery may also commonly be seen with enterotoxemia caused by *Clostridium perfringens*, type A, B, or C, *Clostridium difficile, Lawsonia intracellularis*,[5] attaching effacing *Escherichia coli, Campylobacter jejuni*, coccidiosis, malignant catarrhal fever (MCF), arsenic toxicity, and oak toxicity. Inflammation results in malabsorption, maldigestion, osmotic effects, and, in acute disease, changes in intestinal motility. Because most water absorption in the horse occurs in the cecum and colon, inflammatory typhlitis and colitis are the major causes of diarrhea in the horse (Boxes 7-2 and 7-3). The neonatal foal commonly develops small intestinal enteritis.

7.1.1.2

Box 7-2 Causes of Diarrhea in Horses (Except Neonates; see Chapter 19 for Neonates)

7.1.1.2.1

COMMON CAUSES

Colitis or typhlitis

Salmonellosis

Enteritis, unknown cause

Potomac fever (equine monocytic ehrlichiosis)

Endotoxemia or gram-negative sepsis

Overfeeding or sudden change in diet

Clostridium difficile,

7.1.1.2.2

LESS COMMON CAUSES

Eosinophilic gastroenteritis

Renal failure, uremia

Necrotizing enterocolitis

Heart failure

Enterotoxemia *(Clostridium perfringens*, mainly type A)

Lawsonia intracellularis, (mainly foals and weanlings), proliferative enteropathy

Intestinal lymphosarcoma

Cathartics or laxatives

Parasympathomimetics

Chronic granulomatous bowel disease

Proximal enteritis

Peritonitis

Intussusception

Sand, gravel, or enterolith in gut lumen

Gut stenosis

Antibiotic use

Rhodococcus (Corynebacterium) equi, gut infection (mainly foals)

Cryptosporidiosis (mainly foals)

Giardiasis (mainly foals)

Toxins or poisonous plants (see Box 7-3)

7.1.1.2.3 UNCOMMON CAUSES

Hepatic failure

Cholelithiasis

Vascular aneurysm

Combined immunodeficiency

Agammaglobulinemia

Lactose intolerance (mainly foals)

Campylobacter jejuni, (mainly foals)

Colorectal polyps

Anaphylaxis

Vitamin A deficiency

Tularemia

Snake bite, insect or spider sting or bite

Histoplasmosis

Hydroallantois

Hyperlipidemia

Internal abdominal abscess

Pheochromocytoma

Viral arteritis

Besnoitiosis (globidiosis) (exotic)

Irritation of the bowel with a foreign body such as sand may result in either low-grade recurrent colic or diarrhea. Weight loss may also be evident with a large amount of sand. Sand accumulation in the large bowel of the horse may be suspected when there is evidence of a significant amount of sand in the feces or when sand is auscultable

with a stethoscope over the ventral abdomen. Irritation probably causes diarrhea through creation of an inflammatory response and altered motility.

Osmotic diarrhea, results from any disease causing maldigestion and/or malabsorption. Any osmotically active solute can produce diarrhea in normal animals if given in quantities sufficient to surpass the intestinal capacity for digestion or absorption. Disaccharides are natural examples. Osmotic cathartics such as dioctyl sodium sulfosuccinate (DSS) hold water in the intestine and act as fecal softeners. Magnesium phosphates and sulfates and other divalent and trivalent cations and anions are poorly absorbed and thus are effective laxatives and cathartics.

Osmotic diarrhea can be associated with ingestion of osmotically active poorly absorbed solutes, overloading of the intestine with carbohydrates or lipids beyond the amount that can be digested and absorbed, sudden dietary changes resulting in marked shifts in gut flora and resulting bacterial action on ingested substrate (e.g., grain overload), or bowel disease in which surface area is diminished or digestion interfered with in some manner. Lactase deficiency, secondary to rotavirus or *C. difficile*, infections, may result in osmotic diarrhea in foals.[6] This results in increased concentration of undigested and/or unabsorbed nutrients entering the lower bowel, increased bacterial fermentation, and an increase in the concentration of osmotically active particles. Unfavorable electrochemical gradients prevent resorption of water. Mucosal digestive enzyme levels are often decreased with any disease involving the small intestine, resulting in maldigestion. When osmotic diarrhea is suspected in mature animals, dietary modification to basic roughage should be tried as part of the nonspecific therapy. Sodium and potassium are normally present in roughly equal amounts in feces and (with a little ammonium) make up the vast majority of cations in the feces. Concentrations of sodium and potassium in feces and osmotically active nonelectrolytes influence fecal water. In general, osmotic diarrheas diminish when the animal is fasted. When the offending substance is reintroduced, diarrhea occurs.

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7.1.1.3

Box 7-3 Toxic Causes of Diarrhea in Horses

Phenylbutazone toxicity

Blister beetle toxicity (cantharidin)

Salt poisoning

Selenium toxicity

Slaframine toxicity (slobber factor)

Amitraz toxicity

Propylene glycol toxicity

Dioctyl sodium sulfosuccinate (DSS) toxicity

Sulfur toxicity

Phosphorus toxicity

Nicotine, Black Leaf 40 toxicity

Reserpine toxicity

Arsenic toxicity

Mercury toxicity

Monensin, lasalocid, or salinomycin toxicity

Organophosphate toxicity

7.1.1.3.1 PLANT TOXINS

Oleander poisoning

Japanese yew *(Taxus cuspidata)*, poisoning

Castor bean poisoning

Avocado poisoning

Thorn apple *(Datura stramonium)*, toxicity

Potato poisoning

Heath (Ericaceae) poisoning

Algae poisoning

Acorn or oak poisoning

Hypericum (St. John's wort, Klamath weed) poisoning

Agrostemma githago, (corn cockle) poisoning

Mycotoxicosis

Pimela poisoning (St. George disease) (exotic)

Grass sickness (exotic)

Secretory diarrheas, are most important in neonates[4] (enteropathogenic *E. coli*), but many strains of *Salmonella*, associated with colitis in large animals may produce enterotoxins that stimulate secretion. Enterotoxins act by stimulating cyclic adenosine monophosphate (AMP) or other intracellular messengers to promote secretion of chloride, sodium, and other electrolytes into the gut lumen. Water is carried with these electrolytes and osmotically retained. The hallmark of secretory diarrheas is the large volume of feces produced.

Examples of secretory diarrheas are enterotoxigenic *E. coli*, and many strains of *Salmonella*, and *C. perfringens. Salmonella*, and other invasive organisms produce inflammation that may induce prostaglandin-mediated secretion as well. Secretion may occur with viral diarrhea by a different mechanism, as damaged mature (absorbing) villus cells are replaced by immature (secreting) crypt cells.[7] A good example is rotavirus.

Decreased intestinal transit time, associated with increased peristalsis and/or decreased segmentation appears to occur in many bowel diseases because of bowel irritation. *Peritonitis*, is a major cause of bowel inflammation and should always be explored as a contributing cause of diarrhea, especially when fecal output volume is scant. Abnormal motor patterns have been demonstrated to occur with many infectious diarrheas and may be a bowel response to irritation and/or increased intraluminal volume. Elimination of gut contents thus appears to be a normal gut defense mechanism against infection and probably should not be pharmacologically alleviated in acute infectious diarrheas. Primary motility disorders of animals are not well recognized; diarrhea associated with nervous or excited animals may be the best example of this type. In general, fecal volume associated with motility disorders is not great.

Increased hydraulic pressures, from the blood to the lumen also decrease net absorption of fluid. These can result from decreased oncotic pressure (hypoalbuminemia), increased capillary hydrostatic pressure (heart failure or portal hypertension as with liver disease), or decreased lymphatic drainage associated with inflamed or blocked lymph vessels or nodes (lymphosarcoma). These mechanisms are most commonly associated with chronic diarrhea, but acute inflammation can also result in diarrhea associated with this mechanism.

Two or more of these mechanisms are probably at work in most diarrheal diseases. Therapy of diarrhea is therefore nonspecific, except when the actual causative agent can be identified. Diagnosis of a specific causative agent is most important when diarrhea is caused by an infectious agent, so that appropriate therapeutic steps can be taken before chronicity develops, spread of disease can be prevented, and an accurate prognosis can be made.

In mature horses, small intestinal diseases such as granulomatous bowel disease or duodenitis or proximal jejunitis (anterior enteritis) may not be associated with diarrhea, and diseases of the stomach almost never cause diarrhea. Most significant diarrheal disease in adult horses involves the large colon because this is the principal site of water absorption. The exception to this is the neonatal foal, in which primarily small intestinal diseases such as rotavirus infection and cryptosporidiosis may cause severe diarrhea.

The frequency of defecation is usually increased when diarrhea is present, and defecation is most frequent when the colon or rectum is irritated. When these areas are involved, *tenesmus*, (straining) may result. Tenesmus can also occur with hepatic failure in ruminants and in horses and ruminants with rectal tears or strictures, vaginitis, retained placenta, dystocia, intussusception, urolithiasis, rabies, and diseases involving the nervous system when there is retention of feces or urine. Severe rectal irritation can lead to straining and rectal prolapse.

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In ruminants, abnormalities such as grain overload (toxic indigestion) resulting in ruminal osmotic changes can produce diarrhea, as can changes in abomasal pH such as occur with type II ostertagiasis. Diarrhea in ruminants is frequently caused by forestomach problems (Boxes 7-4 and 7-5). The colon and remainder of the distal bowel are involved in diseases such as salmonellosis. Gram-negative infections and resulting endotoxemia, found in conditions such as coliform mastitis and septic metritis, are relatively common causes of nonspecific diarrhea. Foals with septicemia also commonly develop nonspecific diarrhea associated with SIRS. Diarrhea may be (1) a manifestation of a primary disease (bovine viral diarrhea [BVD]; Johne's disease; *C. difficile*), (2) one of the signs of a generalized disease (MCF, uremia), or (3) secondary to toxemia (coliform mastitis, septic metritis, septicemia).

7.1.2 Nonspecific Fluid Therapy for Diarrhea

Dehydration, electrolyte losses, and acid-base abnormalities can occur rapidly when diarrhea is present. Symptomatic treatment to correct these problems is an important component of nonspecific therapy in animals with diarrhea. Very often the cause of diarrhea remains undetermined, yet symptomatic correction of hypovolemia, dehydration, and acid-base and electrolyte abnormalities can result in a return to normal function, particularly if the diarrhea is acute and severe. Fluids and electrolytes can be given orally or parenterally. Oral fluids can be given rapidly and inexpensively. Oral fluids should be isotonic or hypotonic. The degree of dehydration should be estimated as a percentage of body weight. Mild dehydration is usually considered less than 5%; moderate, 5% to 8%; and severe, over 8%. Thus a severely dehydrated 450-kg patient with an estimated 10% dehydration (weakness, cold extremities, sunken eyes, decreased urine output, decreased elastic skin rebound, weak pulse, rapid heart rate) requires 45 L of fluids.

The best way to determine electrolyte needs is to take a plasma or serum sample before initiating fluid therapy. Electrolyte requirements can be estimated; with diarrhea, mixed water and electrolyte losses occur, so that sodium-containing fluids are usually required to replace lost sodium and improve blood volume (see also Fluid and Electrolyte Balance, Chapter 22). Unless the acid-base status can be measured, the safest sodium-containing fluids are balanced polyionic fluids such as Ringer's or lactated Ringer's solution. Normal saline is a satisfactory alternative in most cases, but the relatively high concentration of chloride ions in saline can aggravate a preexisting metabolic acidosis unless hypochloremia is also present. In calves with severe metabolic acidosis, use of fluids containing sodium bicarbonate is indicated. In horses, it is best not to include gram quantities of sodium bicarbonate in fluids unless there is good evidence that a severe metabolic, strong ion acidosis exists (such as hyperchloremia). Flow rates for administering isotonic intravenous fluids should be kept as slow as possible to avoid fluid overload, pulmonary edema, and excessive diuresis. When the patient is shocky, flow rates close to 20 mL/kg/hr or faster may be required for administration of isotonic crystalloid fluids, but in general rates below 10 mL/kg/hr are desirable, especially once hypovolemic shock has been addressed. Hypertonic saline (7% NaCl) may be given rapidly intravenously at a dose of 4 to 5 mL/kg. When a colloid fluid is required to combat low plasma protein levels, hetastarch can be used. It is available as 6% hetastarch in lactated Ringer's or normal saline. See Neonatal Diarrhea, Chapter 20, Fluid and Electrolyte Balance, Chapter 22, and Fluid Therapy, Chapter 44, for more details on fluids and acid-base balance.

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7.1.2.1

Box 7-4 Causes of Diarrhea in Ruminants (Except Neonates; see Chapter 20 for Neonates)

7.1.2.1.1

COMMON CAUSES

Parasitism, worms

Coccidiosis

Salmonellosis

Colitis or typhlitis

Enteritis, unknown cause

Indigestion (spoiled feed, overfeeding, or sudden change)

Displaced abomasum (B)

Abomasal torsion (B)

Peritonitis

Intussusception

Sepsis or toxemia

Johne's disease

Enterotoxemia

Grain overload (rumen acidosis)

Bovine viral diarrhea (B)

Winter dysentery (B)

Liver failure

Malignant catarrhal fever (B)

Molybdenosis or copper deficiency

Heart failure

Uremia, renal failure

Xylazine, following large doses

Cathartics or laxatives

Parasympathomimetics

Toxins or poisonous plants (see Box 7-5)

7.1.2.1.2

LESS COMMON CAUSES

Amyloidosis

Giardiasis (mainly calves)

Intestinal obstruction, partial

Intestinal neoplasia

Traumatic reticuloperitonitis (hardware)

Vagal indigestion

Selenium deficiency (white muscle disease)

Cecal dilation (B)

Liver abscess

Brisket disease (high-altitude disease) (B)

Sarcocystosis (B)

Bluetongue (O)

Bovine leukosis (BLV) (B)

7.1.2.1.3 UNCOMMON CAUSES

Fat necrosis (B)

Abomasal impaction

Duodenal ulcers

Systemic candidiasis

Vitamin A deficiency

Volvulus, root of mesentery

Water intoxication (B)

Cholelithiasis

Cobalt deficiency

Zinc deficiency (baldy calf) (B)

Hydrops allantois (B)

Lethal trait A 46, keratogenesis imperfecta (parakeratosis) (B)

Zygomycosis, mucormycosis

Pregnancy toxemia

Bacillary hemoglobinuria

Rumen flukes, paramphistomosis

Pancreatic adenocarcinoma

Bee or wasp sting

Pseudorabies

Rift Valley fever (exotic)

Rinderpest (exotic)

Schistosomiasis (exotic)

Theileriosis (East Coast fever) (exotic)

Wesselsbron disease (exotic) (B, O)

Heartwater (exotic)

B, Bovine; *O*, ovine

7.1.2.2

Box 7-5 Toxic Causes of Diarrhea in Ruminants

Arsenic poisoning

Sulfur poisoning

Salt poisoning

Propylene glycol

Levamisole

Monensin

Polybrominated biphenyl

Sodium bicarbonate

Aflatoxin

Herbicide

Zinc

Phosphorus toxicity

Nicotine (Black Leaf 40) toxicity

Copper

Chlorpyrifos (Dursban)

Phosphate fertilizer

Lincomycin

Trichothecene (T-2 toxin)

Plant toxins

Oak (acorn poisoning)

Senna occidentalis, (coffee weed)

Selenium accumulators

Slaframine (blackpatch diseased legumes, slobber factor)

Mycotoxicoses

Helenium (sneezeweed, bitterweed)

Solanum (nightshade)

Pyrrolizidine alkaloid (*Senecio, Crotalaria, Amsinckia*, species)

Brassica (mustards, crucifers, cress)

Oleander poisoning

Japanese yew *(Taxus cuspidata)*, poisoning

Whitehead *(Sphenosciadium capitellatum)*,

Pokeweed *(Phytolacca americana L)*,

Mushroom

Inkweed *(Drymaria pachyphylla)*,

Tung tree (aleurites)

Chinese tallow tree

Kalanchoe (crassulaceae)

Fungal toxicity

Sesbania (rattlebox)

Gutierrezia (broomweed, snakeweed)

Hypericum (St. John's wort; Klamath weed) poisoning

Agrostemma githago, (corn cockle) poisoning

7.1.3

Approach to Diagnosis of Diarrhea in the Horse (for Neonates, see Chapter 19)

1 Take history. Especially note change in diet, deworming program, housing and management, and whether diarrhea is acute or chronic. Note appetite, whether animal is drinking an adequate volume of water, and whether salt is available. Note whether it is a single or multiple case, if there are intercurrent diseases, or if other medications or exposure to toxins is involved. Most antimicrobials have been associated with diarrhea in horses, but especially lincomycin, tetracyclines, and erythromycin. Antimicrobials should be discontinued if diarrhea develops during administration. Most bacterial and protozoal agents rely on altered intestinal microflora to proliferate in the gut and cause diarrhea. Note whether nonsteroidal antiinflammatory agents were used before the development of diarrhea. Many causes of diarrhea can be eliminated from consideration on the basis of history. Find out about housing and whether animals have access to pasture, have access to natural water sources, or are stall confined.

2 Perform physical examination. Take vital signs (often normal in chronic cases). Perform rectal examination unless an infectious contagious agent is suspected. Note weight loss. Systemic signs of toxemia, SIRS, hypovolemia, and dehydration often accompany acute colitis, salmonellosis, equine monocytic ehrlichiosis (Potomac fever), clostridiosis, and many other acute diseases.

3 Examine feces. Perform gross inspection; note whether blood or fibrin is present (see list of causes of dysentery).

a Perform microscopic examination for ova and protozoa, especially for chronic cases. Perform Gram stain of feces. A predominance of gram-positive rods may indicate an anaerobic overgrowth such as occurs with *C. difficile*, infections.

b Perform multiple cultures for *Salmonella, C. difficile*,[8] and *C. perfringens*, if onset is acute, if animal is febrile, or if feces contain fibrin and mucus. A commercial polymerase chain reaction (PCR) test can be used as an aid to evaluate for the presence of salmonellosis.[9] An evaluation for *C. difficile*, and for *C. perfringens*, should be made if the diarrhea is temporally associated with antibiotic administration. Cultures for *C. difficile*, should be performed on selective media (cycloserine-cefoxitin-fructose agar). Recently *Brachyspira pilosicoli*, has been isolated from the feces of weanlings with chronic diarrhea.[10] This warrants further investigation as a cause of diarrhea and failure to thrive in young horses.

c Several enzyme-linked immunosorbent assay (ELISA) kits are available for identification of toxins A (enterotoxin) and B (cytotoxin) of *C. difficile*, in feces. A stool cytotoxin cell culture is available for toxin B.[11,12] Toxin B cell culture testing is considered the gold standard.[13]

d Isolates of *C. perfringens*, should be examined for the ability to produce beta 2–toxin, as these strains are most often associated with gastrointestinal disease.[14] Beta 2–toxin is found by PCR. In addition, a commercial fecal ELISA is now available for detection of alpha-toxin, beta-toxin, and epsilon-toxin at the California Animal Health and Food Safety Laboratory (San Bernardino). This allows diagnosis of *C. perfringens*, types A, B, C, and D.

e Fecal occult blood (if positive, see list of causes of melena and blood in feces, pp. 106 and 107).

f Fecal osmolality, sodium, and potassium concentrations (optional). Electrolyte concentration in feces is roughly twice the sodium plus potassium. When this value is much lower than the measured osmolality of the feces, the difference is an osmolar gap caused by osmotically active nonelectrolytes, and osmotic diarrhea is confirmed.

g Check for sand by placing some feces in a bucket of water, mixing thoroughly, and decanting the water. If a radiographic unit with the appropriate power capability is available, abdominal radiographs can be taken to detect the presence and amount of sand. Ultrasound of the ventral abdomen can be used to diagnose the presence of sand, although this requires considerable expertise.

h A PCR test for feces is available at University of Minnesota Diagnostic Lab and the University of California Molecular Laboratory for detection of *L. intracellularis*, organisms in weanlings and yearlings with diarrhea, weight loss, general malaise, and hypoalbuminemia.[15] Also see serum test described later.

i *Rhodococcus equi*, can cause diarrhea in 3-week- to 6-month-old foals. Diagnostic tests include cultures of transtracheal aspirates, abdominal fluid cytology and culture, and abdominal ultrasonography. Fecal PCR techniques are available on a limited basis.[16]

j If all other cultures are negative and an infectious cause of diarrhea is suspected, the feces should be cultured for *Aeromonas*, species and *C. perfringens*.,[17] A positive culture for *C. perfringens*, should be coupled with an evaluation for the presence of toxins or toxin genes to confirm pathogenicity, as the organism may be cultured as part of the normal flora. Recent reports implicate a novel beta 2–toxin—producing *C. perfringens*, as a potential pathogen in colitis of adult horses.[18] Commercial toxin ELISA tests are now available for alpha-, beta-, and epsilon-toxins (California Animal Health and Food Safety Laboratory, San Bernardino).

4 Obtain blood for the following database:

a Complete blood count (CBC; includes fibrinogen and plasma proteins). Increased fibrinogen indicates inflammation. Decreased proteins indicate protein-losing enteropathy. Thrombocytopenia may indicate a coagulopathy. Neutropenia with or without a toxic, left shift (immature neutrophilia) is often present with infectious and inflammatory causes of acute colitis, indicating SIRS. Elevations in packed cell volume (PCV) and red cell mass are often present, indicating hemoconcentration and/or splenic contraction in horses.

b Acid-base values if condition is acute and dehydrated or toxic. Although acid-base values are not of much use diagnostically in terms of etiology, they allow for initiation of proper nonspecific supportive therapy.

5 Test serum for the following:

a Electrolytes (Na, K, Cl) (nonspecific).

b Serum creatinine and blood urea nitrogen (BUN)—prerenal azotemia is common as a result of dehydration; check again after rehydration. Serum chemistries should be evaluated for liver and other organ disease.

c Albumin and globulin values; hypoalbuminemia is seen with chronic protein-losing enteropathies such as granulomatous bowel disease, with phenylbutazone toxicity (right dorsal colitis), and with acute colitis conditions.

d Specific immunoglobulin (Ig) A, IgM, and IgG levels; immunodeficient individuals may have chronic diarrhea. Elevated globulins may indicate the presence of chronic disease.

e Paired sera for *Neorickettsia risticii*, titer following acute diarrhea with fever. PCR techniques are available to identify the agent in whole blood samples and feces.

f Immunoperoxidase monolayer assay and an immunofluorescence assay (IFA) for *L. intracellularis*, can be done, particularly in weanlings and yearlings. Fecal PCR analyses are now available.

g Clotting times (prothrombin time [PT] and partial thromboplastin time [PTT] or activated clotting time [ACT]) should be monitored as indicators of coagulopathies such as disseminated intravascular coagulation (DIC). Antithrombin III levels can be monitored for the risk of thromboses.

6 Perform paracentesis, especially if signs of colic are present. Evaluate cytology, protein, and fibrinogen values in chronic cases to rule out peritonitis, tumors, and mesenteric abscess.

7 Perform function and absorption tests in chronic diarrhea cases, especially when weight loss is present.

a Oral glucose or xylose small intestine absorption tests (see Chapter 32) for chronic cases, particularly if a high index of suspicion exists because of hypoalbuminemia. If tests indicate malabsorption, either biopsy the gut (or rectum) or assess response to treatment for 60 days following larvicidal anthelmintic dose.

b Perform liver function tests such as sodium sulfobromophthalein (BSP) half-time or serum bile acid concentrations if liver involvement is suspected as a result of elevated liver enzyme levels and/or hypoalbuminemia. Liver enzymes are elevated in many cases of enterocolitis and in these cases do not necessarily indicate primary liver disease (see Chapter 33).

8 Examine tissue.

a Rectal or intestinal biopsy for microscopic examination and fluorescent antibody for immune-mediated diseases (also culture for *Salmonella*). Rectal histopathology is particularly useful in horses with hypoalbuminemia or weight loss.[19]

b Detection of *C. perfringens*, beta 2–toxin from types A or C by immunohistochemistry of gut mucosa is diagnostic on biopsy or postmortem specimens.[20]

c Liver biopsy if indication of involvement in chronic cases.

9 Toxicology.

a Blood lead, liver lead, and liver arsenic concentrations can be measured if toxicity is suspected.[21]

b High-pressure liquid chromatography or gas chromatography-mass spectrometry can be used to detect cantharidin (blister beetle toxin) in urine or gastrointestinal contents.[22]

c Urine and gastrointestinal contents can be evaluated for the presence of oleandrin using thin layer chromatography. Oleander toxicity should be suspected in animals with diarrhea, colic, arrhythmias, and renal disease.[23]

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10 Evaluate response to treatment with undiagnosed *chronic*, diarrhea.

a Alter diet to simple grass hay. Alternatively, a pelleted complete diet can be tried, especially if right dorsal colitis is suspected. Psyllium mucilloid, at 4 oz, and 1 to 2 cups of corn oil can be added to the daily diets of horses with right dorsal colitis.[24,25]

b Stop nonsteroidal drugs such as phenylbutazone if toxicity is possible cause.

c If no protozoa are seen in fecal sample, attempt transfaunation with colon or cecum contents from normal animal (if not available, use feces).

d Attempt to classify into type by rectal biopsy; many changes are nonspecific.

(1) Marked fibrosis and inflammatory changes point to a poor prognosis. Administer potentiated sulfas (5 mg/kg trimethoprim tid is therapeutic dose) and iodochlorhydroxyquin (Rheaform 10 g/450 kg horse/day) for 2 weeks.

(2) Mononuclear cell infiltrate. Administer 20 to 30 mg dexamethasone (Azium) per day, tapering down to 10 mg in 1 week; if response is favorable, continue with 600 to 800 mg prednisolone PO per day, taper over 2 months.

(3) Eosinophilic infiltrate. Administer larvicidal anthelminthic dose of fenbendazole plus corticosteroids as above.

e Transfusion with plasma (1 to 2 mL/kg) in young horses 2 to 12 months of age that may need some additional serum factors. Synthetic colloids, such as hetastarch, can be used in animals with reduced colloid osmotic pressure (hypoalbuminemia), especially if edema is present. Hetastarch has been used at 10 mL/kg.[26]

f Horses with Potomac fever often respond favorably to systemic treatment with tetracycline.

g Metronidazole (15 mg/kg PO tid) can be used empirically, especially if an anaerobic overgrowth is suspected, or when the diarrhea is secondary to antibiotic use.[27]

7.1.4 Approach to Diagnosis of Diarrhea in Ruminants (for Neonates, see Chapter 20)

1 Take history. Especially note diet, appetite, previous deworming and vaccinations, and whether it is an individual or herd problem. In animals less than 1 year of age coccidia, *Ostertagia*, or other helminths should be strongly considered. Determine if onset is acute or chronic. If chronic, first consider diseases such as parasitism, Johne's disease, copper deficiency (molybdenosis), selenium deficiency, liver failure,

and other diseases of individual cows such as bovine leukosis virus (BLV), amyloidosis, heart failure, or uremia.

2 Perform physical examination. Especially note weight loss, fever, systemic signs, rumen activity, and oral lesions. Perform rectal examination. In most acute-onset diseases, vital signs are abnormal, and systemic involvement or oral lesions (especially with BVD) may be obvious.

3 Examine feces.

- a Gross inspection
- b Microscopic examination for ova and parasites
- c Culture for *Salmonella*, if animal is febrile or feces appear inflammatory (fibrin or mucus)
- d Check for fecal occult blood
- e Culture of *Mycobacterium avium*, subsp. *paratuberculosis*, if weight loss is a problem (especially if a herd problem in animals over 2 years of age)

4 Take rectal scrapings of mucus.

- a Make thin smear on slide for acid-fast staining for Johne's disease. Examine under oil immersion lens.

5 Obtain blood for the following:

- a Plasma proteins
- b Fibrinogen
- c In acute cases, electrolytes and acid-base status
- d If a herd problem, copper and selenium status

6 Test serum for the following:

- a BUN
- b Liver enzymes (γ-glutamyltransferase [GGT] and sorbitol dehydrogenase [SDH])
- c Albumin and globulin values
- d Agar gel immunodiffusion (AGID) for BLV (single animals); request gp51 and p24 antibody status
- e If Johne's disease is suspected, perform ELISA test

7 Perform paracentesis. Paracentesis rules out gross peritonitis, but many false-negatives are possible as a result of focal or fibrinous peritonitis.

8 Perform urinalysis for protein to rule out consideration of amyloidosis or other multisystemic immune-mediated disease. Because ruminants normally have a urine pH of 8 or higher, most dipstick tests will give a trace or a 1+ positive reading for urine protein even when the animal's urine is normal.

9 Examine tissue.

a Rectal, intestinal, or mesenteric lymph node biopsy for acid-fast stain for Johne's disease, for culture for *Salmonella*, and for presence of lymphosarcoma

10 Perform feed analysis (herd problem only).

a Copper, molybdenum, and selenium

b Toxins suspected (e.g., mercury, arsenic)

11 Tap abomasum for increased pH; rule out type II ostertagiasis

12 Perform necropsy (herd problem only).

a Pick severely affected individual to examine thoroughly

7.2 COLIC

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Colic, is defined as the manifestation of visceral abdominal pain. Colic may be the result of nongastrointestinal pain, such as urinary tract obstruction (Boxes 7-6 and 7-7). This section discusses colic of gastrointestinal origin. Pain may be acute, chronic, or recurrent. Gas distention or recognizable organic problems such as displacements are most frequently associated with acute colic. Five basic causes in large animals are as follows:

- Distention of gut with fluid, gas, or ingesta
- Pulling on the root of the mesentery (mesenteric tension)
- Ischemia or infarction
- Deep ulcers in the stomach or bowel
- Peritoneal pain (peritonitis)

The horse exhibits colic frequently, because it appears to have a low threshold for pain and is frequently beset by minor digestive disturbances that result in distended bowel. Signs of colic in the horse include restlessness, lying down and getting up, groaning, grunting, rolling, sweating, kicking at the abdomen, or suddenly dropping to the ground in pain. Anorexia and depression often accompany these signs. Horses may develop tachycardia with weak pulse quality and prolonged capillary refill time, cold extremities, and bright red (vasodilatory phase) followed by dark (vasoconstrictive phase or low cardiac output state) mucous membranes if the problem is severe and affects cardiovascular integrity.

7.2.1

Box 7-6 Gastrointestinal Causes of Colic in Horses

7.2.1.1

COMMON CAUSES

Accumulation of intestinal, cecal, or colonic gas

Hypermotility and intestinal spasms

Feed impaction, constipation

Meconium impaction (newborn)

Gastric ulcers (foal)

7.2.1.2

LESS COMMON CAUSES

Thromboembolism

Intestinal foreign body (sand; enterolith; phytobezoar)

Volvulus of small intestine

Pedunculated lipoma with bowel strangulation

Hernia, inguinal, epiploic, umbilical, diaphragmatic

Nephrosplenic ligament bowel entrapment

Ascarid impaction

Massive strongyle infection

Gastric dilation

Anterior enteritis (duodenitis or proximal jejunitis)

Enteritis, impending or active

Peritonitis

Parasympathomimetic drugs

Irritant cathartics

Necrotizing enterocolitis

Psychogenic colic

Rectal tear

Volvulus or displacement of large bowel

Rupture of stomach or intestine

Ileus

Intussusception

7.2.1.3 UNCOMMON CAUSES

Abdominal adhesions

Intramural hematomas of stomach or intestine

Stenosis or stricture of bowel lumen

Botulism

Tetanus

Potomac fever

Exhaustion

Anaphylaxis

Rhodococcus equi (Corynebacterium), gut abscesses

Cribbing or wind sucking

Abdominal fibroma

Segmental ischemic necrosis following mesocolic tearing

Equine viral arteritis

Anthrax with bleeding

Malignant edema (*Clostridium*, species)

Malignant mesothelioma

Gastric or intestinal tumor

Atropine

Vitamin K_3 deficiency (moldy sweet clover)

7.2.1.4 TOXINS

(See also toxins listed under Diarrhea)

Cantharidin toxicity

Dioxin

Trichloroethylene-extracted feed toxicity

Warfarin (dicumarol)

Herbicides

Lead

Nitrophenyl urea (vacor)

Phenylbutazone or other nonsteroidal antiinflammatory drugs

Poison plants (many of those that produce diarrhea also produce colic; see plant toxins listed under Diarrhea)

African horse sickness (exotic)

Grass sickness (exotic)

7.2.2

Box 7-7 Causes of Colic in Ruminants

7.2.2.1

COMMON CAUSES

Increased intestinal gas

Intussusception

Torsion or volvulus of the mesenteric root

Peritonitis

Intestinal foreign body or obstruction

Urolithiasis

Ruptured bladder

Acute pyelonephritis

Abomasal torsion

Abomasal ulcer

Cecal dilation or volvulus

Severe bloat

7.2.2.2 LESS COMMON CAUSES

Cystitis or urinary tract disease

Abomasal bloat (neonates)

Uterine torsion or rupture

Hernia

Parturition, impending

Hypermotility and spasms of gut

Feed impaction

Right displaced abomasums

Acute traumatic reticulitis, abomasitis, or duodenitis

Acute liver disease

Vagal indigestion

Atresia coli (neonates)

7.2.2.3 UNCOMMON CAUSES

Rabies

Rectal tear

Rectal prolapse

Grain overload

Water intoxication

Winter dysentery

Ovarian abscess

Fat necrosis

Cholelithiasis

Intestinal adhesions

Enterotoxemia

Ileus

Intestinal strangulation

Inversion of uterine horn

Malignant edema

Malignant mesothelioma

Ruptured uterine artery

Intestinal neoplasia

Aortic, iliac, or femoral thrombosis

Anaphylaxis

Renal cysts

Ruptured prepubic tendon

Vaginal laceration

Torsion of descending colon

Rinderpest (exotic)

7.2.2.4 TOXINS

Plant poisonings (many of those that cause diarrhea also produce colic; see plant toxins listed under Diarrhea)

Evidence of shock is usually present only when the disease condition is severe and involves infarctive disease (volvulus, torsion, thromboembolism) or advanced visceral distention (extreme flatulence, impaction, or dilation). Foreign bodies such as sand or enteroliths in the large colon may result in *low-grade recurrent colic*., When an enterolith is passed into the transverse colon where it obstructs the bowel, *signs of complete obstruction*, and acute colic ensue. These signs are manifestations of visceral pain, mediated by the sympathetic nervous system. External palpation and pushing on the abdomen of adult horses does not usually elicit pain unless the affected inflamed or dilated viscus is contacted.

In contrast, parietal pain associated with *peritonitis*, usually is responsive to external palpation. Whereas the animal with visceral pain shows active signs of colic, the animal with parietal pain is usually reluctant to move and has a splinted abdomen. Acute peritonitis occurs within minutes after rupture of the stomach or perforation of an ulcer as a result of immediate irritation of serosal surfaces by the acid contents, whereas with rupture of the colon or rectum it may take 12 hours or more before peritonitis is clinically apparent.

Ruminants exhibit colic less frequently than horses, probably because of a higher threshold for pain and because dietary shifts principally affect the rumen; thus intestinal gas pains occur less frequently. Colic with visceral pain (including urinary tract) is manifested by grinding the teeth (odontoprisis or bruxism), grunting or groaning, treading with the hind feet, kicking at the abdomen, restlessness, repeatedly lying down and getting up, anorexia, and depression. With parietal pain caused by peritonitis, ruminants demonstrate abdominal pain by arching the back, splinting, and exhibiting pain on deep palpation of the area. These signs are seen most commonly with traumatic reticuloperitonitis and abomasal ulcers; rarely are these diseases associated with the colic signs described previously.

7.2.3 Diagnosis and Management of Colic in the Horse

1 Take history. Because colic is a common problem in horses, mild to moderate degrees of abdominal pain are often initially treated symptomatically with analgesics and/or laxatives before major diagnostic efforts are undertaken. Most colic of mild to moderate severity responds favorably to symptomatic treatment. In general, severe pain or pain that is unresponsive to analgesics indicates a more serious condition for which more aggressive medical management or surgical correction may be indicated.

Recurrent mild-to-moderate colic *may*, be an indication of a more serious problem such as bowel entrapment or displacement thromboembolism, internal abscess, enterolith, sand or other foreign body,

tumor, gastric ulcer, hypobiotic cyathostomiasis, *Strongylus vulgaris*, larval migration, heavy burden of ascarids, abdominal adhesions, strictured bowel, or urinary tract disease.

2 Perform physical examination. Intestinal causes of colic can often be differentiated from colic associated with other organ systems (Box 7-8) by physical examination findings and laboratory data. Although extraintestinal origins of acute colic are relatively uncommon in the horse, they include mainly abdominal abscesses, tumors, cholelithiasis or cholestatic disease, and genitourinary tract disease and tend to be recurrent. It is important to note the presence or absence of normal intestinal borborygmi and whether or not feces are being passed in determining whether the problem is extraintestinal. Careful auscultation of the thorax should be performed to evaluate for the presence of diaphragmatic hernias or pleural disease. The testicles should be palpated on all stallions to screen for scrotal hernias or testicular torsions. Rectal examination findings often help to determine anatomic location within gut or other site. Abdominal tumors, abscesses, and other masses may be palpable. Although mild to moderate chronic intermittent colic may be of extraintestinal or intestinal origin, most cases of severe unremitting colic indicate gut involvement, often with anatomic displacement.

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7.2.3.0.0.0.1

Box 7-8 Extraintestinal Causes of Colic in Horses

7.2.3.0.0.0.1.1

COMMON CAUSES

Mesenteric abscess

Ovarian tumor, abscess, or hematoma

Parturition

Acute hepatitis (massive necrosis) or hepatic lipidosis

Diaphragmatic hernia

Ruptured bladder (foal)

Uterine torsion

7.2.3.0.0.0.1.2

LESS COMMON CAUSES

Urinary tract or renal disease, including urolithiasis

Pleuritis or pericarditis (referred pain)

Retained placenta

Uterine rupture or retroflexion

Spermatic cord thrombosis or torsion

7.2.3.0.0.0.1.3

UNCOMMON CAUSES

Perirectal abscess

Pheochromocytoma

Purpura hemorrhagica

Biliary atresia

Vaginal or vulvar tear

Cholelithiasis

White muscle disease

Rabies

Rupture of prepubic tendon

Splenitis, splenic abscess, splenomegaly

Cauda equina neuritis with retention of feces or urine

3 Use ultrasound and radiology. Ultrasound may help in locating masses, adhesions, or enlarged liver. It may also be helpful in the diagnosis of gastrointestinal disease, including nephrosplenic entrapment of the large colon and small intestinal distention, and detection of sand from the ventral abdomen may be possible. Ultrasound can be particularly useful in foals and small ruminants because of their size. Radiology can also be useful in detecting enteroliths or sand in adult horses and in some gastrointestinal conditions of foals. Rarely is radiology useful in diagnosing the cause of colic in ruminants, except for urethrographs in sheep and goats to locate a urethral stone.

4 Examine feces. Gross examination of feces should be performed. The presence of sand can often be detected by mixing feces with water in a bucket, then pouring off the water and looking for sediment.

If no feces are passed, a more serious condition is usually indicated, particularly if intestinal sounds are absent.

5 Use laboratory aids. Laboratory aids of immediate benefit in diagnosis and management include PCV and plasma proteins to aid in assessing hydration and vascular integrity and a paracentesis to evaluate abdominal fluid grossly and microscopically. Pain and excitement alone can elevate the PCV, but there is a correlation of elevated PCV (>55%) in colics with nonsurvival. Plasma proteins are not elevated unless blood volume is decreased through shifts in compartmental distribution of body fluids. In colic cases these fluid shifts usually mean that an increased and abnormal amount of extracellular fluid is in the gut lumen, a "third space" where it is of little use in maintaining blood volume. Blood lactate concentration measurement has become routine in evaluation of horses with acute abdominal disease. It is useful in monitoring as an end point to fluid therapy. Some studies have suggested a prognostic role of lactate in horses with colic, although there is marked variability.

Abdominal fluid is normally present in small volume (a few drops to 50 mL); is clear and colorless to yellow; and has a total protein below 2.5 g/dL, specific gravity less than 1.015, little or no fibrinogen (<100 mg/dL), and fewer than 5000 white blood cells (WBCs) per microliter. Elevations in these parameters or increased numbers of neutrophils in peritoneal fluid often indicate inflammation on serosal surfaces. Comparisons of abdominal fluid glucose with serum glucose (greater than 50 mg/dL difference is abnormal) and evaluation of abdominal fluid pH, lactate (as compared with blood lactate), and lactate dehydrogenase (LDH) concentrations can aid in the diagnosis of septic peritonitis.[28] Grossly, fluid changes to cloudy yellow, then to blood-tinged with fibrin clots, and finally to black in color as bowel necrosis and hemolysis of extravasated red blood cells (RBCs) occur. Elevated levels of peritoneal fluid protein are consistently found in anterior enteritis (duodenitis and proximal jejunitis) and provide a useful differential aid, although this finding is also common in cantharidin poisoning. Elevated protein levels are present in peritonitis but accompanied in these cases by elevated numbers of neutrophils. If peritoneal fluid is grossly contaminated with feed material, rupture of a viscus should be considered. Another peritoneal tap in a different location should be undertaken if the possibility of bowel penetration during paracentesis cannot be ruled out. It is not necessary to have abnormal peritoneal fluid before consideration of surgical correction of colic is contemplated. Recently, abdominal fluid lactate has been shown to be predictive of intestinal ischemia secondary to strangulating obstruction and may aid in early detection of intestinal strangulation, rupture, and septic peritonitis.[29]

Many chemical analyses (e.g., lactate) of blood or peritoneal fluid have been recommended as an aid in prognosis and gauging severity of tissue damage. Plasma fibrinogen, as well as peripheral leukocyte counts, can aid in the differentiation of enterocolitis or anterior enteritis from strangulating lesions. Serum electrolyte concentrations and acid-base status are important from a therapeutic standpoint. Serum biochemistries, including liver enzymes, creatinine, and BUN, are important in evaluating for liver and renal compromise. Hyperglobulinemia may be indicative of chronic disease.

6 Evaluate response to treatment. The approach to diagnosis of colic signs is often tied in with management because if the animal's pain cannot be alleviated, surgical intervention and specific diagnosis of displacements, internal hernias, masses, and adhesions are the next steps. The initial diagnosis especially considers the history of deworming and feeding. The findings of the physical examination, including rectal examination and evaluating degree of pain, determine whether additional laboratory workup is indicated. In many cases with mild to moderate pain and no evidence of shock, standard treatment is parenteral administration of an analgesic agent (see Chapter 3) and oral administration of a mild laxative

such as DSS (approximately 1 mL/kg of 5% DSS) or mineral oil (4 L). When a nasogastric tube is passed, the stomach should be checked for reflux and decompressed as needed. The pH of the gastric reflux may indicate primary gastric dilation if acidic, or small intestinal blockage or ileus if alkaline. Dark brown, foul-smelling, and alkaline reflux is often associated with anterior enteritis (duodenitis and proximal jejunitis). If a significant amount of reflux is present, oral medications should be withheld. If cardiovascular function is impaired (poor mucous membrane color and capillary refill, weak pulse, cold extremities, impending shock), sodium-containing fluids should be given intravenously at a rate of 3 to 10 L/hr to a 450-kg horse.

Large amounts of painful gas auscultable in the right flank can be tapped and drawn off, although the risk for peritonitis should be considered. The cecum is trocarized, using a 14- to 16-gauge 6-inch needle inserted through aseptically prepared skin.

The principles of colic management include (1) control of pain, (2) relief of distention, (3) relief of obstruction, and (4) reversal of shock.

7 Perform exploratory surgery. In making a decision concerning management of colic, it is important to separate impending enteritis and peritonitis from bowel disease requiring surgical intervention. Anterior or proximal enteritis can result in prolonged moderate pain and requires constant or frequently repeated analgesic administration and gastric decompression of the foul-smelling, dark reddish-to-brownish stomach contents. However, pain often subsides and is replaced with depression after gastric decompression in horses with anterior enteritis, whereas horses with strangulating lesions often remain in pain. The presence of fever or decreased total WBC count (with neutropenia) may be an indication of impending or ongoing enteritis, in which case surgery may be contraindicated. *Surgery is indicated in the following situations:*, 105 106

a Pain is severe and intractable or nonresponsive or poorly responsive to analgesics.

b Pulse is weak and rate is over 70 beats/min.

c Perfusion is poor, as evidenced by cold extremities, mucous membranes are off color, and capillary refill is poor.

d No gut sounds are auscultated (a lack of fecal production).

e Bowel is markedly distended.

f Large volumes of yellowish alkaline gastric reflux are present.

g Abdominocentesis indicates damaged bowel (blood tinged, increased protein, increased WBCs).

Surgery may be contraindicated in the following situations:,

a Fever

b Neutropenia or marked neutrophilia

c Severe icterus or marked enzyme abnormalities indicating primary liver disease

d Foul-smelling, brownish-red gastric reflux characteristic of proximal enteritis (duodenitis/jejunitis), especially when removal of reflux results in discontinuation of signs of pain

e Evidence of an extraintestinal cause not amenable to surgical correction

f Colitis or diarrhea

g Abnormal behavior or neurologic signs

7.2.4

Diagnosis and Management of Colic in Ruminants

1 Take history. Colic in neonates is most often associated with increased abomasal or intestinal gas and is discussed in Chapter 20. Perforating ulcers are not uncommon as a cause of colic in calves 1 to 6 months of age.

It should be determined whether the onset of colic was acute or whether the colic is chronically recurrent. Few diseases cause recurrent colic in ruminants. Urolithiasis is probably the most common cause of colic in male or neutered male goats and sheep and occurs under varied dietary and environmental conditions. Urolithiasis in cattle occurs most frequently in bulls or steers eating high-grain diets, but silicate stones can occur in very young animals and animals on pasture diet.

2 Perform a physical examination. Take vital signs; with torsion or severe peritonitis, shock signs such as rapid heart rate (>90 beats/min), cold extremities, and weakness may be seen. Tympany can be detected by simultaneous auscultation and percussion. Such causes of colic as cecal dilation, bloat, free gas in the peritoneal cavity, and severe abomasal dilation can be diagnosed in this way (see Figs. 1-3 to 1-5Fig. 1-3). Rectal examination detects such abnormalities as gas in the cecum, uterine abnormalities, urinary tract disease, and intussusception. Observe animal urinating to rule out obstructive urolithiasis.

Ultrasound examination of the abdomen is also useful (see Chapter 32).

3 Examine feces. Observe grossly; intussusception usually has scant dark red (almost black) feces. Scant feces are seen with cecal dilation or displacement.

4 Check preputial hairs and urethral process for sediment and stones. Grit on the preputial hairs is often associated with urolithiasis. Observe animal urinating and check urine for abnormalities. Rule out pyelonephritis.

Radiology and ultrasound can be useful in sheep and goats when urolithiasis is a consideration. Ultrasound can detect a distended bladder, and stones may sometimes be detected. Radiology (lateral view) may detect a stone in the urethra or stones in the bladder. A contrast urethrogram may also be diagnostic.

5 Perform paracentesis to look for peritonitis caused by perforated abomasal ulcer, serosal devitalization, intussusception, or ruptured bladder. Interpret as above for horses, except that normal peritoneal fluid protein concentration can go as high as 5 g/dL in ruminants.

6 Other laboratory aids such as CBC and clinical chemistries are seldom diagnostic in ruminant colic. If grossly abnormal, they may be grounds for formulating a poor prognosis. Intussusception may be associated with neutrophilia (as well as dark feces and colic) in some cases.

7 Symptomatic treatment of colic includes analgesics and, if heart rate is over 90 beats/min, intravenous fluid therapy with a sodium-containing fluid. Take blood sample for electrolytes and acid-base status before initiating fluid therapy.

8 Surgical exploration is indicated if colic is persistent, abdominal distention occurs, the heart rate is over 100 beats/min, feces are scant (especially those that are dark red and indicative of intussusception), there are pings indicating abomasal or cecal displacement or torsion, or the peritoneal fluid indicates bowel devitalization (blood-tinged fluid with elevated protein and WBCs). If surgical exploration is indicated, an important consideration is whether the animal will remain standing under local anesthesia during surgery. It is often best to perform abdominal surgery on animals with colic in left lateral or dorsal recumbency, aided by sedation and restraint, to avoid sudden collapse when painful surgical manipulations are performed. If the left lateral position is selected, use padding to raise the hip and shoulder so that the abdominal viscera can sit in a depression.

7.3

MELENA

BRADFORD P. SMITH,

Melena (dark, tarry feces) is caused by blood in the lumen of the stomach or proximal intestinal tract, resulting in black (digested) blood appearing in the feces (Boxes 7-9 and 7-10). Usually blood is a result of a bleeding ulcer in the stomach or abomasum but may also result from ingestion, oral or pharyngeal bleeding, or coughing up blood that is then swallowed. In ruminants the presence of dark red feces from an intussusception is the main differential to be considered. Blood must stay in the intestinal tract for hours before the hemoglobin is altered and turns black. Small amounts of hemoglobin can be detected by using one of the tests for occult blood. In general, fairly large volumes of blood (1 to 2 L) are required to produce a positive fecal occult blood test in the horse.* A 24- to 48-hour time period is needed for orally administered blood to reach the rectum in the horse. In ruminants, smaller volumes of blood are needed to produce a positive fecal occult test, and a faster transit time is expected.

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7.3.1

Box 7-9 Causes of Melena in Horses

7.3.1.1

COMMON CAUSES

Gastric or duodenal ulcer

Gastric squamous cell carcinoma

Coughing up and swallowing blood

7.3.1.2

LESS COMMON CAUSES

Phenylbutazone toxicity (nonsteroidal antiinflammatory drugs)

Purpura hemorrhagica

Gastroenteritis with bleeding

Warfarin toxicity or other coagulation disorder

Colonic hematomas

Disseminated intravascular coagulation with mucosal hemorrhage

Anterior or proximal enteritis (duodenitis or proximal jejunitis)

Arsenic toxicity

7.3.1.3 UNCOMMON CAUSES

Lupus erythematosus

Factor VIII deficiency, hemophilia A

Histoplasmosis

7.3.2 Box 7-10 Causes of Melena in Ruminants

7.3.2.1 COMMON CAUSES

Abomasal ulcer

Intussusception

7.3.2.2 LESS COMMON CAUSES

Lung abscess with ruptured blood vessel

Oak toxicity

Coccidiosis

Gastroenteritis with bleeding

Arsenic toxicity

Ingestion of blood after parturition

Intestinal parasites

Toxicity from nonsteroidal antiinflammatory drugs

Abomasal torsion or volvulus

7.3.2.3 UNCOMMON CAUSES

Duodenal ulcers

Hemophilia A, factor VIII deficiency

Bacillary hemoglobinuria

Sulfur toxicity

Warfarin poisoning or other coagulation disorder

Narthecium asiaticum maxim poisoning (exotic)

In approaching a diagnosis, rule out pulmonary, oral, or pharyngeal bleeding. Bleeding of gastrointestinal origin can be determined to be caused by mucosal disease or full-thickness bowel disease (such as an intussusception or neoplasia) by examining peritoneal fluid for abnormalities. Abnormalities in peritoneal fluid are usually present in the case of serosal involvement. Bleeding abomasal ulcers are probably the leading cause of melena in ruminants. They can be silent except for the dark feces and weakness if severe anemia develops. In older horses, gastric squamous cell carcinoma is a frequent cause of gastric hemorrhage. Significant bleeding is much less common in foals and calves with gastric ulcers, and melena is rare in foals and calves with gastric ulcers.

Consideration should be given to whether or not the melena is the result of clotting abnormalities associated with such diseases as DIC or warfarin poisoning. In cattle with colic and dark red-to-black feces, intussusception should be considered likely.

When severe anemia develops, there is evidence of blood loss because the decrease in PCV and RBCs is accompanied by a decrease in plasma proteins. Nonspecific therapy for melena consists principally of blood transfusions in life-threatening cases. Sudden, massive gastric or abomasal bleeding may result in anemia and collapse before melena has appeared.

In the foal, gastric ulcers may be treated with histamine-2 (H_2) blockers such as ranitidine or cimetidine. These drugs are probably less effective in ruminants. Their benefit in ruminants with abomasal ulcers is not well understood at present. New drugs such as the hydrogen pump blocker omeprazole are useful and potent gastric pH effectors. Therapy with protectants such as sucralfate (which coats the ulcer) is a viable and clinically useful therapy in the horse. In ruminants, orally administered protectants and antacids are so diluted by the time they reach the abomasum that they are probably of limited benefit.

* Carlson G: Personal communication, 1990.

7.4

BLOOD, FIBRIN, AND/OR MUCUS IN FECES (DYSENTERY)

BRADFORD P. SMITH,

Bloody diarrhea is termed *dysentery*., The presence of fresh blood or clots in the feces is termed *hematochezia*, and is the result of bleeding into the distal intestinal tract. Occasionally blood from the female reproductive tract may appear in or on the feces. Fibrin indicates severe inflammatory bowel disease. Fibrin appears as casts, chunks of yellow-gray material, or mucosa-like sheets. Mucus in feces increases with inflammatory bowel diseases such as salmonellosis. It is often seen when fecal volume is small in animals that are anorectic, in which case the feces are often coated with mucus. This mucous coating can become very obvious in the horse and is not a sign of bowel disease in this case.

Frank blood in feces without diarrhea and other evidence of gastrointestinal dysfunction or systemic illness may be a result of a bleeding disorder, a traumatic foreign body, rectal examination trauma, sadistic rectal trauma, or rectal trauma in a mare from a stallion penetrating the rectum (Boxes 7-11 and 7-12). Many of the diseases listed as causes of melena may also result in gastrointestinal hemorrhage and are therefore listed in both places. If the bleeding is in the distal gastrointestinal tract, fresh blood may be seen in the feces. With diseases midway down the tract, such as intussusception, fecal material is dark red and may appear black until a sample is examined closely and spread on a white surface.

7.4.1

Box 7-11 Causes of Blood, Fibrin, or Mucus in Feces of the Horse

7.4.1.1

COMMON CAUSES

Foreign body

Rectal tear or trauma

Intussusception

Blister beetle (cantharidin) toxicity

Colitis, unknown cause

Salmonellosis

7.4.1.2 LESS COMMON CAUSES

Purpura hemorrhagica

Small strongyle infection (cyathostomiasis)

Colorectal polyps

Eosinophilic gastroenteritis

Acorn or oak poisoning

Arsenic toxicity

Organophosphate toxicity

Warfarin poisoning or other coagulation disorder

Mycotoxicoses

Besnoitiosis (globidiosis) (exotic)

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7.4.2 Box 7-12 Causes of Blood, Fibrin, or Mucus in Feces of Ruminants

7.4.2.1 COMMON CAUSES

Foreign body

Intussusception

Coccidiosis

Salmonellosis

7.4.2.2 LESS COMMON CAUSES

Rectal tear or trauma

Rectal examination trauma

Volvulus, root of mesentery

Malignant catarrhal fever

Enterotoxemia

Bovine viral diarrhea

Arsenic toxicity

Abomasal torsion

Warfarin poisoning or other coagulation disorder

Castor bean *(Ricinus)*, poisoning

Tung tree (Aleurites) poisoning

Solanum, (nightshade, potato) poisoning

Sesbania, (rattlebox) poisoning

Bracken fern

7.5 ABDOMINAL DISTENTION AND CONSTIPATION

BRADFORD P. SMITH,

Abdominal distention may be caused by feed, fluid, gas, feces, or a neoplasm (Boxes 7-13 and 7-14). Pregnancy or extreme obesity may also result in an enlarged abdomen. The physical examination should determine which of these is the most likely cause. Often in ruminants the distention can be seen as primarily left sided, right sided, or bilateral. For example, bloat in ruminants results in a characteristic high left-sided gas distention. It may be primary or associated with vagal indigestion, tetanus, or hypocalcemia. With vagal indigestion the rumen becomes enlarged and fluid-filled, often giving a pear shape to the abdomen as it is viewed from the rear, or a pear shape on the right and an apple shape on the left (“papple” shape) if some degree of bloat is also present. Hypocalcemia and hypokalemia contribute to ileus and may result in constipation and abdominal enlargement. In sheep, abomasal impaction and enlargement associated with abomasal emptying defects can result in an enlarged abdomen with

decreased food intake. When a mass (most commonly an abscess, a tumor, or a fat necrosis [cattle only]) obstructs fecal passage, abdominal enlargement can become severe. With obstructive disease, some degree of colic is almost always present. Ruptured bladder results in a large fluid-filled abdomen, but constipation is not an obvious sign.

7.5.1

Box 7-13 Causes of Abdominal Distention and Constipation in Horses

7.5.1.1

COMMON CAUSES

Ileus

Intestinal foreign body such as enterolith (see Colic)

Peritonitis

Intestinal obstruction, impaction, or gas (see Colic)

Necrotizing enterocolitis (foals)

Torsion or volvulus of gut (see Colic)

Sudden decrease in exercise

7.5.1.2

LESS COMMON CAUSES

Pregnancy

Pelvic mass (abscess, tumor)

Cecal tympany (see Colic)

Hernia, obstructive (see Colic)

Intussusception (see Colic)

7.5.1.3

UNCOMMON CAUSES

Anticholinergics

Opiates

Intrinsic colonic nerve dysfunction

Anorectal pain

Perineal hernia

Hypokalemia

Tetanus

Hypocalcemic tetany

Intramural hematomas on gut

Propylene glycol toxicity

Grass sickness (exotic)

7.5.2

Box 7-14 Causes of Abdominal Distention and Constipation in Ruminants

7.5.2.1

COMMON CAUSES

Pregnancy

Obesity

Vagal indigestion

Grain overload

Bloat

Ileus

Cecal volvulus or dilation with ileus

Peritonitis, traumatic or other cause

Fat necrosis involving rectum or colon

Ruptured bladder (uroperitoneum)

Intestinal obstruction

Pelvic mass (abscess, tumor)

Hypocalcemia

Omasal obstruction or foreign body

7.5.2.2 LESS COMMON CAUSES

Anticholinergics

Intussusception

Abomasal volvulus

Abomasal impaction

Tetanus

Abomasal bloat (calf)

Necrotizing enterocolitis (calf)

7.5.2.3 UNCOMMON CAUSES

Hydrops

Ascites

Torsion of descending colon

Internal herniation, especially diaphragmatic hernia involving reticulum

Displacement of intestine to left of rumen

Stenosis of duodenum

Adhesions of intestine

Bovine leucosis

Intestinal volvulus

Atresia of anus, colon, rectum, or intestine

Abomasal adenocarcinoma

Omental bursitis

Perforated abomasal ulcer

Zinc toxicity

Crude oil toxicity

Diesel fuel toxicity

Propylene glycol toxicity

Larkspur poisoning

The most common causes of decreased fecal output in ruminants and horses are decreased feed intake and dehydration. In such cases the animal will appear gaunt or have a relatively empty abdomen or rumen. Horse feces in cases of prolonged transit are often covered with a layer of tenacious, thick, yellow mucus. When a functional obstruction (ileus, vagal indigestion) or physical obstruction (impaction, foreign body, displaced intestine, fat necrosis) occurs as a cause of constipation, the abdomen is more likely to appear normally full or to become distended. Rectal examination is of great help in determining whether a mass or an obstruction exists because loops of distended small bowel can sometimes be palpated in the latter case.

Radiographs and ultrasound may be valuable to help determine the cause of abdominal distention in foals, calves, and small ruminants. Increased gastrointestinal gas may result in abdominal distention. Abomasal bloat and necrotizing enterocolitis in young animals may best be confirmed with lateral abdominal radiographs.

Dehydration may also result in dry feces but not in abdominal enlargement. When constipation is present and feces are drier than normal, rehydration and correction of hypocalcemia, hypokalemia, and any existing acid-base abnormalities are important parts of correction of the constipation. Other nonspecific therapies for functional constipation include laxatives, cathartics, and cholinergic drugs. When treating constipation, which is usually a secondary problem, it is important to simultaneously attempt to diagnose the primary disease.

In ruminants, when abdominal distention involves the rumen or is caused by pregnancy or obesity, colic is absent. When abdominal distention is the result of obstruction from the pylorus distal, colic is usually present. Abdominal distention and constipation are frequently accompanied by colic in the horse, regardless of anatomic site involved (review the approach to colic).

7.6 REGURGITATION AND VOMITING

BRADFORD P. SMITH,

Regurgitation is the reflux of esophageal, gastric, or rumen contents into the mouth or nose. This may be caused by malfunction of the esophagus or in ruminants as part of the normal physiology for rechewing ingested plant fiber (Boxes 7-15 and 7-16). Vomiting is a coordinated, centrally (medulla) mediated event, usually preceded by nausea (inappetence), increased salivation, or retching. In vomiting the abdominal musculature contracts, the diaphragm is pushed caudally, and the cardia relaxes. The medullary vomiting center can be stimulated by visceral afferent stimuli or through the chemoreceptor trigger zone. Most toxins and drugs that cause vomiting act by directly affecting the chemoreceptor trigger zone. Other than with toxins, most cases of feed returning to the mouth in large animals are examples of regurgitation rather than true vomiting. Vomiting is unusual in both ruminants and horses.

Although regurgitation is a normal phenomenon in ruminants, it is unusual to find excessive regurgitation as a sign of disease. Physical blockage of rumenoreticular outflow by a foreign body, warts, granulomas, or diaphragmatic hernia can cause rumen distention and excessive regurgitation after eating. An esophageal foreign body can cause irritation and result in regurgitation. Animals with facial paralysis may drool feed and saliva on the affected side; this should be differentiated from animals with excessive or abnormal regurgitation. Vomiting or forced regurgitation in ruminants is rare and is seen principally with the toxins listed.

7.6.1 Box 7-15 Causes of Regurgitation and Vomiting in Horses

7.6.1.1 COMMON CAUSES

Choke

Damaged esophagus, foreign body, or diverticulum

Foreign body in pharynx, trachea, or nose

Guttural pouch infection and pharyngeal paresis with nerve involvement

Gastric dilation

Gastric rupture

7.6.1.2 LESS COMMON CAUSES

Snake bite

Tetanus

Tick paralysis

Anterior enteritis (duodenitis or proximal jejunitis)

Gastric stenosis, ulcers

Hydrocephalus, meningitis, encephalitis

Central nervous system trauma

Polyneuritis

Peritonitis

Persistent right aortic arch

Grass sickness (exotic)

7.6.1.3 TOXINS

Phosphorus

α-Naphthyl thiourea (ANTU)

Cyanide

Herbicides

Arsenic

Lead

Nitrophenyl urea (vacor)

Organochlorine

7.6.1.4 PLANT TOXINS

Oleander

Castor bean

Death camas (*Zigandenus*, species)

Algae

Heath (Ericaceae)

7.6.2 Box 7-16 Causes of Regurgitation and Vomiting in Ruminants

7.6.2.1 COMMON CAUSES

Esophageal trauma or foreign body

Oral or pharyngeal foreign body, abscess, or trauma

Salt toxicity (water deprivation-access)

Tumor, papilloma, or other mass in rumen or esophagus

Toxins and poisonous plants

7.6.2.2 LESS COMMON CAUSES

Megaesophagus

Hiatal or diaphragmatic hernia

Esophageal diverticulum

Esophageal reaction to Hypoderma lineatum (B)

Hydrocephalus

Meningitis, meningoencephalitis

Central nervous system trauma

7.6.2.3 UNCOMMON CAUSES

Intestinal neoplasia

Traumatic reticulitis

Tick paralysis

Tetanus

Bluetongue (O)

Peritonitis

Persistent right aortic arch

Pseudorabies

Rift Valley fever (exotic)

7.6.2.4 TOXINS

Methanol or ethanol

Acute oral copper

Phosphorus

Arsenic

Nitrates

Crude oil

Diesel fuel

Snake bite

7.6.2.5 PLANT TOXINS

Solanum, species

Melia, (chinaberry)

Larkspur *(Delphinium*)

Cyanogenic plants

Nitrate accumulators

Death camas (*Zigandenus*, species)

Castor bean

Oleander

Cocklebur

Tremorgenic toxins

Heath (Ericaceae)

Helenium, (sneezeweed, bitterweed)

Hymenoxys, (rubberweed, bitterweed)

Veratrum, (hellabore)

Amianthium, (stagger grass)

Haplopappus, (burroweed)

Psilostrophe, (paper flowers) (O)

Agrostemma githago, (corn cockle)

Kalmia, (laurel)

Kikuyu (exotic)

Ibaraki disease (exotic)

Geigeria, (exotic)

Yellow-wood (exotic)

B, Bovine; *O*, ovine.

Horses have such a marked tone at the cardiac sphincter that vomiting occurs only when extreme intragastric pressures develop, usually in small intestinal obstructive diseases or proximal enteritis. Vomiting in the horse thus often occurs with gastric rupture or terminally with shock. Stomach contents are usually pH 5 or below. Because it is a terminal event, vomiting in the horse is often grounds for rendering a poor prognosis. Abdominocentesis should be performed on a horse after vomiting to rule out gastric rupture. To avoid this sequence of events, decompression using a nasogastric tube should be performed in any horse with evidence of gastric distention (see approach to colic). Regurgitation and vomiting in horses most commonly occur from the nose rather than into the mouth, because of the anatomy of the soft palate. With choke (esophageal obstruction), esophageal regurgitation from the nares consists of mixed feed and saliva.

In foals a few weeks to several months of age, milk returning from the nares is often associated with gastric ulceration, along with signs of colic, lying in dorsal recumbency, hypersalivation, and champing movements of the mouth. In advanced cases with duodenal ulcers, pyloric outflow can be obstructed by scarring, resulting in more pronounced signs. Foals 1 to 6 months of age are most susceptible to gastric ulceration.

Occasionally, neonatal foals without cleft palate have some mild degree of dysphagia with milk regurgitation from the nose for the first 24 to 48 hours of life, which spontaneously corrects. The cause of this is unknown, but it would appear to be a failure of normal swallowing events to be sufficiently strong or coordinated in the newborn. The major ruleout in these cases is cleft palate.

7.6.3

Approach to Diagnosis of Regurgitation and Vomiting

Evaluation of regurgitation or vomiting should include a history to determine possible exposure to toxins or poison plants, which is most likely when multiple animals are affected. Age of the animal limits some considerations; young animals are more prone to meningitis and central nervous system (CNS) trauma, and congenital problems such as esophageal diverticula and persistent right aortic arch are found only in neonates and may not manifest as choke or regurgitation until solid food intake is increased.

The physical examination can determine whether the problem is vomiting or regurgitation. In ruminants, regurgitation often occurs as a result of distention and overfilling of the rumen, resulting in an obviously distended abdomen. Painful pharyngeal lesions can also cause pharyngeal paresis, which results in gagging and regurgitating. In horses the most common causes of feed coming from the nares are spontaneous choke and pharyngeal paresis associated with guttural pouch lesions (see section on dysphagia).

Physical examination should also include passing a stomach tube to determine whether any impediment to passage of ingesta is present (Box 7-17). Endoscopy is useful to visualize esophageal defects. Many endoscopes currently in use are not long enough to reach the stomach of the adult horse. Endoscopy of the rumen is rarely diagnostic, because it is almost impossible to empty it adequately to allow for visualization of a lesion. Ultrasound of the cervical esophagus may also be useful.

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7.6.3.1

Box 7-17 Useful Techniques in Diagnosing Cause of Regurgitation

- Passing of stomach tube
- Endoscopy of pharynx, guttural pouches, esophagus, and stomach
- Ultrasound examination of the cervical esophagus may be helpful
- Radiographs; plain films of pharynx, guttural pouches, esophagus, and stomach
- Radiographs, barium swallows, checking gastric emptying time in horse

In horses and small ruminants radiography, particularly barium contrast studies, can be useful in detecting esophageal abnormalities. In foals, prolonged gastric emptying time may be diagnosed from contrast studies. Normal emptying and movement of contrast media into small bowel occur in less than 2 hours; contrast media reach the large bowel by 3 hours. Radiography may also be useful in detecting diaphragmatic hernia.

The most significant complications of regurgitation and vomiting include aspiration pneumonia, dehydration, and electrolyte imbalances. The marked hypochloremic alkalosis common to most monogastrics is rare in horses and occurs in ruminants mainly with internal vomiting (one type of vagal indigestion) associated with reflux of abomasal contents back into the rumen.

Vomiting, like diarrhea, is often an attempt by the body to rid itself of a noxious or toxic substance. Antiemetics are therefore rarely indicated in vomiting of central origin and rarely effective in regurgitation in large animals.

7.7

DYSPHAGIA (INCLUDING FEED FROM NARES AND EXCESSIVE SALIVATION)

BRADFORD P. SMITH,

Dysphagia, is used here to refer to abnormalities of prehension, mastication, or swallowing. It is associated with diseases of the mouth, lips, pharynx, esophagus, mandible, or masseter muscles or, in the case of neurologic problems, with central or peripheral lesions resulting in malfunction in these areas. Diseases resulting in erosions, ulcers, swellings, crusts, or growths in or on the lips, mouth, or pharynx are discussed under a separate heading. Painful causes of dysphagia such as dental problems require differentiation from oral lesions such as ulcers.

7.7.1

Box 7-18 Causes of Dysphagia in Horses

7.7.1.1

PAIN

Tooth root abscess or periodontal disease

Worn, missing, capped, overgrown, or broken teeth

Foreign body in mouth, pharynx, nose

Oral vesicles, erosions, ulcers, or growths

Pharyngeal abscess, cellulitis, trauma, fistula, or neoplasia

Esophageal choke, trauma

Strangles

Rupture of rectus capitus ventralis muscle

Snake bite

Oral, mandibular, or maxillary fracture, neoplasia, or granulomas

White muscle disease

Epiglottiditis, epiglottic cysts

Trauma or excessive traction to tongue

Hyoid bone injury

Nasal mass (granuloma)

7.7.1.2 OBSTRUCTION

Pharyngeal abscess, cellulitis, trauma, fistula, or neoplasia

Esophageal choke, trauma, megaesophagus

Strangles

Rostral displacement of palatopharyngeal arch

Damaged or abnormal esophagus

Cleft palate

Dorsal displacement of soft palate

Epiglottiditis, epiglottic cysts

Nasal mass (granuloma)

Lymphosarcoma

Purpura hemorrhagica

7.7.1.3 NEUROLOGIC, NEUROMUSCULAR

Yellow star thistle (Nigropallidal encephalomalacia)

Guttural pouch mycosis, infection, or tympany

Megaesophagus

Botulism

Lead toxicity

Rabies

Snake bite

Tetanus

Tick paralysis

Encephalitis, meningitis

Encephalopathy, hepatic

White muscle disease

Cerebrospinal nematodiasis

Electrocution

Transit or lactation tetany

Lymphosarcoma

Myeloproliferative disease

Myotonia

Otitis interna and media

Pontomedullary, brainstem neoplasia, pituitary abscess, trauma, neoplasm

Postanesthetic myasthenia

Herbicide toxicity

White snakeroot (tremetol) toxicity

Moldy corn poisoning

Locoweed *(Astragalus, Oxytropis)*, toxicity

West Nile fever

Borna disease, Near East encephalitis (exotic)

Grass sickness (exotic)

The causes of dysphagia can be divided into three categories: (1) pain induced, (2) neurologic, and (3) obstructive (Boxes 7-18 and 7-19). A fourth category is mechanical interference with prehension and swallowing, but this usually manifests in a manner resembling the manifestation of painful lesions. Particularly in horses, worn, missing, capped, abscessed, overgrown, or broken teeth often result in mechanical interference with chewing, resulting in half-chewed feed being dropped from the mouth (quidding). Observation of the animal as it attempts to eat and a good physical examination, including oral inspection and passage of a stomach tube to rule out choke, are essential in determining the cause of dysphagia. Use of a fiberoptic endoscope to visualize the pharynx, guttural pouches, and esophagus may be helpful. Plain film radiographs and barium swallows may also be indicated to see functional abnormalities in the pharynx and esophagus during swallowing and to rule out fractures of the hyoid or mandible. Ultrasound should also be employed.

Pain is probably the most frequent cause of dysphagia in ruminants and horses. Oral lesions, oral foreign bodies, and poor teeth result in decreased feed intake, in increased salivation, and often in dropping feed from the mouth while attempting to chew. Dental problems are relatively common in sheep and goats. In cattle, pharyngeal injuries from balling guns and paste wormers can result in severe pharyngeal cellulitis, which is manifested by an extended head, ptyalism, foul breath, and a painful, externally palpable, pharyngeal swelling. Mandibular fractures must be ruled out by careful examination, because even nondisplaced unilateral mandibular fractures can result in weak jaw tone, reluctance to eat, and drooling.

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7.7.2

Box 7-19 Causes of Dysphagia in Ruminants

7.7.2.1

PAIN

Oral vesicles, erosions, ulcers, growths (see following section)

Foreign body

Pharyngeal abscesses, cellulitis, or tumor

Traumatic or irritant stomatitis

Snake bite

White muscle disease

Actinobacillosis

Actinomycosis

Worn, missing, overgrown or broken teeth

Periodontal disease or tooth root abscesses

Oral, maxillary, or mandibular neoplasia

Fractured mandible or maxilla

Stomatitis

Necrotic laryngitis (calf diphtheria)

Ruptured or damaged esophagus

7.7.2.2 OBSTRUCTION

Foreign body

Pharyngeal abscess, cellulitis, or tumor

Choke

Snake bite

Actinobacillosis

Oral, maxillary, or mandibular neoplasia

Megaesophagus

Hiatal or diaphragmatic hernia

Cleft palate

Bovine leukosis

7.7.2.3 NEUROMUSCULAR

Listeriosis

Rabies

Tetanus

Botulism

Tick paralysis

Encephalitis, encephalopathy

Brain abscess

White muscle disease

Megaesophagus

Paresis of masseter muscles (mandibular branch of trigeminal)

Bovine leukosis

GM1 gangliosidosis in Friesian cattle

Meningitis

Encephalitis or encephalopathy

Atlantoaxial subluxation or occipitoatlantoaxial malformation

Hypocalcemia
Otitis media and interna
Pontomedullary brainstem neoplasia, trauma, infection, inflammation
Pituitary abscess
Pseudorabies
White snakeroot (tremetol) poisoning
Fireweed *(Kochia scoparia)*, poisoning
Locoweed *(Astragalus, Oxytropis)*, poisoning
Mercury poisoning
Kikuyu poisoning (exotic)
Ibaraki disease (exotic) (B)
Geigeria, poisoning (exotic)
Ephemeral fever (exotic) (B)

B, Bovine.

When dysphagia is associated with loss of large amounts of saliva, metabolic acid-base and electrolyte disorders may develop. Cattle and sheep have saliva high in sodium (136 to 201 mEq/L) and bicarbonate (108 mEq/L), with potassium and chloride values in the 14 to 15 mEq/L range.[30,31] As a result, losses of large amounts of saliva can result in hypovolemia and severe metabolic acidosis. In contrast, horses have relatively high levels of salivary chloride (48 to 82 mEq/L) with relatively low salivary bicarbonate (44 to 52 mEq/L). Equine salivary potassium is 14 to 18 mEq/L, and sodium 54 to 90 mEq/L.[32,33] As a result, horses with esophageal fistulas that lost saliva had a transient metabolic alkalosis.[32]

In the horse a common cause of acute dysphagia is choke (esophageal obstruction), followed in frequency by pharyngeal paresis (neurologic) resulting from lesions in the guttural pouch that affect the pharyngeal nerves. Feed coming from the nose is the most obvious sign of both of these conditions. In choked horses, as a result of the

length and position of the soft palate, feed comes mainly from the nares rather than coming back into the mouth. Choke and other obstructive diseases can be easily identified by using a nasogastric tube, whereas pharyngeal paresis may be associated with a number of neurologic or neuromuscular conditions, such as botulism or guttural pouch mycosis, which require careful differentiation. The most frequent serious problem associated with choke or pharyngeal paresis is inhalation (aspiration, foreign body) pneumonia. Mineral oil or other material that is particularly damaging if it gains entry into the lung should never be used in choke for this reason. In any animal with dysphagia, care must be taken to prevent aspiration pneumonia and to evaluate the thorax periodically.

Animals with facial paralysis often drool from the affected side and may pack feed into the cheek on the affected side. Listeriosis in ruminants is frequently associated with facial paralysis. In horses facial paralysis is usually caused by halter trauma or a blow to the head.

7.8

ORAL VESICLES, EROSIONS, ULCERS, OR GROWTHS

BRADFORD P. SMITH,

Oral lesions are found with many conditions (Boxes 7-20 and 7-21). In general, they result in some degree of dysphagia or reluctance to eat because of pain. The lesions include vesicles, erosions, ulcers, crusts, or growths in or on the lips, tongue, gums, palate, or pharynx. Oral lesions are often associated with champing and increased amounts of saliva being observed on the lips or running from the mouth. When the volume of saliva is increased, the condition is called *ptyalism*, and the animal may be observed swallowing repeatedly. *Pseudoptyalism*, refers to a normal volume of saliva that because it is not swallowed is visible to the observer and may be confused with dysphagia (see previous section).

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7.8.1

Box 7-20 Conditions Accompanied by Oral Vesicles, Erosions, Ulcers, or Growths in Horses

7.8.1.1

COMMON CAUSES

Vesicular stomatitis

Phenylbutazone toxicity

Yellow bristle grass (*Setaria lutescens*, or *Setaria glauca*) ulcers

Other plant awn stomatitis

Oral foreign body

7.8.1.2

LESS COMMON CAUSES

Irritant or caustic chemical stomatitis

Periodontal gingivitis

Blister beetle (cantharidin) toxicity

Uremia

7.8.2 Box 7-21 Conditions Accompanied by Oral Vesicles, Erosions, Ulcers, or Growths in Ruminants

7.8.2.1 COMMON CAUSES

Bluetongue (O)

Contagious ecthyma (Orf virus) (O, C)

Bovine viral diarrhea/mucosal disease (B)

Bovine papular stomatitis (B)

Traumatic or irritant stomatitis

Bristle grass (*Setaria lutescens*, or *Setaria glauca*) ulcers

Other plant awn stomatitis

Oral foreign body

Actinobacillosis (woody tongue)

Vesicular stomatitis

7.8.2.2 LESS COMMON CAUSES

Actinomycosis (lumpy jaw)

Cheek abscess

Periodontal gingivitis

Oak or acorn toxicity

Malignant catarrhal fever (B)

Irritant or caustic chemicals

7.8.2.3 UNCOMMON CAUSES

Caprine herpes virus (C)

Necrotic stomatitis

Epidermolysis bullosa

Familial acantholysis (B)

Oral neoplasia

Epitheliogenesis imperfecta

Hereditary zinc deficiency (baldy calf) (B)

Electrical injury

Bovine herpes 2 mammillitis (B)

Elaeophorosis (O)

Chlorinated naphthalene toxicity (B)

Thallium toxicity (O)

Giant hogweed *(Heracleum mantegazzianum)*, toxicity

Lead toxicity

Mycotoxicoses
Ibaraki disease (exotic) (B)
Lumpy skin disease (exotic) (B)
Sweating sickness (exotic) (B)
Sheep and goat pox (exotic) (O, C)
Peste des petits ruminants (exotic) (O, C)

B, Bovine; *C*, caprine; *O*, ovine.

The approach to determining the cause of oral lesions is based on first determining whether the cause is likely to be an infectious disease (Table 7-1). Essentially all these infectious diseases are associated with a fever, although it is short-lived and moderate in the case of bovine papular stomatitis (BPS) and actinobacillosis. Papular stomatitis rarely causes illness and is usually an incidental finding in calves with a different clinical problem. Most of the infectious diseases are associated with additional lesions or symptoms. They can be conveniently grouped into those causing diarrhea and those not usually associated with diarrhea. Of those not associated with diarrhea in North America, BPS, actinobacillosis, and vesicular stomatitis (VS) are most common in cattle; VS in horses; bluetongue in sheep; and contagious ecthyma (CE) in sheep and goats. CE can be readily differentiated from bluetongue because it involves primarily lips and gums and is proliferative, whereas bluetongue involves the tongue and dental pad most severely, is erosive, and is associated with other signs of generalized vasculitis. Laboratory diagnosis in acute cases of VS is done by working with state and federal veterinarians. Because VS is highly contagious and similar in clinical appearance to foot-and-mouth disease, quarantine and proper diagnosis are essential. Bluetongue is diagnosed by serology (AGID), PCR, and virus isolation. CE can be diagnosed serologically, by fluorescent antibody on the impression smear or biopsy of a lesion, and by isolation. Asymptomatic seroconversion to bluetongue is common where *Culicoides*, vectors are active. Congenital defects can result from bluetongue infection of the fetus in sheep, goats, and cattle.

The two most common North American infectious diseases associated with oral lesions and diarrhea in cattle are bovine viral diarrhea/mucosal disease (BVD/MD) and MCF. MCF can usually be differentiated because it most commonly occurs sporadically in single animals and has signs of generalized vasculitis such as bilateral corneal opacity, mucopurulent nasal discharge, enlarged lymph nodes, and very high fever. Dysentery is common in MCF, and some animals exhibit CNS signs or have thickened and cracking skin. Laboratory diagnosis in acute cases of BVD (see Chapter 32) involves fluorescent antibody testing of slides made from ear notch biopsies, lesion swabs, buffy coat, or tissue. Virus isolation from swabs, serum, or blood or a rise in serum titer from acute to convalescent samples is also diagnostic. Asymptomatic seroconversion is also common, and infection of the fetus may result in congenital anomalies, including cerebellar hypoplasia in cattle.

In animals without fever and other signs of systemic involvement, irritants and caustic chemicals should be considered as possible causes of oral lesions. Horses and young calves are susceptible to severe ulceration when consuming hay contaminated with yellow bristle grass, which is armed with barbed bristles.[34] Horses sometimes

develop gingivitis or oral ulcers associated with dry plant awns called *foxtails*, which become embedded into the gums around teeth. Foals and ponies are most susceptible to phenylbutazone toxicity, which can produce oral ulceration. In cattle the surfaces of masses produced by actinobacillosis and actinomycosis sometimes ulcerate. Many cattle without significant disease have one or more small ulcers of traumatic origin from plant awns on the hard palate and in the cleft (sulcus lingualis) where the base and shaft of the tongue meet.

Table 7-1 Infectious Diseases Associated with Oral Lesions in Cattle, Sheep, Goats, and Horses

Disease	Natural Species	Oral Lesions	Other Lesions
Vesicular stomatitis (VS)	Cattle Horse Sheep (rare)	Vesicles for short time, then large ulcers; tongue usually severely involved	Teats and feet may be involved
Bluetongue	Sheep Goat (rare) Cattle (rare)	Large oral ulcers; dental pad and tongue most affected; generalized vasculitis	Coronitis, muscle degeneration, lameness, pulmonary edema, edema of face and ears
Contagious ecthyma (CE; Orf)*	Sheep Goat	Proliferative scabby lesion on lips to fleshy growth on gums	Occasionally on teats of nursing dams
Bovine papular stomatitis*	Cattle	Round, dark red, raised papules on muzzle and on hard palate	Occasionally in esophagus
Foot-and-mouth (exotic)	Cattle Sheep Goat	Vesicles for short time, then large ulcers	Teats and coronary bands often involved
Bovine viral diarrhea/ mucosal disease (BVD/MD)	Cattle	Ulcers in mouth, particularly on hard palate; erosive stomatitis	May have skin lesions; a few have corneal edema or enlarged lymph nodes; pneumonia and lesions in esophagus and gastrointestinal tract common; severe diarrhea
Malignant catarrhal fever (MCF)	Cattle	Erosive stomatitis with ulcers; generalized vasculitis	Purulent nasal discharge, corneal edema, enlarged lymph nodes, ± cracking skin, ± central nervous system signs; severe diarrhea; high fever
Rinderpest (exotic)	Cattle Sheep Goat	Erosive stomatitis	Blepharospasm, severe intestinal involvement, and diarrhea
Alimentary form of infectious bovine rhinotracheitis (IBR) in calves	Cattle	Gray pinpoint pustules on soft palate and occasionally in nares; minimal oral lesions	Rhinotracheitis, conjunctivitis, pneumonia

* Infectious to humans.

7.9 DENTAL ABNORMALITIES

BRADFORD P. SMITH,

Chronic fluorosis is a cause of a variety of dental abnormalities in young animals with developing teeth (Boxes 7-22 and 7-23). Although cattle are most frequently involved, all large animals are susceptible. The teeth may appear mottled, striated, chalky, or hypoplastic or may have defective calcification. In severe cases teeth may be yellow, brown, or black and have multiple caries. Animals of any age may also develop bone lesions associated with chronic fluorosis.

7.9.1 Box 7-22 Causes of Dental Cavities, Abnormalities of Tooth Color, and Loose Teeth in Horses

Periodontal disease

Chronic fluoride toxicity

Dental decay

Fractured teeth

Osteomalacia, osteodystrophy

Halicephalobus (Micronema) deletrix, granulomas of mandible or maxilla

Skeletal neoplasia of mandible or maxilla

Hyperparathyroidism

Tooth root abscess with osteomyelitis, secondary to open infundibulum

Ameloblastoma (odontoma)

Dental stain (black walnut hull ingestion or other compound)

Porphyria is a rare congenital condition of cattle transmitted by a simple autosomal-recessive gene. The teeth often appear pink because of the presence of porphyrins and fluoresce pink, purple, or red when exposed to ultraviolet light. Affected calves often develop photosensitization and anemia. This condition must be differentiated from superficial staining caused by ingestion of black walnut hulls or other compounds with staining properties. 114 115

7.9.2

Box 7-23 Causes of Dental Cavities, Abnormalities of Tooth Color, and Loose Teeth in Ruminants

Chronic fluoride toxicity

Bovine erythropoietic porphyria

Fractured teeth

Osteogenesis imperfecta in Friesians

Osteomalacia, osteodystrophy

Actinomycosis

Skeletal neoplasia of mandible or maxilla

Lymphosarcoma (goat and sheep)

Periodontal disease

Broken mouth (old worn teeth)

Tooth root abscess with osteomyelitis

Ingestion of black walnut hulls or other dental stain

Excessive or uneven wear or loss of teeth is often seen in horses and ruminants as they age. Tooth wear, particularly of incisors, is more rapid in animals on sandy range. Periodontal disease can cause premature loss of teeth (broken mouth) and tends to be most common in sheep in some geographic areas; the cause of this is unknown.[35]

The most common dental disease in horses has been described as periodontal disease.[36] In horses fractured teeth or teeth with a small tract into the root through an open infundibulum often result in tooth root abscesses. This dental decay is a result of hypoplasia of the cementum of the enamel lakes and occurs most frequently in the second and third lower cheek teeth and third and fourth upper cheek teeth.[37] These can cause sinusitis and foul-smelling unilateral nasal discharge if upper cheek teeth are involved or draining tracts to the exterior skin surface if lower cheek teeth are involved.

Most of the other causes of dental abnormalities listed here are bone abnormalities that cause secondary loss of teeth. See Chapter 32 for more details.

7.10 ICTERUS (JAUNDICE)

BRADFORD P. SMITH,

Icterus, and *jaundice*, are synonymous terms referring to the expression of a yellow coloration in the sclera and mucous membranes resulting from increased amounts of bilirubin in tissues and increased serum bilirubin levels (Boxes 7-24 and 7-25). Bilirubin especially stains elastic tissues and is thus most visible in the sclera and vulva. Icterus usually indicates *decreased excretion*, of bilirubin with liver or biliary tract diseases or *increased production*, of bilirubin with hemolytic anemia.

7.10.1 Box 7-24 Causes of Icterus in Horses

7.10.1.1 LIVER

7.10.1.1.1 Common Causes

Pyrrolizidine alkaloid toxicity

Serum-associated hepatitis

Acute hepatitis

Chronic active hepatitis

Cholangitis or cholangiohepatitis

Bile stones, other biliary obstruction

Fasting hyperbilirubinemia

7.10.1.1.2 Less Common Causes

Aflatoxicosis with liver failure

Tyzzer's disease (foals)

Hepatic lipidosis

Hepatic abscess

7.10.1.1.3 Uncommon Causes

Black disease (infectious necrotic hepatitis)

Hemangioma, hemangiosarcoma, angiosarcoma

Cardiac neoplasm

Viral arteritis

Gastric or duodenal ulcers

Severe ascarid infection

Lymphosarcoma

7.10.1.2 HEMOLYTIC ANEMIA

7.10.1.2.1 Common Causes

Immune-mediated hemolytic anemia

Ehrlichiosis *(Ehrlichia equi)*,

Neonatal isoerythrolysis

7.10.1.2.2 Less Common Causes

Piroplasmosis (babesiosis)

Snake bite

Blood transfusion

Erythrocytosis

7.10.1.2.3 Uncommon Causes

Equine viral arteritis

Leptospirosis

Bee or wasp sting

Sulfur toxicity

Trichloroethylene-extracted feed

Iron toxicity

Phosphorus toxicity

Herbicide toxicity

Phenothiazine toxicity

White snakeroot poisoning (tremetol)

Onions

Red maple *(Acer rubrum)*,

Pentachlorophenol toxicity

Oak toxicity

Mycotoxicosis

Surra, *Trypanosoma evansi*, (exotic)

Mal de caderas, *Trypanosoma equinum*, (exotic)

Murrina de caderas, *Trypanosoma hippicum*, (exotic)

The accumulation of conjugated bilirubin results in more pronounced jaundice than does a similar amount of unconjugated bilirubin, with the result that the most pronounced jaundice is usually seen with hepatic or biliary obstructive disease. Laboratory examination of serum for relative amounts of unconjugated (indirect reacting) and conjugated (direct reacting) bilirubin is essential in determining the cause of the icterus. Generally, mainly unconjugated bilirubin levels are elevated with hemolytic anemia. Anorectic horses may have a plasma unconjugated bilirubin of 5 or 6 mg/dL without any evidence of hemolytic anemia or liver disease. Anorectic ruminants also experience a rise in plasma unconjugated bilirubin, often to a level between 0.5 and 2 mg/dL.

In determining the cause of icterus, laboratory tests, including PCV, RBC count, and the liver enzymes SDH and GGT, should be determined. In horses, alkaline phosphatase (AP) may also be useful, although it is not liver specific.

When active hepatocellular damage is occurring, SDH, which is liver specific, and aspartate aminotransferase (AST [SGOT]), which is not liver specific, are found in serum in elevated levels. GGT and AP are more indicative of biliary tract disease or proliferation and tend to rise more slowly but also to remain elevated for a longer period than SDH, which has a short half-life. Elevated levels of GGT or AP are often associated with chronic liver disease, cholangitis, cholelithiasis, or liver flukes. *It is possible to have liver disease without icterus*., Production and elimination of bilirubin are often equal in chronic liver disease, but acute liver disease or liver failure is usually associated with icterus. Although liver function tests such as BSP half-time can be run to determine the extent of liver damage, in most cases a liver biopsy must be taken for histopathologic examination to make a specific etiologic diagnosis of the cause of liver disease.

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7.10.2 Box 7-25 Causes of Icterus in Ruminants

7.10.2.1 LIVER

7.10.2.1.1 Common Causes

- Pyrrolizidine alkaloid toxicity
- Aflatoxicosis
- Fat cow syndrome (fatty liver)

7.10.2.1.2 Less Common Causes

- Acute hepatitis
- Liver flukes
- Infectious necrotic hepatitis (black disease)
- Liver abscess

Cholangiohepatitis

7.10.2.1.3 Uncommon Causes

Sarcocystosis

Hepatic neoplasia

Ruptured gallbladder

Cholelithiasis

Biliary obstruction

Nolina, (beargrass) toxicity

Lantana, toxicity

Agave, toxicity

Wesselsbron disease (exotic) (B, O)

7.10.2.2 HEMOLYTIC ANEMIA

7.10.2.2.1 Common Causes

Leptospirosis

Anaplasmosis

Bacillary hemoglobinuria *(Clostridium hemolyticum)*,

Piroplasmosis, babesiosis (exotic)

7.10.2.2.2 Less Common Causes

Snake bite

Immune-mediated hemolytic anemia

Transfusion reaction

Postparturient hemolytic anemia

Copper toxicity (especially sheep)

Neonatal isoerythrolysis

Yellow lamb disease (*Clostridium perfringens*, type A) (O)

7.10.2.2.3 Uncommon Causes

Anaplasma ovis

Eperythrozoonosis

Bee or wasp sting

Brassica species toxicity

Trichloroethylene-extracted feed toxicity

Iron toxicity

Onion poisoning

Zinc poisoning

Phosphorus poisoning

Mercury poisoning

Fireweed *(Kochia scoparia)*, poisoning

Mycotic lupinosis

	Mycosporum poisoning
	Theileriosis (East Coast fever) (exotic)

B, Bovine; *O*, ovine.

Liver abscesses rarely result in icterus because they rarely damage a sufficient percentage of liver to impair bilirubin clearance. They do cause multifocal hepatic damage and therefore are often associated with increased levels of SDH and AST when in the acute stages of formation.

Hemolytic anemia is characterized by destruction of RBCs either intravascularly or in the reticuloendothelial organs. This increased destruction results in production of bilirubin more rapidly than it can be removed by the liver, resulting in icterus. The specific cause of hemolytic anemia may sometimes be evident, as when autoagglutination is seen (autoimmune hemolytic anemia), *Anaplasma*, bodies are visible in stained RBCs of cattle, or *E. equi*, blue cytoplasmic inclusion bodies are seen in stained neutrophils.

In mature sheep, the most common cause of severe icterus is copper toxicity. In lambs, yellow lamb disease caused by *C. perfringens*, type A is a leading cause.

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8 Chapter 8 Localization and Differentiation of Neurologic Diseases

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8.1 TERMINOLOGY AND DESCRIPTION OF CLINICAL SIGNS OF NEUROLOGIC DISEASE (TABLE 8-1)

Telencephalon (cerebrum, basal ganglia) and diencephalon (thalamus)

Changes in behavior

Changes in the level of consciousness

Dullness, obtundation

Stupor

Coma

Excitement, mania

Seizures (convulsions)

Narcolepsy

Vision disturbance

Blindness in both visual fields (amaurosis)

Blindness in the contralateral visual field (hemianopsia)

Menace reflex deficit

Change in pupil size: small to pinpoint pupils

Circling (toward the side of the lesion)

Head turn (toward the side of the lesion)

Gait usually normal

Abnormal postural reactions (contralateral)

Decreased or absent conscious proprioception

Noticeable ataxia, paresis (weakness), or paralysis are uncommon

Abnormal spinal reflexes

Normal to increased (hyperreflexic) myotactic reflexes

Altered muscle tone

Normal to increased muscle tone (spasticity)

Urinary incontinence (upper motor neuron)

Tremors

Mesencephalon (midbrain)

Changes in the level of consciousness

Dullness (depression)

Stupor

Coma

Narcolepsy

Abnormal posture

Opisthotonos

Decerebrate posture

Abnormal visual or ocular function

Blindness in both visual fields (amaurosis)

Blindness in the contralateral visual field (hemianopsia)

Change in pupil size

Small pupils in early, mild lesions

Dilated, nonresponsive pupils in severe lesions

Menace reflex deficit (ipsilateral)

Anisocoria (asymmetric lesions)

Circling (toward side of lesion—ipsiversive)

Head turn (toward side of lesion—ipsiversive)

Abnormalities of gait (usually contralateral to lesion)

Decreased or absent conscious proprioception

Ataxia

Paresis (weakness)

Paralysis

Abnormal spinal reflexes

Normal to increased (hyperreflexic) myotactic reflexes

Altered muscle tone

Spasticity

Urinary incontinence (upper motor neuron)

Metencephalon (pons, cerebellum)

Abnormal posture

Head tilt

Decerebellate posture

Circling (usually away from side of lesion—paradoxic signs)

Head turn (usually away from side of lesion—paradoxic signs)

Nystagmus (variable—may be constant, positional, direction changing, or disconjugate and may occur in any direction)

Abnormalities of gait

Ataxia

Dysmetria—typically, hypermetria

Abnormal spinal reflexes (occasional)

Normal to increased myotactic reflexes (hyperreflexia)

Altered muscle tone

Normal to increased muscle tone on the opposite side of the body (contralateral spasticity)

Normal to decreased muscle tone on the same side of the body (ipsilateral hypotonus)

Urinary incontinence (upper motor neuron) (rare)

Medulla oblongata

Changes in the level of consciousness

Dullness, obtundation

Abnormal posture

Head tilt (toward side of lesion—ipsiversive)

Circling (toward side of lesion—ipsiversive)

Head turn occasionally (toward side of lesion)

Strabismus—variable

Nystagmus—spontaneous, abnormal (variable—may be constant, positional, direction changing, or disconjugate and may occur in any direction)

Dysphagia

Facial anesthesia, analgesia

Facial paresis or paralysis

Menace reflex deficit

Jaw weakness

Roaring, snoring, dysphonia

Tongue weakness, deviation, or paralysis

Abnormalities of gait—ipsilateral

Decreased or absent conscious proprioception

Ataxia

Paresis (weakness)

Paralysis

Abnormal spinal reflexes

Normal to increased (hyperreflexic) myotactic reflexes

Altered muscle tone

Normal to increased muscle tone

Urinary incontinence (upper motor neuron)

Spinal cord C1-C5

Abnormalities of gait in thoracic and pelvic limbs—ipsilateral

Decreased or absent conscious proprioception

Ataxia

Paresis (weakness)

Paralysis

Abnormal spinal reflexes—ipsilateral

Hyperreflexia in both thoracic and pelvic limbs

Decreased to absent caudal cervical and auricular reflexes

Decreased to absent slap test (horses)

Altered muscle tone

Normal to increased muscle tone

Urinary incontinence (upper motor neuron)

Spinal cord C6-T2

Abnormalities of gait in thoracic and pelvic limbs—ipsilateral

Decreased or absent conscious proprioception

Ataxia

Paresis (weakness)

Paralysis

Abnormal spinal reflexes—ipsilateral

Hyporeflexia in thoracic limbs

Hyperreflexia in pelvic limbs

Decreased to absent caudal cervical and auricular reflexes

Decreased to absent slap test (thoracolaryngeal reflex, horses)

Absent panniculus reflex

Horner's syndrome (ipsilateral)

Altered muscle tone

Decreased muscle tone in thoracic limbs

Normal to increased muscle tone in pelvic limbs

Urinary incontinence (upper motor neuron)

Spinal cord T3-L2

Abnormalities of gait in pelvic limbs only—ipsilateral

Decreased or absent conscious proprioception

Ataxia

Paresis (weakness)

Paralysis

Abnormal spinal reflexes—ipsilateral

Hyperreflexia in pelvic limbs only

Decreased panniculus reflex caudal to lesion

Altered muscle tone—ipsilateral

Normal to increased muscle tone in pelvic limbs

Urinary incontinence (upper motor neuron)

Spinal cord L3-S3

Abnormalities of gait in pelvic limbs only—ipsilateral

Decreased or absent conscious proprioception

Ataxia

Paresis (weakness)

Paralysis

Abnormal spinal reflexes—ipsilateral

Hyporeflexia in pelvic limbs only

Altered muscle tone

Decreased muscle tone in pelvic limbs

Flaccidity of the tail

Urinary incontinence (lower motor neuron)

Fecal incontinence (lower motor neuron)

Peripheral nerve and muscle

Abnormalities of gait

Paresis to paralysis

Decreased or absent conscious proprioception

Ataxia

Paresis (weakness)

Paralysis

Abnormal spinal reflexes—ipsilateral

Hyporeflexia

Altered muscle tone

Decreased muscle tone

Muscle atrophy

Flaccidity of the tail

Urinary incontinence (lower motor neuron)

Fecal incontinence (lower motor neuron)

Table 8-1 Localization of Central Nervous System Lesions According to Major Signs Encountered

Sign or Problem Encountered	Usual Lesion Location
CHANGES IN GAIT AND LOCOMOTION	
Ataxia	Nonspecific; any area of the central nervous system (CNS)
Conscious proprioceptive deficit	Nonspecific; any area of CNS except cerebellum
Knuckling	
Abduction or adduction	
Abnormal postural placement	
Hypermetria	Cerebellum, cerebellar peduncles, spinocerebellar tracts
Circling, or falling to one side	Basal ganglia, cortex, vestibular nuclei, cerebellum
Paraplegia or hemiplegia	Nonspecific
CHANGES IN SENSORIUM AND BEHAVIOR	
Coma or semicoma	Brainstem, thalamus, cortex
Obtundation	Brainstem, thalamus, cortex
Convulsions	Brainstem, thalamus, cortex
Head pressing, propulsive walking	Cortex (frontal lobe), limbic system
Aggression or rage	Limbic system, frontal lobe, amygdala
Inappropriate sexuality	Limbic system
Hyperphagia or hypophagia	Hypothalamus
Diabetes insipidus	Hypothalamus
Head shaking	Unknown, probably peripheral neuropathy
CHANGES IN HEAD POSTURE	
Stiff neck	Meninges, cervical spine
Head tilt	Thalamus, cerebral cortex, medulla, cerebellum
Head tremor	Cerebellum, basal ganglia
Opisthotonos	Cerebellum (rostral vermis), rostral brainstem, cerebrum, cranial nerve VIII
CRANIAL NERVE DYSFUNCTION	
Amaurosis	Cortex, internal capsule, optic chiasm, optic nerve, eye
Anisocoria	Cervical spine, vagosympathetic trunk, mesencephalon (oculomotor nerve nucleus), cranial cervical ganglion, ciliary ganglion, oculomotor nerve
Mydriasis	Oculomotor nerve, brainstem (mesencephalon), eye

Miosis	Vagosympathetic trunk, ciliary ganglia, tectum, brainstem, cervical spinal cord
Ptosis	Facial nerve, vagosympathetic trunk, ciliary ganglion, tectum, brainstem, cervical spinal cord
Strabismus	
Ventrolateral	Cerebellum, vestibular nucleus, oculomotor nerve
Dorsomedial	Trochlear nerve
Medial	Abducent nerve
Nystagmus	
Horizontal	Nerve VII (peripheral)
Vertical or rotatory	Vestibular nuclei, peripheral vestibular receptor, cerebellum, vestibulocochlear nerve
Jaw drop	Metencephalon, trigeminal motor nucleus, trigeminal nerve
Flaccid tongue	Medulla, hypoglossal nerve, hypoglossal nucleus, tongue muscle
Facial paralysis	Medulla, facial nerve, facial muscles
Facial analgesia	Trigeminal nerve (sensory component)
Dry eye	Cranial nerve VII before entering petrous temporal bone
CHANGES IN REFLEXES	
Patellar	L4-L6 spinal cord, femoral nerve, quadriceps femoris muscle
Flexors (forelimbs)	C5-T2 spinal cord segments, radial, ulnar, musculocutaneous and median nerves, and innervated muscles
Flexors (rear limbs)	L6-S2 spinal cord segments (hindlimbs); femoral, ischiatic, peroneal, and tibial nerves; flexor and extensor muscles of the limbs
Triceps	C6-T1 spinal cord segments, radial nerve, triceps muscle
Panniculus	C8 spinal cord segment, thoracodorsal nerve, dorsal column of thoracic spinal cord
Anal	S1-S5 sacral spinal cord segments, pudendal nerve
Ear twitch	Dorsal columns of C1-C3 spinal cord segments; facial nerve, facial nucleus, muscles of ear
Dysuria (dribbling urine)	Spinal cord, pons, pelvic nerves, bladder wall

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The clinical signs of neurologic disease depend on the location of the disease process within the nervous system. Widely varying disease entities may produce similar or identical clinical signs. Seizures, for example, may be the result of metabolic, toxic, traumatic, neoplastic, or other causes. Definitive diagnosis of neurologic disease, therefore, cannot be made on the basis of clinical signs alone. Localization of lesions within the nervous system is the first and key step in developing a differential diagnosis list and a rational diagnostic and therapeutic plan for any animal with signs of neurologic disease. Lesions are localized with the help of the neurologic examination. In this chapter the clinical signs of neurologic disease and the methods and interpretation of the neurologic

examination are described. Fortunately for the veterinarian, the clinical anatomy and the functions of the nervous systems of the various domestic animal species are almost identical. Thus, the clinical signs of neurologic lesions are, for the most part, similar in all these species.

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8.2 DIAGNOSIS OF NEUROLOGIC DISEASES

8.2.1 Signalment

The species, breed, age, and pedigree of an animal are important considerations in the differential diagnosis of neurologic disease. Many diseases are species-specific, particularly in the case of infectious and genetic diseases. Equine protozoal myeloencephalitis, for example, would not be a differential diagnosis in the case of cattle with signs of neurologic disease. Other infectious diseases, such as rabies virus infection, can affect many species. In yet other instances, all species may be affected but may have varying susceptibility to the disease. Such is the case with tetanus caused by *Clostridium tetani* exotoxin; horses and small ruminants are significantly more susceptible to the disease than are cattle. Some diseases not only are species-specific but also have higher incidence in certain breeds of that species. An example of this is equine degenerative myeloencephalopathy, which has been reported in several breeds of horses but has an increased incidence in some breeds, such as the Appaloosa.[1] Examples of the numerous other breed-related neurologic diseases of large animals include cerebellar abiotrophy (Arabian foals), progressive ataxia (Charolais), demyelinating myelopathy (Limousins), neuraxial edema (polled Herefords), neuraxonal dystrophy (Morgans), hydrocephalus (horned Herefords and shorthorns), epileptic seizures and Weaver syndrome (Brown Swiss cattle), ceroid lipofuscinosis (Hampshire sheep), cerebellar abiotrophy, GM1 gangliosidosis (Holsteins), and many others.[2–11] Atlantoaxial malformations most commonly occur in Arabian foals and Holstein calves but are not seen exclusively in those breeds.[12,13]

Disease susceptibility also may be linked to age. Acute lead poisoning, for example, occurs most commonly in calves, whereas adult cattle tend to develop the subacute form of the disease.[14] Some diseases are found in the neonate at birth. A large number of congenital disorders of the central nervous system (CNS) can affect domestic livestock. These diseases have a variable clinical course, depending on the nature of the disorder. Inborn errors of myelin metabolism worsen with age, whereas other developmental conditions may remain stable throughout the animal's life.[15–20] Examples of these disorders are listed in Chapters 51 and 52

A knowledge of the most likely disease entities to occur within individual animals or groups of animals of particular species, breeds, and ages, therefore, can greatly assist the clinician in arriving at a list of likely differential diagnoses and formulating a rational diagnostic and therapeutic plan.

8.2.2 History

Many disorders of the CNS produce characteristic patterns of onset and progression that can have diagnostic importance. Some CNS diseases occur acutely, developing the full range of clinical signs within hours. If the disease is not fatal, the signs either stabilize by 24 hours and remain constant thereafter or improve. Diseases that may display this clinical course include traumatic injuries and some types of toxic, infectious, and metabolic diseases. Diseases with degenerative, neoplastic, and certain viral causes may develop more slowly, requiring days to weeks before the full extent of clinical signs is apparent.[2,21,22]

8.2.3 Diet

The diet of patients with neurologic disease should be evaluated[23–29] (Table 8-2). Common deficiencies of livestock include vitamins A and E, copper, selenium, and magnesium. Vitamin A deficiency occurs in feedlot animals that have no access to green plants; affected cattle become blind and develop seizures. Equine motor neuron disease is seen mainly in horses that are housed without access to pasture and whose diet is deficient in vitamin E.[30] Copper deficiency occurs in ruminants pastured in areas with shale or volcanic soils, which either are deficient in copper or contain high concentrations of molybdenum and sulfur (secondary copper deficiency). The deficiency produces demyelination of the spinal cord in lambs and kids and pathologic fractures of the lumbar spine of rapidly growing calves. Dietary deficiency of calcium in rapidly growing weaned calves also results in vertebral and long bone fractures. Although dietary deficiencies of vital nutrients are commonly associated with the development of neurologic diseases, oversupplementation of certain nutrients also may produce neurologic disorders. Overfeeding of calcium, micronutrient imbalance, protein, and energy to horses, for instance, has been linked to the development of cervical vertebral instability and stenosis (wobbler syndrome) in horses.[31,32]

Table 8-2 Dietary Deficiencies Associated with Neurologic Disorders of Livestock

Dietary Deficiency	Disease Produced	Neurologic Sign
Copper	Demyelination, pathologic fractures of vertebrae	Ataxia, recumbency
Vitamin E	Demyelination	Ataxia, recumbency
Vitamin A	Encephalopathy	Convulsions, blindness
Magnesium	Grass tetany, transport tetany, milk tremors	Convulsions, tremors, ataxia
Potassium	Weakness	Postpartum recumbency
Calcium or phosphorus	Milk fever, pathologic vertebral fractures, tetany	Weakness, ataxia, recumbency, tetany
Vitamin E or selenium	Nutritional myodegeneration	Weakness, ataxia, recumbency, acute death

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8.2.4 Environment

Examination of the patient's environment may provide valuable information about the cause of CNS disease. Outbreaks of botulism and listeriosis have been associated with ingestion of rotting vegetation around haystacks, silos, and feed bunks.[33,34] Plant poisonings are common in livestock, and identification of neurotoxic plants is important whenever multiple animals are affected simultaneously.[34–36] (Table 8-3). Clinical signs of plant poisonings are variable and may include ataxia, hypermetria, head tremors, convulsions, paralysis, coma, or sudden death. Nonplant neurointoxicants of livestock include lead, ethylene glycol, organic mercurials, chlorinated hydrocarbons, organophosphates, salt, sulfur, petroleum distillates, and many others. Dose of the neurointoxicant may be important, with different clinical signs appearing depending on the level of exposure.

Ingestion of high concentrations of organophosphates or carbamates inhibits cholinesterase and produces signs of parasympathetic and neuromuscular activation, including marked ataxia, coma, muscle tremors, salivation, and miotic pupils. When low doses of organophosphates are ingested chronically, however, the result is an axonopathy of spinal cord and medullary neurons. The clinical signs that result are predominantly those of hindlimb paresis and ataxia, which may progress to tetraparesis and recumbency.[37] Ingestion of petroleum distillates (motor oil, gasoline, kerosene) by cattle can induce narcosis. Some petroleum distillates also may contain toxic concentrations of lead. Other sources of lead include paints, batteries, waste dumps, and smelters. Therapeutic and dietary interventions also may result in toxicoses when improperly administered. Overtreatment of cattle with propylene glycol produces profound ataxia, depression, and coma. Ingestion of ammonia or ammoniated feedstuff produces hyperesthesia, excitability, coma, and convulsions. High concentrations of salt in drinking water or, more commonly, lack of fresh water or interruption of the water supply followed by unlimited access to water, can result in laminar necrosis of the cerebral cortex or eosinophilic meningitis.[37] The clinical signs are those of cerebral dysfunction, including blindness, dullness, seizures, coma, and death. Although this syndrome has been reported in cattle and sheep,[38–40] pigs seem to be particularly susceptible.

Table 8-3 Poisonous Plants Producing Neurologic Signs (Also See Chapter 54)

Plant Poisoning	Clinical Signs
Bermuda grass *(Cynodon dactylon)*	Ataxia, head tremors, spasms, recumbency
Water hemlock *(Cicuta maculata)*	Tremors, vomiting, ataxia, sudden death, convulsions, odontoprisis, pupillary dilation, abortions, bloat
Poison hemlock *(Conium maculatum)*	Tremors, vomiting, ataxia, sudden death, abortions, pupillary dilation, bradycardia, coma
Blue green algae *(Aphanizomenon, Anabaena flos-aquae)*	Sudden death, tremors, salivation, miosis, bradycardia
Laburnum *(Laburnum anagyroides)*	Excitement, incoordination, convulsions, death
Milkweed (*Asclepias* species)	Tremors, salivation, ataxia
Larkspur *(Delphinium)*	Ataxia, collapse, recumbency, inability to lift head, tremors of face, flank, and hip; vomiting
Ryegrass ergot *(Claviceps paspali)*	Ataxia, head tremors, truncal ataxia, spasms, recumbency
Tobacco (*Nicotiana* species)	Tremors, salivation, ataxia, convulsions, birth defects
Nightshades (*Atropa* species, *Solanum* species)	Tremors, ataxia, recumbency, convulsions
Monkshood *(Aconitum)*	Restlessness, salivation, paresthesia, irregular heartbeat, recumbency, coma
Locoweed (*Astragalus* species)	Ataxia, weight loss, recumbency, hyperesthesia
White snakeroot *(Eupatorium rugosum)*	Tremors, salivation, convulsions
Rayless goldenrod *(Haplopappus heterophyllus)*	Lassitude, obtundation, arched back, stiff-legged gait, tremors, weakness, collapse
Bracken fern *(Pteridium aquilinum)*	Ataxia, weight loss, strip sweating (horses only)
Horse tail *(Equisetum arvense)*	Ataxia, weight loss, strip sweating (horses only)
Yellow star thistle *(Centaurea solstitialis)*	Facial rigidity, lack of prehension, ataxia, depression (horses only)
Tansy ragwort *(Senecio jacobea)* and groundsel *(Senecio vulgaris)*	Ataxia, obtundation, somnolence, excitability, head pressing (hepatic encephalopathy)
Fiddleneck *(Amsinckia intermedia)*	Ataxia, obtundation, somnolence, excitability, head pressing (hepatic encephalopathy)
Rattlebox *(Crotalaria spectabilis)*	Ataxia, obtundation, somnolence, excitability, head pressing (hepatic encephalopathy)
Death camus (*Zigadenus* species)	Trembling, uncontrolled running, recumbency, opisthotonos, convulsions, vomiting, salivation
Dutchman's breeches *(Dicentra)*	Trembling, uncontrolled running, recumbency, opisthotonos
Buckeye (*Aesculus* species)	Incoordination, twitching, sluggishness
Rape *(Brassica napus)*	Blindness, ataxia, aggressiveness

Cheesewood *(Malva)*	Tremors, worsened by forced exercise, hyperflexion of the hock during movement (stringhalt)
Lupine *(Lupinus)*	Tremors, hyperexcitability, depression
Dandelion *(Taraxacum officinale)*	Hyperflexion of the hock during movement (stringhalt)

Geographic area also may be important in the differential diagnosis of neurologic disease. Certain infectious diseases may be more common in particular areas of the country or even regions within a single state where the conditions for disease vectors are optimal.[41] The travel history of the animal must be considered, as well as the animal's location at the time clinical signs appeared. Travel also may result in increased contact with other animals and greater risk of exposure to infectious diseases. Recent movement of animals onto the premises may be important with respect to the likelihood of infectious diseases such as equine herpesvirus 1 and equine infectious anemia. 121 122

8.2.5 Vaccination and Disease History

When a neurologic problem is evaluated, the vaccination history and previous herd or individual disease problems should be noted. Some vaccines are highly protective, whereas others are less so. Examples of effective vaccines include those for focal symmetric encephalomalacia (enterotoxemia caused by *Clostridium perfringens* type D), rabies, and tetanus. Neurologic disease may be a secondary complication of disease in another organ system. Foals and calves with severe diarrhea, for example, may convulse secondary to hypokalemia, hypernatremia, or hypoglycemia. Preexisting diseases or clinical syndromes should be determined. For example, outbreaks of the CNS form of equine herpesvirus I are often preceded by respiratory disease or abortions in herdmates. Thromboembolic meningoencephalitis of cattle often follows an outbreak of respiratory disease within the herd. Historical evidence of limited colostral intake may be important in the diagnosis of bacterial meningitis of neonates. Bloody diarrhea often precedes the onset of nervous coccidiosis of calves.

8.2.6 Gestational Stage

Hypomagnesemia, eclampsia (hypocalcemia), hypokalemia syndrome, hypophosphatemia (postparturient hemoglobinuria) and nervous ketosis are common causes of recumbency, convulsions, and tremors in adult livestock. These diseases usually occur between the end of the last trimester and the first 2 months after parturition.

8.3 NERVOUS SYSTEM EXAMINATION

8.3.1 General Comments

A thorough physical examination should always precede or be performed concurrently with the neurologic examination. Physical examination may reveal evidence of systemic disease that underlies the neurologic problem—for example, icterus in animals with liver disease resulting in hepatic encephalopathy, unthriftiness in animals on poor diets, or traumatic injuries. In some instances disease of organ systems other than the nervous system may take precedence for diagnosis and treatment. Such may be the case with animals in shock or suffering from other life-threatening cardiovascular or respiratory disturbances. A common practice is to perform a general physical examination followed by a neurologic examination, but many aspects of nervous system

function, such as assessment of mental status and cranial nerve examination, may be carried out during the physical examination.

The neurologic examination should be carried out in a systematic fashion. The exact order of the examination is not important in itself, but procedures that may cause discomfort or pain, such as palpation of the spine, should be left until last. A common system used by many neurologists is to start at the head and progress to the tail.[42] This system is very useful in small animals but may be less so in large animals. Some clinicians prefer to examine the animal standing in the stall initially, then observe the gait. Because large animals are less amenable to handling than the typical cat or dog, another system for the neurologic examination is to begin with procedures that require minimal handling of the animal, such as observation of mental status, posture, and gait, and proceed to those that require greater manipulation: examination of the cranial nerves, assessment of spinal reflexes, and so on. The latter is the system that is described in the following sections. Each individual should develop a system that is effective for him or her, bearing in mind that one goal of the neurologic examination is to induce as little stress in the animal as possible because stress may alter the results of the examination.

Neurologic examination alone rarely leads to definitive diagnosis, but rather helps to answer the questions “Does the animal have neurologic disease?” and “What is the location of the neurologic lesion?” Once these questions are answered, a list of differential diagnoses can be made in light of other information such as the signalment of the animal and the history of the current problem. The diagnostic plan is based on the location of the lesion and the most likely differential diagnoses.

8.3.2 Mentation and Behavior

Initial examination should be done from a distance. The examiner observes the animal's mental state and whether its responses to its surroundings are appropriate. This is done ideally in the animal's usual environment, where it would be expected to be most calm. When this is not possible, the influence of factors such as the stress and excitement of previous travel and the animal's natural fear of unfamiliar surroundings, sounds, and smells must be taken into account. The reports from the animal's usual handler may be informative, if he or she is a good observer and has an understanding of normal behavior in animals. Compare the patient's interaction with its environment to a summary of its previous behavior and to the activities of the herdmates. Normal animals respond to mild stimulation. Most normal animals actively seek food when offered but vigorously avoid needle pricks. All livestock should recognize and fear strangers and should show awareness of the examiner's position. Normal animals change the posture of the head, ears, and eyes as the examiner moves. Depending on previous conditioning, normal behavior may include cautionary moves, avoidance, belligerence, or affection. Animals with decreased mental awareness (obtunded, dull, depressed) have reduced responses that may include lassitude, lack of recognition, unwillingness to rise or lift the head from the ground, head pressing, propulsive walking, lack of appetite, drooped ears, convulsions, stupor, or coma (Fig. 8-1). Systemic illness also may cause dull mentation; thorough physical examination and, perhaps, diagnostic tests including a complete blood count and serum chemistry are important in determining whether systemic disease is present. Furthermore, animals with primary CNS disease tend to have more profound dullness than do those with systemic disease alone. Hyperexcitability, rage, mania, or frantic motor activities are suggestive of a lesion of the limbic system, an assembly of connected groups of neurons (nuclei) and neuronal tracts in the cerebrum, thalamus, hypothalamus, and midbrain that is involved in emotional responses and patterns of behavior. Such animals may strike or kick at inappropriate times, demolish their stalls, bellow, show belligerence, or, if recumbent, struggle violently. The age, species, previous management system, and even the breed of animal are important considerations in the assessment of behavior. Bulls and stallions exhibit behavior that is very different from that of steers and geldings. Beef cattle behave differently than dairy cattle do. Animals that are handled regularly show fewer and milder fearful or aggressive responses than do animals that are handled rarely.

Fig. 8-1 Dull mentation in a horse with cerebral toxicosis caused by sage toxicity (Salvia species).

Changes in mental status are consequences of disease affecting either the cerebrum or the ascending reticular activating system (ARAS). The cerebral cortex is the “seat of consciousness”: conscious perception of both external stimuli (e.g., vision, hearing, touch) and internal stimuli (e.g., abdominal pain) depends on the integrity of the cerebral cortex. Both primary intracranial diseases (e.g., encephalitis, traumatic injury) and extracranial diseases (e.g., metabolic derangements, toxicities) can alter the functions of the cerebral cortex.

The ARAS is composed of a number of neuronal pathways that lie centrally within the brainstem (medulla oblongata, midbrain, and thalamus). The ARAS receives collateral input from all sensory information reaching

the brain, which it conveys ultimately to the cerebral cortex, where it reaches the level of consciousness. The ARAS is important in maintaining the animal's level of consciousness and arousal. The relationship between the cerebral cortex and the ARAS is sometimes described as follows: the cerebral cortex determines the content of consciousness, and the ARAS determines the level of consciousness. Diseases affecting the ARAS tend to produce more profound depression of consciousness, such as coma, than do those affecting the cerebral cortex alone, although this is not an absolute rule. Lesions of the ARAS occur commonly within the midbrain segment of this system, so that other signs of midbrain disease, such as pupillary dilation and loss of the oculocephalic reflexes (see below), often are observed in animals with lesions of the ARAS.

A seizure (convulsion, ictus) is a manifestation of cerebral cortex dysfunction characterized by loss of consciousness or involuntary motor activities. Seizures may be generalized or focal (partial). Generalized seizures are characterized by loss of consciousness and variable degrees of involuntary motor activity, which may include flailing of the limbs, elimination of feces and urine, and nystagmus. Localized involuntary movements with or without obvious alterations of consciousness characterize focal seizures. Alternatively, focal seizures may result in episodes of abnormal or bizarre behavior or momentary lapses of consciousness without collapse or significant motor activity. A third form of seizure is focal with secondary generalization. The onset of the seizure is focal, but seizure activity subsequently spreads throughout the cerebral cortex, resulting in a generalized seizure. Animals with this form of seizure activity exhibit initial focal signs, such as head turning, bellowing, focal tremors, and so on, followed by loss of consciousness and generalized signs of involuntary motor activity, as described previously. In most animals with focal seizures, with or without secondary generalization, the outward manifestation of the seizure is always the same. Rarely, seizures may be preceded by an aura, a period in which the animal exhibits anxiety or restless behavior shortly before the onset of the seizure itself. In most cases of seizures in animals, however, an aura is not observed. A postictal phase, a period of time subsequent to the seizure during which the animal exhibits abnormal behavior such as lethargy, restlessness, or anxiety, is usual after seizures in most animals. The postictal phase usually lasts a few minutes to hours but may last as long as several days. The postictal phase may be the only stage of the seizure observed by the animal's handler. Thus, any animal with a history of episodes of abnormal behavior should be suspected of having seizures. The typical history is that the animal is found in a dull or excited state, without the handler observing the onset of this change of behavior. Additional supporting evidence includes physical injuries such as scrapes and cuts that may have been incurred during the seizure itself.

Abnormalities of cerebral cortex dysfunction are the ultimate cause of seizure activity. During a seizure, groups of neurons in the cerebral cortex exhibit spontaneous electrical activity resulting in the clinical manifestations of focal or generalized seizures. Whereas neurons in the cerebral cortex ultimately become involved, abnormal electrical activity can begin elsewhere in the brain, such as in the brainstem, with subsequent spread of this activity to the cerebrum. Causes of seizures are legion, including alterations in the neuronal environment resulting from metabolic disturbances or toxicities, and the effects of structural brain diseases such as congenital or developmental disorders, traumatic injuries, neoplasia, and inflammatory conditions. Diagnosis of seizures and other states of altered mentation must include a thorough physical examination and screening for metabolic diseases such as electrolyte imbalances and hepatic or renal failure.

Abnormalities in the neurologic examination found between seizures (interictal period) support a diagnosis of primary brain disease and are an indication for diagnostic procedures such as cerebrospinal fluid (CSF) tap. Some toxins cause systemic signs as well as seizures, such as neuromuscular involvement (tremors, weakness) or parenchymal organ failure (icterus, uremia). Such signs, combined with a good clinical history and complete examination of the animal's environment, will help to direct specific toxicologic screening tests.

Narcolepsy is a condition wherein the normal mechanisms of sleep are disturbed. Although sudden onset of rapid eye movement (REM) sleep is one manifestation of narcolepsy, the acute onset of cataplexy—complete paralysis of striated muscles—usually is a more prominent clinical feature. Animals may be observed to suddenly collapse to the ground or to buckle at the knees. Cardiac and respiratory muscles are not affected. Narcoleptic attacks may be difficult to distinguish from seizures but are not accompanied by the involuntary motor activity that characterizes most generalized seizures. In some cases owners observe traumatic injuries to the head, face, and limbs without observing the cataplectic attacks that cause the trauma. Narcolepsy has been reported both in cattle and horses.[43–46]

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8.3.3 Gait

Gait should be evaluated by moving the animal in a straight line, moving it in a tight circle, backing up, and moving it over obstacles such as a curb. Having the patient walk up and down a slope with varying steepness and with the head elevated may reveal more subtle abnormalities. The examination may need to be modified depending on the species of the patient, amenability to handling, and consideration of safety concerns. In general, horses are more tolerant of handling than are ruminants.

Quadrupeds begin walking by protracting the rear limb, followed by the forelimb of the same side, then the opposite rear limb, and finally the opposite forelimb. Gait on a level surface requires integrity of the musculature, motor and sensory components of the peripheral nerves, local spinal reflexes, ascending and descending pathways in the spinal cord, and centers within the brainstem. Dysfunction of any of these areas results in an animal with mild to severe proprioceptive disturbances when standing or walking, which are exacerbated by turning the animal in a circle or stepping it on and off a curb. Animals with cerebral disease usually are able to perform simple motor activities such as walking along a straight path without obvious deficits but exhibit decreased proprioception when they are required to perform complex motor activities, such as walking on slopes or negotiating obstacles such as curbs or ground poles. Performance of such complex maneuvers requires coordination of proprioception and motor activities within the cerebral cortex, basal nuclei, and other CNS centers. Subtle deficits may be elicited by walking and then trotting the patient, or walking or trotting the patient briskly and then stopping suddenly. While a helper is walking the animal in a straight line on a level surface, the examiner should take hold of the tail and pull the animal sharply to one side. The normal animal will move toward the pull but should not stumble or fall. If the tension on the tail is maintained, strength can be assessed. Animals with lesions anywhere within the ascending or descending pathways controlling gait may show decreased proprioception in the form of stumbling, tripping, or crossing the limbs or may be weak. This maneuver also is useful for assessing the symmetry of a lesion. Circling the patient in a wide circle and then a tight circle also may elicit deficits, such as knuckling, stumbling, interference between feet, pivoting on one foot, or wide movements in the outside limb, that are not observed when the animal is walked in a straight line. Assessment of gait is facilitated when animals are halter-broken and can be lead. This is not the case in many ruminants, so the clinician must rely more on observing the animal in its usual environment or in a confined area such as a pen. A handler may drive animals that are not halter-broken, but this should be done with caution; safety of the animal and handler must be the top priority.

A grading system for gait deficits has been described elsewhere,[47] as follows:

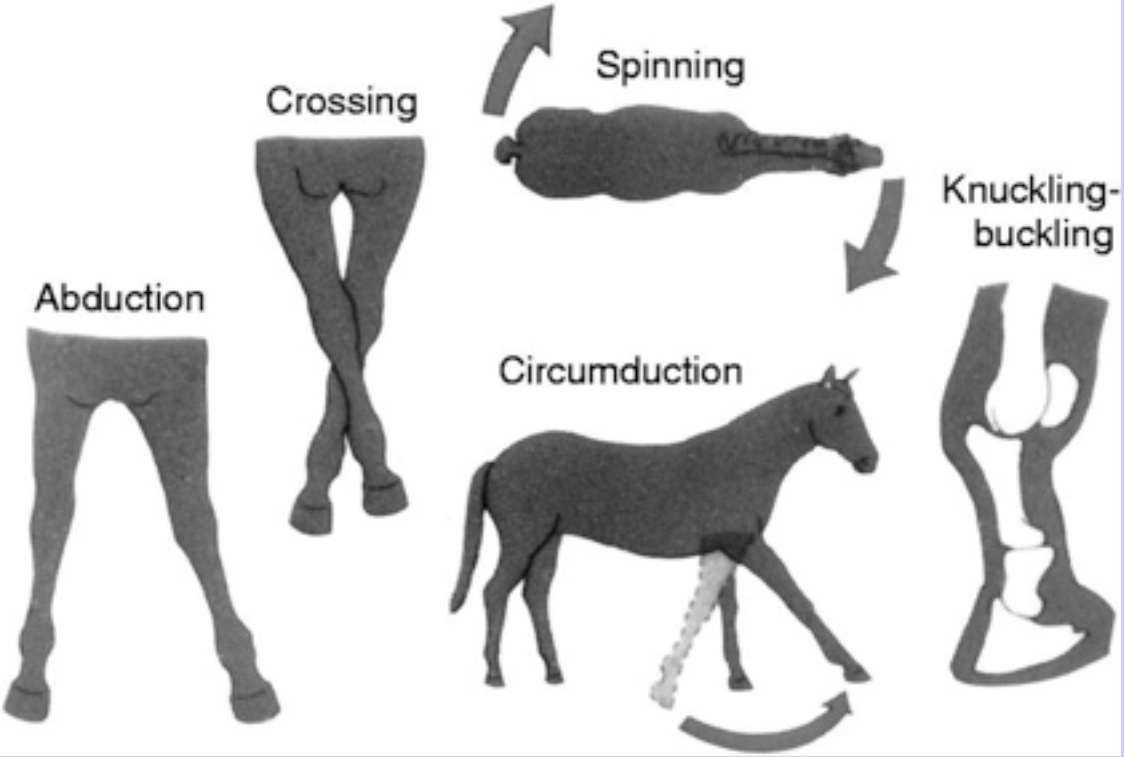
Grade 0:	Normal gait
Grade 1:	Very subtle deficits, observed by only an experienced clinician
Grade 2:	Deficits apparent to an inexperienced clinician
Grade 3:	Deficits apparent to laypersons
Grade 4:	Severe deficits, including stumbling, knuckling at the fetlock, falling
Grade 5:	Recumbency and inability to rise

Proprioception is the sense of position in space. Receptors lie in the skin, joints, and muscles. Ascending pathways run mainly in the dorsal funiculus of the spinal cord, relaying information to centers in the brainstem and cerebral cortex. Descending pathways involved in proprioception are largely similar to those that control gait. The vestibular system and pathways in the spinal cord to and from the vestibular centers in the medulla oblongata and cerebellum also help to control proprioception. Abnormalities of proprioception include knuckling, stumbling, adduction or abduction of the limbs, circumduction, and interference between limbs (Fig. 8-2). Animals with proprioceptive deficits often slap down the feet hard, rather like the gait of a person walking down stairs in the dark, unsure of where the next step is. Walking the animal off a curb or step exaggerates this appearance. When spun in a tight circle, normal animals lift the inside forefoot as the weight shifts. The outside rear leg is put down within a line demarcated by the lateral margin of the trunk. When spun in a tight circle, patients with abnormal proprioception may pivot on the inner forefoot rather than lifting it and replacing it into a normal position. The outside foot may circumduct widely, knuckle, or buckle, and the inside foot may step on the outside foot. Animals with abnormal proprioception worsen when they are required to climb hills or lift the foot over a curb or are walked with the head elevated. The gait of noncompliant cattle may be assessed by observation of maneuvers through corrals, alleys, or a squeeze chute.

Having the animal walk backward tests strength and proprioceptive function further. The normal subject should be able to do so in a smooth, coordinated fashion. Animals with lesions of either the ascending or descending motor pathways may exhibit abnormalities such as foot dragging and weakness, sometimes to the point of “dog-sitting.” Otherwise cooperative animals may be reluctant to move straight backward and will try avoidance maneuvers such as circling to one side or the other in order to avoid it. Such tactics should raise the index of suspicion of a neurologic deficit. Care should be taken when backing an animal with severe neurologic deficits because some animals could fall backward during the procedure. Animals that are uncooperative or that have been little handled may exhibit reluctance to walk backward that is not caused by neurologic disease. Observing the patient's general level of cooperation and having a good history will help the examiner determine whether the problem is caused by neurologic disease or is the result of the animal's lack of compliance.

Cerebellar disease causes generalized ataxia with a rolling, drunken gait. Protraction of the limbs is delayed and limb movements are exaggerated, a condition known as hypermetria. This is often accompanied by opisthotonos, which is a hyperextension of the head and neck, and intention tremor, most easily observed in the head. 124
Purposeful movements, such as reaching out to take food, exaggerate intention tremor, and muscular relaxation, 125
as in a recumbent animal, eliminates it.

Fig. 8-2 Examples of conscious proprioceptive deficits in a horse. The signs of proprioceptive deficits in ruminants are similar.



Spontaneous circling is seen in diseases of the vestibular system, midbrain, and cerebrum. Circling varies from a mild tendency to circle in one direction to tight and compulsive circling, seen particularly with midbrain disease. Circling occurs toward the side of the lesion, except in paradoxic vestibular disease (caused by lesions in the vestibular components of the cerebellum), in which the animal circles away from the side of the lesion. Localization of the neurologic lesion in animals that circle is made on the basis of other neurologic abnormalities, such as the state of consciousness, the presence of proprioceptive deficits, and the presence of signs such as head tilt, spontaneous nystagmus, seizures, or abnormal ocular function.

8.3.4

Conscious Proprioception and Postural Reactions

The integrity of conscious proprioceptive pathways may be tested by means of the postural reactions. Normal animals stand at rest with the limbs in line with the abaxial boundaries of the trunk. When the limbs are moved, normal animals do not permit the limbs to be placed outside of the body axis or across midline. After placement of the limbs in an abnormal position, the neurologically intact animal returns to a normal stance within a few seconds. Animals with conscious proprioceptive deficits allow the limb to remain in the abnormal position for longer than the usual period of time. This can vary from animals in which replacement of the limb into a normal position is slightly slowed to animals that do not try to replace the limb at all. The examiner should cross one of the animal's limbs over the opposite limb, or abduct one limb; the normal response is for the limb to be placed back into the resting position. Normal animals often strongly resist attempts to place the limbs in abnormal

positions. Animals with proprioceptive deficits may spontaneously place the limbs in abnormal positions: excessively adducted, abducted, or even crossed. Abnormalities of proprioception alone are poorly localizing signs, although a couple of generalities may be stated. Unilateral lesions rostral to the medulla oblongata produce mild to moderate proprioceptive and postural deficits in the contralateral limbs. Unilateral lesions in the medulla oblongata or spinal cord produce more severe proprioceptive and postural deficits in the ipsilateral limbs. Lesions of the cerebellum very rarely result in postural deficits.

Additional postural reactions, such as hopping and hemiwalking, can be tested in small ruminants, calves, and some foals. Hopping is tested in the forelimbs by lifting the rear limbs a few inches off the ground by means of a hand and arm placed around the abdomen, flexing one forelimb slightly, and moving the animal away from the side of the flexed forelimb, so that it has to hop laterally on the forelimb still in contact with the ground. It is easiest if the examiner stands in one place and turns clockwise when testing the animal's right forelimb and counterclockwise when testing the left forelimb. Hopping in the rear limbs can be tested similarly, supporting both forelimbs off the ground with an arm around the chest. Hemiwalking is done by supporting both limbs on one side of the body in a slightly flexed position and pushing the animal toward the opposite side so that it must walk laterally on the two limbs still in contact with the ground. Both hopping and hemiwalking should be done with care not to push the patient over. Hopping and hemiwalking involve the same ascending and descending motor tracts involved in gait on a level surface but also require integrity of the cerebral cortex. These maneuvers are abnormal on the ipsilateral side in animals with lesions in the skeletal muscles, peripheral nerves, spinal cord, and medulla oblongata and on the contralateral side in animals with lesions in the midbrain, thalamus, or cerebrum. Animals with cerebral lesions have normal gait on a level surface, but marked deficits in hemiwalking and hopping.

8.3.5 Abnormalities of Posture and the Righting Response

Posture refers to the position of the body and head in space, in relationship to gravity and to each other. Animals adopt slightly different postures when on a sloped surface or an uneven surface compared with posture on a level surface. However, sustained postures such as head tilt (Fig. 8-3), in which one ear is closer to the ground than the other, and head turn (Fig. 8-4), in which the muzzle is turned back toward the trunk, are abnormal. Circling often accompanies head tilt and head turn, and all tend to be toward the direction of the lesion. The exception to this rule occurs in paradoxic vestibular syndrome as a result of involvement of the cerebellar components of the vestibular system, in which head tilt and circling occur in the direction away from the side of the lesion. When proprioceptive deficits accompany circling they are ipsilateral when the lesion is in the medulla oblongata and contralateral when the lesion lies in the cerebrum, thalamus, or midbrain. Head tilt, head turn, and circling reflect the presence of lesions that are unilateral within the neuraxis or are asymmetric.

The righting response is most easily tested in small ruminants and in recumbent large animals (Fig. 8-5). The response is initiated by receptors in the eyes and vestibular labyrinths and by proprioceptive receptors in the joints, tendons, and muscles. Information regarding limb position and balance is relayed ultimately to the cerebral cortex. Descending impulses are initiated in the motor cortex and relayed via the brainstem and spinal cord to the appendicular musculature. The normal response to stimulation is to lift the head, assume sternal recumbency, and rise. The normal horse rises on the forelimbs first, whereas the normal ruminant rises on the rear limbs first. Animals that are reluctant to rise but do so normally after sufficient stimulation may have a disease of the cerebral cortex or the thalamus. Animals that are in lateral recumbency and unable to lift the head from the ground may have lesions in the peripheral or brainstem vestibular centers or in the cervical spinal cord proximal to the C4 spinal cord segment. Unilateral lesions in this area result in an inability to lift the head from the ground when the lesion side is up. When the lesion side is down, the animal can raise the head slightly. Animals with incomplete lesions of the cervicothoracic spinal cord (C7 to T1 spinal cord segments) are able to

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lift the head and neck but may remain recumbent. Animals with lesions of the thoracolumbar and lumbosacral spinal cord (T3 to S3 spinal cord segments) usually can lift the head and neck, arise on the forelimbs, and assume a dog-sitting position when stimulated.

Fig. 8-3 Head tilt caused by vestibular dysfunction in a horse that sustained head trauma.

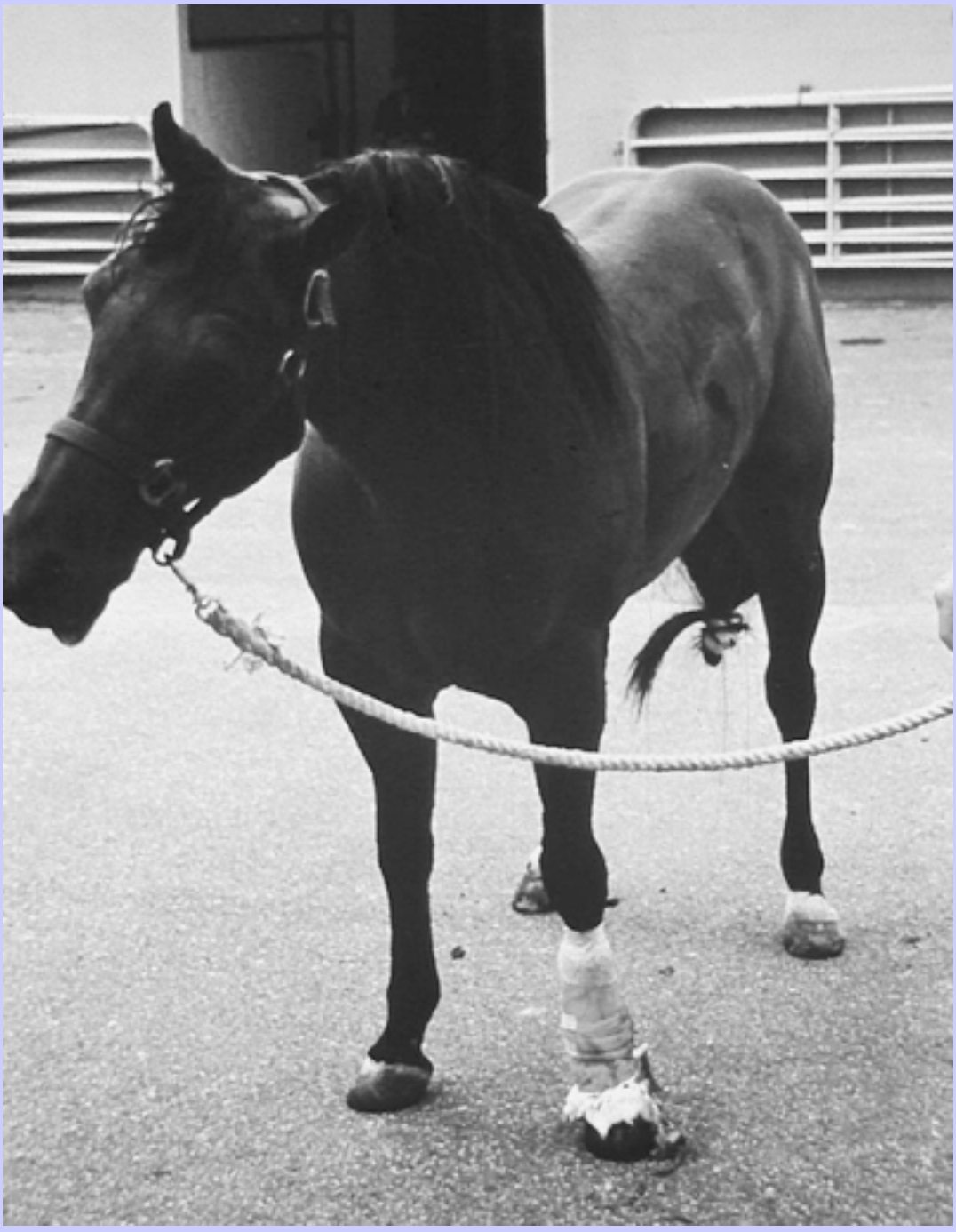
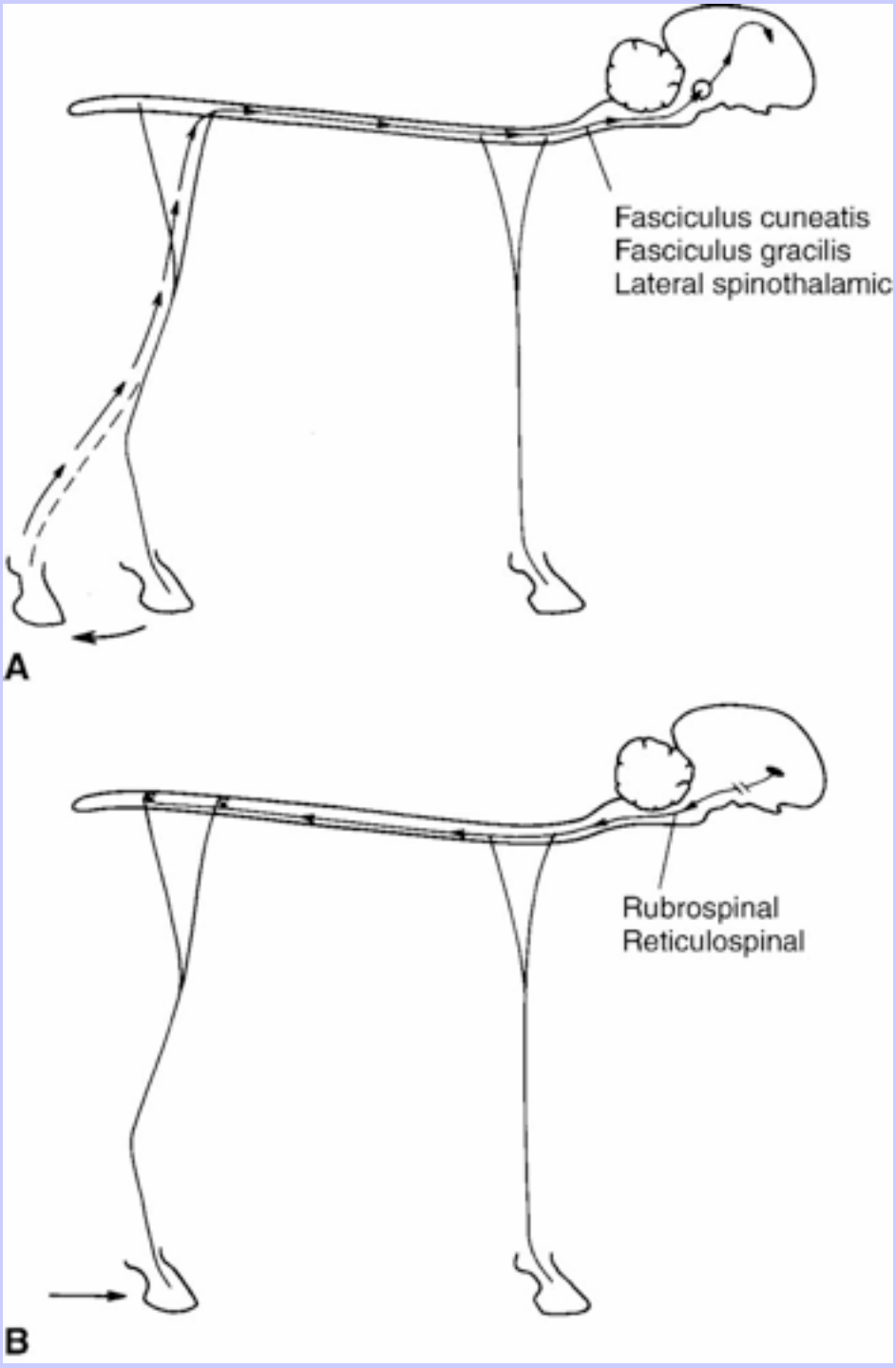


Fig. 8-4 Head turn in a steer with polioencephalomalacia.

Fig. 8-5 **A**, Afferent pathways responsible for providing proprioceptive information to the brainstem and higher centers. **B**, Efferent pathways responsible for providing motor activities to the motor neurons.



8.3.6 Spinal Reflexes

The spinal reflexes are stereotyped responses to specific stimuli. They include the myotactic or tendon reflexes, the panniculus or cutaneous trunci reflex, the perineal reflex, and several others. As their name implies, spinal reflexes depend on the integrity of local spinal cord segments, as well as the peripheral nerves, neuromuscular junctions, and muscles. Lesions in the spinal cord that are located rostral to the spinal origin of the peripheral nerves to the limbs being tested result in normal to increased spinal reflexes and are commonly referred to as *upper motor neuron lesions*. Lesions in the spinal cord segments at the level of the reflex arc or in the peripheral nerves, neuromuscular junctions, or muscles result in decreased spinal reflexes and are commonly referred to as *lower motor neuron lesions*.

It is appropriate at this point to define the terms *upper motor neuron* and *lower motor neuron*. Upper motor neurons are nerve cells whose cell bodies lie within the brain and whose axons terminate at synapses within the brain or in the spinal cord. Disease affecting upper motor neurons results in normal to increased spinal reflexes, as well as ataxia, variable severity of weakness, and sometimes increased muscle tone (spasticity). The nerve cell bodies of lower motor neurons lie in the nuclei of cranial nerves in the brainstem or within the ventral horn gray matter of the spinal cord. Their axons project beyond the CNS, course within the peripheral or cranial nerves, and terminate at neuromuscular junctions. Diseases affecting lower motor neurons result in decreased spinal reflexes, ataxia, moderate to severe weakness, decreased muscle tone, and rapid, pronounced atrophy of the denervated muscles.

8.3.7 Myotactic Reflexes

Myotactic or tendon reflexes are tested by sharply striking the tendon of a specific muscle (or sometimes the muscle itself) and evaluating the strength of the reflex contraction. The ascending component of the reflex arc involves the muscle spindles, which are stretch detectors, sensory fibers in the peripheral nerve, the dorsal nerve root and its ganglion, and the central projection of the sensory nerve fiber onto the ventral horn cell in the same spinal cord segment (Fig. 8-6). The descending component of the reflex arc involves the ventral horn cell (lower motor neuron), the ventral nerve root, the motor fibers in the peripheral nerve, the neuromuscular junction, and the myofibers in the muscle being tested. Lesions in either the ascending or descending components of the reflex arc result in a decreased to absent myotactic reflex. Lesions in the spinal cord above the level of the reflex arc and lesions of the brain result in a normal to increased myotactic reflex.

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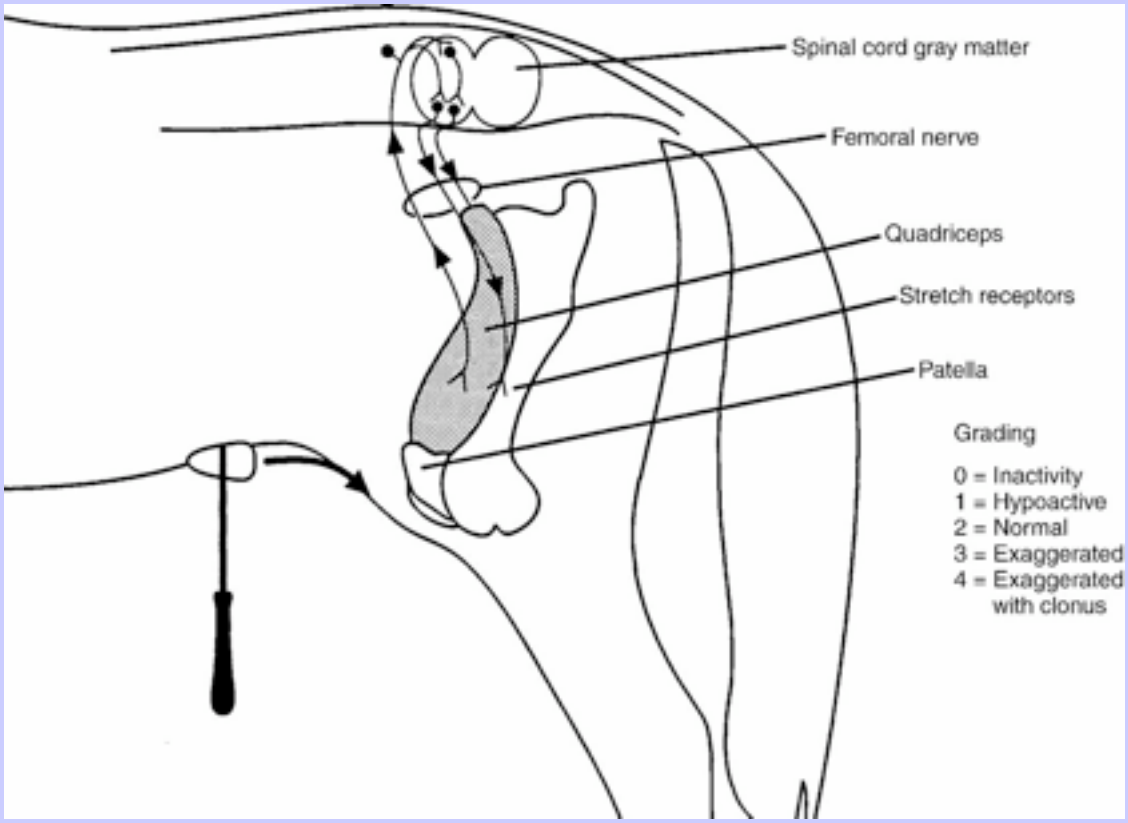
Fig. 8-6 Pathways governing patellar tendon reflex.



The myotactic reflexes can be tested only in the recumbent animal and thus are able to be examined only in a limited number of large animal patients. These reflexes should be tested only in the limbs that are uppermost when the animal is lying on one side. The animal must be turned over to test the limbs on the opposite side. These reflex responses are more subtle than in small animals and may not be elicited in some normal patients. The reflex responses are assigned a qualitative clinical score. One common classification is as follows:

0—No reflex activity

1—Hypoactive

2—Normal

3—Hyperactive

4—Hyperactive and clonic

Clonus is a phenomenon observed with severe upper motor neuron lesions: the response of the muscle being tested is rapid, repeated contractions rather than a single contraction. The innervation of the limbs is listed in Tables 8-4 and 8-5.

8.3.7.1 FORELIMB MYOTACTIC REFLEXES

8.3.7.1.1 Triceps Reflex

Hold the limb moderately flexed at the elbow, and percuss the triceps tendon just above the olecranon using a heavy instrument, such as a balling gun. In smaller subjects a rubber pleximeter can be used, as is done in cats and dogs. The normal response is a contraction of the triceps muscle, leading to retraction of the upper limb and extension of the elbow. The triceps reflex measures the integrity of the radial nerve and the C7 to T1 spinal segments.

Table 8-4 Innervation of the Forelimbs of Large Animals

Spinal Cord Segment	Peripheral Nerve	Muscle(s)
C7	Suprascapular	Supraspinatus, infraspinatus
C6, C7	Subscapular	Subscapularis
C7, C8, T1	Pectoral	Subscapularis, pectoral muscles
C6*, C7, C8	Musculocutaneous	Biceps brachii, coracobrachialis, brachialis
C8, T1, T2	Median	Flexor carpi radialis, deep digital flexor, superficial digital flexor
C8*, T1, T2	Ulnar	Flexor carpi ulnaris, deep digital flexor, superficial digital flexor
C7, C8, T1	Radial	Triceps, extensor carpi radialis, ulnaris lateralis, lateral and common digital extensors
C6†, C7, C8	Axillary	Deltoideus, teres minor, subscapularis, cleidobrachialis
C7, C8	Long thoracic	Serratus ventralis
C8, T1, T2†	Thoracodorsal	Latissimus dorsi
C8, T1, T2	Lateral thoracic	Panniculus

* Contributes innervation in the ruminant only.

† Contributes innervation in the horse only.

Table 8-5 Innervation of the Hindlimbs of Large Animals

Spinal Cord Segment	Peripheral Nerve	Muscle(s)
L3*, L4, L5, L6†	Femoral	Quadriceps
L5*, L6, S1	Cranial gluteal	Gluteals, tensor fascia latae
S1-S5	Caudal gluteal, pudendal	Biceps femoris, middle and superficial gluteals
L5*, L6, S1, S2	Ischiatic, fibular	Lateral digital extensor, long digital extensor, short digital extensor, cranial tibial
L5*, L6, S1, S2	Tibial	Gastrocnemius, popliteus, superficial and deep digital flexor, interosseus
L5*, L6, S1, S2	Pudendal	Retractor penis
S3-Cd5	Caudal rectal	Rectum, anal sphincter, bladder

* Contributes innervation in the horse only.

† Contributes innervation in the ruminant only.

8.3.7.1.2

Biceps Reflex

Hold the limb moderately extended at the elbow and place the supporting hand over the attachment of the biceps muscle on the dorsomedial aspect of the limb at the level of the elbow joint. Percuss the biceps tendon or the taut biceps muscle with a heavy instrument. Contraction of the muscle may be perceived visually or by palpation. A slight flexion of the elbow and extension of the carpus is normal. The test measures the function of the musculocutaneous nerve and spinal cord segments C6 to C8 in ruminants and C7 and C8 in horses.

Lesions rostral to C6 result in general hyperreflexia of both forelimbs and hindlimbs. Lesions located in spinal segments C5 to T2 result in hyporeflexia to areflexia of the forelimbs and hyperreflexia of the hindlimbs.

8.3.7.2

REAR LIMB MYOTACTIC REFLEXES

8.3.7.2.1

Patellar (Quadriceps) Reflex

Flex the stifle moderately, and sharply percuss the middle patellar ligament with a heavy instrument, or a rubber pleximeter in smaller subjects. The normal reflex is a sharp contraction of the quadriceps femoris muscle resulting in extension of the stifle and a forward jerk of the lower limb. The patellar reflex measures the function of the femoral nerve, the quadriceps femoris muscle, and L3 to L5 and L4 to L6 spinal cord segments in the horse and cow, respectively.

8.3.7.2.2 Cranial Tibial Reflex

The cranial tibial reflex is elicited by flexing the hock and sharply striking the belly of the cranial tibial muscle. The reflex consists of a slight extension of the digit. The cranial tibial reflex is mediated through the peroneal and sciatic nerves and spinal cord segments L5 to S2 or L6 to S2 in the horse and the ruminant, respectively. Lesions of the spinal cord anterior to L3 segments result in hyperreflexia, whereas lesions of L3 to L6 spinal segments result in hyporeflexia or areflexia.

The reflex part of the test measures the function of the peroneal, tibial, and sciatic nerves and the function of L6 to S2 spinal segments. The peroneal nerve supplies cutaneous innervation to the dorsolateral aspect of the limb. The tibial nerve supplies innervation to the caudomedial and dorsomedial aspects of the limb.

8.3.8 Flexor Reflexes

The flexor reflexes are elicited in the recumbent large animal. A painful stimulus is applied to the uppermost foot. The normal reflex consists of two phases: (1) a rapid limb flexion, and (2) a slower conscious perception of the stimulus, characterized by attempts to assume sternal recumbency, vocalization, ear and eye movements, violent kicking, and so on. The forelimb flexor reflex tests the integrity of the axillary, median, and musculocutaneous nerves and spinal cord segments C5 through T2, as well as the flexor muscles of the limb. The hindlimb flexor reflex is mediated by means of the sciatic, peroneal, and tibial nerves and the hindlimb flexor muscles.

Spinal cord and peripheral nerve lesions may be localized further by testing the integrity of the sensory innervation of the skin of the limbs. Areas of decreased or absent cutaneous sensation reflect lesions of the peripheral nerves innervating those regions of the skin or of the spinal cord segments in which those sensory nerves terminate. The skin over the trunk and much of the limbs is innervated by more than one peripheral nerve. Some areas of the limbs derive sensory innervation from a single peripheral nerve. These areas are termed the *autonomous zones* for those peripheral nerves. Damage to a peripheral nerve innervating the skin of a limb therefore will result in decreased to absent cutaneous sensation in the autonomous zone for that nerve. This information can be used to localize lesions. Decrease or loss of sensation to an entire limb or to limbs on both sides of the body suggest a lesion affecting several local spinal cord segments, or a transverse spinal cord lesion rostral to the affected limbs.

8.3.9 Other Spinal Reflexes

8.3.9.1 PERINEAL REFLEX

The perineal reflex is elicited by pinching the mucocutaneous junction of the anus. The normal reflex includes tightening of the sphincter muscle and contraction of the ventral tail muscles. Conscious sensation of the stimulus produces avoidance or protective responses that may range from a slight movement of the rear limbs and pelvis to a violent kick. The reflex is mediated by the internal pudendal nerve and spinal cord segments S1 to S5. Lesions in the nerve or in the sacral spinal cord result in a dilated, atonic rectal sphincter that fails to respond to noxious stimuli, as well as fecal impaction in the rectum and a dilated urinary bladder. The bladder is full of urine and dribbles whenever digital pressure is applied through the rectum or vagina. The perineum remains wet and may become irritated (“scalded”) by the continuous overflow of urine.

8.3.9.2

PANNICULUS (CUTANEOUS TRUNCI) REFLEX

The panniculus reflex is a wrinkling or flinching of the skin over the trunk when it is stimulated by light touch or by pinching. The skin over the caudal flank usually is the most sensitive. Run the tip of a closed hemostat over the skin, tap the skin lightly with the hemostat tip, or pinch the skin lightly with the hemostat. The normal response is a skin twitch, together with a conscious avoidance maneuver, such as moving away from the stimulus. The afferent part of the panniculus reflex is mediated through the dorsal nerve rootlets and the segmental spinal nerves that are distributed to the stimulated area. These ascend in the dorsal funiculi of the spinal cord and synapse on the efferent neurons in spinal segments C8 to T1 in ruminants and C8 to T2 in horses. The axons exit the ventral rootlet and form the thoracodorsal nerve, which innervates the cutaneous trunci muscle. The degree of reflex responsiveness varies among the large animal species. Sheep, goats, and many cattle possess a poor panniculus reflex. Horses and Zebu cattle have a well-developed reflex.

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8.3.9.3

CERVICAL REFLEXES

Two reflexes have been described in the cervical area of the horse.[48] The cervical reflex is similar to the panniculus reflex. Tapping or pinching the skin of the caudal half of the cervical region results in a local skin twitch. The pathway is believed to involve the cervical segmental spinal nerves and the local spinal cord segments.

The cervicoauricular reflex is elicited in horses by covering the eye and lightly tapping the skin over vertebrae C1 to C3. As the skin is stimulated in normal horses, the ear reflexively twitches cranially and ventrally, and twitching of the facial musculature at the commissure of the lips is observed. This test measures the integrity of the dorsal funiculi of C1 to C3 spinal cord segments and the facial nerve in the medulla oblongata. The diagnostic usefulness of the test in ruminants is unknown.

Both these reflexes are variable and are not always found in normal animals. Increased experience of the examiner, however, seems to be associated with increased reliability of these reflexes. Both reflexes may be abnormal in animals with lesions affecting the cervical spinal cord, such as equine wobbler syndrome. The cervicoauricular reflex also may be decreased or absent in animals with caudal brainstem lesions involving the facial nerve or with peripheral facial nerve lesions.

8.3.9.4

“SLAP” TEST (LARYNGEAL ADDUCTOR REFLEX)

A sharp slap applied in the saddle region on one side of a horse's thorax results in adduction of the vocal folds of the larynx on the opposite side.[49] This reflex can be palpated as a contraction of the cricoarytenoideus lateralis muscle. Standing on one side of the animal the examiner curls his or her fingers around the dorsolateral aspect of the larynx on the opposite side. A slap is applied to the saddle region on the side on which the examiner is standing. The response is palpated as a small movement under the fingertips of the cricoarytenoideus lateralis muscle on the opposite side of the larynx. It is often useful to have a helper apply the slap rather than to have the examiner do so. The pathway for the reflex is only partially understood. Sensory information from the skin is relayed to the spinal cord in the segmental spinal nerves. The ascending information then crosses the spinal cord and runs rostrally in a contralateral pathway to the origin of the vagus nerve in the nucleus ambiguus in the medulla oblongata. Descending output from the nucleus ambiguus runs in the cervical vagosympathetic trunk and thence to the recurrent laryngeal nerve, which branches from the vagus in the cranial thorax. The recurrent laryngeal nerve runs rostrally alongside the trachea to the larynx.

Thus the pathway for this reflex is almost entirely contralateral to the side on which the stimulus (the slap) is applied. Abnormalities in the laryngeal adductor response are seen in animals that have lesions of the cervical spinal cord but also in those with caudal brainstem lesions, vagus nerve lesions, and lesions of the recurrent laryngeal nerve ("roarers"). The test's accuracy may be limited. In one study there was poor correlation when predicting the presence or absence of cervical spinal cord or brainstem disease.[50] Interpretation of the results depends on the experience of the examiner. It should also be interpreted considering the complete neurologic examination findings. Presence of the response bilaterally is normal. Unilateral absence of the response suggests a lesion in one of the structures described previously. Bilateral absence of the response is harder to interpret because it may be the result of a bilateral lesion or the inability to palpate the cricoarytenoid contraction in a large or heavily muscled horse. The laryngeal adduction elicited in this test also can be observed endoscopically. The laryngeal adductor response tends to fatigue, so it may disappear if tested repeatedly over a short period.

8.3.10 Muscle Mass and Tone

Normal mass and tone of the musculature depends on an intact nerve supply. Primary diseases of muscle and loss of use of a limb secondary to orthopedic disease are often associated with mild to moderate muscle atrophy that develops over weeks to months. Atrophy caused by denervation, however, is more severe and rapid in onset. Visible loss of mass of specific muscles or groups of muscles is most likely caused by damage to the nerve supply to those muscles, either by direct injury to peripheral nerves or injury to the origins of those nerves in the ventral horn gray matter of the spinal cord (Fig. 8-7). Knowledge of the central origins of the nerves to the limbs and the course of those nerves in the periphery can be used to specifically localize neurologic lesions (see Tables 8-4 and 8-5). Electromyography and nerve conduction testing can further be used to help identify muscle denervation and peripheral neuropathies (see Chapter 35). Regeneration of peripheral nerves after an acute insult can occur. Regeneration is accomplished by outgrowths of axonal buds from the proximal stump. The buds either grow along previous peripheral nerve rootlets or generate new neural pathways in concert with proliferation of myelin precursor cells. The rate of growth of the axonal buds has been estimated to be approximately 1 to 4 mm/day.[51]

Muscle tone can be evaluated in the recumbent animal by passively flexing the limbs. Evaluation is not accurate in the standing animal or in animals supported in slings because of resistance from taut bands of connective tissue. In normal animals repeated flexion is accompanied by an increase in the tone in the flexed limb. The limbs of animals with a lower motor neuron deficit remain flaccid. Small ruminants tend to show a greater relative amount of extensor tone in the limbs than do cattle or horses. Evaluation of the test must be conservative because some severely obtunded large animals display generalized hypotonia, even though the lower motor neurons are functional. The cause of the hypotonia is unknown.

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Fig. 8-7 Muscle atrophy in the gluteal muscles in a horse with equine protozoal myeloencephalitis.

The tone of the forelimbs is controlled through spinal cord segments C6 to T1 and the radial, musculocutaneous, median, ulnar, axillary, and long thoracic nerves. The motor tone of the rear limbs is controlled through spinal cord segments L3 to S2 and the femoral, cranial and caudal gluteal, and sciatic nerves. The lower motor neurons to the anus originate in spinal cord segments S1 to S5, via the pudendal nerve. The tail is innervated by the coccygeal segmental spinal nerves.

8.3.11 Examination of Cranial Nerves

Examination of the cranial nerves is most easily carried out by examining the functions of groups of nerves that innervate particular regions of the head rather than performing the examination in a strictly numeric order. For example, examination of vision and other ocular functions such as the menace response, pupillary light reflexes, and physiologic nystagmus reveals the integrity of several cranial nerves, not only II, III, IV, and VI, but also V (sensory to the cornea), VII (motor to the eyelids), and VIII (providing vestibular input to control the functions of III, IV, and VI), as well as centers within the brain.

8.3.11.1 CRANIAL NERVE I—OLFACTORY NERVE

Reliable and specific testing of the sense of smell is difficult in animals. Large animals require an intact sense of smell to eat properly, so it can be inferred that animals with good appetites possess an adequate sense of smell. Having an animal track food moved from side to side in front of the nose may be helpful. Ensure that the food has an appealing odor. Irritating substances such as ammonia should not be used for evaluation of olfactory nerve function; such compounds stimulate nociceptors in the nasal mucosa, which are the dendrites of the maxillary nerve (cranial nerve V), rather than stimulating olfactory receptors innervated by the olfactory nerve. Loss of the sense of smell is more likely to be caused by disease within the nasal passages than by a primary neurologic disease.

8.3.11.2 CRANIAL NERVE II—OPTIC NERVE

Vision is the function of cranial nerve II, the optic nerve. Observing the animal's response to its environment provides a good initial assessment. Does it respond to visual cues, such as movement, or does it walk into objects? Noise may cause the animal to turn its head toward the sound, so the observer must be careful to distinguish such responses from those made in response to visual cues. A maze can be set up using straw bales or other objects, and the animal gently driven through the maze. Normal animals will avoid colliding with objects. Animals that are severely obtunded, however, may walk into objects even when they can see. Thorough evaluation of the complete neurologic examination is necessary to distinguish this from true blindness.

The menace response measures the integrity of the entire visual pathway. The ascending pathway runs from the retina via the optic nerves, midbrain, and internal capsule to the visual areas in the occipital lobe of the cerebrum. Information from the visual cortex is processed and relayed to the motor cortex. The descending pathway of the menace response runs from the motor cortex via the pons to the nucleus of the facial nerve in the medulla oblongata and thence via the facial nerve to the orbicularis oculi muscle. Input to this motor pathway also arises from the cerebellum. The menace test is performed by rapidly advancing the hand toward the eye and observing a reflex closure of the eyelids. In addition to the closure of the eyelids, some animals display a generalized avoidance response characterized by coordinated movement of the head and neck away from the stimulus. The opposite eye may be covered to ensure that only one eye is being stimulated. Care must

be taken not to touch the face or eyelashes. Many authors warn that air currents generated by rapid movement of the hand toward the face can elicit the response even in blind animals, but this has not been our experience. The menacing gesture is directed first at the nasal and then at the temporal parts of the visual field. Blindness in one visual field is termed *hemianopsia*. The menace response measures the integrity of the retina, optic nerve, optic chiasm, midbrain, internal capsule, and occipital cortex. There is approximately 90% crossing over of optic nerve fibers in the optic chiasm of livestock. Animals with a postchiasmal lesion in the internal capsule, midbrain, or occipital lobe will show hemianopsia in the contralateral visual field. In practical terms, lesions central to the optic chiasm cause loss of vision in the opposite eye, with apparently normal vision in the ipsilateral eye.

Menace deficit may be the result of facial nerve paralysis. In such cases the animal does not blink but shows avoidance of the stimulus by pulling the head away. Facial nerve deficits will be apparent in these animals by their inability to close the eyelids under any circumstances and by other signs such as facial drooping on the same side. Animals with cerebellar disease also may display a menace deficit, yet possess normal vision. The precise pathway by which the cerebellum influences the menace reflex is not known, but interruption of this pathway is thought to disrupt upper motor neuron control of the facial nerve, which becomes dysfunctional. Menace deficits resulting from facial nerve or cerebellar disease may be differentiated from deficits in other areas by maze testing. Animals with cerebellar or facial nerve disease retain visual acuity and maneuver through the course successfully. The maze test measures the patient's ability to identify and avoid obstacles. In addition to the optic pathways, the test measures the integrative pathways in the frontal and parietal lobes of the brain, the motor neurons, and the proprioceptive pathways (Table 8-6). Myasthenic diseases (e.g., botulism, hypocalcemia, or hypomagnesemia) result in bilaterally decreased menace and palpebral responses but do not produce blindness.

The pupillary light reflex measures the integrity of the retina, optic nerves, optic chiasm, pretectal and oculomotor nuclei in the midbrain, oculomotor nerve, ciliary ganglia, and constrictor pupillae muscle. The test is performed by shining a bright light into each eye and observing constriction of the pupil in the ipsilateral eye (direct response) and the contralateral eye (indirect response). Reducing the ambient light level may facilitate this test by causing the pupils to dilate. The reflex in large animals is considerably slower than observed in cats and dogs. A “swinging light” test has been recommended in large animals to reduce the blink and startle responses elicited by suddenly shining a bright light into the eyes.[47] A strong light source is slowly shone from one eye to the other while bringing it closer and closer to the head and observing the responses in each pupil. The effects on the pupillary light reflex of lesions at various levels along the visual pathway are shown in Table 8-6.

Unilateral lesions of the cerebral cortex result in blindness of the opposite eye. The pupillary light reflexes usually are normal. If the cortical disease is accompanied by increased intracranial pressure, the oculomotor nerve or nucleus may become dysfunctional because of midbrain compression, resulting in ipsilateral mydriasis.

Table 8-6 Guide to Neuroophthalmologic Lesion Location

	Menace Response		Pupillary Light Response		
Lesion Location	**Ipsilateral**	**Bilateral**	**Ipsilateral**	**Bilateral**	**Maze Test**
Unilateral retina, optic nerve	Absent	Present	Normal	Normal	Abnormal
Bilateral retina, optic nerve, optic chiasm	Absent	Absent	Fixed	Fixed	Abnormal
Unilateral oculomotor nerve	Absent	Present	Dilated nonresponsive	Normal	Normal
Unilateral occipital cortex	Present	Absent	Normal*	Normal*	Abnormal
Bilateral occipital cortex	Absent	Absent	Normal	Normal	Abnormal
Bilateral vagosympathetic trunk	Present	Present	Miotic	Normal	Normal
Bilateral cerebellar cortex	Absent	Absent	Normal	Normal	Normal†

* Assuming that no cortical swelling has occurred.

† Animals walk abnormally but recognize and generally avoid obstacles.

8.3.11.3

CRANIAL NERVES III, IV, AND VI—OCULOMOTOR, TROCHLEAR, AND ABDUCENT NERVES

The position of the globe in the orbit is governed by the activity of the oculomotor, trochlear, and abducent nerves. Dysfunctions of these nerves result in deviation of the globe that is constant in all head positions. Loss of oculomotor nerve function results in a ventrolateral strabismus. Trochlear nerve dysfunction results in rotation of the dorsal aspect of the globe away from the midline (dorsomedial strabismus). In large animals that have horizontal pupils, trochlear nerve lesions cause deviation of the pupil such that the medial aspect of the pupil is dorsal to the lateral aspect. The trochlear nerve crosses the midline twice in the area of the midbrain before exiting the cranial vault. Therefore unilateral lesions could result in contralateral or ipsilateral strabismus, depending on the location of the lesion within the brainstem. Lesions of the trochlear nerve are, in our experience, extremely rare. Loss of abducent nerve function results in medial strabismus with inability to retract the globe, which is best demonstrated by restraining the head of the patient, opening the palpebral fissure, and touching the cornea. The normal reflex is a retraction of the globe with protrusion of the third eyelid.

Function of the oculomotor, trochlear, and abducent nerves also is observed when testing the oculocephalic reflexes. When the head is turned from side to side a horizontal nystagmus is observed, with the fast phase of the nystagmus in the direction of the head movement. The sensory receptors for this reflex lie within the semicircular canals of the inner ear, and they detect angular acceleration of the head. Input from the

semicircular canals is transferred to the vestibular centers in the medulla oblongata and the cerebellum, and thence via the medial longitudinal fasciculus and reticular formation to the nuclei of cranial nerves III, IV, and VI. Lesions of the peripheral or central components of the vestibular system also can result in abnormal eye position (strabismus) and movement (nystagmus), described in more detail later. In such cases, however, the strabismus typically changes when the head and neck are moved, in contrast to the constant deviation of the globe seen with direct lesions to the oculomotor, trochlear, and abducent nerves. Vestibular dysfunction also results in spontaneous nystagmus, which can be used to differentiate these conditions from dysfunctions of nerves III, IV, and VI.

The oculomotor nerve is the motor nerve to the levator palpebrae superioris muscle, the most important of the muscles responsible for elevation of the upper eyelid. Lesions of the nerve cause ptosis (drooping of the upper eyelid) in addition to the signs described previously. Ptosis also can be induced by lesions of the sympathetic nerve supply to the eye because of paralysis of the superior tarsal muscle and in the horse, only, by lesions of the facial nerve, which innervates the levator anguli oculi medialis muscle (see later).[52]

8.3.11.4

CRANIAL NERVE V—TRIGEMINAL NERVE

The trigeminal nerve is sensory to the face and motor to the muscles of mastication. The sensory functions of the trigeminal nerve are tested by lightly stimulating the face using the tip of a closed hemostat. In animals that are head-shy, the examiner can use his or her fingers to stimulate the skin of the face. The forehead is innervated by the ophthalmic branch of the nerve, the upper jaw and muzzle by the maxillary branch, and the lower jaw by the mandibular branch. Each area should be tested specifically. The normal response is one of avoidance using neck, facial, and appendicular musculature; the animal usually pulls the head away and blinks simultaneously. Some areas such as the cheeks, forehead, and chin are normally less sensitive, whereas the periorbital region, the nasal planum, and the lips are very sensitive. The test evaluates the function of the sensory part of the trigeminal nerve, the trigeminal ganglion, the nucleus and spinal tract of the trigeminal nerve, the pontine sensory tract nucleus of cranial nerve V, the thalamus, the sensorimotor cortex, and the motor neurons of the head, which innervate the muscles of facial expression and run in the facial nerve (cranial nerve VII). After the trigeminal nerve enters the lateral aspect of the medulla, axons both ascend and descend through the medulla as the spinal tract of the trigeminal nerve. Ascending information ultimately reaches the sensorimotor cortex, where it is consciously perceived. Descending information projects to the nucleus of the facial nerve in the medulla and also into the first cervical spinal segment. Unilateral loss of facial sensation most commonly results from damage to the peripheral portion of the trigeminal nerve, the trigeminal ganglion in the petrosal bone of the skull, or the contralateral cerebral cortex. Lesions affecting the spinal tract of the trigeminal nerve in the medulla and midbrain would likely be fatal, because they also would affect adjacent respiratory and cardiovascular centers in the brainstem. Patients with bilateral facial hypoesthesia probably have bilateral cerebral cortex disease.

The palpebral reflex is elicited by lightly touching the periorbital area and observing a brisk closure of the eyelids. This reflex reflects the sensory function of the trigeminal nerve and the motor function of the facial nerve and orbicularis oculi muscle. Simultaneous loss of the menace response and the palpebral reflex suggests a lesion in the facial nerve or the orbicularis oculi muscle. Loss of the palpebral reflex with normal menace responses suggests a lesion in the trigeminal nerve or ganglion. Loss of menace response with preservation of the palpebral reflex indicates occipital cerebrocortical dysfunction (cortical blindness) or a cerebellar lesion.

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The jaw should be opened to assess the strength of the masticatory muscles. This measures both the sensory (proprioceptive) fibers of the trigeminal nerve and the motor component of the nerve. Bilateral lesions of the

motor component of the trigeminal nerve result in a dropped jaw. Affected animals may protrude the tongue but can retract it normally when stimulated. Animals with dropped jaws may drool saliva because they cannot trap it within the oral cavity. Unilateral lesions of the trigeminal nerve produce asymmetric jaw closure, with a slight gap between the occlusal surfaces of the teeth on the affected side; these signs, however, are not readily apparent.

8.3.11.5

CRANIAL NERVE VII—FACIAL NERVE

The motor nucleus of cranial nerve VII originates in the middle and ventral part of the medulla oblongata. The motor fibers are distributed to muscles of facial expression. Just as the motor fibers are exiting from the lateral aspect of the brainstem they merge with axons from the parasympathetic facial nucleus. These fibers innervate the lacrimal and salivary glands. They separate from the motor component of the facial nerve as it traverses the petrous temporal bone. Lesions of CN VII located between the brainstem and the petrous temporal bone usually result in “dry eye.” More distal lesions, however, have no effect on tear production. The tone of the facial musculature is examined by palpation of the ears, lips, eyelids, and muzzle. Clinical signs of facial nerve dysfunction include drooped ear and lips, drooling saliva, and retention of food in the cheek pouch on the denervated side (Fig. 8-8). Closure of the eyelids is weak in partial facial nerve lesions and absent in severe lesions. Despite this, there is slight drooping of the upper eyelid (ptosis) because of paralysis of the frontalis muscle, which contributes to eyelid retraction. In species with a soft muzzle (e.g., horses, sheep, and goats), there is a marked deviation of the filtrum away from the side with the lesion after unilateral loss of facial nerve function. The filtrum of affected cattle is not deviated because of the large amount of fibrous tissue in the planum nasale. In chronic facial paralysis the face may be deviated toward the affected side because of atrophy and contracture of the denervated musculature of the face.

8.3.11.6

CRANIAL NERVE VIII—VESTIBULOCOCHLEAR NERVE

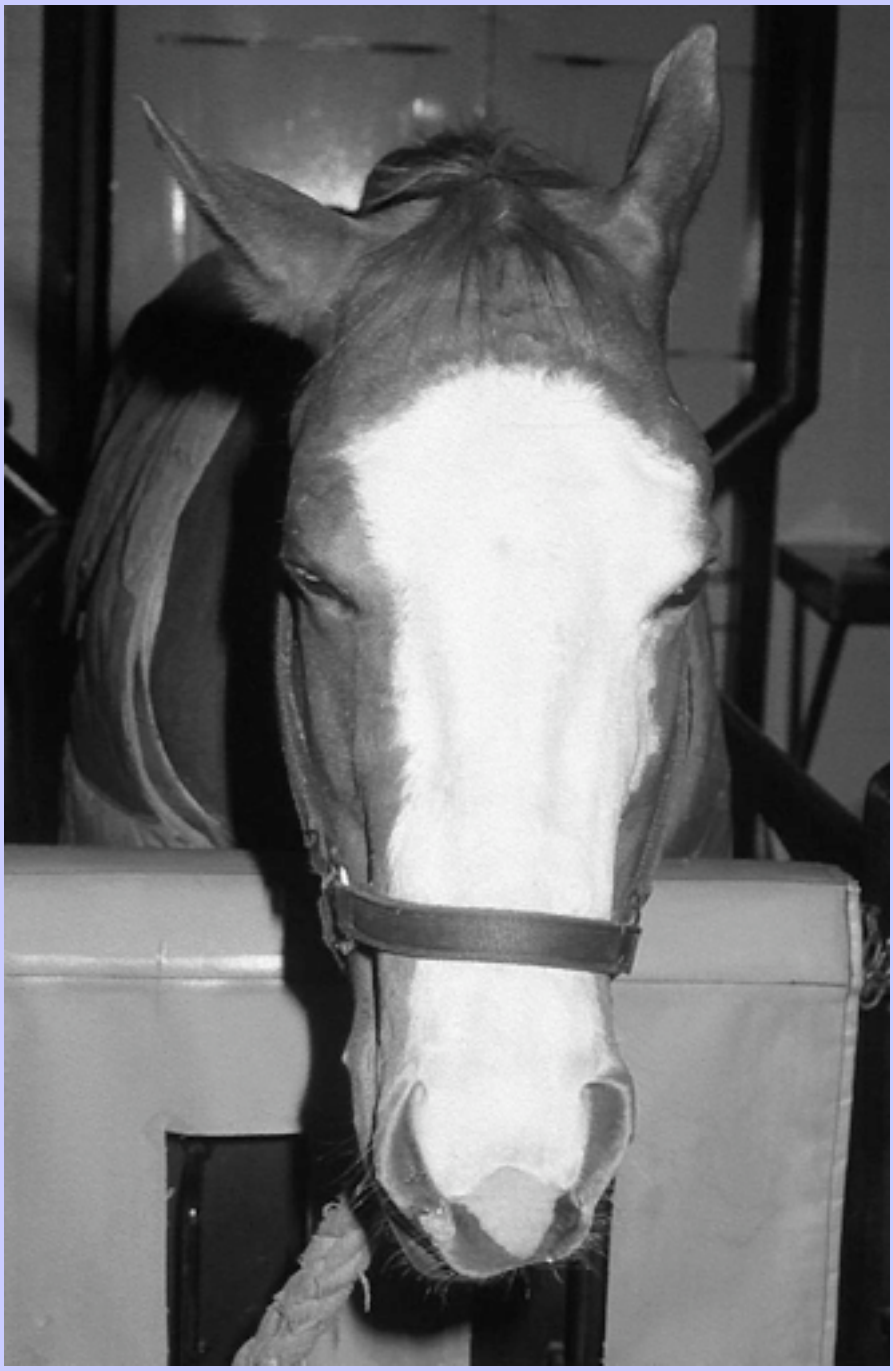
8.3.11.6.1

Vestibular System

The function of the vestibular system, which is composed of the sensory structures in the inner ear (semicircular canals, utriculus, saccule), the vestibular portion of cranial nerve VIII, and the central components of the vestibular system in the medulla oblongata and cerebellum, is tested by assessment of gait, extensor tone, head posture, and eye movements. Signs of vestibular dysfunction include a staggering gait, circling, falling, rolling, head tilt, and spontaneous nystagmus. Signs can be classified as peripheral, central, or paradoxic in type. Lesions affecting the inner ear or cranial nerve VIII result in signs of peripheral vestibular disease. Lesions affecting vestibular structures in the medulla oblongata result in central vestibular signs, and lesions affecting vestibular structures in the cerebellum result in paradoxic vestibular signs. Blindfolding affected patients results in a worsening of clinical signs because of elimination of compensatory mechanisms from optic centers. Recumbent animals with vestibular lesions tend to lie with the side of the vestibular lesion downward. When turned, these animals spontaneously rotate back to the lesion-down position and may strongly resist attempts to turn them over. Animals with unilateral vestibular disorders may have a ventral strabismus in the ipsilateral eye and a dorsal strabismus in the contralateral eye. This sign is seen with either central or peripheral vestibular lesions. Assessment of strabismus should be performed on the standing animal with the head held in normal posture. All species of livestock keep the eyes centered in the orbit when the head is in the neutral position. Cattle and sheep keep the optic plane parallel to the ground when the head is moved. This results in a positional ventrolateral strabismus of the right eye when the head is rotated to the left, and vice versa, and a ventral strabismus

when the head is raised. In contrast, the normal horse and goat maintain the eye in the center of the palpebral fissure in all head positions.

Fig. 8-8 Acute right facial paralysis in a horse with guttural pouch mycosis. Note the drooped right ear and deviation of the muzzle toward the left side.



Bilateral, symmetric lesions of the vestibular system are rare. They do not cause head tilt, nystagmus, or strabismus. Affected animals are reluctant to move. They stand with a base-wide posture, with the head held low, and fall easily when forced to move.

8.3.11.7

CRANIAL NERVES IX, X, AND XI—GLOSSOPHARYNGEAL, VAGUS, AND SPINAL ACCESSORY NERVES

Cranial nerves IX, X, and XI originate in the nucleus ambiguus, a column of motor neurons that extends from the middle to the caudal medulla oblongata, located in a ventrolateral position. They are motor to the muscles of the neck, pharynx, and palate. The vagus nerve contains efferent fibers that stimulate the secretions of glands of the visceral and respiratory mucosa and control forestomach motility in ruminants. The glossopharyngeal and accessory nerves carry afferent fibers from the mucosa of the tongue, larynx, and pharynx. The signs of glossopharyngeal and vagus nerve dysfunction include dysphonia (roaring, snoring), 132
dysphagia, and regurgitation. Animals with pharyngeal paralysis regurgitate food from the nose. Roaring is a 133
characteristic stertorous sound emanating from the larynx. The abnormal sound can be increased by exercise. Functional examination of these nerves should include auscultation of the larynx for stertorous airway sounds, observation of the animal as it swallows, passage of a nasogastric tube to evaluate deglutition, endoscopic examination to evaluate pharyngeal and laryngeal activity, and palpation of the cricoarytenoideus dorsalis muscle for atrophy. The slap test, described earlier, is a test for function of the vagal innervation of the larynx. Specific descriptions of the endoscopic appearance of pharyngeal paralysis and roaring are presented elsewhere (see Chapter 31).

Signs of spinal accessory nerve dysfunction are extremely rare and include atrophy of the trapezius, sternocephalicus, and brachiocephalicus muscles.

8.3.11.8

SYMPATHETIC INNERVATION OF THE HEAD—HORNER'S SYNDROME

Preganglionic sympathetic fibers that innervate structures of the head originate from the first three thoracic spinal cord segments. These fibers emerge with the origins of the nerves that form the brachial plexus. They ascend the neck in the peripheral vagosympathetic trunk to the cranial cervical ganglion under the tympanic bulla, where they synapse with postganglionic sympathetic fibers. The postganglionic fibers are distributed to the smooth muscles of the head through the ciliary nerves, passing through the petrous temporal bone area. Lesions anywhere along the course of the preganglionic or postganglionic sympathetic nerves, in spinal cord segments T1 to T3 or, very rarely, in the upper motor neuron component of the sympathetic pathway in the cervical spinal cord or brainstem (tectotegmentospinal tract) cause a characteristic constellation of clinical signs known as *Horner's syndrome*. Signs include miosis, enophthalmos, ptosis, and increased warmth on the ipsilateral side of the face. In cattle there is a loss of sweating on the ipsilateral side of the planum nasale, whereas in horses there is excessive sweating on the affected side. The enophthalmos is caused by paralysis of the periorbital smooth muscle that normally pushes the globe toward the surface of the orbit. The relaxation of the periorbita results in the sinking of the globe. Miosis is produced by the lack of pupillary dilation in response to normal sympathetic activity.

Diseases that could produce Horner's syndrome in large animals include compressive lesions of the gray matter in the T1 to T3 spinal segments, neoplasms (lymphosarcoma, melanoma, or neurofibroma), mediastinal or thoracic abscesses, abscesses in the cervical sympathetic trunk, esophageal perforations, guttural pouch mycosis, otitis media and interna, and retrobulbar abscesses. Transient Horner's syndrome may occur after

intravenous injection of xylazine. Preganglionic and postganglionic denervation may be differentiated by instillation of 1:1000 epinephrine (0.1 mL) into the eye with the miotic pupil. Pupillary dilation occurs by 20 to 40 minutes in eyes with postganglionic and preganglionic lesions, respectively. This test is unreliable in horses, however, and therefore is not useful in this species. Lesions of the mesencephalon (brainstem) at the level of the rostral colliculus may produce miotic pupils without other signs of Horner's syndrome. This is a common sign in cattle with polioencephalomalacia and lead poisoning.

8.3.11.9 CRANIAL NERVE XII—HYPOGLOSSAL NERVE

The hypoglossal nerve supplies motor impulses to the muscles of the tongue and the geniohyoideus muscle. The cell body of the nerve is located in the dorsomedial aspect of the caudal medulla oblongata. Hypoglossal nerve function is tested by pulling the tongue out of the mouth. Normal animals should have forceful resistance to passive manipulation of the tongue. Lesions of the hypoglossal nerve result in flaccidity of the tongue. With unilateral lesions, the tongue falls out of the mouth away from the side with the lesion. Chronic lesions of the hypoglossal nerve result in deviation of the tongue toward the side of the lesion because of muscle atrophy and contracture on the affected side.

8.3.12 OTHER ASPECTS OF PHYSICAL EXAMINATION OF THE PATIENT WITH NEUROLOGIC DISEASE

Diagnosis of a neurologic disease can often be facilitated by the observation of physical abnormalities in other systems. When one examines animals with chronic ataxia or tetraparesis, the head, neck, and back should be gently manipulated while the spine is palpated for crepitation or swelling. This finding could indicate the presence of a fracture, malformation, or luxation of one or more cervical vertebrae or vertebral osteomyelitis. Do not manipulate the neck whenever there is evidence of acute cervical vertebral trauma. Swelling, bruising, or hair loss on the skin around the head or bleeding from the ears or nose could signify cranial trauma. Hair loss and dermatitis around the perineum and medial thigh may indicate urinary incontinence. In neonates a hairless patch over the dorsum of the spine could indicate a meningomyelocele. Displacement of the sacrum could indicate sacroiliac luxation. Crepitation over coxofemoral or stifle joints of recumbent cattle could indicate a luxation or fracture. If luxation of the coxofemoral joint is suspected, the animal should be rolled on its back, and the length of the two pelvic limbs should be compared while the legs are held in extension. A pelvic examination should be performed in all large animals to detect displacement of the hip joint into the obturator foramen or fractures through the shaft of the ilium. All joints should be passively manipulated to detect dislocations or fractures. The heart should be auscultated for murmurs that could suggest left-sided endocarditis because such lesions can shower bacteria into the meninges. Odors on the breath such as ammonia, ketones, or petroleum distillates could provide clues about possible toxic causes. Identification of concurrent bronchopneumonia may indicate the possibility of thromboembolic meningoencephalitis in cattle or herpesvirus myelitis in horses. The ocular fundus should be examined ophthalmoscopically to detect retinal hemorrhages (trauma), papilledema (increased intracranial pressure), or vasculitis.

8.3.13 Examination of the Neonate

Most of the physical diagnostic techniques described in the preceding paragraph for the adult may be applied in examination of the neonate. Most spinal reflexes of livestock are well developed after birth. In the normal foal under 3 weeks of age, the limbs are hypertonic and hyperreflexic, with occasional myoclonus occurring after percussion of the patellar or triceps tendons. This hyperreflexia is most pronounced in the rear limbs. A lack of

menace response for up to 2 weeks after delivery also has been observed. Nevertheless, foals are visual and aware of their surroundings almost immediately after birth. When restrained the newborn foal relaxes into a trancelike state, periodically awakening and struggling violently before becoming passive again.

The results of daily examinations of 10 normal calves indicated that the spinal reflexes were present by 24 hours after birth. Most cortical responses were developed by 3 weeks of age. Bottle-reared calves aggressively attempt to suck while being examined, including vigorously butting of the handler with the head. Beef calves attempt to escape restraint and do not attempt to suck. See Chapters 15 and 21 for more details on neonates.

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8.4 LOCALIZATION OF CENTRAL NERVOUS SYSTEM LESIONS

Localization of a CNS lesion on the basis of clinical signs is vital because many specific diseases are restricted to particular regions of the CNS. Thus localization of a CNS lesion facilitates both differential diagnosis and specific diagnosis of the disorder. Ancillary diagnostic testing is determined both by the likely differential diagnoses and by the location of the lesion within the nervous system. Once the clinician has located the anatomic site of a neurologic lesion, a list of rule-out diagnoses may be formulated. Additional tests, including CSF analysis, radiography, magnetic resonance imaging (MRI), computed tomography (CT), serology, electroencephalography, brainstem auditory evoked response (BAER), and myelography, can be performed to further characterize the disease.

Lesions can be localized to one of seven regions of the CNS: cerebral cortex and thalamus, midbrain, cerebellum, medulla oblongata, spinal cord, peripheral nerve (either cranial nerves or spinal nerves), and muscle. Further localization to specific areas of these larger structures often can be determined after the neurologic examination.

8.5 LOCALIZATION OF NEUROLOGIC DISEASES BY MAJOR CLINICAL SIGNS

8.5.1 ABNORMAL MENTATION AND BEHAVIOR AND SEIZURES

Decreased mental alertness (dullness, obtundation, stupor, coma) is the most common change of mental status in animals with neurologic disease, although increased responsiveness to external stimuli (anxiety, mania, aggression) sometimes occurs. Altered mentation results from changes in the cerebrum, thalamus, or ARAS. Diseases affecting the ARAS tend to produce severe changes in mentation (stupor, coma), whereas those affecting the cerebrum or thalamus tend to produce a wider range of clinical signs, from slight dullness to coma. In order of worsening severity, decreased mental status in animals can be categorized as follows.

8.5.1.1 DULL, MILD TO MODERATE OBTUNDATION

Animals have decreased responsiveness to their surroundings, may ignore visual and auditory stimuli, may stop interacting with herdmates, and may be inappetent.

8.5.1.2 SEVERE OBTUNDATION

Animals are ambulatory but sometimes appear to be blind and walk into objects. They will respond only to fairly strong stimuli such as very loud noises and vigorous handling.

8.5.1.3

STUPOR

Animals appear to be asleep and will respond only to very vigorous and painful stimuli. Responses even to these stimuli are blunted.

8.5.1.4

COMA

Animals appear to be asleep and will not respond even to the most painful stimuli. Animals in coma are recumbent. They may adopt abnormal posture, particularly decerebrate posturing (opisthotonos, all four limbs rigidly extended), and may have other abnormal signs such as loss of the oculocephalic and pupillary light reflexes.

8.5.1.5

MANIA, ANXIETY

Animals that exhibit abnormally heightened reactions and responses vary widely in the severity of their signs, from mildly overreactive to bellowing, rearing, and attacking people, animals, or objects around them.

8.5.1.6

SEIZURES, COLLAPSE

Episodic abnormalities of behavior or consciousness are usually the result of seizure activity, narcolepsy or cataplexy, or syncopal attacks caused by cardiovascular or respiratory dysfunction. Intermittent toxicities or fluctuating metabolic abnormalities, such as occasionally occur with hepatic encephalopathy, also may cause episodic changes in mentation and behavior. Animals with a history of episodic collapse should undergo a very thorough physical examination to determine whether disease of the cardiovascular system (e.g., cardiac arrhythmias, intermittent hemorrhage) or respiratory system (e.g., laryngeal paralysis) is present. Animals that have seizures usually have a period of abnormal behavior after the seizure (postictal phase of the seizure), whereas those with narcolepsy or cataplexy or nonneurologic causes of collapse usually do not. Seizures and narcolepsy/cataplexy are discussed in more detail later.

Signs of cerebral and thalamic disease are variable in severity and are difficult to distinguish from each other clinically. The thalamus and cerebrum can be thought of as a functional unit, to some extent, because the thalamus is the relay center via which sensory information from the periphery reaches the cerebrum and through which motor impulses from the cerebrum are transmitted to the brainstem motor centers. Diffuse cerebral disease often results from metabolic, toxic, or infectious diseases. Increased intracranial pressure, the consequence of early acquired hydrocephalus, mass lesions within the cranial vault, inflammatory diseases, or cerebral edema, tends to produce signs of diffuse cerebral disease, which can range from mild to severe. Mild to moderate cerebral dysfunction usually results in an animal with decreased mental awareness, or, more rarely, excitement and overreaction. Diffuse disease does not result in circling, and gait on a level surface may appear normal, or almost so. Gait is abnormal, however, when the animal is challenged to ascend or descend slopes, step over objects on the ground, step onto and off curbs, circle, or back up. Both ataxia and paresis become apparent, although the former usually is more obvious. Postural and proprioceptive reflexes and reactions similarly are abnormal. When an animal is walking at normal speed on a level surface, local reflexes in the spinal cord and regulatory information from the red and reticular nuclei in the brainstem control simple gait patterns. Movements that require visual input or complex limb and body integration of movements are initiated in motor centers of the cerebral cortex. The combination of normal gait on a level surface with

obvious proprioceptive and postural deficits should immediately alert the examiner to the likelihood of cerebral or thalamic disease.

Response to visual stimuli, such as an open hand directed toward the face, may be decreased or absent because of involvement of the visual pathways in the cerebral cortex or the internal capsule (see Blindness, later). Pupillary light reflexes and oculocephalic reflexes usually are normal in animals with cerebral disease, except in severe cases. Response to all sensory input to the cerebrum often is decreased, but this is most obvious in the head, where the facial reflex (twitching of the facial skin and superficial musculature in response to tactile stimuli) and the palpebral reflex are decreased to varying degrees. It is common to mistake this for the presence of a second lesion, affecting the trigeminal nerve, facial nerve, or both, but such lesions need not be present to account for these clinical signs. In trigeminal or facial nerve lesions the clinical deficits tend to be more severe than when cerebrocortical disease is present, and mental status is normal when the cranial nerve lesions are peripheral in location. Horses with severe cerebrocortical lesions may fail to retract the tongue after it is pulled from the mouth but can do so when stimulated vigorously. Animals with lesions of the hypoglossal nerve may not be able to retract the tongue at all, or the tongue may be very weak.

The hypothalamus regulates primitive functions such as eating, drinking, cardiovascular function, and sexual behavior. Lesions of the hypothalamus may cause behavioral changes ranging from profound depression, rage, and inappropriate sexual activities to unusual affection, as well as polydipsia, polyuria, bradycardia, and abnormal appetite (pica).

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Seizures are the physical manifestations of spontaneous paroxysmal electrical activity in the brain. Although a focus of abnormal activity may originate in the thalamus or elsewhere in the brainstem, spread of this activity to the cerebral cortex results in the observable seizure activity. When the seizure activity is limited to a small area of the cerebral cortex the seizure that results is focal in type, resulting only in localized abnormal motor activity, such as muscular twitching in the face or in one limb, or episodes of abnormal behavior. More commonly the seizure is generalized, or starts focally and becomes generalized, to the entire cerebral cortex. Generalized seizures cause loss of consciousness, collapse, and generalized tonic-clonic motor activity. The presence of seizures necessitates a localization of the neurologic lesion to the cerebrum, but the initiating cause may lie elsewhere in the brain; the origin may even be extracranial. *Epilepsy* is a term that means repeated seizures of any cause, although it is often used to indicate seizures of unknown cause. The nature of the seizure, whether focal or generalized, is not a reliable indicator of the underlying cause. Congenital or idiopathic epilepsy, such as benign epilepsy of Arabian foals, usually causes generalized seizures. Partial or focal seizures more commonly indicate an acquired cause. Animals with seizures should undergo a complete physical examination, together with diagnostic testing for suspected toxins and underlying metabolic diseases, as well as a thorough neurologic examination to localize any interictal neurologic signs. Further diagnostics, such as CSF analysis and MRI, are performed as indicated after this initial workup.

When cerebral and thalamic disease is lateralized or asymmetric in severity, asymmetry of clinical signs becomes apparent. Circling occurs often, ranging from a tendency to drift toward one side to obvious and persistent circling. Circling caused by forebrain disease remains more a tendency to circle rather than compulsive circling, which occurs in midbrain disease. Even in more severe cases it usually is possible to stop the animal from circling, although it may be very reluctant to turn in the opposite direction. Proprioceptive and postural reaction deficits are present in the limbs on the side of the body opposite to the lesion (contralateral) and vary in severity with the severity of the underlying neurologic disease. A head turn toward the side of the lesion (ipsilateral) may be present, but head tilt is not found. The absence of signs such as head tilt, nystagmus, and strabismus, together with the presence of contralateral proprioceptive and postural reaction deficits, distinguishes forebrain lesions from those affecting the vestibular system. In the latter, head tilt,

nystagmus, and/or strabismus usually are present, and proprioceptive and postural reaction deficits either are absent (peripheral vestibular disease) or are present ipsilateral to the lesion (central vestibular disease, see later).

Specific diseases associated with the cerebrum of ruminants and horses are given in Tables 8-7 and 8-8, respectively.

Table 8-7 Diseases of Ruminants That May Produce Cortical or Thalamic Signs

Disease	Predominant Clinical Signs	Species Affected
Rabies	Obtundation, excitement, aggressiveness, hyperesthesia, analgesia, anesthesia, proprioceptive deficits, recumbency, propulsive walking, head pressing, tenesmus, hypersexuality, salivation	Cow, sheep, goat
Trauma, hematoma, brain edema	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, opisthotonos, facial anesthesia, weak tongue, convulsions, anisocoria (late), head tilt, head pressing, blood from ears or nose, decerebrate rigidity	Cow, sheep, goat
Polioencephalomalacia	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, facial anesthesia, weak tongue, anisocoria (late), head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cow, sheep, goat
Sulfur poisoning	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, facial anesthesia, weak tongue, anisocoria (late), head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cow, sheep, goat
Lead poisoning	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, facial anesthesia, weak tongue, anisocoria (late), head pressing, opisthotonos, odontoprisis, convulsions, decerebrate rigidity	Cow, sheep, goat
Salt poisoning	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, opisthotonos, facial anesthesia, weak tongue, convulsions, anisocoria (late), head tilt, head pressing, decerebrate rigidity	Cow, sheep, goat
Scrapie	Chewing, licking, wool break, depression, weight loss, ataxia, reduced menace, hypertonicity, hyperreflexia, proprioceptive deficit, recumbency, coma	Sheep, goat
Bovine spongiform encephalopathy	Aggression, weight loss, milk production, ataxia, proprioceptive deficit, recumbency, coma	Cow
Border disease	Ataxia, tremors, bunny-hopping	Sheep, goat
Vitamin A deficiency	Obtundation, somnolence, blindness with fixed pupils, ataxia, proprioceptive deficits, facial anesthesia, weak tongue, head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cow, sheep, goat
Brain abscess, meningitis	Recumbency, opisthotonos, blindness, hyperesthesia, stiff neck, proprioceptive deficit, ataxia, head pressing, depression, coma	Cow, sheep, goat

	Plant poisonings	Convulsions, blindness, ataxia, propulsive walking, head pressing, odontoprisis, hyperexcitability, salivation, proprioceptive deficit, sudden death, vomiting, fetal malformations	Cow, sheep, goat	
	Nitrofurazone toxicosis	Hyperirritability, propulsive running, muscular tremors, blindness, convulsions	Cow	135
	Grass staggers	Tremor, ataxia that worsens with excitement or exercise	Cow, sheep, goat	136
	Pseudorabies	Obtundation, ataxia, hyperesthesia, paresthesia, aggressiveness, fear, head pressing, propulsive walking, hypersexuality, salivation, coma, convulsions, recumbency, conscious proprioceptive deficit	Cow, sheep, goat	
	Malignant catarrhal fever	Aggression, rage, proprioceptive deficit, depression, head pressing, blindness, nystagmus, bellowing, mucosal and skin erosions, lymphadenopathy, diarrhea	Cow	
	Caprine arthritis-encephalitis	Obtundation, ataxia, head pressing, convulsions, coma	Goat	
	Maedi-visna	Obtundation, ataxia, head pressing, convulsions, coma	Sheep	
	Sarcocystis species infection	Seizures, blindness, opisthotonos, nystagmus, ataxia, muscular weakness, tremors, hyperexcitability, hypersalivation, recumbency	Cow	
	Brain tumor	Obtundation, facial paresis or paralysis, facial anesthesia or analgesia, head tilt, strabismus, nystagmus, loss of menace, hypermetria, ataxia	Cow	
	Sporadic bovine encephalomyelitis	Blindness, circling, ataxia, proprioceptive deficits, pleural friction rubs, pericardial friction rubs, abdominal tenderness	Cow	
	Urea poisoning	Muscle tremor, bloat, salivation, incoordination, struggling, ataxia, proprioceptive deficit, recumbency, bellowing, coma, convulsion	Cow	
	Ammoniated feed toxicosis	Trembling, fear, uncontrolled running, crashing through objects, coma, convulsion	Cow	
	Diplodiosis	Blindness, ataxia, obtundation, recumbency, convulsions, hyperesthesia	Cow	
	Ceroid lipofuscinosis	Blindness, ataxia, weight loss, coma, convulsion	Cow	
	Hydrocephalus, hydranencephaly, microcephaly, anencephaly	Blindness, ataxia, proprioceptive deficit, ventrolateral strabismus, failure to suckle, dysphonia	Cow, sheep, goat	
	Citrullinemia	Recumbency, coma, convulsions, death by 4 days of age	Cow	

Globoid cell leukodystrophy	Ataxia, proprioceptive deficits, hyperreflexia, depression, coma	Sheep
Infectious bovine rhinotracheitis	Fever, bellowing, coma, convulsions, somnolence, hyperexcitability, hyperesthesia, proprioceptive deficit, recumbency	Cow
Insecticide poisoning (organophosphate carbamate)	Salivation, vaginal discharge, diarrhea, tremors, coma, convulsion, diarrhea, proprioceptive deficit, recumbency	Cow, sheep, goat
Organochlorine poisoning	Tremors, hyperesthesia, recumbency, coma, convulsions	Cow, sheep, goat
Propylene glycol poisoning	Depression, bloat, ataxia, recumbency, proprioceptive deficit	Cow, sheep, goat
Ethylene glycol poisoning	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, facial anesthesia, weak tongue, head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cow, sheep, goat
Nitrofurazone poisoning	Obtundation, proprioceptive deficit, recumbency, convulsion, coma	Cow, sheep, goat
Hypocalcemia	Cow, doe: weakness, ataxia, inappetence, bloat, proprioceptive deficit, cool extremities, weak pulse, bizarre head posture, dysuria	Cow, goat
	Ewe: rigidity; tremors; hyperesthesia; convulsions; rapid, irregular breathing; odontoprisis	Sheep
Hypomagnesemia	Stiffness, hyperexcitability, recumbency, ataxia, proprioceptive deficit, muscle tremors	Cow
Nervous ketosis	Aggressiveness, tremors, ataxia, paresthesia, recumbency, proprioceptive deficit, hyperesthesia, bellowing	Cow
Hypoglycemia	Coma, semicoma, convulsions, blindness, hyperesthesia, cold extremities	Cow, sheep, goat
Nervous coccidiosis	Diarrhea, recumbency, obtundation, somnolence, blindness, proprioceptive deficit, propulsive walking, head pressing	Cow
Hepatic encephalopathy	Hyperexcitability, aggression, rage, odontoprisis, ataxia, proprioceptive deficit, head pressing, coma, convulsions, semicoma, blindness, tenesmus, rectal prolapse	Cow, sheep, goat
Idiopathic epilepsy	Intermittent psychomotor seizures	Cow, goat
Narcolepsy	Sleep state, recumbency, loss of consciousness, loss of motor activity, rapid eye movement	Cow
Propylene glycol toxicosis	Ataxia, obtundation, bloat, characteristic garlic-like odor	Cow, sheep, goat

	Coenuris cerebralis	Blindness, circling, ataxia, conscious proprioceptive deficit, head tilt, recumbency, coma, convulsions	Sheep
	Theileriosis (central nervous system form, exotic)	Depression, hypersensitivity, ataxia, circling, paralysis, convulsions	Cow
	Babesiosis (exotic)	Odontoprisis, ataxia, conscious proprioceptive deficits, coma, convulsions	Cow
	Louping ill (exotic)	Fever, anorexia, obtundation, constipation, muscular tremors, head tremors, hypermetria, ataxia, proprioceptive deficits, hyperexcitability, incoordination, rabbit hopping gait, recumbency, convulsions, coma	Sheep, cow
	Borna disease (exotic)	Head tremors, hyperesthesia, ataxia, anorexia, propulsive walking, coma, convulsions	Cow, sheep, goat
	Sarcocystis	Fever, weight loss, tremors, weakness, diarrhea, loss of hair on the tail switch, abortions	Cow
	Heartwater (exotic)	Hyperesthesia, behavioral changes, muscular fasciculations, hypermetria, ataxia, conscious proprioceptive deficits, head pressing	Cow, sheep, goat
	Trypanosomiasis (exotic)	Ataxia, conscious proprioceptive deficit, somnolence, circling, head pressing	Cow

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Table 8-8 Diseases of the Horse That Produce Cortical Disease

Disease	Predominant Clinical Signs
Hepatoencephalopathy	Aggression, rage, hyperexcitability, odontoprisis, ataxia, proprioceptive deficit, head pressing, convulsions, obtundation, coma, semicoma, blindness, fear, red urine (hemolysis), icterus
Parasitic migration	Head tilt, hyperexcitability, odontoprisis, ataxia, proprioceptive deficit, head pressing, circling, coma, semicoma, blindness, anisocoria, convulsion, tongue dystonia
Rabies	Recumbency, ataxia, proprioceptive deficit, aggression, depression, coma, semicoma, head pressing, circling, propulsive walking, mydriasis, tenesmus, fear, continual chewing
Leukoencephalomalacia	Recumbency, ataxia, proprioceptive deficit, aggression, obtundation, coma, semicoma, head pressing, circling, propulsive walking, mydriasis, tenesmus, fear, continual chewing
Brain abscess, meningitis	Head pressing, blindness, conscious proprioceptive deficit, ataxia, circling, depression, convulsions, hyperexcitability, stiff neck, rigid legs, fever, propulsive walking
Brain tumor	Depression, facial paresis or paralysis, facial anesthesia or analgesia, head tilt, strabismus, nystagmus, loss of menace, hypermetria, ataxia
Trauma, hematoma	Head pressing, blindness, conscious proprioceptive deficit, ataxia, circling, depression, convulsions, hyperexcitability, stiff neck, rigid legs, fever, propulsive walking, blood from ear or nose
Viral encephalomyelitis Eastern equine encephalomyelitis Near Eastern encephalitis Venezuelan equine encephalomyelitis Western equine encephalomyelitis Equine herpesvirus 1	Head pressing, blindness, conscious proprioceptive deficit, ataxia, circling, depression, coma, convulsions, recumbency, hyperexcitability, stiff neck, rigid legs, fever, propulsive walking
West Nile virus	Fasciculations of neck and facial muscles in addition to the other signs
Borna	
Equine protozoal myeloencephalitis	Seizures, head tilt, facial paralysis, circling, nystagmus, dysphagia, facial paralysis, blindness, ataxia, paresis, hyporeflexia, hyperreflexia
Hydrocephalus	Coma, semicoma, blindness, somnolence, head pressing, dysphonia, ataxia, conscious proprioceptive deficit, weak tongue
Idiopathic epilepsy	Intermittent psychomotor seizures, normal interictal periods
Narcolepsy	Intermittent sleeplike states with stress, normal between attacks

Diseases that are restricted to the thalamus are rare in domestic animals. Most lesions affecting the thalamus alone result from infarctions or parasitic migration through the CNS. The thalamus may be involved in multifocal nervous system disease, such as occurs with infectious diseases. The clinical signs of thalamic disease are, for the most part, similar to signs of cerebral dysfunction.

8.5.2 Blindness and Ocular Abnormalities

Blindness may be the result of lesions in the eye, optic nerve, optic chiasm, or central projections of the visual pathways. Ophthalmic examination, including fundic examination, should be part of the routine physical examination. Animals presented with the complaint of blindness should receive a more detailed ophthalmic examination to determine whether primary ocular disease is the cause of the problem (see Chapter 39). Sophisticated diagnostics such as electroretinography (ERG) may be indicated in some animals. When no ocular disease can be found to account for blindness, a lesion in the nervous system is likely to be responsible. Observing the animal's ability to negotiate its environment, particularly in unfamiliar surroundings, and eliciting 137
the menace reflex are the primary methods of determining visual function. Further testing can be performed by 138
setting up a maze of objects for the animal to negotiate, by using different light levels and assessing vision in bright versus dim light, and by blindfolding each eye in turn when unilateral deficits are suspected. Blindfolding should be used judiciously, because of the stress caused to the patient and the risks of worsening clinical signs in animals that do have visual deficits or other deficits such as vestibular dysfunction. Eighty percent to 90% of optic nerve fibers (axons of retinal ganglion cells) cross to the opposite side of the brain in the optic chiasm of ungulates; thus central representation of vision in these species is predominantly contralateral. Fibers that remain uncrossed originate from the temporal aspect of the retina. Lesions in the visual apparatus distal to the optic chiasm (i.e., lesions of the globe, the retina, or the optic nerve) produce ipsilateral visual deficits. Lesions proximal to the optic chiasm produce lesions in the opposite visual field (contralateral hemianopsia). The following discussion refers to severe or complete lesions, because these are most easily understood and described. Partial lesions will produce similar but milder signs, for example, reduced visual acuity rather than complete blindness. Absent or reduced menace reflex also can be caused by lesions of the facial nerve (cranial nerve VII), the cerebellum, or the cerebrum. Animals with facial nerve lesions can see but cannot blink even when the canthi of the eye are touched. Animals with cerebellar disease can see and can blink in response to the examiner touching the periorbital area. Cerebellar disease causes additional signs such as intention tremor, hypermetria, and ataxia. Animals with moderate to severe cerebral disease usually will blink in response to tactile stimulation of the face and periorbital area but appear to have decreased vision and may have a reduced to absent menace reflex (see earlier). Localization of lesions causing blindness is summarized in Table 8-6.

Pupil size and movement of the globes are mediated via cranial nerves II, III, IV, and VI and the sympathetic innervation of the eye. Clinical signs of diseases affecting these nerves are described earlier in the sections on cranial nerves and Horner's syndrome.

8.5.3 Circling

Circling can be a manifestation of lateralized disease in several regions of the brain: the cerebrum and thalamus, the midbrain, or the medulla oblongata. Circling associated with cerebral disease is toward the side of the lesion (ipsiversive) and is thought to result from lesions affecting the deep structures of the cerebrum or thalamic components rather than the cerebral cortex. Animals that circle secondary to cerebral disease often have a head turn toward the side of the lesion in addition to the circling. Whereas gait may appear normal on a level surface, affected animals have proprioceptive and postural reaction deficits on the side of the body contralateral to the lesion. Head tilt and spontaneous nystagmus are not present. Physiologic nystagmus (the oculocephalic reflex) is

normal when the examiner turns the animal's head from side to side. The severity of circling seen with lateralized cerebral disease is variable, from a subtle tendency to marked circling.

Diseases affecting solely or predominantly one side of the midbrain also result in circling. The circling is ipsiversive, occurs without manifestations of head tilt or spontaneous nystagmus, and is accompanied by contralateral proprioceptive and postural reaction deficits. Circling in midbrain disease is compulsive, in contrast to that seen in cerebral disease or vestibular disease. In both cerebral and midbrain disease the animal's level of consciousness usually is decreased, more severely with midbrain than cerebral disease. Midbrain lesions also may cause abnormalities of the oculocephalic and pupillary light reflexes because of the involvement of the somatic and parasympathetic nuclei of the oculomotor nerve (cranial nerve III) and the medial longitudinal fasciculus. The medial longitudinal fasciculus relays sensory information from vestibular centers in the medulla oblongata to the nuclei of cranial nerves III, IV, and VI.

Severe midbrain disease results in decerebrate posture: the animal is unconscious and in opisthotonus (extreme extension of the head and neck) with extensor rigidity of all four limbs. Severe midbrain disease may be the result of traumatic injuries or infectious diseases and particularly is a consequence of increased intracranial pressure from a variety of causes. When intracranial pressure is increased above normal there is a tendency for the occipital lobes of the cerebrum to be herniated caudally, under the tentorium cerebelli. This results in compression of the midbrain and is usually fatal. The presence of decerebrate rigidity warrants a very grave prognosis and the need for immediate and aggressive treatment with agents that decrease intracranial pressure (intravenous mannitol, dimethyl sulfoxide [DMSO], and other diuretics).

8.5.4 Head Tilt and Nystagmus

The presence of a head tilt, wherein one ear is held closer to the ground than the other, indicates disease of the vestibular system. Head tilt usually is accompanied by spontaneous (abnormal) nystagmus and a variety of other clinical signs. Vestibular disease can be classified as peripheral or central. Peripheral vestibular disease occurs when lesions of the vestibular apparatus of the inner ear (utricle, saccule, semicircular canals) are present or when there is abnormality of the peripheral portion of the vestibulocochlear nerve (cranial nerve VIII). Animals with peripheral vestibular lesions have normal mentation but may be extremely disoriented, making assessment of mentation difficult. The head tilt in peripheral vestibular disease is toward the side of the lesion. The vestibular system is involved in the maintenance of normal posture. Unilateral peripheral vestibular dysfunction causes decreased extensor tone in the limbs ipsilateral to the lesion and increased extensor tone in the contralateral limbs, resulting in the clinical signs of leaning, falling, and rolling toward the affected side. Proprioception and postural reactions are normal in peripheral vestibular disease, although they may be hard to evaluate in severe cases and in larger animals. Peripheral vestibular lesions produce a horizontal or rotatory nystagmus, with the fast phase directed away from the side of the lesion. The direction of the nystagmus in relation to the rest of the head is unchanged no matter what the position of the head. Physiologic nystagmus may be absent in severe cases, but more often it is decreased, particularly when the head is turned toward the side of the lesion. The facial nerve runs in proximity to the petrous temporal bone, and facial paralysis may be present in animals with peripheral vestibular disease when the facial nerve also is damaged by the underlying cause, such as may occur in traumatic injuries or severe otitis media or interna. Similarly, involvement of the postganglionic sympathetic nerve to the eye as it courses through the petrous temporal bone results in an ipsilateral Horner's syndrome (ptosis, miosis, enophthalmos, facial sweating in horses, reduced sweating on the nasal planum in cattle).

Lesions within the vestibular centers in the medulla oblongata and cerebellum also cause vestibular dysfunction. Central vestibular disease may produce clinical signs similar to peripheral vestibular lesions but can be

distinguished from the latter by a number of features. Head tilt in central vestibular disease usually is toward the side of the lesion but may be in the opposite direction when the underlying disease involves the cerebellum (paradoxic vestibular syndrome). Similarly, nystagmus may be identical to that seen in peripheral vestibular disease but also may be vertical, diagonal, or different in each eye (disconjugate nystagmus); may change in direction when the position of the head is changed (positional nystagmus); or may be horizontal or rotatory with the fast phase toward the side of the lesion (paradoxic vestibular syndrome). Signs of involvement of the motor and sensory tracts to the limbs as they course through the medulla usually accompany central vestibular disease. Proprioceptive and postural reaction deficits are present in the ipsilateral limbs, together with mild hyperreflexia. The nuclei of cranial nerves V to XII also may be affected by diseases that cause central vestibular lesions. Signs of cranial nerve dysfunction accompanying vestibular abnormalities, other than that of the facial nerve alone, indicate central vestibular disease. Horner's syndrome, however, is not seen in conjunction with central vestibular disease. Decreased mentation often occurs in animals with central vestibular disease, in contrast to the normal mental status of animals with peripheral vestibular lesions.

Animals with either peripheral or central vestibular lesions tend to lean against the walls and may fall when forced to perform a complex motor maneuver. They may adopt recumbency with the lesion side directed down and have poor righting responses, particularly from lesion-side-down recumbency. When positioned so that the lesion side is directed up, they often will roll to a lesion-down position. Blindfolding the patient eliminates visual compensatory mechanisms and therefore increases the severity of the clinical signs (Romberg test). Blindfolding may help in the detection of subtle lesions but should be done with caution because it may result in falling. Animals with vestibular disease occasionally may have slight ventral strabismus in the ipsilateral eye and slight dorsal strabismus in the contralateral eye. This strabismus can be differentiated from the ventrolateral strabismus seen with lesions of the oculomotor nerve because the strabismus accompanying vestibular lesions is mild and changes or disappears when the head position is changed. The strabismus in animals with paralysis of the oculomotor nerve does not change as the head position is altered. In the cow and sheep, evaluation of globe position must be conducted with the head held in normal position because these animals rotate the globe downward when the head and neck are extended. Conversely, the globe is maintained in the center of the palpebral fissure at all head positions in the horse and the goat.

Animals with bilateral vestibular lesions do not have head tilt or nystagmus. The animal stands with the legs base-wide and may fall to either side when the head position is rapidly altered. Affected animals may show a coarse side-to-side head tremor. Bilateral vestibular lesions usually are peripheral in type and are rarely encountered in clinical practice. Central lesions extensive enough to cause bilateral vestibular disease are likely to be fatal.

8.5.5 Incoordination, Hypermetria, Dysmetria, and Intention Tremor

Clinical signs that occur in animals with cerebellar disorders include hypermetria, intention tremor, and truncal ataxia (excessive body sway during movement along a straight path). Conscious proprioceptive fibers do not pass through the cerebellum. Consequently, postural placement of the limbs is normal. Animals with cerebellar disease move the limbs with excessive rate, range, and force. There is a slight delay in lifting the limb from the ground. At the peak of protraction the limbs are lifted too high and too far anteriorly. The legs then hit the ground with excessive force. When the animal is turned, the legs circumduct. The animal may violently thrust the outside rear limb backward and laterally when turned. The forelimbs and the hindlimbs occasionally collide during the turn (interference). At rest the animal stands with the legs abducted, in a base-wide stance. This is not a conscious proprioceptive deficit, however, because the animal consciously returns the limbs to the base-wide posture if the leg position is manually corrected. There is intention tremor, most marked in the head. When the animal attempts to reposition the head, it overshoots the intended position, corrects, and then overshoots again.

The sequence of overcompensation and overcorrection results in a coarse oscillation. The head tremor is most conspicuous when the animal is alert, especially when eating. Intention tremor disappears when the animal is recumbent and the musculature is relaxed. In animals with cerebellar disorders, the extensor muscles of the limbs may be hypertonic, and spinal reflexes occasionally are exaggerated. Foals with cerebellar disease fall backward. This does not usually occur in ruminants. Lesions of the rostral cerebellar vermis can result in opisthotonos. Animals with cerebellar cortical disease may lack a menace response but retain their vision and can negotiate around obstacles. The reason for the menace deficit is unclear, but it is thought to result from disruption of efferent pathways emanating from the occipital (visual) cortex and passing through the cerebellar cortex to the motor nucleus of the facial nerve. Animals with pure cerebellar dysfunction remain bright, alert, and responsive to external stimuli. Animals with very severe lesions of the cerebellum may be recumbent and unable to rise, with decerebellate posture. This posture is characterized by opisthotonos and forelimb extensor rigidity, with normal or flexed hindlimbs. Unlike decerebrate rigidity, animals in decerebellate rigidity have normal mentation and a good prognosis if the underlying disease is not progressive. Cerebellar disease is often bilaterally symmetric, but lateralized lesions cause signs on the ipsilateral side of the body. Diseases that cause spasticity or tremors in livestock are listed in Table 8-9.

Involvement of the vestibular components of the cerebellum (caudal cerebellar peduncle, flocculonodular lobe, and fastigial nucleus) results in signs of paradoxic vestibular syndrome, described earlier.

8.5.6 Abnormalities of Cranial Nerve Function

The normal functions of the cranial nerves are described earlier, in the discussion of the neurologic examination. Cranial nerve dysfunction may be central or peripheral in type, depending on whether the neurologic lesion lies within the central components of the cranial nerves within the brain or in the peripheral portions of the nerves. Clinical signs of cranial nerve dysfunction are ipsilateral to the lesions that cause them.

8.5.6.1 BLINDNESS, STRABISMUS, OCULAR PARESIS OR PARALYSIS, ABNORMALITIES OF PUPIL SIZE OR PUPILLARY LIGHT REFLEXES

Lesions involving cranial nerves II, III, IV, and VI are described earlier, in the discussion of blindness and other visual dysfunctions.

8.5.6.2 FACIAL HYPOESTHESIA OR ANALGESIA, DROPPED JAW

Loss of or decrease in sensory perception on the face, including the inside of the mouth, the nasal planum, the cornea, and the lower jaw area is the result of lesions of the trigeminal nerve. It is important to distinguish this from the signs of contralateral cerebral disease or facial nerve paralysis. In the former case conscious perception of the stimulus is decreased, but animals will respond to vigorous or painful stimuli and usually will blink in response to corneal stimulation. Animals with cerebral disease have decreased mental alertness and may have other signs of cerebral disease, such as seizures, circling, or contralateral hemiparesis. Facial nerve lesions result in an inability to move the muscles of facial expression or blink on the affected side, but animals will avoid stimulation of the face by pulling away the head and neck in a coordinated fashion. Unilateral loss of facial sensation most commonly results from damage to the peripheral portion of the trigeminal nerve, the trigeminal ganglion in the petrosal bone of the skull. Bilateral facial hypoesthesia is most likely caused by cerebral disease rather than trigeminal nerve disease. The mandibular branch of the trigeminal nerve also carries motor innervation to the muscles of mastication from the pontine motor nucleus of the trigeminal nerve. Bilateral involvement of the motor component of the nerve results in a dropped jaw and

inability to prehend and chew food, together with drooling saliva. The muscles of mastication atrophy, most obvious in the masseter and temporalis muscles. Unilateral disease causes atrophy of the denervated muscles, and mild jaw weakness may be appreciated, but the animal can still eat and close the jaw. The most important differential diagnosis for dropped jaw is rabies. A careful history must be taken to ascertain the risk of exposure to this disease as well as whether the animal has been vaccinated. Central lesions in the trigeminal nerve also may involve adjacent structures in the brainstem, such as the facial nerve, the vestibular system, and the long sensory and motor tracts to the limbs.

Table 8-9 Diseases of Spasticity or Tremors in Horses and Ruminants

Disease	Clinical Manifestations	Affected Species
Cerebellar hypoplasia Bovine viral diarrhea Bluetongue Akabane Border disease Wesselbron disease Hereditary	Intentional head tremor, base-wide stance, hypermetria, hypertonia, hyperreflexia, truncal ataxia, menace deficit, opisthotonos	Cattle, sheep, goats
Cerebellar abiotrophy	Intentional head tremor, base-wide stance, hypermetria, hypertonia, hyperreflexia, truncal ataxia, menace deficit, opisthotonos	Cattle, horses
Daft lambs	Recumbency, hypertonicity, hyperreflexia, deafness, intentional head tremors, hypermetria	Sheep
Grass staggers Bermuda Kikiyu Rye grass Mycotic tremorgens Canary Dallis	Hypermetria, hyperreflexia, truncal ataxia, head tremors, base-wide stance, recumbency, ptyalism, hyperexcitability, hyperesthesia	Cattle, sheep, goats
Hypomagnesemia	Hypermetria, hyperreflexia, truncal ataxia, recumbency, hyperesthesia, menace deficit, opisthotonos, aggressiveness, hypertonia	Cattle, horses
Lysosomal storage disease	Intentional head tremor, base-wide stance, hypermetria, hypertonia, hyperreflexia, truncal ataxia, menace deficit, opisthotonos, blindness, aggressiveness	Cattle, goats
Locoism and *Swainsonia* poisoning	Ataxia, conscious proprioceptive deficit, obtundation, intentional head tremor, loss of herd instinct, maniacal behavior, flaccidity of the nose and lips, base-wide stance	All species
Aspergillus clavatus toxicosis	Ataxia, weakness, muscle tremors, hypersalivation, altered behavior, recumbency, opisthotonus, death	Cattle, sheep
Hereditary neuraxial edema	Recumbency, head tremor, good appetite, hyperesthesia, nystagmus, strabismus, muscular fasciculations	Cattle
Bovine familial convulsions and ataxia	Tetaniform seizures, ataxia, hypermetria, hyperreflexia, head tremors, truncal ataxia	Cattle
Maple syrup urine disease	Obtundation, recumbency, opisthotonos, stimulus-induced tetanic spasms, convulsions, generalized decrease of spinal reflexes	Cattle
Solanum dimidiatum	Head tremors, hypermetria, hypertonia, hyperesthesia, weight loss, opisthotonos, recumbency, and convulsions	Cattle

8.5.6.3

FACIAL PARESIS OR PARALYSIS

Lesions of the facial nerve result in ipsilateral atonia or hypotonia of the facial muscles. The clinical signs of facial nerve paralysis in all large animals include ptosis, dropped ear, and absence of the menace response and palpebral reflex. There is accumulation of food in the cheek pouch and commissure of the lips on the ipsilateral side. Affected animals frequently drool saliva from the lip commissure on the affected side. The animal is unable to open the nostril on the affected side during inspiration. The muzzle of the horse, goat, and sheep deviates away from the direction of the neurologic lesion. Deviation of the muzzle is not seen in cattle because of the normal rigidity of the planum nasale. If the neurologic lesion is located between the medulla oblongata and the skull, the ipsilateral eye may be dry because of loss of innervation from the parasympathetic nucleus of cranial nerve VII. Lesions of the central components of the facial nerve in the medulla oblongata also destroy proprioceptive tracts and reticular system neurons, resulting in conscious proprioceptive deficits and, sometimes, decreased mentation. Lesions of the peripheral component of cranial nerve VII result in facial atonia or hypotonia but do not produce obtundation or conscious proprioceptive deficits.

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8.5.6.4

HEAD TILT, SPONTANEOUS NYSTAGMUS, DEAFNESS

Lesions involving cranial nerve VIII, the vestibulocochlear nerve, produce signs of vestibular dysfunction, as described previously. Deafness also may be a consequence of vestibulocochlear nerve disease. Bilateral deafness has been reported in Paint horses, where it may be a heritable defect associated with the gene for white coat color, similar to the situation that exists in a number of breeds of dogs with white or merle coat color. Deafness also can result from severe aural disease. Although bilateral deafness is fairly easy to recognize clinically, unilateral deafness may be less obvious. Inability to localize sound occurs when animals have unilateral deafness and may be suspected when animals alert to sound but do not turn toward the sound. Auditory evoked potentials can be used to determine integrity of the auditory pathway in the inner ear and medulla oblongata.[53]

8.5.6.5

DYSPHAGIA, DYSPHONIA, STERTOROUS BREATHING

Lesions in the nucleus ambiguus (cranial nerves IX, X, and XI) produce dysphonia, inspiratory dyspnea, dysphagia, and neurogenic atrophy of the trapezius, sternocephalicus, and brachiocephalicus muscles. The inspiratory dyspnea is characterized by roaring and snoring. Roaring is a stertor that is made during peak inspiratory flow. It is caused by paralysis of the cricoarytenoideus dorsalis muscle, resulting in a failure to abduct the arytenoid cartilages during inspiration. Additional evidence of paralysis of cranial nerves IX to XI may be obtained by endoscopic examination of the pharynx. Other signs of paralysis of cranial nerves IX to XI include failure to abduct the vocal folds, collapse of the pharynx, dorsal displacement of the soft palate, and inability to swallow a nasogastric tube. Lesions in the peripheral parts of the glossopharyngeal, vagus, and accessory spinal nerves produce similar laryngeal signs but may be differentiated from centrally located lesions by attitude, appetite, and conscious proprioceptive responses. Animals with peripheral nerve deficits remain alert and appetent and do not show conscious proprioceptive deficits, whereas animals with centrally located lesions may be depressed and inappetent and may have proprioceptive and postural deficits. Animals with bilateral lesions in the peripheral nerves are unable to open the glottis during inspiration and display extreme respiratory distress. Peripheral lesions of the accessory nerve that have been present for longer than 1 month may produce neurogenic atrophy of the trapezius, brachiocephalicus, and sternocephalicus muscles. This is frequently accompanied by aspiration pneumonia. Lesions of the visceral efferent component of cranial nerve X in ruminants produce vagal indigestion, which is characterized by ruminal distention with fluid,

ruminal tympany, abomasal stasis, and sometimes a hypochloremic, hypokalemic metabolic alkalosis. This is an important disease of the ruminant gastrointestinal tract. Hypoglossal nerve lesions produce a weak or flaccid tongue. In animals with unilateral lesions, the tongue deviates away from the side with the lesion and is flaccid when it is manually extended from the mouth. After prolonged denervation (1 month or more) the ipsilateral side of the tongue atrophies and the tongues deviates toward the affected side. Horses with lesions in the sensorimotor cortex may also fail to retract the tongue normally; however, the tongue tone is variable, and the animal can retract it if it receives sufficient stimulation. In comparison, the tongue tone is consistently weak in cases of hypoglossal paralysis.

Signs of cranial nerve dysfunction, together with the central origins or projections of the nerves, are summarized in Table 8-10. Diseases that involve the brainstem and cranial nerves are summarized in Table 8-11.

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Lesions of the medulla oblongata can produce severe obtundation, somnolence, or coma as a result of ARAS dysfunction in addition to signs of vestibular dysfunction and functional deficits in cranial nerves V to XII. Other clinical signs of medullary lesions include ipsilateral paresis and conscious proprioceptive deficits as a result of dysfunction in the rubrospinal, reticulospinal, spinothalamic, and spinocerebellar pathways. The spinal reflexes of the ipsilateral limbs are exaggerated, and the extensor muscle tone is increased. Further details are given in the discussion of quadriparesis and hemiparesis, later.

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Table 8-10 Clinical Signs of Cranial Nerve Dysfunction

Cranial Nerve	Central Origin or Projection	Clinical Signs of Dysfunction	Comments
I—Olfactory	Olfactory bulb, limbic system (behavior and emotion centers), cerebral cortex	Loss of sense of smell (anosmia)	Olfactory nerve lesions are rare and difficult to detect clinically.
II—Optic	Optic chiasm, optic tract, lateral geniculate nucleus, optic radiation, occipital cortex	Blindness	See text for additional comments (blindness).
III—Oculomotor	Midbrain somatic and parasympathetic nuclei	Ventrolateral strabismus, ptosis (somatic component); dilated, nonresponsive pupil (parasympathetic component)	
IV—Trochlear	Midbrain	Dorsomedial strabismus	Trochlear nerve lesions are rare and usually accompanied by other signs of midbrain dysfunction.
V—Trigeminal	Pons (motor nucleus), medulla, and rostral cervical spinal cord (sensory tract)	Dropped jaw in bilateral motor paralysis; decrease or loss of sensation to most of the structures of the head and face in sensory nerve disease	Rabies is an important differential diagnosis in animals with a dropped jaw.
VI—Abducent	Rostral medulla oblongata	Medial strabismus (paralysis of the lateral rectus muscle)	
VII—Facial	Medulla oblongata (rostral to middle); motor, sensory, and parasympathetic components	Facial paresis to paralysis (motor component); loss of sense of taste to rostral two thirds of the tongue, loss of sensation on medial aspect of the pinna (sensory components); decreased tear production (dry eye) and decreased salivation (parasympathetic components)	The facial nerve is particularly susceptible to damage in its peripheral course because of its proximity to the middle ear and to the guttural pouch in horses and its superficial location on the face.
VIII—Vestibulocochlear	Medulla oblongata (middle)	Decreased hearing or deafness; vestibular signs (head tilt, nystagmus, falling, rolling)	See description of vestibular disease in text.

IX, X, XI—Glossopharyngeal, vagus, accessory	Medulla oblongata (nucleus ambiguus in middle to caudal medulla and rostral cervical spinal cord)	Dysphagia (IX and X), laryngeal paresis to paralysis (X), atrophy of sternocephalicus, brachiocephalicus, and trapezius muscles (XII)	Rabies is an important differential diagnosis in animals with dysphagia or choke.
XII—Hypoglossal	Medulla oblongata (middle to caudal)	Paresis to paralysis of the tongue	Acute unilateral lesions result in the tongue being deviated away from the side of the lesion. In chronic disease, atrophy and contracture of the affected side of the tongue result in deviation toward the affected side.

Table 8-11 Diseases of the Brainstem and Cranial Nerves

Disease	Location	Clinical Signs and Laboratory Findings
Viral encephalomyelitis, rabies, malignant catarrhal fever (cattle only)	Multifocal brainstem, particularly medulla oblongata	Head tilt, nystagmus, circling, ataxia, proprioceptive deficit, tongue paralysis, anisocoria, dilated nonresponsive pupils, strabismus, paralyzed tongue, dysphonia, dysphagia, plus cortical signs (rage, fright, fear, convulsions); CSF may show pleocytosis (mainly mononuclear cells); high protein
Listeriosis (cattle)	Multifocal brainstem, particularly basal ganglia, metencephalon, and medulla oblongata	Circling, head tilt, facial paralysis, roaring, snoring, dysphagia, obtundation, coma, convulsions, ataxia, proprioceptive deficit; CSF shows pleocytosis (mainly mononuclear); increased protein
Thromboembolic meningoencephalomyelitis (cattle)	Multifocal brainstem and cortex	Circling, nystagmus, head tilt, strabismus, tongue paralysis, dysphagia, facial paralysis, coma, convulsions, obtundation, xanthochromic CSF with increased neutrophils
Peripheral vestibular disease	Petrous temporal bone, membranous labyrinths, vestibulocochlear nerve, also associated with facial nerve paralysis	Head tilt, circling, or leaning toward lesion side, ventrolateral strabismus on ipsilateral side, dorsomedial strabismus on contralateral side, nystagmus (usually horizontal and constant)
Verminous migration	Multifocal brainstem, most commonly thalamus, diencephalon	Circling, nystagmus, head tilt, strabismus, tongue paralysis, facial paralysis, obtundation, coma, convulsions, depression, proprioceptive deficit, bradycardia, salivation, head pressing, hemianopsia; high protein and increased WBCs in CSF
Space-occupying mass Tumor Abscess	Cerebellopontine angle; cranial nerves V, VII, and VIII	Head tilt, strabismus, proprioceptive deficit, facial analgesia, jaw drop, obtundation, coma, strabismus, nystagmus, hyperreflexia, hypertonia, falling or circling toward affected side, blindness on contralateral side, tongue paralysis, hemianopsia, bradycardia, coma, convulsion
Horner's syndrome	C8 to T1 motor neurons (gray matter), spinal roots, vagosympathetic trunk, sympathetic tracts of spinal cord, periorbita	Miosis, enophthalmos, lack of nasal sweat (cattle only), ipsilateral facial swelling (horses only)
Guttural pouch mycosis (horses)	Guttural pouch	Dysphagia, head shyness, head shaking, roaring, dysphonia, protrusion of the tongue from the mouth, epistaxis, head tilt, nystagmus, facial sweating, shivering, Horner's syndrome, colic, facial paralysis

CSF, Cerebrospinal fluid; *WBCs*, white blood cells.

8.5.7 Measurement of Brainstem Function Using Auditory Evoked Potentials

The integrity of the vestibulocochlear apparatus can be examined using brainstem auditory evoked potentials.[53–55] This method examines the averaged waveform that is generated after an auditory click in the ear. The individual signals from a single click stimulus are small and therefore must be amplified by repeating the stimulus (30 to 100 dB, 10 Hz) between 30 and 1000 times and recording the voltage difference between two electrodes placed on the head. The recording electrode is usually placed over the petrous temporal bone, and the reference electrode at the vertex, or elsewhere on the head. The technique of signal averaging is used to eliminate background electrical activity and enhance the specific waveforms generated by the auditory impulse. The response usually is measured for 10 ms after the stimulus is applied. Ablation of the entire cochlear apparatus and vestibular nerve, as might occur with otitis interna, would result in a loss or attenuation of waveform activity after the click stimulus. Injury to the brainstem vestibular nuclei would result in a loss of waves II through VI. Damage to the trapezoid body (pons), lateral lemniscus, caudal colliculus, and medial geniculate body would result in a loss of waveforms III through VI, respectively. Increased latency between the peaks is usually associated with toxic or degenerative diseases of the CNS.

8.5.8 Paresis and Ataxia in Two or Four Limbs

Quadriparesis and hemiparesis are seen with lesions affecting the mid to caudal brainstem (midbrain, medulla oblongata) or the cervical spinal cord (C1 to T2 spinal cord segments). Quadriparesis also can be seen in generalized peripheral nerve or muscle disease, discussed later. Paraparesis results from disease affecting the spinal cord between segments T3 and L2 or the peripheral nerves to the hindlimbs. Disease of the cerebrum and thalamus does not produce appreciable paresis and ataxia when the animal is walking in a straight line on a level surface, but these signs become apparent in the limbs contralateral to the lesion when the animal is asked to circle, back, step over obstacles, or walk on a slope. Localization of the lesion when signs of paresis and ataxia are present depends on the assessment of muscle mass and tone, spinal reflexes, and evaluation of brainstem function, as determined by the presence or absence of signs such as altered mentation, cranial nerve deficits, or vestibular dysfunction.

Quadriparesis and ataxia with normal muscle mass and tone and normal to increased spinal reflexes indicate a lesion in the brainstem or in spinal cord segments C1 to C5. Presence of clinical signs of brain disease will facilitate localization of the lesion to an intracranial site, as described earlier. Lesions in the midbrain cause contralateral postural and proprioceptive deficits, whereas those in the medulla oblongata cause ipsilateral signs. Cerebellar disease causes a truncal ataxia, without significant loss of proprioceptive or postural functions, and with no or mild hyperreflexia of the limbs. Lesions of the thalamus and cerebrum cause minimal to no paresis or ataxia when the animal is gaited on a level surface, but contralateral proprioceptive and postural reaction deficits are present. Altered mentation and other signs of cerebral or thalamic disease are expected, such as circling or cortical blindness. Animals with spinal cord disease have normal mentation. The clinical signs shown by such patients depend on the location of the lesion and the relative amount of damage to gray (cell bodies) and white (myelinated spinal cord tracts) matter. Loss of white matter results in sensory loss, whereas gray matter damage produces lower motor neuron deficits. The sensory losses are either proprioceptive responses or cutaneous sensory deficits. White matter is usually more susceptible to pressure changes than gray matter, so proprioceptive deficits are consistently observed during the first stages of spinal cord disease. Spinal cord diseases may be localized to one of the following five regions: high cervical (C1 to C5), cervicothoracic (C6 to T2), thoracolumbar (T3 to L2), lumbosacral (L3 to S2), and sacrococcygeal (S3 to Cd5) regions. Tables 8-4 and 8-5 list the peripheral nerves and the spinal segments that innervate them.

8.5.9 Cervical Spinal Cord

Animals with incomplete section of the cervical region of the spinal cord display hemiparesis or tetraparesis. The clinical signs include knuckling, stumbling, failure to lift the inside feet when turned in a tight circle, interference, hypermetria, abnormal postural placement responses, crossing over midline when turned, and excessive truncal sway. Animals with more severe lesions of the cervical spinal cord become recumbent and are unable to lift the head from the ground. There is an asymmetric righting response in animals with unilateral lesions. They can raise the head and neck to a variable distance only when lying with the lesion side facing down. Muscle tone and spinal reflexes in the limbs of recumbent animals are exaggerated. The urinary bladder is distended. The animals have difficulty urinating, and afterward the bladder contains a large amount of urine. Animals with complete spinal cord transection anterior to C6 die suddenly as a result of paralysis of the intercostal muscles and the diaphragm.

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Lesions between C6 and T2 spinal segments (brachial intumescence) result in conscious proprioceptive deficits in all four limbs and tetraparesis or tetraplegia. There is hypotonia and hyporeflexia of the forelimbs and hypertonia and hyperreflexia of the hindlimbs. Unilateral lesions result in ipsilateral signs. Lesions of C6 to T2 segments involving white but not gray matter do not produce forelimb hypotonia. Conscious perception of painful stimuli may be depressed in all limbs. Flexor reflexes in the forelimbs may be depressed but are normal in the hindlimbs. The righting responses of the head and neck are normal. Urination is difficult, and the urinary bladder is distended and has a large residual volume. After 1 month or more, lesions of the gray matter of the spinal cord or the peripheral nerves may result in neurogenic atrophy of one or more muscle groups of the forelimbs. Gray matter lesions of T1 to T3 spinal segments may result in Horner's syndrome, which is characterized by miosis, enophthalmos, and ptosis in all species. Unilateral facial sweating occurs in horses; lack of sweating on the planum nasale occurs in cattle. Differentiation of high (C1 to C5) and low (C6 to T2) cervical spinal cord lesions may be difficult in horses, especially when signs are fairly mild.

Lesions of the thoracolumbar region (T3 to L3) result in normal activity of the forelimbs and proprioceptive deficits in the hindlimbs. These deficits are similar to those described previously for the cervical areas and include ataxia, knuckling, stumbling, abduction, adduction, interference, excessive truncal sway, and failure to lift the inside foot when pivoted in a tight turn. With complete lesions, the animal becomes recumbent but intermittently assumes a dog-sitting position, with the forelimbs extended and weight bearing and the hindlimbs flexed. Muscle tone and spinal reflexes are exaggerated in the hindlimbs. The urinary bladder is distended, and residual volume is large. The tone of the urethral sphincter is normal. Young animals with severe spinal cord lesions between T2 and L2 display transient hypertonia of the forelimbs (Schiff-Sherrington syndrome). This condition is caused by interference with inhibitory fibers ascending from the lumbar segments in the dorsal funiculi to the lower motor neurons of the forelimbs.[56] These fibers synapse on the neurons of the brachial intumescence. Hypertonia from this deficit may be differentiated from cervical cord lesions by the lack of conscious proprioceptive deficits in the forelimbs of animals with thoracolumbar lesions.

The lumbosacral region (L3 to S2) of the spinal cord contains lower motor neuron efferents to and general proprioceptive afferents from the pelvic limbs. Lesions in this area result in paraparesis or paraplegia. Affected animals are ataxic and have conscious proprioceptive deficits of the hindlimbs. Patients with complete spinal cord lesions of L3 to S2 exhibit flaccid paraplegia, which is accompanied by hyporeflexia or areflexia of the hindlimbs. With prolonged denervation, neurogenic atrophy of the hindlimb musculature occurs.

Lesions located between L3 and L6 spinal cord segments result in urinary bladder distention and maintenance of a large residual volume. The sphincter tone is intact, but urine is not voided unless the intravesicular pressure

exceeds that of the sphincter. These animals usually have contact dermatitis of the perineum and preputial area because of urine scalding. Lesions located around S1 and S2 segments result in bladder distention and flaccidity. Urine may drip continuously from the urethral orifice. The rate of flow may be increased by manually pressing on the bladder during a rectal examination.

Lesions of the sacrococcygeal (S3 to Cd5) region (cauda equina) produce flaccidity of the tail and anus and, in males, paraphimosis. Lesions in this area also result in desensitization of the tail, penis, vulva, anus, and perineum. The urethral sphincter is dilated, and urine constantly drips from the urethral orifice. The animal does not evacuate the bladder and is unable to defecate, resulting in a large dilated urinary bladder and distention of the rectum with feces.

If the entire neurologic lesion is located caudal to S3, ataxia or conscious proprioceptive deficit is not present. The combination of flaccidity of the tail and anus and the constant urine leakage produces contact dermatitis of the perineum and hindlimbs. Perineal scalding is characteristic of lesions of the cauda equina. Specific diseases of the spinal cord, peripheral nerves, and motor end plate are listed in Table 8-12.

Table 8-12 Diseases of the Spinal Cord, Peripheral Nerve, and Motor End Plate of Large Animals

Disease	Signs	Species Affected
Occipitoatlantoaxial malformation	Ataxia, spasticity, hyperreflexia, crepitation or pain with neck flexion, head tilt, torticollis, proprioceptive deficit, visible swelling or asymmetry	Cow, horse
Fractures and dislocations	Tetraparesis, tetraplegia, paraparesis, paraplegia, hyperreflexia, stiff neck, recumbency, proprioceptive deficit, acute death, crepitation, pain, swelling	All species
Cervical spinal abscesses	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, proprioceptive deficit, sudden death, crepitation, pain, swelling	All species
Myelopathy	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, proprioceptive deficit	Horse
Cervical stenotic myelopathy	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, proprioceptive deficit, strip sweating	Horse
Cervical vertebral instability	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, proprioceptive deficit, sudden death, crepitation, pain	Horse
Spinal tumor (lymphosarcoma, neurofibroma)	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, proprioceptive deficit	All species
Equine rhinopneumonitis	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, proprioceptive deficit, flaccid anus, flaccid tail, dysuria, distended bladder, impacted rectum, urine scalding	Horse
Copper deficiency	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, proprioceptive deficit	Sheep, goat
Cauda equina neuritis	Pruritus in perineum, hair loss in perineum, analgesia in perineum, flaccid tail, flaccid anus, paraphimosis, dysuria, facial palsy, head tilt, leaning, nystagmus	Horse
Ischemic myelopathy (fibrocartilaginous embolism)	Paraplegia, tetraplegia, flaccid tail, flaccid anus, areflexia at site of lesion, hyperreflexia distal to site of lesion, proprioceptive deficit	Horse, sheep
Postanesthetic myelopathy	Paraparesis to paraplegia, ataxia, hypoalgesia, scoliosis	Horse, cattle (calf)
Caprine arthritis-encephalitis virus	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, proprioceptive deficit	Goat

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Segmental myelitis	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, proprioceptive deficit, strip sweating, hyporeflexia, areflexia, lower motor neuron deficit, facial nerve paralysis, jaw drop	Horse
Developmental defects (spina bifida, Arnold-Chiari syndrome, syringomyelia, hemivertebrae, spinal cysts)	Paraplegia, paraparesis, tetraplegia, tetraparesis, hypotonia, atonia, neurogenic atrophy, torticollis, scoliosis, kyphoscoliosis, misshapen tail, absence of skin over dorsal midline	All species
Verminous migration	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, proprioceptive deficit, head tilt, hyporeflexia, areflexia, hyperreflexia, hypertonia, hypotonia	All species
Tetanus	Stiffness, normal reflexes, flashing third eyelid, trismus, bloat, convulsions, coma, raised tail head	All species
Botulism	Flaccidity, ataxia, dysphagia, hyporeflexia, pupillary dilation, facial hypotonia, flaccid tail, flaccid anus	All species
Progressive ataxia	Ataxia, conscious proprioceptive deficit, recumbency	Charolais cattle
Locoism	Ataxia, conscious proprioceptive deficit, recumbency, bizarre behavior	All species
Dying back axonopathies	Hypermetria, hyperreflexia, proprioceptive deficit, flaccid tail, anus, fecal and urine retention, urine scalding, recumbency	All species
Elso heel (spastic paresis)	Affected hindlimb is hyperextended and swings in pendulum fashion; tail head is elevated	Cow
Spastic syndrome (crampy)	Episodic hyperextension of the hindlimb, extension of the limb behind the cow, head and neck extension	Cow
Peripheral nerve injuries	Areflexia, hypotonia, hyporeflexia, atonia, anesthesia, analgesia of a specific area of limbs or trunk, inability to support weight, normal function of limbs distal to denervated site	All species
Ionophore toxicosis (salinomycin, lasalocid, monensin)	Tetraparesis, tetraplegia, ataxia, conscious proprioceptive deficit, colic, cardiac dysrhythmia, sudden death	All species
Periodic hyperkalemia	Episodic tremors, weakness, spasticity during episodes, recumbency	Horse, cow
Myotonia congenita	Episodic weakness, spasticity during episodes	All species
Bromide intoxication	Weakness, ataxia, stumbling, proprioceptive deficit, closed eyelids, drooped head and neck, paraphimosis	Horse
Coyotillo poisoning	Progressive weakness, hypermetria, areflexia	Goat
Humpy back/Coonabaran disease	Arched back, ataxia, conscious proprioceptive deficit, hindlimb stiffness, recumbency	Sheep

Neosporosis	Recumbency, ataxia, conscious proprioceptive deficit, neurogenic atrophy	Calf	
Cycad palm poisoning	Posterior paresis, conscious proprioceptive deficit, elevated tail head, paraparesis, paraplegia	Cow	
Acquired torticollis	Abnormally positioned head and neck	All species	145
Sorghum toxicosis	Ataxia, paraparesis, paraplegia, rabbit-hopping gait, proprioceptive deficit, recumbency, weight loss	Horse, cow	146
Stringhalt	Normal at rest, involuntary hyperflexion of the hock and stifle	Horse	
“Kangaroo” gait	Forelimb weakness, ataxia, proprioceptive deficits (bilateral radial nerve paralysis)	Sheep	
Tick paralysis	Progressive generalized paresis, ataxia, recumbency, flaccid tail, flaccid anus, weak facial muscles	All species	

8.5.10 Muscle Atrophy, Reduced Muscle Tone, Flaccid Paresis, Focal Analgesia

Clinical signs of reduced muscle tone, muscle atrophy, and flaccid paresis indicate peripheral nerve, muscle, or neuromuscular diseases. Signs may be localized to a single limb, as in the case of traumatic peripheral nerve injury; generalized, as in botulism and many myopathies; or multifocal, as in equine protozoal myeloencephalitis and other diseases that attack multiple areas of the CNS, destroying the ventral horn gray matter of the spinal cord, or nuclei of cranial nerves in the brainstem. Details of neuromuscular diseases and the use of ancillary diagnostic testing to localize peripheral nerve, muscle, and neuromuscular disease are described in Chapter 35.

Peripheral nerve lesions, whether of the central components of the nerves in the spinal cord and brainstem or along their peripheral course in the limbs and head, also can result in focal hypalgesia or anesthesia. Knowledge of the autonomous zones for the peripheral nerves innervating the limbs can be used to localize such peripheral nerve lesions.

8.5.11 Urinary Incontinence and Urine Retention

The clinical signs of urinary bladder denervation are variable and depend on the lesion location. Lesions of the sacral segments of the spinal cord produce a flaccid bladder, which distends with a large residual volume. Spontaneous urine leakage occurs continuously from the urethra. Additional urine flow occurs when the abdominal pressure is increased. The urethral sphincter is dilated and atonic. Lesions of the brainstem or spinal cord anterior to S1 produce reflex dyssynergia, a disturbance in coordination of micturition, wherein the facilitatory influence of the bladder stretch receptor (afferents) maintains tonic activity on the efferents of the urethral sphincter. The lack of inhibition of these reflexes from the upper motor neuron pathways produces hypertonicity of the urethral sphincters and results in an impediment to urine flow. There is a high intravesicular pressure and a large postvoiding urine volume. The urine escapes paroxysmally only when the intravesicular pressure exceeds the sphincter pressure. After approximately 1 month of denervation, local spinal reflexes between the sacral afferent and efferent neurons develop in the S1 to S5 segments, and incomplete voiding occurs. In these cases the residual volume remains large, and the normal urination posture is not attained.

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9 Chapter 9 Alterations in Body Weight or Size

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Slowed growth and below-normal weight gain usually happen at the same time, although occasionally they develop separately. By definition a decrease in growth and weight gain is limited to the growing animal. Similar pathogenic mechanisms cause weight loss or an emaciated condition in an adult patient. This arbitrary age division allows the clinician to consider possible causes that are more or less common for a given age-group.

Potential growth and weight gain are genetically determined. They differ according to species, breed, and sex, and marked differences in potential growth exist within a breed. The potential for growth in ruminants is greater in the offspring of multiparous females than in those from primiparous females. The normal or minimum growth and weight gain rates for common breeds of the various large animal species are outlined in the section on assessment of growth and weight gains.

9.1 MECHANISMS OF DECREASED GROWTH AND DECREASED WEIGHT GAIN

Major pathogenic mechanisms that result in decreased growth and decreased weight gain include the following:

- Inadequate dietary intake of essential nutrients
- Infections or inflammation
- Parasitism
- Genetic errors in metabolism or physiologic function
- Concurrent toxicosis
- Environmental causes
- Multiple causes

Inadequate intake of one or more essential nutrients is an important cause of decreased growth. In many cases growing animals are not provided with a sufficient volume of feed to meet their nutrient requirements. Young animals rely on a highly digestible diet that provides energy and essential nutrients for growth. Even animals fed an appropriate volume of a poor-quality milk replacer could suffer from poor growth. Milk replacers formulated with sources of protein, fat, vitamins, and minerals that have limited nutrient digestibility may induce a state of energy, protein, vitamin, or mineral malnutrition. For some young animals, poor-quality forage is the only feed available. Weaned foals and ruminants rely on forages and cereal grains to provide essential nutrients. Hay that has been harvested at a late stage of growth usually has a lower nutrient digestibility compared with young forages. Diets low in digestible energy or protein or both reduce total daily intake in ruminants (Table 9-1) because of the increased turnover time ($T_{½}$) in the gastrointestinal tract and subsequent decreased throughput. This compounds the problems caused by an inadequate intake of digestible nutrients. The digestibility of forages is even lower for horses than for ruminants.

Protein-calorie malnutrition (PCM) is the most common clinical cause of decreased growth and decreased weight gain in young animals. It is characterized by smaller size and lower weight than the normal minimums for age, breed, and sex. Inadequate intake of digestible energy and protein (or essential fatty acids in the neonate primarily adapted to a milk diet) results in inadequate levels of amino acids, fats, and carbohydrates for normal metabolism and growth. Diets that lack any of the other essential nutrients (fatty acids, vitamins, macrominerals, or trace minerals) can also decrease growth. Deficiencies of calcium, phosphorus, and magnesium result in improper skeletal formation. Deficiencies in other macrominerals (e.g., sodium, chloride, potassium), trace minerals (e.g., copper, zinc, manganese, cobalt, iron), and vitamins (e.g., A, D, E, thiamin) cause biochemical dysfunctions that lead to inefficient metabolism and growth. Large animal patients that grow slowly as a result of inadequate diets often have normal or increased appetites until they are terminally ill. Physical findings and clinicopathologic data from animals with PCM often are within the normal range until the disease process is well advanced.

Infections or inflammatory processes are important causes of decreased growth and decreased weight gain in young horses and ruminants. The decrease in growth can be of short duration followed by recovery and compensatory gain (cryptosporidiosis) or can persist (chronic bronchopneumonia). Infections or inflammatory processes can also result in nutrient malabsorption (chronic salmonellosis, acute rotavirus diarrhea), anorexia (pharyngeal abscesses), increased nitrogen turnover, and direct protein losses (gastrointestinal disease). Energy or protein requirements may be increased as a result of infection and inflammation.

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Table 9-1 Maximum Dry Matter Intake (DMI) Related to Forage Quality for Cattle

Forage Quality	Maximum DMI/Day (% Body Weight)	Maximum DMI for 500 kg/Cow/Day (kg)
Poor	1–1.5	5–7.5
Oat straw		
Corn stover		
Average	2	10
Meadow grass hay		
Excellent	2.5	12.5
Alfalfa hay (25% crude fiber)		
Corn silage		

From Maas J: Relationship between nutrition and reproduction in beef cattle, *Vet Clin North Am*, 3:634, 1987.

Parasitism often affects young horses and ruminants and results in decreased growth and decreased weight gain by increasing nutrient requirements, increasing nutrient losses, and/or decreasing nutrient absorption. The animal's metabolic rate and nutrient requirements may also increase as a result of inflammatory and immune reactions that arise secondary to parasitism.

Genetic diseases (α-mannosidosis, dwarfism) result in decreased growth through generalized errors in the genetic code or interference with strategic reactions in one or more metabolic pathways. Congenital cardiac malformations (tetralogy of Fallot, interventricular septal defect) create physiologic inefficiencies that require energy beyond the body's ability to supply it. Congenital renal disease (agenesis, dysplasia, hypoplasia, polycystic kidney disease)

affects homeostatic mechanisms that regulate electrolyte and acid-base balance, results in the production of uremic toxins, and often results in partial anorexia and PCM. Digestive tract malformations including cleft palate, megaesophagus, and brachygnathism can reduce nutrient ingestion and impair growth.

Toxicities, although rare in growing animals, result in decreased weight gain by interfering with metabolic pathways (e.g., ammonia toxicity, zinc-induced copper deficiency with abnormal skeletal development in foals), by causing loss of body reserves (e.g., thiamin deficiency in horses, bone marrow hypoplasia and associated bleeding diatheses in ruminants associated with bracken fern toxicity), by inducing anorexia, or by a combination of mechanisms. The pathogenic mechanisms of many toxins are not yet known.

Environmental factors including extreme heat or cold or high humidity result in decreased growth and decreased weight gain. Extremely cold conditions increase an animal's daily energy requirements. During extremely hot weather feed intake often decreases, which may contribute to decreased growth. Often, environmental conditions influence the development of disease, resulting in a subsequent increase in nutrient requirements in a growing animal (e.g., calves with PCM housed in poorly ventilated or overly humid conditions become much more susceptible to infectious pneumonia).

In many cases a combination of these diverse factors may influence the growth and weight gain of young animals. A period of increased growth rate and weight gain, called *compensatory gain*, often occurs after a period of restricted growth. In growing foals, compensatory gain should be closely monitored to prevent excessively rapid growth and abnormal skeletal development.

Boxes 9-1 and 9-2 list many of the possible causes of decreased growth and decreased weight gain in horses and ruminants, respectively.

9.1.1

Box 9-1 Causes of Decreased Growth and Decreased Weight Gain in Horses

9.1.1.1

COMMON CAUSES

Protein-calorie malnutrition (PCM), inadequate nutrient intake

Extreme environmental factors

Parasitism (*Parascaris equorum*, small strongyles, large strongyles, tapeworms, bots)

Bacterial pneumonia *(Rhodococcus equi, Streptococcus zooepidemicus)*, lung abscessation

Viral pneumonia (equine herpes virus, equine influenza)

Gastric ulcers

Lameness (e.g., physitis, osteochondritis dissecans, contracted tendons, osteomyelitis)

Prematurity, dysmaturity

Diarrhea (*Clostridium*, species, *Salmonella*, species, sand enteropathy, other causes)

9.1.1.2 LESS COMMON CAUSES

Esophageal stricture, megaesophagus (idiopathic, acquired)

Peritonitis

Congenital cardiac and great vessel anomalies

Endocarditis

Jaw pain (fracture, dental abnormality)

Cryptosporidiosis

Selenium deficiency

Copper deficiency

Vitamin A deficiency

Vitamin D deficiency

Thiamine deficiency

Phosphorus deficiency

Osteodystrophy

Lead toxicity

Goiter

Generalized steatitis

Rotavirus infection (foals)

Wound myiasis

9.1.1.3 UNCOMMON CAUSES

IgM-deficiency

Combined immunodeficiency disease in foals

Gonadal dysgenesis, intersex (XO, XXY)

Ammonia toxicity

Sarcocystosis

Fluorosis

Congenital renal abnormalities (hypoplasia, dysplasia, agenesis, polycystic kidney disease)

Hydrocephalus

Myeloproliferative disease

Biliary atresia

Hepatic portosystemic shunt

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9.1.2 Box 9-2 Causes of Decreased Growth and Decreased Weight Gain in Ruminants

9.1.2.1 COMMON CAUSES

Protein-calorie malnutrition (PCM)

Mannheima, Pasteurella, Haemophilus, pneumonia

Ostertagiasis I and II

Coccidiosis

Parasitism (flukes, gastrointestinal worms, lungworms)

Salmonellosis

Bovine virus diarrhea

Hepatic abscessation, liver disease

Rotavirus infection

Diarrhea, undifferentiated

Lameness (sole abscess, foot rot, laminitis, foot warts, osteomyelitis)

Cryptosporidiosis

Enterotoxigenic *Escherichia coli*,

Coronavirus

Selenium deficiency

Copper deficiency (molybdenosis)

Sarcoptic mange

9.1.2.2 LESS COMMON CAUSES

Johne's disease

Cardiac or great vessel anomalies

Hydrocephalus

Myiasis

Ammonia (urea) toxicity

Goiter

Eperythrozoonosis

Arthrogryposis

Thiamine deficiency

Cobalt deficiency

Urachal or bladder abscess

Peritonitis

Pharyngeal abscess, injury

Giardiasis

Osteodystrophy, rickets

Neonatal isoerythrolysis

Immune-mediated anemia

Zinc deficiency

Vitamin A deficiency

Adenovirus infection

Tick infestation

Sarcocystosis

Abomasal ulcers

Severe bovine papular stomatitis

9.1.2.3 UNCOMMON CAUSES

Gonadal dysgenesis, intersex

Brisket disease

Epidermolysis bullosa

Phosphorus deficiency

Osteogenesis imperfecta in Friesians

Calf lymphosarcoma

Granulocytopathy

Congenital porphyria

Hypersensitivity to soy protein

Bacteroides fragilis, diarrhea

α-Mannosidosis

Generalized glycogenosis

Zygomycosis

Mucormycosis

Omental bursitis

Schistosomiasis (exotic)

Trypanosomiasis (exotic)

Hyena disease (exotic)

Lethal skin defects in Japanese black cattle (exotic)

Babesiosis (exotic)

9.1.2.4 TOXINS

Pyrrolizidine alkaloid toxicosis

Herbicide toxicity

Zinc toxicity

Fluorosis

Selenium toxicity

Aflatoxicosis

Ergotism

Iodine toxicity

9.1.2.5 PLANT TOXINS

Cassia, species

Bracken fern

Fescue toxicity

Leucaena leucocephala,

Oxalate toxicity

9.1.3

Approach to the Diagnosis and Management of Decreased Growth and Decreased Weight Gain in Horses

1 Take a general history and a diet history.

a General history

i What is the patient's age? Was the foal born prematurely? Were any congenital defects identified during the initial examination of the foal after birth? Did the foal have any complications from sepsis?

ii What is the stocking density of the herd? Is the foal exposed to a high parasite load in the environment? What is the foal's deworming history? Have there been previous problems with gastrointestinal parasitism on the farm? What is the vaccination history of the mare and the foal? Does the farm have a history of infectious disease agents (*Rhodococcus equi, Streptococcus equi*, subsp. *equi*)? Are there any sick horses on the same farm? Has the foal shown any evidence of systemic illness (diarrhea, nasal discharge, cough, pyrexia)?

iii What type of protection is provided from adverse weather conditions? Are there any toxins in the foal's environment?

b Diet history

i If the foal is nursing, what is the weight condition of the mare? Is the mare producing a sufficient amount of milk for the foal? If the foal is an orphan, what type of milk replacer is the owner using? What is the daily energy and protein intake of the foal? Is the owner mixing the solution properly? Does the foal have access to a creep feed? What is the owner using as a creep feed? How much of the creep feed does the foal consume daily?

ii If the foal is a weanling, when was the foal weaned? Does the foal compete with other foals for feed? Has the owner changed the foal's diet recently? If yes, what changes were made? Does the foal have a good appetite? Has the foal's appetite changed recently?

(1) What type of forage is fed to the foal? What is the quality of the forage? Is there gross evidence of dirt, mold, or weed contamination in the forage? Has a hay analysis been performed on the forage? How much forage is offered to the foal (in weight)? How much forage (in weight) does the foal eat each day? 149 150

(2) What type of supplemental feed is fed to the foal? What is the nutrient composition of the supplemental feed? Is the supplemental feed of high quality? How much of the supplemental feed (in weight) does the foal eat each day?

(3) Is the foal offered a vitamin and mineral supplement? Is the vitamin and mineral supplement offered free choice? How much of the supplement (in weight) does the foal eat each day? Could any nutrients be consumed in a toxic amount? Has the owner provided any supplemental parenteral vitamins or minerals to the foal?

2 Perform a physical examination.

a What is the body weight of the foal (measured by using either a scale or weight tape)? What is the body condition score (BCS) of the foal (see Table 9-21)? Is the foal small, thin, or underweight according to growth charts (Table 9-2, Figs. 9-1 and 9-2)?

b Does the foal show any signs of infectious disease (current or resolved)?

c Does the foal have evidence of a congenital abnormality (cardiac, renal, gastrointestinal, oral)?

d Does the foal have any musculoskeletal abnormalities?

3 Examine the feces.

What is the consistency of the feces? Refer to Chapter 20 for the diagnosis and management of neonatal diarrhea; refer to Chapter 7 if the foal is older and has evidence of diarrhea. Is there evidence of sand in the manure? Perform a fecal egg count. If the foal has a positive fecal egg count, follow the parasite control program recommendations in Chapter 49. If a negative fecal egg count is reported but parasitic infestation is still suspected, repeat the test in 2 to 3 weeks or follow the deworming protocols in Chapter 49. Evaluate the feces occult blood. If the foal has a positive fecal occult blood test, review the medical management for melena in Chapter 7.

Table 9-2 Weight as a Percentage of Mature Body Weight in Horses

Age (Months)	Ponies[4] (%)	Light Horses[1–3,5] (%)	Draft Horses (%)
6	55	46	40
12	75	67	57
18	84	80	75

Fig. 9-2 **A** to **C**, Body weight as a percentage of mature body weight for horses at a given age. A modified from Crampton WW: *J Agric Hortic* 26:172, 1923; **B** modified from Lewis LD: *Feeding and care of the horse*, Philadelphia, 1982, Lea & Febiger; **C** modified from Hintz HF: Factors affecting the growth rate of horses, *Horse Short Course Proceedings*, Texas A&M Animal Agriculture Conference, 1979, College Station, Texas.

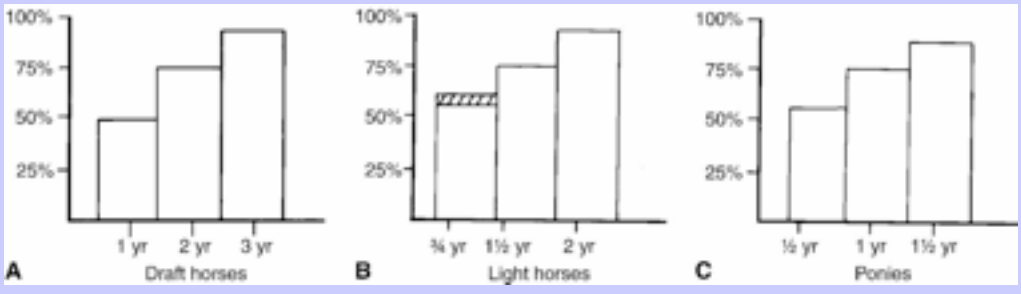
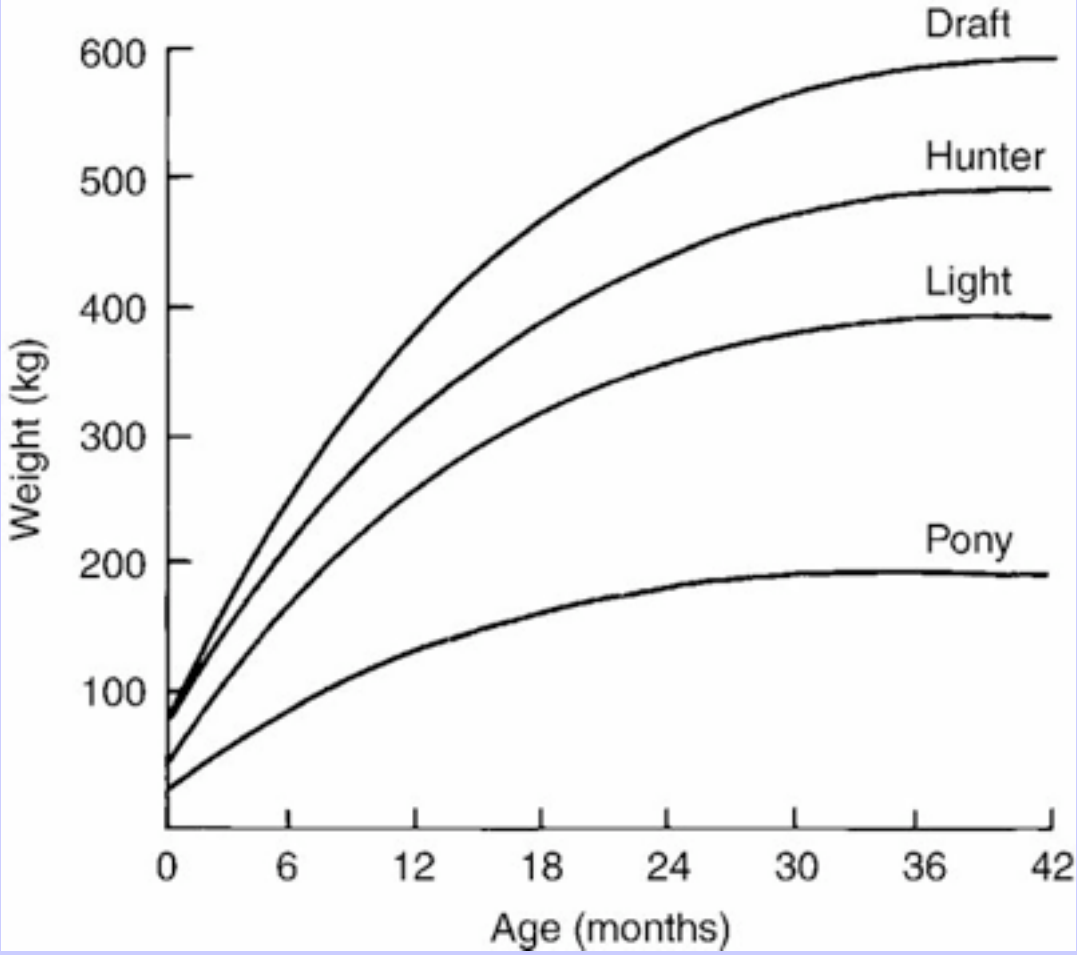


Fig. 9-1 Estimated weight gain of horses of various mature body weights. Modified from National Research Council [NRC]: *Nutrient requirements of horses*, Washington, DC, 1978, National Academy of Sciences, NRC.



4 Perform blood analyses.

a Perform a complete blood count (CBC) and include a plasma protein and fibrinogen concentration. If the foal is anemic, determine the cause of the anemia following the guidelines in Chapter 24. If the foal's CBC indicates inflammation, review Chapters 25 and 26 and select appropriate ancillary diagnostic tests to identify the source of the infection or inflammation.

b Perform a serum biochemical analysis. Evaluate the results for evidence of systemic disease. Serum albumin is usually within normal limits with PCM until the condition is terminal. Serum glucose is usually normal but it may be decreased in neonatal foals with sepsis. Serum glucose may be elevated in stressed animals. Serum urea nitrogen and creatinine concentrations are elevated in foals with renal disease. Serum urea nitrogen decreases in cases of chronic protein malnutrition.

c If the foal has evidence of systemic disease, perform ancillary diagnostic tests to identify the source of the illness, then manage the case with appropriate medical or surgical intervention.

5 Analyze the diet and improve the feeding program.

a Determine whether the energy, protein, mineral, and vitamin content of the diet meets the requirements of the growing foal (Table 9-3).

i Young horses require adequate levels of essential amino acids for growth. Lysine is the first and threonine is the second limiting amino acid in the equine. Growing foals should consume 4.3% of their crude protein requirement as lysine (multiply the crude protein requirement by 4.3%).[6] Growing foals should also consume at least 0.5% threonine (DM) in their diet. Soybean meal and alfalfa hay contain approximately 3.3% and 0.9% lysine (DM), respectively, whereas cereal grains are poor sources of lysine.

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Table 9-3 Daily Nutrient Requirements for Growth in Equines of Various Mature Body Weights

Mature Body Weight (kg/lb)	Category	Weight		Daily Gain		Digestible Energy (Mcal)	Crude Protein (g)	Lysine (g)	Calcium (g)	Phosphorus (g)
		kg	lb	kg	lb					
Ponies 200 kg (440 lb)	Nursing foal (4 months of age)	67	147	0.34	0.75	5.3	268	11.5	15.6	8.7
	Weanling (6 months of age)	86	189	0.29	0.64	6.2	270	11.6	15.5	8.6
	Yearling (12 months of age)	128	282	0.18	0.40	7.5	338	14.5	15.1	8.4
Horses 400 kg (880 lb)	Nursing foal (4 months of age)	135	297	0.67	1.47	10.6	535	23.0	31.3	17.4
	Weanling (6 months of age)	173	381	0.58	1.28	12.4	541	23.3	30.9	17.2
	Yearling (12 months of age)	257	565	0.36	0.79	15.0	677	21.9	30.1	16.7
Horses 500 kg (1100 lb)	Nursing foal (4 months of age)	168	370	0.84	1.85	13.3	669	28.8	39.1	21.7
	Weanling (6 months of age)	216	475	0.72	1.58	15.5	676	29.1	38.6	21.5
	Yearling (12 months of age)	321	706	0.45	1.0	18.8	846	36.4	37.7	20.9

Horses 600 kg (1320 lb)	Nursing foal (4 months of age)	202	444	1.01	2.22	15.9	803	34.5	46.9	26.1
	Weanling (6 months of age)	259	570	0.87	1.91	18.6	811	34.9	46.4	25.8
	Yearling (12 months of age)	385	847	0.54	1.19	22.5	1015	43.6	45.2	25.1

Modified from National Research Council (NRC): *Nutrient requirements of horses*, Washington, DC, 2007, National Academies Press

9.1.3.0.0.0.0.0.0.0.0.1

Box 9-3 Forage and Large Animal Feed Sampling Instructions

9.1.3.0.0.0.0.0.0.0.0.1.1

SAMPLING PASTURE

1. Collect pasture samples from a 1-foot-square area. Sample only the same type of forage that the horses are grazing. Sample 10 to 20 sites.
2. Using scissors, cut the pasture to within 1 inch of the ground. Do not collect soil-contaminated pasture. Cut all samples to a length of 1 inch, and place all samples into a clean bucket.
3. After sampling is complete, mix the samples well and place the forage into a plastic sealable bag (1-gallon Ziplock). Label the bag with the date of sampling, the collection site, and the owner's name.
4. If the sugar and starch content of the sample is of special interest, the sample should be frozen and shipped on ice to the analysis company.

9.1.3.0.0.0.0.0.0.0.0.1.2

SAMPLING HAY USING A CORE HAY SAMPLER

1. Choose 10 to 20 bales randomly from the hay shipment. Only one type of forage should be submitted for analysis in the same container. If more than one type of hay is analyzed, each should be placed into a separate, labeled plastic bag.
2. Use the core hay sampler with a ratchet brace or drill to collect two samples from each bale. Square bales should be sampled from the long end of the bale. Round bales should be sampled along a horizontal line at the curve of the bale. Place all samples into a plastic sealable bag (1-gallon Ziplock), and label the bag with the date, type of hay, and owner's name.

9.1.3.0.0.0.0.0.0.0.0.1.3

SAMPLING HAY BY HAND

1 Choose 10 to 20 bales randomly from the hay shipment. Only one type of forage should be submitted for analysis in the same container. If more than one type of hay is analyzed, each should be placed into a separate, labeled plastic bag.

2 Open the bale, and divide the bale in thirds. Collect a handful of hay from the center of the bale at each site (two samples per bale). Include everything that you have grabbed (including weeds and other plants) in the sample. Cut all samples to a length of 1 inch, and place all samples into a clean bucket. Thoroughly mix the cut hay samples, place the forage into a plastic sealable bag (1-gallon Ziplock), and label the bag with the date, type of hay, and owner's name. Ensure that all parts of the sample (leaves and stems) are included in the final sample.

9.1.3.0.0.0.0.0.0.0.0.1.4

SAMPLING GRAIN OR PELLETED FEED

1 Analysis of two to four samples from 10 bags is recommended to obtain a representative sample of feed. Only one type of feed should be submitted for analysis in the same container. If more than one type of grain or pelleted feed is analyzed, each should be placed into a separate, labeled plastic bag.

2 Open a bag or a bin, and obtain a 2- to 4-ounce sample from two to four locations in the bag or bin. A sample should be obtained from the bottom of the bin or bag to ensure that a sample of the settled feed is analyzed. When multiple bags or bins are sampled, samples from each bin or bag should be placed into a clean plastic bucket. Once all sampling has been completed, the feed sample should be mixed well, and approximately 1 pound of the feed should be placed into a plastic sealable bag (1-gallon Ziplock). Label the bag with the date, type of feed, and owner's name.

ii Milk replacer

If the foal is consuming a milk replacer, review the guaranteed analysis for the nutrient content of the product. Review the mixing instructions with the owner or farm manager. Develop a feeding program appropriate for the foal's age.

iii Forage

The most accurate way to determine the nutrient content of forage or pasture is with an analysis. Forage sampling instructions and forage analysis companies are listed in Boxes 9-3 and 9-4. University Extension services often provide a forage analysis service. If the client does not purchase a large volume of hay, or if analysis cannot be performed, forage tables from the Nutrient Requirement Council reference books (www.nap.edu) or nutrient tables from the Equi-Analytical Laboratories forage laboratory database (www.equi-analytical.com) can be referenced to estimate the concentration of different nutrients in common forages and supplemental feeds. Use the daily nutrient requirement table (see Table 9-3) to recommend the type and amount of forage the foal should consume based on the nutrient content of the forage.

9.1.3.0.0.0.0.0.0.0.0.2

Box 9-4 Feed Analysis Companies

1 Equi-Analytical Laboratories/Dairy One

730 Warren Road

Ithaca, NY 14850

(877) 819–4110; (800) 496–3344

www.equi-analytical.com

www.dairyone.com

2 Cumberland Valley Analytical Services, Inc.

P.O. Box 669

Maugansville, MD 21767

UPS/FedEx: 14515 Industry Drive

Hagerstown, MD 21742

(800) 282-7522

www.foragelab.com

3 Eurofins Scientific, Inc.

P.O. Box 1292

Des Moines, IA 50305

UPS/FedEx: 3507 Delaware Avenue

Des Moines, IA 50313

(800) 880-1038

www.eurofinsus.com

iv Commercial feeds and grain mixes

The guaranteed analysis on the feed tag label provides the nutrient content of certain ingredients. Contact commercial feed companies for the energy content of their product. Make recommendations about the appropriate use of commercial equine feeds, grain, or grain mixes for young growing foals based on the clinical health of the foal.

v Vitamins and minerals

Ensure that the diet meets the vitamin and mineral requirements of the foal. Supplement the diet if necessary.

b If the foal or weanling has a nutrient deficiency, the problem should be corrected by a change in the diet or through appropriate parenteral supplementation.

c If the diet history indicates that nutrients for maintenance and growth have been steadily consumed, the search for another cause of decreased growth and decreased weight gain should continue.

6 Perform ancillary diagnostic tests.

If the cause of the decreased growth and/or poor weight gain has not been determined, additional diagnostic tests should be performed. Possible tests include, but are not limited to ultrasound, radiographs, serum or whole blood trace mineral analysis, and carbohydrate absorption tests (oral D-glucose, D-xylose).

9.1.4

Approach to the Diagnosis and Management of Decreased Growth and Decreased Weight Gain in Ruminants

1 Take a general history and a diet history.

a General History

i What is the age of the animal? When was a decrease in growth observed? How many animals in the herd are affected? What are the ages of the affected animals? Has the herd had historical problems with growth of the young?

ii Identify the problem as acute, subacute, or chronic.

iii Check for signs or history of previous infectious disease.

iv Determine the parasite control procedures for the animal or herd.

v Examine the environment, including feed preparation areas and equipment, for possible toxic substances (e.g., zinc from galvanized buckets).

b Diet history

i Obtain an accurate diet history, including diet information when a milk or milk replacer diet is being fed (birth to 2 or 3 months of age). Note the age and condition of the dam if patient was suckled before weaning. An accurate postweaning dietary history is essential. Suckled animals are developed ruminants at weaning, but hand-reared animals (dairy calves, bummer lambs, and dairy kids) are usually not fully developed ruminants at the time they are weaned from milk.

ii Inspect all forages and concentrates for quality, signs of spoilage, or abnormal color or odor. Has an analysis been performed on the forage? Is the feed formulated appropriately?

iii Because ruminants are often fed in groups, note whether all animals have adequate space to eat simultaneously.

2 Perform a physical examination.

a Determine the patient's age and weight. Check the patient against age and weight charts (Figs. 9-3 to 9-6).

b Carefully note any signs of infectious or parasitic disease.

c Evaluate the animal for any signs of congenital abnormalities.

Fig. 9-3 Minimum growth curve for dairy heifers. From Sniffen CJ: *Feed Manage* 35:37, 1984.

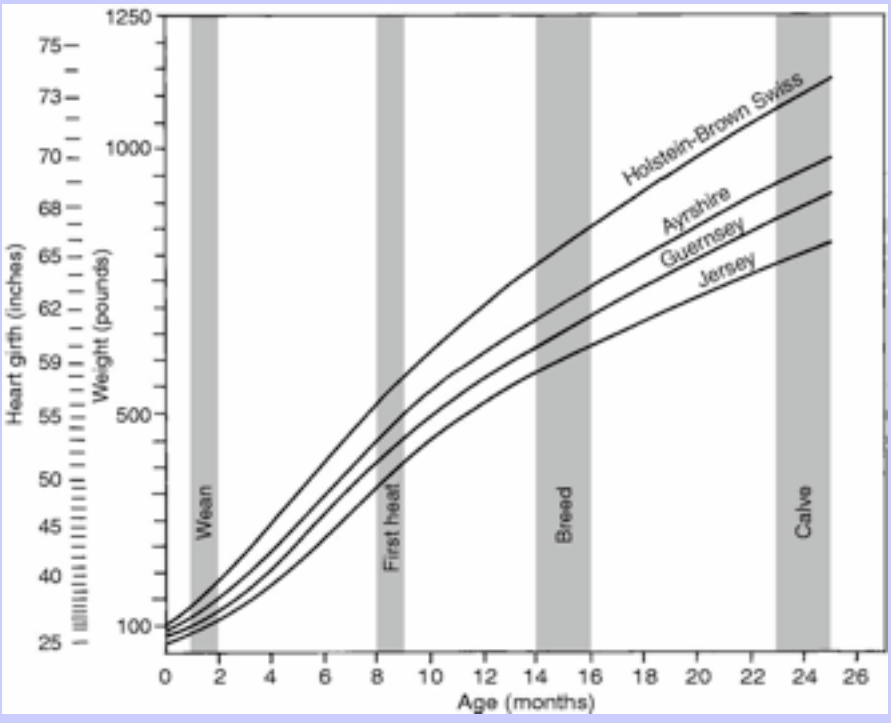


Fig. 9-4 Estimated growth curves for beef cows of various breeds. *AA*, Angus; *CC*, Charolais; *CA*, Charolais × Angus; *FA*, Holstein × Angus. Modified from Nadarajah K, Marlowe TJ, Notter DR: Growth patterns of Angus, Charolais, Charolais X Angus and Holstein X Angus cows from birth to maturity, *J Anim Sci* 59:957, 1984.

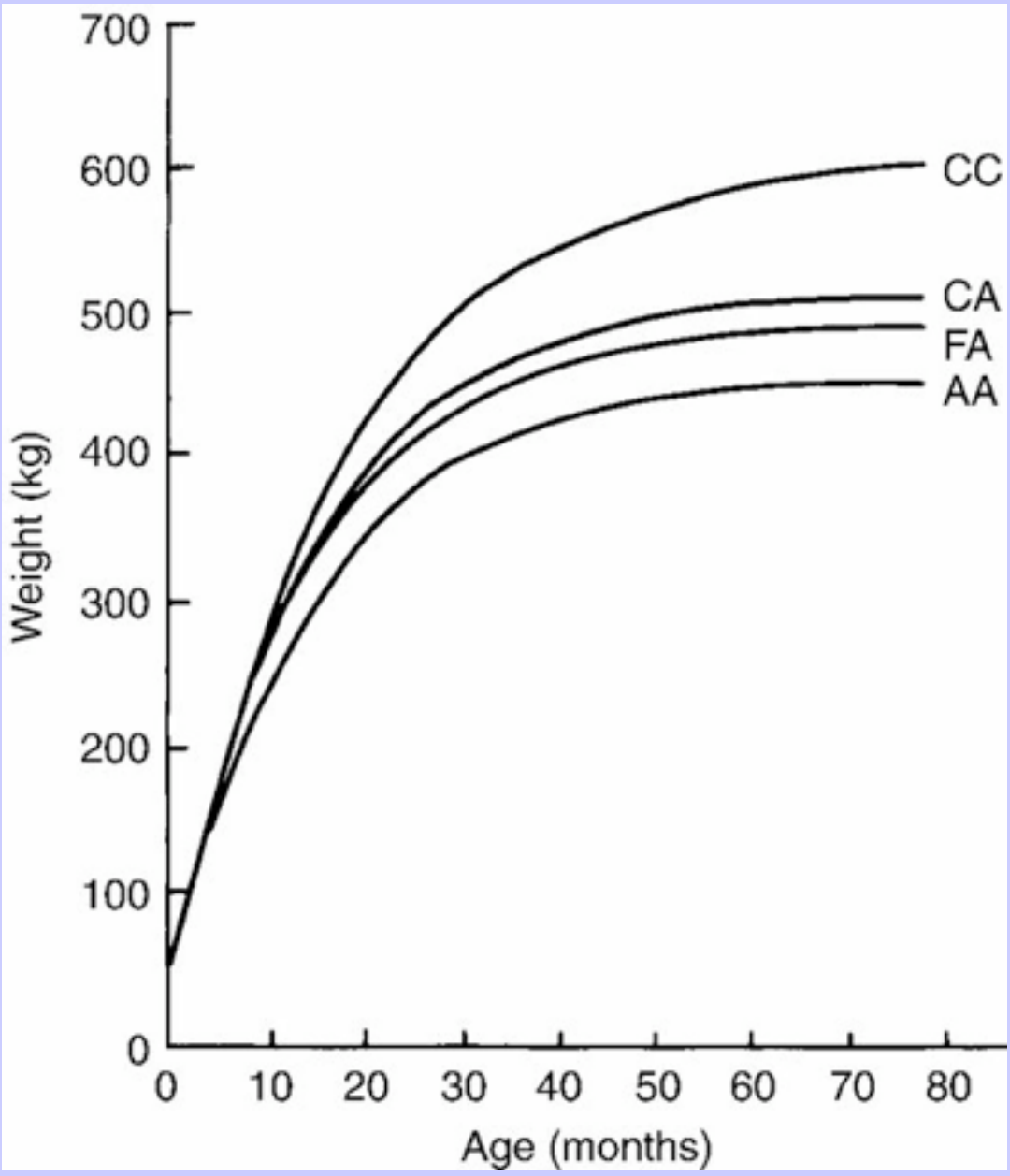
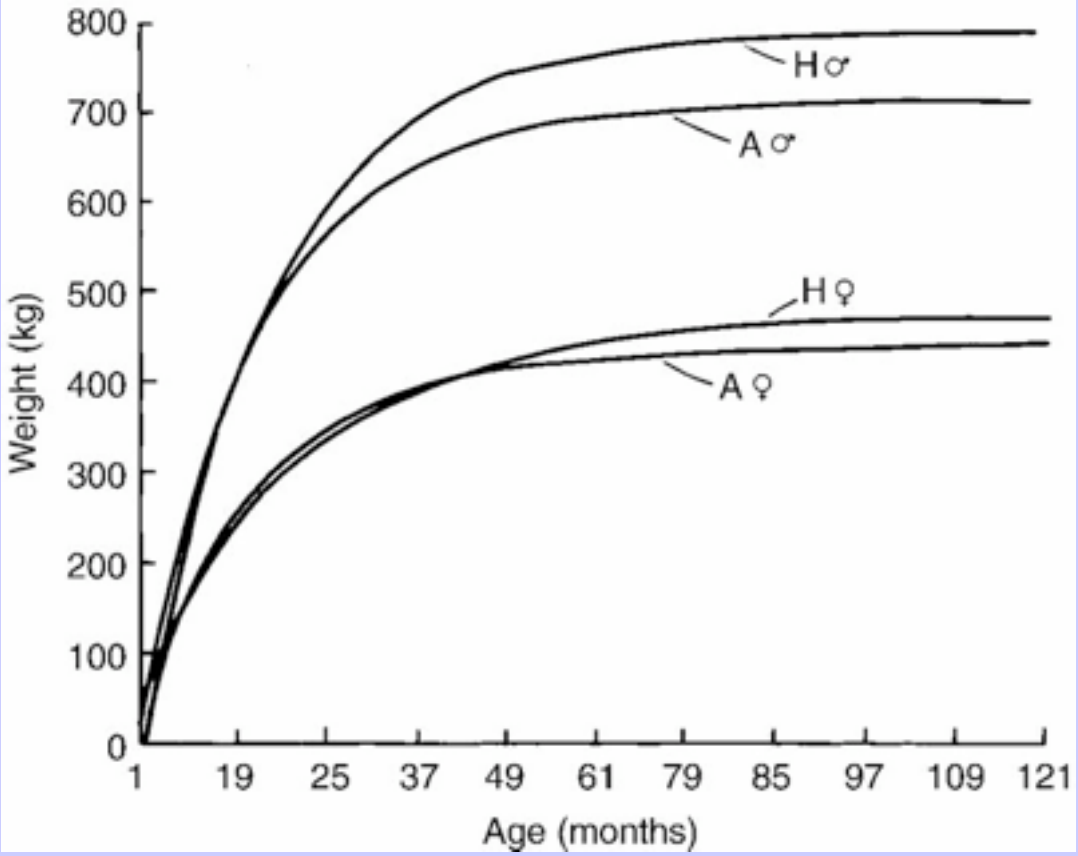


Fig. 9-5 Mean growth curves of Angus *(A)*, and Hereford *(H)*, males (♂) and females (♀). Modified from Brown JE, Brown CJ, Butts WT: A discussion of the genetic aspects of weight, mature weight and rate of maturing in Hereford and Angus cattle, *J Anim Sci* 34:525, 1972.



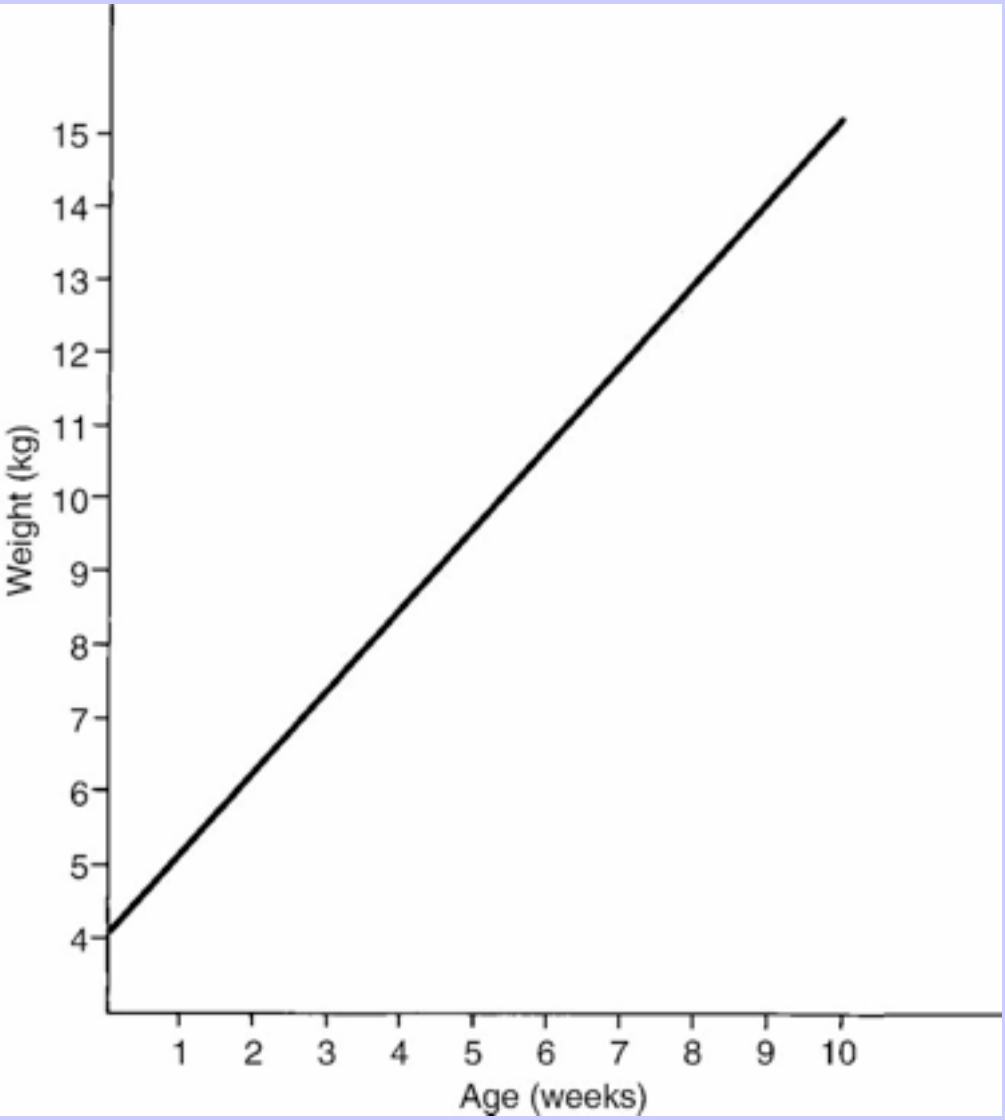
3 Examine the feces.

Perform flotation, sedimentation, and Baermann's procedures to detect patent parasitic infestation. Perform a fecal occult blood test; if the result is positive or if there is evidence of diarrhea, see the section on melena or diarrhea in Chapter 7. If diarrhea is noted in neonatal calves, refer to Chapter 20 for diagnostic and therapeutic management.

4 Perform blood analysis.

a Perform a CBC, including plasma protein and fibrinogen. Calculate the erythrocytic indices, and document and characterize the anemia if present. If a herd problem exists in a selenium-deficient region, measure the whole blood selenium concentration or glutathione peroxidase activity.

Fig. 9-6 Growth curve for young goats. Modified from Morand-Fehr P, Hervieu J, Bas P, Sauvant D: *Proc Third Int Conf Goat Prod Dis* 3:96, 1982.



b Perform a serum biochemical analysis. Serum albumin is decreased late in PCM. Albumin is normally lower in neonates (approximately 1 g/dL less) than in adults. The blood urea nitrogen (BUN) level is often low in ruminants as a result of urea recycling through saliva. Total serum calcium may be decreased with hypoalbuminemia (ionized serum calcium remains normal), anorexia, or hypocalcemic syndromes (milk fever). Serum phosphorus may be increased during severe starvation or decreased with anorexia.

Hypophosphatemia may be the result of dietary deficiency or *Brassica*, feeding, or it may be associated with copper deficiency. Measure serum (plasma) copper if a herd problem exists in a copper-deficient region (or a region with excess molybdenum or sulfate or both). Copper (serum or plasma) concentrations below 0.5 µg/mL (ppm) indicate deficiency. Liver copper levels are even more indicative of status. Serum glucose may be increased with stress or decreased or normal near death.

5 Analyze the diet and improve the feeding program.

Compare nutrient intake with the requirements for maintenance and growth of the various ruminant species (Tables 9-4 through 9-10). If the neonate is being fed a milk diet, evaluate the quality of the product and ensure that the animal's intake meets the dietary requirements (see Tables 9-4 and 9-5). Ensure that the milk replacer is mixed properly. If the ruminant is consuming a grain mix or forage, ensure that the quantity and the quality of the feed are adequate to allow sufficient intake in developed ruminants (see Table 9-1). Forage sampling instructions are listed in Box 9-3. If anorexia is present, look for more specific signs of a primary disease process. If the diet supplies adequate nutrients for maintenance and growth, consider decreased growth and decreased weight gain to be caused by a primary disease condition.

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Table 9-4 Daily Energy and Protein Requirements for 50-kg Calves on a Milk Diet

	Digestible Energy Requirements	Digestible Protein Requirements
Maintenance	45–55 kcal/kg body weight	0.5 g/kg body weight
Gain	300 kcal/100 g gain in body weight*	22 g/100 g of weight gain†
0.5 kg daily gain	1500 kcal	
1 kg daily gain	3000 kcal	

* A 50-kg calf gaining 0.75 kg/day would have a daily energy requirement of 5000 kcal of digestible energy (2750 kcal maintenance + 2250 kcal/0.75 kg of gain).

† A 50-kg calf gaining 0.75 kg/day would have a daily protein requirement of 190 g of digestible protein (25 g of maintenance + 165 g of gain).

Table 9-5 Net Energy (NE) Requirements of Young Lambs on Milk-Replacer Diets*

	Body Weight in Kilograms (Pounds)				
Average Daily Gain (g)	**5 (11)**	**7.5 (16.5)**	**10 (22)**	**12.5 (27.6)**	**15 (33)**
NE_M REQUIRED, KCAL/DAY					
	359	487	603	712	817
NE_G REQUIRED, KCAL/DAY					
100	127	172	214	253	290
150	193	262	325	383	440
200	261	353	438	518	594
250	330	447	555	655	751
300	401	543	674	796	913
350	473	641	796	940	1078
400	547	742	921	1088	1247

From Chiou PWS, Jordan RM: Ewe milk replacer diets for young lambs. IV. Protein and energy requirements of young lambs, *J Anim Sci*, 37:581, 1973.NE_m, Net energy of maintenance; NE_g, net energy of gain.

* Protein requirements for young lambs on a milk-replacer diet are approximately 20 g, 40 g, and 60 g for weight gains of 0, 100, and 200 g/day, respectively.

Table 9-6 Net Energy (NE) Requirements for Growth of Beef Cattle (Mcal/day)

	Body Weight in Kilograms/(NE_m Required)			
Daily Gain (kg)	**200 (4.1)**	**250 (4.84)**	**300 (5.55)**	**350 (6.23)**
Medium-frame steer calves NE_g required				
0.5	1.27	1.50	1.72	1.93
1.0	2.72	3.21	3.68	4.13
1.5	4.24	5.01	5.74	6.45
Growing bulls Weight (kg)/NE_m required	300 (6.38)	400 (7.92)	500 (9.36)	600 (10.7)
0.5	1.72	2.13	2.52	2.89
1.0	3.68	4.56	5.39	6.18
1.5	5.74	7.12	8.42	9.65

Modified from National Research Council (NRC): *Nutrient requirements of beef cattle, 7th revised edition*, Washington, DC, 1996, National Academy of Sciences, NRC.NE_m, Net energy of maintenance; NE_g, net energy of gain.

Table 9-7 Daily Nutrient Requirements for Growth of Dairy Calves

Body Weight (kg)	Body Weight (lb)	Breed	Age (Weeks)	Daily Gain (kg)	Digestible Energy (Mcal/day)	Metabolizable Energy (Mcal/day)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
HEIFERS AND BULLS FED ONLY MILK									
25	55	Small	1	0.2	1.56	1.50	70	6	4
30	66	Small	3	0.4	2.31	2.22	124	7	4
45	99	Large	1	0.2	2.30	2.21	81	8	5
50	110	Large	3	0.6	3.86	3.70	185	9	6
GROWING HEIFERS AND BULLS FED MIXED DIETS									
50	110	Large	3	0.5	5.42	5.20	198	10	6
GROWING DAIRY HEIFERS									
100	220	Small	26	0.5	8.35	8.00	360	16	6
200	440	Small	54	0.5	14.06	13.5	586	20	13
300	660	Small	83	0.5	18.74	18.00	746	23	17
Growing Dairy Bulls									
100	220	Small	26	0.5	8.35	8.0	361	16	8
200	440	Large	24	0.5	13.66	13.1	602	20	13
300	660	Large	38	0.5	18.56	17.8	777	24	18

Modified from National Research Council (NRC): *Nutrient requirements of dairy cattle*, Washington, DC, 1978, National Academy of Sciences, NRC; and from NRC: *Nutrient requirements of dairy cattle*, Washington DC, 2001, National Academy of Sciences, NRC.

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Table 9-8 Protein Requirements for Growth of Beef Cattle (Crude Protein g/day)

	Body Weight in Kilograms			
Daily Gain (kg)	200	250	300	350
Medium-Frame Steer Calves				
0.5	531	588	645	692
1	747	805	861	903
1.5	959	1014	1069	1103

Modified from National Research Council (NRC): *Nutrient requirements of beef cattle, 7th revised edition*, Washington DC, 1996, National Academy of Sciences, NRC.

Table 9-9 Calcium (Ca) and Phosphorus (P) Requirements for Growth of Beef Cattle (g/day)

		Body Weight in Kilograms			
Daily Gain (kg)	**Mineral**	**200**	**250**	**300**	**350**
Medium-frame steer calves					
0.5	Ca	20	21	21	22
	P	11	11	14	15
1	Ca	33	33	32	32
	P	16	16	16	16
1.5	Ca	45	44	42	41
	P	21	21	20	20

Modified from National Research Council (NRC): *Nutrient requirements of beef cattle, 7th revised edition*, Washington, DC, 1996, National Academy of Sciences, NRC.

Table 9-10 Nutrient Requirements for Growth in Sheep of Various Mature Body Weights

Category	Body Weight kg	Body Weight lb	Daily Gain kg	Daily Gain lb	Metabolizable Energy (Mcal)	Total Digestible Nutrients (kg)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
Replacement ewe lambs	30	66	0.23	0.5	2.8	0.78	185	6.4	2.6
	40	88	0.18	0.4	3.3	0.91	176	5.9	2.6
	50	110	0.12	0.26	3.2	0.88	136	4.8	2.4
	60	132	0.1	0.22	3.2	0.88	134	4.5	2.5
Replacement ram lambs	40	88	0.33	0.73	5	1.1	243	7.8	3.7
	60	132	0.32	0.7	6.7	1.5	263	8.4	4.2
	80	176	0.29	0.64	7.8	1.8	268	8.5	4.6
	100	220	0.25	0.55	8.4	1.9	264	8.2	4.8
Finishing lambs (4–7 months)	30	66	0.29	0.65	3.4	0.94	191	6.6	3.2
	40	88	0.27	0.6	4.4	1.22	185	6.6	3.3
	50	110	0.2	0.45	4.4	1.23	160	5.6	3
Early weaned lambs—moderate growth	10	22	0.2	0.44	1.4	0.4	127	4	1.9
	20	44	0.25	0.55	2.9	0.8	167	5.4	2.5
	30	66	0.3	0.66	3.6	1	191	6.7	3.2

Modified from National Research Council (NRC): *Nutritional requirements of sheep*, Washington, DC, 1978, National Academy of Sciences, NRC.

9.2 WEIGHT LOSS

The clinical problem of weight loss suggests that an individual large animal patient or a herd has lost weight over a known period of time. It may also suggest that the patient has reached a subnormal adult weight and size (see section on decreased growth and decreased weight gain, earlier). Late pregnancy, early lactation, and intense exercise are normal physiologic conditions commonly accompanied by mild to moderate weight loss. Late pregnancy can be associated with decreased body condition without actual weight loss, because weight is gained with the conceptus. During pregnancy and lactation the loss of body condition may be mild, resulting in a low normal BCS, or the loss may be severe and can threaten the health of both the dam and the neonate.

Weight loss in adult animals is most commonly associated with one or more of the following circumstances (other causes are listed in Boxes 9-5 and 9-6):

- Anorexia
- Increased nutrient demands
- PCM
- Micronutrient deficiencies
- Parasitism

Anorexia usually occurs secondary to a primary disease. Increased nutrient requirements are associated with normal physiologic conditions (e.g., pregnancy, lactation, exercise, cold weather) and with pathologic processes (e.g., sepsis, trauma, parasitism, burns). Mild to severe PCM is often associated with inadequate feed quality (see Table 9-1) or quantity but can also be caused by increased energy requirements resulting from adverse environmental conditions. Weight loss can also occur with a deficiency of essential micronutrients such as copper, cobalt (vitamin B_{12}), or vitamin A. Parasitism should always be on the differential list in an animal that has lost weight.

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9.2.1

Box 9-5 Causes of Weight Loss in Horses

9.2.1.1

COMMON CAUSES

Protein-calorie malnutrition (PCM)

Parasitism

Dental, jaw abnormalities

Sand enteropathy

Chronic colonic impaction

Gastric ulcers

Right dorsal colitis

Peritonitis

Internal abdominal abscess

Streptococcus equi, (lymph node abscessation, pulmonary or mesenteric abscessation)

Pneumonia (bacterial, viral)

Pleuritis, pleuropneumonia, pulmonary abscessation

Chronic obstructive pulmonary disease

Chronic renal failure

Acute renal failure

Pituitary pars intermedia dysfunction

Neoplasia (alimentary tract)

9.2.1.2 LESS COMMON CAUSES

Guttural pouch infection

Otitis media, interna

Paranasal sinus infection

Oral foreign body

Vesicular stomatitis

Esophageal abnormalities (esophagitis, diverticula)

Gastric squamous cell carcinoma

Duodenal ulcers

Gastric impaction

Lymphocytic-plasmacyte enterocolitis

Eosinophilic enterocolitis

Multisystemic eosinophilic epitheliotropic disease

Granulomatous enteritis

Proliferative enteropathy

Idiopathic diarrhea

Toxic hepatopathy

Chronic hepatitis

Cholelithiasis

Pyrrolizidine alkaloid hepatotoxicity

Amyloidosis

Urolithiasis

Renal tubular acidosis

Glomerulonephritis

Pyelonephritis

Renal neoplasia

Urinary bladder neoplasia

Osteomyelitis

Infectious arthritis

Atrial fibrillation

Cardiac or great vessel anomalies

Congestive heart failure

Endocarditis, pericarditis

Splenic rupture, abscess

Lymphoma, lymphosarcoma

Malignant melanoma

Granulosa cell tumor

Purpura hemorrhagica

Autoimmune anemia or thrombocytopenia

Cauda equina neuritis

Equine motor neuron disease

Nocardiosis

Coccidioidomycosis

Cryptococcosis

Agammaglobulinemia

Anhidrosis

Giardiasis

Aflatoxicosis

Equine adenovirus

Equine viral arteritis

Equine infectious anemia

9.2.1.3 UNCOMMON CAUSES

Rabies

Nigropallidal encephalomalacia

Botulism

Nutritional myodegeneration

Rectus capitus ventralis muscle rupture

Skeletal or vertebral neoplasia

Spinal abscessation

Micronema deletrix, infection of the central nervous system

Rhodococcus equi, infection

Tuberculosis

Pleural mesothelioma

Pneumocystis carinii, pneumonia

Pulmonary aspergillosis

Micropolyspora faeni, hypersensitivity pneumonitis

Testicular neoplasia

Mammary carcinoma

Ovarian adenoma

Pancreatic neoplasia

Malignant mesothelioma

Pulmonary neoplasia

Strongylus vulgaris, thromboembolism

Portal vein shunt

Liver fluke

Theiler's disease

Basophilic enterocolitis

Ileal hypertrophy

Myeloproliferative disease

Pyloric stenosis

Colonic fistula

Prognathia, brachygnathia

Aortic aneurysm

Enzootic cystitis

Polycystic disease

Pheochromocytoma

Hyperparathyroidism

Diabetes mellitus

Systemic granulomatous inflammation

Seborrhea

Bullous pemphigoid

Panniculitis

Lupus erythematosus

Pemphigus foliaceous

Eosinophilic dermatitis

Horsefly-deerfly infestation

Wound myiasis

Steatitis

Goiter

Erythrocytosis

Histoplasmosis

Phycomycosis

Fungal granuloma

Tularemia

Babesiosis

Brucellosis

Phosphorus deficiency

Vitamin A deficiency

Multiple cartilaginous exostoses

Trypanosoma evansi, infection (exotic)

Trombiculiasis (exotic)

Nagana (exotic)

Pseudomonas pseudomallei, infection (exotic)

Uasin Gishu skin disease (exotic)

Besnoitiosis (exotic)

Dourine (exotic)

Glanders (exotic)

Grass sickness (exotic)

Louping ill (exotic)

Trypanosoma equinum, infection (exotic)

Trypanosoma hippicum, infection (exotic)

Stachybotryotoxicosis (exotic)

9.2.1.4 TOXINS

Phenylbutazone, flunixin, and other nonsteroidal antiinflammatory drugs

Vitamin D calcinosis

Zinc

Selenium

Fluoride

Arsenic

Mercury

Vitamin K_3

4-Aminopyridine

Pentachlorophenol

Dioxin

Aflatoxicosis

9.2.1.5 PLANT TOXINS

Yellow star thistle

Red maple leaf

White snakeroot (tremetol)

Plant calcinosis

Thornapple

Crofton weed

Pimela, (exotic)

Swainsonia (exotic)

Birdsville disease (exotic)

Pachysandra paralysis (exotic)

9.2.2

Box 9-6 Causes of Weight Loss in Ruminants

9.2.2.1

COMMON CAUSES

Protein-calorie malnutrition (PCM)

Bacterial pneumonia, pulmonary abscessation

Parasitism (lungworms, gastrointestinal parasites)

Johne's disease (paratuberculosis)

Bovine leukosis

Peritonitis

Ruminal lactic acidosis

Urolithiasis

Pyrrolizidine alkaloid toxicity

Displaced abomasum

Hepatic abscess

Abomasal ulcer

Rotavirus diarrhea

Coronavirus diarrhea

Sarcoptic mange

Foot rot

Pedal osteomyelitis

Sole abscess

Traumatic reticuloperitonitis, pericarditis

Ketosis

Vagal indigestion

Winter dysentery (B)

Salmonellosis

Fat necrosis (B)

Actinobacillosis

Actinomycosis

Pharyngeal, retropharyngeal abscess

Pyelonephritis, cystitis

Selenium deficiency

Bovine virus diarrhea (B)

Coccidiosis

Copper deficiency

Dental abnormalities

Enterotoxigenic colibacillosis

Agammaglobulinemia (failure of passive transfer) in neonates

Fescue toxicity (B)

Anaplasmosis (B)

Septic arthritis

Infectious bovine rhinotracheitis (B)

Intussusception

Leptospirosis

Mastitis, coliform or staphylococcal

Lice or ked infestation

Hepatic abscess

Liver fluke infestation

Pasteurellosis, septicemic

Pregnancy toxemia

Bluetongue (O)

Cryptosporidiosis

Mammary abscess

Wound myiasis

Diarrhea, unknown cause

9.2.2.2 LESS COMMON CAUSES

Rabies

Sarcocystosis (B)

Sodium chloride deficiency

Cardiac or great vessel anomalies

Thymic lymphosarcoma (B)

Tuberculosis

Ulcerative stomatitis

Vesicular stomatitis

Salt toxicity, water deprivation

Psoroptic mange

Postparturient hemoglobinuria

Malignant catarrhal fever

Aspiration pneumonia

Brisket disease

Neoplasia

Omasal impaction

Abomasal impaction

Listeriosis

Pleuritis

Renal amyloidosis

Acute renal failure

Hydronephrosis, urachal abscess, bladder abscess

Dermatophilosis

Glomerulonephritis

Thiamine deficiency

Fluorosis

Esophageal malfunctions

Cobalt deficiency

Coenurosis (gid)

Congenital porphyria

Endocarditis

Aflatoxicosis

Eperythrozoonosis

Mandible, maxilla fracture

Goiter

Lingual injury, abscess

Vena caval thrombosis

Colonic obstruction

Otitis media, externa

Papular stomatitis (B)

Micropolyspora faeni, hypersensitivity pneumonitis

Loss of teeth, periodontal disease

Sinusitis

9.2.2.3 UNCOMMON CAUSES

Buss disease (transmissible serositis) (B)

Neoplasia (other than bovine leukemia virus)

Systemic candidiasis

Local and systemic mycoses

Mycoplasma, arthritis

Ulcerative posthitis, vulvitis (B)

Polycythemia (B)

Phosphorus deficiency

Vitamin A deficiency

Zinc deficiency

Bovine spongiform encephalopathy

Meuse-Rhine-Yssel muscular dystrophy (B)

Epidermolysis bullosa (B, O)

Familial acantholysis

Portal vein anomaly

Granulocytopathy

Pulmonary listeriosis

Cholelithiasis

Bronchobiliary fistula (B)

Hypersensitivity to soy or milk replacer

Diabetes mellitus

Idiopathic granulocytopenia or thrombocytopenia

Endocardial fibroelastosis (B)

α-Mannosidosis (B)

Fungal granuloma

Generalized glycogenosis (B)

GMI gangliosidosis

Hereditary zinc deficiency (B)

Lethal trait A-46, keratogenesis imperfecta (B)

Omental bursitis (B)

East Coast fever (theileriosis) (exotic)

Tick-borne fever (exotic)

Idiopathic sporadic bovine encephalomyelitis (exotic) (B)

Surra (exotic) (B)

Trypanosomiasis (exotic)

Melioidosis, *Pseudomonas pseudomallei*, (exotic)

Petechial fever (exotic) (B)

Besnoitiosis (exotic)

Ibaraki disease (exotic) (B)

Turning sickness (exotic) (B)

Contagious pleuropneumonia (exotic) (B)

Schistosomiasis (exotic)

Louping ill (exotic)

Foot-and-mouth disease (exotic)

Lethal skin defects in Japanese black cattle (exotic)

Echinococcosis (exotic)

Endemic ethmoid carcinoma (exotic)

African bovine malignant catarrhal fever (exotic)

Idiopathic storage disease in cattle (exotic)

Babesiosis (exotic)

9.2.2.4 TOXINS

Selenium

Trichothecene (T-2)

Vitamin D_3

Diesel fuel

Polybrominated biphenyls

Cobalt

Herbicides

Zinc

Furazolidone

4-Aminopyridine

Chlorpyrifos

Toxins associated with crude oil, kerosene

Ergotism

Arsenic

Lead

Mercury

Ethylene glycol

Stachybotryotoxicosis (exotic)

9.2.2.5 PLANT TOXINS

Gossypol (cottonseed)

Helenium, sneezeweed

Acorn, oak

Bracken fern

Perennial broomweed *(Gutierrezia)*,

Cocklebur

Hairy vetch *(Vicia villosa)*,

White snakeroot (tremetol)

Mushroom

Tung tree

Fireweed *(Kochia scoparia)*,

Locoweed *(Oxytropis, Astragalus)*,

Phalaris, species

Bermuda grass

Pimela, species (exotic)

Geigeria, species (exotic)

Cestrum, species (exotic)

Yellow wood (exotic)

Leucaena leucocephala, species (exotic)

B, Bovine; *O*, ovine.

9.2.3

Mechanisms of Weight Loss

Anorexia is the loss of appetite or lack of desire for food; it may be complete or partial. It is a primary mechanism for weight loss of short or intermediate duration. Weight loss results from decreased nutrient intake. When partial anorexia occurs over a long period, the weight loss may be subtle and go unrecognized. Acute, complete anorexia results in more dramatic weight loss.

In domestic species, anorexia is usually associated with a primary disease condition and is regulated by cytokines, including interleukin (IL)-1 and tumor necrosis factor alpha (TNF-α), released during an inflammatory response. Resolution of the primary disease process usually results in a return to voluntary food consumption. Anorexia must be differentiated from dysphagia by observation. The distinction between the conditions that cause anorexia and those that control hunger and satiety is not clear; however, many diseases that cause anorexia also result in dehydration, electrolyte imbalances, and/or acid-base disorders.

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In addition to causing anorexia, many disease processes cause an increase in the nutrient requirements for basal metabolism. Nutrient requirements for maintenance, growth, pregnancy, lactation, and exercise have been well defined for many large animal species. Nutrient requirements in disease have not been adequately evaluated in large animals, and most information is currently extrapolated from humans, laboratory animals, and small animal species. In human patients, published estimates indicate that requirements for energy and protein increase

approximately 10% after elective surgery, 20% with fractures, 30% to 60% with severe infection or sepsis, 40% with peritonitis, and 50% to 110% with major burns.[7,8] In humans, the resting energy expenditure is estimated to increase by 14% for each degree Celsius increase in body temperature.[9] Extrapolation of these data directly to equine and ruminant patients is probably not possible; however, the figures do indicate the degree of change in nutrient requirements as a result of disease. The stress of many disease processes results in an increase in serum cortisol and in glucagon. The decreased insulin/glucagon ratio alters the production of glucose and results in hyperglycemia because of enhanced hepatic gluconeogenesis. An increase in sympathetic activity appears to regulate fat oxidation, the increased release of fatty acids from cellular lipid stores, and the development of hypertriglyceridemia in many patients with sepsis. Protein degradation and a negative nitrogen balance are also hallmarks of the acute response to infection. Weight loss resulting from protein and lipid catabolism is often observed in large animal patients with sepsis, owing to altered metabolic activity and nutrient requirements.

In conditions such as burns, peritonitis, pleuritis, colitis, and granulomatous bowel disease, nutrients (particularly proteins) are lost. In many disease conditions, concurrent anorexia and increased nutrient requirements greatly increase the risk of PCM and weight loss. Certain conditions, such as Johne's disease in ruminants and granulomatous enteritis in horses, are also associated with a malabsorption or malassimilation syndrome. In these types of diseases, nutrients are not efficiently digested and absorbed; anorexia may be absent, and dietary intake may appear normal, but weight loss still occurs.

PCM continues to be a persistent problem in domestic animals. Inadequate ingestion of energy and protein obviously results in weight loss, but PCM and associated weight loss can occur through several other mechanisms. The most direct cause is that the animal receives an inadequate volume of feed to meet their dietary requirements. This can occur as frank underfeeding of all animals or as a consequence of inadequate feeding facilities that create competition among animals for available feed. The latter circumstance occurs most dramatically when animals of varying ages are mixed; the younger animals with the highest requirements are often pushed away by older, dominant individuals.

The quality of the diet, particularly dietary forages such as hay and pasture, is an important factor in the development of PCM and total nutrient intake. Table 9-1 lists guidelines for estimating the maximum daily intake by cattle. It is evident that as forage quality (digestibility) decreases, maximum daily intake decreases because poor-quality feed must remain in the rumen for an increased period of time before it is sufficiently digested to allow passage through the reticuloomasal orifice. Maximum dry matter intake (DMI) as a percentage of body weight is somewhat higher in small ruminants than in cattle. However, the energy requirement per kilogram of body weight is higher in small ruminants than in cattle. Similar estimates for maximum DMI in horses related to forage quality are not available. Horses do not have a pregastric fermentation organ (rumen) and can ingest slightly more of the same quality forage than cattle. Low-quality forages are often the cause of PCM, even when an unlimited quantity is available. The best way to determine the nutrient content of forage, grain, and pelleted feeds is to have the feed analyzed by a forage laboratory. Feed analysis instructions are provided in Box 9-3. Feed tag labels or forage databases can be referenced if a forage analysis is not performed.

Environmental factors can have a major influence on nutrient requirements and can increase the subsequent risk for PCM and weight loss. The most important environmental factor is the ambient temperature. Nutrient requirements for maintenance change with a decreasing ambient temperature as follows:

- *Adult horses:*, Estimated increase in digestible energy (DE) requirements by 2.5% for every degree Celsius below the lower critical temperature (LCT). The LCT for adult horses ranges from 5° C to −15° C, depending on the horse?s adaptation to the environment. In cold temperatures, when the hair coat is wet, the maintenance DE requirement may be increased by as much as 50%.[10]

- *Beef cattle:*, 1% increase in maintenance energy requirements (total digestible nutrients [TDN], net energy of maintenance [NE_m], digestible energy [DE], and metabolizable energy [ME]) for each 1° C drop below 20° C (68° F).
- *Dairy cattle (lactating):*, 25% increase in energy requirements (TDN, net energy of lactation [NE_L]) as ambient temperature drops from 20° C (68° F) to −10° C (14° F).
- *Sheep with 10-cm wool:*, 1% increase in energy requirements (TDN, ME, DE) for each 1° C drop below lower critical temperature (approximately −10° C).

There are also additive effects of wind and rain that increase energy requirements in large animal species. As nutrient requirements increase, the dietary intake must also increase to prevent weight loss associated with PCM. Horses in inclement weather may not be able to consume enough forage to meet their increased energy requirements, and for these animals, dietary fat and limited grain supplementation may be required.

Deficiencies of micronutrients (trace minerals, B vitamins) often result in inefficiencies in basic biochemical pathways. These inefficiencies, if marked, can be associated with weight loss. Genetic errors in metabolism can cause similar disturbances, but these usually manifest as decreased growth and even death in young animals.

Parasitism is a common cause of weight loss in adult domestic animals. The mechanisms by which parasite infestation can result in weight loss include a loss of body fluid and tissues resulting in increased nutrient requirements, competition for nutrients in the gastrointestinal tract, malassimilation and malabsorption, inflammation resulting in increased nutrient requirements, micronutrient deficiencies, and organ or vascular damage from migrating parasite larvae. Anorexia may also develop in the advanced stages of severe parasitism.

9.2.4 Approach to the Diagnosis and Management of Weight Loss in Adult Horses

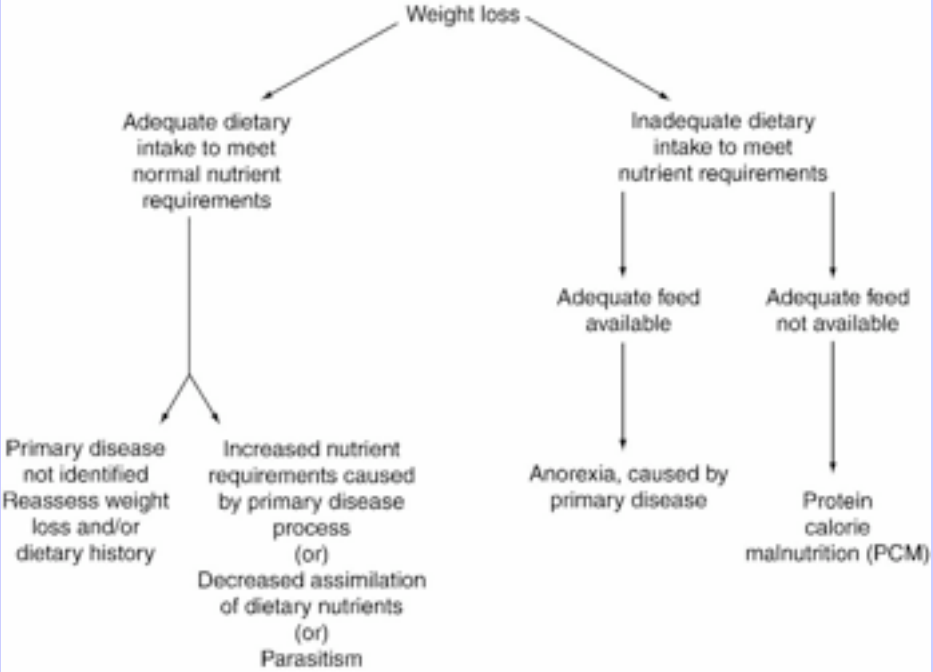
Use the flow sheet in Fig. 9-7 to aid in decision making.

1 Take a general history and a diet history.

a General history

i Is the weight loss affecting one animal, or many animals? If many horses are affected, what is the age range of the affected animals? How long has the caretaker noticed weight loss in the horse? How much weight has been lost? Is this an estimate of weight loss, or have the horse(s) been monitored on a scale or with a weight tape? What is the change in BCS of the horse(s)? Has the diet been changed to manage the weight loss? Weight loss is often suspected but not documented in the initial complaint or history. Acute weight loss of 5% to 10% is significant. Quantitation of weight loss and BCS changes is important.

Fig. 9-7 Flow sheet for classifying conditions associated with weight loss.



If a weight tape will not fit around the girth of the horse, or if the horse has a BCS of 1 to 3, a body weight estimate is made using measurements of the length and girth of the horse.[11–12] Length is measured from the tuber ischium to the point of the shoulder, and girth is measured at the withers, behind the elbows, at the end of expiration.

$$\text{Body weight (kg)} = \frac{\text{Chest girth (cm)}^2 \times \text{Length (cm)}}{11877}$$

The weight of miniature horses should be obtained using a small animal clinic scale. If a scale is not available to weigh a miniature horse, then the following equation can be used to estimate the weight of the miniature horse.[13]

$$\text{Body weight (kg)} = \frac{(3.7 \times \text{Chest girth in cm}) + (2 \times \text{Length in cm}) - 348.5}{2.2}$$

ii Is there any past or current clinical disease in the horse or herd? If so, when was the disease first diagnosed? How many animals were affected? What type of treatment was administered? Was the diet changed during this period of time? Question the caretaker closely about any clinical signs of diarrhea, coughing, dysphagia or polyuria. What is the deworming history of the horse and herd? Has the deworming protocol been changed lately?

b Diet history

i Obtain an *accurate*, dietary history including the type and amount of feed offered (in pounds, ounces) and the amount of feed refused by the horse(s). It is essential that feeds are weighed accurately. Nutrient requirements of adult ponies and horses are listed in Table 9-11. For how long does the horse have access to pasture? What type of grass is available in the pasture? Is the pasture overgrazed? Are any diet supplements fed to the horse? If so, what amount is fed? Does the horse have access to a salt or trace mineral block? How long has this diet been fed? Have there been any changes in the forage offered to the animals? Forage quality is often not consistent between hay shipments. Has a forage analysis been performed on the pasture or hay? If yes, obtain a copy of the analysis for the patient record. Inspect the pasture and all feeds for gross quality, evidence of spoilage, abnormal color or odor, presence of weeds and mold, and quantity of feed the owner has at the facility.

ii How are the horses fed? What type of feeder is used? Are mats placed under the feeders to reduce sand and dirt ingestion? Is there competition among the horses for food? Are there any toxic substances in the horse's environment? What is the water source for the horses? Is the water clean?

2 Perform a physical examination.

a Observe the horse while it is eating forage. Can the horse prehend, masticate, and swallow food normally? Is the horse dysphagic? Does the horse have a good appetite? Is the horse hungry? Are there any signs of neurologic disease?

b Examine the patient closely to identify signs of concurrent disease (e.g., pyrexia, diarrhea, melena, dysphagia, abnormal dentition, icterus, nasal discharge, cough, dyspnea, tachycardia, cardiac murmur, dysuria).

c What are the horse's body weight (scale or weight tape) and BCS (see Table 9-21)?

3 Examine the feces.

What is the consistency of the feces? If the horse has evidence of diarrhea, review the section on diarrhea in Chapter 7. How long are the fibers in the feces? Perform a glove test. Is there evidence of sand in the feces? Horses can have a significant volume of sand in the large intestine while having negative fecal sand test results. Perform a fecal egg count. An enzyme-linked immunosorbent assay (ELISA) may be useful in diagnosing a tapeworm infection. Follow the parasite control program in Chapter 49 if the horse has evidence of fecal parasites or if a parasite infection is suspected despite a negative fecal egg count. Perform a fecal occult blood test; if the result is positive, see the section on melena in Chapter 7.

Table 9-11 Daily Nutrient Requirements of Ponies and Horses of Mature Body Weight

Category	Digestible Energy (Mcal)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
MATURE PONIES, 200 KG (440 LB) OF MATURE BODY WEIGHT				
Maintenance, average activity	6.7	252	8	5.6
Mares, last 90 days of gestation	7.7–8.6	319–357	14.4	10.5
Lactation, first 3 months	12.7–12.2	614–587	23.6–22.4	15.3–14.4
MATURE HORSES, 400 KG (880 LB) OF MATURE BODY WEIGHT				
Maintenance, average activity	13.3	504	16	11.2
Mares, last 90 days of gestation	15.4–17.1	637–714	28.8	21
Lactation, first 3 months	25.4–24.5	1228–1174	47.3–44.7	30.6–28.8
MATURE HORSES, 500 KG (1100 LB) OF MATURE BODY WEIGHT				
Maintenance, average activity	16.7	630	20	14
Mares, last 90 days of gestation	19.2–21.4	797–893	36	26.3
Lactation, first 3 months	31.7–30.6	1535–1468	59.1–55.9	38.3–36
MATURE HORSES, 600 KG (1320 LB) OF MATURE BODY WEIGHT				
Maintenance, average activity	20	756	24	16.8
Mares, last 90 days of gestation	23.1–25.7	956–1072	43.2	31.5
Lactation, first 3 months	38.1–36.7	1842–1761	70.9–67.1	45.9–43.2
MATURE HORSES, 900 KG (1980 LB) OF MATURE BODY WEIGHT				
Maintenance, average activity	30	1134	36	25.2
Mares, last 90 days of gestation	34.6–38.5	1434–1607	64.8	47.3

Lactation, first 3 months	54.4–52.4	2763–2642	106.4–100.6	68.9–64.9

Modified from National Research Council (NRC): *Nutrient requirements of horses*, Washington, DC, 2007, National Academies Press.

4 Perform blood analyses.

a Perform a CBC, including plasma protein and fibrinogen. Examine the results closely for indication of an inflammatory process (e.g., leukocytosis, neutrophilia, leukopenia, neutropenia, hyperfibrinogenemia, decreased plasma protein/fibrinogen ratio [below 10]). Calculate the erythrocytic indices, and characterize anemia, if present.

b Perform a serum biochemical analysis. The serum albumin half-life is approximately 19 days in horses. Hypoalbuminemia may be associated with colitis, internal abscessation, PCM, liver disease, renal disease, and granulomatous bowel disease, among other conditions. Albumin is often within normal limits in PCM until the patient is near death. Globulin (particularly γ-globulins) may be increased with inflammation, and the albumin/globulin ratio may be decreased. The glucose concentration is usually normal or elevated as a result of stress and may also be elevated in horses with pituitary pars intermedia dysfunction (PPID) and equine metabolic syndrome. Hyperlipidemia (serum triglyceride between 100 and 500 mg/dL) is commonly associated with early anorexia and can be present in horses with PPID. Hyperlipemia (serum triglyceride above 500 mg/dL) is a serious condition associated with prolonged anorexia and hepatic lipidosis and is often found in miniature horses, ponies, and donkeys under severe physiologic stress (PCM and lactation). Unconjugated bilirubin levels can rise to 6 or 7 mg/dL with anorexia or decreased food intake. An elevated γ-glutamyltransferase (GGT) (above 25 IU/L) may indicate hepatic disease. Horses with PCM may have a low serum urea nitrogen if the protein malnutrition is prolonged and severe.

5 Analyze the diet and improve the feeding program.

a Determine if the energy, protein, mineral, and vitamin content of the diet meets the nutrient requirements of the horse at their current metabolic state and activity level (see Table 9-11). Include pertinent environmental and management factors in the nutrient requirement calculations. The quality of the feeds should be assessed.

i Forage

The most accurate way to determine the nutrient content of forage or pasture is with an analysis. See Box 9-3 for instructions on how to sample feeds for analysis. Contact a university extension service for forage analysis. If the client does not purchase a large volume of hay, or if analysis cannot be performed, forage tables from the Nutrient Requirement Council reference books (www.nap.edu), or nutrient tables from the Equi-Analytical Laboratories forage laboratory database (www.equi-analytical.com) can be used to estimate the concentration of different nutrients in common forages and supplemental feeds.

ii Commercial Feeds

The guaranteed analysis on feed tag labels provides the nutrient content of certain ingredients. Contact commercial feed companies for the energy content of their products.

b If the horse has a dietary deficiency, the problem should be corrected by a change in the diet or through appropriate supplementation. Contact an equine clinical nutritionist for guidance on ration formulation.

c If the dietary history indicates that adequate nutrients for maintenance and performance have been steadily consumed, continue to search for another cause of the weight loss.

6 Perform ancillary diagnostic tests.

If the weight loss is not caused by inadequate or poor-quality feed, additional diagnostic tests should be performed. Possible tests include but are not limited to ultrasound, gastric endoscopy, radiographs, serum or whole blood trace mineral analysis, serum insulin concentration, carbohydrate absorption tests (oral D-glucose, D-xylose [see Chapter 32]), and appropriate organ biopsy.

Table 9-12 Daily Nutrient Requirements for Dairy Cattle

Body Weight						
(kg)	(lb)	NE_L (Mcal)	Total Digestible Nutrients (kg)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
MAINTENANCE OF MATURE LACTATING COWS						
400	880	7.16	3.15	373	15	13
500	1100	8.46	3.72	432	18	15
600	1320	9.7	4.27	489	21	17
650	1430	10.3	4.53	515	22	18
700	1540	10.89	4.79	542	24	19
MAINTENANCE PLUS LAST 2 MONTHS OF GESTATION OF MATURE DRY COWS						
400	880	9.3	4.1	702	26	18
500	1100	11	4.84	821	31	22
600	1320	12.61	5.55	931	37	26
650	1430	13.39	5.9	984	39	28
700	1540	14.15	6.23	1035	42	30

Modified from National Research Council (NRC): *Nutrient requirements of dairy cattle*, Washington, DC, 2001, National Academy of Sciences, NRC.NE_L, Net energy of lactation.

Maintenance requirements can also be calculated by the following formula: Maintenance NE_L = 0.080 Mcal/kg $BW^{0.75}$

Table 9-13 Daily Nutrient Requirements for Lactating Dairy Cows at Various Production Levels

Daily Milk Production (3.5% Butterfat)						
(kg)	(lb)	NE_L (Mcal)	Total Digestible Nutrients (kg)	Crude Protein (kg)	Calcium (g)	Phosphorus (g)
400 KG OF BODY WEIGHT						
20	44	21	9.23	2	67	48
30	66	28	12.27	2.83	96	66
40	88	34.80	15.31	3.65	116	83
500 Kg Of Body Weight						
20	44	22.26	9.80	2.07	70	50
30	66	29	12.84	2.9	96	68
40	88	36	15.88	3.71	119	85
600 KG OF BODY WEIGHT						
20	44	23.5	10.35	2.2	73	52
30	66	30.4	13.39	2.95	99	70
40	88	37.3	16.43	3.77	125	87
700 KG OF BODY WEIGHT						
20	44	24.69	10.87	2.2	59	54
30	66	31.59	13.91	3	77	72
40	88	38.49	16.95	3.82	94	89

Modified from National Research Council (NRC): *Nutrient requirements of dairy cattle*, Washington, DC, 2001, National Academy of Sciences, NRC.NE_L, Net energy of lactation.

The energy requirement for milk production when only the butterfat content of the milk is known by the following formula:

NE_L (Mcal/kg milk) + 0.360 + (0.0969[fat%]).

9.2.5

Approach to the Diagnosis and Management of Weight Loss in Adult Ruminants

1 Take a general history and a diet history.

a General history

Question the caretaker closely about any clinical signs that might indicate a primary disease (e.g., diarrhea, coughing, dysphagia, polyuria, depression, agalactia). Note if body condition is less than desired. Quantitate the weight loss or BCS if possible. Acute weight loss of 5% to 10% is quite significant. Carefully note the production level of the animal or herd (e.g., pregnancy [single, twins, triplets], lactation [level of milk production]). Evaluate the parasite control program. Does the herd have a history of chronic or recurrent disease (Johne's disease, bovine virus diarrhea, ruminal lactic acidosis, laminitis, mastitis, pneumonia)?

b Diet history

Obtain an *accurate*, dietary history, particularly when signs of a primary disease are absent. Inspect all forages, concentrates, and feed additives for quality, signs of spoilage, abnormal color or odor, and quantity on hand. Be sure the feeding system allows for adequate consumption by all animals and that competition for feedstuffs does not occur. Check to see if the feeding program was changed before the onset of observed weight loss or loss of body condition. The history should include the *weight*, of each feedstuff and supplement fed and consumed per day. The maximum DMI can be estimated according to feed quality for cattle (see Table 9-1). Determine or estimate the nutrient analysis of the feedstuffs being fed. Examine the environment for possible toxic plants or substances.

2 Perform a physical examination.

Examine patients carefully for signs of concurrent disease (e.g., diarrhea, decreased ruminal motility, pyrexia, dysphagia, abnormal dentition, melena, icterus, mastitis, metritis, dyspnea, tachycardia). Is the patient hungry? Weigh the patient (or use a heart-girth measurement) and note the BCS (see Tables 9-18 through 9-20). Observe the patient for signs of muscle wasting and the presence or absence of subcutaneous fat. Test the milk with nitroprusside powder (a positive reaction indicates an acetoacetate concentrate above 5 mg/dL and is diagnostic of ketonlactia and ketonemia), or measure the ketone concentration in the urine. Measure the ruminal pH (pH above 7 is indicative of anorexia). Examine the skin for evidence of lice or keds.

3 Examine the feces.

Perform flotation, sedimentation, and Baermann's procedures to detect patent parasitic infestations. If the feces test positive for occult blood or are very dark, see the section on melena in Chapter 7. If there is evidence of or apparent diarrhea, see the section on diarrhea in Chapter 7.

4 Perform blood analysis.

a Perform a CBC, including plasma protein and fibrinogen. Interpret for evidence of inflammation. Calculate the erythrocytic indices, and characterize the anemia if present. Analyze for blood selenium concentration or glutathione peroxidase activity if a herd problem of weight loss exists in a selenium-deficient region.

b Perform a serum chemistry analysis. The serum albumin half-life is approximately 16½ days in cattle and 14 days in sheep and goats. Hypoalbuminemia is associated with internal abscessation, PCM, liver disease, renal disease, and Johne's disease, among other conditions. In the first two of these conditions, albumin is often normal until the patient is near death, whereas with protein-losing renal or gastrointestinal disease or with failure to make albumin in severe hepatic disease,

hypoalbuminemia is often seen by the time noticeable weight loss occurs. Globulins, particularly γ-globulins, may be increased with inflammation, and the albumin/globulin ratio may be decreased. The serum glucose concentration is usually not helpful in determining the cause or causes of weight loss. An elevated serum GGT (above 25 IU/L) may indicate hepatic disease or, in rare cases, pancreatic disease. Serum BUN is often low with PCM in ruminants because of salivary urea recycling. Serum (total) calcium may be decreased with hypoalbuminemia, anorexia, or hypocalcemic syndromes. Serum phosphorus may be increased during severe starvation or Johne's disease or decreased with anorexia. The serum (plasma) copper concentration may be decreased if a herd problem of copper deficiency exists. Weight loss is particularly associated with copper deficiency when diarrhea is present in a region known to be copper deficient or in a region with excess dietary molybdenum or sulfates or both. A low serum copper concentration (below 0.5 μg/mL or ppm) indicates deficiency. Ketonlactia (above 5 mg/dL), indicated by a positive reaction (blue or purple) of milk with nitroprusside, may be associated with anorexia in ketosis or other conditions. Plasma β-hydroxybutyrate (BHB) concentrations have been reported to be a useful tool in diagnosing *inadequate caloric intake*, in pregnant sheep.[14] Plasma BHB concentrations should be less than 0.8 mmol/L in pregnant ewes consuming adequate energy.[14]

5 Analyze the diet and improve the feeding program.

Is the feed quantity and quality adequate to allow sufficient intake of nutrients (see Table 9-1)? Compare the nutrient intake from the diet with the requirements for the appropriate species (Tables 9-12 through 9-17). Consider any important environmental and management factors in the daily nutrient requirements. Review nutrient analysis profiles on the feeds and total mixed ration (TMR) ingredients. Is the TMR mixed properly? Are grain rations mixed properly? Is too much grain being fed to the animal or herd? Analyze the pasture, forage, or concentrate rations (see Box 9-3). Make appropriate recommendations to optimize the ration. Determine if the patient or patients have a normal appetite. Is anorexia present? If the dietary history and analysis indicate that adequate nutrients have been steadily consumed, the search for a primary cause for the weight loss should be resumed.

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6 Perform ancillary diagnostic tests.

a If the weight loss is not related to the diet, additional diagnostic tests should be performed on the animal or on a number of animals in the herd. Possible tests include but are not limited to trace mineral analyses, ultrasound, and appropriate organ biopsy.

b Pathologic findings of affected ruminants often provide evidence of the effects of a systemic disease or of chronic malnutrition. Ruminants with PCM exhibit serous atrophy of fat in the coronary grooves of the heart and bone marrow at necropsy. Subcutaneous, abdominal, and perirenal fat are not present.

9.3 OBESITY

9.3.1 Mechanisms of Obesity

Obesity is a common problem in domestic species. The prevalence of obesity is increasing in the domestic horse population, and obesity is a significant problem in many ruminant species raised as companion animals. Obese patients (especially ruminants) are at particular risk for reproductive failure or metabolic disease late in pregnancy or during lactation. The risk of obstructive urolithiasis increases in overweight goats and sheep. In

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horses, obesity may be related to a variety of diseases including equine metabolic syndrome, laminitis, and colic associated with strangulating lipomas. Obese horses and ponies that are rapidly losing weight or that are anorexic are particularly susceptible to hyperlipidemia and hyperlipemia.

Table 9-14 Daily Nutrient Requirements for Mature Beef Cows

Reproductive Status	Daily Gain (kg)	Digestible Energy (Mcal/day)	Crude Protein (kg)	Calcium (g)	Phosphorus (g)
MATURE 500-KG (1100-LB) BEEF COW					
Nonpregnant, maintenance	0	18.9	0.63	17	17
Pregnant, third trimester	0.4*	22.4	0.73	25	20
Lactating, 20 lb milk per day	0	29	1.18	38	27
MATURE 600-KG (1320-LB) BEEF COW					
Nonpregnant, maintenance	0	21.6	0.69	20	20
Pregnant, third trimester	0.4*	25.1	0.83	28	23
Lactating, 20 lb milk per day	0	33	1.35	43	31

Modified from National Research Council (NRC): *Nutrient requirements of beef cattle, 7th revised edition*, Washington, DC, 1996, National Academy of Sciences, NRC.

* This gain represents only the growth of the fetus.

Table 9-15 Daily Nutrient Requirements for Bulls: Maintenance and Regaining Body Condition

Weight (kg)	Daily Gain (kg)	Daily Gain (lb)	Digestible Energy (Mcal/day)	Crude Protein (kg)	Calcium (g)	Phosphorus (g)
650	0.6	1.3	32.6	0.96	27	24
700	0.6	1.3	34.3	1	29	26
800	0*	0	27.7	0.88	27	27
800	0.2	0.4	31.2	0.96	27	27

Modified from National Research Council (NRC): *Nutrient requirements of beef cattle, 7th revised edition*, Washington, DC, 1996, National Academy of Sciences, NRC.

* Maintenance only, no gain.

Table 9-16 Daily Nutrient Requirements of Sheep

Body Weight		Weight Change/Day						
(kg)	(lb)	(g)	(lb)	Digestible Energy (Mcal)	Total Digestible Nutrients (kg)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
EWES, MAINTENANCE, MODERATE CONDITION								
60	132	10	0.02	2.7	0.61	104	2.3	2.1
80	176	10	0.02	3.2	0.72	122	2.7	2.8
90	198	10	0.02	3.4	0.78	131	2.9	3.1
EWES, FLUSHLING—2 WEEKS PREBREEDING AND FIRST 3 WEEKS OF BREEDING								
60	132	100	0.22	4.4	1	157	5.5	2.9
80	176	100	0.22	4.9	1.12	171	5.9	3.6
90	198	100	0.22	5.1	1.18	177	6.1	3.9
EWES, NONLACTATING, FIRST 15 WEEKS OF GESTATION								
60	132	30	0.07	3.2	0.72	121	3.2	2.5
80	176	30	0.07	3.6	0.82	139	3.8	3.3
90	198	30	0.07	3.8	0.87	148	4.1	3.6
EWES, LAST 4 WEEKS GESTATION (130%-150% LAMBING RATE EXPECTED) OR LAST 4–6 WEEKS LACTATION SUCKLING SINGLES								
60	132	180 (45)	0.4 (0.1)	4.4	1	184	6	5.2
80	176	180 (45)	0.4 (0.1)	4.9	1.12	202	6.3	6.1
90	198	180 (45)	0.4 (0.1)	5.1	1.18	212	6.4	6.5
EWES LAST 4 WEEKS OF GESTATION (180%-225% LAMBING RATE EXPECTED)								
60	132	225	0.5	5.1	1.17	205	6.9	4
80	176	225	0.5	5.7	1.3	223	8.3	5.1
90	198	225	0.5	6	1.37	232	8.9	5.7
EWES, FIRST 6–8 WEEKS LACTATION SUCKLING SINGLES OR LAST 4–6 WEEKS LACTATION SUCKLING TWINS								
60	132	−25	−0.06	6.6	1.5	319	9.1	6.6
80	176	−25	−0.06	7.4	1.69	344	9.5	7.4
90	198	−25	−0.06	7.6	1.75	353	9.6	7.8
EWES, FIRST 6–8 WEEKS LACTATION SUCKLING TWINS								
60	132	−60	−0.13	7.4	1.69	405	10.7	7.7
80	176	−60	−0.13	8.6	1.95	435	11.2	8.6
90	198	−60	−0.13	9.2	2.08	450	11.4	9

Replacement Ewe Lambs								
30	66	227	0.5	3.4	0.78	185	6.4	2.6
40	88	182	0.4	4	0.91	176	5.9	2.6
50	110	120	0.26	3.9	0.88	136	4.8	2.4
60	132	100	0.22	3.9	0.88	134	4.5	2.5
Replacement Ram Lambs								
40	88	330	0.73	5	1.1	243	7.8	3.7
60	132	320	0.7	6.7	1.5	263	8.4	4.2
80	176	290	0.64	7.8	1.8	268	8.5	4.6
100	220	250	0.55	8.4	1.9	264	8.2	4.8
Lambs Finishing—4–7 Months Old								
30	66	295	0.65	4.1	0.94	191	6.6	3.2
40	88	275	0.6	5.4	1.22	185	6.6	3.3
50	110	205	0.45	5.4	1.23	160	5.6	3
Early Weaned Lambs—Moderate Growth Potential								
10	22	200	0.44	1.8	0.4	127	4	1.9
20	44	250	0.55	3.5	0.8	167	5.4	2.5
30	66	300	0.66	4.4	1	191	6.7	3.2

Modified from National Research Council (NRC): *Nutrient requirements of sheep*, Washington, DC, 1985, National Academy of Sciences, NRC.

Table 9-17 Daily Nutrient Requirements of Goats

Body Weight		Digestible Energy (Mcal)	Total Digestible Nutrients (g)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
kg	lb					
MAINTENANCE, STABLE FEEDING CONDITIONS, MINIMAL ACTIVITY						
30	66	1.59	362	51	2	1.4
60	132	2.68	608	86	3	2.1
90	198	3.68	824	116	4	2.8
MAINTENANCE PLUS LATE PREGNANCY						
30	66	3.33	759	133	4	3.8
60	132	4.42	1005	168	5	3.5
90	198	5.37	1221	198	6	4.2
LACTATION, 4% FAT MILK AND 5-KG MILK PRODUCTION PER DAY						
30	66	9.24	2092	411	17	11.9
60	132	10.33	2338	446	18	12.6
90	198	11.28	2554	476	19	13.3

Modified from National Research Council (NRC): *Nutrient requirements of goats*, Washington, DC, 1981, National Academy of Sciences, NRC.

The mechanism of obesity is invariably a prolonged intake of total dietary energy above that needed for maintenance and either production or exercise. Obesity occurs most commonly in stabled horses fed high-energy feeds such as grain or high-fat supplemental feeds and in horses and ponies on lush pasture. Even horses that are fed a forage diet but have limited access to exercise may gain weight if they consume an excess amount of energy for their body size. Purebred or pet sheep and goats (particularly wethers) tend to be overfed. In dairy cattle, obesity occurs when cattle are fed well above requirements for maintenance and milk production. Poor reproductive performance is often associated with the initiation of obesity and is also a common sequela to obesity. Feeding for high milk production for lengthy periods in production groups predisposes infertile cows to become fat cows. Dry cows with access to high-energy diets are also predisposed to fat cow syndrome. The systemic complications associated with fat cow syndrome (fatty liver), and its diagnosis and treatment, are described in Chapter 33.

9.3.2 Diagnosis of Obesity in Horses and Ruminants

Diagnosis is obvious; it is made by physical examination. Overweight and obese animals have an elevated BCS (7 to 9/9 for horses; 8 to 9/9 for beef cattle; 4 to 5/5 for dairy cattle, sheep, and goats). Palpation of the back, gluteal area, and ribs should be included in the physical examination of sheep and camelids with long wool or fiber and of horses with a long winter hair coat so that a BCS can be accurately assigned. In some animals, external signs of fat deposition may be subtle. In these cases, ultrasonography can be used to identify the extent of deposition of intraabdominal fat in horses and of back fat in cattle. Clinical descriptions of obesity provided

by the body condition scoring system are straightforward (Tables 9-18 to 9-21) and require minimal interpretation.

In some animals, obesity can be mistaken for the normal physiologic condition of pregnancy. In other cases, obesity could be mistaken for a distended abdomen from acute pathologic disease conditions including uroabdomen and peritonitis. A full physical examination should always be performed on a large animal patient before a weight loss ration is fed.

Table 9-18 Body Conditioning Scoring System for Beef Cattle

Group	Score	Definition
	1	Emaciated (Body fat = 3.77%)
		Cow is extremely emaciated with no detectable fat over spinous processes, transverse processes, hipbones, or ribs. Tailhead and ribs project quite prominently.
	2	Poor (Body fat = 7.54%)
Thin condition		Cow still appears somewhat emaciated, but tailhead and ribs are less prominent. Individual spinous processes are still rather sharp to the touch, but some tissue exists along spine.
	3	Thin (Body fat = 11.3%)
		Ribs are still individually identifiable but not quite as sharp to the touch. There is obvious palpable fat along spine and over tailhead and some tissue cover over dorsal part of ribs.
	4	Borderline (Body fat = 15.07%)
Borderline condition		Individual ribs are no longer visually obvious. Spinous processes can be identified individually on palpation but feel rounded rather than sharp. There is some fat cover over ribs, transverse processes, and hipbones.
	5	Moderate (Body fat = 18.89%)
		Cow has generally good overall appearance. On palpation, fat cover over ribs feels spongy, and areas on either side of tailhead now have palpable fat cover.
	6	High moderate (Body fat = 22.61%)
Optimum moderate condition		Firm pressure must be applied to feel spinous processes. High degree of fat cover is palpable over ribs and around tailhead.
	7	Good (Body fat = 26.38%)
		Cow appears fleshy and obviously carries considerable fat. There is a very spongy fat cover over ribs and over and around tailhead. “Rounds” or “pones” of fat are beginning to be obvious. There is some fat around vulva and in crotch.

	8	Fat (Body fat = 30.15%) Cow is very fleshy and overconditioned. Spinous processes are almost impossible to palpate. There are large fat deposits over ribs, around tailhead, and below vulva. “Rounds” or “pones” of fat are obvious.
Fat condition	9	Extremely fat (Body fat = 33.91%) Cow is obviously extremely wasty and patchy and looks blocky. Tailhead and hips are burled in fatty tissue, and “rounds” or “pones” of fat protrude. Bone structure is no longer visible and barely palpable. Animal's mobility may even be impaired by large fatty deposits.

From Spitzer JC: Influences of nutrition on reproduction in beef cattle. In Morrow DA, ed: *Current therapy in theriogenology*, Philadelphia, 1986, Saunders; and modified from National Research Council (NRC): *Nutrient requirements of beef cattle, 7th revised edition*, Washington, DC, 1996, National Academy of Sciences, NRC.

Table 9-19 Body Conditioning Scoring System for Dairy Cattle

Score	Description
1	Individual spinous processes have limited flesh covering and are prominent; the ends are sharp to the touch, and together the processes form a definite overhanging shelf effect to the loin region. Individual vertebrae of the chine, loin, and rump regions are prominent and distinct. Hooks and pin bones are sharp with negligible flesh covering, and severe depressions between hooks and pin bones are noted. The area below the tailhead and between the pin bones is severely depressed, causing the bone structure of the area to appear extremely sharp. (Body fat = 3.77%)
2	Individual spinous processes are visually discernible but not prominent. The ends of processes are sharp to the touch, although they have greater flesh covering, and the processes do not have a distinct overhanging shelf effect. Individual vertebrae of chine, loin, and rump regions are not visually distinct but are readily distinguishable by palpation. Hooks and pin bones are prominent, but the depression between them is less severe. The area below the tailhead and between the pin bones is depressed, but the bone structure is not devoid of flesh covering. (Body fat = 11.3%)
3	Spinous processes are discernible by applying slight pressure. Together the processes appear smooth, and the overhanging shelf effect is not noticeable. Vertebrae of the chine, loin, and rump regions appear as rounded ridges, and hooks and pin bones are rounded and smooth. The area between the pin bones and around the tailhead appears smooth, with no sign of fat deposition. (Body fat = 18.84%)
4	Individual spinous processes can be distinguished only by firm palpation, and together the processes appear flat or rounded with no overhanging shelf effect. The ridge formed by the vertebral column of the chine region is rounded and smooth, but loin and rump regions appear flat. Hooks are rounded, and the span between the hooks is flat. The area around the tailhead and pin bones is rounded, with evidence of subcutaneous fat deposition. (Body fat = 26.38%)
5	Bone structure of the vertebral column, spinous processes, hooks, and pin bones is not visually apparent, and evidence of subcutaneous fat deposition is prominent. The tailhead appears to be buried in fatty tissue. (Body fat = 33.9%)

From Wildman EE et al: *J Dairy Sci*, 65:495–501, 1982; and modified from National Research Council (NRC): *Nutrient requirements of dairy cattle*, Washington, DC, 2001, National Academy of Sciences, NRC.

Table 9-20 Body Condition Scoring System for Sheep

Score	Description
0	Animal is extremely emaciated and at the point of death. No muscular or fatty tissue can be detected between the skin and the bone.
1	The spinous processes are prominent and sharp. The transverse processes are also sharp; the fingers pass easily under the ends, and it is possible to feel between each process. The eye muscle areas are shallow with no fat cover.
2	The spinous processes still feel prominent but also smooth, and individual processes can be felt only as fine corrugations. The transverse processes are smooth and rounded, and the fingers can be passed under the ends with a little pressure. The eye muscle areas are of moderate depth but have little fat cover.
3	The spinous processes are detected only as small elevations; they are smooth and rounded, and individual bones can be felt only with pressure. The transverse processes are smooth and well covered, and firm pressure is required to feel over the ends. The eye muscle areas are full and have a moderate degree of fat cover.
4	With pressure the spinous processes can just be detected as a hard line between the fat-covered muscle areas. The ends of the transverse processes cannot be felt. The eye muscle areas are full and have a thick covering of fat.
5	The spinous processes cannot be detected even with firm pressure, and there is a depression between the layers of fat where the spinous processes would normally be felt. The transverse processes cannot be detected. The eye muscle areas are very full and have a very thick fat cover. Large deposits of fat may be seen over the rump and tail.

From Russel A: Body condition scoring of sheep, *In Pract*, 6:91, 1984.

9.3.3 Treatment of Obesity

Overweight and obese horses and ruminants should lose weight to extend life span and to improve production efficiency. In many cases a reduction in energy intake can be achieved by simply eliminating excess calories from grain or supplemental feeds. Animals that fail to lose weight after 1 to 2 months after a reduction in calories require a more aggressive weight loss program, which may include reformulation of their ration and the gradual implementation of an exercise program. Voluntary activity in animals that are turned out in pasture is rarely high enough to promote weight loss. Obese laminitic horses present a difficult challenge because exercise may not be practical, and weight loss must rely solely on dietary energy restriction.

Horses and companion ruminants that require a managed weight loss program should have the energy content of their diet evaluated by the veterinarian. The actual energy intake should be compared against the energy requirement for the animal's current lifestage (see Tables 9-11 to 9-17). The animal's current calorie intake should be reduced by 10% to 20% at the start of the weight loss program. Dietary protein should not be restricted. Supplemental feeds and treats should be reduced or eliminated from the diet, and only high-quality forage should be fed.

Feeding straw should be avoided because gastrointestinal complications including impaction colic could develop. A vitamin and mineral supplement should be fed during a weight loss program to ensure that the diet

meets nutrient requirements. To prevent boredom, small amounts of forage should be fed frequently. When horses are being fed, hay can be placed in a double hay net or hay bag, or a restricted feeder (The Grazer Hay Feeding Machine) can be used to decrease the rate of intake. The target weight loss goal is between 0.5% and 2% of the original body weight each week. A weight tape should be used to assess the horse's weight if a scale is not available. A BCS should be assigned to the animal at the start of the weight loss program. The body weight and BCS should be assessed every month to track changes in the animal's weight.

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Table 9-21 Body Condition Scoring System for Horses

Score	Description
1	Poor. Animal is extremely emaciated. Spinous processes, ribs, tailhead, tuber coxae, and tuber ischii project prominently. Bone structure of the withers, shoulders, and neck is noticeable. No fatty tissue can be felt.
2	Very thin. Animal is emaciated. There is a slight fat covering over the base of the spinous processes; the transverse processes of the lumbar vertebrae feel rounded. Spinous processes, ribs, tailhead, tuber coxae, and tuber ischii are prominent. Bone structure of the withers, shoulders, and neck is faintly discernible.
3	Thin. Fat buildup is present about halfway on the spinous processes; the transverse processes cannot be felt. There is a slight fat cover over the ribs. Spinous processes and ribs are easily discernible. Tailhead is prominent, but individual vertebrae cannot be visually identified. Tuber coxae appear rounded but are easily discernible; tuber ischii are not distinguishable. Bone structure of the withers, shoulders, and neck is accentuated.
4	Moderately thin. Negative crease can be seen along the back. Faint outline of ribs is discernible. Tailhead prominence depends on conformation; fat can be felt around tailhead. Tuber coxae are not discernible. Withers, shoulders, and neck are not obviously thin.
5	Moderate. Back is level. Ribs cannot be visually distinguished but can be felt easily. Fat around tailhead is somewhat spongy. Withers appear rounded over spinous processes, and shoulders and neck blend smoothly into the body.
6	Moderately fleshy. Slight crease may be seen down the back. Fat over ribs is spongy, and fat around tailhead is soft. Fat is beginning to be deposited along withers, behind shoulders, and along neck.
7	Fleshy. Crease may be seen down the back. Individual ribs can be felt, but there is noticeable filling of fat between ribs. Fat around tailhead is soft. Fat is deposited along withers, behind shoulders, and along neck.
8	Fat. Crease is seen down the back. Ribs are difficult to feel. Fat around tailhead is very soft. Areas along withers and behind shoulders are filled with fat, and neck is noticeably thickened. Fat is deposited along inner thighs.
9	Extremely fat. Obvious crease is seen down the back. Patchy fat appears over ribs. Bulging fat is seen around tailhead along withers, behind shoulders, and along neck. Fat along inner thighs may cause thighs to rub together. Flank is filled with fat.

From Henneke GD, Potter GD, Kreider JL, Yeates BF: Relationship between condition score, physical measurements and body fat percentage in mares, *Equine Vet J*, 15:371, 1983.

Owner compliance is essential during a weight loss program for horses and companion large animals. Owners should be encouraged to keep a weight loss journal and to include digital pictures to assess the animal's BCS during the program. Excessive, rapid weight loss should be avoided. Weight loss programs should be approached with caution in animals that are either pregnant or lactating. Once the animal has achieved the ideal body weight and BCS, it should be placed on a maintenance ration and exercise program that will ensure that the ideal weight is maintained.

In a production management setting the ration should be evaluated and revised to reduce calories while maintaining sufficient energy intake to maximize reproduction or milk production. Care should be taken to ensure the animals consume an adequate concentration of vitamins and minerals to meet their requirements when they are fed an energy-restricted ration.

9.4 PICA

Pica (geophagia) is defined as a depraved or abnormal appetite. It is usually associated with animals that chew or eat wood (fences, trees, buildings), dirt, bones, or other inanimate objects not usually considered feedstuffs. The mechanism or mechanisms of pica are not yet understood. Pica has been associated with PCM, parasitism, obesity, and deficiencies of phosphorus, salt, protein (kwashiorkor), and micronutrients. Diagnosis is by observation or history or both. The main emphasis must be placed on identification and resolution of the primary problem. Pica must be differentiated from abnormal behavior associated with central nervous system diseases, bovine ketosis, and equine behavioral abnormalities associated with boredom.

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10 Chapter 10 Alterations in Urinary Function

Consulting Editors

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10.1 DYSURIA AND STRANGURIA

Dysuria is defined as difficult or painful urination. *Stranguria* is defined as straining to urinate, with the normal rate and flow of voiding being decreased and the effort required to void often increased. These two clinical signs are often present simultaneously in large animals with lower urinary tract disease, and because these signs are often difficult to distinguish from each other, they are considered together in this section. The most common causes of dysuria and stranguria are urethral obstruction, inflammation of the urethra and/or the bladder, and neurologic conditions that prevent normal emptying of the bladder. Adhesions between the bladder and other structures in the abdominal or pelvic cavities can create mechanical interference with bladder emptying, resulting in dysuria and stranguria.

Urinary incontinence is defined as the involuntary voiding of urine. It is most frequently indicative of impaired neuromuscular control of urination. Evaluation of neurologic control of urination is discussed later in this section. Incontinence may also occur with severe cases of lower urinary tract trauma and inflammation. In young animals, congenital abnormalities such as ectopic ureter must be considered in the differential diagnosis for incontinence.

The horse voids urine very actively and forcefully. Both male and female adult horses may briefly groan and strain slightly during normal urination. This should not be misinterpreted as dysuria or stranguria. In other large animal species, urination is more passive, and straining or groaning normally is not observed. Conditions in which a horse may appear to have dysuria include lower urinary tract disease, abdominal pain, peritonitis, pleuritis, severe musculoskeletal disease, or neurologic disease. With any of these conditions, the horse may attempt to posture and urinate but may not be able to increase intraabdominal pressure sufficiently to allow complete voiding.

Signs of dysuria and stranguria include treading, repetitive switching or flagging of the tail, pollakiuria (frequent voiding of small amounts of urine), constant urine dripping, flatulence during voiding, and retention of the urination posture for several seconds after voiding has ceased. Urine scalding of the perineal region or rear legs may be noted in either ruminants or horses with dysuria or stranguria. Vocalization during urination may accompany dysuria, particularly in goats. While straining to void, the affected animal may show forceful contractions of the abdominal musculature. Male horses and ruminants that are experiencing dysuria or stranguria typically stand with the back slightly extended (mild lordosis), with the front legs held further ahead of the body and the hind feet positioned farther behind the body than normal (Fig. 10-1).

Dysuria or stranguria in large animal species may be confused with tenesmus. This is most frequently a dilemma in neonatal foals with a ruptured bladder or meconium impaction. However, with tenesmus the rear feet of the foal are positioned slightly more anteriorly than with stranguria or dysuria. Stranguria may be severe enough in some cases to induce secondary rectal prolapse; therefore, when examining an animal with rectal prolapse, the clinician must establish whether or not the underlying cause might be urinary tract disease.

10.1.1 Approach to Diagnosis of Dysuria and Stranguria

As for other medical problems, the signalment, onset of signs, duration, progression, and response to treatment should be established. Certain signalment and historical data can lend important clues for evaluation of specific causes. For example, urethral calculi should be suspected immediately in castrated ruminants on high-grain diets. A history of one or more horses showing clinical signs of spinal cord disease, respiratory disease, stranguria, or urinary incontinence should immediately lead the practitioner to consider equine herpesvirus-1 myelitis in the differential. A history of dysuria or stranguria that develops after parturition usually indicates an injury to the lower urinary tract. Parturient damage to the normal structure of the vagina and vestibule can increase the animal's risk of subsequent urinary tract infection. A full physical examination should be performed because abnormal urination may be a sign of disease in other body systems, such as those characterized by diffuse muscular weakness. Common causes of dysuria, stranguria, and urinary incontinence are shown in Box 10-1.

10.1.1.1 URINATION (MICTURITION)

When possible the animal should be observed urinating, and a sample of urine should be collected for dipstick urinalysis, measurement of specific gravity, and, when indicated, sediment examination. Urination can be induced in female cattle by gently rubbing the perineum immediately ventral to the vulva (Fig. 10-2). In male cattle, the examiner may induce urination by placing a finger into the preputial cavity and gently rubbing the preputial mucosa. In ewes, urination can be prompted by holding off the nose until the ewe struggles; urination typically occurs at this point. Obviously, this procedure should not be performed on ewes in shock or those with poor cardiac or respiratory function. In horses, goats, and male sheep, the examiner simply has to wait until the animal is ready to void, although urination may be prompted by placing the animal in a freshly bedded stall. Recumbent animals will often void soon after standing.

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Fig. 10-1 Stranguria in an Angus steer with urethral obstruction caused by a urolith.

10.1.1.1.1

Box 10-1 Causes of Dysuria, Stranguria, and Urinary Incontinence in Horses and Ruminants

Urinary calculi

Penile, vaginal, urethral, or preputial trauma

Smegma accumulation (E)

Penile masses or encircling hair rings

Habronemiasis (E)

Ulcerative posthitis and vulvovaginitis (R)

Adhesions of the bladder

Urachal infection or abscesses

Rectovaginal fistula

Hemorrhage into the urinary tract

Ruptured urethra, bladder, or ureter

Viral infections of the genitalia

Vaginal prolapse

Impending parturition

Prolapsed bladder (postpartum)

Urinary tract infection

Urinary calculi

Bladder neoplasia
Estrogen-responsive dysuria (E)
Ectopic ureter
Equine neonatal maladjustment (E)
Cantharidin (blister beetle) toxicosis (E)
Prolonged recumbency
Equine herpesvirus-1 myelitis (E)
Sorghum cystitis (E)
Rabies
Epidural lymphosarcoma
Other forms of severe spinal cord disease
Pelvic or sacral fracture
Laminitis
Myopathy
Painful conditions of the abdomen or abdominal wall
Painful conditions of the thorax or thoracic wall

E, Found only in horses; *R*, found only in ruminants.

Fig. 10-2 Inducing urination in a Jersey cow.

* A detailed discussion of interpretation of urinalysis is covered in Chapter 22.

10.1.1.2

EXAMINATION OF THE GENITALIA

The male's preputial hairs and the female's perineal region should be closely inspected for the presence of blood, exudate, or crystalline debris. The urethral orifice can be visualized in many males, but mild sedation and/or epidural anesthesia may be necessary to induce sufficient relaxation of the retractor penis muscles. In bulls and steers, transrectal massage of the pelvic segment of the urethra may stimulate penile relaxation to enable penile visualization. In prepubescent ruminants, the frenulum often prevents complete exteriorization of the penis for examination of the urethral orifice; general anesthesia may be needed to induce sufficient relaxation. The glans penis and urethral orifice should be carefully examined for masses such as papillomas, evidence of trauma, encircling hair rings and embedded foreign bodies (e.g., grass awns), and lesions of the urethral mucosa. An attempt should be made to exteriorize the penis and examine the urethral process in male small ruminants, as urinary calculi often become enlodged at this site (Chapter 34).

If swelling or pain is found on palpation of the most distal part of the equine penis, it may be necessary to tranquilize the horse so that this area can be examined more closely for signs of habronemiasis, neoplasia, or traumatic injury. An accumulation of smegma, composed of mucus and cellular debris, may cause preputial swelling and dysuria in adult male horses. Smegma usually can be found as a hard, waxy mass in the urethral diverticulum. Preputial swelling without pain or discharge may be seen in equine Cushing's syndrome (Chapter 41).[1]

In the male the penis and the urethra should be palpated percutaneously from the perineum to the sheath. Swelling, pain, abnormal urethral pulsations, and calculi enlodged in the urethra may be detected. Marked swelling along the ventral body wall in a bull or steer with active or recent dysuria or stranguria strongly suggests a urethral rupture. Urethral calculi are most commonly lodged just below the anus in male horses, and these can occasionally be palpated on the midline of the perineum.

The vulva, caudal vagina, and urethral orifice should be visualized and palpated in dysuric or stranguric females. Sacrocaudal epidural anesthesia may facilitate examination if painful lesions are present. In females of breeding age the cervix should be visualized or palpated and the uterus evaluated by palpation or ultrasonography, as the pollakiuria and apparent dysuria that may occur at the onset of parturition may be the primary complaint of a novice or uninformed observer. Previous dystocia can result in sufficient soft tissue trauma, laceration, swelling, and pelvic neuropraxia to induce dysuria or stranguria. The ventrum of the tail, perineum, udder, and hindlimbs should be examined for adhered blood or exudate from the female's reproductive or urinary tract. 171 172

10.1.1.3

RECTAL EXAMINATION

In adult horses and cattle, rectal palpation should be performed when dysuria and stranguria are present. Before examination the clinician should take careful note of the tail and anal tone of the animal; reduction of either or both may indicate underlying neurologic or muscular disease. At the onset the examiner must take care not to place his or her hand and wrist too far forward in the rectum because abnormalities of the trigone and pelvic segment of the urethra may be missed, as may calculi lodged at the junction of the pelvic and perineal segment of the urethra. The caudal extent of the pelvic cavity should be carefully evaluated for masses that might mechanically interfere with voiding. The bladder is typically located on the midline at the level of the pubic brim. Its presence in the caudal pelvic cavity, particularly in the standing animal, may suggest pelvic entrapment of the bladder.

Bladder distension is commonly found in persistently recumbent horses and cattle, and the bladder is often positioned further caudally than in standing animals. In the horse, bladder distention may also be found with abdominal or thoracic pain. Apparently, the abdominal pressure necessary to empty the bladder incites sufficient pain of diseased structures to cause reluctance to void. Musculoskeletal and neurologic disease may also result in bladder distension. These other possibilities should be investigated when bladder distension is detected, yet no primary disease is found in the urinary tract.

A careful rectal examination of the bladder and the proximal urethra of the horse might allow identification of urethral or cystic calculi. Most cystic calculi in the horse are singular and located in the trigone of the bladder and are best palpated with only the hand and wrist in the rectum. If there is a large amount of urine in the bladder, the stone may not be palpable; transrectal ultrasound examination may enable visualization of the stone. Sabulous calculi may be found in horses with stranguria or urinary incontinence, and on rectal examination the clinician may interpret the palpation findings as a bladder tumor or large stone.[2] If a urinary calculus is detected in the horse, an ultrasound examination of the entire urinary tract should be performed, because some horses with cystic calculi may have other stones in one or both kidneys.

10.1.1.4

NEUROLOGIC EXAMINATION

If bladder dysfunction is not caused by structural abnormalities, trauma, or infectious disease, a thorough neurologic examination should be conducted. If neurologic dysfunction is suspected, an attempt should be

made to determine whether the primary lesion is affecting the detrusor muscle or the urethral sphincter muscles of the bladder. This determination is often helpful in localizing the lesion and is important when selecting treatment.

When bladder paralysis is caused by upper motor neuron (UMN) dysfunction, signs of UMN dysfunction may be evident in the rear limbs. The animal frequently postures and strains to urinate but voids only a small amount of urine, because the striated urethral muscles are disinhibited from higher centers and their resultant increased tone impedes urine outflow from the bladder. Frequent, small-volume urine egress from the distended bladder occurs when the animal responds to the urge to void, or when the bladder undergoes reflex contraction.

With severe disease of the sacral spinal cord or sacral nerve plexus, lower motor neuron (LMN) input to the detrusor muscle is impaired or absent. Urinary incontinence is often the predominant clinical sign (e.g., cauda equina neuritis in horses or lymphoma in cattle). The bladder usually is moderately to severely distended, and urine can be expressed easily if pressure is applied to the bladder during rectal examination. With LMN dysfunction urine may also be voided as the animal walks. Voluntary or involuntary voiding is often incomplete, leading to retention of urine in the bladder. This, in turn, increases the patient's risk of urinary tract infection and, in horses, sabulous calculi accumulation in the bladder. Other neurologic signs involving the sacral and coccygeal nerves may be apparent, such as decreased tail and anal tone and atrophy of the gluteal or tailhead musculature. Ataxia of the rear limbs may or may not be present with an LMN bladder. Urethral and bladder pressure profiles can be determined to better assess the location of the lesion.[3–5]

10.1.1.5

URINALYSIS AND URINE CULTURE

If dysuria, incontinence, or stranguria are believed to be caused by an inflammatory disease of the urethra or bladder, the absence or presence of infection should be determined (see section on pyuria).

10.1.1.5.1

Small Ruminants and Neonates

Ultrasonography and transabdominal palpation are useful for evaluation of the urinary tract. In these animals a distended bladder usually can be palpated by simultaneously placing one hand on each side of the caudal ventral abdomen at the level of the pelvic brim and pressing the fingers of each hand toward the abdominal midline. If the bladder has been ruptured, it will be difficult to identify by palpation but ascites can be detected. Digital rectal examination of the pelvic segment of the urethra can be performed in neonatal cattle and horses and in small ruminants. The umbilicus should be carefully palpated in neonates with dysuria or stranguria because urachal abscesses and adhesions to the bladder may impair voiding. An infected urachus will occasionally communicate with the bladder lumen, creating concurrent septic cystitis.

Ectopic ureter(s) should be considered in young animals with persistent urinary incontinence; stranguria and dysuria are less common primary complaints. In affected females, vaginal urine pooling is often present. Vaginoscopic or cystoscopic examination can be performed, but the opening of the ectopic ureter can be difficult to locate during routine examination. Intravenous, positive-contrast pyelography may be required to locate the ectopic structure(s). As for all congenital defects, a careful assessment for defects in other organs should be performed.

10.2 HEMATURIA AND PIGMENTURIA

Hematuria is defined as blood in the urine. It may appear as occult blood detected during urinalysis, as uniformly red-colored urine throughout urination, or as blood clots passed at any phase of urination. If large clots are present, obstruction of the urinary tract may occur, resulting in concurrent stranguria and dysuria. *Pigmenturia* is defined as the presence of abnormal pigment in the urine; in large animals such pigments are usually limited to hemoglobin or myoglobin. Hemoglobin, myoglobin, and blood all cause a positive reaction for blood and protein on a urine dipstick test. Certain oxidizing disinfectants can also trigger a positive reaction for blood on these strips.

Hematuria can be easily distinguished from hemoglobinuria and myoglobinuria if clots of blood are present in the urine. Also, when scattered spots of color change are evident on the blood reagent pad of the urine dipstick, the reaction pattern reflects the presence of small aggregates of red cells having been deposited on the pad. Otherwise, differentiation requires that the discolored urine be centrifuged and the sediment examined. Again, prompt examination of urine sediment after collection is required, as intact red cells in urine may lyse during storage. Hematuria is characterized by red, pink, or brown-colored urine that clears partially or entirely after centrifugation, resulting in a pigmented pellet of sediment. Red cells or red cell “ghosts” are visible in the sediment of animals with hematuria.

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Urine containing hemoglobin is clear to dark red in color, depending on the concentration of hemoglobin in the sample. If visibly discolored, the urine does not clear when centrifuged. Sediment findings vary according to the underlying disease, and hyaline or cellular casts may be seen if pigment nephropathy is present. Animals with hemoglobinuria are often experiencing intravascular hemolysis, which leads to passage of hemoglobin from the plasma into the tubular fluid of the nephrons. The serum or plasma of these animals may be pink in color. Mucous membrane pallor or icterus may be evident, and tachycardia and tachypnea are present when red cell destruction is rapid and extensive. The packed cell volume may be decreased at the time of initial examination, or it may decrease progressively over 12 to 24 hours of monitoring. Release of hemoglobin from red blood cells may result in elevation of the plasma and serum total protein concentration. The clinician should note that hemoglobin is potentially nephrotoxic, and renal function and hydration should be carefully evaluated and monitored in such cases.

Urine containing myoglobin is clear to dark red or brown in color, depending on the concentration of myoglobin in the sample (Fig. 10-3). If visibly discolored, urine containing myoglobin does not clear when centrifuged. Sediment findings are variable but can include hyaline or cellular casts if pigment nephropathy is present. Myoglobin can be differentiated from hemoglobin in urine through ammonium sulfate precipitation, electrophoresis, or spectroscopy. Animals with myoglobinuria have muscle necrosis or injury, which leads to release of myoglobin from damaged muscle cells into the plasma. Myoglobin then passes from the plasma into the tubular fluid. Extensive muscle trauma (e.g., dog attacks, trailer accidents) or primary diseases of muscles can induce myoglobinuria. Affected animals may show abnormal stance or gait or other evidence of muscle swelling, pain, or weakness. The serum activity of the enzymes creatine phosphokinase (CPK), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) is variably increased, depending on the duration and severity of muscle injury. As for hemoglobinuria, the presence of myoglobinuria should alert the clinician to assess and monitor renal function and hydration, as the persistence of myoglobin in the tubular fluid of the nephrons can induce tubular necrosis.

Fig. 10-3 Normal equine urine *(left)* and urine with severe myoglobinuria *(right)*. Urine containing myoglobin is not always so markedly discolored. *Photo courtesy of Paul S. Morley, DVM, PhD, DACVIM.*

10.2.1

Approach to Diagnosis of Hematuria and Pigmenturia

The history should include data on recent infectious diseases, exercise, diet, and treatment. Hematuria after exercise may indicate the presence of erosions in the urinary tract mucosa, anomalous vascular structures, or mucosal trauma from uroliths (Fig. 10-4). Ingestion of certain toxins (e.g., cantharidin, bracken fern) can create hematuria; hemoglobinuria can result from exposure to hemolytic toxins, such as red maple leaves, copper, onions, and certain bacterial toxins. Intravenous infusion of markedly hypotonic or hypertonic fluids, such as water and undiluted dimethyl sulfoxide (DMSO) solution, respectively, can result in intravenous hemolysis and hemoglobinuria. The potential for exposure to gossypol and ionophores should be investigated as a cause of myoglobinuria. Certain viral and bacterial infections, such as streptococcal infections in horses, can induce myopathy and myoglobinuria. A recent history of heavy exertion or abnormally high ambient temperature (heat stroke) may exist in cases of myopathy with myoglobinuria. A previous history of recurrent exercise intolerance or muscle dysfunction may be evident in certain inherited, idiopathic, or diet-associated cases of rhabdomyolysis. Prolonged recumbency, as occurs under general anesthesia, can induce sufficient pressure myopathy to cause myoglobinuria. Rarely, idiosyncratic responses to medications can induce hemolysis or muscle injury, resulting in hemoglobinuria and myoglobinuria, respectively.

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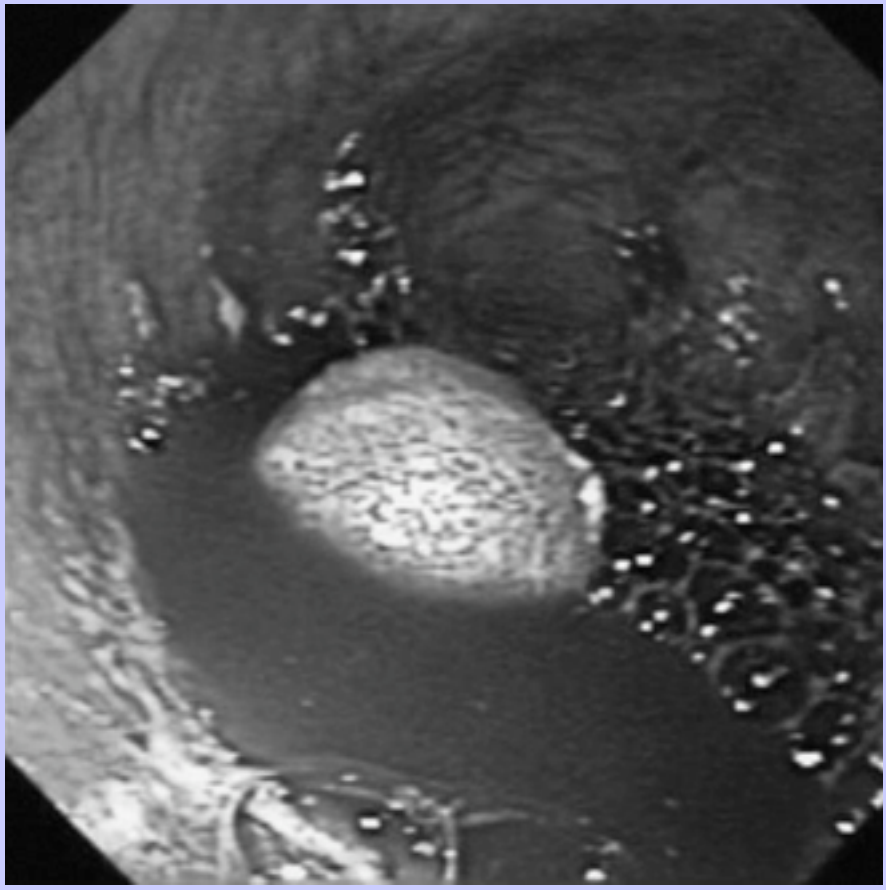
Fig. 10-4 Endoscopic view of a calculus in the lumen of a horse's bladder. Note the presence of hematuria. *Photo courtesy of Carl Soffler, DVM.*



A full physical examination should be conducted. The patient with potential hematuria should be carefully examined for clinical signs suggestive of impaired coagulation. A positive blood reaction on urine dipstick analysis can occur with true hematuria, hemoglobinuria, myoglobinuria, or contamination of the urine with reproductive or fecal blood. Severe vulvitis often develops in female horses and ruminants with profuse diarrhea as a result of chronic contact of the vulvar mucosa with fecal contents. A trace reaction for blood is often evident in the urine of these animals; however, the possibility of hemorrhage from tubular injury caused by hypovolemia should be considered as well. Common causes of hematuria and pigmenturia are listed in Box 10-2.

Lesions of the urethra most often produce hematuria at the beginning of urination, although in a male horse with proximal urethral disease, this hemorrhage may be seen only at the end of urination.[6,7] These geldings and stallions often show hematuria associated with a vascular fistula or cavernosal rupture in the most proximal urethra.[6,7] Hematuria that originates from the bladder is most likely to be seen or appear more pronounced at the end of urination. Hemorrhage originating from the upper urinary tract would likely be more pronounced at the end of urination, but voluminous or continuous hemorrhage in the upper tract might result in hematuria seen throughout urination. If the urine discoloration appears uniform throughout urination and no clots are obvious, the veterinarian must first determine that the discoloration is hematuria and not hemoglobinuria, bilirubinuria, or myoglobinuria. This can be accomplished by routine dipstick urinalysis; urine sediment examination; assessment of the patient's packed cell volume, plasma protein concentration, and serum muscle enzyme activities; and visualization of the color of the plasma and mucous membranes.

Hematuria often accompanies pyuria and bacteriuria in urinary tract infection. If hematuria is confirmed and urinary tract infection or trauma is not the cause, rectal examination may reveal calculi or tumors in the proximal urethra or bladder. Introduction of the hand and wrist into the rectum is usually sufficient for careful palpation of the pelvic segment of the urethra and bladder trigone. Examination of the urethral orifice, along with endoscopic examination of the urethra and bladder, is necessary if the lesion cannot be detected during rectal or physical examination.

During endoscopic examination of the urethra and bladder, if the source of hemorrhage is not apparent, the openings of the ureters and the color of the urine coming from both of them should be visualized. This is best performed after suctioning urine from the bladder and then distending the bladder with air, taking care that bubbling of the urine does not occur. The ureteral opening can be seen dorsally as the scope is first introduced into the bladder. The two openings can be visualized simultaneously by passing the scope farther into the bladder and retroflexing the scope caudally until the entire trigone area is visualized. If hemorrhage is seen to originate from one or both ureteral openings, the next diagnostic step is ultrasound examination the kidneys and ureters, as the hemorrhage has now been localized to the upper urinary tract.

10.3 PYURIA

Pyuria is defined as gross or microscopic purulent exudate in the urine. Dysuria, stranguria, pollakiuria, crystalluria, urine scalding of the perineum, or hematuria may accompany the pyuria. Pyuria may result from septic or nonseptic inflammatory disease. Causes of pyuria are listed in Box 10-3. Normal equine urine is turbid owing to the presence of mucus and calcium-based crystals.

10.3.1

Box 10-2 Causes of Hematuria and Pigmenturia in Horses and Ruminants

10.3.1.1

HEMATURIA

Habronemiasis (E)

Urinary calculi

Vascular anomaly, corpus cavernosum rupture (proximal dorsal urethral hemorrhage in males) (E)

Penile, vaginal, preputial, or urethral trauma

Penile masses, encircling hair rings

Neoplasia

Bleeding diatheses (e.g., warfarin, disseminated intravascular coagulation [DIC])

Cantharidin (blister beetle) poisoning (E)

Enzootic hematuria (R)

Urinary tract infection

Leptospirosis

Nephritis

Aberrant parasite migration within the urinary tract

Exercise-induced hematuria (E)

Renal papillary necrosis (e.g., related to nonsteroidal antiinflammatory drugs [NSAIDs])

Contamination of urine with oxidant disinfectants

Hemorrhage from the reproductive tract in females

Admixture of fecal blood with urine

10.3.1.2 HEMOGLOBINURIA

Intravascular hemolysis:

Intravenous (IV) hypotonic fluid administration

IV hypertonic fluid administration (e.g., dimethyl sulfoxide [DMSO])

Excess water intake, water intoxication

Red maple intoxication (E)

Clostridium hemolyticum infection (redwater)

Onion and *Brassica* species (rape, kale, etc.) intoxication

Leptospirosis

Hepatic failure

Neonatal isoerythrolysis

Copper intoxication

10.3.1.3 MYOGLOBINURIA

Exertional, capture rhabdomyolysis

Toxic myopathies (e.g., *Cassia* species, ionophores, gossypol)

Myopathy associated with streptococcal infections (E)

Clostridial myonecrosis

Viral myopathies (influenza, equine herpesvirus [EHV], bluetongue)

Nutritional myodegeneration

Postanesthetic myoneuropathy

Hereditary, congenital myopathies

E, Found only in horses; *R*, found only in ruminants.

10.3.2

Approach to Diagnosis of Pyuria

The history should be taken, and a complete examination of the entire urinary tract should be performed, including rectal palpation or transabdominal palpation of the bladder. Although cystitis may be characterized by a thickened bladder wall, this is often difficult to detect, and ultrasonographic examination may be necessary to accurately detect this lesion. In males the accessory sex glands should be carefully examined, as exudate from these structures may be admixed with urine. Predisposing factors, such as urinary calculi, dystocia, abnormal urethral or genital structure, and neurologic diseases should always be considered.

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10.3.2.1

Box 10-3 Causes of Pyuria in Horses and Ruminants

Penile, vaginal, urethral, or preputial trauma

Penile masses or encircling hair rings

Ulcerative posthitis and vulvovaginitis (small ruminants)

Viral infections of the genitalia

Rectovaginal fistula

Urinary calculi

Urinary tract infection (urethritis, cystitis, ureteritis, and/or pyelonephritis)

Exudation from the reproductive tract in females

Exudation from accessory sex glands in males

Nephritis

Leptospirosis
Urinary tract neoplasia
Admixture of exudate from the female reproductive tract

Pyuria is confirmed by obtaining a midstream or catheterized urine sample (or both) and quantitating the number of white blood cells and bacteria in the urine sediment. Evaluation of urine sediment within 30 to 60 minutes of collection enables preservation of the greatest cytologic detail. Pyuria is confirmed by the presence of >10 white blood cells per high-power microscopic field of a midstream-voided or catheterized sample. When bacterial infection is the cause, there are typically > 20 organisms visible per high-power field. The cytologic features of urine sediment are greatly influenced by the method of collection, rigor of aseptic technique, and degree of contamination of the prepuce, vulva, and urethral orifice. Catheterization can be used to obtain urine from the bladder of most male and female horses and female ruminants. In male ruminants the urethral recess (diverticulum) prevents retrograde catheterization of the bladder, and collection of a midstream sample is usually the sole option. Cystocentesis of a large animal with a urinary tract infection carries the risk of induction of septic peritonitis.

Quantitative cultures of the samples should be performed soon after collection in order to prevent false increases in the colony count that can occur from bacterial proliferation in the sample during storage. The results of quantitative culture are greatly influenced by the method of collection and the degree of contamination of the prepuce and vulva. In specimens collected by midstream free catch, bacterial counts greater than 1×10^4 bacteria per milliliter of urine are indicative of urinary tract infection if compatible dipstick and sediment examination findings are present. Normal male and female horses have less than 20,000 colony-forming units (CFU) per milliliter of urine on a free catch sample and less than 500 CFU/mL on a catheterized sample.[8] A culture that yields a large number of mixed growth may reflect heavy contamination of the vulva or penis, fecal admixture, or delay before culture was initiated.

Once pyuria is confirmed, the clinician should next determine the location or origin of the pyuria, the cause, and any predisposing conditions. In females the reproductive tract should be evaluated to confirm that it is not the source of the exudate, as mixing of urine and exudate in the urethra and vestibule may result in a spurious diagnosis of pyuria. Similarly, trauma or inflammation of the glans penis or prepuce can result in admixture of exudate with urine, as often occurs in cases of ulcerative posthitis in rams and bucks. Inflammatory diseases of the urethra and bladder usually produce obvious clinical signs of dysuria but minimal to no signs of systemic disease. Low-grade fever may be present in occasional cases of cystitis, but affected animals rarely appear to be systemically ill.

If the pyuria originates from the upper urinary tract (ureters and kidneys), the animal is usually persistently or intermittently febrile and shows systemic signs of disease. Inflammation of the ureter(s) and kidney(s) may result in colic. The rectal examination may reveal enlargement of one or both ureters, pain on palpation, and possibly an enlargement or abnormal shape (or both) of the left kidney. If grossly enlarged, the right kidney occasionally can be palpated per rectum in the horse or cow. In cows and heifers, vaginal palpation may reveal thickening and pain of one or both ureters. Changes suggestive of inflammation are often present on the complete blood count. Although cytologic examination of the urine may indicate pyuria, bacteriuria may be inconsistently found,

particularly if the infection originates from a nephrolith. Casts of exudate, blood, protein, or cellular debris may be seen the urine sediment in cases of pyelonephritis.

An ultrasound examination of both kidneys and ureters should be performed in all animals with evidence of upper urinary tract infection. The technique for ultrasound examination of the urinary tract is described in Chapter 34.

If *Leptospira interrogans pomona* is suspected as a cause of pyuria, urine sediment should be placed on a microscope slide, air dried, and examined by fluorescent antibody for *Leptospira* antigen.[9] Polymerase chain reaction testing for this organism can be performed on urine sediment; in cattle, greater sensitivity may be achieved by obtaining a urine sample after administration of furosemide.[10]

10.4 CRYSTALLURIA

Crystalluria is defined as the presence of crystals in the urine. Calcium carbonate and calcium phosphate crystals are abundant in normal equine urine; these, along with mucus, impart a turbid, slightly opaque quality to normal equine urine. Herbivore urine is normally alkaline, which reduces the solubility of certain calcium- and phosphate-based compounds in urine, inducing crystal development. Small numbers of calcium phosphate, calcium carbonate, or calcium oxalate crystals may be present in highly concentrated ruminant urine. In such cases crystalluria should be considered an incidental finding if the animal is healthy and free from signs of urinary tract disease. However, in male ruminants, heavy or persistent crystalluria may indicate the potential risk of urolithiasis because the combination of highly concentrated urine and urinary mineral precipitation is considered instrumental in calculogenesis. A precautionary review of diet, salt intake, and water management may be indicated in such cases. High dietary intake of calcium and oxalates has been hypothesized to be the cause of heavy calcium oxalate crystalluria in a goat.[11]

Crystalluria presents a medical problem when crystals enlarge through precipitation, causing microscopic or gross traumatic injury to the urinary epithelium and urinary tract obstruction. When crystals coalesce and enlarge to form calculi (uroliths), the calculi may remain occult or cause disease through trauma to and obstruction of the urinary tract. As a result, the clinician usually detects crystalluria in these animals during the diagnostic workup for hematuria, dysuria, stranguria, pyuria, or signs of urinary tract obstruction. It is critical to note that the *absence* of crystalluria does not indicate that the urinary tract is free of calculi or renal mineralization.[12–14] Causes of crystalluria are listed in Box 10-4.

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10.4.1 Box 10-4 Causes of Crystalluria in Horses and Ruminants

Normal calcium-based crystalluria of horses

Highly concentrated or alkaline urine

Urolithiasis

Urinary tract infection

Ethylene glycol intoxication

Intoxication with oxalate-containing plants

Parenteral vitamin C

10.4.2 Approach to Diagnosis of Crystalluria

10.4.2.1 HISTORY

Toxins such as oxalic acid and ethylene glycol can induce calcium oxalate crystalluria, so animal access to oxalate-containing plants and storage areas or garages should be investigated. Administration of high doses of parenteral vitamin C can also induce calcium oxalate deposition in the urinary tract, and a careful history can help to include or exclude these causes from the differential diagnosis list. Previous urinary tract surgery, dystocia, or genital trauma may not directly contribute to crystalluria per se, but abnormal structure of the urinary tract, suture material retained in the tract, or loss of uroepithelial integrity can promote crystal precipitation into calculi.

10.4.2.2 PHYSICAL EXAMINATION

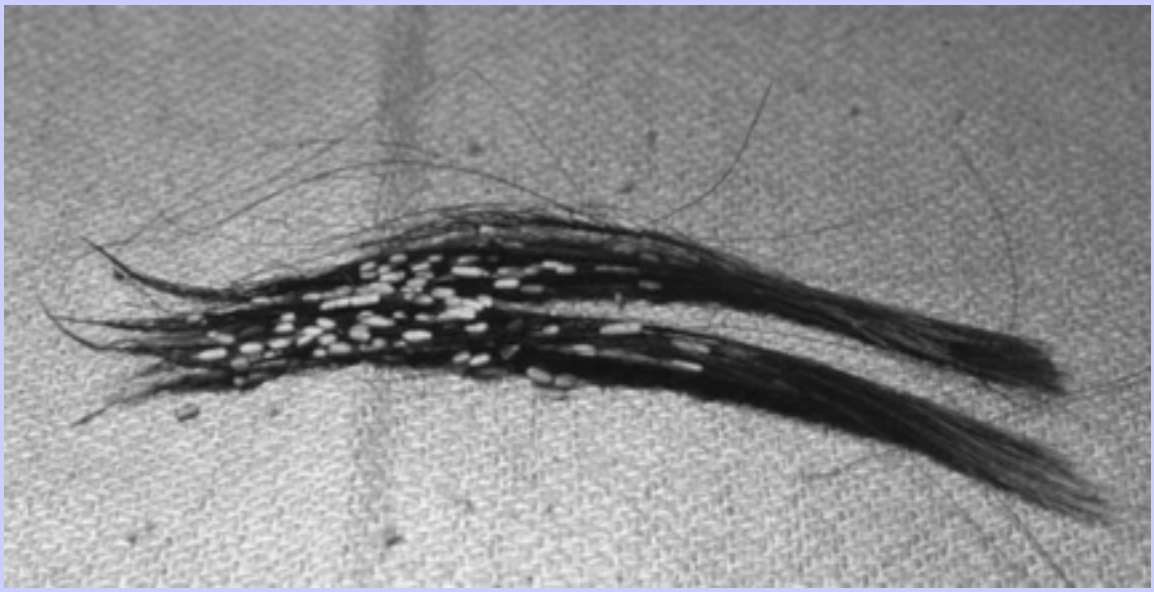
The hairs surrounding the preputial orifice or vulva should be carefully examined for visible crystals that cling to the hair (Fig. 10-5). Animals with dysuria and stranguria or incontinence may have crystals adherent to the hair of the hindlegs or tail as well. The presence of adherent crystals on hair indicates that crystalluria is heavy, and in males, given that imminent or current obstructive urolithiasis is the most important diagnosis to investigate, the clinician should determine whether or not the urinary tract is patent in such instances.

Urinary tract infection can induce microscopic crystalluria, crystal and exudate accumulation on the external genitalia, or, more rarely, calculus formation. Urease-producing bacteria may increase the pH of urine to the point of inducing precipitation of certain minerals suspended in the urine into calculi. In addition, exudation into the infected urinary tract also provides nidi for deposition of urinary minerals. The approach to urinary tract infections is discussed in the previous sections on dysuria, stranguria, and pyuria.

10.5 POLYURIA

Polyuria can be defined as the passage of abnormally large amounts of urine. This may be a normal response when excessive fluid, electrolytes, or both are presented to the tubules of a healthy kidney. It may also occur with renal failure when tubular function is impaired or when enough individual nephrons have been lost that the remaining ones are presented with excess fluid and/or solute. Polyuria is also present in central or neurogenic diabetes insipidus (caused by insufficient secretion of antidiuretic hormone [ADH]), nephrogenic diabetes insipidus (caused by diminished effect of ADH on receptors in the kidney), renal medullary washout (caused by an insufficient interstitial concentration gradient), excessive drinking (polydipsia), liver failure, fluid administration, and certain electrolyte abnormalities. Polyuria may also be evident after urinary tract obstructions have been relieved, a phenomenon termed *postobstructive diuresis*. Causes of polyuria are listed in Box 10-5.

Fig. 10-5 Crystals adherent to the preputial hairs of a steer with urolithiasis. The crystals were analyzed and found to be composed of struvite (magnesium ammonium phosphate).



10.5.1

Approach to Diagnosis of Polyuria

Evaluation of an animal with polyuria should begin with an inquiry about any history of recent disease, drug administration (e.g., diuretics, corticosteroids, xylazine), fluid therapy, change in diet, change in water quality or availability, or known laboratory evidence of renal disease. After completion of the history and a review of the patient's medical records, the initial diagnostic step is to collect a urine sample to measure the osmolality or specific gravity (UspG). If the osmolality is close to the isosthenuric range (UspG of 1.008 to 1.014), and the concentration remains similar to the plasma concentration in the face of dehydration, primary renal disease should be considered as a cause. This is typically confirmed by measuring the serum creatinine concentration, 176
although radionuclide clearance studies and/or 12- or 24-hour urinary creatinine clearance can also be performed. 177
If evidence of renal failure is not evident on these tests, a water deprivation test may be needed to determine the tubules' ability to concentrate urine. This test should be performed in a normovolemic patient with careful monitoring of patient status during the test, because the mild dehydration induced during this test may exacerbate preexisting, occult renal disease.

10.5.1.1

Box 10-5 Causes of Polyuria, Anuria, and Oliguria in Horses and Ruminants

10.5.1.1.1

POLYURIA

Excessive salt or water ingestion

Salt deficiency

Excessive intravenous fluid therapy

Acute or chronic renal failure

Central diabetes insipidus

Nephrogenic diabetes insipidus

Medullary washout

Psychogenic polydipsia

Diabetes mellitus

Liver failure

Postobstructive diuresis

Hyperglycemia

Xylazine

Corticosteroids

Diuretics

Severe deficits of chloride, potassium, or urea

10.5.1.1.2 ANURIA AND OLIGURIA

Dehydration, hypovolemia

Urinary tract obstruction (e.g., urinary calculi)

Rupture of the urethra, bladder, or ureter(s)

Acute or chronic renal failure

10.5.1.1.3 *APPARENT* ANURIA OR OLIGURIA

Painful diseases of the abdomen or abdominal wall

Painful diseases of the thorax or thoracic wall

Recumbency

Neonatal maladjustment

Patent urachus

Encephalopathies

Severe spinal cord disease

Ectopic ureter(s)

As an alternative to the water deprivation test in identifying tubular disease and dysfunction as the cause of polyuria, the fractional clearance (fractional excretion) of sodium in the urine can be measured. This test is performed on simultaneously collected urine and serum samples by measuring the creatinine and sodium in both the serum and the urine. The fractional clearance (Fc_{Na}) of sodium is then determined by the following formula:

$$Fc_{Na}(\%) = \frac{[Na_u]}{[Na_p]} \times \frac{[Cr_p]}{[Cr_u]} \times 100$$

where Na_u is the urine sodium concentration, Na_p is the plasma creatinine concentration, Cr_u is the urine creatinine concentration, and Cr_p is the plasma creatinine concentration. A fractional sodium clearance value above 1% in adult horses is suggestive of primary tubular disease,[15] particularly if the animal's diet and physiologic state are such that avid sodium conservation is expected. Fractional clearance of sodium values of up to 4% have been measured in healthy, lactating dairy cattle.[16] Thus, for this test to be valid, salt intake must be normal, the animal must not be given diuretics, and due consideration of the animal's diet and physiologic state must be given. Intravenous fluid therapy will complicate interpretation of fractional clearance values.

If the UspG or osmolality is less than that of the plasma (1.007), diabetes insipidus, psychogenic polydipsia, and renal medullary washout should be considered. Diabetes insipidus, although rare, has been reported in the horse and may be the result of inadequate secretion of vasopressin (neurogenic diabetes insipidus) or inadequate response to vasopressin in the kidney (nephrogenic diabetes insipidus).[17] However, the patient may simply be

ingesting large amounts of water as a result of high ambient temperature, so interpretation of low UspG requires due consideration of the animal's physiologic state.

10.6 ANURIA AND OLIGURIA

Anuria is defined as the absence of urine production, and *oliguria* is defined as scant or subnormal urine production. Unless the patient's history includes a careful record of urine output, these two disease conditions are often difficult to distinguish at the onset of the evaluation. Furthermore, the difficulties associated with maintaining urine collection devices in large animals make an accurate measurement of urine production difficult in many cases.

The volume of urine produced by healthy large animals varies tremendously according to breed, age, physiologic status, level of exercise, diet, and a multitude of environmental factors. Altman (1961) determined normal urine output for the large animal species to be as follows: horses, 3 to 18 mL/kg/day; cattle, 17 to 45 mL/kg/day; and sheep and goats, 10 to 40 mL/kg/day.[18] Anuria and oliguria frequently become apparent to the clinician when an azotemic animal is diagnosed with a primary disease in which renal function is commonly threatened (e.g., severe diarrhea) and urine output after initiation of fluid therapy is noted to be subnormal or absent.

If urine collection and measurement cannot be performed, the adult animal with potential anuria or oliguria can be closely watched or placed in a stall with minimal bedding or fine, fresh bedding (e.g., sawdust) in order to facilitate detection of urine on the stall floor. When indicated, fluid therapy should be initiated and expectations for urine output predicted based on the rate and route of fluid administration. Animals with painful thoracic or abdominal disease may refrain from urination, and the clinician must remember to evaluate *bladder filling* and not just the volume of urine voided. Recumbent, obtunded foals, particularly males, may not reliably void urine; monitoring bladder fill by ultrasound or placement of an indwelling urinary catheter is recommended. Urachal leakage of urine must be considered in neonates with suspected anuria or oliguria, as these animals may be observed to void less frequently than normal. Animals with encephalopathies or severe spinal cord disease may not be capable of voluntary voiding.

When evidence for anuria mounts, the clinician must determine if the urinary tract is patent and rule out the presence of rupture of the bladder, urethra, or ureters. Repeat physical examination and ultrasound of the upper and lower urinary tract and abdominal cavity is warranted in such instances. Obstructive diseases of the lower urinary tract are typically accompanied by signs of colic and stranguria. However, these signs will not be present if the patient has a preexisting rent in the urinary tract or if the animal is severely obtundent from uremia.

Oliguria is a physiologic adaptation to dehydration and can be expected in animals with prerenal azotemia. Assessment of the urine specific gravity is critical in determining the presence of renal failure in such cases. If urine cannot be collected from the dehydrated animal, fluid therapy should be initiated and the azotemia monitored. Oliguria is a relatively common feature of acute renal failure, particularly if the disease process involves obstruction of the nephron lumen with crystals, cellular debris, or proteinaceous casts. However, the volume of urine produced by the large animal in renal failure can vary greatly according to the patient's hydration status, diet, and the inciting cause. In short, urine production can be normal, increased, or decreased in renal failure. Renal failure is covered in detail in Chapter 34. Causes of anuria and oliguria are listed in Box 10-5.

10.7 UREMIA

Uremia is caused by the presence of excessive urinary constituents in the blood and their detrimental effect on a variety of organ systems. Uremia is defined as the constellation of clinical signs, impaired metabolic processes, and

alteration of the function of multiple organs that occurs as a result of failure to excrete waste products from the body via the urine. Uremia may be the result of either acute or chronic renal failure, retention of urine in the body as a result of urinary tract leakage (e.g., bladder rupture), or both. Various retained toxins are associated with the uremic process, including urea, parathyroid hormone, guanidine, phenolic compounds, and phosphorus.[19,20] The predominant clinical signs of uremia seen in large animals are depression and anorexia. Weight loss, gastrointestinal ulcers, polyuria, polydipsia, melena, and diarrhea are other noticeable effects. Oral erosions or ulcers, gingivitis, diffuse stomatitis, dental tartar, and halitosis may be evident on examination of the oral cavity. Coagulopathy and platelet dysfunction make uremic patients prone to gastrointestinal hemorrhage and impaired clotting during surgery. Pulmonary edema and uremic encephalopathy may develop in rare cases.

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12 Chapter 12 Alterations in Sexual Function

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12.1 ALTERATIONS IN MALE SEXUAL FUNCTION

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Stallions, bulls, rams, and bucks intended to be used as breeding animals need to have (1) normal genital organs, (2) the libido necessary to tease females and gain an erection, (3) the physical ability to mount and intromit the penis into the female's vagina, and (4) an adequate number of morphologically normal, motile spermatozoa in each ejaculate to be considered as satisfactory breeders under natural service conditions. Digression from normal sexual function in males usually is recognized clinically by changes in sexual behavior, abnormalities or diseases of the genital organs, or a decreased pregnancy rate in dams bred. Subfertile males may be responsible for significant economic loss in the livestock industry.

12.1.1 Mechanisms of Altered Male Sexual Function

Sexual function may be altered by any of four major mechanisms: general physical abnormalities, abnormalities of the genital organs, decreased libido, and poor semen quality (Boxes 12-1 and 12-2).

The male must be mobile enough, especially in a pasture breeding program, to locate, tease, mount, and breed estrual females successfully. Musculoskeletal abnormalities may limit reproductive ability or desire. Hindlimb conformation defects in bulls and rams, degenerative joint disease involving the hock in stallions, and foot problems in rams are examples of conditions that may cause enough discomfort to interfere with the normal breeding process or prevent normal mobility, impairing reproductive performance.[1–3]

Congenital or acquired abnormalities of the genital organs, including the penis, prepuce, scrotum, testicles, spermatic cords, or accessory sex glands, can lead to altered sexual function or infertility. Congenital abnormalities such as persistent penile frenulum and penile deviations in bulls may prevent normal intromission.[4] Acquired lesions such as a penile hematoma caused by rupture of the tunica albuginea of bulls at time of service may limit sexual function by causing paraphimosis, adhesions, or sensory nerve damage.[5]

Libido is an essential component of breeding performance but may be difficult to measure during a breeding soundness examination and cannot be evaluated if semen is collected by electroejaculation. Libido has been demonstrated to be an inherited behavioral trait in bulls.[6]

Semen volume, concentration of spermatozoa, percentage of progressive motility, and percentage of morphologically normal spermatozoa are semen parameters commonly measured during a breeding soundness examination. Abnormalities of semen quality associated with decreased fertility in bulls include spermatozoa morphology and, to a lesser degree, motility.[2,4,7]

12.1.2

Approach to Diagnosis of Altered Male Sexual Function

A complete breeding soundness examination and history should be obtained, including number of females bred each year, conception rates, breeding methods (natural service or artificial insemination), and results of previous breeding soundness examinations (Box 12-3). A medical or health history, including medications, vaccinations, and previous illnesses, should be obtained. The animal should be given a general physical examination. Hindlimb conformation and the presence of degenerative joint disease, laminitis, foot abscesses, abnormal foot wear, corkscrew claw defect, weak pasterns, postleggedness, sickle hock, interdigital fibromas (bulls), foot rot, ulcerative dermatitis and pizzle rot (rams), and caprine arthritis-encephalitis (CAE) (bucks) should be noted. An ophthalmologic examination should be done to ensure that the animal has adequate vision and that no significant pathologic condition is present. A special emphasis is placed on identification of squamous cell carcinoma and pinkeye *(Moraxella bovis)* corneal lesions in bulls. Range animals showing weight loss and a decline in reproductive performance should be given an oral examination, and the parasite control program should be evaluated.

The external genital organs should be examined carefully. The penis of the stallion is easiest to examine after an erection is obtained by teasing to an estrual female. In ruminants manual palpation of the penis per rectum or by use of an electroejaculator is suitable in many cases. The penis should be normal in size and shape and free of lesions. In bulls, deviations or other abnormal configurations such as corkscrew penis may occur with use of an electroejaculator and therefore cannot be considered abnormal.[5] Rams and bucks should be carefully examined for abnormalities of the urethral process, including the presence of calculi.[8] The lesions most often observed on the penises of stallions are squamous cell carcinoma and cutaneous habronemiasis.[9,10]

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12.1.2.1

Box 12-1 Causes of Altered Sexual Function in Stallions

12.1.2.1.1

ABNORMALITIES OF THE PENIS

Balanoposthitis

Paraphimosis

Phimosis

Trauma

Hematoma, seroma

Abscess

Urolithiasis

Equine coital exanthema

Tumor (squamous cell carcinoma)

Cutaneous habronemiasis (equine summer sores)

Improper use of stallion rings

12.1.2.1.2 ABNORMALITIES OF THE PREPUCE

Trauma

Foreign body

Preputial stenosis

Balanoposthitis

Tumor (squamous cell carcinoma, sarcoid)

Hematoma

Abscess

Cutaneous habronemiasis

Varicosities of the preputial vein

Equine viral arteritis

12.1.2.1.3 ABNORMALITIES OF THE TESTICLES, SPERMATIC CORD, AND SCROTUM

Testicular hypoplasia, atrophy

Testicular degeneration

Segmental aplasia

Testicular, scrotal neoplasia

Thrombosis of the spermatic cord

Torsion of the spermatic cord

Orchitis, epididymitis

Sperm, parasitic granuloma

Trauma

Hematoma, hematocele

Inguinal, scrotal hernia

Androgen, anabolic steroid effects

Cryptorchidism

Pseudohermaphrodism

Actinomycosis

Chemical irritation of the scrotum

Equine viral arteritis

12.1.2.1.4 LACK OF LIBIDO

Malnutrition, protein-calorie starvation

Testicular neoplasia

Lameness

Trauma, foreign body of the prepuce

Overuse

Equine coital exanthema

Iodine deficiency

Penile trauma, hematoma, abscess

Psychologic impotence

12.1.2.1.5 INFERTILITY

Segmental aplasia of the reproductive tract

Vesicular gland adenitis

Malnutrition, protein-calorie starvation

Testicular degeneration

Testicular hypoplasia, atrophy

Testicular neoplasia

Thrombosis of the spermatic cord

Torsion of the spermatic cord

Urolithiasis

Vitamin A deficiency

Hemospermia

Lameness

Iatrogenic causes, including artificial insemination-associated infertility

Bacterial contamination of the semen

Brucellosis

Trauma, foreign body of the prepuce

Balanoposthitis

Paraphimosis

Orchitis, epididymitis

Sperm, parasitic granuloma

Androgen, anabolic steroid use

Testicular trauma, hematoma, hematocele

Chromosomal abnormalities

Hermaphrodism, pseudohermaphrodism

Cryptorchidism

Ejaculation failure

Frostbite

Abnormalities of spermatogenesis

Sperm storage dysfunction

Iodine deficiency

Heat stress, heat stroke

Inguinal, scrotal hernia

Psychologic impotence

12.1.2.2

Box 12-2 Causes of Altered Male Sexual Function in Ruminants

12.1.2.2.1

ABNORMALITIES OF THE PENIS

Penile deviation (B)

Balanoposthitis

Paraphimosis

Phimosis

Penile-preputial adhesions (B)

Penile hair ring (B)

Penile trauma, hematoma, abscess

Urethral calculi

Ruptured urethra

Persistent penile frenulum (B)

Papillomatosis

Infectious bovine pustular vulvovaginitis (B)

Herpes vulvovaginitis (C)

Ovine ulcerative dermatosis (O)

12.1.2.2.2 ABNORMALITIES OF THE PREPUCE

Abscess, cellulitis

Balanoposthitis

Trauma

Foreign body

Preputial stenosis

Prolapsed prepuce

Ulcerative posthitis (pizzle rot)

Ovine ulcerative dermatosis (O)

12.1.2.2.3 ABNORMALITIES OF THE TESTICLES, SPERMATIC CORDS, AND SCROTUM

Scrotal abscess (O)

Orchitis, epididymitis

Segmental granuloma, spermatocele

Testicular degeneration

Testicular hypoplasia, atrophy

Varicocele

Zinc deficiency

Testicular tumors

Brucellosis (B, O)

Testicular trauma, hematoma, hematocele

Inguinal, scrotal hernia

Cryptorchidism

Actinomycosis

Intersex in polled goats (C)

Pseudohermaphrodism (C)

Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)

12.1.2.2.4

LACK OF LIBIDO

Malnutrition, protein-calorie starvation

Ulcerative posthitis

Vertebral osteophytosis, spondylosis (B)

Zinc deficiency

Lameness

Trauma, foreign body of the prepuce

Prolapsed prepuce (B, O)

Loss of penile sensation (B)

Penile hair ring (B)

Corpus cavernosum vascular shunts (B)

Iodine deficiency

Psychologic impotence

Penile trauma, hematoma, abscess

Persistent penile frenulum (B)

Epididymitis, orchitis (O, C)

Intersex in polled goats (C)

Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)

Obesity

Spondylosis (B)

12.1.2.2.5

INFERTILITY

Testicular degeneration

Orchitis, epididymitis

Trauma, foreign body of the prepuce

Paraphimosis

Heat stress, heat stroke

Penile trauma, hematoma, abscess

Segmental aplasia

Vesicular gland adenitis

Sperm granuloma, spermatocele

Malnutrition, protein-calorie starvation

Testicular hypoplasia, atrophy

Ulcerative posthitis (pizzle rot)

Urolithiasis

Varicocele

Vitamin A deficiency

Zinc deficiency

Manganese deficiency

Iodine deficiency

Hemospermia

Lameness

Iatrogenic, including artificial insemination-associated infertility

Balanoposthitis

Testicular trauma, hematoma, hematocele

Cryptorchidism

Dermatophilosis

Frostbite

Inguinal, scrotal hernia

Psychologic impotence

Hermaphrodism, pseudohermaphrodism

Short retractor penis muscle in Dutch Friesian bulls (B)

Abscess of scrotum (O)

Prolapsed prepuce (B, O)

Penile deviation (B)

Penile-preputial adhesions (B)

Vertebral osteophytosis, spondylosis (B)

Testicular tumors (B, O)

Bulls co-twin with freemartins (B)

Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)

Infectious bovine rhinotracheitis—contaminated semen (B)

Infectious bovine rhinotracheitis—associated dermatitis (B)

Bovine virus diarrhea—contaminated semen (B)

Chromosomal abnormalities (B, O)

Loss of penile sensation (B)

Penile hair ring (B)

Bovine herpesvirus type 1

Corpus cavernosum vascular shunt (B)

Urethral fistula (B)

Cold weather-associated infertility (B)

Papillomatosis, warts (B)

Abnormalities of spermatogenesis

Micropenis, penile hypoplasia (B)

Persistent penile frenulum (B)

Ovine ulcerative dermatosis (O)

Congenital phimosis (O)

Overuse

Chorioptic mange (O, C)

Hexachlorophene toxicity

Gynecomastia (C)

B, Bovine; *C*, caprine; *O*, ovine.

The prepuce should also be examined for lesions. Strictures of the preputial orifice may increase the risk of phimosis or paraphimosis. Bulls of the *Bos indicus* breeds often have a pendulous prepuce that is predisposed to traumatic injury, abscessation, stricture formation, and eversion.[5,11] Ulcerative posthitis (pizzle rot) caused by *Corynebacterium renale* in rams on a high-protein diet is the most common lesion of the prepuce in rams.[12]

The scrotum, testicles, and spermatic cords should be examined for size, consistency, symmetry, and presence of lesions. Two scrotal testicles should be present, each smooth, resilient on palpation, and freely movable. Testes volume and consequently the amount of testicular parenchyma present are highly correlated with daily sperm production in all species. Each gram of testicular tissue should produce 15 to 20 million sperm per day. In ruminants, scrotal circumference has been determined to be highly correlated with testes weight or volume. Yearling beef bulls should have a scrotal circumference of 30 cm or more, depending on the animal's age and breed.[7] In stallions, measurements of total scrotal width and, more recently, testicular volume have been evaluated and correlated to potential daily sperm production. Mature stallions should have a scrotal width of at least 8 cm. Testicular volume in stallions can be determined by the following steps[13]:

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1 Measure the length (L), width (W), and height (H) of each testicle.

2 Volume of each testicle can be determined using the formula:

Testicular volume (cm^3) = 0.5233 × L × W × H

3 Add the volume of each testicle to obtain total testicular volume.

4 Expected daily sperm production (DSP) (in billions of sperm per day) can be calculated using the formula:

Expected DSP = 0.024 × (Total testicular volume in cm^3) – 1.26

12.1.2.3

Box 12-3 Outline of a Breeding Soundness Examination for Diagnosis of Male Infertility

1 Species, breed

2 Age

3 Month of evaluation

4 Breeding history

5 Physical examination

- a General
- b External genital organs
  - (1) Penis
  - (2) Prepuce
  - (3) Testes
  - (4) Scrotum
  - (5) Epididymides

6 Libido

7 Mating ability

8 Semen evaluation

- a Motility
- b Concentration
- c Morphology

	d Volume
9	Microbiologic culture
10	Serologic tests

The epididymides should be palpated for position, size, and presence of lesions. The most common palpable abnormality in rams is epididymitis caused by infection with *Brucella ovis, Actinobacillus seminis*, or *Histophilus ovis*.[8,12,14] A definitive diagnosis is obtained by isolation of bacterial organisms in the semen and serologic testing.

Diseases of the accessory sex glands are diagnosed most frequently in bulls. Vesicular gland adenitis is clinically recognized by the presence of leukocytes in the semen and enlargement, induration, and loss of lobulation noted during palpation and ultrasonographic examination of the glands per rectum.[15,16]

Libido and the ability to mate should be assessed after the physical examination. The male should be teased to a female in estrus. Interest in and interactions with the female and ability to gain an erection, mount, intromit the penis into the vagina (or into an artificial vagina), and ejaculate are noted. Libido and mating ability cannot be evaluated when using an electroejaculator to collect semen from ruminants. Tests for “serving capacity” have been described for bulls.

The evaluation of semen quality is a major part of the breeding soundness examination. Semen from stallions is collected into an artificial vagina. Semen from ruminants may be collected into an artificial vagina or obtained by use of an electroejaculator. Semen collected by electroejaculation usually has a higher volume and a lower concentration of spermatozoa than semen collected by an artificial vagina. Semen quality in ruminants is scored primarily on the basis of motility and morphology.[7] Evaluation of semen from stallions should include determination of volume, concentration, motility, and morphology. The motility of the spermatozoa should be evaluated microscopically on raw and extended semen immediately after collection. In ruminants, bright-field microscopy at ×40 to ×125 magnification is used to detect mass motion or swirling to evaluate gross motility. Changes in sperm concentration, progressive motility, or speed of progression of spermatozoa will decrease or eliminate the swirling effect. Phase contrast microscopy at ×200 to ×500 is used to evaluate motility of individual spermatozoa. Computer-assisted semen analysis (CASA) has become more common in recent years to evaluate motility at larger reproduction facilities.

Concentration can be measured by use of a hemocytometer or a calibrated spectrophotometer. Morphology can be evaluated microscopically, using stained semen samples (e.g., eosin-nigrosin stain) or phase-contrast microscopy.

Ejaculates from stallions may be collected once daily for 5 to 10 days until daily sperm output (DSO) is achieved to fully evaluate potential fertility.[17] However, this is time-consuming, labor-intensive, and expensive. Consequently, most stallions are evaluated by the collection of two ejaculates 1 hour apart, with the total number of progressively motile, morphologically normal spermatozoa in the second ejaculate most critically evaluated.

The age of the stallion or male ruminant being evaluated for potential fertility may influence the semen parameters, measurements of the testicular size, mating ability, and libido. Puberty is attained in the male equine at 18 months, in the bull at 9 to 12 months, and in the ram and buck at 7 to 8 months.[18] Semen parameters and testicular size continue to increase until sexual maturity is reached. The season of the year in which the fertility evaluation is done may affect semen parameters in the stallion, ram, and buck.

Microbiologic samples should be routinely collected when evaluating infertility in the stallion and when evaluating high-risk populations of bulls. Smegma samples should be collected from the prepuce of bulls and cultured for *Trichomonas foetus* and *Campylobacter fetus*. Swabs from the preejaculate and postejaculate urethra, semen, and fossa glandis of stallions should be cultured for potentially pathogenic bacterial organisms, especially *Taylorella equigenitalis, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*.[9] The semen of rams should be cultured for *B. ovis, A. seminis*, and *H. ovis*.[8,12,14] Serologic testing for exposure to equine arteritis virus (EAV), the causative agent of equine viral arteritis (EVA), is important for breeding stallions. In many states, determination of negative serologic status is required before vaccination against the virus may be performed.

Other tests that are occasionally performed to evaluate male reproductive function, health, or pathology include hormone analysis, chemical evaluation of seminal plasma, transmission electron microscopy of semen, karyotype, sperm chromatin structure assay, urethral endoscopy (stallion), and testicular biopsy.

After summarizing the results of the entire breeding soundness evaluation, stallions and male ruminants may be categorized into classifications, such as satisfactory, questionable, or unsatisfactory. In bulls a fourth category of "decision deferred" may be used for young prepubertal bulls or mature bulls that have recently experienced a transient disturbance in spermatogenesis. 197 198

It must be emphasized that the breeding soundness examination is a measure of potential fertility.[19] True fertility can be determined only by the results of breeding trials or by conception and live birthrates in dams bred.

12.2 CYCLIC IRREGULARITY

Steven D. Van Camp

Cyclic irregularity refers to an abnormal interval from the first day of estrus until the first day of the subsequent estrus. The alteration in the cycle length may occur during estrus or during the interestrous interval. Irregular cycles may be related to erroneous estrous detection, seasonal transitions, corpus luteum life span alterations, ovulation derangements, embryo or fetal wastage, or behavioral aberrations. In some cases the cause of the cyclic irregularity is unknown.

Inaccurate heat detection may appear as irregular cycles. Missed heats should be expected if the heat intervals approximate multiples of the normal cycle length (e.g., 42 or 63 days in the cow or mare). Silent heats (no clinical signs of estrus) were found to occur less often than suspected when cows were observed 24 hours a day, although silent heats do sometimes occur. The first ovulation of the season (ewe and doe) and the initial postpartum ovulation in cows usually are silent. Subestrum, weak, or short heats occur more commonly in the early postpartum period in the cow and may be caused by insufficient progesterone priming of the behavior center for optimum expression of estrus.[20]

Artificial insemination records may indicate that breedings are grouped so that two or more cows are bred the same day. This may indicate a failure to determine which animal is actually in heat. Short cycles may also indicate a lack of discrimination between the riding cow and the cow in standing heat. This type of error in estrous detection often results in the same cows being rebred within 3 days.

Anestrus is a particularly important type of cyclic irregularity with several causes. It is dealt with in a separate section of this chapter.

Nymphomania, a state of persistent or frequent heats, is the antithesis of anestrus. Many mares thought to be nymphomaniacal are actually exhibiting some degree of virilism. Frequently their ovaries are small and firm and appear inactive. These mares may actually be aggressive toward the stallion instead of receptive.[21] The cause of this condition may be behavioral rather than endocrine, as previously believed. Passive acceptance of the male, as can be seen in gonadal dysgenesis mares, can be mistaken for nymphomania. Mares with these chromosomal aberrations may accept service by the male, but they do not show the characteristic signs of estrous behavior in his presence. Nymphomania may be seen in cases of hormone-secreting granulosa cell tumors. Nymphomania also may indicate an ovulatory anomaly. Nymphomania in cows and goats is most often associated with ovarian follicular cysts. In ruminants, luteinized cysts, which cause anestrus, are more common.

12.2.1 Mechanisms of Irregular Cycles

Cyclic derangements occur either during estrus or in the interestrous interval. A delay in follicular maturation or ovulation may result in a prolonged proestrus or persistent estrus. This is seen in mares entering or leaving the physiologic breeding season in the transition from or to winter anestrus. It is likely the result of changing patterns of hypothalamic releasing factor and pituitary gonadotropin secretion.[22] Ovarian insensitivity to these substances may also play a role. The tubular tract may be insensitive to the ovarian hormones and may be atypical for the structures present on the ovaries.[23] The estrual behavior and ovarian structures may not correlate in these mares. They may have large follicles without heat or may show heat without large follicles being present. This may be a result of changes in the central nervous system's response to the sex steroids during the transition season.

Failure of ovulation can result in prolonged estrus. Mares frequently form persistent follicles during the transitional seasons. These usually regress with time and are not a long-term cause of infertility.[24] Ovulation failure can result in the development of follicular cysts and frequent or persistent heats in cattle.[25]

Other ovulation irregularities include delayed ovulation and premature ovulation. Delayed ovulation rarely occurs in animals. What may appear to be delayed ovulation is often erroneous heat detection or premature breeding. Similarly, premature ovulation is often misdiagnosed because of inaccurate heat detection. Premature ovulation may be suspected in heat-stressed animals that only show heat for short periods at the peak of estrus, or during the cool of the night.[26]

The mare seems to have a unique type of ovulation anomaly. After having one or more normal cycles, mares may spontaneously have a fertile, diestrous ovulation without signs of estrus. If the new corpus luteum develops after day 10 of diestrus, it has not had time to mature and become sensitive to prostaglandin-induced lysis. Thus the mare skips the next expected estrus and has a prolonged diestrus.[24]

The corpus luteum controls the length of diestrus and the interestrous interval in cycling animals. Premature lysis of the corpus luteum results in a short interestrous interval. If prostaglandin-induced lysis of the corpus luteum is prevented, the corpus luteum persists and a prolonged diestrus results.

Irritation or inflammation of the endometrium may cause premature release of prostaglandin and lysis of the mature corpus luteum, resulting in a short interestrous interval. Irritation of the endometrium late in diestrus may interfere with the action of prostaglandin on the mature corpus luteum, leading to a prolonged diestrus. Intrauterine therapy with irritating solutions may alter the interestrous interval, depending on when they are administered in the cycle. Treatment between 4 and 10 days after ovulation causes a short cycle in the cow.

Intrauterine treatment late in diestrus, 15 to 17 days after ovulation, results in a prolonged cycle, presumably because of a disruption of the synthesis or release of prostaglandin. In both cases the mare comes into heat 7 to 10 days after treatment.[27] Inadvertent intrauterine insemination during diestrus may induce a heat similar to that induced by infusion of other irritating solutions. Thus a split heat or short cycle may be seen.

Prolonged diestrus must be differentiated from early embryonic or fetal death. If embryonic death occurs after the time of maternal recognition of pregnancy (see the section Repeat Breeder), the next heat is skipped and the female returns to heat after a prolonged diestrus. This may last several months in the mare if the fetus is lost after the endometrial cups begin secreting equine chorionic gonadotropin (ECG; see the section Anestrus).

Diseases that cause endometritis may cause cyclic irregularity by two mechanisms. Endometritis results in premature lysis of the corpus luteum, leading to a short cycle. Endometritis also may result in early embryonic death (EED), which may culminate in a prolonged diestrus. Some viral agents, including some modified live vaccine strains, may attack the ovary and corpus luteum directly. The resulting oophoritis can lead to necrosis of the corpus luteum; therefore vaccination around the time of breeding is contraindicated.[28–30] These agents may also cause embryonic death, leading to apparent cyclic irregularity.[30–32]

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12.2.2 Approach to Diagnosis of Irregular Cycles

Clinical evaluation of a case of cyclic irregularity requires a detailed reproductive history, more so than with many other reproductive problems. Examination of breeding records is essential. In dairy cows, errors in estrous detection are indicated when (1) more than 10% of the interestrous intervals are 3 to 17 days or 25 to 35 days long; (2) more than 5% of the cows have two artificial inseminations within 3 days; or (3) cows are calving early or are further in gestation than predicted from the last breeding when examined for pregnancy. Seventy percent of cows should have an interestrous interval of less than 30 days, and 60% should be in the range of 18 to 24 days. The ratio of 18-to-24—day cycles to 38-to-46—day cycles should be 5:1. Evaluation of heat-detection methods is important when dealing with a hand mating or artificial insemination program. Discussing the owner's understanding of the normal reproductive physiology of the species often is enlightening, and client education may be required. Observation of the teasing behavior of the animal is helpful, and examination of the reproductive tract should provide valuable information. Ancillary procedures such as ultrasonography, uterine culture, cytologic studies, and endometrial biopsy are often needed. Prediction of estrus through rectal examination or determination of the progesterone concentration (or both) may help. Progesterone determination on a sample collected at the time of insemination can be useful in evaluating the accuracy of heat detection. With ruminants it may be wise to suggest the use of a teaser, or marker male. Heat-detection aids (e.g., Kmar patches, tail chalk) are effective if applied properly and observed regularly. Serologic and microbiologic evaluation for the diseases known to cause endometritis or EED may need to be done if the source of the problem has not been determined.

Problems with cyclic irregularity can be difficult to decipher (Boxes 12-4 and 12-5). Management plays a large part, and it often is difficult to convince the client of this.

12.3 ANESTRUS

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Anestrus, the lack of ovarian activity, is a sign, not a disease. It may be a normal physiologic phenomenon or a sign of disease. Incorrectly perceived anestrous behavior may be an indication of inefficient heat detection. In adult

animals, pregnancy is the most common differential diagnosis of anestrus and should be ruled out before proceeding with diagnostic tests. Other differential diagnoses are those associated with an active corpus luteum and elevated progesterone levels, and those associated with low progesterone levels and the absence of an active corpus luteum.[33] Sequential ovarian palpations or determinations of the progesterone concentration can be helpful in determining the cause (Boxes 12-6 and 12-7).

12.3.1

Differential Diagnoses and Causes of Anestrus

1 *Pregnancy*. In any animal presented for anestrous behavior, the most important differential diagnosis to rule out is pregnancy. Any invasive diagnostic techniques must be reserved until after pregnancy has been ruled out. Many practitioners have experienced a case in which the history taken from the owner would make pregnancy seem an impossibility and then been surprised to find a healthy fetus.

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12.3.1.0.0.0.1

Box 12-4 Causes of Cyclic Irregularity in Mares

12.3.1.0.0.0.1.1

COMMON CAUSES

Transition season

Erroneous heat detection

Diestrus ovulation

Intrauterine therapy

Diestral endometrial biopsy

Pneumovagina

Endometritis

Pubertal cycles

Early embryonic death

Spontaneous corpus luteum prolongation

Endophyte-infested fescue

Cervical dilation

12.3.1.0.0.0.1.2

LESS COMMON CAUSES

Urovagina

Rectovaginal fistula

Ovarian tumors

Pyometra

Persistent follicles

Split heats

Endotoxemia

Hemorrhagic anovulatory follicles

Old age

Use of Deslorelin implant

12.3.1.0.0.0.1.3

UNCOMMON CAUSES

Contagious equine metritis

Corpus luteum inadequacy

Anabolic steroids

Progesterone therapy

Phosphorus deficiency

Sex chromosome anomalies

12.3.1.0.0.0.2

Box 12-5 Causes of Cyclic Irregularity in Ruminants

12.3.1.0.0.0.2.1

COMMON CAUSES

- Erroneous heat detection
- Endometritis
- Intrauterine therapy
- Cystic ovaries
- Heat stress
- Leptospirosis
- Infectious bovine rhinotracheitis (IBR) (B)
- Bovine virus diarrhea (BVD) (B)
- Campylobacteriosis
- Trichomoniasis
- Embryonic death after maternal recognition of pregnancy

12.3.1.0.0.0.2.2

UNCOMMON CAUSES

- IBR- or BVD-infected semen
- Bluetongue-infected semen
- Zearalenone toxicity
- Ovarian neoplasia
- Corpus luteum inadequacy

Copper deficiency (O, C)

Molybdenum deficiency (O, C)

Iodine deficiency

Phytoestrogen toxicity

B, Bovine; *C*, caprine; *O*, ovine.

12.3.1.0.0.0.3 Box 12-6 Causes of Anestrus in Mares

12.3.1.0.0.0.3.1 COMMON CAUSES

Season (fall, winter)

Poor heat detection

Corpus luteum persistence

Diestrus ovulation

Pregnancy

Early embryonic death after recognition of pregnancy

Fetal death after endometrial cup formation

Psychologic impediments

Maternal behavior

12.3.1.0.0.0.3.2 LESS COMMON CAUSES

Ovarian tumors

Pituitary tumors

Pyometra

Weight loss

Chronic disease

Lactation

Old age

12.3.1.0.0.0.3.3 UNCOMMON CAUSES

Gonadal dysgenesis

Intersex conditions

Progesterone therapy

Nonsteroidal antiinflammatory drugs (NSAIDs)

Phosphorus deficiency

Ovarian hypoplasia

Anabolic steroids

Zearalenone toxicity

Chromosomal abnormalities

2 *Inadequate heat detection*. In nonpregnant, hand-bred, or artificially inseminated animals, the intensity of estrous behavior may be diminished by environmental factors such as high ambient temperature and humidity or poor footing in the paddock. Clinical disease, such as musculoskeletal pain, may also prevent the normal expression of estrual behavior. Too few cycling herdmates may limit the ability to detect cows in heat.

3 *Psychologic problems*. Nervous mares, mares with foals, or dominant, fat, or phlegmatic mares experiencing normal estrous cycles may be reluctant to show estrus. Vigorous teasing with an aggressive stallion may be necessary to elicit estrous behavior in these animals.[34] Sequential ovarian palpations or

determinations of the progesterone concentration (or both) may be useful for predicting the next estrous period.

4 *Energy deficiency*. Inadequate prepartum nutrition or insufficient energy in the ration during lactation in dairy cattle and in postpartum beef cattle nursing a calf can delay the return to estrus after parturition.[35]

5 *Photoperiod*. Photoperiod plays an important role in the cyclic patterns of seasonal breeders such as the mare, ewe, and doe. The mare is a long-day breeder and has a normal anestrous period during the late fall and winter months. A mare that foals early in the year, during the late winter months (e.g., January through March in the northern hemisphere), and has not been kept under artificial lights during the 2 months previous to her foaling date is very likely to revert back into seasonal anestrus after her foal heat. The mare will remain in anestrus until April or May, when natural lighting conditions have been sufficient to stimulate her through the vernal transitional period and into normal cyclicity. The ewe and doe are short-day breeders and are normally anestrous in the spring and early summer, although breed variations occur.[36] Some sheep and goats near the equator have cycles throughout the year, presumably because of the consistency of the photoperiod.[37] The cow is not considered a seasonal breeder, but an increased photoperiod (18 hours of light to 6 hours of dark) has been shown to shorten postpartum anestrus in winter-calving beef cows.

12.3.1.0.0.0.4

Box 12-7 Causes of Anestrus in Ruminants

12.3.1.0.0.0.4.1

COMMON CAUSE

Season (C, O)

Pregnancy

Poor heat detection

Luteal cysts (B, C)

Pyometra

Poor nutrition, energy

Heat stress

Foot and leg problems

Poor footing (B)

Nursing beef cows and ewes (B, O)

Lactation (O)

Freemartinism (B, C)

Intersex conditions (C)

Postpartum period

Heavy lactation

Primiparity

Periparturient disease

12.3.1.0.0.0.4.2

LESS COMMON CAUSES

Mucometra

Hydrometra

Macerated fetus

Mummified fetus

Trichomoniasis pyometra

Anaplasmosis

Johne's disease

Caprine arthritis-encephalitis (C)

Pseudopregnancy (C)

Insufficient number of cycling herdmates

12.3.1.0.0.0.4.3

UNCOMMON CAUSES

- Ovarian tumor
- Segmental aplasia
- Uterine foreign body
- Ovarian hypoplasia
- Zearalenone toxicity
- Phytoestrogenism
- Phosphorus deficiency
- Copper deficiency
- Cobalt deficiency
- Manganese deficiency
- Molybdenum toxicity
- Progesterone implants
- Schistosomiasis (exotic)
- Lumpy skin disease (exotic)

B, Bovine; *C*, caprine; *O*, ovine.

6 *Hypothalamic or pituitary suppression or lack of stimulation.* Poor nutrition, heavy lactation, periparturient disease, hormone-secreting ovarian tumors, weight loss, or inanition associated with chronic disease may prevent stimulation of the pituitary by gonadotropin-releasing hormone (GnRH) from the hypothalamus.[34] Thus the pituitary does not release enough follicle-stimulating hormone (FSH) and luteinizing hormone (LH) for folliculogenesis, estrogen production, and ovulation by the ovaries. The inactive ovaries produce inadequate estrogen to cause behavioral estrus.

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7 *Congenital or hereditary anomalies, including freemartinism in the cow and doe, intersex conditions that occur in polled goats, and gonadal dysgenesis in the mare*. The ovaries of these animals are unable to respond to FSH and LH stimulation from the pituitary. These animals frequently have rudimentary or hypoplastic ovaries and never display estrus.[38]

8 *Abnormal progesterone levels*. Inadequate progesterone exposure of the pituitary or hypothalamus before the first cycle of the season (ewe and doe) or the first postpartum estrus (cow) usually results in a silent heat.[35,39] On the other hand, suppression of the pituitary, the hypothalamus, or both by a high progesterone level can result in ovarian acyclicity or masking of behavioral estrus, or both.

9 *Retained or persistent corpora lutea*. These can occur spontaneously in the mare without evidence of a uterine pathologic condition. The mare is disposed to diestrous ovulations without estrus and the formation of corpora lutea that mask the next expected estrus. These previously cycling mares often demonstrate anestrus of several months' duration during the breeding season.[38] Persistent corpora lutea in the mare may also occur after fetal death while the endometrial cups are still producing ECG. These mares often undergo a 1- to 4-month anestrous period. Corpus luteum persistence can occur when the production or release of the luteolysin prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is prevented. Segmental aplasia of a major portion of a uterine horn may prevent $PGF_{2\alpha}$ from acting on the ipsilateral ovary of the ruminant and may result in corpus luteum persistence.[33]

10 *Fluid, foreign bodies, or pathologic material in the uterine lumen*. Mucometra, hydrometra, and pyometra prevent the release of $PGF_{2\alpha}$ in ruminants.[33] Thus the corpus luteum persists, and perceived anestrus results. Pyometra in the mare may result in anestrus if the endometrial damage is severe enough to prevent production of $PGF_{2\alpha}$.[38] The presence of a mummified or macerated fetus in the ruminant uterus prevents release of $PGF_{2\alpha}$ and results in a persistent corpus luteum and perceived anestrus.[33]

12.3.2 Approach to Diagnosis of Anestrus

Knowledge of the reproductive physiology of the species involved is essential to understanding the cause of anestrus. Determining the cause of anestrus relies on an in-depth general and reproductive history, a thorough physical examination, and evaluation of the estrous detection programs involved. Pregnancy must be ruled out when dealing with any case of anestrus. In dairies using Dairy Herd Improvement Association (DHIA) records, inadequate heat detection must be suspected if the cows are determined to be cycling by palpation or progesterone tests but fewer than 50% of the possible estrous periods are detected; fewer than 70% of the cows are seen to be in heat by 60 days postpartum; and the average number of days to first service is over 80. The reproductive tract of the nonpregnant anestrous animal must be evaluated for any pathologic condition that might prevent estrus. The uterus of the ruminant should be evaluated for the presence of fluid, a macerated or mummified fetus, or a foreign body. Ultrasonography or radiology may aid the diagnosis of these conditions in small ruminants. The ovaries should be evaluated for luteal cysts (ruminants) or neoplasia. Ultrasonography and hormone concentration determination are often helpful if rectal palpation of the ovaries is impossible. If the ovaries appear to be normal in size, an attempt should be made to determine the presence of a functional corpus luteum producing progesterone. On-site milk or serum progesterone test kits are available for mares and ruminants. Sequential tests at weekly intervals may prove helpful in eliminating inadequate estrous detection as the source of the complaint of anestrus.

Some of the DHIA reproductive parameters can be used to assess the efficiency of estrous detection. The percentage of cows in heat by 60 days after parturition, the percentage of cows bred by 90 days after parturition, and the average number of days to first breeding can be used to evaluate the accuracy of heat detection if most cows have been determined to have normal, cycling reproductive tracts.[40] In addition, a 24-day heat-detection trial can be conducted. Of the nonpregnant, cycling cows, 80% to 85% should be found to be in heat within a 24-day period if estrous detection is adequate.

Anestrus is a frequent reproductive complaint. Often a number of causes are involved in a herd problem. The three most important differential diagnoses of anestrus in a herd are pregnancy, poor estrous detection, and inadequate nutrition. Concurrent, nonreproductive disease must be kept in mind when an individual anestric animal is examined.

12.4 REPEAT BREEDER

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Bruce W. Christensen

Managing repeat breeders is often frustrating and expensive. The repeat breeder is an animal that has been bred during three or more successive heat periods without being diagnosed pregnant.[41] An incidence of 10% to 15% repeat breeders is considered acceptable for dairies.[42] The incidence increases with the herd size and the level of milk production and with the use of artificial insemination.[43] This may be an even greater problem in the horse because 5% to 8% of mares lose their pregnancy in the first 4 months of gestation.[43] The use of ultrasonography and embryo collection indicates that the incidence of EED in the mare is likely even higher.[44] The syndrome of repeat breeders in mares is completely different from that in cows. In mares it is often associated with breeding-induced persistent endometritis. This is discussed in detail in Chapter 43.

The causes of repeat breeding are numerous and are related to male, female, and management factors (Boxes 12-8 and 12-9). The pathogenesis of repeat breeding involves either a failure of fertilization or EED.[42] Some etiologies, such as heat stress in the herd, may involve both mechanisms. Fertilization rates are normal in heat-stressed cows that are bred artificially, but heat stress increases the rate of EED. Heat stress can cause failure of fertilization by affecting spermatogenesis in males used in a natural breeding program.[45] When dealing with an individual repeat breeder, it is often wise to begin with the female. When several females are affected, the male should be eliminated as a source of the problem before proceeding. Management errors may be related to either male or female factors.

Fertilization failure is often the cause of repeat breeder syndrome. Studies have demonstrated delayed or inadequate release of LH, and consequent delayed ovulation, in repeat breeder cows compared with those cows showing normal fertility rates.[47] This observation has led to the investigation of GnRH (or its analogues) and prostaglandins as treatment options for repeat breeders, with some success.[48,49] In addition to LH abnormalities, repeat breeder cows showed prolonged duration of estrus, prolonged lifespan of the preovulatory follicle, and a late postovulatory rise in progesterone.[47] These changes negatively contribute to final oocyte maturation and competence in repeat breeder cows compared with unaffected cows.[50] Insulin has been shown to be an important mediator of follicular development, steroidogenesis, oocyte maturation, and subsequent embryo development,[51] and treatment with insulin has been shown to increase fertility in repeat breeder cows.[52] Workers in Japan have linked the repeat

breeder syndrome with abnormal profiles of endometrial epidermal growth factor (EGF). Assays of EGF have been suggested as diagnostic tools, and EGF treatment has been suggested to restore fertility.[53,54]

12.4.1

Box 12-8 Causes of Repeat Breeding in Mares

12.4.1.1

COMMON CAUSES

Transition season

Endometritis

Poor timing of artificial insemination

Pneumovagina

Metritis

Endometrial fibrosis

Poor heat detection

Ovulation failure

Twins

Uterine lymphatic lacunae

Endometrial cysts

Early foal heat breed

Poor uterine clearance

Ventral uterine sacculation

Endophyte-infested fescue

12.4.1.2 LESS COMMON CAUSES

Diestrous breeding

Urovagina

Rectovaginal fistula

Malnutrition

Pyometra

Heat stress

Poor semen quality

Old age

12.4.1.3 UNCOMMON CAUSES

Salpingitis

Hydrosalpinx

Oviductal adhesions

Oophoritis

Uterine neoplasia

Cervical neoplasia

Ovarian neoplasia

Parovarian cysts

Contagious equine metritis

Iodine deficiency

True hypothyroidism

Phosphorus deficiency

Zearalenone toxicity

Intersexuality

Gonadal dysgenesis, sex reversal, trisomy

Other karyotype abnormalities

Teratogenic factors

Vitamin A deficiency

Cervical trauma

Luteal insufficiency

12.4.2

Box 12-9 Causes of Repeat Breeding in Ruminants

12.4.2.1

COMMON CAUSES

Heat detection

Poor timing of artificial insemination

Inadequate or delayed luteinizing hormone surge

Poor artificial insemination technique

Malnutrition

Follicular cysts

Endometritis

Heat stress

Trichomoniasis

Campylobacteriosis

Leptospirosis

Inadequate uterine involution

12.4.2.2 LESS COMMON CAUSES

Poor semen quality

Inadequate male power (not enough males)

Infectious bovine rhinotracheitis (IBR) (B)

Bovine virus diarrhea (BVD) (B)

Bluetongue

Brucellosis

Anaplasmosis

Toxoplasmosis (C, O)

Border disease (C, O)

Selenium deficiency

Phosphorus deficiency

Ureaplasmosis

Urine pooling

Pneumovagina, pneumouterus

Oviductal bursal adhesions

Segmental aplasia

Rectovaginal fistula

Parovarian cysts

Zearalenone toxicity (B, O)

Fescue toxicity

Uterine tumors

Defective embryos

Dietary protein toxicity

12.4.2.3 UNCOMMON CAUSES

Johne's disease

Tuberculosis

Vitamin A deficiency

Zinc deficiency

Manganese deficiency

Cobalt deficiency

Copper deficiency

Molybdenum toxicity

Selenium toxicity

Iodine deficiency

Iodine toxicity (B, O)

Oophoritis

Fat necrosis (B)

Brasilia, toxicity

Ovarian tumors

Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)

Polybrominated biphenyl toxicity (B)

Phytoestrogen toxicity (B, O)

Hydrosalpinx

Salpingitis

Cervical anomalies and cysts

Chromosomal abnormalities (1/29 or 14/20 centric fusions)

Fluoride toxicosis

Segmental aplasia

Uridine monophosphate synthase deficiency

	Delayed ovulation
	Schistosomiasis (exotic)
	Tick-borne fever (exotic)
	Epivag (exotic)
	Leucaena leucocephala, (exotic)
	Besnoitiosis (exotic)
	Maedi, visna (exotic)
	Lumpy skin disease (exotic)
	Onion grass toxicity (exotic)

B, Bovine; *C*, caprine; *O*, ovine.

Early embryonic death also contributes as a cause of infertility in repeat breeders.[42,44] The interval between heats may help distinguish between EED and failure of fertilization. Failure of fertilization usually does not affect the interestrous interval. However, EED may prolong the interestrous interval if the fetal wastage occurs after the time of maternal recognition of pregnancy. Maternal recognition of pregnancy occurs at approximately days 15 to 17 after estrus in the cow, days 11 to 14 in the mare, and days 12 to 13 in the ewe.[55] Animals experiencing EED after pregnancy recognition often have interestrous intervals corresponding to multiples of a normal cycle length. Luteal insufficiency is suspected to cause EED in some repeat breeder cows, and trials of exogenous progesterone supplementation have shown promise for maintaining pregnancy in young late lactation repeat breeders.[56]

12.4.3 Approach to Diagnosis

Clinical differentiation of EED from failure of fertilization is difficult. In addition to evaluation of heat detection and breeding techniques, it is important to obtain a detailed history. When dealing with a herd problem, the clinician begins by evaluating the male or males used or assessing the semen quality and techniques used for artificial insemination. When dealing with an individual repeat breeder, evaluation of the female is the first step.

Evaluation of the male should include evaluation of the animal's physical condition, including the genitalia. The quality of the semen should be checked. The male's libido and ability to mount should be determined by observation or through historic information. Examination of the male for venereally transmitted diseases, such as trichomoniasis and campylobacteriosis in the bull and contagious equine metritis in the stallion, may be

warranted if other factors are ruled out. When dealing with an artificial insemination program, the semen quality should be evaluated and the thawing, transporting, timing, and deposition techniques should be evaluated.

Errors in heat detection and the timing of breeding are major management causes of repeat breeding. Discussing and observing the methods used to determine when an animal should be bred are important in dealing with both the individual animal and the herd. Milk or serum progesterone determinations at the time of breeding have proved helpful in determining the accuracy of heat detection and timing of insemination. In some dairies 40% to 50% of the cows are bred at the wrong time.

Examination of the female or females should begin with evaluation of the body condition. Poor nutrition has been associated with repeat breeding.[57] The reproductive examination should include evaluation of the vulva, vagina, cervix, uterus, oviducts, and ovaries. Poor vulvar conformation may lead to pneumovagina and endometritis, resulting in EED. The spermicidal effect of urine may cause failure of fertilization in the mare or cow that pools urine in the vagina. Cervical canal occlusion can prevent fertilization. An abnormal uterine environment may also lead to repeat breeding. Large volumes of pus and debris associated with a postpartum metritis may cause failure of fertilization because of its effect on sperm. Endometritis with minimal intraluminal pus rarely causes failure of fertilization but often results in EED. Unlike ruminants, the mare may continue to display estrus while experiencing pyometra. The volume of pus present in the uterus is likely to cause failure of fertilization. Hydrosalpinx or salpingitis may lead to failure of fertilization by blocking sperm or ovum passage. Ovulation abnormalities such as delayed ovulation or ovarian cyst formation may result in failure of fertilization. Whenever possible, including a uterine culture, cytologic smear, and endometrial biopsy as part of the examination is likely to help determine the cause of the infertility.

Differentiation of EED from failure of fertilization in repeat breeders has been facilitated by the use of embryo flushing techniques and ultrasonography. Collection of unfertilized ova indicates failure of fertilization; collection of degenerating embryos indicates very early embryonic death. In ruminants, failure to collect ova or embryos may indicate oviductal blockage resulting in failure of fertilization. This is not the case for mares because they usually retain unfertilized ova in the oviducts.

Ultrasonic determination of pregnancy in the mare and cow has made very early detection of pregnancy possible. Loss of an embryo after detecting it with ultrasound at 10 days of gestation confirms EED. Pregnancy wastage can be confirmed later in gestation with sequential rectal palpations of the reproductive tract or ultrasonic evaluation. Hormone assays are also helpful for confirming embryo or fetal loss.

An assay for ECG, previously called *pregnant mare serum gonadotropin* (PMSG), can be used to determine if a mare was pregnant long enough to stimulate formation of the endometrial cups and ECG production. ECG can be detected at about 40 days of gestation with these kits. The endometrial cups continue to produce ECG until 120 to 150 days of gestation even if the fetus dies. Therefore ECG can be used to confirm EED but not failure of fertilization. Progesterone determination cannot be used to confirm pregnancy in the mare or ruminants. However, it can be used to confirm nonpregnancy if the progesterone level is low early in the expected gestation. A bovine early conception factor test can be used to confirm fertilization, but it does not rule out EED later.

The fetally derived hormone-metabolite estrone sulfate has been used to determine the presence of a live fetus. It is detectable in the serum or urine of the dam if the fetus is alive after 45 days of gestation in the doe, 70 days of gestation in the ewe, 100 days of gestation in the mare, and 120 days of gestation in the cow.[58,59] Thus a decline in estrone sulfate indicates death of the fetus. Estrone sulfate is probably most helpful in confirming fetal loss in the doe and ewe because other techniques are available in the larger species.

Infertility associated with repeat breeding is a perplexing clinical problem. The economics involved often do not warrant pursuing the cause. If the cause is determined, therapy often is unrewarding.

Boxes 12-8 and 12-9 list the causes of repeat breeding in mares and ruminants. The causes have been divided into expected frequencies of occurrence.

12.5 PREGNANCY LOSS

Patrick M. McCue

Mats H.T. Troedsson

Pregnancy loss refers to the failure of a conceptus to be maintained successfully to term. Pregnancy loss may be classified as early embryonic death (EED), abortion, or stillbirth, depending on the gestational stage when the pregnancy loss occurred. EED is the death of a conceptus before organogenesis is complete (approximately 55 days in horses, 45 days in cattle, and 34 days in sheep).[60] *Abortion* refers to pregnancy loss after the completion of organogenesis. *Stillbirth* refers to the delivery of a nonviable fetus at or near term.

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12.5.1 Early Embryonic Death

The exact incidence of EED in any species is difficult to determine because most losses occur before pregnancy can be routinely diagnosed. Embryonic death early in pregnancy usually results in reabsorption of the embryonic tissues and fluids. Consequently, EED cannot be distinguished from failure of fertilization in most instances. However, despite the lack of clinical evidence, EED probably accounts for the largest percentage of reproductive wastage in large animals. The incidence of EED has been estimated at 5% to 24% in mares,[61] 30% to 35% in cows,[62] and 20% to 30% in ewes.[63] The rate of EED is much higher in subfertile or repeat breeder females and in older females.

Loss of the embryo before maternal endocrine recognition of the pregnancy (i.e., days 14 to 16 in the mare, days 15 to 17 in the cow, and day 12 in the ewe and doe) results in return to estrus at the normal time. Embryonic loss after this critical period may result in persistence of the corpus luteum in horses, pseudopregnancy in goats, or irregular returns to estrus in cattle.

Chromosomal and genetic defects of the oocyte, sperm, or embryo; a poor oviductal or uterine environment; endocrine dysfunction; and maternal stress are all considered important factors in the pathogenesis of EED.[61,64] Infectious agents such as *T. foetus* and *C. fetus* subsp. *venerealis* in cattle[64] and *Streptococcus zooepidemicus* and other bacteria in horses[65] can cause EED. Endogenous release of $PGF_{2\alpha}$ during the corpus luteum—dependent stage of gestation may result in luteolysis and subsequent embryonic loss or abortion in any large animal species. Luteal insufficiency associated with low plasma progesterone concentrations has been suggested as a possible cause of EED in horses, cattle, and sheep, although scientific evidence is limited.[62,66,67]

12.5.2 Abortion

The rate of abortion after pregnancy diagnosis at 60 days of gestation has been estimated to be approximately 10% in horses[68] and 3% to 4% in cattle.[69] Fetal death may result in abortion (expulsion of the fetus from the

uterus) or retention of the fetus in the uterine lumen, with subsequent fetal maceration or mummification. In animals with a corpus luteum—dependent pregnancy for all or most of gestation (cows, goats, llamas), death of the fetus usually results in the abortion of an autolyzed fetus because of a delay between the time of fetal death and lysis of the corpus luteum. In species that do not depend on a corpus luteum for maintenance of pregnancy for most of gestation (e.g., mares and ewes), fetal death causes an immediate decrease in placental progesterone production and rapid expulsion of a relatively nonautolyzed fetus. Mummification is characterized by fluid reabsorption from a fetus retained in a sterile uterine environment. Fetal mummification is most common in multiparous species with a corpus luteum—dependent pregnancy (e.g., sows) and is rare in uniparous species that are corpus luteum independent for most of gestation (e.g., mares). *Maceration* refers to the degenerative changes that occur in a fetus after retention in a nonsterile uterine environment. Fetal maceration may be associated with significant maternal endometrial damage.

12.5.2.1

HORSES

Equine abortions may be characterized as infectious or noninfectious in origin. Most equine abortions occur secondary to placental dysfunction. One of the most commonly diagnosed infectious causes of abortion in horses is equine herpesvirus type 1 (EHV-1).[68] Abortion caused by EHV-1 usually occurs after 7 months of gestation and accounts for 10% to 15% of all diagnosed equine abortions. Exposure of pregnant mares to EAV may lead to abortion within 1 to 3 weeks after initial viral exposure. Abortion may be caused by vasculitis, edema, and necrosis in the endometrium and allantochorion.[70] There is no evidence that exposure to EAV at breeding can cause a mare to abort later in gestation. Abortion rates may range from 10% to 70% during an outbreak.

Consumption of Eastern tent caterpillars (larva of *Malacosoma americanum*) by mares causes abortion after approximately 40 days of gestation. The syndrome has been named *mare reproductive loss syndrome* (MRLS). Pregnancy loss at 40 to 150 days of gestation is characterized by hyperechoic amniotic and allantoic fluids on ultrasonographic examination along with a dead or dying fetus.[71,72] Near-term abortions are characterized by histologic lesions in the placenta and umbilical cord. In many cases, endometrial cultures are positive for non—beta-hemolytic streptococci and *Actinobacillus* species. Diagnosis of MRLS is currently based on four variable factors: placental lesions, culture of characteristic bacteria from fetal tissues, conformation of increased caterpillar exposure, and diagnostic elimination of other known causes of abortion (John Roberts, personal communication). The microscopic lesions observed in natural late-term MRLS cases are primarily the result of host response to bacterial infection, with the primary isolates being non—beta-hemolytic streptococci and actinobacilli.

During an outbreak in central Kentucky in 2001 and 2002, a variety of nonspecific lesions were reported that included placental edema, fetal pneumonia, and hemorrhages in the heart and placenta. During this outbreak, inflammation of the umbilical cord (funisitis), specifically the amniotic segment, was observed in 78% of cases.[73] Funisitis was also observed in three cases necropsied during a 2006 Florida outbreak. The lesion is initiated as a suppurative to pyogranulomatous response between the outer circumferential stroma and the outer tunica adventitia of major umbilical vessels and progresses outward to involve or ulcerate the amniotic surface of the umbilical cord (John Roberts, personal communication). Other causes of equine abortion such as noninfectious umbilical cord lesions, leptospirosis, and EHV should be ruled out by appropriate diagnostic tests. In addition, if a horse farm encounters unilateral endophthalmitis or pericarditis in the general population, MRLS should be elevated as a differential diagnosis for unsolved abortions.[74,75]

Nocardioform actinomycete a filamentous, branching bacillus, has recently been identified as a significant cause of chronic placentitis and subsequent late-term abortion, stillbirth, and premature birth.[76] *Leptospira* species have also been identified as a significant cause of equine abortion in Kentucky.[77] Bacterial and fungal abortions in mares are primarily caused by infections that ascend through the cervix, causing placentitis and subsequent fetal infection. The bacterial organisms most commonly cultured from aborted fetuses include *Streptococcus* species, *Escherichia coli, Pseudomonas* species, *Klebsiella* species, and *Staphylococcus* species. The most frequently recovered fungi are *Aspergillus* species.

The most common noninfectious cause of equine abortion is twin pregnancy.[68] Inability of the uterus to support two fetuses to term because of insufficient placental support may result in abortion at any stage of gestation but is most common after 7 months. Early diagnosis of pregnancy using ultrasonography allows for highly successful manual reduction of one twin if done before day 16 of pregnancy. This technique has significantly reduced the incidence of abortion caused by twin pregnancies.

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12.5.2.2

RUMINANTS

Infectious bovine rhinotracheitis—infectious pustular vulvovaginitis (IBR-IPV) virus and bovine virus diarrhea—mucosal disease (BVD-MD) virus are two of the most common viral causes of abortion in cattle.[78] Bacterial abortions caused by *Brucella abortus, Arcanobacterium (Actinomyces) pyogenes, Bacillus* species, *Listeria monocytogenes, E. coli, Leptospira* species, and *Pasteurella haemolytica* and fungal abortions caused by *Aspergillus* species and *Mucor* species usually result from hematogenous spread and localization in the placenta.[79] Protozoal abortion, caused by *Neospora* organisms, has recently been recognized as a significant cause of abortion in cattle worldwide.[80] Epizootic bovine abortion (EBA) is a common cause of third-trimester abortion in susceptible heifers and cows inhabiting the foothills of the Sierra Nevada mountain range of California, Nevada, and Oregon.[81] The vector for EBA is the argasid tick *(Ornithodoros coriaceus)*, but the causative agent has not been identified.

Campylobacteriosis (vibriosis), caused by *C. fetus* and *C. fetus* subsp. *jejuni*, and enzootic abortion of ewes caused by *C. psittaci* are the most common infectious causes of abortion in sheep.[82] They are characterized by abortion in the last 4 to 6 weeks of gestation, premature births, stillbirths, and birth of weak, infected lambs. *C. psittaci* is also the most common cause of infectious abortion in goats in the United States.[83]

Noninfectious causes of large animal abortion include genetic or chromosomal factors, maternal stress, inadequate nutrition, vitamin or mineral deficiencies, ingestion of poisonous plants or other toxins, hormonal factors, environmental factors, physical factors, and certain medications.

12.5.2.2.1

Box 12-10 Causes of Pregnancy Loss in Mares

12.5.2.2.1.1

COMMON CAUSES

Impaired oviductal and uterine environment (EED)

Chronic endometritis (EED, Ab)

Embryonic defects (EED)

Endometrial fibrosis (EED, Ab)

Twinning (Ab)

Equine herpesvirus type 1 (EHV-1) (Ab)

Bacterial placentitis (*Streptococcus* species, *Escherichia coli, Pseudomonas* species, *Klebsiella*, species, *Staphylococcus* species) (Ab)

Fungal placentitis (Ab)

Umbilical cord abnormalities (Ab)

12.5.2.2.1.2

LESS COMMON CAUSES

Endotoxemia (EED, Ab)

Leptospirosis (Ab)

Mare reproductive loss syndrome (MRLS) (EED, Ab)

Fetal anomalies (Ab)

Maternal stress, other disease (EED, Ab)

Chromosomal abnormalities (Ab, EED)

Fescue toxicity (EED, Ab)

Advanced maternal age (EED)

Equine viral arteritis (Ab)

Equine infectious anemia (Ab)

Uterine torsion (Ab)

Endocrine factors (EED)

Malnutrition (EED, Ab)

Drug-induced causes (EED, Ab)

Premature separation of the placenta (Ab)

Fetal asphyxia (Ab)

Placental insufficiency (Ab)

12.5.2.2.1.3

UNCOMMON CAUSES

Ehrlichia risticii (Potomac horse fever) (Ab)

Uterine body pregnancy (Ab)

Endometrial adhesions (EED)

Taylorella equigenitalis (contagious equine metritis) (EED)

Uterine lymphatic lacunae, cysts (EED, Ab)

Hyperlipemia (Ab)

Lymphosarcoma (Ab)

Iatrogenic causes (EED, Ab)

Fetal diarrhea syndrome (Ab)

Ergot toxicity (EED, Ab)

Brucellosis (Ab)

Mycobacterium infection (Ab)

Corynebacterium pseudotuberculosis (Ab)

Rhodococcus equi (Ab)

Mycoplasma infection (Ab)

Coccidioidomycosis (Ab)

Histoplasmosis (Ab)

Babesiosis (Ab)

Vitamin A deficiency (Ab)

Iodine deficiency (EED, Ab)

Granulosa theca cell tumors (Ab)

Cryptococcosis (Ab)

Sorghum, Sudan grass (Ab)

Locoweed (*Astragalus* species)

Hoary alyssum poisoning (Ab)

Salmonella abortus equi (Ab)

Ab, Abortion; *EED*, early embryonic death.

12.5.3 Approach to Diagnosis of Abortion

A definitive diagnosis is reached in 20% to 40% of bovine abortions,[60] 50% to 60% of equine abortions,[68] and 30% to 40% of sheep abortions.[84] The generally low diagnostic success is a result of the complexity of the condition (Boxes 12-10 and 12-11). Abortion involves disease in the maternal, placental, and fetal compartments individually or together, and all these compartments have to be examined thoroughly. In addition, a “triad” of

determinants for animal disease has to be considered: (1) the presence of a pathogenic organism, (2) the environment in which a host lives, and (3) the susceptibility of the host to the disease.[85] To enhance diagnostic success, information and samples must be collected from the fetus, placenta, dam, and herd. A thorough history should be obtained, including the gestational age of the fetus; reproductive, medical, and vaccination history of the dam and other individuals in the herd; previous abortions and diagnoses; new arrivals to the herd and contacts of the animal with other herds; potential causes of maternal stress; possible access to toxins and poisonous plants; and sources of water and nutrition.

A physical examination that includes all body systems should be performed on the dam. Samples should be collected from the vagina, uterus, or both for culture and cytologic studies. Examination of the reproductive system should include palpation or ultrasonography of the reproductive tract per rectum, speculum examination of the vagina, and digital examination of the cervix. Paired serum samples from the dam and other females in the herd (10 animals or 10% of the herd, whichever is greater) may also help demonstrate an immunologic response to an infectious agent. Maternal serologic testing is generally most useful if paired samples are submitted, combined with accurate information about the animal's vaccination history. However, postabortion titers from cows that aborted can be compared with titers from unaffected cows in the herd at a similar stage of lactation. Demonstration of a fourfold rise in titer between acute and convalescent serum samples suggests recent exposure to an agent, but the presence of antibodies does not necessarily indicate that the agent caused the abortion. An exception can be made for brucellosis and leptospirosis, for which a high titer from a single sample can be diagnostic.

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12.5.3.1

Box 12-11 Causes of Pregnancy Loss in Ruminants

12.5.3.1.1

COMMON CAUSES

Campylobacter infection (B: EED; O, C: Ab)

Epizootic bovine abortion (B: Ab)

Arcanobacterium (Actinomyces) pyogenes (B: Ab)

Bacillus species (B: Ab)

Bovine protozoal abortion (Neospora species) (B, C: Ab)

Infectious bovine rhinotracheitis—infectious pustular vulvovaginitis (IBR-IPV) virus (B: EED, Ab)

Leptospirosis (B, O, C: Ab)

Trichomoniasis (B: EED, Ab)

Brucellosis (B, O, C: Ab)

Bovine virus diarrhea (BVD) (B: EED, Ab)

Toxoplasmosis (O, C: EED, Ab)

Border disease (O, C: EED, Ab)

Chlamydiosis (O, C: Ab)

Embryonic defects (B, O, C: EED)

Bacterial abortion (B, O, C: Ab)

12.5.3.1.2 LESS COMMON CAUSES

Twinning (B: Ab)

Prenatal asphyxia (B, O, C: Ab)

Akabane virus (B, O, C: Ab)

Q fever *(Coxiella burnetii)* (O, C: Ab)

Mycotoxicosis (B, O, C: Ab)

Anaplasmosis (B, O, C: Ab)

Ureaplasma infection (B, O: EED, Ab)

Mycoplasma infection (B, C: Ab)

Chromosomal abnormalities (B, O, C: EED, Ab)

Malnutrition, protein-calorie starvation (B, O, C: EED, Ab)

Bluetongue (B, O: EED, Ab)

Haemophilus somnus (B: Ab)

Tuberculosis (B: Ab)

Uterine torsion (B: Ab)

Water deprivation-salt toxicity (B, O, C: Ab)

Selenium deficiency (B, O, C: Ab)

Mycotic, fungal abortion (B, O, C: Ab)

Salmonellosis (B, O, C: EED, Ab)

Nitrate-nitrite poisoning (B, O: Ab)

Drug-induced causes (B, O, C: EED, Ab)

Endotoxemia (B, O, C: EED, Ab)

Cache Valley virus (B, O: EED, Ab)

Maternal stress (O, C: Ab)

Pregnancy toxemia (O, C: Ab)

Umbilical cord, placental abnormalities (B, O, C: Ab)

Fetal anomalies (B, O, C: Ab)

Deficiency of uridine monophosphate synthase (DUMPS) (B: EED)

Listeria (B, O, C: Ab)

12.5.3.1.3 UNCOMMON CAUSES

Pine needle poisoning (B: Ab)

Chlorinated naphthalene toxicity (B: Ab)

Osteopetrosis (B: Ab)

Lathyrus poisoning (B, O, C: Ab)

Cobalt deficiency (B: EED, Ab)

Yersinia pseudotuberculosis (B, O, C: Ab)

Death camas (*Zigadenus* species) (O: Ab)

Foxglove (B: Ab)

Phosphate fertilizer toxicity (O: Ab)

α-Mannosidosis (B, O, C: Ab)

Ergot toxicity (B, O: EED, Ab)

Iodine deficiency (O, C: EED, Ab)

Hydrops fetalis (B, O: Ab)

Iatrogenic causes (B, O, C: EED, Ab)

Lead toxicity (B, O: EED, Ab)

Liver fluke disease (B, O, C: Ab)

Locoweed (*Astragalus, Oxytropis* species) (B, O, C: EED, Ab)

Ryegrass poisoning (B, O: Ab)

Sarcocystis infection (B, O, C: Ab)

Veratrum poisoning (O, C: EED, Ab)

Vitamin A deficiency (B, O, C: Ab)

Polybrominated biphenyl toxicity (B: EED, Ab)

Broomweed (*Gutierrezia* species) (B, O, C: Ab)

Bacillary hemoglobinuria (B, O: Ab)

Tetraglymia glabrata (O: Ab)

Copper deficiency (O, C: Ab)

Caprine herpesvirus infection (C: Ab)

Habitual abortion in Angora goats (C: Ab)

Ab, Abortion; *B*, bovine; *C*, caprine; *EED*, early embryonic death, *O*, ovine.

For optimal diagnostic efficiency, the entire aborted fetus and placenta should be submitted to a diagnostic laboratory for necropsy. If this cannot be done, a prompt necropsy should be performed, and collections of fetal, placental, and maternal samples should be submitted to a diagnostic laboratory (Table 12-1).

A systematic necropsy must be performed on the aborted fetus. Fetal age and development may be assessed by measuring crown-rump length, hair patterns, and color. Meconium staining of the skin suggests uterine fetal distress. The condition of the fetus, including the degree of autolysis, should be noted. A careful examination for fetal anomalies (e.g., cerebellar hypoplasia, hydrocephalus, cleft palate, cardiac anomalies) should be performed. Histopathologic samples should be immersed in a volume of 10% buffered formalin (or Bouin fixative) equivalent to 10 times the volume of tissue. Samples for culture, virus isolation, and fluorescent antibody tests should be submitted on ice in separate sterile containers. A sample of abomasum and stomach contents should be aseptically collected for culture. Fetal heart blood or thoracic fluid may be collected for serologic evaluation. A late-term fetus is immunologically competent, and high titers may indicate activity of a pathogenic agent. Serologic testing of fetal fluids can be useful both in detecting a nonspecific active fetal immune response (total immunoglobulin [IgG]) and for titers against a specific antigen.

The fetal membranes should be examined for size, weight, degree of autolysis, condition, and completeness. 206

Samples of placental tissue, especially areas with lesions, should be collected for histologic examination, impression smears, bacterial culture, virus isolation, and fluorescent antibody tests. The equine placenta should be examined for integrity, lesions, and distribution of chorionic villi. The normal equine placenta is everted after expulsion, with the allantoic surface presented outward and chorioallantois ruptured at the site of the cervical star. Blood may be collected from the free end of the cord. The allantoic surface should be examined for abnormalities such as multiple allantoic pouches that may indicate compromised fetal circulation.[86] The chorionic surface of the placenta should be examined for lesions and distribution of chorionic villi. Areas of avillous chorion are normally observed in association with the cervical star, narrow folds over large vessels, and 207

areas opposing endometrial cups. Absence of chorionic villi over a circumscribed area is characteristic of twins and represents the region where two placentas were in contact. The region of the placenta adjacent to the cervix should be examined for loss of chorionic villi and the presence of inflammatory exudate, a hallmark of ascending infection.

Table 12-1 Tissue Samples to Be Submitted for Diagnosis of the Cause of Abortion

	Preservation Method	
Source	**Chilled or Frozen**	**Fixed***
Aborted fetus	Lung, liver, kidney, spleen, thymus, skeletal muscle, heart, heart blood, abomasum, and stomach contents	Lung, liver, kidney, spleen, thymus, skeletal muscle (diaphragm), heart, adrenal gland, lymph node, brain
Placenta	Allantochorion (ruminants: cotyledons and intercotyledonary areas), allantoamnion, amniotic fluid, cord blood	Allantochorion (ruminants: cotyledons and intercotyledonary areas), allantoamnion
Dam or herd	Paired serum samples, vaginal or uterine swabs	

* 10% Formalin or Bouin fixative should be used.

The cotyledons and intercotyledonary spaces of the ruminant placenta should be carefully examined for lesions. Autolytic changes of the placenta may be difficult to interpret. Some normal features of the bovine placenta must be kept in mind.[69] Amniotic plaques are present on the inner surface of the amnion and on the umbilical cord. They are most prominent at 3 to 7 months of gestation. Necrotic areas of the chorioallantois in the tips of the uterine horns are also normal and caused by insufficient vascularization to that area. Mineralization of the placenta is normal during the first months of gestation but may reflect placental injury associated with infection at the end of gestation.

All aborted fetuses and placental tissues should be handled with care, and tissues not submitted to a diagnostic laboratory should be burned or buried. Dams that have aborted should be isolated from the remainder of the herd.

12.6 FESCUE TOXICOSIS

James P. Brendemuehl

Tall fescue (*Festuca arundinacea* Schreb.) is a cool-season, seed-propagated, perennial grass that is grown in many regions of the United States. It is traditionally recognized to be the most widely grown pasture grass in the humid areas of the southeastern and northwestern United States. Recent surveys have demonstrated endophyte-infected forage in more than half of all forage samples tested in all geographic areas of the United States.[87,88] An endophytic fungus, *Neotyphodium coenophialum*, has been shown to be widely spread wherever tall fescue is grown.[88] Undesirable signs in animals grazing tall fescue have been associated with the presence of the asymptomatic fungal endophyte (also see Chapter 54).

12.6.1 Clinical Manifestations of Fescue Toxicosis

Agalactia or hypogalactia is the most commonly reported clinical sign in mares grazing endophyte-infected fescue.[89,90] Mares grazing endophyte-infected fescue show significantly lower prolactin concentrations than mares grazing endophyte-free forage. Hypoprolactinemia associated with endophyte ingestion would inhibit normal mammary development in the prepartum period. Prolactin concentrations increase in the immediate prepartum period in the mare and return to baseline levels several weeks postpartum. Episodic increases in prolactin associated with nursing by the foal suggest the requirement of prolactin to maintain lactogenesis.[91] Suppression of prolactin by ergopeptines during the prepartum period in the cow reduced milk yields but had no effect after lactogenesis had been established. Therefore it appears that the endophyte reduces milk yield postpartum because of reduced intake.

Calving rates are decreased by the presence of endophyte in tall fescue.[92] Ewes grazing endophyte-infected fescue demonstrated a prolonged interval to conception after introduction of the ram compared with ewes on endophyte-free pasture.[93] Necropsy results and time to return to estrus indicated embryonic mortality as a cause. Mares grazing endophyte-infected fescue demonstrated increased embryonic loss rates, prolonged luteal function, and decreased per-cycle pregnancy rates compared with mares grazing endophyte-free pastures.[94]

Puberty in heifers is delayed by grazing endophyte-infected tall fescue. Progesterone concentrations were additionally decreased in heifers grazing endophyte-infected fescue, indicating luteal function was impaired.[95] Altered luteal function caused by endophyte exposure could possibly affect cyclicity and reduce pregnancy maintenance.

Mares grazing endophyte-infected tall fescue demonstrate a significant incidence of prolonged gestation, agalactia, dystocia, poor foal viability, and retained and thickened placentas.[89,96] Foals born to mares grazing endophyte-infected tall fescue are typically weak at birth with characteristic signs of dysmaturity, including overgrown hooves, irregular dental eruption, lanugo, and flexor laxity. Foal weights are significantly greater in endophyte-exposed mares despite reduced muscle mass. At birth, concentrations of triiodothyronine, progestagens, adrenocorticotropic hormone, and cortisol were significantly lower in foals from mares grazing endophyte-infected fescue.[97]

Endocrine alterations in pregnant mares grazing endophyte-infected fescue are a depression in prolactin, [89,90,97,98] thyroxine,[99] progestogens,[89,97,98] and relaxin.[100] Progesterone concentrations did not differ in mares that experienced early embryonic death, indicating an effect of the endophyte other than impaired luteal function.[94] Total progestogen concentrations were reduced with endophyte exposure of pregnant mares only after day 300 of gestation.[101] Short-term exposure of late-gestation mares to endophyte-infected fescue results in significant decreases in prolactin and progestogens.[101] At birth, concentrations of total progestogens were significantly reduced in mare jugular, foal jugular, and umbilical artery plasma, indicating reduced fetal and placental progestogen synthesis.[97]

Placental alterations in mares associated with consuming endophyte-infected fescue include premature separation of the allantochorion, increased allantochorion weight and thickness, and retained placenta.[89,96,98] Transabdominal ultrasonography demonstrated a significant increase in uteroplacental thickness in endophyte-infected mares. However, this was not observed until an average of 8 hours before the onset of labor. Premature

separation of the allantochorion was detected in conjunction with the increase in placental thickness. Histologic evaluation of the allantochorion revealed a significant increase in the splanchnic mesoderm caused by edema.

12.6.2

Approach to Diagnosis of Fescue Toxicosis

Definitive diagnosis of fescue toxicosis involves identification of the causative endophytic fungus in forage or seed samples by microscopic examination (Boxes 12-12 and 12-13). Ergopeptine concentrations may additionally be determined by high-pressure liquid chromatography analysis or specific enzyme-linked immunosorbent assay (ELISA). A presumptive diagnosis of fescue toxicosis can be made in cattle based on expression of the characteristic clinical signs of hyperthermia, excessive salivation, long, rough hair coat, necrosis of the tail and ear tips, and fat necrosis in association with consuming fescue forage. Hypoprolactinemia is supportive of the diagnosis, but the assay is not commercially available.

A presumptive diagnosis of fescue toxicity in the pregnant mare is based on the observation of failure of normal mammary development for gestational stage. Prolongation of gestation is commonly reported as well. An accurate breeding history should include dates of breeding, dates of confirmed pregnancy diagnosis, and absence of parturition at the anticipated time. A history of recent exposure to fescue pasture or hay is supportive. In tall fescue-endemic areas, pastures that contain tall fescue grass should be considered infected with the endophyte unless specific testing has confirmed otherwise. Determination of total plasma progestogen concentrations is a sensitive indicator of endophyte exposure after 300 days of gestation.[101]

12.6.2.1

Box 12-12 Manifestations of Fescue Toxicity in Mares

Agalactia, hypogalactia

Hypoprolactinemia

Decreased relaxin prepartum

Prolonged gestation

Early embryonic death

Cyclic irregularity

Dystocia

Premature allantochorion separation

Allantochorion edema

Increased placental weight

Retained placenta

Corpus luteum persistence

Decreased pregnancy rates

Decreased total progestagens prepartum

Poor neonatal viability

Reduced colostral immunoglobulin G (IgG) absorption

Neonatal hypoadrenalism

Neonatal hypopituitarism

Neonatal hypothyroidism

Fetal oversize

Hirsutism

Hyperhidrosis

12.6.2.2

Box 12-13 Manifestations of Fescue Toxicity in Ruminants

Agalactia, hypogalactia

Reduced calf birth weight

Hypoprolactinemia

Reduced serum cholesterol

Reduced conception rates

Reduced pregnancy rates

Early embryonic death

Cyclic irregularity

Delayed return to cyclicity postpartum

Dystocia

Hyperthermia

Hyperpnea

Hirsutism

Reduced weight gain

Photosensitization

Necrosis of the digits

Necrosis of the ears and tail

Fat necrosis

Management of a mare suspected of endophyte exposure should consist of removing the mare from the suspected pasture or hay source and maintaining the mare in a stall or dry lot under close observation. High-quality hay, preferably legume, should be provided. Because of the increased incidence of dystocia in mares grazing endophyte-infected tall fescue, close monitoring of the mare and attendance at parturition is critical to minimize risk to the mare and loss of the foal. Removal of mares from infected fescue by day 300 of gestation has been demonstrated to alleviate the toxic effects on the mare and foal. Removal after day 300 carries an increased risk of prolonged gestation, agalactia, dystocia, and neonatal death. Induction of parturition is not recommended because of the high incidence of fetal dysmaturity, fetal oversize, and failure of pelvic relaxation associated with endophyte exposure. Elective cesarean section deliveries of postdate gestation mares have resulted in significantly higher foal survival rates than spontaneous deliveries.

Where removal of pregnant mares from infected fescue is not practical or mares are inadvertently grazed on endophyte-infected fescue beyond the recommended stage of gestation for removal, pharmacologic intervention

is warranted. Several DA_2 dopamine receptor antagonists—perphenazine,[103] fluphenazine,[100] and domperidone[104]—and the dopamine depletor reserpine[105] have been investigated prophylactically to prevent or therapeutically to treat clinical fescue toxicosis. Perphenazine[103] and fluphenazine[100] have demonstrated mixed success in preventing toxicosis in restricted clinical trials. Reserpine[105] was ineffective in preventing prepartum agalactia and prolonged gestation but was sufficient to resolve postpartum agalactia. Domperidone[106] has demonstrated efficacy in both the prevention and treatment of clinical fescue toxicosis in clinical trials involving large numbers of mares in numerous locations.

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12.7 PROLONGED GESTATION

Bruce W. Christensen

Many factors influence the duration of gestation in horses and ruminants. Normal variations in length of gestation have been attributed to genetic, nutritional, and environmental factors.[107,108] The species, breed, and sex of the fetus, ambient temperature, and length of photoperiod are among factors that, within normal variations, affect the duration of gestation.[107–110] The duration of pregnancy in thoroughbred mares ranges from 310 to 374 days,[110] in dairy cows from 275 to 292 days, in beef cows from 271 to 310 days, in ewes from 143 to 155 days, and in does from 146 to 155 days.[111] Prolonged gestation periods are those that exceed the normal gestational variation attributable to genetic, nutritional, and environmental factors. In pathologic prolonged gestation there is an impediment to the mechanisms that terminate gestation and initiate parturition. Pathologically prolonged gestation has been attributed to genetic, infectious, and toxic factors[112] as well as to manipulation of the embryo.[113,114]

Of the several forms of prolonged gestation with genetic causes in cattle, the best described forms have been observed in Guernsey and Holstein cattle.[108,109,112,115] In each the fetus fails to initiate parturition at term because of fetal adrenal hypoplasia. Prolonged gestation, from 3 weeks to 3 months beyond normal term, has been observed in a number of dairy cattle breeds.[116] Graves, Hansel, and Krook[115] described a Holstein fetus of 441 days' gestation in which the pituitary pars distalis was aplastic and the adrenal and thyroid glands were severely hypoplastic. Two different types of fetuses have been associated with prolonged gestation in cattle.[107] In the first type, fetuses had a large skeleton and excessive growth of epidermal organ structures such as hair and hooves but no obvious deformities. The second type of fetus was mature or immature and exhibited cranial and central nervous system anomalies; growth ceased at about 7 months of gestation. Both types of calves had hypoplastic or absent adrenal glands. These anomalies have been observed to be inherited as an autosomal recessive trait.[108,112]

Several infectious agents have been incriminated in prolonged gestation in ruminants. Bluetongue virus, bovine diarrhea virus, and border disease virus may cause severe cerebral lesions in the fetus, resulting in the absence of a hypothalamus and pituitary stalk. Again, by virtue of the lack of adrenocorticotropic hormone, the sequence of events necessary for parturition does not occur.[112]

The last decade has seen an increase in the use of assisted reproductive techniques in cattle in the form of in vitro procedures and somatic cell nuclear transfer (“cloning”). Although these techniques offer advantages for reproducing important genetic lines, they still have many accompanying complications that have yet to be overcome. Besides increased pregnancy loss, increased birthweight of calves, and increased incidence of dystocia and perinatal losses, another of these complications is prolonged gestation in recipient cows compared with embryo transfer recipient and artificially inseminated cows.[113] This technology has great potential for manipulating and preserving superior genetic potential.[117] The cow has been the most successfully cloned animal to date, but such

cloning still has a low success rate (0% to 10%).[118,119] This is an extremely active area of research and it is likely that with further understanding the current pitfalls surrounding in vitro procedures and nuclear transfer will be overcome and use of the techniques will become more commonplace.[119]

Veratrum californicum contains the teratogenic agent cyclopamine. When pregnant ewes ingest cyclopamine on the fourteenth day of gestation, their fetuses lack a pituitary gland or have a malformed hypothalamic stalk. These defects result in prolonged gestation by virtue of secondary adrenal hypoplasia.[112]

Prolonged gestation in mares has been cited as an indication for induction of parturition.[120,121] However, the clinical significance of prolonged gestation in mares is undetermined because there is no apparent correlation between duration of gestation and readiness for birth. Dysmature neonatal foals have resulted from gestations of normal and longer than normal durations; alternatively, 399 days' gestation resulted in births of normal twin foals.[122] Prolonged gestation in the mare has not generally been associated with excessively large foals and dystocia.[123] Therefore, in the absence of clinical signs that warrant induction of parturition in a high-risk pregnancy and the fulfillment of criteria for induced parturition, there is no reason to perform elective parturition induction in mares in which gestation is prolonged.

12.7.1

Approach to Diagnosis of Prolonged Gestation

Approach to the diagnosis of prolonged gestation in mares and ruminants is essentially similar (Boxes 12-14 and 12-15). If the client is concerned about what is apparently prolonged gestation in an otherwise normal dam, an accurate breeding history should be obtained. Because no pathognomonic clinical or laboratory findings are associated with prolonged gestation, the diagnosis is predicated on the history and a general physical examination of the dam. The overall condition of the dam should be determined. In addition to the reproductive history, exposure to infectious agents and toxic plants should be determined. The most important anamnestic factors are breeding dates, dates of confirmed pregnancy examinations, and absence of parturition at the expected time. The reproductive tract should be examined for the gravid uterus and evidence, although tenuous, of the term or near-term fetus. Diagnostic ultrasonography can be incorporated into the workup to enhance the assessment of viability and fetal well-being by determination of fetal heart rates, fetal size and movement, uteroplacental thickness, and estimation of allantoic fluid volume.[124–126] Parturition should not be induced unless the objective is fetal survival in the face of a high-risk pregnancy.[126] Otherwise, the mare should be examined and, if appropriate, the owner assured that the gestation is probably normal and that patience will likely result in a normal foal with adequate colostrum and passive immunity.[127]

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12.7.1.1

Box 12-14 Causes of Prolonged Gestation in Mares

Fescue toxicity

Fetal mummification

Delayed embryonic development

12.7.1.2

Box 12-15 Causes of Prolonged Gestation in Ruminants

Fetal mummification

Fetal hypothalamic-hypophysial-adrenal axis disorder

Autosomal recessive genetic disorder affecting Holstein and Guernsey cattle (B)

Vitamin A deficiency (B)

Veratrum album toxicity (B)

Veratrum californicum toxicity (cyclopamine) (O)

High environmental temperature (B)

Fescue toxicity

Hydrops amnii (B, O)

Bluetongue (B, O)

Bovine virus diarrhea (B)

Border disease (O)

Salsola tuberculata toxicity (Grootlamsiekte [exotic]) (O)

Akabane virus (exotic) (B, O)

Somatic cell nuclear transfer (B)

B, Bovine; *O*, ovine; *C*, caprine.

12.8

DYSTOCIA

Mats H.T. Troedsson

Dystocia is defined as difficult parturition; it may be a sign of either maternal or fetal conditions that impede fetal passage through the birth canal.[128] Dystocia in mares and ruminants is more likely to be attributable to fetal causes such as malpresentation, malposition, and malposture than to maternal conditions[128,129] (Boxes 12-16 and 12-17). The overall incidence of dystocia and incidences of types of dystocia vary among the species and breeds within a species.[130] Cattle, especially first-calving heifers and larger breeds, are more commonly affected by dystocia; the overall incidence of bovine dystocia ranges from 3% to 25%.[128] The incidence of dystocia among thoroughbred mares is 4%,[129] and in does, 3% to 5%.[131] The incidence of dystocia is generally greater in sheep than in goats.[132] Dystocia represents an emergency situation that commands prompt resolution to afford the optimum prognosis for dam and fetus. Reposition, traction, fetotomy, and cesarean section are the obstetric procedures available for the management of dystocia.[133] The economics of large animal practice often play a significant role in determining which course to pursue in resolving dystocia. The lives of the dam and the fetus may be at risk. Although the objective should be the survival of both, unless otherwise advised by the owner and if conditions are not prohibitive, the well-being of the dam and her reproductive potential should have priority over the fetus.

12.8.1

Box 12-16 Causes of Dystocia in Mares

12.8.1.1

COMMON CAUSES

Malpresentation

Malposition

Malposture

Abortion

Arthrogryposis

Twinning

12.8.1.2

LESS COMMON CAUSES

Fescue toxicity

Preterm parturition

Torticollis

Vaginal, vulvar obstructions (hematoma, callus, abscess, tumor)

Pelvic injury, fracture

12.8.1.3 UNCOMMON CAUSES

Fetopelvic disproportion

Congenital defects

Hydrocephalus

Uterine dorsoretroflexion

Uterine torsion

Hydrops of fetal membranes

Rupture of prepubic tendon

Fetal mummification, maceration

Vaginal prolapse

Abdominal, inguinal hernia

Uterine inertia

Induction of parturition

Premature separation of chorioallantois from endometrium

Uterine laceration

12.8.2 Box 12-17 Causes of Dystocia in Ruminants

12.8.2.1 COMMON CAUSES

Fetopelvic disproportion (B, common; C, O, uncommon)

Malpresentation

Malposition

Malposture

Twins, triplets (B)

Uterine torsion

Periparturient hypocalcemia (B)

Failure of cervix to dilate (B, O; rare in C)

Lymphedema

12.8.2.2 LESS COMMON CAUSES

Preterm parturition

Abortion

Congenital defects (fetal monsters)

Hydrops of fetal membranes (B, O)

Emphysematous fetus

Hydrocephalus (more common in B than O, C)

Extremity ankylosis (more common in B than O, C)

Breeding immature, young, small-for-age females

Obesity (B)

Pregnancy toxemia (O, C)

Uterine inertia

Fetal mummification, maceration

Uterine, cervical, vaginal obstruction

Retained fetus

Pelvic fracture

Vaginal prolapse

12.8.2.3 UNCOMMON CAUSES

Phytoestrogen toxicity (B, O)

Rectovaginal constriction of Jersey cattle (B)

Uterine rupture

Abdominal, inguinal hernias

Lipomatosis (B)

Lupine poisoning, arthrogryposis (B)

Polybrominated biphenyl toxicity

Bovine fetal tumors

Rupture of prepubic tendon (B)

Hereditary edema, lymphedema in Ayrshire calves

Prolonged gestation (B, O)

Chlorinated naphthalene toxicity

B, Bovine; *C*, caprine; *O*, ovine.

Although parturition has been divided into three distinct stages for descriptive purposes, the stages overlap clinically, and normal parturition is observed as a continuous process.[129] The equine fetus is lying in a ventral or ventrolateral position with head and forelimbs flexed during late gestation.[134] During the first stage of parturition the fetus plays an active role, along with myometrial contractions, in assuming correct extremity posture as it positions itself for delivery through the birth canal. The second stage of parturition commences with rupture of the chorioallantois and culminates in delivery of the fetus. Myometrial contractions continue during third-stage parturition, which ends with the expulsion of the placenta. In the mare parturition is a forceful, explosive act. The time between rupture of the chorioallantoic membrane and delivery of the fetus is normally about 20 minutes.[128] Separation of the fetal membranes from the endometrium may occur within 1 to 2 hours after the second stage of parturition commences; therefore the retained fetus must be delivered quickly or it will asphyxiate. Fetal expulsion in the ruminant is not quite as explosive as in the mare; second-stage parturition in the bovine usually requires ½ hour to 4 hours.[128] Ewes and does require a range of ½ hour to 2 hours to complete the second stage, or slightly longer if twins or triplets are present.[128] Primiparous animals generally require a longer time to expel the fetus than do multiparous dams.

Dystocia in large animals is often accompanied by forceful straining. The dam may attempt to lie down and stand repeatedly. This is characteristic of dams with dystocia that is caused by fetopelvic disproportion, malposture, or fetal impaction. Alternatively, the dam may stand quietly with minimal or no straining, as in cases of uterine inertia, uterine rupture, or exhaustion associated with prolonged dystocia of any cause. Whatever the presentation of the dam, the attending veterinarian must be prepared for unexpected behavior when attempting to perform obstetric examinations and procedures. The dam, fetus, attendants, and veterinarians must be protected from injury. The dam should be placed in open-ended stocks with movable sides or a straw-bedded box stall. During obstetric examination and manipulation, mares and cows may attempt to get up and lie down, or they may suddenly collapse. Such sudden movements may injure the dam and veterinarian if rigid, closed-end stocks are used. Minimum physical restraint should be used; however, restraint should be sufficient to permit completion of the obstetric examination and procedures with efficiency and safety. General anesthesia followed by elevation of the hind quarter will facilitate safe manipulation and vaginal delivery of a foal in mares with dystocia. This technique, if applied correctly, will likely result in less damage to the mare's reproductive tract.

Little is known about the pharmacokinetics of drugs in pregnant domestic animals. Accordingly, it must be assumed that sedative and anesthetic drugs will depress neonatal and fetal functions at least as much as those of the mare. The effects on myometrial activity of drugs administered to dams experiencing dystocia must also be considered. Acepromazine has little effect on the fetus and is generally considered safe for use in the pregnant mare. However, acepromazine was shown to have a suppressive effect on myometrial activity in cycling mares.[135] Xylazine causes significant fetal cardiovascular compromise in horses and has been reported to stimulate myometrial activity in cows and mares.[135–137] The fetal and myometrial effects of detomidine are similar but of longer duration compared with those of xylazine.[135,136] The effects of detomidine on myoelectrical activity in the uteri of cows and mares treated during the last trimester of pregnancy were dose dependent.[138,139]

As equipment is being organized and the process of evaluating the dam begins, a pertinent reproductive history should be obtained, including the dam's age, her previous breeding history, and the outcomes of previous pregnancies (i.e., abortion, normal parturition, dystocia). Her present gestational status should be determined; has parturition commenced at term, or is it a preterm or postterm delivery? Her udder should be examined to determine the stage of development. Information about the progress of the current parturition should be obtained. The time

since rupture of the chorioallantoic membrane, the duration and intensity of labor, whether fetal membranes or parts have appeared at the vulva, and previous attempts to assist in delivery should be noted. If the dam is recumbent, the veterinarian should determine if she has attempted to or been able to rise. Although a complete examination of the dam is optimum, it should be postponed until after the delivery of the fetus. However, in obtaining the dam's reproductive history, questions about her current physical condition should be included. Such predisposing factors as recent weight loss, systemic disease, and trauma should be considered. She should be assessed for signs of hemorrhage, dehydration, and shock.

After the tail has been wrapped, the perineal area should be thoroughly and gently washed and rinsed. Examination of the dam's reproductive tract may cause some discomfort or pain. Temperance regarding analgesia and sedation must be practiced. Caudal epidural anesthesia (4 to 8 mL of 2% lidocaine or other anesthetic) is often an excellent means of facilitating examination and resolution of dystocia and at the same time minimizing trauma to the dam, fetus, and operator. Lidocaine epidural anesthesia may cause hindlimb weakness and ataxia. Safe and effective analgesia can also be induced by epidural administration of xylazine (0.17 mg/kg diluted in 10 mL physiologic saline). A combination of lidocaine (0.22 mg/kg) and xylazine (0.17 mg/kg) resulted in an onset of analgesia within a few minutes and a duration of over 5½ hours.[140] Although vaginal sensitivity and the Ferguson reflex both are reduced by epidural anesthesia, myometrial contractions and abdominal press are not totally eliminated. General anesthesia will effectively eliminate myometrial contractions and abdominal press. This approach has to be combined with an elevation of the hindquarter of the dam, in order to provide sufficient space for safe manipulation of the fetus. Great care must be taken during the examination of the genitalia and fetus. In addition to the viability of fetus and dam, the dam's future reproductive potential is at risk and must be preserved. The vulva, vestibule, vagina, and cervix should be carefully examined. The location of the fetus in the birth canal, as well as its viability, presentation, position, and posture, should be determined. Schuijt and Ball[141] described a procedure to manually dilate the bovine birth canal before forced extraction is attempted. In the management of dystocia in any species, forced extraction should proceed only after maximal dilation of the caudal reproductive tract in order to minimize the potential for injuries to the dam during parturition (i.e., cervical, vaginal, and vulvar lacerations, hematomas, postparturient vaginal necrosis, and obturator, perineal, and gluteal paralyses).[128,142] Mares are especially susceptible to cervical lacerations, which may have detrimental consequences on the dam's future reproductive performance. Slow traction with continuous palpation of cervical stretching by the attending obstetrician is therefore recommended in equine dystocias.

The integrity of the birth canal, fluids, and fetal membranes serves as an indicator of the length of time the dystocia has persisted and the well-being of the fetus. Generous lubrication is required in all cases of dystocia and should be applied continuously during the management of dystocia to prevent damage to the dam's birth canal. Lubricating preparations consisting of methyl cellulose are superior to those consisting of mineral oil or soaps. Several liters of lubricants should be infused into the bovine and equine uterus by the use of a nasogastric tube.

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Traction or forced extraction can usually be successfully implemented after correction of malpresentation, malposition, or malposture. In equine dystocia, if the foal is still alive and dystocia cannot be relieved quickly (20 minutes) or if it is determined that extensive manipulation will be required, general anesthesia may be induced. Because of the length of the extremities of the foal, mutation is more difficult in the mare than in the cow and requires extensive repulsion to provide adequate room for manipulation. Examination and manipulation can be greatly facilitated by elevating the mare's hindquarters, enabling the fetus and viscera to recede cranially into the mare's abdominal cavity, thereby allowing more room for the operator.[143] If a nonviable fetus cannot be delivered by traction or forced extraction or if the owner is unwilling to select cesarean section, fetotomy can be performed.[133,143] Beyond the delivery of the nonviable fetus, fetotomy is indicated to save the mare and her subsequent fertility.[133] The advantages of fetotomy include avoiding major abdominal surgery (cesarean section) and its

complications and preserving the birth canal because excessively large parts are not forced through it.[128,142–144] At the same time, the primary disadvantage of fetotomy, particularly if not properly performed by an experienced obstetrician, is trauma to the birth canal by instruments, wire, or bone.[128] The indications, equipment, procedures, and complications of fetotomy have been reviewed in several publications.[128,133,142–144]

Cesarean section is indicated for a dam with dystocia when attempts to deliver the fetus by reposition, traction, and fetotomy are unsuccessful or contraindicated, and continued attempts may compromise the fetus, the dam, or her subsequent fertility.[128,130,132,145–152] Cesarean section may be the only rational procedure for delivery of some fetuses (e.g., emphysematous fetuses, deformed fetuses, and bicornuate fetuses). In addition, high-risk pregnancies caused by maternal conditions can be effectively and efficiently managed by cesarean section.[148] The specific indications, procedures, and complications of cesarean section have been reviewed in a number of publications.[128,130,145–152]

Management of a case of dystocia is not complete until a systematic examination, focusing on the dam's reproductive tract, has been conducted. Complications during dystocia involving the reproductive tract and other body systems can affect the outcome of the case.[128,153–155] As much as possible, examination of the dam's reproductive tract should rule out the presence of another fetus in the uterus or abdominal cavity.[128] The most common reproductive injuries incurred by dams during parturition include cervical, vaginal, and vulvar lacerations, hematomas, postparturient vaginal necrosis, and uterine hemorrhage.[142,155,156] Gastrointestinal complications, such as constipation associated with unwillingness to defecate, postpartum perineal inflammation, and bruising or rupture of entrapped or compressed segments of the gastrointestinal tract, can follow parturition in the mare.[155] Musculoskeletal and neurologic complications have been reported after parturition in cows and mares.[128] Retained placenta, delayed uterine involution, metritis, and laminitis may result from normal parturition but are more likely sequelae of dystocia.[128,155,157]

The signs associated with normal progression of each of the stages of parturition must be explained carefully to clients and farm managers. It is only through understanding the clinical signs associated with events of normal parturition that clients become proficient at recognizing abnormal events and know when to seek professional assistance.

12.9 RETAINED FETAL MEMBRANES

Mats H.T. Troedsson

Retained fetal membranes represent the failure of the entire or partial placenta to be expelled within physiologic time limits. Although variation exists among species regarding the duration of time that must pass before a placenta is considered retained, the condition is one of the most common complications occurring in animals after parturition.[158]

12.9.1 Retained Fetal Membranes in Mares

The anatomic structure of the equine placenta is described as diffuse, epitheliochorial, and microcotyledonary. It is composed of the allantochorion, the allantoamnion, and the umbilical cord.[159] During most normal foalings, the separation of fetal membranes from the endometrium and their subsequent expulsion occur within ½ hour to 3 hours of the delivery.[158] The incidence of retained fetal membranes is 2% to 10% in the mare, with a higher

incidence in draft horses than in lighter horse breeds.[158] The cause of retained fetal membranes remains unclear, but it is believed that allantochorionic microcotyledons near the tip of the nongravid uterine horn have failed to separate as a result of an endocrine unbalance, a disturbance in normal myometrial contractions, or any swelling at the site of microcotyledons[160] (Box 12-18). Diagnosis of retained fetal membranes in the mare is straightforward when it is based on the observation of membranes hanging from the vulva beyond 3 hours after foaling. However, if the fetal membranes fall cranially over the pelvis, they remain within the uterus without being visible, and the diagnosis must be made using vaginoscopy or ultrasonography or by digital intrauterine examination. If an early diagnosis of complete or partial retention of fetal membranes has been missed, the diagnosis may be made 1 to 2 days after foaling. At this time, clinical signs indicative of metritis are often present (i.e., fever, depression, colic, and/or laminitis).

After their expulsion, the fetal membranes should be stored until they can be scrutinized to determine if they are complete. The clinician should rinse the fetal membranes with water and, on a flat surface, thoroughly examine them for completeness.[161] Evidence that a part of the placenta is retained in the uterus or that an area of microvilli has been sheared off and retained in the endometrial crypts is an indication for digital endometrial examination or ultrasonographic examination, and institution of appropriate therapy (see Chapter 43, Retained Fetal Membranes).

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12.9.1.1

Box 12-18 Causes of Retained Fetal Membranes in Mares

12.9.1.1.1

COMMON CAUSES

Dystocia

Preterm parturition

Abortion

Endometritis, metritis

Twinning

Induced parturition

Stillbirth

12.9.1.1.2

LESS COMMON CAUSES

Fetotomy

Cesarean section

Placental edema at uterine horn tip

Placentitis

Drugs

Prolonged gestation

Fescue toxicity

Poor condition, poor environment, fatigue, increasing age, and other debilitating conditions

Hypocalcemia

Dropsy of fetal membranes

Entrapped placenta

12.9.2 Approach to Diagnosis of Retained Fetal Membranes in Mares

12.9.2.1 HISTORY

Many cases of retained fetal membranes follow episodes of dystocia, cesarean section, and fetotomy. An increased incidence of retained fetal membranes has been reported in mares that abort after the seventh month of gestation.[162] However, no increase in the incidence of retained fetal membranes associated with abortion, stillbirth, twinning, and delivery of a weak or diseased foal was observed if it occurred without dystocia.[163]

12.9.2.2 PHYSICAL EXAMINATION

Fetal membranes must be examined after their expulsion to determine their entirety and integrity. Tears, missing areas of tissue, and areas of chorionic surface devoid of microvilli should be considered evidence of partly retained fetal membranes, and immediate action should be taken to enhance expulsion of retained tissue and minimize complications.

Vital signs may be normal early in cases of retained fetal membranes. A rectal examination should be performed to determine the degree of uterine involution. Aseptic intrauterine palpation can be performed to determine the area and extent of retention and the integrity of involved tissues and fluid.[161] Systemic signs of dehydration, septicemia, toxemia, and laminitis may accompany fetal membranes retained for 24 to 36 hours.[164] Occasionally mares with retained fetal membranes show signs of colic. Therapeutic approaches for retained fetal membranes in mares are discussed in Chapter 43.

12.9.3

Retained Fetal Membranes in Ruminants

The anatomic structure of the ruminant placenta is described as cotyledonary and epitheliochorial.[158] It is composed of the allantochorion, the allantoamnion, and the umbilical cord. Fetal membranes are considered pathologically retained in the cow if they are not expelled by 8 to 12 hours after calving.[158] The incidence of retained fetal membranes in dairy cattle is 3% to 12% after normal parturition.[165] Dairy cows are more commonly affected than beef cows.[165] The incidence of retained fetal membranes may exceed 50% after abnormal parturition or abortion and in brucellosis-infected herds.[165] The retained placenta itself is relatively innocuous, but the condition is important because cows with retained fetal membranes experience an increased incidence of postpartum complications such as metritis, pyometra, ketosis, mastitis, delayed conception, and abortion.[166,167] The principal cause of retained placenta in cattle is a disturbance in the loosening process between the fetal cotyledons and the maternal caruncles[168] (Box 12-19). The processes that lead to successful loosening and separation of the placentome occur during the months preceding parturition. Many infectious and noninfectious factors are believed to disrupt the separation and expulsion processes. An endocrine causal relationship does not appear to exist.[169]

Clinical signs of retained fetal membranes in the doe and ewe are similar to those in the cow. The placenta of the ewe and doe is considered retained if it is not expelled within 24 hours after parturition.[170] The incidence of retained placentas in does is 6.4%.[171] Placental retention for longer than 24 hours may cause metritis in ewes and does. Inadequate dietary selenium and inadequate nutrition and exercise during gestation have been seen as factors predisposing does to retained placentas.[171] There have been several reports on factors that predispose to retained fetal membranes.[158,165–168,172,173] Many infectious and noninfectious factors apparently contribute to the disruption of the process of loosening and separation of the placentome. Accordingly, it has been suggested that a retained placenta should be considered to be a sign of an underlying disease.[174]

12.9.3.1

Box 12-19 Causes of Retained Fetal Membranes in Ruminants

12.9.3.1.1

COMMON CAUSES

Multiple births

Induced parturition

Placentitis (bacterial, fungal infection)

Hypocalcemia

Abortion

Stillbirth

Dystocia

Abnormal gestation length

12.9.3.1.2 LESS COMMON CAUSES

Injury, inflammation, or edema of placentome

Cesarean section

Uterine torsion

Necrotic placentome secondary to uterine and systemic disease

Excessive weight gain during dry period

Uterine atony

Dropsy of fetal membranes

Entrapment of separated placenta

Prostaglandin $F_{2\alpha}$ deficiency

Trace mineral deficiencies (selenium and iodine)

Vitamin deficiencies (carotene, vitamins A and E)

Mineral deficiencies, imbalances (calcium and phosphorus)

Heat stress

Increasing age

Nitrate toxicity

High milk production

12.9.4 Approach to Diagnosis of Retained Fetal Membranes in Ruminants

12.9.4.1 HISTORY

A review of accurate breeding records correlates retention of fetal membranes with the duration of pregnancy. Gestational periods of abnormal lengths result in a higher incidence of retained placenta than do normal-term parturitions. Induced parturition, twinning, and late-term abortions have been associated with retained fetal membranes in cows. Many periparturient diseases and conditions affect the incidence of retained fetal membranes.[158,165–168,172,173]

12.9.4.2 PHYSICAL EXAMINATION

In cows that have calved spontaneously and without problem after a normal gestation period, little illness tends to be associated with retained fetal membranes, and treatment may be unnecessary. Transient decreases in appetite and milk production may be observed.[165] However, metritis, toxemia, and septicemia may be observed when retention of fetal membranes is associated with gestation of abnormal length, dystocia, nutritional deficiencies, or certain infectious diseases. Metritis affects up to 90% of cows with retained fetal membranes.[172] For considerations for the treatment of retained fetal membranes in cows, see Chapter 43.

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12.10 ALTERATIONS IN LACTATION

Bruce W. Christensen

The mammary glands are modified cutaneous glandular structures considered accessory reproductive organs that function to secrete milk for the nourishment of the young.[175] The mammary glands are located in the prepubic region in the mare, cow, ewe, and doe. The cow's udder is composed of four mammary glands, whereas in the doe, ewe, and mare the udder has two mammary glands. One teat serves each mammary gland, and in the cow, ewe, and doe each teat has one streak canal. The mare has two streak canals per teat.

The mammary glands are ectodermal in origin, and most of their fetal development occurs during the first half of gestation.[176] Except for growth that occurs in association with some of the anomalous conditions of the mammary gland or as a result of the deposition of fat, there is little growth of mammary tissue between birth and puberty. Further mammary gland development occurs with each estrous cycle after the onset of puberty. Development of the duct system is primarily attributable to estrogen. Progesterone is the principal stimulant to development of secretory tissue. However, neither estrogen nor progesterone alone or in combination can cause optimum mammary gland growth and development.[177] Insulin, cortisol, thyroxine, prolactin, and growth hormone are necessary for full mammary gland development. During pregnancy the mammary gland attains maximum development under the control of pituitary, ovarian, adrenal, and placental hormones.[178] During parturition a process of interrelated neuroendocrine processes initiates lactogenesis, the production of milk. The secretion of milk and its release from the mammary gland after parturition depend on the availability of appropriate amounts of the hormones named previously, especially prolactin and oxytocin.

In addition to mastitis, conditions that manifest themselves as alterations in the mammary gland and lactation are fairly common in ruminants and horses. Problems caused by conditions that affect the mammary gland are often multifactorial in that they compromise the well-being of the patient, the nutrition of the offspring, and ultimately the economics, especially in commercial dairies.

12.10.1

Enlarged Mammary Gland

Many conditions and diseases of the mammary gland cause swelling or enlarging of the gland[179] (Boxes 12-20 and 12-21). Enlargement may involve one or more of the glands of the udder. However, the enlarged mammary gland is not necessarily inflamed. Several anomalies of the mammary gland cause noninflammatory enlargement of the gland (e.g., gynecomastia and precocious udder development).[179–181] It is important to determine whether the enlargement of the gland is attributable to an infectious or a noninfectious cause. Trauma is probably the most likely cause of noninfectious inflammation of the mammary gland. Mastitis, with which a large number of organisms have been associated, is the most common cause of mammary gland inflammation (see Chapter 36).

Evaluation of a patient with an enlarged mammary gland should include the medical and reproductive histories. The age and sex of the animal may limit the considerations. Gynecomastia is seen in young bucks, rarely in rams and bulls, and never in stallions.[179,181] Congenital anomalies such as stenotic or absent teat canals are not determined until parturition occurs and lactation commences.[179] The animal should be given a complete physical examination, with emphasis on the affected mammary gland. Examination of the gland should include observation, palpation, and expression of its contents. Cytologic and bacteriologic examination of the secretion from the mammary gland may be helpful in determining the cause and establishing the prognosis of enlarged mammary glands. In postpartum cows the most common causes of enlarged mammary glands are periparturient udder edema and mastitis. Mastitis occurs most often in mares after weaning. Trauma to the udder is more likely to be problematic in cows and goats than in ewes and mares because the udder is more pendulous in the former.[179] Undesirable udder traits of genetic origin occur in the goat (e.g., hanging or saclike udder, polythelia, and blocked teat).[182] Lacerations, superficial contusions, and seromas are detected by close examination of the affected gland. Diagnoses of other injuries may rely on examination of the gland's secretion for evidence of increased cellularity and hemorrhage. Mammary gland neoplasia is rare in mares, cows, and small ruminants.[179,183–185]

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12.10.1.1

Box 12-20 Causes of Enlarged Mammary Glands in Mares

12.10.1.1.1

COMMON CAUSES

Mastitis

Abscessation

Periparturient udder edema (physiologic)

Gland distention associated with weaning

12.10.1.1.2 LESS COMMON CAUSES

Trauma (contusion, hematoma, seroma, laceration)

Neoplasia (malignant melanoma, carcinoma)

Cutaneous histoplasmosis *(Histoplasma farciminosus)*

12.10.1.2 Box 12-21 Causes of Enlarged Mammary Glands in Ruminants

12.10.1.2.1 COMMON CAUSES

Mastitis

Periparturient udder edema

Abscessation

Trauma (contusion, hematoma, seroma, laceration)

Pendulous udder (B, C)

Blind quarters (aplastic duct) (B)

12.10.1.2.2 LESS COMMON CAUSES

Eczema

Urticaria (irritants, caustic chemicals; contact dermatitis; insect bites)

Sarcoptic and psoroptic mange

Primordial mammarian tissue swelling (accompanies witch's milk)

Photosensitization

Sunburn

Frostbite

Cowpox (B)

Pseudocowpox (B)

Goat pox

Contagious ecthyma (orf) (C, O)

Furunculosis, abscesses

Staphylococcal folliculitis

Papillomatosis, warts

Caprine arthritis-encephalitis (C, O)

Zearalenone toxicity

Neoplasia (lymphosarcoma, malignant melanoma [C], squamous cell carcinoma [C])

Milk allergy (B)

Tuberculosis (B)

Ovarian neoplasia

Caseous lymphadenitis (O, C)

Cutaneous lipomatosis

Enzootic mycobacterial nodular-ulcerative mammillitis (B)

Bovine herpesvirus mammillitis (BHV-2) (B)

Precocious udder development (B, C)

Udder cysts (C)

Gynecomastia (C)

Pseudopregnancy (C)

Foot-and-mouth disease (exotic)

B, Bovine; *C*, caprine; *O*, ovine.

12.10.2 Udder Edema

Udder edema, one of the most common causes of enlarged mammary glands, results from the excessive accumulation of intercellular fluid in the mammary gland (Box 12-22). The disorder is observed during the late gestation and early postpartum periods and is common in both horses and ruminants, but it is probably more frequently seen in dairy cattle. One study reported an udder edema incidence of 18% in dairy cattle, of which less than 1% required veterinary treatment.[186]

Two forms of udder edema are seen in cattle.[187] In the physiologic or acute form, there is edema of the mammary gland during the late gestation and early postpartum periods.[187] The entire udder is usually symmetrically involved, and the edema may involve adjacent abdominal and perineal areas.[187] The condition is usually not obviously painful but may cause the cow some difficulty in lying down and walking because of the mammarian swelling. Chronic bovine udder edema differs from the acute form in that affected cows develop udder edema within 6 weeks after calving, and the edema may persist for several months.[187] The swelling may be localized in the form of plaques on the ventral aspect of the rear of the udder, or it may involve the ventral abdominal wall.[187]

Udder edema is a relatively common condition of dairy goats.[188] Two-year-old does kidding for the first time are most commonly affected; however, all ages can be affected. Affected does usually have colostrum at parturition, but within a few hours the udder is warm, hard, and agalactic.

Broodmares affected with udder edema have generalized ventral edema during the last 1 to 2 weeks of gestation and for as long as 2 to 3 days after foaling. The extent of ventral edema varies, ranging from local swelling of the udder and immediately adjacent subcutaneous tissues to a generalized swelling that may extend from posterior to the mammary glands forward, along the ventral abdomen and thorax, to the axillary or pectoral area. In the mare such edematous accumulations are referred to as *plaques of edema*. Affected brood mares seem to be uncomfortable and reluctant to move. Younger broodmares, especially primiparous mares affected with udder edema, appear to be in more pain than older mares, and some of the mares so affected refuse to allow their foals to suckle.

12.10.2.1 Box 12-22 Causes of Udder Edema

12.10.2.1.1 MARES

Periparturient udder edema (physiologic)

12.10.2.1.2 RUMINANTS

Periparturient udder edema (physiologic)

Hereditary predisposition

Overfeeding of grain prepartum

Excess dietary protein

Obesity

Excess dietary sodium, potassium

Hypomagnesemia (chronic udder edema)

Disturbances in udder blood and lymph circulations

Excessively long dry period

Anemia

12.10.3 Agalactia

Any disease or condition that adversely affects the dam has the potential to compromise lactation. Agalactia, the failure of lactation after parturition, may be attributable to a primary endocrinologic or mammary gland problem, or it may be secondary to any of a multitude of systemic conditions and diseases (Boxes 12-23 and 12-24). True agalactia may be attributable to mammary gland anomalies or inadequacies among the numerous endocrinologic factors of development and pregnancy. Agalactia may be a complication of many conditions. In some animals the conditions to which agalactia is secondary manifest as alterations in a specific system, whereas other animals with agalactia may demonstrate such signs as fever, weight loss, anorexia, and anemia. Inadequate nutrition is rarely the cause of clinically observed agalactia. Fescue grass toxicity, caused by ingestion of the ergot alkaloid-

producing *Acremonium coenophialum*, is an important cause of agalactia and hypogalactia[189,190] (see Fescue Toxicity).

Agalactia should not be confused with failure of milk ejection (milk letdown). Administration of oxytocin may enhance milk letdown but does not affect milk production. Oxytocin stimulates a release phenomenon that acts on previously secreted and stored milk. Although somatotropin may increase milk production in a normally lactating cow, its effect on agalactia has not been adequately studied.

Inexperienced or nervous mares with adequate milk are often reluctant to allow their offspring to nurse, in part because of the mare's inexperience. Such nervous mares need not necessarily be primiparous mares. Although not allowing their offspring to nurse is usually a manageable behavior problem, the mare's udder should be examined for evidence of periparturient edema, inflammation, and painful conditions. 215 216

12.10.3.1

Box 12-23 Causes of Agalactia and Hypogalactia in Mares

12.10.3.1.1

COMMON CAUSES

Mammary aplasia, hypoplasia

Abscessation

Mastitis

Abortion

Premature birth

Postpartum complication

12.10.3.1.2

LESS COMMON CAUSES

Endocrine dysfunction

Nutritional deficiencies, malnutrition

Neoplasia

Squamous cell carcinoma

Malignant melanoma

Pituitary adenoma

Lymphosarcoma

Other tumors

Fescue toxicity

Trauma to mammary gland

Periparturient disease

Dystocia

Anemias

Severe toxicity

12.10.3.2 Box 12-24 Causes of Agalactia and Hypogalactia in Ruminants

12.10.3.2.1 COMMON CAUSES

Mammary aplasia, hypoplasia

Mastitis

Abscessation

Caseous lymphadenitis (udder involvement) (C, O)

Caprine arthritis-encephalitis (CAE; hard udder) (C, O)

12.10.3.2.2 LESS COMMON CAUSES

Endocrine dysfunction

Malnutrition

Water deprivation
Self-sucking (B, C)
Trauma
Chapped teats; teat dip irritation (B, C)
Milk allergy
Neoplasia
Malignant melanoma (C)
Lymphosarcoma
Squamous cell carcinoma
Carcinomas
Fescue toxicity
Papillomatosis
Mycoplasmal agalactia (C, O)
Anemias
Severe toxicity

B, Bovine; *C*, caprine; *O*, ovine.

12.10.3.3 APPROACH TO DIAGNOSIS OF AGALACTIA

An accurate reproductive history should be obtained. It should be determined whether the dam is primiparous or multiparous. If primiparous, is she manifesting anxiety in the presence of her offspring? If multiparous, has she been agalactic at previous parturitions? Has she sustained recent trauma, perhaps during parturition, or was there exposure during gestation to infectious diseases or toxic plants? After a history has been determined

and the dam and neonate have been observed, attempts to facilitate the youngster's suckling might be indicated. Is the dam agalactic, or does she simply refuse to let the neonate suckle? Such measures as twitching or tranquilizing the nervous and inexperienced mare may resolve that problem. If assessing the dam's behavior toward her offspring does not resolve the problem, a thorough physical examination should be initiated. The objective now should be to rule out or incriminate infectious and inflammatory conditions contributing to the agalactic state. The dam herself may be systemically affected, or the problem may be localized in the udder or a mammary gland.

In listing causes of agalactia and hypogalactia in Boxes 12-23 and 12-24, we included only those that have a direct effect on the anatomic integrity of the mammary gland or its function. Abnormalities involving any system may compromise lactation.

12.10.4

Galactorrhea and Precocious Mammary Gland Development

Galactorrhea, the abnormal manifestation of lactation (not the secretion of true milk), occurs occasionally from the primordial mammary gland of young foals and ruminants, including neonates.[179] The serous secretion occurs in association with swelling of mammarian tissue in males and females and may be caused by transplacental transmission of maternal steroid hormones[191] (Box 12-25). The secretion is popularly known as *witch's milk*.

12.10.4.1

Box 12-25 Causes of Galactorrhea and Precocious Mammary Gland Development in Horses and Ruminants

Impending abortion

In utero death of one twin fetus

Spontaneous (inappropriate prolactin secretion)

Placental separation

Zearalenone toxicity

Pregnancy (especially multiple fetuses)

Suckling

Pseudopregnancy (caprine)

Ascending infection during pregnancy, placentitis

Ovarian tumors

Precocious mammary gland development and galactorrhea occur in pregnant and nonpregnant mares and in some of the ruminant species. Such premature udder development and subsequent lactation have been observed in nonpregnant and nonsuckled doelings and heifers.[179,192] Udder development and subsequent lactation have been observed in young nonpregnant heifers and does being suckled by other young animals.[179] In addition to the continued stimulation of suckling, other causes of premature mammarian development and lactation may be trauma and diseases of the pituitary, ovarian, and adrenal glands.[179] Zearalenone toxicity has been implicated in precocious mammary gland development and lactation in heifers.[193] Milk production is nonphysiologic in that it is of insufficient quality and quantity and does not justify milking the affected animals. There is no evidence that such abnormal development compromises normal lactation after parturition.[179]

Inappropriate lactation has been observed at various stages of pregnancy in most domestic species.[179] The most common cause of galactorrhea is abortion. Lactation may commence before or even without expulsion of the dead fetus. Lactation during pregnancy has also been observed in association with multiple fetuses, placentitis, and ovarian tumors. Accordingly, premature mammary gland development during gestation should be considered a warning of impending abortion, and the dam should be examined. Occasionally, pregnant mares develop mammarian enlargement during middle to late gestation that spontaneously regresses.[190] Some of these mares begin to lactate before parturition. It must be kept in mind that premature lactation, and subsequent loss of colostrum, is one of the most important causes of failure of passive transfer of immunoglobulins.[194]

Gynecomastia, the abnormal development of the male's mammary glands, has been observed in bucks in which rudimentary mammary glands and associated teats underwent development.[179,192] The aberrant structures, located on both sides of the buck's scrotum, can secrete up to 1 L daily of a substance that resembles milk. The cause is presumed to be endocrine imbalance but has not been determined. Lofstedt and colleagues[195] reported adrenal neoplasia as a cause of lactation in a wether.

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11 Chapter 11 Alterations in the Skin

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11.1 GENERAL APPROACH TO DISEASES THAT ALTER THE SKIN

It is important to remember that the skin has a limited repertoire with regard to its presentation; many diseases with various causes may manifest with similar lesions. However, certain patterns of response to disease are also recognized. In order to manage skin problems successfully, the veterinarian must use a systematic approach by obtaining a complete history, performing a thorough physical examination, and, when appropriate, using one or more simple diagnostic techniques.[1] The following sections discuss the materials and methods necessary to perform techniques commonly used to diagnose large animal skin disease.

11.1.1 History

To obtain a differential diagnosis list, all the questions listed on the sample history form (Fig. 11-1) should be answered. Often it is helpful to repeat the questions to the owners at a later time or to give them a history form to complete at their leisure, which allows greater opportunity to remember details relevant to the skin disease. The goals should be to determine the initial features of the skin disease, how the problem has progressed, and what factors have influenced its progression to the present state.

11.1.2 Physical Examination

The diagrams and terms listed on the sample form (Fig. 11-2) may serve as a useful guide for recording the physical findings. The animal's overall condition should be assessed and a general physical examination should be performed to determine if the disease is limited to the skin or if systemic signs of disease are also present. The distribution, morphology (e.g., papules, nodules, wheals, patches of alopecia), and size of skin lesions should be noted. The mucous membranes also should be examined, and the skin surface palpated to determine features not readily noted visually (e.g., crusts beneath the hair, dryness, ability to epilate hairs, and presence of peripheral lymphadenopathy).

The practitioner's goal should be to describe accurately the animal's clinical appearance in a written record for future reference.

11.1.3 Diagnostic Techniques

For most of the techniques that follow, a good-quality microscope equipped with ×4, ×10, ×40, and ×100 objectives is recommended.

11.1.3.1 SKIN SCRAPINGS

Skin scrapings are used primarily to demonstrate microscopic ectoparasites, specifically mites. Scraping is a quick, simple, inexpensive diagnostic technique that is more useful in ruminants than in horses because equine

mite infestations are relatively uncommon. The materials needed to perform a skin scraping are a sterile container, mineral oil, a medical grade spatula (Fisherbrand Microspatula with Flat-Ended Blade, catalogue no. 21-401-20, Fisher Scientific; www.fisherscientific.com), glass slides, and cover slips. Although a No. 10 scalpel blade may be used, a medical grade spatula will not cut the skin in cases of sudden movement of the horse, yet is just fine enough to be able to scrape deep enough to find *Demodex* species mites, if indicated. If the hair coat is thick, a small area should be clipped before scraping. Multiple superficial scrapings that cover large surface areas should be performed, as well as several scrapings covering a small area that are deep enough to create capillary oozing. The collected material should be placed in a container until it can be examined microscopically. Some of the sample can then be placed on a glass slide and finely dispersed in enough mineral oil to provide a confluent layer without air bubbles beneath a cover slip. The slide should be scanned systematically with the ×10 objective. If something of significance is noted, the ×40 objective can be used to examine the specimen in more detail.

11.1.3.2

DERMATOPHYTE CULTURE

The materials necessary to perform a dermatophyte culture include dermatophyte test medium, mosquito forceps, a medical grade spatula, and sterile empty containers such as evacuated blood collection tubes. The forceps should be sterile, and each lesion to be sampled should be wiped gently with either water or isopropyl alcohol (there is some controversy as to which is better; I use water out of concern that the alcohol may inhibit fungal growth on the culture medium) to remove as many bacterial and fungal contaminants as possible and allowed to dry. Multiple small, scaling, and slightly crusted lesions should be sampled; the samples should be stored in individual containers. Broken hairs, scales, and crusts from the periphery of the lesions are collected (because dermatophytes cause peripherally expanding lesions). A spatula may be useful for scraping scales and debris from the skin surface. The forceps are used to pluck broken hairs.

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Fig. 11-1 Sample dermatologic history form.

DERMATOLOGY HISTORY FORM

Owner_____ Date_____

Animal's name_____ Case #_____

Age of animal_____

Age when purchased_____ Age when skin problem started_____

Where on the body did the problem start?_____

What did the skin problem look like initially?_____

How has it spread or changed?_____

What season did the problem start?_____

Is the problem seasonal or year round?_____

If seasonal, what seasons is the disease present?_____

Does the animal itch?_____ If so, where?_____

Do any animals contacting the affected animal have skin problems?_____

Do any people in contact with the animal have skin problems?_____

Is fly control used?_____ If so, describe_____

Do any relatives of this animal have skin problems?_____ If yes, explain_____

List injectable, oral, or topical medications that have been used before and after onset of the disorder_____

Which medications were of benefit?_____

Which medications aggravated the condition?_____

Describe the environment where the animal is kept, including bedding_____

What is the animal fed?_____

Any additional information you feel is relevant to the skin disease_____

Fig. 11-2 Sample dermatologic physical examination form.

DERMATOLOGY PHYSICAL EXAMINATION FORM

Date_____

Distribution of lesions:

_____

_____

_____

Primary lesions (circle):

Macule	Patch	Papule
Pustule	Vesicle	Bulla
Wheal	Nodule	Tumor

Secondary lesions (circle):

Scale	Erosion	Excoriation
Fissure	Ulcer	Lichenification
Erythema	Alopecia	Hyperpigmentation
Crust	Comedone	

Pruritus_____ Epilation_____

Skin thickness_____ Skin tone_____

Hair coat_____ External parasites_____

Diagnostic workup:

Skin scrapings_____

KOH preparation_____

Dermatophyte culture_____

Acetate tape prep_____

Dermatophilus prep _____

Histopathology_____

Immunofluorescence_____

Microfilarial prep_____

Bacterial culture & sensitivity_____

Differential diagnosis:_____

Initial therapy:_____

If the clinician's practice performs its own fungal cultures, the samples should be removed from the containers with a sterile forceps in a clean working area and gently pressed onto, but not buried beneath, the culture medium. The top of the culture dish or vial should be loosely replaced to allow sufficient ventilation for the culture to grow. Most dermatophytes grow at room temperature, except for some strains of *Trichophyton verrucosum*, which requires incubation at 37° C (98.6° F). The colony usually first appears in 5 to 7 days, although all cultures should be allowed to incubate for 3 weeks before a negative result is declared.

Dermatophyte test medium is an amber-colored Sabouraud's dextrose agar containing phenol red, a pH indicator, and several antibacterial and antifungal agents to inhibit growth of contaminant organisms. Dermatophytes preferentially use the protein in the medium as they begin to grow, producing alkaline metabolites that cause the medium to turn red. The dermatophyte colony is typically a white to beige, powdery to fluffy growth; the colonies are never dark colored. Most saprophytic (contaminant) fungi metabolize the carbohydrates first, producing acidic metabolites that do not change the color of the medium. It should be stressed that after the carbohydrate source has been depleted, saprophytes use the proteins and produce a red color change.

Positive identification of a dermatophyte is made in most instances if a white to beige, powdery to fluffy colony begins to appear on the medium at the same time or within 24 hours of the appearance of a red color change in the medium (Fig. 11-3). An infrequently encountered exception to this rule is growth of the saprophyte *Scopulariopsis brevicaulis*, a tan to light brown, smooth or mealy colony that produces a concurrent red color change in the medium. It is essential to check the cultures daily to determine if the red color change and colony growth occur nearly simultaneously. If any doubt exists about the type of colony growth, the sample should be submitted to a diagnostic laboratory for specific identification.

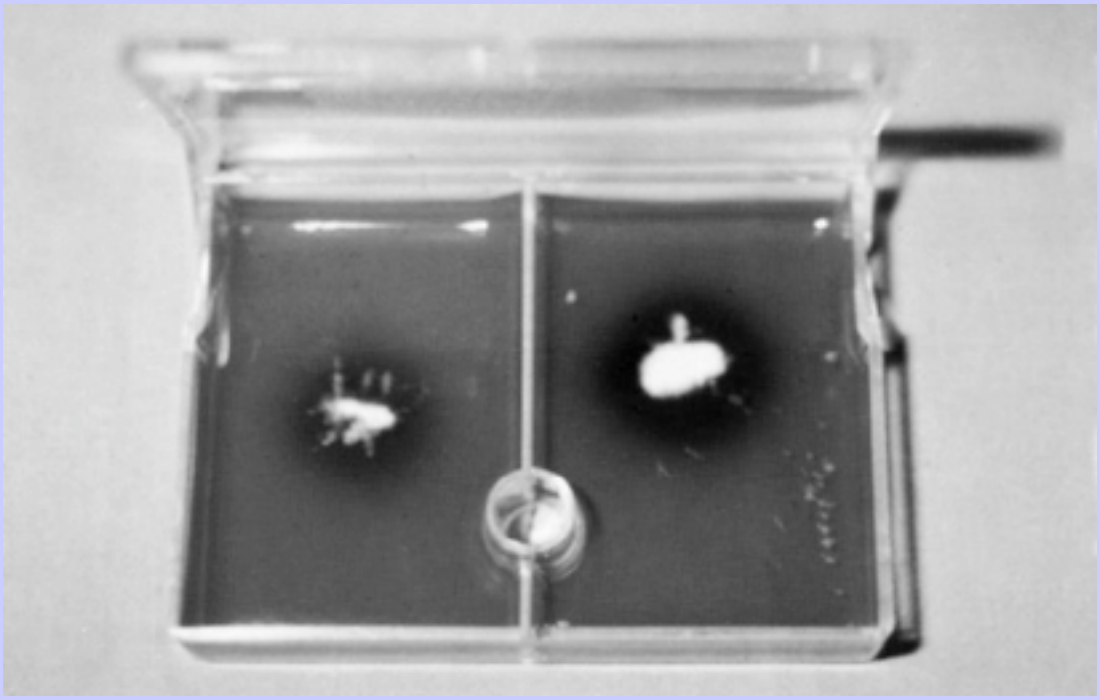
11.1.3.3

POTASSIUM HYDROXIDE PREPARATION

A potassium hydroxide (KOH) preparation may permit immediate diagnosis of dermatophytosis. However, examination of KOH preparations requires considerable experience, as fungal elements may be easily overlooked (false-negative result) and numerous artifacts such as fibers, cholesterol crystals, or oil droplets may be mistaken for fungal elements (false-positive result). It is always advisable to perform a dermatophyte culture in conjunction with a KOH preparation.

The materials necessary to perform a KOH preparation include mosquito forceps, a medical grade spatula, a sterile empty container, glass microscope slides, cover slips, a Bunsen burner, and clearing solution. As with a dermatophyte culture, it is important to sample several lesions to increase the chances of obtaining a diagnostic sample. Hairs and scales are collected from the periphery of the lesions with the mosquito forceps and the spatula. The samples are stored in the sterile container until a microscopic examination can be performed. A drop of the KOH clearing solution is placed on a glass slide, hairs and scales are added to the solution, and a cover slip is placed over the material. The slide should be scanned systematically with the ×10 objective for abnormal-appearing hairs with a fuzzy internal structure. If these features are noted, a higher-powered objective should be used for more detailed examination. A positive result with a KOH preparation demonstrates hyphae, which usually are uniform in width and septate. Beadlike chains of arthroconidia may be seen as well (Fig. 11-4).

Fig. 11-3 Positive result on dermatophyte culture. Growth of light-colored colony and simultaneous red color change are shown on dermatophyte test medium (right half of culture plate). Growth of dermatophyte on rapid-sporulating medium is shown on left half of culture plate.



The purpose of the clearing solution is to dissolve the hard keratin and bleach the melanin of the hair shaft so that the fungal hyphae and arthroconidia can be identified more readily. Care should be taken not to spill any clearing solution on the microscope because it can damage the lenses. Several types of clearing solutions are available. If 15% KOH is used, the slide should be heated for 15 to 20 seconds to facilitate clearing before examination. As an alternative, the preparation can be allowed to stand at room temperature for 30 minutes before viewing.

11.1.3.4

ACETATE TAPE PREPARATION

Acetate tape preparations for parasites are used primarily to diagnose infection with *Oxyuris equi*, although they may also be used to diagnose *Chorioptes* species. The materials required to perform an acetate tape preparation include acetate (nonfrosted) tape, mineral oil, and glass microscope slides. A piece of the tape is pressed over several areas in the anal and perianal region when looking for *O. equi* or over an affected region that has been lightly clipped when looking for *Chorioptes* species. The tape is then placed with the adhesive side down on a line of mineral oil that was placed lengthwise on a glass microscope slide. The purpose of the oil is to help clear the debris and facilitate examination of the preparation for parasites. The preparation is scanned with the ×10 objective for organisms.

11.1.3.5

DERMATOPHILUS PREPARATION

This test is used as an aid in identification of *Dermatophilus congolensis*. Crusts should be removed from the patient and the excess hair carefully trimmed from the crusts with a small pair of scissors. The crusts are minced with the scissors and mixed with several drops of saline on a glass slide. After the crusts have softened in the saline for several minutes, they should be crushed with the tip of an applicator stick. The excess debris is removed, and the slide is allowed to air dry. The slide should then be heat fixed; stained with Gram, Giemsa, or Wright stain; and examined for the characteristic bacteria. *D. congolensis* organisms are gram-positive, branching, filamentous bacteria that divide horizontally and longitudinally, forming parallel rows of cocci (zoospores) that commonly are described as resembling "railroad tracks" (Fig. 11-5).

11.1.3.6

CYTOLOGIC STUDIES

Cytologic studies are of value when dealing with crusts, scales, pustules, vesicles, nodules, or tumors. They can quickly indicate the presence of infectious organisms and provide a rough assessment of the spectrum of cell types present in a lesion (e.g., neoplastic, acantholytic, or inflammatory). The surface of the lesion should be gently shaved (if necessary); particular care must be taken not to rupture fragile pustules and vesicles or remove crusts. Crusts and scales are best evaluated by performing a superficial scrape with a spatula, placing the material on a microscope slide, heat-fixing, then staining with Gram, Giemsa, or Wright stain. Alternatively, acetate tape may be used to collect the material, and instead of placing the tape on a slide that has mineral oil (as is done when looking for parasites), the tape is placed on a slide on which several drops of the "blue" solution from the Wright stain have been placed. Scan for areas of interest with the ×4 objective, then use the ×100 objective with immersion oil.

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Fig. 11-4 Positive result on potassium hydroxide (KOH) preparation. Note the small, spheric fungal elements (arthroconidia) on the hair shaft.

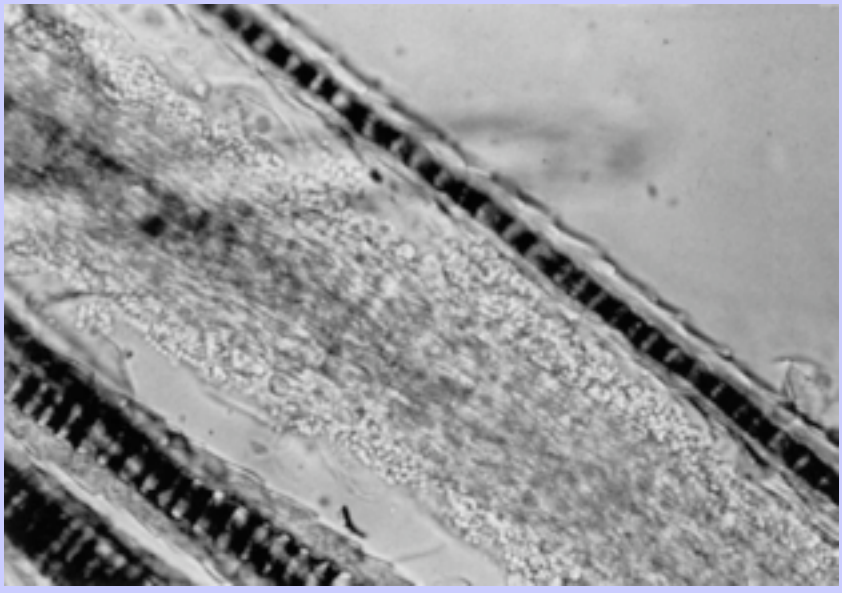
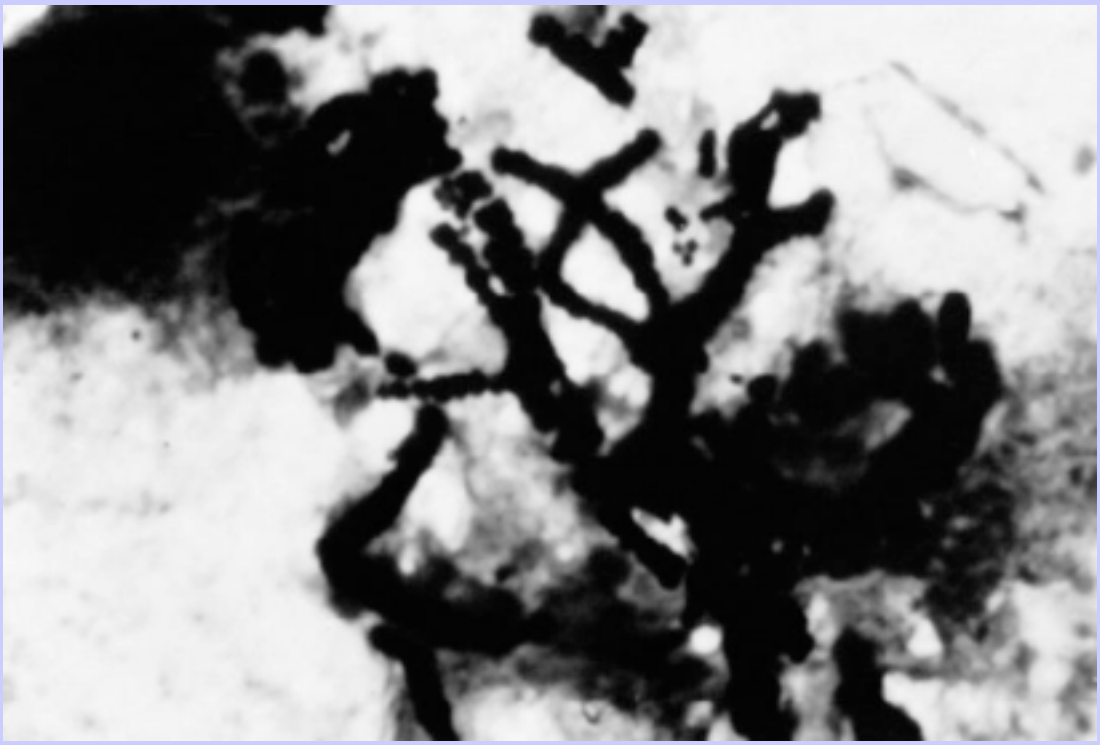


Fig. 11-5 Positive result on *Dermatophilus* preparation. *Dermatophilus congolensis* is a large, gram-positive, filamentous bacterium that divides horizontally and longitudinally, forming parallel rows of cocci (zoospores) that are commonly described as "railroad tracks."



Cytologic evaluation of intact pustules and vesicles is best accomplished by gently opening an intact lesion with the tip of a sterile No. 15 scalpel blade or 25-gauge needle and smearing the contents on the surface of a glass slide. The slide should be air dried, heat fixed, stained with one of the previously mentioned stains, and examined. Nodules, tumors, and swellings are best evaluated by fine-needle aspiration. A 25- or 22-gauge needle on a 12-mL syringe is introduced into the mass, and negative pressure is applied. Several passes through the mass at different angles should be performed. After negative pressure has been released, the needle is removed from the mass. The needle is then removed from the syringe, the syringe is filled with air, and the needle is reattached. The contents of the needle are pushed out onto glass slides, which are subsequently dried, fixed, and stained as described previously.

11.1.3.7

BIOPSY FOR ROUTINE HISTOPATHOLOGIC EXAMINATION

The following materials are needed to perform a skin biopsy:

- 6-mm and 4-mm biopsy punches

- No. 15 scalpel blade
- Sharp scissors
- Curved mosquito forceps
- Needle holders
- No. 2-0 or 3-0 nonabsorbable suture
- 2% lidocaine
- 3-mL syringe with a 22- to 25-gauge needle
- Tongue depressor or cardboard
- Gauze
- 10% buffered formalin

It is very important *not* to surgically prepare a lesion that is going to be biopsied for histopathologic examination. Shaving and scrubbing remove crusts and epithelial tissue that may be important in reaching a diagnosis. Cutaneous infections caused by biopsies taken in this manner are extremely uncommon. If the clinician is concerned about infections, surgically prepare the site *after* the biopsy has been taken, before suturing.

Local anesthesia is sufficient for obtaining most skin biopsies. A 22- to 25-gauge needle is inserted at the margin of the lesion until the bevel is buried in the subcutaneous tissue beneath the lesion. The 2% lidocaine (0.5 to 1 mL) is injected, allowing 1 to 2 minutes for the anesthetic to take effect. Infiltration of the dermal or epidermal tissue with lidocaine should be avoided because this causes artifactual changes in the specimen.

Four techniques can be used to biopsy skin: the excisional, wedge, punch, and elliptic techniques. When the lesion to be sampled is a single nodule, the ideal biopsy technique is excisional because the lesion can be eliminated at the same time the histologic diagnosis is made. If the lesion is a tumor and too large to be excised, a generous wedge biopsy should be performed, which ideally extends from the margin to the center and includes the full depth of the lesion.

Most lesions can be sampled with a 6-mm biopsy punch. A disposable biopsy punch* usually can be used to obtain two or three biopsies before its edge is dulled and it must be discarded. The punch is placed directly over the lesion and rotated in a continuous circular motion while pressure is applied until the blade of the punch is in the subcutaneous tissue. If the punch has cut to a sufficient depth, when it is removed the tissue sample is free of the adjacent dermis and remains only loosely attached to the underlying subcutaneous tissue by a thread of connective tissue. A small pair of curved mosquito forceps is used to gently grasp the subcutaneous part of the biopsy and elevate it from the surrounding tissue. The specimen is then cut free with a pair of sharp scissors. It is important to avoid handling the epidermal and dermal parts of the sample during this procedure to minimize artifactual changes in the tissue sample. The sample is gently blotted to remove any surface hemorrhage and immediately placed in 10% buffered formalin for fixation. The site from which the sample was taken may then be cleaned with an antiseptic solution and closed with either two simple interrupted sutures or a cruciate stitch using No. 2-0 or 3-0 nonabsorbable sutures.

Although punch biopsies are convenient and easy to use, they are not appropriate for vesicular, bullous, and ulcerative lesions. For these lesions the method of choice is a surgical elliptical biopsy. The biopsy of vesicular and bullous lesions should encompass the entire lesion. Biopsy of samples of ulcerations should include abnormal tissue, the leading edge of the lesion, and normal tissue. Because an ulcer lacks epithelial tissue, the leading edge where epithelium remains may be the most rewarding in providing a histologic diagnosis. Thus the skin is biopsied so that the long axis of the ellipse crosses perpendicular to the leading edge of the ulcer (Fig. 11-6). It is important to mount surgical elliptical biopsies before placing them in formalin or they will curl during fixation, resulting in distortion of the histologic features during sectioning. To mount the specimen, the subcutaneous surface is placed on a small piece of a wooden tongue depressor or cardboard while gentle pressure is applied to the tissue so that it adheres to the surface; then the specimen is placed in the formalin.

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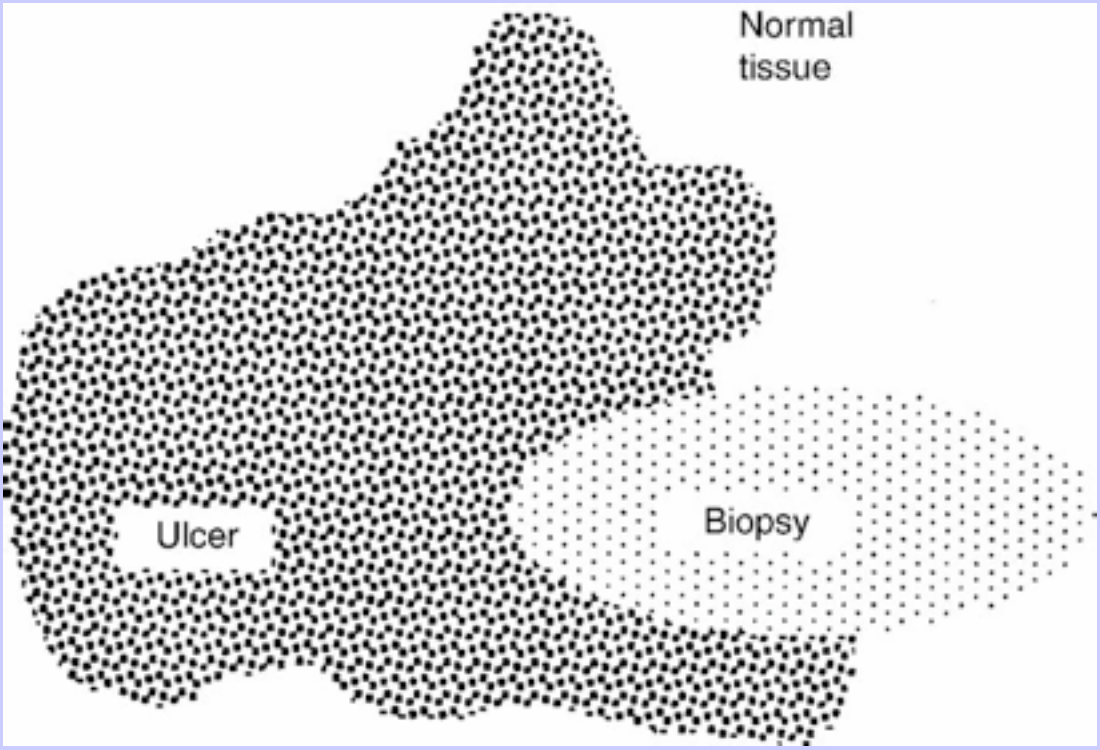
Fig. 11-6 An ulcerative lesion should be biopsied in an elliptical fashion, using a No. 15 scalpel blade, so that the long axis of the ellipse crosses perpendicular to the leading edge of the lesion.



Ideally biopsy specimens should be submitted to a veterinary histopathologist with special interest and training in dermatopathology. Submission of adequately biopsied specimens of properly chosen lesions is the clinician's responsibility. To further increase the chances of securing clinically valuable information from the biopsy samples, the clinician must also provide the pathologist with a concise history of the skin problem, physical findings, a description of the morphology and location of the lesions, and a list of differential diagnoses. When the suspected clinical diagnoses are provided, the pathologist's efforts can be directed specifically toward confirming or ruling out those diagnoses.

* Baker's Biopsy Punch, Chester A. Baker Laboratories, Miami, FL.

11.1.3.8

BIOPSY FOR IMMUNOPATHOLOGY

Immunopathology may be used as an adjunct to conventional histologic testing when the clinician suspects that the patient has an immune-mediated skin disease. The two methods used are direct immunofluorescence, which requires a special medium for fixation (Michel's fixative), and immunoperoxidase techniques, which may be performed on the paraffin block prepared for the histopathologic study (i.e., the formalinized tissue section). The materials and the technique for biopsy for immunopathology are essentially identical to those for a routine histologic examination. Administration of corticosteroid medications within 3 weeks of testing may be associated with false-negative test results. It is advisable to bisect biopsy samples along their long axis, submitting half for direct immunopathology and half for histopathologic examination. It should be borne in mind that histopathology of the lesions, rather than immunopathology, is often the more accurate of the two methods in the diagnosis of autoimmune diseases; thus if faced with the choice (because of financial reasons or paucity of lesions) the clinician should always choose the former.

11.1.3.9

MICROFILARIAL PREPARATION

The microfilarial preparation technique is applicable to the diagnosis of cutaneous onchocerciasis in horses, stephanofilariasis in cattle, and elaeophorosis and parelaphostrongylosis of sheep and goats. After selecting the lesion to be sampled, a 6-mm punch biopsy is used to obtain the tissue sample in the same manner as for the histopathologic biopsy. The tissue should be split, and half preserved in 10% buffered formalin for routine histologic studies. The other half is placed on a dampened gauze sponge in a tightly closed container until the preparation can be performed. A small piece of the tissue that includes the dermis is placed on a glass slide and minced with a razor blade; a few drops of nonbacteriostatic saline are added. Bacteriostatic saline, which kills the microfilaria and thus makes their identification more difficult, should not be used. The specimen is incubated at room temperature for 15 minutes. The slide is then scanned with the ×4 objective along the margins of the tissue debris while the clinician searches for indication of motion in the saline. If the characteristic whiplash movement of the parasite is noted, a higher-powered objective should be used. If the preparation result is negative, a small amount of water is added to a Petri dish, the glass slide is rested on two wooden sticks above the water, and the cover is replaced on the dish. The preparation should be incubated for several hours or overnight and reexamined. The Petri dish helps prevent the sample from drying out.

11.1.3.10

BACTERIAL CULTURE

The method of bacterial culture depends on the type of lesion. All haired lesions should be gently shaved. Nodules and tumors should be cultured by aseptically excising the lesion or by obtaining a generous wedge of the tissue. To prevent culture contamination by surface bacteria, the nodules should be gently shaved, washed with an antiseptic soap, and dried with a sterile gauze pad. A perilesional injection of 2% lidocaine is used to anesthetize the tissue. The sample is placed in a transport medium and sent to a microbiology laboratory for culture. A papular eruption (rash) is best cultured by obtaining a sterile 6-mm punch biopsy of skin.

Crusts may be lifted up and the underside cultured via a sterile Culturette. Ulcerative lesions should not be cultured because any bacteria isolated are more likely to be opportunistic rather than primary pathogens. If the lesions are fluctuant (vesicles, pustules), the overlying skin can be opened gently with a No. 15 blade and some of the contents of the lesion transferred with the blade to the tip of a sterile culture swab. It is advisable

to avoid placing the swabs directly on the skin surface, particularly when sampling small lesions, because nonpathogenic bacteria from the skin surface may be inadvertently cultured.[1]

11.1.3.11 SUBCUTANEOUS AND DEEP FUNGAL CULTURE

Subcutaneous and deep fungal cultures should be performed on nodules, tumors, and swellings. The technique is identical to that described for bacterial culture of these lesions.

11.2 PRURITUS

11.2.1 Definition

Pruritus is an unpleasant sensation that provokes the desire to scratch. It is designated a primary cutaneous sensation, along with heat, cold, pain, and touch. There are two broad categories of pruritus. Physiologic or spontaneous itch is a sharp, well-defined, pruritic sensation that is sufficiently intense to prompt scratching but that does not result in significant irritation of the skin; this is a frequent daily occurrence in normal individuals. Pathologic itch is the less well-defined pruritus that occurs in a variety of primary and secondary skin disorders and in systemic diseases. It is an intense cutaneous discomfort that provokes vigorous scratching.[2]

11.2.2 Mechanisms of Pruritus

The investigation of the mechanism of pruritus has been primarily in laboratory animals and humans. It is presumed that much of this knowledge is applicable to other animal species. Pruritus is a distinct sensory quality transmitted from an arborizing network of nerve endings situated at or near the dermoepidermal junction. The sensation is carried to the spinal cord through small, unmyelinated C fibers. The fibers enter the dorsal root of the spinal cord and ascend in the ventrolateral spinothalamic tract through the posterior ventral nucleus of the thalamus to the sensory cortex. The pruritic sensation may be modified in the sensory cortex by behavioral factors or competing stimuli.[3,4]

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Many physical and chemical stimuli can evoke pruritus, and many substances have been implicated as mediating pruritus in humans. Examples of these mediators, which are assumed to have importance in domestic animals as well, include the following[4]:

- *Histamine*. Histamine has been regarded as the classic mediator of pruritus. Histamine is present in mast cells in the dermis and in blood basophils. An intradermal injection of histamine produces pruritus within 20 to 50 seconds. Because many pruritic disorders respond poorly to antihistamines given either therapeutically or prophylactically, histamine is not believed to be the sole mediator of pruritus.
- *Endopeptidases*. Examples include trypsin, papain, and kallikrein.
- *Prostaglandins*(*E series* and *endoperoxidases*). Prostaglandins induce pruritus by potentiating the release of proteases from keratinocytes and leukocytes and by lowering the threshold and increasing the duration of histamine-induced pruritus.
- *Endogenous opioid peptides*. Opiates may potentiate preexisting pruritus. The opiate antagonist naloxone hydrochloride has an attenuating effect on the histamine-induced component of pruritus.

- *Substance P*. Substance P is a neurotransmitter found in the central and peripheral nervous systems. When introduced intradermally, it elicits a pruritic response.

Many factors can potentiate existing pruritus. Neurologic factors such as boredom and fatigue can potentiate a pathologic itch and possibly transform a physiologic itch into a pathologic itch. Local axonal reflexes can potentiate pruritus; that is, if a second stimulus is applied to an area close to one that is pruritic, the second stimulus, irrespective of its type, is perceived as an itch. In addition, skin with chronic dermatitis has limited perception of stimuli, and any stimulus applied to the affected region may be perceived as either a burning sensation or an itch. This phenomenon is known as "conversion itch." Secondary bacterial infections, vasodilatation, and inflammation result in a local increase in proteases that potentiate pruritus.[3]

Pruritus can be diminished by several nonpharmacologic mechanisms, the most common being application of competing stimuli. Pruritus is a minor sensation compared with the other primary sensations of heat, cold, touch, and pain; thus local application of a competing stimulus to a pruritic area often suppresses the pruritic sensation. Scratching is an example of a competing stimulus. Scratching may relieve pruritus by disturbing the rhythm of afferent impulses traveling toward the central nervous system. An alternative theory is that scratching may cause transient damage to nerve fibers that convey the pruritic sensation. Unfortunately the effect is short-lived because the epidermal damage induced by scratching causes the release of epidermal proteases that may later increase the degree of pruritus. Centrally acting factors such as diversions or distractions can also diminish the perception of pruritus by providing competing stimuli directly to the cortex rather than locally to the skin.[3]

11.2.3

Approach to the Diagnosis of Pruritus

Pruritus is the most common sign of cutaneous disease. Most often in large animals it is caused by ectoparasites or a hypersensitivity reaction, or both (e.g., *Culicoides* hypersensitivity), but it may also be caused by cutaneous bacterial or fungal infections (e.g., dermatophytes, *Malassezia* species) (Box 11-1). Because pruritus may be a feature of a more generalized disease process, it is important to take the patient's general health into account. Hypersensitivity reactions, which are commonly pruritic, may or may not be limited to the skin. For example, anaphylaxis is a life-threatening hypersensitivity reaction that may manifest as pruritus in its early stages. Other pruritic skin diseases include immune-mediated diseases such as pemphigus foliaceus; direct irritation by chemicals; and photoactivated dermatoses. It is helpful to formulate a differential diagnosis by considering each of these broad categories of diseases and using historic information, other cutaneous signs, and appropriate diagnostic tests to narrow the list of differential diagnoses.

11.2.3.1

Box 11-1 Most Common Causes of Pruritus in Horses and Ruminants

11.2.3.1.1

ECTOPARASITES

Culicoides species (horses)

Other flying insects

Lice

Psoroptes cuniculi (goats)

Psoroptes ovis (sheep)

Sarcoptes scabiei (ruminants)

Chorioptes species (horses and cattle)

11.2.3.1.2 HYPERSENSITIVITY (HORSES)

Atopic dermatitis

11.2.3.1.3 INFECTIOUS

Staphylococcal pyoderma (horses)

Dermatophytes

The following steps are a guide to the diagnosis of pruritus in the horse and ruminant:

1 History and physical examination (see Fig. 11-1).

a Determine if the pruritus is a seasonal or year-round problem. A seasonally recurrent pruritic disease tends to suggest either seasonal exposure to a parasite (e.g., lice in the winter, flies in the summer) or a seasonal environmental allergen (e.g., pollens) as the cause. Determine the level of fly exposure for the animal that is pruritic in the warmer months.

b Determine if the pruritus is generalized or localized, and if localized, what areas of the body are affected. For example, photoactivated dermatoses are limited to the white-haired regions.

c Determine if contact animals of the same and different species are affected or unaffected. The presence of multiple pruritic animals is suggestive of a contagious disease (e.g., dermatophytes, ectoparasites) or a disease of common exposure *(Culicoides)*. A single pruritic animal among a group of unaffected animals is more likely to be experiencing a hypersensitivity reaction (drug or environmental).

d Determine what topical and systemic medications were given to the patient both before and after the onset of the problem. Medications given before onset may be the cause of the pruritus, and those given after onset may interfere with the results of diagnostic tests.

e Determine whether all the cutaneous lesions can be attributed to self-trauma or if other primary cutaneous changes are present (e.g., wheals, nodules, pigmentary changes).

f Determine whether, on close inspection, the coat shows evidence of small but grossly visible parasites such as lice or their eggs.

2 The most useful diagnostic tests are skin scrapings, acetate tape preparations, dermatophyte culture plus KOH preparation, *Dermatophilus* preparation, microfilarial preparation, biopsy for routine histopathologic examination, and intradermal skin testing (see Chapter 40).

11.3 NODULES, TUMORS, AND SWELLINGS

11.3.1 Definition

A nodule is a circumscribed, solid elevation larger than 1 cm in diameter that does not deform when palpated. Nodules extend into the deeper layers of the skin and are usually the result of cellular infiltrates in the dermis or subcutis. *"Tumor"* is a less precise term that usually refers to a neoplastic, nodular enlargement of the skin or subcutaneous tissue.[3] The term *"tumor"* is most commonly used to describe very large nodular neoplasms. In addition to nodules and tumors, swellings include elevated lesions that pit with pressure (wheals) and fluctuant lesions (cysts and abscesses).

11.3.2 Mechanisms of Nodule, Tumor, and Swelling Formation

Nodular lesions can be subdivided into inflammatory and neoplastic lesions. Inflammatory nodules are composed of a massive mixed cellular infiltrate involving the dermis, the subcutis, or both. The inflammatory infiltrate may contain variable numbers of neutrophils, histiocytes, lymphocytes, plasma cells, and eosinophils. Cellular infiltration usually is stimulated by the presence of foreign material, and the nature of that material influences the composition of the inflammatory infiltrate. The foreign material may be infectious (parasite, bacteria, or fungi) or noninfectious (fibrin, crystalline material, or other inert substances). Grossly visible nodules develop as the masses of inflammatory cells accumulate in the tissues to phagocytize or wall off the foreign material. As the lesion enlarges, the dermis and subcutis are obliterated by the inflammatory infiltrate and the overlying epidermis may become atrophic, resulting in ulceration of the nodule's surface.

Most cutaneous and subcutaneous neoplasms form nodular lesions. Cutaneous and subcutaneous neoplasms may either arise from a cell type of the epidermis, dermis, or subcutis or less commonly metastasize from another tissue of origin. Cytologically and histologically neoplasms are composed of a uniform population of pleomorphic cells with variable atypia. Neoplasms may stimulate a secondary inflammatory reaction.

Swellings include solid lesions, such as nodules and tumors, as well as urticaria, cysts, and abscesses. Urticarial lesions (wheals, hives) are often transient, localized, inflammatory lesions caused by a vascular reaction in the dermis in which vasodilatation results in fluid transudation with or without erythema. The fluid is not compartmentalized but dispersed evenly throughout the dermal tissue. The result is an elevated lesion that, unlike a nodule, pits with pressure and often dissipates within minutes to hours as the fluid is resorbed. Typically a sparse, perivascular infiltrate that is usually lymphocytic is seen, although the infiltrate may be dense and intermingled with eosinophils. Urticaria is usually well circumscribed, although with confluence the edema may assume geometric shapes.

A cyst (Latin for *sac*) is an epithelium-lined cavity containing fluid or semisolid material.[3] A cyst usually presents as an elevated, smooth, well-circumscribed, fluctuant mass. Cutaneous cysts usually are lined by

adnexal epithelium (hair follicle, sebaceous or apocrine epithelium) and are filled with cornified cellular debris and sebaceous or apocrine secretions.

An abscess is a localized, fluid-filled, fluctuant lesion; if large enough, it may be ballotted. It results from a dermal or subcutaneous accumulation of the debris of dead cells and tissue elements liquefied by the proteolytic and histolytic enzymes elaborated by polymorphonuclear cells (e.g., pus). Abscesses most commonly result from localized infection, although they occasionally result from septicemia or may be sterile.

11.3.3

Approach to the Diagnosis of Nodules, Tumors, and Swellings

Nodules, tumors, and swellings may arise from a variety of cutaneous disorders and, in rare cases, as signs of a systemic disease. The major categories of diseases that should be considered when forming a differential diagnosis include hypersensitivity reactions, infectious diseases, sterile inflammatory diseases, and neoplasia (Box 11-2). The primary systemic diseases that should be considered are amyloidosis, lymphosarcoma, and anaphylaxis.

The following steps are a guide to the diagnosis of nodules, tumors, and swellings in horses and ruminants:

1 History (see Fig. 11-1). Pay particular attention to:

a Signalment. Older animals are at greater risk for cutaneous neoplasia (e.g., gray horses and melanomas). However, neoplasia is not restricted to older animals; equine sarcoids are frequently recognized in horses as young as 3 years of age.

11.3.3.0.0.0.0.0.0.1

Box 11-2 Most Common Causes of Nodules, Tumors, or Swellings in Horses and Ruminants

11.3.3.0.0.0.0.0.0.1.1

HORSES

11.3.3.0.0.0.0.0.0.1.1.1

Infectious

Corynebacterium pseudotuberculosis

Habronema species

Sporotrichosis

11.3.3.0.0.0.0.0.0.1.1.2

Neoplasia

Sarcoid

Squamous cell carcinoma

Melanoma

11.3.3.0.0.0.0.0.0.1.1.3 Sterile, Nonneoplastic

Eosinophilic granuloma

Exuberant granulation tissue (proud flesh)

Urticaria (hives)

11.3.3.0.0.0.0.0.0.1.2 RUMINANTS

11.3.3.0.0.0.0.0.0.1.2.1 Infectious

C. pseudotuberculosis

Hypoderma species (warbles)

Sporotrichosis

Actinobacillosis

Actinomycosis

11.3.3.0.0.0.0.0.0.1.2.2 Neoplasia

Squamous cell carcinoma

Fibroma or fibrosarcoma

Epidermal inclusion cysts

11.3.3.0.0.0.0.0.0.1.2.3 Sterile, Nonneoplastic

Urticaria (hives)

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b Number and progression of lesions. If one or only a few lesions are present, hypersensitivity to arthropod bites should be considered, particularly if there is rapid onset of the lesion. Rapid onset of generalized lesions such as urticaria suggests a differential diagnosis of drug, flying insect, environmental (pollen), or (rarely) food allergies.

c A recent history of systemic illness, which might suggest that the lesion is a bacterial abscess.

2 Physical examination (see Fig. 11-2). In particular:

a Determine by palpation if the cutaneous lesions are nodules, tumors, or swellings.

b Inspect the lesion or lesions closely for evidence of cutaneous parasitism (ticks, breathing pores associated with *Hypoderma* larvae, yellow granules associated with cutaneous habronemiasis).

c Determine if the lesions are painful or pruritic (e.g., evidence of excoriations).

3 Perform fine-needle aspiration for cytologic studies.

4 Perform biopsy for histopathologic examination.

5 Perform bacterial culture and sensitivity.

6 Perform subcutaneous and deep fungal cultures.

7 Perform dermatophyte culture and KOH preparation.

11.4 ULCERATIONS AND EROSIONS

11.4.1 Definition

An ulcer is a cutaneous defect that results from a complete loss of the epidermis and usually part of the underlying dermis.[3] Ulcers often heal with scarring that is caused by destruction of dermal collagen. An erosion is a cutaneous defect that results from a partial loss of the epidermis that does not penetrate beneath the basal laminar zone. Because an erosion does not involve the dermis, it heals without leaving a scar. Because the epidermis is a cutaneous barrier to invading microorganisms, ulcers and erosions often are secondarily infected.

11.4.2 Mechanisms of Ulcer and Erosion Formation

Ulcers and erosions are secondary lesions. Primary lesions develop spontaneously and are a direct reflection of underlying disease. Secondary lesions evolve from primary lesions or are artifacts induced by excoriation or external trauma. Primary lesions that may lead to the formation of ulcers and erosions include fluid-filled lesions such as pustules and vesicles. Rupture of these fragile lesions results in epidermal destruction and erosion or ulcer formation. Swellings such as abscesses and cysts may also rupture, resulting in ulceration, but these primary lesions are more stable and often remain intact. Nodules and tumors may become secondarily eroded or ulcerated. As the nodule or tumor enlarges, the mass exerts pressure on the overlying epidermis, leading to epidermal atrophy and ultimately a break in epidermal confluence, resulting in ulceration and erosion. The most common cause of ulceration and erosion is pruritus, which induces excoriation and hence epidermal destruction. Ulcers and erosions may also result from external trauma, such as epidermal destruction arising from mechanical, thermal, or chemical causes (Box 11-3).

11.4.3 Approach to the Diagnosis of Ulcerations and Erosions

To diagnose the cause of an ulcer or erosion, the clinician must first determine the primary lesion that resulted in ulceration and erosion. Ulcers and erosions occurring secondary to pustules and vesicles, to swellings such as

abscesses and cysts, to nodules and tumors, to pruritus, and to external trauma must be differentiated. The list of differential diagnoses relevant to each of these groups of primary lesions is then considered.

11.4.3.1

Box 11-3 Most Common Causes of Ulcerations and Erosions in Horses and Ruminants

11.4.3.1.1

IMMUNE-MEDIATED

Adverse drug reaction

Contact irritant or hypersensitivity

Photosensitivity

Purpura hemorrhagica (horses)

Vasculitis

11.4.3.1.2

INFECTIOUS

Dermatophilosis congolensis

Habronema species (horses)

Viral diseases (in ruminants, for example, infectious bovine rhinotracheitis, vesicular stomatitis, bovine herpes mammillitis)

11.4.3.1.3

NEOPLASIA

Squamous cell carcinoma

The following steps are a guide to the diagnosis of ulcerations and erosions in horses and ruminants:

1 History (see Fig. 11-2)

a Determine if the animal is pruritic.

b Determine if the animal has been subjected to external trauma (mechanical, thermal, or chemical).

c Determine what topical and systemic medications were given to or used on the patient before the onset of the problem. Use of certain topical agents may suggest a diagnosis of contact dermatitis, whereas administration of systemic medications may suggest a drug hypersensitivity.

2 Physical examination (see Fig. 11-2)

a Examine the oral cavity and mucocutaneous junctions for lesions. Oral or mucocutaneous lesions (or both) in the horse might suggest accidental ingestion of a vesicant, or the rare diagnosis of bullous pemphigoid. In a ruminant these lesions often are seen with viral infections.

b Look for evidence of excoriation, suggesting that the ulcerations and erosions have occurred secondary to pruritus.

c Look for evidence of primary lesions such as pustules, vesicles, nodules, tumors, or swellings, which may have preceded the ulcerations and erosions.

3 Biopsy for routine histopathologic examination

4 Biopsy for direct immunofluorescence testing

11.5 PAPULES, PUSTULES, AND VESICLES

11.5.1 Definition

A papule is a solid, circumscribed, elevated lesion up to 1 cm in diameter. Papules are essentially small nodules that do not extend beneath the dermis. A pustule is a fluctuant, circumscribed, elevated accumulation of pus (inflammatory cells and often necrotic debris) up to 1 cm in diameter (e.g., a small abscess). Pustules are frequently associated with infectious diseases, although sterile pustular diseases (such as pemphigus foliaceus) exist. A vesicle is a fluid-filled, acellular, circumscribed, elevated lesion up to 1 cm in diameter. A bulla is a vesicle that is larger than 1 cm in diameter. All these lesions can be either follicular or nonfollicular in orientation, depending on the underlying cause. Pustules and vesicles are rarely seen clinically because of their fragility and hence their susceptibility to rupture. Because papules are solid lesions, they are more stable and therefore more commonly encountered.

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11.5.2 Mechanisms of Papule, Pustule, and Vesicle Formation

Papules usually form as a result of an infiltrate in the dermis, which can be either cellular or noncellular. Cellular infiltrates may include inflammatory or neoplastic cells, although neoplastic papular lesions are relatively uncommon in large animals. Inflammatory infiltrates may be mixed, containing variable numbers of neutrophils, histiocytes, lymphocytes, plasma cells, and eosinophils, or one cell type may predominate. The composition of the inflammatory cells is influenced by the underlying cause of the papule, and the possible causes are extensive. Noncellular papular infiltrates include substances such as edema fluid, amyloid, and proliferative collagen. Epidermal hypertrophy may contribute to or be the sole cause of papule formation.

Pustules form as the result of an intraepidermal, subcorneal, or, less commonly, subepidermal accumulation of inflammatory cells. Infiltration of inflammatory cells, particularly polymorphonuclear leukocytes, leads to the release of proteolytic enzymes that liquefy tissue elements and result in the formation of a fluctuant lesion. Eosinophils, acantholytic cells, and infectious organisms may also be noted in a pustule, depending on the underlying cause. The stimulus leading to pustule formation is most commonly infectious, although pustules can result from noninfectious causes such as hypersensitivity reactions and autoimmune disease.

Vesicles form either at the dermoepidermal junction (subepidermal) or in the epidermis (intraepidermal) as a result of destruction of the basement membrane zone or confluence of intercellular edema (spongiosis). Clinically the two types of vesicles are indistinguishable. Vesicles form as the result of some viral diseases, during severe inflammatory reactions (allergic contact dermatitis), or with cutaneous physical damage (mechanical, chemical, or thermal). In pemphigus foliaceus, autoantibodies presumably bind to transmembrane proteins between the epidermal cells, causing disruption of epidermal intercellular attachments. The result is intraepidermal cleft formation that leads to vesiculation. In bullous pemphigoid, complement-activating antibodies bind to antigens in the basement membrane zone, causing degranulation of mast cells, chemotaxis of neutrophils and eosinophils, and release of tissue-destructive enzymes that injure the basement membrane zone. The result is loss of dermoepidermal adherence and vesicle formation.[3] Vesicles are transient, fragile lesions and therefore are rarely recognized clinically. If they are not destroyed by surface trauma, rapid infiltration by inflammatory cells transforms a vesicle into a pustule.

11.5.3

Approach to Diagnosis of Papules, Pustules, and Vesicles

Although papules, pustules, and vesicles may look somewhat similar on a cursory physical examination, the clinician must differentiate among the three and determine which of the lesions are present. Examination with a hand lens may help. The differential diagnoses relevant to papules, pustules, and vesicles are not necessarily the same (Box 11-4). In all cases it is important to determine if disease is limited to the skin or if the animal's general health is compromised as well.

11.5.3.1

Box 11-4 Most Common Causes of Papules, Pustules, and Vesicles in Horses and Ruminants

11.5.3.1.1

HORSES

11.5.3.1.1.1

Hypersensitivity—Usually Papules

Culicoides species

Other flying insects

11.5.3.1.1.2

Infectious—Papules or Pustules

Staphylococcal pyoderma

Dermatophilosis congolensis

11.5.3.1.1.3

Immune-Mediated

Pemphigus foliaceus—papules or pustules

Bullous pemphigoid—vesicles

11.5.3.1.2 RUMINANTS

11.5.3.1.2.1 Ectoparasites—Usually Papules

Sarcoptes scabiei

Psoroptes cuniculi (goats)

Lice

11.5.3.1.2.2 Infectious

Viral diseases (e.g., vesicular stomatitis)—vesicles

Staphylococcal pyoderma (goats)—pustules or papules

Papular lesions have the most extensive differential diagnoses:

- Hypersensitivity reactions. Parasitic hypersensitivities are the most common (e.g., *Culicoides* hypersensitivity), although drug and (rarely) food hypersensitivities should also be considered. Many hypersensitivity reactions are pruritic.
- Parasites. Some species simply irritate the skin with their bites (e.g., horn fly [*Haematobia irritans*]) without inducing a hypersensitivity reaction.
- Infectious diseases (bacterial, fungal, and viral). Typically papules caused by infections have a follicular orientation.
- Certain neoplastic diseases (papillomas or sarcoids).
- Uncommon causes, including autoimmune diseases, such as pemphigus foliaceus, and diseases of uncertain cause, such as equine sarcoidosis.

Pustules are most commonly associated with bacterial infections, although fungi and, in rare cases, parasites (*Demodex* species) can cause pustule formation. Sterile pustular diseases are less frequently seen (drug eruptions, sterile eosinophilic folliculitis of cattle)[5] but should be included in the differential diagnoses. Vesicles are rapidly infiltrated by inflammatory cells and transformed into pustules. Diseases commonly associated with vesicles include viral diseases of ruminants, autoimmune diseases, contact dermatoses, and burns.

The following steps are a guide to the diagnosis of papules, pustules, and vesicles in horses and ruminants:

1 History (see Fig. 11-1)

a In particular, determine whether the lesions are pruritic, painful, or asymptomatic.

b Determine if contact animals of the same and different species are affected or unaffected. If contact animals are affected, a contagious problem should be considered: fungal (dermatophytosis), bacterial (dermatophilosis), viral (contagious ecthyma), or parasitic (*Culicoides* hypersensitivity).

c Trace the temporal course of development. Rapid onset of lesions may suggest a hypersensitivity reaction.

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d Check for seasonality. A seasonal problem suggests a parasitic or hypersensitivity (pollens) cause. Lice are a problem in the winter, trombiculidiasis tends to occur in the fall, and most of the flying insects are present in the spring, summer, and early fall.

e Determine what topical and systemic medications were given to or used on the animal before the onset of the problem. Use of certain topical agents may suggest a diagnosis of contact dermatitis, whereas administration of systemic medications may suggest drug hypersensitivity.

f Determine if the animal has been subjected to external trauma (thermal or chemical).

2 Physical examination (see Fig. 11-2)

a Gently palpate the lesions to determine if they are solid (papules) or fluctuant (pustules or vesicles).

b Note if the lesions have a follicular orientation, suggesting an infectious cause.

c Check for lesions involving the oral cavity and mucocutaneous junctions.

d Look for evidence of excoriation, suggesting that pruritus is a feature of the disease.

e Inspect the coat closely for small but grossly visible parasites such as lice or their eggs.

f Inspect contact animals for evidence of disease.

3 Skin scrapings of papular lesions

4 Cytologic studies

5 Dermatophyte culture and KOH preparation

6 *Dermatophilus* preparation

7 Bacterial culture and sensitivity

8 Microfilarial preparation

9 Biopsy for routine histopathologic examination

10 Biopsy for direct immunofluorescence testing

11.6 SCALING AND CRUSTING

11.6.1 Definition

Scale is a visible accumulation of fragments of the horny layer of the skin (stratum corneum); it represents the final product of epidermal keratinization.[3] The process of forming the stratum corneum is termed *cornification*. Histologically scale is recognized as hyperkeratosis and can be subdivided into parakeratosis (cornification with nuclear retention) or orthokeratosis (cornification without nuclear retention). In some conditions parakeratosis and orthokeratosis may be present together. Grossly the scale varies in appearance. The color may be white, silver, yellow, brown, or gray. The consistency may be bran-flake—like, powdery, coarse, greasy, or dry. Scale can be either loose or adherent to the skin or hair shafts.

Crusts are composed of variable amounts of serum, cells (leukocytes, erythrocytes, keratinocytes), fibrin, infectious agents (bacteria and fungi), debris, and/or medications. They often cover erosions or ulcerations. Heaped-up crusts are referred to as *vegetations*. On the basis of their histologic composition, crusts may be subdivided into cellular, serocellular, serous, and hemorrhagic types.

11.6.2 Mechanisms of Scale and Crust Formation

Scale results from increased desquamation (exfoliation) of the stratum corneum. Exfoliation is the final stage of keratinization, the process by which the permanent population of cells of the basal layer of the epidermis divides, undergoes specific patterns of differentiation, and progresses toward the surface, where it is shed.[3,5] Excessive exfoliation and scale formation occur when the rate of keratinization is accelerated; when trauma to the surface of the epidermis (chemical, mechanical, or thermal) loosens the stratum corneum; or when the structures sustaining epidermal intercellular cohesion (such as transmembrane proteins) are destroyed, resulting in a loss of cohesion between epidermal cells.

Because crusts are composed primarily of serum and cells, their presence on the skin surface implies that vascular and epidermal permeability has increased to permit their formation. Serum and inflammatory cells are released into the tissues from the dermal vasculature, then cross the epidermis to the skin surface either through erosions or ulcerations or by permeating between the intercellular spaces. The exudate dries on the skin surface, in combination with any medication or debris that was already present on the hair or skin, to form the visible crust. Desquamating keratinocytes may be swept up in the exudate and become part of the crusts. Bacteria frequently invade crusts after they have formed and will be noted on histologic examination, even though they may not be a factor in the pathogenesis. Fungal organisms, when present, are more likely to be important to the pathogenesis of the underlying disease process.

11.6.3 Approach to Diagnosis of Scaling and Crusting

The most important factor in determining the underlying cause of scale or crust formation in either a horse or a ruminant is to determine if the patient is pruritic and if some or all of the lesions are induced by self-trauma. If pruritus is a feature, the approach to diagnosis of pruritus should be used because all pruritic diseases can cause scale and crust formation. If the patient is not pruritic, the most important differential diagnoses include infectious diseases (particularly dermatophilosis and dermatophytosis), nutritional disorders, toxicities, autoimmune disease (pemphigus foliaceus), cutaneous filariasis, photosensitization, irritant contact reactions or

burns, and diseases of uncertain cause (for example, in equine patients, sarcoidosis, aural plaques, and primary seborrhea) (Box 11-5).[3,6] Viral diseases are important nonpruritic causes of scaling and crusting in ruminants, although they usually are associated with ulceration and erosion with involvement of the oral cavity and mucocutaneous regions.

11.6.3.1

Box 11-5 Most Common Causes of Scaling and Crusting in Horses and Ruminants

11.6.3.1.1

ECTOPARASITES

Sarcoptes scabiei (ruminants)

Psoroptes cuniculi (goats)

Psoroptes ovis (sheep)

Lice

Chorioptes species (horses and cattle)

11.6.3.1.2

INFECTIOUS

Dermatophilosis congolensis

Staphylococcal pyoderma

Dermatophytosis

11.6.3.1.3

IMMUNE-MEDIATED

Pemphigus foliaceus (horses and goats)

Photosensitization (horses)

11.6.3.1.4

NUTRITIONAL

Zinc deficiency (ruminants)

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The following steps are a guide to the diagnosis of scaling and crusting in horses and ruminants:

1 History (see Fig. 11-1)

a In particular, determine if the patient is pruritic.

b Determine if contact animals of the same or different species are affected. If they are, a contagious problem should be considered: fungal (dermatophytosis), bacterial (dermatophilosis), viral, or parasitic.

2 Physical examination (see Fig. 11-2)

a Look for evidence of excoriation, suggesting that pruritus is a feature.

b Inspect the coat closely for small but grossly visible parasites such as lice or their eggs.

c Inspect contact animals for evidence of disease, suggesting a contagious cause.

3 Skin scrapings

4 Acetate tape preparations

5 Dermatophyte culture and KOH preparation

6 *Dermatophilus* preparation

7 Biopsy for routine histopathologic examination (careful histologic examination of scale and crusts is essential to the search for the underlying cause of their formation)

8 Microfilarial preparation

9 Biopsy for direct immunofluorescence testing

10 Bacterial culture and sensitivity

11.7 ABNORMAL COAT LENGTH AND DENSITY

11.7.1 Definition

Abnormalities in coat length and density can be subdivided into decreased coat length and density (alopecia, hypotrichosis) and increased coat length and density (hirsutism, hypertrichosis). Hirsutism, or excessive body hair, is far less common than alopecia, which is an absence of hair from areas where hair is normally present. Alopecias are usually classified as scarring (cicatricial) or nonscarring (noncicatricial). In cicatricial alopecias the hair follicles are destroyed, and hair loss is permanent because neogenesis of the hair follicle does not occur in an adult mammal. In nonscarring alopecias the hair follicles are retained; therefore the potential for regrowth remains. Both alopecia and hirsutism may be complete or partial, diffuse or focal, and congenital or acquired.

11.7.2 Mechanisms of Development of Abnormal Coat Length and Density

A basic understanding of the dynamics of hair structure and development is essential to an understanding of the mechanisms associated with pathologic changes in coat length and density.

The hair follicle and the sebaceous and apocrine glands are epidermal appendages. The hair follicle forms during fetal development as a downgrowth of epidermal cells toward a group of mesenchymal cells that ultimately become the dermal papillae. The sebaceous and apocrine glands begin as buds of epithelium from the sides of the developing hair follicle.

Hair is composed of keratin and is the product of the hair follicle. The hair shaft is the part of the hair that emerges from the skin surface. The hair root is the part of the hair in the follicle. The hair bulb is a knob of epidermal cells that attaches the follicle to the dermal papilla. Both the hair follicle and the shaft have distinct layers. There are two types of hair follicles: simple and compound. A simple hair follicle produces a single hair. A compound hair follicle produces multiple hairs with bundles of hairs sharing a common skin opening and a single follicle down to the level of the sebaceous gland. Below the sebaceous gland the follicle branches so that each hair has its own hair bulb. Horses and cattle have only simple follicles. Goats and sheep have a mixture of simple and compound hair follicles (Fig. 11-7).[3,5]

The normal hair growth cycle is divided into three repeating stages: anagen, catagen, and telogen, with the size and shape of the follicle changing during each stage (Fig. 11-8). The amount of time a follicle spends in each phase varies with the species, breed, individual, and body region. In addition, it is influenced by factors such as photoperiod, stress, and disease. Anagen is the active phase of hair growth. Catagen is the transition stage from the growing to the resting state. Catagen is short, and the hair quickly enters the telogen phase, in which hair growth stops. As the follicle reenters anagen, a new hair grows up beside the old and dislodges it. The signal that stimulates progression from telogen to anagen is unknown.

Coat abnormalities may result from a multitude of endogenous and exogenous factors that can modify the normal pattern of hair growth and development.

The length, density, and texture of the coat of a normal animal are determined genetically, and a variety of hereditary defects result in coat abnormalities. These defects may cause changes in hair length, density, or quality. Coat quality may be abnormal at birth or may become apparent sometime before 6 months of age. A given defect may alter the number of follicles present in the skin, or the number of follicles present may be normal but there may be genetic alterations in the way the hair is produced. Altered hair production may manifest as an increased or a decreased growth rate or as structural deformities that result in weak hair shafts that break easily.

Nutritional imbalances can affect growth and maintenance of the coat in various ways, depending on the species. Nutritional deficiencies may result in a shift of greater numbers of follicles into telogen, thus increasing shedding. Dietary carbohydrate and protein deficiencies reduce the length, diameter, and strength of hair. Supplementing the diet with carbohydrate and protein releases protein for keratin formation, provides energy to use protein, and maintains mitotic activity in the hair matrix. Fatty acid deficiencies affect lipid production in the skin, leading to a dry coat with increased fragility. A variety of vitamin and mineral deficiencies may also result in poor hair growth or quality.

Inflammatory skin diseases frequently result in hair loss. Infectious inflammatory processes such as dermatophytosis and pyoderma are usually directed specifically at the hair or hair follicle. Inflammatory processes directed elsewhere may still affect the hair follicle by sweeping it up as an “innocent bystander.”

Hormonal effects on hair growth are complex. Thyroid hormones, corticosteroids, sex hormones, melanocyte-stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), growth hormone, and prolactin all affect hair growth. The effect of a single hormone may be modified in the presence of other hormones, and the

importance or effect of any one hormone on hair growth may differ from species to species. Hormonal variations affect the hair coat quality and length by altering the period of time that hair follicles spend in any given part of the cycle, by influencing the rate of hair growth, and by inducing follicular atrophy. External factors such as changes in the photoperiod influence hair growth by altering hormonal levels.

Trauma to the skin is a frequent secondary cause of hair loss. Self-trauma induced by pruritus is the most common cause of alopecia. Hairs may be lost either from trauma to the hair shaft, resulting in breakage, or from trauma to the dermis, resulting in destruction of the hair follicle. In the former case, the hair regrows once the source of trauma has been removed. In the latter case, hair loss is permanent.

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Fig. 11-7 Longitudinal section of a compound hair follicle.

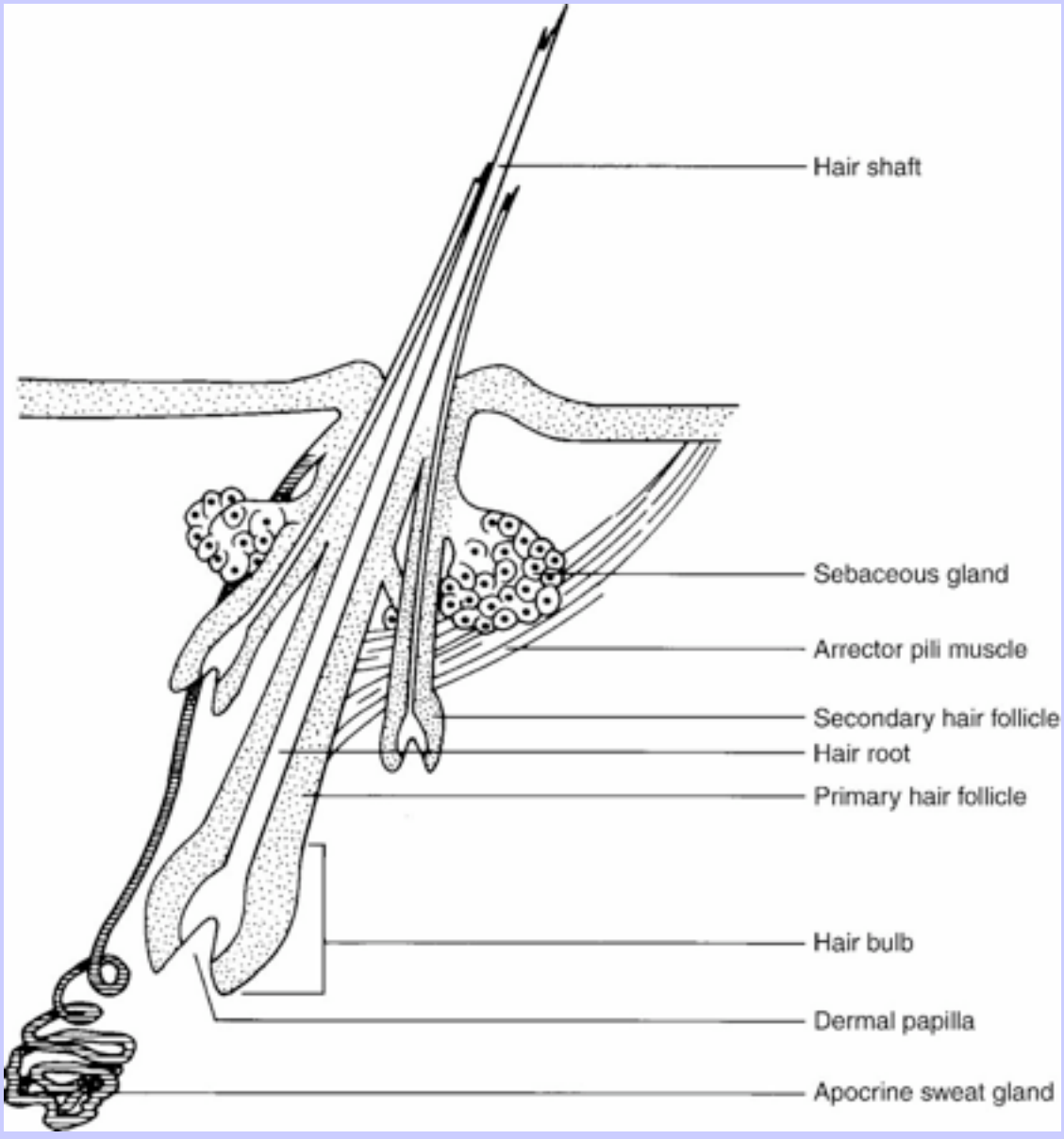
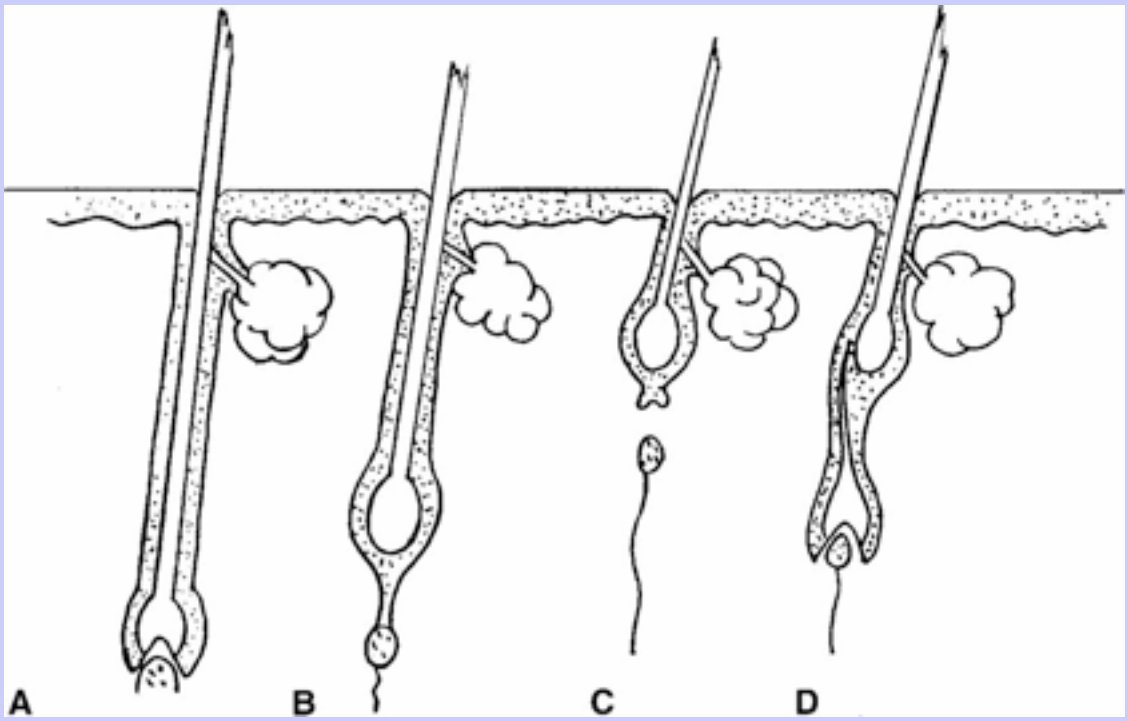


Fig. 11-8 Stages of the hair growth cycle. **A** Anagen. **B** Catagen. **C** Telogen. **D** Early anagen.



A variety of factors can result in hair loss by causing an abrupt shift of hairs into the telogen phase. Recognized causes of telogen effluvium include stress from high fever or severe illness and parturition.

11.7.2.1

Box 6-18 Causes of Abnormal Peripheral Pulse in Horses

11.7.2.1.1

COMMON CAUSES

Dehydration

Shock

Toxemia

Congestive heart failure

Electrolyte imbalances

Acid-base disorders

Hypertension

Hypotension

Exercise

Fever

Laminitis

Aortic regurgitation

Cardiac arrhythmias

11.7.2.1.2 UNCOMMON CAUSE

Aortic cardiac fistula

Peripheral arteriovenous shunt

Patent ductus arteriosus

11.7.2.2 Box 6-19 Causes of Abnormal Peripheral Pulse in Ruminants

11.7.2.2.1 COMMON CAUSES

Dehydration

Shock

Toxemia

Congestive heart failure

Electrolyte imbalances

Acid-base disorders

Fever

Cardiac arrhythmias

11.7.2.2.2 UNCOMMON CAUSES

Patent ductus arteriosus

Aortic regurgitation

Peripheral arteriovenous shunt

11.7.3 Approach to Diagnosis of Abnormal Coat Length and Density

The differential diagnosis of abnormalities resulting in *increased* coat and length density is relatively limited and does not provide much of a diagnostic dilemma for the clinician. In the horse increased coat length and density is an acquired abnormality associated with equine hyperadrenocorticism.[3] In ruminants defects are congenital and are either the result of an in utero infection (border disease) or a breed-specific hereditary defect.[5]

The differential diagnoses of *decreased* coat length and density are extensive. The initial step is to determine if the alopecia is congenital, implying a hereditary defect, or acquired. If the abnormality is acquired, the clinician must determine if it is a primary alopecia or secondary to another cutaneous abnormality such as pruritus or ulceration. If alopecia is the result of another primary cutaneous abnormality, the clinician should focus on the differential associated with that primary abnormality. Finally, to help provide a prognosis for hair regrowth, the clinician should biopsy to determine if the alopecia is scarring (cicatricial) or nonscarring (noncicatricial). Regardless of the underlying cause and its resolution, hair will not regrow with a cicatricial alopecia because by definition the hair follicle has been destroyed. In a noncicatricial alopecia the potential for hair regrowth remains if the underlying cause for hair loss can be identified and resolved (Box 11-6).

The following steps are a guide to the diagnosis of decreased coat length and density in horses and ruminants:

1 History (see Fig. 11-1)

a Determine whether the lesions are congenital or acquired. If they are congenital, determine if any related animals are affected and if the lesions have progressed since birth.

b If the alopecia is acquired, determine if the animal is pruritic and if other cutaneous lesions have been observed.

c Determine if the animal's diet is nutritionally complete.

d Determine if the animal has been exposed to any toxic substances.

e Determine if contact animals of the same or different species are affected. If contact animals are affected, a contagious problem such as dermatophytosis or dermatophilosis should be considered. Because feed and environment are also shared, dietary deficiencies and toxicities should be included in the differential diagnosis.

11.7.3.0.0.0.0.0.0.1

Box 11-6 Most Common Causes of Abnormal Coat Length and Density in Horses and Ruminants

11.7.3.0.0.0.0.0.0.1.1

Alopecia*

- Dermatophytosis
- Staphylococcal pyoderma (horses)
- Alopecia areata (horses, cattle)
- Drug reaction
- Congenital hypotrichosis (cattle)
- Onchocerciasis (horses)

11.7.3.0.0.0.0.0.0.1.2

Increased Coat Length

- Pars intermedia pituitary dysfunction (horses)
- Congenital hypertrichosis

* Alopecia without pruritus, crusts, or other clinical signs.

f Determine what medications have been given systemically or applied topically to the patient. Use of certain topical agents, along with a history of an inflammatory stage preceding or coincident with the alopecia, may suggest a diagnosis of contact dermatitis. Administration of systemic medications may suggest that the cause is a drug hypersensitivity.

g Determine if the animal has been subjected to any stresses that might provoke a telogen effluvium.

2 Physical examination (see Fig. 11-2)

a Check for evidence of disease in organ systems other than the skin. Does the animal appear thin and malnourished, suggesting hair loss related to a dietary deficiency? Is it febrile or suffering from a severe systemic disease, suggesting a telogen effluvium?

b Can the hairs be epilated readily from the coat? If not, hair loss may be caused by trauma (self-induced or external). If so, underlying nutritional, hormonal, or stress-related causes of alopecia are more likely.

c Look for evidence of excoriation, suggesting that self-trauma is the cause of the hair loss.

d Determine whether the lesions are generalized or localized, either to particular areas of the body or to certain hair colors (e.g., black hair follicle dystrophy). Note if the hair loss has a symmetric pattern.

e Inspect the coat closely for small but grossly visible parasites such as lice or their eggs.

f Inspect contact animals for evidence of disease.

3 Microscopic examination of the ends of affected hairs (squared or broken ends suggest that the hair loss is traumatically induced; tapered ends suggest an abnormality in the hair follicle, growth cycle atrophy, or an inflammatory process such as dermatophytosis)

4 Skin scrapings

5 Acetate tape preparations

6 Dermatophyte culture and KOH preparation

7 Microfilarial preparation

8 Biopsy for routine histopathologic examination (sagittal sections should be evaluated to determine the proportion of hairs in the anagen, catagen, and telogen phases; for the presence or absence of inflammation and infectious organisms; and for evidence of scarring, which suggests a poor prognosis for hair regrowth; cross-sections of the biopsy specimen should be evaluated in noninflammatory alopecias to determine the number of hair follicles present per given area)

The following steps are a guide to the diagnosis of increased coat length and density in horses and ruminants:

1 Horses demonstrating increased coat length and density should be evaluated with appropriate laboratory tests for hyperadrenocorticism.

2 Lambs with increased coat length and density should be evaluated for evidence of border disease.

3 Cattle with increased coat length and density probably have hereditary hypertrichosis.

11.8 ABNORMAL PIGMENTATION

11.8.1 Definition

The following terms are used when discussing pigmentation and pigmentary abnormalities.[3]

- *Melanin* is a brown-black, light-absorbing, insoluble pigment formed in many organisms by specialized cells called *melanocytes*.

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- *Hyperpigmentation* is an excessive tissue deposition of pigment, usually melanin.
- *Hypopigmentation* refers to less than normal pigmentation and can be congenital or acquired.
- *Leukoderma (hypomelanosis)* is a partial or total acquired loss of melanin pigment from the skin. The term *vitiligo* also refers to an acquired loss of melanin from the skin but is often reserved for a specific type of leukoderma found in humans.
- *Leukotrichia* is an acquired loss of pigment from the hair.
- *Albinism* is a congenital lack of pigment in all tissues.

11.8.2 Mechanisms of Pigmentation Abnormalities

Cutaneous pigmentation results from the interaction of melanocytes and keratinocytes. The degree of “baseline” pigmentation observed in an animal is genetically controlled. Melanocytes are of neural crest origin and migrate from this site during embryologic development. They are present in nearly all tissues but occur in the highest numbers in the epidermis, mucous membrane epithelium, dermis, hair follicles, leptomeninges, uveal tract, and retina. Epidermal melanocytes are found in the basal cell layer, and each melanocyte is presumed to supply melanin to 10 to 20 keratinocytes. Melanin is usually found in the deeper layers of the epidermis, although darkly pigmented animals may have melanin throughout the epidermal layers.

Melanocytes produce membrane-bound organelles called *melanosomes* that fuse with vesicles containing the enzyme tyrosinase. Melanin, a black-brown pigment, is produced from tyrosine in the presence of tyrosinase and copper. It is deposited on the protein matrix in the melanosomes. Once melanosomes are fully melanized, they disperse to the periphery of the dendrites of the epidermal melanocytes, and the dendritic tips are phagocytized by keratinocytes. Melanin is also synthesized and transferred to cells of the hair shaft during the anagen phase.[3]

In general, mechanisms associated with pathologic pigmentary disturbances in large animals are poorly understood. Hyperpigmentation results from increased amounts of melanin in the epidermis or dermis or both. The melanin may be present in melanocytes, keratinocytes, or melanophages (dermal macrophages that have phagocytized melanin pigment). Hyperpigmentation is an uncommon problem in horses because most normally have darkly pigmented skin. Hyperpigmentation may be reversible: with removal of the pigment-promoting stimulus, it tends to decline over time to the baseline level.

MSH may stimulate hyperpigmentation. MSH acts by affecting the levels of cyclic adenosine monophosphate (cAMP), resulting in increased tyrosinase activity. MSH also causes increased dispersion of melanosomes into melanocyte dendritic processes, where they are phagocytized by keratinocytes. Increased levels of ACTH,

estrogens, progesterones, and androgens may also have effects on pigmentation, although the importance and mode of action in large animals is not clear.

Inflammation from a variety of causes and persistent cutaneous trauma from friction induce hyperpigmentation. Stimuli that may be factors in large animals include physical cutaneous damage (trauma, friction), chemicals (primary irritants, allergic sensitizers, photosensitizers), infectious agents, and nutritional disturbances.

Hypopigmentation is the result of a decreased amount of melanin in the epidermis or dermis (or both) and may be congenital or acquired (depigmentation). Possible mechanisms include decreased melanin production (defects in melanocyte migration during embryogenesis or disorders of melanin synthesis), decreased dispersion of melanin granules (defective transfer of melanin to keratinocytes), and increased loss of melanin (accelerated desquamation of epidermal melanin, epidermal pigment loss caused by disruption of the basement membrane with resultant pigment incontinence, or immunologic destruction of melanin or melanocytes).

Several congenital genetic abnormalities that result in partial or total hypopigmentation have been identified in large animals. Albinism is a recessive condition in which a normal complement of melanocytes is present but a biochemical defect results in lack of ability to synthesize tyrosinase, so that melanin is not produced. There is complete lack of melanin in all tissues in a true albino. Pseudoalbinism, in which there is ocular pigmentation, may be more common. Other genetic disorders include abnormal melanosome production and abnormalities in melanocyte development and migration from the neural crest (piebaldism).[3,5]

Acquired hypopigmentation (leukoderma) may be caused by several factors, including genetic abnormalities, trauma, inflammation, dietary imbalances, hormonal influences, and immunologic disorders. In some cases acquired hypopigmentation is idiopathic. Juvenile Arabian leukoderma appears to have a genetic basis because of the predilection for the Arabian breed and the occurrence of the disease in young animals.[6] Trauma and inflammation are the most common factors associated with depigmentation, particularly in the horse. The intensity of the inflammatory reaction may bear little relation to the degree of postinflammatory leukoderma. Dietary abnormalities, particularly molybdenum toxicity and copper deficiency, are associated with faded or washed out coat color in food animals. Severe protein deficiency, such as occurs in kwashiorkor in humans, can lead to deficient melanin pigmentation. Melatonin is a hormone produced by the pineal gland that antagonizes MSH, thus causing decreased pigmentation, although an association with pathologic hypopigmentation in large animals has not been documented. Immunologic destruction of melanocytes has been documented in humans and is suspected of being a factor in acquired hypopigmentation in the dog but has not yet been documented in large animals. Idiopathic leukodermas are noted in all species.

Leukotrichia is the result of decreased amounts of melanin in the hair shaft. In most cases the pathogenesis is speculative, and the actual factors are unknown. Melanocytes in the hair bulbs can be affected independently of melanocytes in the epidermis, and leukotrichia without a coexistent leukoderma is common. Leukoderma, however, is usually accompanied by leukotrichia; thus, when the two conditions ae seen in combination, their pathogenesis is the same. Several leukotrichias that occur independently of leukoderma appear to be genetically induced because of breed predilections (e.g., reticulated leukotrichia of quarter horses and spotted leukotrichia of Arabians). In addition, viral infection is suspected as one of the causes of hyperesthetic leukotrichia of horses.

11.8.3 Approach to Diagnosis of Pigmentation Abnormalities

The initial approach to diagnosis of pigmentary abnormalities is to determine whether the defect is congenital or acquired. Congenital pigmentary abnormalities are almost always caused by a genetic defect, whereas acquired abnormalities most commonly do not have a hereditary basis. If the abnormality is acquired, the clinician must

determine if it is a primary pigmentary abnormality or if it is associated with some other pathologic change such as inflammation or trauma. If associated changes are a feature of the disease, differential diagnosis should focus on the initial pathologic changes (Box 11-7).

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11.8.3.1

Box 11-7 Most Common Causes of Abnormal Pigmentation in Horses and Ruminants

11.8.3.1.1

LOSS OF PIGMENTATION

Burns and other trauma

Idiopathic leukotrichia and leukoderma (horses)

Copper deficiency (ruminants)

11.8.3.1.2

INCREASE IN PIGMENTATION

Pruritus

Melanoma

The following steps are a guide to the diagnosis of pigmentation abnormalities in horses and ruminants:

1 History (see Fig. 11-1)

a If the pigmentary change is congenital, determine if related animals are affected and if the lesions have progressed or regressed since birth. Take note of the patient's signalment and determine if that breed has been documented to have congenital pigmentary abnormalities.

b If the pigmentary change is acquired, determine if the animal has been subjected to cutaneous trauma that could result in posttraumatic pigmentary change. Determine if other cutaneous lesions in addition to the pigmentary changes have been observed (e.g., inflammation, ulceration).

c Determine if the animal's diet is nutritionally complete and balanced.

d Determine if the animal has been exposed to any toxic substances.

e Determine if contact animals of the same or different species are affected. Because feed and environment are shared, if contact animals are affected, dietary imbalances and toxicities should be included in the differential diagnosis.

f If the affected animal is a horse, determine what parasiticidal agents have been administered and if they are effective in the treatment or prevention of onchocerciasis.

2 Physical examination (see Fig. 11-2)

a Check for evidence of disease in organ systems other than the skin. Does the animal appear thin and malnourished, suggesting a pigmentary change secondary to a dietary deficiency or toxicity?

b If the patient's problem is hypopigmentation, examine the coat closely to determine if leukoderma, leukotrichia, or both are present.

c Look for evidence of other cutaneous lesions (inflammation, ulceration) that could result in postinflammatory pigmentary changes.

3 Microfilarial preparation

4 Biopsy for routine histopathologic examination (affected, unaffected, and marginally affected areas should all be biopsied and labeled appropriately for histologic comparison).

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13 Chapter 13 Musculoskeletal Abnormalities

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13.1 LAMENESS AND STIFFNESS

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Lameness, is the term used to describe a condition in which an animal is incapable of normal locomotion. Generally lameness is characterized by an inability to maintain a normal gait, manifested by asymmetry in movement, apparent incoordination or weakness, and inefficient or ineffective motion of the limbs. Lameness usually can be assessed only when the animal is moving under its own power, although lameness severe enough to cause an inability to bear weight can be assumed at a standstill. The onset of lameness can be acute (e.g., fracture), chronic (e.g., degenerative joint disease), or acute on chronic (e.g., catastrophic fracture secondary to stress fractures).

13.1.1 Mechanisms of Lameness and Stiffness

The ultimate effects of any cause of lameness are restricted movement of the limbs or body, reduced performance, and abnormal gait. Causes of lameness are generally associated with conditions of the musculoskeletal system or nervous system. Most causes of lameness have both a musculoskeletal component (e.g., atrophy of the supraspinatus and infraspinatus muscles) and a neurologic component (e.g., suprascapular neurapraxia). Some causes of lameness have only a musculoskeletal component (e.g., upward fixation of the patella) and are not principally associated with either afferent nerve signs (i.e., pain) or efferent nerve signs (i.e., motor dysfunction). Similarly, other causes of lameness are solely related to a motor nerve deficit (e.g., radial neurapraxia).

Unlike the usual definition of lameness, “stiffness” refers to a generalized restriction in freedom of movement in a limb, the neck, or back. Stiffness is manifested by a limited range of motion by a joint, reduced length of stride, or decreased flexibility during bending or turning. For example, cellulitis and soft-tissue swelling in the area of the tarsocrural joint can cause restricted freedom of movement of the hindlimb and an apparent lameness, yet there may be no specific musculoskeletal or neurologic cause. Stiffness may have either congenital or acquired causes, and the clinical signs may be mild and transient or severe and persistent. Stiffness may or may not be associated with pain.

13.1.2 Approach to Diagnosis of Lameness and Stiffness in Horses

The lameness examination is the most commonly performed assessment of the musculoskeletal system in the horse. The examination should be well planned, consistent, and thorough. Knowledge of all diseases capable of causing lameness is not required, as long as the examiner maintains an open mind and objectivity during the examination (Box 13-1). The goals of the lameness examination are to determine which limbs are affected, differentiate between supporting limb and swinging limb lameness, and to establish the musculoskeletal and/or neurologic components producing the lameness.

1 History. The lameness examination begins with the client interview. A summary of the important historical features of the lameness should include answers to basic questions about the following:

- Onset (e.g., When was the last time the horse was seen sound? Was the lameness acute in onset, or did it have a slow, insidious onset?)
- Characteristics of the lameness (e.g., Is the lameness seen more in hand, at the lunge, or under saddle?)
- Associated or inciting factors (e.g., injury) that may have contributed to or caused the lameness
- Changes in the characteristics, intensity, and duration of the lameness
- Responsiveness to treatment (e.g., Has the horse received any type of treatment, and if so what was the response?)
- Time since the last hoof trimming and shoeing, and whether or not the horse's shoeing was changed

In addition, the signalment and the activity that the horse undertakes (e.g., jumping vs. racing) should be ascertained and may be a guide in determining potential causes of the lameness (e.g., stress fractures are more common in racing thoroughbreds, and osteochondrosis is more commonly diagnosed in young animals).

2 Observe from a distance—stationary phase. Observing the horse from a distance while it is stationary permits an assessment of the horse's conformation, position, and posture. The horse should be viewed from the front, from behind, and from both sides. From the front, special note should be made of any abnormality in the following: *217*

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- Conformation. A number of conformational abnormalities have been associated with lameness (e.g., upright pastern conformation predisposes to pastern disease and foot lameness; offset or bench knees predispose to carpal disease; and straight through the hocks or postlegged conformation predisposes to upward fixation of the patella, suspensory desmitis, and fetlock disease). Poor conformation can affect the young horse when it is put into training or can cause a slow insidious onset of lameness. Recognizing these conformational abnormalities at the time of examination can be helpful in diagnosing potential causes of lameness. When a horse is evaluated for purchase, recognition of poor conformation should be noted and discussed as a source of future lameness problems.

13.1.2.0.0.0.0.0.1

Box 13-1 Causes of Lameness and Stiffness in Horses

13.1.2.0.0.0.0.0.1.1

COMMON CAUSES

Infections of the foot

Bruised or punctured sole

Hoof wall defects

Fractures

Septic (infectious) arthritis

Laminitis

Secondary (degenerative) joint disease

Navicular disease

Osteomyelitis

Fibrotic or ossifying myopathy

Rhabdomyopathy (tying up)

Sprain

Strain

Tenosynovitis

Contracted tendons (flexural deformity)

Ankylosis or arthrogryposis

Osteochondrosis or bone cyst

Cruciate or meniscal rupture

Luxation or subluxation (dislocations)

Upward fixation of the patella (locking patella)

Sesamoiditis

Muscle injury, soreness, bruise, trauma, compartment syndrome

Subcutaneous abscess, cellulitis

Angular limb deformities

Disruption of the suspensory apparatus (broken down)

Postanesthetic equine myasthenia

Tendon rupture, damage, tendonitis (bowed tendon)

Osteomalacia, osteodystrophy (rickets)

Bucked shins

Epiphysitis (physeal injuries)

Purpura hemorrhagica

13.1.2.0.0.0.0.0.0.1.2

LESS COMMON CAUSES

Shivers (shivering)

Borreliosis (Lyme disease)

Equine monocytic ehrlichiosis (Potomac fever)

Chronic selenium toxicity

Hemangioma, hemangiosarcoma, angiosarcoma

Skeletal neoplasia

Rabies

Spondylitis, discospondylitis

Spinal or vertebral neoplasia

Vertical column malformation

White muscle disease (nutritional myodegeneration)

Gunshot injury

Corynebacterium pseudotuberculosis,

Hypothyroidism (goiter)

Actinobacillosis

Hyperparathyroidism

Ulcerative lymphangitis

Myotonia congenita

Vesicular stomatitis

Fistulous withers (*Brucella abortus*, or other organisms)

Sporadic equine lymphangitis

Acute necrotizing equine vasculitis (with or without thrombocytopenia)

Peripheral arteriovenous fistula

Hypertrophic osteopathy or osteodystrophy

13.1.2.0.0.0.0.0.0.1.3

UNCOMMON CAUSES

Nocardiosis

Cutaneous blastomycosis

Pemphigus foliaceus

Tuberculosis

Multisystemic postexhaustion syndrome

Generalized steatitis

Cutaneous vasculitis

Sterile nodular panniculitis

Multiple clotting defects in ill foals

Salmonellosis

Factor VIII deficiency (hemophilia A)

Idiopathic equine aplastic anemia

Idiopathic equine thrombocytopenia

Hemimelia (radial, tibial, ulnar hypoplasia, agenesis)

Lupus erythematosus (rheumatoid arthritis)

Phycomycosis

13.1.2.0.0.0.0.0.0.1.4

POISONS, TOXINS, DEFICIENCIES, AND EXCESSES

Moldy sweet clover poisoning

Strychnine toxicity

Tetrachlorodibenzodioxin (dioxin) toxicity

Warfarin (Dicumarol) toxicity

Vitamin K—induced renal toxicity

Calcinosis resulting from plant poisoning

Zinc toxicity

Phosphorus toxicity

Phosphorus deficiency

Vitamin D toxicity

Locoweed-associated limb deformities or stringhalt-like gait

Chronic fluoride toxicity

- Position of the head (e.g., tilted, turned)
- Distribution and equality of muscle mass along the neck and trunk
- Topographic symmetry of the front limbs, from the dorsal region of each scapula to the hoof

From the rear, the height and mass of the hip musculature and the symmetry between the hindlimbs should be assessed. From each side, abnormalities in stance (e.g., camped out in front) or load bearing (e.g., dropped elbow) and the position of the head and neck (e.g., hyperflexed poll) should be compared.

3 Physical examination and palpation. Palpation enables a closer inspection of the horse and identification of abnormalities that may or may not otherwise be noticed. A thorough examination of the musculoskeletal system not only allows for identification of palpable abnormalities but also offers the opportunity for the practitioner to refine the identification of normal structures; subtle abnormalities cannot be appreciated unless the examiner is skilled at recognizing normal anatomy. There are also many instances in which normal structures palpate abnormally but are not necessarily associated with lameness (e.g., flexor tendon sheath [windpuffs, windgalls] and palmar or plantar MCPJ pouch effusion [wind puffs]). The examination should be conducted consistently and thoroughly starting with the cervical neck and concluding at the tail. Abnormal findings should be described to identify their location on the limb, their size, and their orientation relative to normal anatomic landmarks.

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Palpation of the upper limb is often limited to the overlying muscle mass, with an identification of any atrophy, hypertrophy, pain, or fibrosis. Articular structures and surrounding ligamentous structures can be difficult to palpate because of the overlying muscle. Deep palpation of the thoracolumbar and gluteal musculature can provide clues to potential hindlimb lameness and tack or rider issues. The pelvis, iliac

arteries, and sublumbar musculature can be evaluated by rectal palpation while the horse is standing quietly; movement or crepitation can be assessed while swaying the horse from side to side.

Particular attention should be directed toward palpation of the limbs. The majority of lameness will originate from the carpus distally in the front limb. Common sources of lameness in the hindlimb can be identified from the stifle distally. All palpable structures should be evaluated, including skeletal structures, synovial structures (joints, tendon sheaths, and bursa), and soft-tissue structures (tendons and ligaments). This portion of the examination can be performed using different methods, either by palpating each tissue in one pass of the limb or by making multiple passes of the limb, palpating each tissue structure separately. Regardless of the preferred technique, a consistent and complete examination should be performed. Once the limbs have been palpated in the weight-bearing position, the examiner should palpate them in the non—weight-bearing position. This allows for separation of the soft-tissue structures and facilitates deep palpation of the suspensory apparatus. Comparing limbs is often useful for distinguishing an abnormality from an unusual or unique conformation.

The relative size, shape, and condition of the feet (e.g., contracted heel, scuffed toe), length of heel, and pattern of shoe wear (e.g., thinner branch on the outside of the shoe than on the inside) give clinically significant but often overlooked clues to the site and cause of lameness. Evaluation of the feet with hoof testers is mandatory; most lameness arises from problems in the forefeet.

Certain signs indicating trauma (e.g., wounds, swelling, hair loss, pain) may lead to more important findings such as underlying evidence of a fracture (e.g., bony crepitus, warm or cold areas, bony protuberance).

4 Observe from a distance—mobile phase. Observations made from a distance while the horse is moving can be evaluated critically once clues provided by the history, and observations made of any postural deformities, direct the practitioner's attention to a specific area of the horse's body. This part of the examination is conducted while the horse is moving in at least two gaits, the walk and the trot. Sometimes it is also helpful diagnostically to observe the horse move at other gaits (e.g., canter) or while under saddle. It may also be beneficial to observe the horse on different surfaces (hard and soft) to amplify different lamenesses. If possible, the horse should be evaluated under similar conditions as that under which it performs.

At a walk the horse should be observed moving toward and away from the examiner. The break-over point of the foot at the toe, the arc of the foot flight, the distance covered by the foot in the swing phase, and the placement of the foot should be evaluated for each limb and should be compared between pairs of limbs. Although many abnormalities often can be observed only during a trot, some conditions may cause a subtle alteration in gait that can be observed only at a walk (e.g., fibrotic myopathy).

If a fracture is suspected (e.g., nondisplaced long-bone fracture) or if there is the possibility of exacerbating preexisting trauma, this part of the examination should either be abbreviated or not performed at all to preclude further damage or trauma. In such cases, immediate radiographic or other definitive diagnostic tests should be performed (Box 13-2).

Recognizing the asymmetric movement of the head and neck for frontlimb lamenesses, and the asymmetric movement of the pelvis for hindlimb lamenesses, is a common method of lameness identification. Hindlimb lamenesses often present the greatest challenge.

Sound horses at a trot show a perfect sinusoidal pattern for all midline body locations including the head, withers, and tuber sacrale. The height of these structures falls from the beginning of the diagonal stance phase, reaching the lowest position at mid stance, then rising to the highest level at or shortly after the end of the stance phase (suspension). Correlating head and neck movement with the correct front limb lameness is relatively easy. It is well recognized that the head is elevated during the stance phase of the lame limb, with an increase in downward motion during the stance phase of the sound limb—"down on sound." Lameness can also be recognized by changes in the distal limb, including changes in the motion of the metacarpophalangeal joint (MCPJ). During the stance phase, the hyperextension of the MCPJ is decreased with increasing lameness in the lame limb, whereas in the contralateral sound limb an increase is seen. With respect to stride length and foot flight, with forelimb lameness the caudal phase of both the lame and the sound limbs becomes shortened whereas the cranial phase remains unchanged. In the hindlimbs the opposite is seen; the cranial phase is shortened and the caudal phase remains unchanged. This may be explained by the significantly decreased suspension phase following the lame diagonal. In the forelimbs the arc of the lame front foot is unchanged, but there is an increase in the arc of the sound front foot. In the hindlimbs, the arc of the foot flight in the lame hindlimb is lower than the sound limb in most cases. The change in maximal hoof height during the swing phase appears to be the result of changes in trunk height and is no indication for reduced flexion in the upper joints or an effort to reduce the pain when the hoof lands. Medial (winging) or lateral (paddling) deviation of the distal limb during the flight phase can result in interference and trauma to other limbs and potential lameness. Conformational abnormalities, most commonly, toeing-in or toeing-out, give rise to an alteration in the point of break-over and a change in the flight of the distal limb. Poor foot balance caused either by poor conformation or by poor trimming can result in similar flight patterns.

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13.1.2.0.0.0.1

Box 13-2 Causes of Spontaneous Fractures in Horses and Ruminants

Pathologic fractures

Subclinical stress fractures

Tumors

Infection

Inflammation

Osteoporosis

Copper deficiency

Molybdenum excess

Phosphorus deficiency

Protein deficiency

Osteomalacia

Osteodystrophy (rickets)

Rapid growth

Lactation

Advanced pregnancy

Plaiting, describes adduction of the lame limb directly in front of or lateral to the opposite limb. In the front limbs, plaiting is commonly the result of faulty conformation, but in the hindlimbs it is more commonly associated with lameness. This pattern of travel is often associated with upper limb lameness but can also be seen with distal hock or high suspensory disease.

A dampening effect also appears to occur as an adaptation to lameness. This effect is more pronounced in the hindlimb than in the frontlimb. Flexion of the shoulder and hock joints actually increases during weight bearing in the lame limb. This is probably an increase in the function of the shock-absorbing mechanism. The increased flexion cannot be related to increased loadings but has to be attributed to a gentler braking of the flexion by the extensor muscles. In such a way, the loading of the lame limb with the body weight occurs more gradually, reducing the peak forces in the hoof.

The tuber coxae are typically the landmark of choice in evaluating hindlimb lamenesses. Because the tuber coxae are more laterally located, the pattern is different from that seen in the head. Also, because the hindlimbs lack closely located segments, such as the neck and head, an enhancement of the vertical movements must be found in a rotation of the back around a longitudinal axis. Such a rotation is indicated by different vertical displacements of one tuber coxae during both stance phases. The vertical movement of the tuber coxae exhibits a characteristic pattern of a double-waved, slightly asymmetric line during one stride. The lowest point of the hip is reached in the middle of the stance phase of the right contralateral limb. The highest point of the hip is reached shortly after the stance phase of the contralateral limb, just before the stance phase of the left hindlimb.

Kinematic studies have more clearly defined the notion of “hip hike,” and “hip drop” and have recorded regular patterns of pelvic movement in lame horses. Consistent findings in the overall pelvic movement in the lame horse include less downward movement during the midstance phase and less upward movement at the end of and after the stance phase of the lame limb. This can give the appearance of an overall pelvic elevation during the stance phase of the lame limb as compared with pelvic height during stance of the sound limb; a similar exaggerated pattern is seen in the tuber coxae. The tuber coxae also exhibit less downward movement during the midstance phase and less upward movement at the end of the stance phase in the lame limb. More notably, there is more downward movement during midstance of the sound limb (midflight of the lame limb), and more upward movement at the end of stance of the sound limb (impact of the lame limb), giving rise to the notion of a “hip hike.” These changes result in an increase in the overall vertical movement of the tuber coxae on the lame side as compared with the sound side. Clinically, many find it easier to identify the exaggerated excursion of the tuber coxae to identify the side of the lameness.

Lateral movement or drifting of the hindend can also be seen in horses with unilateral hindlimb lameness. Horses tend to drift or move away from the side of the lameness. Subtle lameness with an absence of asymmetric pelvic movement may present with a consistent drifting to one side or the other.

Thorough and useful systems for grading the severity of lameness are available. Most systems are designed to enable the practitioner to compare how lameness changes with time, assess the characteristic of lameness among horses, and accurately record information and communicate information to other veterinarians. Simple and consistent schemes that are easy to remember and modify can be developed (Table 13-1).

Once the initial standing and mobile examinations are completed and the affected limb is identified and the lameness graded, isolating the specific region of the limb is the next goal of the lameness examination. Manipulative tests or stressing of articulations and associated soft-tissue structures can provide additional information as to the location of the source of lameness. Flexion and extension tests are designed to stress selective regions of the limb and observe the effects of the manipulation on the lameness. These tests are also commonly performed on the sound horse to reveal potential areas of concern particularly during prepurchase examinations. Flexion and extension manipulations also enable an assessment of range of motion. Interpretation of these tests should be approached with caution. They are seldom specific for one particular joint. For example, the fetlock flexion test not only stresses the fetlock joint but also places stress on the proximal and distal interphalangeal joints; the hock flexion test also flexes and stresses the stifle joint because of the presence of the stay apparatus. If a flexion tests results in a positive response, the horse should be walked out of the response and observed before additional manipulations. Occasionally exacerbation of the lameness will persist for an extended period of time, which changes the baseline lameness and clouds the interpretation of additional manipulations.

It is common for horses to be presented with multiple lamenesses. Secondary lameness or compensatory lameness is the result of increased stress or overloading of the other limbs in response to the primary lameness. This most commonly occurs in the contralateral limb but can also occur between front limbs and hindlimbs. The secondary lameness can also be the result of shifts in body mass that produce an apparent or phantom lameness. Phantom lameness is less severe than the primary lameness. The following guidelines can be used to aid in the differentiation between a real or compensatory and an apparent or phantom lameness.

- Address most severe lameness first.

- Horses with primary hindlimb lameness and apparent or phantom contralateral frontlimb lameness. Each lameness should be considered as real.

Table 13-1 A Five-Grade Lameness Scheme

Grade	Description
1	An inconsistently observable lameness visible under special circumstances (in a circle, flexion tests, hard surface, etc.)
2	A consistently observable lameness visible only under special circumstances (in a circle, flexion test, hard surface, etc.)
3	A consistently observable lameness at a trot in a straight line
4	A consistently observable lameness at a walk
5	A non—weight-bearing lameness; horse is unable to use the leg
Modified from the *American Association of Equine Practitioners Newsletter*, March:12, 1983.	

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- Horses with a primary forelimb lameness and apparent or phantom ipsilateral hindlimb lameness. Each lameness should be considered as real.
- Primary forelimb lameness may produce asymmetric pelvic movement causing the perception of a contralateral hindlimb lameness. Example: left foreleg lameness (head elevation) causing apparent or phantom right hindleg lameness (hip drop).
- Horses with a primary forelimb lameness and apparent contralateral hindlimb lameness. Block out frontlimb lameness first.
- Primary hindlimb lameness (≥3 to 5/5) can mimic ipsilateral forelimb lameness. Example: A horse shows a cranial load shift during the stance phase of lame limb that causes the head and neck to shift forward and nod down, giving the perception of ipsilateral lameness—"down on sound."
- Horses with a primary hindlimb lameness and apparent ipsilateral forelimb lameness. Block out the hindlimb lameness first.

Assumptions as to the cause of a horse's lameness based solely on the physical examination and visual inspection should be avoided unless obvious signs, for example severe swelling or crepitus, are present. After the physical and visual examination, evaluation of the horse with diagnostic analgesia is mandatory for the accurate isolation and diagnosis of equine lameness. A thorough knowledge of anatomy and the structures desensitized by blockade of the appropriate peripheral nerves or synovial structures is essential (Table 13-2). *When performing perineural analgesia it is important to remember to block from distal to proximal*., An improvement in gait indicates a favorable response to a nerve or joint block; complete elimination of gait asymmetry is unusual and generally should not be expected after intraarticular or peripheral nerve analgesia. If necessary, improvement in gait can be confirmed by repeating the successful block the next day. By that time residual effects from multiple blocks performed previously should be absent.

Common local anesthetics used in horses include 2% solutions of lidocaine, mepivacaine, and bupivacaine. These solutions all share a common mechanism of action, specifically the ability to block or inhibit nociceptive nerve conduction by preventing the increase in membrane permeability to sodium ions. Lidocaine and

mepivacaine are considered to be fast acting and have a duration of action of 1½ to 3 hours and 2 to 3 hours, respectively. Bupivacaine on the other hand is intermediate in onset and has a much longer duration of action of 3 to 6 hours. Mepivacaine is reportedly less irritating to tissues than lidocaine.

Table 13-2 Structures Desensitized by Commonly Performed Nerve Blocks

Nerve Block	Nerve(s) Affected	Structures Desensitized*
Palmar (plantar) digital	Palmar (plantar) digital	Heel bulbs; frog; bars; navicular bone and bursa; palmar regions of the third phalanx, distal interphalangeal joint, sole, and soft tissues
Abaxial sesamoid	Palmar (plantar)	Coronary band, interphalangeal joints, lamellar and solar corium
Low palmar (volar)	Palmar, palmar metacarpal†	Skin of medial and lateral pastern, metacarpophalangeal joint, proximal sesamoids, flexor tendons, tendon sheath
High palmar (volar)	Palmar, palmar metacarpal†	Skin and deep structures of palmar cannon region (flexor tendons, suspensory ligament except origin, interosseous ligaments of splint bones)
High two-point	Lateral palmar, medial palmar	Origin of suspensory ligament

* Includes all structures listed up to and including the particular block; first structure listed in each block is also the area that can be tested with point pressure to evaluate the effectiveness of the block.

† For hindlimbs, additional anesthetic (i.e., ring block) is needed at the level of the particular perineural block to achieve the desired effect.

Intrasynovial analgesia can be used to more specifically isolate a lameness to a joint, tendon sheath, or bursa. It can be used in combination with perineural analgesia or alone depending on the suspected source of the lameness. Proper patient restraint and strict aseptic technique including aseptic preparation of the skin, wearing sterile gloves, and use of a new bottle of anesthetic are imperative to avoid iatrogenic synovial sepsis. Lameness may be erroneously associated with a joint if intraarticular analgesia of several joints is performed within a short period of time; ample time (30 to 60 minutes) must be allowed between joint blocks to allow for adequate articular desensitization.

When performing intrasynovial analgesia it is not necessary to follow the distal to proximal rule. If intraarticular analgesia of a proximal joint results in no improvement in the lameness, immediate follow-up with distal limb perineural blocks is still possible. Exceptions to this rule exist with intrasynovial analgesia to the foot. When performing intrasynovial analgesia of the distal interphalangeal joint (DIPJ) or navicular bursa, it is important to take into consideration the volume of anesthetic used and the timing at which the lameness is reevaluated. The recommended volume of anesthetic for the DIPJ is 4 to 5 mL, and for the navicular bursa 3 to 4 mL. Once injections into these structures have been performed, the horse should be evaluated at 5-minute intervals to help with the interpretation of the response to the block.

Significant improvement in experimentally induced lameness to the navicular bursa can be seen at 5 minutes after intraarticular anesthesia of the DIPJ with 5 mL of 2% mepivacaine hydrochloride. Amelioration of bursal lameness is mostly likely caused by diffusion of the anesthetic into the bursa via an indirect or functional communication, or by diffusion of anesthetic into the periarticular tissues. The proximal palmar pouch of the

DIPJ lies in close proximity to the palmar digital (PD) neurovascular bundles as they course along the medial aspects of the collateral cartilages, making it possible for anesthetic diffusion to block nerve conduction at that level.

Experimentally induced solar toe pain can also be ameliorated by intraarticular blockade of the DIPJ with 10 mL of mepivacaine hydrochloride. The structures innervated by the deep branch of the PD nerves include the DIPJ, navicular bursa, distal navicular ligament, laminar corium, and corium of the sole. The DIPJ capsule contacts the PD neurovascular bundle, and a local anesthetic injected into the DIPJ likely desensitizes the PD nerves below the level of the coronary band, and the structures innervated by them.

Variable responses are also seen with blockade of the DIPJ when different volumes of anesthetic are used. Blocking the DIPJ with 6 mL of mepivacaine (Carbocaine) results in significant improvement in lameness originating from the dorsal margin of the sole; however, lameness originating from the palmar sole shows no improvement. Using 10 mL of Carbocaine reduces lameness originating from the dorsal margin of the sole, as well as the palmar heel regions of the sole, but only after 30 minutes. The difference in response to analgesia of the DIPJ in attenuating pain at the dorsal margin of the sole versus the angles of the sole may be because these regions are innervated by different branches of the PD nerve. This may help distinguish between pain arising from the DIPJ or the navicular apparatus and palmar solar pain.

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In contrast to the responses seen with blocking the DIPJ in the presence of navicular bursa disease, blocking the navicular bursa with 3.5 mL of mepivacaine hydrochloride in the presence of experimentally induced DIPJ lameness results in a significant improvement in lameness but only after 30 minutes. Experimentally induced lameness from the dorsal sole is improved by blockade of the navicular bursa; lameness originating from the palmar sole does not show significant improvement.

Knowledge of the previously described responses to intrasynovial analgesia of the DIPJ and the navicular bursa is helpful in localizing and interpreting lameness commonly seen in the horse. The anatomy and close approximation of the associated nervous and synovial structures of the foot give rise to a diffusion gradient associated with perisynovial infiltration of local anesthetic to peripheral nerves and variable responses to intrasynovial analgesia. Similar responses can be encountered with intraarticular analgesia of the carpus and distal tarsal joints. Instillation of anesthetic into the middle carpal joint and the tarsometatarsal joints can result in desensitization of the proximal suspensory ligament, a common site for soft-tissue injury and lameness in the horse.

Once the lameness has been described and localized, a radiographic or ultrasonographic examination can be performed as the next step to confirm a clinical diagnosis. Radiography should be performed using proper technique, an ideal film/screen combination, and multiple views to construct a thorough study (Table 13-3). Comparing radiographs of affected and unaffected limbs can help confirm or refute a suspected abnormality, evaluate the severity of the disease, and identify possible bilateral limb involvement.

Although standard radiographic techniques are well documented and described, ultrasound is becoming more and more popular and useful in musculoskeletal imaging. Indications for ultrasonographic evaluation of a lameness include diagnosis of soft-tissue injuries, including muscular, vascular, tendon, tendon sheath, ligament, joint capsule, or bursal defects; evaluation of articular surfaces (articular cartilage thickness, osteochondritis dissecans lesions); assessment of fluid accumulation (synovial effusions, seromas, or sepsis); evaluation of bony surfaces; monitoring of the progression of healing; and monitoring of the effects of training on soft-tissue injuries such as tendonitis or desmitis.

When radiographic or ultrasonographic techniques are nondiagnostic, other methods such as thermography, nuclear scintigraphy, treadmill evaluation, computerized videographic gait analysis, force plate evaluation, computed axial tomography (CAT), or magnetic resonance imaging (MRI) may be useful. University hospitals and major regional referral centers are often the only locations where these adjunctive procedures can be performed because the procedures are expensive and technically complex and they require specialized equipment and experienced personnel. However, even these techniques have limitations; for example, nuclear scintigraphy may not identify the origin of an insidious (e.g., osteochondrosis) or chronic lameness as successfully as an acute lameness.

Table 13-3 Recommended Radiographic Views of Extremities

Radiographic Series	Minimum Radiographic Views
Distal extremity (navicular)	45 degrees DP, 65 degrees DP (2), LM, flexor tangential*
Pastern	45 degrees DP, LO, MO, LM
Fetlock	45 degrees DP, LO, MO, LM, flexed LM
Metacarpal or metatarsal	DP, LO, MO, LM
Carpus	DP, LO, MO, LM, flexed LM, flexed skylines (distal radius, proximal and distal rows of carpal bones)
Tarsus	0 degrees DP, 10 degrees DP, LO, MO, LM
Radius-ulna or tibia-fibula	Cr-Cd, LO, MO, LM
Elbow	Cd-Cr, LO, LM, patellar (delete patellar)
Shoulder	ML
Stifle	Cd-Cr, LM, flexed LM, Cd 30° L-CMO, patellar skyline

Cd-Cr, Caudocranial; *Cd 30,° L-CMO*, caudal 30-degree lateral-craniomedial oblique; *Cr-Cd*, craniocaudal; *DP*, dorsopalmar (dorsoplantar); *LM*, lateromedial; *LO*, lateral oblique; *ML*, mediolateral; *MO*, medial oblique.

* View to highlight the flexor cortical margin of the navicular bone (50 degrees proximal palmaropalmaro distal oblique).

13.1.3 Approach to Diagnosis of Lameness and Stiffness in Ruminants

1 History. An accurate history is the first step in reaching a correct diagnosis of the cause of lameness in ruminants (Box 13-3). For example, although stiffness can occur at any time in life, it occasionally occurs at birth (e.g., arthrogryposis); therefore acquired and congenital signs can be differentiated on the basis of a complete history. Furthermore, other ruminants on a property may demonstrate similar clinical signs, and the onset and duration of signs may be important diagnostically. It also is useful to examine the environment and determine how the ruminant could have been traumatized or injured. Finally, any evidence of systemic disease manifested by fever, anorexia, or depression should be determined.

2 Observe from a distance—stationary phase. Next, the ruminant should be observed standing to assess posture and stance. For example, a cross-legged stance may indicate an abnormality of the medial claw of the hoof. A dairy cow with painful heels in the hind feet may stand with its heels over the gutter while in a stanchion. Alternatively, a ruminant resting its feet farther forward than usual may have a painful toe region. Small ruminants with problems in both front feet may attempt to move around on their carpi.

3 Observe from a distance—mobile phase. In ruminants these observations are usually made while walking rather than trotting the animal. This enables the examiner to identify the affected limb; to determine whether the lameness is a supporting-leg or swinging-leg lameness; and to assess how much of the lameness is solely mechanical and how much is associated with pain.

4 Palpation. The most important part of lameness examination in ruminants is examination of the foot. As with horses, most lameness in ruminants involves the foot. The examiner should look closely between toes, around the coronary band, and at the hoof wall. The sole should be pared with a hoof knife to identify discoloration or draining tracts beneath the sole or into the corium. A black discoloration may indicate infections of deeper structures of the foot. Applying pressure to the sole with a hoof tester or tapping over the wall may elicit pain. 222 223

The limb should also be palpated to detect swelling, heat, or soreness, which may indicate inflammation from infection or soft-tissue trauma. Crepitation found by manipulating the limb may indicate a fracture or dislocation. Stiffness or pain on joint flexion may indicate joint disease, either septic or degenerative.

Flexion tests and nerve blocks are not used for diagnosis as routinely in ruminants as they are in horses, but they may be useful in certain instances. The technique is similar to that described for horses, but the location of the nerves is different. Radiographs are not necessary in most cases, although they can identify bony or articular lesions that may not be readily apparent or palpable. Examination of synovial fluid obtained by arthrocentesis can be used to differentiate septic from traumatic arthritis.

13.2 POSTURAL DEFORMITIES

***Carter E. Judy*,**

***John Maas*,**

A postural deformity in horses or ruminants is an abnormal stance caused by neurologic deficit, pain, or a musculoskeletal problem. Postural deformities can range from subtle conformational faults such as broken forward foot axis to severe and unusual positions, such as when the animal is camped out in front. Inability to bear weight on a limb, asymmetric angles between joints, and lateral or medial deviations in the alignment of limbs are examples of postural deformities. Often the postural deformity itself is specific for certain diseases and conditions (Table 13-4).

13.2.1 Mechanisms of Postural Deformities

Postural deformities can be either congenital or acquired and result from maldevelopment, trauma, or disease (Box 13-4). Congenital deformities may be caused by tendon contracture or laxity, osseous malformation, and hypoplasia or aplasia of osseous structures or soft tissues. Acquired deformities are most often caused by trauma or disease. Disuse atrophy secondary to an unrelated musculoskeletal abnormality can result in abnormal posture. 223 224

Occasionally diseases affecting proprioception and consciousness may cause an abnormal stance that appears as a postural deformity (e.g., head pressing) but is unrelated to neurologic pain or a musculoskeletal problem.

Table 13-4 Examples of Postural Deformities and Possible Origins

Postural Defect	Likely Site of Origin
Contracted heels	Foot; flexor tendons
Bucked knees	Suspensory ligament
Dropped elbow	Motor nerves to forelimb; olecranon
Tiptoe stance	Foot; flexor tendons; interphalangeal joints
Non—weight-bearing	Foot; any long bone; any limb articulation
Broken down (hyperextension) fetlock; dropped fetlock	Suspensory apparatus
Toe-out hindlimb and elevated hip	Coxofemoral joint; femoral neck
Basewide behind	Coxofemoral joint; femoral neck
Hyperextension of stifle and hock	Patella
Camped out in front	Bilateral forefeet
Carpal valgus	Distal metaphysis, physis, epiphysis, or carpal bones
Stiffly elevated head	Withers; cervical spine
Shifting weight between forefeet	
Recumbency	Any long bone; feet; spinal cord; myopathy

13.2.2

Approach to Diagnosis of Postural Deformities in Horses

A history can help the examiner determine if a postural deformity is congenital, as with arthrogryposis, or acquired. Because most postural deformities in horses arise from traumatic injuries or overuse, a complete lameness examination is essential. Occasionally a postural deformity does not cause lameness; in these instances the veterinarian must consider nontraumatic causes associated with abnormal development, improper nutrition, and seemingly unrelated disease such as carpal valgus deformity.

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13.2.2.1

Box 13-3 Causes of Lameness and Stiffness in Ruminants

13.2.2.1.1

COMMON CAUSES

Infections of the foot

Hoof defects

Interdigital dermatitis (infectious foot rot)

Underrun heel

Papillomatous digital dermatitis (foot warts)

Rusterholz ulcer, granuloma of sole

Laminitis

Corkscrew claw and other growth abnormality

Interdigital fibroma

Overgrown feet

Bruised or overworn sole

Puncture wound

Septic infectious arthritis

Contracted tendons

Arthrogryposis

Chlamydial arthritis of sheep

Caprine arthritis-encephalitis in goats

Fractures

Blackleg

Muscle abscess

Mycoplasma polyarthritis of sheep and goats

Osteomyelitis

Ruptured anterior cruciate ligament

Ligament rupture (e.g., torn collateral ligament of stifle)

13.2.2.1.2

LESS COMMON CAUSES

Erysipelothrix, arthritis

Vesicular stomatitis

Secondary (degenerative) joint disease

Luxations and subluxations

Sprain

Strain

Hygroma

Spinal abscess

Spinal lymphosarcoma

Osteomalacia

Bluetongue virus in sheep (coronitis and myopathy)

Dorsal fixation of the patella (bovine)

Septic tenosynovitis

Angular limb deformities

Malignant edema

Malignant catarrhal fever

Muscle injury

Ruptured tendon

13.2.2.1.3 UNCOMMON CAUSES

Sporadic bovine encephalomyelitis

Ulcerative lymphangitis

Salmonellosis

Dactylomegaly in shorthorn cattle

Bovine virus diarrhea (coronitis)

Physeal injuries (epiphysitis)

Clotting factor deficits

Hyperparathyroidism

Phycomycosis

Neoplasia

Angioneurotic edema

Hemimelia (radial, tibial, ulnar, hypoplasia, or agenesis)

Melioidosis (exotic)

Ibaraki disease (exotic)

Ephemeral fever (exotic)

African bovine malignant catarrhal fever (exotic)

Akabane disease (exotic)

Foot-and-mouth disease (exotic)

Lumpy skin disease (exotic)

13.2.2.1.4 POISONS, TOXINS, DEFICIENCIES, AND EXCESSES

Nutritional myodegeneration (white muscle disease selenium deficiency)

Fescue foot (ergot poisoning)

Polybrominated biphenyl (PPB) toxicity

Acorn calves

Kaley-pea poison in cattle

Calcinosis caused by plant poisoning

Sweet clover poisoning

Copper deficiency

Locoweed toxicity

Lupine alkaloid poisoning

Zinc deficiency

Nicotinic acid toxicity

Hemlock poisoning

Sweet vernal grass poisoning (exotic)

13.2.2.2

Box 13-4 Causes of Postural Deformities in Horses

13.2.2.2.1

COMMON CAUSES

Infections of the foot

Hoof wall defects

Fractures

Septic (infectious) arthritis

Secondary (degenerative) joint disease

Laminitis

Angular limb deformities

Osteomyelitis

Sprain

Strain

Tenosynovitis

Contracted tendons (flexural deformity)

Laxity of flexor tendons in foals

Tendon rupture, damage, tendonitis (bowed tendon)

Upward fixation of the patella (locking patella)

Epiphysitis

Septic tenosynovitis

Muscle injury, soreness, bruise, trauma, compartment syndrome

Navicular disease

Congenital

Cuboidal bone hypoplasia

13.2.2.2.2 LESS COMMON CAUSES

Disruption of the suspensory apparatus (broken down)

Lateral or medial patellar luxation

White muscle disease (nutritional myodegeneration)

Brucellosis

Sesamoiditis

Hypertrophic osteopathy or osteodystrophy

Ankylosis or arthrogryposis

Luxation or subluxation

Snakebite

Equine monocytic ehrlichiosis (Potomac fever)

Spondylitis, discospondylitis

Spinal or vertebral neoplasia

Tick paralysis

Vertebral column malformation

Nigropallidal encephalomalacia (star thistle poisoning)

Postanesthetic equine myasthenia

Abscess caused by *Clostridium perfringens*,

Hyperparathyroidism

Osteomalacia, osteodystrophy (rickets)

13.2.2.2.3 UNCOMMON CAUSES

Lupus erythematosus (rheumatoid arthritis)

Osteochondrosis

Cruciate or meniscal rupture

Patellar ligament injury

Malnutrition

Splenic rupture

Neonatal maladjustment

Subcutaneous abscess, cellulitis, foreign body

Vesicular stomatitis

Bucked shins (dorsal metacarpal disease)

Hemimelia (radial, tibial, ulnar hypoplasia, agenesis)

Botulism (shaker foal)

Myotonia congenita

Skeletal neoplasia

Shivers (shivering)

Borreliosis (Lyme disease)

13.2.2.2.4 POISONS, TOXINS, DEFICIENCIES, AND EXCESSES

Vitamin A deficiency

Vitamin D toxicity

Strychnine toxicity

Phosphorus deficiency

Chronic fluoride toxicity

Chronic selenium toxicity

13.2.2.3 Box 13-5 Causes of Postural Deformities in Ruminants

13.2.2.3.1 COMMON CAUSES

Congenital

Crooked calf syndrome (lupinosis)

Syndactyly

Hemimelia (radial, tibial, ulnar hypoplasia)

Osteogenesis imperfecta

Dactylomegaly in Shorthorns

Contracted tendons

Idiopathic deformities

Angular limb deformities

Shortened long bones (acorn calves)

Acquired hoof wall defects

Infections of the foot

Secondary contracted tendons

Muscle atrophy caused by denervation

Fractures

Luxations

Severed or ruptured tendons

Septic arthritis with ankylosis

Arthritides (e.g., mycoplasma, caprine arthritis-encephalitis, septic arthritis)

Osteomalacia

Rickets

Epiphysitis

Septic tenosynovitis

Chronic laminitis

Degenerative joint disease

Hypertrophic osteopathy

Hyperparathyroidism

Osteomyelitis

Ruptured gastrocnemius (goats)

Ruptured peroneus tertius

Upward fixation of the patella (locking patella)

13.2.2.3.2 POISONS, TOXINS, DEFICIENCIES, AND EXCESSES

Primary copper deficiency or secondary copper deficiency (molybdenosis) (e.g., physitis, spontaneous fractures)

Selenium poisoning

Fluoride poisoning

Phosphorus deficiency

Monensin toxicity

Calcinosis caused by plant poisoning

Locoweed-associated limb deformities

Diagnosis of the cause of a postural deformity begins with a detailed description of the deformity and assessment of the position and asymmetry of the anatomic structures involved. If the nature and severity of the deformity cannot be determined by direct observation, palpation and manipulation of the affected structure are required. Radiography and ultrasonography also can assist in the diagnosis and provide information on which to base treatment recommendations and prognosis.

13.2.3 Approach to Diagnosis of Postural Deformities in Ruminants

Because of the many differences in husbandry and management practices between ruminants and horses, most postural deformities in ruminants are congenital or arise from dietary nutritional imbalances or plant poisonings

(Box 13-5). Traumatic injuries play a smaller role, except in dairy cattle, which commonly slip on concrete and injure themselves. History, visual inspection, manipulation, and palpation are important in the diagnosis of postural deformities in ruminants. In addition, other ruminants in the herd with similar abnormalities should be identified. Plant, feed, soil, and water samples should be taken to identify toxins that may have been ingested, resulting in the deformity. Often the signalment helps rule out certain breed- or species-specific genetic defects. Because goats jump off heights, they are subject to numerous fractures, sprains, and luxations, including unilateral or bilateral rupture of the gastrocnemius tendon.

13.3 SWELLINGS AND ENLARGEMENTS (SOFT AND HARD TISSUE)

***Carter E. Judy*,**

***John Maas*,**

Swellings and enlargements consist of soft tissue (e.g., tendon) or hard tissue (e.g., osseous) and can occur anywhere on an animal's body. Generally, clinically significant swellings and enlargements associated with the musculoskeletal system occur on the limbs.

Swellings and enlargements can be further divided into two principal groups, depending on whether or not they are associated with a specific anatomic structure. For example, a soft fluctuant swelling in the region of the left carpus may be caused by an abnormality of the antebrachialcarpal joint (e.g., septic synovial effusion) or may not involve the joint at all (e.g., subcutaneous abscess). Although lameness can be associated with such a swelling, clearly it is important to determine the cause of the abnormality because the one involving the joint may require the more immediate treatment.

13.3.1 Mechanisms of Swellings and Enlargements

The mechanism by which swelling or enlargement develops depends on the tissue involved (Box 13-6). Soft-tissue swelling often is produced by trauma, inflammation, infection, or neoplasia; it can consist of interstitial fluid (e.g., edema), fluid within an open space (e.g., synovial hernia), or a localized accumulation of cells or fibrous tissue. Localized edematous swelling commonly is caused by inflammation and/or obstruction of venous blood or lymph flow. Generalized edema is usually the result of increased hydrostatic pressure caused by circulatory failure or an altered capillary-tissue osmotic gradient stemming from hypoalbuminemia. Fluctuant swellings such as hematoma, synovial effusion, a purulent abscess, or a plasma-filled cyst contain free fluid. Granulation tissue, fibrous scar tissue, and tumor cells are the most common constituents of firm soft-tissue swellings. Rupture of supporting or confining structures (e.g., prepubic tendon rupture) can result in unusual forms of soft-tissue swelling caused by herniation of internal organs.

Many factors influence new bone formation. Trauma and infections initiate bony enlargement (e.g., callus) by disrupting the periosteum, producing inflammation and eventually ossification. The extent of periosteal new bone formation depends on the cause of the stimulus and the size of the affected area. Remodeled bone may also arise from nontraumatic events, usually associated with altered metabolism or neoplasia. Bony enlargements associated with the metaphysis and physis in young, growing animals are usually secondary to a combination of nutritional and traumatic factors. For example, dietary calcium, phosphorus, and vitamin D imbalance can lead to abnormal bone growth. A bony swelling develops gradually and may become noticeable only after it enlarges, interferes with normal function, or becomes a source of lameness.

13.3.1.1

Box 13-6 Causes of Swellings and Enlargements in Horses

13.3.1.1.1

SOFT TISSUE

Septic (infectious) arthritis

Secondary (degenerative) joint disease

Sprain

Strain

Hygroma

Tenosynovitis

Osteochondrosis

Suspensory desmitis or sesamoiditis

Infections of the foot

Insect or snake bites

Cellulitis

Abscess

Herniation

Neoplasia

Capped hock

Hematoma

Phycomycosis

13.3.1.1.2 HARD TISSUE

Secondary (degenerative) joint disease

Fracture

Sequestrum

Osteomyelitis (periosteal new bone formation)

Epiphysitis

Luxation or subluxation

Osteochondroma

Osteomalacia (rickets)

Bucked shins (dorsal metacarpal disease)

Hypertrophic osteopathy

Ankylosis or arthrogryposis

Calcinosis caused by plant poisoning

Selenium toxicity

13.3.2 Approach to Diagnosis of Swellings and Enlargements in Horses

1 History. A history should determine the number of horses involved, the duration of clinical signs, and the possibility that traumatic events or environmental factors are responsible for causing a swelling or enlargement. In addition, changes over time in the appearance and size of the swelling or enlargement can be informative.

2 Inspection and palpation. The location of the swelling and its proximity to anatomic structures often reveal the tissue involved and the probable cause of the condition. For example, swelling around a joint may indicate arthritis, periarthritis, or hygromas. Tendon swelling may indicate tendonitis or ruptured tendons. Swelling over ligaments may indicate rupture, subluxation, or inflammation around a ligament.

Muscle swelling results from abscessation or fascial tears. Subcutaneous swelling may indicate hematomas, edema from inflammation around a ligament, or cellulitis. Bony enlargements often can be localized to the shaft of a bone (e.g., periosteal callus) or the ends of a bone (e.g., metaphyseal flaring). Periarticular new bone may be readily apparent (e.g., ringbone) or may not be found even on deep palpation. New bone formation also can be found associated with the axial skeleton and head.

Palpation of a swelling can determine its consistency and association with anatomic structures. Osseous swelling indicates calcification, proliferation of bone, or fracture. Firm soft-tissue swelling indicates inflammation, abnormal proliferation of soft tissue (e.g., granulation, tumor), or herniation.

Warmth, redness, and pain associated with swelling indicate active inflammation. While new bone is forming, the swelling may be soft and sensitive to palpation. Cold and insensitivity to palpation suggest inadequate blood supply and possibly ischemia (e.g., gangrene).

Lameness caused by an injury or condition that results in a hard swelling or enlargement may be accentuated by performing a stress test, such as trotting the horse in hand after direct pressure on the swelling. Intraarticular anesthesia may substantially reduce a lameness caused by joint effusion associated with periarticular new bone.

3 Radiography, ultrasonography, and alternative imaging techniques. In addition to identifying definitively the nature of an osseous swelling or enlargement, radiography can gauge the severity and progression of the disease and help establish a therapeutic plan and prognosis. Ultrasound often can determine the position (e.g., depth, area) and volume of a soft-tissue swelling and the optimum site for aspiration or biopsy. Thermography may help to identify subtle heat production secondary to inflammation and increased blood flow, before onset of a swelling, allowing for early treatment. Nuclear scintigraphy may help to localize the cause of swellings and identify whether they are bony or soft tissue in origin (e.g., tarsal effusion secondary to a sustentaculum tali osteomyelitis). CAT scanning is useful for evaluating bony swellings, especially of the head when swellings of the mandible and maxilla may be related to infected teeth and the determination of which teeth are involved is necessary before surgical intervention. MRI may prove useful for accurate imaging of soft-tissue masses that cannot be accurately characterized with other diagnostic techniques.

4 Cytology, microbiology, and histology. A fine-needle aspiration, using aseptic techniques, should be performed to obtain samples for microbiologic culture (e.g., bacterial and fungal) of soft-tissue swellings. If the material is very viscous, a large-gauge needle may be required. Fluid collected for cytology should be placed in tubes containing ethylenediaminetetraacetic acid (EDTA) to prevent clotting before analysis. Tissue samples obtained by biopsy should be placed in 10% buffered formalin.

13.3.3 Approach to Diagnosis of Swellings and Enlargements in Ruminants

1 History. The history should indicate the duration of a swelling and whether it is congenital or acquired (Box 13-7). The rate of growth of a mass may be significant. The signalment of the ruminant sometimes gives a clue to the origin of the swelling; other ruminants in the herd should be examined for similar signs. Systemic manifestations (e.g., fever, anorexia, depression, and elevated pulse and respiratory rates) may indicate such things as blackleg, malignancies, and septic abscesses.

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13.3.3.0.0.0.1

Box 13-7 Causes of Swellings and Enlargements in Ruminants

13.3.3.0.0.0.1.1

SOFT TISSUE

Septic arthritis

Mycoplasma arthritis

Caprine arthritis-encephalitis in goats

Hygroma

Tenosynovitis

Papillomatous digital dermatitis (foot warts)

Chronic tendonitis

Ruptured tendon

Foot rot

Gangrene of the foot

Fescue foot

Neoplasia

Bee stings

Snake bite

Abscess

Hematoma

Capped hock

Interdigital fibroma

Skin neoplasia

Granulomas (such as woody tongue)

Habronemiasis

Phycomycosis

13.3.3.0.0.0.1.2 HARD TISSUE

Osteomyelitis (periosteal new bone formation)

Septic arthritis

Secondary (degenerative) joint disease

Epiphysitis

Sequestrum

Lumpy jaw (actinomycosis)

Rickets

Fracture

Tumoral calcinosis

Osteosarcoma

Calcinosis circumscripta

Traumatic stifle injury with fibrosis

Primary or secondary copper deficiency (molybdenosis) (e.g., physitis, spontaneous fractures)

2 Inspection and palpation. The origin of a swelling may be identified by the density and position of the mass on the ruminant. Masses over joints may represent hygromas or distention caused by synovial effusion. Skin masses may be edematous or parasitic nodules or neoplastic tumors. Muscle masses could be abscesses, herniations through torn fascia, or, in rare cases, neoplasia. Lymph nodes are most frequently enlarged because of abscessation, but neoplasia must be considered. Foot masses include interdigital fibromas and granulation tissue from chronic infections. Large osseous masses indicate calcification, bone proliferation, or a foreign body. When drainage is present in the center of a firm mass, a bone sequestrum is very likely. Firm soft-tissue masses may be granulomatous tissues, neoplasia, or a connective tissue scar.

3 Radiography and ultrasonography. (See comments for equine section.)

4 Cytology, microbiology, and histology. In some cases the density and location of a mass will be diagnostic and eliminate other possible diagnoses, but in many cases a microscopic examination of the tissue is necessary. Tissue can be obtained by needle aspiration, biopsy, or sometimes complete excision. Abscesses can simply be lanced, drained, and flushed. Unidentified tissue should be sectioned and stained for histopathologic examination and, in some cases, cultured.

13.4 PARESIS AND WEAKNESS

***Richard A. Lecouteur*,**

Paresis, may be defined as a deficit of voluntary movement. It may be monoparesis (paresis of a single limb), paraparesis (paresis of both pelvic limbs), tetraparesis (paresis of all four limbs), or hemiparesis (paresis of a thoracic and pelvic limb on the same side). Paresis results from disruption of the voluntary motor pathways that extend from the cerebral cortex, through the brainstem and spinal cord, to the motor unit (peripheral nerve, neuromuscular junctions, and muscle fibers). Complete loss of voluntary movement is referred to as *paralysis (plegia)*., Voluntary movements must be differentiated from reflex movements on the basis of neurologic examination findings and general observations.

Weakness, may be defined as impairment of strength and power. Most authors use the terms *paresis*, and *weakness*, synonymously; however, this may be confusing in some circumstances. For example, weakness may occur in the absence of paresis in some disorders of the nervous system, and weakness may result from many disease processes that do not primarily involve the nervous system (e.g., heart failure, respiratory insufficiency). The clinical signs of weakness may vary considerably and may include paresis, gait abnormalities, dysphagia, regurgitation, dyspnea, and dysphonia. Weakness may be present at rest or may occur after exercise. The distribution of involvement may be local, regional, or generalized. In addition, there may be gross deformities of muscle mass (e.g., atrophy, hypertrophy, skeletal deformities) associated with weakness.

This section focuses on paresis and weakness caused by conditions that affect the motor unit (Box 13-8). Diseases of other systems (e.g., respiratory and cardiovascular diseases or central nervous system disorders) that may result in paresis and weakness are discussed separately in other sections. 227 228

13.4.1 Box 13-8 Causes of Paresis and Generalized Weakness in Horses and Ruminants

Anemia

Cardiovascular disease

Chronic inflammatory disease

Drug-related conditions

Electrolyte disorders

Endocrine or metabolic disorders

Exhaustion

Fever or sepsis

Gastrointestinal disease

Motor unit disease

Neoplasia

Nervous system disease

Nutritional disorders

Respiratory system disease

Trauma

Toxicities

13.4.2

Mechanisms of Paresis and Weakness

Voluntary movement is initiated by the cerebral cortex. Muscular activity occurs subconsciously after activation of successively lower levels of the nervous system: basal nuclei, midbrain, pons and medulla, cerebellum, brainstem, spinal cord, and motor unit. The function of these lower levels is vital, and without their input voluntary movements become impossible.

Monoparesis (or monoplegia) is a common problem in horses and ruminants. It may be caused by dysfunction of the lower motor neuron or neuromuscular junction. Monoparesis is commonly caused by trauma to a nerve or plexus, although neoplasia (e.g., lymphoma, neurofibroma) and inflammation or infection (e.g., early stages of rabies) of peripheral nerves have been reported to cause monoparesis.

Bilateral pelvic limb paresis, ataxia, or paralysis may occur as a result of a neurologic disorder localized to the spinal cord caudal to the T2 spinal cord segment. Various congenital vertebral and spinal cord malformations may result in pelvic limb paresis. Equine protozoal myeloencephalitis and equine degenerative myeloencephalopathy may result in lameness, weakness, and ataxia that may progress to tetraparesis. Musculoskeletal disorders resulting only in bilateral pelvic limb weakness and paresis are unusual. Possible causes include trauma (e.g., postcalving or postfoaling paralyses caused by lumbosacral nerve root compression or contusion), vascular disorders (e.g., thrombosis), and early stages of an infectious disorder that may progress to tetraparesis.

The causes of tetraparesis are numerous and include progression of many of the disorders mentioned previously. Outbreaks of intoxication with *Clostridium botulinum*, occur sporadically in horses and ruminants; the condition results in a flaccid paralysis that starts with the pelvic limbs and progresses cranially. Depending on the amount of toxin involved, large numbers of animals may be affected. Polyneuropathies (congenital and acquired) and polymyopathies (congenital, metabolic, infectious, and immune-mediated) are causes of tetraparesis.

Muscle weakness may result either from a primary neuromuscular disease or disorders that affect muscle secondarily. In the latter category, problems of horses and ruminants that commonly result in weakness include poor diet, underfeeding, toxicity, and anorexia. Systemic diseases and disorders such as dehydration, low circulating blood volume, anemia, and metabolic abnormalities (e.g., acidosis or alkalosis) also may result in weakness. Disorders of bones (e.g., fractures) and joints (e.g., septic arthritis) affecting one limb also may affect the contralateral limb through overuse or misuse, and weakness of the contralateral limb may result.

Primary neuromuscular diseases usually are classified on the basis of the anatomic component of the motor unit that is involved. Such diseases broadly are subdivided into neuropathies (disorders of the neuron, its cell body, axon, and/or Schwann cells [myelin]); junctionopathies (disorders of the neuromuscular junction); myopathies (disorders of muscle fibers); and neuromyopathies (disorders of both the neurons and the muscle fibers).

Dysfunction of the motor unit results in lower motor neuron signs, seen clinically as muscle weakness. The expression of this weakness may vary considerably, and the distribution of involvement may be local, regional, or generalized. Atrophy, hypertrophy, and skeletal deformities may accompany the muscle weakness. Any patient with some form of clinical weakness should be viewed as potentially having a motor unit disorder. That the patient is “weak merely because it is sick” should not be readily assumed without meticulous evaluation of the motor unit.

13.4.3 Approach to Diagnosis of Paresis and Weakness in Horses

Establishing a diagnosis requires an informed and coordinated approach to defining a problem list through associations and direct observations (i.e., a diagnostic plan) (Box 13-9).

1 Signalment. Breed, age, sex, and use of the horse.

2 History. Feeding program, vaccination and deworming schedules, course of complaint, response to treatment, and possibility of exposure to toxins or trauma.

3 Physical examination. Presence and distribution of abnormal findings on physical and neurologic examinations should be recorded. Normal functions must be known before abnormal functions may be recognized. Abnormal functions must be recognized because neurologic diseases are manifested clinically almost entirely by dysfunction. It is uncommon for the clinical signs to include readily detectable anatomic changes. Therefore a clinician must rely on clinical signs of abnormal function to identify the location of the neurologic dysfunction.

   The first step in locating a neurologic lesion is to determine the level of the abnormality along the longitudinal plane of the neuraxis (i.e., brain, spinal cord, or motor unit). The second step is to further localize the lesion within an anatomic region (e.g., motor unit should be further localized to peripheral nerve, neuromuscular junction, or muscle). The third step is to determine the location of the lesion in the transverse plane at the appropriate longitudinal level (e.g., left or right side).

4 Minimum database. Complete blood count, serum biochemistry panel (including electrolyte determinations), fecal analysis, and urinalysis. Measurement of muscle-specific serum enzymes, such as creatine kinase (CK), as well as aspartate aminotransferase (AST) and lactic dehydrogenase (LDH) may be helpful in identifying neuromuscular disorders in which myonecrosis is a principal pathologic feature. Elevated serum enzyme activities may help to differentiate myopathies from other neuromuscular disorders. Immunologic procedures for the detection of myoglobin that are becoming available may provide a sensitive means of detecting myolysis in the future.

5 Specific diagnostic tests

   a Electrodiagnostic testing. Electromyography (EMG) involves the detection and characterization of electrical activity (potentials) recorded from a patient's muscles. A systematic study of individual muscles permits an accurate determination of the distribution of muscles affected by a pathologic process.

   b Nerve and muscle biopsy examination. This procedure evaluates the morphology of portions of the motor unit and may differentiate neuropathies, junctionopathies, and myopathies. In some instances, results of muscle biopsy analysis may provide a definitive diagnosis (e.g., polysaccharide storage myopathy of horses).

13.4.4 Approach to Diagnosis of Paresis and Weakness in Ruminants

The approach to the diagnosis of disorders causing paresis and weakness in ruminants is essentially the same as that for horses (Box 13-10). Differences may be encountered as a result of the intended use of ruminants. Most ruminants live in a herd setting, and the level of human supervision and care of the herd will vary. In some cases animals will be monitored daily for signs of abnormal behavior, whereas in other cases animals may not be observed for varying periods of time. Infectious diseases, disorders arising from nutritional problems, parasites, or toxicity may progress to affect several individuals before a problem is noticed. Signalment, history, and a physical and neurologic examination are essential to determine first if the paresis and weakness are neurologic in origin and second to make a neuroanatomic diagnosis. These findings should be combined with a knowledge of diseases and disorders that produce this clinical picture in order to arrive at a diagnosis.

13.4.4.1

Box 13-9 Causes of Paresis and Weakness in Horses

13.4.4.1.1

DEGENERATIVE

Equine degenerative myeloencephalopathy

13.4.4.1.2

ANOMALOUS OR CONGENITAL

Hydrocephalus

Vertebral and spinal cord malformations

13.4.4.1.3

METABOLIC

Exertional rhabdomyolysis

Hyperkalemic periodic paralysis

Hypothyroidism

Hyperthermia

Hypocalcemia

Hypokalemia

Equine hepatic lipidosis

Vitamin A deficiency

13.4.4.1.4

NUTRITIONAL

Malnutrition, vitamin E (selenium) deficiency

13.4.4.1.5

NEOPLASTIC

Brain or spinal cord tumor

Lymphosarcoma

Melanoma

Leukemia

13.4.4.1.6 INFECTIOUS OR INFLAMMATORY

Encephalitis, myelitis

Equine protozoal myeloencephalitis

Diskospondylitis

Botulism

Rabies

Ehrlichiosis

Tuberculosis

Rhinopneumonitis

Hepatoencephalopathy

Tick paralysis

Cerebrospinal nematodiasis

Equine protozoal myeloencephalitis

13.4.4.1.7 TOXIC

Snake bite

Plant poisons (star thistle poisoning, oleander, moldy corn poisoning, white snake root, locoweed, larkspur, delphinium, onion, moldy sweet clover)

Vitamin D

Phosphorus

Heavy metals (lead, arsenic)

13.4.4.1.8 TRAUMATIC

Vertebral fracture or luxation

13.4.4.1.9 VASCULAR

Postanesthetic hemorrhagic myelopathy

13.4.4.2 Box 13-10 Causes of Paresis and Weakness in Ruminants

13.4.4.2.1 ANOMALOUS OR CONGENITAL

Progressive degenerative myeloencephalopathy of Brown Swiss cattle

Progressive ataxia of Charolais cattle

Inherited progressive spinal myelinopathy of Murray Grey cattle

Inherited myophosphorylase deficiency in Charolais cattle

13.4.4.2.2 METABOLIC

Acidosis

Ketosis

Vagal indigestion

Urolithiasis

Hypocalcemia

Hypomagnesemia

Anemia

Hypothermia

13.4.4.2.3 NUTRITIONAL

Vitamin E (selenium) deficiency

Polioencephalomalacia (thiamine deficiency)

Malnutrition

Viral or bacterial diarrhea

Water intoxication or salt poisoning

13.4.4.2.4 NEOPLASTIC

Spinal vertebral neoplasia (usually lymphoma)

13.4.4.2.5 INFECTIOUS OR INFLAMMATORY

Salmonellosis

Parasitism

Cryptosporidiosis

Coccidiosis

Colibacillosis

Anaplasmosis

Pneumonia

Peritonitis

Encephalomyelitis

Mastitis

Botulism

Tick paralysis

Rabies

Sepsis

Gastrointestinal ulceration

Bovine spongiform encephalopathy

13.4.4.2.6 TOXIC

Lead poisoning

Snakebite

13.4.4.2.7 TRAUMATIC

Lightning strike

Gunshot wound

Vertebral fracture or luxation

13.5 MUSCLE SPASMS AND MYOCLONUS

***Richard A. LEcouteur*,**

Muscle spasms are sudden, transient, and involuntary contractions of a single muscle or group of muscles, attended by pain and loss of function. Often all the muscles affected by a spasm are supplied by a single nerve. A painful, tonic, spasmodic muscular contraction is often referred to as a *cramp*.,

Myoclonus, may be defined as a disturbance of neuromuscular activity characterized by abrupt, brief, rapid, jerky, arrhythmic, asynergic, involuntary contractions involving portions of muscles, entire muscles, or groups of muscles, regardless of their functional association. The movements may be single or repetitive (10 to 50 per minute) and are similar to those that follow stimulation of a muscle. Myoclonus is seen primarily in muscles of the limbs, where involvement is often diffuse or widespread. Myoclonus also may be present in facial or masticatory muscles and muscles of the tongue, larynx, and pharynx. Myoclonus usually disappears during sleep.

This section describes muscle spasm and myoclonus as specific clinical signs associated with dysfunction of the musculoskeletal system.

13.5.1 Mechanisms of Muscle Spasms and Myoclonus

Spasms usually are of reflex origin and may result from irritation or stimulation at any level of the nervous system from the cerebral cortex to the muscle fibers. In most cases, however, spasms are caused by peripheral irritation affecting either muscles or nerves. Pain may cause either tonic or clonic spasms of muscles, especially should the painful stimulus be focal or discrete. Mechanical irritation may cause a localized spasm. There may be prolonged and characteristic muscle spasm associated with the hyperirritability of nerves and muscles in tetany or tetanus. Spasms may follow injury or irritation of peripheral nerves, particularly during the process of regeneration. Spasms may also result from irritation or diseases affecting cortical centers in the brain, motor nuclei in the brainstem, or descending motor pathways in the spinal cord.

There has been much discussion regarding the pathologic process underlying myoclonic movements. Whereas originally it was thought that the neural discharge that excites the muscular contraction of myoclonus was confined to the motor unit, it is now known that myoclonus also may result from dysfunction of the brain (cerebral cortex, brainstem, basal nuclei, thalamus, etc.), spinal cord, peripheral nerve, neuromuscular junction, or the muscle itself, alone or in combination. A variety of processes evidently lead to hyperexcitability of the cerebral cortex, subcortical structures, or even the lower motor neurons alone. Myoclonic movements or muscle spasms may occur in a variety of conditions. They have been observed in association with encephalitis, meningitis, toxic and postanoxic states, metabolic disorders, degenerative diseases, and vascular and neoplastic conditions. Myoclonus has also been reported in association with lesions of peripheral nerves, nerve roots, and spinal cord.

Specifically, disturbances in plasma electrolyte concentrations, certain drugs, toxins, and poisons may elicit involuntary muscle activity. In general, the mechanism that is common to all causes of spasm or myoclonus involves an inappropriate stimulation of a nerve or muscle cell, causing the cell to fire a series of action potentials, resulting in muscle contraction. For example, toxins may act directly on the muscle cell membrane to stimulate the release of calcium into the cell from the sarcoplasmic reticulum, thereby causing involuntary muscle contraction. Alternatively, some toxins may cause efferent neurons to release neurotransmitter across the neuromuscular junctions, thereby stimulating receptors on the muscle cell membrane.

13.5.2

Approach to Diagnosis of Muscle Spasms and Myoclonus in Horses

A broad spectrum of diseases may be associated with muscle spasms or myoclonus in horses (Box 13-11). A thorough investigation is needed to achieve an accurate diagnosis.

1 History. A comprehensive history including evaluation of the environment and stablemates, description of any traumatic episodes, and any potential drug or toxin exposure.

2 Physical examination. Complete lameness and neurologic examinations should be done as extensions of a thorough physical examination.

3 Minimum database. Complete blood count, serum biochemistry panel (including muscle enzyme determinations), and cerebrospinal fluid analysis should be performed. In the case of muscle spasm and myoclonus, elevation in muscle enzymes may indicate secondary muscle damage rather than a primary muscle disease. A tetany panel, including serum calcium, phosphorus, and magnesium determinations, may be completed. Hypocalcemia may be a cause of muscle spasms in lactating horses, exhausted endurance horses, or horses transported long distances.

4 Specific diagnostic tests.

a Electrodiagnostic testing. A systematic study of individual muscles using EMG permits an accurate determination of the distribution of muscles affected by a pathologic process.

b Nerve and muscle biopsy examination. This procedure evaluates the morphology of portions of the motor unit and may differentiate neuropathies, junctionopathies, and myopathies. In some instances results of muscle biopsy analysis may provide a definitive diagnosis (e.g., phosphorylase deficiency of Charolais cattle).

13.5.2.0.0.0.0.0.0.1

Box 13-11 Causes of Muscle Spasms and Myoclonus in Horses

13.5.2.0.0.0.0.0.0.1.1

ANOMALOUS OR CONGENITAL

Myotonia congenita

13.5.2.0.0.0.0.0.0.1.2

METABOLIC

Hyperkalemic periodic paralysis

Hypocalcemia

Hypoglycemia

Hypothermia

Exhaustion

Shivering

13.5.2.0.0.0.0.0.0.1.3 NEOPLASTIC

Insulinoma

13.5.2.0.0.0.0.0.0.1.4 INFECTIOUS OR INFLAMMATORY

Tetanus

Rabies

Equine influenza

Tick-borne encephalitis

Meningitis

13.5.2.0.0.0.0.0.0.1.5 IDIOPATHIC

Neonatal maladjustment syndrome

13.5.2.0.0.0.0.0.0.1.6 TOXIC

Strychnine

Organochlorines

Chlorinated hydrocarbons

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231

13.5.2.0.0.0.0.0.0.2 Box 13-12 Causes of Muscle Spasms and Myoclonus in Ruminants

13.5.2.0.0.0.0.0.0.2.1 ANOMALOUS OR CONGENITAL

Congenital posterior paralysis of Danish red calves

Inherited congenital myoclonus (formerly known as neuraxial edema) of polled Herefords and their crossbreeds

Maple syrup urine disease in polled Herefords and their crossbreeds

Lethal spasms in Jersey and Hereford calves

Congenital brain edema in Herefords

13.5.2.0.0.0.0.0.0.2.2 METABOLIC

Hypomagnesemia

Hypocalcemia

Hypoglycemia

13.5.2.0.0.0.0.0.0.2.3 INFECTIOUS OR INFLAMMATORY

Tetanus

Rabies

Pseudorabies

Meningitis

Coccidiosis

13.5.2.0.0.0.0.0.0.2.4 TOXIC

Chlorinated hydrocarbons

Strychnine

Cocklebur

Buckeye

13.5.3 Approach to Diagnosis of Muscle Spasms and Myoclonus in Ruminants

The approach to diagnosis of muscle spasms and myoclonus in ruminants is essentially the same as that described for horses (Box 13-12). In ruminants a tetany panel (consisting of serum calcium, phosphorus, and magnesium determinations) should be completed in any animal exhibiting these signs. In lactating cattle on grass pasture, and in sheep transported long distances, hypomagnesemia and hypocalcemia, respectively, are highly suspected initially. Several infectious (e.g., rabies, pseudorabies), toxic, and inherited causes of muscle spasms and myoclonus should be suspected in ruminants. In postparturient animals and animals with wounds or bites, or animals recently castrated or tail docked, tetanus should be considered as a possible cause of muscle spasms and myoclonus.

13.6 Suggested Readings

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14 Chapter 14 Collapse and Sudden Death

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James R. Turk

The ruminant or horse that collapses and dies within 24 hours while being observed or is found dead with no premonitory signs of illness is often a diagnostic challenge. In these situations clients often are distressed and frequently pressure the veterinarian to declare an immediate diagnosis. Sudden death in the absence of observed clinical illness is usually the most perplexing. Obligation to clients necessitates a systematic approach to derive a specific causative diagnosis, to determine the source and extent of the problem, and to recommend corrective measures. These goals are best accomplished by delineating the characteristics of normal animals within the herd and analyzing the distribution of the disease with respect to time, place, and a variety of exposure factors and environmental influences. These factors are then correlated with necropsy results and additional diagnostic testing.

14.1 COLLAPSE VS. SUDDEN DEATH

Collapse is easily identified as a state of extreme prostration and depression. However, sudden death has a somewhat tenuous meaning, lending itself to subjective impression. The timing parameter used to define sudden death ranges from 1 to 24 hours from the onset of the fatal episode. Some veterinarians restrict the definition to a narrower time span. The 12- to 24-hour interval is sometimes selected to coincide with the frequency of owner observation of the livestock. For our purposes sudden death means clinically unexplained, rapid death (12 to 24 hours) occurring during normal activity in apparently healthy animals. Generally a condition of this nature is associated with fatal dysfunction of the cardiovascular, nervous, respiratory, or gastrointestinal (GI) system. In addition, perturbations in general cellular metabolism (cyanide or hydrogen sulfide) may result in peracute death.

14.1.1 Approach to Diagnosis of Sudden Death

The causes of sudden death are investigated in much the same way as for any disease. The accompanying tables of differential diagnoses include infectious, metabolic, nutritional, physical, cardiovascular, toxic, and miscellaneous causes of sudden death. Diagnostic laboratories provide an array of tests and analytic procedures based on the needs of veterinarians in their service areas. Use of these facilities to support a definitive diagnosis is essential in sudden death cases. Diagnosis is rarely based on a single item of evidence and usually requires input from multiple testing procedures. Unless the cause of death is apparent, some important considerations required for effective use of a diagnostic laboratory include the following:

1 A detailed history, which consists of the herd incidence, management changes, past medical problems, vaccination records, new additions to the herd, a complete description of the environment, and a recognition of the frequency of animal observation. Owners and managers may not be candid for fear of being considered negligent. Inconsistencies among involved parties should be carefully evaluated. Recent changes in management practices should be scrutinized, including feeding habits and whether there have been any illnesses in commingled animals. Animals trailed or transported for long distances or introduced onto unfamiliar ranges often are poisoned by plant species normally avoided by indigenous livestock. The likelihood of foul play should be considered without creating undue alarm. Assigning blame should be left to the discretion of owners. Consideration of disgruntled former employees and equine insurance claims are particularly critical situations that may have legal implications. The precise cause of death is crucial for insured livestock (mostly horses) because of exclusion clauses in many insurance policies. Heavily

insured horses should be subjected to a detailed, documented, and witnessed diagnostic evaluation. Toxicologic testing is especially critical in these cases. Evaluation of the environment before the animal is moved is necessary to eliminate questionable procedures in insurance claim cases. Evidence of struggling in the immediate area indicates a more protracted illness in contrast to collapse and death without a struggle. Suspicions should be aroused when evidence suggests the animal may have been dragged or carried to the current location.

2 The appropriate specimen is required by the diagnostic laboratory to perform the requested examination. Many cases of sudden death are attributed to central nervous system dysfunction; therefore it is necessary to remove the brain. Busy practitioners frequently do not take the time to remove this organ. There is a higher-than-normal probability of a poison being involved in sudden death cases, especially in equine insurance claims. For toxicologic examination, toxicants remaining in the GI tract must be considered, together with those in the major excretory organs, the liver and kidneys. 232 233

3 The correct amount and preservation of the sample depends on the specific test. Medicolegal cases demand that stringent photographic and written documentation, witnessing, and chain-of-custody protocol be followed during necropsy and sample collection. The amount of the sample is particularly important for chemical analysis. Sending insufficient quantities of sample may preclude multiple testing procedures. In general, 100 to 200 g of tissue or ingesta, 50 mL of urine, all fluid from both eyes, and 5 to 10 mL of blood or serum suffice for most analytic procedures. A midsagittal cut through the brain is performed to allow freezing of one half for chemical analysis and formalin preservation of the other. When poisoning is suspected, samples from possible sources such as feed, water, baits, poisonous plants, and suspect materials should be submitted. Usually 1 kg of each is adequate. Samples submitted for chemical analysis should be frozen in individual containers and labeled with date, location, and identity of the specimen. Specimens for bacteriology and virology are to be packaged separately and chilled. Dry ice should be avoided because gaseous carbon dioxide may kill some infectious agents. Tissues for histopathologic examination require fixing in 10% formalin with tissue slices 4 to 5 mm thick. Suspected poisonous plants are properly preserved by placing them in a plastic bag with wet paper towels or by drying them between sheets of paper.

14.2 CAUSES OF COLLAPSE AND SUDDEN DEATH

14.2.1 Infectious Causes of Sudden Death in Horses (Box 14-1)

Foal actinobacillosis is an acute fulminant septicemia caused by *Actinobacillus equuli*, a gram-negative bacterium found in the upper respiratory tract, feces, and genital tract of normal adult horses. Predisposing factors to foal septicemia with any agent include prematurity, failure of passive transfer, dam malnourishment during gestation, and environmental stress. A characteristic histologic finding is multiple bacterial emboli in renal glomerular capillaries without inflammatory infiltrate in neonatal foals. Acute anthrax may be rapidly fatal to horses after a period of excitement, depression, convulsions, and coma. Isolating the causative agent from blood confirms the diagnosis. Babesiosis is an erythrocytic parasite that may cause death within 24 hours. Identification of the organism in blood smears or complement fixation testing for parasite antibodies confirms the diagnosis.

14.2.1.1

Box 14-1 Infectious Causes of Collapse and Sudden Death in Horses

Acute colitis

Babesiosis

Botulism*

Clostridial myopathy

Clostridium difficile, diarrhea

Clostridium perfringens, enterotoxemia

Clostridium sordellii, dysentery

Equine monocytic ehrlichiosis (Potomac fever)

Guttural pouch mycosis (hemorrhage from)

Hemorrhagic enterotoxemia in foals

Neonatal septicemia

Neonatal diarrhea

Salmonellosis*

Tyzzer's disease

* Likely to involve several animals.

Acute clostridial disease involving *Clostridium septicum, Clostridium chauvoei, Clostridium novyi*, and *Clostridium perfringens*, has been associated with intramuscular injections of various parenterals such as ivermectin, vitamin B complex, prostaglandin, antihistamines, and flunixin meglumine when asepsis has been ignored. Clostridial myopathies also are associated with deep stab or puncture wounds. Botulism in foals (shaker foal syndrome) is caused by *Clostridium botulinum*, (usually type B). Toxin may sometimes be demonstrated in feed and gut contents. The organism may be cultured from tissues or gut contents in toxico-infectious cases.

Clostridium sordellii, should be suspected in cases of foals having a history of colic, bloody diarrhea, and death within a few hours.[1] *C. perfringens*, type C may induce a hemorrhagic enterotoxemia and death in foals as young as 4 days.[2] Severe intestinal lesions are caused by the beta-toxin produced by this species. Organisms may be demonstrated in smears of intestinal contents. *C. perfringens*, type D also induces sudden death in the most aggressive foals in group-feeding situations. Similar enterotoxemia also has been associated with toxin-producing *Clostridium difficile*,[3] and *Bacteroides fragilis*.,[4]

Equine monocytic ehrlichiosis (Potomac fever), caused by *Ehrlichia risticii*, is a severe colitis with diarrhea and dehydration, followed by ileus, endotoxemia, and death in adult horses. Diagnosis is based on clinical findings and antibody and antigen detection using immunofluorescent antibody (IFA) and enzyme-linked immunosorbent assay (ELISA) methods, respectively. Guttural pouch mycosis often results in nonfatal intermittent unilateral epistaxis. Occasionally a single episode of severe epistaxis from rupture of an aneurysm in the internal carotid artery may result in sudden death. Necropsy reveals blood in the nasal passages and guttural pouch with a diphtheritic plaque in the dorsocaudal aspect of the medial compartment. Salmonellosis is responsible for many cases of acute enterocolitis, especially when several animals are involved. The peracute syndrome may resemble colitis-X in mature horses with a course of 6 to 12 hours. Horses may die before diarrhea develops. Postmortem diagnosis is based on isolation of *Salmonella*, species from bowel contents, bowel wall, and/or associated lymph nodes. Tyzzer's disease is a rapidly developing fatal hepatitis of foals. The incidence is sporadic, and, because of the peracute development, clinical signs may not be observed before death. Diagnosis is based on histologic demonstration of the bacilli in bundles within hepatocytes surrounding necrotic areas.

14.2.2 Infectious and Parasitic Causes of Sudden Death in Ruminants

Infectious causes of sudden death range from acute septicemias and toxemias to rupture and release of abscess contents into the systemic circulation (Box 14-2). A liver abscess rupturing into the caudal vena cava; endocarditis, especially of the right atrioventricular valve, with subsequent pulmonary thromboembolism; and the rupture of a pituitary abscess are occasional causes of sudden death in individual animals. Acute anthrax and the clostridial infections, as well as ingestion of their preformed toxins, are more common causes of sudden death in ruminants. Anaplasmosis may cause sudden death in mature cattle under stress, without apparent icterus. 233
In these cases anthrax may be mistaken for anaplasmosis because of the gross enlargement of the spleen. 234
Anaplasma, organisms may be demonstrated in blood smears, whereas newer diagnostic methods involve indirect fluorescent antibody and DNA probes. Of all domestic animals, cattle are the most susceptible to clostridial infections in which tissue invasion is present (blackleg). Because of this, vaccination status is important to ascertain. In addition, a fluorescent antibody test and isolation of the bacterium confirm the diagnosis. *C. perfringens*, of various types is responsible for heavy losses caused by enterotoxemia in calves, lambs, kids, and feedlot cattle in apparent good health and on full feed. *C. perfringens*, type D has been associated with focal symmetric encephalomalacia in lambs.[5] *Coliform*, mastitis may result in peracute systemic disease and rapid death if not treated early. Diagnosis is based on culture of the organism from the affected gland. *Leptospira*, may cause an acute septicemia with hemolytic anemia and rapid death in young ruminants. Demonstration of leptospires in fresh urine or by immunohistochemical staining of tissues may assist in making the diagnosis. The course of listeriosis in sheep and goats is rapid, and death may occur in 4 to 48 hours after the appearance of clinical signs.[6] Bacteriologic culture (isolation) or immunohistochemical staining of the organism in tissues is diagnostic. Acute fascioliasis *(Fasciola hepatica)*, occurs seasonally in sheep and may cause sudden death within 6 weeks of initial infection. Anaerobic conditions induced by flukes in hepatic parenchyma predispose ruminants to the highly fatal clostridial hepatopathies such as *Clostridium hemolyticum*, infection. Evidence of fluke infection is grossly visible. Peracute malignant catarrhal fever (MCF) is a sporadic cause of sudden death in cattle that is usually associated with contacting ovine carriers, but most animals with MCF have

diarrhea, keratitis, and other obvious clinical signs for days before death occurs. A septicemic form of mycoplasmosis has induced rapid death in kids.[7] Isolation of the causative organism is diagnostic. Sudden death is the usual manifestation of septicemic pasteurellosis in lambs. Pseudorabies is a consideration in sudden death cases of ruminants having contact with infected swineherds in the Midwestern United States. Brain for microscopic examination and virus isolation should be submitted to confirm the diagnosis. Acute septicemic salmonellosis mainly affects young ruminants and may result in death within 24 hours. Acute septic metritis usually occurs secondary to complications of parturition. Endotoxic shock and rapid death may occur in severe cases. Thromboembolic meningoencephalomyelitis caused by *Haemophilus somnus*, is a peracute septicemic disease of young calves. Many cattle die without showing clinical signs. It may be associated with prior respiratory problems in the herd or feedlot. Typical lesions or isolation of the causative organism is diagnostic. Adult lymphosarcoma associated with bovine leukemia virus can be a cause of sudden cardiac death when neoplastic cells infiltrate the cardiac conduction system.

14.2.2.1

Box 14-2 Infectious and Parasitic Causes of Collapse and Sudden Death in Ruminants

Abscess rupture at liver hilus or pituitary

Anaplasmosis* (B)

Anthrax*

Black disease, infectious necrotic hepatitis

Blackleg

Botulism*

Bovine lymphosarcoma

Clostridium hemolyticum, bacillary hemoglobinuria, redwater*

Clostridium perfringens, enterotoxemia

Coliform mastitis

Endocarditis

Leptospirosis

Listeriosis (C, O)

Liver flukes (O)

Malignant catarrhal fever (B)

Mycoplasmosis (C)

Neonatal septicemia

Neonatal diarrhea

Pasteurellosis, septicemic* (O)

Pseudorabies

Salmonellosis*

Septic metritis

Thromboembolic meningoencephalomyelitis* (B)

B, Bovine; *C*, caprine; *O*, ovine.

* Likely to involve several animals.

14.2.3 Metabolic and Nutritional Causes of Sudden Death in Horses

Hypocalcemia in horses is most common in lactating mares, but it also occurs after transit. Animals may develop tetany, synchronous diaphragmatic flutter (thumps), muscle tremors, and sweating. Low serum calcium is diagnostic. White muscle disease (nutritional myodegeneration) is associated with selenium and vitamin E deficiency. Sudden death in adult horses after severe exercise is attributed to degenerative lesions in cardiac and skeletal musculature. Death in foals may occur within hours from pulmonary edema and heart failure. Diagnosis is based on measuring whole blood and/or liver selenium and vitamin E concentrations.

14.2.4 Metabolic and Nutritional Causes of Sudden Death in Ruminants

Metabolic and nutritional diseases often are not considered in cases of sudden death. The primary lesion in a disorder of cattle known as “falling disease” is progressive fibrosis of the myocardium. Sudden deaths characteristic of the disease are attributed to exercise-induced heart failure.[8] Rapid development of hypocalcemia

usually is associated with the onset of lactation in cattle, with stressful circumstances in older lactating ewes, or with transport associated with fasting and weather stress. Hypomagnesemia also may develop under similar conditions, especially in ewes and cows in heavy lactation and on lush grass pastures. Polioencephalomalacia occurs most commonly in animals raised under intensive production techniques and can sometimes be traced to excessive sulfates in the diet and/or water. The clinical course tends to be most rapid in sheep. Severe cases of ruminal lactic acidosis, especially in animals unaccustomed to high levels of soluble carbohydrate in the diet, may induce death within 24 hours. Nutritional myodegeneration of the heart is a frequent cause of sudden death in young ruminants born to dams fed selenium-deficient diets during gestation. Diagnosis is based on histopathology and measurement of liver selenium concentration. Some cases of sudden death associated with myocardial necrosis are idiopathic.[9]

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14.2.5 Cardiovascular Causes of Sudden Death in Horses

Diagnosis of sudden death caused by cardiovascular failure depends on a careful and methodic technique (Box 14-3). Usually a single animal is affected. Necropsy is necessary to identify the location and characteristics of the lesion, and further analysis may be necessary to establish the exact cause of death. Aortic ring (root) rupture in stallions usually is seen early in the breeding season, occurring immediately after servicing a mare. Rupture of the aorta may occur just distal to the aortic valve, resulting in cardiac tamponade and rapid death. Acute central nervous system embolism results from detached thrombi originating from endocarditic lesions or accidental intracarotid injection. Cerebral hematoma also can result from intracarotid injection. Endocarditis, especially of the aortic valve, may result in coronary thromboembolism and myocardial infarction. Coronary occlusion as a result of damage induced by *Strongylus vulgaris*, larvae can be diagnosed by the presence of the larvae in the coronary thrombus. Massive abdominal or thoracic hemorrhage is found at necropsy, and the cause may be difficult to ascertain.[10] Racehorses mostly die from severe hemorrhage in the thorax. Myocarditis in horses up to 4 years of age resulting from recent respiratory infection may be diagnosed with histopathologic examination. Pericardial rupture and the associated heart damage is a result of violent trauma. Splenic rupture and fatal hemorrhage rarely occur because of the protection afforded by the thoracic wall. Massive thrombi of verminous origin have been observed in young horses that die suddenly while exercising. Uterine arterial rupture involving ovarian, uteroovarian, uterine, or external iliac arteries is observed in older mares, with death ensuing in 30 minutes to 20 hours' postpartum.

14.2.6 Physical Causes of Sudden Death in Horses

Fatal air embolism can result from any open vein above the heart. Open needles or catheters and severe head wounds involving teeth and sinuses have resulted in sudden death from air emboli. Air is aspirated into the vein by the Venturi effect from blood surging past a portal and creating the necessary negative pressure to aspirate air into the vein. Between 700 and 6000 mL of air may produce a fatal air embolus in the right cardiac ventricle, where it obstructs the pulmonary artery. Cecal or colonic rupture in parturient mares results in sudden death within 8 hours.[11]

14.2.7 Physical Causes of Sudden Death in Ruminants

Physical causes of sudden death often display gross evidence indicative of the diagnosis. Abomasal bloat occurs in calves and lambs drinking excessive quantities of warm milk replacer at infrequent intervals. Abomasal ulcers occasionally may perforate and cause rapid death in calves or adult cattle. Ruminal bloat is one of the more common physical causes of sudden death in intensively raised ruminants. When differentiating postmortem from

antemortem bloat, note that bloat is the primary cause of death when there is congestion and hemorrhage in the anterior parts of the carcass and edema in the scrotal and ventral perineal areas. Bloat and hypersalivation are the most consistent clinical signs seen in cases of choke. Attempts to swallow firm fruits, tubers, or green ears of corn may occlude the esophagus and result in rapid ruminal tympany and death.

Sudden death is a major concern in feedlots because most such deaths occur in cattle near market weight. GI disturbances are seen with a high frequency in cattle in the late stages of the feeding program. Sudden death is the result of interactions among factors such as rumen acidosis, bloat, and endotoxemia.

14.2.7.1

Box 14-3 Cardiovascular Causes of Collapse and Sudden Death in Horses

Aortic ring (root) rupture

Central nervous system embolism

Coronary occlusion

Endocarditis

Massive abdominal or thoracic hemorrhage

Myocarditis

Pericardial rupture

Splenic rupture

Thrombi of verminous origin

Uterine arterial rupture

Exposure to high-voltage currents in the form of lightning or electrical transmission wires may cause instantaneous death. The diagnosis of lightning strike is based on a history of an electrical storm, linear singe marks, food in the mouth, several animals dead in the same vicinity, and evidence of lightning damage in the immediate environment. Gunshot wounds may be deliberate or accidental, but in any case involving sudden death the head or heart is the usual target. Bullets may pass through or lodge in obscure locations, making retrieval difficult. Radiography can assist in locating a bullet. Heatstroke is a sporadic condition characterized by hyperthermia and collapse. High humidity, dehydration, obesity, and poor heat tolerance associated with young or old age are all factors that predispose animals to overheating. Summer slump induced by consumption of endophyte-infected fescue potentiates the heat intolerance. Internal bleeding may cause sudden death when a uterine artery is ruptured during parturition. This is readily apparent on necropsy. Tracheal edema, or “honker” syndrome, of feeder cattle is seen sporadically in feedlot cattle of the southern plains during hot weather. The

pathoanatomic basis of this syndrome is extensive edema of the mucosa and submucosa of the lower trachea, with attendant dyspnea and obstructive asphyxiation. Increased respiratory movements stimulated by hot weather or exercise trigger the clinical illness, especially in heavy cattle during the latter part of the feeding period.[12] Traumatic reticuloperitonitis or reticulopericarditis is associated with lack of oral discrimination in cattle. Sudden death occurs because of acute hemorrhage or dysrhythmia when the heart is punctured.

14.2.8

Toxic Causes of Sudden Death in Horses

Toxic causes of sudden death are frequently related to management practices. An increase in specific disease syndromes or sudden death in a population of livestock with common potential exposures suggests involvement of a toxicant. Investigation of the premises and a familiarity with poisonous plants and pesticides used in the practice area should help narrow the list of possible causative agents (Box 14-4).

Horses ingesting a lethal dose of the avicide 4-aminopyridine have died within 2 hours of the onset of clinical signs. Diagnosis is based on chemical analysis of stomach contents. Fatal doses of arsenic-containing pesticides may induce cardiovascular collapse and death in horses within hours of ingestion. The presence of edema and fluid in the GI tract suggests the diagnosis, and chemical analysis of GI tract contents, liver, or kidney confirms it. Black flies swarm where swiftly flowing water provides the aeration necessary for the development of larvae. 235
Massive attacks of these blood-sucking insects can rapidly kill livestock because a toxin present in the saliva of 236
the flies increases capillary permeability.[13] Cantharidin poisoning can occur after ingestion of 4 to 5 g of blister beetles. Lesions suggestive of cantharidin toxicosis include blistering and ulceration of mucous membranes of the GI and urinary tracts and myocardial degeneration and necrosis. Sustained hypocalcemia and hypomagnesemia are features of the clinical pathology consistent with blister beetle poisoning. Identification of blister beetles in the hay and chemical analysis of urine and GI contents are suitable for diagnostic confirmation. In the past, ferrous fumarate, present in digestive inoculate and administered to foals immediately after birth, resulted in death in some cases in 12 to 96 hours. This illustrates the acute toxicity of iron to young animals in particular. Lesions induced were those of gross liver damage. *Fusarium moniliforme*,–contaminated corn causes rapid death in horses after the sudden onset of bizarre neurologic deficits and behavioral effects. The lesion of this mycotoxin-induced leukoencephalomalacia is liquefactive necrosis in the subcortical white matter.

14.2.8.1

Box 14-4 Toxic Causes of Collapse and Sudden Death in Horses*

4-Aminopyridine

Arsenic

Black flies

Cantharidin*

Ferrous fumarate

Fusarium monoliforme,–associated mycotoxicosis

Insulin and potassium
Monensin*
Nitrogen dioxide
Organophosphate and carbamate insecticides
Toxic plants
Acer rubrum (red maple),
Blue-green algae*
Cicuta, species (water hemlock)
Conium maculatum, (poison hemlock)
Cyanogenic plants
Melilotus, species (sweet clover)
Nerium, species (oleander)
Nicotiana, species (tobacco)
Ricinus communis, (castor bean)
Taxus, species (Japanese yew)
* Likely to involve several animals.

High intravenous doses of insulin[14] and potassium[15] induce sudden death without significant lesions. Chemical detection is often overlooked and very difficult to perform and interpret in cases of deliberate poisoning. Immediate analysis of blood and circumstantial evidence of needle punctures in the jugular furrow are of diagnostic value. Monensin is quite toxic to horses, and fatal poisoning can occur within 12 hours of ingestion of poultry feed containing 100 g/ton or cattle premixes containing 300 g/ton. Lesions related to heart failure are

seen on postmortem examination. Tissues collected for microscopic examination should include heart and diaphragm. Chemical analysis of feed samples and stomach contents will confirm exposure. Toxic gases such as nitrogen dioxide, hydrogen sulfide, and carbon monoxide may be responsible for sudden death in horses housed in poorly ventilated buildings with associated gas sources nearby. Organophosphate and carbamate insecticides may induce acute intoxication and death within hours. Diagnosis is based on a history of exposure, determination of acetylcholinesterase activity in the caudate nucleus of the brain, and chemical detection of specific compounds in gut contents.

Circumstances surrounding toxic plant ingestion and diagnosis of intoxication are described in the ruminant section of this chapter. Ingestion of wilted *Acer rubrum*, (red maple) leaves may induce massive methemoglobinemia, causing marked tissue anoxia and death.[16] Red maple poisoning usually occurs during the late summer and early fall when trees are in full leaf. Ready access to wilted leaves follows windstorms. *Ricinus communis*, or castor bean, is also unique to this section. Seeds of this plant contain a phytotoxin called ricin, which causes severe enteritis and rapid death in horses. About 150 beans (50 g) are sufficient to kill a 450-kg horse. Diagnosis can be verified by finding a toxic amount of ingested seeds in the gut contents.

14.2.9 Toxic Causes of Sudden Death in Ruminants

Intoxication of livestock is frequently suggested as a simple explanation for very complex situations involving sudden death. Suspicions are warranted when a large number of animals die suddenly within a short time. Toxicants should be considered when the appearance of a disease or sudden death is temporally associated with a change in the environment (Box 14-5). An accurate diagnosis in many of these cases requires qualitative and quantitative analyses for suspect poisons. Selecting toxicants for which to analyze requires reasoned judgment supported by an extensive investigation of the environment and postmortem findings.

The avicide 4-aminopyridine usually is formulated with corn, making it a palatable poison for nontarget herbivorous livestock. Diagnosis is confirmed by chemical analysis of rumen contents or urine. Anticoagulant intoxication may induce sudden death when hemorrhage occurs in the cranial vault, abdominal cavity, pericardial sac, mediastinum, or thorax. The antemortem or postmortem sample for chemical analysis is whole blood or liver. Failure to detect an anticoagulant is not unusual because of the time lag between consumption and presence of the clotting defects, as well as the metabolism of the compound. Arsenic derivatives are a significant hazard to ruminants, especially in areas where such chemicals are widely used as cotton desiccants. Postmortem findings are consistent with microvascular injury to the GI tract. Diagnosis is confirmed by chemical analysis of rumen contents, liver, or kidney. In rare cases large doses of botulinum toxin may cause sudden death in ruminants. Sources of the toxin include the bones of dead animals eaten by osteophagic livestock, poultry carcasses in manure fed to cattle, stagnant pond water, animal tissues in silage or baled hay, and improperly ensiled silage or haylage.

Acetylcholinesterase-inhibiting agents such as the carbamate and organophosphate pesticides can kill livestock within hours. Agricultural practices result in the use of these pesticides in close proximity to livestock. This situation may lead to disaster. Acetylcholinesterase activity in the caudate nucleus of the brain is readily determined and interpreted, and specific compounds may be identified in rumen contents. Toxic gases such as carbon monoxide, hydrogen sulfide, and nitrogen dioxide become important differentials for sudden death in ruminants housed in poorly ventilated buildings, particularly over waste pits. Chlorinated hydrocarbon pesticides do not enjoy the widespread use they once did; however, old containers remain in obscure locations on many farms. When acute intoxication with these compounds is suspected, samples for analysis should include liver, brain, and rumen contents. In subacute cases fat and milk are appropriate samples. Copper toxicosis is a frequent cause of sudden death in sheep and has been reported in cattle fed chicken litter.[17] Cattle feeds normally contain

twice as much copper as sheep feeds and may cause copper toxicosis in sheep. Copper from treated fence posts also may poison sheep that either chew the posts or ingest contaminated forage in the vicinity. Samples required for chemical confirmation consist of whole blood or serum and liver. Close proximity of livestock to petroleum exploration and production activities in the major oil-producing states results in a variety of clinical problems, including sudden death.[18] Consumption of the more volatile petroleum constituents may induce rapid bloating and coating of the respiratory membrane when these substances are aspirated into the lungs. Gossypol toxicosis reportedly causes death without premonitory signs in calves (occasionally cows) and lambs fed cottonseed products containing this toxic pigment.[19,20] Poisoning appears abruptly after livestock have been fed the gossypol-containing ration for a period of weeks to months. Sudden death is attributed to heart failure. Postmortem examination reveals edema, centrilobular hepatic necrosis, and an enlarged heart. Ionophores may induce sudden death in species exposed to large overdoses, but delayed death is the usual course. Conditions conducive to lethal overdose include insufficient mixing or top dressing with monensin- or lasalocid-supplemented mineral. Degenerative-to-necrotic lesions in the heart are compatible with a diagnosis of ionophore poisoning.

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14.2.9.1

Box 14-5 Toxic Causes of Collapse and Sudden Death in Ruminants*

4-Aminopyridine (Avitrol), an avicide

Anticoagulants

Arsenic

Botulism*

Carbamates

Carbon monoxide

Chlorinated hydrocarbons

Copper (B, O)

Crude oil

Gossypol*

Hydrogen sulfide gas*

Ionophores*

Lead*

Metaldehyde

4-Methyl-imidazole, bovine bonkers syndrome (B, O)

Nicotine sulfate

Nitrogen dioxide gas*

Organophosphates

Selenium, parenteral overdose

Strychnine

Urea, nonprotein nitrogen*

Water deprivation, sodium ion toxicity

Toxic plants

Aconium, species (monkshood)

Asclepias, species (milkweed)

Blue-green algae*

Calycanthus fertilis, (bubby bush) (B)

Cicuta, species (water hemlock)

Conium maculatum, (poison hemlock)

Cyanogenic plants

Delphinium, species (larkspur) (B)

Drymaria pachyphylla, (inkweed)

Halogeton glomeratus, (halogeton) (O, B)

Kalmia, species (laurels)

Kochia scoparia, (summer cypress)

Laburnum anagyroides, (golden chain tree)

Lupinus, species (lupine) (O)

Melilotus, species (sweet clover)

Nerium, species (oleander)

Nicotiana, species (tobacco)

Nitrate-accumulating plants

Perilla frutescens, (perilla mint)

Phalaris, species (canary grass) (O)

Sarcobatus vermiculata, (greasewood) (B, O)

Solanum, species (nightshades)

Taxus, species (yew)

Xanthium, species (cocklebur) (B, O)

Zigadenus, species (death camas) (O)

B, Bovine; *O*, ovine.

* Likely to involve several animals.

Acute lead intoxication is another differential from the list of possibilities in sudden death cases. Lead poisoning is the most common toxicosis in cattle. Blood, liver, and kidneys are suitable specimens for lead analysis. Metaldehyde is an uncommon poison for ruminants; however, intoxication in cattle has occurred in low wetland areas where the chemical is used as a molluscicide. The palatability of metaldehyde baits promotes ingestion. Ammoniation of high-quality forage such as forage sorghum and Sudan grass, cereal grain, brome, and fescue hays is responsible for bovine bonkers syndrome, reportedly caused by the formation of 4-methyl-imidazole.[21] This sporadic intoxication causes central nervous system derangement and rapid death in cows and nursing calves. Ruminants may be poisoned by nicotine sulfate from ingestion of solution, treated foliage, and food or water from contaminated containers. The onset and progression of the syndrome are rapid, and death may occur within hours. Detection of nicotine in urine is easily performed by most toxicology laboratories. Iatrogenic selenium toxicosis and death in young ruminants can result from parenteral administration of excess doses. Rapid onset of violent tetanic seizures ending in death characterizes strychnine toxicosis. Samples suitable for chemical analysis include rumen contents, liver, and urine.

Urea toxicosis is a frequent cause of sudden death in feedlot livestock. In one particular case, 48 feedlot steers died within 2 days of delivery of a new lot of feed supplemented with urea.[22] Unusually high rumen pH, excess ammonia in serum, rumen contents, and eyeball fluid support the diagnosis. Water deprivation, with attendant sodium ion intoxication, is a known cause of sudden death in ruminants.[23] Some cases occur in hot weather, but frozen water supplies in cold weather can be equally as devastating.

Poisonous plant problems frequently present a unique set of circumstances associated with their ingestion. Overgrazing of pastures is probably the most significant factor affecting the ingestion of toxic plants. Other situations conducive to poisonous plant ingestion include lack of suitable forage in periods of drought and the incorporation of toxic forbs in hay or greenchop. Plants normally avoided because of poor palatability may become acceptable when frosted or sprayed with herbicide. Toxic plants also may be the first green plant available early in the spring, when livestock are hungry for anything green and succulent. Livestock trailed or transported for long distances without food or water and then suddenly introduced to new pasture may fail to avoid toxic plants and often will eat anything within immediate reach. In general, diagnosis of plant poisoning is based on availability, grazing evidence or presence in the hay, and the existence of plant parts in the rumen contents. Diagnostic lesions are usually lacking, and analytic methods for toxic components are severely limited.

Aconitum, species (monkshood) rarely are a cause of sudden death because of their limited availability. 237
Delphinium, species (larkspur), however, are closely related to monkshood and 238 are responsible for more cattle losses in the western United States than any other poisonous plant. Larkspur grows in dense stands in the mountainous West and is readily consumed, especially during an early stage of growth. Mature stands are less palatable and not as toxic. Cattle poisoned by larkspur often are found close to a stand, collapsed and bloated. Death from the cardiotoxic and neuromuscular blocking effects may occur within a few hours of ingestion. Sheep are less susceptible to larkspur and are seldom poisoned by it, partly because of their different grazing habits.[24] *Asclepias*, species (milkweed) contain either cardioactive glycosides or neurotoxic compounds.[25] The most toxic species reside in the western and southwestern United States. These plants are not very palatable but are somewhat less objectionable when dried. Livestock will graze them in a drought, but the biggest problem is contamination of hay or greenchop. Blue-green algae may cause sudden death in all classes of livestock within minutes of ingestion of toxins from certain neurotoxic species. Toxins from other hepatotoxic species may require 24 hours to induce death. Toxic blooms occur sporadically during certain environmental conditions of

late summer and fall. Diagnosis is usually based on a history of exposure to a concentrated bloom, but some laboratories perform chemical and bioassays.

Calycanthus, species (bubby bush) contain an alkaloid similar in structure and mechanism of action to strychnine. These species are of minor importance to the livestock industry in the Southeast and West but have induced death in cattle. Seeds and other plant parts may be identified in rumen contents. *Cicuta*, species (water hemlock) may induce violent convulsions and death within an hour. Intoxication is most common in early spring, when plants growing along waterways are easily uprooted and the tuberous parts are eaten. A single root system from a large plant can kill a cow. This is one of the most toxic plants in North America, and it has been responsible for the deaths of numerous livestock and humans. *Conium maculatum*, (poison hemlock) grows throughout the United States. Cattle are most sensitive, and sheep are relatively resistant. Poisoning is usually associated with heavily grazed pastures.

Cyanogenic glycosides are present at toxic concentrations in more than 250 plant genera, including *Sorghum*, *Prunus*, *Triglochin*, and *Linum*,. Ruminants are especially susceptible to these glycosides, as they possess the microorganism enzyme systems necessary for rapid liberation of hydrocyanic acid. Death may occur within 15 to 30 minutes of ingestion. Hyperoxygenated venous blood will be cherry red and slow to clot, and rumen contents may have the odor of almond extract. Samples of forage, blood, and rumen contents should be collected immediately, placed in airtight containers, and frozen for analysis. Negative results are often questionable because of the highly volatile nature of hydrogen cyanide. *Drymaria pachyphylla*, (inkweed) has caused sudden death in cattle in the southwestern United States. The differential diagnosis in this part of the country includes anthrax. Diagnosis is based on examination of rumen contents for plant parts.

Halogeton glomeratus, is a soluble oxalate-containing plant that grows best in disturbed soil along roadsides in the western intermountain states. *Sarcobatus vermiculata*, (greasewood) grows in semiarid regions of the West. It also contains toxic levels of soluble oxalate. Unadapted sheep are most frequently intoxicated with these plants, and death may occur within 9 to 11 hours of onset of intoxication. Sudden death results from hypocalcemia and inhibition of cellular respiration. Postmortem findings include hemorrhagic rumenitis, hydrothorax, ascites, and the presence of oxalate crystals in the kidney and rumen wall. *Kalmia*, species (laurel) are an occasional problem in winter or early spring, when they are the only conspicuously green plant available. Laurel grows in the wild in the eastern and western regions of the United States. Death may occur in 12 to 14 hours. Fragments of glossy, leathery leaves may be visible in rumen contents. *Kochia scoparia*, (summer cypress or burning bush) sporadically causes a thiamine-responsive polioencephalomalacia in cattle. *Laburnum anagyroides*, (golden chain tree) is a large ornamental shrub considered to be the second most poisonous plant in Great Britain. It also grows in much of the United States. The shrub contains quinolizidine alkaloids that may induce rapid death from respiratory failure. *Lupinus*, is a genus with about 200 species in North America. There is considerable seasonal variation in toxicity, with the toxic species presenting a problem when plants are very immature or when they have reached the seedpod stage. Acute intoxication and rapid death are likely only when large quantities of seeds are ingested within a short time. Toxic species cause more deaths in sheep than any other plant in Montana, Idaho, and Utah. Improperly cured hay and silage derived from *Melilotus*, species (white and yellow sweet clover) may cause sudden death in cattle when hemorrhage occurs in the cranial vault, pericardial sac, mediastinum, or thorax. Induction of the disease requires consumption of the moldy forage for several weeks to allow sufficient depletion of vitamin K—dependent clotting factors. *Nerium*, species (oleander) are widely cultivated in the South and West. Toxic in the green or dry state, these plants may border hay fields, and significant mortality of livestock may occur when dropped leaves or trimmings are incorporated into forage. Livestock often are poisoned when prunings are mixed with grass clippings and the bitter taste is disguised. Diagnosis is based on evidence of consumption and identification of plant parts in rumen contents.

The genus *Nicotiana*, contains toxic species of wild and cultivated tobacco. Poor palatability usually hinders consumption; however, opportunities for intoxication and death sometimes occur in areas of the West where forage is scarce and in parts of the country where tobacco is cultivated. Nitrate-accumulating plants include certain annuals, weeds, and cool-season crops and grasses. Notable examples include pigweed, lamb's-quarters, Sudan grass, and oat hay. Under the right environmental conditions most plants can accumulate toxic concentrations of nitrate. Plant-associated nitrate poisoning is a serious problem only in ruminants because of the nitrate-reducing ability of rumen microbes. Onset of nitrate intoxication is rapid, and death may result within 6 to 24 hours of rapid ingestion of a toxic dose. Diagnosis is based on a brownish cast to the viscera and blood, together with chemical analysis of serum, aqueous humor, and forage for nitrate concentration.

Acute bovine pulmonary emphysema is associated with an abrupt change from dry range forage to lush green pasture high in L-tryptophan concentration. Less commonly, the pulmonary toxins of *Perilla frutescens*, (perilla mint) can induce dyspnea and death in a few hours. Necropsy reveals incomplete collapse of lungs that are heavy and firm, with froth-filled airways. Histologic examination shows a proliferation of type II pneumocytes. *Phalaris*, species (canary grass) recently were reported to have caused sudden collapse and death of sheep in California.[26] Sheep that had been grazing a field containing canary grass were herded a short distance when six ewes collapsed and died. Bilaterally symmetric, greenish-grey discoloration was seen in the midbrain. The same gross discoloration also was seen in the renal cortex. Microscopic examination confirmed the presence of intracytoplasmic accumulation of this granular pigment. *Solanum*, species (nightshades) grow throughout the United States, especially in waste areas and overgrazed pastures. Rapid ingestion of large quantities of highly toxic fruit can result in coma and rapid death. *Taxus*, species (yew) poisoning in ruminants commonly results in sudden death. Poisoning is most likely to occur when ruminants are pastured adjacent to residential areas where yew is a common ornamental shrub. Diagnosis is based on evidence of exposure and identification of yew leaves in rumen contents. *Xanthium*, species (cocklebur) are most toxic at the cotyledonary stage of growth. These species may induce death in calves within 12 hours of onset of clinical intoxication. Hypoglycemia and centrilobular hepatic necrosis are consistent findings. *Zigadenus*, species (death camas) are of major importance to sheep grazing on western ranges. These plants begin growth in early spring, presenting a significant hazard at this time.[27]

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14.2.10 Miscellaneous Causes of Sudden Death in Horses

Allergic reactions capable of causing sudden death include rupture of warble fly larvae. Warble fly larvae are seldom able to penetrate equine skin, and the fully matured larvae either die or are killed when the horse is saddled or harnessed. Anaphylactic shock results, and pulmonary edema and foam in the airways are found on necropsy. Penicillin or other antibiotics may cause an anaphylactic reaction with a similar outcome.

Perinatal sudden death may occur in foals as a result of meningeal hemorrhage caused by birth trauma. The sudden onset of profuse, watery diarrhea and rapid development of hypovolemic shock characterize colitis-X. A severe necrotic typhlitis is seen at necropsy, with destruction of colonic and cecal mucosa. Diaphragmatic rupture and hernia are associated with violent exercise or trauma, with or without bowel herniation. Electrocution occurs when a horse chews through or comes into contact with an uninsulated hot wire while well grounded. Death is instantaneous, usually with negative necropsy findings. Lightning strike may reveal burning or singeing of skin, hair, or underlying tissue. GI maladies that may cause sudden death include volvulus, intussusception, torsion, incarceration, gastric rupture from grain overload, tympanites, and small intestine rupture from ascarid impaction.

Gunshot wounds may be another cause of sudden death that is surprisingly difficult to verify, as bullet retrieval is necessary to establish the diagnosis. Finding the bullet lodged in tissue is a time-consuming task at best. Heat or work stress is seen in horses in hot, poorly ventilated quarters or in poorly conditioned horses overworked in hot, humid weather. Collapse and coma are followed by death in a few hours. Necropsy reveals skeletal and cardiac muscle damage, GI ulceration, and renal necrosis. In pregnancy, unrecognized and untreated torsion of the gravid uterus may result in sudden death.

Exercise-induced respiratory tract injury may cause sudden death in well-conditioned horses.[28] Epistaxis and pulmonary hemorrhage occur at the peak of training, with most cases being of little concern. However, in fatal cases horses that die immediately after exercise often have subpleural hemorrhages in the caudal lung lobes, and rupture of these hematomas has resulted in extensive intrathoracic hemorrhage and sudden death. Rupture of lung tissue while exercising also may result in fatal hemorrhage.

Serum sickness (acute hepatitis) can be traced to administration of biologics of equine origin 50 to 90 days before the onset of clinical signs. Death may occur within 12 to 48 hours. The main lesion seen is liver necrosis with discoloration and accentuation of the lobular pattern on the cut surface. Fracture of the junction between the basisphenoid and basioccipital bone usually results from rearing over backward and striking the poll on the ground.

14.2.11 Miscellaneous Causes of Sudden Death in Ruminants

Fatal anaphylaxis occurs in sensitized animals after parenteral use of drugs or vaccines. This is most common with the penicillins and vaccines containing gram-negative bacteria or cell walls. Anaphylactic shock also may be an outcome of blood transfusion reactions. Immune-mediated hemolytic anemia (neonatal isoerythrolysis) from ingestion of colostrum-containing antibodies against a neonate's erythrocytes may induce sudden death if the specific antibody concentration is sufficiently high. A sudden death syndrome occurs in feeder cattle on high-concentrate diets. It usually occurs in warmer months and is limited to cattle fed high-concentrate rations for several weeks.[29] A malignant tumor that has been associated with sudden death is the thymoma, or thymic lymphosarcoma, seen most commonly in old goats. It appears as a large, pale, fleshy mass in the cranial mediastinum.[30]

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15 Chapter 15 The Peripartum Period

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15.1 THE PERIPARTUM EQUINE

15.1.1 ASSESSMENT OF THE MARE DURING LATE GESTATION

Wendy E. Vaala

Guy D. Lester

It has been estimated that between 25% and 40% of mares that are bred do not produce a live foal.[1–4] Many factors contribute to this poor outcome, including infertility, early fetal loss, abortion, stillbirth, and perinatal death.[2] During late gestation, two of the most important causes of reproductive loss are fetoplacental infection and complications of delivery including dystocia and perinatal asphyxia.[2,5] As mares age, their pregnancy and foaling rates decline and their foals experience higher morbidity and mortality rates and decreased athletic ability.[1,3]

A 1997 National Animal Health Monitoring System (NAHMS) study of 7320 foals estimated a mortality rate of 1.7% within the first 48 hours of a live birth.[6] This includes an estimate of euthanasia and spontaneous deaths. Sepsis, asphyxia, and dysmaturity, including prematurity and postmaturity syndromes, are the leading causes of neonatal foal mortality during the first two weeks of life. Despite dramatic advances in neonatal intensive care, many foals still die, not because their primary problem is untreatable, but because veterinary intervention was delayed, delivery was unattended, neonatal compromise was not recognized in a timely fashion, or critical care was unavailable or not economically feasible. Foals surviving severe peripartum illness often experience increased morbidity associated with chronic infections, suboptimal growth, or developmental orthopedic disease. Therefore the focus of equine neonatology has shifted from a strictly therapeutic approach to a preventative one. This new direction emphasizes assessment of fetoplacental well-being during late pregnancy. The three periparturient events that have the most devastating effect on neonatal survival are hypoxia, infection, and derangement of in utero development. These events can result in behavioral abnormalities, multiorgan system failure, neonatal death, abnormal fetal development, or premature delivery.

Many of the periparturient events associated with increased fetal and neonatal morbidity and mortality have been identified in the mare (Box 15-1). In human obstetrics, prepartum detection of placental dysfunction and fetal distress has become an important factor influencing the management of the last stages of pregnancy and the newborn infant. Following the lead in human perinatology, clinicians are developing biochemical and biophysical techniques for monitoring fetoplacental well-being in the pregnant mare.[7–10] Mares with high-risk pregnancies should be identified early, treated appropriately, and monitored carefully through the birth process. Accurate assessment of fetal well-being is complicated and difficult in the human being. Fetal monitoring in the equine species is less developed and is handicapped by the size of the dam and fetus.

Vaala has suggested that mares experiencing problem pregnancies be assigned to one of three categories: (1) mares with histories of abnormal pregnancies, deliveries, or newborn foals; (2) mares at risk for a problem with the current pregnancy because of systemic illness or reproductive abnormality; (3) mares that have no apparent risk factor but that experience an abnormal periparturient event.[10] A list of important perinatal risk factors is presented in Box 15-2. Ideally, mares with high-risk pregnancies should receive some type of late gestation fetal monitoring or at least be carefully watched during late gestation and attended at the delivery. Personnel attending the delivery of a high-risk foal should be trained in resuscitation techniques.

A variety of biochemical and biophysical parameters can be measured in the late-term mare or fetus. Measurement of maternal progestagen concentrations in plasma may provide an indicator of fetal well-being. Maternal progestagen concentrations are relatively stable between days 150 and 315 of gestation, rising sharply over the remainder of the pregnancy before a large fall in the last 1 to 2 days before parturition. Progestagens are synthesized by the fetus and by the uteroplacental tissues. Two abnormal progestagen patterns have been described.[11–14] In acute maternal illnesses, such as colic or torsion of the uterus, the progestagen concentration declines hours to days before abortion. In these mares progestagen concentration may fall to less than 2 ng/mL.[14] In chronic disease states, such as laminitis or placentitis, there is a premature rise in the plasma progestagen concentration that can persist for weeks before abortion or premature delivery.[11] It has been suggested that a premature increase in maternal progestagens could reflect hastened or precocious fetal maturation. Removal of the stressful event can lead to normalization in progestagen concentrations and the subsequent delivery of a normal-term foal. Progesterone radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) can be used to quantitate progestagens. Measurement of progestagens may be indicated to determine the need for progestin supplementation.[15]

An ELISA has been developed to measure equine fetal protein, and elevated concentrations were associated with twinning, placentitis, premature placental separation, uterine trauma, and fetal death.[10,16] Additional studies are required before this test can be applied accurately in a clinical setting. Another reproductive hormone that holds promise as a marker of fetoplacental well-being and periparturient complications in the mare is relaxin. The placenta is the primary source of relaxin in horses.[17] In healthy pregnant mares relaxin concentrations increase from about day 80 to a peak of 80 to 100 ng/mL at day 175, which persists until birth.[18,19] In mares with problematic pregnancies, low relaxin levels during late pregnancy have been indicative of placental insufficiency associated with a variety of causes including fescue toxicosis,[20] oligohydramnios, placentitis, and pituitary neoplasia.[21]

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15.1.1.1

Box 15-1 Common Causes of Abortion, Stillbirth, and Perinatal Death in Horses

15.1.1.1.1

INFECTIOUS PROBLEMS (IN ORDER OF FREQUENCY)

Fetoplacental infection

Bacterial infections

Viral infections

Fungal infections

Unidentified causes

15.1.1.1.2 NONINFECTIOUS PROBLEMS (IN ORDER OF FREQUENCY)

Neonatal asphyxia not associated with dystocia

Neonatal asphyxia associated with dystocia

Placental edema

Premature placental separation

Twin pregnancies

Contracted foal syndrome

Other congenital malformations

Umbilical cord abnormalities

Placental villous atrophy

From Giles RC, Donahue JM, Hong CB, et al: Causes of abortion, stillbirth, and perinatal death in horses: 3527 cases (1986-1991), *J Am Vet Med Assoc* 203:1170, 1993.

15.1.1.2 Box 15-2 Conditions Associated with the High-Risk Foal

15.1.1.2.1 MATERNAL CONDITIONS

15.1.1.2.1.1 Past History

Foals with neonatal isoerythrolysis, neonatal maladjustment syndrome, congenital malformations

Prematurely born, postterm foals that appear premature, or asphyxiated foals

Dystocia or premature placental separation

Foal rejection

Recent exposure to infectious diseases associated with abortion and stillbirths, such as equine herpesvirus, viral arteritis, *Leptospira* species

15.1.1.2.1.2 Systemic Problems

Fever

Anemia or hypoproteinemia

Endotoxemia

Gastrointestinal crisis, such as large bowel torsion

Malnutrition

Severe systemic infection

Laminitis

Prolonged recumbency from a variety of neurologic or musculoskeletal problems

Excessive medication administration

Prolonged transport before parturition

15.1.1.2.1.3 Reproductive, Mammary Gland, or Localized Problems

Severe endometrial fibrosis

Hydrops allantois or amnii

Purulent vaginal discharge

Prepubic tendon rupture

Pelvic injuries

Agalactia, such as from grazing on fescue pastures

Failure to produce good-quality colostrum

Premature lactation

15.1.1.2.2 ABNORMALITIES OF LABOR OR DELIVERY IN CURRENT PREGNANCY

Premature parturition

Abnormally long gestation

Prolonged labor

Induction of labor

Dystocia

Early umbilical cord rupture, umbilical cord abnormality

Cesarean section

Premature placental separation

15.1.1.2.3 NEONATAL ABNORMALITIES

Meconium-stained fluid or neonate

Placental disease—e.g., placentitis, villous atrophy, edema

Twins

Orphan

Delay in or lack of intake of colostrum

Dysmaturity or prematurity

Exposure to infectious diseases, such as influenza

Trauma (birth, predators, mother)

Adverse environmental conditions

Failure to be up and nursing by 2 to 3 hours of age

Congenital abnormalities

Weakness, poor appetite

Several studies have demonstrated that ultrasound-guided transabdominal amniocentesis and allantocentesis can be performed relatively safely in the late-gestation mare as long as the procedure is performed aseptically and multiple attempts are not made.[10,22] However, the clinical usefulness of fetal fluid analysis in the horse remains to be determined. Studies attempting to relate the phospholipid profile in amniotic fluid with equine fetal lung maturation have been inconclusive to date.[10,22,23] Transabdominal-guided ultrasound amniocentesis has been used to detect experimentally induced equine herpesvirus 1 (EHV-1) fetal infection in utero.[24] This technique holds promise as a diagnostic aid to detect specific fetal diseases and as a potential therapeutic avenue to deliver medication in utero.

Electrolyte concentrations in prepartum mammary secretions may be monitored to predict impending parturition in the mare. As parturition approaches, the mammary concentration of sodium decreases and concentrations of potassium and calcium increase. An elevation in calcium concentration to over 40 mg/dL (10 mmol/L) is considered the most reliable indicator of readiness for birth and may be used to help determine whether elective induction or cesarean section should be performed. The increase in calcium occurs over the last 72 hours of gestation.[25,26] Test strips are commercially available to measure calcium and magnesium concentrations in a field setting (Predict-a-Foal test, Animal Health Care Products, Vernon, CA; FoalWatch kit, Chemetrics, Calverton, VA). The mammary concentration of potassium increases and the mammary sodium concentration decreases over the final 7 days of the gestational period. The mammary concentration of potassium typically exceeds that of sodium between 1 and 5 days before foaling. This has been used by some as a predictor of birth, although a recent study concluded that the use of mammary electrolyte concentrations was not reliable because of individual variability both in raw concentrations and in percent changes.[27]

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An arbitrary scoring system using calcium, sodium, and potassium concentration in the mammary secretions to assess fetal maturity has been described.[26] False-positive results—that is, values that inaccurately predict imminent foaling—have been associated with vaginal discharge, placentitis, and premature lactation. False-negative results occur commonly in mares with systemic illness or in animals that have undergone general anesthesia. In many mares the changes in the electrolytes occur only within hours of delivery, so if monitoring is

not performed frequently, the changes will be missed.[10,27,28] The decision on whether or not to induce parturition in a mare should not be based on the results of this type of testing alone.

Fetal heart rate (FHR) monitoring is routinely used in the human fetus to detect fetal distress, particularly hypoxia, during late gestation and labor and delivery. Doppler ultrasound is the most common technique used for FHR monitoring; this technology has been adapted for use in the mare.[29] First the fetal heart is located using an ultrasound transducer, then the Doppler transducer is placed on the mare's abdominal wall directly over the fetal heart. Fetal movement is detected by a pressure transducer or by a hand placed on the mare's abdomen. Continuous FHR monitoring for at least 10 minutes is preferred to better detect abnormalities in heart rate and rhythm. Use of M-mode echocardiography makes it easier to obtain an FHR measurement because of the rapid motion of the normal equine fetus. Heart rate is normally regular and decreases from greater than 120 beats per minute (bpm) before day 160 of gestation to between 60 and 90 in late gestation.[8,29–31] An average of 10 heart rate accelerations (25 to 40 bpm) was observed in a 10-minute period; 95% of these were associated with fetal movement.[29] Cardiac accelerations in response to fetal movement are an indicator of fetal well-being. Cardiac rhythm should be regular. Persistent bradycardia is associated with fetal distress and is mediated by a vagal response to hypoxemia. Severe tachycardia and arrhythmias have been associated with impending fetal demise. Although persistent fetal tachycardia and bradycardia suggest fetal compromise, normal heart rate alone does not guarantee that the fetus is healthy. Prolonged periods of fetal inactivity in the absence of maternal sedation are also suggestive of fetal compromise.

A fetal electrocardiogram (ECG) may also be used to assess FHR and fetal heart rhythm after day 150 of gestation.[30,31] The procedure is relatively easy to perform. The left arm electrode is placed on the dorsal midline of the mare at the lumbar region, and the left leg electrode is placed 15 to 20 cm cranial to the mare's udder on the ventral midline. The hair should be clipped, and ample gel or alcohol should be placed to ensure good contact of the electrodes. Poor fetal signals may result from poor electrode contact or placement, fetal movement, or electrical interference.[10]

Transabdominal ultrasonography allows noninvasive evaluation of the intrauterine environment and fetal well-being. A biophysical profile (BPP) using five parameters is used in women to evaluate fetal distress late in pregnancy.[32,33] The BPP evaluates the following: fetal tone, fetal movement, fetal breathing, FHR reactivity (i.e., increased FHR during fetal activity), and amniotic fluid volume. The BPP was predicated on the theory that during asphyxia the most complex activity, FHR reactivity, disappears first, followed sequentially by fetal breathing, fetal movements, and fetal tone. Decreases in fetal fluids are associated with chronic intrauterine stress and hypoxia, dysmaturity, and placental insufficiency.[34]

Transabdominal ultrasonography can be used in the mare to evaluate the equine fetus after day 90 when the gravid uterus contacts the ventral abdominal wall. This technique is used more commonly during the second and third trimesters. Recent studies have focused on the development of a modified BPP using FHR reactivity, fetal activity, fetal breathing movements, qualitative and quantitative fetal fluid assessment, evaluation of placental integrity, and measurement of fetal size. Transducers with lower frequencies (2 to 4 MHz) are required because of the deep tissue penetration needed. The mare's ventral midline must be cleaned and clipped from the level of the umbilicus caudally to the mammary gland, and a viscous coupling gel applied. Minimal maternal restraint is usually required. Chemical sedation should be avoided because drugs such as xylazine and detomidine induce fetal bradycardia and retard fetal movement.

In the pregnant mare, transabdominal ultrasonography has been used to detect twins, document fetal position, estimate fetal size using fetal aortic diameter, evaluate fetal activity, evaluate placental integrity, determine fetal

fluid clarity and volume, and monitor FHR and fetal breathing. After 9 months of gestation most fetuses are in an anterior presentation and are unlikely to change that presentation before delivery.[35] The mean fetal thoracic aortic diameter averages between 2.2 and 2.5 cm in horse fetuses.[8] Fetal activity increases with advancing gestational age, and FHR decreases. During late gestation the equine fetus should demonstrate good tone and moderate activity with only brief episodes of inactivity (<20 min). During the last month of gestation the FHR averages between 60 and 90 bpm with transient bouts of tachycardia (25 to 40 bpm above baseline) observed during or immediately after fetal activity. Fetal breathing is characterized by excursion of the diaphragm between the thorax and the abdomen, with accompanying ribcage expansion. Regular breathing movements are observed intermittently in most late-term fetuses. It is difficult to differentiate fetal from maternal breathing movements. The maximum ventral fetal fluid pocket depths average 8 cm for amniotic fluid and 13 cm for allantoic fluid.[8] Excessive fetal fluid accumulation is observed in cases of hydrops. Markedly decreased amounts of fetal fluids have been associated with placental dysfunction and the birth of a dysmature, hypoxic foal. As gestation advances, fetal fluids increase in turbidity. Sudden increases in turbidity may be associated with meconium passage, hemorrhage, or inflammatory debris. Average uteroplacental thickness viewed transabdominally ranges between 8 and 15 mm.[8] Thicker uteroplacental units may indicate placental edema, placental separation, or placentitis. Areas of separation between the uterus and chorion appear as black anechoic areas.

Transabdominal real-time ultrasonography can provide both structural and functional information about the health and environment of the fetus. Because of the depth of penetration required, 2- to 4-MHz transducers should be used. As in other procedures involving ultrasonography, familiarity with the normal appearance of the placenta and fetus is essential to detect abnormalities. Details on how to perform the evaluation can be found in other texts.[29,36–38] In the mare this procedure has been used in late gestation to determine fetal position, estimate fetal size, evaluate the placenta and fetal fluids, detect premature placental separation, and assess fetal movement and viability.[10,37] Overall, fetal activity tends to increase with advancing gestational age; periods of inactivity longer than 15 minutes may indicate the need for further evaluation. A BPP has been developed that uses several parameters to establish an idea of the size and overall health of the equine fetus.[9,29,39] The parameters include fetal weight, as estimated by the fetal aortic diameter (mean 2.1 cm at 300 days' gestation to 2.7 cm at term), heart rate, movement, uteroplacental thickness (mean 1.26 ± 0.33 cm), qualitative allantoic fluid appearance, and allantoic volume estimation. Additional studies are needed to establish the validity of this profile in predicting fetal health or compromise in a larger group of mares.

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15.1.2 EFFECTS OF PLACENTAL INSUFFICIENCY

The effects of uteroplacental vascular insufficiency on the newborn depend on the severity of placental compromise and the severity and duration of prenatal and perinatal asphyxia. Conditions associated with chronic asphyxia in the large animal fetus include chronic placentitis, villous atrophy, twin and postterm pregnancies, ingestion of endophyte-infected fescue grass by the pregnant mare,[40] and ingestion of ponderosa pine by pregnant cattle.[41]

If decreased uteroplacental blood flow is long-standing, growth is concomitantly inhibited in the fetus. The pattern of growth retardation associated with chronic placental insufficiency is usually asymmetric. This type of growth retardation is characterized by visceral wasting with relative preservation of fetal length and head circumference. Affected human infants are expected to be long and thin, with loss of subcutaneous fat and a large head relative to the body size. The same is probably true in the large animal neonate. It has long been recognized that twin equine neonates and other abnormally small foals tend to have heads that are disproportionately large for their small, wasted bodies.[42]

In placental vascular insufficiency the fetus has the ability to avoid overgrowing its nutrient supply and to maximize organ growth. Under metabolic stress there is a fetal antiinsulin response, with loss of fat and glycogen stores and muscle mass. Associated with the decrease in uteroplacental blood flow is an increase in uterine and fetal vascular resistance, and redistribution of cardiac output, with a greater percentage of blood flow going to organs such as the brain and heart. Unless uteroplacental insufficiency is very severe, brain growth continues at a relatively normal rate. In the human fetus the redistribution of cardiac output also results in decreased blood flow to the lung and kidney and decreased production of fetal urine and lung liquid, two major components of amniotic fluid. A decrease in amniotic fluid volume is therefore associated with chronic fetal asphyxia. The regulation of these adaptations is not completely understood, but corticosteroids, catecholamines, and vasopressin, among others, play a role.[43,44]

It is thought that repeated episodes of hypoxemia during gestation slowly deplete cardiac glycogen stores and impair the ability of the heart to effectively pump blood during subsequent hypoxemic episodes, such as during labor. The newborn with depleted glycogen stores may also be at increased risk of developing hypoglycemia and hypothermia. Meconium aspiration and persistent arterial hypertension in the newborn period are secondary to chronic fetal hypoxia. Immature skeletal ossification, particularly of the carpal and tarsal bones, has also been associated with growth retardation in the foal.[42]

There are certain advantages associated with fetal adaptation to chronic placental insufficiency. Growth-retarded premature human infants have a lower incidence of hyaline membrane disease than babies of the same gestational age who are appropriately sized.[45] Presumably, fetal hormones, such as the corticosteroids and catecholamines that are released in response to nutrient deprivation, stimulate the early maturation of the lung and surfactant system. Accelerated neurologic maturity has also been documented, along with accelerated pulmonary maturity.[46] Therefore the fetus that has been chronically exposed to an adverse in utero environment may be in some ways more tolerant of premature delivery and independent life outside the uterus than the “normal” fetus that is abruptly displaced through induction of labor or cesarean section. The low-birthweight fetus therefore represents a successful adaptation to a nutrient-deprived environment. Its smaller size, decreased metabolic needs, and early organ maturation actually place it at lower risk for hypoxic injury at birth and aid its transition to independent life after delivery.[44] Further discussion of the characteristics, treatment, and prognosis of growth-retarded premature foals may be found in Chapter 19.

Premature lactation, purulent vaginal discharge, previous history of growth-retarded foals, advanced maternal age, and prolonged gestation are problems that should raise the suspicion of chronic uteroplacental insufficiency. The labor and delivery should be attended to minimize the chances of acute asphyxia. The newborn animal should be examined for evidence of growth retardation, infection (particularly in utero acquired pneumonia secondary to placentitis), and metabolic and acid-base derangements. Ample colostrum should be administered, and body temperature and blood glucose should be monitored closely.

One author has suggested that intrauterine growth retardation is unlikely to pose any substantial additional threat to the neurodevelopment of premature human infants unless it is accompanied by chromosome abnormalities, severe perinatal asphyxia, or hypoglycemia, or unless growth retardation is very severe.[47] Human infants that display characteristics of asymmetric growth retardation commonly “catch up” by late infancy or early childhood. Similar observations have been made in the foal. Many mildly to moderately growth-retarded newborn foals have also done well after discharge from the hospital and have grown to a normal size. Problems secondary to an immature musculoskeletal system, such as angular limb deformities, have been the most

common complications noted in these individuals, but careful orthopedic management can result in a successful outcome.

15.1.3 PLACENTITIS

Placentitis is a common cause of reproductive losses in horses in the United States. During the 1998-1999 foaling season in Kentucky, 24.7% of cases of aborted, stillborn, and premature foals were associated with placentitis.[48] The most common cause of placentitis is ascending infection from the lower urogenital tract via a relaxing cervix. A far less common route of infection is the hematogenous avenue, resulting in a diffuse or multifocal placentitis. Most cases of placentitis are the result of bacterial infection caused by typical equine pathogens including *Streptococcus equi* subsp. *zooepidemicus, Enterobacter agglomerans, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. In Kentucky and some other regions a slightly different form of placentitis has been recognized and is characterized by focally extensive placentitis located predominantly at the base of the placental horns at the junction of the horns and the body of the placenta. The affected area is covered with thick, tenacious, brown mucoid exudate, and the underlying chorionic villi are necrotic and absent or reduced in size. This form is associated with infection with a group of gram-positive, branching, filamentous *Nocardioform*-like organisms.[48]

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Clinical signs of placentitis include vaginal discharge that may be evident on the mare's vulva, tail, or inner thighs, premature udder development, and precocious lactation. Premature udder development is the result of placental compromise, fetal stress, a precocious increase in maternal progestagen concentration, and enhanced fetal adrenocortical activity. Despite even voluminous vaginal discharge, most mares with placentitis do not become febrile and do maintain a normal appetite. The dam's hemogram and fibrinogen concentration usually remain within normal limits. Transrectal ultrasound can be used to identify placental separation and uteroplacental thickening of the caudal uterine body. This region is most commonly involved in mares with ascending placental infection. Measurement of the combined thickness of the uterus and placenta (CTUP) is established. This measurement increases from approximately 6 mm at 7 months of gestation to 10 to 12 mm at term.[49,50] A measurement greater than 12 mm at 11 months or greater than 15 mm at 12 months is consistent with placental pathology.[49] Measurement of CTUP alone can be misleading, and a recent recommendation involved monitoring of the CTUP by ultrasound along with determination of the maternal progestagen concentrations to give a more accurate assessment of fetal well-being.[11] Transabdominal ultrasonography can be used to evaluate other areas of the placenta to detect loss of placental integrity or increased uteroplacental thickening. Measured using transabdominal ultrasound, the uteroplacental unit should be <16 mm during late gestation. Other signs suggestive of placentitis include increased fetal fluid echogenicity, which may be the result of hemorrhage, purulent exudate of the brown mucoid material associated with *Nocardioform* placentitis.[51] If placentitis is severe enough to alter placental function, reduced fetal movement, loss of heart rate variability, and absolute fetal bradycardia indicate fetal compromise.

Samples of vaginal discharge should be cultured, and Gram stains performed. The goal of maternal therapy is to treat the placental infection and maintain the pregnancy, provided there is no evidence of severe fetal distress or demise. In many cases, because the infection is of long duration, the fetus has been chronically stressed and therefore is relatively mature for its gestational age and better prepared to tolerate premature birth. If placentitis is suspected, after delivery the foal should be considered a high-risk individual. Commonly encountered problems in the newborn foal that was exposed to placentitis are pneumonia, uveitis, growth retardation, incompletely ossified bones, and, sometimes, systemic sepsis.

15.1.4 MANAGEMENT OF THE HIGH-RISK LATE-GESTATION MARE

Each mare should receive a complete physical examination, and a complete foaling history should be obtained. She should be evaluated regularly for clinical signs of impending parturition (sacroiliac ligament and perineal relaxation, mammary development, and mammary secretion electrolyte concentration). The reproductive tract may be evaluated by rectal palpation, and transabdominal ultrasonography may be performed at regular intervals to detect changes in the fetus, fetal fluids, or placenta. Prolonged periods of starvation are best avoided to prevent maternal hypoglycemia.[10] Estimation of progestin concentrations in the maternal circulation, using a commercial progesterone assay, is recommended.[11]

When treating the pregnant mare for any medical or surgical condition, there are two patients to consider: the dam and the fetus. Any illness or disease that affects the mare's cardiovascular system has the potential to affect placental perfusion and the integrity of the fetoplacental unit. Hypotension, endotoxemia, and hypoxemia are examples of conditions that can alter uteroplacental blood flow and jeopardize the pregnancy. Diseases that stimulate prostaglandin production have the potential to initiate labor and delivery. Illnesses that produce prolonged periods of anorexia in the late-term mare can also lead to premature delivery. The effect of various drugs on the placenta and fetus should be considered when treating the pregnant mare. If delivery is not imminent, then many drugs will pass through the placental and fetal circulation and be cleared by the maternal liver and kidneys. Because of the epitheliochorial nature of the mare's placenta, some drugs will not cross the placental barrier at all. If drugs are administered to the mare and the fetus is delivered shortly thereafter, then the neonate must rely on its renal and hepatic function to process, degrade, and excrete those drugs. In most instances, as long as fetal well being and placental integrity are closely monitored, the goal of most therapies is to treat the maternal condition and maintain the pregnancy as long as possible to achieve an acceptable degree of fetal maturation. Early data derived from late pregnant mares indicated that penicillin and gentamicin did not readily cross the fetal membranes.[52,53] However, recent studies using microdialysis probes inserted into the allantoic fluid of normal mares reported therapeutic concentrations of penicillin and gentamicin in the allantoic fluid after 22,000 IU/kg of potassium penicillin G (intravenous [IV] administration q6h) and 6.6 mg/kg gentamicin (IV q24h).[54] Studies in two mares with experimentally induced bacterial placentitis again confirmed passage of both drugs across the placenta. The combination of trimethoprim-sulfadiazine (30 mg/kg orally [PO] bid) and the phosphodiesterase inhibitor pentoxifylline (8.5 mg/kg PO bid) also readily crosses the fetal membranes in both healthy mares and in animals with experimental placentitis.[53,55] In many cases medical treatment of the placental infection and prolongation of pregnancy is associated with a good outcome. Maternal treatment includes systemic antibiotics, flunixin meglumine, and altrenogest.[10] Because of the usual presence of mixed gram-positive and gram-negative placental and fetal infections, a broad-spectrum antibiotic that reaches therapeutic levels in the fetus and fetal fluids should be selected. Therapeutic options include penicillin and gentamicin, trimethoprim-sulfonamide, and ceftiofur. Low doses of flunixin can be administered to decrease inflammation and prevent prostaglandin-mediated induction of delivery. Regumate (altrenogest) (10 to 20 mL PO q24h) is given to help maintain the pregnancy. If there are large areas of placental thickening, IV dimethyl sulfoxide (DMSO) (0.5 to 1 g/kg) can be administered to decrease placental edema. Pentoxifylline has also been administered in attempts to improve placental perfusion.

If premature delivery appears unavoidable, then one or two doses of maternal steroids can be used with the hope of stimulating and accelerating fetal lung maturation through enhanced surfactant production. In the high-risk mare, it is very important that the delivery be attended by knowledgeable personnel and that all supplies, drugs, and equipment required for diagnosing and correcting a dystocia and stabilizing the mare and foal be organized and close at hand. A spontaneous, vaginal delivery is generally preferred in the high-risk mare, because of both

the profound problems associated with the untimely delivery of a premature foal and the complications sometimes associated with induced labor or cesarean section.[56,57] (See Chapter 19, Prematurity.) There are instances, however, when an induced birth or cesarean section is indicated or preferred.

Induction of parturition should be considered with the following:

- Severe fetal distress noted on prenatal assessment
- Evidence of premature placental separation or a history of premature placental separation associated with dead or asphyxiated foals
- Hydrops allantois and/or amnion
- Unproductive stage I labor
- Uterine inertia
- Impending prepubic tendon rupture
- Life-threatening maternal illness

Indications for cesarean section may include the following:

- Pelvic injury or abnormality resulting in obstruction of the birth canal
- Gastrointestinal crisis requiring surgery
- Severe dystocia
- Insufficient, thickened placenta associated with fescue toxicity in the mare
- Catastrophic and terminal illness or injury in the mare, such as gut rupture or fractured limbs

If induction of parturition or cesarean section is elected, every effort should be made to ensure that the fetus is mature and is ready to be born; the usual result of induction at an inappropriate time is a nonviable newborn. Three essential criteria are a gestation of longer than 330 days, good-quality colostrum in the udder, and softening of the cervix.[56] The scheduling needs of the veterinarian or owner should never be the only criterion used for determining the timing of delivery. A slow continuous oxytocin infusion administered at a rate of 1 unit/minute usually results in delivery within 20 to 40 minutes.[10] Alternatively, multiple IV or intramuscular injections of 10 to 20 units of oxytocin every 10 minutes have been recommended.[56,58] Other investigators have shown that smaller IV doses of oxytocin (2.5 IU administered every 15 to 20 minutes until rupture of the chorioallantois or a total of 20 IU of oxytocin has been administered) is an effective, and perhaps more physiologic, method of induction.[59]

Induction of parturition in the mare has been associated with more violent, painful contractions than spontaneous labor and a higher incidence of premature placental separation and neonatal asphyxiation. Cesarean section also predisposes to neonatal peripartum asphyxia. Maternal hypotension secondary to general anesthesia and the weight of the maternal abdominal contents on the aorta and vena cava may both compromise uteroplacental circulation. For further details concerning anesthesia of the late-term mare, the reader is referred to other texts.[60,61] The management of a mare with hydrops amnion was recently described.[62] Abdominal support was used

along with nonsteroidal antiinflammatory drugs and altrenogest to maintain the pregnancy up until day 321, when spontaneous delivery occurred. The delivery was complicated by uterine inertia, maternal postpartum hypovolemic shock, and cardiac arrhythmias, but both mare and foal survived.

15.2 THE PERIPARTUM RUMINANT

John K. House

The peripartum period is a high-risk period for the fetus and dam. Approximately 5% to 10% of the annual calf crop and 15% to 20% of the annual lamb crop in the United States dies before weaning.[63,64] Between 50% and 70% of neonatal mortality occurs in the first 3 days of life, with dystocia, starvation, and hypothermia responsible for 50% to 60% of these losses.[64,65]

Reduced fetal viability often reflects mismanagement of maternal nutrition and/or the maternal environment during the last trimester of pregnancy and/or the prepartum and peripartum periods. Investigation of perinatal morbidity and mortality should begin with assessment of maternal management. Some of the more common causes of stillbirth and perinatal mortality are listed in Box 15-3.

Forty percent to 60% of stillbirths are associated with dystocia. Calves that survive dystocia are more likely to have edema of the head and tongue, making suckling difficult. They are also weak and exhausted and likely to be recumbent for a longer period of time and expose themselves to more fecal pathogens.[66] Dystocia affects the uptake of immunoglobulins by the calf, and calves that survive dystocia are more likely to become sick in the first 45 days of life.[67] Maternal variables correlated with dystocia and consequently calf mortality at birth include parity and conformation. Dystocia and stillbirths in heifers are most commonly secondary to fetopelvic incompatibility. Fetopelvic incompatibility accounts for a lower proportion of dystocias in multiparous cows, but weak labor secondary to hypocalcemia, uterine torsion, and incomplete cervical dilation are more common in older cows.[68] In a large study of Holstein calving records, 8.3% of calves born to heifers were stillborn compared with 3.6% of calves born to multiparous cows.[69] Dam pelvic diameter is an important determinant of dystocia for heifers.[70] Pelvic measurements can be used to identify abnormally small or abnormally shaped pelvises. Large frame size of the dam correlates with a reduced risk of dystocia; however, continued selection for large frame size tends to select for larger birthweight and dimensions of calves.[71] Age at first calving for heifers is not correlated with risk of dystocia as long as heifers are fed and managed to achieve appropriate growth and stature before calving.[72–74] The risk of dystocia in heifers is increased by poor nutrition in the last trimester.[75] Appropriate nutrition and management of replacement heifers to achieve appropriate size and stature at parturition reduces maternal and neonatal losses by reducing the incidence of dystocias. Maternal consequences associated with calving difficulty and delivery of a stillborn calf include decreased milk production and reduced reproductive efficiency. Reductions in milk production ranging from 100 to 400 kg have been reported to be associated with the birth of a stillborn calf. If the stillborn calf is delivered by cesarean section, the reduction in milk yield is in the order of 300 to 500 kg.[69] Delivery of a stillborn calf is also associated with depressed conception rates, increased services per conception, and delayed conception.

Use of calving ease bulls over primiparous cows helps to reduce the incidence of dystocia and subsequently mortality during parturition. The heritability of calving ease is relatively low; estimates of maternal calving ease range from 0.03 to 0.24,[68,76,77] and paternal heritability is approximately 0.147. Despite the relatively low heritability of calving ease, selection for calving ease should not adversely affect other production parameters in dairy cattle, as the genetic correlation between calving ease and other dairy production traits are generally close to

0.[68] Calving ease evaluations are intended to increase the use of artificial insemination (AI) for heifers. To facilitate sire selection most breed associations provide guidelines regarding calving ease or expected progeny difference for calf birthweights. An example of such a scheme is the calving ease and reliability values assigned to AI Holstein bulls. In this system the calving ease score is the expected percentage of difficult births predicted for calves delivered by primiparous cows.[78] The reliability score provides an indication as to the number of births that were considered in deriving the calving ease score. The higher the reliability score, the larger the number of observations the calving ease score is based on and the more likely it is that the calving ease prediction will accurately reflect the outcome.

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15.2.1

Box 15-3 Common Causes of Stillbirth and Perinatal Death in Ruminants[63,64,124,125]

Dystocia

Cold stress

Pneumonia (lambs)

Nutrition

Energy deficiency

Protein deficiency

Pregnancy toxemia

Copper excess or deficiency

Iron excess

Iodine excess or deficiency

Selenium deficiency

Vitamin A deficiency

15.2.1.1

INFECTIOUS

Viruses

Infectious bovine rhinotracheitis virus

Bovine virus diarrhea

Border disease

Bluetongue

Akabane virus

Cache Valley Virus

Bacteria

Hemophilus somnus

Brucella abortus

Leptospira species

Clostridium perfringens types C and D

Streptococcus species

Campylobacter species

Listeria monocytogenes

Yersinia pseudotuberculosis

Histophilus ovis

Brucella ovis

Campylobacter fetus var *fetus*

Protozoa

Neospora

Toxoplasma gondii

Tritrichomonas foetus

Fungus

Aspergillus species

Rickettsia

Chlamydia species

Coxiella burnetii

15.2.1.2 TRAUMA

Obstetric trauma

Castration, tail docking

15.2.1.3 TOXINS

Plant toxins

Monterey pine *(Pinus radiata)*

Perennial broomweed *(Gutierrezia microcephala)*

Locoweed *(Astragalus lentiginosis)*

Lupines *(Lupinus sericeus*and *Lupinus caudatus)*

Poison hemlock *(Conium maculatum)*

Chemical toxins

Nitrate

15.2.1.4 CONGENITAL

Epitheliogenesis imperfecta

Cardiac abnormalities (ventricular septal defects, tetralogy of Fallot)

Internal hydrocephalus

Cerebellar hypoplasia

Arthrogryposis or cleft palate

β-Mannosidosis

Spider lamb syndrome

α-Mannosidosis

Bovine citrullinemia

Bovine maple syrup urine disease

Management variables that influence the risk of dystocia and perinatal mortality include stocking density of preparturient cows, timing of calving, and cow grouping. In a study of 123 beef herds the dystocia rate was highest for cows housed in a barn and decreased progressively through barn-and-yard, barn-and-pasture, and pasture-only calving location categories.[79] The most common cause of dystocia in penned heifers was vulval constriction, whereas dystocias in paddocked heifers were most commonly associated with malpresentations.[80] Calving beef heifers 6 weeks before cows has been recommended to allow the heifers longer to recover and conceive after calving than cows.[81] In a herd level comparative study this practice was associated with a higher incidence of dystocia and stillborn calves.[79] Presumably because of better nutritional management, heifer dystocia rate is reduced the longer heifers are maintained as a separate group from cows before calving.[79]

Fetal variables that influence the risk of mortality include sex, size, and number. Calves born to primiparous cows, twins, and bull calves are more likely to die at birth than calves born from multiparous cows, single calves, and heifer calves.[82,83] Low and high birthweight calves are at greater risk of mortality than average birthweight calves.

[82] Small calves experience greatest mortality at parities greater than one, and large calves at first parity.[72] Fetal viability may be compromised in utero by a number of infectious agents. Common infectious agents associated with abortion and or birth of weak calves are listed in Box 15-3. Manifestations of disease in the newborn are dependent on the time of exposure to the infectious agent.

Environmental stress before or around the time of parturition can compromise the fetus or neonate. Heat stress affects fetal viability by impeding calf growth in the last trimester of pregnancy[84] and by depressing colostral quality[85] and immunoglobulin transfer.[86] Uterine blood flow and placental mass are reduced and endocrine profiles altered when cattle are heat stressed during the last trimester of pregnancy. Heat stress during the last 3 weeks of pregnancy lowers dry matter intake, contributing to a negative energy balance at this time, promoting mobilization of body fat and ketogenesis. Transfer of immunoglobulins to colostrum is impaired, and the concentration of protein, casein, lactalbumin, fat, and lactose in colostrum is reduced.[85] Cold, windy, and wet conditions also adversely affect calf survival. The magnitude of the effect of climate on neonatal survival depends on the age of the dam, sex and size of the calf, and incidence of dystocia in the herd.[82] Cold stress sufficient to cause hypothermia in calves leads to subcutaneous hemorrhages and delayed absorption of colostral immunoglobulins.[87]

Maintenance of adequate nutrition throughout pregnancy is essential to provide for the growing fetus and to maintain a healthy dam capable of delivering and nursing the fetus. Pregnancy toxemia, hypocalcemia, protein energy malnutrition, micronutrient deficiencies, and obesity may all impair the health of the fetus directly, or indirectly by affecting the health or capacity of the dam to deliver the fetus. Protein energy malnutrition and copper deficiency have been associated with impaired fertility, weak calves, and high calf mortality.[88]

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15.2.2 Assessment of Fetal Viability

Fetal viability is rarely evaluated during the prepartum period in production animals, but it is a serious consideration when the prepartum dam is diseased or debilitated. Assessment of fetal viability is diagnostically challenging, but a number of methods are available to evaluate the fetus and fetal environment. During the physical examination of cattle, uterine blood flow, uterine tone, and presence of a vaginal discharge may be evaluated via rectal palpation and a vaginal speculum examination. Reduced fremitus in the uterine arteries and increased uterine tone may be appreciated by rectal palpation after fetal death. Abdominal ultrasound is useful for examining the uterus, placenta, and fetuses of small ruminants. The uterus and placenta of cattle can be examined by transrectal ultrasound, but examination of the fetal calf via transrectal or transabdominal ultrasound is often compromised by limited access. Fortnightly ultrasound of the uterus and placenta of recipient cows carrying cloned calves is conducted to detect evidence of hydroallantois and placental edema in these high-risk pregnancies.[89] After fetal death, some of the following may be observed: thickening of the uterine wall, increased echogenicity of chorioallantoic and amniotic fluid, altered fetal posture, altered contour of the amnion, and reduced definition and ultimately reduced size of the caruncles.[*] Examination of the fetus may reveal gross congenital abnormalities, and ultrasound of the fetal chest allows visualization of a beating heart and determination of FHR. The normal heart rate of full-term lambs is 108 to 126 bpm.[90] Measuring the heart rate of fetal calves is more difficult than in small ruminants but can be achieved via transabdominal Doppler using a 1.5-Mhz probe. The normal heart rate of full-term calves is 90 to 125 bpm.[91] In human medicine FHR is used as a measure of fetal viability. FHR accelerations associated with fetal movement are considered a sign of fetal well-being, and persistent bradycardia or tachycardia a sign of fetal stress.[92] Normal FHR patterns of ruminants need to be characterized in more detail before FHR measurements are used for prenatal clinical assessment of ruminant fetal well-being.[93]

Fetal loss associated with abnormal placentation occurs sporadically and is reflected by alterations in volume and composition of allantoic and amniotic fluid. In a study of 60 cases of bovine hydrops, 88% were hydroallantois, 5% hydramnios, and 7% a combination of both.[94] Hydroallantois is often associated with disease of the uterus and hydramnios with genetic or congenital defects of the fetus (Dexter cattle with bulldog calves, Angus calves with osteopetrosis, Guernsey calves with pituitary hypoplasia or pituitary aplasia).[95] The concentration of sodium and chloride in allantoic fluid of cattle during the last 12 weeks of gestation is normally low (Na = 52 ± 20 mmol/L and Cl = 17 ± 11 mEq/L) and concentration creatinine concentration is high (1224 μg/mL ± 458).[96] With hydroallantois, allantoic fluid sodium and chloride concentrations rise toward extracellular fluid concentrations (Na = 116 ± 13 and Cl = 81 ± 12 mEq/L), and allantoic creatinine concentration decreases (193 ± 73 μg/mL).[96] Normal amniotic fluid has electrolyte concentrations similar to those of plasma (Na = 132 ± 7 and Cl = 115 ± 8 mEq/L) and a lower creatinine concentration than allantoic fluid (70 ± 26 μg/mL).[96] Cows with hydroallantois are also often hyponatremic and hyperglycemic.[94,97]

Estrone sulfate is a marker of a viable fetoplacental unit and has been used to assess fetal viability in cattle.[98] Estrogen synthesized by embryonic tissue is converted to estrone sulfate by the endometrium, which contains the enzyme sulfotransferase. Estrone sulfate assays can be used to diagnose pregnancy in small ruminants after 50 days[99] and in cattle after 100 days.[100] Estrone sulfate may be measured in plasma or milk[84,100]; baseline values are low after fetal loss, regardless of the stage of pregnancy. Compromise of the fetoplacental unit reduces estrone sulfate production. In a study of the effects of heat stress on pregnant cattle, plasma estrone sulfate concentrations were significantly lower throughout pregnancy in cows that gave birth to low-birthweight calves.[84] Plasma concentrations of estrone sulfate rise slowly during the second trimester of pregnancy from 0.74 ng/mL to 3.66 ng/mL from day 90 to day 210 of pregnancy. The last trimester of pregnancy is associated with a rapid rise in the concentration of estrone sulphate to 13.36 ng/mL at approximately 10 days before parturition.[101]

In human medicine, diagnosis of surfactant deficiency is based on the ratio of two phospholipids in amniotic fluid, lecithin (L) and sphingomyelin (S). If the L/S ratio is greater than 2, the surfactant system is mature and respiratory distress syndrome is rare.[102] The L/S ratio in amniotic fluid collected from cattle may also be used to assess surfactant system maturity,[103] providing a measure of readiness for birth, but is rarely employed in clinical veterinary medicine. Crude surfactant harvested from bovine lungs at a slaughterhouse has been used intratracheally with calves that appeared to be in respiratory distress shortly after birth.[104]

* Dr. JD Rowe, UC Davis, personal communication.

15.3 INDUCTION OF PARTURITION IN RUMINANTS

Manipulation of parturition may be considered for maternal, fetal, or management reasons. Fetal viability after induced parturition is variable among species. The viability of calves induced within 14 days of anticipated calving date is good.[105] Viability of lambs and kids induced more than 5 days before anticipated parturition date is poor.[95] Absorption of colostral immunoglobulins by premature calves is reduced, so colostral transfer should be monitored closely in induced neonates.[106] Induction of parturition or cesarean section is often necessary to prevent mortality of small ruminants with pregnancy toxemia.[107] Fetal viability is often improved by induction of parturition with dexamethasone; however, delivery of the fetuses via cesarean section is often necessary because of the debilitated state of the dam. Secretion of glucocorticoid hormones from the adrenal cortex increases markedly during the final days of gestation. The prenatal increase in fetal glucocorticoid secretion plays an important role in the cascade of

endocrine events leading to parturition and stimulates maturational events in the lungs, liver, kidney, and gastrointestinal tract in preparation for postnatal life.[108]

Steroids stimulate production of surfactant phospholipids by alveolar type II cells, enhance the expression of surfactant-associated proteins, reduce microvascular permeability, and accelerate overall structural maturation of the lungs.[109] Administration of 10 mg of flumethasone and 25 mg of dinoprost to pregnant cows 30 hours before elective cesarean section increases the L/S ratio, improving lung function and reducing complications associated with respiratory acidosis in the calf.[110] Induction of parturition has been used to reduce the incidence of dystocia in herds or breeds experiencing a high incidence of dystocia associated with fetomaternal disproportion.[111] Large birthweights are strongly correlated with fetomaternal disproportion.[112,113] Induction of parturition within 14 days of anticipated calving date is associated with good calf viability and a 3.2-kg reduction in birthweight of beef calves.[105]

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Exogenous glucocorticoids, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), or a combination may be used to induce parturition in cattle (dexamethasone 20 to 30 mg alone or in combination with 25 mg $PGF_{2\alpha}$) and in sheep and goats (10 to 20 mg dexamethasone and/or 15 mg $PGF_{2\alpha}$).[95] Glucocorticoids are more effective than prostaglandin for inducing parturition in sheep.[114] A lower incidence of dystocia and higher viability of calves has been reported in cattle induced with glucocorticoids compared with cows induced with prostaglandin.[115] Cows treated with dexamethasone or prostaglandin within 14 days of anticipated calving date usually calve within 72 hours of treatment.[105] Combination of dexamethasone with prostaglandin increases the efficacy and reduces the interval to parturition (36 hours).[116,117] Retention of fetal membranes is a common complication of induced parturition in cattle.[118] Retention of fetal membranes may be associated with reduced first service conception and subsequent pregnancy rates.[119] Treatment of cows with prostaglandin at calving was reported to reduce the incidence of retained fetal membranes,[120] but subsequent studies have failed to support this.[116,121] Induction of cattle by administration of 25 mg of triamcinolone (Opticortinol) at day 270 followed by treatment with dexamethasone and prostaglandin 6 days later appears to reduce the incidence of retained fetal membranes associated with induction.[118,122] Coliform mastitis is an uncommon complication observed after induced parturition.[123]

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16 Chapter 16 Perinatal Adaptation, Asphyxia, and Resuscitation

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16.1 PERINATAL ADAPTATION

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At birth the fetus must successfully make a series of structural and physiologic changes to survive. Perinatal mortality is often attributable to cardiovascular, pulmonary, thermoregulatory, or metabolic physiologic abnormalities. Dystocia and severe birth asphyxia compromises physiologic transitions, increasing the risk of neonatal mortality. Compromised neonates that survive the birth process are less likely to consume adequate colostrum and are subsequently more likely to die of hypothermia and infectious diseases. A good review of physiologic mechanisms of adaptation at birth is presented by Kasari.[1]

The placenta functions as the respiratory organ of the developing fetus; efficiency of oxygen transfer to the fetus is increased by the high oxygen affinity of fetal vs. adult hemoglobin.[2] In utero the potential spaces of alveoli and the tracheobronchial tree are distended with fluid secreted by pulmonary tissue.[3] Oxygenated blood is delivered to the fetus via the umbilical vein, which anastomoses with the portal vein near the liver, and approximately two thirds of the blood flow is shunted via the ductus venosus directly into the caudal vena cava.[1] The caudal vena cava drains into the right atrium, where over 50% of the volume shunts directly into the left atrium via the foramen ovale.[1] The relatively hypoxic in utero environment causes constriction of pulmonary vessels and dilation of the ductus arteriosus.[1] Because pulmonary arterial resistance is higher than systemic arterial resistance, nearly 70% of pulmonary artery flow is shunted via the ductus arteriosus into the aorta, with the remainder perfusing the lung.[4] Left ventricular output is distributed to the systemic circulation via the aorta. The two umbilical arteries arise from the aorta in the region of the last lumbar vertebra to carry predominantly venous blood back to the placenta via the umbilicus.

At birth some of the lung fluid is evacuated through the trachea during spontaneous delivery.[5] When the umbilicus ruptures, asphyxia triggers reflex gasping, respiratory movements, and increased peripheral vascular resistance.[4] The majority of lung fluid is absorbed through alveolar walls in the initial stages of ventilation.[5] This mechanism is prompted by activation of adrenaline-mediated β-adrenergic receptors in the pulmonary epithelium.[6] The rapidity of lung fluid absorption by the body is optimized at thoracic pressures between 35 and 40 cm H_2O.[5] Pulmonary ventilation reduces pulmonary vascular resistance, promoting perfusion of the ventilated alveolar tissue.[1] The increased O_2 saturation of blood stimulates closure of the ductus arteriosus within 4 to 5 minutes of birth.[4] The foramen ovale functionally closes within 5 to 20 minutes of birth when increased pulmonary venous return raises blood pressure in the left atrium, reversing the right-to-left shunt.[4] The septum secundum, a thin fold of tissue that lies in close apposition to the foramen, acts as a valve closing the opening. Healthy calves have mean pulmonary arterial pressures ranging from 40 to 82 mm Hg immediately after birth, declining to 22 to 25 mm Hg by 2 weeks of age.[7] Systemic arterial pressure is approximately 100 mm Hg, and arterial saturation is greater than 90%.[1]

Transient mild metabolic and respiratory acidosis is observed after rupture of the umbilical cord as a result of anaerobic glycolysis in poorly perfused tissues during the transition between placental oxygen delivery and establishment of respiratory function. The mild acidosis is normally corrected within 1 to 4 hours of birth.[8] Anatomic closure of the foramen ovale and ductus arteriosus may take several weeks.[4] Normal blood gas values for the calf during the immediate postpartum period are presented in Table 16-1.

Dystocia is commonly associated with prolonged hypoxia and acidosis. Hypoxia and acidosis maintain constriction of pulmonary arterioles, and the subsequent maintenance of high pulmonary vascular resistance favors continuation of in utero right-to-left vascular shunts, which contributes to systemic hypoxia. After dystocia neonates are less active, slow to stand, slow to nurse, and prone to hypothermia and hypogammaglobulinemia. The normal duration of stage 2 labor (from appearance of fetal membranes at the vulva to delivery of the fetus) in ruminants is generally shorter in multiparous animals (approximately 30 minutes) than primiparous animals (approximately 60 minutes).[9] Fetal viability is improved with early intervention; multiparous animals should be assisted after 30 to 60 minutes of stage 2 labor, and primiparous animals after 60 to 90 minutes.[10]

The range in ambient temperatures over which newborn animals are able to maintain homeothermy is much narrower than in growing or adult animals. Neonates are more susceptible to fluctuations in environmental temperature because of their large surface area—to-mass ratio, evaporation of amniotic fluid, and limited caloric reserves. Starvation and hypothermia is the second leading cause of death of neonatal lambs.[11] Neonatal mortality increases with decreasing ambient temperature and with increasing precipitation on the day of birth.[12] Thermoneutrality is maintained by shivering and metabolism of brown adipose tissue. Normally at birth blood glucose concentration in calves ranges between 50 and 60 g/dL, rising to 100 mg/dL within the first 24 hours of life.[1] Lambs born in warm weather can survive for up to 4 days without supplemental nutrition. Severe weather stress may increase energy requirements by 500% and deplete the energy reserves of newborn lambs in 6 to 16 hours.[13] Starvation exacerbates the effects of environmental stress by reducing the available substrates for heat production, and energy depletion leads to hypoglycemia. Administration of glucose to hypothermic neonates before and during warming is important to avoid deaths from cerebral hypoglycemia induced by increased use of glucose by peripheral tissues.[14] Warming hypothermic lambs by immersion in 38 ° C water is more efficient than infrared lamps or wrapping them in cotton cloth.[15]

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Table 16-1 Arterial and Venous Blood Gas Values for Newborn Calves

	Parameters					
	Calf Age	pH	Po_2	Pco_2	HCO_3^-	Base Excess
Venous*	1 hour	7.219 (0.05)	N/A	41 (5.9)	24.2 (2.7)	–2.9 (3.2)
Arterial†	1 hour	7.3 (0.05)	58.43 (11.61)	50.40 (5.27)	23.52 (2.78)	N/A

Values represent mean with standard deviation parenthesis. *N/A,* Not available.

* Blood was taken from the brachial artery while the calf was in lateral recumbency (N = 30).[73]

† Blood taken from the jugular vein immediately post partum.[8]

No intrauterine transfer of immunoglobulin (Ig) occurs in ruminants; hence, at birth, neonatal ruminants are agammaglobulinemic and immunologically naive. Infectious disease is the leading cause of morbidity and

mortality in calves greater than 3 days of age.[16] Failure of passive transfer (FPT) increases the risk of neonatal mortality.[17] Colostrum provides a concentrated source of energy and immunoglobulins. Immunoglobulins are concentrated in colostrum by an active, receptor-mediated transfer of IgG_1 from the blood of the dam across the mammary gland secretory epithelium beginning several weeks before parturition.[18] Colostral IgG_1 concentrations may be 5 to 10 times the maternal serum concentrations. IgM, IgA, and IgG_2 concentrations in colostrum are much lower.[19] The large numbers of leukocytes also contribute to providing passive immunity to the newborn.[20] Methods of assessing passive transfer and management of FPT are discussed in detail in Chapter 53.

16.2 ACUTE ASPHYXIA IN THE NEONATE

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Peripartum asphyxia can lead to encephalopathy, ischemic renal failure, and varying degrees of gastrointestinal (GI) dysfunction, the most severe form being necrotizing enterocolitis (NEC). The encephalopathy is most commonly referred to as *hypoxic ischemic encephalopathy* (HIE). The diagnosis of peripartum asphyxia syndrome relies on prepartum transabdominal ultrasonography of the fetoplacental unit, postpartum placental and neonatal foal examination, and immediate assessment of creatinine and presuckle glucose in the foal after delivery. Patient survival may depend on management of central nervous system (CNS), GI, and renal dysfunction.

Any process that results in impairment to placental blood flow or gas exchange can produce asphyxia. These changes in moderation are both normal and critical for postnatal adaptation through a phenomenon known as *ischemic preconditioning*. Essentially, brief episodes of ischemia, as can occur with myometrial contractions, induce partial protection against subsequent episodes of severe ischemia. This is likely mediated through inducible nitric oxide and can also be triggered by hypoxia and volatile inhaled anesthetic agents.[21] Disease develops when episodes of ischemia and/or hypoxia are severe or prolonged. Asphyxia is a multifactorial disease process that develops when tissue oxygenation is disrupted. It is most commonly encountered when pregnancy and labor are complicated by problems resulting in impaired oxygen delivery to fetal tissues, on either a short-term or a long-term basis. Peripartum asphyxia has been associated with rapid, seemingly uncomplicated deliveries, dystocia, induced delivery, cesarean section, premature placental separation and other placental abnormalities, umbilical cord abnormalities, twinning, meconium staining, postdate pregnancy, and severe maternal illness.[22] Asphyxia may also occur in the neonatal period; causes include severe hemorrhage, resulting in hypovolemia and shock, and severe cardiorespiratory dysfunction, as in severe pneumonia, cardiac malformations, pulmonary hypertension, and airway obstruction.

The overall incidence of the condition in the foal is not known, because of the high incidence of unmonitored and unobserved deliveries and the diagnostic confusion of asphyxial problems with other perinatal problems.[23] In a recent study of causes of equine perinatal death, complications of birth, including asphyxia, dystocia, and trauma, were listed as the second most common cause of death after infection (19% of 3527 cases). This figure does not include acute placental or umbilical cord abnormalities, problems that also could have caused acute fetal asphyxiation.[23]

Peripartum asphyxia produces HIE, ischemic renal failure, and varying degrees of NEC. Diagnosis relies on prepartum transabdominal ultrasonography of the fetoplacental unit, postpartum placental and neonatal foal

examination, and immediate assessment of creatinine and presuckle glucose in the foal after delivery. Patient survival depends on management of CNS, GI, and renal dysfunction.[24]

16.2.1 Pathophysiologic Considerations

Perinatal asphyxia describes an episode of impaired oxygen delivery to cells from hypoxemia (decreased oxygen concentration in blood) and or ischemia (decreased blood flow to tissues) around the time of birth. Pure hypoxemia implies a decrease in oxygen concentration in the blood with preservation of blood flow, which allows organs to respond by increasing their efficiency in extracting oxygen from the circulation. The effects of hypoxemia and ischemia are not identical, but they are difficult to distinguish clinically. Ischemia is far more devastating and results in anaerobic metabolism, increased lactate concentrations, and intracellular acidosis and is a preamble for reperfusion injury. Metabolites of anaerobic metabolism, such as lactic acid, cannot be removed from the tissues until blood supply is restored. As a result, severe acidosis may develop locally, which interferes with cellular function and may cause irreversible cell damage.

In general terms, preterm animals are far more tolerant of periods of hypoxia than adult animals. In utero the mammalian fetus adapts to a relatively hypoxic environment by increased oxygen affinity of fetal hemoglobin, increased ability to extract oxygen from the blood, and a greater tissue resistance to acidosis. Hemoglobin in the fetal foal is structurally similar to adult hemoglobin, but the fetal erythrocyte carries increased concentrations of 2,3 diphosphoglycerate, causing a leftward displacement of the sigmoidal hemoglobin-oxygen dissociation curve and an increased affinity for oxygen.[25] Fetal compensatory mechanisms against increasing asphyxia include bradycardia, decreased oxygen consumption, anaerobic glycolysis, and reflex redistribution of blood flow with preferential perfusion of the brain, heart, and adrenal glands at the expense of circulation to kidneys, gut, liver, lungs, and muscle.[26] The shunting of blood away from kidneys and the gut during in utero asphyxia is likely centrally mediated via the α-adrenergic component of the sympathetic nervous system.

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The extent of tissue injury depends on whether the asphyxial insult is acute or chronic, or partial or complete, and whether the neonate is premature or full term. Severe in utero hypoxia can lead to prolonged hypoperfusion and reduced metabolism with an associated and sequential loss of fetal reflexes, with the most oxygen-demanding fetal activities disappearing first. Fetal reflexes are lost in the following order: (1) fetal heart rate reactivity (the ability to increase heart rate in response to fetal activity), (2) fetal breathing, (3) generalized fetal movements, and (4) fetal tone.

An episode of perinatal asphyxia may not result in immediate cell death but can induce a complex cascade of events that can lead to delayed damage.[27] The two key processes of neuronal injury after asphyxia are neuronal necrosis and apoptosis.[28] After asphyxia there is a latent phase that occurs with reperfusion; this phase involves an initial recovery of cerebral energy metabolism. A secondary phase takes place between 6 and 15 hours after the asphyxial insult and is characterized by the accumulation of cytotoxins, seizures, cytotoxic edema, and failure of cerebral oxidative metabolism. Without sufficient energy, cellular ion pumps eventually fail, with accumulation of sodium, chloride, water, and calcium intracellularly (cytotoxic edema), and excitatory amino acid neurotransmitters in the brain, such as glutamate and aspartate, extracellularly. Neonates appear to be more susceptible to glutamate-mediated excitotoxicity than adults. Glutamate injection into specific regions of the brain results in neuronal injury identical to that seen after hypoxia-ischemia, and glutamate antagonists can prevent cell death from anoxia. At high extracellular concentrations, glutamate acts as a neurotoxin and mediates opening of ion channels that permit sodium to enter cells, followed by an influx of chloride ions and water, resulting in osmotic lysis and immediate neuronal death.[29,30] Glutamate also mediates delayed cell death by provoking calcium influx through depolarization-induced opening of calcium channels and by direct stimulation

of *N*-methyl-D-aspartate (NMDA) receptors that open additional calcium channels.[29,30] High intracellular levels of free calcium result in activation of lytic enzyme systems that attack the structural integrity of the cell, generation of free radicals, and impairment of mitochondrial function, resulting in delayed neuronal death. Because of the important role of calcium in regulation of cellular function, drugs such as NMDA and calcium antagonists that prevent calcium influx into damaged cells are being investigated to help reduce delayed ischemic brain injury.

Oxygen free radicals are generated during the reperfusion phase of hypoxic-ischemic injury. It is thought that these radicals contribute to brain injury by their ability to induce free fatty acid peroxidation.[31] The physical integrity of the circulation is often severely compromised after a period of ischemia. It is suspected that oxygen-derived free radicals are at least partially responsible for the increased capillary permeability, edema formation, and tissue damage that commonly follows the restoration of blood flow to ischemic tissues.[32] Severe asphyxial insults tend to produce widespread neuronal necrosis, whereas milder episodes are more likely to induce apoptosis. The latter is an active but noninflammatory response characterized by cell shrinkage, nuclear pyknosis, chromatin condensation, and genomic fragmentation.

16.2.2 Potential Postnatal Sequelae of Birth Asphyxia

The consequences of an episode of asphyxia can be far-reaching and profound. Many organ systems can be adversely affected and contribute to the commonly observed clinical signs of weakness and depression in the neonate. Management can be difficult and complex, but with good supportive care, dramatic recoveries can be made in even severely affected individuals. Unfortunately, it is virtually impossible at the onset of treatment to predict either the severity of injury or the prognosis. Chronic asphyxia in premature individuals or those with sepsis carries the poorest prognosis for intact neurologic survival.

Clinical signs related to the asphyxial injury may not appear until hours or days after the insult. Blood volume abnormalities, such as severe hypovolemia, occurring at delivery may not be obvious until several hours later. Blood pressure may actually be normal at first because capillary capacitance beds are constricted by substances such as catecholamines and angiotensin II. Then as the peripartum stresses decrease over time, circulating hormone levels fall and progressive hypotension and acidosis often develop.[23]

Table 16-2 lists specific clinical conditions and organ system derangements that have been associated with asphyxial injury. Table 16-3 presents therapies for specific organ system dysfunction.

16.2.2.1 CENTRAL NERVOUS SYSTEM

Numerous terms are used in the literature to label foals with hypoxic ischemic brain injury. The term *hypoxic-ischemic encephalopathy* is preferred by some, but other terms include *neonatal maladjustment syndrome; dummy, barker,* or *wanderer foals;* and *perinatal asphyxia syndrome*. Risk factors for asphyxial injury are numerous and include placental insufficiency, placentitis, premature placental separation, maternal illness, umbilical cord diseases (e.g., torsion, funisitis, thrombosis), exogenous induction of labor, dystocia, caesarean section,[33] and a range of postnatal causes including airway obstruction and hemorrhage. Mild asphyxia produces transient tissue ischemia with potentially reversible damage. Prolonged ischemia results in disruption of tight junctions in the capillary endothelium and leakage of osmotic agents and fluid into surrounding brain interstitium, causing vasogenic edema.[34] Brain necrosis occurs and is accompanied by increased intracranial

pressure, progressive brain swelling, reduced cerebral blood flow, and exacerbation of existing ischemia. In critically ill foals, cerebral edema has been associated with cerebellar herniation.[35]

Additional brain injury occurs as a result of repeated seizures, which are common during severe encephalopathy. Repeated seizures cause brain injury through (1) hypoventilation and apnea resulting in hypoxemia and hypercapnia, (2) elevation in arterial blood pressure and cerebral blood flow, (3) progressive neuronal injury because of excessive release of excitatory amino acids such as glutamate, and (4) depletion of the brain's limited energy stores to support seizure activity.

Neonatal foals suffering from HIE display a wide spectrum of neurologic signs that are mostly related to cerebral dysfunction. These include jitteriness, hyperalertness, stupor, somnolence, obtundation, lethargy, hypotonia, clonic seizures, extensor rigidity, hypertonia, subtle seizures, tonic posturing, coma, death, aimless wandering, head pressing, loss of affinity for the dam, inability to find the udder, abnormal vocalization (barking, high-pitched cry), loss of suckle, dysphagia, decreased tongue tone, odontoprisis, blindness, anisocoria, mydriasis, nystagmus, eye deviation, head tilt, head and neck turn, irregular respiration, apnea, abnormally slow respiratory rate, proprioceptive deficits, and spastic dysmetric gait. Blindness is a relatively common complication of perinatal asphyxia and postnatal anoxia from seizure activity and results in extensive gray and white matter injury affecting optic radiations and the visual cortex.[36] In a smaller number of affected foals there may be signs of brainstem or spinal cord involvement. Foals with HIE exhibit a variety of seizure-like activities. Seizures can vary in clinical severity from subtle, which may not be recognized as seizure activity, to generalized and severe (see Seizures, Chapter 19). Jitteriness is associated with mild hypoxia and is not a true seizure but a movement disorder consisting of tremors that can be stopped by gentle restraint. Subtle seizures are called *motor automatisms* and are characterized by paroxysmal events including eye blinking, eye deviation, nystagmus, pedaling movements, a variety of oral-buccal-lingual movements such as intermittent tongue protrusion (so-called “chewing gum fits”), sucking behavior, purposeless thrashing, and other vasomotor changes such as apnea, abnormal breathing patterns, and changes in heart rate. Tonic posturing is another subtle seizure activity characterized by symmetric limb hyperextension or flexion and may be accompanied by abnormal eye movements and apnea. Clonic seizures are true epileptiform seizures with a distinct electroencephalogram (EEG) signature and are characterized by rigid jerky motions that cannot be suppressed by restraint.

Table 16-2 Clinicopathologic Conditions Associated with Peripartum Asphyxia[74]

Organ or System Affected	Clinical Signs	Laboratory Findings	Pathologic Lesions
Central nervous system (CNS)	Hypotonia, hypertonia, seizures, coma, loss of suckle, proprioceptive deficits, apnea	Increased intracranial pressure, increased blood-brain barrier permeability and albumin quotient	CNS hemorrhage, edema, ischemic necrosis
Renal	Oliguria, anuria, generalized edema	Azotemia, hyponatremia, hypochloremia, abnormal urinalysis	Tubular necrosis
Gastrointestinal	Colic, ileus, abdominal distention, bloody diarrhea, gastric reflux	Occult blood (+) feces and reflux, pneumatosis intestinalis	Ischemic mucosal necrosis, enterocolitis, ulceration
Respiratory	Respiratory distress, tachypnea, dyspnea, rib retractions	Hypoxemia, hypercapnia, respiratory acidosis	Hyaline membrane disease, atelectasis, meconium aspiration, pulmonary hypertension
Cardiac	Arrhythmia, weak pulses, tachycardia, edema, hypotension	Hypoxemia, elevated myocardial enzymes	Myocardial infarcts, valvular insufficiency, persistent fetal circulation
Hepatic	Icterus, abnormal mentation	Hyperbilirubinemia, elevated liver enzymes	Hepatocellular necrosis, biliary stasis
Endocrine: adrenals, parathyroids	Weakness, apnea, seizures	Hypocortisolemia, hypocalcemia	Necrosis, hemorrhage

Table 16-3 Drugs Used to Treat Foals with Peripartum Asphyxia[74]

Organ System	Clinical Sign	Drug Therapy
CNS	Seizures	Diazepam: 0.11-0.44 mg/kg IV
		Phenobarbital: 2-10 mg/kg IV q12h; give slowly, monitor serum levels
		Pentobarbital: 2-10 mg/kg IV
	CNS edema	DMSO: 0.5-1 g/kg IV as 20% solution over 1 hr; can repeat q12h
		Mannitol: 0.25-1 g/kg IV as 20% solution over 15-20 min; q12-24h
	Antioxidants	*N*-acetylcysteine: 70 mg/kg IV as 10% solution; q6h
		Vitamin E: 20 IU/kg SC sid
		Thiamine: 10 mg/kg added to IV fluids sid
	NMDAantagonist	Magnesium sulfate: 0.05 mg/kg/h loading dose and then 0.025 mg/kg/hr as IV infusion
Renal	Oliguria, anuria	Dopamine infusion: 2-10 µg/kg/min; monitor blood pressure and pulse
		Furosemide infusion: 0.25-2 µg/kg/hr or 0.25-0.5 mg/kg IV q1-6h; monitor serum electrolytes and hydration status
		Mannitol: 0.5-1 g/kg IV as 20% solution over 15-20 min.
		Dobutamine infusion: 2-15 µg/kg/min; use if cardiac dysfunction is contributing to hypotension and poor renal perfusion
		Fenoldopam: 0.04 µg/kg/min
Gastrointestinal	Ileus, GI distention	Erythromycin: 1-2 mg/kg PO q6h; 1-2 mg/kg/hr as IV infusion q6h
		Cisapride: 10 mg PO q6-8h
		Metoclopramide: 0.25-0.5 mg/kg/hr infusion q6-8h
	Ulcers	Sucralfate: 20-40 mg/kg PO q6h
		Ranitidine: 5-10 mg/kg PO q6-8h, 1-2 mg/kg IV q8h
		Cimetidine: 15 mg/kg PO q6h; 6.6 mg/kg IV q6h
		Omeprazole: 2 mg/kg PO q24h

Cardiac	Hypotension	Dopamine infusion: 2-10 µg/kg/min
		Dobutamine infusion: 2-15 µg/kg/min
		Digoxin: 0.02-0.035 mg/kg PO q24h if cardiac failure is suspected
Respiratory	Hypoxemia	Intranasal, humidified oxygen: 2-10 LPM
	Apnea	Caffeine: loading dose, 10 mg/kg PO; maintenance dose, 2.5-3 mg/kg PO q24h
Endocrine	Hypocortisolemia	ACTH (depot): 0.26 mg IM q8-12h
Immune	FPT, leukopenia	Hyperimmune plasma: 10-20 mL/kg IV; monitor serum IgG and WBCs

ACTH, Adrenocorticotropic hormone; *CNS,* central nervous system; *DMSO,* dimethyl sulfoxide; *FTP,* failure of passive transfer; *GI,* gastrointestinal; *IgG,* immunoglobulin G; *IM,* intramuscular; *IV,* intravenous; *LPM,* liters per minute; *NMDA, N*-methyl-D-aspartate; *PO,* by mouth; *SC,* subcutaneous; *sid,* once per day; *WBCs,* white blood cells.

Not all neurologic abnormalities in large animal neonates are the result of peripartum asphyxia. Other causes of neonatal neurologic disease include the following:

- Metabolic disorders: hypocalcemia, hypomagnesemia, hyponatremia, hypernatremia, hyperosmolality (e.g., hyperlipidemia, hyperglycemia), severe azotemia, hepatoencephalopathy
- Infectious conditions: septic meningitis, septicemia or endotoxemia, equine herpesvirus 1 (EHV-1) infection
- Malformation: hydrocephalus, agenesis of the corpus callosum, vertebral and spinal cord malformations, cerebellar abiotrophy, occipitoatlantoaxial malformation
- Cranial or vertebral trauma
- Toxins

The diagnosis of HIE is unfortunately often done by exclusion. In foals in which there is a clear history of an asphyxial insult, such as dystocia or prolonged stage 2 labor, or that were delivered through cesarean section, the accuracy of the diagnosis should be extremely high. In foals with signs of neurologic disease when there has been no obvious asphyxial insult and when other known causes of brain dysfunction have been ruled out, a diagnosis of HIE should be made with some degree of skepticism. It has been suggested that the term *neonatal encephalopathy* may be more appropriate than HIE for such foals, as the cause may be unclear.

An important but uncommon cause of neurologic signs in neonatal foals is bacterial meningitis. A normal leukogram or the absence of severe leukopenia, neutropenia, and toxic neutrophil changes help rule out septic conditions. A cerebrospinal fluid (CSF) tap is indicated to rule out meningitis in foals in which signs of infection coexist with neurologic signs. Septic meningitis produces an increased nucleated cell count, protein concentration, and IgG index in the CSF. Hypoxic brain damage may result in an increased albumin quotient in the CSF compatible with increased blood-brain barrier permeability. It is also important to remember that foals with postasphyxial encephalopathy are susceptible to infection and that the two conditions often coexist without bacterial involvement of the CNS. The differentiation between HIE and congenital brain anomalies can be very difficult. The most common anomalies include hydrocephalus and hydranencephaly and are

presumptively diagnosed on the basis of persistence of neurologic abnormities or definitively through computed tomography (CT) or magnetic resonance imaging (MRI). Normal serum chemistries help rule out metabolic disturbances.

Currently, suggested treatment of CNS dysfunction in asphyxiated large animal neonates includes seizure control, nursing care to prevent self-trauma, and judicious fluid therapy to avoid overhydration and hypoglycemia or hyperglycemia. Maintenance of effective perfusion and oxygen delivery is the central component of management. Diazepam is used initially to control seizures because of its rapid onset of action. Phenobarbital is used to control severe or repeated seizures. Foals receiving high doses of anticonvulsants should have their vital signs monitored closely because the combination of diazepam and phenobarbital can produce respiratory depression, loss of thermoregulatory control, and hypotension.

A large number of additional therapies are used in the management of foals with suspected postasphyxial brain injury. These therapies are used in the absence of efficacy data and may add little to the principles of therapy described previously. Interstitial cerebral edema is a pathologic feature in a small number of foals. Intravenous dimethyl sulfoxide (DMSO; 0.5 to 1 g/kg of a 10% to 20% solution, slowly over 1 to 2 hours) has been advocated for its ability to reduce brain swelling, intracranial pressure, and inflammation and to act as a diuretic.[22] The osmotic agent mannitol has also been used to reduce cerebral edema and to act as a free radical scavenger. These drugs likely exert little benefit in the control of intracellular edema. To prevent exacerbation of cerebral edema, fluid therapy should be conservative, and sudden changes in osmolality should be avoided. Controversy surrounds the benefits of glucose administration. Hyperglycemia immediately after prolonged hypoxic ischemic injury has been associated with severe neonatal brain injury.[37] Other studies suggest that glucose administration after global hypoxic injury may offer neuroprotection by stimulating insulin release and by reducing glycolysis, free radical formation, and glutamine-mediated injury.[38] Therefore the safest recommendation is to maintain serum glucose concentration within a normal range. *N*-acetylcysteine is a potent antioxidant and antiinflammatory agent that has also been shown to be of benefit in experimental models of neonatal brain injury.[39] A dose rate of 70 mg/kg (as a 10% solution) IV every 6 hours has been suggested in affected neonatal foals. Thiamine is a required cofactor for several important mitochondrial enzymes involved with neuronal metabolism and can attenuate oxygen free radical damage in experimental ischemic brain damage.[40] Thiamine (10 mg/kg sid) is commonly used in foal practice but again in the absence of efficacy data. Other vitamin treatments used by some include vitamin E and vitamin C.

Magnesium sulphate infusion is yet another therapy used to attenuate postasphyxial brain injury in foals. Magnesium is recognized as an inhibitor of NMDA receptor—mediated calcium entry into cells and a membrane stabilizer preventing the persistent membrane depolarization that occurs as a consequence to disruption of the Na/K ATPase pump.[41] Experimental and clinical data regarding the use of magnesium sulphate are conflicting. A recent report not only failed to demonstrate any neurologic benefit of magnesium in postasphyxiated human neonates, but raised the possibility that the therapy could have unexpected cardiovascular and neuromuscular complications.[41] As with many of these agents, any potential effect may be realized only if the treatment is administered before or immediately after the insult.

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16.2.2.2

CARDIOPULMONARY EFFECTS

The response of pulmonary vasculature to hypoxia and acidemia includes increased pulmonary vascular resistance, pulmonary hypertension, increased atrial pressure, and persistent right-to-left flow of blood across fetal pathways (e.g., patent ductus arteriosus, foramen ovale). The neonatal pulmonary circulation reflexively

constricts in response to hypoxemia and acidosis.[42] This pulmonary vasoconstriction results in increased pulmonary vascular resistance, pulmonary hypertension, and increased right atrial pressure. If pulmonary arterial pressure exceeds systemic pressure, right-to-left blood flow may result in the reestablishment of fetal circulation (right-to-left flow through the ductus arteriosus and foramen ovale). Persistent fetal circulation (PFC) is associated with severe hypoxemia unresponsive to oxygen therapy owing to severe right-to-left shunting of unoxygenated blood away from the lungs.

When PFC patterns exist, hypoxemia is exacerbated. During asphyxia-induced pulmonary vasoconstriction, substrate delivery to the pneumocytes is impaired and surfactant production decreases with secondary pulmonary atelectasis. Perinatal asphyxia may adversely affect the respiratory control centers of the brain and result in hypoventilation (increased carbon dioxide), secondary to periods of apnea or abnormal breathing patterns.

Adequate surfactant production is dependent on adequate function of the type II pneumocytes and the ongoing delivery of lipid precursors by the blood. If pulmonary blood flow is compromised, surfactant production may stop, and a secondary surfactant deficiency may result.[23,43] The altered permeability characteristics of the lung that have been associated with asphyxial injury also interfere with the function of surfactant, predisposing to atelectasis.[44]

If asphyxia induces in utero passage of meconium, then the fetus may aspirate meconium. Meconium can cause mechanical obstruction of airways, resulting in suffocation or regional lung atelectasis. Partial obstruction produces a ball-valve phenomenon with distal air trapping, ventilation-perfusion mismatching, alveolar overdistention and possible rupture, interstitial emphysema, and pneumothorax.[45] Meconium also induces chemical pneumonitis accompanied by alveolar collapse and edema.[46] The free fatty acids in meconium displace surfactant, resulting in additional atelectasis and decreased lung compliance.[47] See Chapter 19, Respiratory Distress, for further information. Adverse effects of asphyxia on myocardial function include reduced myocardial contractility, left ventricular dysfunction, tricuspid valve insufficiency, and cardiac failure. As a result of cardiac insufficiency the foal may develop systemic hypotension, further impairment of renal blood flow, and decreased pulmonary perfusion. In the human infant, perinatal asphyxia has been associated with myocardial and papillary muscle ischemia and infarction, with decreased myocardial contractility, tricuspid valve insufficiency, and congestive heart failure often resulting. Cardiac isoenzymes may be increased. Treatment is directed at correcting hypoxemia, acidosis, and hypoglycemia and maintaining cardiac output and blood pressure. Inotropic drugs, such as dopamine and dobutamine, are commonly used.

If pulmonary hypertension develops, thoracic radiographs show diminished vascular markings as a result of pulmonary hypoperfusion. Surfactant dysfunction produces diffuse lung atelectasis and a diffuse reticulogranular parenchymal pattern with air bronchograms. Meconium aspiration may produce perihilar infiltrated and focal atelectasis. Echocardiography helps identify arrhythmias.

Support of the respiratory system involves maintenance of oxygenation and ventilation of the patient. Mild to moderate hypoxemia can be treated by increasing the amount of time the foal spends in sternal recumbency or standing and by administering modest flows of humidified intranasal oxygen (2 to 8 L/min [LPM]). Foals with severe hypoxemia and hypercapnia (Pa_{O_2} <40 mm Hg; Pa_{CO_2} <65 mm Hg) require positive pressure ventilation. Respiratory stimulants are used to treat periodic apnea and abnormally slow breathing patterns associated central depression of the respiratory center. Caffeine is used most frequently to stimulate the respiratory neuronal activity and increase receptor responsiveness to elevated carbon dioxide concentrations. Overdosing with respiratory stimulants leads to excessive CNS, myocardial, and GI stimulation resulting in

agitation, seizures, tachycardia, hypertension, colic, and diarrhea. Caffeine is the safest of the methylxanthines to use.

16.2.2.3

RENAL EFFECTS

During asphyxia, redistribution of blood flow away from the kidneys frequently results in decreased renal perfusion and acute tubular necrosis. The renal effects of asphyxia in foals are likely underreported, as overt signs of failure are rare. Transient changes in urine output are often overlooked, particularly when the foals are on fluid therapy. In human infants, oliguria (<1 mL of urine per kilogram of body weight per hour) is the most common clinical sign of acute renal failure; it has also been observed in asphyxiated foals.[22,23] Other signs of renal ischemic damage include peripheral edema, elevated concentrations of serum creatinine and urine γ-glutamyltransferase (GGT), and electrolyte disturbances such as hypocalcemia, hyponatremia, and hypochloremia resulting from renal tubular damage. The oliguric animal should be identified by careful monitoring of fluid intake and output to avoid fluid overload and edema formation. Based on studies in other neonates, renal blood flow and urine output may be increased by the use of low to moderate doses of dopamine (2 to 10 μg/kg/min infusion) or dobutamine (2 to 10 μg/kg/min infusion). Higher doses of dopamine are contraindicated to avoid peripheral vasoconstriction and a decrease in renal blood flow.[22] Therefore, blood pressure and urine output should be carefully monitored during infusion of these substances. The dopamine-1 receptor agonist, fenoldopam, when administered at a low dose (0.04 μg/kg/min infusion) has no effect on system hemodynamics but did cause an increase in urine output in healthy neonatal foals.[48] Diuretics, such as furosemide (0.5 to 2.5 mg/kg/hr as an infusion, or 1 mg/kg intramuscularly [IM] or intravenously [IV] q12h) and mannitol (0.25 to 1 g/kg as 20% solution, infused slowly IV over 1 to 2 hours), have also been successfully used to improve urine output in asphyxiated foals.[22]

16.2.2.4

GASTROINTESTINAL EFFECTS

Hypoxia results in reduced mesenteric and splanchnic blood flow and varying degrees of intestinal ischemia. The most severe form of intestinal dysfunction is NEC. (See the discussion of abdominal distension in Chapter 19.) During GI ischemia, mucosal cell metabolism diminishes and production of the protective mucous layer ceases, allowing proteolytic enzymes to begin autodigestion of the mucosal barrier. Bacteria within the lumen can then colonize, multiply, and invade the bowel wall. Intramural gas is produced by certain species of bacteria, and pneumatosis intestinalis develops. Possible complications include intestinal rupture, pneumoperitoneum, severe bacterial peritonitis, and septicemia.[49] Reflux and feces may be positive for blood. 257
Generalized sepsis often accompanies NEC. As a result of varying degrees of intestinal dysmotility, some 258
foals develop intussusceptions that can be imaged with ultrasound.

Many asphyxiated foals demonstrate mild signs of GI malfunction, including meconium impactions and intolerance to enteral feeding (delayed gastric emptying, abdominal distension, diarrhea, and colic). Colic, bloody diarrhea, and sudden death have been observed secondary to extensive intestinal mucosal sloughing in severe cases. Ileus associated with hypoxic gut damage can result in bowel distention and colic. Nasogastric decompression relieves proximal gut distention. Enema administration stimulates distal colonic function and encourages passage of gas. Metoclopramide and erythromycin may improve gastric emptying and upper GI function. Metoclopramide infusion (0.25 to 0.3 mg/kg infusion, qid) has been suggested to improve gastric emptying and improve small intestinal motility.[22] Cisapride and erythromycin have been used to stimulate small and large intestinal motility. Be certain to allow adequate time for healing of damaged bowel before using prokinetics in a compromised foal. Sonographic examination of the abdomen helps rule out the presence

of intussusceptions and other obstructive lesions before motility modifiers are administered. Severe large bowel distention may require percutaneous trocarization. Alternatively, exploratory celiotomy may be performed, but the multisystemic derangements often make such animals poor surgical risks.

To reduce the risk of NEC, asphyxiated foals should have enteral feeding reduced or withheld until intestinal motility has returned. Reassuring signs include manure passage, normal borborygmi, and stable vital signs (temperature, blood pressure). Enteral feeding should be started cautiously with fresh mare's milk or colostrum. Foals with severe GI dysfunction should have enteral feeds withheld and should be started on parenteral nutrition. Because intestinal ischemia may predispose to ulceration, histamine-2 (H_2) blockers (cimetidine, ranitidine), proton pump inhibitors (omeprazole), or cytoprotective agents (sucralfate) are recommended.

16.2.2.5 HEPATIC AND ENDOCRINE FUNCTION

Hypoxic liver damage produces an increase in hepatocellular and biliary enzymes. Affected neonates are usually icteric. Impaired hepatic function renders the neonate more susceptible to alteration in glucose homeostasis and can result in decreased hepatic defense mechanisms and increased susceptibility to sepsis. Endocrine organ damage associated with hypoxia includes adrenal gland hemorrhage and necrosis with hypocortisolemia. Parathyroid damage may result in hypocalcemia. Pancreatic injury and abnormal insulin activity can occur.

16.2.2.6 IMMUNE DYSFUNCTION

Maladjusted foals are at increased risk for FPT because of their abnormal nursing behavior. Serum IgG levels should be evaluated, and colostrum and/or plasma administered to treat FPT.

16.2.3 Supportive Care and Prognosis of the Acutely Asphyxiated Foal

A summary of therapies for specific organ dysfunction associated with peripartum asphyxia is presented in Table 16-3. Blood glucose, blood gases, and fluid and acid-base balance should be monitored closely. In severely affected animals, both arterial and central venous pressures are monitored. Nursing care must be carefully performed to avoid secondary infection.

Prognosis varies with the severity and duration of clinical signs. In one intensive care unit, 70% of asphyxiated foals recover, with most making a complete recovery. A poor prognosis was associated with foals that failed to show any signs of improving neurologic function in the first 5 days after delivery; foals that remained comatose or experienced severe, recurrent seizures; and foals that developed septicemia.[22]

16.3 RESUSCITATION OF THE NEONATE

John K. House

Assisted deliveries are usually associated with moderate to severe fetal stress. Survival of the compromised fetus is facilitated by prompt initiation of supportive care. Prior preparation of a “crash box” or “crash cart” (Fig. 16-1) expedites location of the necessary supplies and equipment. Passage and subsequently aspiration of meconium often accompany fetal stress. Suction, if available, is useful for clearing the airway but should be used judiciously as prolonged pharyngeal and tracheal aspiration induces vagally mediated bradycardia.[50] Vigorously rubbing the

skin over the legs stimulates a somatic-respiratory reflex and may help initiate respiratory effort.[51] Thermoregulation is important, as recovery from acidosis is delayed by hypothermia.[52] Cold stress leads to increased metabolic needs and produces hypoxia, hypercarbia, metabolic acidosis, and potentially hypoglycemia—metabolic sequelae that resuscitation is aimed at correcting.[53] Weak fetuses are often born with strongly beating hearts but have difficulty initiating adequate inspiratory efforts to expand their lungs. Positive pressure ventilation is required to overcome surface tension in alveoli and the elastic recoil of lung tissue. Fluid within alveolar spaces and the lumen of the tracheobronchial tree is absorbed into the pulmonary interstitium most efficiently at thoracic pressures between 35 and 40 cm H_2O.[5] Less pressure is usually needed for succeeding breaths. Intrathoracic pressure that exceeds 40 cm H_2O increases the risk of damaging the alveolar epithelium. Observation of chest wall movement is a more reliable sign of appropriate inflation pressures than pressure readings from a manometer. Nasal insufflation with oxygen does not facilitate resorption of lung fluid and is largely ineffective.

If an endotracheal tube and a laryngoscope are available the fetus should be intubated. Placing a rigid stylet in the endotracheal tube and positioning the neonate in sternal recumbency with head and neck extended makes intubation easier. Calves may also be intubated blindly via palpation of the larynx. Ventilation of asphyxiated newborn neonates with 100% oxygen is usually recommended, but experimental work with newborn pigs and a study in humans suggest room air may be as effective.[54,55] Ventilation with a pulmonary resuscitation bag (Ambu bag) with a pressure relief valve set at 42 cm H_2O avoids inadvertent overinflation.[56] If a laryngoscope and an endotracheal tube are not available, positive pressure ventilation can be achieved using an esophageal feeding tube. The tube is passed into the esophagus with the fetus in right lateral recumbency. The distal end of the tube is located approximately one third of the distance “down” the neck. The esophagus is compressed distal to the end of the tube, with one hand taking care not to trap the trachea, and the muzzle is gripped with the other hand to seal the nares. The operator then blows into the tube and, providing the esophageal and muzzle seals are good, air is delivered into the lungs.[57] Direct mouth-to-mouth resuscitation is unhygienic and delivers air mainly into the abomasum. Respiratory stimulant (analeptic) drugs, such as doxapram hydrochloride, may be used to stimulate respiration in neonates but should be used judiciously, as the stimulatory action of the drug is nonselective. Convulsions may be observed with repeated administration, increasing the demand for O_2 in an already hypoxic neonate.[58] Analeptics should not be used as a substitute for ventilatory support.

Fig. 16-1 Supplies for a “crash box.”

Ambu bag
Oxygen mask
Oxygen cylinder, regulator, and pressure relief valve
Nasal insufflation tubing
Endotracheal tubes
Laryngoscope
KY jelly
Brown gauze, umbilical tape, and adhesive tape
Razor
IV catheters, T-ports, PRNs, and suture
J wire
Needles and syringes
Emergency surgery pack, scalpel blades and surgical gauze
Fluids (saline, lactated Ringer's, and dextrose), administration and extension sets
Blood collection tubes and needles
Drugs (epinephrine, lidocaine, prednisolone, doxapram, sodium bicarbonate, calcium chloride, and dopamine) (observe necessary storage requirements)

Progressive hypoxia and tissue acidosis lead to bradycardia, decreased cardiac contractility, and eventually cardiac arrest. If apnea progresses to cardiopulmonary arrest, artificial circulation in the form of cardiac massage needs to be provided, along with positive pressure ventilation. Cardiac massage in lambs and kids is performed by compressing the ventral thorax behind the elbows between the thumb and two fore fingers. Cardiac compressions in calves is achieved by placing the patient in lateral recumbency and compressing the ventral thorax behind the elbows against a sandbag placed under the calf in a position opposite the resuscitator's hands. Effectiveness of cardiac compressions may be monitored by checking for a palpable pulse and by observing changes in mucous membrane color. When available, an electrocardiograph is useful to monitor the electrical activity of the heart. Abdominal wrapping is used in human and small animal medicine during cardiopulmonary resuscitation to improve myocardial perfusion by returning pooled venous blood from the abdomen and limbs to the central compartment and by reducing the runoff of arterial blood to the caudal periphery.[59] Treatment with epinephrine is recommended for asystole or if the heart rate stays below 60 beats/minute. Epinephrine increases systemic vascular resistance, redistributing circulation away from the periphery to the cerebral and myocardial circulation, and increases myocardial contractility, heart rate, and cardiac output. Epinephrine is initially administered at a dose of 0.02 mg/kg either intravenously or intratracheally (via the endotracheal tube). There are reports of cases in the human literature in which there was no response to this dose but responses were observed to doses as high as 0.2 mg/kg.[60] High-dose epinephrine therapy may increase the risk of acute renal failure and intracranial hemorrhage and is not recommended as a primary treatment.[53] Peak plasma concentrations of epinephrine are achieved 60 seconds after

endotracheal administration. Plasma concentrations of epinephrine after endotracheal administration are approximately 10 times lower than those achieved with intravenous administration, so intravenous access should be established as soon as possible.[61] Administration of large doses of epinephrine endotracheally to compensate for the reduced absorption is associated with prolonged hypertension and is not recommended.[62] In an emergency the endotracheal route of drug administration may be used for other lipid-soluble drugs such as lidocaine or atropine but should not be used for non—lipid-soluble drugs.[63] When drugs are administered by the endotracheal route, they should be instilled as deeply as possible into the tracheobronchial tree using a catheter inserted beyond the tip of the endotracheal tube.[64] Dilution of the drug in 1 to 2 mL of saline may aid drug delivery. Rapid intravenous infusion of warm isotonic fluid (lactated Ringers 20 to 40 mL/kg) increases the circulating fluid volume and may help to compensate for the increased vascular volume. The use of sodium bicarbonate, atropine, and calcium chloride in cardiopulmonary resuscitation of neonates is controversial. A basic protocol for resuscitation of the newborn is presented in Fig. 16-2.

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Fig. 16-2 Resuscitation of the neonate.

The rationale for sodium bicarbonate administration in the presence of lactic acidosis is to increase extracellular pH and thereby improve cardiac function, perfusion and oxygenation of peripheral tissues, intracellular pH, and lactate metabolism.[65] Sodium bicarbonate administration is associated with production of carbon dioxide; correction of the acidosis requires removal of the CO_2, which is dependent on adequate ventilation and pulmonary blood flow. If pulmonary ventilation or pulmonary blood flow is inadequate, administration of sodium bicarbonate will result in hypercarbia. Excessive administration of sodium bicarbonate causes alkalemia and a right shift in the oxygen-hemoglobin dissociation curve, reducing oxygen availability to tissues. Paradoxic CNS acidosis has been documented in association with bicarbonate administration during cardiopulmonary resuscitation,[66] and acute intracellular potassium shifts secondary to sodium bicarbonate therapy may be associated with an increased incidence of cardiac arrhythmias.[67] Administration of sodium bicarbonate is recommended only if adequate ventilation has been established and when all other measures have not been successful.[68] The dose is 1 to 2 mEq/kg administered by slow intravenous injection. Because catecholamines are inactivated by bicarbonate and because calcium will precipitate when mixed with bicarbonate, intravenous catheters should be flushed between infusions of drugs.[64]

Use of atropine in resuscitation is based on its peripheral effects as a competitive antagonist of acetylcholine, reducing vagal tone and increasing conduction through the atrioventricular node. The effect of atropine is dependent on the degree of vagal stimulation that is causing the bradycardia. Vagal stimulation is not the cause of bradycardia in hypoxic newborns; therefore a response is unlikely. Possible deleterious effects of atropine administered at therapeutic doses are increased myocardial oxygen consumption and precipitation of atrial and ventricular tachyarrhythmias.[69] In low doses atropine stimulates the medullary vagal nuclei, causing paradoxic bradycardia with slowing of atrioventricular conduction.[70]

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The belief that increasing the availability of calcium during cardiac arrest might improve myocardial function led to inclusion of calcium chloride in cardiopulmonary resuscitation protocols. Calcium has been implicated as a cause of postresuscitation cerebral ischemia, as high levels of calcium promote prolonged vasoconstriction, exacerbating cerebral and myocardial hypoperfusion.[71] Currently administration of calcium chloride is recommended only in cases of known hypocalcemia and hyperkalemia.

16.3.1 Postresuscitation Care

After resuscitation it is important to closely monitor cardiopulmonary function. Steroids have been recommended to reduce postischemic cerebral edema via preservation of membrane integrity, inhibition of prostaglandin and free radical formation, lysosomal membrane stabilization, and preservation of vascular membrane permeability, but there is no documented evidence demonstrating their effectiveness.[72] The β_1-agonist dopamine may be administered via a continuous slow intravenous infusion (2 to 10 µg/kg/min) if peripheral perfusion is poor, as indicated by decreased capillary refill, absent or decreased pulses, cool extremities, tachycardia, and oliguria. Infiltration of dopamine into tissues can produce local tissue necrosis. Dopamine, like epinephrine, is inactivated in alkaline solutions and should not be administered in sodium bicarbonate.[64] Serum electrolytes, blood gases, and blood glucose should be periodically monitored if laboratory support is available, and appropriate fluid therapy administered to correct deficits. Positioning the newborn in sternal recumbency and provision of oxygen via nasal insufflation helps the compromised neonate maintain blood oxygen saturation. Body temperature should be monitored closely, and heating lights and pads provided. During the course of the first 24 hours of life the newborn should receive approximately 15% of its body weight in colostrum. If the coordination of the newborn is questionable, colostrum should be tube-fed to avoid

aspiration. Immunoglobulins are often absorbed poorly by the compromised neonate, so passive transfer should be evaluated at 18 hours of age and plasma administered if the plasma immunoglobulin concentration is less than 400 mg/dL.

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17 Chapter 17 Initial Management and Physical Examination of the Neonate

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17.1 APPROACH TO THE HIGH-RISK OR COMPROMISED NEONATAL FOAL

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The abnormal large animal neonate often presents diagnostic and management challenges to the veterinarian. Familiarity with neonatal characteristics and behavior, as well as with neonatal disease processes, is critical for a successful outcome. Despite dramatic advances in neonatal intensive care, many foals still die, not because their primary problem is untreatable, but because veterinary intervention was delayed, delivery was unattended, neonatal compromise was not recognized in a timely fashion, or critical care was unavailable or not economically feasible (Box 17-1). It is absolutely essential to recognize abnormalities *early* in the course of the disease process. Large animal neonates are born with few nutritional, physiologic, or immunologic reserves. Any condition that prevents them from standing and nursing soon after birth represents a potentially fatal condition. Unfortunately, signs of illness in the neonate are frequently vague and nonlocalizing. Many high-risk newborn animals look relatively good during the first hours after birth. This “grace period” is often followed in 12 to 24 hours by a worsening of condition because of the specific disease process itself as well as disruption of normal adaptive processes. The presence of one localizing sign such as diarrhea may obscure the fact that other organ systems are involved as well. Multiple problems in the same individual seem to be the rule rather than the exception.

Many weak foals begin to fade as a result of a series of problems that need to be systematically addressed. Therefore diagnosis on the basis of physical examination alone is extremely difficult. Prompt collection of a complete database (history, hematologic assessment, clinical chemistries, immunoglobulin status, radiographs, and ultrasonography) is often necessary to form a realistic idea of the neonate's problems and prognosis. The veterinarian must initiate treatment for the specific disease process while addressing the unique metabolic demands and physiologic instability of the newborn.

Another neonatal tendency that is extremely important in dictating the time course of clinical diagnosis, monitoring, and intervention is the rapidity with which changes in condition can occur, either for better or worse. Even a short delay in institution of therapy can make the difference between success and failure. The placentation of the large animal fetus does not allow transfer of immunoglobulins from mother to fetus in utero, and the newborn is dependent on the ingestion of colostrum shortly after birth for the majority of its immunoglobulins. Even with a normal level of circulating immunoglobulin, the immune system of the neonate is not as effective as that of the adult, and if failure of passive transfer of immunoglobulins occurs (see Chapter 53), the neonate is at higher risk for acquiring severe, generalized infections. A foal should be considered high risk if any of the abnormal periparturient events listed in Box 17-1 have been observed.

17.2 EXAMINATION OF THE POSTPARTUM MARE AND PLACENTA

When accompanying a sick newborn foal, the mare should be evaluated thoroughly, and a complete foaling history should be acquired (see Chapter 15).

If available, the fetal membranes should be weighed and examined for integrity, abnormal thickening, discharges, villous atrophy, and other abnormalities. The placenta should be scrutinized systematically for valuable information about the in utero environment.[1,2] Fetoplacental infection, associated with bacterial, viral, and fungal agents, is one of the most important causes of abortion, stillbirth, and perinatal mortality in the equine species.[3] Normal placental weight for thoroughbreds ranges from 4.5 to 6.4 kg (10 to 14 lb) or about 11% of the foal's body weight[4]; placentas that weigh over 6.4 kg should be considered potentially abnormal (edema or placentitis), and those that weigh less than 4.5 kg may be incomplete or have severe villous atrophy.

Cases of chronic placentitis are usually recognized by thickening and discoloration of the chorion. Because most intrauterine infections begin as an ascending placentitis of the chorioallantois, the area of discoloration and thickening originates at the cervical star and extends up the body of the placenta. Acute cases of placentitis may require histopathologic examination for a diagnosis.[5] If placentitis is suspected, fetal fluids or membranes should be cultured, and sections of amnion and chorioallantois should be saved in formalin for histopathologic examination. Organisms most commonly associated with endometritis may also be associated with placentitis. Pathogens include *Streptococcus zooepidemicus, Leptospira* species, *Escherichia coli*, nocardioform actinomycetes, fungi, *Pseudomonas aeruginosa, Streptococcus equisimilis, Enterobacter agglomerans, Klebsiella pneumoniae,* and alpha-hemolytic *Streptococcus*.[6,7] Diffuse placentitis is associated with hematogenous spread of infection such as seen with *Leptospira* infection. Nocardioform placentitis is characterized by focally extensive placentitis at the base of the placental horns at the junction of the horns and the body of the uterus.[7] The affected placenta is usually covered with thick, tenacious brown exudate. Fungal placentitis often results in a sticky brown mucoid exudate covering parts of the chorion and is often associated with the birth of a small, emaciated foal.[5] Sabouraud's agar should be used to isolate suspected fungal pathogens. A direct smear of the exudate can be examined with Gomori's methenamine silver stain.[6] *Aspergillus* and *Mucor* species are the most common fungal pathogens isolated.[8] Systemic fungal infection of the foal is relatively rare.

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17.2.1

Box 17-1 Periparturient Events Associated with High-Risk Neonates

17.2.1.1

PREPARTUM EVENTS

Premature udder development and/or precocious lactation in the dam

Severe maternal illness

Severe maternal malnutrition

Exposure to endophyte-infected fescue within 2 months of delivery

Inadequate prenatal maternal immunization

Advanced maternal age

17.2.1.2 PARTURIENT EVENTS

- Premature delivery
- Prolonged gestation
- Premature placental separation
- Meconium staining of fetus, placenta, and/or fluids
- Agalactia
- Severe dystocia
- Cesarean section
- Induced delivery
- Grossly abnormal or heavy placenta (>11% of foal's body weight)

17.2.1.3 POSTPARTUM EVENTS

- Failure of neonate to stand and nurse within 3 hours of delivery
- Low Apgar score
- Abnormal physical examination findings including generalized weakness, poor suckle, severe angular limb deformities, enlarged or bleeding umbilicus, patent urachus, respiratory distress, diarrhea, colic, or other signs of localized infection

Pending culture results, the foals from grossly abnormal placentas should be considered at high risk of being infected. Such foals should have a blood culture submitted and their leukogram and creatinine concentration evaluated. Prophylactic treatment with broad-spectrum antibiotics is indicated.

If the chorioallantois is unusually heavy, it may fail to rupture at the cervical star, resulting in premature or abnormal placental separation with the rupture of membranes occurring near the base of one horn. Foals may experience bouts of hypoxia associated with such deliveries. Early postpartum treatment with drugs, such as dimethyl sulfoxide (DMSO) or mannitol, to decrease cerebral edema is indicated at the first signs of neonatal hypoxic ischemic encephalopathy (i.e., dummy foal syndrome).

Adenomatous hyperplasia of the allantois may appear as hyperplasia and hypertrophy of the epithelial cells of the allantois with the formation of intraepithelial glands. More severely affected membranes may have raised firm tan nodules on the allantoic surface of the chorioallantois.[9] These lesions consist of dilated, anastomosing glands surrounded by loose, collagenous stroma. Inflammatory changes are thought to be secondary to the adenomatous dysplasia. The cause of this lesion is not known, but it is seen with chronic placentitis, placental edema, and fetal diarrhea.[6,9] Umbilical cord abnormalities may also affect the fetus.[10] Granular debris and golden meconium particles on the amniotic portion of the cord suggest local inflammation. An excessively long umbilical cord (normal range is 36 to 83 cm) may result in strangulation of the fetus with evidence of edema and vascular occlusion around the head and neck. If there is excessive twisting of the cord, there may be compromised fetal circulation and/or obstruction of the urachus. Urachal obstruction may contribute to urachal patency or bladder rupture. An unusually short cord is prone to premature rupture and hemorrhage and may predispose the foal to hypoxic injury.

The mare's udder, milk, and reproductive tract should be carefully examined. After birth the quality of colostrum may be assessed by visual inspection (thick, sticky) or by colostrometer (specific gravity <1.060 is normal) (see Chapter 53). A full, distended udder usually indicates that the foal is not nursing adequately, but in rare instances it may accompany mastitis. In mares with mastitis the milk may appear normal on visual inspection. A flaccid and empty udder may indicate either an aggressively nursing foal or a mare that is not lactating sufficiently. One way to distinguish the two is to muzzle the foal for 1 to 2 hours and then check the amount of milk in the udder.

The mare's reproductive tract should be evaluated if there is a history of vaginal discharge, retained placenta, or traumatic birth or if the mare appears sick or febrile. The mare's appetite and manure production should be monitored. Postpartum mares are at increased risk for developing gastrointestinal disease. Causes of colic in the postpartum mare include impaction of the large colon or cecum, cecal rupture, large colon displacement, large colon torsion, rectal prolapse with rupture of the mesocolon, ischemic necrosis of the descending colon, diaphragmatic herniation of abdominal viscera into the thorax, rupture of the uterine artery, hematoma formation within the broad ligament or uterine wall, peritonitis secondary to uterine trauma, rupture, or prolapse, and metritis.

Diagnostic aids include a careful history of events surrounding delivery. Prepartum maternal problems such as hydrops or prepubic tendon rupture and ventral abdominal hernia formation predispose to specific problems. Hydrops, if severe, can result in uterine rupture, leading to postpartum peritonitis. Prepubic tendon rupture and rectus abdominis damage can produce intraperitoneal inflammation leading to intraabdominal adhesions, bowel trauma, and peritonitis. A history of dystocia increases suspicions of intrauterine trauma, uterine rupture, metritis, and peritonitis. Dystocias have also been associated with bowel damage including cecal rupture. If the mare experienced rectal prolapse, she is at increased risk for rupture of the mesocolon and secondary disruption of blood supply to the descending colon resulting in intestinal ischemic necrosis and peritonitis. Retained fetal membranes increase the risk of metritis and secondary peritonitis.

It is common practice to feed mares a laxative diet following parturition to reduce the risk of impaction. The mare should be dewormed within 24 hours after delivery to reduce the foal's parasite exposure.

17.3 RESTRAINT OF THE FOAL

The uncooperative nature of many neonatal foals can seriously limit the quality of care provided, and identification of effective restraint techniques often becomes a concern equal in importance to medical therapy. In general, procedures should be performed as quickly and quietly as possible. For minor procedures such as venipuncture, most foals can be successfully restrained in the standing position, with the foal held against a wall or in a corner of

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the stall. One of the restrainer's arms is placed around the foal's chest, and the opposite hand grasps the tail base and holds the tail up over the rump. If foals are held too tightly, they tend to collapse, then leap forward. Alternatively, most foals stand well when both ears are held tightly at the base; this technique also provides excellent access to the jugular vein.

For procedures that are more involved and time-consuming, it is highly recommended that foals less than 2 weeks of age be placed in lateral recumbency. The use of local anesthetic placed with a small needle facilitates catheter placement and arterial blood gas collection. Additional details concerning foal restraint can be found in other texts.[11]

17.4 PHYSICAL EXAMINATION OF FOALS

Guy D. Lester

17.4.1 Physical Appearance and Bodyweight

The degree of physical maturity should be considered in relation to the estimated gestational age. This assessment should be made in light of the variable gestational length in horses. Typically, gestational length is calculated from the time of insemination through birth, which overestimates the true gestational period by as much as 7 days. The mean gestational period in thoroughbreds is approximately 340 to 342 days, with 95% of mares foaling at 327 to 357 days.[12] There are a number of factors that influence this period, including breed, gender, and the time of year. Colts on average have a gestational length that is approximately 1.5 to 2.5 days longer than that of fillies. They also are slightly heavier, are slower to stand, and have a heavier placenta.[13] Mares that develop a pregnancy early in the breeding season have longer pregnancies than those that conceive late in the season. This can affect gestational length by as much as 10 days.[12,14] In some but not all breeds it has been suggested that dam, sire, and dam's sire play a role in determining gestational period.[15] Physical characteristics of immaturity include low birthweight, small body size, short and shiny hair coat, doming of the head, periarticular laxity, and droopy ears. Foals with a shortened gestational period and signs of physical immaturity are termed *premature,* whereas foals that are physically immature in the face of an appropriate gestational length are termed *dysmature*. Foals born after 356 days should be regarded as postterm. Such foals are distinguished from foals that are postmature, a condition of increased morbidity as a consequence of failing placental function.[15] Postmature foals tend to have a lean and lanky physical appearance. Numerous factors influence a foal's body weight at birth including breed, gender, gestational age, and intrauterine environment. Estimates of body weight for newborn thoroughbred foals for the purpose of drug calculation range between 40 and 55 kg, although many healthy foals may well exceed this range.

17.4.2 Foal Behavior

Normal foals achieve sternal recumbency with a raised head within minutes of birth. They also should be highly responsive to a range of tactile, visual, and auditory stimuli within 5 minutes of delivery.[16] Attempts to rise should begin within 30 minutes. Initial attempts may be unsuccessful, but most foals are standing with control by 1 hour of age (mean 57 minutes; range 15 to 165 minutes).[17] Initially the stance is characteristically wide-based, with moderate truncal swaying both forward and backward and from side to side. The suck reflex should be present within minutes of birth and should be vigorous by 30 minutes. After a period of adjustment the normal foal will eventually discover the mare's udder and begin sucking. This is typically achieved before 2 hours (mean 111 minutes; range 35 to 420 minutes); most foals have sucked twice by 2½ hours of age. Sucking periods vary

in duration between 1 and 5 minutes and are interspersed with periods of sleep that last approximately 7 minutes. A foal that spends long periods at the udder may not be getting an adequate intake of milk.

It is important to watch the foal during sucking to confirm appropriate teat contact and swallowing movements. The foal should also be observed after sucking for evidence of nasal regurgitation of milk. The normal neonatal foal spends approximately one third of its life recumbent; this is in contrast to the adult horse, which spends 5% to 10% of a 24-hour period in recumbency. An important part of the physical examination is assessment of the foal's attitude. Normal foals are bright, alert, and very responsive to environmental stimuli. They should be curious and demonstrate frisky play at as early as 2 hours of age. Galloping can be observed by as early as 6 to 7 hours of age. Normal parameters for the foal are listed in Tables 17-1 to 17-3.

Recommendations to clients as to when veterinary intervention should be sought vary from practice to practice. The "1-2-3" rule is often quoted: the foal should be standing by 1 hour after birth, the foal should have sucked by 2 hours, and the placenta should be cleared by 3 hours. Some have translated this into a "2-4-6" rule for clients: seek veterinary attention if the foal has not stood by 2 hours, the foal has not sucked by 4 hours, or the placenta has not been cleared by 6 hours. These recommendations are used only as a rough guide and will obviously be influenced by peripartum conditions and client experience.

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Table 17-1 Normal Physical Examination Parameters of the Neonatal Foal and Calf

Parameter	Foal	Calf
Gestational age	241 days (327-365) <320 days = premature	278-282 (Holstein) 281-282 (Shorthorn) 292 (271-310) Brahma
Time to suckling reflex (stimulated by placing a finger in the mouth)	2-20 min	2-20 min
Time to stand	57 min (15-165 min) <2 hr abnormal	60-158 min 60-228 min without dam
Time to nurse from mother	111 min (35-240 min) <3-4 hr abnormal	104 min
Body temperature	37° C-38° C (99° F-102° F) AM nonstressed value	37° C-38° C (99° F-102° F)
Heart rate	1-5 min postfoaling <60 beats/min 6-60 min postfoaling 80-130 beat/min Day 1-5 80-120 beats/min	90-110 beats/min
Respiratory rate	Postfoaling for 30 min 60-80 breaths/min 1-12 hours in sternal recumbency 30-40 breaths/min	

Table 17-2 Normal Hematology Reference Values for Neonatal Foals

	Gestational Age (Premature Foals)			Postnatal Age (Term Foals)	
Parameter	**300-309 Days Mean**	**310-319 Days Mean**	**320-334 Days Mean**	**1 Day Mean ± SD**	**2-7 Days Mean ± SD**
RBC ($\times 10^6$/μL)	9.6	10.1	11.3	10.5 ± 1	9.26 ± 0.8
Hb (g/dL)	13.1	14.1	13.2	14.4 ± 1.1	13.2 ± 1.2
PCV (%)	41	42	43	42.0 ± 3.6	36.5 ± 3.1
MCV (fl)	42.7	42.2	38.6	40.2 ± 3.6	39.4 ± 2.3
MCH (pg)	14	14.4	11.8	13.6 ± 1.1	14.5 ± 1.1
MCHC (%)	32.4	33.8	30.5	33.8 ± 2	36.2 ± 1.1
Icterus index (u)				40.0 ± 15	30.3 ± 15
Total plasma protein (g/dL)				6.1 ± 0.8	6.4 ± 0.6
Fibrinogen (mg/dL)				243 ± 74	310 ± 90
Total WBC/μL	5000	6800	4900	8632 ± 2570	9075 ± 2200
Neutrophils/μL	1230	1540	1940	6381 ± 2225	6528 ± 2000
Bands/μL			2960	<50	50
Lymphocytes/μL	3720	5090		2021 ± 2225	2203 ± 575
Monocytes/μL				222 ± 160	305 ± 145
Eosinophils/μL				0	22
Basophils/μL				8	17
Neutrophil:lymph ratio	0.33	0.3	0.66	3.16	2.96

Hb, Hemoglobin; *MCH*, mean corpuscular hemoglobin; *MCHC*, mean corpuscular hemoglobin concentration; *MCV*, mean corpuscular volume; *PCV*, pack cell volume; *RBC*, red blood cell; *WBC*, white blood cell.

Table 17-3 Normal Serum Biochemical Reference Values for Normal-Term Postnursing Foals

	Age	
Parameter	**1 Day Mean ± SD**	**4–7 Days Mean ± SD**
Sodium (mEq/L)	139.7 ± 6	139.5 ± 4.2
Potassium (mEq/L)	4.4 ± 0.9	4.5 ± 0.4
Chloride (mEq/L)	103.5 ± 3	101.3 ± 4
Bicarbonate (mEq/L)	22.9 ± 3.4	34.3 ± 2.1
Calcium (mg/dL)	11.7 ± 1.1	11.4 ± 0.8
Inoganic phosphorus (mg/dL)	5 ± 0.85	6.4 ± 0.8
Magnesium (mg/dL)	2.2 ± 0.35	2.7 ±0.15
Glucose (mg/dL)	136 ± 40	150 ± 30
BUN (mg/dL)	18.9 ± 4.3	13.6 ± 536
Creatinine (mg/dL)	2.3 ± 0.6	1.3 ± 0.3
Total bilirubin (mg/dL)	4.3 ± 2.2	4.4 ± 1.1
Direct bilirubin (mg/dL)	0.5 ± 0.2	0.8 ± 0.4
Indirect bilirubin (mf/dL)	3.8 ± 1.5	3.5 ± 1.1
Alkaline phosphatase (IU/L)	2282 ± 1100	1949 ± 1100
GGT (IU/L)	29.6 ± 15	18.3 ±7.3
ADH (IU/L)	2 ± 0.9	2 ± 0.9
AST (SGOT) (IU/L)	154 ± 55	225 ± 60
LDH (IU/L)	487 ± 100	490 ±100

AST, Aspartate aminotransferase (SGOT); *BUN,* blood urea nitrogen; *GGT,* γ-glutamyltransferase; *LDH,* lactate dehydrogenase; *SDH,* sorbitol dehydrogenase.

A potentially critical consequence to a delay in the onset of feeding is failure of passive transfer of maternal immunoglobulin. Foals should be supplemented with 20 mL/kg of good-quality colostrum by bottle or tube ideally before 6 hours of age. Measurement of serum immunoglobulin G (IgG) should be made between 12 and 18 hours of age. A normal foal that has consumed adequate amounts of colostrum will have a serum IgG measurement substantially greater than 800 mg/dL. Failure of passive transfer is generally defined as a serum IgG less than 400 mg/dL; partial failure of passive transfer is used when the serum IgG is between 400 and 800 mg/dL. Many authors have identified an association between low serum IgG and morbidity and mortality, most commonly caused by sepsis. Tetanus prophylaxis, in the form of antitoxin (1500 IU), should be administered to foals with untreated failure of passive transfer.

A modified Apgar score has been used in foals to semiquantitate the severity of signs that occur in response to peripartum asphyxia (Table 17-4).[18] In human neonatal practice the acronym stands for activity, pulse, grimace,

appearance, and respiration. The modification used in equine practice refers to appearance, pulse, grimace, attitude, and respiration. Appearance refers to oral mucous membrane color; pulse is self-explanatory and uses 60 beats per minute (bpm) as a cutoff; grimace is assessed in response to stimulation of the nasal mucosa, the inside of the pinnae, and the region over the thoracolumbar area adjacent to the spine; attitude reflects the degree of muscle tone; and respiration refers to ventilation rate and rhythm, with 30 breaths per minute as the cutoff. Each category is scored from 0 to 2 points, with a score of 10 being optimal. A score of 0 to 3 indicates marked depression; 4 to 6, moderate depression; and 7 to 8, mild asphyxial injury. Normal foals have a score of 9 or 10. Ideally the modified Apgar calculation should be made within the first minute after birth, but certainly within 15 minutes of delivery. Repeating the score 4 minutes later is recommended. Foals with low scores typically require aggressive resuscitation, whereas mildly affected foals may respond to vigorous rubbing, stimulation of the nasal mucosa, and limb movement.

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Table 17-4 Apgar Score: Assessment of Neonatal Asphyxia[19]

Parameter	0 Points	1 Point	2 Points
APPEARANCE	Gray or blue mucous membranes	Pale pink mucous membranes	Pink mucous membranes
PULSE (beats per minute [bpm])	Absent	<60, irregular	60, regular
GRIMACE			
Nasal stimulation Ear tickle Thoracolumbar stimulus	No response No response No response	Grimace Head and neck motion Head and neck motion	Strong grimace, sneeze Ear tickle, head shake Attempt to stand with head, neck, limb motion
ATTITUDE (muscle tone)	Limp, lateral recumbency	Semisternal, some limb flexion	Sternal
RESPIRATION (breaths per minute)	Absent	<30, irregular	30, regular, can whinny

17.4.3

Maternal Behavior

Any intervention should be made in consideration of the impact it may have on the relationship between the mare and the foal. Maternal behavior toward the foal is instinctive and can be modified or disturbed through excessive veterinary intervention. Maternal recognition is largely dependent on smell, and treatments may alter foal odor, thereby interfering with the normal bonding process. Separation of foal and mare may be unavoidable if necessary treatments are to be provided; however, maintenance of an environment in which the mare has continual access to her foal with respect to sight and smell is ideal. It is important to distinguish refusal to suck from true rejection; the latter commonly involves aggression toward the foal. Mares may be reluctant to allow the foal to suck if they are experiencing pain from udder edema, pelvic or perineal disease, or primary gastrointestinal problems. In addition, uterine contractions associated with passage of the fetal membranes may also cause transient discomfort in the mare. Management is dependent on recognition and treatment of the underlying problem. This may include provision of analgesia, local therapy of the udder (heat therapy, massage), and oxytocin (10 to 15 IU given intramuscularly [IM]) to facilitate milk letdown. Tranquilization with acepromazine may also be helpful.

Maiden mares commonly, and multiparous mares occasionally, demonstrate signs of confusion, fear, and anxiety with the arrival of a newborn foal. This usually results in sudden movement of the hindquarters away from the foal as it attempts to find the udder, mare squealing, and heightened sensitivity. Mares may attempt to bite or kick the foal if they are unable to escape. This is accentuated by placement into a busy or noisy environment, typical of many veterinary practices in spring. The most successful approach to managing anxious mares is through a combination of a low-stress environment, tranquilization, and patience. It is important to avoid threatening verbal or physical punishment, as this only heightens the mare's anxiety. The use of a grazing muzzle or hobbles may be needed to reduce the risk to the foal from kicking or biting.

Risk factors for foal rejection include first birth, a history of previous rejection, disruption to the environment (e.g., forced separation, noise), and breed.[20,21] Rejection may occur more often in Arabian mares and more commonly within certain family lines within the breed.[21]

17.4.4 Body Temperature

Rectal temperature in foals reportedly ranges from 99° F to 102° F (37.2° C to 38.9° C) during the first 4 days after birth.[17] The upper end of the normal range, which is approximately 1° F (0.6° C) above the upper end of the adult range, is strongly influenced by environment and exercise. Temperature can be variable in foals with systemic sepsis; in the early stages of sepsis the rectal temperature is commonly within the normal range or mildly elevated. Foals in septic shock usually have a low rectal temperature, and those with localized infection often are febrile.

17.4.5 Cardiovascular System

Physical assessment of the cardiovascular system includes examination of visible mucous membranes, palpation of peripheral arterial pulses, assessment of extremities for warmth, detection of limb or ventral edema, and cardiac auscultation. In the foal, preferred sites for subjective assessment of pulse rate, regularity, and strength include the dorsal metatarsal artery, the brachial artery, and the carotid artery. The dorsal metatarsal artery is easily palpated in healthy foals on the lateral aspect of the third metatarsal bone. The brachial artery is palpated at the level of the medial collateral ligament of the elbow joint. Reduced pulse pressure can be caused by a range of diseases including systemic sepsis, perinatal asphyxia, and prematurity. Indirect blood pressure monitoring is most commonly performed using an automated oscillometric device with a cuff positioned around the base of the tail or over the dorsal metatarsal artery.[22] These devices reasonably reflect direct pressure measurements when used carefully with several repetitions. There are important limitations of indirect or direct blood pressure measurement in overall assessment of the cardiovascular system. In healthy foals the correlation between arterial blood pressure and cardiac output, one of the best available parameters to assess circulatory function, is acceptable but decreases significantly when there is altered systemic vascular resistance—a circumstance that is likely common to several common diseases. Recent descriptions of noninvasive methods to measure cardiac output, such as volumetric echocardiography, have shown good correlation with more robust but invasive techniques in anesthetized foals. The question remains if this correlation will be sustained in critically ill foals.

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Cardiac auscultation is an important part of the physical examination of the newborn foal. This should include auscultation of both the left and right hemithorax. The heart rate can be highly variable in neonates and is dependent on age. Immediately after delivery the rate is around 60 bpm (range of 40 to 80 bpm), and it increases over the first several hours of life to approximately 120 bpm. This should stabilize to within a range of 80 to 100 bpm during the first week. Increases associated with activity and excitement should be expected. Cardiac

arrhythmias occur commonly during the first hour after birth in apparently healthy neonatal foals; most arrhythmias are restricted to the initial 15 minutes of postpartum life. These include atrial premature contractions, paroxysmal atrial fibrillation, atrioventricular block, ventricular premature contractions, and ventricular tachycardia.[23–25] Most are attributable to hypoxia and high vagal tone. Cardiac arrhythmias after an hour of age should be considered abnormal.

Cardiac murmurs are also commonly auscultated in foals during the early neonatal period. The vast majority are localized to the left heart base and are considered to be physiologic rather than pathologic. The presence of a continuous murmur is consistent with patency of the ductus arteriosus. In most foals the systolic component of the murmur is louder and therefore more obvious than the diastolic component. The murmurs are therefore often described as *holosystolic*, with a point of maximal intensity on the left hemithorax, in the third intercostal space, and at the level of the scapulohumeral joint. Audible continuous murmurs are unlikely to persist for more than 3 days; however, the systolic component of the altered flow may linger for a week or longer in normal animals. It is commonly believed that many neonatal systolic murmurs with a point of maximum intensity over the left outflow tract may be a result of left ventricular ejection rather than flow through the ductus arteriosus. This would be similar to physiologic flow murmurs commonly heard in young adult horses. There are a number of observations that should prompt referral for echocardiographic assessment. These include persistence of any loud murmur, particularly if it is radiating or associated with a precordial thrill, and any signs of cardiac disease including weakness, cyanosis, pulmonary edema, ascites, or unexplained dependent edema. Bacterial endocarditis is rare in the neonate but certainly in older foals should be considered if the cardiac murmur is associated with fever, leukocytosis, and hyperfibrinogenemia. Many congenital heart defects have been reported in foals, with a wide variation in clinical signs and age of presentation. The most common congenital heart abnormality is a ventricular septal defect. Myocardial dysfunction has been reported in association with systemic sepsis in foals. Cardiac troponin I (cTnI) and the cardiac isoenzyme of creatine kinase (CKMB) are both elevated in foals with sepsis, although the elevation does not accurately predict survival.[26]

17.4.6 Respiratory Tract

The respiratory rate, rhythm, and depth should be assessed as part of the physical examination of the neonate. The respiratory rate and tidal volume are markedly increased during the first 60 minutes of postnatal life. Rates approaching 80 breaths per minute are not uncommon during this time, after which there should be a steady decrease to approximately 30. Respiratory rhythm will vary with the level of consciousness. In foals with hypoxic-ischemic brain disease, periodic breathing patterns are common, including Cheyne-Stokes and erratic rhythms that may include lengthy apneic pauses, occasionally exceeding 30 seconds. *Cheyne-Stokes respiration* refers to periods of apnea and hypopnea that alternate with periods of hyperventilation. Both respiratory frequency and tidal volume are affected.[27] It is possible that periodic breathing may contribute to the pathology associated with the syndrome. Auscultation of the respiratory tract is an essential part of the examination but can be misleading. Moist rales are normally present throughout the respiratory cycle after birth because of residual fluid within the airways. Asymmetry of air movement and end-inspiratory crackles are also normal findings as a result of simple atelectasis of the dependent lung during lateral recumbency. These typically resolve within minutes of standing. Conversely, foals can have significant lung disease yet few abnormal findings on thoracic auscultation. Added to this problem is the absence of cough and nasal discharge in many neonates during the early phases of lower airway disease.

Thoracic trauma and rib fracture can occur as a complication of second-stage labor. Costochondral dislocation can occur in as many as 20% of births. Fractures of the rib shaft occur far less commonly and can on rare occasions cause significant clinical disease and death. This can include hemothorax, lung laceration and

pneumothorax, and pericardial and myocardial puncture. Diagnosis is by observation of thoracic wall symmetry and synchrony, palpation, and imaging (ultrasound or radiography). Management is typically conservative unless displacement of shaft fragments is identified over key underlying structures.

17.4.7 Oral Cavity and Nasal Passages

Oral mucous membranes should be assessed for color, moisture, and refill time. Normal foals have membranes that are moist, are pale pink, and have a capillary refill time (CRT) of approximately 1.5 to 2 seconds. Given the importance of the intestinal system in the genesis of neonatal sepsis, it is recommended that the veterinarian have clean hands, or preferably be gloved, during this part of the overall examination. In the initial stages of systemic sepsis the membranes develop a bright red color with a brisk CRT. This is usually accompanied by episcleral congestion and reddening of the coronary bands. As septic shock ensues, the membranes darken and the refill time becomes prolonged. The presence of mucosal hemorrhages is most consistent with disseminated intravascular coagulation (DIC) associated with advanced systemic sepsis. A rare cause of mucosal petechial hemorrhages is neonatal alloimmune thrombocytopenia. Affected foals may demonstrate prolonged bleeding after routine venipuncture. A subset of affected animals may also have oral and lingual vesicles and ulcers and widespread ulcerative dermatitis with crusting. These foals are typically weak and are reluctant to suck from the dam because of oral pain. The condition appears to be self-limiting and resolves within 2 weeks, presumably because of removal of alloantibodies. Icterus of the oral mucous membranes can occur in association with bacterial or viral sepsis, as a consequence to hemolysis (as in neonatal isoerythrolysis or certain clostridial infections), or as a benign process, idiopathic neonatal hyperbilirubinemia. In hemolytic diseases of the newborn the yellow discoloration of the membranes is often superimposed on pale membranes. Blue or blue-gray discoloration of the membranes can occur with severe hypoxemia or circulatory collapse. Cyanosis can result from pulmonary or cardiac causes. The nasal passages should be examined for fluid or discharge. The presence of orange to brown fluid at the nares immediately after birth is consistent with meconium aspiration. Passage of meconium into the amniotic sac indicates prepartum stress.

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Dental problems are uncommon in newborn foals with the exception of problems associated with facial deformities, such as maxillary prognathism, mandibular prognathism, and campylorrhinus. The central incisors usually erupt during the first 5 to 7 days of life. The middle incisors rise between 4 and 6 weeks of age, but the corner incisors do not erupt until 6 to 9 months. In miniature horses and ponies the eruption of the middle and corner incisors is delayed at 4 months and 12 to 18 months, respectively. The 12 temporary molars are present at birth or erupt within the first week of life. *Maxillary prognathism* or *parrot mouth* describes the condition in which the mandible is shorter than the maxilla, producing an overjet or overbite. The condition may affect the incisors, check teeth, or both. It is the most common congenital oral malformation of foals. The incidence has been reported to be 2% to 5%. Severe manifestations of the condition often coexist with other developmental abnormalities. A genetic basis is suspected (simple autosomal recessive) but has not been definitively established. *Mandibular prognathism* or *sow mouth* describes the condition in which the maxilla is shorter than the mandible, producing an underbite. It occurs less commonly than the maxillary equivalent. *Campylorrhinus (wry nose, wry face)* describes the condition in which the premaxilla and nasal septum are deviated laterally. The condition may occur singularly or in combination with other deformities, such as wry neck, cleft palate, and maxillary or mandibular prognathism. If the deviation is severe, the foal may have great difficulty in sucking from the mare. There may also be problems with breathing. However, in most foals the deviation is mild and represents a simple but obvious cosmetic defect. As with other facial deformities a heritable basis is possible; therefore breeding is not recommended. Cleft palate is an uncommon congenital defect of foals that results from incomplete fusion of the lip and/or secondary palate during the early gestational period. It has an estimated incidence of 0.1% to 0.2% of all births. Almost all clefts occur in the secondary palate, the horizontal partition dividing oral and nasal cavities. The secondary palate includes all of the soft palate and most of the hard palate,

with the majority of the defects restricted to the soft palate. The basis of this congenital defect is not known but could include a heritable component and/or exposure of the developing fetus to infection, toxins, or nutritional disturbances.

The most common clinical sign is nasal regurgitation of milk immediately after sucking. Foals with small-palate defects may have intermittent milk drainage from the nostril and consequently escape diagnosis during the neonatal period. There are rare reports of cleft palates being initially diagnosed in adult horses. Most will develop an aspiration pneumonia that can be difficult to identify in its early stages because of immaturity of cough receptors. Surviving foals will typically be poorly grown and ill-thrifty. The diagnosis is usually straightforward and centers on an appropriate history and signalment. Confirmation is through palpation using the third finger or by direct inspection of the oral cavity. Smaller defects may be detected by endoscopic examination of the nasal passages or through the oral cavity under anesthesia. Oral palpation is recommended for all sick neonatal foals before commencing potentially costly treatment.

The presence of milk at the nares after feeding is not considered pathognomonic for a cleft palate. Many foals with this condition do not have the defect but rather delayed or altered coordination of the swallowing reflex. Clinical signs may be noted as early as a few hours of age and persist variably from hours through weeks. The basis of the condition is not known, but generalized weakness, hypoxic-ischemic brain disease, and nutritional myodegeneration (white muscle disease) have all been suggested as possible causes (Box 17-2). Soft-palate displacement may also occur in newborn foals as a result of a persistent frenulum between the ventral aspect epiglottis and base of the tongue or with hypoplasia of the epiglottis.[28] Chronically affected foals develop signs consistent with aspiration pneumonia, including cough, ill-thrift, and failure to grow. The diagnosis is confirmed through endoscopy of the nasopharynx; persistent dorsal displacement of a flaccid soft palate and dorsal collapse of the nasopharynx are typical findings. The palate will not replace during attempts to swallow. The procedure is important to rule out congenital defects of the palate and epiglottis, although endoscopy of the oral cavity under short-acting anesthesia may be necessary to rule out more obscure problems such as persistent frenulum or epiglottic hypoplasia. Radiography and ultrasound are useful diagnostic tests to confirm the presence and extent of a ventral consolidating pneumonia. Pharyngeal and subepiglottic cysts are uncommon in newborn foals but when present may be associated with dysphagia and nasal regurgitation of milk. Other clinical signs may include a respiratory noise, cough, and dyspnea. Diagnosis is by endoscopy and radiography. Treatment options include ablation using sharp dissection, laser ablation, or a snare.[29] Esophageal diseases are rare in the newborn foal. Reported conditions include congenital dilatation or ectasia, tubular or cystic esophageal duplication, megaesophagus, motor dysfunction, and stricture. Most descriptions are in foals outside of the neonatal period.

17.4.7.1

Box 17-2 Differential Diagnoses of Nasal Regurgitation of Milk

Cleft palate

Persistent dorsal displacement of the soft palate

Pharyngeal and subepiglottic cysts

White muscle disease

Hyperkalemic periodic paralysis

Guttural pouch tympany

Prematurity or dysmaturity

Forced bottle feeding

Esophageal disease

17.4.8 Eyes and Associated Structures

Several ocular features are unique to the newborn foal. These include a round pupil, reduced corneal sensitivity, prominent lens Y sutures, and persistence of blood in hyaloid artery remnants. The optic disc tends to be round rather than oval and has smooth margins. Normal newborn foals lack the ability to completely close their eyelids (lagophthalmos).[30] Entropion is one of the more common ocular problems in newborn foals. The condition primarily affects the lower lid and involves inward rolling of the lid margin such that the eyelid hairs may cause abrasion to the cornea. It rarely occurs as a primary event and is usually secondary to dehydration or emaciation. Temporary eversion using vertical mattress sutures or staples is highly effective at reducing the risk of corneal damage; a less preferred method involves subcutaneous injection of procaine penicillin into the lid. Surgical treatment for entropion is rarely indicated and should be reserved for older foals only. Corneal ulceration occurs commonly in sick neonatal foals. An important feature of the newborn foal is significantly reduced corneal sensitivity when compared with adult horses.[31] This may in part explain why the signs of corneal disease in foals differ markedly from similarly affected adults. Cardinal signs of keratitis, including blepharospasm, photophobia, and excessive lacrimation, are often absent in the early stages of disease in neonates. There are a number of risk factors for corneal abrasion in foals, including the high prevalence of entropion, the propensity for prolonged recumbency, and the frequency of seizures and colic. The key to management is early recognition. In many hospital practices daily fluorescein staining is part of the routine management of most sick foals. The frequent use of lubricating ointments may also play an important prophylactic role in preventing eye disease.

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Careful examination of the globe may reveal signs of iridocyclitis. This can be unilateral or bilateral and usually is regarded as an ocular manifestation of systemic sepsis. In very young foals the presence of fibrin or hypopyon may indicate in utero bacterial exposure, often caused by placental infection. Likely the most common cause of blindness during the neonatal period can be directly or indirectly linked to asphyxial brain injury. In many of these foals the loss of vision is attributable to cortical disease, as pupillary light reflexes are usually preserved. The prognosis for future vision is usually good. Cortical blindness can also result from prolonged generalized seizures. The menace response is not a reflex and is considered to be a learned behavior in newborn foals. The characteristic eyelid blink and ocular retraction may be absent during the first 1 to 2 weeks of postnatal life, but most foals still demonstrate head withdrawal in response to a threatening hand gesture, assuming an adequate level of alertness. Neonates should blink when a bright light is directed into the eye (bright light blink or dazzle reflex) and should have brisk direct and consensual pupillary light reflexes.

There may be a slight ventromedial rotation of the eyeballs in normal foals; this persists for the first month.[16] Spontaneous nystagmus in any direction is abnormal, but vestibular nystagmus is present when the head is moved in a horizontal plane in healthy foals. The fast phase of the nystagmus is in the direction of head movement. Subconjunctival and scleral hemorrhage is a feature of foals born after dystocia. This can be an

important warning sign of impending postasphyxial problems such as hypoxic-ischemic encephalopathy. The sclera should also be examined for signs of blood vessel congestion, a feature of sepsis, and for icterus. The differential diagnosis for neonatal icterus is discussed elsewhere. Most foals with an abnormally small globe (congenital microphthalmos) are blind, have a reduced palpebral fissure, and have a prominent nictitans.[30] The condition may be unilateral or bilateral, and it has been suggested that thoroughbred foals may be more commonly affected.[30] Foals are at increased risk for ulceration resulting from associated entropion. Microphthalmia has been reported to occur along with mandibular prognathism and cleft palate in foals exposed to griseofulvin during the second month of gestation.[32] Congenital cataracts are relatively common eye defects in foals. Veterinarians should be careful not to misinterpret lens sutures as cataracts. These Y-shaped sutures may persist for up to a year. Assuming a normal retina, an absence of uveal tract inflammation, and an appropriate demeanor, most of these foals are candidates for surgery. Other abnormalities include atresia of the nasolacrimal system, dermoids, retinal dysplasia, and optic nerve hypoplasia.

17.4.9 Ears

Ear problems occur uncommonly in foals. It is, however, important to examine the inside of the pinnae for dermal ecchymotic or petechial hemorrhages. Foals with systemic sepsis may develop these lesions.

17.4.10 Thyroid Gland

Hypertrophy of the thyroid gland (goiter) can occur in response to deficient or excess dietary iodine. One of the more common reasons for thyroid gland enlargement in neonatal foals is excess iodine supplementation during pregnancy.[33] There are reports of neonatal goiter when seaweed was incorporated into the diet of broodmares[34] or when pellets that had been formulated with excessive iodine were fed to mares.[35] Dysmature foals with thyroid hyperplasia and concurrent musculoskeletal problems have been identified in western Canada and the northwestern United States.[36,37] The syndrome results in hypothyroidism and may be related to the feeding of diets that are high in nitrate or low in iodine to mares during pregnancy. Thyroid hormone is an important cofactor in maturation of the respiratory system, and hypothyroidism has been linked to respiratory failure in a newborn foal.[38] In older foals, enlargement of the thyroid has been associated with dietary iodine deficiency and low circulating levels of T_4.[33] Newborn foals have baseline T_3 and T_4 levels that are considerably greater than those of adult horses.[39] These levels decline over the first 12 days after birth. Normal day-old foals have a doubling of T_3 at 3 hours and a 16% increase in total T_4 at 6 hours after TSH administration.[40]

17.4.11 Neck and Back

There are a number of congenital anomalies that affect the alignment of the vertebral column. These include atlantoaxial malformations, scoliosis, kyphosis, lordosis, and combined anomalies, such as kyphoscoliosis. Atlantoaxial malformations may occur with or without cervical scoliosis or signs of spinal cord compression. Arabian foals are most commonly affected, and a familial predisposition has been suggested.[41] There may be palpable abnormalities of the atlas and axis and altered head carriage. The diagnosis is confirmed using radiography, with which a range of abnormalities is seen including atlantooccipital fusion, hypoplasia of the dens, and axis malformation. Prognosis is very poor, as many foals have signs of ataxia and paresis involving all four limbs at birth. Some animals may have normal neurologic function. Foals with severe kyphosis or kyphoscoliosis often have underlying malformation of the thoracic vertebrae.[42]

17.4.12 Gastrointestinal Tract

Borborygmi should be easily heard in healthy neonates. Assessment of abdominal size and shape is part of the routine physical examination. This is critical in assessment of the foal with abdominal pain or decreased urine output. In contrast to small animals, in neonatal foals abdominal palpation is usually unrewarding. In small foals with relaxed abdominal muscles it may be possible to palpate meconium impactions and the urinary bladder. When abdominal distention is present, it is important to determine if it is a result of fluid or gas accumulation. Ultrasound has become an essential tool in the assessment of abdominal distention.

The routine administration of an enema is performed commonly in healthy newborn foals in an attempt to reduce the straining associated with the passage of meconium. Various methods are used, with commercial glycerine phosphate—based products the most common. These are relatively easy to administer, although care should be taken to avoid direct trauma to the rectal mucosa with the applicator tip. Most veterinary practices probably use gravity enemas of 400 to 800 mL of warm soapy water delivered through a soft tube, such as a canine stomach tube or male urinary catheter. Acetylcysteine retention enemas are not administered routinely, but rather in foals with resistant meconium impactions.

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Coprophagy is observed in normal foals from birth through 5 to 6 months of age.[43–45] Most foals demonstrate coprophagy by 7 days of age. The consumption of feces is not driven by hunger, and foals have a selective preference to consume feces of their dams. The most likely basis for coprophagy is as a mechanism to populate the intestinal tract with bacteria, fungi, and protozoa essential for digestion of an herbivorous diet. Coprophagy precedes the passage of protozoa in foal feces and the development of the syndrome known as “foal heat diarrhea.” This is a benign diarrheal disease of newborn foals and should not require treatment.

17.4.13 Umbilicus

Breakage of the umbilical cord occurs naturally within 5 minutes of birth, with the natural break typically 2.5 to 7 cm beneath the body wall. Immediate postpartum transfusion of blood from the placenta to the foal is important, although the process is essentially complete within minutes, assuming establishment of a respiratory rhythm. Premature breakage of the cord can result in significant blood loss—up to one third of the circulating fetal blood volume.[46] Hemorrhage should therefore be controlled with a commercial clamp or umbilical tape. Prolonged attachment of the cord is unlikely to be a significant problem, although blood flow between the placental membranes and the foal is partly gravity dependent, such that blood could flow preferentially from foal to membranes if the foal is above the level of the placenta. Manual breakage of the umbilical cord is recommended if it remains attached for more than 8 minutes. The preferred method for manual cord breakage is to grasp the placenta side of the cord while holding the foal side of the cord with the other hand to prevent excessive traction on the abdominal wall. Gently twist and pull from the placenta side such that the breakage will occur at the natural site of detachment. The umbilical cord should not be cut, as this does not promote normal retraction of the umbilical structures. The cut umbilical stump usually remains prominent, often with detectable pulse, and is more likely to be associated with hemorrhage or patency of the urachus. Bleeding from the umbilicus can also occur after apparent closure if the foal is straining to either defecate or urinate. Clamping or tying off the stump again can reduce this. The exposed umbilical stalk is a portal for bacterial entry. Any manipulation of the cord should be performed with clean, gloved hands. Routine disinfection of the stump is strongly recommended during the first 2 days of postnatal life or until the stump has dried. Most hospitals use 0.5% chlorhexidine solution as the preferred dipping agent, but some advocate a 2% iodine solution for use by clients, as its use can be verified by the characteristic iodine staining.

The appearance of the umbilical stump changes over the first few days after birth. The external stump should be examined for size and moisture. A complete assessment of the umbilical remnants requires ultrasound. The most common problems of the umbilical stump are patency of the urachus and infection. Tearing of the urachus as it moves through the body wall can produce a circle of cellulitis around the stump because of leakage of urine into the tissues.

Umbilical hernias occur relatively commonly in foals. The condition is generally considered to be a congenital defect with a likely hereditary basis, although umbilical infection may be an important postnatal predisposing factor in some foals. In a study from the Netherlands 19 of 44 Dutch Warmblood foals had a palpable abdominal wall defect varying between 2 and 6 cm at the time of birth.[47] In all but one of these foals the defect had closed by 4 days of age. Of interest was that approximately 28% of the foals developed a defect at 5 to 8 weeks of age. These were considered to be true umbilical hernias in that a hernial sac with contents was palpable in addition to the abdominal wall defect. The group included both foals with and foals without a palpable abnormality at birth. In a retrospective study of hospitalized foals it was concluded that the defect was more likely to occur in fillies than in males and that the condition was more common in thoroughbreds than in standardbreds.[48] Most clinicians recommend delay in treatment, as some defects will close spontaneously. Several techniques have been described for repair and vary from external clamps to surgical herniorrhaphy. Rare complications are associated with umbilical hernias or their repair. These include enterocutaneous fistulas, umbilical abscessation, and intestinal incarceration.[49,50]

17.4.13.1

Diagnosis of Umbilical Disorders Using Ultrasound

JOHN E. MADIGAN

Ultrasonography has been used to quantitatively correlate umbilical structural changes with age in foals. Mean diameters for selected umbilical structures derived from 13 foals ranging from 6 hours to 4 weeks of age have been reported.[50a] Foals may be examined in a stall adjacent to their dams and near the stall door. Foals are made to lie down without sedation, using the method shown in Fig. 17-1. Foals will usually become quiet and still within a few minutes of recumbency. All ultrasound examinations are performed with the foal in left lateral recumbency with the ultrasound machine behind the examiner (Fig. 17-2).

Fig. 17-2 includes a diagram of the anatomic locations of the structures examined during the ultrasound evaluation. A 5- to 8-cm-wide strip of hair can be clipped along the ventral midline, extending from the umbilical stump cranial to the xiphoid to facilitate examination of the umbilical vein. In addition, an area 5 cm by 5 cm caudal to the umbilical stump is clipped to visualize the umbilical arteries and urachus. The ultrasound examination is performed with a 7.5-MHz sector scanning transducer; a built-in standoff is preferred. Eight views of the umbilical vessels and linear measurements of the vertical and horizontal dimension of each vessel can be taken. This allows examination of the umbilical vein (three views) and umbilical stump (one view) (Fig. 17-3), and urachus/umbilical arteries (four views) (Fig. 17-4). The umbilical vein is visualized at a site approximately 1 cm cranial to the umbilical stump (view 1); another view taken approximately halfway between the umbilicus and the liver (view 2) and at a point where the vein curves away from the body wall and angles toward the liver (view 3). A single cross-sectional view of the external umbilical stump is made at the body wall. The combined urachus/left and right umbilical artery is visualized in a single cross-sectional view just caudal of the umbilical stump. The comparative mean umbilical vessel diameter normal data is summarized in Table 17-5. All but one of the ultrasound views demonstrated a significant reduction in mean vessel diameter over the first 7 days of life in normal foals; only the urachus and

umbilical arteries in a single structure remain static during the first week of life. Enlargements in these structures are suggestive of inflammation, infection, or hematoma and should be correlated with clinical signs and laboratory findings for choosing an optimal treatment plan.

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Fig. 17-1 Procedure for placing neonatal foals in lateral recumbency for umbilical ultrasound. **A,** The foal is restrained by placing the arms around the neck area and rump and holding the tail. **B,** The left forearm of the handler is placed against the head of the foal, and the head is folded back toward the rump area while pressure is applied to the rear quarters with the other arm. **C,** The foal leans backward and sags toward the handler, becoming recumbent. **D,** The foal is allowed to sag to the ground and is kept in the folded position until completely recumbent and relaxed. **E,** The front legs are then grasped with left hand and the forearm is placed on the neck area. The rear legs are held with the right hand. **F,** The foal is held steady in this position until blindfolded and struggling stops. The foal is in left lateral recumbency.

17.4.14 Urogenital System

Urine is one of the most important indicators of health in foals. Normal neonatal foals produce a large volume of urine relative to their bodyweight; estimated at 148 mL/kg/day, this value is approximately fivefold to tenfold greater than that of a healthy adult horse on a per kilogram of bodyweight basis.[51] The urine should be light in color and low in specific gravity. Any foal observed to pass thick, concentrated urine should be assessed closely. The first passage of urine after birth occurs around 8-9 hours of age.[52] Colts will pass urine earlier than fillies, at approximately 6 hours of age in colts and 11 hours in fillies. Disruption to the urinary tract occurs relatively commonly and can be difficult to diagnose early in the clinical course. Rupture of the urinary bladder during delivery occurs more commonly in colts than in fillies, although postpartum disruption to the tract in sick or hospitalized foals has no gender bias.[53,54] Signs often include prolonged straining, passage of small volumes of urine, progressive abdominal distention, lethargy, and weakness.

In colt foals the inguinal and scrotal region should be palpated for swelling and testicular descent. Inguinal and scrotal hernias occur relatively commonly but rarely result in clinical signs. Preputial edema may be present. Most congenital hernias are indirect, unilateral, and easily reducible and spontaneously resolve by 3 to 4 months of age. Positioning the foal on its back facilitates manual reduction. A figure 8 support wrap can assist in keeping the hernia reduced. Surgical correction is recommended if spontaneous resolution is delayed, if the hernia increases in size, or if signs of colic develop. Certain breeds appear to be at increased risk for herniation, including Tennessee Walking Horses and standardbreds. A rent in the parietal vaginal tunic can lead to subcutaneous dissection of intestinal loops; this requires surgical reduction, herniorrhaphy, and unilateral castration.[55] Although such rents are extremely uncommon in foals, signs of colic can occur if herniated loops of intestine strangulate.

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Fig. 17-2 Ultrasound evaluation of equine umbilical structures. Diagram depicts the positioning of the ultrasonographer and the assistant and the selected anatomic locations recommended for ultrasound examination.

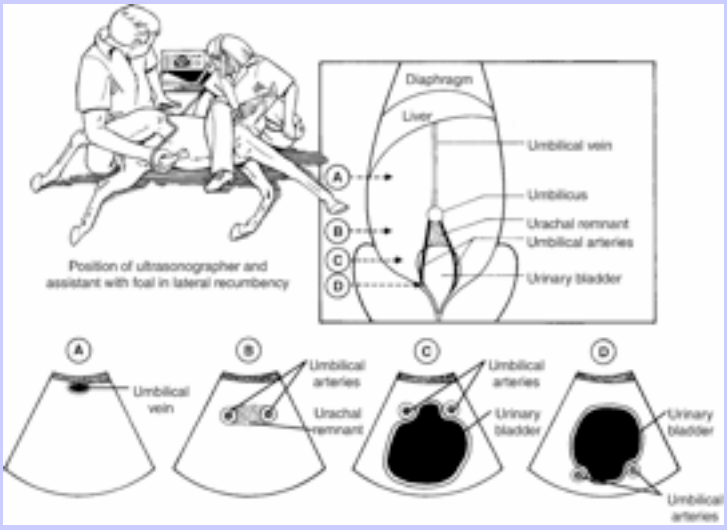

Fig. 17-3 Ultrasonogram images of four views of umbilical structures: umbilical vein views 1 **(A),** 2 **(B),** and 3 **(C),** and umbilical stump **(D).** Refer to the text for the definition of the views.

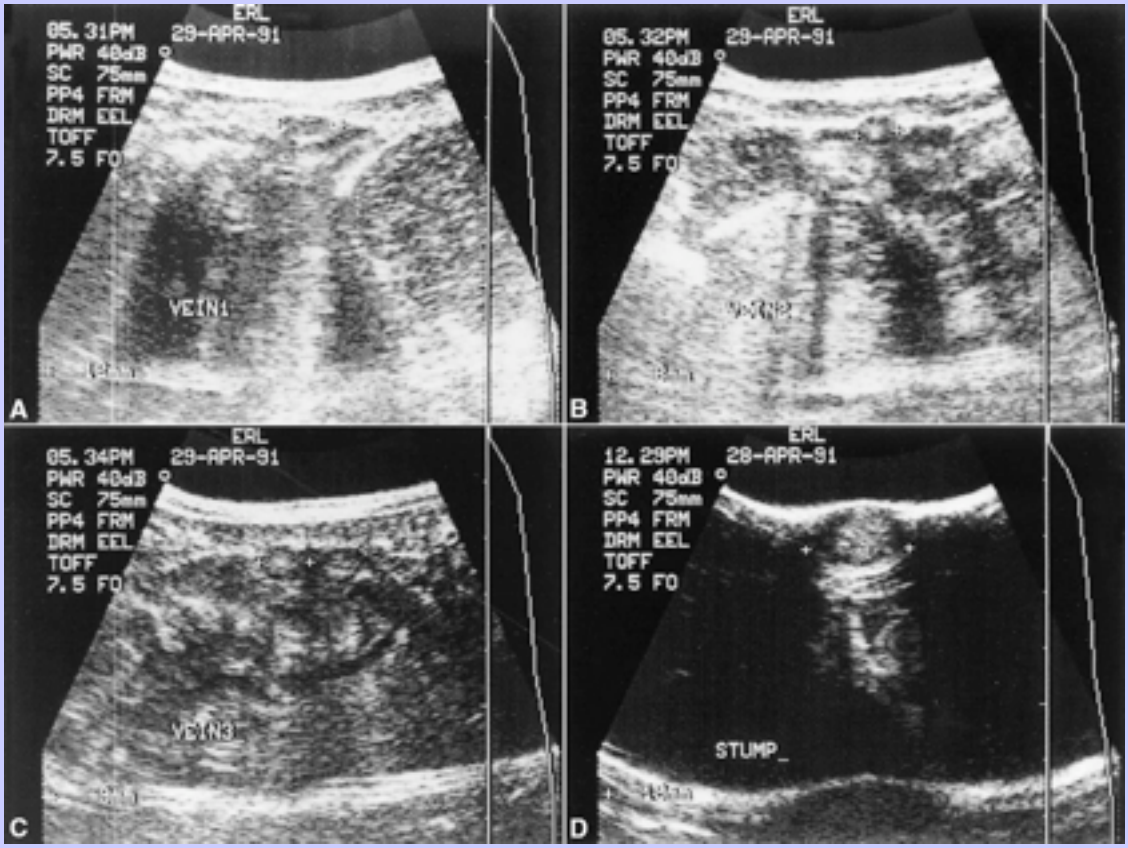

Fig. 17-4 Ultrasonogram images of four views of umbilical structures: urachus **(A),** umbilical arteries views 1 **(B),** 2 **(C),** and 3 **(D).** Refer to the text for the definition of the views.

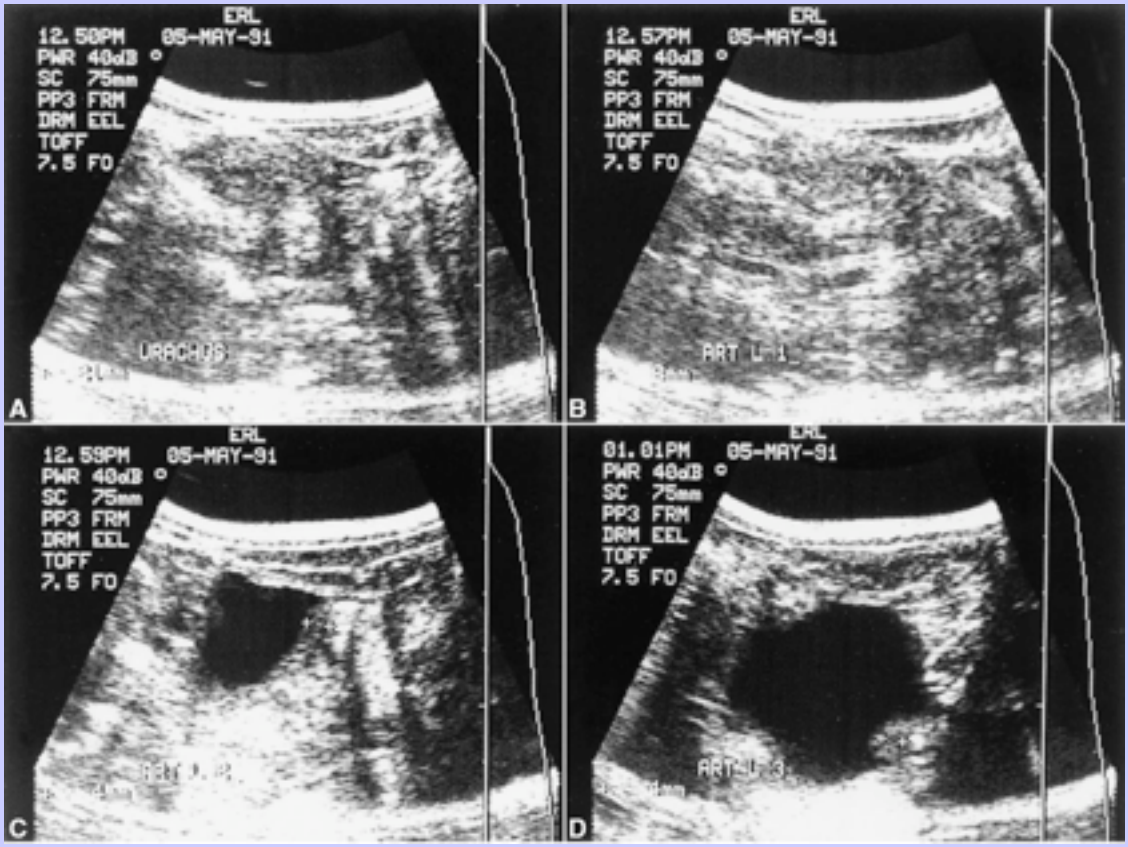

Table 17-5 Comparative Mean Umbilical Vessel Diameters (mm) for 31 Clinically Normal Foals on the First and Seventh Days of Age (Mean ± SD)

	Postnatal Age		
Vessel	**2-24 Hours**	**7 Days**	***p* Value**
UMBILICAL VEIN			
View 1 (range)	8.3 ± 3 (5-18.5)	5.8 ± 1.5 (4-11.5)	p <.0001
View 2 (range)	7.5 ± 1.4 (5–11)	5.4 ± 0.8 (4–7)	p <.0001
View 3 (range)	8.3 ± 1.4 (6–11)	5.4 ± 1.3 (3.5-10.5	p <.0001
Overall (range)	8 ± 2.1 (5-18.5)	5.6 ± 1.3 (3.4-11.5)	p <.0001
Umbilical stump (range)	15.5 ± 2.7 (10.5-20.5)	12.5 ± 2.3 (7.5-18)	p <.0001
Urachus + arteries (range)	17.7 ± 2.7 (13.5-24)	17.8 ± 2.6 (13–25)	p =.4781
UMBILICAL ARTERIES			
View 1 (range)	7.8 ±1.7 (4.5-13)	6.4 ± 1.5 (4–10)	p <.0001
View 2 (range)	7.4 ± 1.6 (4-13.5)	6.7 ± 1.3 (4-10.5)	p <.002
View 3 (range)	7.1 ± 1.6 (4-12.5)	6.5 ± 1.4 (3.5-9.5)	p <.01
Overall (range)	7.5 ± 1.6 (4-13.5)	6.5 ± 1.4 (3.5-10.5)	p <.0001

At the time of birth most testes lie within the inguinal canal. The extraabdominal gubernaculum typically limits movement into the scrotum. The mass of gubernaculum can easily be mistaken for the testicle. Monorchidism has been reported in foals, and affected colts are usually mistaken as cryptorchids.[56] Congenital abnormalities of the penis are rare. Failure to drop the penis during urination can occur as a consequence of preputial edema, a common complication in colts that are straining to defecate or urinate. The free part of the penis is normally fused to the internal lamina of the prepuce for up to 1 month of age. This can make exteriorization of the penis difficult. “Kinking” of the penis has been described, resulting in stranguria or pollakiuria.[57] Correction was achieved through manual straightening of the penis.

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17.4.15 Musculoskeletal System

Supplementation of foals with selenium is recommended for those born in known selenium-deficient regions when mares have not been supplemented during pregnancy. Severe rhabdomyolysis has been reported in newborn foals, usually associated with selenium deficiency.[58] Glycogen branching enzyme deficiency is an inherited cause of mortality in quarter horse foals.[59] Clinical signs are variable and include seizure, persistent recumbency, respiratory failure, and cardiovascular collapse. Authors of the original report suggested that the generalized nature of the clinical signs would likely lead to a false diagnosis of other, more common neonatal diseases.

Because of the rapid growth that occurs in the first months of life, any orthopedic condition must be identified and immediately managed in order to achieve a successful long-term outcome. Palpation of synovial structures is

a critical part of the foal physical examination, regardless of whether lameness or synovial distention is present. Persistent recumbency, a common feature of generalized sepsis, can make detection of joint infection difficult. Synovial sepsis is a common manifestation of bacterial infection, and most affected foals will be lame with obvious joint distention and heat on palpation. Diagnosis is confirmed through synoviocentesis. An elevated synovial fluid white blood cell (WBC) count (>20,000 cells/μL), a predominance of neutrophils (>90%), and an elevated protein concentration (>4 g/dL) all point toward sepsis. Osseous infection can also be difficult to identify in its early stages. Common sites include the stifle, hock, and distal physis of the cannon bone. Osteomyelitis should be suspected in any foal with lameness and edema, heat, and pain on palpation of the overlying tissues. Trauma by the mare is often suspected, but osseous infection should always be considered, particularly in foals with other manifestations of sepsis (e.g., omphalitis, diarrhea, uveitis). There may or may not be effusion in adjacent joints, and if present it could reflect either an extension of the septic process or a nonseptic “sympathetic” effusion. The management of synovial and bone infection is discussed elsewhere.

Contractural deformities of the limbs occur commonly in newborn foals. These are considered to be congenital and may result from a variety of causes including malpositioning within the uterus. If the foal is able to stand and ambulate, most mild deformities of the carpus, fetlock, and coffin joint will resolve within 4 to 5 days without specific treatment.[60] Moderately to severely affected foals often require splinting in combination with medical therapy in order to achieve a successful outcome in the shortest possible time. Foals with persistent or prolonged recumbency are very susceptible to secondary problems, the most important being sepsis and corneal abrasion. Medical therapy often includes judicious use of oxytetracycline and nonsteroidal antiinflammatory drugs. Rupture of the common digital extensor within the synovial sheath may occur in foals with contractural or flexural deformities. This should be suspected in foals with a soft, nonpainful swelling over the dorsolateral aspect of the carpus. Gait may appear stilted, and there may be knuckling of the fetlock. Most foals quickly regain extensor function, and the long-term prognosis is good.

Hyperextension or joint laxity is common in premature and dysmature foals. The most common presentation involves dropping of the fetlock, hyperextension of the pastern, weight bearing on the heel bulbs, and tipping upward of the toe. Again, most foals improve spontaneously over 3 to 4 days, but heel extensions and light padding to protect the heels from bruising will hel more severely affected foals. Hyperextension of the carpus is also observed in some foals.

Angular limb deformities are also frequently encountered in practice; the most common deviations are carpal and tarsal valgus and fetlock varus. Examination should include observation at rest from front and rear, paying careful consideration to any external rotation of the limbs, which may give a false impression of limb valgus. In weak or premature foals there may be limb deviation resulting from ligamentous laxity; this is best assessed through limb palpation including flexion and observation of the foal at the walk. If the limb can be straightened manually, then the deviation is due to ligamentous laxity or delayed ossification of the cuboidal bones.[60] There is a variety of conservative and surgical approaches to these foals.

Laminitis with sloughing of the hoof capsule can occur in neonatal foals; however, it is rare and is typically associated with significant systemic disease. Polydactylism is a duplication of all or part of the digit. This condition can occur as a single defect or as part of a group of congenital anomalies. Surgery may be indicated when the condition occurs as a single entity, not only to improve the cosmetic appearance but also to reduce the risk of lameness at a later age.

17.5 POSTPARTUM ASSESSMENT, PHYSICAL EXAMINATION, AND CARE OF NEWBORN RUMINANTS

John K. House

17.5.1 Neonatal Behavior

Calves and lambs normally have a head-righting reflex almost immediately after birth. Sternal recumbency is usually attained within 2 to 3 minutes, followed rapidly by attempts to stand, at 10 to 20 minutes for lambs and 15 to 30 minutes for calves.[61,62] Hypoxic neonates may struggle and appear bright initially but have difficulty maintaining sternal recumbency, have depressed or absent suck reflex, are slow to stand or remain recumbent, and develop a depressed mentation within hours. After experimentally induced hypoxia, nonviable hypoxic calves had heart rates (118 ± 36 bpm) and body temperatures (39.6° C ± 0.2° C) similar to those of viable calves but lower respiratory rates (14 and 18 versus normal 49 ± 12).[61] In cattle the average time from birth to standing and nursing varies according to breed. The average time from birth to standing and nursing for beef calves is 35 and 81 minutes, respectively. Dairy calves take approximately twice as long.[63] Small ruminants are generally quicker to stand and nurse than calves, with most lambs standing within 30 minutes[62] and nursing within 90 minutes of birth. Failure of the newborn to nurse may result from reduced neonatal vigor, poor mothering, poor maternal conformation, or adverse conditions such as slippery flooring. Calves have difficulty locating teats on low-slung udders (less than 45 cm from the ground)[64] and difficulty nursing from teats greater than 35 mm in diameter.[65] Observation of interaction between the newborn and dam in the immediate postnatal period allows early recognition of the compromised neonate and facilitates timely intervention if maternal conformation or behavior threatens to impede the neonate's efforts to nurse.

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Abnormal neonatal behavior in the immediate postnatal period is commonly secondary to perinatal hypoxia. Resuscitation of the newborn is discussed in Chapter 16. In utero infections and congenital neurologic abnormalities should also be considered as possible causes of abnormal neonatal behavior. Collection of sera before feeding colostrum is useful for diagnosing in utero infections. Precolostral serum immunoglobulin concentrations in calves are very low (IgM 0.126 ± 0.015 mg/mL, IgG 0.044 ± 0.003 mg/mL).[66] Elevated serum concentrations of immunoglobulins before ingestion of colostrum may be observed with in utero infections.[66] Specific serologic tests are available for Cache Valley virus, Akabane virus, bovine virus diarrhea (BVD) virus, *Neospora* species infection, *Toxoplasma* infection, and bluetongue virus.[67] Teratogens and inherited diseases that may cause the birth of weak neonates are listed in Box 15-3.

Tube-feeding colostrum during the first 12 hours of life is appropriate if free-choice consumption is questionable. Drying, warming, and tube-feeding colostrum may revive weak newborn lambs and kids. Tube-feeding dairy calves 3 L of colostrum at birth is recommended, as failure of passive transfer is high (61%) in dairy calves left to nurse their dams.[68]

Table 17-6 Normal Hematology Reference Values for Neonatal Calves[118,119]

	Age			
Parameter	**Birth**	**24 Hours**	**48 Hours**	**3 Weeks**
RBC (×10^6/μL)	9.35 ± 1.02	8.17 ± 1.34	7.72 ± 1.09	8.86 ± 0.68
Hb (g/dL)	12.86 ± 1.85	10.93 ± 2.05	10.49 ± 1.8	11.32 ± 1.02
PCV (%)	41 ± 6	34 ± 6	32 ± 6	35 ± 3
MCV (fl)	43.2 ± 2.4	41 ± 2.8	41.1 ± 2.3	39.1 ± 1.9
MCHC (g/dL)	31.3 ± 1.1	32.1 ± 0.8	32.6 ± 1.0	32.8 ± 1.6
Total WBC/μL	13.99 ± 5.73	9.81 ± 2.8	7.76 ± 1.95	8.65 ± 1.69
Neutrophils/μL	10,940 ± 5,700	6480 ± 2660	4110 ± 2040	2920 ± 1140
Bands/μL	100 ± 150	310 ± 460	210 ± 450	10 ± 30
Lymphocytes/μL	2980 ± 2730	2730 ± 820	2850 ± 880	5050 ± 800
Monocytes/μL	590 ± 660	230 ± 210	350 ± 280	620 ± 330
Eosinophils/μL	0	20 ± 40	20 ± 30	20 ± 40
Basophils/μL	0	0.02 ± 0.05	0.02 ± 0.05	0.02 ± 0.04
TP (g/dL)	4.8 ± 0.3	6.4 ± 0.7	6.4 ± 0.7	6.4 ± 0.3
Fibrinogen (mg/dL)	258 ± 138	288 ± 105	335 ± 116	283 ± 147
Urea nitrogen (mg/dL)	6.36 ± 2.36	7.52 ± 2.13	6.93 ± 3.13	
Creatinine (mg/dL)	4.14 ± 1.27	1.69 ± 0.35	1.27 ± 0.24	
Total bilirubin	0.34 ± 0.66	1.28 ± 0.5	0.89 ± 0.41	
Sodium (mEq/L)	141 ± 3.77	135 ± 2.86	135 ± 3.68	
Potassium (mEq/L)	6.1 ± 1.86	5.46 ± 0.56	5.63 ± 0.96	
Chloride (mEq/L)	97.39	95.76	95.28	
Calcium (mg/dL)	12.24 ± 1.64	10.22 ± 1.2	10.65 ± 0.56	
Phosphorus (mg/dL)	8.16 ± 1.39	7.22 ± 0.87	7.46 ± 0.87	
Creatinine phosphokinase (U/L)	83 ± 42	531 ± 532	256 ± 364	
Aspartate aminotransferase (U/L)	18 ± 19	99 ± 18	72 ± 25	
γ-Glutamyltransferase (U/L)	8 ± 3	1761 ± 1058	846 ± 517	

Hb, Hemoglobin; *MCH,* mean corpuscular hemoglobin; *MCHC,* mean corpuscular hemoglobin concentration; *MCV,* mean corpuscular volume; *PCV,* packed cell volume; *RBC,* red blood cell; *TP,* total plasma protein; *WBC,* white blood cell.

17.5.2 Maternal Behavior

Failure of maternal bonding is more common with primiparous dams, with multiple offspring, and after delivery via caesarean section. Restraint and patience often pay off. Reluctant dams will often accept the calf after several days of restrained feeding in which the dam is placed in a crush two or three times a day to allow the calf to nurse. Maternal bonding in sheep is mediated by an olfactory mechanism.[69] Parturition alters the release of monoamines, amino acids, and oxytocin within the olfactory bulb, stimulating an attraction to amniotic fluid and acceptance of the lamb.[70] Artificial vaginocervical stimulation with a gloved hand induces similar alterations in the release of monoamines, amino acids, and oxytocin within the olfactory bulb and is useful for triggering formation of maternal bonds to foster lambs for at least 27 hours postpartum.[70]

17.6 PHYSICAL EXAMINATION

An initial assessment of the sick neonate should be made to determine if there is a need for immediate intervention and stabilization. Particular attention should also be paid to identification of any congenital malformations. The key to conducting a thorough physical examination is the development of a systematic approach. Normal parameters for calves are listed in Table 17-6.

17.6.1 Examination from a Distance

The physical examination begins with examination from a distance with assessment of behavior, body condition, and stance. Drooping of the head and ears is an early sign of illness. Sick calves spend increasing amounts of time recumbent and are less inclined to drink. In beef calves, lambs, and kids this may be reflected by udder distention in the dam. With dairy calves the calf feeder reports the calf requires stimulation to stand and fails to drink. Resting respiratory rate and effort are assessed before the calf is handled. Abdominal contour should be noted, with consideration of the neonate's reported appetite; an apparently normal abdominal contour may be abnormal if the calf has not eaten for several days. Observing the neonate navigate its environment provides a simple assessment of vision.

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17.6.2 Physical Appearance, Bodyweight, and Body Condition

Congenital disorders may cause subtle changes in physical appearance and behavior. For example, Saler calves with β-mannosidosis have moderately domed heads, mild superior brachygnathism, and a slight head tremor.[71] Similarly, in utero infections that lead to growth retardation may be reflected by low birthweight and poor body condition.

17.6.3 Body Temperature

Rectal temperature in calves ranges from 99° F to 102° F (37.2° C to 38.9° C) during the first 4 days after birth. Calves with sepsis are often febrile; however, absence of a fever does not rule out sepsis. Calves in septic shock

may have subnormal temperatures. Premature calves are prone to hypothermia.[72] Hyperthermia during the first week of life has been reported to be common in cloned calves.[73]

17.6.4 Cardiovascular System

Peripheral pulses in the tail and brachial arteries should be strong and regular, and the peripheral extremities warm. Mucous membranes should be moist and pale pink with a CRT of <2 seconds. Gray or cyanotic mucous membranes are associated with severe hypoxia (i.e., PaO_2 < 35 to 40 mm Hg) and/or circulatory collapse as seen with hypotensive, endotoxic, or hypovolemic shock. Cardiac and pulmonary causes of cyanosis must be distinguished. Cyanosis secondary to cardiac causes reflects right-to-left shunting of blood, as may be observed with tetralogy of Fallot or ‘Eisenmenger's complex.

Dyspnea and coughing are often the predominant clinical signs of congestive heart failure in calves. Close examination may reveal distention of the jugular veins and brisket edema, but if heart failure is predominantly left sided these signs may be absent. Cardiomyopathy secondary to selenium deficiency or gossypol, monensin, or lasalocid toxicity may manifest as a syndrome of sudden death during periods of excitement precipitated by feeding or moving calves out of hutches into group pens.[74]

Cardiac arrhythmias are observed sporadically in neonates, often associated with diarrhea. Metabolic acidosis secondary to losses of electrolytes and water causes a transcellular shift of potassium ions into the extracellular fluid in exchange for hydrogen ions.[75] As serum potassium increases (>5.5 mEq/L), aberrations in cardiac excitability occur and are manifested as progressive atrial standstill, progressing to ventricular fibrillation and asystole.[76] Tachyarrhythmias may be observed in calves with cardiomyopathies, ionophore toxicosis,[77] or hypomagnesemia.

The most common cardiac defect in the large animal neonate is a ventricular septal defect, but a variety of other malformations have been described and are discussed in Chapters 6 and 30. Ancillary tests for evaluating the cardiovascular system are discussed in Chapter 30.

17.6.5 Respiratory Tract

The respiratory rate and effort of breathing in neonates are best observed from a distance so that the stress of restraint does not influence the assessment. Lung sounds of neonates are typically easier to hear than those of adults; however, lung sounds do not always correlate well with the severity of pulmonary pathology present. Thoracic percussion is also easier to perform in the neonate and can be useful to identify the presence of cranioventral consolidation. Animals with few or no audible thoracic abnormalities may have severe respiratory disease. The rate and effort of breathing are important to consider in the physical assessment of respiratory function. When available, chest radiology, thoracic ultrasonography, and arterial blood gas analysis are useful ancillary diagnostic tools.

Lung disease in the newborn is usually diffuse and is the result of infection acquired in utero or postpartum and/or lung atelectasis associated with immaturity, recumbency, or surfactant dysfunction. Signs of lung disease include increased work of breathing characterized by nostril flare, rib retractions, and increased abdominal effort. A cough and nasal discharge, salient features of respiratory disease in older neonates, are infrequent findings in newborns with lung disease.

Conditions that cause partial occlusion of the upper airway, such as necrotic laryngitis, often induce pronounced inspiratory stridor. Expiratory stridor and increased and prolonged expiratory effort are usually associated with lower airway disease. A malodorous breath may be present with necrotic pharyngeal injuries, necrotic laryngitis, or aspiration pneumonia. Age is an important signalment for respiratory disease in calves. Enzootic pneumonia is common in calves between 4 weeks and 6 months of age but uncommon in calves less than 4 weeks of age. Outbreaks of pneumonia in calves less than 4 weeks of age are occasionally observed in calves fed milk contaminated with *Mycoplasma* species.[78,79] This scenario is one of the risks associated with feeding calves unpasteurized "hospital milk." *Mycoplasma* pneumonia in calves may be associated with arthritis, tenosynovitis, otitis media,[79] and decubital abscesses.[80] Clinical signs associated with mycoplasma otitis include cranial nerve 7 and 8 deficits, unilateral or bilateral ear droop, ptosis, epiphora, head tilt, and recumbency in severely affected calves. Aspiration pneumonia is common in calves less than a week of age, often reflecting inappropriate feeding practices (large holes in teat nipples or poor esophageal tubing technique) or pharyngeal dysfunction.

Periodic apnea and abnormally slow respirations are often the result of metabolic disturbances (e.g., hypoglycemia, hypocalcemia), hypothermia, advanced prematurity, or hypoxia-induced suppression of the respiratory center. Calves with metabolic acidosis usually have an increased respiratory rate with long, deep breaths reflecting respiratory compensation. Tachypnea may be a response to high ambient temperatures, pain, or stress. Congenital defects of the respiratory system in ruminants are rare.

17.6.6 Oral Cavity and Nasal Passages

Hyperemic membranes accompanied by scleral injection are the hallmark of early sepsis. Petechiae on the oral or nasal mucous membranes are consistent with sepsis or thrombocytopenia induced by type II BVD. Ecchymotic hemorrhages may be observed on the sclera with type II BVD infections, with DIC, or after birth trauma. Cleft palate is the most common congenital defect observed in ruminants. Calves with cleft palate may have milk run from the nose and are prone to developing aspiration pneumonia.

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17.6.7 Eyes and Associated Structures

Eyes should be examined for the presence of entropion, ectropion, corneal abrasions or ulcers, uveitis and hyphema, congenital cataracts, microphthalmia, corneal dermoids, scleral injection, and scleral hemorrhage. Scleral hemorrhage is usually the result of birth trauma and can take several weeks to resolve. Icterus is uncommon in neonatal ruminants but may be observed with hemolytic or hepatic disease.

A common cause of corneal edema and ulceration, conjunctivitis, and lacrimation in lambs is acquired or congenital entropion. Acquired entropion is associated with self-trauma, dehydration, or prematurity and the lack of periorbital fat. Entropion should be corrected promptly before serious corneal ulceration and keratitis develop. Mild cases may respond to subcutaneous injections of procaine penicillin G into the lower eyelid. Refractory cases may require placement of vertical or horizontal mattress sutures in the eyelid to correct the problem. The affected eye should be stained to detect concurrent corneal ulceration. Varying degrees of miosis secondary to pain and ciliary body spasm is common. Treatment after correction of entropion includes topical administration of 1% atropine to dilate the pupil and relieve ciliary body spasm and topical antibiotics to prevent bacterial infection.

Uveitis may be observed in the newborn animal exposed to an infected uterine environment or may be a result of generalized infection acquired after birth. Scleral injection suggests and fibrin in the anterior chamber is highly indicative of sepsis.

17.6.8 Ears

Bilateral drooped ear carriage is a common observation in sick calves and should prompt a closer examination. Unilateral ear droop may be observed with otitis and facial nerve paralysis. *Mycoplasma* species, *Pasteurella* species, and *Haemophilus* species are reported to cause otitis in calves. Clinical signs may include facial and vestibular nerve deficits and a purulent discharge from the ear. Calves infected with *Mycoplasma* species may also have tenosynovitis and respiratory disease.

Poor perfusion is reflected by cold extremities. A high incidence of pinna abscesses usually reflects contamination of equipment used to place ear tags.

17.6.9 Neck and Back

Several congenital anomalies affect the alignment of the vertebral column. These include atlantoaxial malformations, scoliosis, kyphosis, lordosis, and combined anomalies such as kyphoscoliosis. Atlantoaxial malformations may occur with or without cervical scoliosis or signs of spinal cord compression. Holstein calves affected by the hereditary condition complex vertebral malformation may display a range of abnormalities that include retarded growth, malformation of the head (dysplasia or palatoschisis), bilateral symmetric flexion of the carpal and metacarpophalangeal joints, posterior arthrogryposis, and interventricular septal defects. Of these, growth retardation, vertebral malformation, and symmetric arthrogryposis are the most consistent findings.[81]

17.6.10 Gastrointestinal Tract

Much can be learned about gastrointestinal function by observing abdominal contour, appetite, and fecal consistency and volume. A normal abdominal contour and vigorous appetite associated with the passage of an appropriate volume of pasty stool suggest normal gastrointestinal function. Congenital defects of the gastrointestinal tract occasionally observed in ruminants include cleft palate, poor jaw conformation (brachygnathism, inferior and superior), atresia coli, atresia recti, and atresia ani. The spiral loop of the ascending colon (spiral colon) is the most commonly affected segment of intestine in calves.[82] Neonates with atresia often have a distended abdomen and a history of a declining appetite. Astute owners may notice the lack of or reduced volume of feces.

In contrast to the adult, in the large animal neonate the rectal palpation of the abdominal structures is of limited value. External palpation of the abdomen can be more rewarding, depending on the cooperation of the individual and the tenseness of the abdominal musculature. In calves it is usually possible to palpate enlargement of the umbilical vein and arteries. The inguinal rings and umbilical area should also be palpated for hernias.

Infectious diarrhea is the leading cause of mortality in calves between 3 and 21 days of age. Typically more than one pathogen is involved and the physical examination provides no indication of the causative agent. Fecal pH may be used as an indicator to distinguish secretory diarrhea (enterotoxigenic *E. coli*) from diarrhea associated with malabsorption and maldigestion. Secretory diarrhea produces an alkaline pH, whereas malabsorption and maldigestion are associated with an acidic fecal pH.[83] Small amounts of blood may be observed in the feces of healthy calves. Passage of blood and fibrin is associated with inflammatory bowel disease induced by pathogens such as *Salmonella* and coronavirus that damage the gastrointestinal mucosa. Infectious agents that cause diarrhea and the ancillary tests available to establish an etiologic diagnosis are discussed in Chapter 20.

Abnormal forestomach function in neonatal ruminants, as in adults, is often reflected by altered abdominal contour as described in Chapter 32. Left and right abomasal displacement and abomasal torsion are observed sporadically in calves. Succussion (simultaneous auscultation and percussion) is useful for delimiting the boundaries of distended visci. Passage of a stomach tube helps distinguish rumen and abomasal distention and facilitates collection of a ruminal fluid sample. A putrid odor to neonatal ruminal fluid is common with putrefactive indigestion when milk is delivered to the rumen in greater quantities than normal by escaping the esophageal groove or via excessive backflow from the abomasum. Reflux of abomasal contents into the reticulum and rumen, independent of feeding, occurs in connection with abomasal inflammation and obstructions.[84] Evaluation of ruminal fluid pH and renin activity are useful for distinguishing abomasal reflux from esophageal groove overflow. Ruminal fluid pH is usually ≥7 with rumen putrefaction, and low to normal with abomasal reflux.[84] Chymosin (renin) is normally present in abomasal juice, and renin activity in ruminal fluid suggests abomasal reflux.[85] Renin activity is measured by adding 2 mL of ruminal juice to 2 mL of whole milk on a CMT (California Mastitis Test) plate. Presence of renin in the ruminal fluid causes coagulation of the casein in the milk. Chloride ion concentration in ruminal fluid from calves is higher than in adults (55 to 102 mmol/L in calves[86] and 25 mmol/L in adults[84]), possibly reflecting the high chloride content of milk (45 mmol/L); therefore the chloride concentration of ruminal fluid is not useful for identifying abomasal reflux in calves.

Abdominal radiographs and/or ultrasound examination can be helpful in diagnosing abdominal problems in the neonate and in distinguishing causes of abdominal distention.[87–89] Transabdominal ultrasonography can be used to locate a suitable site for abdominocentesis. Normal peritoneal fluid from calves has a higher nucleated cell count than that of adult cattle (3350 cells/μl vs 1371 cells/μl). Total protein concentration in peritoneal fluid of calves is similar to that of adults (2.5 g/dL vs 3.1 g/dL).[90]

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17.6.11 Umbilicus

Umbilical cord remnant infections represent an important problem in neonates.[91] The infection generally develops during the first 2 weeks of life. Complications associated with umbilical infections include septicemia, septic arthritis, and osteomyelitis.[92] The umbilicus should be examined closely for patency, increased size, moistness or discharge, and tenderness. Abdominal palpation, using both hands and pressing together, is useful for evaluating the umbilicus of ruminants. Enlargement of the umbilical arteries can be palpated coursing caudally toward the bladder, and enlargement of the umbilical vein coursing cranially to the liver. Application of pressure caudal to the xiphoid often elicits a soft grunt from calves with a septic umbilicus and associated peritonitis. Extensive adhesion of bowel to inflamed umbilical structures produces a large, easily palpable intraabdominal mass. Common abnormalities of the calf umbilicus include umbilical hernias, omphalophlebitis, external umbilical abscess, urachal abscess, and omphaloarteritis. Patent urachus is uncommon in calves.

Ultrasound examination of the intraabdominal umbilical structures is a useful ancillary diagnostic tool. Ultrasonography of the umbilical structures of calves has been described by Watson and colleagues.[93] Ultrasound examination of the calf is performed with the calf standing; occasionally the umbilical vein is easier to identify with the patient in left lateral recumbency. The anatomy of the umbilicus of calves differs slightly from that of foals, necessitating alterations in ultrasound technique. In both species the umbilical vein courses from the umbilicus to the liver, which in the calf is located on the right side as opposed to midline in the foal. Also, in cattle the umbilical arteries and urachus retract into the abdominal cavity when the cord ruptures and thus cannot be identified in the external umbilical stalk in normal calves.[93] The umbilical vein of calves is scanned from the umbilical stalk to the liver along the right abdominal wall. The umbilical vein enters the liver

caudoventral to the gallbladder. The umbilical arteries are most easily located adjacent to the urinary bladder and cannot normally be identified much beyond the apex of the urinary bladder unless they are enlarged and abnormal. Identification of a urachal remnant in calves is abnormal.[93]

Literature on the efficacy of navel treatment at reducing calf mortality is divided. In a study of 104 dairy farms, a farm policy of navel treating newborn calves had no significant effect on calf mortality rates. A significant beneficial effect was observed when the navels of calves that had assisted deliveries were dipped with chlorhexidine; other navel treatments such as iodine tended to be associated with increased odds of dying.[94] Navel treatment with iodine was associated with significantly higher mortality in another study of 48 farms; however, the association of navel treatment with mortality on these farms may have reflected the response of producers to high neonatal mortality rather than indicating that iodine navel treatment is a risk factor for calf mortality.[95] Prophylactic administration of antibiotics to young calves has been associated with an increased incidence of diarrhea[96] and increased calf mortality.[97]

17.6.12 Urogenital System

Neonates on a milk-based diet normally produce large volumes of dilute urine. Normal urine osmolarity in the 2- to 3-day-old calf has been reported to be 286 to 391 mOsm/L, and urine volume voided per day 34 mL/kg/day.[98]

Congenital defects associated with the urogenital system in calves include ovarian aplasia, duplication of the cervix in Hereford cattle, persistence of the hymen (white heifer disease), and rectovaginal constriction in Jersey cattle. Congenital urolithiasis has been described in calves and lambs. Calcium oxalate is the most commonly reported congenital form of urolithiasis and may be associated with other congenital abnormalities.[99] A report of renal oxalosis in a number of Beefmaster calves suggests a possible recessively inherited metabolic defect resulting in primary hyperoxaluria in this breed.[100] Freemartins (XX/XY chimeras) occur in over 90% of bovine[101] and 1% of ovine[102] female heterosexual twins. Typically freemartins are sterile and have hypoplastic ovaries and internal tubal genitalia; the external genitalia normally are not affected. Males should be examined for cryptorchidism and male pseudohermaphroditism, and both sexes for evidence of hermaphroditism (gonads of both sexes).

Rupture of the urinary bladder at parturition is uncommon in ruminants. Clinical signs of a ruptured bladder include dysuria, stranguria, progressive abdominal distention, and depression. A percussion wave may be felt with ballottement of the distended abdomen. Ancillary tests including abdominal ultrasound, abdominocentesis, and assessment of serum and peritoneal electrolytes are useful to verify the diagnosis.

Hemodynamically mediated renal disease is observed sporadically in calves after chronic enteritis.[103] Prolonged reduced renal perfusion secondary to hypovolemia may lead to ischemia and acute tubular necrosis. Failure to thrive after apparent recovery from diarrhea may reflect compromised renal function.

17.6.13 Musculoskeletal System

The musculoskeletal system should be examined for evidence of birth trauma including fractured ribs, long bones, and mandibles, brachial plexus injuries, and soft-tissue trauma including an edematous head and tongue from prolonged compression in the pelvic canal. Strenuous manipulation during a dystocia can also result in Salter-Harris type 1 fractures characterized by disruption of the distal physis in one or more limbs. Femoral nerve paralysis occurs as a sporadic complication of dystocias associated with “hip lock” in calves.[104]

All four legs should be examined for both flexural and angular limb deformities. Although most mild-to-moderate limb deformities correct themselves in a few days, others may need splinting for a successful result. In severe cases of congenital contracture, which are often associated with dystocia, even heroic measures, such as surgical resection of flexor tendons, may provide little or no benefit.

Any heat, swelling, edema, or pain around the joints or physes, or lameness, should be noted. *A swollen joint should be considered infected until proven otherwise*. In older neonates, metabolic bone disease should be considered as a differential diagnosis for lameness associated with flaring of the physis. Diets high in energy and protein that have low calcium and high phosphorus promote rapid weight gain, increasing the physical load on metabolically compromised growing bones. Damage to the growing physis may result in the subsequent development of angular limb deformities. Calcium deficiency in calves leads to reduced mineralization of bone. The transverse processes of the lumbar vertebrae become soft and bend when palpated. Copper deficiency causes metabolic bone disease that is manifested by physitis and brittle bones, reflected by a propensity to develop spontaneous fractures. 278 279

Skeletal muscle myopathy is an important differential diagnosis for lame neonatal ruminants. Lambs and kids with selenium and/or vitamin E deficiency are often mentally bright, are reluctant to stand, and walk with a stiff gait and cry when forced to move. Evaluation of serum creatinine phosphokinase, blood selenium, and plasma vitamin E concentrations is useful to confirm the diagnosis. In regions deficient in selenium, nutritional myodegeneration can be a major cause of death in neonates if the dam was not supplemented with selenium during pregnancy. Nutritional myodegeneration has also been observed when selenium levels are adequate but α-tocopherol levels are low.[105,106] The concentration of vitamin E in sheep colostrum is 5 to 11 times higher than in milk; sheep colostrum appears to be an important source of vitamin E for lambs, as vitamin E is transferred poorly across the placenta. Nutritional myodegeneration secondary to vitamin E deficiency is observed when pregnant ewes are maintained on forage low in vitamin E. Vitamin E–associated nutritional myodegeneration may be prevented by supplementing lambs and kids at birth with α-tocopherol (500 IU orally)* or by supplementing ewes during pregnancy either with a single dose of 500 mg IM 2 weeks before lambing or via dietary supplementation, delivering 150 mg daily for 3 to 4 weeks before lambing.[106] Neonatal nutritional myodegeneration associated with selenium deficiency may similarly be prevented by supplementing neonates at birth (2.5 to 3 mg of selenium per 45 kg) or by supplementing the dam during pregnancy and is discussed further in Chapter 42.

The skull should be examined for excessive doming of the forehead and symmetry. A moderately domed forehead is most commonly the result of intrauterine growth retardation rather than hydrocephalus. The entire vertebral column should be examined for scoliosis, kyphosis, and lordosis and other malformations. Arthrogryposis is characterized by multiple skeletal malformations, including severely contracted limbs and malformations of the vertebrae, and has been associated with the ingestion of toxins, such as locoweed and Sudan grass, by the pregnant mare.[107,108]

Umbilical hernias are the most common congenital malformation. The greatest danger associated with a hernia is strangulation of a portion of the gastrointestinal tract outside the body wall, with compromise of its vasculature. Umbilical hernias in cattle do not tend to close spontaneously and are believed to be hereditary.[109] Dwarfism is a relatively common inherited problem in most cattle breeds. Osteopetrosis has been reported in Angus, Hereford, and Simmental breeds of cattle.[110] Syndactyly is considered an inherited disorder in Holstein-Friesian cattle, and affected animals are also predisposed to hyperthermia.

* East N: Personal communication, University of California, Davis, Calif.

17.6.14 Neurologic Examination of Neonatal Ruminants

Neurologic disease in neonates during the perinatal period often results from birth asphyxia, congenital disease, or sepsis. Congenital central nervous system (CNS) abnormalities in the large animal neonate may be inherited or may result from in utero infections, toxins, and other environmental factors. Hydrocephalus, hydranencephaly, and anencephaly may occur in calves. In the calf, both Akabane and bluetongue virus may cause hydranencephaly and other problems, including arthrogryposis and premature births. Hydrocephalus is fairly common and appears to be inherited as a simple autosomal recessive trait in many breeds. Internal hydrocephalus may result from a simple recessive gene or congenital BVD infection. Fetal infection with BVD virus may result in a number of other problems, including cerebellar dysplasia, ocular defects, hypomyelinogenesis, and intrauterine growth retardation. Cerebellar hypoplasia may also result from an autosomal recessive gene and is seen in a number of cattle breeds.

Disorders of amino acid metabolism that result in primarily neurologic signs include maple syrup urine disease[111,112] and citrullinemia.[113] Maple syrup urine disease is analogous to branched chain keto acid decarboxylase deficiency and results in clinical signs of extensor spasms, weakness, dullness, recumbency, and opisthotonos shortly after birth. The most striking lesion of the CNS histologically is widespread spongy vacuolation in the white and gray matter of the brain. Citrullinemia, an inborn error of metabolism of the urea cycle, was reported in five neonatal Friesian calves.[113] The calves appeared normal for a short period after birth, but at 24 hours to 5 days of age they developed progressive neurologic signs of depression, tremors, seizures, and opisthotonos, which were followed by death.

Congenital myoclonus (neuraxial edema) is an autosomally recessive inherited disorder of polled Herefords.[114] Clinical signs included premature delivery, inability to stand after birth (with the majority remaining in lateral recumbency), normal mentation, and prominent sensory stimuli-induced myoclonic jerking of the whole body with extension of the head and limbs. The majority of affected animals also display traumatic hip lesions, presumably as a result of the severe myoclonic contractions. Severe alterations in spinal cord glycine-mediated neurotransmission result from a marked decrease or defect in glycine receptors and an increase in neuronal (synaptosomal) glycine uptake. Alterations are also present in the major inhibitory system (γ-aminobutyric acid [GABA] receptors) in the cerebral cortex.[115] Storage diseases in cattle, usually inherited as autosomal recessive genes, include α-mannosidosis in purebred Angus, β-mannosidosis in Salers, GM-1 gangliosidosis in inbred Friesians, neuronal lipodystrophy in Beefmasters, and ‘“shaker calf syndrome” in horned Hereford calves. The last condition was recently recognized as an inheritable neurodegenerative disorder characterized by excessive accumulation of neurofilaments within neurons of the central, peripheral, and autonomic nervous systems. Clinical signs included a normal birth but inability to stand unassisted after delivery. Several hours later the calves developed fine generalized tremors, hyperesthesia to tactile stimulation, weakness, ataxia, and aphonia.[116]

Most acquired neurologic disease in neonates is associated with disease in other organ systems. Sepsis and diarrhea are both commonly associated with depressed mentation secondary to toxemia and/or metabolic derangements. Bacterial meningitis is common in neonates after bacteremia; diarrhea, septic arthritis, omphalophlebitis, and uveitis are frequent concurrent clinical problems. The clinical signs of meningitis in neonates—lethargy, anorexia, and recumbency—are nonspecific. Concurrent metabolic derangements may appear to provide an adequate explanation for the observed depressed mentation. In a retrospective study of 32 cases of bacterial meningitis in calves, concurrent metabolic derangements included hyperkalemia (15/25, 60%), respiratory acidosis (11/24, 46%), hypernatremia (3/20, 15%), and hypoglycemia (3/7, 43%).[117] The more classical clinical signs described for bacterial meningitis in older animals—fever, opisthotonus, extension of the

head, convulsions, hyperesthesia, and signs of neck pain—may not be evident or may not be perceived in neonates. Seizures in calves are often subtle, manifested as facial twitches or jaw champing. Common causes of cerebral disease in lambs and kids include polioencephalomalacia and focal symmetric encephalomalacia. Affected animals are typically depressed and blind but have normal pupillary light reflexes. 280

Posterior paresis is common in neonates; causes include border disease, enzootic ataxia, vertebral body abscesses, caprine arthritis encephalomyelitis virus, and vertebral body fractures associated with dietary copper deficiency or calcium phosphorous imbalance. These neurologic problems are discussed in Chapter 35.

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18 Chapter 18 Neonatal Infection

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Infection, both generalized and localized, is an important cause of morbidity and mortality in the large animal neonate; in both calves and foals, bacteria cause most infections. The prognosis of neonatal infection varies considerably depending on the type and severity of infection. The traditional view of sepsis includes a pivotal role for bacterial endotoxins with resultant overactivation of the host immune system and release of endogenous proinflammatory and antiinflammatory mediators. This response could then precipitate a cascade of metabolic and hemodynamic changes that may culminate in multiple organ system failure.[1,2] This traditional model of sepsis has recently been challenged with a decreased emphasis on a primary role of bacterial endotoxins and a new focus on the regulation of Toll-like receptors (TLRs) in generation of the systemic inflammatory response syndrome (SIRS) and the sepsis syndrome.[3] It has been suggested that TLR4, the putative endotoxin receptor, is under a constant state of inhibition. Endogenous factors generated in response to tissue inflammation lead to release of TLRs from inhibition as well as acting as TLR agonists. TLR activation results in a potent proinflammatory response. This model provides a common pathway of SIRS, irrespective of initiating causes (e.g., gram-negative bacteria, gram-positive bacteria, tissue trauma, neoplasia). Although further refinement is needed for acceptance of this model of sepsis, it may provide the window for novel therapies in the prevention and treatment of sepsis.

Much of the information related to sepsis and endotoxemia in horses has been derived from experimental endotoxin bolus or infusion in healthy animals. Endotoxin activates cytokine-mediated procoagulant effects on endothelial cells.[4] The initial response to endotoxin is activation of coagulation.[5] As the inflammatory response progresses, systemic hypercoagulability may progress to hypocoagulability, with fulminant signs of hemorrhage recognized as disseminated intravascular coagulation (DIC).[4] Circulatory failure, perfusion deficits, and an inability of the body to use existing metabolic substrate effectively characterize septic shock, the end point of that continuum. If the neonate survives acute sepsis, localized areas of infection such as pneumonia, uveitis, synovitis, physitis, meningitis, hepatitis, and enteritis may then appear. In the past decade, survival rates of septicemic foals have improved considerably because of advances in early detection procedures and critical care management techniques,[6–11] but it is far preferable to prevent[12] septicemia by using good management techniques and by ensuring that the newborn acquires good colostrally derived immunity. The prognosis for septicemic neonates admitted for treatment in the late stages of the disease remains poor because bacteria are usually already well established in many organs, particularly the bones and joints. In these cases, even if the neonate survives on a short-term basis, a number of chronic complications result in an unfavorable long-term outcome. Foals with adequate transfer of maternal immunoglobulins can still succumb to generalized infection after birth, but animals with partial or total failure of passive transfer (FPT) have a greater risk of morbidity or mortality resulting from infection.[13] See Chapter 53 for details on the detection, prevention, and treatment of FPT.

18.1 ETIOLOGY AND NEONATAL IMMUNITY

Most neonatal infections are caused by opportunistic bacteria that normally live in the genital tract, on the skin, or in the environment of normal horses, cows, sheep, and goats. Infection may be acquired prenatally, through the placenta, from the birth canal, or from the environment after birth. Portals of entry include the respiratory and

gastrointestinal tracts, the placenta, and the umbilicus. A number of abnormalities in the late gestation mare make infection more likely in the neonate (see Chapter 15). Bacterial placentitis is a common cause of premature delivery and infection in the newborn foal; most cases result from ascending infection through the cervix. Perinatal stress, including chronic in utero hypoxia, prematurity, dystocia, and birth asphyxia, renders the neonate more susceptible to infection. Unsanitary environmental conditions, overcrowding, poor ventilation, contamination of the environment with pathogenic bacteria such as *Salmonella* species,[12] and other poor management techniques also predispose to infection.[9]

The propensity for contagious and opportunistic infections in neonates reflects the immature status of their immune system. At birth, foals, calves, lambs, and kids are hypogammaglobulinemic or agammaglobulinemic and immunologically naive. Bovine colostrum contains approximately 45 mg/mL[14] of immunoglobulin and 10^6 leukocytes/mL.[15] Passively derived immunoglobulins enhance neonatal immunity by functioning as neutralizers and opsonins. The association between FPT of immunoglobulins and neonatal infection has been well established in the calf[16,17] and suggested by several studies in the foal.[13,18–20] Colostral leukocytes participate in regulation of the neonate's immune response. Comparison of the immune response of calves fed leukocyte-replete or leukocyte-depleted colostrum indicates that colostral leukocytes enhance humoral immunity and phagocyte function.[21–25] After experimental *Escherichia coli* infection, calves fed leukocyte-replete colostrum recovered more quickly and shed fewer bacteria than calves fed leukocyte-depleted colostrum.[15] Transfer of cellular immunity via colostral leukocytes has also been demonstrated in sheep.[26] Colostral leukocytes are destroyed when colostrum is frozen, pasteurized, or fermented.

The phagocytic and bacterial killing function of neutrophils (polymorphonuclear neutrophils [PMNs]) is a crucial component of the primary immune response against invading pathogens. Despite a larger number of neutrophils in the circulation of normal calves at birth, neutrophils from neonatal calves are functionally less effective than adult cells. Reduced Fc receptor expression in neonatal PMNs may contribute to impaired phagocytosis and antibody-dependent cellular cytotoxicity.[27–29] Depressed PMN bacterial killing[30] may be related to reduced superoxide anion[31] and myeloperoxidase—hydrogen peroxide—halide antibacterial activity.[29] Adult level superoxide activity in fetal PMNs suggests that some of the deficits in neonatal PMN function may be a manifestation of perinatal PMN suppression.[32] Calves have elevated cortisol levels for the first 10 days of life, which may contribute to depression of neutrophil function.[33] Dexamethasone depresses neutrophil phagocytosis, antibody-dependent cellular cytotoxicity, and bacterial killing.[34,35] Undefined serum factors also appear to be important for PMN function, as phagocytosis and bacterial killing by neonatal PMNs is similar to that of adult PMNs when bacteria are opsonized with adult serum but is reduced when bacteria are opsonized with neonatal serum.[30] T helper cells ($CD4^+$) play a central role in humoral and cell-mediated immunologic memory. Lymphokines produced by $CD4^+$ cells, interleukin (IL)-2, IL-4, and interferon gamma (IFN-γ) are essential components of antigen-specific immunity. Virtually all IL-4 and most IFN-γ produced by polyclonally activated adult human $CD4^+$ cells are mediated by a subset of "functional memory cells."[36] Leukocyte production of IL-4 and IFN-γ is reduced in human neonates,[36] and IFN-γ in bovine neonates,[*] possibly reflecting their antigenically naive status. Depressed lymphocyte proliferation and IL-2 activity in the perinatal period correlates with elevated cortisol levels.[33]

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Acquisition of humoral immune competence is age and antigen dependent.[37] Neonates are capable of producing humoral immune responses to good immunogens (protein antigens) but may fail to respond to lesser immunogens (sugars and lipids). Calves less than 3 months of age vaccinated with modified live or killed salmonella vaccines produce an adult-type humoral immune response to salmonella protein antigens but do not respond to salmonella

lipopolysaccharide (LPS).[38] Ingestion of colostrum suppresses the humoral response to some antigens but not to others.[37]

Adverse management and environmental conditions further compromise neonatal immunity. Cold stress depresses neutrophil chemotaxis, and vasoconstriction reduces delivery of leukocytes to peripheral tissues.[39] Protein energy malnutrition in calves is associated with depressed lymphocyte IL-2 activity, lymphocyte proliferation, and humoral immune responses.[33] Micronutrient deficiencies also depress immunity. Selenium, zinc, copper, and vitamin E deficiencies depress lymphocyte and phagocyte function.[40,41]

Inherited defects in immune function are sporadically observed in neonates and should be considered when recurrent or atypical infections are observed—for example, *Pneumocystis carinii* pneumonia in foals. Inherited immunodeficiencies are discussed in Chapter 53.

* VanMetre D: Unpublished data, 2000, University of California, Davis, Calif.

18.2 PATHOGENESIS OF SEPSIS

As discussed earlier, the pathogenesis of sepsis is yet to be fully elucidated.[3] Systemic sepsis can be caused by a range of infectious agents including gram-positive bacteria, gram-negative bacteria, fungi, and viruses. Interaction between viruses, bacteria, or bacterial products and TLRs appears pivotal in the induction of the proinflammatory and antiinflammatory responses.[42] Endotoxin is a mediator of gram-negative sepsis. Endotoxin, the LPS component in the outer cell membrane of gram-negative bacteria, is released whenever the bacterial cell membrane is disrupted, as occurs during rapid growth or cell death. Endotoxin is composed of hydrophilic heteropolysaccharide and hydrophobic lipid. The surface portion of LPS is the O-antigenic determinant consisting of sugar chains that are highly variable among species. Deeper within the LPS molecule is the lipid moiety, which is responsible for most of the endotoxin's biologic activities. Binding of LPS to TLR4 receptors leads to expression of nuclear factor—kappa B (NF-κB)–controlled proinflammatory cytokines and IFN-regulatory factors and type I IFNs.[42] The reticuloendothelial system is responsible for detoxification of endotoxin. Gram-positive bacteria do not produce endotoxin but elaborate lipoteichoic acid and peptidoglycan, which can effect a similar inflammatory response through activation of other TLR receptors, TLR2 and TLR6.[42]

The initiating event in the generalized bacterial sepsis syndrome is the presence of bacteria and/or bacterial products within the circulation. Subsequent binding with surface TLRs and other immune system components triggers intracellular signaling pathways that activate the genes and enzymes responsible for production and maturation of cytokines and IFNs. Proinflammatory products include the cytokines tumor necrosis factor alpha (TNF-α), IL-1, IL-6, transforming growth factor (TGF)–β, and IFN-γ. Antiinflammatory cytokines include IL-4, IL-10, and IL-13. The cascade yields other products including kinins, myocardial depressant factor, β-endorphins, free-radical oxygen species, lysosomal enzymes, and prostaglandins.[1,2,43] Serum TNF concentration has been correlated with clinical criteria of sepsis in calves and foals.[44,45] Many of the inflammatory mediators have direct effects on the vascular endothelium, resulting in increased endothelial permeability. The endothelium also releases two additional substances: endothelium-derived relaxing factor (EDRF), and endothelin-1. EDRF has been identified as nitric oxide (NO) and is responsible for relaxing smooth muscle, depressing myocardial function, decreasing vasopressor responsiveness, and inhibiting platelet aggregation.[46,47] Endothelin-1 is a potent vasoconstrictor. After the increase in vascular permeability, interstitial and pulmonary edema, hypovolemia, and decreased cardiac output develop. Pulmonary and systemic hypotension develops. Splanchnic perfusion decreases,

and coagulation pathways are activated, resulting in varying degrees of DIC. The majority of patients that die of septic shock suffer multiple organ failure.[2]

Respiratory failure is a frequent complication of septic shock. As pulmonary capillary permeability increases, leukocytes accumulate and degranulate in the pulmonary microvasculature, resulting in endothelial damage, increased capillary leakiness, and alveolar flooding. Lung collapse (atelectasis), intrapulmonary shunting, and mismatching of ventilation and perfusion develop. Terminally, hypoxemia, pulmonary hypertension, progressive lung collapse, pulmonary edema, and respiratory failure develop.[2]

Myocardial depression occurs during sepsis. Endotoxin and NO exert a direct inotropic depressant effect on the heart. During early sepsis stimulation of the sympathetic nervous system results in tachycardia, increased cardiac output, improved myocardial contractility, and increased oxygen consumption. As sepsis progresses, there is a decrease in vascular tone and oxygen extraction by peripheral tissues, accompanied by development of metabolic acidosis and anaerobic metabolism. During late sepsis, myocardial failure develops, accompanied by decreased cardiac output and severe hypotension. A recent study reported elevations in the cardiac biomarkers cardiac troponin I and creatine kinase MB in septic foals compared with healthy neonatal foals.[48] The magnitude of either of these markers did not predict outcome.

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Sepsis is best characterized nutritionally by hypermetabolism, catabolism, and protein wasting.[49] During sepsis, intermediary metabolism is disrupted and the foal loses sequentially the ability to use glucose, then fat, and finally protein as energy sources. Elevated concentrations of catecholamines and glucagon contribute to insulin resistance and increased lipolysis. These changes explain the hyperglycemia and lipemic serum occasionally observed in foals with sepsis.

18.3 INFECTIOUS AGENTS ASSOCIATED WITH NEONATAL DISEASE

In all studies conducted in the United States, Europe, and Australia in the past 20 years, gram-negative bacteria have been the predominant cause of infection in large animal neonates, and *E. coli* has been by far the most common bacterial species isolated.[6,7,9,10,50–55] Other common bacterial organisms include *Actinobacillus* species (foals), *Pasteurella* species (calves and foals[56] [rare]), *Klebsiella* species, *Salmonella* species (calves and foals), and less commonly *Pseudomonas* species, *Listeria monocytogenes,*[57] *Clostridium perfringens* and *Clostridium septicum,*[58] *Staphylococcus aureus,* and *Streptococcus* species. Although *Streptococcus* species are most commonly isolated in mixed infections with gram-negative bacteria,[6,7] both alpha- and beta-hemolytic *Streptococcus* species have been isolated in pure culture in foals with large subcutaneous abscesses and physitis and septic arthritis. *Streptococcus pneumoniae* type 3, typically a human pathogen, was identified as the cause of severe respiratory distress in a neonatal foal.[59] Polymicrobial infections are common in calves with septicemia (28%).[52] Surveys examining blood culture results of foals admitted to neonatal intensive care units reflect a trend in the type of bacterial organisms contributing to septicemia. There has been an increase in the number of gram-positive bacterial isolates including *Streptococcus* (alpha and beta) species, *Staphylococcus* species, *Enterococcus* species, and *Clostridium* species.[60] These statistics serve to remind clinicians not to ignore the pathologic significance of gram-positive organisms when selecting an antibiotic regimen for the septic neonate. Although newer antibiotics including some of the cephalosporins, β-lactam antibiotics, and fluoroquinolones have an extended gram-negative spectrum, their gram-positive spectrum may be inadequate for pathogens such as *Streptococcus* species.

Most organisms known to cause placental and fetal disease may cause disease of the newborn. Infectious agents associated with abortion, stillbirths, and birth of weak ruminant neonates are listed in Box 15-3. Infections of neonates contracted in utero are uncommon compared with postnatally acquired infections. Clinical signs of in utero infections are dependent on the age of the fetus at the time of infection and the tissue tropism and virulence of the infecting organism. Abortion storms and outbreaks of perinatal weakness, congenital defects, and mortality are often manifestations of widespread herd or flock infections. Subclinically infected neonates may remain chronically infected, providing a continuing reservoir of infection in the population. Transplacental infection is important in the epidemiology of a number of diseases including Johne's disease *(Mycobacterium paratuberculosis),* bovine virus diarrhea, and bovine leukosis.[61–63]

Although viral agents are most commonly associated with abortion in the mare, viral infections may also occasionally cause disease in the newborn foal. Equine herpes viral infection may result in a weak newborn foal that responds very poorly to conventional supportive care; antemortem diagnosis is very difficult.[64,65] Equine viral arteritis has been reported in neonatal foals.[66,67] Equine influenza may be associated with interstitial pneumonia in foals.[68]

Fungal infections have been observed in neonatal foals. The development of severe, generalized candidiasis has been observed in debilitated or immunocompromised foals undergoing intensive care. A history of prolonged antimicrobial use is common. Diagnosis has been made using blood cultures or cultures of joint aspirates.

18.4 CLINICAL SIGNS

The spectrum of clinical signs associated with septicemia depends on the integrity of the host immune system, the duration of illness, the severity, the route of infection, and the target organs. Early in the clinical course, the clinical signs are usually nonexistent or vague, nonspecific, and easily attributed to other diseases. During the early hyperdynamic phase of sepsis, clinical signs include lethargy, hypotonia, more time spent sleeping, decreased nursing frequency followed by complete loss of suckle reflex, hyperemic mucous membranes with rapid capillary refill time associated with peripheral vasodilation and increased cardiac output, tachycardia, bounding peripheral pulses, extremities that are still warm, tachypnea, and variable body temperature. Capillary leakiness contributes to the early appearance of petechiae on the gums, sclera, inside of the ears, and coronary bands. As soon as the foal's nursing vigor decreases, the mare's udder becomes warm and distended and may stream milk spontaneously. When the weak foal does nurse from the overdistended udder, it often comes away with a milk-stained face owing to the spontaneous milk letdown that it is too weak too swallow. Dehydration develops rapidly, resulting in decreased urine output and constipation. Obviously, the earlier the infection is diagnosed, the better chance the treatment has of being successful. Localizing signs may or may not be present. Prompt and aggressive intervention at this stage of the disease process frequently results in a successful outcome.

During late sepsis, when infection overwhelms the host's immune system, septic shock develops. Affected foals are usually recumbent, dehydrated, and almost moribund. Clinical signs include severe hypotension associated with hypovolemia and decreased cardiac output, tachycardia, altered mentation, cold extremities, weak peripheral pulses, and dry, injected mucous membranes with a toxic ring and prolonged capillary refill time. Hypothermia is common. Gut motility is usually decreased and is accompanied by gastric reflux, abdominal distention, and constipation or diarrhea. Colic may be present if the ileus and abdominal distention are severe. Liver dysfunction is associated with cholestasis and increasing clinical jaundice. Decreased pulmonary perfusion and increased vascular permeability contribute to progressive respiratory compromise. Signs of respiratory distress include tachypnea, dyspnea with nostril flare, rib retractions, and expiratory grunting. Salvage of the patient in late septic shock is

usually not successful. Although an encouraging response to intensive therapy may be noted initially, most neonates presented in late septic shock do not survive.

Fever is inconsistently present in infected foals; the possibility of infection should never be ruled out because of the absence of fever.[6] Foals in septic shock often have a subnormal rectal temperature. In one study diarrhea was the most common early localizing sign in a group of foals with septicemia.[6] The pathophysiologic basis of the diarrhea is not known but may relate to altered intestinal perfusion. *E. coli* is the common cause of systemic sepsis in foals, but it is a rare cause of primary enteric disease. Other signs include seizures (with or without the presence of meningitis or encephalitis), colic, respiratory distress, uveitis, subcutaneous abscesses, joint distention and/or periarticular edema, and umbilical abscessation. The signs of osteomyelitis or physeal infection may be extremely subtle, with no obvious areas of inflammation detectable on the limbs. The only clues may be a reluctance to move, a choppy, stilted gait, and/or an inflammatory hemogram (increased fibrinogen, in particular).

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The time of onset of clinical signs of infection in the neonate depends on whether the infection was acquired in utero or postnatally. Animals infected in utero generally begin to show signs sometime during the first 24 hours of life, whereas postnatally infected animals often appear relatively normal for the first 2 days of life or longer. *Actinobacillus* infections in foals may become apparent somewhat earlier (24 to 48 hours of age) and are commonly characterized by an acute onset of depression, diarrhea, or rapidly distending, painful joint(s). Bone and joint infections in neonates may not be obvious for several days to weeks, and their appearance may either follow an improvement in systemic signs of illness or not be accompanied by any signs of systemic illness.

As with foals, septicemia in ruminant neonates commonly involves multiple organs with the respiratory and gastrointestinal systems most commonly affected.[52] Clinical signs are often nonspecific and may include lethargy, poor suckle reflex, weakness, dehydration, tachycardia, tachypnea, and recumbency. Findings suggestive of involvement of a particular organ system include diarrhea, lameness, omphalophlebitis, neurologic and ocular signs, and cardiac murmurs. Depressed mentation, diarrhea, and dehydration are the most common clinical signs of sepsis in neonatal ruminants, but clinical presentation is variable.[54] Rectal temperature, heart rate, and respiratory rate are poor predictors of sepsis in calves.[54,55] Fecteau and co-workers have developed a clinical score model for predicting sepsis in calves to promote rational antimicrobial use by producers.[55] Criteria included in the model include fecal consistency, hydration status, attitude (mental awareness), and umbilical and scleral vessel assessment. Sensitivity and specificity of the model were 76% and 75%, respectively. In the calves examined by Fecteau and colleagues the presence of severe diarrhea or a localized infection (e.g., infected navel) was associated with an increased probability of bacteremia as determined by blood culture.

18.5 DIAGNOSIS OF BACTERIAL INFECTION IN NEONATES

It is not difficult to diagnose an infected neonate when overwhelming sepsis is present. Bacteria may be observed on a peripheral blood smear in cases of advanced sepsis. Unfortunately, if treatment is instituted at this time, it is unlikely to be successful. Because of the necessity of early diagnosis and treatment of infection for a favorable outcome, a reliable, rapidly available field test to establish the presence of infection would be highly desirable. Such a test is not currently available. Positive blood cultures are the only definitive antemortem proof of bacteremia, but a minimum of 24 hours is usually required for preliminary results.

Because of the difficulty in identifying early sepsis at a treatable stage, a scoring system has been developed for the neonatal foal that incorporates a group of historic parameters, physical examination findings, and laboratory values, which together have been found to be considerably more accurate than any one single parameter in establishing the likelihood of infection.[69] The sepsis score is intended for use as a diagnostic aid only and is not 100% accurate.

False-negative results occur in older foals, and false-positive results are common in foals born prematurely. If the score is low for an individual foal but clinical suspicion of infection is high, antibiotic therapy should be instituted, and further assessment should then be performed.

The white blood cell (WBC) count and differential are important parts of the sepsis score. A number of foals in the early stages of septicemia have a normal total WBC count, but most have either an increased number of immature (band) neutrophils (>50 cells/μL) or toxic changes (Döhle bodies, toxic granulation, vacuolization) in the neutrophils. Foals that die of septicemia generally have very low WBC counts with considerable toxicity, but a low WBC count in a patient with sepsis does not necessarily predict death. The WBC count may undergo dramatic changes in a short period of time, often preceding changes in clinical condition. Foals with infection acquired in utero as a consequence of bacterial placentitis typically are born with elevated WBC counts. There is some evidence that very high WBC counts are positively correlated with successful outcomes. The fibrinogen concentration is also useful in detecting newborn foals that have been infected or exposed to inflammatory placental disease in utero. Fibrinogen values in these cases may be 1000 mg/dL or greater at birth (normal is 300 mg/dL or less), and, again, high values are often positively related to outcome. In the early stages of postnatally acquired infections, fibrinogen values may be only mildly increased (400 to 500 mg/dL), but with increasing chronicity resulting from pneumonia or bone and joint infections, plasma fibrinogen levels may increase dramatically.

Total plasma protein concentration is highly variable and may be influenced by dehydration, catabolism, and ingestion of colostral immunoglobulins. The range of presuckle protein concentration varies so much between foals that it is not a reliable indicator of FPT. IgG determination has been shown to be an important component of the sepsis evaluation, in that low IgG levels have strongly correlated with the presence of sepsis. Severe, overwhelming infections are seen far less commonly in foals with normal immunoglobulin G (IgG) levels (>800 mg/dL) but can occur, particularly in individuals with in utero acquired infections and severe enteric infections caused by pathogenic bacteria such as *Salmonella* species and clostridial intestinal infections. Because serum IgG levels can change dramatically as a result of protein catabolism associated with sepsis, it is often difficult to determine whether hypogammaglobulinemia in a sick foal is the cause or result of sepsis.

Hypoglycemia (glucose <60 mg/dL; <3.3 mmol/L) commonly accompanies generalized infection and is associated with bacterial consumption and reduced glycogen reserves. Serum glucose values can be very low, with the animal showing few signs other than depression and weakness.

The potential application of hematologic evaluation of neonates for early detection of sepsis is illustrated in a study reported by Adams and colleagues.[70] Hematologic values in 35 newborn beef calves were evaluated; five calves subsequently developed clinical signs of sepsis at 3 weeks of age. Comparison of hematologic values from the five diseased calves with values for healthy calves revealed significant differences at each sample collection time (birth, 24 hours, 48 hours, and 3 weeks), although disease was not clinically evident at the three early sample times. 284
Compared 285 with the clinically normal calves the five septic calves had more band neutrophils and a higher neutrophil-to-lymphocyte ratio at birth. At 24 hours the monocyte count was higher, and at 48 hours total leukocyte, mature neutrophil, and monocyte counts and neutrophil-to-lymphocyte ratio were higher in the five calves. At 3 weeks, when clinical signs of disease were detectable in the five calves, the total leukocyte, band neutrophil, and mature neutrophil counts, neutrophil-to-lymphocyte ratio, and plasma total protein and fibrinogen concentrations were higher.[70]

Hematologic abnormalities observed in septic calves with clinical signs of disease are not consistent. In a retrospective study of 25 septic calves a noticeable feature of the pattern of laboratory abnormalities was the contrast of severe clinical signs with minor complete blood count (CBC) and serum biochemical alterations in

numerous calves.[52] Abnormal laboratory findings included neutrophilia or neutropenia, immature neutrophils, toxic neutrophils, and hyperfibrinogenemia.[52] Low serum immunoglobulin concentrations are also commonly observed in calves with sepsis.[52,55] The most common abnormalities observed in calves with DIC include activated partial thromboplastin time (aPTT) and prothrombin time (PT), observation of schistocytes, and elevated fibrin degradation products. Thrombocytopenia is less frequently observed.[71] Abnormalities of the coagulation and the fibrinolytic systems are also common in neonatal foals with sepsis.[72] Prolongation of PT and aPTT are common, as are increased concentrations of fibrin degradation products.[73] Foals with advanced sepsis may show signs of spontaneous hemorrhage or vascular thrombosis.

Lactate measurement is an important indicator of foal sepsis and if taken at admission may provide important prognostic information.[74] Lactate is normally <2.5 mmol/L; levels between 2.5 and 5 mmol/L are typically not associated with acidosis, whereas values<5 mmol/L are often associated with acidosis. Substantial reductions in blood lactate in response to 24 hours of therapy often translate into a favorable outcome.[75] Other abnormal serum chemistries associated with sepsis include metabolic acidosis (bicarbonate <19 mEq/L) resulting from increased anaerobic metabolism and azotemia (creatinine <2 mg/dL) secondary to dehydration as well as primary renal damage. During the terminal stages of septicemia, foals frequently display a mixed respiratory and metabolic acidosis accompanied by hypoxemia. Lipemia and hyperbilirubinemia reflect altered endocrine and hepatic function.

Positive blood cultures are essential to make the diagnosis of septicemia. However, it is clear that treatment cannot be delayed until results of blood cultures are obtained. Although it does not help to make the initial decision regarding therapy, a positive blood culture allows a more accurate prognosis to be given to the owner, provides information about the type of bacteria and its susceptibility pattern, and helps guide the decision as to length of antibiotic treatment.

Blood cultures are easy to perform but must be done carefully for accurate results. The hair should be shaved, and the site of venipuncture surgically scrubbed. Depending on the type of culture bottle or tube, a set amount of blood is withdrawn from the vein aseptically and deposited into both anaerobic and aerobic blood culture bottles. A liquid or solid blood culture medium can be used. One popular culture medium is Columbia broth medium with sodium polyanetholsulfonate as anticoagulant for aerobic cultures (Septi-Chek, Roche Laboratories, Nutley, NJ) and a brain-heart infusion medium for anaerobic cultures. If the medium is not readily available, the sample can be transferred in a yellow-top tube containing anticoagulant citrate dextrose (ACD). Serial cultures are preferred. A clean needle is used for transferring the blood into each bottle. The bottles are then incubated. A positive culture is characterized by marked turbidity, usually within 12 to 48 hours of incubation. The medium with bacterial growth is then Gram stained and plated out for identification and susceptibility testing. Working with a local human hospital may provide the ideal resource when trying to identify bacteria and establish antibiotic susceptibility patterns.

Other samples that can be used for culture in addition to urine and blood are synovial fluid, cerebrospinal fluid (CSF), peritoneal fluid, feces, and transtracheal aspirate. In cases of physeal osteomyelitis a physeal aspirate may be beneficial.

Many referral hospitals perform blood culture on all abnormal neonatal foals on admission, whether or not they received antibiotics previously, and the foals should then be placed on antibiotics if infection is suspected. Bacterial cultures are also taken from specific areas if local infections are suspected (CSF, joint, feces, trachea). With only one blood culture routinely taken per foal, some false-negative results have been obtained, but the number of positive results has been surprising.[6,51] However, foals with in utero—acquired pneumonia have rarely had positive

results on blood culture, and additional culture specimens (e.g., tracheal aspirate) should also be taken. If a fever spike occurs during the hospital stay, if the WBC count changes dramatically, or if the clinical condition of an infected foal deteriorates, the blood is recultured. The development of resistant infections has been observed in both community- and hospital-acquired infections, and their prompt detection is very important.

18.6 THERAPY FOR BACTERIAL INFECTION

Antibiotic therapy is currently the cornerstone of treatment of neonatal infection. Because sepsis can progress with devastating speed in the neonate, antibiotic therapy should be started as soon as sepsis is suspected. Broad-spectrum coverage should be initiated pending culture results, anticipating the preponderance of gram-negative bacteremia, the reemergence of gram-positive pathogens, and the possibility of polymicrobial infections. Bactericidal drugs are favored for treatment of sepsis in neonates because of the immaturity of the neonatal immune system. Immaturity of mechanisms involved in drug absorption, distribution, biotransformation, and excretion contribute to altered pharmacokinetics of antimicrobials in neonates. Implications of altered pharmacokinetics in neonates include the potential for suboptimal therapeutic concentrations, toxic effects, and, of importance in food animals, violative residues if adult dosing regimens are employed. In general terms, antimicrobials have longer elimination times in neonates (less than 2 weeks of age) than in adults and therefore larger doses are administered with a longer dosage interval to achieve similar peak and trough antimicrobial concentrations. More complete discussions of antibiotic therapy in neonatal foals[10,76,77] and food animals can be found in other texts.[78–81] The use of immediate antimicrobial therapy in advanced cases of sepsis is controversial. It has been suggested that lysis of circulating bacteria could further contribute to endotoxin load, hastening circulatory collapse and death. In vitro data indicate that β-lactam antibiotics, such as ceftiofur or ampicillin, but not aminoglycosides, may lead to an increase in endotoxin concentration.[82]

The duration of antibiotic therapy in infected neonates depends on the clinical status of the patient and what type of infection has been documented. One week to 10 days of therapy may be adequate for suspected but undocumented sepsis if the CBC, fibrinogen, and patient are normal at the end of therapy. A minimum of 2 weeks of treatment is suggested in blood culture—positive patients with no evidence of localized infections. Three to 4 weeks (or more) of antibiotic treatment are often required when the infection has localized, particularly in the joints or lungs. Therapy is usually discontinued when the WBC count, fibrinogen, and radiographs have returned to normal. Although there has been concern about the use of aminoglycoside antibiotics in the neonatal foal, the well-hydrated neonatal foal tolerates these drugs very well, even after extended periods of treatment (2 to 4 weeks).

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Established sepsis in the neonate carries a poor prognosis, with less than 12% survival of calves with sepsis in a referral hospital.[52] Client education to facilitate early recognition and treatment of neonates with sepsis improves outcome and reduces cost.

18.6.1 Antimicrobial Therapy in Foals

The combination of a penicillin and an aminoglycoside, such as gentamicin (6.6 mg/kg given intravenously [IV] or intramuscularly [IM] once per day [sid]) or amikacin (21 to 25 mg/kg IV or IM, sid), provides good antimicrobial coverage. Some clinicians have used gentamicin at 6.6 mg/kg twice per day (bid) as long as in-hospital monitoring is available. Amikacin is often preferred to gentamicin because it seems to be less nephrotoxic and less likely to be associated with the development of resistant bacterial infections.[10,77,83] Ideally, peak and trough serum aminoglycoside concentrations are monitored to ensure that the proper dose and dosing interval are used, but this is not often possible in a field setting. Unfortunately, no studies have been conducted in the foal to determine the specific peak and trough serum concentrations resulting in optimal survival rates in

individuals with sepsis.[84] Based on work in other species a target peak concentration of 15 to 30 µg/mL and trough concentration of 1 to 3 µg/mL have been suggested.[85] During long-term aminoglycoside therapy, efforts are made to prevent dehydration, and the patient's urinalysis and serum creatinine are monitored at least weekly.

Other antibiotics that may be useful in the empirical treatment of the infected neonate include certain third-generation cephalosporins, such as ceftiofur (2.2 to 4.4 mg/kg IV or IM bid), cefotaxime (20 to 30 mg/kg IV or IM three times per day [tid]), ceftriaxone, and ceftazidime. In studies of susceptibility patterns of bacteria cultured from foals undergoing treatment in intensive care units, antibiotics such as ampicillin, kanamycin, and tetracycline were of very little value for treatment of gram-negative infections. Twenty percent to 40% of isolates were resistant to trimethoprim-sulfonamide (TMS) combinations (15 mg/kg bid IV, orally [PO]), ceftiofur (2.2 to 6.6 mg/kg IM bid), chloramphenicol (25 to 50 mg/kg IV or PO four times per day [qid]), and ticarcillin-clavulanate (50 mg/kg IV, tid or qid).[7,9,51,86] Some, however, have reported success with tetracyclines in the management of osseous infection. A susceptibility pattern should document that the organism is indeed susceptible before these antibiotics are selected for use. Fluconazole may be effective in treatment of localized and generalized candidiasis. One recommended dosage for foals is a loading dose of 400 mg followed by 200 mg at 24-hour dosing intervals.[10]Q See Chapter 45 for further discussion of antibiotics.

18.6.2 Antimicrobial Therapy in Neonatal Ruminants

Common medical conditions in neonatal calves that require antimicrobial therapy include diarrhea, pneumonia, bacteremia, omphalophlebitis, osteomyelitis, meningitis, and septic arthritis.

Bacteremia is a common problem in debilitated neonatal ruminants. Rapid recognition and treatment of sepsis improves the likelihood of a successful outcome. Blood culture studies of debilitated calves indicate that gram-negative bacteria account for approximately 80% of bacterial isolates; *E. coli* is the most common species of bacteria isolated.[52,54,87] In a study of 190 recumbent calves on a large calf-raising facility, 31% were determined to have bacteremia. *E. coli* accounted for 51% of the isolates; other gram-negatives, 25%; gram-negative anaerobes, 5.9%; gram-positive cocci, 11.8%; and gram-positive rods, 5.9%.[87] Empiric antimicrobial therapy should include a gram-negative and gram-positive spectrum. Other considerations pertinent to antimicrobial selection include the pharmacokinetics and pharmacodynamics of the drug in neonates, likelihood of antimicrobial resistance, and potential for violative antimicrobial tissue residues. Determination of antimicrobial susceptibility (minimal inhibitory concentration [MIC]) before therapy is desirable but often not possible. Alternatively, a drug may be selected and given at a dosage that has been shown to be effective for ≥90% of similar isolates tested (MIC 90%). The objective of measuring antimicrobial MIC' is to facilitate antimicrobial selection that is likely to achieve a therapeutic concentration of drug for the target pathogen. The MIC data are of limited value without information on serum and tissue concentrations attainable using the intended drug dose. Data regarding microbial susceptibility to antimicrobial drugs are provided in Table 18-1, and pharmacologic data regarding the volume of distribution, half life, and breakpoint MICs of common antimicrobial drugs are presented in Table 18-2. The data presented in the tables are intended as a guide. Being from different studies, they reflect the magnitude of differences that may be observed over time and among sources. The data reflect intravenous administration. The half-life of drugs is often longer after intramuscular injection, reflecting absorption rate—dependent elimination.[114]

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Table 18-1 Antimicrobial Susceptibility Data for Bacterial Pathogens from Bovine Sources

Organism (No. of Isolates)	Antimicrobial	% Susceptible	MIC (µg/mL)		
			50%	90%	Range
PASTEURELLA HEMOLYTICA					
(n=461)[98]	Ampicillin	60.5	0.25	32	≤0.03->64
(n=89)[99]	Ampicillin		4	16	0.25->16
(n=421)[100]	Ampicillin		128	128	
(n=461)[98]	Ceftiofur	100	≤0.03	0.06	≤0.03-0.13
(n=50)[101]	Ceftiofur		0.0078	0.015	≤0.003-0.03
(n=121)[102]	Enrofloxacin		0.06	0.06	0.03-0.12
(n=461)[98]	Erythromycin	5.4	4	4	≤0.03->64
(n=89)[99]	Erythromycin		2	16	0.5->16
(n=421)[100]	Erythromycin		4	4	
(n=243)[103]	Florfenicol			1	
(n=89)[99]	Gentamicin		1	2	0.25–8
(n=421)[100]	Gentamicin		2	4	
(n=89)[99]	Kanamycin		4	16	2->16
(n=89)[99]	Penicillin G		8	16	4->16
(n=461)[98]	Spectinomycin	83.5	32	64	0.5->128
(n=89) [99]	Spectinomycin		12	32	8->32
(n=421)[100]	Spectinomycin		8	16	
(n=89)[99]	Sulfadimethoxine		200	400	12.5->400
(n=421)[100]	Sulfadimethoxine		256	256	
(n=461)[98]	Sulfamethazine	46.2	128	512	0.5->512
(n=461)[98]	Tetracycline	57	1	32	≤0.06-64
(n=89) [99]	Tetracycline		16	16	0.5->16
(n=421)[100]	Tetracycline		32	64	
(n=461)[98]	Tilmicosin	69.1	4	8	0.06-16

(n=89)[99]	Tylosin		16	16	8->16
(n=421) [100]	Tylosin		64	128	
PASTEURELLA MULTOCIDA					
(n=318)[98]	Ampicillin	88.1	0.25	8.0	≤0.03->64
(n=32)[99]	Ampicillin		1	16	0.25->16
(n=158) [100]	Ampicillin		2	4	
(n=318)[98]	Ceftiofur	100	≤0.03	0.06	≤0.03-0.25
(n=50) [101]	Ceftiofur		0.0078	0.0078	≤0.003-0.0078
(n=108)[102]	Enrofloxacin		0.015	0.03	≤0.008-0.06
(n=318)[98]	Erythromycin	16	2	8	≤0.03->64
(n=32)[99]	Erythromycin		4	16	1->16
(n=158)[100]	Erythromycin		4	4	
(n=183)[103]	Florfenicol			0.5	
(n=32)[99]	Gentamicin		1	4	0.25->8
(n=158)[100]	Gentamicin		4	8	
(n=32)[99]	Kanamycin		4	16	1->16
(n=32)[99]	Penicillin		4	16	0.12->16
(n=158)[100]	Penicillin		2	4	
(n=318)[98]	Spectinomycin	76.4	32	128	0.13->128
(n=32)[99]	Spectinomycin		12	32	4->32
(n=158)[100]	Spectinomycin		8	16	
(n=32)[99]	Sulfadimethoxine		400	400	100->400
(n=158)[100]	Sulfadimethoxine		256	256	
(n=318)[98]	Sulfamethazine	27.4	128	512	0.5->512
(n=318)[98]	Tetracycline	71.1	0.5	16	≤0.06->32
(n=32)[99]	Tetracycline		16	16	1->16
(n=158)[100]	Tetracycline		2	16	
(n=318)[98]	Tilmicosin	58.9	4	8	0.25-32
(n=32)[99]	Tylosin		16	16	16->16
(n=158)[100]	Tylosin		32	64	
HAEMOPHILUS SOMNUS					

(n=109)[98]	Ampicillin	90.1	0.06	1	≤0.03->64
(n=109)[98]	Ceftiofur	100	≤0.03	0.06	≤0.03-0.13
(n=59)[101]	Ceftiofur		≤0.0019	≤0.0019	≤0.0019
(n=104)[102]	Enrofloxacin		0.015	0.03	≤0.008-0.5
(n=109)[98]	Erythromycin	88.9	0.25	2	≤0.03->32
(n=34)[103]	Florfenicol			0.5	
(n=109)[98]	Spectinomycin	87.1	8	32	≤0.13->128
(n=109)[98]	Sulfamethazine	35.8	256	512	≤0.5->512
(n=109)[98]	Tetracycline	98.2	0.5	1	≤0.03-32
(n=109)[98]	Tilmicosin	90.4	2	4	≤0.03-32
MYCOPLASMA BOVIS					
(n=20)[104]	Enrofloxacin		0.1	0.25	0.05-1
(n=100)[103]	Florfenicol			0.5	
(n=20)[104]	Oxytetracycline		1	2.5	0.1-10
(n=20)[104]	Tylosin		1	5	0.025->100
***MYCOPLASMA MYCOIDES* SUBSP *MYCOIDES* SMALL COLONY TYPE**					
(n=20)[105]	Florfenicol		1	2	0.25-8
(n=20)[105]	Oxytetracycline		0.5	1	0.125-4
(n=20)[105]	Spectinomycin		8	16	4->128
(n=20)[105]	Tilmicosin		0.015	0.03	<0.008-0.25
FUSOBACTERIUM NECROPHORUM					
(n=21)[106]	Ampicillin		1.6	2.3	
(n=68)[107]	Ampicillin	100			
(n=17)[108]	Ceftiofur	100	≤0.062	≤0.062	≤0.062
(n=68)[107]	Chloramphenicol	100			
(n=21)[106]	Erythromycin		3.1	6.3	
(n=12)[103]	Florfenicol			0.25	
(n=21)[106]	Oxytetracycline		0.08	0.2	
(n=365)[109]	Penicillin	96			
(n=68)[107]	Penicillin	100			
(n=21)[106]	Penicillin G		0.1	1.9	

(n=365)[109]	Tetracycline	99			
(n=68)[107]	Tetracycline	100			
(n=21)[106]	Tylosin		3.1	6.3	
CLOSTRIDIUM PERFRINGENS					
(n=67)[109]	Chloramphenicol	99			
(n=67)[109]	Penicillin G	93			
(n=67)[109]	Tetracycline	70			
OTHER*CLOSTRIDIA*					
(n=109)[109]	Chloramphenicol	99			
(n=109)[109]	Penicillin	90			
(n=109)[109]	Tetracycline	77			
FUSOBACTERIUM NECROPHORUM* SUBSP *FUNDILIFORME					
(n=16)[106]	Ampicillin		1.3	2.7	
(n=16)[106]	Erythromycin		3.1	6.3	
(n=16)[106]	Oxytetracycline		0.2	4.1	
(n=16)[106]	Penicillin G		0.2	0.8	
(n=16)[106]	Tylosin		4.7	21.3	
BACTEROIDES MELANINOGENICUS					
(n=11)[103]	Florfenicol			0.25	
BACTEROIDES FRAGILIS					
(n=29)[108]	Ceftiofur	69	1	16	≤0.0625-≥16
(n=192)[109]	Chloramphenicol	99			
(n=192)[109]	Penicillin G	15.9			
(n=192)[109]	Tetracycline	77.3			
NON–BACTEROIDES FRAGILIS					
(n=12)[108]	Ceftiofur	58	2	16	0.125-≥16
(n=114)[109]	Chloramphenicol	100			
(n=114)[109]	Penicillin G	89			
(n=114)[109]	Tetracycline	96			
PEPTOSTREPTOCOCCUS ANAEROBIUS					
(n=57)[107]	Ampicillin	100			

(n=12)[108]	Ceftiofur	100	0.25	2	0.125-2
(n=57)[107]	Chloramphenicol	100			
(n=193)[109]	Chloramphenicol	100			
(n=57)[107]	Penicillin	97			
(n=193)[109]	Penicillin	96			
(n=57)[107]	Tetracycline	100			
(n=193)[109]	Tetracycline	100			
ESCHERICHIA COLI					
(n=24)[99]	Ampicillin		4	16	1->16
(n=40)[101]	Ceftiofur		0.25	0.5	0.13-1
(n=24)[99]	Gentamicin		1	2	0.5->8
(n=24)[99]	Oxytetracycline		16	16	1->16
(n=24)[99]	Spectinomycin		16	32	8->32
(n=24)[99]	Sulfachlorpyridazine		200	400	12.5->400
ARCANOBACTERIUM (ACTINOMYCES) PYOGENES					
(n=42)[110]	Ampicillin		0.025	0.05	≤0.0125-0.05
(n=42)[110]	Benzylpenicillin		≤0.0125	0.25	≤0.0125-0.05
(n=42)[110]	Ceftiofur		0.78	1.56	0.39-1.56
(n=42)[110]	Chloramphenicol		1.56	1.56	0.39-1.56
(n=42)[110]	Erythromycin		0.025	0.025	≤0.0125-0.025
(n=42)[110]	Florfenicol		1.56	1.56	0.78-1.56
(n=42)[110]	Gentamicin		1.56	1.56	0.2->100
(n=42)[110]	Oxytetracycline		6.25	25	0.2–25
(n=42)[110]	Tilmicosin		0.05	0.05	≤0.0125-0.05
***SALMONELLA* SPECIES**					
(n=9)[99]	Ampicillin		16		2->16
(n=48)[99]	Ampicillin		16	16	0.5->16
(n=28)[101]	Ceftiofur		1	1	0.6-2
(n=9)[99]	Gentamicin		0.5		0.5-4
(n=48)[99]	Gentamicin		0.5	2	0.25-8
(n=9)[99]	Oxytetracycline		2		1->16

(n=48)[99]	Oxytetracycline	16	16	1->16
(n=9)[99]	Spectinomycin	12		8->32
(n=48)[99]	Spectinomycin	32	32	12-32
(n=9)[99]	Sulfachlorpyridazine	150		50->400
(n=48)[99]	Sulfachlorpyridazine	400	400	12.5->400
(n=48)[99]	Sulfamethoxine	400	400	12.5->400

Table 18-2 Pharmacokinetic Parameters of Antimicrobial Drugs in Calves and Adult Cattle

Drug	Neonate Vd (L/kg)	Adult Vd (L/kg)	Neonate $T_{½}$	Adult $T_{½}$ (hr)	Breakpoint (µg/mL)
Ampicillin	0.5[111]		3.8 r	0.95[81]	≤2
Ceftiofur	0.385[112]	0.3[112]	16.1 hr[112]	7[112]	≤2[100]
Enrofloxacin		1.46		6.4 [81]	≤0.25
Erythromycin		1.7[113]		3.2[81]	≤2[100]
Florfenicol	0.907[89]	0.35[114]	3.8 hr[89]	2.9[114]	≤0.5
Gentamicin	.42[115]	.21[115]	2.9[115]	1.7[115]	≤4[100]
Oxytetracycline	2.48[116]	0.8[116]	13.5[116]	10.3[116]	≤4
Penicillin G	0.77[117]		0.98[117]	0.7[81]	≤1[100]
Spectinomycin					≤32[98]
Sulfadimethoxine		0.31[118]		12.5[118]	≤100[100]
Sulfamethazine		0.44		8.2[81]	≤32
Sulfadiazine	0.72[119]	0.75	4.4[119]	2.5[120]	
Tilmicosin		2		4.18	≤4[98]
Trimethoprim			1 day = 8.4 hr 7 days = 2.1 hr 42 days = 0.9 hr[119]		
Tylosin	4.4[121]	4.4[121]	2.31[121]	1.26[121]	≤5[100]

Vd, Volume of distribution.

Antimicrobial drugs with a gram-negative spectrum of activity include third-generation cephalosporins (ceftiofur), TMS, fluoroquinolones (enrofloxacin), aminoglycosides, sulfonamides, and tetracyclines. Although florfenicol has a gram-negative spectrum, the MIC90 for *E. coli* is very high at 25 mg/mL.[88] Intramuscular injection of florfenicol (20 mg/kg IM) fails to reach the MIC90 value in plasma, and intravenous injection (11 to

20 mg/kg IV) exceeds the MIC90 value for only 60 minutes.[89–91] The National Cattlemen's Association (NCA) recommends that “until further scientific information becomes available alleviating safety and efficacy concerns, aminoglycoside antibiotics should not be used in cattle except as specifically approved by the FDA” (*Herd Health Memo,* No. 9, p. 82, 1993–1994). The bacteriostatic action and frequency of antimicrobial resistance to tetracyclines and nonpotentiated sulfonamides limits their effectiveness in neonates with sepsis. TMS may be used to treat sepsis in neonatal calves, but its half-life rapidly declines as ruminal function develops. In ruminating (6- to 8-week-old) calves, subcutaneous or oral administration of TMS leads to high serum levels of sulfadiazine but little or no serum trimethoprim.[92] Bacterial resistance to TMS is less common than resistance to sulfa drugs alone but still may be high.[54,93] Fluoroquinolones such as enrofloxacin are bacteriocidal and have an appropriate gram-negative spectrum of activity suitable for treatment of gram-negative sepsis. *However, in the United States, enrofloxacin is conditionally licensed for treatment of respiratory disease in beef cattle*. In countries where it is legal to use enrofloxacin for treatment of neonatal sepsis, a dosage rate of 2.5 to 5 mg/kg every 24 hours has been suggested as appropriate for calves.[94] Enrofloxacin has demonstrated good efficacy in the treatment of *E. coli* septicemia, *Salmonella* enteritis, and *Mycoplasma* and *Pasteurella* pneumonia in calves.[95–97] Prolonged administration of enrofloxacin (weeks) is not recommended, as it produces articular erosions in immature animals of other species. Ceftiofur has an appropriate antimicrobial spectrum, is bacteriocidal, and has been used to treat calves with sepsis with good clinical results using a dose of 5 mg/kg twice a day.* The label dose of 1 mg/kg once a day may not achieve minimal inhibitory tissue drug concentrations for some bacteria commonly isolated from neonates. Deviation from the labeled dose requires implementation of a withholding period. Information regarding drug withholding times for extra-label use of antimicrobials is available from the Food Animal Residue Avoidance Databank (FARAD), and a database of U.S. Food and Drug Administration (FDA)–approved drugs is accessible via the World Wide Web (http://www.farad.org/index/html).

* George L: Personal communication, 1998, University of California, Davis, Calif.

18.6.3

Circulatory Support

Maintenance or restoration of effective circulating volume is a top priority in cases of sepsis. Aggressive intravenous fluid therapy is the mainstay of cardiovascular support and should be administered at the maximal rate tolerated by the foal. Severe septic shock may require fluid rates of 40 to 80 mL/kg/hr. Volume expansion should be achieved using a balanced electrolyte solution (crystalloid) or plasma (colloid). Colloid solutions are preferred and may reduce the incidence of pulmonary and systemic edema during fluid resuscitation. Infusion of crystalloid solutions equivalent to 0.5 to 1.5 times the estimated blood volume of the patient has been used, but hemodilution is a common consequence.[122] If hemodilution is severe, or if hypotension or vasoconstriction continue or recur, additional fluid administration in the form of colloid, such as plasma, or hypertonic crystalloid fluid should be considered. Additional discussion of hypertonic saline administration may be found in Chapter 44 and in other references.[123,124]

When fluid resuscitation alone is inadequate to improve cardiovascular function and restore acceptable blood pressure, pharmacologic intervention using sympathomimetic agents is necessary. Peripheral and cardiac adrenergic receptor downregulation necessitates the use of larger doses of pressor agents than usual. In patients that are hypotensive, dopamine with its combined α- and β-adrenergic and dopaminergic activity is preferred. Higher doses are required for patients in severe septic shock. If the foal fails to respond to high doses (>10 to 15 μg/kg/min) then norepinephrine, a more potent α-adrenergic agent, can be tried. Recently, NO has been shown to play a role in sepsis-induced hypotension. IV administered new methylene blue, an NO antagonist, has been used to try and reverse severe life-threatening hypotension. If oliguria continues in spite of restoration of circulating volume, diuretics such as furosemide or mannitol are used to promote renal vasodilation and urine flow.[122]

Because most foals with sepsis are hypoglycemic, a slower continuous infusion of dextrose-containing solutions should be run simultaneously with the rehydration fluids. Avoid too rapid an infusion of dextrose to avoid hyperglycemia, which can induce an osmotic diuresis that further exacerbates the dehydration.

Treatment with antiprostaglandin drugs has been found to counteract a number of the clinical and hemodynamic changes associated with endotoxemia and septic shock, including the decrease in cardiac output and systemic hypotension. They have little effect, however, on the leukopenia, thrombocytopenia, or coagulopathies that develop in septic shock.[122] Based on the effect of these drugs in models of endotoxemia in the adult horse[125,126] and neonatal calf[127] and of septic shock in other species,[122] they would be expected to be of some benefit in treatment of the septic large animal neonate. Pharmacokinetic studies of flunixin meglumine in neonatal foals suggest that, in spite of prolonged elimination of flunixin in healthy newborn foals, the physiologic activity appears similar to that in the adult, and the adult dose of 1.1 mg/kg of body weight would be appropriate in at least some patients.[128] Lower doses of flunixin meglumine, 0.25 mg/kg IV tid may be effective in ameliorating some of the signs of endotoxemia. Other treatments include plasma administration from hyperimmunized donors to treat not only FPT but to provide opsonins and improve foal neutrophil function. Plasma also represents an ideal colloid for rapid volume expansion.

Other therapies include naloxone, an opiate antagonist, which has been used experimentally to counteract the detrimental vasodilatory effects of endorphins released during sepsis. An NO inhibitor, new methylene blue, has been used to treat refractory hypotension in septic patients.[46,47] Pentoxifylline, a methylxanthine derivative, has been used for treatment of conditions characterized by inadequate regional blood flow.[129,130] The drug increases red cell deformability, reduces blood viscosity, decreases platelet aggregation, and decreases thrombus formation. Pentoxifylline administration also results in decreased plasma fibrinogen, increased action of plasminogen activators, and antithrombin III, decreased platelet thromboxane synthesis, and increased prostaglandin 1-2 synthesis. The net effect of the drug is to increase regional blood flow and inhibit coagulation. When the drug was used in animal models of endotoxic shock, it increased overall survival rates and prevented endotoxin-induced renal failure, synthesis of TNF, and coagulopathies. Horses that received the drug showed a decrease in packed cell volume (PCV) and red blood cell (RBC) sedimentation rate and beneficial effects of RBC deformability. IV doses used experimentally in horses include a single bolus of 7.5 mg/kg of body weight followed by a continuous infusion of 1.5 mg/kg/hr.[129]

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Polymyxin B administered at low, nontoxic doses is a new investigational treatment modality being used to neutralize systemic endotoxin. Low doses of the drug result in decreased concentrations of circulating endotoxin, improved immune function, and decreased mortality rates among shock patients. Polymyxin B binds and neutralizes endotoxin in vitro and has been shown to removed endotoxin from the circulation in vivo. Use of this drug in the horse is investigational. A suggested dose is 6000 IU/kg diluted in 300 to 500 mL of 5% dextrose and given as a slow intravenous infusion.

18.6.4 Immunologic Support

When FPT of antibodies accompanies neonatal infection, plasma is routinely used to increase immunoglobulin levels. From 1 to 4 L of plasma have been infused IV to raise IgG levels, but the optimum amount is not known. Important factors influencing the amount of plasma indicated include the total IgG content of the plasma and the specific antibody concentration against foal pathogens, as well as the degree of circulatory impairment of the neonate. The efficacy of plasma in the prevention or treatment of septicemia in foals has not been established as of this writing. See Chapter 53 for more information on treatment of FPT.

Several immunologic products are currently under investigation as potential treatments of foal septicemia; their efficacy has not yet been proven. These include serum or plasma containing high levels of antibodies to the common core structures of LPS,[126,131] and granulocyte colony-stimulating factor, which markedly increases WBC counts in foals.[132] Monoclonal antibodies to TNF and other inflammatory mediators may also be of use in the future.[133]

Bovine colostrum supplements are commercially available. Immunoglobulin content varies among products and should be considered when comparing prices. Colostrum supplements generally fail as colostrum substitutes because of the relatively low mass of immunoglobulin delivered per dose.[134] In two separate clinical trials, peak serum immunoglobulin concentrations were not significantly different in calves fed 3 or 4 L of maternal colostrum with or without colostrum supplement.[134,135] Administration of a colostrum supplement before 18 hours of age is indicated when an adequate supply of colostrum is not available. If a colostrum supplement is to be used as a colostral substitute, multiple doses are required to deliver a minimum of 100 g of immunoglobulin.

18.6.5 Supportive Therapy

Nutritional support of neonates with sepsis is critical. Gram-negative bacterial sepsis disrupts intermediary metabolism, increases metabolic rate, and sequentially hinders use of carbohydrates, lipids, and finally protein for energy. Endotoxin release precipitates a neurohormonal cascade of events mediated by TNF and increased levels of catecholamines, glucocorticoids, and glucagon. Elevated concentrations of antidiuretic hormone, aldosterone, and thyroxin and low levels of insulin accompany low perfusion states associated with septic shock. Sepsis results in glycolysis, lipolysis, and proteolysis, increased urinary excretion of potassium and nitrogen, and water and sodium retention. Suppressed insulin production and peripheral insulin resistance result in glucose intolerance and hyperglycemia. During sepsis the transport, oxidation, and clearance of free fatty acids (FFAs) is impaired owing to a deficiency of the carrier peptide carnation and decreased lipoprotein lipase activity. Lipemia develops. The final fuel source becomes protein degradation. Uremia, production of false neurotransmitters, hepatoencephalopathy, and neurologic signs occur when excessive amino acid degradation overwhelms hepatic metabolic capacity.

Provision of adequate nutrition is vital for a successful outcome in the treatment of infected neonates. Poor nutritional support leads to debilitation, a poorly functioning immune system and poor healing, persistent infection, and other complications, such as decubital ulcers. The healthy newborn foal requires 15% to 25% of body weight in milk per day. Foals that are too weak to nurse from the mare or a bottle should be tube-fed a minimum of 10% of their body weight per day in milk administered in small feeds every 2 to 3 hours. Because many sick foals have poor gut function, enteral nutrition is not a viable option initially. If a foal is not consuming at least 10% of body weight in milk within the first 36 to 48 hours, it should be started on parenteral nutrition using a formula containing dextrose, lipids, amino acids, vitamins, and trace minerals. Solutions of 5% to 10% glucose can be administered to help maintain a normal blood glucose level. These solutions provide temporary nutritional support but do not contain nearly enough calories for long-term nutritional support. It would require 35 L of a 5% dextrose solution per day to provide a 50-kg foal with adequate calories (120 kcal/kg/day). The use of a combination of oral and parenteral nutritional support has considerable merit in treating the infected neonate.

Foals with sepsis are susceptible to pulmonary dysfunction because of a variety of factors including dependent lung atelectasis, pneumonia, pulmonary edema, and surfactant dysfunction. The focus of respiratory support is to minimize ventilation and perfusion mismatching. Fluid therapy helps increase left ventricular, left atrial, and

diastolic pressures to create more uniform lung perfusion. Recumbent foals should be turned and repositioned frequently to minimize dependent lung atelectasis and pulmonary edema formation. Mild to moderate hypoxemia can be treated with humidified intranasal oxygen (2 to 10 L/min). Severe hypoxemia (P_{O_2} < 50 mm Hg), despite oxygen supplementation, and persistent hypercapnia (P_{CO_2} <65 to 70 mm Hg) require positive pressure ventilation with positive end expiratory pressure (PEEP) to prevent further lung collapse, reduce interstitial edema, and prevent respiratory muscle fatigue. Debilitated foals with sepsis that require mechanical ventilation and nasotracheal intubation are at increased risk for nosocomial infections. Nebulization using bronchodilators, wetting agents, and mucolytic agents, accompanied by coupage therapy, also helps relieve foals with respiratory distress and facilitates removal of tracheal secretions.

The nursing care of the neonate with sepsis is very important. Maintenance of body temperature; fluid, blood gas, and acid-base balance; and a clean environment is critical for a successful outcome. Every neonate undergoing intensive care, regardless of its primary problem, should be monitored closely for fever spikes, neutropenia, increasing lethargy, and localizing signs of infection that could indicate early sepsis or a different, bacterial infection resistant to the antibiotics being used.

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18.7 PROGNOSIS AND COMPLICATIONS OF SEPTICEMIA AND RELATED INFECTIONS

If a large animal neonate has FPT and is septicemic with several organ systems involved, its long-term outcome must be considered guarded, even with intensive nursing care.[8] A recent study reported a short-term survival rate of 81% for neonatal intensive care unit survivors.[11] Secondary complications that often accompany multifocal bone and joint infections may exert an adverse effect on the final outcome. A retrospective study that examined the factors associated with prognosis for survival and athletic use in foals with septic arthritis showed that with treatment the prognosis for survival was favorable, whereas the prognosis for ability to race was unfavorable. Approximately 78% of treated foals survived, and a third of those foals raced. Multisystem disease, isolation of *Salmonella* species from synovial fluid, involvement of multiple joints, and synovial fluid neutrophil count <95% were associated with a poor prognosis.[136] If blood cultures are negative and localized infection (enteritis, pneumonia) is present, the outcome can be much more positive with aggressive therapy. If in utero acquired infections in the foal are treated appropriately early in the clinical course and good IgG levels are attained by the newborn, the outcome can be quite favorable (>75% survival).

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19 Chapter 19 Manifestations and Management of Disease in Foals

Guy D. Lester

19.1 MATURITY

Guy D. Lester

19.1.1 GESTATIONAL PERIOD

In contrast to most other domesticated species, in mares the duration of the gestational period is highly variable. The gestational age is typically calculated from the day of insemination to the day of parturition, a value that may overestimate the true gestational period by as much as 7 days. The mean gestational length in the thoroughbred is consistently reported to be 340 to 342 days,[1–5] but the range of normal gestational ages is wide, with an estimated 95% confidence interval of 327 to 357 days.[1] The mean duration of pregnancy also appears to be relatively consistent across breeds: Friesians, 332[6] or 338[7] days; Arabians, 332 days[8]; Dutch Freiberger mares, 336 days[9]; draught breeds, 343 days[7]; Haflinger ponies, 341 days; Fjord ponies, 342 days; Shetland ponies, 337 days[7]; and ponies in England, 333[5] or 325 days.[10] Several factors appear to determine the length of gestation in mares. Colts on average have a longer gestation than fillies, with a reported difference of 1.5 to 2.5 days.[2–4,6] Colts are also heavier, have a heavier placenta, and take longer to stand.[4] The time of conception within the breeding season affects the duration of the gestational period. Mares that conceive early in the breeding season have longer pregnancies than those bred toward the end of season. This difference may be as great as 10 days.[1,2] An influence of mare, sire, and dam's sire on gestational length was recently reported in Friesian mares[6] and an effect of sire was reported in Freibergers.[9] A study of thoroughbreds concluded that dam, in addition to foal gender and month of conception, but not sire, had a significant effect on the duration of pregnancy.[2] The age or parity of the mare does not appear to have an influence,[2,3] but maternal age has been correlated with decreasing foal birthweights. Twinning is also an important cause of shortened gestational periods and in utero growth retardation.[11]

The terminology associated with birth maturity in most species is straightforward but is difficult in horses because of the variability in normal gestational length. Retrospective studies report wide variability in gestational age but unfortunately do not report physical characteristics or foal survival. Gestational ranges of 305 to 365 days, 315 to 387 days, and 286 to 370 days have been described.[2,3,12] The term *"premature"* in other domesticated animals and in human beings refers to the birth of an infant or animal after a gestational period shorter than normal. A premature human infant is now defined as one who is delivered at least 21 days before the mean pregnancy duration of 266 days. The use of a gestational age to classify equine prematurity has been described, with the most commonly used definition being a foal born before 320 days of gestation.[5] This definition was based on significantly lower birthweights and poor outcomes of foals born before 320 days.[13] It could also be argued that foals born outside the lower 95% confidence interval of the normal gestational period would best fit the classification of premature; this would be less than 325 days in thoroughbreds, using data extrapolated from Hintz and others.[3] It is clear that any precise classification of prematurity based solely on estimated gestational age would falsely classify a small number of appropriately mature animals. There are similar difficulties in classifying animals that have experienced a longer than normal gestational period. Again,

using the upper confidence interval limits from thoroughbreds, foals born after 356 days could be regarded as postterm. A distinction should be made between postterm and postmature, the latter describing a condition of increased neonatal morbidity as a consequence of failing placental function.

Dysmaturity is a term commonly used to describe foals that have experienced some degree of intrauterine growth retardation (IUGR). Such foals typically demonstrate some signs of physical immaturity, such as a low birthweight. Dysmature foals can have shortened, normal, or prolonged gestation lengths. Other terms used to classify foals with incomplete maturation include *viable* and *nonviable*[13] and *ready* and *unready for birth*.[14] In a review of terminology, Koterba suggested the terms *viable* and *nonviable* were inappropriate because outcomes of premature foals are heavily influenced by access to facilities and the value of the animal.[13] The concept of *readiness for birth* was used to categorize foal outcomes based primarily on the degree of maturation of the fetal hypothalamus-pituitary-adrenal (HPA) axis. Although this plays a critical role in determining postpartum survival, other factors, including the degree of physical maturation and the consequences of an adverse intrauterine environment, are also relevant in determining the ultimate outcome.[13] Premature maturation of the HPA axis often takes place at an inappropriate developmental stage for some body systems, causing asynchrony of organ maturation and postnatal problems.[15] Extending the concept of readiness for birth, Rossdale introduced the term *twilight foals* to describe those foals with accelerated but incomplete maturation of the HPA axis at the time of birth.[5,16]

The physical characteristics associated with prematurity include a low birthweight and small body size, a short and shiny haircoat, a prominent rounded head, periarticular laxity, and droopy ears. Foals typically have moderate flexor laxity with elevation of the toe, but some have contracture of the fetlock. Muscle development is usually poor. Most demonstrate generalized weakness and hypotonia and have difficulty in standing. Severely premature foals may have lids naturally sutured closed and little hair covering their bodies. Many have difficulty in maintaining body temperature, blood pressure (BP), and blood glucose.

Dysmature foals commonly experience some degree of IUGR. This is usually reflected by the birth of a foal that is small for its gestational age. The average relative weight of the term foal to its dam is approximately 10%. Postmature foals usually have an acceptable birthweight with a large frame but poor muscle development. This gives the foal a lanky appearance. In contrast to premature animals, fetlock contracture is common, although laxity can be present. Consistent with their prolonged gestation, postterm or postmature foals often have erupted incisors and a long haircoat. In term foals the central incisors typically erupt during the first 5 to 7 days of postnatal life.

19.1.2 CAUSES OF PREMATURE DELIVERY

The pregnant uterus is highly responsive to contractile agents such as oxytocin and prostaglandins throughout gestation. Consequently, one of the most important causes of premature birth and perinatal morbidity and mortality is the induction of labor with exogenous oxytocin or prostaglandins. The adverse consequences of premature induction of parturition were identified in a study in which parturition was induced either before 300 days' gestation or between 300 and 320 days' gestation.[17] The overall survival rate was only 5%, with the youngest surviving animal delivered after 318 days' gestation. Other surviving foals were all delivered after 320 days' gestation. The decision to prematurely terminate a pregnancy may be made deliberately in the “normal” mare, or the termination may be necessary because of significant maternal disease. The latter frequently involves delivery of a compromised and often premature foal by cesarean section. Chemical induction of parturition sometimes occurs when late pregnancy intestinal problems are misinterpreted as ineffective labor. Premature

birth can occur as a sequela to placental problems, including placental infection, edema, and/or detachment (premature placental separation). Placental insufficiency as a result of twinning is another cause of IUGR.

The consumption by pregnant mares of tall fescue pasture infected with *Neotyphodium coenophialum* leads to range of abnormal signs including prolongation of gestation, perinatal mortality, and agalactia.[18] The large skeletal frame of the postmature foal predisposes mares to dystocia. The delay in parturition may be caused by toxin-induced interference with fetal corticotropin-releasing hormone (CRH) and delay in maturation of the HPA axis. Foals born to mares grazing endophyte-infected fescue pasture have normal thyroxine and reverse T_3 but reduced triiodothyronine levels compared with control foals.[19] This is also consistent with failure of cortisol-induced maturation of thyroid function. A syndrome of congenital hypothyroidism has been reported in foals in Western Canada.[20] Signs include prolonged gestation, dysmaturity, and a range of musculoskeletal abnormalities including flexural deformities, delayed ossification, and mandibular prognathism. The specific cause has not been determined, although consumption of diets that contain nitrate or are deficient in iodine is suspected.[21]

19.1.3 MATURATION OF THE FETAL HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The maturation of several organ systems coincides with changes in the fetal HPA axis.[15] Fetal cortisol is critical for organ maturation, but if the fetus is exposed too early in gestation or to too large a quantity IUGR may occur. The fetus is protected from cortisol during much of gestation. The type 2 isoform of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) converts excess biologically active cortisol into inactive cortisone in the placenta, thereby reducing the exposure of the fetus. The postnatal adrenal gland, under the influence of ACTH from the pituitary, can readily synthesize cortisol from cholesterol and pregnenolone (P5). Several important enzymes are required for this conversion, including 3β-HSD, P450scc, and P450C17. These enzymes are either inhibited or deficient during most of pregnancy, again protecting the developing fetus from excessive cortisol. Consequently during the majority of gestation the major products of steroidogenesis are progesterone and the 5α-reduced progestagens and not cortisol.[22] Foals, like other species studied, undergo enhanced adrenal activity before birth. This is reflected by high plasma cortisol and ACTH concentrations in term newborn foal plasma in the first hours after birth.[23] There is also a substantial change in the amount and localization within the adrenal gland of 3β-HSD, P450scc, and P450C17 around the time of birth.[24]

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The trigger(s) for the process that results in fetal cortisol production, organ maturation, and birth are not known. Data from sheep indicate that upregulation of CRH messenger ribonucleic acid (mRNA) in the fetal hypothalamus and proopiomelanocortin in the fetal pituitary is a key initiating event.[15,25] At the same time there is upregulation of adrenocorticotropic hormone (ACTH) receptors and key steroidogenic enzymes in the fetal adrenal glands. The consequence is a progressive increase in circulating ACTH and cortisol in the fetus. The rise in fetal cortisol has a direct effect on the placenta to increase prostaglandin H synthase 2, leading to secretion of prostaglandins such as prostaglandin E_2 (PGE_2).[15,25,26] Prostaglandins further stimulate the fetal HPA axis, stimulate placental 11β-HSD-1 (which favors the production of cortisol from cortisone), and also facilitate the conversion of estrogen from pregnenolone. It is not known if these events occur in the pregnant mare, but they do appear to be consistent across most species studied.

An important difference between equids and other species is the timing of these events before parturition.[15] In pregnant ewes, maturation of the HPA axis occurs during final 20 days of a 150-day gestation. In contrast, the production of significant fetal cortisol appears to occur during the final 48 to 72 hours of pregnancy in mares.[27] Several important maturational events appear to be tightly associated with the prepartum increase in ACTH and

cortisol.[22] These include changes in red blood cell (RBC) and white blood cell (WBC) parameters, most notably a large increase in the neutrophil-to-lymphocyte ratio (N:L).[27,28] Hepatic and renal glucose-6-phosphatase, a key enzyme of gluconeogenesis, also increases sharply around the time of birth,[29] coinciding with increases in hepatic and skeletal muscle glycogen stores.

The prepartum rise in plasma cortisol likely induces deiodination of the outer ring of T_4 to produce the biologically active triiodothyronine (T_3).[30] Adequate levels of T_3 are required for a number of biologic functions including postnatal thermogenesis. Normal term foals have very high levels of thyroid hormones, including T_3, at the time of birth.[31] These levels decline over the initial weeks or months of postnatal life. A relationship between circulating T_3 levels and cortisol was reported in premature, dysmature, and mature foals,[16] and the increase in T_3 appears to be dependent on maturation of the HPA axis.[32] Both cortisol and T_3 are critical for lung maturation, particularly the normal postpartum reabsorption of lung liquid.[32]

19.1.4 ACCELERATED MATURATION OF THE FETAL HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Several factors can induce premature maturation of the fetal HPA axis. Hypoxemia is a potent stimulator of the axis in sheep, with rises in fetal ACTH and cortisol.[33] The HPA axis can also be manipulated using exogenous glucocorticoids; betamethasone is commonly administered to women in danger of preterm birth in order to hasten HPA maturation and therefore improve the chances of postnatal survival. Poor nutrition before and after conception in sheep produces a shortened gestational period and hastened maturation of the fetal HPA axis.[25] Placental and/or fetal infection also can accelerate maturation of the HPA axis. The cytokines induced by infection increase prostaglandin synthesis and decrease metabolism. Prostaglandins exert a range of actions in addition to promoting cortisol production.

The stimuli associated with precocious HPA axis maturation in foals are not well described. The exception is infection of fetal membranes, in which foals are often delivered preterm with laboratory findings consistent with axis maturation. Spatial and nutritional deprivation resulting from a thoroughbred foal placed in a pony uterus using embryo transfer also leads to premature maturation of the fetal adrenal.[10,34]

Unfortunately, many late-term maternal diseases do not appear to have a significant effect on foal maturity. Hypoxemia associated with anesthesia and colic surgery in pregnant mares during the final 60 days of pregnancy results in a high rate of preterm delivery of compromised foals that did not survive.[35] It is likely that the insult in these cases was so severe that the interval between surgery and delivery was inadequate for maturation of the axis to occur. Another important consideration in determining outcomes would be the effect of hypoxia and/or ischemia on other fetal organ systems.

19.1.5 TREATMENT OF THE AT-RISK LATE PREGNANT MARE

Unfortunately, the administration of corticosteroids to the pregnant mare appears to have little effect on maturation of the fetal HPA axis, at least when doses considered safe are used.[5] Direct injection of $ACTH_{1-24}$ to the fetus results in increased fetal cortisol, but the effect is dependent on gestational age, with maximal responses occurring at around day 313 and with no measurable benefit when administered before day 295.[27] Direct administration of CRH, ACTH, or betamethasone to the fetus using ultrasound-guided intramuscular (IM)

injection results in increased maternal progestagen levels consistent with maturation of the fetal adrenal gland.[36,37] The procedure itself can lead to abortion in a small number of mares. Exogenous $ACTH_{1–24}$ administered to late pregnant pony mares had an impact on both gestational length and fetal maturation.[38] Depot $ACTH_{1–24}$ given to mares at 300, 301, and 302 days of gestation produced a shortened gestational length and lower birthweight but evidence of HPA axis maturation. A confounding effect in this study was the time of conception, with the most significant findings observed in mares bred later in the breeding season.

It is preferable to maintain the fetus in utero to ensure not only adequate HPA axis maturation but also effective ossification and maturation of other body systems. Consequently, the primary focus of therapy for a mare with placental infection is to eliminate the pathogenic organisms, reduce inflammation, and maintain the pregnancy. The specific management of placentitis is not the focus of this chapter, but treatment may involve broad-spectrum antibiotics, nonsteroidal antiinflammatory drugs, pentoxifylline, β_2-adrenoreceptor agonists, and altrenogest. The efficacy of altrenogest use in mares with placentitis has been questioned.[22]

The termination of postterm pregnancies is a difficult decision for practitioners, particularly with the emotional response that is common in many owners. Given the wide variation in gestational range it is almost always in the best interests of the foal to let the pregnancy continue. If facilities are available then rectal and transabdominal ultrasound assessment of the fetus and chorioallantois should be made, looking carefully for thickening or detachment of the fetal membranes. Ideally any induction of parturition should be based on appropriate changes in physical characteristics of the mare and in milk electrolytes. Mares grazing endophyte-infected tall fescue can be medicated with dopamine receptor antagonists, such as domperidone.[18]

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19.1.6 LABORATORY ASSESSMENT

The laboratory data will indirectly reflect the degree of HPA axis maturation. Premature or dysmature foals that fail to survive often have minimal cortisol secretion in the face of adequate endogenous ACTH. Furthermore, the change in plasma cortisol in response to exogenous $ACTH_{1–24}$ (0.125 mg IM) is inconsistent and usually inadequate.[23] The foal with incomplete adrenal maturation will have low total white cell and neutrophil counts and an N:L that is characteristically less than 1:1.[28] It is important to determine if sepsis is present as neutropenia is also a common feature of this condition. Evidence of shifting toward immature cell types and neutrophil toxicity should indicate primary sepsis or prematurity or dysmaturity complicated by sepsis. Premature foals that fail to improve their total WBC and neutrophil counts over the initial 24 to 48 hours of treatment have an even poorer prognosis for survival. Changes in red cell indices have also been reported in nonstressed preterm foals.[28] Most notable is an elevated mean corpuscular volume in preterm foals. An elevated plasma fibrinogen concentration is considered to be a good prognostic factor in premature foals as it often reflects prepartum exposure to bacterial infection. Induced or spontaneously delivered term foals have a significantly higher plasma glucose concentration than premature foals.[39] Plasma creatinine levels are often elevated in newly born preterm or dysmature foals as a result of placental dysfunction. This increase is independent of foal renal function. Measurement of low cortisol levels coupled with increased progestagens would provide further evidence that effective maturation of the HPA axis has not occurred in the foal before birth.[40]

19.1.7 ESTABLISH A PROGNOSIS

The prognosis for survival of a prematurely delivered foal is dependent on a range of factors including the gestational age, the reasons for delivery, complications associated with delivery, available resources (facilities

and expertise), and financial limitations of the owner. Survival of very premature foals (280 to 300 days) would typically require a history of chronic in utero stress with resultant precocious maturation of the HPA axis and critical organ systems. The majority of such foals would still require a lengthy and costly period of hospitalization and experience a range of complications, some of which could be life-threatening. Foals delivered prematurely as a consequence of chemical induction of parturition without evidence of chronic in utero stress or via cesarean section typically have a high mortality rate even when delivered close to calculated due dates. Foals delivered under these circumstances before 300 days will almost certainly die, irrespective of available resources.

A complete blood count (CBC) and fibrinogen estimation are key factors in determining short-term prognosis. A normal or elevated neutrophil count, N:L, or total WBC count is a positive indicator for survival, as these values typically reflect maturation of the HPA axis. In a survey of 135 neonates admitted to the University of Florida with a gestational age of ≤320 days, short-term survival was in part predicted by total WBC count, neutrophil count, lymphocyte count, and the N:L at presentation.[41] The N:L of surviving premature foals (12.5:1) was well above that reported for both normal term foals (2.5:1) and nonsurviving premature foals. Many of the surviving animals were exposed to confirmed or suspected placental infection. Outcome was not affected by gestational age (surviving foals 311 days and nonsurvivors 307 days). These data confirm that in utero stress, with hastened maturation of the HPA axis, is a good prognostic factor for survival in foals that are delivered preterm. In many foals the greater the neutrophil count the better the outlook, at least in terms of short-term survival. A high plasma fibrinogen concentration is also considered to be a positive factor. Reevaluation of the white cell indices on day 2 for appropriate increases also supports a favorable prognosis.

A history of placental infection appears to be a positive factor when predicting survival in preterm foals. One obvious downside is that many of these foals are born with aspiration pneumonia (a result of in utero aspiration of contaminated amniotic fluid) and/or systemic sepsis. This, coupled with the fact that many foals have an impaired immune system, warrants the use of broad-spectrum antimicrobial therapy.

Consideration should also be given to the long-term outcomes of preterm foals. These animals are at risk for significant and permanent musculoskeletal problems as a result of bone and ligamentous immaturity. Foals that survive the neonatal period are smaller than their peers, and this difference will often remain noticeable when they are weanlings and yearlings. The differences may be less obvious at 2 years and older. Other common complications, such as pneumonia, will further reduce the growth rate in the first 6 months of life. There is nothing to indicate that premature fillies will experience fertility problems as adults.

19.1.8 CLINICAL PROGRESSION

The clinical progression usually reflects the degree of endocrinologic maturity, additional perinatal stresses, and the extent of physical maturity. Typically, foals born prematurely but chronically exposed to an appropriate in utero stress such as placental infection will appear weak and depressed in the immediate postpartum period. Some will require resuscitation. After a longer than normal period of postural adaptation they will usually manage to stand but will often require assistance. Suckle reflex and appetite may be reduced or absent, and many will need to be fed initially via nasogastric tube. They will frequently have trouble maintaining their body temperature and blood glucose levels. After the initial 24-hour period many of these foals demonstrate improvement both in physical strength and mentation. Their appetite for milk will often exceed that of a healthy term foal. Foals with inadequate maturation of the HPA axis will frequently require immediate resuscitation. They may mimic the clinical progression of in utero stressed premature foals until 12 to 18 hours of age. This initial period after delivery can be deceptive, with many foals showing degrees of improvement, which often promote owner optimism. The rise of hormones accompanying delivery may lead to improvement in alertness

and strength. However, after this period a range of progressive abnormalities develop. These include systemic weakness, depression, seizures, respiratory failure, and intolerance to feeding. Cardiovascular collapse may ensue, the first sign of which is a reduction in the intensity of peripheral pulses, followed by a reduction in urine flow, development of subcutaneous edema, and deteriorating neurologic function. Poor tissue perfusion leads to lactate accumulation and a mixed metabolic and respiratory acidosis. Death will certainly occur without aggressive support, and even with high-level intensive care the mortality rates are very high.

19.1.9 TREATMENT OF THE PREMATURE OR DYSMATURE FOAL

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It is critical to perform a thorough physical examination, as problems of altered maturity can involve many organ systems. Successful outcomes are dependent not only on careful management of identified problems but also in predicting the problems that may arise in the hours, days, or weeks to come. Most premature and dysmature foals experience some degree of pulmonary insufficiency. Factors that predispose these foals to respiratory problems include structural and functional immaturity, a naïve and potentially immature immune system, altered pulmonary vascular reactivity, a highly compliant rib cage, and a propensity for prolonged or persistent recumbency. Final maturation of the respiratory system appears to be highly dependent on a functional HPA system. Arterial blood gas (ABG) analysis is an important tool in the assessment of respiratory function, and the lower arterial oxygen concentration in term newborn foals is further decreased in dysmature or premature foals. Extrapulmonary shunts account for more than 30% of the cardiac output, in contrast to <10% in normal full-term foals.[42] Ventilation-perfusion mismatching also occurs because of a poorly reactive pulmonary vasculature and dependent atelectasis. Deficiency of lung surfactant is not likely to play a primary role in the respiratory dysfunction in most premature or dysmature foals, as it is usually fully developed in most foals by 300 days, but it could be delayed until after 340 days in some foals.[43] The most severe form of respiratory failure is neonatal respiratory distress syndrome (RDS), a disease characterized by progressive respiratory failure, severe hypoxemia and hypercapnia, coma, and death. A diffuse severe alveolar pattern is a classic radiographic finding. Intervention would ideally involve mechanical ventilation, bovine or synthetic surfactant, and glucocorticoids; however, outcomes are extremely poor, irrespective of the level of care. Fortunately RDS is relatively uncommon; most premature foals will, however, demonstrate a less severe manifestation of lung dysfunction characterized by reduced ventilation capacity, tachypnea, hypoxemia, and varying levels of hypercapnia. These foals are very susceptible to dependent lung atelectasis from recumbency. Most foals will benefit from supplemental intranasal oxygen with initial flow rates of 5 L/min recommended. Adjustment in flow rate is dictated by positive changes in ABG analyses or improvement in ventilation rate and depth. It is important to avoid prolonged periods of lateral recumbency in order to minimize the impact of atelectasis. If the foal is unable to stand, then placement in sternal recumbency is recommended. This is made easier by use of a specially constructed V-pad.

Failure of the cardiovascular system is common in foals with partial or incomplete maturation of the HPA axis. Management is challenging in part because of inconsistent responses to standard inotrope and vasoreactive therapy. Successful treatment is reliant on early detection of reduced perfusion. This is reflected clinically by cool extremities, the presence of limb and ventral edema, and darkening of the mucous membranes with prolongation of the capillary refill time. As failure ensues, peripheral pulses will become difficult to palpate, blood pH will fall, and there will be increases in plasma lactate and anion gap. Indirect (or direct) measurement of mean BP along with determination of blood lactate will help guide therapy. An initial approach to the treatment of failing perfusion may involve intravenous plasma followed if necessary by dopamine (3 to 5 μg/kg/min) and/or dobutamine infusion (5 to 20 μg/kg/min). The volume and type of fluids given should be carefully monitored, as fluid overload and hypernatremia are common. Urine output should be appropriate for the volume of fluids administered, and anuria or oliguria should be treated aggressively. This may include low-dose

dopamine or fenoldopam infusion, furosemide boluses or infusion, or mannitol infusion. Establishment of urine flow is critical in terms of survival.

Signs of gastrointestinal (GI) tract dysfunction are rarely evident on initial assessment of premature or dysmature foals; however, most will not tolerate aggressive force-feeding. These foals commonly develop intestinal stasis with reduced fecal passage, gas accumulation, and gastric distention. The combination of prolonged asphyxia and prematurity is also a risk factor for the development of necrotizing enterocolitis (NEC). Feeding should be restricted to very small volumes (e.g., 10 to 20 mL hourly) until the foal appears to be systemically stable. Concurrent parenteral nutrition (PN) is indicated in order to prevent loss of body weight. Foals should be monitored closely for signs of GI dysfunction irrespective of feeding volume or frequency. Such monitoring includes assessing fecal passage, monitoring for changes in abdominal size (assessed using a measuring tape), testing for gastric reflux if a nasogastric tube is in place, and frequently assessing with transabdominal ultrasound.

Premature and dysmature foals are susceptible to hypothermia. Thermogenic mechanisms develop late in gestation and are related to circulating T_3 levels. As discussed previously, thyroid hormone generation is closely tied to maturation of the HPA axis. Consequently problems with thermogenesis are exacerbated in preterm foals with incomplete adrenal function. Body temperature needs careful management, as rapid warming may result in peripheral vasodilatation and possible cardiovascular collapse. Initially the foal should be covered by blankets and removed from any drafts. Intravenous and oral fluids should be warmed before use. Once the foal begins to demonstrate vigor, heat lamps and circulating warm-water blankets can be used.

Premature and dysmature foals often have inadequate gluconeogenic enzyme activity and limited glycogen stores at the time of birth. Consequently most will have difficulty maintaining a normal blood glucose concentration. This is managed acutely by infusion of 10 mL/kg of a 10% dextrose solution over several minutes, followed by a constant infusion at about 6 mg/kg/min (approximately 200 mL/hour of a 5% dextrose solution to a 30-kg foal). Blood glucose should be monitored regularly to avoid hyperglycemia. Some foals with persistent hyperglycemia benefit from insulin supplementation.

Skeletal maturity is assessed by radiographing a carpus and a tarsus for evidence of incomplete ossification (Fig. 19-1). Accelerated ossification does not appear to be a feature of foals born prematurely after exposure to chronic in utero stress. Incomplete ossification coupled with periarticular laxity predisposes the premature or dysmature foal to long-term skeletal problems. Foals with incomplete ossification and more than 30% reduction of the central and/or third tarsal bones with pinching or fragmentation of the dorsal aspects of affected bones commonly develop degenerative joint disease and have a guarded prognosis for future athletic performance. Restriction of exercise is recommended in order to minimize collapse of developing carpal or tarsal bones, but forced recumbency may predispose the foal to or exacerbate pulmonary disease. Furthermore, normal load bearing encourages ossification. Periarticular laxity predisposes the premature foal to angular limb deformities that facilitate abnormal load bearing and increase the risk of cuboidal bone crush injury of the carpus or hock. Splinting and attention to hoof care are recommended if angular limb deviation develops. In most cases flexural deformities and laxities improve over time. Dorsal splints are recommended for flexural deformities involving the fetlock, and heel extensions are helpful to foals with flexural laxity.

There are several reasons why colostral transfer of maternal immunoglobulin may not occur in premature foals. Mares may have lactated prematurely or not at all, and the foal may not be able to suck. It is crucial to ensure that the premature neonate receive ample amounts of high-quality colostrum (>20 mL/kg) in the first 6 hours after birth, although the intestinal tract may not be capable of efficient colostral uptake or may not tolerate large volumes of liquid. Consequently, plasma transfusion is often used even in foals less than 18 to 24 hours of age.

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A serum immunoglobulin G (IgG) level should be measured to confirm successful transfer of immunity (>800 mg/dL).

Fig. 19-1 **A**, Lateral tarsus of a 1-day-old, 305-day gestational age colt. Note the lack of ossification of the small tarsal bones. **B**, Lateral tarsus of the same foal as in **A**, at 3 weeks of age, showing irregular ossification. Without the initial radiograph, increasing ossification could have been confused with bone lysis and osteomyelitis. The foal is reported to be sound at 6 months of age.

The use of glucocorticoid therapy in the management of prematurity is controversial. Dexamethasone has been used in human medicine because of its potency, but it is associated with adverse side effects including hypertension, hyperglycemia, and catabolism.[44] Hydrocortisone has a shorter half-life and lower biologic activity and is as effective for improving lung function in preterm human infants without the side effects of dexamethasone.

19.2 WEAKNESS AND/OR DEPRESSION

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When confronted with a neonate with the primary complaint of weakness with or without accompanying depression, a number of differential diagnoses must be ruled out (see Box 20-1). The gestational and postnatal age of the neonate should be established. If weakness has been present since birth, then in utero acquired bacterial or viral infections, birth asphyxia and trauma, chronic placental problems, and congenital anomalies should be placed higher on the list of differential diagnoses. Lethargy and loss of suckle are often the first signs of neonatal illness. A full udder on the dam accompanies poor nursing behavior in the neonate. If the neonate is depressed and has injected mucous membranes and hyperemic coronary bands, then sepsis is the primary differential diagnosis and the most life-threatening. If the neonate is relatively bright but is becoming a "dishrag," consider peripartum hypoxia and early signs of hypoxic-ischemic encephalopathy. If the newborn shows signs of physical immaturity such as tendon laxity and silky hair coat, then weakness may be a result of progressive fatigue, hypothermia, hypoxia, and/or hypoglycemia. Unfortunately, many weak foals begin to fade as a result of multiple problems. Glycogen branching enzyme deficiency in certain quarter horse and Paint lineages is associated with a range of abnormal signs that could include persistent recumbency.[45]

If weakness is present without accompanying depression, then several other differential diagnoses should be considered. Neuromuscular diseases include botulism, white muscle disease, and congenital myopathies. Botulism is an infection acquired via the GI tract. Consequently, signs appear in neonates that are usually 10 days of age or older. Although most cases of nutritional myodegeneration (NMD) occur during the first year of life among rapidly growing large animal neonates, an in utero form of NMD may occur, resulting in clinical signs in affected foals soon after birth. If weakness is detected in one or more limbs immediately after birth, peripheral nerve and muscle damage associated with birth trauma should be ruled out. Foals with rupture of the gastrocnemius muscle will be unable to rise or stand unsupported.[46]

It should be determined whether any drugs or anesthetics were administered to the dam before or at the time of delivery, as many agents cross the placenta and can exert depressive and other adverse effects on the fetus. For example, one study reported that phenylbutazone administered to normal pregnant mares crossed the placenta and resulted in substantial concentrations of phenylbutazone and its active metabolite oxyphenbutazone. Although clinical signs of phenylbutazone toxicity were not noted in the foals postnatally,[47] adverse effects are possible, particularly if other problems are present. Drug-induced neonatal depression is particularly important after cesarean deliveries. Maternally administered anesthetics and analgesics can suppress respiration and heart rate in the newborn. In horses, both xylazine and detomidine cause maternal and fetal bradycardia and reduced cardiac output.[48,49] These effects cause a reduction in placental perfusion and fetal oxygenation. If the newborn shows depression associated with maternal administration of these drugs, yohimbine can be given as an antagonist. Weakly basic drugs, when given to the mare, tend to concentrate in the fetus. Diazepam is an example of such a drug that crosses the placenta rapidly and accumulates in the fetal circulation, resulting in lethargy, hypotonia, and hypothermia in the neonate after delivery. Flumazenil has been used to reverse the sedative effects of benzodiazepines. Maternal systemic illnesses of various types may also result in a weak newborn.

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Many neonatal disorders are associated with severe electrolyte and metabolic derangements. Weakness is a common clinical manifestation of hypoglycemia, metabolic acidosis, hyponatremia, hypernatremia, and hyperkalemia. Such abnormalities may occur before or at the time of birth, and laboratory assessment of the weak newborn is essential for accurate diagnosis. Young foals with hypocalcemia can have stiff gait, muscular tremor, tachycardia, sweating, muscular tremor, and recumbency.[50] Profound weakness associated with metabolic acidosis is commonly observed in foals with diarrhea. Correction of the acidosis by intravenous administration of bicarbonate usually produces rapid improvement.

A number of congenital bacterial, fungal, and viral infections that cause abortions and stillbirths may also result in the birth of a live, weak neonate. Clinical manifestations of fetal infections depend on the age of the fetus and virulence and trophism of the infecting agent (see individual diseases).

Generally, weakness secondary to uroperitoneum, renal, and liver failure, postnatally acquired infections, and neonatal isoerythrolysis (NI) is not expected to appear during the first 24 hours of age. Rather, foals with NI are usually presented between 24 and 72 hours of age, foals with uroperitoneum at 2 to 5 days of age or older, and neonates with postnatally acquired infections most commonly at 2 to 5 days of age or older.

NMD associated with selenium and/or vitamin E deficiency may produce localized (dysphagia) or generalized paresis.

Paraplegia and tetraplegia are commonly associated with spinal cord compression. Compression of the spinal cord in neonates most commonly results from vertebral body malformations, osteomyelitis, or fractures. Most malformations involve the occipital condyles of the skull and the first two cervical vertebrae (OAAM). Generally, vertebral body malformations occur sporadically; genetic, nutritional, and environmental factors have been implicated. Osteomyelitis and vertebral body abscess may be a sequela to bacteremia after neonatal sepsis or pneumonia. *Rhodococcus equi* vertebral osteomyelitis with or without associated pulmonary infection has been reported in foals.[51] Leukocytosis and hyperfibrinogenemia are commonly observed in neonates with vertebral body abscesses. In most instances vertebral abscesses do not infiltrate the pachymeninges so the cerebrospinal fluid (CSF) either is normal or has a mild elevation of protein and/or a mild pleocytosis.

A complete neurologic examination is an important component of the workup of the weak neonate. In particular, it should be noted if the weakness is accompanied by signs of depression and diffuse cerebral disease. Limb reflexes should be tested to establish whether components of the spinal reflex pathways are involved in the disease process (sensory nerve, lower motor neuron, neuromuscular junction, muscle). For example, foals with severe spinal cord hemorrhage may have relatively normal mentation, but spinal reflexes may be greatly diminished and profound weakness may be present. Animals with other types of spinal cord disease (e.g., trauma, vertebral malformations) may also show weakness and ataxia yet appear clinically to have normal cerebral function. Virtually any severe systemic disease such as generalized infection can cause both profound depression and weakness in a neonate without the presence of actual brain pathology. Primary neurologic disease in neonates is rare; commonly, neurologic dysfunction is associated with multisystemic disease. A thorough comprehensive physical examination and workup are required to define a problem list and formulate an appropriate management plan. A CBC, blood cultures, and assessment of immunoglobulin status provide an indication of the likelihood of sepsis. Hypoxia and metabolic acidosis are ruled out by assessing ABG status, and electrolyte disturbances and hypoglycemia are evaluated by measuring serum electrolytes and blood glucose concentration. Collection of CSF to assess the central nervous system (CNS) is usually performed when disease in other organ systems that may account for the altered mental state has been ruled out and no improvement in the patient's condition is observed after correction of electrolyte, blood gas, and metabolic derangements.

19.3 SEIZURES

19.3.1 IDENTIFICATION OF NEONATAL SEIZURE ACTIVITY

Seizures may be generalized or partial, depending on the part of the cerebral cortex affected by abnormal electrical activity. Involuntary muscle activity, opisthotonos, paddling, and extensor rigidity are signs associated with a generalized convulsion. In the neonate, more subtle neurologic signs may also be associated with seizure

activity. In the human infant, particularly the premature infant, the neuromuscular system is not fully developed at birth and is therefore unable to fully express the abnormal electrical activity in cerebral neurons. Abnormal breathing patterns, lip smacking, chomping, rapid eye movements, small limb movements, and tremor may be the only signs indicating seizure activity in the human infant. Similar signs in the abnormal neonatal foal have also been attributed to seizure activity.[52]

In the large animal neonate, several conditions should be distinguished from seizure activity. Bizarre movements associated with rapid eye movement (REM) sleep, particularly prominent in the premature foal, are frequently confused with seizure activity by the inexperienced observer. Signs can be very similar and include rapid eye movements, rhythmic paddling of the limbs, and chomping. The two conditions can be distinguished by attempting to arouse the animal; if activity is associated with REM sleep, the animal should be easily aroused to full consciousness. A foal that is simply resisting restraint in lateral recumbency may also appear to be having a seizure, and violent paddling of the limbs and occasionally opisthotonos are noted. If confusion exists as to the cause of the activity, the animal is encouraged to stand, and its behavior is then evaluated. Finally, in the foal the cataplexy-narcolepsy syndrome may be confused with convulsions. This “fainting foal syndrome” was first described in 1924 in three Suffolk foals that showed signs within a few hours after birth,[53] and a familial occurrence was recently reported in miniature horse foals.[54] Any exciting stimulus, including petting and restraint, can trigger the attacks, in which affected foals suddenly appear to be asleep, with flaccid limbs yet open eyes.

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Once seizure activity is identified, the cause of the seizures should be identified, if possible. A complete history is obtained, including a detailed description of the delivery process, and complete physical and neurologic examinations are performed. Any signs of trauma, infection, or congenital malformations should be noted. Evaluation of hematologic data and IgG status, combined with historical and physical examination parameters, results in an assessment of the likelihood of sepsis. Blood glucose and serum electrolyte concentrations should be determined promptly. A chemistry panel, blood gas analysis, bacterial cultures of blood and other body fluids, and possibly CSF analysis and skull radiographs, complete the database in most cases.

Before attempting to collect CSF (see Chapter 35), the benefit of the information likely to be obtained must be weighed against the small risk to the patient and the inconvenience of having to analyze the sample within 30 minutes of collection. In the large animal neonate, as in the adult, either the atlantooccipital or lumbosacral site may be used. Depending on the state of consciousness of the neonate, local anesthesia with manual restraint or light sedation, or general anesthesia may be required to obtain the fluid. For collection of fluid from the atlantooccipital site, a 20-gauge, 1½-inch needle with a clear hub may be used. A change in resistance is felt when the needle penetrates the dural membranes, and CSF appears in the plastic hub as soon as the subarachnoid space is entered. Approximately 5 to 10 mL of fluid may be removed safely from foals.[52]

Urinary reagent strips can be used to rapidly obtain general information on the fluid. If blood is detected, the sample should be spun down after the cytologic examination. RBCs contaminating the sample will settle, and the supernatant should be colorless. If hemorrhage occurred before the procedure, the sample remains xanthochromic (yellow). Glucose should be present in “trace” or “+” amounts in the normal sample. Negative values in the adult suggest severe meningitis but in the neonate may also be caused by profound hypoglycemia. The total protein level is increased in neonatal foal CSF compared with the level in the CSF of the adult horse, averaging 1.38± 0.5g/L (138±50 mg/dL) during the first 40 hours after delivery,[55] and slight xanthochromia is often present. Immaturity of the blood-brain barrier is postulated as one reason for the difference in CSF protein between adult and neonatal animals.

Vascular accidents in the neonate are tentatively diagnosed on the basis of a xanthochromic sample, elevated total protein levels, increased numbers of erythrocytes, and microscopic identification of erythrophagocytosis (best). CSF analysis is most useful in determining the presence of septic meningitis. Elevation of the total protein level (>150 mg/dL) and neutrophil count in addition to a positive Gram stain and bacterial culture results in a straightforward diagnosis of bacterial meningitis, and the prognosis is considered poor for the animal.[56] However, infection in the CNS can be difficult to detect until the process becomes generalized, and the lack of positive cultures and Gram stain does not rule out CNS infection. An elevated albumin quotient suggests increased blood-brain permeability and can be seen in both hypoxic-ischemic brain injury and meningitis, but an elevated IgG index indicates increased intrathecal IgG production and is more compatible with a diagnosis of meningitis.[57]

Ultrasonography and computed tomography (CT) are important procedures for evaluating anatomic causes of seizures (hemorrhage, infarct, malformations) in the human infant. Because the fontanelles are usually closed in the large animal neonate, ultrasound imaging is of limited or no use. Premortem diagnosis of agenesis of the corpus callosum and associated malformations was made using CT scanning in a foal that had an abnormally shaped head and seizures refractory to anticonvulsant therapy.[57] Identification of the specific abnormalities early in the clinical course allowed the owners to make a more informed decision regarding the treatment of the foal, and the clinicians to acquire valuable information regarding the prognosis associated with a specific malformation in the horse.

19.3.2 TREATMENT OF SEIZURES

Generalized seizures should be controlled immediately. Diazepam is often the initial drug chosen for seizure control because of its rapid effect. A dose of 5 to 20 mg for a 45-kg neonate is slowly administered, and its effect monitored. In some individuals one dose controls the seizure, and repeat seizures are not observed, whereas in others, multiple doses at frequent intervals may be necessary. In these animals other longer-acting anticonvulsants are often required.

Phenobarbital acts by raising the seizure threshold, and its peak effect is seen at approximately 30 minutes. An initial dose of 10 to 20 mg/kg diluted in saline and given intravenously (IV) over 15 minutes has been used successfully to control seizures in clinical patients. This initial dose is followed by a maintenance dosage of 10 mg/kg IV every 12 hours. Oral tablets may also be used. The major side effect of phenobarbital in foals has been mild sedation and ataxia. Interactions between phenobarbital and other drugs usually involve induction of the hepatic microsomal enzyme system. Weaning from anticonvulsant therapy should be gradual to avoid recurrence of seizure activity.

Phenytoin has also been used for seizure control in the newborn foal. The initial dose is 5 to 10 mg/kg IV followed by 1 to 5 mg/kg every 2 to 4 hours. This dosage resulted in effective seizure control in several foals unresponsive to both diazepam and phenobarbital, but it also appeared to cause marked depression in some patients. Little is known about the pharmacokinetics of the drug in the large animal neonate.

Pentobarbital anesthesia has also been used to control seizures, but its use has been associated with marked respiratory depression, hypotension, hypothermia, and prolonged anesthesia. Xylazine is also a potent sedative in the foal, but its side effects have also included markedly depressed cardiovascular and respiratory function and prolonged recovery in abnormal foals. Neither pentobarbital nor xylazine is recommended for seizure control in the foal unless no other agents are available.

19.3.3 CONDITIONS ASSOCIATED WITH SEIZURES

CNS dysfunction in asphyxiated large animal neonates is discussed in Chapter 16. Disorders of sodium can also cause seizures in young foals; these are discussed in detail in Chapters 22 and 44.

19.3.3.1 Meningitis

Although bacterial meningitis may occur as a primary entity, it more commonly is a result of generalized sepsis in neonates with failure of passive transfer (FPT). Agents that cause meningitis are the same as those that cause septicemia, most commonly bacteria such as *Escherichia coli*, *Enterobacter* species, *Salmonella* species, and *Streptococcus* species. Because clinical signs of meningitis are easily confused with hypoxic ischemic encephalopathy (HIE) and septicemia without localization in the CNS, diagnosis depends on CSF analysis (see Chapter 35). Treatment recommendations for treating bacterial CNS infections may be found in Chapter 35. Although there is one report on the successful treatment of two neonatal foals with suspected meningitis using third-generation cephalosporins,[58] in many cases, once the diagnosis is made the infectious process is often well advanced both in the brain and in other tissues, resulting in a poor outcome.

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19.4 RESPIRATORY DISTRESS

Wendy E. Vaala

Guy D. Lester

The transition from the fluid-filled lung of the fetus to an organ that is responsible for efficient gas exchange is both rapid and complicated. The process can be complicated by a number of factors, including prematurity or dysmaturity, aspiration of meconium or milk, and bacterial, viral, or fungal infection. A highly compliant chest wall, an inefficient immune system, and failure to derive adequate antibody from colostrum (partial or total FPT) are additive factors that predispose the neonate to respiratory problems.

The detection of respiratory disease in the newborn foal can be difficult. Thoracic auscultation can be highly misleading. Minute ventilation (frequency × tidal volume) is increased in the healthy neonate, resulting in easily heard bronchovesicular sounds. There is no need to accentuate breath sounds with rebreathing techniques. During the first few hours after birth, fluid can normally be auscultated throughout both lung fields and within the trachea. End-inspiratory crackles are commonly heard over the dependent lung during and shortly after rising from lateral recumbency. This is presumably because of simple atelectasis. Foals with respiratory disease will frequently have abnormal lung sounds, such as crackles and wheezes, but neonates with even severe pulmonary disease will occasionally have little detectable abnormality during auscultation. Clinical signs that are often associated with pulmonary tract disease in older foals and adult horses are frequently lacking in the sick neonatal foal. Fetal foals develop and mature in a relatively hypoxic environment within the uterus and therefore are more likely to tolerate postnatal hypoxemia than older foals or adults. Cough is also uncommon, likely owing to a postnatal delay in maturation of irritant receptors within airway and delayed onset of the laryngopharyngeal cough reflex. This is clinically relevant in that aspiration of milk into the lower airway associated with force-feeding can go undetected for several days. Of additional importance is that the respiratory rate and rhythm frequently do not accurately reflect arterial concentrations of oxygen or carbon dioxide. This is particularly relevant in foals that are showing signs suggestive of asphyxial injury, where rising arterial CO_2 concentrations occur in response to hypoventilation

and fail to cause an increase in minute ventilation. In these foals the primary drive for ventilation is arterial O_2 rather than CO_2.

In the absence of ABG data or radiographic information, the clinician must rely on vague signs, such as restlessness and agitation, increased respiratory rate, or respiratory distress. Historical information may also aid in diagnosis. This should include an estimation of gestational age, recognition of any maternal problems (e.g., fever, dystocia, placentitis, or prepartum vaginal discharge), the presence or absence of meconium staining of amniotic fluid, and an assessment of colostral quality and quantity. Failure to make an early identification of pulmonary disease often results in unfavorable outcome, with chronic pneumonia resulting. Malformations, inflammation, or other abnormalities of the upper respiratory tract can cause clinical signs of respiratory distress, stridor, and dysphagia and result in lower respiratory tract problems as well. Several nonrespiratory conditions also cause clinical signs that mimic respiratory disease.

The ideal diagnostic tools for investigation of neonatal respiratory disease include ABG analysis and thoracic radiography. ABG analysis is the most sensitive clinical tool used to assess lung function. The sample is usually collected from the dorsal metatarsal artery, easily palpated in most foals on the lateral aspect of the third metatarsal bone. Alternative sites include the brachial artery, located at the level of the medial collateral ligament of the elbow joint, and the carotid artery, but hematoma formation is a common sequel to aspiration from the latter site. The sample will remain useful for up to 90 minutes in a capped plastic syringe at room temperature.

Interpretation of the ABG sample involves consideration of the amount of struggling and position of the foal during sample collection. Normal ABG values for neonates of different postnatal and gestational ages are presented in Table 19-1. Lateral recumbency can reduce the Pa_{O_2} by as much as 30 mm Hg. The sample needs to be handled appropriately, paying strict attention to avoidance of air contamination, which will artificially increase the Pa_{O_2} and decrease Pa_{CO_2}. The inspired oxygen concentration must also be considered when analyzing ABG values. With supplemental oxygen, Pa_{O_2} is increased variably, depending on the inspired oxygen concentration (Fi_{O_2}), the amount of pathology present (particularly the extent of right-to-left shunting), the respiratory rate and tidal volume of the foal, and whether the oxygen is delivered by nasal insufflation. A flow rate of 10 L/min, delivered by nasal insufflation, increased the Pa_{O_2} to 298 ± 69 mm Hg in the normal, term newborn foal[59]; this flow rate was thought to approximate an Fi_{O_2} of 1.[60] In the induced premature foal the Pa_{O_2} increased only to 111 ± 35 mm Hg.[59] If the respiratory rate of a foal is rapid and shallow, the supplemental oxygen will be "diluted" by room air because of the large quantity of room air entering the upper respiratory tract, and the concentration of alveolar oxygen will probably be much less than 100%. The two most common respiratory-derived ABG derangements include hypoxemia with normocapnia or hypocapnia and hypoxemia with hypercapnia. It is important to distinguish acute from chronic hypercapnia. Acute hypercapnia is associated with a more substantial drop in blood pH and may lead to circulatory collapse and coma, particularly if accompanied by acute hypoxemia. Chronic exposure to elevated CO_2 permits adaptation and more subtle clinical effects. The change in pH is less dramatic, primarily because of enhanced bicarbonate reabsorption in the proximal tubules of the kidney. This effect begins within 6 to 12 hours of exposure to increased concentrations of CO_2 and is maximal by 3 to 4 days. Hypercapnia can be exacerbated by fever or the administration of carbohydrates or bicarbonate. The latter is often clinically relevant and highlights the danger of giving large amounts of sodium bicarbonate to foals with pulmonary disease.

Interpretation of blood gas values of venous blood (see Table 19-1) can be very deceptive and should be restricted to evaluation of metabolic conditions (e.g., metabolic acidosis) and not pulmonary gas exchange. To avoid problems associated with regional blood sampling, peripheral venous blood should be taken from a free-flowing jugular vein, because the metabolic status of the head is usually stable. To obtain a sample representative of the whole body, mixed venous blood is drawn from the right atrium. Determination of mixed venous blood oxygen

saturation is a good test for assessing the overall adequacy of oxygen delivery to tissues because it reflects the balance between oxygen delivery and oxygen use.

Table 19-1 Normal Blood Gas Values for Foals*

	Arterial					Venous			
Age-Group	O_2 (mm Hg)	CO_2 (mm Hg)	pH	Base Excess	HC^-_3 (mEq/L)	O_2 (mm Hg)	CO_2 (mm Hg)	pH	HC^-_3 (mEq/L)
Immediate post-foaling†	40-50	52-60	7.2-7.3	+2	24-26	—	—	—	—
2 hours†	68 ± 10	49 ± 2	7.37 ± 0.01	+4	26 ± 2	42 ± 2	56 ± 2	7.33 ± 0.01	28 ± 2
4-12 hours‡	75 ± 5	47 ± 2	7.39 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 2
24 hours‡	81 ± 6	48 ± 2	7.4 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 3
1-3 days‡	90 ± 6	148 ± 2	7.4 ± 0.01	+6	28 ± 2	43 ± 2	52 ± 2	7.38 ± 0.01	29 ± 2
4-14 days‡	86 ± 5	45 ± 2	7.41 ± 0.01	+6	28 ± 1	38 ± 2	53 ± 2	7.38 ± 0.01	31 ± 2
Premature† birth	39 ± 5	55 ± 4	7.27	−3	24 ± 1	—	—	—	—
(320-330 days' gestation)—1 hour	52 ± 4	48 ± 3	7.33	−1.3	25 ± 1	—	—	—	—

* Lateral recumbency.

† Data from Leipold HW, Hiraga T, Dennis SM: Congenital defects of the bovine musculoskeletal system and joints, *Vet Clin North Am (Food Anim Pract)* 9:93, 1993.

‡ Data from Scott PR, Penny CD, Murray LD: A field study of eight ovine vertebral body abscess cases, *N A Vet J,* 39:105, 1991.

Several factors need to be considered when evaluating foal thoracic films. Thoracic radiographs are routinely taken only in the standing or recumbent lateral position in foals, with dorsoventral positioning reserved for the anesthetized or very depressed foal. Thus interpretation can be limited because of positioning limitations. If the neonate has been in lateral recumbency for extended periods of time, atelectasis may result in diffuse or localized interstitial infiltrates that usually resolve once lung reexpansion occurs. It can be very difficult to accurately distinguish bacterial pneumonia from atelectasis and pulmonary edema on the basis of radiographic appearance alone. In these cases additional diagnostic aids (cultures, hematology, necropsy) should be used in conjunction with radiology to reach an accurate diagnosis. A false overinterpretation of disease is common because of motion artifact, caused by a combination of long exposure times, poor patient compliance, and high spontaneous ventilation rates. When the radiographic appearance of the lung fields is evaluated, the type of infiltrate (interstitial,

nodular, alveolar, mixed), severity, and location (diffuse, perihilar, cranioventral, craniodorsal, caudodorsal, caudoventral) should be noted. Other soft-tissue structures (including the heart, vessels, and diaphragm) and bones (ribs, vertebrae, long bones) should also be evaluated.

Serial thoracic radiographs are useful in monitoring the progress of a respiratory condition. Radiographic changes may either follow or precede changes in clinical condition, and major changes can occur surprisingly rapidly (Fig. 19-2). Clinical signs of pneumonia frequently resolve much earlier than chest radiographs and hemograms return to normal. Unfortunately, both ABG analysis and radiography are difficult to perform in field situations.

Ultrasonographic evaluation of the foal's thorax can yield useful information in a variety of disease processes, including pleural effusion, such as hemothorax or pleuritis, bronchopneumonia, or abscessation. It is also the preferred method for diagnosing rib fracture or dislocation and congenital heart disease and thus is often a useful technique to differentiate cardiac and pulmonary causes of hypoxemia.[61]

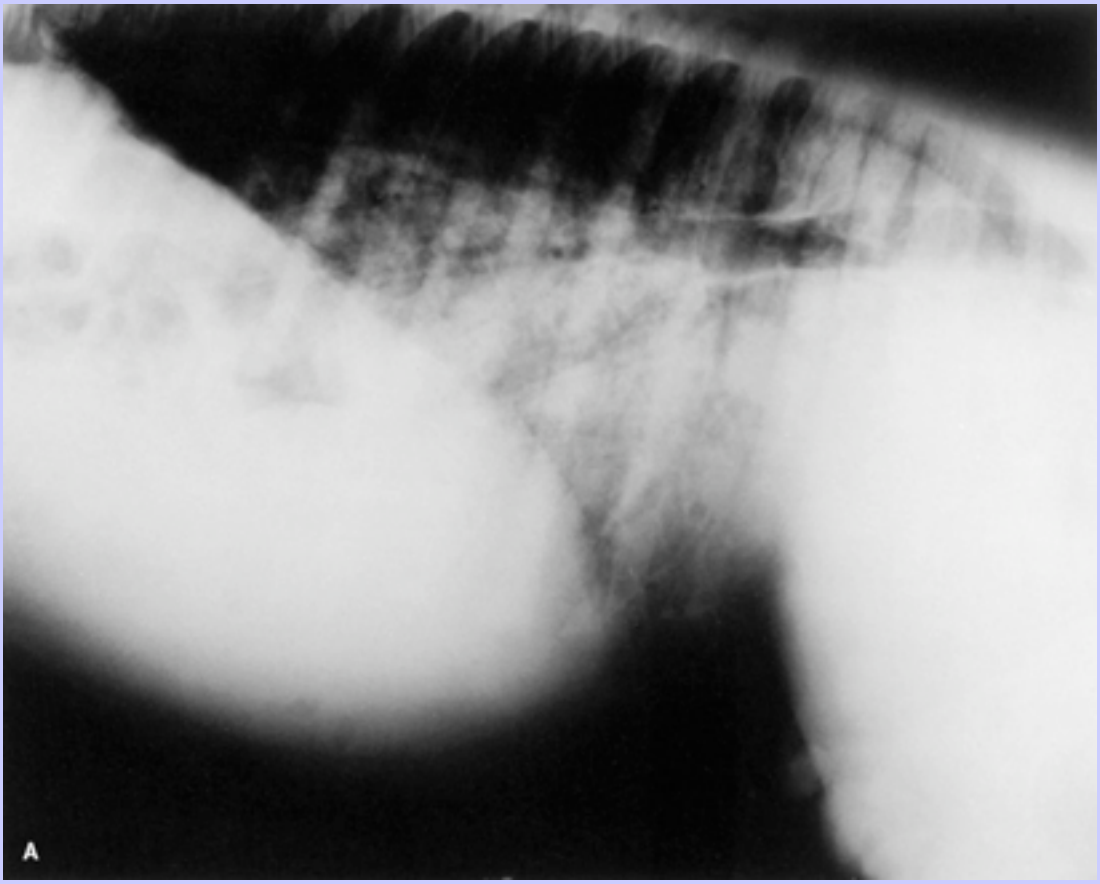
19.4.1 SPECIFIC RESPIRATORY CONDITIONS

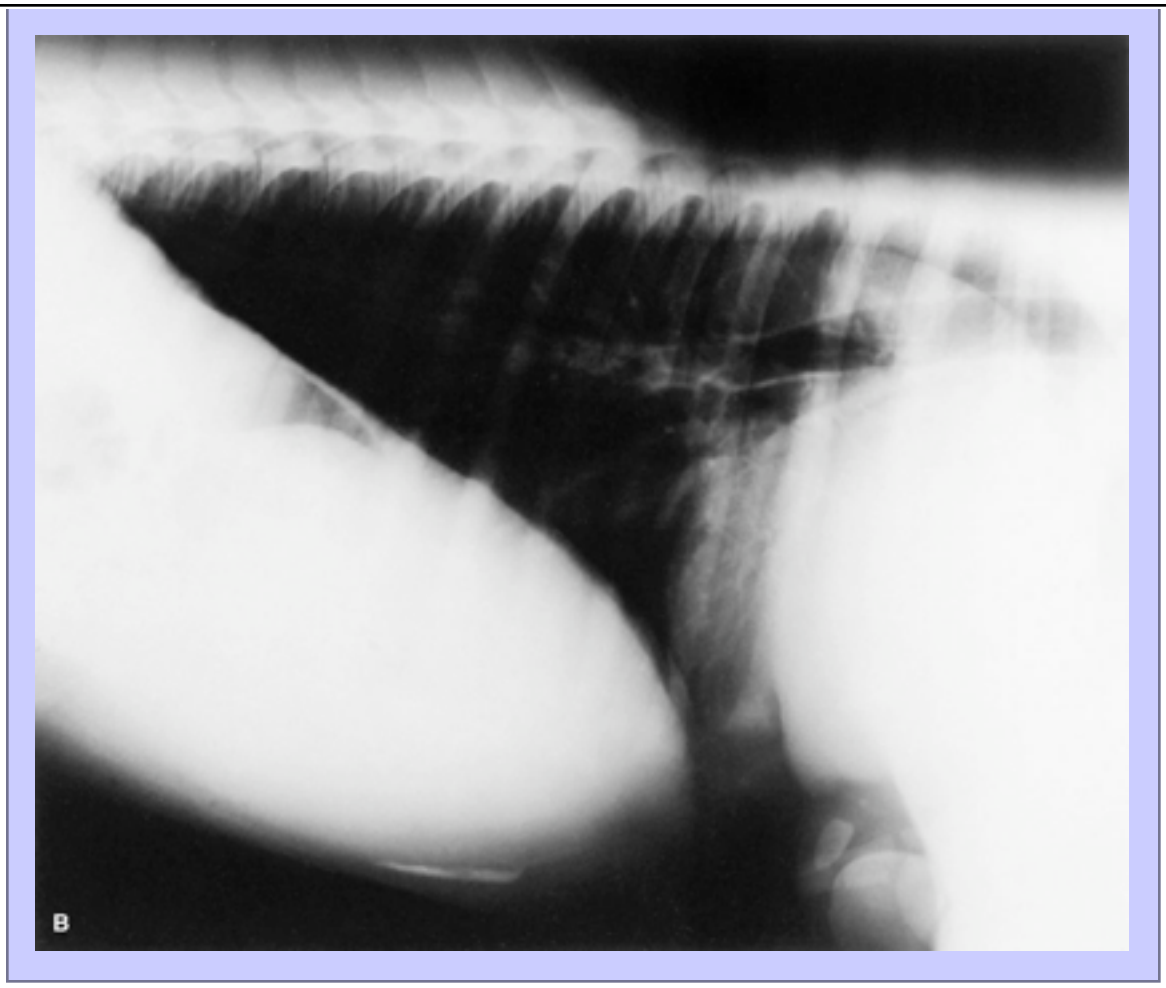
19.4.1.1 Upper Respiratory Tract Disorders

Upper respiratory tract disorders are relatively uncommon in neonates. Conditions affecting pharyngeal and laryngeal function are important, as they predispose to aspiration pneumonia. Dyspneic neonates also have difficulty nursing and are subsequently likely to become malnourished. Congenital defects of the upper respiratory tract include collapsed trachea, stenotic nares, choanal atresia, epiglottal cyst, and guttural pouch tympany (foal). There have also been recent reports of dorsal displacement of the soft palate (DDSP) as a cause of acute dyspnea, stridor, and dysphagia in neonatal foals.[62,63] Endoscopic examination of the upper airways of these foals revealed that the dorsally displaced soft palate was edematous, flaccid, and redundant. To varying degrees, flaccidity and swelling of other pharyngeal and laryngeal structures (e.g., arytenoid cartilages, epiglottis, or palatopharyngeal arch) were also noted.[63] Both medical[63] and surgical[62] treatment of the condition have been suggested. In one study, medical management with antiinflammatory drugs, enteral feeding via nasogastric tube, and broad-spectrum antibiotics (for the coexisting aspiration pneumonia) resulted in dramatic and permanent resolution of the problems within 2 to 4 days. The cause of these abnormalities remains unknown at this time but may involve primary pharyngeal and palatal muscular laxity.[63]

Impaired pharyngeal and laryngeal function may result from physical deformation or neuromuscular disorders. Pharyngeal and laryngeal injuries are often associated with improper application or use of damaged feeding tubes and oral medication equipment. Compression of the larynx by a retropharyngeal abscess or mass tends to cause inspiratory dyspnea; aspiration pneumonia is a common sequela. Partial occlusion of the upper airway induces turbulent airflow and subsequently mucosal edema. Placement of a tracheostomy tube provides an alternate, sometimes lifesaving, airway and rests the inflamed mucosa.

Fig. 19-2 **A**, Standing lateral chest radiograph of a 7-day-old thoroughbred filly with severe angular limb deformities that experienced an acute onset of severe respiratory distress and cyanosis after a walk outside the stall. Intubation and 100% oxygen administration raised the Pa_{O_2} to only 48 mm Hg. Severe pulmonary interstitial disease is present in the caudoventral lung fields, and the tentative diagnosis was bacterial pneumonia. No modifications were made in the treatment regimen (the same antibiotics being given for a wound were continued), and over the following 24 hours the filly clinically improved. **B**, Repeat radiographs taken 3 days after the first ones revealed marked resolution of the infiltrates. The diagnosis remains open, but pulmonary edema was suspected.





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NMD, hyperkalemic periodic paralysis, and botulism may induce laryngeal paresis. Dysphagia and subsequent aspiration pneumonia are common sequelae of pharyngeal and laryngeal dysfunction associated with NMD and botulism. Exercise- and excitement-induced respiratory stridor has been described in foals with hyperkalemic periodic paralysis.[64]

Collapsed trachea is a rare congenital or acquired condition. Clinical signs include an intermittent honking cough, stridor, and dyspnea with mild exercise. There is no stenosis of the trachea; rather, a dynamic dorsoventral collapse during inspiration. The caudal cervical and cranial thoracic sections of the trachea in the area of the thoracic inlet are most frequently affected. Acquired tracheal collapse is commonly associated with fractured ribs and compression of the trachea at the thoracic inlet by the subsequent bony callus.

Diagnosis of most upper airway disorders can usually be made with a combination of radiography and endoscopy. A 7-mm outside diameter (OD) endoscope is usually small enough to pass through the ventral meatus of horse and pony foals that weight over 30 lb. An integral part of the diagnostic approach to the neonate with suspected upper airway obstruction is assessment of the lungs for aspiration pneumonia. If the primary upper respiratory problem is not corrected and normal nursing is allowed, the pneumonic process will likely persist and become chronic.

19.4.1.2

Respiratory Infection

Bacterial infection of the lower respiratory tract most commonly occurs during or shortly after birth but can also take place before parturition through aspiration of contaminated amniotic fluid. This may take place in mares with bacterial placentitis. In the newborn foal, pneumonia can result from direct aspiration or inhalation of bacteria or from the hematogenous spread of organisms in foals that are bacteremic. The most common bacterial organisms that have been associated with pulmonary disease in foals are identical to those that cause systemic sepsis. The most common isolates include *E. coli*, *Klebsiella pneumoniae*, *Pasturella* species, *Actinobacillus* species, and *Streptococci* species. Less common isolates include, but are not limited to, *Salmonella* species, *Enterobacter* species, *Pseudomonas* species, *Serratia marcescens*, *Staphylococcus* species, and *Yersinia pseudotuberculosis*.

The diagnosis of pneumonia involves identification of the causative organism. Isolation of bacteria can be attempted from blood culture or from culture of amniotic fluid or placental tissue if in utero infection is suspected. Lower airway culture can be difficult, as a tracheal aspiration can be dangerous in a compromised neonate. An alternative method involves passage of a guarded swab through a nasotracheal tube into the lower airway. The tip of the nasotracheal tube can also be cultured if it has been present in the airway for a prolonged period. A CBC and measurement of an acute phase protein, such as fibrinogen, may support a diagnosis of infection but will not be helpful in localization of infection to the respiratory tract. The treatment of bacterial lung disease involves a combination of respiratory support techniques and antibiotic therapy. The neonatal foal readily develops dependent atelectasis in lateral recumbency. Consequently, positioning in sternal rather than lateral recumbency results in improved ventilatory capacity and higher arterial oxygen tension. Broad-spectrum antibiotic therapy should be commenced as soon as lung disease is suspected. A good choice is a β-lactam antibiotic, such as penicillin or ampicillin, combined with an aminoglycoside. The emergence of *E. coli* resistance to gentamicin in certain regions may limit its future use. The third-generation cephalosporins, such as ceftiofur, ceftazidime, ceftriaxone, and cefotaxime, have distinct advantages over aminoglycosides in the treatment of bacterial pneumonia. They have superior penetration into the lung, and effective tissue concentrations are easily achieved by intravenous or intramuscular routes. Because premature discontinuation of antibiotic therapy has resulted in relapse in a number of cases, repeat radiographs and hematology (complete blood cell count and plasma fibrinogen) are highly recommended before discontinuation of antibiotic therapy. A minimum course of therapy of 3 to 4 weeks' duration is not unusual in cases of severe pneumonia. Premature foals with pneumonia should be monitored particularly closely for the development of bacterial pneumonia resistant to the antibiotics being used.

Several viruses have been documented as causes of pneumonia in the neonatal foal. These include equine herpesvirus type 1 (EHV-1) and type 4 (EHV-4), equine influenza, equine viral arteritis virus, and adenovirus. Of these, EHV-1 is the most common. Herpesviral pneumonia is frequently fatal, even in the face of aggressive supportive therapies such as mechanical ventilation. The antiviral drug acyclovir has been used. The difficulty is establishing a diagnosis early in the course of treatment. Several factors appear common to EHV-1–infected foals, but none should be considered pathognomonic. These include leukopenia with neutropenia and lymphopenia, and depletion of the myeloid cell lines on cytologic examination of bone marrow aspirates. The presence of dilated retinal vessels and a red discoloration to the optic disc on fundic examination has also been suggested as a common antemortem finding. Infection with adenovirus can be a problem in any immunocompromised foal, especially Arabian foals with severe combined immunodeficiency (SCID) syndrome.

In utero infection with *Histoplasma capsulatum* can result in placentitis, abortion, or birth of an infected foal with multiple organ disease, including granulomatous pneumonia. An antemortem diagnosis can be difficult to establish but is aided by tracheal aspirate and bronchoalveolar lavage when characteristic yeastlike organisms (3 to 5 µm in diameter) are seen within macrophages. Neonatal and maternal serum should be positive for anti-*Histoplasma* antibodies using an agar gel immunodiffusion test. The disease has been successfully treated in adults using amphotericin B, but reports of neonatal survival are lacking. Infection with *Candida* species (especially *Candida albicans*) is an infrequent complication in foals with chronic bacterial infection. Lengthy antimicrobial use is an apparent risk factor for infection, and many cases begin with oral candidiasis. The diagnosis is based on a history that often includes persistent low-grade fever, worsening respiratory disease or the development of synovitis, and isolation of the organism through blood culture. Successful treatment of neonatal candidiasis has been achieved with ketoconazole, amphotericin B, or fluconazole.

19.4.1.3

Meconium Aspiration Syndrome

In utero asphyxia or umbilical cord occlusion can result in fetal passage of meconium into amniotic fluid. Hypoxia induces a redistribution of blood flow away from less vital organs, including the gastrointestinal tract, resulting in mesenteric vasoconstriction and secondary intestinal ischemia. Transient hyperperistalsis and anal sphincter relaxation occur, thereby allowing passage of meconium. Meconium aspiration may occur before, during, or immediately after delivery as a result of fetal gasping. Meconium can produce a variety of clinical signs including mechanical airway obstruction (ball-valve effect) and regional air trapping, chemical pneumonitis and alveolitis, alveolar edema, and displacement of surfactant by free fatty acids in meconium, leading to decreased lung compliance, small airway obstruction, and focal atelectasis.[65–67] These events lead to increased pulmonary vascular and airway resistance and ventilation-perfusion mismatching. Meconium may also enhance the growth of bacterial species within the respiratory tract, resulting in secondary bacterial pneumonia. It may be difficult to differentiate meconium aspiration from bacterial pneumonia, especially if the birth was unattended. Occasionally, chronic placentitis is associated with both bacterial pneumonia and meconium aspiration.

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If meconium has been aspirated into the pharynx, then gentle suctioning of the nasal and oral cavities is recommended. The ideal time to suction the airways is while the animal is still in the birth canal, before it has taken its first breath. If the foal shows signs of meconium aspiration below the vocal cords, nasotracheal intubation and careful, aseptic suctioning are recommended. Intranasal oxygen should be administered during suctioning. ABG analysis dictates what long-term respiratory and metabolic support is necessary. Mild to moderate hypoxemia can be treated with humidified intranasal oxygen (2 to 10 L/min). Severe hypoxemia with accompanying hypercapnia requires positive pressure ventilation (PPV) and is associated within increased mortality. If surfactant displacement and secondary atelectasis is contributing to hypoxemia, continuous positive airway pressure (CPAP) alone may improve oxygenation while avoiding any unnecessary increase in peak airway pressure. Exogenous surfactant administration has been advocated to treat the surfactant dysfunction, although efficacy data are lacking. Intravenous dimethyl sulfoxide (DMSO) (0.5 to 1 gm/kg) administered as a 10% solution may help reduce alveolar and interstitial edema. Systemic antibiotic therapy is recommended to prevent secondary bacterial pneumonia. Good airway hygiene and coupage are crucial.

A diagnosis of meconium aspiration is based on a history of meconium-contaminated amniotic fluid and a meconium-stained newborn. Radiographs typically show a ventrocranial distribution of pulmonary infiltrate characteristic of aspiration. Clear, brownish fluid may drip from the nose.

19.4.1.4

Milk Aspiration

Aspiration of milk into the lower airway may occur as a complication of a wide range of conditions. Most foals that aspirate milk also demonstrate nasal regurgitation of milk. Unfortunately the decreased sensitivity of the upper and lower airway to foreign material may make diagnosis of milk aspiration difficult. Aspiration can occur in foals with cleft palate, persistent DDSP, botulism, HIE, or generalized weakness resulting from sepsis or prematurity. Iatrogenic contamination of the airway can occur when bottle-feeding is forced or if the foal is too weak or sleepy to receive feeding. Substantial and sometimes fatal pneumonia can result from inappropriate placement of a nasogastric tube.

The diagnosis of milk aspiration is supported by historical data (nasal regurgitation of milk), physical examination findings (abnormal lung and tracheal sounds), and laboratory data (inflammatory leukogram, elevated fibrinogen, hypoxemia). Radiographic examination commonly reveals a heavy, perihilar, and/or ventrally located interstitial density with or without air bronchograms.

The treatment of milk aspiration involves long-term, broad-spectrum antimicrobial therapy and prevention of further contamination of the airway. The underlying cause should be pursued diagnostically and treated. This may necessitate the use of further diagnostic tests, including endoscopy and plain and contrast radiography. Enteral feeding through a nasogastric or esophagostomy tube is indicated until the underlying problem has been resolved. Persistent or intermittent DDSP in the neonate frequently resolves over time, but this may take weeks to months.

19.4.1.5

Pneumothorax[68] and Hemothorax

Pneumothorax is usually an iatrogenic sequela of PPV of diseased lungs, but it may occur spontaneously or as a result of birth trauma or from ruptured bullae within the lung parenchyma. During mechanical ventilation uneven alveolar ventilation leads to alveolar rupture and dissection of air into the interstitium. The air moves along bronchioles and other lung structures to pleural surfaces, forming blebs. This air may rupture into the pleural space. The condition should be strongly suspected if the respiratory condition suddenly worsens while an animal is being ventilated. Clinical signs may include respiratory distress, shift of cardiac point of maximum impulse, cyanosis, and hypotension. Although auscultation may reveal decreased breath sounds, it may be misleading because of the wide referral of breath sounds. Percussion is usually fairly unremarkable, unless the condition is very severe. Radiographs are indicated to confirm the diagnosis, but, if radiology is unavailable or the animal is very distressed, a direct needle aspiration is diagnostic and therapeutic.

Pneumothorax may be treated conservatively if no distress is associated with the air leak and the condition appears stable. Stress should be minimized. Chest tube insertion is indicated in human infants with continuing air leak, if underlying pulmonary disease is causing respiratory distress, and in those patients receiving mechanical ventilation. A trocar catheter is sterilely introduced into the chest cavity, and the catheter is secured, with the suture material crisscrossed tightly around the catheter. Suction is applied at −15 cm H_2O after confirmation of chest tube position by chest radiograph. Suction is discontinued when the tube has drained no air for 24 to 48 hours and when extrapulmonary air has been resolved radiographically for 24 to 48 hours. The tube may then be placed under a water seal for an additional 24 hours, and if no air accumulates the tube may be removed.

Hemothorax is occasionally noted in the large animal neonate. It has occurred secondary to unstable fractured ribs, with puncture of the lung parenchyma resulting in hemorrhage into the pleural space. Occasionally

hemothorax may remain undiagnosed until clinical signs of anemia, hypovolemia, or shock appear in the young animal.

19.4.1.6 Idiopathic or Transient Tachypnea in the Neonate

A syndrome observed in Clydesdale, thoroughbred, and Arabian neonatal foals has been the combination of fever and tachypnea. The condition appears to be more frequent during hot, humid weather conditions. The pathogenesis of the condition is unknown, but it is speculated that it results from a transient problem in central or peripheral control of thermoregulation and/or respiratory rate and pattern.

Affected foals are usually of normal gestation and experience a normal birth. Most display normal activity for a variable period after birth, with a sudden onset of clinical signs. Occasionally a foal may show mild signs of CNS derangement (e.g., lack of affinity for the mare, wandering). There are usually no signs of pulmonary abnormalities as assessed by thoracic radiographs or ABG analysis. Body temperature is variable among foals, ranging from 102° F to 108° F (39° C to 42.2° C). A generally poor response to antipyretics has been noted. The respiratory rate and breathing pattern often resemble panting (respiratory rate >80 breaths/min). The condition usually resolves spontaneously within a few days to weeks.

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Before idiopathic tachypnea is diagnosed, it is extremely important to rule out a pneumonic process or other pulmonary abnormality, other forms of infection, metabolic acidosis, and other causes of an increased respiratory rate. Hematology, chest radiographs, and arterial blood gases should be within normal limits, and bacterial cultures should be negative.

Treatment is directed at controlling the body temperature; body clipping, alcohol baths, and maintenance of a cool environment are the most effective methods. If infection cannot be entirely ruled out, antibiotic therapy should be used.

19.4.1.6.1 Treatment of Respiratory Distress

It is beyond the scope of this book to provide detailed information on the respiratory support of the large animal neonate, and the reader is referred to other articles and texts for additional information on mechanical ventilation and other topics.[69–71] Oxygen therapy is extremely useful in the treatment of the large animal neonate with respiratory disease. The decision as to when to institute oxygen therapy is somewhat subjective and is based both on clinical signs and on blood gas analysis. Increased respiratory rate, labored respiration, increased intercostal and abdominal muscle activity, and restlessness are considered indications for a trial of oxygen therapy. A Pa_{O_2} <55 to 60 mm Hg in lateral recumbency is considered an objective indication for oxygen therapy, although many foals with a Pa_{O_2} of 50 to 55 mm Hg on room air that were recovering from pneumonia apparently did well and displayed no signs of hypoxia. If blood gas analysis is not available, clinical signs indicating a favorable response to oxygen therapy include a decrease in effort of breathing, decrease in respiratory rate, and a more comfortable-appearing animal. An absence of response may indicate a nonrespiratory origin of the clinical signs, severe lung pathology, a cardiac malformation resulting in right-to-left shunting of blood, or inadequate inspired oxygen concentration.

The inspired oxygen concentration is most easily increased by nasal insufflation using a bias flow of humidified oxygen. Although an oxygen-delivery mask can be used, its presence interferes with nursing or feeding, and it may be poorly tolerated by the alert foal. Depending on the severity of disease and size of the

individual, oxygen is initially delivered at a flow rate of about 5 L/min, and the response is noted. The catheter tip should be advanced into the nasopharynx, and the opposite end should be secured to the nostril using tape or sutures in active foals. The actual oxygen concentration delivered to the alveoli depends on several factors, including the position of the tube and the depth and rate of breathing. Oxygen therapy should be directed at maintaining a Pa_{O_2} of 80 to 100 mm Hg, and the flow rate should be adjusted according to blood gas results. Oxygen therapy should be on a continuous basis, and weaning from support should be done gradually. Transtracheal oxygen delivery may beneficial in larger foals, hypoxemic neonatal foals that have a very rapid, shallow breathing pattern, and foals with severe pulmonary disease that are unresponsive to nasal insufflation.[72] A percutaneous catheter system is placed using local anesthetic and is secured to the skin. The distal location of the catheter bypasses a substantial volume of dead space, and probably results in a higher alveolar oxygen concentration. One advantage of this method of oxygen delivery has been the ability to provide long-term oxygen therapy to unrestrained foals.[72]

Unfortunately, oxygen therapy is not effective in correcting hypoventilation, and if hypercapnia is progressive and accompanied by signs of increasing respiratory distress, some type of mechanical ventilatory support is usually indicated. This decision to provide mechanical ventilation must take into account several considerations, including the worth of the individual, the commitment of the owners, the facility and manpower availability, and the type of disease process present.

Regardless of the level of respiratory support provided, the importance of meticulous respiratory supportive technique cannot be overemphasized. Maintenance in sternal position, frequent turning from side to side, regular coupage, and use of proper suction technique are all very important components of respiratory support.

19.5 DISTENDED AND/OR PAINFUL ABDOMEN

Wendy E. Vaala

19.5.1 APPROACH TO DIAGNOSIS

The large animal neonate with a painful or distended abdomen can present a diagnostic challenge to the clinician. Medical and surgical causes of colic and GI disease in the foal include ileus and bowel distention associated with peritonitis, hypoxic gut damage and metabolic disturbances, enteritis caused by dietary changes, viral infections and bacterial pathogens, gastroduodenal ulcer disease (GDUD), impaction associated with ascarid infections, intussusception, thromboembolic disease, small intestinal volvulus, colon torsion, uroperitoneum, strangulating abdominal hernias, and congenital GI lesions. The clinical challenge is to distinguish medical from surgical lesions to permit rapid and appropriate therapy. Abdominal surgery in young foals, particularly neonates, is associated with increased morbidity and mortality and a higher incidence of intraabdominal adhesion formation when compared with surgery in mature horses.[73] Medical causes of GI disease such as enteritis and peritonitis carry an increased risk of generalized sepsis and death if the patient's cardiovascular status and metabolic parameters are not monitored and stabilized in a timely manner.

Box 19-1 lists some of the more common conditions associated with the acute abdomen in large animal neonates. Physical examination findings can be very similar between neonates requiring surgical intervention and those with only an infectious problem, such as enteritis. If abdominal distention is present, every effort should be made to identify its cause. Because the neonatal foal is considerably smaller than the adult, some of the diagnostic techniques routinely used in the adult (rectal palpation, assessment of shape of abdomen) are of limited value in

assessing the acute abdomen in the neonate. Bilateral, tympanitic distention of the paralumbar fossae is suggestive of generalized ileus or large bowel obstruction (e.g., meconium impaction). Other diagnostic aids including abdominal radiographs, transabdominal ultrasonography, abdominal ballottement, and transcutaneous abdominal palpation are not practical in the adult but are useful diagnostic tools in the newborn foal. Abdominal ultrasound is a critical diagnostic procedure in horses of all ages.

The approach to the neonate with a painful or distended abdomen should include a complete history, including any abnormalities noted during the perinatal period, the type and dose of any analgesics previously administered, and whether there is history of diarrhea in other foals or horses on the farm. The age of the foal helps determine the risk of certain conditions. Young foals less than 2 weeks of age are more likely to experience colic caused by meconium retention, peritonitis associated with generalized sepsis, hypoxic gut damage, uroperitoneum, and congenital deformities including lethal white syndrome (e.g., mesenteric aganglionosis), inguinal and scrotal hernias, and atresia of the anus or colon.[74–76] We have also seen increasing numbers of young foals with clostridial enteritis that are presented for treatment for colic. Older foals are more likely to suffer from intussusceptions, enteritis, gastroduodenal ulceration, and thromboembolic disease.[74,75]

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19.5.1.1

Box 19-1 Causes of Abdominal Distention

19.5.1.1.1

OBSTRUCTION

Foreign body (hairballs in calf)

Malformation (atresia coli, recti, ani)

Intussusception

Volvulus, torsion or strangulation

19.5.1.1.2

UROPERITONEUM

Ruptured bladder (uncommon)

Torn or necrotic urachus, ureter

19.5.1.1.3

PERITONITIS

Generalized infection

Devitalized bowel

Perforated gastric or intestinal ulcer

Severe umbilical infection

19.5.1.1.4 GAS AND FLUID ACCUMULATION IN ABOMASUM, INTESTINAL TRACT

Intolerance to diet

Ileus

Gastric, abomasal, duodenal ulceration

Necrotizing enterocolitis

Ruminal bloat

19.5.1.1.5 MISCELLANEOUS

Hemoperitoneum

Ruptured umbilical vessels

Ruptured spleen or liver

Congenital tumor

19.5.1.1.6 ASCITES

Severe liver or renal failure

Severe hypoproteinemia

The neonate's age at the onset of abdominal distress also may provide diagnostic clues. For example, foals with meconium impaction or congenital GI malformations such as atresia coli tend to be presented for treatment during the first 12 to 36 hours of age, whereas foals with uncomplicated ruptured urinary tracts are usually presented at about 3 days, when the abdomen is visibly distended. The character, quantity, and frequency of defecation and urination should be determined. Surgical GI lesions such as intussusception and large colon displacement have occurred secondary to enteritis. On the other hand, in the early stages, enteritis alone can cause severe abdominal distention or severe pain, in the absence of diarrhea. NEC and clostridial enteritis can be particularly painful conditions. Most foals with ruptured urinary bladders display abnormalities in urination, but in some cases normal micturition has been noted. Reduction in urine output from a neonate with a distended abdomen is not pathognomonic for uroperitoneum. Urine volume is typically reduced as a result of dehydration

secondary to a variety of abnormalities, including GI disease.[77] The colic associated with uroperitoneum is not usually severe.

Assessment of the degree of pain being exhibited is an important part of the examination of the neonate with a distended abdomen. Foals more commonly show signs of abdominal discomfort than do calves. In a retrospective study of foals undergoing exploratory celiotomy, uncontrollable pain and severe abdominal distention were the primary reasons the animals were taken to surgery. Sever abdominal pain can also occur in foals with non-surgical lesions, such as sever enteritis, making the decision for surgical exploration difficult in some cases.[78] However, persistent tachycardia in a neonate with a heart rate in excess of 150 beats per minute (bpm) despite administration of analgesics and in the absence of fever is suggestive of a surgical GI lesion.

The degree of compromise to the cardiovascular and pulmonary systems should be assessed. A neonate with an abdominal crisis is often in need of immediate stabilization because of shock secondary to endotoxemia or hypovolemia. Exploratory celiotomy in neonates that receive inadequate presurgical supportive therapy is associated with a number of complications, including poor tolerance to anesthesia. The degree of respiratory compromise secondary to the abdominal problem should also be considered, particularly if the animal is a surgical candidate. For example, foals with long-standing uroperitoneum may have pleural effusion and pulmonary abnormalities as well as serum electrolyte abnormalities, all of which may predispose to anesthetic problems (hypoxemia, hypercapnia, cardiac arrhythmias).

It is very important to establish the likelihood of generalized or localized infection such as enteritis. Generalized sepsis can interfere with the function of many organ systems, including the GI tract. The first signs of enteritis are often severe abdominal distention and colic, with diarrhea becoming apparent a few hours to days later (Fig. 19-3); the severity of these signs may warrant surgical exploration of the abdomen. Leukopenia may be observed in foals with septicemia, enteritis, peritonitis, and surgical GI lesions. An unexplained metabolic acidosis may also indicate impending enteritis.

Additional information on the physical examination of the abdomen and GI tract can be found in Chapter 17. It is difficult to distinguish fluid accumulation in the large colon from accumulation in the peritoneal cavity using physical examination alone, and additional diagnostic procedures are usually required to distinguish the two (see later). In general, nasogastric intubation in the neonatal foal does not seem to be as useful a diagnostic technique as it is in the adult horse. Gastric reflux can be difficult to obtain, even if the stomach appears markedly distended on radiographs, and a moderate amount may be obtained in cases of ileus. If large volumes of reflux are obtained, however, obstructive disease (e.g., of the pylorus and small intestine) is considered more likely.[78]

Neonates with enteritis, uroperitoneum, and other abdominal problems can have markedly deranged serum electrolyte concentrations (hyperkalemia, hyponatremia, and metabolic acidosis are typical). Failure to recognize the severity of these abnormalities or adequately treat them can result in the death of the patient.

Abdominal radiographs can be very helpful in identifying segments of the intestinal tract that are distended, fluid in the peritoneal cavity, and the composition of ingesta in the GI tract (e.g., sand, meconium) (Figs. 19-4 and 19-5). A good knowledge of normal radiographic anatomy of the intestinal tract is important for accurate interpretation (Fig. 19-6). Adequate radiographs are obtained in foals up to 250 kg if available radiograph equipment includes a grid, rare earth screens, and sufficient milliampere-second (mAs) (5 to 28) and kilovolt peak (kVp) (75 to 95) levels. With experience in viewing normal and abnormal abdominal radiographs, the likelihood of an obstructive lesion versus simple ileus can be established in some but not all cases. The presence of erectile, distended loops of small intestine is most consistent with a diagnosis of obstructive disease. Intramural gas is suggestive of NEC. It can be very difficult to differentiate large colon torsion or displacement

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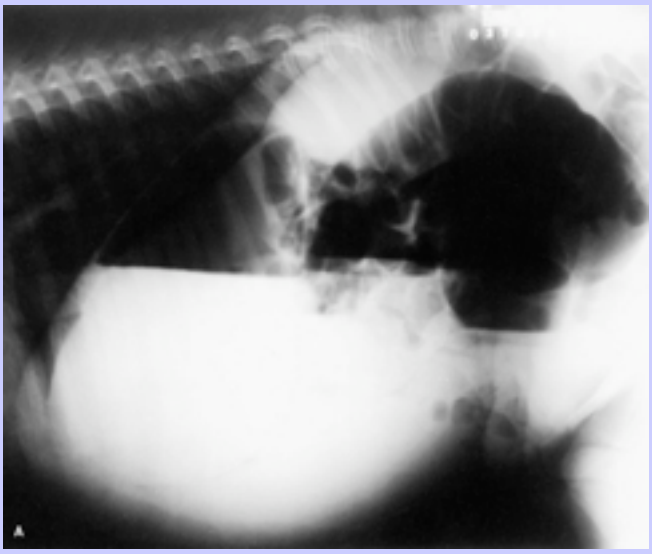
from simple gas and fluid distention secondary to ileus. Contrast radiography can help to define the location and nature of GI problems such as duodenal stricture and abnormalities of the small colon or rectum. Further details on the radiographic diagnosis of abdominal disorders are contained in other articles. [78a,78b,78c,78d]

Fig. 19-3 **A**, Abdominal radiograph (standing) of a 48-hour-old foal that was presented with meconium impaction and a distended abdomen. The foal also had a metabolic acidosis, hypoglycemia, and leukopenia. Note the gaseous distention of the large intestines, which was suggestive of ileus and possibly obstruction. **B**, Standing abdominal radiograph of the same foal 24 hours later after passage of diarrhea. Following removal of the meconium, profuse bloody diarrhea was observed, suggesting enteritis. With passage of the diarrhea, gas distention resolved.



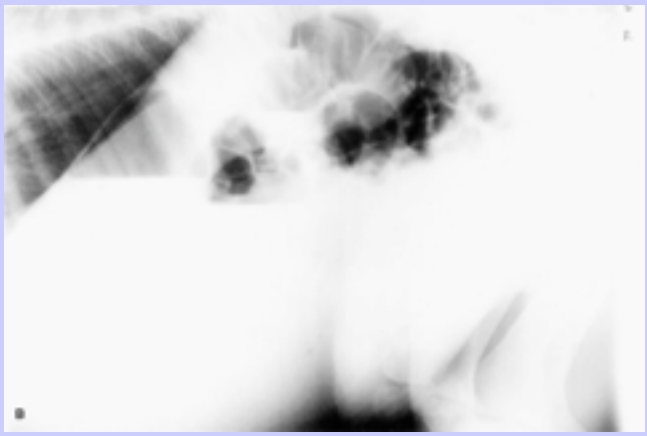


Fig. 19-4 Sand accumulation in the ventral colon of a 1-month-old foal with chronic diarrhea and intermittent colic.

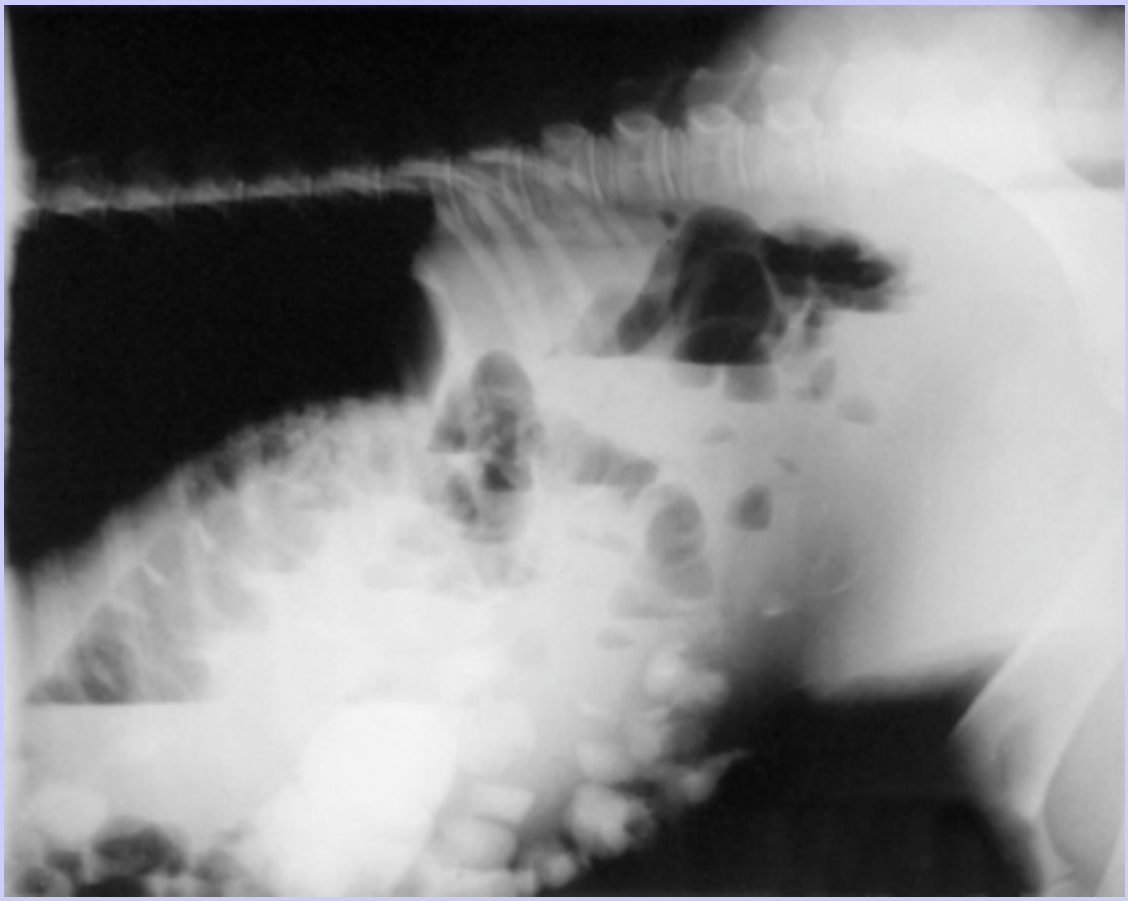
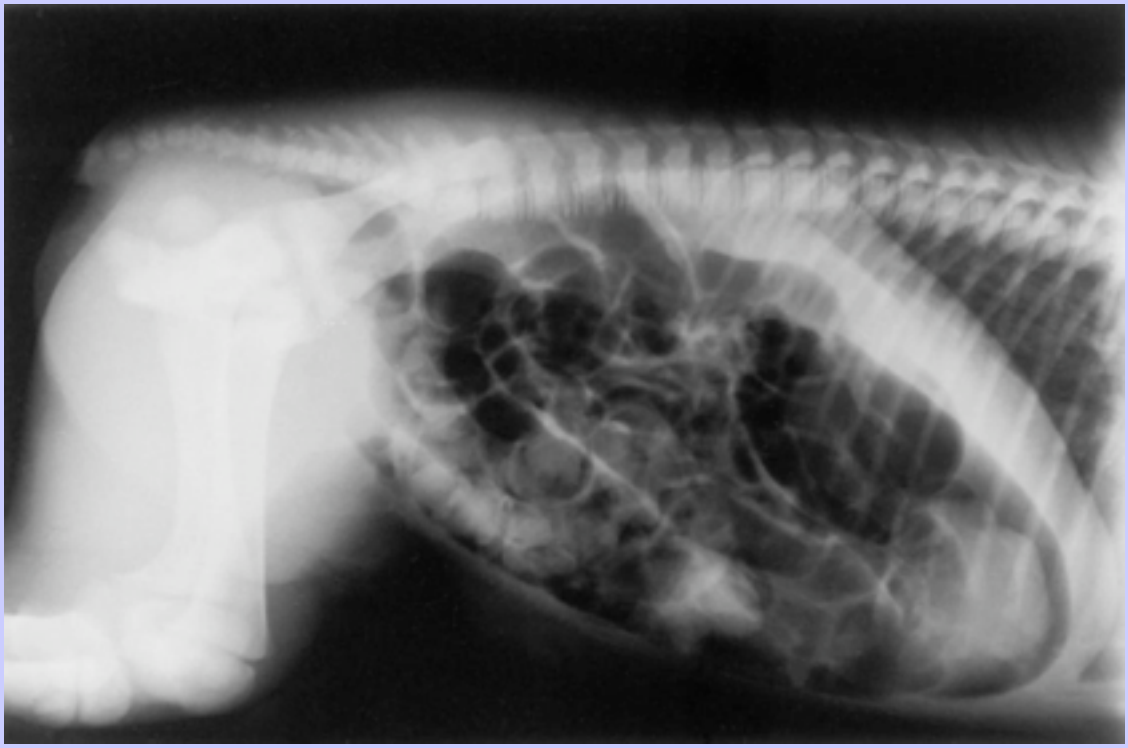


Fig. 19-5 Abdominal radiograph (lateral recumbency) of a 7-hour-old miniature horse foal with atresia ani, showing meconium packed into a gas-distended large colon. The extent of the atresia proximally from the anus is not visible.



Abdominal ultrasonography can be of value in diagnosing certain conditions that may be contributing to a distended or painful abdomen, including fluid-distended small and large intestine, ascarid impaction, intussusception, colonic impaction, uroperitoneum, and abnormalities of the umbilical vessels and urachus. Ultrasonography also permits characterization of small intestinal motility, distention, and bowel wall thickness. Healthy foals have flaccid, fluid-filled loops of small intestine. The presence of rounded, distended loops of small intestine is suggestive of an ileus, enteritis, or possible small bowel obstructive disease. The location, amount, character, and echogenicity of free peritoneal fluid can also be determined (Fig 19-7).[61,79,80] A large accumulation of peritoneal fluid with increased echogenicity (or fibrin) is suggestive of peritonitis, whereas an excessive volume of hypoechogenic peritoneal fluid is suggestive of uroperitoneum.

In our opinion, except in a couple of specific conditions, peritoneal taps are of limited value in diagnosis of the acute abdomen in the neonate. Extreme caution should be exercised to avoid perforating the bowel while attempting to acquire a sample of peritoneal fluid, particularly if intestinal distention is present. The intestine of the neonate is easily ripped by inadvertent perforation with a needle or teat cannula, even if the neonate is well restrained. It is probably safest to perform the procedure using ultrasonography to image the fluid pocket and the needle position. Foals with uroperitoneum are the ideal candidates for abdominocentesis. Clear yellow, urine-like

peritoneal fluid is easily and safely obtained in these patients because the excessive volume of peritoneal fluid allows the abdominal viscera to float well above the ventral floor of the abdomen.

Fig. 19-6 Normal standing abdominal radiograph in a neonatal foal. Note the prominent fluid line in the stomach and the presence of gas in various portions of the tract.

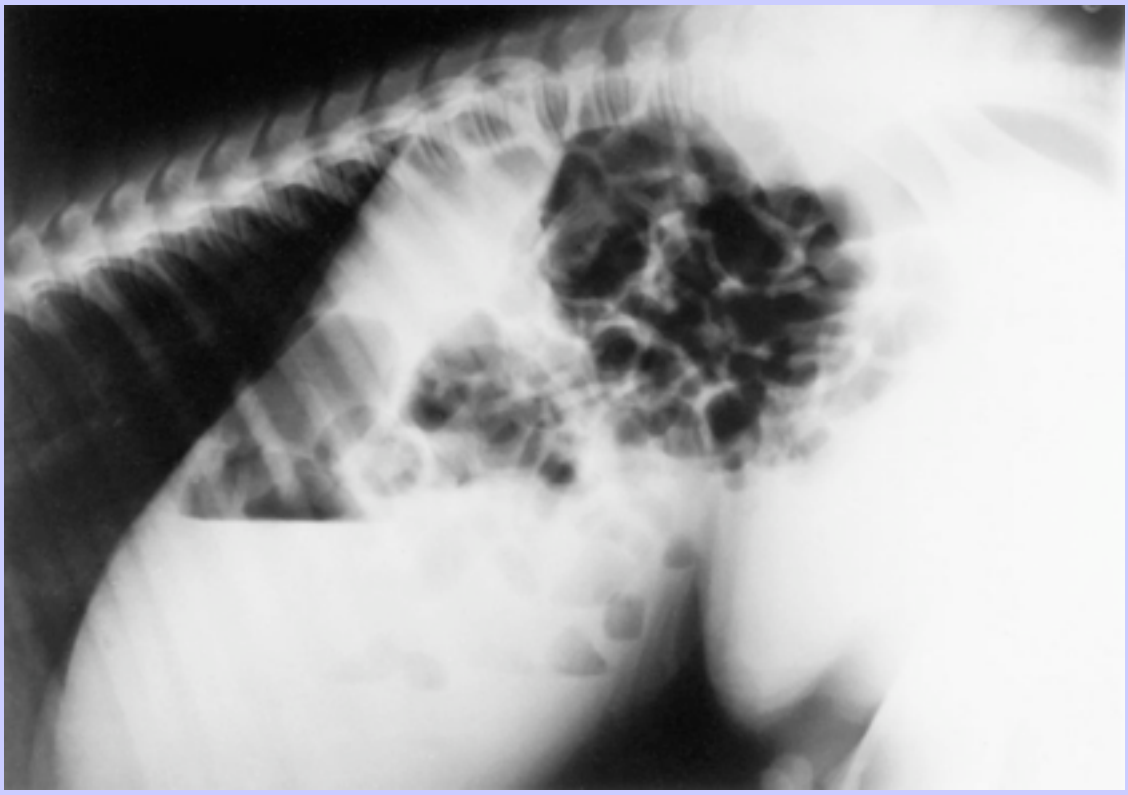


Fig. 19-7 Ultrasound view of the caudal abdomen of a 24-hour-old premature foal with a torn urachus, showing (from top to bottom) the ventral abdominal wall, free abdominal fluid (black), the urinary bladder (oval structure to the right), and small intestinal loops (cross-sectional view).

Normal peritoneal fluid is similar to that in the adult, except that the normal WBC count is lower (1500 cells/µl or less).[81] Cytologic examination should also be performed to determine the cell types present and to detect the presence of bacteria and toxic neutrophils (suggesting peritonitis) and fecal material (suggesting either

inadvertent gut tap or bowel rupture). The total protein and WBC count may be elevated in a variety of conditions. These include severe enteritis; urachal, umbilical, or severe bladder infection; and primary peritonitis, in addition to conditions in which there is ischemic bowel requiring surgical resection. On the other hand, as in the adult, normal peritoneal fluid has accompanied a number of surgical intestinal lesions, such as large colon displacement. Therefore peritoneal fluid analysis is of limited value in distinguishing the surgical patient but can be useful in the diagnosis of peritonitis. In addition, peritoneal fluid analysis usually results in a straightforward diagnosis of uroperitoneum. In virtually all cases of uroperitoneum observed to date, peritoneal creatinine level was greater than the serum level (usually >2:1). Also, the acquisition of free-flowing blood from the abdominal tap usually allows a diagnosis of hemoperitoneum.

Endoscopy of the upper and lower GI tract of the foal can be performed if appropriately sized equipment is available (8 to 10 mm OD, 180 to 250 cm long).[77] The esophagus and stomach can be examined for erosion, ulceration, perforation, and other abnormalities. Suspected impactions or malformations of the rectum and small colon can also be examined.[74]

In summary, accurate identification of foals with acute abdominal problems requiring surgery can be very difficult even with the use of ancillary diagnostic procedures, and mistakes are commonly made because there are no clear-cut and consistent differences between medical and surgical cases. Findings suggestive of the need for surgical exploration include severe and unrelenting pain and persistent tachycardia.

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19.5.2 SPECIFIC CONDITIONS

19.5.2.1 Meconium Impaction

Meconium impaction is the most common cause of colic in the newborn foal. This condition is more common in colts because of the narrow pelvic canal. Many foals show some degree of straining and discomfort while passing meconium, but in most instances it is passed uneventfully by 24 to 48 hours of age. The meconium most commonly becomes impacted in the rectum or small colon. The clinical signs associated with meconium impaction in the otherwise normal foal include repeated attempts to defecate, straining with the back arched, swishing of the tail, and restlessness. Nursing stimulates defecation through an oral-anal reflex, so signs of discomfort may appear shortly after each milk meal. If left untreated, meconium impactions lead to varying degrees of abdominal distention. The foal's abdomen becomes gas distended, with tympany detected over the paralumbar fossa. Digital examination often reveals a rectum packed with hard fecal balls. Occasionally, the impaction is located more proximally (large or small colon) and radiography or ultrasonography is required for diagnosis.

Low doses of analgesics such as dipyrone (10 to 22 mg/kg IV), flunixin meglumine (0.25 to 1 mg/kg IV), and butorphanol (0.01 to 0.1 mg/kg IV) may be required to prevent self-trauma during colicky episodes. Xylazine may exacerbate gut stasis and can cause respiratory depression, and it should be used with caution in newborn foals. A gravity enema with mild soap and warm water or a commercial Fleet enema usually results in prompt evacuation of the meconium. Refractory meconium impactions may respond to acetylcysteine retention enemas.[82] The supplies and procedure for a retention enema are as follows: Mix together 150 mL water, 6 g of acetylcysteine powder, and 20 g of sodium bicarbonate (baking soda). Insert a well-lubricated 12 or 14 French, cuffed Foley urinary catheter into the rectum and inflate the cuff. Slowly infuse 120 to 180 mL of the retention enema solution. Plug the end of the catheter. Tape the catheter loosely to the foal's tail. Leave in place a minimum of 15 minutes, then deflate the cuff and remove the catheter. This procedure can be repeated several times. Care must be taken to avoid traumatizing the rectal mucosa by stiff tubing or multiple enemas

with harsh detergents. Clinical signs associated with meconium impaction in the compromised foal may be absent. In asphyxiated or premature individuals that are receiving little or no enteral feeding, meconium may remain in the large colon for days, gradually forming into hard concretions that are diagnosed by palpation or radiographs or at postmortem examination. In these cases the routine administration of an enema is often ineffective in mobilizing the impaction because it is high in the large colon. Additional therapy includes intravenous fluids, oral fluids, and laxatives (60 to 120 mL of mineral oil with ½ to 1 oz of psyllium, 60 to 120 mL of milk of magnesia). If the gas distention becomes severe, transcutaneous bowel trocarization can be pursued. We avoid the use of Dioctyl sodium sulfosuccinate (DSS) as an oral cathartic because it can cause excessive irritation, resulting in diarrhea and colic. Analgesics may also be helpful in controlling the neonate's discomfort and in reducing the risk of self-trauma. Although most meconium impactions can be successfully treated with aggressive medical therapy, those few foals that are refractory to treatment or display uncontrollable pain are candidates for surgical intervention.

19.5.2.2

Uroperitoneum

Uroperitoneum is a relatively common cause of abdominal distention and depression in the neonatal foal. The condition predominates in males but may occur in females as well. Uroperitoneum may be congenital or acquired. The congenital form occurs as a result of failure of the dorsal wall of the bladder to close during development.[83] The most common cause of uroperitoneum is a ruptured urinary bladder, but other sites in the urinary tract may also leak, including the ureters, urachus, and urethra. Most cases of ruptured bladders are presumed to occur during parturition because of external pressure on a distended bladder. This form occurs most commonly in colts. Uroperitoneum can also occur secondary to ischemic necrosis or infection of the urinary bladder or urachus in the compromised foal.[78] Critically ill, recumbent foals may rupture their bladders while being lifted and turned with a full bladder or as a result of chronic overdistention associated with the generalized disease state. Foals with botulism may also rupture their bladders secondary to bladder atony and chronic overdistention. Older foals of either sex may experience bladder rupture secondary to focal infection of the umbilical arteries and/or urachus, or ischemic necrosis of the apex of the bladder.

Clinical signs of uroperitoneum are rarely noticed before 48 to 72 hours of age, particularly if the foal is not being watched closely. The first signs may be urinary incontinence or frequent attempts to urinate, with only small amounts voided. Sometimes, particularly in those animals that experience rupture sometime after birth, there is a history of a period of normal urination, which at some point stopped or became abnormal. Loss of suckle, mild colic, and increasing abdominal distention are usually accompanied by worsening depression and increasing heart and respiratory rate. If the condition is allowed to persist, foals become increasingly weak and dyspneic and may be presented in cardiovascular collapse. Fillies with ruptured ureters have been reported to have a characteristic protruding perineum, presumably as a result of retroperitoneal accumulation of fluid.[84]

Laboratory findings commonly associated with uroperitoneum are elevated serum creatinine and blood urea nitrogen (BUN), hyperkalemia, hyponatremia, hypochloremia, and metabolic acidosis. These changes are probably a result of the normal diet of the foal (milk being relatively high in potassium [25 mEq/L] and low in sodium [12 mEq/L]) and the third spacing of urine in the peritoneal cavity. With urine potassium concentration relatively higher than serum levels, and with urine sodium concentration lower than serum levels, the net effect of partial equilibration of serum with peritoneal fluid across a semipermeable membrane is hyponatremia and hyperkalemia, along with an inability to excrete the waste products of metabolism. Hyperkalemia may be severe enough to induce potentially fatal bradyarrhythmias. In hospitalized foals that developed uroperitoneum as a secondary complication, these typical electrolyte abnormalities are not consistently observed. Because most of those foals were receiving replacement intravenous fluids (high in

sodium, low in potassium) and very little milk, it was theorized that intake has a great influence on the electrolyte abnormalities associated with uroperitoneum.[85] On the other hand, the electrolyte abnormalities typically associated with uroperitoneum are not pathognomonic for that disorder. Foals with renal failure, blocked urethra, white muscle disease, and enteritis have shown the same electrolyte changes.

A diagnosis of uroperitoneum often can be made quickly using transabdominal ultrasound and a 5- or 7.5-MHz transducer to visualize large volumes of free, nonechogenic fluid within the abdomen and a small, irregularly shaped, collapsed bladder. Abdominocentesis usually produces a free flow of peritoneal fluid that has a low cell count, low specific gravity, and at least twice the creatinine concentration of peripheral blood. If the creatinine is the same in both serum and peritoneal fluid, other explanations for the clinical signs should be investigated. The WBC count, total protein, and cytology of the fluid should also be determined. Most uncomplicated cases of ruptured bladders have fairly normal values for peritoneal fluid. In some cases, however, an increased WBC count and total protein and the presence of bacteria may suggest peritonitis. This may be a result of the urine in the abdomen, but more commonly there is a primary ongoing infectious problem (necrotic urachus or bladder, enteritis), and the prognosis becomes worse. If laboratory facilities are not available, new methylene blue can be injected into the bladder using a urinary catheter, and a few minutes later a sample of peritoneal fluid should have a blue discoloration if a ruptured bladder is present. However, this technique may not allow detection of other causes of uroperitoneum such as a ruptured ureter or distal urachus. Positive contrast cystography using a 10% solution of water-soluble media may be helpful in detecting the location of the urinary tract leakage. The ability to obtain urine on catheterization of the urinary bladder does not rule out uroperitoneum. Hematology and blood cultures should be performed to detect primary or secondary sepsis.

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Treatment of uroperitoneum is surgical repair. However, the foal with uroperitoneum should not be rushed to surgery without first carefully stabilizing it. Serum electrolytes and blood gases should be run to determine the extent of hyperkalemia, hyponatremia, and acidosis present. Although the total amount of water in the body is usually grossly increased by the peritoneal accumulation of urine, effective circulating volume may be drastically reduced. If the eyeballs are sunken and the pulse quality and capillary refill time are poor, aggressive fluid therapy is indicated to support the circulation. This is best performed by concurrently removing as much fluid as possible from the abdomen with a teat cannula, 14G catheter, or peritoneal dialysis catheter to avoid worsening fluid overload and respiratory distress. The fluids of choice to treat the typical electrolyte alterations associated with uroperitoneum are saline, dextrose, and possibly sodium bicarbonate solutions, depending on the degree of acidosis present. In most instances continuous dextrose infusion is effective in decreasing the serum potassium level to an acceptable level, but values should be rechecked before anesthesia is induced. Insulin and dextrose may also be used to treat hyperkalemia, but the patient must be monitored for hypoglycemia. One suggested regimen is regular insulin at 0.1 to 0.2 U/kg subcutaneously (SC) or IV accompanied by a continuous intravenous dextrose infusion (4 to 8 mg/kg/min). Some individuals also have pleural fluid accumulation and atelectasis secondary to the abdominal distention, so oxygenation and ventilation during and after surgery should be closely monitored. Broad-spectrum antibiotics should be started immediately after samples are taken for culture if infection is suspected.

The prognosis for uncomplicated ruptured urinary bladders is usually good (>80% survival), provided the animal is stabilized before anesthesia. The presence of concurrent septicemia carries with it a considerably poorer prognosis.[85] In one retrospective study among foals with uroperitoneum, 100% of those foals with a negative sepsis score lived and only 57% of foals with a positive sepsis score survived.[85]

19.5.2.3

Gas or Fluid Accumulation in the Gastrointestinal Tract: Ileus

Abdominal distention and colic secondary to excessive gas and/or fluid accumulation in all or a portion of the GI tract are common complications in the compromised neonate undergoing intensive care. The exact mechanisms responsible for the presumably altered GI motility are not well defined. Ileus is associated with the absence of intestinal sounds, abdominal distention, and intolerance of oral feeds characterized by gastric reflux. Auscultation of reduced GI borborygmi does not always correlate with the degree of intestinal compromise and decreased motility. Transabdominal ultrasonography helps identify absence of intestinal motility and the location and degree of intestinal distention. Ileus and the attending abdominal distention can cause severe colic and can induce respiratory distress in a weak or premature foal with preexisting pulmonary compromise.

Metabolic and infectious causes of ileus in the foal include hypokalemia, hypocalcemia, hypoxic-ischemic bowel injury, bowel obstruction, peritonitis, enterocolitis, and endotoxemia. Hypokalemia is associated with anorexia, diarrhea, and renal loss. Hypocalcemia is associated with prematurity, decreased dietary intake, excessive bicarbonate administration, diuretic therapy, and those conditions such as asphyxia, toxemia, and sepsis that stimulate release of cortisol and catecholamines. Peripartum hypoxia results in a preferential decrease in blood flow to the gut and kidneys. Poor perfusion of the intestines leads to varying degrees of mucosal damage and decreased motility. Severely damaged bowel requires a period of gut rest to allow healing to occur before oral feeds are resumed. Premature resumption of enteral feeding is associated with colic, maldigestion, diarrhea (often bloody), and translocation of intraluminal bacteria across damaged bowel wall into the bloodstream. Some of the more common causes of bowel distention in the neonate include meconium retention, intussusception, ascarid impaction, and small intestinal volvulus. Peritonitis may be associated with intraabdominal abscessation, severe enteritis or GDUD, and generalized septicemia. The most common causes of enteritis in foals include rotavirus, *Clostridia* species, *Salmonella* species, and dietary changes. Endotoxemia is usually part of generalized septicemia. Chronic bowel distention, regardless of the cause, further impedes return of normal gut motility. In the foal, aerophagia, particularly in the struggling or hypoxic neonate, often results in gas distention that is not easily removed through a nasogastric tube, because gas tends to move quickly through the GI tract (Fig. 19-8). Abdominal distention is also commonly observed during mechanical ventilation in the foal and as a result of overfeeding in the calf. Foals with botulism are often intolerant of enteral feeding, probably because of altered GI motility. Use of certain milk replacers can result in bloat, colic, and diarrhea, even in the apparently healthy orphan neonate. Discontinuation of or a decrease in the amount of enteral feeding and, if possible, increased activity of the patient usually result in resolution of the problem.

Abdominal radiographs reveal gas-distended loops of small or large intestine and may identify bowel obstruction. Sonographic examination permits evaluation of bowel wall thickness, peritoneal fluid volume and echogenicity, gut patency, intramural gas accumulation, location and degree of intestinal distention, and presence or absence of motility. An abdominal sonogram should be performed to rule out the presence of an intussusception or other obstructive lesion before any prokinetic therapy is initiated.

Management of ileus includes nasogastric decompression, cessation or reduced volume and frequency of enteral feeds if gastric reflux is present, parenteral alimentation if enteral feeding cannot be maintained at a rate of at least 10% of body weight per day, enema administration to relieve distal meconium or fecal retention, correction of any underlying electrolyte abnormalities, exercise for ambulatory foals, and judicious use of prokinetic agents. The gut atrophies without enteral feeding. Glutamine and butyrate are essential fuels for the small and large bowel respectively and have been added to enteral formulas for people and some oral

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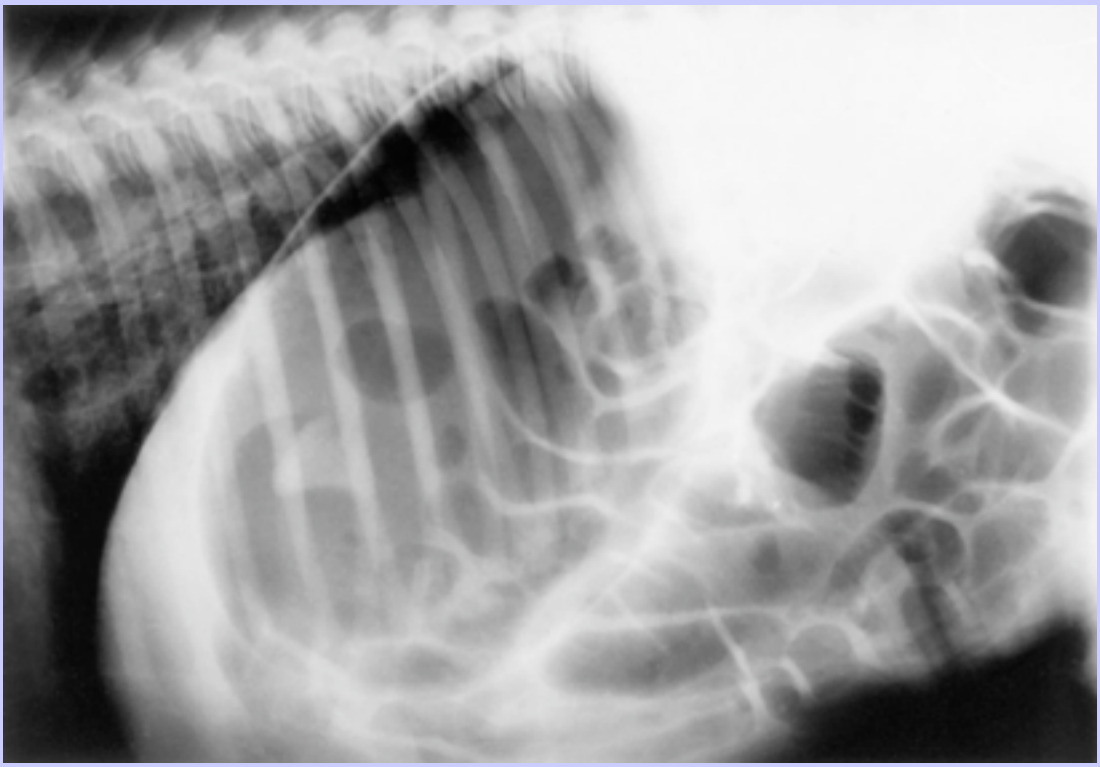
fluid replacement formulations for animals to help maintain and restore enterocyte health.[86] Prokinetic drugs should not be used when bowel obstruction or compromised bowel integrity is suspected. Prokinetic agents that have been used include metoclopramide, bethanechol, and erythromycin. There have been anecdotal reports of small intestinal intussusception after prokinetic use in neonatal foals.

Fig. 19-8 Marked gastric and generalized small intestinal gas distention in a septic, collapsed, 3-day-old thoroughbred colt. There is no evidence of obstruction. The patient was treated with supportive therapy and recovered.



19.5.2.4

Surgical Gastrointestinal Lesions

Most types of displacement, torsion, volvulus, and entrapments that occur in the adult horse may also occur in the neonatal foal, although probably at a lower frequency (Fig. 19-9). Large colon displacement, intussusception, and small intestinal volvulus have also been observed secondary to enteritis and colitis.

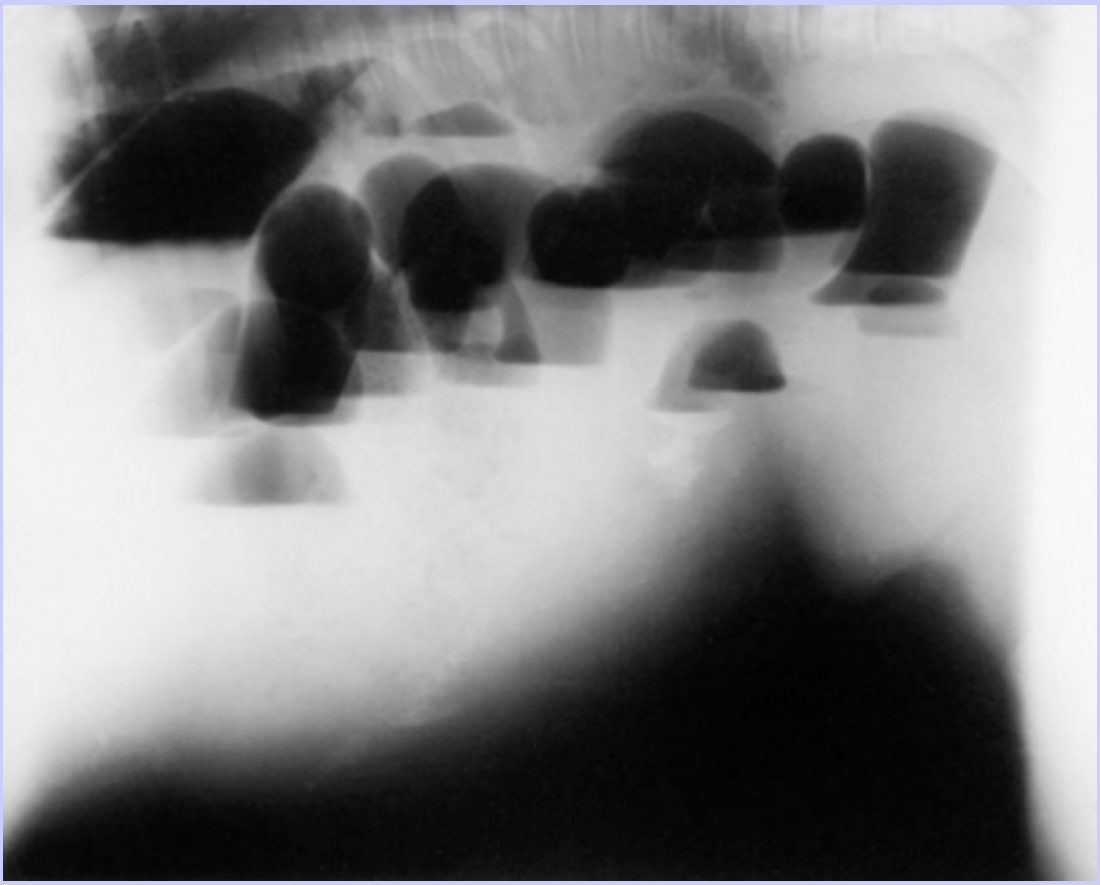
Surgical correction of congenital GI defects may be attempted. Atresia ani, atresia recti, and atresia coli have been well documented in the foal, and intestinal aganglionosis has been observed in association with recessive lethal white foals, which are usually the products of mating between two overo paint horses.[76] Acute colic, progressive abdominal distention, and lack of meconium staining after repeated enemas have been the most common findings in newborn foals with atresia coli. Barium enemas may be of use in identifying foals with a short small colon but may also be misleading.[87] Surgical exploration of the abdomen offers definitive

diagnosis of the severity of the malformation and the possibility of correction, but the owner should be informed before surgery of the high frequency of inoperable lesions and the high failure rate after reattachment.[87] Before any surgery is contemplated, a thorough physical examination should be performed to identify any other congenital malformations. Surgical correction of atresia ani is often successful, particularly if the atresia is limited only to a persistent membrane blocking the anus and the anal sphincter is normal. The prognosis for atresia coli is guarded. Poor intestinal motility, technical difficulties of attaching bowel segments that are so different in size, anastomosis breakdown, and peritonitis after surgery are common complications.[87] An inguinal hernia is another congenital lesion occasionally requiring surgical intervention. Such hernias occur in colts and may be caused by compression during parturition. Most congenital inguinal hernias are handled conservatively because the condition is often self-limiting by the time the foal is 3 to 6 months old. Treatment includes daily manual reduction of the hernia and frequent observation to detect possible bowel strangulation. Indications for surgical intervention in foals with congenital hernias include rupture of the common vaginal tunic, persistent colic, severe edema of the prepuce and scrotum, and trauma to the skin overlying the hernial sac. Surgical hernias are difficult to reduce manually, and loops of intestines are often palpable in the subcutaneous tissues of the scrotum and medial thigh.[88] Unilateral castration is usually performed on the affected side.

Other GI lesions in foals that may require an exploratory laparotomy include intussusception, small or large intestinal volvulus, and mechanical obstruction (e.g., food or ascarid impaction, phytobezoar, fecalith). Intussusceptions are reported in young horses less than 3 years of age. An intussusception is formed when one segment of intestine and its mesentery invaginates into the lumen of the adjacent bowel immediately aboral to it. The invaginated segment is called the *intussusceptum*, and the enveloping segment is called the *intussuscipiens*. Small intestinal intussusceptions can involve the jejunum, ileum, or ileocecal junction. Other sites of obstruction include cecocecal and cecocolic junctions. Intussusceptions are most common in foals less than 6 weeks old.[89]

Causes of intussusception include segmental motility differences (e.g., a hypermotile section of bowel adjacent to an atonic segment of bowel) and local changes in the bowel wall (e.g., abscessation). Causes of altered peristalsis include enteritis, heavy ascarid infestation, mesenteric arteritis, and sudden dietary changes.[90] Changes in the bowel wall have included granulomas, papillomas, and intramural leiomyoma. *Anoplocephala perfoliata* has been associated with ileocecal intussusceptions. Clinical signs include varying degrees of discomfort depending on the site of obstruction and its duration. Abdominal pain can be severe but is often low grade and intermittent, accompanied by decreased manure production. Ultrasonography is a useful diagnostic aid. Sonographically the cross-sectional view of the intussusception reveals a target-like pattern with a thick hypoechoic rim. The outer rim is created by severe edema of the entering and returning bowel walls of the intussusceptum.

Fig. 19-9 Standing abdominal radiograph of a 3-week-old foal that was presented with signs of severe pain. Note the multiple, erectile loops of distended small intestine with fluid lines. Obstructive disease was suspected. On surgical exploration of the abdomen, obstructing adhesions secondary to a previous surgery were found.



Treatment involves surgical exploration. Early cases can be manually reduced, followed by surgical resection. Because of the ileum's tenuous blood supply and the inaccessibility of the ileocecal junction, intussusceptions involving the ileum are usually treated with a side-to-side jejunostomy or ileocecostomy. Ileoileal intussusceptions have been reported to have a better prognosis than jejunal or ileocecal intussusception. Foals that have multiple sites of intussusception have a poor prognosis.

Volvulus may involve the small or large intestines. Small intestinal volvulus is the most common, especially among foals between 2 and 4 months of age. Signs include abdominal distention, gastric reflux, persistent tachycardia, severe pain, and sonographic evidence of uniform, severe bowel distention with bowel wall edema (>3 to 4 mm) and absence of motility. As expected, survival is poorer following correction of strangulating versus nonstrangulating lesions. Strangulating lesions of the small intestines are associated with poor survival compared with large intestinal lesions and have a higher incidence of fatal complications.

Parasitic migration and abrupt dietary changes are among conditions thought to predispose to volvulus development.

Surgical colic in foals carries a poorer long-term prognosis than in adult horses. One study[91] examined the survival rate among 67 foals <150 days of age that underwent colic surgery. The most common lesions requiring a celiotomy were small colon impaction, large colon impaction, jejunal volvulus, and ascarid impaction. A poor prognosis was associated with strangulating lesions. Foals less than 14 days of age experienced more early postoperative complications and suffered poor long-term survival because of adhesion formation. Only 25% of foals less than 14 days of age survived in the short term compared with a survival rate of 71% in foals older than 14 days of age.

Another study[92] examined the outcome among 119 young horses less than 1 year of age that underwent exploratory celiotomy. Among all foals the most common cause for surgery was small intestinal strangulation. Uroperitoneum and meconium impaction were the most common conditions in neonatal foals, and intussusception and enteritis were more common among older foals. Significant elevations in packed cell volume (PCV) (37% to 54%), heart rate (80 to 134 bpm), nucleated cell counts, total protein in peritoneal fluid (3.1 to 32.8 × 10^3/μL, 2.9 to 4.9 g/L), and rectal temperature (38.2° C to 39.2° C) were observed in nonsurvivors compared with survivors. Nonsurvivors had significantly decreased serum bicarbonate, chloride, sodium, and venous pH values. Thirty-three percent of foals that survived surgery had evidence of intraabdominal adhesions.

19.5.2.5

Necrotizing Enterocolitis

NEC has been described in equine neonates.[93] It is a syndrome of acute intestinal necrosis.[94] In human infants, prematurity is the single greatest risk factor, with only a small percentage of affected infants being full term. The causes of NEC are not well defined, but predisposing factors include ischemic hypoxic gut injury, presence of intraluminal bacteria, and enteral feeding. After GI ischemia, mucosal cell metabolism diminishes and the protective mucous layer is lost. This allows enzymes to break down the mucosal barrier, and intraluminal bacteria can then invade and multiply within the bowel wall. Enteral feeding provides substrate for the bacteria. Pneumatosis intestinalis develops, and the bowel frequently ruptures. Abdominal signs include abdominal distention, tenderness, ileus, and ascites. The condition may appear as a fulminant, rapidly progressive disease or progress at a much slower pace.[94,95] One affected equine neonate was premature and was undergoing treatment for respiratory distress when the abdominal crisis occurred. Another was a term foal that had experienced a prolonged delivery and was presented at 24 hours of age because of weakness and abdominal pain. Abdominal distention and abdominal pain, followed by ventral colon rupture, were noted in both foals.[93]

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Clinical signs associated with varying degrees of hypoxic, ischemic gut injury include ileus, gastric reflux, colic, lethargy, abdominal distention, and diarrhea. Reflux and feces may be positive for blood. Generalized sepsis often accompanies NEC. NEC should be distinguished from intestinal ileus secondary to other neonatal diseases, other surgical GI lesions, bacterial or viral enterocolitis, and intolerance to a milk diet. Although no single laboratory test is specific for NEC, the abdominal radiograph often reveals pneumatosis cystoides intestinalis, bowel wall edema, and an abnormal gas pattern consistent with ileus. Ultrasonography may reveal intramural gas accumulation. If intestinal perforation has occurred, pneumoperitoneum and septic peritonitis may also be noted.[93,94] Intestinal perforation is associated with a poor prognosis.

19.5.2.6

Gastrointestinal Ulceration

GDUD in the older suckling foal is covered in greater detail in Chapter 32. GI ulceration has also been associated with a number of neonatal diseases, including asphyxiation, enteritis, and septicemia.[96] The most significant form of the disease in this age group is cardiac gland disease—ulceration in the cardiac gland mucosa immediately beneath the margo plicatus. Ulceration presumably occurs in response to altered perfusion and may result in perforation and fatal peritonitis. In endoscopic surveys of neonatal foals in the United States, England, and Ireland, approximately one half of foals less than 3 months of age had evidence of gastric squamous mucosal ulceration.[97,98] The prevalence of lesions was greatest in 2- to 9-day-old foals and 30- to 59-day-old foals. In the young foals, typical lesions were golden-colored crusts in the squamous mucosa next to the margo plicatus along the greater curvature in association with diffuse ulceration and erosion and, commonly, squamous epithelial desquamation.[98] In one of these studies, foals that had a previous disorder (e.g., diarrhea, illness, transport) were more likely to have a glandular mucosal lesion than those that had not (9% vs 4%).[98]

The clinical signs of bruxism, excessive salivation, and colic that are commonly associated with GDUD in the 1- to 4-month-old foal are rarely observed in the neonatal foal. Frequently, gastric perforation is the first indication of the problem. Perforated and bleeding gastric ulcers have been diagnosed as early as 24 hours of age. There is also a high incidence of abomasal ulceration in calves, but rarely do they become symptomatic unless perforation occurs. Currently the cause and pathophysiology of the condition in the neonatal period is not known. Because of the difficulty of diagnosing the condition without specialized endoscopic equipment and the often catastrophic consequences of subsequent perforation or pyloric or duodenal stricture formation, antiulcer medications are often used prophylactically in the compromised neonatal foal. Foals at highest risk for ulcers are sick neonates that are not recumbent and foals with hypoxic gut damage, enterocolitis, and painful orthopedic conditions. Foals that are chronically recumbent frequently maintain a high pH that may a result of ileus and enterogastric reflux.[99] In normal foals the mean hourly baseline gastric pH ranged from 3.2 to 3.7. Milk intake had a dramatic but transient alkalinizing effect on pH. H_2 blockers including ranitidine and omeprazole significantly raised gastric pH. Ranitidine administered IV at 2 mg/kg or orally at 6.6 mg/kg significantly raised gastric pH.

Initial therapy includes the use of H_2 blockers (cimetidine 15 to 20 mg/kg orally [PO] q6h; ranitidine 6 to 8 mg/kg PO q8h), cytoprotective agents (sucralfate 20 mg/kg PO q6h), and a new class of drugs, proton pump inhibitors (omeprazole 4 mg/kg PO q24h). Omeprazole is highly effective and has the advantage of once-daily administration. Treatment regimens should continue for a minimum of 21 to 28 days. In acute stages some foals receive additional pain relief from over-the-counter antacid solutions (10 to 20 mL q3-4h). Some foals are in too much pain to nurse and benefit from withholding enteral feeds temporarily and maintaining them on a brief course of parenteral alimentation using a mixture of amino acids, lipids, dextrose, electrolytes, and vitamins. Currently recommended dosages for antiulcer medications are listed in Chapter 32.

19.5.2.7

Hemoperitoneum

Hemoperitoneum is a relatively uncommon cause of abdominal distention in the large animal neonate. The structures most commonly responsible for the hemorrhage are the umbilical vessels and the liver or spleen when ruptured secondary to trauma. Occasionally other structures such as a ruptured granulosa cell tumor may bleed.[100] Depending on the cause and severity of the hemorrhage, clinical signs relating to hypovolemia and

anemia may be mild or severe and may appear shortly after birth or in the older foal. Diagnosis of hemoperitoneum is based on the retrieval of free-flowing blood on peritoneal tap and the detection of free fluid in the abdomen. Ultrasound examination may be of benefit in detecting the source of the bleeding. Of critical importance, regardless of the source of the hemorrhage, is prevention of hypovolemic shock, and intensive patient monitoring and intervention are often indicated. Whole blood replacement may be necessary. If an internally bleeding animal with an unstable cardiovascular system is rushed to surgery without prior stabilization, profound shock may occur, and a poor outcome usually results.

19.6 DIARRHEA IN NEONATAL FOALS

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John E. Madigan

Diarrhea occurs commonly in foals of all ages and represents one of the most common medical conditions requiring veterinary intervention. The approach to diagnosis can be difficult, and establishment of a definitive diagnosis in a field setting is uncommon. The veterinarian must therefore consider a number of factors in order to construct a list of most likely causes. These factors include the age of the affected animal, the numbers of foals affected, the volume and character of the feces, and the duration of signs. Some limited diagnostic tests can be used to rule in or out many of the common causes of foal diarrhea.

In some foals, diarrheal diseases are associated with signs of colic. The abdominal pain can be severe and can mimic that seen in foals with strangulating intestinal lesions, making case management difficult. Colicky signs frequently precede the onset of diarrhea. Passage of a nasogastric tube is as important in colicky foals as it is in adults. Foals with intestinal ileus or inflammatory diseases of the small intestine commonly produce large volumes of gastric fluid on reflux. The control of pain is required in order to reduce the chances of injury and to facilitate evaluation. Intramuscular butorphanol can be very helpful in providing pain relief in foals with colitis. α_2-Adrenergic agonists should be used with caution in neonates because of their depressive effect on the cardiopulmonary system. If they are to be used, then start with lower doses or consider combining with butorphanol. Nonsteroidal antiinflammatory drugs should be avoided until a diagnosis is established. Neonatal foals generally tolerate flunixin well but require a slightly larger dose rate but reduced frequency when compared with older animals.[101,102]

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There are many causes of diarrhea in young foals, including bacteria and bacterial toxins, viruses, nutritional factors, parasites, and antibiotic use. Normal physiologic adaptive processes can also produce diarrhea in most foals.

19.6.1 DIFFERENTIAL DIAGNOSES

19.6.1.1 Bacteria

E. coli is the most important mediator of systemic sepsis in newborn foals but is not a common primary cause of diarrhea in this age group. Some reports implicate an association between *E. coli* and diarrhea in foals. Enterotoxigenic *E. coli* was isolated from a 3-day-old diarrheic foal from Virginia.[103] The isolate was of the 0101 serotype, was heat labile-like—toxin positive, but negative for heat stabile. Earlier inoculation studies indicated that F4 (formerly K88)-positive *E. coli* was not likely to cause diarrhea in foals, although it may have a synergistic role in foals infected with other potential pathogens, such as rotavirus.[104,105]

Intestinal disease mediated by clostridial toxins occurs in foals worldwide. The toxins are most commonly derived from biotypes A and C of *Clostridium perfringens* or from *Clostridium difficile*. Classic intestinal clostridiosis of foals is caused by *C. perfringens* biotype C and is characterized by colic, rapid dehydration, cardiovascular collapse, and hemorrhagic diarrhea. The disease occurs most commonly in foals less than 10 days of age, and often less than 36 hours of age. It is associated with a high mortality, and outcomes are rarely influenced by treatment.[106] Death may occur rapidly, and occasionally it occurs before any diarrhea has been passed. Biotype C produces both alpha- and beta-toxins, along with variable amounts of enterotoxin. Cases can occur sporadically or as outbreaks and on some farms occur annually, presumably associated with carriage in specific mares. Biotype A of *C. perfringens* has become well recognized as a specific cause of foal diarrhea over the past decade. Biotype A produces alpha-toxin and enterotoxin and is associated with a slightly lower mortality rate than biotype C. Affected foals are more likely to respond to directed or supportive care.[106] The development of clinical signs is rapid, and diarrhea may or may not contain blood; in ‘our experience passage of bloody diarrhea is common but usually very transient. Reported risk factors for *C. perfringens* diarrhea in neonatal foals in Colorado include breed (stock horse type); birth on dirt, sand, or gravel; housing in stalls or on dry lots during the first 3 days of life; and maternal feeding practices. Feeding a low-grain diet prepartum was associated with a decreased risk of neonatal disease.[107] Hematologic findings are consistent with toxemia. This includes hemoconcentration; an initial leukopenia, characterized by a neutropenia with a left shift to immature forms and toxicity; and a lymphopenia. In chronic cases a rebound leukocytosis and hyperfibrinogenemia may develop. Altered coagulation may be evident clinically through prolonged bleeding or spontaneous hemorrhage or through a propensity to develop thrombosis.

A definitive diagnosis of *C. perfringens* diarrhea is rarely established in practice. The diagnosis is usually based on signalment, clinical features, and outcome, rather than on detection of specific clostridial toxins. Positive fecal culture is strongly supportive, noting that healthy foals may shed low numbers of *C. perfringens*. Identification of toxin is ideal but is limited because of availability of appropriate commercial assays. Fecal enterotoxin detection assays are available but lack sensitivity, particularly with biotype C isolates. Biotyping of *C. perfringens* isolates after culture can be achieved using polymerase chain reaction (PCR) analysis for toxin gene sequences. This may be helpful in increasing the accuracy of the diagnosis but again falls short in establishing a definitive cause. Fecal Gram stain is easy to perform and may support an early clinical suspicion of disease if there are abundant numbers of large gram-positive organisms or spores present.

Clostridium difficile can produce an identical clinical syndrome to *C. perfringens,* although it appears to be more variable with respect to fecal blood. It also occurs as sporadic cases or as clusters or outbreaks. It is important to recognize that clostridial infection can produce a severe inflammatory syndrome that is restricted to the small intestine and may not cause diarrhea. Affected foals can present with signs that mimic strangulating small bowel disease including severe abdominal pain, gastric reflux, and sanguineous peritoneal fluid. Two principal toxins can be liberated from *C. difficile*, an enterotoxin (toxin A) and a cytotoxin (toxin B). Both nontoxigenic and toxigenic strains exist and can be differentiated only after culture using molecular techniques. Consequently, commercial toxin tests (available for both toxin A and toxin B) are recommended in addition to fecal culture to establish a diagnosis. As with *C. perfringens* cases, a fecal Gram stain can also increase suspicion. Hematologic changes associated with *C. difficile* infection can mimic those associated with *C. perfringens* disease.

Most cases of clostridial enterocolitis require aggressive medical intervention, irrespective of clostridial type. Antimicrobial therapy should be both specific and broad spectrum. Targeted antimicrobial treatment typically includes both metronidazole and penicillin. The majority of affected foals require, at minimum, intravenous

crystalloid solutions; some also benefit from plasma or synthetic colloids and inotrope and vasopressor therapy. Additional therapies include *C. perfringens* biotype C and D antitoxin, di-tri-octahedral smectite clay, and lactase enzyme replacement.[108,109] The use of *C. perfringens* antitoxin and toxoid is off-label and not without some risk. Pretreatment with antihistamines before antitoxin has been suggested.[108] Prevention of clostridial enterocolitis centers on hygienic housing practices and avoidance of overfeeding of late pregnant mares. Affected foals and their mares should be isolated and strict protocols instituted to limit cross-contamination. Administration of *C. perfringens* type C and D toxoid to pregnant mares has been used with anecdotal success on farms with recurrent problems with *C. perfringens* biotype C. The use of prophylactic metronidazole is highly controversial but understandable on properties with a high disease prevalence. Some isolates of *C. difficile* are reportedly resistant to metronidazole,[108] and although this appears to be dependent on geographic location, the widespread prophylactic use could promote resistance. Prophylactic use of probiotic preparations has also been commonly recommended but is difficult to justify on the basis of limited and conflicting efficacy data.[110,111]

Bacteroides fragilis is a gram-negative anaerobic rod and occurs in both enterotoxigenic and nonenterotoxigenic forms. Enterotoxigenic strains of *B. fragilis* have been incriminated with diarrhea in several species including lambs, calves, pigs, humans, and foals.[112] Enterotoxigenic *B. fragilis* was isolated from young foals (aged 2 to 60 days) with diarrhea.[113] Half of these foals had other potential pathogens detected, including *Salmonella* or rotavirus. In a study reviewing 20 isolates of *B. fragilis* from hospitalized foals with diarrhea, only four had the enterotoxin gene.[112] The most common isolate from foal feces was a nonenterotoxigenic strain, casting doubt as to clinical relevance.

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Enterococcus (group D *Streptococcus*) *durans* has also been implicated as a cause of diarrhea in several species including foals.[104] Similarly, *Aeromonas hydrophila* was isolated more commonly from foals with diarrhea than from control animals, suggesting a potential role in foal diarrhea.[114]

R. equi is an important cause of pulmonary disease in foals. Although abdominal involvement appears common, the relevance of *R. equi* as a significant primary enteric pathogen in terms of number of animals affected is likely small. An intestinal syndrome has been directly attributed to *R. equi* that involves necrosis of the small intestinal Peyer's patches and multifocal thickening and necrosis of the cecum and large intestine.[115] The changes include multiple areas of intestinal ulceration with a thin covering of fibrin and neutrophils. There is also an associated mesenteric lymphadenopathy. The diagnosis of *R. equi* ulcerative colitis is difficult for a variety of reasons. In contrast to *Salmonella* infection, in which recovery of the organism from the feces has significance, the recovery of *R. equi* is common in asymptomatic animals. Up to 100% of foals older than 2 weeks of age may shed large numbers of the bacteria ($>10^4$ colony-forming units [cfu] per gram of feces).[116]

Salmonella infection of neonatal foals is also associated with high mortality. As with clostridial infection, cases can occur sporadically or as part of an outbreak. Mares provide the most important source of *Salmonella* to newborn foals, but it is rare that both mare and foal develop clinical disease. Clinical signs can become apparent by 24 hours of age but are more common in older foals. The severity of signs is related to virulence of the serotype involved, inoculation dose, and level of host immunity. In contrast to adult infections, detectable bacteremia occurs commonly in affected foals. Consequently foals that may survive the initial intestinal or systemic disease remain at risk for secondary complications that include osteomyelitis, synovitis, meningitis, uveitis, hepatitis, or pyelonephritis. In some foals these complications may not become clinically apparent until days or weeks after resolution of enteric disease. Therefore appropriate and sustained broad-spectrum antibiotic therapy is important in foals known to be affected. The selection of antibiotic should be

based on known sensitivity patterns, understanding that in vitro sensitivity may not accurately translate into clinical efficacy because of the intracellular location of *Salmonella*. For example, the limited distribution of aminoglycosides can lead to therapeutic failure despite often promising in vitro sensitivity.

19.6.1.2

Viruses

Rotavirus is generally considered to be the most common cause of infectious diarrhea in foals. There are seven known groups of rotavirus (A through G), and many different serotypes within each group. Group A is the primary cause of rotaviral diarrhea in foals, with G3 being the most common serotype. Rotaviruses have the ability to change their surface proteins over time, and this rearrangement of gene segments takes place during co-infections with other strains. This leaves the possibility for many variations of the virus.

Transmission may be direct from animal to animal or indirect through fomites. Disease occurs after a short incubation period. Experimentally, this period may be as brief as 48 hours.[117] Rotavirus replicates within the intestine and invades the lining of the proximal small intestine, causing villous cell death and a resultant loss of absorptive area. Diarrhea may result from several mechanisms: (1) a loss of absorptive capacity coupled with a decrease in lactase production can lead to an osmotic load of undigested lactose delivered to an immature hindgut; (2) a compensatory crypt cell proliferation may cause an increase in intestinal secretion; and (3) the virus produces an enterotoxin that causes or contributes to the development of diarrhea. The putative viral enterotoxin and cytotoxin, NSP4, is a nonstructural glycoprotein of rotavirus that is released from virus-infected enterocytes.[118] NSP4 is a noncompetitive inhibitor of the Na-glucose symporter and also enhances intestinal chloride secretion.

Disease can be seen between 2 and 160 days of age but is most common in foals less than 60 days old. Indeed, most clinical infections probably occur between 5 and 35 days of age. The presence and severity of diarrhea are highly dependent on the degree of hindgut maturation. Consequently, infection in foals less than 2 weeks of age may result in life-threatening watery diarrhea, whereas infected older foals may have minimal or no diarrhea because of effective colonic compensation of osmotic and fluid loads. Diarrhea when present is often watery but is nonfetid in odor.

There is serologic evidence that broodmares may have an important role in propagation of the virus within a herd. Infections can occur as isolated cases or as outbreaks following periods of overcrowding and stress. Shedding after infection is usually complete by 10 days after the cessation of clinical signs but may occur intermittently for up to 9 months.[119] The virus can persist in the environment for up to 9 months, and disinfection usually necessitates the use of substituted phenolic compounds.

The diagnosis of rotaviral diarrhea is based on an appropriate signalment, clinical signs, and detection of the virus in feces. Tests include electron microscopy and commercial immunoassays (latex agglutination or enzyme-linked immunosorbent assay [ELISA]). Virus is shed in large concentration early on during infection.[120] Central to the management of affected foals is maintenance of hydration through enteral and/or intravenous fluid therapy. Bismuth subsalicylate is commonly administered to foals with diarrhea, irrespective of the underlying cause.

Prevention involves good hygiene and reduction in crowding. Vaccination of mares during pregnancy has yielded variable results in terms of efficacy.[121,122] Some evidence suggests that vaccination may at a minimum delay the onset of disease, thereby reducing both the severity and duration of diarrhea. Limited data from Japan indicate a potential benefit of bovine colostral immunoglobulin powder in the prevention of

rotaviral diarrhea.[123] A commercial egg-protein—derived supplement has also been used in foals to reduce the prevalence of neonatal diarrhea, but controlled research data are lacking.

Coronavirus can also cause diarrhea in foals during the neonatal period, although it appears to be very uncommon.[124–127] The few reports of clinical disease indicate that disease caused by coronavirus can be very severe. Antemortem diagnosis can be made using electron microscopy, serology, or commercial fecal-capture ELISA. As with rotaviral infection, shedding is greatest in the early stages of disease. Adenovirus is unlikely to play an important role in foal diarrhea, with the exception of foals with severe, combined immunodeficiency syndrome.[128]

19.6.1.3 Parasites

Strongyloides westeri is a common parasite of foals, with early infection of the foal occurring through mare's milk. Experimental studies have indicated that higher numbers of infective larvae than are found in milk are needed to produce diarrhea.[129] In addition, foals with high egg counts (prepatent period 8 to 14 days) are often asymptomatic. *S. westeri* is susceptible to a variety of anthelmintics, including ivermectin.[130] *Eimeria leuckarti* is commonly found in feces of foals from approximately 30 to 125 days of age.[131] It is unlikely to be a cause of diarrhea in foals.[132]

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Cryptosporidium parvum is not considered to be an important pathogen of foals in terms of numbers of animals diseased. Based on epidemiologic studies the parasite appears to be concentrated in some breeding operations.[133] Foals diseased with *Cryptosporidium* shed enormous numbers of infective oocysts into the environment. The parasite is considered to be coccidian-like but differs from coccidia in terms of size (4 to 6 μm diameter compared with 23 to 34 μm for other coccidia), host specificity (not host specific), pathogenesis (invades only epithelium), and drug sensitivity (resistant to many drugs). Infection is by the fecal-oral route. The oocysts can survive in the soil or water for months. They do not require a period of sporulation outside of the host to become infective. In a study of asymptomatic foals in Ohio and Kentucky, it was reported that between 15% and 31% of foals were shedding *Cryptosporidium* and that shedding began between 4 and 19 weeks of age and persisted no more than 14 weeks.[134] All shedding had ceased by weaning and was not identified in adult horses. Each generation of the *Cryptosporidium* lifecycle is brief, with maturation occurring in as little as 12 hours. Consequently, the prepatent period is very short, approximately 72 to 96 hours. Although not determined in foals, a heavily infected calf can shed approximately 50 billion oocysts within a 7-day period.

The diagnosis is usually made through microscopic examination of the feces. Acid-fast or Ziehl-Neelsen stains are required to detect oocysts. Immunofluorescence assays and flow cytometry techniques have also been described. *C. parvum* infection may be seen with concurrent enteric or systemic infections. The disease is generally self-limiting in immunocompetent animals. Historically the pharmacologic control of *Cryptosporidium* has been difficult, but paromomycin, nitazoxanide, or azithromycin may be efficacious.

Giardia may be found in normal foals, with infection rates reported to be 17% to 35%. *Giardia* is present in all age groups, and it is believed foals acquire infection from nursing mares. Concurrent infection with *Cryptosporidium* and *Giardia* may be observed. Disease should be suspected if large numbers of parasites are seen on fecal analysis. Affected animals should respond within a few days to treatment with metronidazole; failure to respond should alert to other pathogens.

19.6.1.4

Nutrition

Nutritional causes of diarrhea include overingestion of milk (as might occur when the mare and foal are separated and rejoined) or overfeeding orphaned or sick foals. Overwhelming the ability of the small intestine to digest and absorb results in presentation of milk to the colon, where it is fermented and produces osmotically active sugars and acids.[135] In a controlled study of foals less than 5 days of age, an elemental isotonic diet (Osmolyte) produced diarrhea in healthy foals when fed as the sole source of nutrition. Older foals fed a similar diet apparently did not develop diarrhea.* Caution should be exercised in using elemental diets designed for humans in the foal without adequate prior testing of tolerance to the diet. Orphan foals and foals fed commercial mare milk replacer may experience diarrhea associated with these diets. Foals that are fed raw cow's milk frequently experience diarrhea and failure to thrive. Cow milk replacer uncommonly causes diarrhea but remains a less than ideal replacement. In contrast, foals fed goat's milk grow well and rarely develop diarrhea, although they may develop a metabolic alkalosis of minimal to no clinical significance.

Transient lactase deficiency has been proposed in foals.[137–139] An oral lactose tolerance test is conducted by a 4-hour fast and administration of 1 g/kg of body weight in a 20% solution of α-lactose powder and observation of an increase of plasma glucose of 35 mg/dL by 90 minutes.[139] It has been postulated that agents such as rotavirus that damage epithelial cells may cause prolongation of the diarrhea because of temporary lactase deficiency (lactase is produced in mucosal cells). Lactase and cellulobiase are present at birth and decline after 4 months of age.[140]

* Kohn CA: Personal communication.

19.6.1.5

Foal Heat Diarrhea

Diarrhea developing during days 5 to 14 of life has been termed *"foal heat diarrhea"* because of the time relationship to the occurrence of postfoaling estrus in the mare. Diarrhea has developed in foals in this age group that have been raised separated from the dam on a consistent diet and isolated from pathogens, so it does not appear to be causally related to estrus. There is no demonstrable change in the composition of mare's milk during this time period.[141] *S. westeri* has been investigated and is not the causative agent of foal heat diarrhea.[129] The most likely cause of foal heat diarrhea is the establishment of normal flora in the hindgut. Foal heat diarrhea is typically preceded by coprophagy 2 to 3 days before the onset of diarrhea.[142] Classic foal heat diarrheas are mild and require no specific therapy. Continued diarrhea, fever, or depression with signs of reduced sucking activity on the mare should raise concern about other causative agents and should prompt appropriate diagnostic testing and treatment.

19.6.1.5.1

Clinical Pathology and Diagnostic Imaging

In addition to the fecal tests described under specific causes, tests for signs of systemic involvement are indicated in foals with frequency and amounts of diarrhea that may produce dehydration or in foals with fever and depression and/or loss of suck reflex. CBCs may indicate toxemia or systemic sepsis with neutropenia and shifting to immature forms. Computation of a sepsis score is indicated in foals with diarrhea that are less than 7 days of age. Assessment of renal function through BUN, creatinine, and urinalysis may reveal renal azotemia of prerenal or renal origin and warrant prolonged fluid therapy.

Assessment of electrolyte and acid-base balance is warranted in neonatal diarrheas, because hyponatremia caused by losses in the GI tract and renal compromise can be significant. Prolonged diarrhea can lead to significant metabolic acidosis, requiring fluid and bicarbonate replacement (see p. 355). Fecal culture and determination of fecal leukocytes and occult blood are additional diagnostic tests that may indicate a more severe disease condition. Fecal leukocytes are common in diseases caused by enteroinvasive pathogens, such as *Salmonella*. Ultrasound and radiography are also helpful at differentiating enteritis or colitis from other causes of colic or abdominal distention.

19.6.1.5.2

Treatment and Prognosis

The three main components of therapy for diarrhea in the neonatal foal consist of (1) fluid therapy (either oral or intravenous), (2) intestinal protectants and adsorbents, and (3) antibiotics if indicated to treat suspected bacteremia or clostridiosis. Sodium-containing isotonic intravenous fluids are an important component of diarrhea therapy in the compromised neonate. Potassium is lost in severe diarrhea and, if hyperkalemia is not present, should be supplemented by adding 15 to 20 mEq/L of KCl to fluids. Foals that are not nursing normally may have hypoglycemia and may need glucose-containing fluids. Acid-base correction by volume expansion and replacement of bicarbonate can be lifesaving and blood pH and calculated bicarbonate concentrations should be monitored frequently when significant intestinal fluid losses occur.

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In general terms, milk should not be withheld from foals with diarrhea. The clear exceptions are foals with colic and those with bloody diarrhea. The foal can be muzzled for 8 to 12 hours while the mare is milked out, and the foal provided oral fluids through stomach tube or a bottle if a suck reflex is present. Although labels of electrolyte replacers do not always specify “for use in foals,” many preparations used in calves (see Table 20-9) have been used successfully in foals. Most of these preparations provide insufficient energy and should be used for short intervals of no more than 24 to 36 hours unless PN of some type is provided to maintain blood glucose levels.

Intestinal protectants may be all that are required in uncomplicated cases or may be used in conjunction with other therapies. Bismuth subsalicylate, kaolin or pectin, and activated charcoal have been used for this purpose. Suggested advantages of bismuth subsalicylate[90] are its neutralization of bacterial toxins and antisecretory effect through its local antiprostaglandin activity.[143,144]

Systemic antibiotics should be used in the neonate with diarrhea that may be septicemic or may have compromised immunity. Blood cultures (see Chapter 18) should be obtained before initiation of antimicrobial therapy. Antibiotics with a spectrum against gram-negative and gram-positive organisms should be used. In general terms, renal toxicity associated with aminoglycoside use is uncommon in clinical practice. The clear exception are foals that are dehydrated, most commonly because of ongoing losses through diarrhea. Consequently the monitoring of renal function is indicated when potentially nephrotoxic drugs are used.

Plasma therapy for hypoproteinemia associated with FPT or protein-losing enteropathy is useful to maintain plasma oncotic pressure and expected protein binding of medications. Diarrheic foals with albumin levels below 2 g/dL or total plasma protein levels less than 4.2 g/dL may benefit from plasma therapy.

19.6.1.5.3 Prevention and Control

Prevention is best accomplished by minimizing density of populations of horses, separating of age groups, providing appropriate sanitation and hygiene (see Chapter 46), and obtaining adequate colostrum of good quality (see Chapter 53).

19.7 LAMENESS AND RELUCTANCE TO WALK

John E. Madigan

Guy D. Lester

19.7.1 INFECTIOUS LAMENESS

19.7.1.1 Etiology

Septic arthritis, septic physitis, and osteomyelitis as a complication of or sequel to bacteremia produce lameness and reluctance to move. Terminology to describe this condition has included “joint-ill,” “navel-ill,” septic physitis, septic polyarthritis, and septic epiphysitis.[145] Blood-borne bacteria from a previous illness or concurrent with an active nidus of infection produce infection in synovial membranes, growth plates, or periarticular bone. Sources of infection include primary bacteremia with or without FPT[146] (see Chapter 53), pneumonia, umbilical infection, enteritis, and extension of local infection from penetrating wounds. Thirty eight of 140 foals with confirmed septic arthritis demonstrated evidence of umbilical disease. In foals, bacteria that produce septic arthritis include the causative agents of systemic sepsis: *E. coli, Klebsiella* species, *Actinobacillus equuli, Salmonella* species, *R. equi,* and *Streptococcus* species.[146] A review of 78 foals with septic arthritis ranked the frequency of isolation of bacterial agents. Gram-negative bacteria were cultured from 51 of 78 foals. In addition, the probability of susceptibility of these isolates to various antibiotics was determined. Blood culture produced more bacterial isolates, although joint aspiration yielded bacteria in 69% of foals sampled.[147] Bacterial species cultured from blood and synovial fluid were identical in 16 of 88 foals. Negative cultures occurred in 31% of foals with later confirmed septic arthritis.[147] Gram-negative bacteria were more common in younger foals, and gram-positive infections became increasingly more common with advancing age of the foal.[147]

19.7.1.2 Clinical Signs and Differential Diagnoses

Signs may be extremely variable. Sudden onset of lameness in one leg in an apparently healthy neonate with or without joint distention, pain, or edema may be noted. Other presentations may be observed, consisting of sudden onset of lameness with systemic signs of illness or evidence of multiple joint distention, pain, and edema in a neonate with obvious illness and a diagnosis of septicemia. Prematurity or FPT should raise the index of suspicion. The chief differential diagnosis is trauma; lameness is often attributed by the owner to the dam's stepping on the newborn. Any neonate less than 45 days of age with sudden onset of lameness should be considered infected until proven otherwise.

19.7.1.3

Clinical Pathology and Radiology

Diagnosis may be obvious, with signs of septicemia, a positive sepsis score, and a swollen, hot, and painful joint. Peripheral leukocyte counts, rectal temperature, level of alertness, and appetite may be normal with localized infections. Joint aspiration may reveal normal synovial fluid if the infection is in the early stages of synovial membrane inflammation or physeal or bone involvement.[145] Synovial fluid with greater than 10,000 WBCs/μL and greater than 70% neutrophils indicates that infection is likely.[146] Cytology and Gram stain of the synovial fluid may further aid diagnosis. Thin, turbid, or brown synovial fluid with increased leukocytes is considered evidence of infection.[145] Culture of synovial fluid is often negative, even when infection is present. Improved recovery of bacteria may be obtained with thioglycolate broth or brain-heart broth with an agar slant and sodium polyanethole sulfonate (SPS) to prevent clotting and inhibit aminoglycoside and trimethoprim antibiotics.[148] Normal synovial fluid does not rule out septic physitis or osteomyelitis.[145] Careful examination of high-quality radiographs is important for the detection of bone lysis in cases of osseous infection. Initial radiographs may be normal because the degree of damage is often not detectable for 10 to 14 days after initial infection occurs.[145] Radiographic features of septic arthritis include soft-tissue swelling, widening or collapse of the joint space, osteoporosis, and osteosclerosis. Repeat radiographs taken at 3- to 7-day intervals are valuable for assessing the degree of damage if lameness persists.[145] Ultrasound may be used to confirm involvement of the joint and rule out periarticular or tenosynovial infection to avoid iatrogenic contamination of the joint during arthrocentesis. Joint distention and hyperechogenic fragments in the synovial fluid are suggestive of septic arthritis. Normal synovial fluid is anechoic. Bone scans or CT may facilitate early detection.

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19.7.1.4

Pathophysiology

Hematogenous spread of bacteria resulting in bone infection may follow a variety of pathways.[145] A nidus of infection may develop at the junction of cartilage and subchondral bone. The low pressure, slow flow, and reduced oxygen pressure of the blood supply at cartilage-bone junctions may predispose to establishment of infection in these areas. Level of immunity and degree of maturation of bone of the foal may be additional predisposing factors.[145] Destruction of the epiphysis and extension of infection into the joint may be primary in some cases, rather than starting as a primary synovial membrane infection that spreads to the epiphysis and physis. A classification has been proposed to reflect the various pathogeneses of infection (see Box 19-2). Infection of the small bones of the tarsus has been reported to be more common than that of the carpus,[149] and the metaphysis of ribs and vertebral bodies may be involved.[146] Synovitis produces severe inflammation and depletion of the cartilage matrix and collagen framework, which can cause irreversible damage.[145,146] Eburnation of cartilage leads to exposure of subchondral bone and extension of infection in bone.[145]

19.7.1.4.1

Box 19-2 Causes of Acute Abdomen in Foals

19.7.1.4.1.1

MECONIUM IMPACTION

Primary

Secondary to sepsis or asphyxia

19.7.1.4.1.2 OBSTRUCTION

Malformation (atresi coli, recti, ani)

Intussusception

Volvulus, torsion, strangulation

Foreign body

19.7.1.4.1.3 UROPERITONEUM

Ruptured bladder

Torn or necrotic urachus, ureter

19.7.1.4.1.4 PERITONITIS

Generalized infection

Devitalized bowel

Perforated gastric, intestinal ulcer

Severe umbilical infection

19.7.1.4.1.5 GAS/FLUID ACCUMULATION IN GASTROINTESTINAL TRACT

Aerophagia

Dietary intolerance

Ileus

Gastric/intestinal ulcer

Necrotizing enterocolitis

19.7.1.4.1.6 ASCITES

Severe liver or renal failure

Severe hypoproteinemia

19.7.1.4.1.7 MISCELLANEOUS

Hemoperitoneum

Ruptured umbilical vessels

Ruptured spleen or liver

Congenital tumor

19.7.1.5 Treatment

Aims of treatment are to remove the infectious agent, protect and minimize cartilage damage, and minimize secondary osteoarthrosis. If partial or complete FPT has occurred, an additional aim is to provide immunoglobulins through plasma transfusion (volume dependent on IgG concentration, but 2 or more liters IV may be required).[145] Treatment described for bacteremia should be used promptly. Umbilical ultrasound should be performed, because many infections may be not be visible externally. Systemic antibiotics provide adequate levels of antibiotic in normal and inflamed joints.[145,150] Antibiotics or antibiotic combinations with both gram-negative and gram-positive spectrum should be used initially, with selection modified by culture results. Ampicillin or a first-generation cephalosporin in conjunction with amikacin or gentamicin has had a good probability of antimicrobial sensitivity.[147] The third-generation cephalosporin ceftiofur may be used as monotherapy. Antimicrobials (antibiotics) should be continued for at least 3 weeks. Joint lavage with 1 to 3 L of balanced polyionic buffered (pH-adjusted) fluids helps to remove bacteria and inflammatory mediators that damage cartilage and improves outcome.[147] An infected joint is a medical emergency, and treatment should be carried out immediately after clinical diagnosis of probable sepsis, even before all cultures and clinical pathology test results are back. Arthrotomy or arthroscopic lavage for joints with fibrin and debris has been advocated and appears effective.[148,151] Delivery of antibiotics to chronically infected tissues via regional limb perfusion or intraosseous infusion has been described.[152] Confinement and limb immobilization may decrease pain, inflammation, and cartilage damage. Short-term use of nonsteroidal antiinflammatory drugs such as flunixin or phenylbutazone at prescribed dosages may be indicated, although the risk that these agents will induce gastric ulceration in foals is well described.

19.7.1.6 Prognosis

Duration, extent of bone involvement, and degree of damage affect the prognosis. A recent study determined that 79% of foals with septic arthritis had IgG levels less than 8 g/L (800 mg/dL). Infection of multiple joints, delay in onset of treatment, and presence of concurrent bony lesions on radiographs were associated with a poorer prognosis.[147] In one study, 67% of foals with septic arthritis were discharged when treatment was initiated within 24 hours of the onset of clinical signs.[147] Better outcomes were observed when treatment included joint lavage. Of foals treated for septic arthritis, 26% went on to perform their intended function.

If FPT has occurred and multiple joints are involved, the prognosis is poor because, in foals with FPT and lameness, multiorgan involvement is common.[146] Initial detection should warrant a guarded prognosis. The long duration of treatment and sometimes costly multiple therapeutic modalities should be discussed with the owner at the outset. Reevaluation of the patient at regular intervals is indicated. Recurrence after cessation of therapy sometimes occurs.

19.7.2 NONINFECTIOUS LAMENESS

Rhabdomyolysis in foals deficient in vitamin E and selenium may be precipitated by stress such as septicemia. Affected foals are reluctant to move, paretic, and occasionally dysphagic. Pelvic limb muscles are often palpably firm. Elevated serum creatinine kinase and electrolyte disturbances of hyponatremia and hyperkalemia may be observed.[153]

In foals, rupture of the common digital extensor tendon may be present at birth or may develop within a few days of life. Rupture occurs within the carpal synovial sheath and produces swelling over the dorsolateral surface of the carpus at the level of the intercarpal and carpometacarpal joints. Palpation of the fibers reveals tearing of the tendon. Splinting of the limb for 3 to 4 weeks usually results in healing.[154] 320 321

Contracture of joints or tendons of the limbs produces difficulty in movement and predisposes to FPT by impeding the ability to adequately nurse. Degree of contracture varies from mild to severe and may be associated with scoliosis and/or torticollis.[155] Foals with congenital contracture of tendons of the front limbs may spontaneously rupture the common digital extensor tendon. Conservative therapy consisting of splinting the front limbs to induce tendon laxity may be helpful.

19.7.2.1 Developmental Causes

Incomplete ossification of the cuboidal bones (see Fig. 19-1) of the carpus and tarsus of newborn foals is considered to be related to the development of flexural and angular deformities of the foal.[156] Twins, premature foals, foals that are small for gestational age, and foals with in utero acquired infection are likely to have incomplete ossification of cuboidal bones at birth.[156,157] Radiographic analysis and grading of the degree of ossification have been suggested for these foals.[157] Foals with substantially reduced ossification may damage bone with limb loading. Limited exercise may be prudent until ossification begins to increase radiographically, which can be within 7 days. Hypothyroidism (see Chapter 41) has been identified in foals with angular limb deformities, contracted tendons, and tarsal bone collapse.[158,159]

19.8 PATENT URACHUS, OMPHALITIS, AND OTHER UMBILICAL ABNORMALITIES

John E. Madigan

19.8.1 PATENT URACHUS

Patent urachus is a persistence after birth of the tubular connection between the bladder and umbilicus. The urachus drains the bladder into the allantoic sac during gestation. Urine flow should gradually change, with some urine entering the amniotic sac through the urethra in later gestation. At birth, with umbilical cord rupture the urachus should be closed, and urine should be voided through the urethra. Foals with a patent urachus may dribble urine from the urachus during or after urination or may simply have a constantly wet umbilical stump.

19.8.1.1 Etiology

Various causes have been suggested for failure of the urachus to close and completely involute. Early severance or ligation of the umbilical cord, inflammation, infection, and excessive physical handling of the neonate have been implicated.[160] Rather than being the original cause for hospital admission, patent urachus develops as a complication of hospitalization in a significant percentage of foals in neonatal intensive care. Weakness of abdominal musculature may contribute to the problem in sick foals.

19.8.1.2 Clinical Signs and Differential Diagnosis

Differential diagnoses include concurrent infection of the navel (omphalophlebitis). Ultrasound may assist the diagnosis and determine the involvement of umbilical arteries or vein.[161] Moist hairs around the umbilicus and visualization of fluid coming from the navel are diagnostic. Ultrasound examination of the internal structures of the umbilicus is strongly recommended.

19.8.1.3 Clinical Pathology

Identification of concurrent infection is essential. A complete physical examination should be performed. If abnormalities are noted, serum IgG, CBC, and urinalysis are helpful for detecting susceptibility to infection and presence of systemic or urinary tract infection.

19.8.1.4 Pathophysiology

Congenital patent urachus caused by excessive torsion on the umbilical cord in utero occurs in 6% of normal foals.[162] The obstruction of the urachus caused by the torsion causes retention of urine in the bladder and overdistends the proximal urachus, which interferes with normal involution.[162] Infection of umbilical structures or the urachus itself may result in inflammation and failure to completely involute. In a review of 16 cases of umbilical cord infections in foals, 13 of the foals had patent urachus.[163] The majority of these foals had acquired patent urachus after birth, with the youngest age of onset being 3 days and the mean age of onset being 12 days. Excessive manipulation and improper lifting of the foal's abdomen in the presence of high urethral sphincter tone may force urine within the bladder out into the involuting urachus. In our experience, farms have experienced outbreaks of patent urachus when procedures (such as tests for FPT) have been

implemented that require handling of foals in the first 12 to 24 hours of life. A similar cause may be responsible for the increased incidence of patent urachus in hand-reared calves.

19.8.1.5 Treatment and Prognosis

Therapy consists of either conservative management through monitoring or medical treatment for infection and cauterization of the urachus with iodine, phenol, or silver nitrate sticks applied into the urachus. Persistence of urine dribbling despite cauterization, the detection of involvement of other umbilical structures through ultrasound, and a rent in the urachus that produces subcutaneous swelling are indications for surgery. Not all foals that have persistent patent urachus have an infected umbilicus. Use of general anesthesia and removal of the entire urachus to the tip of the bladder are performed in foals with an infected or enlarged urachus. Associated arteries and veins should be ligated and removed if they are infected or necrotic. Merely ligating the exterior stump can trap organisms and cause infection. In our neonatal unit the majority of patients with acquired patent urachus respond to conservative therapy. Late-onset patent urachus (5 days of age) may be more refractory to conservative therapy.[163] Complications are uncommon but may include bladder necrosis and uroperitoneum caused by extension of infection and inflammation of the urachus.

19.8.1.6 Prevention

Allowing the umbilical cord to rupture without ligation or the careful use of specific umbilical clamps after birth has been suggested to decrease the incidence of patent urachus. Minimum handling of neonates and careful restraint may prevent pressure buildup in the bladder and subsequent patent urachus.

19.8.2 OMPHALITIS AND OMPHALOPHLEBITIS

19.8.2.1 Definition and Etiology

Omphalitis is inflammation of umbilical structures that may include the umbilical arteries, umbilical vein, urachus, or tissues immediately surrounding the umbilicus. The umbilicus consists of three types of structures and undergoes functional and anatomic changes at birth. Two umbilical arteries connect internal iliac arteries to the placenta. These later regress and become the round ligaments of the bladder. One umbilical vein connecting the placenta to the liver and porta cava regresses to become the round ligament of the liver within the falciform ligament. The urachus connects the fetal bladder to the allantoic cavity. 321 322

Umbilical abscess or infection of any of the three components of the umbilicus may produce local infection or be a source of septicemia. The source of infection is most commonly the external environment, coupled with FPT. Omphalophlebitis may extend the length of the umbilical vein into the liver and result in liver abscessation.

19.8.2.2 Clinical Signs and Differential Diagnosis

When the umbilicus is enlarged and draining purulent material, infection is easily noted. In other cases the umbilicus may be dry and larger in diameter than expected. In addition, neonates may have a completely normal-appearing, dry external navel and be severely ill from infection of the urachus, umbilical arteries, or vein. In a neonate with sepsis without external signs of infection, involvement of the umbilicus can be difficult to determine. The presence of pain on palpation of the umbilicus indicates inflammation. Ultrasound aids in

the detection of involvement of the urachus or arteries and vein.[161] The umbilical area of neonates less than 20 days of age with fever of unknown origin should be scanned. Hematoma developing after umbilical rupture may produce distention of the umbilical stump shortly after birth.

Overt signs of infection include heat, swelling, purulent discharge, or pain. Concurrent signs of systemic infection such as joint infection, pneumonia, diarrhea, meningitis, or uveitis may be noted. Infection in more than one umbilical vessel in the neonate is common, and urachal involvement is frequent. Umbilical abscessation that is walled off and does not involve deeper structures is a less severe problem and may be treated with drainage without surgical removal of the entire umbilicus. The depth of involvement may be determined by standing behind the neonate and pressing the hands together above the umbilicus to detect internal masses and painful areas.

19.8.2.3

Diagnostic Methods

In addition to detection of overt umbilical inflammation as described, ultrasonography may aid in evaluating a normal-appearing navel.[164] The umbilical vein, arteries, and urachus may be imaged in the newborn (see Chapter 18). The umbilical arteries leave the umbilical stalk and course on the outer edges of the urachus in a parallel fashion.[164] In the foal the urachus connects the apex of the bladder with the umbilicus and is located along the midline immediately adjacent to the body wall. Persistent dilation of the umbilical vein or arteries with a hypoechoic-to-echogenic fluid is seen with infection. If ultrasound is performed by a skilled ultrasonographer familiar with normal ultrasonographic findings of the umbilicus, there is an excellent correlation between surgical and ultrasound findings.[164]

19.8.2.4

Treatment and Prognosis

Early treatment with antibiotics and supportive care as described for the septicemic foal (see Chapter 18) may allow resolution before development of abscessation and distention of the urachus or the umbilical arteries and vein. Established infection, which may occur within 24 hours, may necessitate surgical removal of involved structures in addition to medical therapy.[163] When omphalophlebitis extends into the liver, the umbilical vein may be marsupialized to facilitate drainage and flushing. The prognosis is very good when adequate passive transfer of colostral immunoglobulins has occurred and when joints or other structures are not involved. Sequelae such as renal abscessation, joint or bone infection, peritonitis, and other complications described for septicemia may develop if therapy is started too late or discontinued prematurely.

19.8.3

ANEMIA AND ICTERUS

John E. Madigan

19.8.3.1

Definition and Etiology

Anemia in the neonate should be interpreted in the context of the realization that normal hematologic values of the neonate may vary from those of the adult. In foals, values of hemoglobin and PCV are similar to those in adult horses but decrease during the first weeks and months of life to below those in adults.[165] Foals have low iron stores during the first 5 months of life; this is reflected in decreased serum ferritin concentration, increased serum total iron binding capacity, and decreasing mean corpuscular hemoglobin concentration.[166]

Microcyte production is observed rapidly after birth.[166] Absolute RBC and total blood volume decrease at between 2 days and 2 weeks of age and then progressively increase.[167]

In addition to frank blood loss from an injury, diseases causing anemia in the neonate include NI, non-NI immune-mediated hemolytic anemia, blood loss caused by gastric ulcer or ovarian cyst rupture producing hemoperitoneum, anemia of chronic disease associated with localized infections, piroplasmosis, and equine infectious anemia.

19.8.3.2 Clinical Signs and Differential Diagnosis

Rapidly developing anemias such as those associated with NI produce signs of weakness, pale or jaundiced mucous membranes, fever, and depression. Hemoperitoneum produces weakness and pale mucous membranes. Suspected drug-induced, immune-mediated hemolytic anemia and thrombocytopenia have been reported in the foal.[168] Intestinal parasitism does not normally lead to anemia during the neonatal period. Chronic localized infection may produce anemia of chronic disease.

19.8.3.3 Clinical Pathology

Intravascular hemolysis may produce hemoglobinuria and hemoglobinemia. Icterus develops when the ability of the liver to conjugate bilirubin is exceeded. Mainly, indirect bilirubin is elevated. Anisocytosis is observed in responsive anemias. Nonspecific stimulation of bone marrow may produce a leukocytosis.

19.8.3.4 Therapy

Determination of the nature of the anemia may allow specific treatment. NI is discussed in Chapter 53. Drug-induced or autoimmune anemias may be treated with corticosteroids (0.05 to 0.1 mg of dexamethasone per kilogram twice a day IM or IV). Blood transfusion after cross-match may be indicated when anemia develops rapidly or PCV drops below 14%. Massive red cell destruction may trigger disseminated intravascular coagulation, and the actual cause of death may be a result of activation of the clotting system by RBC destruction and reticuloendothelial system removal.[169] Associated conditions such as metabolic acidosis and hypoglycemia should be corrected. Anemia of chronic disease requires correction of the primary disease condition.

19.8.4 FEVER

John E. Madigan

19.8.4.1 Definition and Etiology

Fever (rectal temperature >38.9° C [102° F]) as a clinical sign must be interpreted differently in neonates than in the adult because of the variations of anticipated response to systemic illness, temperature regulation control differences, and susceptibility to environmental changes in temperature. In foals with septicemia, fever (> 38.9° C [102° F]) was present in fewer than 30% of cases, and hypothermia was noted in approximately 20%.[56] Consequently fever is considered an unreliable clinical sign for determination of sepsis in neonates. Older foals with localized infection such as in joints or bone are more likely to have fever.

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19.8.4.2 Differential Diagnosis

The chief differential diagnoses for fever in neonates are fever caused by infections with viral or bacterial pathogens, seizures with subsequent generation of heat by muscular overactivity, pyrogens generated from hemolysis in NI, and environmentally induced hyperthermia. The condition of transient tachypnea of the newborn may produce significantly elevated temperatures in warm environments.[170] Neonatal foals have a rapid respiratory rate that appears to be an attempt at heat loss through a panting type of mechanism. Extreme care must be used in attributing the pyrexia and fever to transient tachypnea syndrome alone by ruling out the presence of infection through physical examination, chest radiographs, blood gases, and computation of a sepsis score. Pathophysiology is similar to that in the adult and is discussed thoroughly in Chapter 4.

19.8.4.3 Treatment and Prognosis

Although a conservative approach to fever in older animals may be appropriate, the presence of a fever in a neonate warrants rigorous diagnostic evaluation and aggressive therapeutic intervention. The immaturity of the neonatal immune system, the high fatality rate, and the frequency of devastating sequelae to bacterial infection warrant a complete examination of the neonate.

Because fever may be beneficial to the animal, the need to administer antipyretics to the febrile neonate is controversial. Body temperatures lower than 40.8° C (105.4° F) are not considered detrimental unless they are associated with heat stroke or seizures,[171] in which case cooling and antipyretics are indicated. Because many antipyretics are antiprostaglandins that can cause deleterious GI and renal effects, these agents should be used judiciously. Dipyrone is often used in neonates in our clinic for antipyretic response because it lacks most of the adverse GI side effects found with most nonsteroidal antiinflammatory drugs. Correction of the initiating cause and maintenance of fluid balance are also important. Prognosis depends on immunoglobulin status and stage of disease when treatment is initiated. Significant fatality rates occur in neonates with bacterial infections. Transient tachypnea has an excellent prognosis, with neonates becoming normothermic within 2 to 3 weeks of age. Clipping a long and thick haircoat, using fans in stalls, and removing the animal from direct sunlight may reduce heat stress to the neonate.

19.8.5 CYANOSIS

John E. Madigan

19.8.5.1 Definition and Etiology

Cyanosis is the purple-blue coloration observed on mucous membranes or skin caused by reduced or poorly oxygenated hemoglobin in blood.[172] Causes for this condition include congenital heart disease, respiratory impairment, or any circulatory condition that produces a right-to-left shunt. The degree of cyanosis depends on the arterial oxygen saturation, hemoglobin concentration, pH, peripheral circulation, and temperature of the neonate.[172] Shock and hypothermia are important causes of peripheral cyanosis (see Box 20-4).

19.8.5.2 Pathophysiology

The affinity of hemoglobin for oxygen is reflected in the standard oxyhemoglobin dissociation curve. This curve is similar for neonates but is affected by the amount of 2,3-diphosphoglycerate (DPG) in the erythrocyte. The foal does not have a fetal hemoglobin but has decreased amounts of 2,3-DPG, which causes oxygen to bind more tightly to hemoglobin and thus to be released in lesser amounts to the tissues.[173] Severe hypothermia and acidosis cause the oxygen dissociation curve to shift to the right and therefore contribute to tissue hypoxia. Cyanosis can be either central or peripheral.[172] Peripheral cyanosis results from increased peripheral extraction of oxygen from normally saturated blood or a significant decrease in the perfusion to an extremity.[172] In the neonate, causes include septic shock and severe hypothermia. Central cyanosis is more common in neonates and is related to congenital heart disease that causes right-to-left shunting or severe respiratory conditions that result in hypoxia. Paroxysmal atrial fibrillation in three foals with cyanosis shortly after birth is described.[174]

19.8.5.3 Treatment

Examination and clinical pathologic evaluation for metabolic causes of cyanosis, hypothermia, and cardiac abnormalities should be conducted. History, medication use, auscultation, thoracic radiographs, and arterial blood gases are useful in determining the degree of the respiratory component of cyanosis. Therapy for respiratory causes is discussed in the sections on respiratory distress. Electrocardiography and echocardiography may be required for identification of cardiac anomalies. Circulatory compromise caused by hypothermia, hypoglycemia, and shock requires aggressive fluid therapy, respiratory support, and environmental temperature correction.

19.8.6 OLIGURIA AND STRANGURIA

John E. Madigan

19.8.6.1 Definition and Etiology

In the neonate, urination is usually observed within 6 to 10 hours after birth. Frequency of voiding is every few hours. Urine volume produced in the foal is approximately 148 mL/kg/day.[175] Urine specific gravity is low (1.001 to 1.012) because of the high water content of milk. Specific gravity readings of 1.018 to 1.025 are approaching maximum in concentrated urine.[176]

The major causes of slow or painful discharge of urine (stranguria) in neonatal foals are ruptured bladder, bacterial cystitis, urachitis, and reduced urine production (oliguria) resulting from reduced renal perfusion. Pollakiuria, dysuria, and cystitis are complications occasionally observed with urachal abscesses.[176]

19.8.6.2 Pathophysiology

Ruptured bladder (see also Chapter 34) occurs most frequently in male foals and is believed to be caused by occlusion of the male urethra during birth, a full bladder, and great pressures during birth when the mare pushes to expel the fetus. Inadequate pressure flow to the kidney producing oliguria may be caused by

congenital cardiac anomalies, asphyxia, sepsis, diarrhea, or endotoxemia. Straining from cystitis can be severe and can mimic meconium impaction. Infection of the bladder may be associated with urachal infection. Inappropriate antidiuretic hormone (ADH) secretion occurs in stressed human infants, resulting in decreased urine production and electrolyte abnormalities. During periods of reduced glomerular filtration rate (GFR), drugs excreted by the kidney may accumulate, resulting in toxicity. Inability to excrete a water load associated with excessive fluid therapy may result in fluid accumulation and pulmonary or generalized edema. Uroperitoneum may result in stranguria or oliguria. Postrenal obstruction syndromes are rare in the neonate. 323
Ectopic ulcers have been reported in foals[177] as a cause of incontinence and hydronephrosis. A syndrome of 324
apparent pain on attempting the first urination is observed in some male foals; urinary bladder catheterization for 1 to 3 days may resolve the problem.

19.8.6.3

Clinical Signs

A carefully obtained history of events of the birth and neonatal period is important. Observation of defecation, posture during urination, frequency, and estimated amounts of urination should be noted. Excessive stretching of the front legs, dorsoventral flexion of the back, and colic may be observed with uroperitoneum. Detection of oliguria requires careful observation or catheterization of the bladder to determine presence of urine and amount of urine production. Free catch of urine and examination for WBCs aid in diagnosis of cystitis.

Azotemic neonates with oliguria have signs of depression, dehydration, poor pulse quality, prolonged capillary refill, reduced jugular distensibility, and retracted eyeballs. Elevated levels of serum urea and creatinine may be observed with uroperitoneum, often with concurrent electrolyte abnormalities of hyponatremia, hyperkalemia, and hypochloremia. If the presence of uroperitoneum is suspected, abdominocentesis should be performed. The fluid can be analyzed for potassium and creatinine and compared with serum values. Urea rapidly equilibrates between abdominal fluid and serum. Peritoneal fluid creatinine levels will be 1.8 to 2 times those of serum with uroperitoneum. A syndrome of high creatinine in newborn foals associated with maternal conditions or events of birth and without renal disease has been reported. Serial creatinine determinations reveal a gradual decline toward normal values over several days. Consequently a single serum creatinine determination should not be used to determine prerenal, renal, or postrenal uremia in the foal.

19.8.6.4

Treatment

Administration of balanced electrolyte solutions such as lactated Ringer's solution or saline and determination of urine production are important. Specific electrolyte and acid-base disturbances should be corrected slowly. Prolonged ischemia of the kidneys may result in permanent renal parenchymal damage. Lack of urine production after restoration of fluid balance should be an indication for diuretic therapy with furosemide (0.5 to 2 mg/kg IV) or osmotic diuresis with mannitol (0.25 to 0.5 mg/kg IV over 20 minutes and repeated in 4 hours if no response occurs). If adequate urine production has not developed, administration of dobutamine (2 to 10 g/kg/min) or dopamine (2 to 5 μg/kg/min) may be attempted. Treatment of concurrent sepsis, endotoxemia, hypoproteinemia, respiratory distress, or other abnormality should be attempted. If adequate urine flow is not produced, maintenance levels of fluids should be administered to prevent fluid overload. Body weight determinations three to four times a day help to prevent overhydration by detecting fluid accumulation. Urinalysis and clearance calculations may add further insight to the origin and degree of primary renal involvement. Progressive development of uremia and generalized edema is associated with a poor prognosis. When oliguria is present, serial BUN and creatinine determinations should be performed and urine production monitored. Recumbent neonates may be catheterized and urine production quantitated.

19.8.7 HEART MURMUR

John E. Madigan

19.8.7.1 Definition and Etiology

Heart murmurs in the neonate may be heard normally before physiologic closing of the ductus arteriosus during the first 1 to 5 days of life. Other causes of murmurs include congenital anomalies, severe anemia, and infectious valvular disease.

19.8.7.2 Clinical Signs and Differential Diagnosis

Physical examination for other signs of heart disease helps determine the severity of the murmur. Jugular pulse, weak or irregular arterial pulse, and palpable thrill indicate a serious condition. Signs of weakness, cyanosis, and tachypnea are indications of poor cardiac performance. Timing and location of the heart murmur should be determined. The electrocardiogram (ECG) may reveal atrial or ventricular enlargement. Thoracic radiography may aid in determining heart size and in detecting pulmonary edema or distended pulmonary vessels. Echocardiography may reveal atrial or ventricular enlargement, thickened ventricular walls, anomalous orientations of outflow tracts, or ventricular septal defects (VSDs).[178]

Patent ductus arteriosus (PDA) produces a continuous murmur localized over the left heart base.[179] The diastolic component may not be heard with auscultation over other parts of the heart. As pulmonary hypertension develops, the murmur is shortened to a holosystolic type with normal arterial pulse. Large shunting of blood produces a bounding arterial pulse caused by wide fluctuations of systolic and diastolic pressures.[179] The ECG is normal unless atrial enlargement is present and increasing QRS amplitudes are observed.[178] Radiographs may reveal an enlarged heart with increased vascularity caused by left-to-right shunting of blood. Echocardiography may reveal an increased left atrial and left ventricular diastolic dimension or volume and hyperdynamic septal and left ventricular wall systolic motion (depending on the degree of right-to-left shunt).[178] Catheterization and angiography may further delineate the degree of shunting.[180] Recent studies have indicated the ductus architecture changes days before birth, which prepares the ductus for closure. Triggering factors for closure include increased blood oxygenation and lower pressures resulting from vasodilation of pulmonary vasculature at birth.

VSD produces a large, harsh, holosystolic murmur that is loudest on the right cranial region of the thorax and is softer over the left heart base.[181] The ECG may be normal or may show increased amplitude of the QRS, with larger shunts and alterations in chamber size. Radiography may reveal heart size increase, left atrial enlargement, and dilated pulmonary vasculature.[178] Two-dimensional echocardiography may show aortic and septal discontinuity.[178] Injection of saline bubbles into the left ventricle and observation of bubbles in the right atrium or ventricle document a left-to-right shunting of blood.[178] Tetralogy of Fallot or other types of complex malformations often produce loud murmurs and are associated with cyanosis, weakness, fatigue, and stunted growth.[182] Tetralogy of Fallot produces a systolic ejection murmur heard at the left heart base.[178] Electrocardiography may reveal negative QRS complexes in leads I, II, and aVF, suggesting right ventricular hypertrophy.[178] Echocardiography may reveal a thickened right ventricular wall, septal echo dropout in the area of the VSD, rightward displacement of the aortic root, and an abnormal pulmonary outflow region.[178]

Saline injection into the jugular vein demonstrates right-to-left flow from the right ventricle to the left ventricle or the aorta.

19.8.7.3 Treatment

PDA has been treated by chemical closure using indomethacin in human neonates, but it has not been used in veterinary medicine.[183] Other global antiprostaglandins, including flunixin meglumine, have been used in attempts to assist with chemical closure of the ductus arteriosus in foals. The efficacy of this procedure has not been determined. Minimal fluid administration is also suggested to be of assistance. VSDs may pose few problems if the degree of shunting is small. Other complex cardiac anomalies producing murmurs may be treated symptomatically for a short time, but the long-term prognosis is extremely poor.

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19.9 SUPPORTIVE CARE OF THE ABNORMAL NEONATE

Wendy E. Vaala

The vulnerability of neonates to contagious and opportunistic pathogens is amplified by adverse environmental conditions. Maintenance of a “friendly” environment is a crucial component of neonatal medicine. Any condition that prevents them from standing and nursing within 3 hours of delivery represents a potentially fatal condition. Forced recumbency alone interferes with pulmonary function; contributes to dependent lung atelectasis and increases the risk of pneumonia; compromises GI function and predisposes to constipation; increases the risk of aspiration after milk meals; exacerbates preexisting musculoskeletal weakness and favors tendon contracture; delays absorption of colostral antibodies and calories, which increases the risk of infection and hypoglycemia; predisposes to decubital sores; and contributes to poor hygiene, urachal patency, and omphalitis. Supportive care is aimed at protecting the patient from self-inflicted injury, maintaining fluid, electrolyte, and metabolic homeostasis, providing adequate caloric intake, and preventing nosocomial infections.

If recumbent, foals should be kept on soft, absorbent bedding (mattress covered in synthetic fleece, straw on top of a deep bed of shavings or rubber mats) and turned and assisted to stand every 2 hours. If the foal is thrashing, it should be manually restrained to prevent self-trauma. Padded walls and strategic placement of pillows help protect the recumbent patient. Using a temporary barrier between the mare and recumbent foal facilitates treatment of the foal yet keeps the dam within sight, sound, touch, and smell of her foal, which fosters good bonding. The foal's eyes are prone to injury with the development of entropion, corneal edema, and ulceration. To prevent these injuries artificial tears or another sterile ocular lubricant should be applied topically every few hours. If entropion develops it should be corrected promptly using one or two vertical mattress sutures. A small bleb of procaine penicillin injected into the lower eyelid provides temporary improvement for mild cases of entropion.

If the animal's body temperature is less than 100° F (37° C), efforts should be made to warm it by raising the environmental temperature, using radiant heat lamps, applying blankets, and using heating pads judiciously. An effective heat pack can be made by placing a wet towel inside two rectal sleeves and microwaving to the desired temperature. The hot pack remains dry and can be nestled alongside the foal's abdomen. If the animal is wet, it should be dried off to reduce convective heat loss. Volume expansion to restore normal cardiovascular function, peripheral circulation, and systemic BP is an essential part of the warming process. Rewarming the periphery only with external heat without simultaneously warming the core can produce peripheral vasodilation with cardiovascular collapse. The thermoneutral zone for a term foal is 23° to 25° C (73° F to 77° F).[185]

Generalized seizure activity should be controlled as soon as possible. Diazepam at 5 to 20 mg IV, given slowly to effect to a 45-kg foal, is an appropriate first choice. If seizures are severe or recurrent, then phenobarbital should be administered (3 to 10 mg/kg IV slowly over 5 to 10 minutes). Multiple doses of diazepam can cause respiratory depression and should be avoided.

Respiratory rate, effort of breathing, mucous membrane color, heart rate, and fluid balance are quickly assessed to establish the need for immediate intervention and stabilization. Depending on the type and severity of the animal's condition, postural drainage, suction, oxygen therapy, or PPV may be indicated. If shock, severe dehydration, or metabolic derangements, such as hypoglycemia, are present, fluid therapy should be initiated as soon as an intravenous catheter is placed and secured. Table 19-2 highlights the significance of abnormal physical examination findings.

19.9.1

NEONATAL CHARACTERISTICS INFLUENCING FLUID AND DRUG THERAPY[186]

It is often observed that neonatal animals are more “sensitive” to the actions of drugs administered at normal adult dosage levels (on a mg/kg bwt basis) and less tolerant of inappropriate fluid administration than adult animals. Differences between neonatal and adult animals in drug effects generally can be attributed to differences in drug distribution, metabolism, or excretion. Some general characteristics of the neonatal period include better absorption of drugs from the GI tract, less drug binding to plasma proteins, increased apparent volume of distribution of drugs that are distributed in the extracellular fluid (ECF) volume, increased permeability of the blood-brain barrier, and slower elimination (i.e., longer half-life) of many drugs. It is important to remember, however, that the foal and the calf are relatively precocious newborns, and much of the data on neonatal differences were generated in considerably less mature species. For instance, glomerular filtration rate (GFR) reaches adult values at 2 days of age in calves versus at least 14 days of age in puppies. Studies of the development of renal function in foals,[187] as well as indirect evidence provided by pharmacokinetic studies of antibiotic agents eliminated primarily by renal excretion,[188] suggest that full-term, 2- to 4-day-old foals also have relatively mature renal function. For a more detailed discussion of neonatal drug disposition, the reader is referred to other texts.[186,189,190]

In the neonate, the relative volumes of fluid differ from those in the adult. Total body water in the equine neonate constitutes 70% to 75% of the total body weight, versus approximately 60% in the adult horse. During growth the intracellular fluid compartment remains relatively consistent with regard to size, whereas the ECF compartment decreases as a percentage of body weight, with an increasing body fat percentage. In the 2-day-old foal, ECF volume was 394 ± 29 mL/kg, blood volume was 151 ± 32.8 mL/kg, and plasma volume was 94.5 ± 8.9 mL/kg; at 4 weeks at age, ECF volume was 348 mL ± 45 mL/kg and plasma volume was 61.9 ± 5.9 mL/kg.[191] In another study, in a 1-week-old term foal, ECF volume was 44 ± 1.3% of body weight and plasma volume was 6.5 ± 1% of body weight. The ECF volume at 3 weeks of age had decreased to 28 ± 2% of body weight.[192]

Although the neonate has a higher percentage of total body water than the adult, it is more vulnerable to water loss than the adult for several reasons, including increased basal metabolic rate; relatively greater surface area, predisposing to increased heat and water losses; and reduced urine concentrating ability.

Table 19-2 Physical Examination: Normal and Abnormal Parameters

Parameter	Normal Finding	Abnormal Observation
Attitude	Bright, alert	Depression: sepsis, hypoxia, pain, metabolic disturbances (acidosis, hypoglycemia) Seizures: hypoxic brain damage or meningitis
Body tone	Erect head and neck posture	Hypotonia: sepsis, immaturity, hypoxia Extensor rigidity: hypoxia, meningitis
Suckle reflex	Present <20 min after birth	Absent or weak with sepsis, immaturity or hypoxia
Body temperature	37.2° C-38.6° C (99° F-102° F)	Fever with well-established infection, hypothermia with acute sepsis Temperature instability with prematurity
Mucous membranes	Pink, moist	Pale membranes: anemia from excessive umbilical cord hemorrhage, blood loss into body cavities associated with birth trauma, hemolysis due to NI or DIC Icteric: liver disease, EHV-1 infection, sepsis, NI Cyanotic: shock, hypoxia Hyperemic: sepsis
Capillary refill time	<2 seconds	2 seconds with dehydration, shock
Petechiation	Absent	Present with DIC, sepsis
Pulse	70–100 bpm, regular	Tachycardia: fever, pain, shock, sepsis, hypocalcemia Bradycardia: severe septic shock, hypothermia, hypoglycemia, hyperkalemia
Pulse quality	Strong peripheral pulses	Hypotension: hypovolemic and septic shock; hyperkinetic pulses during early sepsis
Respiration	30–40 breaths/min, regular	Tachypnea: stress, pain, fever, lung disease, acidosis; slow, irregular rate with apnea caused by hypoxia, prematurity
Nostril flare, rib retractions	Absent	Increased with impending respiratory failure, pneumonia
Lung sounds	Easily heard all over chest	Rales, rhonchi, ventral dullness with pneumonia, consolidation, atelectasis
Eyes, eyelids	Clear cornea, no entropion	Blepharospasm, miosis, lacrimation, corneal edema and ulceration with self-trauma during recumbency and entropion
Abdominal distention; borborygmi	Distention absent; borborygmi heard on both sides of abdomen	Distention with ileus, hypoxic gut damage, meconium impaction, uroperitoneum, enteritis; borborygmi decreased with ileus and increased with enteritis
Fecal volume, consistency; color	4–6 oz two to four times per day; pasty; yellow or tan color	Constipation with meconium impaction, dehydration Diarrhea: sepsis, hypoxic gut damage, diet changes

Urine volume, concentration	4–6 mL/kg/hr; dilute, with specific gravity usually <1.020	Decreased volume with renal failure, hypoxic kidney damage, dehydration, ruptured bladder
Umbilicus	Dry, small	Moist and inflamed because of infection, urachal patency
Joints	No distention or lameness	Warm, distended joints, lameness with septic synovitis
Limbs	Straight with mild carpal valgus common	Tendon laxity with immaturity; carpal and fetlock contracture associated with fetal malpositioning, hypothyroidism, plant toxins

DIC, Disseminated intravascular coagulation; *NI,* neonatal isoerythrolysis; *EHV,* equine herpesvirus.

19.9.2

BASIC FLUID THERAPY IN THE FOAL

The goal of fluid therapy is to expand vascular volume in an attempt to restore and maintain cardiovascular function, improve organ perfusion pressure, and correct dehydration, acid-base balance, osmolality, and electrolyte disturbances. Fluid therapy is a crucial part of the supportive care of the abnormal neonate. In assessment of the need for fluid therapy, both the state of hydration (sunken eyeballs, decreased skin turgor, dry mucous membranes, generalized weakness, decreased urine output) and the state of circulating volume (heart rate, pulse quality, capillary refill time, temperature of limbs, BP) should be assessed. If the losses are very acute, gross abnormalities in effective circulating volume may not yet be reflected in decreased skin turgor or sunken eyeballs, but heart rate or pulse quality may be abnormal. On the other hand, pulse quality and perfusion may be relatively normal in a neonate with severely sunken eyes and reduced skin turgor. Neonates that appear very thin and malnourished may actually be very dehydrated; with fluid therapy alone, their appearance can dramatically change in a short period. In sick foals fluid therapy should replace existing deficits while supplying maintenance requirements. A foal with moderately to severely sunken eyes is estimated to be 8% to 10% (of body weight) dehydrated. The estimated fluid deficit in a 40-kg animal that is 10% dehydrated would be approximately 4 L.

Laboratory parameters are useful for formulating a fluid therapy plan. Serum electrolyte concentrations may be life-threateningly deranged in foals with a condition such as uroperitoneum or enteritis, and knowledge of specific values can be of great benefit in selection of an appropriate fluid. The affordability of portable blood chemistry analyzers (e.g., IRMA Blood Analysis System, Diametrics Medical, St. Paul, Minn.) makes determination of electrolyte values feasible even in field situations. Poor nursing in a neonate can be detected by measurement of urine specific gravity. The normal nursing foal produces large quantities of dilute urine (specific gravity 1.000 to 1.012). In some cases, laboratory values can be misleading. For example, PCV or total plasma protein is often within the normal range in clinically dehydrated neonates.

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The fluid therapy plan is calculated to supply maintenance needs and to replace deficits and current losses. Calculation of fluid deficits is based on the following equation:

$$\textbf{Replacement fluid deficits}\,(L) = \%\ \textbf{Dehydration} \times \textbf{Body weight}\,(\text{kg})$$

Table 19-3 lists fluid replacement volumes for foals based on clinical assessment of dehydration.

Foals experiencing septic or hypovolemic shock may require fluid administration rates of 40 to 80 mL/kg/hr initially until their BP is stable. Normal BP ranges are as follows:

Systolic BP = 80 to 120 mm Hg

Diastolic BP = 65 to 90 mm Hg

Mean BP = 70 to 100 mm Hg

BP can be easily measured indirectly using the coccygeal artery and the noninvasive Doppler or oscillometric method.[193]

The maintenance fluid requirement for a newborn foal is approximately 4 to 6 mL/kg/hr (200 to 300 mL/hr for a 50-kg foal). Maintenance fluid administration in large animal neonates at the rate of approximately 100 mL/kg/day has usually resulted in adequate fluid balance and good urine output, in the absence of fluid deficits or increased fluid losses. If severe diarrhea is present, the daily fluid requirements can reach 15 to 20 L (500 mL/kg/day) or more.

If an animal is mildly to moderately dehydrated and the GI tract is not seriously compromised, fluid requirements can be provided by the enteral route, using milk or commercially available dextrose and electrolyte mixtures. However, if the gut is abnormal or if moderate-to-severe dehydration is present, the intravenous route is the preferred method of fluid administration.

Many types of intravenous catheters are suitable for use in the large animal neonate. Teflon catheters tend to be more thrombogenic than Silastic or polyurethane catheters and therefore should be replaced at more frequent intervals. A 5-inch long, 16-gauge Teflon catheter (Abbocath, Abbott Hospitals, North Chicago, Ill.) placed in the jugular vein and a 2-inch, 16-gauge Teflon catheter (Quik-Cath, Baxter Healthcare Corporation, Deerfield, Ill.) placed in the cephalic vein have both worked well to deliver intravenous fluids to foals. Short catheters placed in peripheral veins can be difficult to maintain and are not suitable for large-volume, rapid fluid replacement. I prefer to use a long-term, 16-gauge, 8-inch, polyurethane catheter (Arrow Catheter, Arrow International, Reading, Penn.) inserted in the jugular vein. This catheter is inserted over a flexible J-wire and can be left in place for 2 to 3 weeks. The use of polyurethane catheters reduces the incidence of thrombophlebitis and eliminates the need for frequent catheter replacement. Smaller-diameter catheters may be more suitable for lambs and kids. Regardless of the type used, it is essential to use aseptic techniques for catheter placement and to secure the catheter firmly to the skin. A combination of superglue and sutures has been very effective in keeping the catheters in place. Catheter sites are kept as clean as possible, and the site of venipuncture and the vein are watched closely for signs of infection. Specific information on catheter placement and maintenance can be found in other texts.[194,195]

Table 19-3 Calculation of Fluid Deficits

Severity of Dehydration	% Dehydration	Fluid Deficits for 50-kg Foal
Mild	5–6	2.5–3 L
Moderate	7–8	3.5–4 L
Severe	10	5 L

The intraosseous infusion technique is an alternative method for rapid delivery of fluids in the critically ill neonate when IV access is not possible. This procedure uses the intramedullary vessels in the bone marrow to gain access to the central circulation. A description of this technique is described in other texts.[196] The optimum type of intravenous fluid administered depends on the electrolyte and acid-base status of the patient. Fluids are available as either crystalloids (e.g., polyionic fluids such as Plasmalyte, Normosol, lactated Ringer's, saline) or colloids (e.g., plasma, hetastarch). Polyionic fluids are usually used for rapid rehydration and maintenance fluid therapy. These fluids should be isotonic (osmolality 270 to 300 mOsm/L). In most circumstances, in the absence of appropriate laboratory services the use of a balanced electrolyte solution such as lactated Ringer's or Plasmalyte is satisfactory to replace fluid deficits. Saline solutions may be a more appropriate choice in certain situations: foals with diarrhea are often hyponatremic and hypochloremic; premature foals with immature renal and endocrine function conserve electrolytes poorly and have a tendency to become hyponatremic and hypochloremic; foals receiving diuretics often require additional sodium chloride. Other exceptions to this rule include animals with hyperkalemia, in which potassium-containing fluids are best avoided, and animals with hypernatremia, in which controlled slow reduction of body sodium content is required.

Fresh or frozen plasma is often more effective than crystalloid fluids for volume expansion in seriously ill neonates. Endotoxemia and sepsis produce inflammatory changes in vessel walls. Capillary endothelial permeability is increased, resulting in increased extravasation of fluid and albumin from the capillaries into the interstitium. Rapid infusion of large volumes of crystalloids reduces colloidal oncotic pressure while transiently increasing intravascular hydrostatic pressure. These forces favor movement of fluid out of vessels. Colloidal solutions contain large—molecular—weight molecules that do not freely pass though the capillary membrane. Therefore colloid administration results in increased plasma oncotic pressure, increased plasma volume, and more effective improvement in circulating blood volume. There are synthetic colloids (e.g., dextran, hetastarch) and natural colloids (e.g., plasma, whole blood). Plasma has several advantages over synthetic colloids. It is a good source of protein, opsonins, complement, clotting factors, and immunoglobulins. The disadvantages of plasma include the possibility of an anaphylactic reaction and the need to thaw frozen plasma, which makes it less suitable when rapid fluid resuscitation is necessary. An effective, commercially available synthetic colloid is hetastarch (Hespan, DuPont Pharma, Wilmington, Del.). Hetastarch has been used successfully for rapid fluid resuscitation in equine patients and has caused few adverse reactions.[197]

If a neonate remains hypotensive in spite of volume expansion and fluid replacement, pressor agents such as dopamine and dobutamine may be indicated. Dopamine, with its combined α- and β-adrenergic and dopaminergic activity, is preferred. Higher doses will be required for patients in severe septic shock. If the foal fails to respond to high doses (>10 to 15 μg/kg/min), then norepinephrine, a more potent α-adrenergic agent, can be tried. Safe and effective infusion of these agents requires continuous monitoring and some type of infusion pump. Recently, nitric oxide (NO) has been shown to play a role in sepsis-induced hypotension.[198] IV administered new methylene blue, an NO antagonist, has been used to try to reverse severe life-threatening hypotension.

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The rate of fluid administration is determined by the degree of dehydration, severity of cardiovascular compromise, and maintenance requirements. Most normal foals can tolerate rapid fluid infusion, but asphyxiated, septic, or premature foals may be oliguric and therefore far less tolerant of overzealous fluid administration. In these cases generalized edema may result. A general rule of thumb is to replace one half the calculated deficit in the first 6 hours of fluid therapy and the rest over 12 to 24 hours. A flow rate of 20 mL/kg/hr or higher (40 to 80 mL/kg/hr) may be needed to treat hypovolemic or septic shock.

In any depressed, weak, or seizuring animal, blood glucose levels should be checked, because hypoglycemia is one of the most frequently observed metabolic derangements accompanying many neonatal diseases. The rapid blood glucose reagent strips and hand-held Glucometers are very useful in making this determination in a field setting. For treatment of hypoglycemia a continuous infusion of 5% to 10% dextrose is sufficient to reach and maintain adequate blood glucose levels in most neonates. Hypertonic glucose boluses (25% to 50%) may aggravate preexisting CNS insults and frequently result in rebound hypoglycemia 30 to 40 minutes after infusion. Therefore they should be avoided. One regimen for treating hypoglycemia is 10% dextrose infusion administered at 5 to 10 mL/kg fairly rapidly, followed by a continuous infusion to supply 4 to 8 mg/kg/min (approximately 5 mL/min of 5% dextrose for a 40-kg neonate). The appropriateness of the therapy should be judged by frequent blood and urine glucose determinations. If hyperglycemia results, the rate of infusion or concentration of solution is decreased (to deliver perhaps 2 mg/kg/min) but not stopped.

Another metabolic derangement commonly observed in the large animal neonate is metabolic acidosis. This disorder may be caused by accumulation of acid, by loss of buffers from the body, or by a combination of the two. Whenever possible, treatment should be directed at correcting the underlying cause of the acidosis. Acidosis caused by low cardiac output or decreased peripheral oxygen delivery should be treated by measures to increase tissue perfusion (e.g., plasma volume expansion, cardiac inotropes, nasal oxygen insufflation). In this type of acidosis there is no actual loss of bicarbonate from the body, and bicarbonate therapy often produces disappointing results and adverse reactions. If respiratory dysfunction is present, considerable caution should be exercised in the use of sodium bicarbonate. Bicarbonate functions as a buffer only in an “open” system in which carbon dioxide can be transported to the lungs and eliminated.[199] Profound fluctuations in BP and cerebral blood flow, intracranial hemorrhage, and decreased oxygen delivery to tissues are possible adverse effects of sodium bicarbonate infusion in human beings.[200] In many mildly to moderately acidotic neonates, simple volume expansion with isotonic fluids alone is very effective in correcting the base deficit by improving perfusion. Other more compromised individuals need more aggressive support of the cardiovascular system. Mild acidosis (HCO_3 deficit 5 to 10 mEq/L) associated with dehydration, can be corrected by simple rehydration. Bicarbonate supplementation is recommended when HCO_3 deficits are >10 mEq/L (serum HCO_3 <15 mEq/L) or whenever the pH is <7.2. Bicarbonate deficits can be calculated using the following equation:

$$\text{Bicarbonate deficit (mEq)} = 0.6 \times \text{Body weight (kg)} \times \text{Base deficit (mEq)}$$

An isotonic bicarbonate solution is preferred because excessive bicarbonate administration results in increased CO_2 production, leading to respiratory embarrassment and increased risk of CNS acidosis and hemorrhage. Isotonic bicarbonate can be made by adding 150 mL of 8.4% bicarbonate solution to 850 mL of sterile water, or 200 mL of 5% bicarbonate solution to 800 mL of sterile water. Bicarbonate solutions should be given slowly. Hyperkalemia is often observed with metabolic acidosis because of the transcellular shift of potassium ions into the ECF in exchange for hydrogen ions.[201] As the metabolic acidosis is corrected, the hyperkalemia resolves. Bicarbonate solution should not be combined with any calcium containing solution or precipitation will occur.

The effect of the bicarbonate replacement therapy should be monitored closely, and the dose adjusted accordingly. Neonates with severe diarrhea because of ongoing losses of bicarbonate through the feces may need considerably more than the calculated deficit to maintain an adequate blood pH until the diarrhea subsides. As in any type of fluid therapy, a plan is devised, the animal's response to the plan is monitored, and changes are made accordingly.

Hypokalemia can occur in anorexic foals, foals with diarrhea, and those receiving diuretic therapy. Potassium (K) supplementation can be estimated using the following equation:

$$\text{Replacement K (mEq)} = 0.4 \times \text{Body weight (kg)} \times \text{K deficit (mEq)}$$

Potassium can safely be added to fluids at a rate of 20 to 30 mEq/L. The rate of potassium administration should not exceed 1 mEq/kg/hr. If acidosis is present, hydrogen ions are exchanged for intracellular potassium ions, resulting in a relative increase in serum K. As the acidosis is corrected there will be an influx of K ions back into cells, resulting in potential hypokalemia, which must be anticipated during fluid therapy.

19.9.3 NUTRITIONAL SUPPORT OF THE ABNORMAL NEONATAL FOAL

Provision of adequate nutritional support to the compromised neonate is an essential part of critical care but often becomes a major management problem. Reasons for the common failure to provide adequate nutrition to the neonate include underestimating the needs of the ill, stressed animal; a disinterest in nursing on the part of the sick neonate; the need to use alternate methods and routes of delivery for continued oral feeding; and a GI tract that is compromised and intolerant of nutrient intake.

Nutrition of the premature or sick neonate is a science that is in its early stages of development even in human neonatology; much less is known in veterinary medicine. The exact nutritional requirements for optimum growth of the normal-term foal have not even been defined, let alone for the premature, growth-retarded, or debilitated animal whose caloric, protein, mineral, and vitamin requirements might be very different.

Measurements of milk production of mares combined with data concerning the free-choice milk intake of normal orphan foals and premature and sick foals recovering from various illness suggest that a figure of 125 to 150 kcal/kg/day or even higher is close to the normal caloric intake.[202] Healthy full-term foals nurse an average of 2 minutes, seven times an hour,[203] consume between 20% and 30% of their body weight in mare's milk daily, and gain 0.5 to 1.4 kg/day. On this diet a 50-kg foal would consume 10 to 12.5 L of milk a day to receive 120 to 150 kcal/ kg/day. Nutritional requirements may be even higher in disease states such as generalized septicemia, pulmonary disease, or thermal stress or after surgery.

If there is no medical contraindication for oral feeding, and if the GI tract is functional, then enteral nutrition is the preferred and most effective route of nutritional supplementation. Enteral feeding is more physiologic and stimulates normal gut maturation, growth of intestinal villi, production of crypt cells, and hepatic and biliary secretions and brush border disaccharidase enzyme activity. Enterocytes rely on absorption of volatile fatty acids (VFAs) such as glutamine and β-hydroxybutyrate from the gut lumen as their primary energy source. Therefore, even in foals that must be fed parenterally, small volumes of enteral feeds are given to “feed the gut” to prevent gut atrophy.

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Foals that are not nursing from the mare can be fed by bottle, bucket, or nasogastric tube. If an effective swallow reflex is present, then bottle-feeding can be used. Udder-bumping and teat-seeking behavior can be stimulated by allowing the foal to approach the bottle from behind and under the handler's armpit. This technique also reduces the risk of aspiration by preventing overextension of the head and neck. Bucket-feeding allows the foal to drink with its head and neck in a flexed position and is helpful for foals with a weak swallow reflex or foals destined to be hand-raised. Milk should be introduced in a shallow handheld bowl and the foal encouraged to suckle the finger or nipple as its head is lowered into the milk. “On demand” feeding is ideal but often impractical and labor intensive. Foals less than 7 days of age should be fed every 2 hours.

Nasogastric intubation is required if ineffectual swallowing and suckling are present. A small-bore flexible silicone tube (5 to 7 mm internal diameter) with a weighted tungsten end is preferred. Individual choice dictates whether the tube is passed for each feeding or left indwelling. Indwelling tubes can be sutured to the nares or

taped to half a tongue depressor, which is then taped to the foal's muzzle and/or fleece halter. Tubes should be sealed between feedings to prevent aerophagia. Recumbent foals should be maintained in sternal recumbency immediately after tube-feeding to reduce the risk of gastroesophageal reflux and aspiration.

If the foal's mother is available and milk production is adequate, free-choice nursing is optimal. A nurse mare is probably the next best substitute. Popular enteral formulas include mare's milk, goat's milk, and artificial milk replacers. Mare's milk is preferred. Goat's milk is acceptable and is higher in fat, total solids, and gross energy than mare's milk Foals raised on goat's milk occasionally become constipated. Cow's milk is not as digestible but can be used if additional sugar is added and some of the fat is removed. This can be accomplished by using 2% skim milk and adding 20 g of dextrose per liter of milk. Various artificial milk replacers are available. The ideal replacer should have 22% crude protein, 15% fat, and less than 0.5% fiber on a dry matter basis. Complications associated with enteral feeding include colic, abdominal distention, diarrhea, constipation, flatulence, misplacement of the nasogastric tube, aerophagia, nasal and pharyngeal irritation from the tube, and aspiration pneumonia.

Delayed gastric emptying and gastroduodenal dysmotility can be improved in some foals with metoclopramide given IV as a slow infusion (0.25 mg/kg/hr) or orally (0.3 to 0.6 mg/kg q4-6h). Overdosage is associated with excitement. Other prokinetic agents are erythromycin (1 mg/kg PO four times per day [qid] or given as a 30-minute infusion qid), which works throughout the GI tract, and cisapride (0.1 to 0.2 mg/kg PO or per rectum q6h), which also affects the entire gut. All prokinetic agents are contraindicated if GI obstruction is suspected. Diarrhea is treated symptomatically with oral bismuth subsalicylate (1 to 2 mL/kg PO q4-6h) and/or loperamide (0.1 to 0.2 mg/kg PO q6h). Diarrhea may also respond to administration of active culture yogurt or an intestinal inoculant containing lactobacillus organisms. Nasopharyngeal irritation from repetitive tubing can be treated with insufflation of a nasopharyngeal spray containing prednisone, Furacin, glycerin, and DMSO.

More details on the feeding of both orphan and sick neonatal foals are contained in review papers[202,204–207] and in Chapter 50.

19.9.4 PARENTERAL NUTRITION

During the past years, PN has been more frequently used to supply at least a portion of the daily nutritional requirements to critically ill foals and calves. PN is indicated whenever feeding via the gut is inadequate or contraindicated. Candidates for partial or total PN include individuals with chronic diarrhea, those with GDUD (foal), a variety of postsurgical patients, foals with botulism, premature and infected animals, and other individuals with GI tracts poorly tolerant of enteral feedings.

PN involves administration of hypertonic solutions containing dextrose, amino acids, lipids, vitamins, electrolytes, and trace minerals. These PN solutions must be administered continuously through a jugular catheter. Complications include metabolic disturbances such as hyperglycemia, hypoglycemia, glucosuria, osmotic diuresis, hyperlipemia, azotemia, and imbalances of trace minerals, vitamins, and electrolytes. Catheter-related problems include thrombosis, phlebitis, and sepsis. Commonly used stock solution for PN include 50% dextrose, 8.5% or 10% amino acids, and 10% or 20% lipid emulsion. Sample calculations are as follows:

Initial Formulation for a 50-kg Foal	
Glucose	10 g/kg/day = 450 g = 900 mL of 50% dextrose
Amino acid	2 g/kg/day = 90 g = 900 mL of 10% amino acid
Lipid	1 g/kg/day = 45 g = 450 mL of 10% lipid
Calories Provided	
Glucose	3.4 kcal/g; 450 g = 530 kcal
Amino acid	4 kcal/g; 90 g = 360 kcal
Lipid	9 kcal/g; 45 g = 495 kcal
Total calories	2385; 53 kcal/kg/day

Source of Calories
Glucose = 64%
Amino acid = 15%
Lipid = 21% (foals should not receive more that 50% of nonprotein calories from lipids)

Nonprotein Calories/Gram of Nitrogen
NP calories = 2025
6.35 g protein = 1 g nitrogen
90 g amino acid = 14.4 g nitrogen
Nonprotein calories/ g of nitrogen = 2025/14.4 = 140.6 (to prevent catabolism of protein for energy, the ratio should be between 100 and 200)

Supplements
Multivitamin concentrate (pediatric formula), trace mineral (MTE-5), KCL 20 to 40 mEq/L

Foals receiving PN should have their blood and urine glucose monitored. Serum glucose concentration should remain >80 mg/dL and <180 mg/dL. Serum should be checked for gross lipemia. Heparin can be administered at 10 units/kg as an intravenous bolus to treat lipemia. The amount of glucose, lipid, and amino acids can be varied for each individual foal. Foals must be weaned onto and off of PN slowly. All intravenous lines must be checked

routinely for signs of infection. Additional information regarding the use of PN in foals is presented in other articles.[207]

At the present time, the applications of PN are on a fairly short-term basis compared with human medicine—usually 2 to 3 weeks at the most. Most commonly, parenteral and enteral nutrition has been used in combination; parenteral nutrient delivery is used to supplement, not totally replace, oral intake. Enteral nutrition helps to maintain the intestinal mucosa. Prolonged total PN is associated with reduced intestinal epithelial cell renewal, villous atrophy, and decreased enzymatic activity.[208]

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Although PN can be expensive and difficult to manage, the benefits, such as prevention of a catabolic state or starvation, improved body condition at discharge, and better healing, can far outweigh the drawbacks. Details concerning the use of PN compounds can be found in other references[209] and in Chapter 50.

19.10 NOSOCOMIAL AND ZOONOTIC INFECTIONS

Immunologically naive neonates are particularly susceptible to opportunistic and contagious pathogens. Nosocomial infections increase mortality and amplify environmental contamination, perpetuating further dissemination of the infecting organism. Prevention of nosocomial infection requires attention to detail. Patients may be exposed to pathogens via environmental contamination, biologic vectors, equipment, and personnel. Provision of a pathogen-free environment requires disinfection between patients and verification of disinfection via culture. Control of vermin is important, as birds, rodents, and insects have all been implicated in dissemination of infectious pathogens. Equipment (shovels, brushes, nasogastric tubes, etc.) function as vectors if not disinfected between stalls and/or animals. And, most important, personnel have to appreciate their potential role in nosocomial infections. Personnel schedules need to take into consideration the workload demands and the implications such demands may have on infectious disease control over all 24 hours of each day. Separate personnel for management of infected and high-risk patients is desirable. Attention to detail, basic hygiene, and common sense prevail. Washable footwear, disinfectant footbaths, patient-specific protective clothing, and hand washing between patients are infectious disease control protocols that have been successfully applied in controlling infectious disease outbreaks in veterinary hospitals. Many of the pathogens that affect neonates are potentially zoonotic (*salmonella, cryptosporidium, giardia,* and *clostridium*); personal hygiene is in the interest of the health care provider and the patients.

19.10.1 IMMUNE SYSTEM SUPPORT: PLASMA AND COLOSTRUM

Controversy persists as to what serum IgG concentration is protective for newborn foals. There is little argument, however, that healthy foals have postsuckle IgG exceeding 1000 to 2000 mg/dL within 24 hours of birth. There is also agreement that there is a correlation between very low IgG concentrations (IgG <200 mg/dL) and increased foal morbidity and mortality. By definition, IgG <200 mg/dL is complete FPT, and IgG between 200 and 800 mg/dL is partial FPT. Causes of FPT include poor-quality colostrum, failure to ingest adequate colostrum, and inability to absorb adequate amounts of colostral immunoglobulins. Mares produce an average of 1.5 to 2 L of colostrum. Ideally, foals should receive a minimum of 1 L of good-quality colostrum within the first 8 hours of life. In addition to IgG, colostrum contains IgA for local gut immunity, IgM, high caloric density, growth factors, lactoferrin, laxative properties, and leukocytes. If fresh or frozen colostrum is not available, some sources of lyophilized IgG products for oral administration have a longer shelf life and do not require freezing. These products are expensive and may have variable absorption. Regardless of the product, a rule of thumb is to administer a minimum of 40 g of IgG (or 1 g/kg of body weight) to colostrum-deprived foals. Always measure serum IgG concentrations to determine if the supplementation was adequate.

Plasma administration becomes necessary if the foal's IgG is low and the foal is too old to absorb colostrum or gut function is abnormal. I recommend IgG supplementation for any foal with a serum IgG <200 mg/dL regardless of its health status or environment. If the foal's IgG is between 200 and 800 mg/dL, I recommend IgG supplementation if one or more of the following conditions exist:

Gestation length <320 days, or signs of prematurity or dysmaturity

Difficult delivery (e.g., dystocia, premature placental separation, meconium staining)

Grossly abnormal or heavy placenta (>11% of foal's body weight)

5- and 10-minute Apgar scores <6

High environmental stresses including overcrowding and poor farm hygiene

Anticipated transportation off the farm within 7 to 10 days of foaling

Failure to stand and nurse within 3 hours of delivery

Abnormal physical examination within 24 hours of birth; significant abnormalities include generalized weakness, injected mucous membranes, poor suckle, severe angular limb deformities, enlarged umbilicus, patent urachus, colic, meconium retention, increased respiratory effort, other signs of localized infection

Poor postpartum surveillance

Plasma is administered through an aseptically placed catheter using a blood administration set with an in-line filter. The volume of plasma to give depends on the foal's IgG, the desired IgG, the foal's body weight, and the IgG in the plasma and the general health of the foal. The old rule of thumb for plasma administration for FPT is 20 mL/kg or approximately 1 L for a 45-kg foal. In healthy foals, 1 L of plasma with IgG of 1200 mg/dL raises the serum IgG 200 to 250 mg/dL. The same amount of plasma has less effect in foals with sepsis. Ill foals require relatively more plasma because the serum half-life of IgG is less, IgG may be sequestered in intravascular spaces or at sites of inflammation, and IgG may be catabolized more readily. A complete discussion of FPT and its treatment is presented in Chapter 53.

Plasma should be administered at an average rate of 10 mL/kg/hr. Give the first 100 mL slowly, and monitor the foal's pulse, respiratory rate, and temperature. Possible transfusion reactions and treatment for such reactions are listed in Table 19-4.

19.10.2 RESPIRATORY SUPPORT

Thoracic radiographs and ABG analysis help determine the severity of lung disease. Lateral radiographs with the foal standing or recumbent help characterize the nature and extent of pulmonary pathology. Diffuse pulmonary

infiltrates occur with bacterial and/or viral pneumonia and atelectasis. Cranioventral and caudoventral pulmonary infiltrates are seen with aspiration pneumonia and bacterial bronchopneumonia. Nodular infiltrates suggest discrete abscessation.

ABG analysis determines the degree of pulmonary dysfunction. Portable blood gas machines now make blood gas analysis easy and affordable. The preferred site for arterial puncture is the great metatarsal artery. A small 25-gauge needle attached to a heparinized 1- or 3-mL Luer slip syringe is used. Hypoxemia (Pa_{O_2} <60 mmHg) with a normal Pa_{CO_2} is caused by ventilation-perfusion mismatching, right-to-left shunting, low inspired O_2, and impaired gas exchange. Hypoxemia accompanied by elevated concentrations of CO_2 is usually the result of hypoventilation caused by respiratory muscle fatigue, central depression of the respiratory center, or neuromuscular weakness as with botulism. Mild hypoxemia can be improved by positioning the laterally recumbent foal into a sternal position. Oxygen supplementation is best administered through a soft nasal cannula inserted into the nasal passage to the level of the medial canthus. The cannula can be sutured or taped to the external nares. Humidified oxygen is administered using a tank or wall oxygen source and a humidifier filled with distilled water. Oxygen flows between 2 and 10 L/min are regulated using a flowmeter. Flow rates are adjusted to keep the Pa_{O_2} between 70 and 100 mm Hg. Long oxygen lines attached to a surcingle allow even ambulatory foals to benefit from continuous oxygen therapy.

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Table 19-4 Transfusion Reactions: Signs, Causes, Therapy

Signs of Reaction	Cause	Treatment
Hemolysis, hemoglobinuria, hemoglobinemia	Incompatibility between donor RBCs and recipient's plasma	Stop transfusion; give IV fluids; cross-match for suitable donor
Fever, chills	Allergic or nonspecific reaction to donor protein	Give antipyretics
Allergic reaction, urticaria	Recipient reacts to soluble antigens in donor's plasma	Slow transfusion, give antihistamine
Anaphylactic reaction, respiratory distress, hypotension, shock	Anaphylaxis	Stop transfusion, give epinephrine (5–10 mL of 1:10,000 epinephrine via IV or SC route)
Circulatory overload, hypertension, pulmonary edema, cardiac dysfunction	Excessive volume expansion	Stop or slow transfusion; give diuretic
Endotoxemia, fever, tachycardia, tachypnea, leukopenia	Contaminated transfusion	Stop transfusion, give Banamine, and antibiotics

IV, Intravenous; *RBCs,* red blood cells; *SC,* subcutaneous.

Mechanical ventilation is necessary for persistent hypoxemia that is refractory to nasal insufflation or is accompanied by Pa_{CO_2} >70 to 75 mm Hg. A long, cuffed nasotracheal tube is required, as is a ventilator capable of delivering tidal volumes of 10 to 15 mL/kg, respiratory rate of 15 to 25 breaths per minute, proximal airway pressure between 18 and 25 cm H_2O, end expiratory pressure (PEEP) of 0 to 10 cm H_20, and an inspired oxygen concentration between 0.21 and 1.0. Ventilators that allow the foal to breathe spontaneously between preset ventilator-delivered breaths are tolerated the best by the foal. Guidelines regarding ventilatory support for foals

are presented in other review articles.[70] More recently there have been investigations using noninvasive mechanical ventilation in neonatal foals.[72]

Foals have a poorly developed cough reflex. Tracheobronchial secretion removal may be enhanced using chest coupage and nebulization with mucolytic agents such as acetylcysteine or dilute bicarbonate solution. Ultrasonic nebulizers using solutions or an Equine Aero Mask using metered dose aerosol inhalers can be used.

Chemical respiratory stimulants can be used to stimulate the central respiratory center. Theophylline, caffeine, and aminophylline are xanthine derivatives commonly used as bronchodilators but can also be used to improve diaphragmatic contractility and to treat periodic apnea associated with hypoxia and prematurity. The safest stimulant is caffeine: loading dose of 10 mg/kg PO once per day (sid) followed by 2.5 mg/kg PO sid as a maintenance dose.

19.10.3 ANTIBIOTIC THERAPY

Foals that become ill or compromised during the first few days of life are at increased risk for infection. Because of the neonate's immature immune system, localized infections tend to become systemic, leading to septicemia. This explains how foals with diarrhea can develop uveitis and septic joints. Antibiotics are administered to foals for two reasons: prophylactically to prevent infection, and therapeutically to treat existing infection. The most serious infections are those caused by gram-negative bacteria (e.g., *E. coli, Klebsiella, Salmonella, Pasteurella, Actinobacillus)*. The most common gram-positive pathogen is *Streptococcus* species, which are often encountered as part of a mixed infection involving the respiratory tract and umbilicus. Occasionally, anaerobic infections (e.g., *Clostridium, Bacteroides)* are encountered as causes of umbilical infections, diarrhea, or aspiration pneumonia.

When antibiotics are used prophylactically, the oral and intramuscular routes of administration can be considered. Penicillin or ampicillin and an aminoglycoside administered IM or IV are good choices if the risk of infection is great. Ceftiofur (IM) or trimethoprim-sulfamethoxazole (PO) are reasonable choices. Prophylactic antibiotics should be given for 3 to 5 days or until the risk factors for sepsis are gone. Once sepsis is confirmed, intravenous administration is the preferred route because gut absorption is too variable. Antibiotic therapy should be continued for a minimum of 7 to 10 days. If localized infections develop, then antibiotics may need to be given for 2 to 3 weeks. In cases of abscess formation and bone infections, therapy is often extended for 1 to 2 months.

19.10.4 TRANSPORT AND REFERRAL

A decision should be made early in the clinical course as to whether the neonate can be taken care of at the farm or whether it should be referred to a neonatal intensive care facility for treatment. If the support staff on a farm are experienced and committed to provision of good nursing care and if appropriate diagnostic facilities are available, many mildly to moderately ill individuals can be successfully treated on the farm and recover within 2 to 4 days. When the neonate is more compromised and in need of considerable supportive care, including 331
continuous intravenous fluid therapy and oxygen supplementation, a more rational decision is to refer, if the 332
animal's value warrants the expense. The sicker or more immature the neonate, the more complications it is likely to develop during the course of treatment. It is much better to refer a sick neonate early in the course of disease, rather than as a last resort before death.

If a decision is made to refer the animal, the method of transport is extremely important to the outcome of the case. If the foal is recumbent and is showing signs of hypothermia and/or respiratory distress, consider shipping

the foal ahead of the mare in a heated vehicle. The mare can be stripped of colostrum and then sedated. Colostrum can be sent with the foal. The mare can be sent later, once the foal's condition has been evaluated and stabilized at the referral clinic. Save and send the placenta with all compromised foals. Recumbent foals can be restrained in SUVs and cars by wrapping them in a sleeping bag or blanket. Ideally, an attendant should travel with any weak, recumbent, or potentially recumbent foal.

Cold foals can be warmed during transport by increasing the inside temperature of the vehicle and by placing water bottles or heat packs beside the foal. Body temperature, blood glucose, and oxygenation must be maintained during the trip. In the hypoglycemic patient, a continuous glucose infusion during the trip is far better than a glucose bolus given before departure.

If the foal is dyspneic, administer intranasal oxygen at 3 to 6 L/min using an indwelling intranasal cannula. Portable oxygen tanks can be rented from home care pharmacies with a veterinarian's prescription. A recumbent foal should be kept sternal and turned every 2 hours to minimize dependent lung atelectasis. If the foal is apneic or demonstrating an unusually slow respiratory rate, consider a loading dose of caffeine (10 mg/kg) given PO or per rectum before transport.

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20 Chapter 20 Manifestations and Management of Disease in Neonatal Ruminants

John K. House

Alison A. Gunn

20.1 WEAKNESS AND/OR DEPRESSED MENTATION

John K. House

If weakness has been present since birth, in utero acquired bacterial or viral infections, birth asphyxia and trauma, chronic placental problems, and congenital anomalies should be considered on the list of differential diagnoses. A number of congenital bacterial, fungal, and viral infections that cause abortions and stillbirths may result in the birth of a live, weak neonate. In cattle, brucellosis, salmonellosis, leptospirosis, listeriosis, *Escherichia coli*, *Corynebacterium* species, and *Aspergillus* species may cause placentitis and disease in the newborn. In sheep, in utero infection with chlamydia, *Campylobacter, Coxiella,* bluetongue virus, and border disease may cause disease in the newborn. Congenital viral infections of neonates are listed in Box 20-1. Clinical manifestations of fetal infections depend on the age of the fetus and the virulence and trophism of the infecting agent (see individual diseases).

Neonatal calves with storage diseases primarily affecting the nervous system may appear reasonably normal for a short period after birth and then show progressive signs of neurologic dysfunction, including tremors, spasms, depression, recumbency, and coma. Differential diagnoses for weakness and depressed mentation after a period of apparently normal strength and mentation include sepsis, electrolyte and acid-base disturbances, hypoglycemia, and hypothermia. A complete history is obtained, including a detailed description of the delivery process, and complete physical and neurologic examinations are performed. Any signs of trauma, infection, or congenital malformations should be noted. Evaluation of hematologic data and immunoglobulin G (IgG) status, combined with historical and physical examination parameters, results in an assessment of the likelihood of sepsis. Blood glucose, blood gas, and serum electrolyte concentrations should be determined promptly. Blood cultures and cerebrospinal fluid (CSF) analysis are useful for verifying central nervous system (CNS) involvement and targeting antimicrobial therapy.

For collection of fluid from the lumbosacral space, a 20-gauge, 1- to 2-inch needle with a clear hub may be used. A change in resistance is felt when the needle penetrates the dural membranes, and CSF appears in the plastic hub as soon as the subarachnoid space is entered. Approximately 5 to 10 mL of fluid may be removed safely. Urinary reagent strips can be used to rapidly obtain general information on the fluid. If blood is detected, the sample should be spun down after the cytologic examination. Red blood cells contaminating the sample will settle, and the supernatant should be colorless. If hemorrhage occurred before the procedure, the sample remains xanthochromic (yellow). Glucose should be present in “trace” or “+” amounts in the normal sample. Negative values in the adult suggest severe meningitis, but in the neonate may also be caused by profound hypoglycemia. CSF analysis is most useful in determining the presence of septic meningitis. Elevation of the total protein level (>150 mg/dL) and neutrophil count in addition to a positive Gram stain and bacterial culture results in a straightforward diagnosis of bacterial meningitis, and the prognosis is considered poor for the animal.[1] Infection in the CNS, however, can be difficult to detect until the process becomes generalized; the lack of positive cultures and Gram stain does not rule out CNS infection. An elevated albumin quotient suggests increased blood-brain permeability and can be seen in both hypoxic-ischemic brain injury and meningitis, but an elevated IgG index indicates increased intrathecal IgG production and is more compatible with a diagnosis of meningitis.

20.2 MENINGITIS

Depressed mentation is a common presenting sign in neonates with sepsis. Although bacterial meningitis may occur as a primary entity, it more commonly is a result of generalized septicemia in neonates with failure of passive transfer (FPT). Agents that cause meningitis are the same agents that cause septicemia, most commonly the gram-negative enteric bacteria such as *E. coli, Enterobacter* species, and *Salmonella* species. In a review of 32 cases of meningitis in calves by Green and Smith,[1] the clinical signs of CNS disturbance observed were lethargy, recumbency, anorexia, loss of suckle reflex, coma, opisthotonos, convulsions, tremor, and hyperesthesia. Leukocytosis and a left shift were evident in 11 of 15 calves (73%). Concurrent metabolic problems were common and included hyperkalemia, respiratory acidosis, hypernatremia, hyponatremia, hypomagnesemia, and hypoglycemia. Analysis of CSF revealed pleocytosis, xanthochromia, turbidity, and high total protein concentration. Cytologically, neutrophils predominated in the CSF in calves with acute disease. Mononuclear cells dominated in calves with chronic disease. Microscopically, bacteria were evident in 10 of 22 (45%) of the antemortem CSF samples, and bacteria were isolated from slightly more than half (11 of 19). All of the calves in this review died.[1] In my experience treating calves in a hospital environment, the mortality rate is high; however, aggressive early treatment can be successful. The economics and welfare implications of treating commercial calves in a field setting are questionable. Empiric antimicrobial therapy for meningitis in neonatal calves should include a gram-negative and positive spectrum. Antibiotics enter the CSF predominantly via passive diffusion down a concentration gradient. The major determinant of CSF penetration is lipid solubility. Lipophilic agents diffuse via transcellular pathways; peak concentrations in CSF occur relatively rapidly, and entry into CSF is affected minimally by the presence of inflammation. In contrast, hydrophilic agents enter the CSF through paracellular pathways; their transport depends on the opening of tight junctions, and peak concentrations are relatively delayed.[2] Only one report documents the pharmacokinetics of an antimicrobial agent in CSF in calves. Table 20-1 lists CSF-to-blood concentration ratios (penetration) derived from multiple species for a handful of antimicrobial drugs available for use in cattle.

20.2.1 Box 20-1 Differential Diagnoses for the Weak or Depressed Large-Animal Neonate

20.2.1.1 Bacterial Infection: in Utero or Postnatally Acquired

Septicemia

Joint and bone

Enteritis

Pneumonia

Meningitis

Peritonitis (primary or secondary)

20.2.1.2 Congenital Viral Infection

Bovine virus diarrhea virus (B)

Bluetongue virus (B, O)

Infectious bovine rhinotracheitis virus (B)

Akabane virus (B)

Parainfluenza (B)

Caprine herpes (C)

Border disease virus (O)

Equine herpesvirus (E)

Equine viral arteritis (E)

20.2.1.3 Prematurity/Postmaturity

Weak calf syndrome

Bacterial or fungal placentitis

Insufficient fetoplacental matching (twin foals)

20.2.1.4 Birth Asphyxia

Placentitis

Dystocia

Cesarean section

Premature placental separation

Induced parturition

20.2.1.5 Birth trauma

Brachial plexus injuries

Fractured rib, pneumothorax, hemothorax

Ruptured bladder

20.2.1.6 Congenital Malformations

Cardiac malformations

Central nervous system malformations (e.g., hydrocephalus, hydranencephaly)

Angular limb deformities

Arthrogryposis

20.2.1.7 Metabolic Derangements

Hypoglycemia

Hyponatremia

Hypokalemia or hyperkalemia

Hypocalcemia

Acidosis (respiratory or metabolic)

Uroperitoneum (with electrolyte abnormalities)

Renal failure

20.2.1.8 Severe Anemia

Blood loss

Neonatal isoerythrolysis

20.2.1.9 Brain Disease

Hemorrhage

Ischemia, edema, necrosis

Traumatic injury

Meningitis

Malformations

Narcolepsy-cataplexy syndrome (intermittent weakness)

20.2.1.10 Spinal Cord Disease

Spinal cord hemorrhage

Vertebral malformation (e.g., atlantooccipital)

Vertebral abscessation or osteomyelitis

Vertebral fracture or other trauma to spinal cord

20.2.1.11 Peripheral Nerve and Muscle Disease

White muscle disease

Tetanus

Congenital myopathy, polymyositis

Neuropathy of spinal roots or peripheral nerves

Botulism (foal)

Collagen disorder

Aminoglycoside-induced neuromuscular blockade

20.2.1.12 Liver Disease

Hepatitis

Severe hypoxic insult

Tyzzer's disease (foals >2 weeks old)

Toxin (iron fumarate given to foals)

20.2.1.13 Storage Disorders

Maple syrup urine disease

Citrullinemia

Shaker calf syndrome (neurofilament accumulation)

GM1 gangliosidosis

20.2.1.14 Ingestion of Drugs or Toxins

Transplacental transfer of anesthetics and sedatives

Inadvertent oversedation of neonate

20.2.1.15 Gastrointestinal Disease

Gastrointestinal ulceration

Necrotizing enterocolitis

B, Bovine; *C,* caprine; *O,* ovine.

Table 20-1 Cerebrospinal Fluid—to-Blood Concentration Ratios (Penetration) of Antibiotics Available for Treatment of Meningitis in Calves[2,3]

	Concentration CSF/Concentration Serum (%)	
Antimicrobial*	**Human**	**Animals**
Ampicillin	13–14	8–12
Florfenicol		46 (calves)
Gentamicin	0–30	21–25
Penicillin	5–10	5–6
Trimethoprim-sulfamethoxazole	<41	35–39

CSF, Cerebrospinal fluid.

*The list is not conclusive, reflecting the paucity of available data.

In a CSF pharmacokinetic study of florfenicol in calves the maximum concentration of florfenicol attained in CSF was 4.67 ± 1.51 μg/mL following a single intravenous dose of 20 mg/kg. The levels remained above the minimum inhibitory concentration (MIC) for *Haemophilus somnus* over a 20-hour period.[3] This concentration is below the MIC_{90} for *E. coli*. Bacteriocidal antibiotics are proposed to be more effective for treatment of meningitis in humans, and it is recommended that the concentration of antibiotic in the CSF should be maintained at 10 times the MIC of the target pathogen.[2] Ceftiofur may be used to treat meningitis in calves. In one calf, I measured the concentration of ceftiofur in CSF 28 hours after initiation of treatment with 10 mg/kg twice per day (bid). The concentration of ceftiofur in CSF at this time was 1.27 μg/mL, which happened to be five times the MIC of the *E. coli* isolated from the CSF of the calf. Unfortunately, owing to the lack of CSF pharmacokinetic data in cattle, antimicrobial treatment of meningitis is an inexact science.

20.3 METABOLIC ACIDOSIS

Profound weakness associated with metabolic acidosis is commonly observed in calves with diarrhea and sporadically in kids ("floppy kid syndrome") and calves without other clinical signs of disease.[4,5] Correction of the acidosis by intravenous administration of bicarbonate produces a rapid recovery. An improvement in mentation and strength should be observed within 12 hours; persistent depression is likely to reflect incomplete correction of acidosis, sepsis, hypoglycemia, hypernatremia, or hyponatremia.

20.4 HYPOGLYCEMIA

Hypoglycemia is a common sequela to withdrawal of milk for more than 48 hours, especially in cold weather. Affected calves are weak or recumbent but appear to be normally hydrated or minimally dehydrated.[6] They are often emaciated and can occasionally have neurologic signs including facial twitches, convulsions, opisthotonus, and coma. They will respond to infusion of 5% glucose, but often this response is temporary, especially in calves with severe malabsorptive disease. It is important to rapidly restore adequate energy intake to ensure resolution of these cases. Starvation and hypothermia resulting from mismothering are common causes of weakness in neonatal lambs. Similarly, weakness, poor body condition, and increased susceptibility to infectious diseases are observed with protein-calorie malnutrition induced by feeding poor-quality or incorrectly mixed milk replacers.[7]

20.5 HYPONATREMIA

Hyponatremia occurs when loss of isotonic fluid through the gastrointestinal tract is replaced by free water or hypotonic solutions. The latter often occurs when too much water is added when making up an oral electrolyte solution. Hyponatremia may also occur when isotonic oral electrolyte solutions are administered to calves with compromised sodium absorption capacity. This may be a result of severe pathologic changes or an inadequate level of agents that facilitate sodium cotransport within the oral electrolyte solution. Hyponatremia results in a fluid shift from the extracellular space to the intracellular compartment along the osmotic gradient, and the resultant swelling of the cells can result in neurologic disturbances, depression, disorientation, and even convulsions.[8] Hyponatremia should be considered in calves with serum sodium <132 mmol/L; calves with serum sodium <120 mmol/L have severe hyponatremia.

The goal of therapy is to restore serum sodium levels to >125 mmol/L over the first 6 hours and then to restore to normal levels over 24 hours.[8] In hypovolemic calves the initial treatment should be achieved using normal saline, and in normovolemic calves hypertonic saline should be used for the initial treatment, as the administration of large fluid volumes will exacerbate cerebral edema. If the calves are also suspected to be acidotic, this should be corrected with sodium bicarbonate solutions of appropriate tonicity.

The amount of sodium required in the first 6 hours to raise the sodium level to 125 mmol/L can be calculated as follows[8]:

$$\text{Sodium } \backslash(\text{mmol}) = (125 - \text{Measured serum sodium } \backslash[\text{mmol} / \text{L}]) \times \backslash(0.6 \times \text{Body weight } \backslash\ \backslash[\text{kg}])$$

Calves should then be maintained on a sodium-containing isotonic fluid, such as normal saline or lactated Ringer's, and treated with oral electrolyte solution as appropriate. The sodium level should be monitored frequently in the first 24 hours because of unknown losses through the gastrointestinal tract as well as unknown kidney function in a severely dehydrated patient.

20.6 HYPERNATREMIA

Hypernatremia is defined as a serum sodium concentration over 152 mmol/L (although only levels greater than 170 mmol/L have been associated with nervous dysfunction[9]). Hypernatremia occurs secondary to improper mixing of oral electrolyte solutions[8] or from the use of high—sodium-content milk replacer when there is limited access to

fresh water; consequently it is often farm-specific. Rapid development of hypernatremia results in fluid moving from cells into the extracellular fluid and produces cellular dehydration. Neurologic signs include lethargy, weakness, depression, coma, and death. Treatment of hypernatremia involves fluid therapy with a stepwise reduction in serum sodium concentration. A gradual reduction of serum sodium is indicated, as a rapid drop in serum sodium promotes a fluid flux into the brain, exacerbating cerebral edema and resulting in death.[8] Intravenous fluids are adjusted to contain concentrations of sodium approximately equal to the patient's sodium plasma concentration.[10] The goal is to reduce plasma sodium by less than 5 mEq/L/day over the first 48 hours by slow excretion through the kidneys. The volume given should be that to provide rehydration and cover maintenance and ongoing losses. The solution may include sodium bicarbonate if the calf is acidotic. Sodium should be added to any oral fluids (e.g., milk replacer) until plasma sodium levels approach normal so that the concentration is approximately equal to the intravenous fluids. Seizures may be observed if the drop in plasma sodium is too rapid. Cerebral edema may be treated with 25% solution of mannitol at 1 g/kg given intravenously (IV) over 30 minutes or an oral solution of glycerin given at 1 g/kg diluted 1:1 with water.

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20.7 NEUROMUSCULAR AND MUSCULOSKELETAL DISEASE

Primary neuromuscular or musculoskeletal disease should be considered when weakness is not associated with depressed mentation. Weakness associated with micronutrient deficiencies results from myodegeneration (white muscle disease, selenium, and vitamin E) or demyelination (copper, enzootic ataxia). If weakness is detected in one or more limbs immediately after birth, peripheral nerve and muscle damage associated with birth trauma should be ruled out (see Box 20-1). Femoral nerve paralysis may be observed in calves after a “hip lock” dystocia.[11] A condition resembling congenital myasthenia gravis has also been described in Brahman calves.[12]

Nutritional myodegeneration associated with selenium or vitamin E deficiency may produce paresis that is localized (dysphagia) or generalized. Neonatal small ruminants appear to be particularly susceptible. Affected lambs may be unable to rise. Others can stand but may be unable to nurse because they are unable to raise their heads. Diagnosis is based on clinical signs, increased serum creatinine kinase concentration, and reduced whole blood glutathione peroxidase and/or selenium concentrations. (See Chapter 42.) Vitamin E deficiency is observed when pregnant ewes are fed stored forage low in vitamin E; the clinical signs in affected lambs are identical to those of selenium deficiency, but selenium status is adequate. As vitamin E is labile, serum should be harvested quickly after blood collection, frozen, wrapped in aluminum foil, and sent via express mail on ice.

Paraplegia and tetraplegia are commonly associated with spinal cord compression. Compression of the spinal cord in neonates most commonly results from vertebral body malformations, osteomyelitis, or fractures. Generally, vertebral body malformations occur sporadically; genetic, nutritional, and environmental factors have been implicated.[13,14] In older calves, underlying metabolic bone disease (copper, vitamin D, or phosphorous deficiency) may increase the propensity for fractures to occur. Osteomyelitis and vertebral body abscess may be sequelae to bacteremia after neonatal septicemia[15] or pneumonia.[15] The frequent isolation of *Arcanobacterium (Actinomyces) pyogenes* from vertebral body abscesses in ruminants suggests that chronic respiratory infections is more frequently the source in these species.[16,17] Vertebral body abscesses in lambs are occasionally a sequela to infected docking wounds. Leukocytosis and hyperfibrinogenemia are commonly observed in neonates with vertebral body abscesses. In most instances vertebral abscesses do not infiltrate the pachymeninges, so the CSF either is normal or has a mild elevation of protein and/or a mild pleocytosis.[15,16]

Differential diagnoses for paresis in goat kids include caprine arthritis-encephalitis virus (CAEV) and enzootic ataxia. Enzootic ataxia is also common in lambs. Progressive ataxia and paresis or paralysis is a feature of both

diseases. There are two forms of enzootic ataxia (swayback): the neonatal and the delayed types. In the neonatal condition animals are affected at birth; in the delayed type, signs of incoordination appear at 14 to 30 days of age.[18] Most affected neonates are afebrile, bright, and alert and will continue to eat if it is physically possible. Enzootic ataxia is associated with low liver copper content and, occasionally, low serum copper concentration.[19] It has been proposed that reduction in the activity of the copper-dependent enzyme cytochrome oxidase impairs phospholipid synthesis and subsequently myelin production. Microcytic anemia and increased fragility of bones may be observed in more chronic cases.[20] The copper, molybdenum, and sulfur content of the maternal diet should be evaluated and adjustments made for copper deficiency or molybdenum or sulfur excess. (See Chapter 41.)

Goat kids with the neurologic form of CAEV will have mild to moderate fevers and evidence of cerebral involvement. Cerebral signs commonly identified include depression, head tilt, torticollis, and circling.[21] Evidence for CAEV would include CSF pleocytosis and increased CSF protein and a positive CAEV (agar gel immunodiffusion [AGID]) test or enzyme-linked immunosorbent assay (ELISA). Both the neurologic form of CAEV and enzootic ataxia carry a poor prognosis.

A complete neurologic examination is an important component of the workup of the weak neonate. In particular, it should be noted whether the weakness is accompanied by signs of depression and diffuse cerebral disease. It should be remembered that strength is preserved if ataxia is caused by cerebellar disease. Limb reflexes should be tested to establish whether components of the spinal reflex pathways are involved in the disease process (sensory nerve, lower motor neuron, neuromuscular junction, muscle). Animals with other types of spinal cord disease (e.g., trauma, vertebral malformations, enzootic ataxia) may also show weakness and ataxia yet appear clinically to have normal cerebral function. Virtually any severe systemic disease such as generalized infection can cause both profound depression and weakness in a neonate without the presence of actual brain pathology. Intermittent signs of severe weakness and depression may be caused by the narcolepsy-cataplexy syndrome. (See Chapter 33.)

20.8 RESPIRATORY CONDITIONS

20.8.1 EXAMINATION AND ANCILLARY DIAGNOSTICS

Assessment of the pattern and effort of breathing is a very important part of the examination of the respiratory system. Any obvious abnormal noises associated with respiration should be noted. Inspiratory stridor is often a feature of extrathoracic airway obstruction, and increased abdominal effort on expiration often indicates pulmonary disease causing reduced lung compliance. Absence of cyanosis is not a reliable indicator of adequacy of oxygenation in the neonate, because the partial pressure of oxygen may reach very low levels (<35 to 40 mm Hg) before cyanosis is observed. Fever, cough, and nasal discharge are usually absent in the early stages of pneumonia in the neonate.

Diagnosis of most upper airway disorders can usually be made with a careful physical examination in combination with radiography and/or endoscopy (Box 20-2). An integral part of the diagnostic approach to the neonate with suspected upper airway obstruction is assessment of the lungs for aspiration pneumonia. If the primary upper respiratory problem is not corrected and normal nursing allowed, the pneumonic process will likely persist and become chronic.

20.8.1.1

Box 20-2 Causes of Respiratory Distress

20.8.1.1.1

Airway Obstruction

Choanal atresia (nasopharyngeal atresia)

Laryngeal edema

Tracheal malformation: stenosis, collapse

20.8.1.1.2

Developmental Disorders

Pulmonary hypoplasia

Diaphragmatic hernia

20.8.1.1.3

Lung Parenchymal Diseases

Pneumonia (bacterial or viral)

Atelectasis

Hyaline membrane disease

Pulmonary edema, congestion

Aspiration syndromes

Air leaks (e.g., pneumothorax)

Pulmonary hemorrhage

Transient tachypnea syndromes

20.8.1.1.4

Nonpulmonary Causes

Congestive heart failure

Central nervous system lesions

Metabolic derangements (e.g., acidosis, hypoglycemia)

Severe anemia

Hypovolemia

Persistent pulmonary hypertension

Birth asphyxia

Pain, abdominal crisis

Fever, high environmental temperatures

Excitement

Pleural effusion (e.g., pleuritis)

Endotoxemia and gram-negative sepsis

Thoracic radiographs are helpful in diagnosing the presence of respiratory disease and in determining the type and extent of pulmonary involvement. Shortly after birth the smaller vessels posterior to the heart and in the caudodorsal lung fields should be clear. The heart, posterior vena cava, and aorta should be clearly defined. When the radiographic appearance of the lung fields is evaluated, the type of infiltrate (interstitial, nodular, alveolar, mixed), severity, and location (diffuse, cranioventral, caudodorsal) should be noted. Other soft-tissue structures (including the heart, vessels, and diaphragm) and bones (ribs, vertebrae, long bones) should also be evaluated. Thoracic radiographs are routinely taken in the standing or recumbent lateral position in calves. Cranioventral consolidation is a common feature of infectious pneumonia in calves. Radiographic changes may either follow or precede changes in clinical condition, and sometimes major changes can occur surprisingly rapidly. Clinical signs of pneumonia frequently resolve much earlier than chest radiographs and hemograms return to normal.

Table 20-2 Normal Blood Gas Values for Calves

Age-Group	O_2 (mm Hg)	CO_2 (mm Hg)	pH	HCO^-_3 (mEq/L)
1 hour	58.43 ± 11.61	50.40 ± 5.27	7.30 ± 0.05	23.52 ± 2.78
4 hours	62.30 ± 9.27	47.92 ± 3.97	7.34 ± 0.03	24.49 ± 2.35
12 hours	67.23 ± 9.32	45.36 ± 3.97	7.38 ± 0.03	25.74 ± 2.37
24 hours	70.53 ± 11.47	44.04 ± 3.45	7.40 ± 0.03	26.44 ± 1.87
48 hours	63.85 ± 10.82	45.25 ± 3.69	7.42 ± 0.01	27.98 ± 1.91

Ultrasonographic evaluation of the thorax is useful for identification of pleural effusion, pulmonary consolidation, pleuritis, and chest wall abscesses and for detecting congenital heart defects.

Arterial blood gas concentrations provide a measure of respiratory function. The optimal site for collection of arterial blood samples from neonatal calves is the brachial artery.[22] The calf is placed in lateral recumbency, with one hand on the neck and the other pulling the upper leg caudally. The brachial artery is located on the proximomedial aspect of the elbow of the lower limb. The area over the artery is thoroughly scrubbed and the artery stabilized by placing the index and second fingers of one hand above and below the proposed site of puncture. The arterial blood sample is collected using a 25- or 27-gauge ¾-inch needle and a 3-mL syringe.[22] Normal arterial blood gas values for neonates of different postnatal and gestational ages are presented in Table 20-2.

Several factors can interfere with accurate interpretation of blood gases in the neonate. First, significant inaccuracies can occur if the blood sample is collected, handled, or measured improperly. The most common artifact is the introduction of room air into the sample, with an artificially increased Pa_{O_2}, decreased Pa_{CO_2}, and more alkaline pH resulting. The position of the patient and amount of struggling during sample collection cay also potentially cause transient changes in all blood gas values. The inspired oxygen concentration should also be considered when analyzing arterial blood gas values. With supplemental oxygen, Pa_{O_2} is increased variably, depending on the inspired oxygen concentration (Fi_{O_2}), the amount of pathology present, particularly the extent of right-to-left shunting, and the respiratory rate and tidal volume.

Common patterns of derangement include hypoxemia (Pa_{O_2} <70 mm Hg) with low or normal Pa_{CO_2} and hypoxemia with hypercapnia (Pa_{CO_2} >50 mm Hg). If there is hypercapnia and resulting respiratory acidosis, ventilation is inadequate or pulmonary pathology is severe, impairing diffusion of CO_2. Hypoventilation may reflect lack of surfactant in the premature neonate, compromised muscle function (white muscle disease), or neurologic dysfunction with altered chemosensitivity resulting in inappropriate ventilatory responses to changes in blood gas values. Clinical signs must be evaluated along with blood gas analysis if the most appropriate therapy is to be chosen.

Interpretation of blood gas values of venous blood can be very deceptive and should be restricted to evaluation of metabolic conditions (e.g., metabolic acidosis) and not pulmonary gas exchange. To avoid problems associated with regional blood sampling, peripheral venous blood should be taken from a free-flowing jugular vein, because the metabolic status of the head is usually stable.

Transtracheal aspiration provides a sample for both cytologic and microbiologic analysis. (See Chapter 31 for specific details on technique and interpretation.) If the neonate is in respiratory distress, this technique can further compromise the patient. When mycoplasma or chlamydia infection is suspected, the laboratory needs to be notified, as specific media and growth conditions are required to isolate these pathogens. Viral infections are diagnosed directly by viral isolation (cell culture) or indirectly by demonstrating the presence of a virus (polymerase chain reaction [PCR] and fluorescent antibody techniques) or an immunologic response to a virus (seroconversion). Specific tests available for respiratory viral pathogens are discussed in Chapter 31.

20.8.2 UPPER RESPIRATORY TRACT DISORDERS

Conditions that affect pharyngeal and laryngeal function are important, as they predispose to aspiration pneumonia. Dyspneic neonates also have difficulty nursing and are subsequently likely to become malnourished. Congenital defects of the upper respiratory tract include collapsed trachea, stenotic nares, choanal atresia, and epiglottal cyst. Impaired pharyngeal and laryngeal function may result from physical deformation or neuromuscular disorders. Sporadic outbreaks of pharyngeal and laryngeal injuries are often associated with improper application or use of damaged feeding tubes and/oral medication equipment. Compression of the larynx by a retropharyngeal abscess or mass tends to cause inspiratory dyspnea. Edema and necrosis of the larynx may be observed with infectious bovine rhinotracheitis virus infections in neonatal calves.[23,24] *Fusobacterium necrophorum* typically causes necrotic laryngitis in weaned calves but sporadically infects neonates after pharyngeal trauma.[25] Partial occlusion of the upper airway induces turbulent airflow and subsequently mucosal edema. Placement of a tracheostomy tube provides an alternate, sometimes lifesaving, airway and rests the inflamed mucosa.

Nutritional myodegeneration and botulism may induce laryngeal paresis. Dysphagia and subsequent aspiration pneumonia are common sequelae of pharyngeal and laryngeal dysfunction. Collapsed trachea is a rare congenital or acquired condition. Clinical signs include an intermittent honking cough, stridor, and dyspnea with mild exercise. There is no stenosis of the trachea; rather a dynamic dorsoventral collapse during inspiration. The caudal cervical and cranial thoracic sections of the trachea in the area of the thoracic inlet are most frequently affected. Acquired tracheal collapse is commonly associated with fractured ribs and compression of the trachea at the thoracic inlet by the subsequent bony callus. Treatment of collapsed trachea in the calf by surgical reconstruction has been attempted, but the prognosis is poor.[26–29]

20.8.3 RESPIRATORY INFECTION

A number of respiratory disease syndromes may be observed in neonatal calves. Pneumonia in calves less than 3 days of age typically reflects aspiration of milk subsequent to inappropriate feeding practices or pharyngeal dysfunction (white muscle disease). A mixture of gram-positive, gram-negative, and anaerobic bacteria may be introduced into the lungs, inciting a severe inflammatory response necessitating broad-spectrum antimicrobial and antiinflammatory therapy.

Mannheimia hemolytica and *Pasteurella multocida* infrequently cause pneumonia in calves less than 2 weeks of age. Outbreaks of respiratory disease in this age group may be associated with mixed infections with *Mycoplasma bovis* or may be secondary to bovine virus diarrhea (BVD) infection. Respiratory disease is most common in calves more than 4 weeks of age, with the peak incidence observed after weaning in intensive calf rearing operations. Bovine respiratory syncytial virus, infectious bovine rhinotracheitis virus, BVD virus, *Mycoplasma* species infection, and bovine coronavirus may all produce respiratory disease in neonatal calves.

Viral infections increase the risk of opportunistic bacterial infections by their immunosuppressive effects and damage to the respiratory epithelium and pulmonary clearance mechanisms. Pleuritis is an uncommon feature of most neonatal respiratory infections but may be a manifestation of a generalized polyserositis with specific pathogens such as mycoplasma infections of ruminant neonates[30] and occasionally *Pasteurella* infections in lambs.[31]

Environmental risk factors include extremes of temperature, poor ventilation, dust, ammonia, and overcrowding. A number of pathogens capable of causing respiratory disease are shed in milk. These include *Mycoplasma* species,[30,32,33] CAEV,[34,35] and *Salmonella* Dublin. The practice of feeding mastitic milk (hospital milk) to neonates increases the risk of disease transmission. Rapid growth of salmonella in warm milk quickly produces a lethal challenge. *Salmonella* Dublin is an invasive salmonella serotype host adapted to cattle; calves commonly develop septicemia, and respiratory disease may be the predominant clinical manifestation. *Mycoplasma* species infection typically produces acute polyserositis; goat kids infected with *Mycoplasma mycoides* subsp. *mycoides* (large colony type) are often in pain, febrile, and reluctant to stand and have multiple hot, swollen joints. Approximately 50% of kids develop pneumonia or pleuropneumonia manifested by an increase in respiratory rate and auscultable lung sounds.[30] Pasteurizing goat milk at 56° C for 1 hour kills *Mycoplasma* species and CAEV. Outbreaks of *Mycoplasma* pneumonia in calves are usually caused by feeding waste milk contaminated with *M. bovis*. Clinical signs include increased rate and effort of breathing associated with pneumonia, joint and tendon sheath distention reflecting polyserositis and auricular discharge, and a head tilt reflecting otitis media interna.[32] *Mycoplasma* organisms are susceptible to antimicrobial agents that affect DNA, RNA, protein synthesis, or the integrity of the cell membrane. *Mycoplasma* organisms are not susceptible to agents that interfere with synthesis of folic acid or that act on the cell wall. Tylosin, tetracyclines, erythromycin, tilmicosin, florfenicol, aminoglycosides, and fluoroquinolones have been shown to have activity against one or more *Mycoplasma* species.[36] However, the efficacy of antimicrobial therapy in eliminating the organism is limited, and although animals may recover, chronic infections may persist. Numerous antimicrobials are labeled for the treatment of respiratory disease caused by *Pasteurella, Mannheimia,* and *Hemophilus* in cattle. Treatment protocols are reviewed in Chapter 31.

CAEV produces a number of disease syndromes in goats including mastitis, arthritis, encephalitis, and pneumonia. Encephalitis and subclinical respiratory disease typically occur in kids 2 to 4 months of age and occasionally in kids as young as 1 month of age.[34,37]

20.8.4 NEONATAL APNEA AND IRREGULAR BREATHING PATTERNS

Periods of apnea in the neonate are commonly associated with nonrespiratory factors, including infection, CNS disorders, hypothermia, and metabolic conditions such as hypoglycemia. Seizure activity may be expressed by changes in breathing rate and pattern, and neonatal asphyxia may induce respiratory depression, whether or not cerebral lesions are present.[38] Neonatal respiratory distress may also cause apnea resulting from respiratory center depression or diaphragmatic fatigue. There are two mechanisms of apnea: central apnea, resulting from cessation of diaphragmatic activity, and obstructive apnea, resulting from obstruction of the airway, usually at the pharyngeal level.

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20.9 ABDOMINAL DISTENTION

20.9.1 RUMINAL BLOAT

Ruminal bloat is uncommon in calves less than 5 weeks of age because of the relatively undeveloped state of the neonatal rumen. Causes of ruminal bloat in calves include ruminal putrefaction, obstruction of the cardia or esophagus, and vagal indigestion (Box 20-3).

If milk arrives in the rumen in greater quantities than normal by escaping the esophageal groove, it can be subjected to putrefactive decomposition by proteolytic bacteria. Normally the rumen of neonatal calves has a stable aerobic bacterial population. Anaerobic conditions are rapidly established when appreciable amounts of fermentable substances enter the rumen.[39] Clinical signs include diarrhea, poor development, rough haircoat, and recurrent bloat. Reducing the volume of milk fed per feeding, feeding from nipples rather than buckets, and introducing calf starter to promote ruminal development help prevent the condition. A course of oral antibiotics (500 mg oxytetracycline) once daily for 3 or 4 days may help affected calves by killing the putrefactive gut flora.

Bloat is occasionally observed as a complication of severe bronchopneumonia in calves as a consequence of swollenmediastinal lymph nodes compressing the esophagus or compression or inflammation of the vagus.[40] Relief of ruminal distention is important for return of ruminal function. Chronic ruminal bloat may be relieved by placement of a ruminal fistula (Buff's screw trocar). Correct placement of the screw, as described by Dirksen and colleagues,[41] reduces the risk of inducing peritonitis. The rumen must be bloated so that it lies firmly against the body wall as the trocar is screwed into place. The site for the trocar is shaved and scrubbed, a small skin incision is made, and the trocar is quickly and forcefully screwed into the belly wall and rumen. After removal of the stylet, the outer rim of the trocar is kept under constant outward tension so that the ruminal wall is held tightly against the parietal peritoneum by the last ridge of the screw. To fix the trocar in this position, gauze soaked in antibiotic should be wrapped around the stem of the trocar between the outer rim and the body wall.[41]

20.9.1.1 Box 20-3 Causes of Abdominal Distention

20.9.1.1.1 Obstruction

- Foreign body (hairballs in calf)
- Malformation (atresia coli, recti, ani)
- Intussusception
- Volvulus, torsion or strangulation

20.9.1.1.2 Uroperitoneum

- Ruptured bladder (uncommon)

Torn or necrotic urachus, ureter

20.9.1.1.3 Peritonitis

Generalized infection

Devitalized bowel

Perforated gastric or intestinal ulcer

Severe umbilical infection

20.9.1.1.4 Gas and Fluid Accumulation in Abomasum, Intestinal Tract

Intolerance to diet

Ileus

Gastric, abomasal, duodenal ulceration

Necrotizing enterocolitis

Ruminal bloat

20.9.1.1.5 Miscellaneous

Hemoperitoneum

Ruptured umbilical vessels

Ruptured spleen or liver

Congenital tumor

20.9.1.1.6 Ascites

Severe liver or renal failure

Severe hypoproteinemia

20.9.2 ABOMASAL ULCERS

Abomasal ulcers are usually asymptomatic in young calves, but if perforation occurs peritonitis and shock rapidly develop. Clinical signs of abomasal ulcers in calves include abdominal distention, pain on abdominal palpation, expiratory grunt, drooling saliva, bruxism, and melena. Less commonly a syndrome of chronic abdominal pain is observed after abomasal perforation.[42] Absence of inflammatory changes suggest the gut is unlikely to be perforated or necrotic. Severe hypoproteinemia is common with diffuse peritonitis presumably because of the combination of poor colostral uptake and loss of protein into the abdominal exudate. Obtaining peritoneal fluid from normal calves is difficult; if peritonitis is suspected, collection of abdominal fluid is facilitated by locating pockets of peritoneal fluid via abdominal ultrasound.

Clinically more abomasal ulcers seem to appear during or shortly after a period of weather-induced stress.[43] Lilly proposes that this may be associated with higher endogenous cortisol secretion.[44] Perforating abomasal ulcers in calves have also been associated with *Clostridium perfringens* abomasitis,[45] copper deficiency, dietary changes, mycotic infections, and abomasal bezoars.

Perforated abomasal ulcers are repaired surgically by a right paracostal approach. The ulcers are commonly located on the midpart of the fundus, on the greater curvature of the abomasum. Prognosis is guarded (40%).[43]

20.9.3 ABOMASAL DISPLACEMENT

Abomasal displacement is rare in neonatal ruminants. Clinical signs include reduced appetite, poor weight gain, recurrent tympany (left side), and diarrhea. An association of left-sided abomasal displacement with pneumonia in calves suggests that altered vagal function may be involved in the pathogenesis of the condition.[46,47] Typically, left-sided abomasal displacement in calves occurs between 6 and 14 weeks of age, but younger calves may be affected. Displacement of the abomasum is diagnosed by auscultation and percussion; affected animals may have a hypochloremic metabolic alkalosis. Correction can be attempted by rolling the calf on its back or via surgery.

20.9.4 ABOMASAL TYMPANY

Acute abdominal distention, colic, depression, and sudden death have been reported in neonatal calves with abomasal ulcers, abomasitis, and abomasal tympany. Possible sequelae to abomasal dilation include abomasal torsion, perforation, and rupture. Numerous causes have been postulated, including dietary changes, in particular the addition of coarse roughage feeds; abomasal bezoars; copper deficiency; and various microorganisms. Roeder and co-workers isolated *C. perfringens* type A from a group of eight calves affected by this syndrome[45] and subsequently experimentally reproduced the disease by intraruminal inoculation of the organism.[48] *Campylobacter* species have been incriminated in other studies. Histopathologic evaluation of abomasums from 38 affected calves at necropsy revealed that 31 contained abundant gram-positive bacteria associated with the damaged abomasal mucosa.[49] *Campylobacter*-like organisms were demonstrated in nine and *C. perfringens* in 14 of the 38 cases.[49] Studies of range cattle in west central Nebraska and Wyoming suggest subclinical trace

mineral deficiencies of copper and/or selenium may be involved in the pathogenesis of the condition in this region.[44]

Onset of clinical signs is rapid; affected animals become anorectic, depressed, or occasionally restless. Signs of abdominal discomfort including treading on the spot and kicking at the abdomen are observed in approximately half of the cases. On physical examination splashing and metallic sounds are heard on succussion of the distended abdomen, and passage of a stomach tube fails to relieve the distention. Fecal output is reduced, and occasionally melena is observed. Early in the clinical course calves are likely to have a marked metabolic alkalosis; however, rapid deterioration and onset of shock are common and accompanied by metabolic acidosis. Observation of metabolic acidosis carries a poor prognosis.

Management of abomasal tympany requires rapid relief of the abomasal distention. Paracentesis through the right flank often fails to completely drain the abomasum and carries a high risk of inducing peritonitis.[50] Kumper[51] describes good results with paracentesis using a 14 gauge, 50-mm needle when the calf is turned upside down and the abomasum is deflated by inserting a needle in the highest point of the distended abdominal wall between the umbilicus and xiphoid. Twenty of 21 calves with abomasal tympany were successfully managed without complications using this technique. Repeated paracentesis carries a high risk of inducing peritonitis; if after paracentesis the calf's condition deteriorates or tympany recurs, a right flank laparotomy is performed to correct a possibly torsed abomasum.[51] Intravenous fluids are administered to correct dehydration, electrolyte, and metabolic derangements.

A decreased prevalence of abomasal tympany and ulceration were reported in neonatal calves from herds having a history of these problems after implementation of a *C. perfringens* vaccination program.[44,52]

Abomasal bloat is a significant problem in artificially raised lambs. Feeding systems that allow lambs to drink large quantities of milk replacer at infrequent intervals and housing lambs on litter are predisposing factors.[53,54] Proliferation of lactobacilli, *E. coli*, and *C. perfringens* has been implicated in the disease process.[54,55] Fermentation of sugars contained in milk replacer produces carbon dioxide, distending the abomasum.[56] Lambs may die within hours from acute abdominal tympany compromising vascular return and respiration. Early treatment of bloated lambs with oral doses of antibiotics is sometimes an effective treatment. Addition of 0.1% formalin (37% formaldehyde) to milk replacer reduces the incidence of the condition.[55]

20.9.5 INTESTINAL ATRESIA

Intestinal atresia is the most common cause of abdominal distention in calves in the first week of life.[42] Typically calves are born normally but develop progressive abdominal distention shortly after birth. Signs of mild colic are occasionally observed. The spiral loop of the ascending colon is usually the site of atresia.[57] Other congenital abnormalities may be present (18% of cases).[57] Pregnancy diagnosis by palpating the amniotic sac before 40 days of gestation may cause colonic atresia in cattle[58]; however, an autosomal recessive inheritance in Holstein cattle has recently been proposed.[59] Surgical repair by resection of the distended proximal blind end and anastomosis of the proximal segment of intestine to the descending colon has been described, but breeding affected animals is not recommended.[57] Long-term survivors are likely to have loose feces and do not tend to grow well.[57]

20.9.6 INTUSSUSCEPTION

Intussusception occurs most commonly in the jejunum, but the frequency of ileocecal and colon intussusceptions appears higher in calves than in adults.[60] Commonly there is a history of diarrhea. Clinical signs may include intermittent colic, absence of feces, and melena; however, these are inconsistent. The inconsistency of clinical signs and inability to perform a rectal examination makes the diagnosis more difficult in calves than in adults.[60] Abdominal ultrasound may be useful. The prognosis after surgical correction is strongly influenced by the duration of the condition before correction.

Twisting of the intestinal mass around the cranial root of the mesentery is a rare event but occurs more frequently in calves than in adults.[60] Clinically the condition is characterized by a sudden onset of severe colic (kicking at the abdomen, dropping to the ground) that rapidly progresses (abdominal enlargement, tachycardia, tachypnea, reduced or absent fecal passage) to signs of shock and recumbency. Early diagnosis and rapid surgical correction, using either a right paralumbar or ventral midline, together with a supportive fluids approach allow for a good prognosis.

20.10 DIARRHEA

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Herd management variables that affect the risk of neonatal death losses in housed calves include efficiency of passive transfer, calf nutrition and environmental management (pathogen exposure), calving area sanitation, and cow vaccination status and health. Successful calf rearing is based on good management. A goal of less than 5% death loss from diarrhea is achievable. With neonatal death losses in pasture or range animals it is important to evaluate the dystocia rate, physical management, and nutritional status of the calving and nursing herds; the cleanliness of the calving and nursing areas; the provision of shelter from wind; and any biosecurity risks.

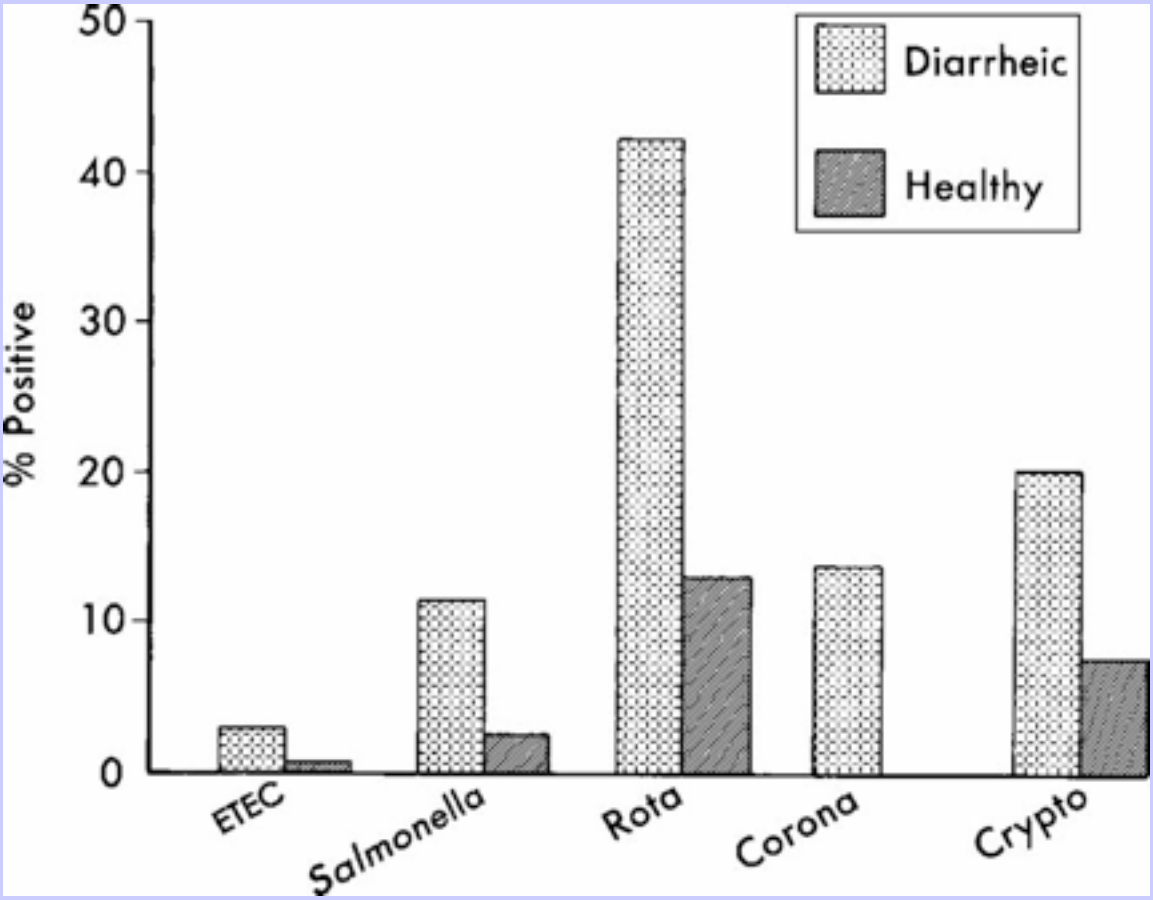
Rotavirus, *Cryptosporidium,* coronavirus, enterotoxigenic *E. coli* (ETEC), and *Salmonella* are recognized as the major pathogens associated with diarrhea in calves (Table 20-3). Rotavirus, *Cryptosporidium,* coronavirus, and ETEC are common pathogens in beef calves (Fig. 20-1).[61–64] *Salmonella* is more frequently implicated in intensive calf-rearing systems.[63–65] Enteropathogenic strains of *E. coli* are occasionally implicated in calf diarrhea; the true prevalence of disease associated with these strains is unknown because of the lack of routine definitive diagnostic tests. Torovirus has recently been associated with neonatal calf diarrhea in Canada, the United States, and Europe.[66–69] BVD is infrequently associated with diarrhea in young calves.[70,71] Various other agents have been implicated as causes of neonatal diarrhea, but their importance in the field situation is unknown (see Table 20-3). The incidence of the various etiologic agents varies with the age of the calf, and this is useful in establishing the likelihood that a particular agent is involved (Fig. 20-2). It is usually impossible to make a definitive etiologic diagnosis on clinical grounds. It is possible to detect signs of straining or passage of frank blood and mucus that suggest the presence of colitis, implicating possible *Salmonella,* coronavirus, BVD, enteropathogenic *E. coli* (EPEC), or coccidial infection.

Table 20-3 Evaluation of the Pathogenicity of Various Infectious Agents as Gauged by Their Ability to Experimentally Produce Diarrhea in Calves, Field Surveys of the Incidence of Infection in Diarrheic and Healthy Calves, and Similarity in the Distribution of Intestinal Pathology and the Infectious Agent

	Experimental Production of Diarrhea			
Agent Name	**Gnotobiotic Calves**	**Conventional Calves**	**Isolated with Higher Frequency from Diarrheic Calves**	**Organism Associated with Intestinal Pathology**
Bacterial				
Enterotoxigenic *Escherichia coli*		+	++/–	+
Enterohemorrhagic *E. coli*	+	+/–		++++
Salmonella species	++	+	+	
Campylobacter fecalis		+		
Campylobacter coli		++	––	
Campylobacter jejuni		++	+/–	
Clostridium perfringens				
Type A	+	–	+	+
Type C	+			++
Clostridium sordelli	+			
Viral				
Rotavirus	++	++	+++	+++
Coronavirus	+++	+	+	+++
Bovine virus diarrhea	+	+++		+
Bovine torovirus (Breda virus)	+++		+	+
Calicivirus	+	–	+	+
Parvovirus		+/–		+
Astrovirus		–		
Parasitic				

Cryptosporidium species	++++	++	+
Eimeria species	++		+
–, Negative finding; +, positive finding.			

Fig. 20-1 Common enteropathogens in dairy calves. The comparative incidence of isolation from diarrheic and normal calves is shown. From Snodgrass DR, Terzolo HR, Sherwood D, et al: Aetiology of diarrhoea in young calves, *Vet Rec* 119:31, 1986.



20.11 PATHOGENESIS

Diarrhea can be the result of either increased secretion or decreased absorption. Bacteria such as ETEC and, to some extent, *Salmonella* cause neonatal diarrhea by secreting enterotoxins that stimulate increased intestinal secretions.[72,73] These changes are thought to be mediated by cyclic adenosine monophosphate (AMP) or cyclic guanosine monophosphate (GMP), calmodulin, and changes in protein kinase activity.[74,75] The cell's structure is not affected, but the activity of the membrane pumps is altered, and secretion of chloride, sodium, and potassium is

increased.[76] Sodium absorption linked to glucose and amino acid transport across the mucosal epithelium is not affected.[77,78] Bovine ETEC does not stimulate intestinal bicarbonate secretion.[76]

Protozoa and enteric viruses cause neonatal diarrhea as a result of the destruction of the absorptive villous epithelial cells.[79–82] Diarrhea results because intestinal digestive secretions continue while absorption is impaired.[83,84] In rotavirus and coronavirus infections this is further exacerbated by compensatory hyperplasia of the crypt cells. The crypt cells have secretory functions, and their multiplication adds to the secretory load.[83] Rotavirus can also stimulate intestinal secretion both at a cellular level and by stimulation of the enteric nervous system. This is associated with the viral nonstructural protein NSP4.[85,86]

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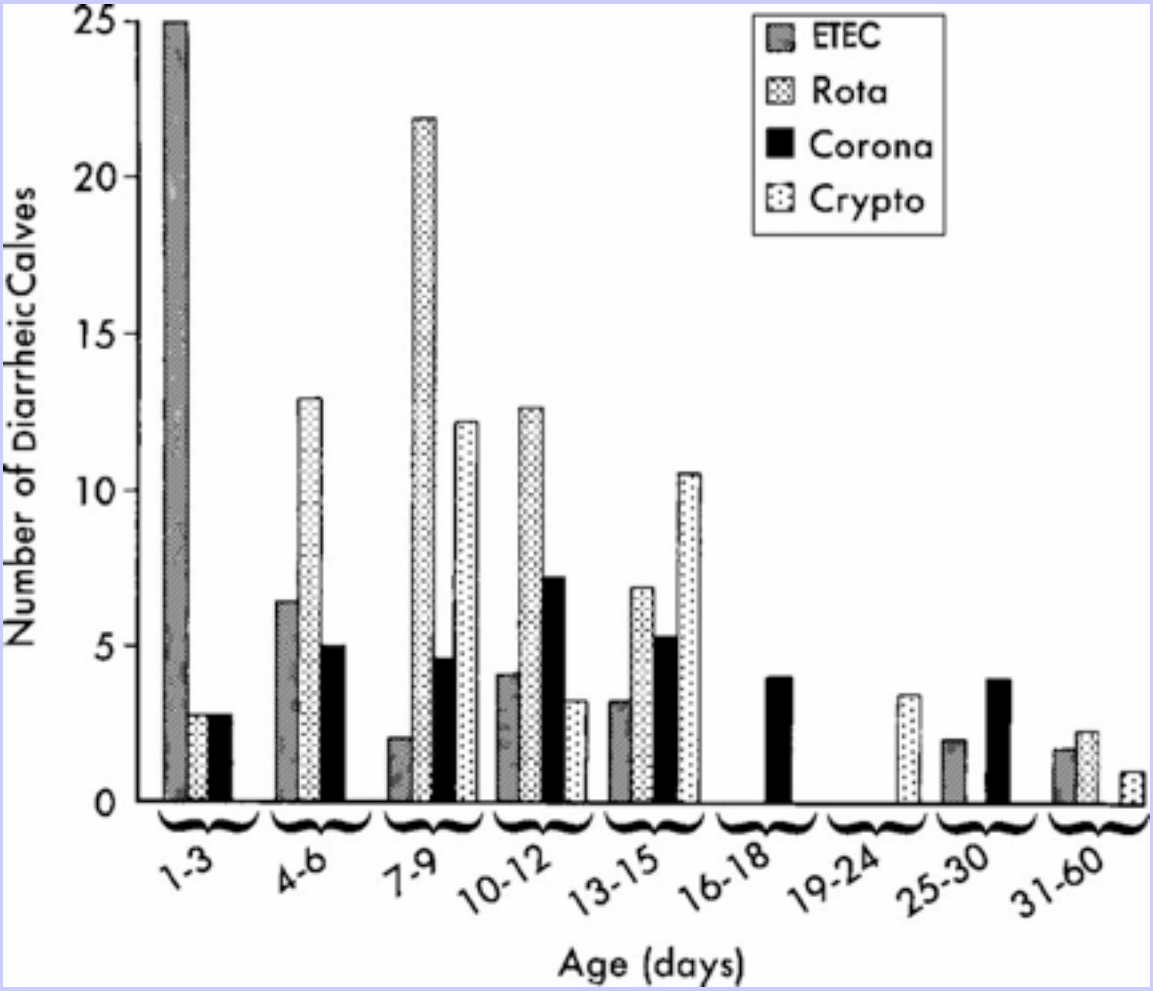
Fig. 20-2 Age incidence of isolation of different enteropathogens from diarrheic beef calves. The data are based on a retrospective records survey of 245 diarrheic calves admitted to the Western College of Veterinary Medicine over a 2-year period.



Continued feeding may result in more nutrients presented to the small intestine than the damaged villi can absorb.[87,88] Excess nutrients are fermented in the large intestine, promoting bacterial overgrowth[74,89] and generation of organic acids and other deleterious compounds. The osmotic effect of the unabsorbed nutrients drags water into the gut and contributes to the diarrhea.[83] Marked inflammation is a feature of salmonellosis and clostridiosis. This contributes to diarrhea by increasing mucosal pore size and hydraulic pressures within the intestinal wall, by destroying absorptive cells, and by increasing prostaglandin production, which in turn stimulates secretory mechanisms within the enterocytes.[74,83]

On an individual animal basis, diarrhea is significant because of fluid and electrolyte losses. As long as the neonate can compensate for these losses it will remain fairly bright and continue to suck. If the losses exceed intake, systemic effects of dehydration (salt and water loss) or acidosis are seen. Fluid is lost preferentially from the vascular compartment,[90,91] and cardiovascular collapse results. Acidosis has several causes including fecal loss of bicarbonate, endogenous synthesis of L-lactic acid in response to dehydration and poor tissue perfusion, and D-lactic acid production through bacterial fermentation of undigested or malabsorbed milk within the gastrointestinal tract.[92–97] Acidosis contributes to the calf's malaise by increasing vascular resistance and impairing cardiac function by direct effects and by inhibiting the action of catecholamines. Esophageal groove function may be compromised in acidotic calves, promoting ruminal drinking with the consequences of further production of D-lactic acid in the rumen and subsequent ruminal acidosis.[97,98]

The neonate becomes depressed, loses its suck reflex, and becomes weak; if the disease progresses, recumbency and coma may develop. One cause of death is believed to be heart failure as a result of myocardial potassium imbalance caused by the combined effects of potassium losses into the gastrointestinal tract and the redistribution of potassium from the cells to extracellular fluid as a result of acidosis.[99–101] Hypothermia will also contribute to cardiac failure. In cases of ETEC, *Cryptosporidium,* rotavirus, and coronavirus infections, correcting the fluid, electrolyte, and acid-base imbalances restores the neonate's ability to walk and suck. A residual degree of malaise may persist, which can be attributed to inflammation within the gut wall and damage to the integrity of the mucosal barriers, allowing invasion of enteric microbes or their toxins. If malabsorption persists, cachexia can develop—particularly if milk continues to be withheld as part of therapy—and death from malnutrition or hypoglycemia may occur.

Salmonella organisms are invasive and release endotoxins in the systemic circulation. *Clostridium* organisms produce exotoxins. Both endotoxins and exotoxins have profound systemic effects that are often directly responsible for malaise, microcirculatory failure, and cardiovascular collapse. Correcting fluid and electrolyte disturbances in these infections will aid the neonate but will not overcome the effects of toxemia or bacteremia.

20.12 ETIOLOGY

20.12.1 Bacteria

20.12.1.1 ESCHERICHIA COLI

E. coli are part of the normal flora of the bovine gastrointestinal tract. Pathogenic strains of *E. coli* possess virulence attributes that are involved in the pathogenesis of disease. Virulence attributes include adhesins, enterotoxins, and cytotoxins. Pathogenic strains of *E. coli* may be shed by adult cattle with transmission to

neonates by the fecal-oral route. Sick neonates amplify environmental contamination via prolific fecal shedding.

20.12.1.2 ENTEROTOXIGENIC *E. COLI*

ETEC possess two virulence factors: fimbriae (pili) and enterotoxins. F5 (K99) and/or F41 fimbriae mediate adherence, and thermolabile (LT) and thermostable (STa and STb) enterotoxins stimulate a secretory response by intestinal crypt cells. Although some bovine-origin ETEC produces LT, most strains that cause diarrhea in neonatal calves produce STa heat-stable enterotoxin.[102] The STa enterotoxin and F5 antigen are plasmid-mediated virulence factors. Susceptibility to ETEC is age dependent according to the binding specificity of pili antigens to immature enterocytes.[103] Disease is typically observed in calves less than 3 days of age; however, concurrent infection with rotavirus may extend this window to 7 to 14 days of age.[104,105] Intestinal cells of calves older than 2 days of age acquire natural resistance to F5 adhesion.[103] Despite this, F5-positive *E. coli* organisms have been isolated from healthy 4- to 12-week-old calves and F5-positive ETEC organisms are shed in feces for several weeks after experimental infection of newborn calves.[106]

20.12.1.3 ATTACHING AND EFFACING *E. COLI* AND SHIGA TOXIN–PRODUCING *E. COLI*

Attaching and effacing *E. coli* (AEEC) and Shiga toxin—producing *E. coli* (STEC) have been identified as causes of diarrhea and dysentery in calves.[107,108] Disease is mediated by cytotoxic damage to the intestinal mucosa. Lesions may be observed in the ileum, cecum, and colon.[109] AEEC (Vero or HeLa toxin—producing) induces a mucohemorrhagic colitis, with petechial or ecchymotic hemorrhages in the wall of the colon and rectum.[110–112] *E. coli* organisms that carry this toxin often belong to O serogroups 5, 26, 111, and 118.[111,113] Naturally occurring outbreaks have been reported in 2-day- to 4-week-old calves.[114] The most common clinical sign is diarrhea, but dysentery, abdominal pain manifested by bruxism, and dehydration are seen in some cases.

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STEC serotypes associated with dysentery in calves include O5:H–, O26:H11, O111:H–, O113:H21.[115] These serotypes may produce Shiga toxins—those that are immunologically similar to the Shiga toxin produced by *Shigella dysenteriae* (Stx1) and those that are immunologically distinct from *S. dysenteriae* Shiga toxin (Stx2).[116] Bovine STEC produces STx1, STx2, or both.[117] AEEC, which causes disease and does not produce enterotoxins or Shiga toxin, is referred to as *enteropathogenic E. coli* (EPEC).

The prevalence of AEEC and STEC in calves and the incidence of disease caused by these strains are not clearly defined, as most diagnostic laboratories do not routinely screen for AEEC and STEC. In a study aimed at determining the clinical significance and prevalence of AEEC in Swiss cattle, fecal swabs of 93 cattle from two farms with calf diarrhea and of 54 cattle from two similar farms without clinical problems were screened for AEEC by PCR assay and colony-blot hybridization. On average, 21% of all cows were positive for AEEC by PCR, without differences between farms with and without diarrhea problems. By contrast, AEEC was detected by PCR in 60% of animals younger than 2 years from farms with diarrhea problems, whereas only 32% of comparable control animals from farms without clinical problems had AEEC.

20.12.1.4

SALMONELLA

There are over 2200 reported serotypes of *Salmonella*, yet fewer than 2% of these account for approximately 80% of the disease reported in livestock.[118] In cattle, over 95% of *Salmonella* associated with disease is in serogroups B, C, D, and E. *Salmonella* induces a wide spectrum of disease in cattle of all ages ranging from inapparent subclinical infections to acute fulminant bacteremia, endotoxemia, and death. The variable manifestations of disease reflect the tissue trophisms of different *Salmonella* serotypes and the influence of challenge dose and host immunity. Common clinical signs associated with salmonellosis include fever, diarrhea, anorexia, depressed mentation, and dehydration. Many of the clinical signs are associated with endotoxemia. Systemic signs of endotoxemia include, fever, tachypnea, tachycardia, scleral injection, leukopenia or leukocytosis, and weakness. Some serotypes, particularly *Salmonella typhimurium,* have a tendency to induce severe inflammation of the bowel mucosa, resulting in dysentery and passage of fibrin and mucosal casts. Fluid, electrolyte, and protein loss may progress rapidly and become life-threatening if not corrected. With severe disease animals rapidly become emaciated because of the catabolic state induced by release of tumor necrosis factor alpha (TNF-α). Sequelae occasionally observed after invasive *Salmonella* infections in neonates include septic osteoarthritis and meningitis.

Immunity to *Salmonella* changes rapidly during the first 3 months of life. At 2 weeks of age the LD_{50} for some virulent strains is 10^5,[119] at 6 to 7 weeks is 10^7, and at 12 to 14 weeks is $10.^{10}$,[120] In contrast, administration of 10^{10} *Salmonella* to 24- to 28-week-old calves failed to induce clinical signs of disease.[120] The numbers cited reflect the influence of age on immunity but should not be interpreted as absolute. Different age predilections, manifestations of disease, and virulence are observed among *Salmonella* serotypes and among different strains of the same serotype.[121,122] Although adults may serve as carriers and a source of infection of *Salmonella* Dublin infection in neonates, disease in adults is less common in mature cattle compared with calves. In contrast, *S. typhimurium* tends to manifest disease in an epidemic manner, causing illness in all age groups.

Calves on endemically infected farms are commonly exposed to *Salmonella* in the first few days of life.[123] *Salmonella* exposure may occur via contaminated colostrum or milk; surface contamination of teats and udder, personnel, or equipment; or the environment. Chronically infected carriers may shed 2.5×10^8 *Salmonella* organisms in milk per day (25 kg of milk containing 10^5 *Salmonella* per milliliter).[124] Feeding utensils and personnel often play a significant role in transmitting *Salmonella* between calves.[125] Salmonella infects the salivary glands and is shed in saliva and nasal secretions.[126,127] Adequate cleaning and disinfection of feeding and medicating utensils is necessary to remove *Salmonella* contamination. *Salmonella* is sensitive to most disinfectants, but removal of contaminating organic debris is imperative, as the activity of disinfectants is reduced by the presence of organic matter.[128]

20.12.1.5

CLOSTRIDIA

Although clostridia are not commonly considered a major pathogen causing neonatal calf diarrhea, a number of reports associate clostridial infections with enteritis and abomasitis.

C. perfringens is the most important cause of clostridial enteric disease in calves. Some types of *C. perfringens* (mainly type A) are consistently recovered from the intestinal tracts of animals and from the environment, whereas others (types B, C, D, and E) are less common in the intestinal tracts of animals and can

occasionally be found in the environment in areas where disease produced by these organisms is enzootic.[129] Disease is usually precipitated by management factors that lead to the proliferation of the organism within the gastrointestinal tract or attenuated digestion of clostridial toxins within the lumen of the alimentary tract.

C. perfringens type A has been associated with acute hemorrhagic abomasitis in neonatal calves. Clinical signs include acute abdominal distention, colic, depression, and sudden death. Onset of clinical signs is rapid; affected animals become anorectic, depressed, or restless. Signs of abdominal discomfort are observed in approximately half of the cases and include treading on the spot and kicking at the abdomen. On physical examination splashing and metallic sounds are heard on succussion of the distended abdomen; passage of a stomach tube fails to relieve the distention. Fecal output is reduced, and melena may be observed. Gross pathology may include abomasal ulcers, abomasitis, and abomasal tympany.[45,48] Trace mineral deficiencies of copper and/or selenium may also be involved in the pathogenesis of the condition.[44] A decreased prevalence of abomasal tympany and ulceration was reported in neonatal calves from herds having a history of these problems after implementation of a *C. perfringens* vaccination program.[44,52] Enterotoxemia caused by *C. perfringens* type A has been described in 2- to 4-month-old calves, with the condition observed more often in beef calves than in dairy calves.[130] The disease is characterized by a high case fatality rate, sudden deaths, lesions of necrotic and hemorrhagic enteritis of the small intestine, and, most often, an absence of other clinical signs.[131]

C. perfringens type B is not commonly associated with neonatal diarrhea in calves. *C. perfringens* type C infections are most frequently observed in neonates less than 10 days of age.[132] Newborn animals are typically most susceptible, perhaps because of ready colonization of the gut by *C. perfringens* in the absence of well-established normal intestinal flora.[129] Alteration of the flora by sudden dietary changes may also be an inciting factor in type C infections. Vigorous, healthy calves develop hemorrhagic, necrotic enteritis and enterotoxemia, often accompanied by evidence of abdominal pain and neurologic signs that may include frenzied bellowing, aimless running, tetany, and opisthotonus. Death may be peracute, occasionally without other clinical signs, but may also follow a clinical course of several days.

20.12.1.6 CAMPYLOBACTER SPECIES

The clinical significance of *Campylobacter* species in calf scours is inconclusive. *Campylobacter* species are part of the normal intestinal flora. Experimental challenge studies have demonstrated the capacity of *Campylobacter jejuni* to cause enteritis in calves.[99,133–135] However, there is a paucity of convincing reports that demonstrate a causal association in naturally occurring cases.

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20.12.2 Viruses

Intestinal viruses multiply within enterocytes. As the epithelial cells are destroyed, villous atrophy develops. The various agents cannot be readily separated on clinical grounds. Diarrhea can vary in severity from soft to watery feces.

20.12.2.1 ROTAVIRUS

Rotaviruses are the most common cause of neonatal diarrhea in calves.[136,137] Affected calves are generally 5 days to 2 weeks of age, although disease can occur at 24 hours, particularly in colostrum- deprived calves (see

Fig. 20-2).[138,139] This age predilection is thought to occur because many cows secrete antirotavirus antibody in their colostrum, which confers local protection against rotavirus attack until antibody levels in milk decline 48 to 72 hours postpartum.[140,141] Resistance to infection is not age dependant, but age-dependant resistance to clinical disease has been demonstrated.[142] Several possible mechanisms are associated involved in age dependence. Age restriction may be related to immunity, as neutralizing antibodies increase with age and virus exposure. The expression of intestinal mucins and the rate of epithelial cell replacement and fluid absorption are also age dependent and have been shown to affect rotavirus infection and disease expression.[143]

Rotavirus invades small intestinal villous epithelial cells; the attack is usually self-limiting because of destruction of target cells.[82] Enterocytes are lost to the gut faster than they can be replaced from the crypts. The shrunken villi are initially covered by squamous and cuboidal cells from the crypts; the villi gradually regenerate as these differentiate into absorptive columnar epithelium.[82,144] Intestinal secretions are increased owing to the compensatory hyperplasia of crypt cells and enterotoxigenic activity of the viral nonstructural protein NSP4.[85,86] Both increased secretory load and impaired absorption resulting from villous hypoplasia contribute to the diarrhea. It is thought that virulent strains replicate more quickly and infect a larger area of epithelium. Difference in rotavirus replication rates in the gut and age-dependent differences in the rate of enterocyte loss and natural replacement rate may explain the differences in clinical outcome. Concurrent infection with ETEC has also been shown to cause clinical signs at a later age than with a single infection of either agent alone.[145]

Rotavirus of calves, lambs, kids, pigs, foals, mice, and children is morphologically identical. Infections are classified by the antigenic properties and/or sequence of the genes encoding the viral capsid proteins. Viral protein (VP) 6 is used to separate them into seven antigenically distinct serogroups, A through F. Rotaviruses from serogroups A, B, and C have been isolated from cattle, and serogroup A is the most common cause of diarrhea in calves. Group B rotaviruses have been isolated from calves and adult cattle; however, there is less information regarding their significance and prevalence in cattle.[146–150] Group B rotavirus is more common in lambs than in calves.[151] Group C rotavirus has been isolated only from adult cattle.[149] The serotype and/or genotype of capsid proteins VP7 and VP4 are also used to differentiate the viruses into a number of G-types (glycoprotein) and P-types (protease sensitive protien).[152] A range of both serotypic and genotypic diversity and virulence has been reported within serogroup A.[142,153–155] Rotavirus is shed in the feces of infected animals, and transmission is primarily fecal-oral. Clinical signs occur 1 to 3 days after infection and last for 5 to 9 days. Virus excretion commences with the onset of clinical signs and continues for 3 to 7 days.[142,156] Adult cows can be subclinically infected and intermittently shed the virus during pregnancy and especially at parturition.[157–159] It is likely that this is the most common source of infection, with carrier cows infecting their calves and then these calves infecting other calves.[160] Calves from carrier cows have a significantly higher risk of clinical disease, and the birth of calves from known carrier cows has been associated with the beginning of an outbreak. Recovered calves can become reinfected and shed virus.[161]

The environment may be an important source of infection. Rotaviruses can survive in fresh water for more than 2 weeks at 23° C and for months in water or soil <5° C.[162] They are also stable in feces and effluent for up to 9 months and therefore are likely to remain in calving areas from year to year.[163]

20.12.2.2 CORONAVIRUS

Bovine coronavirus commonly causes diarrhea in calves 5 days to 1 month of age.[63,68,164,165] Disease can occur within 24 hours in colostrum-deprived calves and has also been recorded in calves up to 5 months of age.[166] Respiratory infections are common in older calves and may be important in the epizootiology of enteritis.[166]

Calves may be infected with coronavirus by the oral or respiratory route.[156] Fecal shedding commences 3 days after infection and persists for up to a week; nasal shedding can be detected 2 days after infection and persists for 2 weeks. Once infected, calves initially excrete high levels of virus and are potent sources of contamination. Infection persists for weeks in apparently recovered calves, and these excrete low levels of virus for weeks.[167] Subclinical infection is common. Disease is more common in the winter months, and coronavirus survives in the environment from year to year.

Calves may be infected by virus shed by persistently infected cows.[168] Coronavirus has been detected in the feces of more than 70% of clinically normal cows.[159] The rate of virus excretion increases at parturition and in the winter months.[157,169] Calves born to carrier animals are at a significantly increased risk for developing diarrhea.[157]

All BCV isolates are believed to belong to a single serotype.[169a] Differences in hemagglutination-inhibition characteristics have been used to classify strains as types 1 through 3.[169b]

The pathology of coronavirus is often more severe than that of rotavirus, resulting in a mucohemorrhagic enterocolitis. The virus infects both the small and large intestine. In the spiral colon there is widespread destruction of the cells of the colonic ridges.[79,81] Virus replication occurs in the surface epithelium, especially in the distal half of the villi, resulting in stunting and fusion of the villi. Immature cells replace epithelial cells, and in severe infection there can be areas of complete desquamation. Intestinal secretions continue, and absorption is impaired by reduced surface area. Undigested lactose accumulates in the intestinal lumen, often resulting in a secondary bacterial overgrowth, fermentation, lactate production, and an osmotic imbalance that draws fluid into the intestinal lumen. Most infections are self-limiting because the virus rarely attacks crypt epithelial cells.[168] In response to infection the mitotic rate of crypt cells increases, producing immature cells that are more resistant to virus infection and that migrate up the villi to replace the damaged cells.

In experimental challenge studies, diarrhea develops 48 hours after infection. Calves are initially depressed and anorectic for the acute phase and may become dehydrated and pyrexic in a severe infection.[168] Severe infections can result in death from dehydration, acidosis, shock, and cardiac failure. Respiratory signs are generally mild. Rhinitis, sneezing, and coughing may occur. Lesions may be found in the lungs, but clinical signs of pneumonia are rare, except when secondary infection occurs.

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20.12.2.3 BOVINE VIRUS DIARRHEA VIRUS

BVD virus occasionally causes diarrhea and thrombocytopenia in young calves outside the confines of the persistently infected disease model.[70,71] Colostral antibodies generally protect young calves from BVD infection, but disease may occur as a result of FPT or the introduction of novel BVD strains with new cattle or

viral mutation in persistently infected home-grown cattle. BVD is also thought to exacerbate infections caused by other pathogens.[170] It has also been implicated in necrotic enteritis, an acute enteritis of 7- to 12-week-old beef calves reported in the United Kingdom.[171] Affected calves usually show oral ulcerations, particularly on the hard and soft palates. The buccal papillae are often blunted, and the tips may be ulcerated.[172] Some variants of the virus produce intestinal bleeding, petechiation, ecchymosis, or prolonged bleeding from venipuncture sites secondary to thrombocytopenia.[70,173–175] Hematologic findings often include leukopenia and thrombocytopenia. The disease must be differentiated from other causes of enteritis that are complicated by bovine papular stomatitis infection. Bovine papular stomatitis is common in neonatal calves. It produces oral lesions that are hyperemic and red, with a central white area of necrosis and often a raised rim of proliferating epithelial cells. These lesions often involve the mucosa around the molars. They are usually of little consequence, and their importance lies in the fact that they may be confused with BVD. One feature that helps identify BVD ulcers is that they lack the zones of epithelial proliferation seen in bovine papular stomatitis.

20.12.2.4 BOVINE TOROVIRUS (BREDA VIRUS)

Bovine torovirus has been detected worldwide[176–179] and has recently been implicated as an important cause of calf diarrhea.[66,67] Initially known as *Breda virus,* it is part of the Coronaviridae family. It has been relatively infrequently reported because it is difficult to recognize by electron microscopy and it cannot as yet be grown in cell culture, which has precluded the development of routine immunospecific diagnostic tests.[66] Laboratory studies using PCR testing have implicated it as the sole pathogen isolated in 25% to 30% of fecal samples from calves with diarrhea under 6 weeks of age.[66,67] It is also found in the feces and nasal secretions of asymptomatic animals,[66,68] suggesting that the epizootiology is likely to be similar to that of rotavirus and coronavirus, with asymptomatic carriers acting as reservoirs of infection within a herd.[157] It is mainly a disease of calves less than 3 weeks of age, with diarrhea commencing as early as 1 to 3 days after birth,[178,179] but clinical signs have been observed in animals up to 10 months of age.[67,180] Clinically it produces mild to moderate diarrhea in calves under both experimental and field conditions.[179,181] The virus infects the small and large intestines, affecting differentiating epithelial cells in the crypts of the intestinal villi.[179,180] Clinical signs develop 24 to 72 hours after experimental infection.[179] It has also been isolated from the respiratory tract of cattle and associated with respiratory signs in calves at 1 month and 4 to 6 months of age.[182]

20.12.2.5 OTHER VIRUSES

Calicivirus, astrovirus, adenovirus, parvovirus and picobirnavirus have all been associated with neonatal calf diarrhea.[183–187] The pathogenicity and contribution of these viruses to field outbreaks is uncertain.

20.12.3 Protozoa

20.12.3.1 CRYPTOSPORIDIUM

Two species of *Cryptosporidium* have been identified in cattle: *Cryptosporidium parvum* in the intestine and *Cryptosporidium andersoni* in the abomasum.[188] The two species have morphologically distinct oocysts and

differ genetically.[189] *C. andersoni* is a parasite of calves postweaning and has not been associated with neonatal diarrhea.

There are several subgenotypes of *C. parvum,* many of which appear to be host-specific and could represent distinct species.[188,190] These genotypes include type 1, which is found in human sources, and type 2, which is considered to be zoonotic and can be isolated from cattle, sheep, and goats.[190] Calves generally become infected between 1 and 4 weeks of age and display clinical signs for 4 to 14 days. Animals of all ages can be infected, but diarrhea is mainly associated with calves preweaning.[191] Cryptosporidial infections are asymptomatic in cattle older than 4 months of age. *C. parvum* mainly infects the distal small intestine, but lesions are also found in the cecum and colon and occasionally the duodenum.[192] The parasite invades the superficial cells of the mucosa in the intestine but is surrounded by an invagination of the host cell membrane and remains extracytoplasmic. Parasitic invasion of the mucosa leads to epithelial destruction and mild to moderate villous atrophy, with microvillous shortening and destruction. This leads to impaired nutrient digestion and transport and a resulting malabsorption diarrhea.

Affected calves often show no sign other than diarrhea but can show depression, dehydration, and anorexia.[193] Pyrexia and tenesmus have been noted.[194,195] Variable levels of morbidity have been reported, and mortality is generally low.[193,194,196] Other pathogens can be involved and are likely to contribute to the severity of the disease. Affected calves can take 4 to 6 weeks to recover. Cryptosporidiosis occurs less frequently in suckler calves at pasture, but when these calves are affected outbreaks were reported to be more severe than found in dairy calves, with mortality rates up to 30%.[188] High mortality rates have been attributed to lack of herd immunity in seasonal calving herds in which the transmission cycle is broken. Neutralizing antibodies in colostrum and milk reduce infectivity by immobilizing the parasite, blocking invasion, inhibiting adhesion to host cells, or having direct cytotoxicity for *Cryptosporidium* sporozoites.[197] High mortality rates have also been associated with concurrent low levels of selenium, inadequate nutrition, presence of concurrent enteric infections, and specific management practices.[188]

Transmission is fecal-oral, by ingestion of an encysted, sporulated oocyst. Transmission can be direct from host to host, by ingestion of contaminated food or water, and probably mechanically via flies.[198] A study of oocyst shedding in experimentally infected neonatal calves demonstrated prepatent and patent periods ranging from 3 to 6 and 4 to 13 days, respectively.[199] However, oocyst excretion has been described at as early as 2 days of age, which means that calves are susceptible to infection during or shortly after birth.[200] The parasite is capable of autoinfection, sporulating within the intestine and immediately infecting adjacent cells. This can result in protracted clinical illness and relapses. The ability to autoinfect results in huge parasite burdens after very small infective doses. Oocyst excretion has been described at as early as 2 days of age, which means that calves are susceptible to infection during or shortly after birth.[200] Calves aged 1 week to 4 months of age are most likely to be actively shedding significant numbers of oocysts, with peak shedding occurring at 1 to 3 weeks of age.[191,199–201] Infected calves can shed in excess of 10^6 oocysts g^{-1} of feces.[199,202] *C. parvum* oocysts have also been isolated from adult cows, with herd prevalence ranging from 7%–100%.[191,203–205] Mean shedding intensity reported for adult cows has ranged from 3 to 900 oocysts g^{-1} of feces.[205–207] It is likely that carrier cows are a source of infection of young calves.

The most critical factor affecting environmental oocyst survival is the temperature. Drying of oocysts has been shown to dramatically reduce their viability and infectivity in mice.[208,209] Oocysts can enter watercourses and ground water by direct contact with cows or from runoff of rain or irrigation water from pastures and manure

storage areas.[188,210] *Cryptosporidium* oocysts have been shown to survive in water for at least 12 weeks at 4° C.[211] Oocysts are resistant to chlorination of water and most disinfectants.[188] They have also been shown to survive in silage.[212] Wildlife may be a significant reservoir for *C. parvum* and may act as a method of amplification and infection in the environment.[203,213,214]

Cryptosporidia cause diarrhea and sometimes death in 3- to 30-day-old lambs. Protracted infections and mortality are most common in lambs infected in the first few days of life, as age resistance is seen after about 3 weeks of age.[92,215–217] Cryptosporidiosis has also been described in goats; it affected 5- to 20-day-old kids, signs lasted from 3 to 7 days, relapses were not uncommon, and there was a moderate mortality rate.[218] Cryptosporidia are resistant to all commonly available antimicrobial and anticoccidial agents and most disinfectants and can survive for long periods in the environment.

People working with diarrheic neonates should be warned of the risk of zoonotic disease. An outbreak of cryptosporidiosis has been described in caregivers in a veterinary hospital treating diarrheic calves. Affected people suffered from watery diarrhea, cramping, flatulence, and headache.[219] One person became infected as a result of handling soiled clothing.

20.12.3.2 GIARDIA

Giardia is often found in diarrheic calves in association with other pathogens, but its relevance as a pathogen in its own right is unclear. Several authors have documented cases of diarrhea in which *Giardia* infection has been implicated as the causative agent either by itself or in conjunction with *C. parvum* and rotavirus.[220–222] Affected calves are at least 2 weeks old, and often older than 1 month of age, with infection often becoming chronic and lasting for several months.[200,220,223–225] *Giardia* has a prepatent period of 7 to 8 days, and the delayed interval between birth and infection is likely to relate to high levels of colostral protection against *Giardia* but low protective levels in milk.[226] Many calves were shown to have a poor specific immune response to the infection, accounting for the chronicity of the infection.

The significance of *Giardia* as a primary pathogen has been questioned by the observation of similar or lower rates of infection in calves with diarrhea compared with asymptomatic calves.[200,227] Treatment of affected calves with fenbendazole reduces the duration but not the number of diarrhea episodes.[222]

20.12.3.3 COCCIDIOSIS

Thirteen species of *Eimeria* have been reported in cattle.[228] *Eimeria bovis* and *Eimeria zuernii* have historically been the most common pathogenic species; however, there are increasing reports of *Eimeria alabamensis* causing disease.[229–231] Transmission is fecal-oral. Infected animals pass unsporulated oocysts in their feces that sporulate and become infective. The sporulated oocysts are protected from the environment by a double cyst wall.[232] Moist, temperate, cool conditions favor sporulation, and oocysts can survive for several years. Sporulated oocysts can resist freezing to −8° C for several months but are destroyed by high temperatures and dry conditions within a few weeks.[233] Under optimal conditions sporulation can occur within a few days. The prepatent period of the two main pathogenic species is 15 to 20 days, and the patent period is approximately 11 days. *E. alabamensis* has a prepatent period of only 8 days and a patent period of 5 days.

Calves start shedding at about 1 month of age and shed for 3 to 4 months. *E. bovis* and *E. zuernii* schizonts first reproduce in the lower small intestine, then produce second-generation schizonts and gamonts in the cecum and colon, where they attack crypt cells.[228] These latter stages induce both local and more extensive lesions.

Outbreaks of disease in calves and lambs are often related to overcrowded and confined conditions. Up to 95% of infections are subclinical, causing decreased growth rates that are often unnoticed.[234] Clinical disease can be chronic or acute and is generally found in calves aged 3 weeks to 6 months, although animals 2 years of age or older may be affected. In beef cattle the most common reports of clinical disease are associated with weaning stress.[235] Clinical signs may include diarrhea, ill thrift, increased susceptibility to pneumonia, tenesmus, increased mucus in feces, and hematochezia. Pyrexia, dehydration, and anemia may also be observed. The disease is usually self-limiting without reinfection. Chronic disease is often underdiagnosed.[234] Calves appear weak and listless, with pasty feces, drooping eyes, and a staring coat. Fecal oocyst count is low or negligible. Disease results from continual reinfection as a result of a heavily contaminated environment.

20.12.4 Nutritional Diarrhea

Producers often express the opinion that scours is caused by calves consuming too much milk. However, there is no documented research in healthy calves to support this. Calves fed 16% to 20% of body weight per day or allowed ad libitum access to milk have not developed problems with diarrhea.[236,237] However, in studies in which calves are also infected with enteric pathogens, the diarrhea and depression were exacerbated by feeding normal amounts of whole cow's milk in the early stages. Villous atrophy as a result of attack by an enteropathogen reduces the ability of the calf to digest nutrients,[84,88] and this predisposes to gastrointestinal overload with fermentation of milk in the large intestine. Deliberate underfeeding of healthy calves also predisposes to diarrhea.

Studies in Scotland have shown that poor clotting ability of milk is associated with diarrhea and abdominal distention in calves aged 1 to 3 weeks of age in beef suckler herds.[238–240] Milk should clot within 7 minutes when incubated with rennet; the milk from the affected cows took at least 1 hour to clot and in some cases >24 hours. Diarrhea may be a result of the rapid passage of undigested milk through the bowel or secondary to infection by enteric pathogens facilitated by the conditions created in the bowel. Milks with poor clotting ability were shown to have low ultrafilterable calcium levels and low total magnesium levels.[240] Calves responded to treatment with 30 mL of 1 molar solution of CaCl administered three times daily by mouth (PO) and relapsed when this treatment was stopped. The majority of the milk samples clotted when 100 µL of 1 mol/L calcium chloride solution was added before the addition of rennet. The exact cause of the impaired clotting ability was not determined. The diet of one group of affected cows was shown to be low in calcium.[238,239] After a mineral mixture containing additional calcium was added to the diet of these cows, the clotting time was reduced to ≤12 minutes; treatment of the calves was stopped, and there was no recurrence of clinical symptoms.[238]

Calves seem to experience more problems with diarrhea on certain milk replacers. One study showed that calves performed well on milk replacers containing soy protein when healthy but that during an outbreak of salmonellosis there was better weight gain and less mortality in calves fed whole milk.[241]

20.13 ESTABLISHING AN ETIOLOGIC DIAGNOSIS

An etiologic diagnosis is useful in selecting specific diagnostic and preventative regimens for bacterial infections. Establishing an etiologic diagnosis for viral infections will allow establishment of specific control methods and development of an appropriate vaccination strategy. Diagnosis of salmonellosis, cryptosporidiosis, and giardiasis can have public health implications. Once an agent has been identified, one of the major problems is in interpretation of whether or not that agent is responsible for diarrhea in the individual or herd, because most agents can also be found in a percentage of normal calves (see Fig. 20-1).

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20.13.1 Sample Collection

Appropriate selection of diagnostic specimens is required to achieve a meaningful diagnosis. Best results are obtained when fresh samples and specimens are collected from calves early in the course of disease. When possible, a fresh necropsy is informative, as it provides an opportunity to relate the presence of pathogens to a disease process. This is required to establish causality. The quality of the information gathered is to a large extent determined by the quality of the samples submitted to the diagnostic laboratory. Autolysis and bacterial invasion of gut mucosa begin within 5 minutes of death. Autolysis is a common cause of poor tissue sections for histopathology; this may reflect a prolonged postmortem interval or poor tissue preparation, handling, or transport. To avoid autolysis, formalin needs to distribute into the lumen of intestinal sections; therefore intestinal specimens should be no longer than an inch long and the tissue-to-formalin ratio should be no greater than 1 to 10.

20.14 DIAGNOSTIC TESTS

20.14.1 Bacterial Pathogens

20.14.1.1 ESCHERICHIA COLI

E. coli is a normal inhabitant of the gastrointestinal tract. Isolation of *E. coli* from fecal samples or gut contents is therefore of no significance unless the isolates are demonstrated to possess virulent attributes that are consistent with the clinical and/or pathologic presentation. Virulence attributes include adhesins, enterotoxins, and cytotoxins. ETEC adheres to enterocytes in the jejunum and ileum.[242] On gross pathology, ETEC is associated with fluid-distended loops of bowel without enteritis.[243] Calves infected with ETEC have a mild inflammatory reaction in the small intestinal wall and some villous atrophy. In fresh specimens, sheets of gram-negative bacilli can be seen adhering to the small intestinal wall.[242] Definitive diagnosis of enterotoxigenicity rests on demonstration of the ability of the *E. coli* to dilate intestinal loops.[244] ETEC can also be identified by the presence of F5 (K99) using antigen-specific immunoassays including latex agglutination,[245] ELISA,[246] fluorescent antibody,[247] slide agglutination,[247] and rapid dipstick tests. A potential limitation of immunoassays is the specificity of the antibodies used; strains of ETEC using non-F5 fimbriae will not be detected by these tests.[108,248]

AEEC and STEC mediate disease by cytotoxic damage to the intestinal mucosa. Diagnosis of *E. coli* infection may be achieved using phenotypic differentiation of pathogenic strains from nonpathogenic normal flora *E. coli* via bioassays or immunoassays for toxins and fimbriae. Immunoassays have been developed to identify

the presence of Stx1 and Stx2 in feces as a presumptive test for the detection of STEC in cattle feces.[249–251] An alternative approach to identify and differentiate ETEC, AEEC, and STEC is to use PCR to identify virulence-associated genes commonly found in these *E. coli* strains (F5, F41, enterotoxin, intimin, Stx1, and Stx2).[117] The significance of STEC, EPEC, and AEEC in bovine enteritis is unknown because of a lack of appropriate assays for routine detection and because of the widespread presence of verotoxin-producing *E. coli* strains in healthy cattle that complicate the interpretation of detecting fecal shedding in sick animals.[252–254] Demonstration of verotoxin in cultures from bovine enteritis is not sufficient to imply a causative association.

20.14.1.2

CLOSTRIDIUM SPECIES

C. perfringens has been associated with enterotoxemia and hemorrhagic abomasitis in calves.[129,131] *C. perfringens* organisms are normal flora of the gastrointestinal tract; therefore isolation of *C. perfringens* from feces is not in itself diagnostic. Pathogenic strains of *C. perfringens* produce exotoxins; five of these (alpha-, beta-, epsilon-, and iota-toxins and enterotoxin) are involved in the pathogenesis of disease.[129] The complete pathogenesis of enterotoxemia and abomasitis has yet to be completely elucidated. Production of specific toxins can be demonstrated only in a proportion of cases.[255] Isolation of toxin-positive *C. perfringens* from intestinal contents does not confirm a clinical diagnosis of bovine enterotoxemia, because almost as many *C. perfringens* isolates from normal calves produce toxin and because toxin production cannot be demonstrated in as many as 40% of affected calves.[256]

A fresh necropsy is required to definitively diagnose clostridial enteritis. Observing many gram-positive bacilli in the mucosa associated with hemorrhagic enteritis is suggestive of clostridial enterotoxemia. Quantitative bacterial counts of intestinal contents at the site of the lesion have proven to be one of the most reliable methods for diagnosing enterotoxemia.[131] A *C. perfringens* count greater than 10^6/mL of intestinal contents is consistent with a diagnosis of enterotoxemia.[131] Demonstrating the presence of *C. perfringens* toxins or the capacity to produce toxins provides support for the diagnosis. Tests for detecting toxins or the bacteria's capacity to produce toxins include bioassays, immunoassays, western blot, and PCR assay.[257] The basis of the bioassay is to demonstrate protection of mice using antitoxin. *C. perfringens* enterotoxin is produced during sporulation. In vitro detection of enterotoxin-production capacity of a *C. Perfringens* isolate using western blot or immunoassays requires sporulation to occur. In vitro techniques to induce sporulation are not 100% efficient, so detection of enterotoxin using these methods is less sensitive than PCR is at detecting the genes required to produce enterotoxin.[258]

20.14.1.3

SALMONELLA SPECIES

Salmonellae are capable of causing disease in cattle of all ages. Neonatal infections are common. The classic pathologic lesion is fibrinous or fibrinonecrotic to ulcerative enteritis.[259] The severity of lesions is usually greatest in the distal small intestine and proximal large bowel. Hypertrophy of the mesenteric lymph nodes is a common finding.[260] Serosal hemorrhages may be observed in the small and large intestines. Septic infarcts in the kidneys and inflammation of the gall bladder are less common findings. Pneumonia is a common finding with *Salmonella* Dublin infections, and gangrenous necrosis of distal extremities may also be observed.[261] Bacteremia is a feature of neonatal salmonellosis and may manifest as osteomyelitis and/or meningitis.

Isolation of *Salmonella* from feces of calves with diarrhea is consistent with a diagnosis of salmonellosis but in itself does not necessarily establish causality, as *Salmonella* may be isolated from the feces of apparently

healthy calves.[262] Isolation of *Salmonella* from tissues at necropsy is indicative of invasive salmonellosis. A definitive diagnosis of salmonellosis is based on the clinical presentation, pathologic lesions, and isolation of *Salmonella* from tissues at necropsy.

There are numerous methods for isolating and detecting the presence of *Salmonella*. These include direct culture, enrichment cultures, PCR, immunoseparation, and immunoassays.

The process of directly inoculating tissues or other samples onto plating media, except in the case of acute infections, is usually nonproductive. Typically, with subclinical infection the number of salmonellae shed in feces is low relative to the high number of other bacteria. Fecal samples should be inoculated into selective-enrichment media for optimal recovery of *Salmonella*. Selective-enrichment broths are formulated to selectively inhibit other bacteria while allowing *Salmonella* to multiply to levels that may be detected after plating. Internal organs that are normally sterile do not need to be inoculated onto selective media; rather, they should be inoculated onto nonselective (blood agar) or weakly selective (MacConkey agar) media.

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Rapid detection methods have been developed to expedite the detection of salmonella. These methods include electrical conductance and impedance, immunologic techniques, nucleic-acid—based assays, and PCR assay. These methods generally take 24 to 52 hours to screen for or detect and identify salmonella organisms. Most of these tests, and particularly the enzyme-linked immunologic techniques, require 10^5 cells per milliliter for reliable results. Accordingly all these tests involve a preenrichment stage, and some also involve a selective-enrichment culture.[263] When *Salmonella* is causing disease, clinically affected calves may shed 10^9 *Salmonella* organisms per gram of feces.[264] Detection of *Salmonella* in clinical samples when it is the inciting cause of the disease process is not normally difficult when multiple samples are collected from a representative sample of the affected population.

20.14.2 Viral Enteropathogens

Viruses are usually identified by direct examination of the feces, immunoassays, or fluorescent antibody examination of intestinal mucosa. Molecular techniques involving PCR and reverse transcriptase—PCR (RT-PCR) have been described for most pathogens but are not routinely available in all diagnostic laboratories. Electron microscopic examination of feces is not a sensitive means of detecting virus particles, but it has the advantage that many different types of viruses can be detected, including those such as parvovirus that are not recognized as common causes of diarrhea. The recent development of relatively inexpensive immunoassay diagnostic test kits makes these an attractive option; limited test-specific data regarding test sensitivity and specificity limit the application of some of these tests.

20.14.2.1 CORONAVIRUS

Coronavirus replication occurs in the epithelial cells of the distal half of the villi of the lower small intestine and colon. Infected cells die, slough, and are replaced by immature cells. In the small intestine these changes result in stunting and fusion of adjacent villi, and in the large intestine they lead to atrophy of the colonic ridges. On histopathology the tall columnar epithelial cells are replaced by cuboidal and squamous epithelial cells, and in severe infections there may be areas of complete desquamation.[265] Virus is shed in respiratory secretions and feces. There are several methods for detecting bovine coronavirus virus in feces. These include isolation of the virus in cell culture,[266] electron microscopy,[267] immunoelectron microscopy,[166] immunoassays[159,246,268–271] and molecular techniques including dot blot hybridization assays[272] and RT-PCR

assay.[273,274] Isolation of bovine coronavirus using cell culture techniques is not often performed in diagnostic laboratories, as the technique is difficult and requires viable virus (fresh samples or shipped on dry ice).[275] Electron microscopy has been used as a standard diagnostic method for bovine coronavirus. Although the intact virion of bovine coronavirus is fairly characteristic in appearance, it is not uncommon for the identifying surface projections of the virus to be lost during sample preparation or storage, making it difficult to properly identify virus particles by electron microscopy.

Numerous ELISA assays have been described for the detection of BCV antigen in feces. Several companies have developed commercial kits using this technology. The use of monoclonal antibodies rather than polyclonal antibodies is reported to increase the sensitivity and specificity of bovine coronavirus ELISAs.[271] The limit of detection for ELISA assays ranges from 10^4 to 10^7 virions per milliliter of feces.

A one-step RT-PCR assay, targeting a 730-bp fragment of the nucleocapsid gene of bovine coronavirus, and a nested PCR assay, targeting a 407-bp fragment of the nucleocapsid gene have been developed to detect bovine coronavirus. Compared with an antigen capture ELISA, the limit of detection for the RT-PCR and nested PCR assays was 10^5 virions/mL and 10^3 virions/mL, respectively, compared with 10^7 virions/mL for the ELISA.[276,277]

20.14.2.2

ROTAVIRUS

Bovine rotavirus infects enterocytes of the intestinal villus. Infected cells are predominantly in the distal third to half of the villus. The age at the time of infection influences the distribution of the virus in the gastrointestinal tract and the number of virions shed in feces. In experimental challenge studies, infection of day-old calves resulted in a uniform distribution of virus throughout the small intestine.[278] Challenge of 10-day-old calves led to a patchy distribution of the virus with maximal viral load observed in the mid small intestine.[278] Villous stunting is more pronounced in young calves.

Methods for detection of rotavirus include cell culture, fluorescent antibody staining, electron microscopy, immunoelectron microscopy, immunoassays, electrophoretic procedures, and RT-PCR assay.[146–150,245,246,269,279–281] Bovine rotavirus is difficult to isolate in cell cultures because of the cytotoxic nature of feces and fecal filtrates and because the virus is inconsistent in production of cytopathic effects.[280] The fluorescent antibody technique is simple, rapid, and specific; however, rotaviral antigen is usually difficult to detect within 24 to 72 hours after the onset of diarrhea because rotavirus-infected epithelial cells are rapidly shed from the tips of the villi.[282] Comparative studies evaluating methods of detecting rotavirus in feces show comparable test results between antigen capture assays (ELISA, latex agglutination) and electron microscopy.[245,269,280,283] Direct immunofluorescence testing of fecal samples corresponds well (90%) with electron microscopic examination for rotaviruses when samples are collected during the 24 hours after the onset of diarrhea,[284] but have poor agreement (33%) for field specimens submitted to a diagnostic laboratory.[280]

20.14.2.3

BOVINE VIRUS DIARRHEA

BVD virus rarely causes diarrhea in neonatal calves.[71] Sporadic disease may be observed in persistently infected calves. Pathologic lesions include ulceration of the oral cavity, particularly on the hard and soft palates, and blunting of the buccal papillae.[172] Erosions may be observed in the esophagus, and necrosis of Peyer's patches may be observed in the ileum. Thrombocytopenia has been observed with BVD type II

infections. Outbreaks of neonatal disease have been observed with this strain. Petechial and ecchymotic hemorrhages are a feature of this condition.[70,174,175] Hematologic findings often include leukopenia and thrombocytopenia.

Several options are available for the detection of BVD; these include virus isolation,[285,286] RT-PCR assay,[287] immunohistochemistry,[288] and antigen capture ELISA.[289] Assays; the latter two are used in most commercial laboratories. Maternal antibodies reduce the sensitivity of the ELISA assay in young calves.[287]

20.14.2.4 BOVINE TOROVIRUS (BREDA VIRUS)

Bovine torovirus produces cytolytic infections of villi and crypt enterocytes in the small and large intestine.[290] 348
Bovine torovirus does not grow in tissue culture, cell culture, or embryonated eggs.[291] Therefore the large- 349
scale preparation of reference antisera and antigens for the development of diagnostic tests has been precluded. Torovirus is capable of causing diarrhea in cattle, with disease observed most frequently in calves less than 3 weeks of age.[68,179,181,292–294] Like other enteric viruses, bovine torovirus has been detected in feces of normal calves; therefore detection of the virus in feces from diarrheic cattle cannot be interpreted as causal. The lack of diagnostic reagents has limited the study of bovine torovirus, leaving questions about its epidemiology and relative importance in calf diarrhea.[67] Diagnostic methods that have been used to detect bovine torovirus include electron microscopy, immunofluorescence, antigen capture ELISA, and RT-PCR assay.[67,179]

20.14.3 Protozoa

20.14.3.1 EIMERIA SPECIES

Eimeria species are host-specific. *E. bovis* affects primarily the mucosa of the cecum and the proximal part of the large intestine, whereas *E. zuernii* affects the mucosa of the cecum as well as the entire large intestine, including sometimes the rectum.[295] The clinical signs of bovine coccidiosis are associated with the final stages of the eimerian life-cycle and commence shortly before oocyst shedding. Gross lesions in the cecum and large intestine range from having semiliquid contents, little or no blood, and few areas of epithelial sloughing to having extensive hemorrhage and large areas of epithelial sloughing and necrosis of the mucosa.[295] The serosal surface is often reddened opposite the affected mucosal area, and the submucosa and external muscular layers are often thickened by edema.

Oocysts usually can be recovered 2 to 4 days after the onset of diarrhea.[296] Oocysts can be identified microscopically by direct smear, flotation, or centrifugation methods. The oocysts of *E. alabamensis* are smaller and less distinctive than oocysts of other coccidian but are approximately 4 times larger than cryptosporidia. Oocyst counts of 5000 or more per gram of feces are considered significant in cattle.[232] Identification of oocysts in feces is not diagnostic for clinical coccidiosis, because the parasite is frequently detected in small numbers in the feces of healthy cattle.[297] When scour problems are being investigated, multiple samples should be collected for oocyst counts to provide an indication as to the level of infection within the group. The potential for discord between clinical signs and fecal shedding limits the diagnostic utility of a single sample from an individual animal.

20.14.3.2

GIARDIA

Giardia infection is not associated with changes in intestinal villous height or crypt depth. However, transmission electron microscopy has been used to demonstrate a reduction in microvillous surface area.[298] Diagnostic methods for detection of *Giardia* include direct microscopy, immunomagnetic separation, fluorescent antibody staining,[221,299] ELISA,[300] and PCR assay.[301] When direct microscopy is used, fecal samples should be examined within 24 hours of collection. Concentration of trophozoites and cysts via density gradient centrifugation or filtration followed by fluorescent antibody staining is the diagnostic method used in most veterinary epidemiologic studies of *Giardia* in calves.[200,302,303] Other immunoassays and PCR techniques are emerging in human diagnostic laboratories.[300,301]

20.14.3.3

CRYPTOSPORIDIA

C. parvum infections are mainly concentrated in the distal small intestine, but lesions may also be found in the cecum and colon, and occasionally in the duodenum.[304] The pathologic findings associated with *Cryptosporidium* are a mild to moderate villous atrophy, villous fusion, and changes in the surface epithelium with infiltration of mononuclear cells and neutrophils in the lamina propria.[304]

Calves infected with *C. parvum* usually develop diarrhea in 72 to 96 hours; diarrhea is observed for 8 to 23 days,[305] during which oocysts are excreted in feces. Oocysts are stable in feces for many days at room temperature.[306] Laboratory methods for the diagnosis of cryptosporidial infections include microscopic examination of fecal smears or fecal preparations, immunoassays, and PCR assay. Cryptosporidia oocysts are small (4 to 6 μm in diameter) and are easily missed on a fecal smear. Because fecal smears do not concentrate the oocysts, this technique is less sensitive than fecal flotation. Concentration of the protozoa is achieved by salt[307] or sugar flotation. Special stains may be used to facilitate detection of cryptosporidia during microscopic examination. Differential staining techniques are useful to distinguish *Cryptosporidium* oocysts from other fecal components (especially some yeasts) of similar size and shape.[308–311]

A number of immunoassays have been developed for the detection of cryptosporidia. The detection thresholds of the different methods have been reported to be 3×10^5 oocysts/g for a monoclonal antibody—based antigen capture ELISA, compared with 1×10^6 oocysts/g detected by examination of acid-fast stained fecal smears and 1×10^3 oocysts/g detected by indirect immunofluorescence.[312] The detection threshold may be further enhanced by using a combination of immunomagnetic separation coupled with immunofluorescent microscopy. With this combination it is possible to detect as few as 10 oocysts/g.[313] Several dipstick immunoassays have also been developed. The detection threshold for this technology is reported to be 1×10^3 oocysts/g.[314] This technology offers the potential for rapid, cost effective detection of cryptosporidia in fecal specimens.

Molecular techniques have been described for detection and typing of cryptosporidia.[190,315] The capacity to differentiate the different genotypes makes this approach useful for epidemiologic studies of cryptosporidia.[315]

20.15 RISK FACTORS FOR NEONATAL CALF DIARRHEA

It is important to identify risk factors, both to set up effective preventive programs and to initiate control in the face of a disease outbreak. The cause of calf diarrhea is multifactorial; consequently it is common for several factors to contribute to the outbreak and perpetuation of disease in a herd.

20.15.1 Dystocia

Dystocia is associated with neonatal calf diarrhea in more intensive beef and dairy systems[62,316] and is a risk for preweaning mortality, with over 40% of preweaning deaths occurring in calves born to cows with dystocia.[317–319] Dystocia affects the ability of the calf to suckle colostrum, resulting in decreased serum IgG levels; consequently calves that survive dystocia are two to four times more likely to become sick in the first 45 days of life.[320–322] Stocking density of preparturient cows, timing of calving, breed, and cow grouping all influence the risk of dystocia.[323] Calves that experience dystocia are likely to have edema of the head and tongue, making suckling difficult. They are weak, exhausted, and likely to be recumbent for longer, increasing exposure to fecal pathogens.[164] Low- and high-birthweight calves are at greater risk of mortality.[318] Small calves experience greatest mortality at parities greater than one, and large calves at first parity.[324] There is no direct effect of preparturient nutrition on the subsequent incidence of neonatal calf diarrhea. Increased feed intake precalving will increase calf birthweight but does not increase the risk of dystocia unless cattle become obese.[325–327] Weight loss is associated with prolonged labor, increased dystocia, and increased perinatal mortality.[327,328]

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20.15.2 Dam Parity

Calves born to first- and second-parity cows have increased mortality compared with those born to older cows, and the risk of diarrhea in calves born to heifers is 3.9 times greater than in those born to cows.[318,329,330] Heifers have an increased risk of dystocia, lower colostrum quality, and inferior mothering ability.[320,321,330–332] The stocking density of heifers is often increased before calving to facilitate observation, with the consequence of exposing their calves to a greater environmental pathogen load. These factors are all likely to contribute to increased morbidity, and consequently the percentage of heifers in the herd will affect the risk of diarrhea. Calves from carrier heifers shedding rotavirus and bovine coronavirus are more likely to develop clinical disease than calves born to carrier cows.[157] Studies in dairy herds have shown that there is a positive correlation between the number of young stock in the herd, the overall herd size, and herd production with the risk of neonatal calf diarrhea.[333–335]

20.15.3 Colostrum Management

Many studies have shown that FPT results in increased risk of neonatal calf diarrhea in beef and dairy herds.[336–342] Calves are able to absorb immunoglobulins only for a limited time after birth, and the subsequent serum Ig concentration is determined by the perinatal state of the calf, timing of colostrum ingestion, and the mass of immunoglobulin consumed.[343] Colostrum also provides local (enteric) immunity, with the major benefits lasting for approximately 3 to 4 days after birth.[344–346] After this period, milk contains little immunoglobulin and most colostral antibody has been cleared from the intestine. Colostral antibodies protect against rotaviral infections in

the first 4 days of life[140,141]; in contrast, anti-F5 (K99) *E. coli* antibody is present in low amounts in unvaccinated cows,[347] and enteric *E. coli* infections are usually seen in very young calves. After 4 days the protective effects of colostrum are primarily a result of systemic antibodies, and there is evidence that these can leak back into the gut and probably give limited long-term protection against diarrhea.[348]

Colostral quality is affected by colostral volume, genetics, nutrition, parity, and climate. Beef breeds have been shown to have a significantly higher IgG concentration than dairy breeds, and this was attributed to differences in the onset of lactogenesis and colostral volume[349]; however, studies comparing colostral quality between beef breeds or between dairy breeds have not shown a consistent result.[320,321,332,350–355] Beef cows have a significantly smaller prepartum decline in serum IgG compared with dairy cows, but the resulting colostral IgG concentration is higher because of the significantly lower volume produced. However, the combination of low volumes and increased turbidity may limit the calf's ability to take in sufficient immunoglobulin, especially if the calf is weak. Recent studies in beef cattle have shown an increased incidence of FPT in specific genotypes, with different haplotypes determining receptors for neonatal Ig absorption.[356,357] This would indicate that FPT is more prevalent in specific lines of cattle rather than in breeds per se. First- and second-calving beef and dairy cows have a lower colostral immunoglobulin concentration than cows of third parity and above.[352,354,358–360] This is reflected in significantly lower mean serum IgG concentration found in calves born to beef heifers and second-parity cows.[320,321,330–332]

The biggest effect of nutrition on colostral quality is its effect on colostral volume, with increasing volume resulting in dilution of immunoglobulins.[359] Severe nutritional restriction has no effect on IgG levels other than an increased concentration associated with a decrease in colostral volume.[321,361–365] Similarly, nonlactation period length appears to have little effect, although a prolonged dry period may result in increased volume in mature cows.[355,359,366]

Passive transfer is also influenced by climate, with both hot and cold extremes leading to decreased immunoglobulin concentration, intake by the calf, and immunoglobulin absorption.[339,355,367–371]

20.15.4 Beef Cow Herd Management

In beef herds, high stocking rates in the calving area and the use of one calving area are major risks for neonatal calf diarrhea.[372,373] The practice of leaving nursing dams and calves with calving cows further increases stocking rates and promotes disease transmission.[338] The weather at calving affects both pathogen survival and calf comfort; shelter in the nursing area is associated with decreased mortality resulting from neonatal calf diarrhea.[329] Major calf scour pathogens can survive in the environment for months or years in cool, wet conditions, and consequently both the incidence and the mortality from diarrhea increase with prolonged use of the same paddock or a longer calving season, and the incidence of diarrhea increases as the calving season progresses.[319,329,330] Adverse weather conditions cause cows to move to shelter and shade, concentrating cows and calves in small contaminated areas. Calves born into a contaminated environment potentially become infected during or shortly after birth and shed enteropathogens even when they remain clinically normal. This further increases the environmental load of infectious agents, infecting adult cattle as well as calves. The outcome of host-pathogen interactions is largely influenced by the pathogen challenge dose and the age of the animal, with clinical disease becoming more common both in younger neonates exposed to higher pathogen numbers (Fig. 20-3).

Farms that purchase replacement calves aged less than 4 weeks have an increased mortality from neonatal calf diarrhea.[329] Purchased calves may introduce new pathogens, challenging a susceptible population. Stress from transport and arrival at a new location may increase shedding and predispose to clinical disease, increasing the environmental pathogen load. The risk of pathogen introduction increases when introduced calves from multiple properties are commingled before introduction.

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Fig. 20-3 Cow on a farm with a high incidence of neonatal diarrhea. Note that the mud is so deep around the feeders that it covers the cow's hocks. As a result the teats will be contaminated by manure and enteric pathogens.

20.15.5 Intensive Calf-Rearing Systems

Intensively reared calves have an increased risk of diarrhea associated with housing, nutrition, and weaning. Variables that have been observed to increase the risk of scours include feeding milk once versus twice a day within 14 days of birth,[374] placing preweaned heifers in groups of seven or more, using damp versus dry bedding,[374] a male having primary responsibility for the care and feeding of preweaned heifers, calves not receiving hay or other roughages until >20 days old, and feeding mastitic or antibiotic milk versus whole milk.[375] Use of individual calf hutches has been reported to increase the risk of scours but to reduce mortality.[374]

Factors significantly associated with a decreased risk of cryptosporidial infection included ventilation in calf rearing areas, daily addition of bedding, feeding of milk replacer, daily disposal and cleaning of bedding, and use

of antibiotics. Postweaning practices that reduced risk of infection included moving animals after weaning, cleaning soiled bedding, and using antibiotics and ionophores as preventive measures. Maternity management factors that reduced risk of infection included using fresh colostrum to feed calves and having a concrete floor in the calving area. General management factors that influenced risk included the total number of dairy cattle, the total number of other species of agricultural animals on the farm, and the distance of the barn water source from the septic system.[376] It is likely that many of these factors in all categories will also increase the risk of infection with other enteric pathogens.

20.16 HERD STRATEGIES TO PREVENT NEONATAL DIARRHEA

Management practices that reduce the risk of calf scours also promote good health, improve growth rates, and reduce the risk of transmitting other enteric pathogens such as *Mycobacterium paratuberculosis*. The principles of prevention are as follows:

1 Minimize pathogen exposure.

2 Ensure adequate colostral intake.

3 Boost specific and nonspecific immunity.

4 Promote farm biosecurity.

20.16.1 Minimizing Pathogen Exposure

Enteric pathogens may be shed in large numbers by calving cows, scouring calves, and asymptomatic cohorts, especially those up to 4 months of age. All enteric pathogens can survive in the environment for months or years in moist damp conditions. Other sources of infection include people who have treated or handled infected calves; contaminated water; contaminated colostrum, milk, or solid feed; and equipment that has been used to feed or medicate infected calves.*

20.16.1.1 MINIMIZING PATHOGEN EXPOSURE IN DAIRY HERDS

Strategies to prevent disease in dairy calves focus on calving cows in a clean environment, removing calves from cows at birth, feeding adequate good-quality colostrum, placing calves in a clean, dry environment separate from other stock, feeding good-quality milk or milk replacer, providing adequate shelter, and providing access to water and high-quality calf pellets. Microbial contamination is an important determinant in the quality of colostrum and milk. Good sanitary practices are required for the harvest, storage, and feeding of both products. Microbial contamination of colostrum compromises passive transfer and in the case of pathogens such as *Salmonella* may lead to a direct pathogen challenge. Similarly, feeding milk with a high bacteria count increases the risk of diarrhea.

In dairy systems, where calves are reared by hand, the number of young stock on the farm and the incidence of respiratory disease are positive predictors for calf diarrhea.[333] Cleanliness of the calving area is important; bedding should be changed between each calving, and large numbers of cows should not be cycled through a few stalls.[333] Before calving the udder and the perineum of the cow should be cleaned. The calf should receive adequate colostrum.[373] In recent years the use of calf hutches has gained widespread acceptance for managing calves after they have been separated from their dam. This system provides individual isolated housing for

each calf. Cleaning is facilitated because the hutches can be moved to new sites between calves. Keeping preweaned calves in groups larger than six puts them at increased risk for diarrhea.[335]

Cleaning and disinfection after each calf batch plays an important role in reducing contamination in housed calves. The key to decontamination is the physical cleaning. Physical removal of organic contamination through scrubbing is preferred to application of high-pressure sprays, which can aerosolize organisms, allowing dissemination. On smooth, ideal surfaces physical removal of visible contamination by thorough washing with soap and water removes 99% of the microbial load (two logs). However, on typical housing surfaces washing removes only 90% (one log). Application of disinfectant after washing is important to eliminate remaining pathogens and to prevent bacterial pathogens from proliferating. Physical cleaning cannot be replaced by applying disinfectants in larger quantities, as organic material neutralizes most disinfectants. Disinfectant solutions are applied following cleaning. With regard to disinfectants, pathogen elimination is time dependent.[380] Other important variables that influence the effectiveness of disinfectants and rate of pathogen reduction include concentration, temperature, pH, and water hardness.

In addition to cleaning between batches, it is important to clean nipple buckets and other feeding utensils between each feed. Separate equipment should be used to administer oral electrolytes and colostrum. *Salmonella* and coronavirus are shed in saliva and can contaminate equipment used for oral medication. Washing with warm soapy water is required to remove the fat residue left by milk and colostrum handling equipment.

Several microbial characteristics should be considered when disinfecting equipment that comes into contact with calves. Rotavirus is susceptible to sodium hypochlorite but is relatively resistant to many common disinfectants, such as chlorhexidine. Because as a nonenveloped virus it is not affected by soaps, washing with soap alone may actually spread the virus around on the washed surface.[381] Coronavirus is an enveloped single-stranded RNA virus and is not as stable in the environment as rotavirus. Because of their envelope, these viruses retain infectiousness better at lower than at higher relative humidity[382] and are considerably more sensitive to soaps and common disinfectants than are nonenveloped viruses. *Cryptosporidium* can autoinfect the original host; consequently, the infectious dose can be exceedingly small. In the environment, cryptosporidia are extremely resistant to most veterinary disinfectants except 5% ammonia, 6% hydrogen peroxide, or 10% formalin.[208,383,384] They survive very well in water, requiring 4 to 11 weeks to decline by one log.[385] On the other hand, cryptosporidia are susceptible to drying, with oocyst infectivity declining in 1 to 4 days.[209]

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The most readily cleaned surfaces are made of smooth impervious materials such as plastic and varnished wood (Table 20-4). Usually buildings are cleaned and then either disinfected or fumigated.[386] Many disinfectants are inactivated by organic matter; viruses, coccidia, and particularly cryptosporidia may be resistant to their action (Table 20-5). Disinfectants may also be toxic and are best applied by personnel wearing rubber gloves and respirators (if indoors). In general, potent phenolics such as cresol (cresylic acid) are very useful for disinfecting dirty surfaces because they are not inactivated by organic matter and are effective against gram-negative organisms and viruses. The phenolics are highly toxic and leave lingering odors. Hypochlorite solutions (5 g of available chlorine per liter) have a broad spectrum of action but are rapidly inactivated by organic matter. They would be useful as a final disinfectant on previously cleaned surfaces. Because hypochlorite is unstable, it is unlikely to leave toxic residues. Iodophors are not very effective against rotavirus, particularly if organic matter is present. Virkon, a newer disinfectant and cleaner containingpotassium monopersulfate as the active ingredient, is effective for all pathogens except cryptosporidia. Normally a 1% solution is used and is prepared by mixing 10 g of powder with 1 L of water.

Contact time should be a minimum of 10 minutes. Virkon has the advantage of having a detergent action that facilitates cleaning.

Table 20-4 Ability of Bacteria to Persist on Various Types of Surfaces Found in Farm Buildings

	Total Bacterial Count per 100 cm^2	
Material	**Uncleaned**	**Cleaned**
Brick	76,000	
Painted wood	34,000	
Block board	116,000	
Ply board	77,000	23,000
Fiber board	57,000	
Chip board	35,000	
Formica	29,000	
Polystyrene	29,000	
Metal		14,000
Concrete		13,000
Plastic	16,000	100
Varnished wood	5000	

Modified from Morgan-Jones SC: In Collins E, et al: *Disinfectants: their use and evaluation of effectiveness,* London, 1981, Academic, p 199.

Table 20-5 Efficacy of Disinfectants Against Enteropathogens

Group	Compound	Efficacy		
		Gram-Negative Bacteria	Rotavirus	Cryptosporidia
Phenolics	Hexachlorophene	+	++	
	Triclosan	+	++	
	Cresol (coal tar derivation)	++	++	–
	Phenol	±	–	
Halogens	Povidone-iodine	+	–	–
	Hypochlorite	+	+	
Biguanides	Chlorhexidine	++	–	
Aldehydes	Formaldehyde*	+	+	+
	Glutaraldehyde	+		
Quaternary ammonium	Benzalkonium chloride	+	+	–
	Cetrimide	+		
Ammonia	Ammonia			+
Oxidizing agent	Potassium monopersulfate	+	+	–

Based on information in references 408, 446–451.

++, Highly effective, not inactivated by organic matter; +, moderately effective, inactivated by organic matter; ±, some effect; –, little effect.

* Requires long contact time—18 hours to kill cryptosporidia.

Formaldehyde is one of the few agents that is effective against cryptosporidia. It requires a long contact time and is highly toxic. It is usually used for terminal fumigation in buildings that can be tightly sealed. Formaldehyde gas is best generated by heating paraformaldehyde (5 g/cubic meter of building) in an electrically heated pan at 204° C. Some manufacturers of paraformaldehyde provide pans specially designed for this purpose. The pans should be placed no more than 30 m apart and arranged so that electricity to the pan can be controlled from outside the building. There must be a safety mechanism to ensure that the pan does not overheat and cause a fire. The building must be sealed for at least 24 hours and cannot be entered until it has been thoroughly ventilated. Formaldehyde gas can also be generated by boiling formalin or by adding potassium permanganate to formalin. The latter method generates a violent chemical reaction and carries risks of explosion. Formalin aerosol generators are ineffective.[387] After cleaning and disinfection one should allow a rest period for the building to ventilate before reintroducing calves. It is very important that cleaning and

disinfection be thorough. Attention should also be given to rodent control because rodents can be a reservoir for *Salmonella*.[388]

* References 126,157,159,188,206,377–379.

20.16.1.2 MINIMIZING PATHOGEN EXPOSURE IN BEEF HERDS

In beef herds, calving areas should be located to take advantage of natural shelter and drainage and rotated from year to year to avoid pathogen buildup.[330,372,389,390] Pregnant cattle are moved into a clean paddock no more than 2 weeks before the start of calving. It is best that cows and heifers are managed separately until their calves are at least 1 month old. This gives the opportunity to provide better feed to the heifers and to minimize infection between the groups. Confined, wet, or muddy areas should be avoided for calving cows, and if they need to be used the stocking rate should be decreased. Feed-out areas should be rotated and separated from watering points to encourage dispersal. When pasture for calved cows is limited, supplementary feed should be fed to dry cows to ensure enough freshpasture for calving and nursing cows. Clean water should be available in a trough that is accessible to cows and calves. Chronically sick animals, weak calves, and cows with no milk should be removed from the calving paddock and kept isolated from the herd.

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Grazing and reproductive management have a significant impact on pathogen load. Where appropriate to grazing management, calving paddocks should be left vacant during the summer. For producers that manage periparturient cows in smaller calving paddocks to facilitate supervision, the emphasis should be on minimizing the stocking density in the calving paddock by removing cows and calves shortly after parturition.[372,389] Alternatively, pregnant cows can be moved away from cows with calves every 1 to 2 weeks or more frequently in large herds. Young calves in the calving paddock will markedly increase the rate of pathogen buildup and the subsequent challenge to newborn calves. Moreover, the increased stocking rate will amplify stress, affecting both transfer of passive immunity and the ability of young calves to rest. Often, calving areas are small because of the perceived need to assist cows with dystocia.[390] Well-grown and appropriately fed heifers mated to suitable sires can minimize this need. Beef cows with calves at foot should be moved from the calving paddock into nursing groups that have a maximum age range of 4 weeks and a low stocking rate. Groups should not be mixed until all calves are at least 4 weeks old.[372,389,390] Reproductive management influences pathogen load by determining the age spread of the calves. Sick calves amplify environmental contamination. A prolonged calving period leads to a buildup of contamination so that calves born later in the calving period experience an increased pathogen challenge. It is desirable to maintain a calving period that is less than 60 days.

20.16.2 Ensure Adequate Colostral Intake

The principles of colostrum feeding and evaluation are discussed in detail elsewhere (see Chapter 53). In general, colostrum deprivation is seen in 25% to 50% of dairy calves[391–393] but is much less common in single suckle beef operations.[394] Colostrum deprivation, poor mothering, and early separation of dam and calf are the major causes of failure of transfer in dairy calves. Beef calves are usually mothered well,[395–397] and volume of colostrum produced, which is strongly influenced by nutrition, is one limiting factor.[361,398,399] Thus adequate colostrum intake is best ensured in dairy calves by assisted sucking of the dam or hand feeding 2 to 3 L of colostrum within 2 to 4 hours of birth. If colostrum is given by stomach tube, 4 L (10% of body weight) should be administered because the efficiency of absorption is reduced. In beef cattle adequate nutrition during late

pregnancy is important. The calving area should be carefully monitored, and any calves that fail to suck within 6 hours of birth should be caught and tubed with colostrum. In herds where both dystocia and neonatal disease is a problem, it may be advisable to administer colostrum after calving to all calves that have an assisted birth.

20.16.3 Boosting Specific and Nonspecific Immunity

20.16.3.1 ENTEROTOXIGENIC *E. COLI*

The protective efficacy of ETEC bacterins is well documented.[400–403] Because ETEC scours occurs during the first 3 days of life, the neonate does not have time to mount a protective immune response to vaccination. Protection is afforded by vaccinating cows in late gestation so as to ensure high concentrations of anti-K99 colostral antibodies. Good maternal management is required to ensure that the calf receives the maternal antibodies. Antipilus antibodies block the adhesion of the pathogen to enterocytes and subsequently prevent disease.[401] In general it is recommended that the vaccines are given 6 and 3 weeks before calving. Studies with some vaccines have shown that the vaccine is still effective if the priming dose is given 18 months before calving and boosting is carried out in the second half of gestation.[404] Clinical experience in beef farms with severe outbreaks of *E. coli* F5 (K99) diarrhea indicates that vaccinating cows that are more than 10 days from parturition can give considerable protection against death from ETEC infection.

Products containing monoclonal antibodies against F5 (K99) antigen have been shown to reduce the severity of diarrhea when calves are experimentally challenged a few hours after receiving the product.[405] In field situations, however, monoclonal products can have a low efficacy, presumably because a single dose provides only a short period of enteric protection. Antibody supplements are expensive, and vaccination of the dam to boost colostral immunity will usually be more cost-effective. On farms experiencing an outbreak of neonatal diarrhea caused by F5(K99) *E. coli,* there may be a place for the use of these products until vaccinated cows begin to calve. However, short-term administration (once a day for first 3 days of life) of an antibiotic to which the *E. coli* is susceptible is also highly effective in preventing diarrhea in herds experiencing outbreaks of ETEC.

20.16.3.2 SALMONELLA

The successful reduction of *Salmonella* prevalence in livestock on a national level via implementation of a *Salmonella* control program emphasizing immunoprophylaxis with modified live and killed *Salmonella* vaccines indicates the potential benefits that can be derived from the application of effective *Salmonella* vaccines.[406] *Salmonella* vaccine studies in cattle have focused on *Salmonella* bacterins and attenuated modified live *Salmonella*.

There are conflicting reports regarding the efficacy of *Salmonella* bacterins. The reported efficacy of *Salmonella* bacterins ranges from good to ineffective.[407–415] The overall consensus of these reports is that vaccination of cattle with *Salmonella* bacterins provides partial protection against *Salmonella* challenge. In the only reported controlled field trial an autogenous *Salmonella* bacterin was not found to have any effectiveness.[415] Anaphylactic reactions are occasionally reported in cattle vaccinated with *Salmonella* bacterins. The cause of these reactions is unknown but has been suggested to be associated with the lipopolysaccharide content of these products. Similar allergic-type reactions in humans caused by *Salmonella* bacterin vaccination during typhoid outbreaks are well documented.[416]

Several naturally occurring and genetically manipulated attenuated *Salmonella* strains have been used to immunize cattle against salmonellosis. The most widely tested genetically altered *Salmonella* mutant vaccines in cattle are the auxotrophic strains. Aromatic amino acid (aro) and purine (pur) auxotrophs of *Salmonella* are attenuated and have decreased virulence.[417–423] Comparative vaccine trials indicate that modified live attenuated *Salmonella* vaccines provide greater protection against virulent *Salmonella* challenge than *Salmonella* bacterins.[413,423,424] Vaccination with modified live *Salmonella* vaccines attenuates the severity of clinical signs and pathologic lesions and reduces *Salmonella* shedding and mortality.[406,419,425]

Calves immunized with modified live *Salmonella* vaccines are protected from homologous and heterologous *Salmonella* serotypes when challenged within 3 weeks of vaccination.[426–428] Live *Salmonella* vaccines induce transitory T-cell independent nonspecific protection that disappears about 1 month after immunization following clearance of the organisms from the reticuloendothelial system. Thereafter, protection against oral challenge is species- and serotype-specific, with recall of immunity presumably involving specific antigen recognition.[429,430]

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The level of passive protection of calves achieved by feeding colostrum from vaccinated cows is questionable. Several reports suggest that immune colostrum provides passive protection, but others report no protective effect. In trials in which protection was achieved, calves were challenged at 1 week of age; trials in which no protection was observed involved challenging calves at 3 weeks of age, suggesting that the duration of passive immunity associated with colostral transfer is relatively short. Considering that many calves are exposed to *Salmonella* in the first week of life, colostral protection may be useful.

20.16.3.3 ROTAVIRUS AND CORONAVIRUS

Bovine coronavirus is associated with several diseases in cattle. All BCV isolates are believed to belong to a single serotype.[169a] Differences in hemagglutination-inhibition characteristics have been used to classify strains as types 1 through 3.[169b] There are seven serogroups of rotavirus, with group A accounting for the majority of pathogenic isolates. Members of the group A rotaviruses are further classified according to antigenic and genetic differences in their outer capsid proteins, G and P. Both of these proteins are involved in neutralization of infectivity in vitro and in vivo.[433] In the United States eight G serotypes and genotypes and four P serotypes and genotypes have been identified in cattle isolates.[153] The genome of rotavirus is composed of 11 gene segments that can be exchanged among isolates when animals are infected by more than one virus at the same time.[434] Genetic reassortment can generate new progeny viruses that can evade what was once a protective immune response, thus allowing persistence of rotavirus in susceptible populations.[433]

Two approaches have been taken with immunoprophylaxis against rotavirus and coronavirus infections in calves. The first approach involves oral vaccination of neonatal calves with a modified live vaccine. Calves begin producing detectable levels of local secretory IgM within 4 to 6 days of vaccination.[435] Calves are resistant to challenge from the initial appearance of local IgM antibodies.[435] In order to consistently elicit an effective immune response, the vaccine must be administered orally, immediately after birth, and before the calf has nursed because the colostrum of most cows contains virus-neutralizing antibodies that interfere with the vaccine.[436] There are conflicting reports of efficacy with these type of vaccines. In double-blind field studies that include vaccinated and nonvaccinated calves the vaccine was not shown to be effective.[437]

Conversely, when all calves were either vaccinated or not vaccinated in sequential comparisons, morbidity and mortality were significantly reduced.[437]

The second approach involves intramuscular vaccination of pregnant cows with either modified live vaccine or inactivated viral vaccines to stimulate high levels of specific viral neutralizing antibodies in colostrum and milk during the first several days of the calf's life. Infectious viral particles are neutralized within the gut lumen, preventing infection of intestinal villous enterocytes. One advantage of passive immunization is the fact that cross-protection between serotypes is less of a problem. This is because vaccination of a mature cow that has had natural rotavirus exposure leads to cross-serotype stimulation of heterotypic antibodies.[438] Single serotype vaccination therefore stimulates antibody production to a wide range of rotavirus serotypes, negating the need for multivalent rotavirus vaccines. Passively absorbed anti-bovine rotavirus IgG1 antibodies are transferred to the small intestinal lumen, where they protect against experimental challenge.[439] Antigen sensitized maternal lymphocytes also confer partial protection against challenge with virulent bovine rotavirus.[440] Colostrum and milk with a high virus-neutralizing antibody titer are highly protective while being consumed by the calf. For example, administering 400 mL of immune colostrum daily to calves from days 2 to 12 reduced the incidence of diarrhea from 41% to 3% in one study.[441] The concentration of rotavirus- and coronavirus-neutralizing antibodies in milk of vaccinated cows falls below protective levels by 3 to 7 days after parturition.[442–444] Rather than complete protection, the manifestations of passive immunity to bovine rotavirus that are often noted are (1) a delay of a few days in the onset of clinical signs, (2)a reduced severity of clinical signs, and/or (3) a reduction in the length of the period of viral shedding associated with infection.[445] Although there are reports of successful field trials involving bovine rotavirus— and bovine rotavirus-coronavirus—vaccinated cows,[402,446,447] negative esults have also been reported.[448] A common problem with commercial vaccines on the market in the United States and Europe is a lack of vaccine-specific data supporting efficacy claims. Protection correlates with serum titers; independent studies have sometimes failed to demonstrate effective seroconversion with some products.[449]

20.16.4 Nonspecific Immunity

20.16.4.1 DIET

The microbial quality of the diet is an important factor in preventing diarrhea. Calves that are fed milk from mastitic quarters or antibiotic-containing milk are at increased risk for diarrhea.[335] After fresh colostrum feeding, young calves have less diarrhea if placed on whole cow's milk rather than on other diets. Pasteurizing surplus colostrum and waste milk reduces the incidence of diarrhea in animals on these diets.[450] It is also important to offer a good-quality calf starter from approximately 2 to 3 days of age; at first little will be ingested, so offer small amounts and keep it fresh.

Some producers routinely administer vitamin A to neonatal calves. Many, but not all, studies in children indicate that supplementation can reduce the incidence of diarrhea in areas in which clinical and subclinical vitamin A deficiency is endemic.[451] In cattle, vitamin A deficiency is most likely when a diet of unsupplemented straw and grain is fed. Calves born to cows fed good-quality green forage or cattle receiving a vitamin A supplement should not require supplementation—particularly if they received adequate colostrum. Enteric absorption of vitamin A is diminished in calves with cryptosporidiosis, so the systemic route should be used in calves with this type of infection.[452]

20.16.4.2 BIOSECURITY

Infectious diseases are often purchased with brought-in stock. Operations that buy calves for rearing purposes should be encouraged to buy from as few sources as possible. Direct purchase from one farm is best; assembling collections of calves through auction markets should be avoided if possible.

20.16.5 TREATMENT OF INDIVIDUAL CALVES

20.16.5.1 Examination

Physical examination of the diarrheic calf is the first step in establishing therapeutic needs. It is important to determine the presence of any intercurrent disease. Treatment of uncomplicated cases of diarrhea depends on the estimation of dehydration, severity of acidosis, likelihood of intercurrent infection, presence or absence of hypothermia, and hypoglycemia. The severity of dehydration is gauged from the eyeball position and skin tent (Table 20-6). In acute diarrhea the degree of enophthalmus is the most reliable indicator of dehydration, but because the position of the eye within the orbit is also dependent on body fat stores, the skin tent in the cervical region may be the most reliable in calves with chronic diarrhea or cachexia.[453] Skin tent can be measured over the eyelids and neck. Best results are obtained when the neck is held straight and the skin of the midneck is tented in the direction of the long axis of the neck to avoid the natural skinfolds that run across the neck. Some have claimed a relationship exists between severity of dehydration and acidosis. However, this has not been borne out in studies of diarrheic calves.[454] Instead, acidosis can be gauged from the calf's sucking or drinking drive, the degree of weakness, and the age of the calf (Fig. 20-4).[454,455] Estimation of severity of acidosis either from laboratory or physical findings is very important to the successful therapy of severely depressed calves. Rectal temperature measurement will determine whether or not the calf is hypothermic.

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Heart rate is variable in diarrheic calves. Bradycardia (<90 beats/min) is clinically important and may indicate the presence of hypothermia, hypoglycemia, or hyperkalemia. Cardiac arrhythmias occur[455] and are usually a result of severe hyperkalemia (K^+ above 8 mEq/L) (Fig. 20-5). Hyperkalemic arrhythmia can usually be differentiated from arrhythmia resulting from cardiomyopathy (selenium deficiency) because the heart rate is not elevated. The presence of bradycardia or arrhythmia indicates the need for immediate fluid therapy with bicarbonate-containing solutions to prevent death.

Body condition is usually good at the start of an attack of diarrhea. Poor condition often indicates chronic infection, mismothering, or poor feeding programs, which may be exacerbated by milk withdrawal for therapeutic purposes.

It is important to check for intercurrent infections, which are easily missed even with careful examination. The lungs should be examined for signs of pneumonia; the navel palpated for pain, swelling, and wetness; and the joints checked for signs of distention and lameness. The boundary between calves in which the primary insult is septicemia with a secondary diarrhea and those in which primary diarrhea is complicated by septicemia is blurred. Calves that are recumbent, under a week of age, have lost their suck reflex, or have evidence of intercurrent infection are more likely to be septicemic and require concurrent antibiotic therapy.[456] Calves in which septicemia has progressed to produce signs of meningitis (e.g., extended neck with reluctance to flex neck), joint involvement, or ophthalmic signs (congested scleral vessels withhypopyon or iridospasm) have a

poor to very poor prognosis. It is best to identify these cases before instituting therapy so that the owner can decide whether treatment is economically feasible.

Table 20-6 Guidelines for Assessing Dehydration in Neonatal Calves

% Dehydration	Eyeball Sunkenness	Neck Skin Tent (Seconds)	Mucous Membranes
0	None	<1	Moist
1–5	None to slight	1–4	Moist
6–8	Slight separation of eyeball and globe	5–10	Tacky
9–10	Gap, <0.5 cm, between eyeball and orbit	11–15	Tacky to dry
11–12	Gap, 0.5 to 1 cm, between eyeball and orbit	16–45	Dry

The laboratory is useful for quantifying metabolic disturbances in diarrheic calves. Blood gas analysis will accurately determine the degree of metabolic acidosis. This is not routinely available to most practitioners. However, it may be worthwhile to make special efforts to get measurements when setting up a fluid therapy protocol for your area or when dealing with cases that fail to respond to treatment. Blood can be collected into a heparinized syringe and the syringe capped, placed in a Styrofoam cup surrounded by ice, and transported 4 hours or more to a laboratory. Alternately, the practice laboratory may have a total CO_2 (Harleco) analyzer or access to serum bicarbonate estimation as part of the serum chemistry profile. Total CO_2 or bicarbonate is a useful index of the severity of metabolic acidosis. Blood glucose can be readily determined using a hand-held Glucometer.

20.16.5.2

Fluid Therapy

The most common causes of death in diarrheic calves are dehydration and acidosis.[457] The immediate objective in treating depressed diarrheic calves is to restore them to a normal systemic state. In some calves it may also be necessary to correct hypoglycemia or hypothermia, restrict milk intake, or give antibiotics.

The estimated severity of dehydration can be combined with estimates of losses through diarrhea and for the maintenance of essential functions to give the total daily fluid requirement (see Table 20-6). The hydration status of the calf can be estimated from the degree of enophthalmus, the degree of skin tent on the neck, and evaluation of the mucous membranes (see Table 20-6). The volume (L) required to replace the deficit is determined as follows:

$$\text{Volume}\,(\text{L}) = \%\ \text{Dehydration} \times \text{Calf body weight}\,(\text{kg})$$

The ongoing losses through diarrhea should be estimated from the nature and volume of the diarrhea. Fecal losses can range from 1 to 6 L in diarrheic calves.[458] Maintenance requirements have been estimated at 50 to 100 mL/kg/day.[6,458] The degree of hydration and the volume of feces passed should be reassessed daily, and the treatment adjusted accordingly. Only 60% to 80% of oral fluids are absorbed, and this needs to be accounted for in the calculation.[459]

Bicarbonate requirements can be calculated from base deficit values (based on blood gas measurements or estimated from physical findings) as follows:

$$\text{Bicarbonate}\,(\text{mmol}) = \text{Body weight}\,(\text{kg}) \times \text{Base deficit}\,(\text{mmol}/\text{L}) \times 0.5$$

A chart of bicarbonate requirements for various body weights and base deficit values is available (Table 20-7).

Measurements of serum total carbon dioxide content or bicarbonate are also reliable estimates of bicarbonate requirements.[460] Bicarbonate requirements are as follows:

$$\text{Bicarbonate}\,(\text{mmol}) = \text{Body weight}\,(\text{kg}) \times (30 - \text{TCO}_2) \times 0.6$$

For example a 40-kg calf has a serum bicarbonate or TCO_2 of 10 mmol/L. The calf has a bicarbonate deficit of 30 mmol/L – 10 mmol/L = 20 mmol/L, so 40 kg × 20 mmol/L × 0.5 = 400 mmol bicarbonate required to replace existing deficits. Ongoing diarrhea may require additional bicarbonate.

Calves that are unwilling to suck and that are severely depressed are best treated with intravenous fluids. Calves that are only moderately depressed may also be treated with intravenous fluids if the condition is worsening rapidly. Catheterization is easier if a No. 15 scalpel blade is used to nick the skin. If it proves very difficult to catheterize the calf, it can be suspended upside down so that blood will pool and distend the jugular veins. The calf's neck should be clipped and prepared before inversion, and the calf laid flat as soon as the catheter is placed. It should be possible to place a catheter in less than a minute even in severely dehydrated calves using this technique. Once the catheter is placed, fluids can be administered. If the calf is hypothermic the fluids should be warmed before administration because cold fluids can decrease cardiac output and may kill a critically ill calf. Fluids can be warmed by a number of methods; one convenient technique is to run the fluids through a coil of tubing immersed in a bucket of hot water (check the temperature regularly) on the way to the calf.

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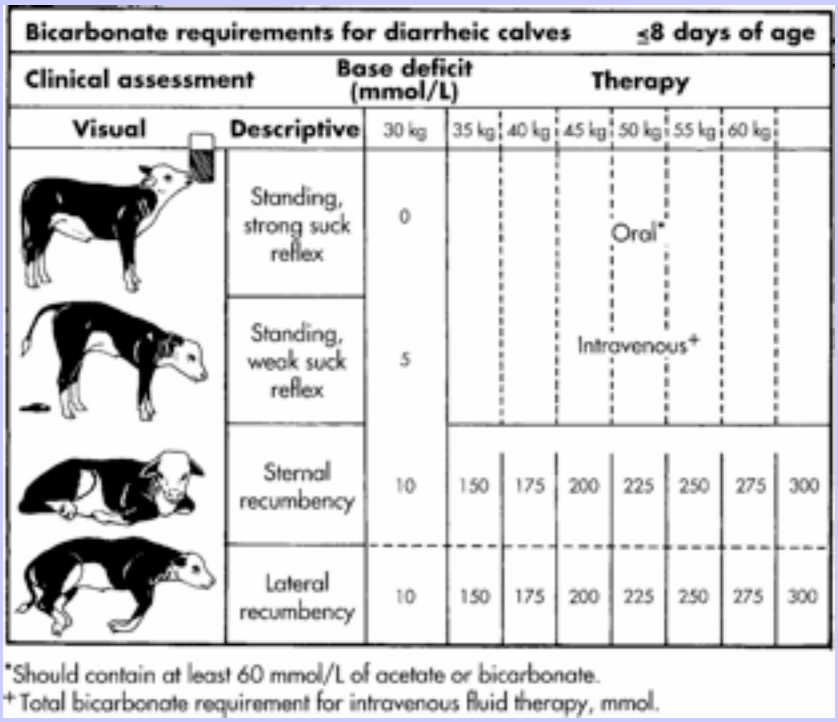
Fig. 20-4 Prediction of severity of metabolic acidosis from body position, strength of suck reflex, and age.



Bicarbonate requirements for diarrheic calves ≤8 days of age

Clinical assessment		Base deficit (mmol/L)	Therapy						
Visual	Descriptive	30 kg	35 kg	40 kg	45 kg	50 kg	55 kg	60 kg
	Standing, strong suck reflex	0	Oral*						
	Standing, weak suck reflex	5	Intravenous+						
	Sternal recumbency	10	150	175	200	225	250	275	300
	Lateral recumbency	10	150	175	200	225	250	275	300

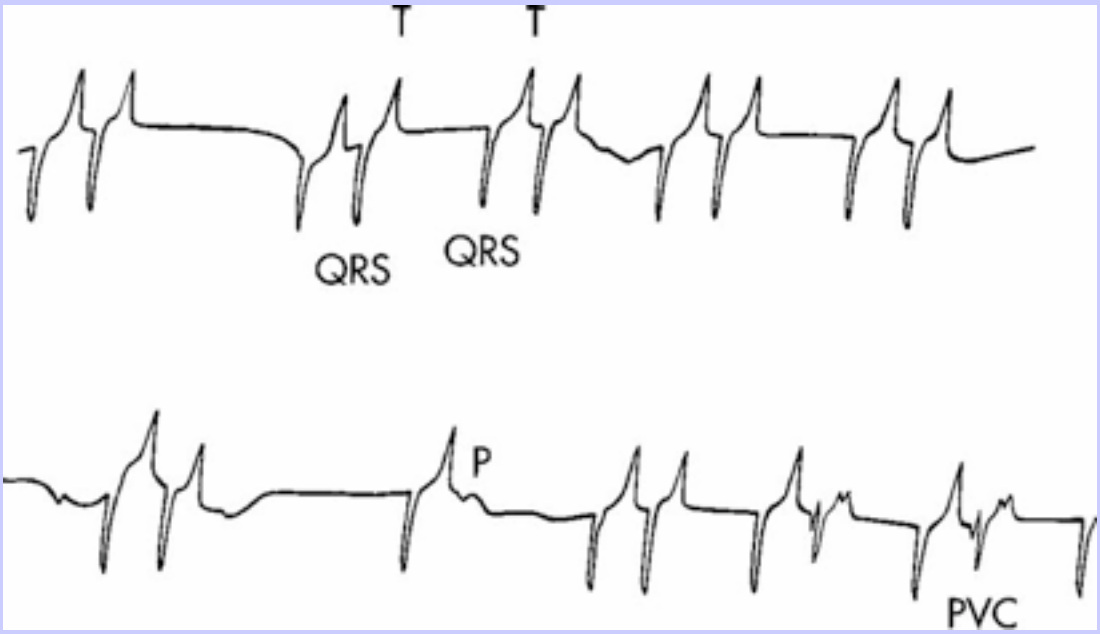
*Should contain at least 60 mmol/L of acetate or bicarbonate.
+Total bicarbonate requirement for intravenous fluid therapy, mmol.

Bicarbonate requirements for diarrheic calves >8 days of age

Clinical assessment		Base deficit (mmol/L)	Therapy						
Visual	Descriptive	30 kg	35 kg	40 kg	45 kg	50 kg	55 kg	60 kg
	Standing, strong suck reflex	5	Oral*						
	Standing, weak suck reflex	10	Intravenous+						
	Sternal recumbency	15	225	262.5	300	337.5	375	412.5	450
	Lateral recumbency	20	300	350	400	450	500	550	600

*Should contain at least 60 mmol/L of acetate or bicarbonate.
+Total bicarbonate requirement for intravenous fluid therapy, mmol.

Fig. 20-5 Bradycardia and atrial standstill in a severely hyperkalemic diarrheic calf. Heart rate is 84 beats/min. There is bigeminy, and the T waves are abnormally large. There is only one P wave, and it is not conducted. Serum potassium was 8.9 mmol/L, and sodium 116 mmol/L.



Although saline-based fluids are suitable for rehydration (Table 20-8), most severely depressed calves are acidotic, and more consistent recovery is obtained if an alkalizing agent is also used. A wide variety of alkalizing agents is available (lactate, acetate, gluconate), but clinical trials show that only bicarbonate is consistently effective in severely acidotic calves (Fig. 20-6).[93,461] Many diarrheic calves require large amounts of bicarbonate to correct their acidosis.[91] An isotonic solution (156 mmol/L) of bicarbonate can be readily made by dissolving 13 g of sodium bicarbonate (baking soda) in 1 L of water.[462] Sodium bicarbonate solutions can be mixed with saline; there is a possibility that precipitates may form if bicarbonate is mixed with calcium-containing solutions such as Ringer's.

Some clinicians may prefer to rehydrate the neonate first and then reconsider the need for bicarbonate if it is not up and sucking within 12 hours of therapy. However, this is time-consuming. It is not always necessary to completely correct acidosis; blood pH from 7.25 to 7.45 has little adverse affect (normal calves have a venous blood pH of 7.34, bicarbonate of 30 mmol/L, and a base excess of 5 mmol/L).

Ideally, dehydration and acidosis should be corrected over a 24-hour period. However, it is unusual to see problems when the fluid and acid-base deficits are corrected over 4 hours, although the calf may continue to improve after this period. Rapid resuscitation techniques include the administration of either hypertonic saline dextran or hypertonic sodium bicarbonate. Hypertonic saline dextran (7.2% saline containing 6% dextran 70) administered at 4 mL/kg of body weight during a 4-minute period concurrently with an isotonic alkalizing oral

electrolyte solution is effective in resuscitating dehydrated calves with diarrhea.[463,464] Hyperosmotic sodium bicarbonate solutions may also be used to rapidly resuscitate acidotic dehydrated calves.[465] The base deficit can be corrected by administering 8.4% sodium bicarbonate IV at a rate of 1 mL/min/kg over 15 minutes.[466,467] Hypertonic fluids should always be given concurrently with an isotonic oral electrolyte solution. After 24 hours of appropriate therapy, one would expect the calf to be standing and show a good suck reflex. Persistent depression is usually a sign of uncorrected acidosis or toxemia.

Table 20-7 Calculation of Bicarbonate Requirement from Calf Body Weight and Severity of Acidosis

Calf Weight (kg [lb])	Base Deficit (mmol/L)	Bicarbonate Requirements (mmol)	Volume in Liters 1.3% $NaHCO^{-}_{3}$ (L)*
30 (66)	5	75	0.5
	10	150	1.0
	15	225	1.5
	20	300	1.9
35 (77)	5	88	0.5
	10	175	1.1
	15	263	1.6
	20	350	2.3
40 (88)	5	100	0.6
	10	200	1.3
	15	300	1.9
	20	400	2.6
45 (99)	5	113	0.7
	10	225	1.4
	15	338	2.1
	20	450	2.9
50 (110)	5	125	0.8
	10	250	1.6
	15	375	2.4
	20	500	3.2
55 (121)	5	138	0.9
	10	275	1.8
	15	413	2.7
	20	550	3.6
60 (132)	5	150	1.0
	10	300	1.9
	15	450	2.9
	20	600	3.8

* Isotonic 1.3% sodium bicarbonate solution is prepared by adding 13 g of sodium bicarbonate to 1 L distilled water (155 mmol of bicarbonate per liter).

Table 20-8 Fluids Commonly Used in Intravenous Therapy

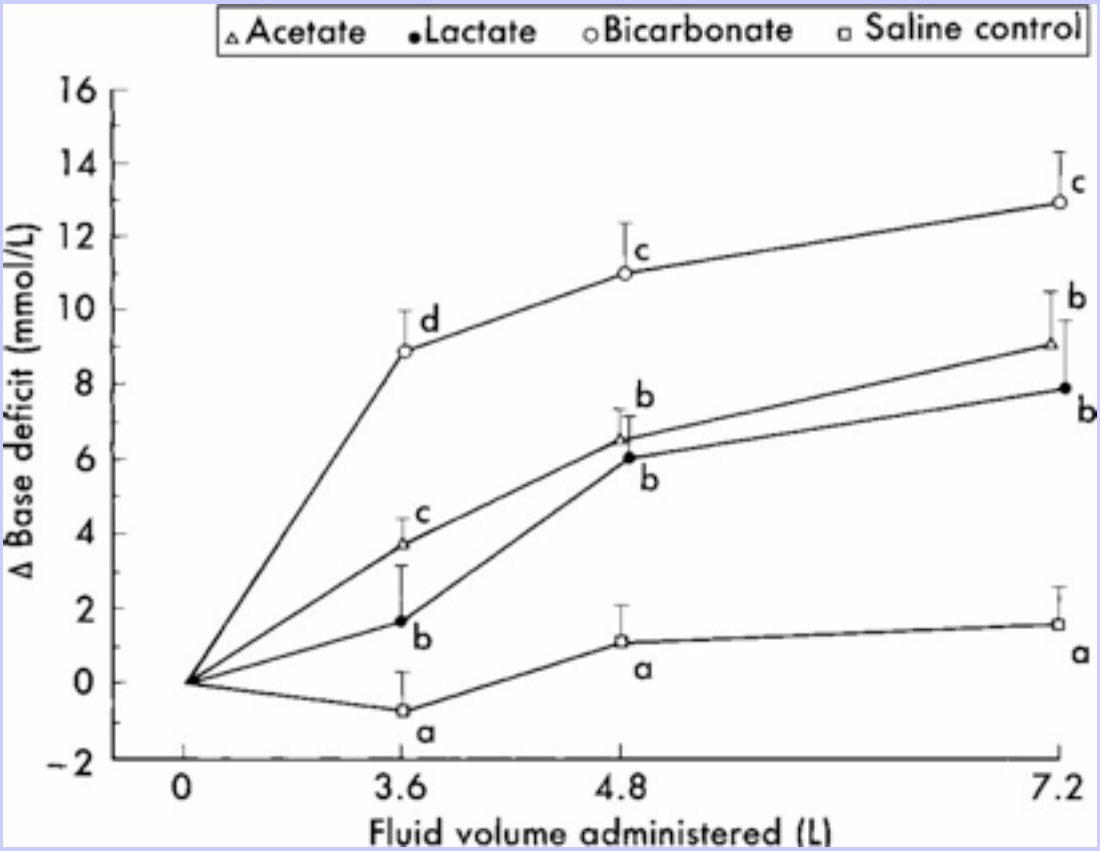
	Concentration (mmol/L)									
Item	**Na^+**	**K^+**	**Ca^{++}**	**Mg^{++}**	**Cl^-**	**HCO^-_3**	**$Lactate^-$**	**$Acetate^-$**	**$Gluconate^-$**	**Glucose**
0.9% saline	155				155					
1.3% sodium bicarbonate*	156					156				
Ringer's	147	4	5		156					
Lactated Ringer's†	130	4	3		107		30			
Ionalyte (diluted)†	139	10		3	101			55		167
Normosol R†	140	5		3	98			25	25	
Plasmalyte 148†	140	5		3	98			27	23	
5% dextrose (D_5W)‡										278

* Do not mix sodium bicarbonate with calcium-containing solutions; precipitates may form. Mixtures of 1.3% sodium bicarbonate and saline are usually used for treating recumbent diarrheic calves.

† Multiple electrolyte solutions are equivalent, with the exception that one should be careful of using Ionalyte in severely hyperkalemic neonates. All are suitable for rehydrating neonates that can stand.

‡ Intravenous fluids are often spiked with 50% dextrose to give a final concentration of 5% dextrose in the drip when hypoglycemia is suspected.

Fig. 20-6 Comparison of the alkalizing effect of various bases in diarrheic calves with severe dehydration and acidosis. At the start of the trial, all calves were at least 8% dehydrated and had a mean blood pH of 7.032 and a base deficit of 18 mmol/L. All calves received a total of 7.2 L of fluid containing 102 mmol/L of saline plus 50 mmol/L of the sodium salt of the respective alkalizing agent. Letters (a, b, c, d) are statistically different ($p < .5$) from one another at that point. From Kasari TR, Naylor JM: Clinical evaluation of sodium bicarbonate, sodium L-lactate, and sodium acetate for the treatment of acidosis in diarrheic calves, *J Am Vet Med Assoc* 187:392, 1985.



Most diarrheic calves are not markedly hypoglycemic, but glucose supplementation is needed to treat severe hypoglycemia (glucose concentrations <2 mmol/L or <36 mg/dL). Severe hypoglycemia is treated by adding glucose to the intravenous fluids to a final concentration of 2.5% to 5%. Severe hyperkalemia is seen in some dehydrated diarrheic calves, but this responds to rehydration (restores renal perfusion and dilutes out potassium) and correction of acidosis (redistributes potassium into the cells). Nutritional support is not needed

if the calf is in good body condition but should be given if the calf is emaciated or if the calf has been deprived of milk for more than 3 days.

There are increased losses of potassium in diarrhea; the significance of this is uncertain, although potassium depletion can result in weakness. Usually there is no need to add potassium to intravenous fluids; the majority of calves respond to infusion of saline and 1.3% sodium bicarbonate. After 12 to 24 hours of intravenous fluid therapy most calves start on oral electrolyte solutions. These usually contain 10 to 30 mmol of potassium per liter. Clinical trials comparing the efficacy of low and high potassium solutions have not been reported.

Once the calf is able to nurse or drink, therapy is usually switched to oral electrolytes. This is also the route of choice for treatment of mildly affected calves on the farm. Calves with weak suck reflexes and calves that are unused to hand-feeding can be administered electrolytes using an esophageal feeder. Oral electrolyte solutions need to supply sufficient sodium to facilitate normalization of extracellular fluid deficits, nutrients to facilitate absorption of sodium from the intestine, alkalizing agents to treat metabolic acidosis, and supplemental energy.[468] The first two requirements depend on the coupled active transport of glucose and sodium ions across the brush border membranes of enterocytes, which results in passive absorption of water and other electrolytes.[469] This function remains largely intact in calves with ETEC diarrhea, but when there is endothelial damage it may be impaired. Certain amino acids (glycine, L-alanine, L-glutamine) enhance the absorption of sodium and water,[469] as do acetate and propionate.[470] In order to effectively combat acidosis, oral electrolyte solutions need to contain 50 to 80 mmol of alkalizing agent per liter. Acetate, lactate, citrate, gluconate, and bicarbonate are all used as alkalizing agents. Bicarbonate combines with hydrogen ions directly, whereas the other agents remove hydrogen ions during their metabolism within cells.[458] Electrolyte solutions that contain >40 mmol of bicarbonate or citrate per liter have marked adverse effects on milk clotting.[471] Bicarbonate raises abomasal pH, whereas citrate binds calcium, and so the presence of either interferes with the normal clotting of milk in the abomasum. Breakdown of abomasal milk clots results in the gradual release of some nutrients into the small intestine. Bicarbonate also reduces milk digestibility. A reduced growth rate was recorded when electrolyte solutions with bicarbonate were fed to milk-fed calves.[472] Solutions containing bicarbonate may also alkalize the gastrointestinal tract of milk-fed calves and promote bacterial overgrowth in the small intestine as well as ETEC attachment and toxin production.[473] Acetate is the best alkalizing agent to include in electrolytes that are to be fed to calves that are still receiving milk; it has excellent alkalizing ability and does not interfere with milk clotting in the abomasum. Any of the commonly used alkalizing agents are likely acceptable for calves held off milk.[471]

A wide variety of oral electrolyte preparations are on the market, and different products are suited to different situations. Almost all the products contain water and electrolytes and are suitable to use for rehydration (Table 20-9). Beware of products that are designed for medicating hundreds of liters of water; the final solution is often very dilute (<10 g of electrolytes per liter) and will not rehydrate sick calves. These products are often marketed as “boosters” and “stress relievers.” Glucose and glycine are usually added to oral electrolyte solutions to facilitate sodium absorption. Research in people has shown that adding glycine to solutions containing 110 mmol/L of glucose aids rehydration. It is probable, however, that there is little additional benefit to supplementing solutions that contain more than 200 mmol/L of glucose with glycine. Solutions that contain large amounts of glucose are hyperosmolar and are absorbed more slowly than isotonic solutions, but the differences are too small to be clinically important.[474] The ionic composition also affects absorption; mixtures containing sodium chloride and citrate, bicarbonate, or acetate have improved absorption over chloride salts alone. Oral electrolyte solutions are almost completely absorbed in healthy calves, but absorption can be as low as 60% in severe *E. coli* diarrhea.[475]

The ability to counteract acidosis varies greatly among oral electrolytes. Some have a net acidifying effect, whereas others alkalize blood (Fig. 20-7). These differences are therapeutically important and are responsible for differences in survival rates among products. Highly alkalizing solutions give the best results. One study showed that it was more important that an electrolyte solution contain bicarbonate than chloride.[476] This is particularly important in older calves. Recently there has been interest in adding glutamine to oral electrolyte solutions because it is an important fuel for the gastrointestinal tract and can promote mucosal repair.[477–479] However, studies show that oral electrolytes containing glutamine as the sole amino acid are no more effective in diarrheic calves than other well-designed solutions that use glycine as the amino acid.[480] Psyllium has been added to some oral electrolyte solutions for a number of perceived benefits, but controlled studies show no clinical advantages, although there may be some moderation of bacterial fermentation within the gastrointestinal tract.[481,482]

Table 20-9 As-Fed Composition of Some Available Oral Electrolyte Solutions for Calves

Product	Company	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	HCO_3^- (mmol/L)	Acetate (mmol/L)	Citrate (mmol/L)	Propionate (mmol/L)	Glucose (mmol/L)	Glycine (mmol/L)	Alkalising Ability (mEq/L)	Additional Contents
Advance Arrest	MS Specialty Nutrition	46	7	?	?	?	?	?	97	0	?	Protein and minerals
Advance Pro-Lyte Plus	MS Specialty Nutrition	117	23	?	?	0	?	0	200	?	?	Probiotics and protein
ASGOLD	Volac	84	10	74	19	0	0	0	103	0	19	Fecal bulking agents and vitamins
Blue Ribbon	Merrick's Inc.	156	20	?	?	?	?	?	200	?	?	Probiotics
Bluelite C	TechMix, Inc.	48	34	57	0	0	?	0	?	0	?	
Bounce Back	Manna Pro	150	9	122	37	0	0	0	166	0	37	
Calf Goldlyte	Bio-Vet	154	27	92	?	0	?	?	?	?	?	Vitamins, minerals and probiotics
Calf Quencher	Vedco	142	24	80	86	0	0	0	399	0	0	
Calf Restart One-4	TechMix, Inc.	261	153	?	0	0	?	0	?	0	?	Immunological and dietary protein, additional water-soluble carbohydrates (energy), probiotics, vitamins and minerals
Calf-Gel 95	Van Beek Scientific LLC	42	9	?	?	0	?	?	?	0	?	Mucopolysaccharides and vitamins
C.H.E.E.R.S.	Nouriche Nutrition Ltd.	90	30	50	0	?	?	?	40*	40	?	
Comeback	AgriPharm	112	24	?	0	0	?	0	?	?	?	
Deliver with Dialine	AgriLabs	77	14	16	37	0	4	0	82	0	49	Fecal bulking agents
Deliver extra with Dialine	AgriLabs	95	19	?	?	0	?	?	?	0	?	Glutamine, probiotics, psyllium and natural vitamin E
Diaque	Boehringer Ingelheim	87	12	54	?	?	?	0	155	7	?	Probiotics and fecal bulking agents
Electrate	Bimeda	165	10	103	0	82	0	0	142	0	82	
Electrolyte with Thickener	DVM Formula (Vets Plus)	110	20	50	80	0	0	0	132	25	80	Fecal bulking agents
Electrolytes Plus Supplement	Sav-A-Caf (Milk Products)	137	7	?	18	0	0	0	249	30	18	Kaolin, probiotics and additional energy as starch
Ener-Lyte	Aspen	132	19	?	?	0	0	0	?	0	?	Probiotics, vitamins, minerals and bulking agents
Entrolyte	Pfizer Animal Health	106	23	46	80	0	0	0	166	22	80	Additional amino acids
Entrolyte HE	Pfizer Animal Health	100	23	45	78	0	0	0	449	38	78	
EPIC Calf Electrolyte	Bioniche Animal Health	99	20	86	0	57	0	0	?	0	57	Immunoglobulins and immune co-factors
Formula 911	Advantech	132	19	?	?	0	0	0	?	?	?	Probiotics, vitamins and minerals

Hydrafeed	Vet Pharm	115	11	62	86	0	14	0	96	32	128	Protein, fibre and lactose (glucose and galactose)
Hydra-Lyte	Vet-A-Mix	85	30	45	0	60	10	0	368	16	90	
Hy-sorb	Bimeda	113	9	64	38	0	9	0	53	38	66	
Land O Lakes Electrolyte System Base	Land O Lakes	99	21	?	0	0	?	0	?	0	?	Vitamins
Land O Lakes Electrolyte System Base + Add pack	Land O Lakes	140	21	?	40	0	?	0	?	?	?	Vitamins
Lifeaid Extra	Norbrook	90	25	60	0	20	7	10	175	0	50	
Nutri-Sorb	AgriPharm	70	16	63	23	0	0	0	125*	0	23	Glutamine and psyllium
One Day Response	Farnam	81	10	?	?	0	?	0	?	0	?	Psyllium and additional energy as fat
Re-sorb	Pfizer Animal Health	80	26	80	0	0	2	0	129	45	5	
Revitilyte	Bomac Vets Plus, Inc.	110	20	50	80	0	0	0	174	25	80	Starch
Revitilyte-Gelling	Bomac Vets Plus, Inc.	110	20	50	80	0	0	0	132	25	80	Starch as a gelling agent

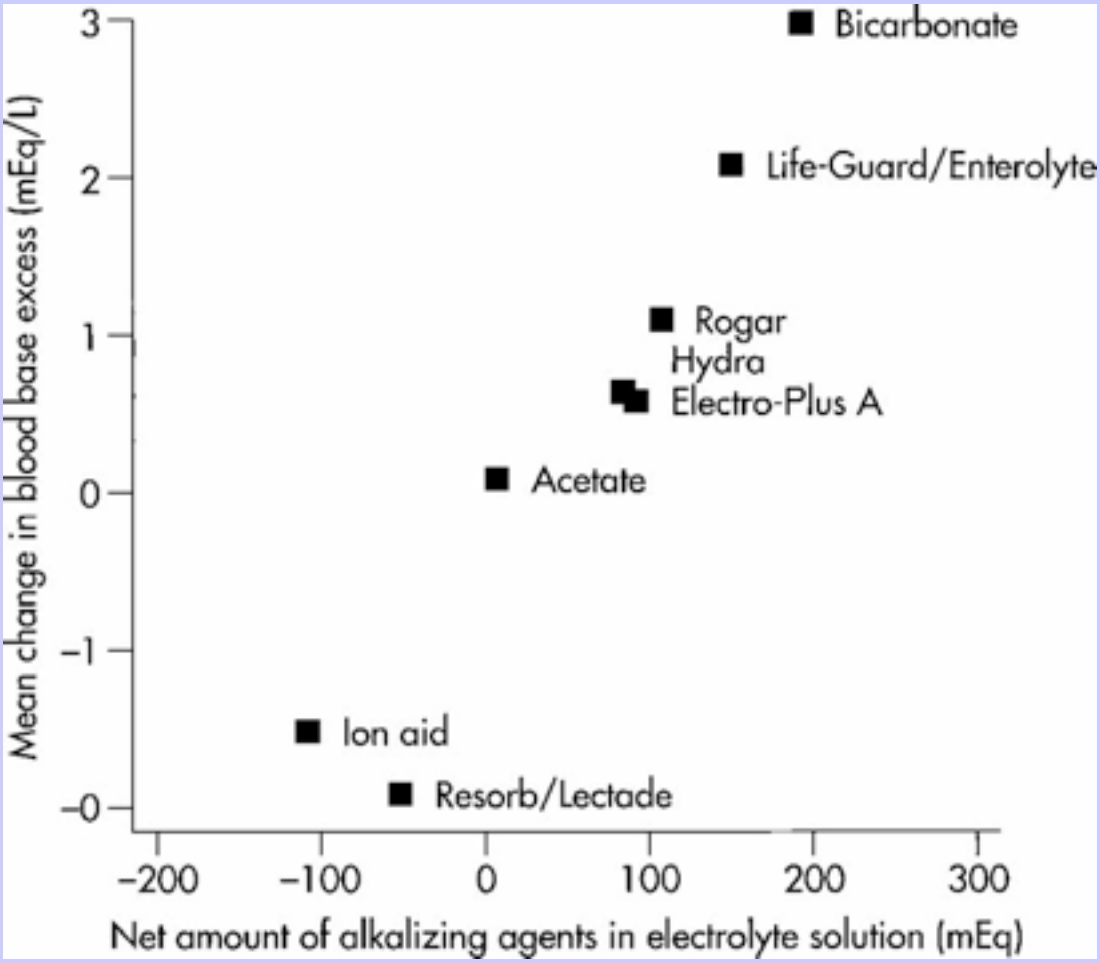
Updated table based on Naylor JM: Oral electrolyte therapy, *Vet Clin North Am Food Anim Pract* 15:487, 1999. Calculated from information listed in the Compendium of Veterinary Products, 2007 and product labels. Additional information obtained from Jones C, Kehoe S and Heinrichs J: Comparison of some available oral rehydration products. Pennsylvania State University, 2006, Department of Dairy and Animal Science, http://www.das.psu.edu/pdf/electrolytetable.pdf.

Note: Concentrations of calcium, magnesium, phosphate, and sulfate not included. Molarities assume that all compounds dissociate completely in solution. Where a maximum and minimum value for a compound was provided the mean value has been used.

?, Published information insufficient to provide reasonable estimate.

* Contain maltodextrins (glucose polymers). It has been assumed that these will be completely digested to provide glucose.

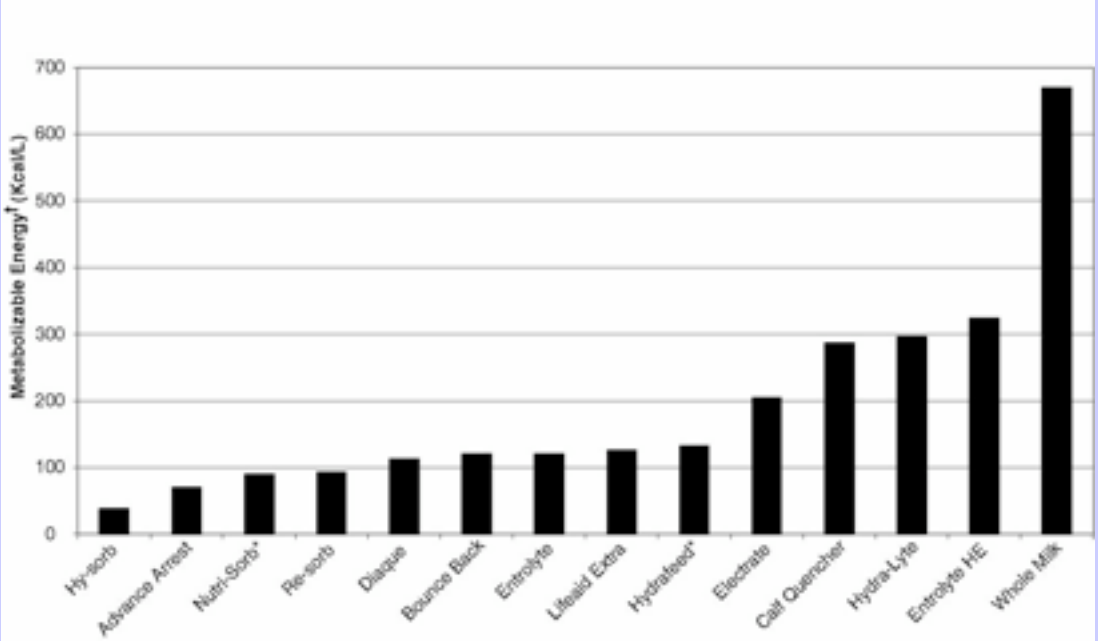
Fig. 20-7 Comparison of the alkalizing abilities of various oral electrolyte solutions. The Y axis shows the mean alkalizing effect after administration of one treatment (1.9 to 2.25 L) of the fluid to healthy calves, and the X axis shows the net amount of alkalizing agents in the solution. Bicarbonate and acetate are experimental solutions. (Life-Guard/Enterolyte is manufactured by SmithKline Beecham Labs, Rogar is Rogar STB's electrolyte powder, Hydra is manufactured by Vetrepharm, Electro-Plus A by Pitman-Moore, Ion Aid by Syntex, and Re-Sorb by Beecham.) *Modified from*Proc 14th World Congr Dis Cattle *1:362, 1986.*



The other problem to be considered in the chronically scouring calf is the need for nutritional support. Maintenance metabolizable energy requirements for a 50-kg calf are about 2000 kcal, and 3500 kcal are required to support a weight gain of 0.5 kg/day. These requirements can be met by 3.3 and 5.7 L of whole

cow's milk, respectively. Comparative studies indicate that weight loss in calves fed oral electrolytes are inversely proportional to the energy content of the solutions.[483] Assuming a 4-L daily intake and 100% digestibility of oral electrolyte nutrients, regular electrolyte solutions supply between approximately 15% and 25% of energy needs. As a result, diarrheic calves that are held off milk for prolonged periods lose weight[484] and can become emaciated. When maintaining body condition is a concern and little milk or solid food is being ingested, then a high-energy oral electrolyte should be fed. Products such as Enterolyte HE provide about 50% of energy requirements if fed twice a day (total intake 4 L) and about 75% if fed three times a day (total intake approximately 6 L). The energy content of various oral electrolyte solutions is presented in Figure 20-8.

Fig. 20-8 Comparison of the energy contents of various oral electrolyte solutions. Milk is also shown for comparative purposes. *ME estimated from water-soluble carbohydrate composition. †ME estimated from glucose and other water soluble carbohydrate composition of as-fed electrolyte solution assuming 1g (cry matter) of carbohydrate = 4kcal. This figure assumes electrolyte solutions are fed to neonatal calves prior to rumen development. (See text for manufacturers.)



20.16.5.2.1

MILK WITHDRAWAL

Milk withdrawal can reduce the severity of diarrhea and depression in severe scours. This is because malabsorption exacerbates diarrhea through the osmotic effect of unabsorbed milk nutrients and also promotes bacterial overgrowth and possibly malfermentation with production of organic acids. Milk also

has a trophic effect on epithelial cells and maintains higher gastrointestinal tract enzyme activities as well as providing protein for repair of damaged intestinal epithelium.[470] In experimental trials, continued feeding of milk maintained weight gain; however, when calves were fed enough milk to fully meet their requirements and the undrunk milk was tube-fed, calves initially had greater inappetence.[472,485] Withdrawal of milk without a high-energy alternative can rapidly result in cachexia and malnourishment.[472] In many calves, particularly the less severely affected, there is often a considerable degree of residual absorptive capacity; enough to support body weight gain if limited amounts of milk are fed. Milk withdrawal is recommended if the calf is depressed and not interested in sucking. In most cases electrolyte therapy will restore a calf's vigor and sucking drive within 1 to 2 days. Milk can then be reintroduced in small amounts (e.g., 1 L given two to four times daily). However, forced feeding (by tubing or drenching), dysfunction of the reticular groove reflex, or reflux of abomasal contents may result in ongoing acidosis because of production of D-lactate from fermentation of carbohydrates entering the reticulorumen.[98] If the calf is not interested in drinking or gets depressed when reintroduced to milk, a high-energy oral electrolyte preparation can be tried instead. Studies indicate that diarrheic calves have a generalized malabsorption rather than specific lactose intolerance.[88] Thus it may be more important to manage calves with milk intolerance by giving smaller amounts of milk in each feed instead of changing carbohydrate source. There is little point in withdrawing milk from calves that remain alert and interested in nursing; it is unlikely to result in clinical improvement. This is particularly likely to be the case when the calf receives whole cow's milk in frequent small quantities, that is, by natural sucking of the dam.

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20.16.5.3 Role of Antimicrobials

There is some controversy regarding the use of antimicrobials for the treatment of calf scours. Reports questioning the use of antimicrobial therapy cite lack of efficacy, potential for adverse effects, potential for violative residues, and selection for antimicrobial resistance. Conversely, there are reports describing attenuation of clinical disease, reduced pathogen shedding, and lower mortality after the use of antimicrobials to treat scouring calves.

20.16.5.3.1 THERAPEUTIC TARGETING

Bacterial pathogens associated with neonatal calf diarrhea include *Salmonella* and *E. coli*. During disease outbreaks caused by these pathogens antimicrobial use may be targeted at the specific pathogen. Beneficial responses to antimicrobial therapy have also been reported in field trials involving undifferentiated pathogens.[486,487] Calves with diarrhea often have increased coliform bacterial numbers in the small intestine, regardless of cause,[488–490] and this colonization is associated with altered small intestinal function, morphologic damage, and increased susceptibility to bacteremia.[490] Calves with diarrhea are more likely to have FPT or partial FPT, and this group of calves, in turn, is more likely to be bacteremic.[491,492] Blood cultures indicate that gram-negative bacteria account for approximately 80% of bacterial isolates. *E. coli* is the species most commonly isolated.[491,493,494] In a study of 190 recumbent calves on a large calf-raising facility, 31% were determined to be bacteremic; *E. coli* accounted for 51% of the isolates; other gram-negatives, 25%; gram-negative anaerobes, 5.9%; gram-positive cocci, 11.8%; and gram-positive rods, 5.9%.[491]

Antimicrobial therapy may therefore be targeted at a specific bacterial enteric pathogen isolated from sick calves or in severely ill calves (as manifested by reduced suckle reflex, >6% dehydration, weakness,

inability to stand, or clinical depression) may be used prophylactically to manage the risk of bacteremia. For this application, emphasis should be directed toward gram-negative organisms, particularly *E. coli*.

20.16.5.3.2

ANTIMICROBIAL SUSCEPTIBILITY

Antimicrobial susceptibility testing of fecal isolates is not a good predictor of clinical outcome. Three studies have reported no correlation between in vitro antimicrobial susceptibility of fecal *E. coli* and *Salmonella* species isolates and clinical response to antimicrobial treatment.[495–497] Antimicrobial efficacy is best evaluated by the clinical response of a number of calves to treatment, with calves randomly assigned to treatment groups, rather than by the results of in vitro antimicrobial susceptibility testing performed on fecal *E. coli* isolates.[498]

Antimicrobial susceptibility testing has more clinical relevance for predicting the clinical response to antimicrobial treatment when applied to bacteria isolated from blood or tissues of bacteremic calves because the MIC break points are based on achievable antimicrobial concentrations in human plasma and MIC_{90} values for human *E. coli* isolates, which provide a reasonable approximation to achievable MIC values in calf plasma and MIC_{90} values for bovine *E. coli* isolates.[498] Even within a given herd there will be a diversity of bacteria isolated from bacteremic calves, so the collection of blood cultures and assessment of antimicrobial susceptibility does not necessarily provide information applicable to the next case.

20.16.5.3.3

ANTIMICROBIAL SAFETY

A number of antimicrobials have been demonstrated to produce deleterious effects when administered orally to healthy milk-fed dairy calves. The addition to milk replacer powder of procaine penicillin (2 to 60 mg/kg of milk replacer) increased the incidence and duration of diarrhea and decreased growth rate compared with untreated controls in a total of 36 milk-fed calves.[499] Penicillin is not labeled for treatment of calf scours and has an inappropriate antimicrobial spectrum to prevent or treat calf scours. Administration of neomycin sulfate (300 mg PO q24h for the first 4 days of life) tended ($p = .060$) to increase the proportion of calves developing diarrhea (99/233 = 43%) compared with the proportion in an untreated control group (58/174 = 33%).[500] Administration of neomycin sulfate (25 mg/kg PO q6h, n = 10), ampicillin trihydrate (12 mg/kg PO q8h, n = 6), or tetracycline hydrochloride (11 mg/kg PO q12h, n = 6) for 5 days increased the occurrence of diarrhea and decreased glucose absorption through unknown mechanisms compared with untreated controls (n = 6).[501] Two other studies did not observe adverse side effects in calves administered tetracycline hydrochloride (40 mg PO q12h; 11 mg/kg PO q12h).[502,503]

20.16.5.3.4

EFFICACY OF ORAL ANTIMICROBIAL THERAPY

The response to oral antimicrobial therapy is variable, with many formulations failing to demonstrate a beneficial effect.[498] Apramycin administered PO at either 20 or 40 mg/kg significantly decreased mortality.[487] Trials with orally administered neomycin reduced the duration of diarrhea but did not reduce mortality.[504,505] Similarly, trials with orally administered ampicillin failed to demonstrate a significant reducccction in mortality.[506] The results of trials with orally administered trimethoprim have been variable, with no significant improvement in outcome observed in a large field trial[507] and a significant reduction in mortality observed in an experimental *Salmonella* challenge study in which calves were administered 5 mg or

trimethoprim per kilogram and 25 mg of sulfadiazine per kilogram PO daily for 5 days.[508] Orally administered amoxicillin trihydrate has been demonstrated to reduce mortality and the duration of diarrhea when administered at a dose of 10 mg/kg PO q12h.[77,509]

In an epidemiologic study of *Salmonella* in dairy calves conducted in the United States, feeding medicated milk replacer and hay to calves from 24 hours of age to weaning was associated with a reduced risk of *Salmonella* shedding.[510] This observation contradicts an experimental study in which feeding chlortetracycline in milk replacer increased the severity of disease and the rate and duration of *Salmonella* shedding.[511] Similarly in another experimental trial, daily drenching of calves with 50 mg or 100 mg of chlortetracycline failed to alter the excretion pattern or the number of organisms excreted by calves infected orally with 10^6 *S. typhimurium*.[512]

20.16.5.3.5

EFFICACY OF PARENTERAL ANTIMICROBIAL THERAPY

Antimicrobial drugs with an appropriate gram-negative spectrum of activity include third-generation cephalosporins (ceftiofur), potentiated penicillins (amoxicillin), trimethoprim-sulfonamide (TMS) combinations, aminoglycosides, sulfonamides, florphenicol, and tetracyclines. There is a paucity of efficacy data to support the use of aminoglycosides, tetracycline, nonpotentiated sulfonamides, and florphenicol.

Ceftiofur has an appropriate antimicrobial spectrum, and therapeutic drug concentrations can be maintained with once-daily dosing. In an *S. typhimurium* challenge experiment, intramuscular administration of ceftiofur hydrochloride (5 mg/kg q24h for 5 days) reduced the severity of clinical signs and reduced fecal shedding of *Salmonella*. The MIC of the challenge strain in this experiment was 1 μg/mL, and the therapeutic protocol maintained plasma concentrations above this concentration for the duration of therapy.[264]

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Potentiated sulfonamides have been evaluated in ETEC and *Salmonella* challenge experiments. Mortality in 2- to 3-week-old calves medicated with trimethoprim-sulfadiazine (in a 1:5 ratio) for 5 days 24 hours after *Salmonella* Dublin oral challenge was reduced.[508] Administration of either sulfadiazine or trimethoprim alone did not reduce mortality.[508] Trimethoprim may be used to treat sepsis in neonatal calves, but its half-life rapidly declines as ruminal function develops. In ruminating (6- to 8-week-old) calves, subcutaneous or oral administration of trimethoprim-sulfadiazine leads to high serum levels of sulfadiazine but little or no serum trimethoprim.[513]

Intramuscular administration of amoxicillin reduced mortality in *Salmonella* Dublin—challenged calves.[514] In a comparative trial of amoxicillin and trimethoprim-sulfadiazine, both drugs were found to have equal efficacy in reducing adverse clinical signs of disease when dosage regimens were based on the MIC of the pathogen.[515]

The frequency of bacteremia is sufficiently high that treatment of calves with diarrhea that are severely ill (as manifested by reduced suckle reflex, >8% dehydration, weakness, inability to stand, or clinical depression) should include routine treatment against bacteremia, with emphasis on treating potential *E. coli* bacteremia.[498] Parenteral administration of a broad-spectrum β-lactam antimicrobial—ceftiofur (5 mg/kg intramuscularly [IM] q24h), amoxicillin (10 mg/kg IM q12h), or trimethoprim-sulfadiazine (20 mg of sulfadiazine per kilogram with 5 mg of trimethoprim per kilogram IV or IM, q24h for 5 days)—is recommended for treating calves with diarrhea and systemic illness. (Note that these are off-label doses and

require an extended meat withholding period.) Antimicrobial therapy is not recommended for calves with diarrhea and no systemic illness (normal appetite for milk or milk replacer, no fever).[498]

20.16.5.4 Antiprotozoal Drugs

Drugs reported to have some efficacy against *Cryptosporidium* in calves include, halofuginone,[516–522] paromomycin,[523,524] decoquinate,[525,526] and β-cyclodextrin.[527] Halofuginone is licensed for treatment of calves in Europe and appears to be the most efficacious. The efficacy of decoquinate is questionable, with the only controlled clinical study failing to demonstrate a beneficial therapeutic effect with daily treatment at 2 mg/kg/day.[526] A trial of lasalocid for treatment of *Cryptosporidium* infection has been conducted. Using a toxic dose of 8 mg/kg was found to reduce the shedding of cryptosporidia; however, the calves suffered adverse side effects. At a dose of 0.8 mg/kg, lasalocid was not effective.[528] The registered dose for preventing coccidiosis in calves is 1 mg/kg per head per day.

Coccidiosis is uncommon in calves less than 6 weeks of age. In hand-reared calves coccidiostats (lasalocid, amprolium, or decoquinate) may be added to milk replacer. Prophylactic options for beef calves are restricted to coccidiostat medicated pellets (monensin, lasalocid, amprolium, or decoquinate) or water (amprolium or sulfonamides). Therapeutic options include amprolium or sulfonamides such as sulfadimidine.

Both fenbendazole (5 mg/kg PO once daily for 3 days) or albendazole (20 mg/kg PO once daily for 3 days) have been shown to be effective treatments for *Giardia*.[222,298,529] Because of the high level of subclinically affected animals, all cows and their dams need to be treated, and reinfection is likely to occur unless calves are removed from environmental sources of infection.

20.16.5.5 Antiinflammatory Drugs

A nonstatistical trend toward decreased morbidity has been reported in a study evaluating the benefits of a single or double injection of flunixin meglumine in scouring calves.[530]

20.16.5.6 Probiotics

Probiotics are foods or drugs containing live microbes that are expected to confer beneficial physiologic effects to the host animal through microbial actions. Bacterial and fungal species included in these products include *Enterococcus faecium*, *Lactobacillus acidophilus, Lactobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidum*, *Streptococcus salivarius* subsp. *thermophilus, Aspergillus oryzae*, and *Candida pintolopesii*. General mechanisms of action that have been ascribed to probiotics include competition for receptor sites on the intestinal surface, immune system stimulation, excretion of antimicrobial substances, and competition with pathogens for intraluminal nutrients.[531]

The number of controlled clinical trials evaluating probiotic formulations in calves is limited. In one report, feeding antimicrobial resistant *Streptococcus faecalis* to calves reared on an antibiotic-containing diet reduced *Salmonella* intestinal colonization of calves.[532] An improvement in weight gain and a reduction in diarrhea have been reported when calves were fed either 3×10^9 *Bifidobacterium pseudolongum* or *L. acidophilus* daily

from 1 to 56 days of age or a cell mixture containing 10^{10} colony forming units (cfu) of *Bacillus thermophilum*, 10^{10} cfu of *Enterococcus faecium*, and 10^{9} cfu of *Lactobacillus acidophilus* for 28 days.[533]

20.16.5.7 Intestinal Protectants

Several products that include intestinal protectants are marketed for treatment of calves with scours. Intestinal protectants include bismuth subsalicylate, kaolin or pectin, and activated charcoal. There are no efficacy data available regarding the use of kaolin in scouring calves. Suggested advantages of bismuth subsalicylate are its neutralization of bacterial toxins and antisecretory effect through its local antiprostaglandin activity.[534,535]

20.16.5.8 Prognosis

The prognosis for recovery decreases with the severity of depression. Severe hypothermia and the presence of intercurrent disease are grounds for a guarded prognosis.[536–538] An initial examination should be performed. Calves with a primary problem of septicemia are not usually worth treating because of the poor prognosis. The severity of dehydration, hypothermia, and acidosis should be estimated. Recumbent calves are usually treated IV with a saline-based rehydrating fluid (0.9% saline, Ringer's, lactated Ringer's, and so on) and isotonic sodium bicarbonate (especially for older and comatose calves). Calves that can suck are treated with oral electrolytes that contain 50 to 80 mmol/L of alkalizing agent. Products that use mainly acetate as the alkalizing agent are best for calves that are still drinking cow's milk (small quantities, frequently). Any alkalizing agent is likely effective in calves held off milk.

20.16.6 SUMMARY

Calf scours is caused by a variety of infectious agents. At the present time, the need to make a definitive diagnosis of ETEC and *Salmonella* infections has been established; these diseases can be controlled with antibiotics and prevented by vaccination.[539] There are public health implications to the diagnosis of cryptosporidiosis and salmonellosis. New vaccines may help control rotavirus and coronavirus infections. Treatment of diarrhea in neonates is primarily based on correcting dehydration and acidosis through the use of oral and intravenous electrolytes. Only in the case of bacterial infections can direct action be taken against the invading organism, but antibiotics may still be useful in preventing secondary bacteremias. Colostrum feeding will help reduce diarrhea in the first days of life. Management is very important in the control of diarrhea, and because infectious agents are almost always present at some exposure level, the underlying theme is to minimize the level of pathogen exposure and stress on the calf. In approaching a problem of neonatal death losses, the areas to be examined should include calf immunoglobulin status, calf feeding, calf housing, cleanliness of environment, calving area, cow vaccinations, diagnosis of specific infectious agents, and treatment protocols.

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20.17 LAMENESS AND RELUCTANCE TO WALK

John K. House

20.17.1 SEPTIC ARTHRITIS

Septic arthritis may result from direct trauma or contamination of the joint, extension from periarticular infection, or hematogenous spread from another site. Systemic sites of infection include enteritis, pneumonia,

and inflamed umbilical structures. FPT increases the risk of sepsis. Destruction of the epiphysis and extension of infection into the joint are common and may be primary in some cases, rather than resulting from a primary synovial membrane infection that spreads to the epiphysis or physis. The most common pathogens isolated from septic joints of neonatal calves are enteric organisms including *E. coli* and *Salmonella* species. *Streptococcus* species, *Staphylococcus* species, and *A. pyogenes* are less common isolates. *A. pyogenes* is the most frequently isolated organism from joints of older calves.[540–542]

Bacteria commonly isolated from septic joints in lambs include *Streptococcus* species, coliforms, *A. pyogenes, Erysipelothrix rhusiopathiae,* and *F. necrophorum*.[455] Predisposing factors include poor docking hygiene and contaminated sheep dip. Sporadic outbreaks of polyarthritis in lambs, kids,[30,543,544] and calves[545] are associated with *Chlamydia* and *Mycoplasma* species infections. Chlamydia infections may occur in utero or postnatally; *Mycoplasma* infections often result from ingestion of *Mycoplasma*-contaminated milk.

Diagnosis of septic arthritis is based on the combination of clinical signs, radiographic examination, bacterial culture, and cytologic analysis of synovial fluid. A bacterium is isolated in only 60% of cases of septic arthritis in bovine medicine.[546] Synovial fluid cytologic analysis is useful for the differentiation between infectious and noninfectious arthritis. Trauma is the chief differential diagnosis. Lambs and kids with septic arthritis often fail to nurse and may have significant weight loss. Typically, polyarthritis caused by *Mycoplasma* species and *Chlamydia* is associated with high fevers and respiratory and occasionally neurologic disease. High morbidity and mortality are common. Conjunctivitis is commonly observed with chlamydial infections.[543] Cytologic findings consistent with septic arthritis include a synovial fluid total protein concentration greater than 4.5 g/dL, a nucleated cell count greater than 25,000 cells/mL, a polymorphonuclear cell count greater than 20,000 cells/mL, and a percentage of polymorphonuclear cells of greater than 80%.[547] Chlamydial inclusions may be found in Giemsa-stained smears of synovial cells and the organism isolated from joint fluid or plasma in early cases.[543] Isolation of *Mycoplasma* species requires specific media (Hayflick's media) and microaerophilic conditions. Normal synovial fluid does not rule out septic physitis or osteomyelitis, because the infection may be in the physis or small tarsal bones.

Careful examination of high-quality radiographs is important for the detection of bone lysis indicating infection. Initial radiographs may be normal because the degree of damage is often not detectable for 10 to 14 days after initial infection occurs. Radiographic features of septic arthritis include soft-tissue swelling, widening or collapse of the joint space, osteoporosis, and osteosclerosis. Ultrasound may be used to confirm involvement of the joint and rule out periarticular or tenosynovial infection to avoid iatrogenic contamination of the joint during arthrocentesis. Joint distention and hyperechogenic fragments in the synovial fluid are suggestive of septic arthritis. Normal synovial fluid is anechoic.

Acute septic arthritis in neonatal ruminants may be treated effectively via joint lavage combined with systemic and local antimicrobial treatment. Typically, however, neonatal ruminants are presented with a chronic disease process. Treatment options include joint lavage or arthrotomy to remove destructive inflammatory products and long-term antimicrobial therapy. Joint lavage is rarely efficacious in the treatment of chronic septic arthritis in calves, as accumulation of fibrin and pocketing of purulent material often make adequate joint drainage impossible.[548] Joint lavage may be facilitated via use of a rigid arthroscope or, in the case of simple joints (elbow and stifle), arthrotomy.[549] Empirical antimicrobial therapy should include a gram-negative and gram-positive spectrum. Culture of synovial fluid facilitates antimicrobial selection.

Therapeutic synovial concentrations of penicillin, oxytetracycline, ampicillin, and cephapirin can be attained in inflamed and normal joints of calves after systemic administration.[550–553] The distribution of trimethoprim-

sulfadiazine, penicillin, oxytetracycline, and cephapirin in joints is not enhanced or reduced by inflammation.[550–552] Penicillin, trimethoprim, and sulfadiazine equilibrate in 0.5 to 1 hour, and oxytetracycline in 4.5 to 6 hours.[551] The subsequent decline in antibacterial drug concentration in synovial fluid parallels that in serum.[550] Synovial inflammation accelerates distribution of antimicrobial drugs into joints[551] but has little effect on the peak drug concentration achieved in synovial fluid.[550,551] The peak concentration of ampicillin in synovial fluid after a single intramuscular injection of ampicillin trihydrate at a dose of 10 mg/kg is higher in normal and inflamed synovial fluid than in sera.[553] There are few bovine-derived data regarding the distribution of the newer generation antimicrobials into synovial fluid after systemic administration. Studies in other species suggest that most classes of antibacterial drugs are capable of crossing the synovial membrane. Synovial tissue is very vascular and does not have a basement membrane. In humans, synovial fluid concentrations of most antibacterials generally average at least 60% to 70% of serum drug concentrations at the time of peak serum concentrations and frequently exceed those in serum immediately before the subsequent systemic dose in patients with septic arthritis.[554] Antimicrobial dosing is targeted to achieve a peak antibacterial concentration that exceeds the MIC of the infecting organism by fivefold to tenfold.[554] The duration of therapy is dependent on the antimicrobial sensitivity of the pathogen and the immune status of the patient; prolonged (4 to 8 weeks) antimicrobial therapy is commonly required.

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In a review of 81 cases of septic arthritis in cattle, a 72% recovery was achieved with a combination of surgical treatment (opening of the joint capsule; debridement; and excision of the synovium, infected cartilage, and bone), joint immobilization, and systemic antibiotic therapy. Of cattle treated conservatively with systemic and intraarticular antimicrobials, 43% recovered.[555]

20.17.2 NONINFECTIOUS LAMENESS

Neonatal ruminants that have nutritional myodegeneration often have a stiff, stilted gait. Lambs and kids may have difficulty nursing if they are unable to lift the head and may cry with pain when assisted to stand (see Chapter 42). Contracture of joints or tendons of the limbs produces difficulty in movement and predisposes to FPT by impeding the ability to adequately nurse. Degree of contracture varies from mild to severe and may be associated with scoliosis and/or torticollis. Conservative therapy consisting of splinting the front limbs to induce tendon laxity may be helpful. Calves with severe digital flexor tendon contractures often require surgical resection of one or both digital flexor tendons, followed by bandaging or casting and stall rest for 3 to 4 weeks.

20.18 UMBILICAL ENLARGEMENT

The umbilicus consists of three types of structures and undergoes functional and anatomic changes at birth. Two umbilical arteries connect internal iliac arteries to the placenta. These later regress and become the round ligaments of the bladder. One umbilical vein connecting the placenta to the liver and porta cava regresses to become the round ligament of the liver within the falciform ligament. The urachus connects the fetal bladder to the allantoic cavity.

20.18.1 PATENT URACHUS

Patent urachus is a persistence after birth of the tubular connection between the bladder and umbilicus. The urachus drains the bladder into the allantoic sac during gestation. Urine flow should gradually change, with some urine entering the amniotic sac through the urethra in later gestation. At birth, with umbilical cord rupture the

urachus should be closed, and urine should be voided through the urethra. Neonates with a patent urachus may dribble urine from the urachus during or after urination or may simply have a constantly wet umbilical stump.

Differential diagnoses include concurrent infection of the navel (omphalophlebitis). Ultrasound may assist in making the diagnosis and determining the involvement of umbilical arteries or vein. Moist hairs around the umbilicus and the presence of fluid coming from the navel are diagnostic. A complete physical examination should be performed. If abnormalities are noted, serum IgG, complete blood count, and urinalysis are helpful for detecting susceptibility to infection and presence of systemic or urinary tract infection. Surgical resection of the urachus to the tip of the bladder is the treatment of choice. Associated arteries and veins should be ligated and removed if they are infected or necrotic. Merely ligating the exterior stump can trap organisms and cause infection.

20.18.2 OMPHALITIS

Omphalitis is inflammation of umbilical structures that may include the umbilical arteries (omphaloarteritis), umbilical vein (omphalophlebitis), urachus, or tissues immediately surrounding the umbilicus. Umbilical abscess or infection of any of the three components of the umbilicus may produce local infection or be a source of septicemia. The source of infection is most commonly the external environment, coupled with FPT. Bacteria isolated from calf umbilical cord remnant infection include *A. pyogenes, E. coli,* and *Proteus* and *Enterococcus* species. The urachus is the most commonly affected structure in calves, and the umbilical arteries the least.[556] Omphalophlebitis may extend the length of the umbilical vein into the liver and result in liver abscessation.

When the umbilicus is enlarged and draining purulent material, infection is easily noted. When the urachus is fixed to the abdominal wall, calves are prone to cystitis and may show signs of pollakiuria and dysuria. In other cases the umbilicus may be dry and larger in diameter than expected. Some neonates may have a completely normal-appearing, dry external navel and be severely ill from infection of the urachus, umbilical arteries, or vein. In a neonate with sepsis without external signs of infection, involvement of the umbilicus can be difficult to determine. Abdominal palpation of the umbilical vein and arteries is a useful, simple, and effective means of assessing their size and of detecting pain associated with these structures. Inflamed structures may be identified by standing behind the neonate and pressing the hands together above the umbilicus. Ultrasound is also a useful ancillary diagnostic aid.[557] Persistent dilation of the umbilical vein or arteries with a hypoechoic-to-echogenic fluid, intraluminal gas, and wall thickening are findings consistent with infection. In calves the urachus normally retracts up into the abdomen at birth, and ultrasonographic identification of a urachal remnant is abnormal.[558]

Overt signs of infection are heat, swelling, purulent discharge, and pain. Concurrent signs of systemic infection such as joint infection, pneumonia, diarrhea, meningitis, or uveitis may be noted. Calves with urachal abscesses may show signs of dysuria or pollakiuria.[559,560] Infection in more than one umbilical vessel is common in the neonate, and urachal involvement is frequent. Umbilical abscessation that is walled off and does not involve deeper structures is a less severe problem and may be treated with drainage without surgical removal of the entire umbilicus.

Early treatment with antibiotics and supportive care may allow resolution before development of abscessation and distention of the urachus or the umbilical arteries and vein. Established infection usually necessitates surgical removal of involved structures in addition to medical therapy.[556] When omphalophlebitis extends into the liver, the umbilical vein may be marsupialized to facilitate drainage and flushing.[561] Prognosis is improved when adequate passive transfer of colostral immunoglobulins has occurred and when joints or other structures

are not involved. Sequelae such as renal abscessation, joint or bone infection, peritonitis, and other complications described for septicemia may develop if therapy is started too late or is discontinued prematurely.

20.19 ANEMIA

Anemia in the neonate should be interpreted in the context of the realization that normal hematologic values of the neonate may vary from those of the adult. In calves the incidence of anemia (hemoglobin <10 g/dL) is quite high, ranging from 15% to 30% in many herds.[562,563] The characteristics of the anemia include normocytosis, normochromia, and poikilocytosis. Anemia is reported to be secondary to iron deficiency.[562,563] Potential causes are reduced amounts of iron in milk, poor placental transfer of iron, and decreased intestinal absorption. Anemic calves with poikilocytosis have similar levels of serum iron, total iron binding capacity, and marrow iron and plasma copper levels compared with normal calves.[564] Anemic calves do not appear to have an increased incidence of disease or decreased growth rates.[565] An overall higher plane of nutrition versus iron supplementation alone produces higher PCVs and hemoglobin levels.[564] Calves less than 6 weeks of age have three types of hemoglobin in various amounts (adult 28%, fetal 40%, and neonatal 25%). The poikilocytosis may be a function of erythrocyte membrane defects or maturation transitions.[564]

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In addition to frank blood loss from an injury, diseases causing anemia in the neonate include blood loss caused by gastric ulcer, anemia secondary to bone marrow necrosis, and anemia of chronic disease associated with localized infections. Hemolytic anemia may be due to neonatal isoerythrolysis (NI) or non-NI immune-mediated hemolytic anemia.[566] NI is caused by ingestion of maternal colostrum containing antibodies to one of the neonate?s blood group antigens. The dam may produce these antibodies after exposure to specific foreign blood group antigens during previous pregnancies or unmatched transfusions. It is uncommon in calves but has occurred after vaccination of pregnant cows against anaplasmosis or babesiosis. The presence of red cell antigens in the vaccine causes the production of antierythrocyte antibody, primarily against the A and F systems.[567] Cows mated to bulls carrying these red cell antigens may have hemolytic disease develop in their A- and F-positive calves after ingestion of colostrum-containing alloantibodies.

Hemolytic disease processes produce signs of weakness, pale or jaundiced mucous membranes, fever, and depression. Blood loss produces weakness and pale mucous membranes. Intestinal parasitism does not normally lead to anemia during the neonatal period. Intravascular hemolysis may produce hemoglobinuria and hemoglobinemia. Icterus develops when the ability of the liver to conjugate bilirubin is exceeded. Mainly, indirect bilirubin is elevated. Anisocytosis is observed in responsive anemias. Nonspecific stimulation of bone marrow may produce a leukocytosis.

Anemia has also been reported in calves infected with BVD virus, secondary to bone marrow necrosis.[568]

Determination of the nature of the anemia may allow specific treatment. Blood transfusion may be indicated when anemia develops rapidly or PCV drops below 14%. Associated conditions such as metabolic acidosis and hypoglycemia should be corrected. Anemia of chronic disease requires correction of the primary disease condition.

20.20 FEVER

Differential diagnoses for fever in neonates include bacterial or viral infections, excitement, seizures with subsequent generation of heat by muscular overactivity, and environmentally induced hyperthermia. Fever is an unreliable indicator of sepsis in neonatal calves.[569] Neonates with sepsis often have a normal or subnormal

temperature. Older ruminants with localized infection such as in joints or bone are more likely to have fever. Fever may be beneficial. The need to administer antipyretics to the febrile neonate is controversial. Body temperatures lower than 40.8° C (105.4° F) are not considered detrimental unless they are associated with heat stroke or seizures, [570] in which case cooling and antipyretics are indicated. Because many antipyretics are antiprostaglandins that can cause deleterious gastrointestinal and renal effects, these agents should be used judiciously. Correction of the initiating cause and maintenance of fluid balance are also important.

20.21 CYANOSIS

Cyanosis is the purple-blue coloration observed on mucous membranes or skin caused by reduced or poorly oxygenated hemoglobin in blood.[571] Cyanosis may be caused by congenital heart disease, respiratory impairment, or any circulatory condition producing a right-to-left shunt (Box 20-4). The degree of cyanosis depends on the arterial oxygen saturation, hemoglobin concentration, pH, peripheral circulation, and temperature of the neonate.[571] Shock and hypothermia are important causes of peripheral cyanosis. The affinity of hemoglobin for oxygen is reflected in the standard oxyhemoglobin dissociation curve. This curve is similar for neonates but is affected by the amount of 2,3-diphosphoglycerate (DPG) in the erythrocyte. Calves' erythrocytes have higher levels of 2,3-DPG, but the higher levels do not affect the affinity of hemoglobin for oxygen. A separate fetal hemoglobin exists in calves to increase affinity for oxygen.[572] Severe hypothermia and acidosis cause the oxygen dissociation curve to shift to the right and therefore contribute to tissue hypoxia. Cyanosis can be either central or peripheral.[571] Peripheral cyanosis results from increased peripheral extraction of oxygen from normally saturated blood or a significant decrease in the perfusion to an extremity.[571] In the neonate, causes include septic shock and severe hypothermia. Central cyanosis is more common in neonates and is related to congenital heart disease that causes right-to-left shunting or severe respiratory conditions that result in hypoxia. Examination and clinical pathologic evaluation for metabolic causes of cyanosis, hypothermia, and cardiac abnormalities should be conducted. History, medication use, auscultation, thoracic radiographs, and arterial blood gases are useful in determining the degree of respiratory component to cyanosis. Echocardiography may be required for identification of cardiac anomalies.

20.21.1 Box 20-4 Causes of Cyanosis

20.21.1.1 Cardiovascular Origin

Tetralogy of Fallot

Tricuspid atresia

Truncus arteriosus

Pentalogy of Fallot

Double outlet right ventricle

Single ventricle

Eisenmenger complex

Ventricular septal defect

Patent ductus arteriosus

20.21.1.2 Respiratory Causes

Alveolar hypoventilation

Drug-induced central nervous system (CNS) depression

CNS trauma or hemorrhage

Hypoglycemia or hypocalcemia

Altered neurologic function of spinal nerves (of respiratory muscles)

Thoracic cage abnormalities: pneumothorax, fractured ribs

Diaphragmatic hernia

Upper airway obstruction

Restrictive pleural space disorders: hemothorax, pleuritis

Hypoplastic lung

20.21.1.3 Impaired Diffusion

Pulmonary: pneumonia, edema, atelectasis

Shunting

Anatomic (congenital heart defects)

Pathologic: pulmonary hypertension

Ventilation-perfusion mismatch

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20.22 HEART MURMUR

Heart murmurs in the neonate may be heard normally before physiologic closing of the ductus arteriosus during the first 1 to 5 days of life. Other causes of murmurs include congenital anomalies, severe anemia, and infectious valvular disease. Physical examination for other signs of heart disease helps determine the severity of the murmur. Jugular pulse, weak or irregular arterial pulse, and palpable thrill indicate a serious condition. Dyspnea, cyanosis, tachypnea, and failure to gain weight are common signs of congenital heart disease in calves. Timing and location of the heart murmur should be determined. Thoracic radiography may aid in determining heart size and in detecting pulmonary edema or distended pulmonary vessels. Echocardiography may reveal atrial or ventricular enlargement, thickened ventricular walls, anomalous orientations of outflow tracts, or ventricular septal defects (VSDs).

Patent ductus arteriosus (PDA) produces a continuous murmur localized over the left heart base. The diastolic component may not be heard with auscultation over other parts of the heart. As pulmonary hypertension develops, the murmur is shortened to a holosystolic type with normal arterial pulse. Large shunting of blood produces a bounding arterial pulse caused by wide fluctuations of systolic and diastolic pressures. Radiographs may reveal an enlarged heart with increased vascularity as a result of left-to-right shunting of blood. Echocardiography may reveal increased left atrial and left ventricular diastolic dimension/volume and hyperdynamic septal and left ventricular wall systolic motion (depending on the degree of right-to-left shunt).

VSD produces a large, harsh, holosystolic murmur that is loudest on the right cranial region of the thorax and is softer over the left heart base. Radiography may reveal heart size increase, left atrial enlargement, and dilated pulmonary vasculature. Two-dimensional echocardiography may show aortic and septal discontinuity. Injection of saline bubbles into the left ventricle and observation of bubbles in the right atrium or ventricle document a left-to-right shunting of blood. Tetralogy of Fallot or other types of complex malformations often produce loud murmurs and are associated with cyanosis, weakness, fatigue, and stunted growth. Tetralogy of Fallot produces a systolic ejection murmur heard at the left heart base. Echocardiography may reveal a thickened right ventricular wall, septal echo dropout in the area of the VSD, rightward displacement of the aortic root, and an abnormal pulmonary outflow region. Saline injection into the jugular vein demonstrates right-to-left flow from the right ventricle to the left ventricle or the aorta.

20.23 ICTERUS

Icterus is a relatively uncommon finding in neonates that may be observed with sepsis, anorexia, liver disease, and hemolytic anemia. Liver disease in the neonate may be caused by exposure to hepatotoxins or sepsis-producing bacterial hepatitis, or it may be secondary to hypoxia. *C. perfringens* type A has been implicated in an enterotoxemic condition in nursing lambs, kids, and calves that is characterized by icterus, hemoglobinuria, anemia, and intravascular hemolysis.[45]

20.24 FAILURE TO THRIVE: CACHEXIA AND WEAK CALF SYNDROME

John Maas

Neonates that are born weak or fail to grow as anticipated pose important problems. In the foal, twins, prematurity, hypothyroidism, and congenital heart or other organ defects may produce failure to thrive. Infections acquired

shortly after birth that produce chronic pneumonia, nephritis, endocarditis, arthritis, or gastric ulcers are a cause of morbidity in the neonatal period.

In calves the weak calf syndrome has been reproduced by feeding low-protein diets to prepartum cows that subsequently calved in environments in which the temperature was well below the thermoneutral zone for calves.[573] The dietary recommendation for crude protein intake for third-trimester pregnant cows and heifers is 0.9 kg (2 lb) of total crude protein per day. This is particularly important for heifers and cows calving early in the spring calving season, when temperatures well below freezing can occur. Cold rains also can produce the hypothermic conditions that aid in precipitating this syndrome.

Cows weighing 450 kg (1000 lb) therefore need to consume 9.9 kg (20 lb) dry matter of good- to excellent-quality hay that is 10% crude protein or more. A quadratic equation has been developed to predict crude protein (CP) intake of the dams if their serum total proteins, urea nitrogen, and creatinine are known.[574] This equation predicts the daily crude protein intake on a continuing basis.

$$\begin{aligned}\text{Daily CP consumption (kg)} &= 0.1806 + 0.04327(\text{BUN}) \\ &\quad -0.33497(\text{creat}) + 0.06963(\text{TP}) \\ &\quad -0.00025(\text{BUN})^2 + 0.06049(\text{creat})^2 \\ &\quad -0.00666(\text{BUN} \times \text{creat})\end{aligned}$$

where *BUN* is serum urea nitrogen (mg/dL), *creat* is serum creatinine (mg/dL), and *TP* is serum total protein (g/dL).

Also, the use of this formula could predict CP intake for pregnant heifers and pregnant cows. This relationship may prove to have important clinical applications when weak calf syndrome or protein-calorie malnutrition is suspected and the gestation diet of the dams is not available for analysis (as under some range conditions). Supplements such as molasses licks that contain urea may tend to overestimate CP intake.[575]

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21 Chapter 21 Colostrum Substitutes and Milk Replacers

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In recent years research in the area of colostrum substitutes and milk replacers has focused on improving the quality of these products so that calf performance can be enhanced and rearing costs can be minimized. The goals of the dairy calf feeding program are to achieve optimum growth rates, develop a strong immune system, minimize health disorders, stimulate and optimize ruminal development, and control the cost of feeding the preweaning calf.

21.1 CALVES

21.1.1 Digestive Physiology of the Preruminant Calf

The gastrointestinal physiology of the newborn calf is poorly developed, and the calf is unable to digest a variety of feedstuffs normally fed to ruminant animals. The gastrointestinal tract of newborn calves undergoes maturation during the first 3 weeks of life and continues to grow and mature for an extended period of time. Because the young calf is technically a monogastric, the diet must be easily digestible and consist of predominately high-quality, human-grade feedstuffs.

The size and proportion of the calf stomach compartments change dramatically during the first few weeks of life and are affected by diet.[1] At birth the reticulorumen makes up approximately 30% of the stomach capacity, although it is nonfunctional. The omasum at birth makes up 10%, and the true stomach or abomasum makes up 60%. The abomasum is the only truly functional part of the four stomach compartments in the newborn. By 4 weeks of age, the reticulorumen makes up slightly more than half the total, the omasum remains about the same at 12%, and the true stomach makes up approximately 36%. By 16 weeks of age the reticulorumen makes up more than two thirds of the total stomach tissue weight. The omasum still makes up about the same proportion (18%). At this point the abomasum makes up only 15%. It has actually grown in size, but relative to the other compartments, it has become less important. The reticulorumen is now the predominant stomach system, having grown in size and in functionality.

In the ruminant animal the enzymes produced by ruminal microorganisms are largely responsible for the breakdown of simple and complex carbohydrates as well as fiber. However, at birth the rumen is nonfunctional, with little tissue development and no microbial population. In the absence of a rumen microbial population, the calf depends on digestive enzymes released primarily from the abomasum, pancreas, and small intestine for the digestion of fats, carbohydrates, and protein. Consequently, preruminant calves cannot efficiently digest complex carbohydrates and fiber.

In the young calf, liquids can bypass the rumen and flow directly to the abomasum through the esophageal groove. The esophageal groove forms when muscular folds from the reticulorumen come together, stimulated by sights and sounds calves associate with feeding and a reflexive response to swallowing. Any liquid (milk or water) consumed while the calf is excited by the anticipation of feeding bypasses the rumen and enters the abomasum. On the other hand, when the calf drinks in response to thirst, liquid enters the rumen instead of the abomasum. The esophageal groove forms whether calves are fed from a nipple bottle or from an open pail.[2] Closure of the esophageal groove also may be stimulated by drenching calves with sodium bicarbonate, which

may be useful in administering pharmaceuticals to the abomasum directly. Riek[3] demonstrated that a dose of 60 mL of a 10% sodium bicarbonate solution stimulated closure of the esophageal groove in 93% of calves tested.

During the first feeding of colostrum, the esophageal groove closes, and colostrum passes directly into the abomasum.[4] The liquid forms a clot as a result of the action of chymosin, pepsin, and hydrochloric acid. Chymosin, also known as *rennin,* is the enzyme that specifically binds with the casein protein of colostrum or milk. This clotting action causes the casein and fat in colostrum to form a curd or hard lump. This lump of fat and protein will be digested slowly and emptied into the small intestine over the next 12 to 18 hours. The stomach and small intestine produce limited amounts of enzymes in the first 48 hours of life. Curd formation allows the digestive tract, which has limited digestive capacity, to slowly yet efficiently digest the nutrients fed and to totally assimilate them, thus preventing digestive scours caused by delivery of undigested nutrients to the large intestine. The second feeding of colostrum or transition milk adds to the already formed curd in the stomach. This system allows the calf to receive a steady supply of nutrients over the first 24 to 48 hours of life as long as it is fed casein-containing liquids.[5]

The fraction of the colostrum that does not form a curd is whey. Whey is passed to the small intestine for digestion and absorption. Whey is composed of water, minerals, lactose, and a variety of proteins. Immunoglobulins are one of the important protein groups in whey obtained from colostrum. Immunoglobulins 367
from ruminants generally have the same features as other mammalian immunoglobulins. Established 368
classes of immunoglobulins are immunoglobulins G1 (IgG1), G2 (IgG2), M (IgM), and A (IgA); all are secreted at high concentrations into colostrum. Immunoglobulins pass out of the abomasum to the small intestine within 10 minutes after feeding, allowing them to be quickly absorbed into the bloodstream of the calf. The rapid absorption of these essential immunoglobulins is critical because no placental transfer of immunoglobulins from the dam occurs.

Digestion of carbohydrates by the newborn calf is relatively poor; the exception is lactose, or milk sugar. Calves younger than one month of age are limited in their ability to use starch, maltose, sucrose, or dextrin because they lack sufficient quantities of the necessary digestive enzymes. By three weeks of age, there is a marked improvement in the ability of the calf to digest starch. After this period there is also an increased ability to digest vegetable proteins.

Within a few days of birth the rumen begins to develop a microbial population. The number and types of bacteria that develop are a function of the type of feeds the calf eats. When the calf eats dry feed, the esophageal groove does not function and the feed enters the rumen. Inoculation of the rumen with microorganisms is by way of the environment, hair coat, bedding, and feeds eaten. The types of ruminal microbes that proliferate are those that best digest and use the feedstuffs being consumed. In addition to feed, ruminal microbes require water in order to grow properly and to digest feedstuffs. If water is not provided to the calf in early life, ruminal microbial growth will be limited. The neural stimulus that forms the esophageal groove does not generally function when water is fed separately from milk or milk replacer feeding. Therefore, much of the water that a calf drinks enters the rumen and is available to support growth of ruminal microbes.

21.1.2 Colostrum Substitutes

The first few weeks of life are critical to the growth and long-term performance of a dairy calf; however, during this period active antibody production does not occur to any extent in the bovine neonate. After birth the calf normally receives colostrum for a first feeding—and in many farm situations, for several feedings up to 3 days of age. From the perspective of the newborn calf, colostrum quality is determined primarily by IgG content and by cleanliness, or the absence of pathogenic bacteria. Cows produce colostrum with a wide range of IgG, and

studies of bacteria in colostrum show that keeping colostrum clean between harvest and feeding the calf can be difficult on many farms.[6,7] In addition to consistency and convenience, colostrum substitutes offer a method of breaking disease transmission cycles for Johne's disease and other infections that may be transmitted through colostrum and milk.

In the United States, colostrum products that contain immunoglobulins are regulated by the U.S. Department of Agriculture (USDA) Center for Veterinary Biologics. Two classes of colostrum substitute are recognized: supplement products that are unable to raise the blood concentration of IgG above 10 mg/mL and typically contain less than 100 g of IgG per dose, and colostrum replacer products that are able to raise serum IgG concentration above 10 mg/mL and contain at least 100 g of IgG per dose plus fat, protein, vitamins, and minerals needed by the newborn calf. When choosing colostrum substitutes consider both the IgG concentration of the product and the absorption efficiency of ingredients.

The primary sources of IgG in colostrum substitutes are dried colostrum, whey, or blood serum. The ingredients of the product and methods using in processing these ingredients can affect the ability of the product to provide absorbable IgG to calves. Apparent efficiency of IgG absorption (AEA) is used to compare the proportion of IgG absorbed to the amount fed. Supplement and replacer products based on bovine serum have an AEA similar to maternal colostrum (20% to 35%). Products based on colostrum or whey have a variable AEA, ranging from 5% to 25%, with an average of approximately 15%.

Colostrum supplements can be used to increase the amount of IgG fed to calves when only low- or medium-quality colostrum is available.[8] However, supplements cannot replace high-quality colostrum.[9] When a supplement is added to low-quality colostrum, the IgG is often absorbed poorly, and antibody absorption is reduced compared with high-quality maternal colostrum. Colostrum replacer contains more immunoglobulin than supplement products and provides more antibodies than poor- or moderate-quality colostrum. In research trials, calves fed colostrum replacer have performed as well as calves fed maternal colostrum with no differences in IgG levels, efficiency of IgG absorption, incidence of scours, or growth rates.[10,11]

Also note that feeding large quantities in a single feeding can reduce absorption efficiency. Therefore it is more beneficial to feed colostrum or a substitute with a higher IgG concentration than to try to feed more of a low IgG solution (by increasing the amount of powder or volume fed). Adding a second or third feeding of low IgG colostrum also is preferred to increasing the volume fed in a single feeding.

Some colostrum supplements include *Escherichia coli* antibody. This can be misleading, causing producers to believe that if they feed this product, it will protect their calves from *E. coli* as well as provide successful passive transfer. These products are designed to provide antibodies specific for *E. coli*, but because of the many different strains of *E. coli* present in different areas of the country and on different farms, these antibodies likely offer little protection.

Colostrum substitutes should be fed according to the manufacturer's instructions; some products are mixed with water and fed in an extra feeding, others are added to colostrum, and the number of feedings recommended may vary.

High-quality maternal colostrum is still the “gold standard” for feeding newborn calves. However, colostrum supplement and replacer products can be valuable tools to increase calf immunity when colostrum supplies are limited or disease eradication is desired. Colostrum supplements can be used to increase the amount of IgG fed to calves when no source of high-quality colostrum is available; however, supplements cannot replace high-quality colostrum. On the other hand, colostrum replacer contains greater levels of IgG and other nutrients and

provides an effective, convenient method of providing passive immunity to calves when maternal colostrum is not available.

21.1.3 Milk Replacer Quality and Formulation for the Dairy Calf

The period of time between colostrum feeding and the beginning of solid food consumption is highly dependent on the management of the individual dairy farm. Often the calf consumes a liquid-only diet for the first 2 weeks of life. Despite dry feeds (grains) being offered, very little, if any, are consumed for the first 7 to 10 days. Therefore the liquid feeding portion of the rearing program is very important to the health and initial growth of the calf.

More than 60% of the dairy calves in the United States are fed milk replacers for most or all of their liquid feeding period.[12] The dairy calf is typically fed a milk replacer for 6 to 8 weeks, at which point it is weaned. Calves can be weaned at any age from 3 weeks on, depending on the health and management of the animal. It is recommended that calves be weaned by 6 weeks of age, with a goal for most of the calves, most of the year, being 4 to 5 weeks of age at weaning. The United States national average in 2002 was 8.4 weeks[13]; however, many progressive farms regularly and successfully wean all calves at 4 to 5 weeks.

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Convenience and economics are the two major factors that have driven the increase in use of milk replacers. Feeding milk replacer is often more convenient than feeding whole milk or pasteurized waste milk because calves are generally housed in different areas on the farm than the milking cows, and the transport of saleable or waste milk is difficult. This issue becomes more pronounced with larger farms. Often, supplying transition milk from the dam to the calf up to the time the milk is saleable is all that is possible from a labor and management standpoint. Milk replacer powder is easily stored and can be mixed in exact quantities to provide milk for each feeding. Another benefit of milk replacers is the ability to limit the spread of diseases, such as Johne's, that can be transmitted through milk.

Milk replacers can be manufactured with a variety of ingredients and levels of nutrients to match the management requirements of a wide variety of farms. Various additives that cannot be easily used in whole milk or waste milk feeding systems can be supplied in milk replacers to improve the nutrition and health of the calf.

One major reason for the use of milk replacers is the cost savings over the alternative of using whole milk. Savings are realized because milk replacers are composed primarily of byproducts of the cheese industry. Casein removed for dried skim milk production, and casein and fat removed for cheese production, carry much of the original value of the whole milk. The whey that remains is less valuable, and although demand for it in the world market is growing, it still commands a much lower price than skim milk. The trend for increased use of milk replacers will likely remain as long as the price differential between milk and milk replacers exists.

21.1.3.1 PROTEIN

The composition and quality of a milk replacer influence the growth, health, and overall performance of the calf. Composition and nutrient levels vary greatly among products. Protein sources are the most expensive ingredients in milk replacer. As a result, manufacturers continually seek less expensive ingredients. The source of milk replacer protein changes in response to ingredient cost and may include a variety of milk and nonmilk proteins. Milk replacers used in the United States are typically composed of whey and whey protein concentrate compounds. Dried whey contains 12% crude protein, mainly lactalbumin, and 74% lactose. Delactosed whey has higher protein content (20% to 26%) because some of the lactose in whey is removed. Whey protein concentrate is produced by ultrafiltration of liquid whey to remove lactose and other soluble

components and contains approximately 34% crude protein. Skim milk is rarely used in appreciable amounts in the United States because of the high cost. This is often not the case in other countries, depending on the agricultural economics situation. However, as new technologies continue to increase the value of whey proteins for use in human foods, skim milk is occasionally substituted for whey in the United States. Dried skim milk contains approximately 34% protein. Casein (85% protein) may also be used in milk replacer (sometimes listed on the label as dried milk protein or sodium caseinate).

The amino acids provided by various sources of protein differ in composition and in bioavailability. Availability depends on the method and conditions of processing and can vary greatly between feeds and processors. Milk proteins are typically more digestible (92% to 98%) and contain a more favorable profile of amino acids than nonmilk proteins. Compared with milk proteins, vegetable proteins (85% to 94% digestible) often contain more crude protein, but their amino acid content is not as desirable. Some soy-based milk replacer contains added lysine and methionine to improve the amino acid profile. Most soy isolates or concentrates used today are highly digestible to the young calf. Egg protein contains a favorable profile of amino acid acids, and most products are highly digestible. Manufacturers use available data to best fortify the product in an economical manner. Some evidence suggests that the amino acid composition of whey is actually more correct for meeting the calf's requirements for optimum growth than the amino acid composition of skim milk. In either case, research trials using skim milk or whey protein have proven both to be completely satisfactory in meeting the needs of the newborn calf for growth.[14]

Vegetable proteins in milk replacer are primarily of soy origin, but wheat and potato proteins also may be used. The soy proteins include soy protein isolates, soy protein concentrates, and chemically treated soy flours. Soy flour (50% protein) is obtained by grinding defatted soy flakes that have been heated to remove trypsin inhibitor or washed in aqueous ethanol to remove glycinin and β-conglycinin. These modifications improve digestibility and reduce allergic reactions. Soy protein concentrate (67% protein) is produced by washing defatted soy flakes with aqueous alcohol to remove the soluble carbohydrates. Isolated soy protein (85% protein) is produced by washing defatted soy flakes in alkali followed by acid precipitation and alkali resolubilization of the extracted protein. Wheat gluten (modified wheat protein) is derived from wheat flour by wet processing or milling and contains 80% protein. Milk replacers with 33% of total protein or without wheat gluten have resulted in comparable calf gains.[15] Modified potato protein is not common in the United States but is used in other countries. This protein is separated from water used to isolate potato starch and dried (80% protein).

Animal proteins, including plasma and eggs, also are used to replace some of the whey protein concentrate in milk replacers. Many of the amino acids in these ingredients are at very high levels compared with milk proteins. Animal plasma is a concentrated protein source obtained by removing red and white blood cells from fresh, whole blood. The resulting plasma is dried and contains 78% protein. Egg protein may be provided from spray-dried whole egg or a combination of whole egg and egg albumin. Whole egg contains high fat levels and 54% protein.

Bovine or porcine plasma products can be used successfully as partial replacements for milk proteins.[10] In addition to supplying a highly digestible source of protein, plasma proteins also supply a source of immunoglobulins that may have a beneficial effect in the calf's intestinal lumen. Morbidity and mortality were reduced in calves fed whey-based milk replacer containing bovine or porcine plasma compared with calves fed milk replacer based solely on whey.[16,17] There is limited dairy calf research on egg proteins, and it appears that the processing of the egg protein can have a dramatic impact on the outcome. Average daily gain and feed efficiency are generally somewhat lower for calves fed egg protein, particularly in the preweaning period.[18]

The performance and cost of these plasma and egg products has been intermediate to all-milk replacers and soy-based replacers.

Historically the rennet coagulation test and crude fiber content were used to evaluate milk replacer quality. These are no longer valid methods to evaluate quality, as the rennet coagulation test merely identifies the presence of casein in the milk replacer. A soft clot indicates that more than 15% of the protein is casein, a firm clot means that more than 50% of the protein is casein. However, most modern milk replacers are based on whey protein, which does not clot when mixed with rennet. Whey protein has been fully researched and is an excellent source of protein for calves; at least one study showed that whey protein was better than skim milk protein. Therefore failure to form a clot does not indicate poor protein quality in milk replacer; it does show that casein is not present. Milk replacers containing plant proteins are often higher in protein content to counteract their lower digestibility relative to milk proteins. Most soy protein isolates or concentrates used today are highly digestible to the young calf. Unmodified wheat or soy flours, potato protein, meat solubles, and fish proteins are among the least desirable ingredients in a dairy calf milk replacer. Milk protein contains no fiber, and in the past, crude fiber levels above 0.2% were considered evidence of a plant protein source. However, highly processed soy protein can contain little to no fiber and other nonmilk sources such as plasma and egg contain no fiber. Also, it is very difficult to accurately detect crude fiber at the low levels found in milk replacer.

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The ingredients listed on the milk replacer tag should be listed in descending order of predominance as specified by the U.S. Food and Drug Administration (FDA) regulation 21CFR501.4. However, many states use a Uniform State Feed Bill that does not specify the need to list ingredients in order of predominance. In these states most companies do list ingredients in order of predominance to facilitate comparison of products. It is important to read and understand the ingredients in a milk replacer in order to compare and evaluate products. Some soy protein compounds and other highly processed ingredients are patented, and labels may bear the registered name and not the generic protein name (such as *soy isolate* or *concentrate*).

21.1.3.2

ENERGY

Energy in milk replacers is derived primarily from lactose and fat. The effects of milk replacer energy content are not always clear in practical applications because of interactions with environmental temperature, energy derived from dry calf starter, stage of ruminal development, and differences in metabolic efficiency of fat- and carbohydrate-derived energy. The thermal neutral zone for a young calf ranges from 10° C to 25° C. During periods of extreme stress, which include cold temperatures for calves housed outside, the energy intake of the calf should be increased to account for increased maintenance energy needs. This can be accomplished by increasing the amount of replacer fed daily by 30% to 50%, increasing grain consumption, or increasing the fat content of the replacer. Fats added to calf milk replacers are mainly edible animal fats, with some use of vegetable fats such as palm oil or refined coconut oil (digestibility 92% to 96%). The animal fats used can be lard or white grease (digestibility 88% to 96%).[19] It is important to note that when dry matter intake from milk is increased, it will substitute potential dry matter intake from grain. The long-term effects of this will be decreased grain intake and delayed ruminal development.

21.1.3.3

ADDITIVES

One obvious reason to use milk replacers is that nutrient fortification and additives for the promotion of growth and health can be incorporated without extra steps. This includes extra vitamins and minerals along

with various other additives. All macrominerals and microminerals are supplemented in milk replacer, as are vitamins A, D, and E and the B vitamins needed by preruminant calves.

The most common additives found in milk replacers today are lasalocid and decoquinate, for the prevention of coccidiosis, and oxytetracycline and neomycin, which aid in the prevention of bacterial scours. Milk-fed dairy calves often respond favorably to oral antibiotics with increased weight gains and improved feed efficiency, but often the level of antibiotics fed is less than what is required to effectively decrease scours. Antibiotics must not be used as a substitute for good management. In addition, continued public concern about the use of antibiotics in animal feed makes it likely that this option may be discontinued in the future. Feeding antibiotics in milk replacer requires a withdrawal period before slaughter, and bull calves intended for sale must not be fed medicated milk replacer.

A number of alternatives to antibiotics, such as probiotics (also called *direct-fed microbials*), yeast, oligosaccharides, and functional proteins, are now available in milk replacer. Many of these products have not been thoroughly researched, and results of research so far have been variable. Probiotics are live cultures of naturally occurring microorganisms. The most common probiotic ingredients are lactic acid-producing bacteria. In theory, probiotics can improve dry matter intake, weight gain, feed efficiency, and disease resistance. Research so far suggests a modest improvement in average daily gain and feed efficiency when probiotics are fed to young calves. It seems that probiotics would be most beneficial when calves are stressed and normal bacteria populations are disrupted. Keep in mind that probiotics are living organisms; follow the instructions for storage, and use products before their expiration dates. In addition, probiotic additives should not be used with medicated milk replacer because the antibiotics may kill the probiotic organisms.

Another category of additives is the prebiotics, which are structural carbohydrates that cannot be digested by ruminants but are excellent nutrient sources for beneficial bacteria in the calf's digestive tract. Examples include resistant starches, polysaccharides, pectins, and gums. The mode of action varies for different types of prebiotics. Prebiotics that are becoming more common in calf feeds are fructooligosaccharides (FOS) and mannanoligosaccharides (MOS), which are complex sugars isolated from the cell wall of yeast. Some pathogens, including *E. coli* and *Salmonella,* will readily and preferentially bind to these indigestible compounds rather than the intestinal wall. Once they bind, the bacteria cannot detach themselves, so they are passed out of the body with other undigested feedstuffs. In addition, beneficial bacteria in the intestine may use these oligosaccharides. Research has shown that these compounds are beneficial in reducing the severity of scours.[20] One study showed that calves fed a product containing the FOS allicin (an extract of garlic) and probiotic cultures and calves fed antibiotic had similar fecal scores.[21] However, no calves in this study were fed control milk replacer (with no additive), so it is impossible to determine if fecal scores were improved compared with calves that were not treated. Another group of researchers compared calves fed galactosyl-lactose (an oligosaccharide derived from whey), antibiotic, or no additive. In this study calves fed galactosyl-lactose or antibiotics were similar and tended to have more normal fecal scores and fewer days scouring than control calves.[22] In addition, calves fed galactosyl-lactose gained more weight than control calves. Although results so far are promising, peer-reviewed research into oligosaccharides is scarce at this time, and additional research is needed to support growth promotion claims.

Yeast is another common direct-fed microbial. *Saccharomyces cerevisiae* is the most frequently used yeast species and may be fed live or dead. Yeast cells are rich sources of protein, nucleotides, and B vitamins. They also stimulate beneficial bacteria and ruminal fermentation and assist in fiber digestion. A review of microbial additives concluded that adding yeast cultures to calf diets could result in no change or a modest improvement in feed intake, weight gain, and feed efficiency.[23] Performance depends on the specific conditions of each situation. However, yeast cultures do tend to increase microbial growth in the rumen, which may have benefits

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in promoting ruminal development. One study reported that adding live yeast to milk replacer fed to calves with failure of passive transfer resulted in fewer days with scours than in control calves.[24]

A final type of antibiotic alternative is a group of proteins known as *functional proteins,* which can cause a physiologic response in the body. Some are able to survive the ruminal environment intact; others are released during digestion. The most well known of the functional proteins are the immunoglobulins. Research has shown that immunoglobulins from the blood are recycled into the intestine.[25] This means that providing immunoglobulins in colostrum or injecting immunoglobulins into the blood can help to boost immunity in calves. Both of these methods have been researched and found effective. In addition, plasma protein fed in milk replacer may provide antibodies that enhance the immune system locally in the intestine. Research with plasma protein seems to indicate that calves under stress benefit from these additional antibodies, whereas healthy, nonstressed calves usually do not benefit.

21.1.4 Enhanced Milk Replacer Feeding Systems

Many companies now offer high-protein, low-fat milk replacers (protein greater than 24% and fat less than 20%) that provide additional protein for increased growth. It is important to pay close attention to the feeding instructions for these milk replacers. Young growing ruminants will respond favorably to increasing amounts of dietary protein if additional energy and other nutrients are also provided. However, the efficiency of using this additional protein is reduced as levels increase. Calves must be fed more than in conventional programs, and the amount fed to each calf may need to be adjusted as the calf grows. To make these feeding programs cost-effective, the increased cost of high-protein milk replacer and the extra cost to feed more dry matter must be offset by long-term improvements in growth or decreased overall heifer production costs, possibly including reduced age at first calving. Thus far, research does not support long-term improvements in health or performance resulting from enhanced feeding during the preweaning period.[26] Typically, changes to the calf feeding program alone cannot achieve these long-term cost-reduction goals. Changes in the feeding and management of older calves and heifers must occur as well and will far outweigh any small changes in the preweaned calf feeding program. Calves also must be managed more carefully when feeding for higher rates of gain, as they may be more susceptible to nutritional scours, especially when milk replacer is fed at greater than 12.5% solids and water availability is limited. Grain intake often is reduced in early life with higher rates of milk replacer feeding, thereby limiting ruminal development. Often this feeding strategy results in restricted growth after weaning and produces calves that are similar in size to conventionally fed calves by 4 to 6 months of age, thereby eliminating any advantage in early growth.

21.1.5 Summary

It is noteworthy that much of the current research related to milk replacers is done by individual manufacturers, with less done in the public domain. This means that much of the peer-reviewed journal research is dated and often may not account for modern feed manufacturing technology. Recommended ranges of nutrients as shown in Table 21-1 are broad in many cases to account for some of these differences and to account for variety of protein sources and energy content in milk replacer products. Many farms want high rates of growth in their young calves and need milk replacers with marginally increased nutrient density, whereas others want only economy. The milk replacer industry has a variety of products to meet the needs of these various customers. As with most purchased items, quality is related to price.

Table 21-1 Nutrient Recommendations for Dairy Calf Milk Replacers from the National Research Council[29]*

Nutrient	Recommended Concentration
Crude protein	18-24
Fat	10-22
Calcium	1
Phosphorus	0.7
Potassium	0.65
Magnesium	0.07
Sodium	0.40
Chloride	0.25
Sulfur	0.29
Iron (ppm)	100
Cobalt (ppm)	0.11
Copper (ppm)	10
Manganese (ppm)	40
Zinc (ppm)	40
Iodine (ppm)	0.50
Selenium (ppm)	0.30
Vitamin A (IU/lb)	25,000-35,000
Vitamin D (IU/lb)	5000-7500
Vitamin E (IU/lb)	50-125

* Percentage of dry matter unless otherwise indicated.

Although milk replacers are important in the dairy feed industry today, keep in mind that many studies show that only 24% of growth before weaning can be accounted for by the energy provided in milk replacer. Calf starter makes up the remaining 76% of the energy for body weight gain in the first 2 months of life. It is important to note that overfeeding milk replacer, either in amount or concentration, will primarily replace dry matter intake that would normally come from grain. This will slow ruminal development and be less economical for the producer. In addition, scours, which cause the greatest amount of calf mortality and morbidity preweaning,[27] are greatly diminished postweaning. This occurs regardless of age at weaning and is more closely related to ruminal development and diet than age.

21.2 FOALS

The use of a milk replacer for foals becomes necessary when the mare has an inadequate milk supply or when the foal is orphaned at an early age. Milk replacers for foals should contain 18% to 22% crude protein, 12% to 16% crude fat, and 10% to 11% total solids. They should be highly digestible, easily reconstituted, and palatable.

Orphan foals should be fed milk replacer from 1 day of age (after receiving colostrum within 24 hours of birth) to a minimum of 1 month of age.[28] General guidelines for feeding foal milk replacers can be found in Table 21-2. Feeding less often than recommended may reduce growth rate as a consequence of inadequate milk replacer intake. It is important that foals receive the recommended amount of milk replacer powder daily so that starvation from underfeeding or diarrhea from overfeeding is avoided.

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Table 21-2 Typical Feeding Recommendations for Foal Milk Replacers[28]

Age (days)	Number of Feedings per Day	Approximate Amount (mL/meal)	Amount of Water (mL/day)	Total Amount of Powder (g/day)
0-3	12	300	3000	480
4-5	8	500	3500	560
6-7	8	770	5300	860
8-10	8	1000	7000	1100
11-14	6	1660	8625	1335
15-21	4	3225	11,130	1750
>21	3-4	?	>15%-20% BW	>2.5% BW

BW, Body weight.

21.3 LAMBS AND KIDS

Milk replacers for lambs and kids are generally used to raise multiples or orphans but are used by dairy operations as well. Most principles discussed in the section on calves apply to lambs and kids. Milk replacers for lambs usually contain 21% to 24% crude protein and 24% to 30% crude fat. The lactose level in lamb milk replacers should not exceed 25%, as higher levels may result in abomasal bloat and diarrhea. Milk replacers for lambs are generally fed cold ad libitum from automatic nipple feeders. Lambs fed warm milk replacer a limited number of times during the day drink too much at each feeding and may develop abomasal bloat.

Creep feed can be offered to lambs after 1 week of age. It should contain 17% to 20% crude protein, be highly digestible, and be fed fresh daily. The introduction of creep feed at an early age helps the lamb develop a fully functional rumen by 35 to 40 days of age.

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22 Chapter 22 Clinical Chemistry Tests

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Laboratory data are discussed here in relation to case management. The focus is on interpretation of an abnormal finding in the typical clinical situation. An in-depth pathophysiologic explanation of these alterations is beyond the scope of this section. Should additional information be required, a textbook on veterinary clinical pathology should be consulted.[1,2]

All samples should be submitted with specific objectives in mind. In general, these objectives fall into one of the following categories:

- Evaluating organ system involvement or functional impairment
- Confirming a diagnosis or ruling out a disease condition
- Assessing response to therapy
- Formulating a more accurate prognosis

22.1 SUBMISSION OF LABORATORY SAMPLES

22.1.1 Veterinary Diagnostic Services

The clinician must be aware of inherent limitations of laboratory evaluation in certain clinical settings. In general, veterinary diagnostic laboratories are preferred to general medical laboratories, because human medical laboratories may be less familiar with animal diseases and the responses of animals to disease. There may also be differences in test methodology and interpretation. These species differences can cause confusion when results are evaluated on the basis of human criteria that may not apply to animals.

Various desktop or portable hand-held point-of-care devices are available to veterinarians for determination of serum chemistry, electrolytes, and acid-base balance. Many of these devices use self-contained strips, cartridges, or rotors and thus reduce errors associated with the maintaining, measuring, and mixing of reagents. In addition, some of these devices can use whole blood rather than serum or plasma. Some devices require refrigerated storage of reagent cartridges, which must then be warmed to room temperature for use. There are relatively few independently published data comparing the results obtained with these point-of-care devices and those obtained with standard laboratory procedures. A widely used hand-held device (iSTAT) has been shown to yield comparable results for blood electrolyte concentrations and acid-base balance in dogs and horses.[3] However, it was noted that the correlation' between results from this device and from standard laboratory techniques was poor for sodium in the dog and for hematocrit in the horse. Portable point-of-care devices can provide rapid, accurate, and relatively inexpensive results. As technology continues to improve, it can be anticipated that there will be wider and more general application of these devices in many large animal practice settings. Important requirements are the establishment of normal values with these devices for our large animal species of important age or production groupings as well as clear definition of the limitations and possible idiosyncratic reactions in certain species or clinical settings.

22.1.2 Selection of Procedures

Selection of specific laboratory tests fosters logically integrated thinking and concentrates on evaluation of the primary medical problems. However, the sophisticated autoanalyzers used by large commercial laboratories can perform a wide battery of tests quickly and efficiently with little additional cost. These panels may be broadly defined (e.g., a general large animal health panel) or may offer a more focused evaluation of a specific organ system (e.g., liver, kidney, or muscle). The clinician must ensure that the panel selected contains all the appropriate tests for a thorough evaluation of the individual patient's medical problems.

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The following recommendations for diagnostic panels are intended to provide a clear indication of organ damage and/or dysfunction. The most directly applicable diagnostic procedures are listed under “Recommended,” and additional procedures that may be of benefit in certain circumstances are listed under “Optional.”

22.1.2.1 GENERAL PANEL

The broadly based general chemistry panel should provide a balanced evaluation of the most likely medical problems.

22.1.2.1.1 Recommended

Glucose

Blood urea nitrogen (BUN)

Creatinine

Creatine kinase (CK)

Aspartate aminotransferase (AST)

Sorbitol dehydrogenase (SDH)

γ-Glutamyltransferase (GGT)

Alkaline phosphatase (ALP)

Bilirubin (direct, indirect, and total)

Total protein

Albumin

Globulin

Albumin/globulin ratio (A/G ratio)

Bicarbonate or total carbon dioxide (total CO_2)

Sodium

Potassium

Chloride

Calcium

Phosphate

22.1.2.1.2 Optional

Venous or arterial blood gases

Ionized calcium

22.1.2.2 MUSCLE PANEL

The muscle panel should detect active skeletal and cardiac muscle destruction (rhabdomyolysis) and the degree of secondary renal damage. The possible causative factors are evaluated as optional procedures, depending on the history, clinical findings, or special circumstances. Muscle biopsy with special staining may be critical to the diagnosis of specific muscle diseases such as polysaccharide storage myopathy, immune mediated myopathy, and mitochondria myopathy. Special tests for muscle function and the genetic basis for some myopathies are discussed in the section on muscles (Chapter 42).

22.1.2.2.1 Recommended

CK

AST

Muscle biopsy

Urinalysis

BUN or creatinine

22.1.2.2.2 Optional

Blood selenium

Venous blood gases

DNA analysis (hyperkalemic periodic paralysis, glycogen branching enzyme deficiency)

Calcium (ionized and total)

Magnesium

Fractional excretion of:

Sodium

Potassium

Chloride

22.1.2.3 LIVER DISEASE PANEL

The liver panel should detect active damage to the hepatic parenchyma, involvement of the biliary system, and alteration in hepatic function.

22.1.2.3.1 Recommended

SDH

AST

GGT

ALP

BUN

Blood glucose

Fibrinogen

Total protein

Albumin

Globulin

Bilirubin (direct, indirect, and total)

Complete urinalysis

22.1.2.3.2 Optional

Liver ultrasound

Liver biopsy

Bile acids

Blood ammonia

Clotting panel

22.1.2.4 RENAL DISEASE PANEL

The kidney panel should provide a rough quantitative estimation of compromised renal function and should indicate the location and nature of the damage to the urinary tract.

22.1.2.4.1 Recommended

BUN

Creatinine

Calcium

Phosphate

Protein or albumin

Complete urinalysis

22.1.2.4.2 Optional

Renal ultrasound

Renal biopsy

Urine culture

Urine/plasma osmolality ratio

Urinary CK/creatinine ratio

Fractional excretion of:

Sodium

Potassium

Chloride

Endogenous creatinine clearance

Sulfanilate clearance

22.1.2.5 GASTROINTESTINAL DISEASE PANEL

The gastrointestinal disease panel should include evaluation of acid-base status, fluid and electrolyte balance, and renal function, which are common complicating features of gastrointestinal diseases. Additional optional or special diagnostic procedures may be necessary in calves or foals with neonatal diarrhea, in horses with colic, and in ruminants with gastrointestinal stasis or displacement.

22.1.2.5.1 Recommended

Packed cell volume (PCV)

Total plasma protein (TPP)

Sodium

Potassium

Chloride

Calcium (ionized and total)

Venous blood gases, pH, bicarbonate

Anion gap

BUN

Creatinine

Glucose

Peritoneal fluid cytology

Fecal occult blood

Fecal parasites

Ruminal fluid pH

22.1.2.5.2 Optional

Peritoneal fluid (glucose and pH)

Serum immunoglobulin

Plasma lactate (D and L forms)

Fecal protozoa

Fecal culture

Fecal *Clostridium difficile* toxin

Fecal cytology

Rectal biopsy

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Absorption test:

Glucose

Xylose

22.1.3 Metabolic Profiling

The health status and productivity of dairy cattle, swine, and other food animals maintained in large confined groups involve a fragile balance between metabolic events, nutrition, agents of disease, management, and environmental factors. In these production units the health status of the herd as a whole is of paramount importance. Subclinical disease or nutritional imbalance may contribute to suboptimal productivity. Most productivity problems in these settings are multifactorial. Defining and finding solutions to these problems can be a difficult and complicated task. Sequential assessment of weight gains, body conditions scores, milk quality, and milk production are useful measures of the presence of subclinical production disorders but do not identify the cause. Metabolic profiling is a tool that has been employed in some situations. Blood samples are drawn from a number of individuals as representative of the group as a whole. Some have recommended the submission of pooled serum samples from representative individuals, much like the use of bulk tank tests as a reflection of the general level of mastitis in a herd. Sampling may be done routinely and sequentially. In dairy cattle this may be

done during gestation or lactation but frequently focuses on the periparturient period when a combination of nutritional and metabolic events often contributes to costly production disorders.

Metabolic profiles might include most of the parameters listed under the recommended general panel (p. 376), with the addition of magnesium, total cholesterol, nonesterified fatty acids (NEFA) and β-hydroxybutyrate (BOHB). BOHB, NEFA, and cholesterol may provide an indication of energy balance, whereas BUN, creatinine, total protein, albumen, and CK may be helpful in assessing protein status. In certain settings, trace minerals or fat-soluble vitamins may be important indicators of underlying nutritional problems. Metabolic profiling is not a substitute for careful clinical examination, analysis of husbandry practices, and ration analysis, but it may play a useful role in some modern large- scale operations in which a variety of subclinical problems can quickly translate into financial disaster.

22.2 SOURCES OF VARIATION IN NORMAL VALUES

22.2.1 Laboratory

One of the most commonly overlooked sources of variation in clinicopathologic data is the difference in results obtained by different laboratories. This can result in fivefold to tenfold differences in the normal range of certain enzyme activities between laboratories using similar but not identical methodologies. In the past there was marked variation in the units of measure used to express the activities of different serum enzymes. The standard method of representing serum enzyme activity is in international units per liter (IU/L), which is used in this text. Correction factors for converting the commonly used but older units of measure to international units are given in Table 22-1. The normal values given in Tables 22-2 and 22-3 are those used at the University of California Veterinary Medical Teaching Hospital or are from the literature.[2,3] It is always best to use normal values and reference intervals established for the species, age, and production type by the diagnostic laboratory to which samples are submitted.

Table 22-1 Conversion of Conventional Units to International Units

Component	Conventional Unit	Multiply By	International Unit (IU)
CHEMISTRY			
Ammonia	µg/dL	0.5872	µmol/L
Bilirubin	mg/dL	17.1	µmol/L
Cholesterol	mg/dL	0.02586	mmol/L
Creatinine	mg/dL	88.4	µmol/L
Glucose	mg/dL	0.05551	mmol/L
Lactate	mg/dL	0.111	mmol/L
Urea nitrogen	mg/dL	0.357	mmol/L
ELECTROLYTE			
Sodium	mEq/L	1	mmol/L
Potassium	mEq/L	1	mmol/L
Chloride	mEq/L	1	mmol/L
Calcium	mg/dL	0.2495	mmol/L
Magnesium	mg/dL	0.4114	mmol/L
Phosphorus	mg/dL	0.3229	mmol/L
BLOOD GAS			
Po_2	mm Hg	0.1333	kPa
Pco_2	mm Hg	0.1333	kPa
Bicarbonate	mEq/L	1	mmol/L
Tco_2	mEq/L	1	mmol/L
PROTEIN AND HEMATOLOGY			
Protein	g/dL	10	g/L
Albumin	g/dL	10	g/L
Fibrinogen	mg/dL	0.01	g/L
Hemoglobin	g/dL	10	g/L
Iron	µg/dL	0.1791	µmol/L
Transferrin	mg/dL	0.01	g/L
Haptoglobin	mg/dL	0.01	g/L
HORMONE			
Cortisol	µ/dL	27.59	nmol/L

Triiodothyronine (T_3)	ng/dL	0.01536	nmol/L
Thyroxine (T_4)	µg/dL	12.87	nmol/L

From Kaneko JJ, Harvey JW, Bruss ML, eds: *Clinical biochemistry of domestic animals,* ed 5, New York, 1997, Academic.

kPa, Kilopascal; Po_2, partial pressure of oxygen; Pco_2, partial pressure of carbon dioxide; Tco_2, total carbon dioxide.

22.2.2 Species

There is relatively modest variation among species for most clinicopathologic parameters. Notable exceptions are plasma electrolyte concentration, erythrocyte potassium concentration in some breeds of sheep, and serum bilirubin concentration, which is higher in horses than in other species. BUN is a less reliable indicator of renal function in ruminants and horses than creatinine because urea nitrogen can be metabolized by the intestinal microflora. Donkeys and burros have a much higher GGT level than horses and cattle.

22.2.3 Breed

Significant differences in hematologic parameters exist between hot-blooded and cold-blooded horses. Hot-blooded horses include most of the athletic breeds of horses (the thoroughbred, quarter horse, standardbred, and Arabian breeds). Cold-blooded horses include the pony and draft breeds. Cold-blooded horses have lower red cell values both at rest and after exercise and maintain a slightly lower leukocyte count; they also have lower resting and fasting indirect bilirubin concentrations.

Table 22-2 Clinical Chemistry: Normal Range for Large Animals

Component	Unit	Equine	Bovine	Ovine	Caprine
CHEMISTRY					
Total bilirubin	mg/dL	0.5-2.3	0-0.1	0.1-0.2	0-0.1
Direct	mg/dL	0-0.6	0	0	0
Indirect	mg/dL	0.2-2	0-0.1	0-0.12	0-0.1
Cholesterol	mg/dL	75-150	80-120	52-76	80-130
Creatinine	mg/dL	0.9-2	0.9-1.3	0.8-1.3	0.7-1
Glucose	mg/dL	89-112	33-66	56-92	53-81
Fibrinogen	mg/dL	100-400	100-600	100-500	100-400
Protein (total serum)	g/dL	5.8-7.7	6.8-8.6	6.6-8.6	6.8-8.3
Albumin	g/dL	2.3-3.6	3-4.3	2.7-3.7	3.2-3.8
Globulin	g/dL	1.7-4.7	3-4.9	2.8-5.4	3.1-4.8
Urea nitrogen	mg/dL	12-27	8-23	14-37	19-31
ENZYME					
ALP	IU/L	86-285	27-107	50-300	27-210
AST	IU/L	138-409	43-127	60-280	46-161
CK	IU/L	119-287	105-409	100-547	104-219
GGT	IU/L	8-22	15-39	40-94	34-65
LDH	IU/L	162-412	697-1445	238-440	123-392
LDH-1	%	6.3-18.5	39.8-63.5	45.7-63.6	29.3-51.8
LDH-2	%	8.4-20.5	19.7-34.8	0-3	0-5.4
LDH-3	%	41-65.9	11.7-18.1	16.4-29.9	24.2-39.9
LDH-4	%	9.5-20.9	0-8.8	4.3-7.3	0-5.5
LDH-5	%	1.7-16.5	0-12.4	10.5-29.1	14.1-36.8
SDH	IU/L	0-8	12-53	18-77	2-57
ELECTROLYTE					
Sodium	mEq/L	132-146	132-152	139-152	142-155
Potassium	mEq/L	2.4-4.7	3.9-5.8	3.9-5.4	3.5-6.7
Chloride	mEq/L	99-109	97-111	95-103	99-110
Calcium	mg/dL	11.2-13.6	9.7-12.4	11.5-12.8	8.9-11.7
Phosphorus	mg/dL	3.1-5.6	5.6-6.5	5-7.3	6.5
Magnesium	mg/dL	2.2-2.8	1.8-2.3	2.2-2.8	2.8-3.6

Osmolality	mOsm/kg	270-300	270-300	N/A	N/A
Anion gap	mEq/L	6-15	14-20	N/A	N/A
ACID-BASE (VENOUS BLOOD)					
pH		7.32-7.44	7.31-7.53	7.32-7.54	N/A
P_{CO_2}	mm Hg	38-46	35-44	37-46	N/A
Bicarbonate	mEq/L	20-28	17-29	20-25	N/A
T_{CO_2}	mEq/L	24-32	21-32	21-28	26-30
SPECIAL					
Red cell acetylcholinesterase	IU/L	450-790	1270-2430	640	270
Ammonia	µg/dL	13-108	N/A	N/A	N/A
BSP ($t_{½}$)	min	2-3.7	2.5-4	1.6-2.7	2.1
Serum iron	µg/dL	73-140	57-162	166-222	N/A
TIBC	µg/dL	200-262	63-186	N/A	N/A
Lactic acid	mmol/L	1.11-1.78	0.56-2.22	1.00-1.33	N/A
Ketones					
Acetone	mg/dL	N/A	0-10	0-10	N/A
Acetoacetate	mg/dL	N/A	0-1.1	N/A	N/A
BHB	mg/dL	N/A	0-10	N/A	N/A

Data from Kaneko JJ, Harvey JW, Bruss ML, eds: *Clinical biochemistry of domestic animals,* ed 5, New York, 1997, Academic; Duncan JR, Prasse KW: *Veterinary laboratory medicine,* ed 3, Ames, Iowa, 1994, Iowa State University Press; and the Normal Values Clinical Pathology Laboratory, Veterinary Medical Teaching Hospital, University of California at Davis, 2000.

ALP, Alkaline phosphatase; *AST,* aspartate aminotransferase; *BHB,* β-hydroxybutyrate; *BSP ($t_{½}$),* bromsulphalein clearance halftime; *CK,* creatine kinase; *GGT,* γ-glutamyl transferase; *LDH,* lactate dehydrogenase; *N/A,* not applicable; *P_{CO_2},* partial pressure of carbon dioxide; *SDH,* sorbitol dehydrogenase; *T_{CO_2},* total carbon dioxide; *TIBC,* total iron-binding capacity.

Table 22-3 Serum Protein Electrophoresis: Normal Range for Large Animals

Component	Unit	Equine	Bovine	Ovine	Caprine
Total protein	g/dL	5.2-7.9	6.74-7.46	6.0-7.9	6.4-7.0
Albumin	g/dL	2.6-3.7	3.03-3.55	2.4-3	2.7-3.9
Globulin	g/dL	2.62-4.04	3-3.48	3.5-5.7	2.7-4.1
α1	g/dL	0.06-0.7	N/A	N/A	N/A
α2	g/dL	0.31-1.31	N/A	N/A	N/A
α	g/dL	N/A	0.75-0.88	0.3-0.6	0.5-0.7
β1	g/dL	0.4-1.58	N/A	0.7-1.2	0.7-1.2
β2	g/dL	0.29-0.89	N/A	0.4-1.4	0.3-0.6
β	g/dL	N/A	0.8-1.12	N/A	N/A
γ_1	g/dL	N/A	N/A	0.7-2.2	N/A
γ_2	g/dL	N/A	N/A	0.2-1.1	N/A
γ	g/dL	0.55-1.9	1.69-2.25	N/A	0.9-3
Albumin/globulin (A/G) ratio		0.62-1.46	0.84-0.94	0.42-0.76	0.63-1.26

Data from Kaneko JJ, Harvey JW, Bruss ML, eds: *Clinical biochemistry of domestic animals,* ed 5, New York, 1997, Academic; and Duncan JR, Prasse KW: *Veterinary laboratory medicine,* ed 3, Ames, Iowa, 1994, Iowa State University Press.

N/A, Not applicable.

22.2.4 Age

There are several important differences in hematologic and clinical chemistry between neonatal and adult animals. The effects of age have been studied most carefully in horses and cattle. Suckling neonatal animals tend to have lower BUN, slightly lower total protein and globulin, moderately higher GGT and phosphate, and markedly greater alkaline phosphatase than do adult animals.

22.2.5 Sex

With the obvious exception of sex hormone concentrations, there are few recognized differences in clinical chemistry values between sexes. In most domestic animals the intact male tends to have a slightly higher erythrocyte count, hemoglobin concentration, and PCV than the female or neutered male. This sex-related difference has been demonstrated most clearly in the horse.

22.2.6 Factors Influencing Results or Their Interpretation

Many factors influence the reliability and interpretation of results obtained by laboratory analysis. Sample collection and handling are very important factors. The sample collection site (e.g., jugular vein, mammary vein, tail vein, or carotid artery) can have an important effect on the results of tests such as blood gas evaluation, glucose, or ketones. The choice of anticoagulants depends on whether the samples are to be submitted for serum, plasma, or whole blood determinations. The specific sample requirements for the most commonly ordered clinical chemistry determinations are listed in Table 22-4. Serum is required for most chemistry determinations, and serum separator tubes work very well in most settings. There have been some indications that results of some serum hormone assays may be influenced by collection of blood in serum separator tubes. Heparin is the anticoagulant of choice for most chemical determinations requiring plasma. In former times fluoride-oxalate was the anticoagulant of choice for blood glucose determination, because it halts glycolysis by the red cells. However, fluoride may interfere with certain chemical procedures (specifically the glucose oxidase method for blood glucose determination) and should be used only for blood lactate determination or in selected circumstances in which glucose determinations are required and samples must be held for some period of time without refrigeration. Citrate is the anticoagulant of choice for clotting tests and blood typing. Ethylenediaminetetraacetic acid (EDTA) is the anticoagulant most often used for hematologic evaluation. Both citrate and EDTA are chelating agents, which may interfere with a wide variety of chemical determinations.

Table 22-4 Recommended Anticoagulants for Hematologic or Clinical Chemistry Evaluation

Anticoagulant	Specimen	Test or Procedure
Ethylenediamine tetraacetic acid (EDTA)	Whole blood Whole blood Plasma	Complete blood count, cross-match, platelet count Blood selenium Refractometric protein and fibrinogen
	Peritoneal fluid	Fluid analysis
	Bone marrow	Hematologic evaluation
	Synovial fluid	Fluid analysis
Heparin	Whole blood	Blood pH, blood gases
	Plasma	Electrolytes, osmolality
	Synovial fluid	Mucin clot test
Fluoride and oxalate	Plasma	Lactate
Citrate	Whole blood	Blood typing
	Plasma	Coagulation tests (PT, PTT, factor analysis)
None, serum separator tubes	Serum	Most chemistries, electrolytes, osmolality Protein electrophoresis
		Hormones (cortisol, T_3, T_4)
		Immunoglobulins (IgG, IgM, IgA)

Modified from Brobst DF, Parry BW: Normal clinical pathology data. In Robinson NE, ed: *Current therapy in equine medicine,* ed 2, Philadelphia, 1987, Saunders.

PT, Prothrombin time; *PTT,* partial thromboplastin time; T_3, triiodothyronine; T_4, thyroxine.

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Samples should be submitted as soon after collection as possible, but circumstances may require storage of some samples for 12 to 24 hours. For collection of serum, whole blood should be allowed to clot before refrigeration. Serum should be separated from the red cells immediately after clot formation and then kept refrigerated. Samples should be stored in clean containers free from exposure to sunlight, medications, or chemicals. If whole blood is left at room temperature for longer than 60 minutes, blood glucose will be falsely low as a result of red cell glycolysis. Storage of whole blood may result in in vitro hemolysis, with the potential for misleading increases in the serum or plasma enzymes AST and lactate dehydrogenase (LDH) due to hemolysis. Failure to separate serum or plasma from the red cells within an hour of collection may lead to leakage of erythrocyte potassium and a falsely elevated serum or plasma potassium concentration.

Stress, transportation, excitement, and handling produce physiologic responses in animals that affect a variety of hematologic and biochemical parameters. This is most evident in the horse, which shows marked increases in red cell mass and to a lesser extent plasma protein concentration in response to excitement, exercise, or catecholamine administration. The red cell count and hemoglobin concentration can increase by as much as 50%,

whereas plasma protein concentration may increase by 1 to 2 g/dL. Leukocytosis is induced as the marginating leukocyte pool is mobilized into the general circulation. Prolonged stress results in the release of endogenous corticosteroids, which produce the typical “stress response” in the leukogram. A similar leukogram is found in race horses some 4 to 6 hours after racing. The combination of catecholamine and glucocorticoid release associated with stress, transport, and excitement, as well as with many gastrointestinal catastrophes, may result in markedly elevated blood glucose concentrations (up to 400 mg/dL). Modest elevations (twofold to fourfold increase) in muscle-derived enzymes occur in association with prolonged transport or endurance exercise.

Large losses or compartmentalization of sodium-containing fluid accompanies many systemic disorders, particularly digestive problems such as diarrhea, colic, displacement of viscera, excessive sweat losses, and some urinary tract diseases. These forms of dehydration lead to decreases in plasma volume, which are indicated by moderate-to-marked increases in the PCV and TPP concentration. The concentration of other compounds dissolved in the plasma may also increase as a result of decreases in the plasma volume. The concentrations of compounds that are largely protein-bound, such as calcium, are generally closely related to protein concentration. More than 50% of serum calcium is bound to albumin. Increases or decreases in plasma protein concentration normally result in proportional changes in total serum calcium concentration, whereas the physiologically active ionized calcium may remain unchanged.

Diseases that cause a reduction in effective circulating fluid volume often also cause alterations in renal function. This so-called “prerenal azotemia” results in moderate to marked elevation in BUN and creatinine. Although this is generally considered primarily a prerenal azotemia, real pathologic changes in the kidneys often are associated with the systemic processes initiated by these disorders. Reevaluation of renal function (urinalysis BUN, creatinine) in these patients during the course of disease is important because it affects prognosis, response to fluid administration, and the potential for nephrotoxicity and systemic toxicity of a variety of chemotherapeutic agents.

Fasting laboratory data are important for evaluation of many disease conditions in human and small animal patients. Truly fasting conditions are rather difficult given the large and complex gastrointestinal tract of most herbivores and are thus seldom used. The feeding of animals in relation to sample collection can, however, have an impact on the data obtained. Hay feeding in horses is reported to affect sodium, potassium, and protein concentrations within the first few hours after feeding. Animals feeding on lush green pasture or large amounts of silage may have slightly different parameters from those fed high-concentrate rations. The anion-cation balance of the ration has an impact on relative serum electrolyte concentration, acid-base balance, and urine pH and urinary electrolyte excretion. Lactescent (cloudy) plasma may be observed in samples from nursing foals or calves. The fluid intake of the normal nursing neonate may range from 100 mL/kg/day to more than 250 mL/kg/day. This high fluid intake is reflected by a commensurately high output of urine with a low specific gravity and low osmolar content.

The administration of certain medications may have an impact on some laboratory parameters. Tranquilization may be necessary for restraint and safe sample collection. The practitioner should be aware that tranquilizers often decrease red cell mass and plasma protein concentration. This is particularly true of the phenothiazine-derivative tranquilizers when used in the horse. Xylazine administered to large animals produces a modest catecholamine release, which may be evidenced by the slight sweating response seen in many horses sedated with this drug. Glucose concentration will increase modestly in response to the xylazine-induced catecholamine release. Repeated intramuscular injections with certain antibiotics (especially erythromycin and tetracycline) or other preparations that are locally irritating may produce slight-to-moderate elevations in muscle-derived serum enzyme activities. Intravenous administration of certain drugs and compounds such as dimethyl sulfoxide

(DMSO) can produce intravascular hemolysis and hematuria. The amount of hemolysis in these circumstances is relatively small and of little consequence, except that it can cause confusion as to why hemoglobinuria occurred.

22.3 FLUID AND ELECTROLYTE BALANCE

22.3.1 Packed Cell Volume and Total Plasma Protein

Changes in the plasma volume generally are reflected by changes in the PCV and the TPP concentration. In dehydrated humans, changes in the PCV are believed to be the more reliable guide to changes in plasma volume because substantial protein fluxes into and out of the circulation have been shown to occur. However, in most animal species the range of normal for the PCV is much wider than for the TPP concentration. This is particularly true of horses, in which excitement, pain, or catecholamine release can produce variable mobilization of splenic erythrocytes, making it difficult to obtain a truly resting PCV. For these reasons, precise quantitative estimation of a change in plasma volume using these parameters is more complex and less reliable in large animal species. As plasma volume increases or decreases, the change in the PCV is always less than the change in the TPP concentration. However, a large disparity in the changes in the PCV and the TPP concentration in a patient with a history of loss of sodium-containing fluid and clinical evidence of reduced effective circulating fluid volume suggests blood or protein loss. Marked increases in the PCV with a normal-to-low TPP concentration frequently are encountered in animals with acute protein-losing enteropathies such as salmonellosis or equine toxic enteritis. In horses undergoing treatment for diarrhea, the excessive administration and retention of sodium-containing fluids is a key factor in the development of edema and hypoproteinemia. Blood loss generally results in a decrease in both PCV and TPP concentration.

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22.3.2 Serum Sodium

The serum sodium concentration is a function of the exchangeable cation content (i.e., the exchangeable sodium [Na] in the extracellular fluid [ECF] volume plus the exchangeable potassium [K] in the intracellular fluid [ICF] volume relative to total body water), as indicated in the following formula:

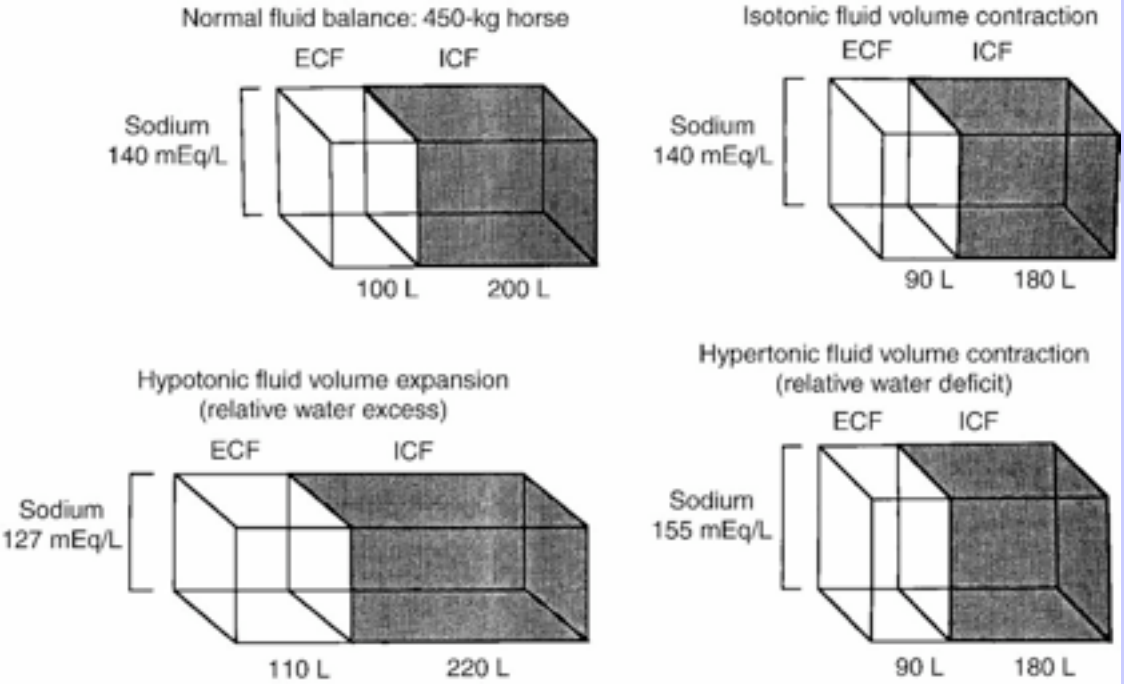
$$\text{Serum Na}\,(\text{mEq}\,/\,\text{L}) \simeq \frac{\text{Exchangeable}\,(\text{Na} + \text{K})}{\text{Total body water}}$$

Changes in the sodium concentration reflect the net changes in this relationship and often do not represent accurately the changes in sodium balance. Changes in water balance are thus primarily responsible for changes in the serum sodium concentration. Hyponatremia is an indication of a relative water excess, whereas hypernatremia is an indication of a relative water deficit.

Dehydration is defined as a loss of body water (fluid volume contraction). It occurs in a variety of clinical circumstances. The serum sodium concentration provides a means of categorizing dehydration in a physiologically meaningful way. Hypertonic dehydration, which occurs when water losses exceed the losses of sodium and potassium, is indicated by hypernatremia. The response of horses to feed and water deprivation is an example of this form of dehydration. Isotonic dehydration occurs with a balanced loss of water and electrolytes —that is, approximately 140 to 150 mEq of sodium plus potassium (Na + K) for each liter of water lost. Because the relative water balance has not changed, the serum sodium concentration remains unchanged despite the accumulation of what may have been a substantial sodium deficit. The early stages of acute diarrhea and the dehydration of heavily sweating endurance horses are examples of isotonic dehydration. Hypotonic dehydration occurs when the losses of exchangeable cations (Na + K) exceed the net change in water balance; this condition

is indicated by hyponatremia. Hypotonic dehydration often is seen in animals with subacute or chronic diarrhea that develop substantial water and electrolyte deficits but then replace part of the water deficit through water consumption. Fig. 22-1 shows the compartmental distribution of fluid between the ECF volume and the intracellular fluid (ICF) volume in four situations.

Fig. 22-1 Compartmental distribution of fluid between the extracellular fluid (ECF) volume and the intracellular fluid (ICF) volume in a 450-kg horse with normal fluid balance; with isotonic fluid volume contraction; with hypotonic fluid volume expansion; and with hypertonic fluid volume contraction. Modified from Kaneko JJ, Harvey JW, Bruss ML, eds: *Clinical biochemistry of domestic animals,* ed 5, New York, 1977, Academic.



22.3.2.1

HYPONATREMIA

Hyponatremia is often but not invariably associated with conditions that cause sodium depletion such as vomiting, diarrhea, excessive sweat losses, and adrenal insufficiency. The fluid losses in these conditions are most often hypotonic or isotonic, and initial fluid and electrolyte deficits do not result in hyponatremia until water intake, renal water retention, or both disturb the balance between the remaining exchangeable cations and the total body water.

The accumulation of sodium-containing fluid in body cavities or the gut lumen caused by ascites, peritonitis, or rupture of the bladder or by displacement, torsion, or volvulus of the gut is referred to as a *third-space problem*. When such accumulations develop rapidly, the plasma volume is reduced, and the serum sodium

concentration subsequently may decrease as compensating renal responses cause water retention. Rupture of the bladder in neonatal foals is associated with marked hyponatremia and hypochloremia. As fluid intake continues and dilute urine accumulates in the abdomen, sodium, chloride, and other ions are drawn from the rest of the ECF into this accumulating fluid. No sodium or chloride has been lost from the body, and the observed decreases in the electrolyte concentration are caused by changes in the relative water balance. The neurologic signs seen in these foals are largely caused by the effects on the central nervous system of the rapidly developing and marked hypotonic hyponatremia. Progressively severe neurologic disturbances may be seen as the serum sodium concentration falls below 115 mEq/L and then below 100 mEq/L. The severity of the neurologic abnormalities is a function of both the rate at which hyponatremia develops and the absolute degree of hyponatremia. Neurologic disturbances can occur iatrogenically if excessive amounts of free water (usually given as 5% dextrose) are administered to patients with altered renal function.

Mastitis results in an increased loss of sodium in the milk, and a low-grade mastitis problem in a dairy herd on a marginal dietary salt intake may result in sodium depletion and medullary washout. Decreased milk production, polyuria, hyposthenuria, and a low urine sodium level may be noted, although the serum sodium concentration may remain within the lower range of normal.

The most common causes of hyponatremia are listed in Box 22-1. Marked hyperlipidemia or hyperproteinemia produces a falsely low sodium concentration value because lipid or protein occupies a significant volume in the serum or plasma sample and because sodium is present only in the aqueous phase. This potential cause of hyponatremia is indicated by an increase in the osmolar gap between measured and calculated osmolality. The use of direct ion-specific electrodes for electrolyte determinations avoids this potential cause of a falsely low sodium concentration value.

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22.3.2.1.1

Box 22-1 Causes of Hyponatremia

22.3.2.1.1.1

COMMON CAUSES

Relative water excess

Loss of sodium-containing fluid (decreased effective circulating volume)

Diarrhea

Excessive sweating

Blood loss

Fluid drainage

High-volume gastric reflux

High-volume pleural drainage

Adrenal insufficiency

Sequestration of fluid (third-space problems)

Peritonitis

Ascites

Ruptured bladder

Torsion or volvulus of the gut

Excessive administration of 5% dextrose to patient with renal disease

False hyponatremia

Hyperlipidemia

Hyperproteinemia

Hyperglycemia

22.3.2.1.1.2

UNCOMMON CAUSES

Water retention with normal effective circulating volume

Psychogenic polydipsia

Renal disease

Inappropriate antidiuretic hormone secretion

Marked hyperglycemia causes a reduction in the measured serum sodium concentration of approximately 1.6 mEq/L for every 100 mg/dL increase in the glucose concentration. Increases in the plasma glucose concentration generate osmotic forces that result in the movement of cellular water into the ECF, diluting the plasma sodium concentration.

22.3.2.2

HYPERNATREMIA

Hypernatremia can occur in the initial stages of diarrhea, vomiting, or renal disease if water loss exceeds electrolyte loss (Box 22-2). When water losses are replaced by increased water consumption, enhanced renal water retention, or both, the serum sodium concentration decreases. Food and water deprivation in normal horses and cattle is associated with substantial reduction of renal and fecal output, but continued cutaneous and respiratory insensible water loss may result in hypernatremia. In this case the hypernatremia is the result of a primary water loss. Hypernatremia may occur transiently as a result of sodium excess after administration of hypertonic saline or sodium bicarbonate if water intake is restricted or impaired. Hypernatremia has been reported in calves fed an inappropriately mixed oral electrolyte replacement solution as their only fluid intake.[4] The hypernatremia observed with salt poisoning in cattle and swine is the result of water restriction in animals that have been maintained on a high-salt intake.

22.3.3

Serum Potassium

The serum potassium concentration is influenced by factors that alter internal balance (the distribution of potassium between the ECF and the ICF) and those that change external balance (potassium intake and output). Changes in the serum potassium concentration occur in a wide variety of clinical circumstances and have profound neuromuscular effects that are largely the result of changes in cell membrane potential. The responses to dehydration and acid-base imbalance often complicate the evaluation of the potassium concentration. For example, calves with acute diarrhea often develop potassium depletion because of excessive losses and inadequate intake, but the serum potassium concentration of these animals usually is normal to increased as the result of renal shutdown and the metabolic acidosis induced by dehydration, sodium depletion, and hypovolemia. Hypokalemia may become evident only as other fluid and electrolyte losses are replaced.

22.3.3.1

Box 22-2 Causes of Hypernatremia

22.3.3.1.1

COMMON CAUSES

Pure water losses

- Panting
- Water deprivation

Sodium excess (water restriction)

- Salt poisoning
- Feeding only electrolytes, no free water

22.3.3.1.2

UNCOMMON CAUSES

Water loss exceeds electrolyte loss

- Vomiting
- Diarrhea
- Burns
- Intrinsic renal disease
- Diuretics
- Diabetes insipidus
- Central
- Nephrogenic
- Hypertonic saline or sodium bicarbonate administration
- Mineralocorticoid excess

Measuring the erythrocyte potassium concentration is relatively easy and has been suggested as an aid in assessing the need for potassium supplementation in racehorses with recurrent muscle disease. However, experimental studies in horses indicate that the erythrocyte potassium concentration does not always accurately reflect potassium deficits.

22.3.3.2

HYPOKALEMIA

Hypokalemia may result from depletion of the body's potassium stores or from a redistribution of potassium from the ECF into the ICF space (Box 22-3). Hypokalemia is most commonly seen with altered intake and absorption and with excessive potassium losses from the gastrointestinal tract caused by vagal indigestion, torsion of the abomasum, ileus, or diarrhea. Excessive renal loss may result from mineralocorticoid excess, certain diuretics, or altered renal function, as reported in horses with renal tubular acidosis. Marked hypokalemia develops when reduced dietary intake caused by anorexia is associated with excessive potassium losses.

Hypokalemia without potassium depletion results from the movement of extracellular potassium to the intracellular space. This form of hypokalemia occurs in response to an acute alkalosis and to the

administration of insulin or glucose. Overzealous and rapid administration of sodium bicarbonate can produce an alkalosis with a profound and rapidly developing hypokalemia. Animals with moderate potassium deficits that are vigorously treated with sodium bicarbonate to correct a coexisting mild metabolic acidosis may be particularly prone to this problem. The initial response to catecholamine administration is a modest, transient increase in potassium caused by α-adrenergic stimulation, which often is followed by hypokalemia caused by β-adrenergic receptor responses.

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22.3.3.2.1

Box 22-3 Causes of Hypernatremia

22.3.3.2.1.1

COMMON CAUSES

22.3.3.2.1.1.1

Altered External Balance*

Vomiting

Vagal indigestion with internal vomiting

Diarrhea

Third-space problems (gut or abomasal torsion or volvulus; peritonitis)

Excessive sweat losses

Dietary deficiency

Prolonged anorexia

22.3.3.2.1.1.2

Altered Internal Balance

Metabolic alkalosis

22.3.3.2.1.2

UNCOMMON CAUSES

22.3.3.2.1.2.1

Altered External Balance

Mineralocorticoid excess

Diuretics

Renal tubular acidosis

Postobstruction diuresis

22.3.3.2.1.2.2 Altered Internal Balance

Excessively rapid bicarbonate administration

Insulin and/or glucose administration

Catecholamine administration or endogenous release

* *External balance* refers to the relative changes in potassium intake and output; *internal balance* refers to the distribution of potassium between the extracellular and the intracellular fluid compartments.

22.3.3.3 HYPERKALEMIA

Hyperkalemia may develop in vitro as a result of hemolysis or leakage of erythrocyte potassium after storage of whole blood (Box 22-4). The release of potassium from leukocytes or platelets into the serum after clot formation is a potential cause of hyperkalemia if marked leukocytosis or thrombocytosis is present. Hyperkalemia also results from renal potassium retention in Addison's disease, acute renal failure, and renal shutdown. A number of factors contribute to the movement of intracellular potassium into the ECF, resulting in hyperkalemia. Hyperkalemia often is associated with metabolic acidosis, particularly when the acidosis results from volume depletion and is complicated by renal shutdown. Hyperkalemia has been reported in animals with massive muscle necrosis, but neither hyperkalemia nor metabolic acidosis is a common feature in horses with exertional rhabdomyolysis. Vigorous short-term exercise of horses at high intensity results in a marked but transient hyperkalemia (9 to 10 mEq/L) that may be associated with the profound lactic acidosis seen with anaerobic workloads.[5] Potassium returns to normal within minutes, and often a modest hypokalemia occurs later in the recovery period. Episodic hyperkalemia and muscular weakness are associated with the condition known as *hyperkalemic periodic paralysis* (HYPP).[6] HYPP is inherited as an autosomal-dominant trait in horses, with a specific quarter horse lineage[7] (see Chapter 42 for a more complete discussion of this disorder). The disease is the result of a single DNA base pair substitution that leads to the production of an abnormal voltage-regulated sodium channel at the cell membrane.[8] Sudden marked increases in the serum potassium concentration, up to 8 to 9 mEq/L, are the result of transcellular movement of potassium and are associated with profound electrocardiographic abnormalities and fluid shifts.

22.3.3.3.1 Box 22-4 Causes of Hyperkalemia

22.3.3.3.1.1 COMMON CAUSES

False hyperkalemia

In vitro hemolysis

Prolonged storage of blood (over 6 hours) without separation of serum or plasma

Altered external balance

Hypovolemia with renal shutdown

Altered internal balance

Metabolic acidosis

Vigorous exercise

22.3.3.3.1.2 UNCOMMON CAUSES

False hyperkalemia

Markedly elevated leukocyte or platelet count

Altered internal balance

Hyperkalemic periodic paralysis in quarter horses

Diabetes mellitus

Tissue necrosis

Renal disease

Addison's disease

22.3.4 Serum Chloride

Alterations in the chloride concentration usually are associated with nearly proportional changes in the sodium concentration as the result of changes in relative water balance. In addition, the chloride concentration tends to vary inversely with the bicarbonate concentration; therefore, when disproportionate changes in the chloride concentration relative to sodium occur, significant acid-base imbalances should be anticipated. Disproportionate

increases in chloride are associated with a normal-to-low anion gap hyperchloremic metabolic acidosis, but they also are seen as a result of the compensating responses for a primary respiratory alkalosis (Box 22-5). A striking hyperchloremic metabolic acidosis has been reported in horses with renal tubular acidosis.[9,10] Disproportionate decreases in chloride relative to sodium characteristically are seen in metabolic alkalosis but also may be seen as part of the compensating response for chronic primary respiratory acidosis (Box 22-6). Hypochloremic metabolic alkalosis is a common feature in many digestive disorders of ruminants and is caused by loss of chloride-rich fluids or sequestration of such fluids in the abomasum and forestomachs.

22.3.5 ## Osmolality

Measurement of the serum osmolality provides an indication of relative water balance in much the same way as the serum sodium concentration does. In most circumstances these parameters are closely correlated. Comparing the measured osmolality with the calculated osmolality, as determined from the measured concentrations of the major solutes in serum (sodium, glucose, and urea), provides a means of determining if the serum water content deviates widely from normal or if foreign, low—molecular-weight substances are present in the blood. The difference between the measured osmolality and the calculated osmolality is called the *osmolar gap*. Decreases or increases in the osmolar gap could indicate laboratory error, but increases of more than 10 mOsm/kg generally are the result either of a decrease in the serum water content (caused by hyperlipidemia or hyperproteinemia) or of the presence of abnormally high concentrations of low—molecular-weight substances in the serum. These substances can include a variety of exogenous and potentially toxic compounds such as mannitol, ethanol, methanol, propylene glycol, ethylene glycol, isopropanol, ethyl ether, acetone, trichloroethane, and paraldehyde.

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22.3.5.1 ### Box 22-5 Causes of Hyperchloremia

22.3.5.1.1 #### WITH PROPORTIONAL INCREASE IN SODIUM

22.3.5.1.1.1 ##### Common Causes

Relative water deficit

Panting

Water deprivation

Salt poisoning

22.3.5.1.1.2 ##### Uncommon Causes

Vomiting

Diarrhea

Burns

Intrinsic renal disease

Diuretics

Diabetes insipidus

Central

Nephrogenic

Hypertonic saline administration

Mineralocorticoid excess

22.3.5.1.2 WITHOUT PROPORTIONAL INCREASE IN SODIUM

22.3.5.1.2.1 Common Causes

Hyperchloremic metabolic acidosis

Renal tubular acidosis

22.3.5.1.2.2 Uncommon Cause

Compensation for respiratory alkalosis

22.3.5.2 Box 22-6 Causes of Hypochloremia

22.3.5.2.1 WITH PROPORTIONAL DECREASE IN SODIUM

22.3.5.2.1.1 Common Causes

Relative water excess

Diarrhea

Excessive sweating

- Blood loss
- Fluid drainage
- High-volume gastric reflux
- High-volume pleural drainage
- Sequestration of fluid (third-space problems)
  - Peritonitis
  - Ascites
  - Ruptured bladder
- Renal disease

False hypochloremia

- Hyperlipidemia
- Hyperproteinemia
- Hyperglycemia

22.3.5.2.1.2 Uncommon Causes

Psychogenic polydipsia

Inappropriate antidiuretic hormone secretion

Adrenal insufficiency

22.3.5.2.2 WITHOUT PROPORTIONAL DECREASE IN SODIUM

22.3.5.2.2.1 Common Causes

Metabolic alkalosis

Exhaustive disease syndrome

Abomasal torsion

Vagal indigestion with internal vomiting

Response to furosemide in horses

22.3.5.2.2.2 Uncommon Cause

Compensation for respiratory acidosis

22.3.6 Serum Calcium

Calcium plays a vital role in many of life's processes, including maintenance of neuromuscular excitability, permeability of cell membranes, conduction of nerve impulses, muscle contraction, and blood clotting. For these reasons the serum calcium concentration or, more correctly, the ionized calcium concentration normally is maintained within a relatively narrow range, despite wide variation in intake and output. Calcium metabolism is regulated by dietary factors, vitamin D and its active metabolites, and the hormones parathormone and calcitonin. The serum calcium concentration is maintained by adjusting intestinal absorption, renal excretion, and mobilization of available calcium from the large stores in bone. Calcium exists in the serum in three forms: ionized calcium, complexed calcium, and protein-bound calcium. Ionized calcium, which normally constitutes 40% to 60% of the total calcium, is the physiologically active form of calcium. Protein binding (protein-bound calcium normally constitutes 40% to 50% of the total calcium) can cause confusion. Hyperalbuminemia may result in a modest hypercalcemia, whereas hypoproteinemia, especially hypoalbuminemia, regularly results in a moderate hypocalcemia. The ionized calcium concentration generally remains within normal limits, despite increases or decreases in total calcium associated with the change in protein concentration. The acid-base balance has additional influence on the amount of ionized and protein-bound calcium. Alkalosis reduces ionized calcium and increases protein binding, whereas acidosis produces the opposite effect. Ion-specific electrodes are available for determining the ionized calcium level, which can be very useful if blood samples are handled appropriately. Most diagnostic laboratories provide the total serum calcium value, which is composed of ionized, complexed, and protein-bound calcium.

22.3.6.1

HYPOCALCEMIA

Large increases or decreases in the serum calcium concentration generally are the result of a failure in the normal mechanisms of calcium homeostasis rather than a reflection of absolute calcium deficits or calcium-phosphorus imbalances. Hypocalcemia occurs with some frequency in domestic animals, particularly in high-producing dairy cattle near the onset of lactation. In cattle the serum calcium concentration normally decreases to less than 8 mg/dL with the stress of parturition and the onset of lactation (Box 22-7). Failure to mobilize sufficient calcium to maintain serum calcium results in the clinical syndrome of parturient paresis (see Chapter 41 for a more detailed discussion of this syndrome). Most animals are recumbent with a calcium level of 6 mg/dL or less, and fatalities may occur if the level drops below 4 mg/dL. Parturient paresis is associated with a normal to increased serum magnesium level, hypophosphatemia, and hypocalcemia. Change in the cation-anion balance in the diet of dairy cattle during the periparturient period has modest effects on the acid-base balance and enhances calcium mobilization from storage sites, thus reducing the incidence of milk fever in cows at high risk. Grass tetany is associated with marked hypomagnesemia and modest hypocalcemia, whereas the inorganic phosphorus level remains within the normal range.

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22.3.6.1.1

Box 22-7 Causes of Hypocalcemia

22.3.6.1.1.1

COMMON CAUSES

Parturient paresis (milk fever)

Grass tetany

Hypoalbuminemia (decreased total calcium; ionized calcium may remain unchanged)

Fat necrosis

Lactation tetany

Transport tetany

Synchronous diaphragmatic flutter

Blister beetle toxicosis (cantharidin)

Acute renal failure

Anorexia in lactating cows

22.3.6.1.1.2

UNCOMMON CAUSES

Acute toxemia and associated anorexia in lactating dairy cows

Hypoparathyroidism

Exertional rhabdomyolysis

Malignant hyperthermia

Pancreatic disease

Oxalate toxicity

Tetracycline administration

Furosemide administration

Alkalosis induced by excessive bicarbonate administration

Systemic diseases resulting in anorexia (e.g., traumatic reticuloperitonitis, ketosis, and displaced abomasum) or acute toxemic conditions (e.g., coliform mastitis, septicemia, or aspiration pneumonia) that produce anorexia in lactating cattle frequently result in hypocalcemia. Hypocalcemia also is seen in sheep on marginal rations if stressed by inclement weather or when being moved. Hypocalcemia is seen in cattle with fat necrosis, presumably as the result of incorporation of calcium with the fat as a form of soap. Horses with exhaustive disease syndrome or transit tetany often develop decreases in ionized calcium with resultant muscle cramps and synchronous diaphragmatic flutter, which generally respond to intravenous calcium administration. Horses, cattle, and sheep usually respond initially to acute renal tubular damage with mild hypocalcemia and hyperphosphatemia.

22.3.6.2

HYPERCALCEMIA

Marked hypercalcemia, with a serum calcium level ranging from 14 to 20 mg/dL, and modest hypophosphatemia frequently are observed in horses with chronic renal failure that are fed a high-calcium diet such as alfalfa hay (Box 22-8). In these horses, blood samples collected in standard EDTA tubes may actually clot. This occurs because the serum calcium concentration is so high that there is insufficient EDTA to bind all the calcium, and some free calcium is available to complete the clotting process. Vitamin D intoxication can develop as a result of excessive dietary supplementation or the ingestion of certain plants such as *Cestrum diurnum* (day blooming jasmine) and *Solanum malacoxylon,* which contain toxic quantities of vitamin D analogs. Primary hyperparathyroidism is exceedingly rare in large animals, but pseudohyperparathyroidism with hypercalcemia occasionally can develop in animals with tumors that produce protein substances with

parathormone-like biologic activity. This has been reported in a few animals with lymphosarcoma or gastric squamous cell carcinoma.

22.3.6.2.1 Box 22-8 Causes of Hypercalcemia

22.3.6.2.1.1 COMMON CAUSES

- Chronic renal failure in horses
- Hypervitaminosis D
  - Excessive dietary supplements
  - Plant intoxication
    - *Cestrum diurnum* (day blooming jasmine)
    - *Solanum malacoxylon*
- Excessive or too rapid intravenous administration of calcium

22.3.6.2.1.2 UNCOMMON CAUSES

- Neoplasia (pseudohyperparathyroidism)
  - Lymphosarcoma
  - Gastric squamous cell carcinoma
- Hyperparathyroidism

22.3.7 Serum Phosphorus

Phosphorus is found primarily in the skeleton and teeth in close association with calcium in the intricate and dynamic crystalline structure of bone. Intracellularly, phosphate plays an essential role in the degradation and synthesis of many compounds. Also, as adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP), it is the primary form of energy storage and transfer required for almost all of life's processes. Phosphorus in the ECF exists primarily as the buffer pair H_2PO^{-3} and HPO^{-4} and plays a role in acid-base balance. Like calcium, phosphorus is regulated by dietary factors, the active metabolites of vitamin D, and the hormones parathormone and calcitonin. Imbalances of calcium and phosphorus or the presence of

compounds that bind these substances in the gut can produce serious imbalances that are not always evident on analysis of serum samples. Measurement of urinary output or creatinine clearance ratios for calcium and phosphate are simple and helpful procedures. They provide an indication of an imbalance while more definitive procedures such as ration analysis are contemplated.

22.3.7.1

HYPOPHOSPHATEMIA

Serum phosphorus concentrations are not always an accurate guide to phosphate balance, but dietary deficiencies of phosphorus are frequently manifested by hypophosphatemia. Hypophosphatemia is a common feature in cattle with parturient paresis (see also Chapter 41) and horses with chronic renal failure (Box 22-9). It has been reported in animals with experimental oxalate toxicity, in chronic wasting states, or with starvation. Postparturient hemoglobinuria is a disorder of cattle, primarily lactating dairy cattle, that often is associated with diets low in phosphorus. Although marked hypophosphatemia is often reported, it is not an invariable feature of this disorder.

22.3.7.2

HYPERPHOSPHATEMIA

Age-related differences exist in the normal range of serum phosphorus concentration. Young animals have much higher values than adults, with values for neonates commonly up to 7 to 9 mg/dL. The serum phosphate concentration declines progressively with age. Hyperphosphatemia is seen in animals with vitamin D toxicity, transiently in horses after long-distance endurance rides, and initially in horses with acute renal failure (Box 22-10).

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22.3.7.2.1

Box 22-9 Causes of Hypophosphatemia

22.3.7.2.1.1

COMMON CAUSES

Chronic renal failure in horses

Parturient paresis in cattle

Postparturient hemoglobinuria

22.3.7.2.1.2

UNCOMMON CAUSES

Brassica toxicity

Inadequate dietary intake

Starvation or chronic wasting diseases

Hyperparathyroidism, pseudohyperparathyroidism

22.3.7.2.2

Box 22-10 Causes of Hyperphosphatemia

22.3.7.2.2.1

COMMON CAUSES

Acute renal failure

Nutritional secondary hyperparathyroidism (excess phosphate intake)

Endurance exercise in horses

Higher normal range in neonates

22.3.7.2.2.2

UNCOMMON CAUSES

Acute rhabdomyolysis

Vitamin D toxicity

22.3.8

Serum Magnesium

Disturbances of magnesium metabolism occur principally in cattle and sheep. Complex nutritional and environmental interactions contribute to a variety of clinical syndromes attributed to magnesium deficiency and the onset of tetany in grazing animals.

22.3.8.1

HYPOMAGNESEMIA

Hypomagnesemia is reported in cattle with grass tetany and in sheep with grass staggers (Box 22-11) (see also Chapter 41). A serum magnesium level below 1.8 mg/dL is considered low; values below 1 mg/dL are considered severe and are likely to be associated with clinical signs. Hypomagnesemia caused by dietary magnesium deficiency has been reported in calves reared in confinement and fed a milk diet exclusively.

22.3.8.2

HYPERMAGNESEMIA

Hypermagnesemia occurs infrequently but may be seen with overzealous administration of Epsom salts ($MgSO_4$), either orally as a drench by means of nasogastric intubation or as an enema for the treatment of digestive disorders (Box 22-12). Intravenous administration of magnesium produces muscle relaxation but does not alter consciousness, and hypertonic $MgSO_4$ solutions are not considered a humane means of euthanasia.

22.3.8.2.1 **Box 22-11 Causes of Hypomagnesemia**

22.3.8.2.1.1 **COMMON CAUSES**

- Grass tetany
- Winter tetany
- Grass staggers
- Calves on a milk-only, magnesium-deficient diet
- Endurance exercise

22.3.8.2.1.2 **UNCOMMON CAUSE**

- Undernutrition

22.3.8.2.2 **Box 22-12 Causes of Hypermagnesemia***

- Epsom salt ($MgSO_4$) overdose given orally or as an enema
- Intravenous administration of magnesium in excessive amounts

* Hypermagnesemia is an uncommon condition in large animals.

22.4 ## ACID-BASE IMBALANCE

Using the traditional approach to acid-base balance, the four primary acid-base imbalances and their compensating responses are presented in Table 22-5. Acidosis is associated with an increase in the hydrogen ion concentration (decreasing pH), whereas alkalosis is caused by a decrease in the hydrogen ion concentration (increasing pH). When the primary imbalance is associated with a change in the bicarbonate concentration, the acid-base imbalance is called a *metabolic disorder*. The compensating response for a metabolic acid-base imbalance is mediated by the respiratory tract, which alters the partial pressure of carbon dioxide (P_{CO_2}) to counterbalance the primary imbalance and to partly restore the pH toward normal. Primary respiratory imbalances are related to changes in alveolar ventilation, which result in an increased P_{CO_2} in respiratory acidosis and a decreased P_{CO_2} in respiratory alkalosis. The compensating response for these primary respiratory acid-base imbalances is mediated by the kidneys through alterations in the excretion or retention of hydrogen ions and bicarbonate. Heparinized blood samples for acid-base evaluation must be drawn anaerobically and sealed immediately. Arterial blood samples

should be submitted for evaluation of primary respiratory disorders and for evaluation of ventilation in patients under general anesthesia. Venous blood samples are easier to obtain and provide reliable data for most primary metabolic acid-base abnormalities.

Blood gas analysis should be done as soon after collection as possible. However, appropriately collected blood samples yield reliable results for as long as 4 hours if held in ice water. The patient's rectal temperature should be provided to the laboratory so that corrections can be made for variation in body temperature. Changes in body temperature have a major impact on the partial pressure of oxygen (P_{O_2}) as well as the P_{CO_2} but relatively little effect on estimations of bicarbonate or base balance. During brief exercise at maximal intensity, the temperature of the central venous blood may exceed the rectal temperature by as much as 3° C. In these circumstances, the central blood temperature is more appropriate than the rectal temperature for correcting blood gas determinations. The blood sampling site (arterial, venous, or capillary blood) has a significant impact on the blood gas values obtained.[11] Arterial blood samples yield higher values for pH and lower values for P_{CO_2} than venous blood, but the bicarbonate is higher in venous blood. The use of blood gas data for evaluation of acid-base imbalances in animals has been reviewed.[12,13] In addition, an excellent review of the traditional and nontraditional approaches to evaluation of acid-base balance as related to fluid therapy in small animals has application to many large animal situations and is well worth reading.[14]

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Table 22-5 Acid-Base Imbalances and Compensatory Responses

Disorder	ph	$[H^+]$	Primary Imbalance	Compensatory Response
Metabolic acidosis	↓	↑	↓ $[HCO_3^-]$	↓ P_{CO_2}
Metabolic alkalosis	↑	↓	↑ $[HCO_3^-]$	↑ P_{CO_2}
Respiratory acidosis	↓	↑	↑ P_{CO_2}	↑ $[HCO_3^-]$
Respiratory alkalosis	↑	↓	↓ P_{CO_2}	↓ $[HCO_3^-]$

$[HCO_3^-]$

, Bicarbonate concentration; P_{CO_2}, partial pressure of carbon dioxide.

22.4.1 Metabolic Acidosis

Metabolic acidosis is characterized by a decrease in pH and bicarbonate concentration. Metabolic acidosis is traditionally thought to be produced by the addition of hydrogen ions or the loss of bicarbonate ions. The most

common causes include the lactic acidosis of ruminal overload, hypovolemia associated with loss or compartmentalization of sodium-containing fluid, ketoacidosis in ketosis and pregnancy toxemia, loss of bicarbonate-rich saliva with oral diseases or esophagostomy in cattle, gastrointestinal loss of bicarbonate as a result of diarrhea, and renal failure, which may result in decreased ability to excrete hydrogen and thus to retain bicarbonate (Box 22-13). Other causes include ingestion of certain drugs or toxic compounds such as salicylate, methanol, ethylene glycol, or paraldehyde. Increased ventilation provides the compensating respiratory response for metabolic acidosis, and a decline in the P_{CO_2} generally begins within minutes. This temporarily minimizes the fall in blood pH, but long-term correction of metabolic acidosis requires renal bicarbonate retention and enhanced acid excretion. Complete correction of metabolic acidosis may be difficult in patients with intrinsic renal disease or those with diseases such as renal tubular acidosis that impair the ability of the kidneys to excrete acid or retain bicarbonate, or both.

22.4.2

Metabolic Alkalosis

Metabolic alkalosis is characterized by an increase in pH and bicarbonate. It occurs fairly commonly in domestic animals, particularly in association with digestive disturbances in ruminants. An initiating process capable of generating alkalosis is necessary and must be coupled with additional factors to maintain metabolic alkalosis. Generation of metabolic alkalosis is traditionally thought to be caused by excessive hydrogen loss, bicarbonate retention, or contraction alkalosis (Box 22-14). Contraction alkalosis occurs when the ECF volume is reduced because of loss or sequestration of fluids high in sodium and chloride but without proportionate loss of bicarbonate. This is a contributing mechanism for the generation of the metabolic alkalosis reported in heavily sweating endurance horses and in response to the diuretic furosemide in the horse. The most common causes of increased hydrogen ion loss are the gastrointestinal losses caused by salivary secretions in ponies after surgical esophagostomy[15]; massive gastric reflux associated with anterior enteritis, ileus, or small bowel obstruction in horses; and sequestration of fluid in the abomasum and forestomach associated with a variety of gastrointestinal displacements or functional disturbances (vagal indigestion) of ruminants. Continuous salivary losses in horses after surgical esophagostomy result in transient metabolic acidosis followed by progressive metabolic alkalosis. Most of these disorders cause significant dehydration and sodium, chloride, and potassium deficits.

22.4.2.1

Box 22-13 Causes of Metabolic Acidosis

22.4.2.1.1

COMMON CAUSES

Rumen overload (lactic acidosis)

Ketosis

Pregnancy toxemia

Hypovolemic shock

Acute diarrhea

Colic with strangulated bowel

Strangulating abomasal torsion

Peritonitis

Uroperitoneum (ruptured bladder)

Exercise above anaerobic threshold (normal response in horses)

22.4.2.1.2 UNCOMMON CAUSES

Renal failure

Renal tubular acidosis

Urea toxicity

Salicylate toxicity

Methanol toxicity

Paraldehyde toxicity

Ethylene glycol toxicity

The factors responsible for maintaining metabolic alkalosis involve impaired renal bicarbonate excretion. These factors are associated with the renal response to decreases in the effective circulating fluid volume, chloride depletion, or potassium depletion. Renal tubular sodium resorption is enhanced in response to hypovolemia. Maintenance of electroneutrality requires that sodium resorption in the proximal tubule be accompanied by a resorbable anion, whereas in the distal tubule, sodium resorption is associated with the secretion of another cation, usually hydrogen or, to a lesser extent, potassium. Chloride is the only resorbable anion normally present in appreciable quantities in the proximal tubular fluid. In metabolic alkalosis, plasma bicarbonate is increased and the chloride concentration is generally decreased as the result of disproportionate chloride losses. The relative lack of the resorbable anion chloride in the proximal tubule thus allows a larger amount of sodium to reach the distal tubule, where aldosterone and other factors enhance hydrogen or potassium loss into the tubular lumen in exchange for sodium. Potassium depletion reduces or eliminates potassium exchange as a means of sodium retention, thus placing greater emphasis on hydrogen ion exchange. Because renal hydrogen excretion is linked with bicarbonate resorption, the excess bicarbonate cannot be eliminated, and metabolic alkalosis is maintained. This is the reason for the *paradoxic aciduria* seen in some patients with metabolic alkalosis, and it is

the reason these patients respond when given intravenous fluids containing chloride and potassium. The compensating respiratory response to metabolic alkalosis is hypoventilation, resulting in an increase in the P_{CO_2}. Excessive bicarbonate administration is an additional potential cause of metabolic alkalosis. Most normal animals can tolerate large doses of bicarbonate, and excesses are rapidly eliminated by renal excretion.[16] However, patients with decreases in effective circulating fluid volume, particularly when coupled with potassium or chloride deficits, may not tolerate a bicarbonate load because renal clearance of excess bicarbonate is likely to be impaired. Attempts to alter the acid-base balance, and thereby affect the athletic performance of racing horses, by prerace administration of high doses of sodium bicarbonate—containing "milk shakes" has become a major concern around the world. This has stimulated substantial research on the acid-base balance of horses before and after racing. In many racing jurisdictions stringent prerace or postrace standards for blood pH or bicarbonate levels (or both) have been enacted to control this practice. The prerace administration of the diuretic furosemide is allowed in some racing jurisdictions. This drug results in a mild metabolic alkalosis with increased bicarbonate, and allowances for this may be included in some regulations. Racing supplements (which may contain sodium bicarbonate), bicarbonate precursors, and diets that supply a high cation-anion balance also have the potential to produce a significant metabolic alkalosis.

22.4.2.2

Box 22-14 Causes of Metabolic Alkalosis

22.4.2.2.1

COMMON CAUSES

- Sequestration of fluid in the abomasum and forestomach in ruminants
- Gastric reflux in horses with ileus
- Massive sweat loss in horses (endurance horses)
- Chloride depletion
- Potassium depletion
- Contraction alkalosis (extracellular fluid volume contraction without bicarbonate loss)
- Salivary loss of chloride in horses with esophagostomy
- Use of diuretics (especially furosemide)

22.4.2.2.2

UNCOMMON CAUSES

- Excessive bicarbonate supplementation or therapy
- Mineralocorticoid excess

Vomiting

22.4.3

Respiratory Acidosis

Respiratory acidosis is characterized by a decrease in pH and an increase in P_{CO_2}, which develop because of decreased effective alveolar ventilation. CO_2 diffuses through the lungs much more readily than oxygen; thus diseases that compromise ventilation normally result in decreases in P_{O_2} before significant increases in P_{CO_2} develop. The most common causes are acute upper respiratory obstruction and primary pulmonary diseases, including pneumonia, pneumothorax, and chronic obstructive lung disease (Box 22-15). Diseases or drugs that affect the respiratory center of the central nervous system also may produce respiratory acidosis, as can general anesthesia. The compensating response for respiratory acidosis is renal retention of bicarbonate. This response requires days to develop and is seen only in chronic respiratory acidosis. Exogenous bicarbonate does not correct respiratory acidosis and should not be administered to affected patients.

22.4.3.1

Box 22-15 Causes of Respiratory Acidosis

22.4.3.1.1

COMMON CAUSES

Primary pulmonary disease

Obstruction of the upper airway

Laryngeal edema

Aspiration pneumonia

Pneumonia

Pneumonia and pleuritis complex

Pneumothorax

Chronic obstructive pulmonary disease

Depression of the respiratory center of the central nervous system

General anesthesia with inappropriately assisted ventilation

Drugs

Opiates

Anesthetics

Tranquilizers

Central nervous system diseases

22.4.3.1.2 UNCOMMON CAUSES

Cardiac arrest

Muscle weakness or dysfunction

Tetanus

Botulism

Myasthenia

Severe hypokalemia

Neonatal respiratory distress syndrome

22.4.4 Respiratory Alkalosis

Respiratory alkalosis is caused by hyperventilation, which may be stimulated by hypoxemia associated with pulmonary disease, congestive heart failure, severe anemia, or neurologic disorders (Box 22-16). The initial compensating response to acute respiratory alkalosis is a modest decline in the ECF bicarbonate concentration, the result of cellular buffering. Subsequent renal responses result in a decrease in the ECF bicarbonate concentration through reduced renal bicarbonate resorption. The decline in bicarbonate may be offset by chloride retention; thus hyperchloremia and decreased P_{CO_2} may be associated with compensated respiratory alkalosis, as well as with compensated metabolic acidosis. Compensating responses for chronic respiratory alkalosis that lasts several weeks actually may be sufficient to return pH to normal.

22.4.5

Mixed Acid-Base Imbalances

Mixed acid-base disorders occur when several primary acid-base imbalances coexist.[17] Metabolic acidosis and alkalosis can coexist, and either or sometimes both may occur with either respiratory acidosis or respiratory alkalosis. The following factors should be considered when evaluating possible mixed acid-base disorders:

1. Compensating responses to primary acid-base disturbances do not result in overcompensation.
2. Compensating responses rarely correct pH to normal. A normal pH in a patient with an acid-base imbalance is an indicator of a mixed acid-base disturbance.
3. A change in pH in the opposite direction to that predicted for a known primary disorder indicates a mixed disturbance.
4. Bicarbonate and P_{CO_2} always deviate in the same direction with primary acid-base disturbances. If these parameters deviate in opposite directions, a mixed abnormality exists.
5. If the change in the anion gap does not approximate the change in bicarbonate, a mixed acid-base imbalance should be suspected.

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Mixed acid-base abnormalities occur with some frequency in domestic animals and often are overlooked. The practitioner must be aware of the potential for mixed acid-base imbalances to correctly interpret blood gas data in complex clinical situations.

22.4.5.1

Box 22-16 Causes of Respiratory Alkalosis

22.4.5.1.1

COMMON CAUSES

- Hypoxemia
  - Pulmonary diseases
  - Congestive heart failure
  - Severe anemia
- Stimulation of the respiratory center of the central nervous system
  - Psychogenic hyperventilation
  - Excitement, fear, transport, pain
  - Gram-negative septicemia

Neurologic disorders

22.4.5.1.2 UNCOMMON CAUSES

After correction of metabolic acidosis

Inappropriate mechanical ventilation

Salicylate toxicity

22.4.6 Anion Gap

The anion gap can be an extremely helpful tool for categorizing causal factors in acid-base imbalances and may prove a useful prognostic guide in animals with serious digestive disorders. The anion gap can be calculated as the difference between the major cations (sodium plus potassium) and the measured anions (chloride plus bicarbonate). The anion gap normally is 12 to 16 and provides an approximation of the so-called “unmeasured anions.” These are anions that are not measured routinely in the clinical laboratory; they include the anionic equivalents of plasma proteins (particularly albumin), sulfate, phosphate, lactate, ketones, and a variety of inorganic anions. Significant differences exist in the normal range of the anion gap among species, and there also may be age-related differences. Foals are reported to have a larger anion gap than adult horses.

Hypoalbuminemia and hyperchloremic metabolic acidosis are the most common causes of a decrease in the anion gap resulting from decreases in unmeasured anions. The cause of normal to low anion gap hyperchloremic metabolic acidosis often can be differentiated on the basis of the serum potassium concentration. Animals with hyperchloremic metabolic acidosis associated with gastrointestinal fluid losses or renal tubular acidosis most often manifest hypokalemia, whereas hyperkalemia generally is seen in patients with decreased mineralocorticoid secretion (Addison's disease) or renal failure with renal shutdown. Decreases in the anion gap can be seen with increases in cationic proteins associated with polyclonal gammopathy or multiple myeloma. Decreases in the anion gap also result from overhydration caused by decreases in the protein concentration and changes in the relative concentration of plasma sodium and chloride.

Most commonly, high anion gap acidosis is associated with accumulation of a metabolizable acid such as lactic acid associated with anaerobic exercise, grain overload, or hypovolemic shock. The commonly employed laboratory procedures for the determination of lactate only measure the L form of lactate. Microbial fermentation in the gastrointestinal tract may result in the production of both the D and L forms of lactate. It has recently been shown in milk-fed calves and kids that accumulation of D-lactate is a major factor in the profound acidosis associated with certain digestive disorders. Unfortunately, at present, determination of D-lactate requires special procedures that may not be readily available. Ketoacidosis, uremic acidosis, and poisoning with a variety of anionic poisons result in increases in nonmetabolizable acids that are also causes of an increased anion gap. When a high anion gap metabolic acidosis is found, a thorough search for the potential causes of the accumulated unmeasured anions is indicated. The anion gap also is useful for identifying mixed acid-base imbalances. A mixed metabolic acid-base imbalance should be suspected when the change in the anion gap does not approximate the change in bicarbonate. Increases in the anion gap can be associated with dehydration and

contraction alkalosis caused by changes in the protein concentration and the relative concentration of plasma sodium and chloride.

22.4.7 Bicarbonate and Total Carbon Dioxide

Bicarbonate accounts for approximately 95% of the measured CO_2; thus the total CO_2 (TCO_2) or "CO_2 content" of serum or plasma provides a measure of metabolic changes in the acid-base balance. Most automated chemistry profiles now provide the bicarbonate level directly, whereas some may still provide the TCO_2. Bicarbonate or TCO_2 is decreased in metabolic acidosis and increased in metabolic alkalosis. However, the bicarbonate or TCO_2 values provide only a crude indication of acid-base status. When acid-base abnormalities are suspected, appropriate samples should be submitted for blood gas determination.

22.4.8 Buffer Base, Standard Bicarbonate, and Base Excess or Base Deficit

The terms *buffer base, standard bicarbonate,* and *base excess* (or *base deficit*) represent derived calculated estimates of the metabolic component of acid-base balance. The buffer base indicates the sum of all the buffer anions in blood under standardized conditions. The standard bicarbonate is the plasma bicarbonate concentration that would be found under specific conditions that eliminate respiratory influences on the values obtained. The base excess or base deficit often is supplied in routine assessment of acid-base balance; it indicates the deviation of bicarbonate from normal. The calculated base deficit provides a means of estimating the amount of bicarbonate required to correct metabolic acidosis. The bicarbonate estimate is calculated by multiplying the base deficit by the probable bicarbonate space (about 40% to 60% of body weight), as in the following equation:

$$\text{mEq } HCO_3 \text{ needed} = \text{mEq base deficit} \times \text{kg body weight} \times 0.5$$

22.4.8.1 NONTRADITIONAL OR STRONG ION APPROACH TO ACID-BASE BALANCE

Peter Stewart first described the quantitative physiochemical approach to acid-base balance over 25 years ago.[18,19] In this approach acid-base balance is determined by three independent variables: strong ion difference (SID), the partial pressure of CO_2, and the total concentration of nonvolatile weak acids (A_{tot}), the principal components of which are plasma proteins and inorganic phosphate. Bicarbonate and pH are dependent variables determined by these three independent variables. Several studies have attempted to adapt Stewart's approach for practical application in human and veterinary medicine.[14,20–27] Most of these studies used rather old human values for A_{tot} and Ka. Experimentally determined species-specific A_{tot} and Ka data are now available for horses, cattle, dogs, and humans.[28–30]

Peter Constable refined Stewart's model and developed an approach that he called the *simplified strong ion model* of acid-base equilibrium.[31] Constable assumed that plasma ions act either as strong ions, volatile buffer ions (HCO^{-3}), or nonvolatile buffer ions. Plasma pH is determined by five independent variables: PCO_2, SID, the concentration of individual nonvolatile plasma buffers (albumin, globulin, and phosphate), ionic strength, and temperature. The simplified strong ion model explains many of the anomalies when the Henderson-Hasselbalch equation is applied to plasma and is algebraically simpler than Stewart's model.

Strong electrolytes are assumed to be completely dissociated in aqueous solution and chemically nonreactive. The SID is simply the difference between the total concentration of strong cations (sodium, potassium, and

magnesium) and the total concentration of strong anions (chloride, sulphate, lactate, acetoacetate, and B-hydroxybutyrate). Sodium, potassium, and chloride are normally the principal determinants of SID. The SID is synonymous with buffer base and as such can be considered as roughly equivalent to the metabolic component of the traditional approach to acid-base balance. In fluids with little or no protein, such as cerebrospinal fluid (CSF), bicarbonate concentration is the same as the SID. Abnormalities in P_{CO_2} are viewed in essentially the same manner in both the traditional and nontraditional approaches to acid-base balance. Plasma albumen makes up the majority of A_{tot}. The A_{tot} exists in both dissociated A^- and undissociated HA forms. A decrease in A_{tot} resulting from hypoalbuminemia causes an alkalosis with an increase in bicarbonate, whereas hyperalbuminemia has the opposite effect. Increases in A^- can cause an increase in anion gap, whereas decreases in A^- result in a decrease in anion gap. Change in protein concentration may potentiate or ameliorate the effects of alterations in SID on acid-base balance.

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When protein and inorganic phosphate remain within the normal range, acid-base balance is controlled by changes in P_{CO_2} mediated by the respiratory system, whereas changes in SID are largely under the control of the kidneys. Heavy sweat loss in an endurance horse, displaced abomasum in a cow, or the prerace administration of the diuretic furosemide in a race horse produces metabolic alkalosis. In each case the alkalosis is the result of a disproportionate loss of chloride relative to sodium, yielding hypochloremia and an increase in SID. Correction of the alkalosis is brought about by the provision of chloride, generally as sodium chloride or potassium chloride. This results in a decrease in SID and thus a return of the dependent variables (bicarbonate and pH) toward normal. Metabolic acidosis with a large base deficit is generally treated with sodium bicarbonate. In the strong ion approach to treatment the rationale for the administration of sodium bicarbonate is to provide the strong cation, sodium, without a strong anion. Other metabolizable anions could be substituted for bicarbonate and achieve similar effects.

Calculation of SID is simple and provides useful insight in patients with metabolic acid-base disturbances. Factors that influence SID range from changes in free water, to sodium-chloride imbalances that result from excessive losses or disproportionate retention of sodium or chloride, to the accumulation of strong organic anions. Organic acidosis can be produced by the accumulation of exogenous as well as endogenous anions. The anion gap does not always accurately predict the presence of unmeasured strong anions. Mathematic methods have been developed as a means for the detection of unmeasured anions[18,32] and more recently for the calculation of the simplified strong ion gap.[33]

Both the traditional and the nontraditional or strong ion approaches to acid-base balance have proven useful to address practical problems in both research and medical settings. The traditional approach to acid-base balance is more widely accepted and user-friendly. The strong ion approach may provide a better understanding as to why the bicarbonate concentration is changing as it integrates acid-base and electrolyte disorders. The strong ion approach has recently gained wider acceptance from members of the human critical care community, who have found it useful for the analysis of the complex fluid, electrolyte, and acid-base problems of patients in intensive care units. Several easy-to-use computer or calculator programs have been developed for the mathematically challenged that facilitate implementation of the strong ion approach to acid-base balance.

22.5 SERUM ENZYMES

Some of the common and less common causes of elevated serum enzyme activity are listed in Box 22-17.

22.5.1 Box 22-17 Causes of Elevated Serum Enzymes

22.5.1.1 ELEVATION OF SORBITOL DEHYDROGENASE (SDH)

22.5.1.1.1 Common Causes

- Severe anoxia
- Acute liver failure
- Liver abscess
- Secondary to damaged bowel
  - Strangulating intestinal lesion
  - Acute toxic enteritis
- Chronic liver failure

22.5.1.1.2 Less Common Causes

- Acute and severe anemia
- General anesthesia
- Anoxia

22.5.1.2 ELEVATION OF γ-GLUTAMYLTRANSFERASE (GGT)

22.5.1.2.1 Common Causes

- Acute liver failure
- Chronic liver failure
- Pyrrolizidine alkaloid toxicity

Aflatoxicosis

Cholangiohepatitis

Cholelithiasis

Liver flukes

22.5.1.2.2 Uncommon Causes

Higher normal range in young animals

Fatty liver

22.5.1.3 ELEVATION OF ALKALINE PHOSPHATASE (ALP)

22.5.1.3.1 Common Causes

Acute liver failure

Chronic liver failure

Pyrrolizidine alkaloid toxicity

Cholangiohepatitis

Cholelithiasis

Liver flukes

22.5.1.3.2 Uncommon Causes

Higher normal range in young animals

Fatty liver

22.5.1.4 ELEVATION OF CREATINE KINASE (CK)

22.5.1.4.1 Common Causes

Exertional rhabdomyolysis (azoturia, myositis, tying-up)

Polysaccharide storage myopathy

Streptococcus equi–associated myopathy

Nutritional myodegeneration (selenium, vitamin E deficiency)

Postendurance ride multisystemic disorder

Alert downer cow syndrome (muscle crush syndrome)

Malignant hyperthermia

Malignant edema

Prolonged recumbency with inability to rise

22.5.1.4.2 Uncommon Causes

Normal postexercise modest increase

Acute cardiomyopathy

Purpura hemorrhagica

Equine influenza

Sarcosporidiosis

Local irritation from intramuscular injections

22.5.1.5 ELEVATION OF LACTATE DEHYDROGENASE (LDH)

22.5.1.5.1 Common Causes

- Muscle disease
  - Exertional rhabdomyolysis (azoturia, myositis, tying-up)
  - Polysaccharide storage myopathy
- *Streptococcus equi*–associated myopathy
  - Nutritional myodegeneration (selenium, vitamin E deficiency)
  - Postendurance ride multisystemic disorder
  - Alert downer cow syndrome (muscle crush syndrome)
  - Malignant hyperthermia
  - Malignant edema
- Liver disease
  - Acute liver failure
  - Chronic liver failure
  - Cholangiohepatitis
  - Cholelithiasis
- In vitro hemolysis

22.5.1.5.2 Uncommon Causes

- Hemolytic anemia

Acute cardiomyopathy

Purpura hemorrhagica

Equine influenza

Sarcosporidiosis

Local irritation from intramuscular injections

Fatty liver

22.5.1.6 ELEVATION OF ASPARTATE AMINOTRANSFERASE (AST)

22.5.1.6.1 Common Causes

Muscle disease

Exertional rhabdomyolysis (azoturia, myositis, tying-up)

Polysaccharide storage myopathy

Streptococcus equi–associated myopathy

Nutritional myodegeneration (selenium, vitamin E deficiency)

Postendurance ride multisystemic disorder

Alert downer cow syndrome (muscle crush syndrome)

Malignant hyperthermia

Malignant edema

Liver disease

Acute liver failure

Chronic liver failure

Cholangiohepatitis

Cholelithiasis

Liver flukes

In vitro hemolysis

22.5.1.6.2 Uncommon Causes

Hemolytic anemia

Acute cardiomyopathy

Purpura hemorrhagica

Equine influenza

Sarcosporidiosis

Local irritation from intramuscular injections

Fatty liver

22.5.2 Sorbitol Dehydrogenase

SDH is a liver-specific enzyme in all large animal species, and increases in this enzyme indicate hepatocellular damage and leakage of enzymes. Increases in SDH also are seen with obstructive or strangulating gastrointestinal lesions and with acute toxic enteritis as a result of liver damage associated with absorption of bacteria or their toxins (or both) from the damaged bowel into the portal circulation. This enzyme is a sensitive indicator of liver damage, and modest increases may be seen with anoxia, acute anemia, or general anesthesia. The half-life of SDH in the circulation is short (a matter of hours), and elevations indicate active and ongoing liver damage. This enzyme is not stable when stored at room temperature, but refrigerated samples may yield useful results after several days of storage.

22.5.3 Creatine Kinase

CK is a highly sensitive and specific indicator of muscle damage in domestic animals. Although CK is found in both cardiac and skeletal muscle, elevations of this enzyme most commonly are associated with exertional myopathies (rhabdomyolysis) and also are seen as musculoskeletal manifestations of systemic disease. Intramuscular injections, vigorous exercise, or prolonged shipping may result in modest releases (up to a fourfold increase over resting values) of CK into the circulation without producing histologic evidence of muscle damage. Endurance exercise may lead to moderate elevation of CK (2000 to 15,000 IU/L) in some horses that show no recognizable sign of exertional myopathy. The half-life of this enzyme in the circulation is very short (2 hours in horses and 4 hours in cattle), and even marked elevations in CK may return to normal within 12 to 24 hours after a single muscle insult. Although marked elevation of CK can be a guide to the extent of muscle damage, the short half-life and the potential for continuing myonecrosis have a marked influence on the enzyme activity observed at any point in time. A persistent elevation of CK suggests a process resulting in active and continuing muscle damage and provides grounds for resting athletic horses. Elevated CK provides no information on the factors responsible for the rhabdomyolysis. Hemolysis may produce falsely high values for CK.

22.5.4 Aspartate Aminotransferase

AST is found in high concentration in a variety of tissues, including skeletal and cardiac muscles, the erythrocytes and kidneys, and the liver. This enzyme is a nonspecific indicator of tissue damage and tends to be less sensitive to mild insults than the tissue-specific enzymes SDH and CK. The half-life of AST in the circulation is relatively long, and elevations may persist for as long as 10 days after an episode of myonecrosis or liver damage. As a general rule, extensive muscle necrosis tends to produce much higher elevations of AST than severe liver necrosis. This enzyme is most useful when compared with the tissue-specific enzymes as determined sequentially over the time course of a disease process. Elevations of CK and AST indicate muscle damage, whereas elevations of SDH and AST indicate liver damage. Marked but transient elevations of CK and SDH are associated with a single insult to the muscles and liver, respectively, whereas AST increases gradually and remains elevated for a much longer time. Thus a moderate to marked increase in AST in an animal with progressively declining SDH or CK indicates that some tissue damage occurred within the past 7 to 10 days but also that the process may no longer be active. This often is a favorable prognostic indicator. Persistent elevation of or a progressive increase in CK or SDH and AST over time indicates an active, continuing process of tissue damage, and the prognosis is more guarded. AST is relatively stable at room temperature, but hemolysis or lipemia may interfere with the assay.

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22.5.5 γ-Glutamyltransferase

GGT is an important marker of hepatobiliary disorders and cholestasis in large animals. GGT is quite stable, and reliable results can be obtained from samples submitted several days after blood samples have been drawn, provided the serum is refrigerated. The activity of this enzyme is highest in the cells of the periportal region of the liver, in the pancreas, and in the renal tubular cells. Pancreatic diseases resulting in inflammation and necrosis are relatively rare in large animal species. Damage to the renal tubular cells leads to a release of GGT into the tubular lumen and the urine. Because this enzyme is a relatively large molecule, it is not resorbed into the systemic circulation, and renal tubular damage does not result in elevated serum GGT activity. Increases in GGT relative to creatinine in the urine have been used as an index of acute renal tubular damage. However, the validity of the normal range for this ratio in horses has been questioned.

In large animal species an elevation in serum GGT is one of the more reliable indicators of damage to the liver and biliary obstruction. Disease processes such as pyrrolizidine alkaloid intoxication, chronic active hepatitis, cholangiohepatitis, and cholelithiasis produce liver damage, primarily in the periportal region, leading to marked and persistent elevation of GGT activity in the serum. In these instances, elevations in serum ALP activity generally are associated with the increase in GGT. Two syndromes, fatty liver syndrome in dairy cows and hyperlipemia syndrome of periparturient mares of pony and miniature horse breeds, are associated with liver damage, which is often reflected by elevation of GGT.

Most suckling neonatal large animals have high levels of GGT activity in their serum. This is the result of absorption of maternal GGT, which is present in relatively high levels in the colostrum. Elevation of GGT in neonates should be regarded as a normal finding unless it is associated with other evidence of liver disease. The normal range of serum GGT activity for burros, donkeys, and asses may be substantially higher (two to three times) than the normal range of serum GGT activity for horses. Caution should therefore be used when evaluating this enzyme in these species. Elevation in serum GGT activity has been reported in thoroughbred racehorses that are performing below expectations. The reasons for the increase in GGT are not known, but horses often respond to a period of rest or reduction in workload. These horses show little histologic evidence of liver damage, and other indices of liver damage and dysfunction usually are within normal limits. The stress of training may be associated with an elevated GGT. Certain trainers, often highly successful trainers, appear to have a disproportionately large number of horses with elevations of this enzyme. The normal range for GGT of thoroughbreds in race training may be slightly higher than that of normal sedentary horses.

22.5.6 Alkaline Phosphatase

ALP is used in most species as a marker for intrahepatic or extrahepatic obstruction of the biliary system. The enzyme is also released by osteoblasts from metabolically active bone. This may be the reason that young, rapidly growing animals normally have high levels of serum ALP. Elevations in ALP are also reported in cases of rickets and healing fractures. The intestinal isoenzyme of ALP is very similar to the ALP isoenzyme found in neutrophils. Elevations in the ALP activity of abdominal fluid in horses with intraabdominal disease may reflect the release of this enzyme from the neutrophils rather than being a specific marker of damage to the bowel.

ALP has been useful for evaluating liver disease in large animals, particularly in horses with pyrrolizidine alkaloid intoxication, chronic active hepatitis, and cholangiohepatitis, and in some patients with cholelithiasis. A profound elevation in ALP activity is thought to reflect periportal liver damage and biliary obstruction in these patients. A moderate to marked elevation in ALP may be observed in a wide range of disorders resulting in hepatic necrosis and intrahepatic cholestasis. Because this enzyme is not organ specific in large animals, elevations in ALP activity must be interpreted in relation to more organ-specific enzymes such as SDH and GGT.

22.5.7 Other Enzymes

Lactate dehydrogenase is found in relatively high concentrations in a variety of organs and tissues of the body from the heart, liver, muscle, and kidney to the erythrocytes and leukocytes. An elevation in serum LDH enzyme activity must be evaluated in relation to other, more organ-specific enzymes. LDH isoenzyme analysis can be helpful in differentiating organ system damage, but the analysis is time-consuming and not always available. An elevation in LDH activity is expected in hepatic necrosis and serves as an indicator of an active disease process. Extensive muscle damage and rhabdomyolysis tend to result in a more massive release of enzyme and much higher serum enzyme activity. A modest elevation in LDH may be seen in some hemolytic disorders and some

cases of leukemia. Blood samples must be handled with care, because hemolysis results in falsely elevated serum LDH activity.

Glutamic dehydrogenase and ornithine carbamoyltransferase are two enzymes that are reported to be sensitive indicators of hepatic necrosis in ruminants. Alanine aminotransferase (ALT) is an important liver-specific enzyme that has wide application in small animals and is often included in automated chemistry profiles. This enzyme has not been useful for evaluation of liver disease in large animal species, and occasionally horses with marked rhabdomyolysis and no other evidence of liver disease show an elevation in serum ALT activity.

22.6 BILIRUBIN

Bilirubin is a breakdown product of the heme component of the hemoglobin molecule. Bilirubin exists in the serum in two forms and is responsible for the yellow color known as *icterus,* or *jaundice,* of the mucous membranes. Unconjugated, prehepatic, albumin-bound bilirubin is also known as *"indirect-reacting" bilirubin,* as determined by the van den Bergh reaction. Indirect-reacting bilirubin must be taken up by the liver cells, where it is conjugated and then excreted in the bile. Conjugated bilirubin is known as *"direct-reacting" bilirubin,* as determined by the van den Bergh reaction. Horses normally have a much higher serum bilirubin level than ruminants, and hot-blooded horses have a higher bilirubin level than cold-blooded horses of the pony and draft breeds. The horse also differs from ruminants in that horses often develop moderate icterus in response to fasting or anorexia associated with 392
many systemic diseases. The increase in the bilirubin concentration in these horses is caused almost entirely by an 393
increase in unconjugated (indirect-reacting) bilirubin, and within a few days the bilirubin can increase from the normal range up to 6 to 8 mg/dL. Therefore the total serum bilirubin concentration is of little diagnostic value in the ill horse unless both the direct- and indirect-reacting bilirubin values are determined.

Total serum bilirubin is elevated in animals with hemolytic anemia, and this increase is caused largely by an increase in indirect-reacting bilirubin (Box 22-18). The degree to which bilirubin is elevated in hemolytic anemia is a function of the rate of red cell destruction and the capacity of the liver to excrete the newly formed bilirubin. The total bilirubin rarely exceeds 10 mg/dL in hemolytic anemia. An exception is the hemolytic anemia of neonatal isoerythrolysis in newborn foals, which often is associated with marked clinical icterus. In these foals the serum bilirubin may exceed 25 mg/dL, a variable but substantial proportion of which (40% to 60%) is likely to be direct-reacting bilirubin.

The second major cause of clinical icterus and increased serum bilirubin is liver failure. Liver failure results in impaired uptake and excretion of bilirubin. Acute liver failure caused by hepatic necrosis results in marked to moderate increases in both direct- and indirect-reacting bilirubin. In horses with acute liver failure, bilirubin often exceeds 10 mg/dL, and this increase is caused primarily by increases in indirect-reacting bilirubin. Direct-reacting bilirubin rarely exceeds 25% of the total bilirubin in the horse, and increases of this magnitude suggest an intrahepatic or extrahepatic biliary obstruction. With chronic liver failure, icterus is more variable, and total bilirubin rarely exceeds 10 mg/dL. Liver failure in ruminants, particularly chronic liver failure, is associated with a much less striking elevation in serum bilirubin than occurs in horses. In the absence of hemolytic anemia, a bilirubin value above 2 mg/dL indicates impaired hepatic function in ruminants.

22.6.1 Box 22-18 Causes of Elevated Serum Bilirubin

22.6.1.1 ELEVATION OF TOTAL SERUM BILIRUBIN

22.6.1.1.1 Common Causes

Hemolytic anemia

Liver failure

Secondary to systemic disease or anorexia in horses

22.6.1.1.2 Uncommon Cause

Chronic liver failure in cattle

22.6.1.2 ELEVATION OF INDIRECT-REACTING BILIRUBIN

22.6.1.2.1 Common Causes

Secondary to systemic disease or anorexia in horses

Liver failure

Hemolytic anemia

22.6.1.2.2 Uncommon Cause

Chronic liver failure in cattle

22.6.1.3 ELEVATION OF DIRECT-REACTING BILIRUBIN

22.6.1.3.1 Common Causes

Liver failure

Cholelithiasis

Cholangiohepatitis

Neonatal isoerythrolysis

22.6.1.3.2 Uncommon Cause

Hemolytic anemia

22.7 GLUCOSE

The concentration of glucose in the blood normally is regulated by the hormones insulin and glucagon, but it is influenced by several other factors as well.

22.7.1 Hypoglycemia

Fasting usually does not result in hypoglycemia except in neonatal animals (Box 22-19). Newborns have limited energy reserves, and any disease, injury, congenital defect, maternal rejection, agalactia, or management error that limits energy intake can result in marked hypoglycemia associated with profound depression, even coma. Rapid, semiquantitive field tests for blood glucose (Dextrostix* and Chemstrip BG†) provide a practical means of early recognition of this problem. Hypoglycemia may be seen in animals with acute toxic enteritis, coliform mastitis, septicemia, and colic associated with strangulated bowel, as well as in the later stages of endotoxemia and in some horses with exhaustion after prolonged exercise. Hypoglycemia is a reasonably consistent feature with primary ketosis and fat cow syndrome in cattle, with pregnancy toxemia in sheep and goats, and in hyperlipemia syndrome, which is seen primarily in pregnant or lactating ponies.

* Ames Division, Miles Laboratories, Inc., Elkhart, Ind.

† Boehringer Mannheim Diagnostics, Inc., Indianapolis, Ind.

22.7.2 Hyperglycemia

Hyperglycemia may be seen with excitement, transportation, or stress and probably is mediated by increases in catecholamine and glucocorticoid hormones (Box 22-20). The stress and pain of acute severe colic in horses frequently results in hyperglycemia, and elevations of blood glucose above 250 mg/dL are associated with a poor prognosis in such cases. Endotoxemia initially results in a transient hyperglycemia that may be followed by marked hypoglycemia in the terminal stages of the toxemia. The later stages of Cushing's syndrome in horses generally are associated with a non—insulin-responsive hyperglycemia and glycosuria. Similar changes can be induced transiently when exogenous glucocorticoid hormones are administered at a high dose rate. Insulin-responsive diabetes mellitus rarely occurs in large animals but has been reported in association with destructive pancreatic lesions.

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22.7.2.1 Box 22-19 Causes of Hypoglycemia

22.7.2.1.1 COMMON CAUSES

Inappetence in newborns

Pregnancy toxemia

Endotoxic shock (late stages)

Hepatic failure

22.7.2.1.2 UNCOMMON CAUSES

In vitro glycolysis by red cells

In vitro glycolysis by eperythrozoonosis

22.7.2.2 Box 22-20 Causes of Hyperglycemia

22.7.2.2.1 COMMON CAUSES

Acute severe colic in horses

Stress and excitement

Cushing's syndrome

Glucocorticoid administration

Xylazine administration

22.7.2.2.2 UNCOMMON CAUSES

Too rapid administration of dextrose

Diabetes mellitus

22.8 CREATININE

Creatinine is derived from the cyclic use of phosphocreatine, the muscle energy store, resulting in the production of inorganic phosphate and creatinine. In the resting animal this process occurs at a relatively constant rate. The absolute muscle mass and level of physical activity may influence the rate of creatinine production and thus the serum concentration. Starvation, with loss of muscle mass, may result in a slightly reduced serum creatinine level, whereas serum creatinine may be slightly higher in muscular, athletic individuals than in sedentary animals.

Creatinine is distributed throughout the body water and is not reused. Creatinine is normally excreted by the kidneys, primarily by glomerular filtration. In azotemic patients a substantial part of creatinine is metabolized and excreted by nonrenal routes. Serum or urine creatinine concentrations determined by the standard alkaline picrate reaction may be falsely elevated by the presence of noncreatinine chromogenic compounds in the serum. These chromogens include glucose, fructose, ascorbic acid, hippuric acid, urea, ketones, and several other compounds. The contribution of these compounds can be reduced or eliminated, and most automated chemical laboratories use such methodology. However, if inappropriately high creatinine is reported in patients without other evidence of renal failure, the method of creatinine measurement should be ascertained.

Alterations in renal blood flow caused by decreases in effective circulating fluid volume (hypovolemia) produce an elevation in serum creatinine and BUN; this can be considered a prerenal azotemia (Box 22-21). It occurs with some frequency in animals with acute enteritis, peritonitis, acute heart failure, massive blood loss, and some forms of colic and in horses with exhaustive disease syndrome. An important point is that many of these disorders initiate the release of inflammatory mediators, which may cause renal damage and impaired renal function above and beyond that associated with impaired renal blood flow and hypovolemia. Prerenal azotemia usually is seen in animals that are dehydrated and volume depleted and that have a history of loss or compartmentalization of sodium-containing fluid. Prerenal azotemia often can be marked (creatinine level above 6 mg/dL), but if uncomplicated, it generally responds rapidly to fluid replacement therapy. Urine production, the urine sodium concentration, and the fractional excretion of sodium usually are low, and the urine specific gravity usually is elevated. The ratio of urine to plasma urea or creatinine, as well as the urine-to-plasma ratio of osmolality, are reported to be higher in horses with prerenal azotemia compared with renal azotemia.[16]

The serum creatinine concentration provides a crude measure of the glomerular filtration rate. However, serum creatinine, like BUN, is not a very sensitive or early indicator of changes in renal function. In ruminants, creatinine is a more reliable indicator of renal failure than BUN. Urea nitrogen can be secreted in saliva and metabolized by the ruminal microflora; this frequently results in a disparity between BUN and creatinine levels in ruminants with renal failure. Although small increases in creatinine may be seen with progressively compromised renal function, nearly two thirds to three fourths of the nephrons must be nonfunctional before the serum creatinine level clearly exceeds the normal range. Both acute and chronic renal failure are usually associated with elevated creatinine. Acute renal failure, especially in animals with anuria or oliguria, is usually associated with progressive daily changes in blood parameters. In contrast, blood parameters of animals with chronic renal failure tend to remain relatively constant. A transient but markedly elevated serum creatinine has been observed in some newborn foals that have no other evidence of compromised renal function. Many of these foals are born to mares that had medical problems before parturition. Alterations in placental function may allow the accumulation of creatinine in the foal's circulation. In most of these otherwise normal foals this marked elevation in serum creatinine resolves within the first few days of life.

22.8.1

Box 22-21 Causes of Elevated Creatinine

22.8.1.1

COMMON CAUSES

Prerenal azotemia

Reduced renal perfusion

Hypovolemia

Congestive heart failure

Dehydration after endurance exercise

Renal azotemia

Acute renal failure

Chronic renal failure

Postrenal azotemia

Urolithiasis

Renal calculi

Ureteral calculi

Urethral calculi

Ruptured bladder

22.8.1.2 UNCOMMON CAUSES

False azotemia

Noncreatinine chromogens in serum or plasma

Perirenal abscess

Renal carcinoma

Renal dysgenesis

Carcinoma of the bladder

Postexhaustion multisystemic syndrome in horses

Severe exertional rhabdomyolysis with myoglobinuria

Severe intravascular hemolysis with hemoglobinuria

Intoxication or poisoning

Heavy metal poisoning

Nonsteroidal antiinflammatory drug intoxication

Aminoglycoside intoxication

22.9 BLOOD UREA NITROGEN

The term *blood urea nitrogen* is ingrained in the veterinary literature, despite the fact that urea nitrogen determinations usually are performed on serum or plasma samples. This is of little consequence, because the actual difference in urea concentrations of whole blood and serum or plasma is relatively small. Urea provides a nontoxic means of excreting ammonia generated by amino acid catabolism and the intestinal microflora. It is distributed throughout the body water. In the intestine, urea is broken down by urease, which is produced by the intestinal microflora, and the nitrogen, as ammonium ion, is recycled to the liver. Urea is excreted by the kidneys, primarily by glomerular filtration.

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22.9.1 Box 22-22 Causes of Decreased Blood Urea Nitrogen

22.9.1.1 COMMON CAUSES

Liver failure

Neonatal animals (BUN is normally lower than in adults)

22.9.1.2 UNCOMMON CAUSES

Low-protein diet

Anabolic steroid administration

Urea production occurs almost exclusively in the liver, and liver failure is frequently associated with a decrease in BUN (Box 22-22). Urea nitrogen tends to be low in nursing animals because of their high fluid intake and urine output and their anabolic state of rapid growth. Urea nitrogen may be reduced slightly in animals given anabolic steroids or fed diets low in protein but of adequate calorie content.

Starvation or other processes that result in rapid tissue catabolism such as fever, burns, or corticosteroid administration may result in modest increases in BUN (Box 22-23). BUN, along with creatinine, provides a crude index of altered renal function in most animal species. BUN is influenced more directly by dietary factors than is creatinine, and creatinine is generally a better guide to renal failure. This is particularly true in ruminants, in which BUN may remain within normal limits in animals with marked impairment of renal function. With these considerations in mind, the discussion of prerenal, renal, and obstructive causes of azotemia in the section on creatinine apply to BUN.

22.10 SERUM PROTEIN

The serum or plasma proteins consist of albumin and globulin fractions. These are discussed in Chapter 26.

22.10.1 Box 22-23 Causes of Increased Blood Urea Nitrogen

22.10.1.1 COMMON CAUSES

Prerenal azotemia

Reduced renal perfusion

Hypovolemia

Congestive heart failure

Dehydration after endurance exercise

Renal azotemia

Acute renal failure

Chronic renal failure

Postrenal azotemia

Urolithiasis

Renal calculi

Ureteral calculi

Urethral calculi

Ruptured bladder

22.10.1.2 UNCOMMON CAUSES

Gastrointestinal bleeding

Perirenal abscess

Renal carcinoma

Renal dysgenesis

Carcinoma of the bladder

Postexhaustion multisystemic syndrome in horses

Severe exertional rhabdomyolysis with myoglobinuria

Severe intravascular hemolysis with hemoglobinuria

Intoxication or poisoning

Heavy metal poisoning

Nonsteroidal antiinflammatory drug intoxication

Aminoglycoside intoxication

22.11 URINALYSIS

Urinalysis can be an extremely useful diagnostic tool, providing information on many systemic disorders. It is essential in the evaluation of primary renal disease. Urine normally is collected as a voided sample or after catheterization. Voided urine samples are safe and easy to collect but are easily contaminated. Catheterization is preferred for bacteriologic evaluation, but the resultant mild trauma may result in a slight increase in urine red cells and protein. Because of the urethral diverticulum at the level of the pelvis, it is difficult to successfully catheterize male ruminants. Urethral obstruction is common in male small ruminants, and percutaneous aspiration may be the

only way to obtain a urine sample in affected animals. Urinalysis should be performed as soon after collection as possible (within 30 minutes) to avoid degeneration of cellular elements, changes in pH, or bacterial overgrowth. If this is not possible, samples should be refrigerated. Urine volume and composition are influenced by feed and water intake, salt supplementation, environmental factors, exercise, stress, systemic disease, and drug administration. Urine samples collected after administration of a diuretic are dilute and unsuitable for routine urinalysis. The tranquilizer xylazine, which is often used to assist in the catheterization of male horses, may alter the results of the urinalysis because it produces diuresis as a result of glycosuria.

22.11.1 Specific Gravity

Specific gravity is defined as the weight of urine relative to the weight of distilled water. The specific gravity of serum is approximately 1.008 to 1.012. The urine specific gravity is an indicator of renal function, because it reflects the action of the renal tubules and collecting ducts on the glomerular filtrate by providing an estimation of the number of particles dissolved in the urine. It is usually measured by refractometry. Urine dipsticks with reagent pads for estimating the urine specific gravity in humans should not be used for this purpose in domestic animals, because a poor correlation has been reported compared with refractometry in large animals.[26] Normal animals have the capacity to dilute their urine specific gravity to less than 1.010 and to concentrate to greater than 1.050. The normal range reported for most adult large animals is 1.020 to 1.050. Suckling neonatal animals normally produce a very dilute urine with a specific gravity below 1.010. Although this could represent immature renal function, it more likely reflects their high-volume fluid intake, because normal neonates can concentrate their urine if fluids are withheld.

Failure to produce a concentrated urine, as reflected by a specific gravity below 1.020, in the face of dehydration is an indication of altered renal function, which may be caused by primary renal disease, diabetes insipidus, medullary washout, or nephrogenic diabetes insipidus. With severe and chronic sodium depletion, tubular sodium may be insufficient to sustain normal countercurrent mechanisms for water resorption. This process is called *medullary washout* and has been reported as a cause of polyuria in lactating dairy cattle on a salt-deficient diet. At least 50% of renal function must remain for highly concentrated urine to be produced. Isosthenuria, a urine specific gravity that remains around 1.010 despite variation in hydration, occurs when renal disease progresses to the point at which renal function is reduced to less than a third of normal. Altered renal function in these animals is usually reflected by a moderate to marked elevation in BUN and creatinine levels and by other changes in the urinalysis. Hyposthenuria occurs when the specific gravity remains below 1.010; this indicates altered release of or response to antidiuretic hormone, as occurs with diabetes insipidus, medullary washout with chronic sodium depletion, nephrogenic diabetes insipidus, psychogenic polydipsia, and chronic liver failure in some horses.

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22.11.2 pH

The normal range of urine pH for adult herbivores is alkaline, with values ranging from 7 to 9. Neonatal foals tend to have a slightly acid urine with a pH below 7. Aciduria in adults may be seen in postrace samples collected from racehorses, after prolonged fasting, with ketosis in ruminants, or in response to metabolic acidosis. A paradoxic aciduria frequently is seen in ruminants with hypochloremic, hypokalemic metabolic alkalosis, as was explained earlier. Urine pH is also influenced by the cation-anion balance of the diet.

22.11.3 Protein

Protein normally is not detected in urine, although a false-positive protein reaction may be noted on urine dipsticks if the sample is strongly alkaline. Urine with a positive reaction for protein on dipsticks should be checked for protein by a chemical method. Proteinuria should be evaluated in relation to the other findings in the urinalysis. Persistent and strongly positive reactions for protein in the absence of leukocytes, red cells, bacteria, or casts suggest glomerular protein loss, as in glomerulonephritis or amyloidosis. The presence of bacteria and leukocytes with proteinuria suggests sepsis in the urinary tract, whereas hemorrhage or inflammation in the urogenital tract often is associated with proteinuria.

22.11.4 Glucose

Glucose is not found in the urine of normal large domestic animals unless the blood glucose level increases above the renal threshold, which is thought to be approximately 100 to 140 mg/dL in ruminants and approximately 160 to 180 mg/dL in horses. The causes of hyperglycemia and glycosuria were described in a previous section; they include Cushing's syndrome, stress, and catecholamine or glucocorticoid hormone release. Hyperglycemia and glycosuria can be created iatrogenically when glucose-containing fluids are administered at an excessive rate. Glycosuria is a fairly consistent finding in sheep with enterotoxemia type D (pulpy kidney). The presence of glycosuria without hyperglycemia strongly suggests renal tubular damage resulting from a toxic or ischemic insult.

22.11.5 Occult Blood

Both myoglobin and hemoglobin give a positive reaction on urine occult blood dipsticks. In most instances proteinuria shows a positive result as well. A tentative clinical impression sometimes can be formed to differentiate myoglobin from hemoglobin in dark urine if the sample is shaken vigorously in a closed, transparent container. Myoglobin tends to produce a brown foam, whereas hemoglobin produces a reddish foam. Hemoglobinuria caused by intravascular hemolysis is generally associated with clinical and hematologic evidence of a hemolytic anemia. Hematuria may result in a positive occult blood reaction if lysis of some of the intact red blood cells has occurred. This is likely to happen if the urine is very dilute or if it is held at room temperature for an extended period before analysis. False-positive reactions can occur if microbial peroxidase or oxidizing contaminants are present.

22.11.6 Myoglobin

Myoglobinuria should be associated with clear clinical and clinicopathologic evidence of extensive muscle damage. The ammonium sulfate precipitation method of differentiating hemoglobin from myoglobin is imprecise and frequently fails to detect myoglobin in the dark, coffee-colored urine of horses with severe rhabdomyolysis. Accurate differentiation of these compounds in urine requires more sophisticated procedures.

22.11.7 Cells

The normal range for cells generally is considered to be up to five red cells or leukocytes per high-power field. An increased number of erythrocytes indicates hematuria, which may be caused by neoplasia, trauma, inflammation, or coagulopathy. Pyuria, an increase in urine leukocytes, indicates an inflammatory process, and

when associated with bacteriuria it indicates a septic process in the urinary tract. The presence of sheets or rafts of transitional cells suggests neoplasia.

22.11.8 Casts

Casts are accumulations of protein and cellular material that form in the renal tubules, and when present in the urine, they indicate renal damage or tubular disease. Casts can consist of erythrocytes, leukocytes, or renal tubular cells. As cellular degeneration proceeds, the cell type is more difficult to determine, and the casts become granular and then waxy. Hyaline casts are noncellular and are formed from mucoprotein. They may be seen with glomerulonephritis, fever with passive congestion, or severe dehydration with altered renal blood flow.

22.11.9 Crystals

The crystalline structures in the urine of large animals are those usually associated with an alkaline urine. Calcium carbonate crystals normally are found in abundance in horse urine, particularly if the horse has been fed alfalfa hay. Triple phosphate and calcium oxalate crystals are frequently observed in relatively small numbers. The major crystals involved in urolithiasis of feedlot cattle is struvite ($Mg\ NH_4PO_4 \cdot 6H_2$). In the western United States silicate stones are most common in livestock under range conditions. Carbonate and oxalate stones are common causes of urolithiasis in small flocks of backyard sheep and goats fed alfalfa hay.

22.11.10 Bacteria

Bacteria sometimes are seen in small numbers in voided urine samples and may represent surface contaminants. Bacterial infections of the urinary tract usually are associated with significant pyuria. When this is noted, a catheterized sample (horse) or clean midstream catch (ruminant) should be obtained for Gram stain, culture, and sensitivity testing. Results from ruminant samples must be carefully interpreted, because male ruminants routinely urinate within the prepuce, thus heavily contaminating samples. Fortunately, urinary tract infections in male ruminants and horses are rare.

22.11.11 Urine Creatinine Clearance Ratio

Urinary electrolyte excretion is affected by a variety of factors, including dietary intake, alterations in renal function, and specific hormones that regulate renal electrolyte excretion. Determination of electrolyte concentrations from randomly collected urine samples is easily done and can be clinically useful when these concentrations are compared with serum concentrations. The presence of substantial amounts of sodium in the urine of an animal with hyponatremia suggests excessive renal sodium loss caused by altered renal function or hormonal control. However, marked variation in the rate of urine production can lead to serious problems in the interpretation of urine electrolyte concentrations. The standard physiologic methods of determining renal electrolyte clearance are complicated by the need for quantitative urine collection and are not well suited to most practical clinical situations. One means of overcoming these difficulties is expression of the renal electrolyte clearance relative to the endogenous creatinine clearance. Expression of the renal clearance as a ratio eliminates the need for quantitative urine collection. This derived value is known as the *creatinine clearance ratio* or the *fractional excretion* (FE) and is calculated by the following formula:

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$$FE = \frac{\text{Urine}(X)}{\text{Serum}(X)} \times \frac{\text{Serum}(C)}{\text{Urine}(C)} \times 100$$

where *X* represents the electrolyte concentration and *C* represents the creatinine concentration.

The FE fluctuates somewhat during the day in relation to physical activity and feed and water intake. However, under standardized conditions, there is close agreement between the FE determined from single random samples of blood and urine and that based on samples quantitatively collected during a 12- to 24-hour period.[16] The FE of electrolytes has a very wide range of normal values. The principal sources of this variation are differences in dietary intake and environmental or experimental conditions. The FE of electrolytes has been useful for detecting specific dietary deficiencies or imbalances. Dietary salt deficiency is associated with an extremely low FE of sodium and chloride, whereas the plasma concentration of these ions generally remains within normal limits. In a similar fashion, dietary calcium and phosphorus imbalances seldom are reflected by the serum concentrations of these ions. Calcium deficiency and phosphorus excess are relatively common dietary problems in large animals and result in a low FE for calcium and a high FE for phosphorus. There are technical problems with the determination of the urine calcium concentration in horses because of their normally alkaline urine and the resultant precipitation of calcium carbonate in the urine. Mixed urine samples from horses must be acidified (hydrochloric acid can be used) to solubilize the calcium.

Increases in the FE of sodium are noted with renal tubular damage and impaired sodium resorption. The sodium FE increase has been a useful indicator for the differential diagnosis of prerenal azotemia, which almost invariably results in a low sodium FE, from the azotemia caused by primary renal disease, in which the FE for sodium often is markedly increased.

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23 Chapter 23 Collection and Submission of Samples for Cytologic and Hematologic Studies

Debra Deem Morris

23.1 BLOOD

Accurate assessment of hematologic data depends heavily on the proper collection, preparation, and transportation of blood samples. Factors that must be considered are the most appropriate venipuncture site, proper restraint, the correct technique, the type of anticoagulant, the necessary volume of blood, and the handling of the samples before laboratory analysis. Many of these factors are determined by the test or tests to be performed.

23.1.1 Venipuncture Site and Technique

Because they are large and easily accessible, the jugular veins most often are used in horses and small ruminants. In adult cattle the subcutaneous abdominal (milk) vein and coccygeal (tail) vein also are easily accessible. The disadvantages of using a milk vein are the danger to the operator and the relatively common occurrence of hematomas. In horses, alternate sites for collection are the cephalic, lateral thoracic, and saphenous veins.

Blood should be drawn from animals at rest under conditions of least excitement to minimize physiologic variations in cell counts. Evacuated tubes (Vacutainer*) that contain the appropriate anticoagulant and their needles are most convenient for collecting blood. These tubes must be filled to capacity to ensure the proper blood-to-anticoagulant ratio. The chosen vein is raised by digital occlusion proximally; an 18- to 20-gauge, 1½- to 2-inch needle is then plunged through the skin into the vein at approximately a 30-degree angle. A clean venipuncture is important to avoid contamination of the blood by tissue thromboplastin, which encourages clot formation and invalidates hemostatic function tests.

The coccygeal vein in cattle is punctured between the sixth and seventh coccygeal vertebrae, where the caudal folds end[1] with the tail directly over the animal's back. The needle is inserted at a right angle to the skin to bone and then is withdrawn gradually while vacuum is applied to the syringe until sufficient blood has been obtained. This technique should not be used to collect blood for hemostatic testing.

Blood for hemostatic tests should be carefully transferred to the anticoagulated vial to prevent hemolysis. Because goat erythrocytes are very sensitive to hemolysis, a Vacutainer is not recommended for blood collection in goats.[2]

* Becton Dickinson, Inc., Rutherford, NJ.

23.1.2 Anticoagulants

An anticoagulant must be added to all blood samples collected for hematologic examination, because cell counts and morphology cannot be evaluated in clotted blood. Commonly used anticoagulants include ethylenediamine tetraacetic acid (EDTA), heparin, and sodium citrate. The minimum amount of blood needed for most routine blood studies is 2 mL. Regardless of the volume withdrawn, the proper blood-to-anticoagulant ratio must always be maintained.

The preferred anticoagulant for the complete blood count (CBC) is EDTA at a concentration of 1 to 2 mg/mL. An excessive EDTA concentration causes erythrocyte shrinkage and may invalidate the packed cell volume, mean corpuscular volume, and mean corpuscular hemoglobin concentration.[2] Vacutainers contain the appropriate amount of EDTA for the full volume of blood; therefore these tubes should be allowed to fill until the vacuum stops. In addition to the CBC, EDTA-anticoagulated blood is suitable for platelet counts, total plasma protein levels, and plasma fibrinogen determinations.

Trisodium citrate (3.8% aqueous solution) is used to anticoagulate blood to be used for hemostatic function tests.[3] It should be used in a 1:9 proportion with blood.

23.1.3 Handling and Transportation of Samples

The vial containing blood and anticoagulant should be inverted several times to ensure adequate mixing. Blood samples for hematologic studies (CBC) are best processed as soon as possible after collection. If delay is expected, the samples should be refrigerated at 4° C (39.2° F). Air-dried blood smears for the differential count should be prepared immediately if samples must be held longer than 2 hours. If refrigerated, the remainder of the blood sample produces an acceptable CBC for 24 hours. Cold packs and an insulated container should be used to transport blood samples to a laboratory. Blood smears can be held for several days before staining with Wright stain or any modified Romanovsky stain.

Blood samples for laboratory examination of the hemostatic system must be collected and handled with special care to prevent platelet clumping and activation of coagulation. If blood is collected into a Vacutainer, discarding the first tube ensures that the sample does not contain tissue fluids.[3] Optimally the samples are placed on ice and delivered to the laboratory within 1 hour of collection. If the sample must be stored for several hours, plasma should be collected immediately by centrifugation (800 to 1000 g for 15 minutes), harvested with a plastic pipette, and frozen, preferably at −70° C (−94° F). Platelet counts must be performed immediately. The platelet count may be estimated by examining a peripheral blood smear and comparing the number of platelets per oil immersion field with the number of red or white cells.

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23.2 BONE MARROW

Air-dried smears can be made directly from a bone marrow aspirate or after the sample has been anticoagulated with EDTA. Because the volume of most aspirates is less than 0.5 mL, it is better to collect the sample in a syringe containing 1 to 2 drops of EDTA solution than to place it in a tube containing proportionately too much anticoagulant. Anti coagulant may not be required if smears can be made immediately after collection. These aspirates and smears should be handled as outlined for blood samples to be used for hematologic studies.

A bone marrow core must be preserved by placing it in a 10% neutral buffered formalin solution. Impression smears may be made from these samples by gently rolling them on a clean glass slide before placing them in the formalin solution.

23.3 LYMPH NODE ASPIRATES

Air-dried smears of lymph node aspirates are handled in the same manner as blood smears for the differential count.

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24 Chapter 24 Alterations in the Erythron

Debra Deem Morris

The erythron is composed of all data pertaining to erythrocytes in the peripheral blood. In most instances the routine complete blood count (CBC), which includes microscopic evaluation of a blood smear, provides the data discussed in this chapter. After evaluation of the CBC, additional data on the erythroid compartment may be necessary, such as can be obtained from staining for Heinz bodies, the Coombs' test, or the erythrocyte fragility test. All pertinent tests associated with erythroid diseases are discussed in this chapter except bone marrow analysis.

Any description of hematologic alterations in large animals would be incomplete without a brief discussion of the unique features of the equine erythron. To correctly interpret hematologic data, the practitioner must appreciate the characteristics that distinguish the horse from other domestic animals.

1 *Unstable packed cell volume (PCV)*. The horse has a highly innervated muscular spleen that normally contains up to one third of the potentially circulating red cell mass. On adrenergic stimulation (which normally accompanies exercise, excitement, or blood loss), the spleen contracts and releases its reservoir of erythrocytes into the peripheral circulation, causing the PCV to increase by as much as 50%. For this reason the resting PCV of horses is highly unstable and must be evaluated serially under different levels of excitement. Also, the response of the spleen to massive hemorrhage precludes using the PCV to estimate the magnitude of blood loss for at least 24 hours.

2 *Rouleau formation*. Equine erythrocytes show a tendency for marked rouleau formation (aligning like stacked coins), which causes cells to separate rapidly from plasma (high erythrocyte sedimentation rate). This characteristic necessitates thorough mixing of blood in the sample vial before analysis and must be differentiated from autoagglutination (see p. 402).

3 *Icteric plasma*. Although hyperbilirubinemia causes plasma to become more intensely yellow or orange, equine plasma is normally yellow (icteric).

4 *Lack of peripheral signs of regeneration*. Equine erythrocytes are retained in the bone marrow until hemoglobin synthesis is complete; thus polychromasia (reticulocytosis), macrocytosis, and other peripheral blood signs of bone marrow regeneration are extremely rare in horses. The erythron of anemic horses cannot be assessed by peripheral blood alone.

5 *Howell-Jolly bodies*. Small numbers of these eccentric erythrocytic inclusions normally are found in equine blood. Their presence does not indicate a responsive anemia, as in other species.

24.1 ANEMIA

Anemia is functionally defined as decreased oxygen-carrying capacity of the blood. The most accurate laboratory indication of anemia is a drop in the PCV or hematocrit below the normal range. The PCV must always be interpreted in light of the animal's hydration status and level of excitement, especially in horses. Because goats have very small erythrocytes (Table 24-1), the PCV in these animals must be determined by microhematocrit centrifugation (12,000 g for 5 minutes) to prevent plasma trapping in the erythrocyte column.[1] This is the most accurate method of PCV determination in all species.

The three pathophysiologic mechanisms for the development of anemia are blood loss, increased erythrocyte destruction (hemolysis), and inadequate erythrocyte production. In the first two instances the bone marrow is normal and responds by increased erythropoiesis (regenerative or responsive anemias). In ruminants, regenerative anemias are attended by the appearance of immature erythrocytes in the peripheral blood. Inadequate erythrocyte production is caused by a bone marrow abnormality, and by definition the anemia is nonregenerative. Often anemia in large animals is caused by a combination of pathophysiologic mechanisms (Boxes 24-1 and 24-2).

24.1.1 Alteration in Mean Corpuscular Volume

The mean corpuscular volume (MCV) is a reflection of mean erythrocyte size, as expressed in the following equation:

$$\text{MCV (fl)} = \frac{\text{Hematocrit} \times 10}{\text{Erythrocyte count (millions / } \mu\text{L)}}$$

An *increased* MCV (macrocytosis) indicates a regenerative anemia, because immature erythrocytes are larger than mature ones. Iron deficiency results in a *decreased* MCV (microcytosis), because cells undergo an extra division as a result of inadequate hemoglobin concentration. Inadequate spinning of blood causes a spurious elevation of the MCV by trapped plasma. This is most commonly a problem in goats.

Table 24-1 Normal Values for Erythron Data in Ruminants and Horses

	Cattle	Sheep	Goats	Horses
PCV (%)	24-46	27-45	22-38	32-53
Erythrocytes ($\times 10^6$/L)	5-10	9-15	8-18	6.7-12.9
Hemoglobin (g/dL)	8-15	9-15	8-12	11-19
MCV (fl)	40-60	28-40	16-25	37-58.5
MCH (pg)	11-17	8-12	5.2-8	12.3-19.7
MCHC (g/dL)	30-36	31-34	30-36	31-38.6
Reticulocytes	0	<0.5%	0	0
Erythrocyte diameter (m)	4-8	3.2-6	2.5-3.9	5-6
Erythrocyte fragility (percent NaCl)				
Minimum (beginning hemolysis)	0.52-0.66	0.58-0.76	0.74	0.54
Maximum (complete hemolysis)	0.44-0.52	0.40-0.55	0.44	0.34
Erythrocyte sedimentation rate (mm/1 hr)	0	1-2.5	0	50-60
Erythrocyte life span (days)	160	140-150	125	140-150

MCH, Mean corpuscular hemoglobin; *MCHC,* mean corpuscular hemoglobin concentration; *MCV,* mean corpuscular volume; *NaCl,* sodium chloride; *PCV,* packed cell volume.

24.1.1.1

Box 24-1 Causes of Anemia in Horses

24.1.1.1.1

COMMON CAUSES

24.1.1.1.1.1

Through Blood Loss

Intestinal parasitism (strongylosis)

Ectoparasites (lice, ticks)

Gastric ulcers

Immune-mediated thrombocytopenia

Gastric squamous cell carcinoma

Equine purpura hemorrhagica

24.1.1.1.1.2 Through Hemolysis

Neonatal isoerythrolysis

Equine infectious anemia

Red maple leaf toxicosis

Equine ehrlichiosis

24.1.1.1.1.3 Through Inadequate Erythrocyte Production

Abdominal abscess or other chronic abscess

Chronic pneumonia or pleuritis

Equine purpura hemorrhagica

Equine ehrlichiosis

Lymphosarcoma

24.1.1.1.2 LESS COMMON CAUSES

24.1.1.1.2.1 Through Blood Loss

Disseminated intravascular coagulation

Moldy sweet clover toxicosis

Warfarin toxicosis

Hemophilia A or other congenital factor deficiencies

Guttural pouch mycosis

24.1.1.1.2.2 Through Hemolysis

Onion toxicosis

Autoimmune hemolytic anemia

Babesiosis (piroplasmosis)

Clostridial infections

Incompatible blood transfusion

24.1.1.1.2.3 Through Inadequate Erythrocyte Production

Myelogenous leukemia

Equine viral arteritis

Chronic renal failure (glomerulonephritis)

Radiation toxicosis

Idiopathic aplastic anemia

24.1.2 Alteration in Mean Corpuscular Hemoglobin

The mean corpuscular hemoglobin (MCH) is an estimation of the amount of hemoglobin (Hb) in the blood per erythrocyte. It is calculated according to the following equation:

$$\text{MCH (pg)} = \frac{\text{Hb (g/dL)} \times 10}{\text{RBC count (millions/}\mu\text{L)}}$$

An *increased* MCH may indicate (1) the presence of reticulocytes (immature erythrocytes) in the peripheral blood or (2) hemolysis, either in vivo *or* in vitro. Iron deficiency results in a *decreased* MCH.

24.1.3

Alteration in Mean Corpuscular Hemoglobin Concentration

The MCH concentration (MCHC) is the most accurate of erythrocytic indices. It can be expressed as a percentage or in grams per deciliter:

$$\text{MCHC}(\%) = \frac{\text{Hb}(g/dL) \times 100}{\text{Hematocrit}(\%)}$$

Reticulocytosis (erythroid regeneration) or iron deficiency results in a *decreased* MCHC; hemolysis (in vivo or in vitro) causes an *increased* MCHC. Inadequate spinning of blood produces a spurious reduction in MCHC.

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24.1.3.1

Box 24-2 Causes of Anemia in Ruminants

24.1.3.1.1

COMMON CAUSES

24.1.3.1.1.1

Through Blood Loss

Intestinal parasitism

Ectoparasites (lice, ticks)

Abomasal ulcer (B)

24.1.3.1.1.2

Through Hemolysis

Anaplasmosis

Brassica toxicosis

Onion toxicosis

Bacillary hemoglobinuria

Leptospirosis

Chronic copper toxicosis (O)

24.1.3.1.1.3

Through Inadequate Erythrocyte Production

Lymphosarcoma

Liver abscess

Chronic bovine virus diarrhea

Johne's disease

Chronic pneumonia

Chronic abscessation

24.1.3.1.2 LESS COMMON CAUSES

24.1.3.1.2.1 Through Blood Loss

Moldy sweet clover toxicosis

Disseminated intravascular coagulation

Pulmonary abscess with hemorrhage associated with thrombosis of the posterior vena cava

Severe acute pyelonephritis

24.1.3.1.2.2 Through Hemolysis

Postparturient hemoglobinuria

Immune-mediated hemolytic anemia

24.1.3.1.2.3 Through Inadequate Erythrocyte Production

Chronic renal failure (amyloidosis, pyelonephritis)

Bracken fern toxicosis (also hemorrhage in enzootic hematuria)

Radiation toxicosis

Myelofibrosis (pygmy goats)

B, Bovine; *O*, ovine.

24.1.4 Anisocytosis

Variation in the size of erythrocytes is caused by the presence of macrocytes or microcytes (or both) among normal cells. Slight to moderate anisocytosis is normal in cattle, but marked anisocytosis in ruminants is a sign of regenerative anemia. Macrocytic erythrocytes may be seen at the peak of erythrocyte release during equine regenerative anemia, but in most horses effective regeneration occurs without macrocytosis.[2]

24.1.5 Polychromasia

Variation in color among the cells (using Romanovsky stains) is caused by the presence of reticulocytes that stain bluish because of residual DNA. In ruminants, polychromasia is a sign of regenerative anemia. Reticulocytosis can be quantitated most accurately by using new methylene blue stain, which causes cytoplasmic DNA to appear as blue granules. Insufficient cellular hemoglobin caused by iron deficiency results in decreased staining intensity and increased central pallor of erythrocytes (hypochromia). Hypochromia is difficult to recognize in large animals because their erythrocytes are small.

24.1.6 Poikilocytosis

The presence of abnormally shaped erythrocytes indicates increased erythrocyte fragility or diseases characterized by erythrocyte fragmentation. In rare cases, poikilocytosis may accompany iron deficiency or disseminated coagulopathy in large animals.

24.1.7 Basophilic Stippling

Tiny blue granules occasionally are observed in Romanovsky-stained erythrocytes containing residual DNA. This is a normal feature of regenerative anemia in cattle and sheep. In cattle, basophilic stippling also may indicate chronic lead poisoning.

24.1.8 Howell-Jolly Bodies

Basophilic nuclear remnants commonly are seen in immature erythrocytes during responsive anemia in ruminants. In healthy horses a few Howell-Jolly bodies occur normally.

24.1.9 Nucleated Erythrocytes

Nucleated erythrocytes and metarubricytes occasionally appear in the peripheral blood during the responsive phase of severe anemia in ruminants.

24.1.10 Heinz Bodies

Oxidative stress to erythrocytes causes denaturation of hemoglobin, which precipitates as aggregates, called *Heinz bodies*. Heinz bodies appear as round structures projecting from one edge of the red cell and are most easily visible on new methylene blue preparations. Erythrocytes containing Heinz bodies are susceptible to

intravascular hemolysis and removal in the mononuclear phagocyte system (MPS). Heinz body hemolytic anemia is seen in cattle that have ingested toxic amounts of onions or plants of the *Brassica* genus. Horses develop Heinz body anemia in association with toxicoses caused by phenothiazine, red maple leaves, and, in rare cases, onions.

24.1.11 Autoagglutination

Aggregation of erythrocytes may be observed grossly or microscopically during immune-mediated anemia in horses or cattle. Marked rouleau formation, which occurs normally in horses, may be differentiated from agglutination by diluting the blood sample 1:4 with 0.9% saline. Both rouleau formation and autoagglutination, rarely induced by severe inflammation, are dispersed by saline dilution.

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24.1.12 Increased Erythrocyte Fragility

The erythrocyte fragility test is a measure of the susceptibility of erythrocytes to hemolysis in a range of hypotonic saline concentrations (see Table 24-1). An increase in osmotic fragility is *indirectly* suggestive of immune-mediated anemia; the Coombs' test is more specific.

24.1.13 Positive Direct Antiglobulin (Coombs') Test Result

A positive Coombs' test result indicates the presence of antibodies on the surface of erythrocytes. A positive test result may be found in idiopathic autoimmune hemolytic anemia in any species and in horses with neonatal isoerythrolysis or equine infectious anemia. The Coombs' reagent is a mixture of antibodies directed against immunoglobulins and complement of a certain species. Because the endpoint of this test is agglutination, it cannot be performed on blood that is autoagglutinating. There are many false-negative results.

24.1.14 Erythrocytic Parasites

During the acute stages of bovine anaplasmosis and babesiosis in horses, cattle, sheep, and goats, intraerythrocytic parasites can be found. *Anaplasma marginale* is seen as a round, basophilic inclusion at the edge of cells, present in highest numbers before a hemolytic crisis. *Babesia* trophozoites occur in erythrocytes as round, bizarre, rod-shaped, or typical piriform (teardrop-shaped) structures. Absence of intraerythrocytic parasites does not rule out anaplasmosis or babesiosis.

24.1.15 Clinical Signs of Anemia

The major clinical signs of anemia (e.g., tachycardia, tachypnea, reduced exercise tolerance, and depression) reflect physiologic adjustments to inadequate oxygen transport to body tissues. The PCV level at which clinical signs occur depends on the rate of development, the severity of the anemia, and the physical demands placed on the animal. Other clinical signs depend on the cause and mechanism of anemia development. Anemia is accompanied by mucosal pallor except when it is caused by hemolysis, which results in icterus. Red urine (hemoglobinuria) indicates intravascular hemolysis, which may be accompanied by fever. Melena, hematuria, and petechial hemorrhages may indicate chronic blood loss.

Although diagnosing anemia is easy, determining the cause, which dictates proper treatment, may be complex. The practitioner first must determine the pathophysiologic classification of the anemia and then consider possible causes.

24.1.16 Approach to Diagnosis of Anemia in Horses

1 Take the history. Important factors are the diet, housing, pasture conditions, drug history, date of the most recent Coggins' test, travel history, time course of current signs, and any past illnesses. In considering neonatal isoerythrolysis, the number of the dam's previous foals and their sires must be ascertained.

2 Perform a physical examination. Take note of the mucous membranes. Icterus in horses may be associated with fasting or cholestatic liver disease, as well as hemolysis. Hemoglobinuria, which is uncommon in horses, indicates intravascular hemolysis (this is difficult to distinguish from myoglobinuria; therefore the plasma should be examined). Epistaxis or other signs of bleeding diathesis suggest a source of chronic blood loss. A thorough search should be made for evidence of chronic disease affecting the respiratory and gastrointestinal tracts. Take note of any weight loss and the character of feces. Any chronic inflammatory disease such as abdominal abscess, pneumonia, or lymphosarcoma causes a mild to moderate nonregenerative anemia. Immune-mediated hemolytic anemia often is associated with equine lymphosarcoma.

3 Perform a CBC. *403*

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a PCV is reduced.

b $\frac{\text{PCV}(\%)}{\text{Hb}(g/dl)}$

The ratio of PCV/HB less than 3 suggests intravascular hemolysis (e.g., PCV=15; Hb=6; 15/6 is <3).

c Pink plasma suggests intravascular hemolysis.

d MCV above 60 fl (rare) suggests regenerative anemia.

e Heinz bodies (substantiate by new methylene blue staining) suggest toxicosis caused by phenothiazine, red maple leaves, or wild onions.

f Agglutination (substantiate by diluting blood 1:4 with 0.9% saline) suggests immune-mediated anemia. Perform Coggins' test in adult. In newborn foal, perform hemolytic cross-match with dam.

4 Evaluate leukogram and plasma proteins.

a Neutrophilia, hyperglobulinemia, and/or hyperfibrinogenemia suggests chronic infection.

b Hypoproteinemia may indicate blood loss anemia or an underlying disease causing protein loss (e.g., granulomatous bowel disease or intestinal lymphosarcoma). In horses, gastric squamous cell carcinoma causes chronic blood loss anemia associated with iron deficiency.

5 Perform bone marrow analysis. This is necessary to adequately characterize anemia in horses as regenerative or nonregenerative.

6 Analyze urine. A positive result for occult blood without microscopic hematuria indicates hemoglobinuria (intravascular hemolysis) or myoglobinuria (myopathy). Hemoglobinuria is associated with pink plasma.

Saturated ammonium sulfate usually precipitates and removes color caused by hemoglobin; however, spectrophotometric tests are best for differentiating from myoglobin.[3]

7 Test feces for occult blood. A positive result may indicate gastrointestinal blood loss as a cause of chronic anemia. Gastric ulcers (foals) and gastric squamous cell carcinoma should be considered.

8 Test serum iron and total iron-binding capacity (TIBC). Low serum iron and a high TIBC are consistent with iron deficiency (chronic blood loss). Low serum iron with normal TIBC suggests the anemia of chronic disease.

9 Perform a Coggins' test. A positive result indicates equine infectious anemia.

10 Perform a Coombs' test. A positive result indicates immune-mediated anemia.

24.1.17 Approach to Diagnosis of Anemia in Ruminants

1 Take the history. Note the type of diet, access to pasture, other herd or flock members with clinical signs of systemic disease, immunization status, and exposure to new animals.

2 Perform a physical examination. Icterus in ruminants is rare except in association with hemolysis. Pallor indicates blood loss or inadequate erythrocyte production. Fever may be a sign of hemolysis or of an underlying systemic disease. Most hemolytic anemias in ruminants, *except anaplasmosis,* cause hemoglobinuria. Check the breath for onion odor.

3 Perform a CBC.

- a PCV is reduced.
- b Pink plasma suggests intravascular hemolysis.
- c Regenerative changes indicate blood loss or hemolysis with normal marrow.
- d If no signs of regeneration are present, abnormal bone marrow, acute blood loss (less than 4 days), or acute hemolysis is indicated.
- e Increased Hb, MCH, and/or MCHC with a low PCV indicates intravascular hemolysis.
- f Basophilic stippling without other signs of regeneration may indicate chronic lead poisoning.
- g Heinz bodies suggest ingestion of onions or *Brassica* plants. May need to do new methylene blue stain to observe.
- h Autoagglutination suggests immune-mediated anemia. Perform dilution tests.

4 Evaluate plasma proteins.

- a Hypoproteinemia suggests blood loss.
- b Hyperproteinemia, hyperglobulinemia, and/or hyperfibrinogenemia suggests chronic inflammatory disease.

5 Analyze urine. See discussion under Approach to Diagnosis of Anemia in Horses. Myoglobinuria is associated with clear plasma.

6 Test feces for occult blood. Bleeding abomasal ulcers cause acute or chronic anemia in cattle.

7 Perform bone marrow analysis. This test is necessary in the absence of peripheral blood signs of regeneration.

24.2 ERYTHROCYTOSIS (POLYCYTHEMIA)

Erythrocytosis is defined as an increase in the PCV, erythrocyte count, and hemoglobin concentration above the normal range. Erythrocytosis may be absolute or relative (apparent), caused by hemoconcentration (dehydration, shock) or splenic contraction (Box 24-3). Absolute erythrocytosis (primary or secondary) is caused by increased erythropoiesis that creates a greater total circulating erythrocyte mass.

Primary absolute erythrocytosis (polycythemia vera) is an idiopathic, myeloproliferative disorder associated with a normal partial pressure of oxygen (Po_2) and reduced erythropoietin levels. Secondary absolute erythrocytosis is caused by an increase in erythropoietin. Chronic tissue hypoxia, which may accompany residence at high altitudes, chronic pulmonary disease, and heart defects that produce arteriovenous shunting induce a physiologic or compensatory increase in serum erythropoietin that results in absolute secondary erythrocytosis. Inappropriate elaboration of erythropoietin (normal Po_2) and secondary erythrocytosis rarely occur in chronic renal, hepatic, or endocrine disorders, especially those caused by neoplasia.

In domestic animals, absolute erythrocytosis usually occurs secondary to chronic diseases that produce tissue hypoxia. Primary absolute erythrocytosis and inappropriate secondary erythrocytosis caused by hepatocellular carcinoma have been described in horses.[4] Familial erythrocytosis has been described in cattle, and the source of the increase in erythropoietin has not been identified.[5] Clinical signs of erythrocytosis are vague; they include lethargy, weight loss, mucosal hyperemia, and signs of underlying disease.

24.2.1 Box 24-3 Causes of Erythrocytosis in Large Animals

24.2.1.1 RELATIVE ERYTHROCYTOSIS

Dehydration

Endotoxic shock

Strangulating intestinal obstruction

Salmonellosis

Colitis X (E)

Septic metritis

Septic mastitis (B)

24.2.1.2 ABSOLUTE ERYTHROCYTOSIS

24.2.1.2.1 Common Causes

Congenital cardiovascular disease

Residence at high altitudes

Chronic obstructive pulmonary disease

24.2.1.2.2 Less Common Causes

Familial (B)

Chronic hepatic disease

Hepatoma

Leiomyoma

Hemangioblastoma

Pheochromocytoma

Nephroma

Hydronephrosis

Polycystic kidneys

Nephrocalcinosis

B, Bovine; *E*, equine.

Diagnosis of erythrocytosis is based on persistent elevation of the PCV, hemoglobin, and erythrocyte count in the absence of clinical evidence of shock or dehydration and without response to intravenous fluid therapy. Chronic hypoxia can be ruled out by determining the arterial oxygen concentration. Thoracic radiographs and echocardiography can delineate cardiorespiratory function more thoroughly. Examination of the bone marrow is indicated, although erythroid hyperplasia is not specific for primary or secondary erythrocytosis. In the absence of hypoxemia and a demonstrable disease that could lead to appropriate secondary erythrocytosis, polycythemia vera and inappropriate secondary erythrocytosis must be considered. Renal and hepatic disease should be excluded by determining the serum creatinine, hepatic enzyme, and bile acid levels. The only way to clearly differentiate primary from secondary absolute erythrocytosis is to determine the serum erythropoietin. This is a bioassay that is not routinely available, and it is relatively insensitive to minor changes in erythropoietin concentrations.

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25 Chapter 25 Alterations in the Leukogram

Debra Deem Morris

The leukogram (white blood cell [WBC] count, differential analysis, and WBC morphology) provides extremely useful laboratory data when considered with the history, clinical signs, and physical findings. To fully use the leukogram, the practitioner must know the types of WBCs, their kinetics and functions, and the pathologic and physiologic conditions that can cause deviations from normal. Normal values for leukogram data are given in Table 25-1.

Mature WBCs include neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Immature leukocytes that may or may not be present in the peripheral blood include band or nonsegmented neutrophils, metamyelocytes, myelocytes, and progranulocytes. These immature forms usually are found only in the bone marrow, but they may be released in response to disease.

25.1 LEUKOCYTES

Leukocytes, or WBCs, are divided into two main categories: polymorphonuclear (PMN) leukocytes (granulocytes) and mononuclear leukocytes. PMN leukocytes include neutrophils, eosinophils, and basophils, which are produced in the bone marrow. The mononuclear leukocytes are the lymphocytes and monocytes. Lymphocytes are produced in the bone marrow (the primary source), lymphoid organs (thymus, spleen, and lymph nodes), and gut-associated lymphoid tissues (Peyer's patches, tonsils). Monocytes, the largest of the WBCs, originate in the bone marrow.

25.1.1 Neutrophils

Neutrophils develop in the bone marrow as myeloblasts, progranulocytes or promyelocytes, myelocytes, metamyelocytes, band cells, and segmented neutrophils. Myeloblasts arise from bipotential committed stem cells (colony-forming unit—granulocyte, macrophage) that are derived from pluripotent hematopoietic stem cells.[1]

Myeloblasts, promyelocytes, and myelocytes are capable of cell division, but metamyelocytes, bands, and segmented neutrophils (about 80% of the bone marrow granulocytes) do not divide.[2] The normal interval for progression from myeloblast to mature blood neutrophil is 4 to 9 days, depending on the species. A functional storage compartment of neutrophils exists in the marrow to prevent marrow depletion by the sudden imposition of a greatly increased peripheral use. The storage pool, which is limited to segmented neutrophils and some bands, varies in size among species and is relatively small in adult cattle.[1] A marginal pool of neutrophils adheres to endothelium throughout the microvasculature. Neutrophils in the circulating pool are the only part of the total neutrophil population enumerated by the peripheral blood neutrophil count. In large animals the marginal neutrophil pool is approximately equal in size to the circulating pool.[1]

After entering the bloodstream, neutrophils have a half-life of 6 to 14 hours, depending on the species. The entire blood pool of neutrophils is replaced two to two-and-one-half times per day. Neutrophils move randomly into the tissues by diapedesis through vascular endothelium and do not return to the blood. Neutrophils migrate into tissues within 2 hours of injury, infection, or inflammation. In the absence of such lesions, the neutrophils are destroyed by macrophages of the bone marrow, liver, and spleen or are lost into body secretions and excretions within 96 hours of exiting the marrow.[2]

The major function of neutrophils is to phagocytize and destroy foreign material, especially pathogenic bacteria. Bacterial products and substances released from activated lymphocytes (lymphokines), macrophages, and cellular damage are responsible for attracting the neutrophils, which move by chemotaxis and bind to the foreign particle.[3] Opsonins are protein components of serum that adhere to foreign particles and make them more liable to phagocytosis.[4] Opsonization by specific antibodies increases the rate and magnitude of ingestion for most bacterial organisms. Once drawn into the cell, the bacteria are enclosed in a phagocytic vacuole, which fuses with lysosomes in the neutrophil cytoplasm that release hydrolytic enzymes to destroy the contents. Degranulation, which occurs within 5 seconds of a phagocytic event, can lead to release of lysosomal enzymes into the surrounding milieu and cause tissue destruction.

Gram-negative bacteria are more resistant to digestion in the neutrophil than gram-positive bacteria because of the structure of their outer wall. *Brucella abortus, Mycobacterium paratuberculosis, Listeria monocytogenes,* and some *Salmonella* serotypes are extremely resistant to lysosomal destruction and may survive and multiply within the neutrophil.

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Table 25-1 Normal Values for Leukogram Data (Adult Animals)

	Cattle	Sheep	Goats	Horses
White blood cells ($\times 10^3/\mu L$)	4-12	4-12	4-13	5.4-14.3
Neutrophils ($\times 10^3/\mu L$)	0.6-4	0.7-6	1.2-7.2	2.3-8.6
Bands ($\times 10^3/\mu L$)	0-0.12	Rare	Rare	0-1
Lymphocytes ($\times 10^3/\mu L$)	2.5-7.5	2-9	2-9	1.5-7.7
Monocytes ($\times 10^3/\mu L$)	0.025-0.84	0-0.75	0-0.55	0-1
Eosinophils ($\times 10^3/\mu L$)	0-2.4	0-1	0.05-0.65	0-1
Basophils ($\times 10^3/\mu L$)	0-0.2	0-0.3	0-0.12	0-0.29
Neutrophil/lymphocyte (N/L) ratio	0.3-0.6	0.3-0.7	0.6-3.6	0.8-2.8

25.2 EOSINOPHILS

Eosinophils are produced in the bone marrow and follow the same maturation sequence and kinetics as neutrophils, except that eosinophils arise from the colony-forming unit—eosinophil.[1] There is a large marrow reserve of eosinophils, and their circulatory half-life varies from 30 minutes to 10 hours, depending on the species. Eosinophils also are found in many body tissues, particularly the gut, subcutis, uterus, and respiratory tract, where they have a half-life of 12 days.

Eosinophils are most important in controlling parasitic infections and in regulating inflammatory and allergic reactions. Eosinophils are less efficient phagocytes than neutrophils and provide little host resistance to bacterial infection but are important in protective parasitic immunity.[2] Eosinophils are believed to regulate immediate (type I) hypersensitivity and inflammatory responses by inactivating histamine, leukotrienes, platelet-activating factor,

and other chemical mediators involved in these processes. Other, less characterized effects of eosinophils include tissue damage, augmentation of coagulation and fibrinolysis, and inhibition of granulopoiesis.

25.3 BASOPHILS

Basophils are relatively scarce in the blood of large animal species. The blood basophil resembles the tissue mast cell and is believed to perform similar functions. Basophils are produced in the bone marrow by mitosis of basophilic promonocytes through the same sequential stages of maturation as neutrophils. Basophils have a mean circulatory half-life of about 6 hours. They then enter tissues, where they survive for approximately 10 to 12 days.[1] Mast cells, found in many body tissues, originate from undifferentiated connective tissue mesenchymal cells, especially near blood vessels. There is evidence in some species that mast cells also originate from a precursor in the bone marrow.[1]

Basophils and mast cells contain stored intragranular substances that mediate their function in allergic and inflammatory processes. The most important function of basophils and mast cells is to elicit an immediate hypersensitivity reaction through secretion of vasoactive mediators, including histamine, leukotrienes, platelet-activating factor, and others. Vasodilation, pooling of fluid in tissue spaces, and systemic reactions may occur, with signs of dyspnea, urticaria, coughing, and even severe anaphylactic shock. Eosinophils are attracted to these areas to neutralize the histamine and attenuate the inflammatory response.

25.3.1 Lymphocytes

Lymphocytes are produced in the bone marrow, lymph nodes, thymus, spleen, and Peyer's patches. They are classically divided into two groups: T cells, or thymus-derived lymphocytes, and B cells, or bone marrow—derived lymphocytes. Null cells have been identified in humans and in some animals that lack specific markers for T or B cells.[1] Both T- and B-cell populations are present in the peripheral blood of large animal species, with T cells making up the majority. B cells are few during fetal life but steadily increase to make up about 20% of circulating lymphocytes in most adult domestic animals.[1] Observations in cattle indicate that various inflammatory states are associated with an increase in B cells and a decrease in T cells. Leukemic cows infected with bovine leukosis virus (BLV) and those with persistent lymphocytosis have a higher number of B cells, which constitute up to 97% of lymphocytes.[1] Lymphocytes can recirculate and continue to undergo mitosis. Information on domestic animals is unavailable, but most blood lymphocytes in humans have an average lifespan of 4.3 years.[1]

B lymphocytes transform into plasma cells that produce antibodies under the regulation of T lymphocytes. T lymphocytes are primarily responsible for delayed-type hypersensitivity (DTH), graft and tumor rejection, autoimmunity, and resistance to certain intracellular pathogens. Some types of T cells have a direct cytotoxic function to destroy foreign cells, and null cells express natural killer activity. Lymphocytes produce important immunologic mediators called *lymphokines,* which include macrophage-activating factor, interferons, and interleukins.

The number of lymphocytes in the peripheral blood reflects a balance between cells leaving and entering the circulation; thus changes do not necessarily mean altered lymphopoiesis. In addition to consideration of the total number in the leukogram, lymphocytes can be evaluated by measuring the ratio of T cells to B cells (normal range is 1:1 to 3:1), antibody levels and response to vaccination, in vitro lymphocyte stimulation tests, and skin tests for DTH.

25.3.2 Monocytes

Monocytes are produced in the bone marrow from the colony-forming unit—granulocyte, a macrophage, which differentiates into either myeloblasts or monoblasts (precursors of monocytes).[1] Monoblasts undergo mitosis to promonocytes, then divide one to two more times to produce monocytes. Once released into the blood, monocytes circulate for 1 to 3 days, then enter body cavities and tissues and transform into macrophages. Tissue macrophages survive in tissues for weeks to years. Once in tissue, these macrophages are described as “fixed” or “free.” Free macrophages are found in the peritoneal and pleural cavities, in joints, in alveolar spaces, and at areas of inflammation. Fixed macrophages include Kupffer's cells of the liver, osteoclasts, microglial cells, and macrophages found in the spleen, bone marrow, and lymph nodes.

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The blood monocytes and tissue macrophages constitute the mononuclear phagocyte (reticuloendothelial) system.[1,2] The functions of tissue macrophages include sustained phagocytic activity to remove dead and damaged tissue; microbicidal action against some bacteria, viruses, fungi, and protozoa; regulation of the immune response in both afferent and efferent limbs; tumor defense; regulation of hematopoiesis; tissue repair and remodeling; and secretion of monokines, lysosomal enzymes, and other substances, such as coagulation factors, that have wide-ranging biologic importance. The tissue macrophages are better equipped than neutrophils to combat intracellular organisms and those that cause granulomatous inflammation such as fungal infections, listeriosis, brucellosis, Johne's disease, tuberculosis, and salmonellosis.

Interleukin (IL)-1 and tumor necrosis factor are important macrophage-derived mediators of the inflammatory response.[5] These and other cytokines are released when macrophages are exposed to bacterial products (especially endotoxin), antigens, and injured tissue. IL-1 stimulates bone marrow release of neutrophils and attracts them to areas of bacterial infection or inflammation. Tumor necrosis factor is responsible for many of the physiologic derangements associated with endotoxemia that end in shock, tissue injury, and death.

25.4 GENERAL PRINCIPLES OF LEUKOGRAM INTERPRETATION

When interpreting the leukogram, the practitioner must consider the established normal values for the species, the animal's age and condition, and the species-specific WBC responses. Leukocytosis may be attributed to physiologic or pathologic causes, whereas leukopenia always is considered pathologic.[1,6]

25.4.1 Physiologic Leukocytosis

Physiologic leukocytosis occurs when epinephrine is released, as with stress, excitation, anxiety, or exercise. The elevated WBC count is transient and caused by both neutrophilia and lymphocytosis, although it is primarily the result of temporary mobilization of the marginal neutrophil pool.[2] Corticosteroids, either exogenous or endogenous, cause neutrophilia and lymphopenia. Younger animals may have higher lymphocyte and total WBC counts than those considered normal for adults.[1]

25.4.2 Neutrophilia

Bacterial infection is the most common cause of pathologic neutrophilia (Boxes 25-1 and 25-2). In the acute stage of the infection, a left shift (presence of increased immature neutrophil granulocytes in the peripheral blood) may appear.[1,6] Left shift with concomitant mature neutrophilia is called a *regenerative left shift*. Rebound

neutrophilia often follows neutropenia associated with endotoxemia, and it is usually a good prognostic indicator. Neutrophilia is most pronounced while bacterial infections are being localized, especially with abscess formation. Chronic localized infections rarely are attended by a left shift, and in cattle the neutrophil count may increase only minimally or not at all. Horses with chronic bacterial infections often show only a mild mature neutrophilia attended by lymphopenia and a normal total WBC count.

Neutrophilia may also accompany inflammation caused by neoplasia or severe injury or may arise during the postoperative period. Less common causes of neutrophilia include parasitic and mycotic infections, tumors that cause secretion of endogenous corticosteroids, toxins, and some metabolic diseases such as pregnancy toxemia.

25.4.2.1

Box 25-1 Causes of Neutrophilia in Horses

25.4.2.1.1

Common Causes

Excitement, exercise

Stress, exogenous corticosteroid administration

Chronic pneumonia, pleuritis

Strangles (*Streptococcus equi* infection)

Chronic peritonitis, abdominal abscess

Other internal abscessation

Chronic salmonellosis or colitis

Thrombophlebitis

Purpura hemorrhagica (vasculitis)

25.4.2.1.2

Less Common Causes

Bacterial endocarditis

Cellulitis

Pyelonephritis

Chronic hepatitis, cholangiohepatitis

Cholelithiasis

Lymphosarcoma

Other internal neoplasia

Pituitary adenoma (equine Cushing's syndrome)

Autoimmune hemolytic anemia

Granulocytic leukemia

Systemic fungal infections

25.4.2.2

Box 25-2 Causes of Neutrophilia in Ruminants

25.4.2.2.1

Common Causes

Stress, exogenous corticosteroid administration

Chronic pneumonia

Chronic traumatic reticuloperitonitis

Peritonitis

Internal abscessation

Caseous lymphadenitis (O, C)

Mycoplasmal or chlamydial polyarthritis (O, C)

Chronic pyelonephritis

Chronic metritis

Liver abscesses

Enteritis

Umbilical abscessation

Chronic salmonellosis

Septic arthritis

25.4.2.2.2 Uncommon Causes

Autoimmune hemolytic anemia

Toxins

Pregnancy toxemia (O, C)

Bovine granulocytopathy syndrome

C, Caprine; *O*, ovine.

In large animals the total WBC or neutrophil count may not reflect chronic inflammation; for this reason, examination of neutrophil morphology is paramount in interpreting the leukogram. Bacterial infections, especially those caused by gram-negative organisms, often result in neutrophil cytoplasmic and nuclear alterations, which are referred to as “toxic changes.” These changes occur in the bone marrow and include cytoplasmic foaminess, vacuolation, and/or basophilia; reddish purple “toxic” granules; bluish cytoplasmic inclusions called Döhle bodies; and bizarre giant forms with or without polyploidy. The changes do not accompany other causes of neutrophilia. 407 408

25.4.3 Neutropenia

The usual causes of neutropenia in the large animal species are bacterial septicemia and endotoxemia caused by gastrointestinal disease, metritis, or coliform mastitis (Boxes 25-3 and 25-4). Some viral diseases and anaphylaxis also cause neutropenia.

A degenerative left shift, generally associated with neutropenia, occurs when immature neutrophils appear in the peripheral blood in greater numbers than mature neutrophils. In species other than cattle, degenerative left shift is an extremely poor prognostic sign. Because cattle have a small bone marrow reserve of neutrophils, immature neutrophils appear quickly in the blood during acute inflammatory diseases and often exceed the mature neutrophils. A marked fall in the WBC count commonly is seen in cattle during the developmental stage of an acute localizing inflammatory process such as mastitis or metritis. Once neutrophil production has intensified,

the left shift disappears and mature neutrophilia intervenes. Neutropenia that persists longer than 4 days is a sign of inadequate granulopoiesis, which sometimes occurs subsequent to severe toxemia. Neutropenia apparently is rare in goats.

25.4.3.1

Box 25-3 Causes of Neutropenia in Horses

25.4.3.1.1

Common Causes

Acute salmonellosis

Acute toxic colitis

Acute peritonitis (ruptured viscus)

Gram-negative septicemia, endotoxemia

Neonatal septicemia

Acute pleuritis

Acute metritis

Proximal enteritis (duodenitis, proximal jejunitis)

Equine influenza

Equine herpesvirus type 1 infection

25.4.3.1.2

Less Common Causes

Equine ehrlichial colitis (Potomac fever, *Ehrlichia risticii* infection)

Equine ehrlichiosis (*Ehrlichia equi* infection)

Idiopathic aplastic anemia

Equine viral arteritis

Radiation toxicosis

Myelophthisic disease (e.g., eosinophilic leukemia)

25.4.3.2

Box 25-4 Causes of Neutropenia in Ruminants

25.4.3.2.1

Common Causes

Gram-negative septicemia, endotoxemia

Septic metritis

Septic (coliform) mastitis

Diffuse peritonitis

Ruptured uterus with peritonitis

Ruptured abomasal ulcer

Acute salmonellosis

Acute pneumonia

Toxemia- or toxin-induced bone marrow suppression

Fat cow syndrome (fatty liver)

Clostridial infection

25.4.3.2.2

Uncommon Causes

Bovine virus diarrhea

Bracken fern toxicosis

Trichloroethylene toxicosis

Radiation toxicosis

Idiopathic aplastic anemia

The severity of toxemia is reflected by the number of “toxic” neutrophils and the degree of toxic changes. In diseases that cause severe toxemia, precursor cells in the bone marrow become vacuolated and fail to divide, thereby contributing to the existing neutropenia. This bone marrow hypoplasia subsequent to severe infection and inflammation is seen most often in cattle.

In rare cases, neutropenia may develop subsequent to myelophthisic disease, idiopathic aplastic anemia, myelofibrosis, or bone marrow suppression by drugs, chemicals, or ionizing radiation. Lymphosarcoma may involve the bone marrow in rare cases.

25.4.4

Lymphocytosis

Pathologic lymphocytosis is uncommon, occurring occasionally with chronic viral infections and autoimmune disease processes (Boxes 25-5 and 25-6). Lymphocytic leukemia is rare in large animals. Thirty percent of cattle infected with BLV are leukemic (see Chapter 37), and lymphocytosis may persist in the absence of lymphoma or leukemia. Physiologic lymphocytosis associated with epinephrine release caused by excitement or exercise is common in horses under 2 years of age.

25.4.5

Lymphopenia

Causes of lymphopenia include acute viral diseases, endotoxin release, severe bacterial infection, septicemia, rickettsial diseases, malnutrition, tumors that cause increased release of corticosteroids, and immunodeficiency (Boxes 25-7 and 25-8). Persistent lymphopenia is a poor prognostic indicator. Increasing lymphocyte counts represent recovery.

25.4.6

Monocytosis

Monocytosis occurs with chronic inflammation (Box 25-9). Because the monocyte count is not highly responsive to inflammatory disease in large animals, it is not an especially useful part of the leukogram.[6]

25.4.6.1

Box 25-5 Causes of Lymphocytosis in Horses

25.4.6.1.1

Common Cause

Excitement, exercise

25.4.6.1.2

Uncommon Causes

Lymphocytic leukemia

Equine infectious anemia

25.4.6.2

Box 25-6 Causes of Lymphocytosis in Ruminants

Persistent lymphocytosis (bovine leukosis virus infection)

Lymphocytic leukemia

Chronic infections (pneumonia, peritonitis, pericarditis, liver abscess)

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25.4.6.3

Box 25-7 Causes of Lymphopenia in Horses

25.4.6.3.1

Common Causes

Stress, exogenous corticosteroid administration

Equine influenza

Equine herpesvirus type 1 infection

Endotoxemia, septicemia

Acute peritonitis (gastrointestinal rupture)

25.4.6.3.2

Less Common Causes

Malnutrition, starvation

Equine viral arteritis

Combined immunodeficiency disease

25.4.6.4

Box 25-8 Causes of Lymphopenia in Ruminants

25.4.6.4.1

Common Causes

Stress, exogenous corticosteroid administration

Gram-negative septicemia, endotoxemia

Septic mastitis

Diffuse peritonitis

Ruptured abomasal ulcer

Acute pneumonia

Infectious bovine rhinotracheitis

25.4.6.4.2 Uncommon Causes

Bovine virus diarrhea

Immunodeficiency

25.4.6.5 Box 25-9 Causes of Monocytosis in Large Animals

25.4.6.5.1 Uncommon Causes

Granulomatous disease

Chronic bacterial infections

25.4.7 Monocytopenia

Endotoxin release and viremia may cause monocytopenia. Monocytopenia occurs initially during stress periods associated with corticosteroid release and may be followed by monocytosis.

25.4.8 Eosinophilia

Eosinophilia is uncommon in large animals but may occur with diseases that involve an interaction between antigen, IgE antibody, and mast cells or basophils, such as parasitic infections, allergic respiratory diseases, and dermatoses (Boxes 25-10 and 25-11). Unlike in humans and small animals, visceral larval migrans rarely induces peripheral eosinophilia. Tissue protein breakdown (malignancies, chronic suppurative processes) may cause eosinophilia in rare cases through the release of histamine or eosinophilic chemotactic factor of anaphylaxis from mast cells. Histamine in the blood attracts bone marrow eosinophils to the circulation. For eosinophilia to occur in response to parasitism, a parasite protein must be released and processed by cells infiltrating the tissue site of parasitic lodgment.[1] Thus eosinophilia is unlikely to accompany intestinal parasitism when the parasite is free-living in the lumen.

25.4.8.1

Box 25-10 Causes of Eosinophilia in Horses

25.4.8.1.1

Uncommon Causes

- Internal parasitism
- Cutaneous habronemiasis
- Systemic hypersensitivity reaction
- Lymphosarcoma
- Eosinophilic leukemia

25.4.8.2

Box 25-11 Causes of Eosinophilia in Ruminants

25.4.8.2.1

Uncommon Causes

- Milk allergy
- Atypical interstitial pneumonia
- Acute bovine pulmonary emphysema
- Sarcocystosis
- Toxoplasmosis
- Migrating parasite larvae such as:
  - Lungworms
  - Ascarids
  - Flukes
  - *Trichostronglyus* species

Hypoderma species

Parelaphostronglylus species

Eosinophilic granulocytic leukemia is rare in large animal species but has been reported in horses.[7] The circulation of bizarre, immature eosinophils differentiates this from other causes of eosinophilia.

25.4.9 Eosinopenia

Eosinopenia is difficult to evaluate, because the leukograms of clinically normal animals may contain very few eosinophils. Eosinopenia may occur secondary to an increase in endogenous or exogenous corticosteroids. Eosinopenia also may be seen with active inflammatory processes.

25.4.10 Basophilia and Basopenia

Basophils are rarely seen in the peripheral blood of the large animal species, although they are more frequently encountered than in dogs and cats.[1] Changes in the number of basophils are difficult to interpret. Stress causes a reduction in their number, whereas basophilia may be seen with allergic dermatitis and delayed hypersensitivity reactions.

25.5 APPROACH TO INTERPRETATION OF THE LEUKOGRAM IN HORSES

The equine neutrophil-to-leukocyte (N/L) ratio declines from approximately 2.8 at birth to 1.1 at 1 to 2 months of age and to 0.9 at 6 to 8 months. An N/L ratio near 1 persists through 2 years and increases with age to approximately 2 as lymphocyte numbers are reduced. The total WBC count increases from birth through 3 months of age, is slightly above adult values between 3 months and 2 years of age, and then starts to decline. Physiologic leukocytosis is quite common in horses under 2 years of age.[1]

During chronic and established inflammatory diseases, horses generally have a mature neutrophilia and lymphopenia that may or may not result in leukocytosis.[6] The degree of leukocytosis in chronic suppurative diseases rarely exceeds 20,000/μL. Peracute diseases of the gastrointestinal tract and septicemia (especially in neonates), usually attended by endotoxemia, are characterized by leukopenia and a degenerative left shift, the severity of which is correlated with the prognosis. In the most severe cases the left shift includes myelocytes and neutrophils that show marked “toxic” changes. Survival and recovery are attended by a rebound neutrophilia (with or without left shift) and monocytosis. Neonates have a small neutrophil reserve and have more sluggish granulopoiesis in response to disease.

Lymphopenia and eosinopenia often occur readily in response to stress or corticosteroid administration. Chronic diseases commonly result in a reduction of the lymphocyte count, which may be under 1000/μL during severe systemic stress. The monocyte is not particularly responsive to disease in horses,[1] but the blood monocyte generally decreases acutely and may increase above normal during chronic inflammatory diseases, especially those associated with tissue necrosis.

25.6 APPROACH TO INTERPRETATION OF THE LEUKOGRAM IN RUMINANTS

The general trend is for the WBC count to be higher in calves through 2 years of age and then decline with advancing age. Sheep and goat leukocyte counts increase through 2 to 3 months of age, then decline in adulthood to levels seen at birth. In cattle and sheep, neutrophils exceed lymphocytes at birth, but the ratio is reversed within the first week of life, and this ratio persists as a species characteristic. A reduction in the number of lymphocytes without similar changes in neutrophils produces an N/L ratio near unity in goats over 3 years of age.

Acute inflammatory disease and infection in cattle (e.g., neonatal septicemia, salmonellosis, enteritis, metritis, and coliform mastitis) cause a rapid drop in the WBC count because of migration of mature neutrophils to the site of inflammation, margination of neutrophils, and stress-induced loss of lymphocytes. The bone marrow has a small reserve of mature neutrophils, and immature forms (bands, metamyelocytes) are released into the circulation, creating a degenerative left shift during the first 2 to 3 days of acute inflammation. By the fourth day bone marrow granulopoiesis usually has increased sufficiently to meet the tissue demand for neutrophils, causing a normal leukocyte count with a left shift. If the inflammatory stimulus persists, a mature neutrophilia may develop. Generally the N/L ratio increases without leukocytosis. Severe systemic toxemia or chronic infections (or both) may cause granulopoietic depression and neutropenia.

Approximately 30% of cattle infected with BLV develop a benign persistent lymphocytosis, defined as an absolute blood lymphocyte count over 3 standard deviations above the normal mean for at least 3 months. Although these cells are BLV infected, cattle with lymphocytosis are clinically normal, and most do not develop enzootic bovine lymphosarcoma (EBL).[8] Approximately 50% of cattle with EBL have a mild-to-moderate lymphocytosis, and leukemia is present in 10% to 30% of cases.[1] Lymphocytosis, usually attended by neutrophilia, occurs sometimes as a result of chronic pyogenic conditions such as liver abscess, pericarditis, pulmonary abscess, and traumatic reticuloperitonitis.

The leukogram changes in sheep generally are similar to those of cattle. Parturition and adverse weather conditions induce typical corticosteroid-induced neutrophilia, lymphopenia, and eosinopenia.

Goats differ from cattle and sheep in that the leukogram typically has an equal or slightly greater number of neutrophils than lymphocytes.[1] The total WBC count during inflammatory diseases may attain levels higher than 25,000/μL because of neutrophilia. A regenerative left shift is a common response to subacute or chronic inflammation. Leukopenia is rare.

An inherited syndrome characterized by marked neutrophilia and an increased susceptibility to bacterial infections has been recognized in Holstein-Friesian cattle under 2 years of age.[9] Affected calves have a history of anorexia, weight loss, and failure to thrive, with signs of chronic intermittent pneumonia and diarrhea. Lymphadenopathy, periodontitis, and generalized dermatitis are also features of the syndrome. The neutrophils of these animals are dysfunctional because of a single mutation in CD18 that causes a lack of surface glycoproteins, called β_2-integrins, that are important in cell adhesion processes.[10] Calves that are heterozygous for the defect do not have dysfunctional leukocytes compared with those of clinically normal calves.[11]

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26 Chapter 26 Alterations in Blood Proteins

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Janet K. Johnston

Proteins play an integral role in numerous physiologic processes. Not only are they important to the basic structural integrity of most body tissues, but as enzymes and hormones, they also regulate many of the body's biochemical reactions. Hemostasis, resistance to infection, and acid-base balance depend on protein metabolism. Plasma proteins also act as carriers for other plasma constituents, and albumin provides osmotic pressure to help maintain proper intravascular volume and prevent edema. Because of the central role proteins play in the body's homeostasis and the close relationship between plasma proteins and tissue proteins, much information about the body's response to disease can be obtained by measuring the total plasma protein and its fractions—albumin, the globulins, and fibrinogen.

Filtration between intravascular and extravascular space, metabolic demands, hormonal balance, nutritional status, and water balance determine the plasma protein concentration of an individual at any given time. Through colostrum absorption, passive transfer of immunoglobulins causes a rise in the total protein concentration of the newborn (see Chapter 53). With time, however, the passively absorbed immunoglobulin concentration declines through natural catabolic degradation. The rate of decline varies among species and classes of immunoglobulins. The time required to reach levels that are no longer protective depends on the initial concentration of the immunoglobulin. The total protein concentration also declines over the next several weeks, even though immunoglobulins are actively produced (Fig. 26-1). In adults the protein concentration remains relatively stable. Pregnancy alters plasma proteins because fetal development imposes additional stress on the dam's protein reserve,[1] and the concentration and response of each protein fraction to different stressors vary among species.[2,3] In general, however, albumin decreases and globulin (especially α_2-globulin) increases in response to stress.

Several methods are available for determining the concentration of serum or plasma protein. The biuret test is a simple colorimetric technique that has been widely adapted for use in automated chemical analyzers. It is highly specific for protein, especially in the range of 1 to 10 g/dL. Unfortunately the biuret technique is not precise enough for evaluation of very low levels, such as those found in cerebrospinal fluid. Refractometry is a useful method for rapidly determining the protein level in serum, plasma, or other body fluids because the refractive index of a solution is proportional to its protein concentration. Mild hemolysis or icterus of a solution does not interfere with its accuracy; however, turbid or lipemic solutions may alter the transmission of light and provide inaccurate results.

The concentration of the total plasma protein and of the individual fractions varies among species (Table 26-1). When a dysproteinemia is suspected, the total plasma (or serum) protein concentration, albumin-to-globulin (A/G) ratio, serum protein electrophoresis (SPE) results, and plasma fibrinogen concentration should be evaluated. The A/G ratio can easily be calculated from most automated serum chemistry profiles. Changes in the A/G ratio often are the first indication of dysproteinemia. Because this method of albumin measurement can be inaccurate when values are markedly low,[4] the A/G ratio is most accurately obtained from serum protein electrophoresis.

When the practitioner is confronted with dysproteinemia, SPE is necessary to quantitate the individual protein fractions that make up the total. Fig. 26-2 shows normal equine and bovine SPE results. Albumin is identified as a discrete molecular compound by a sharp, narrow-based peak nearest the anode. The sharpness of the albumin peak is a measure of the quality of the SPE procedure and is used to differentiate polyclonal globulin peaks. The α-, β-, and γ-globulins form broad-based peaks during their migration in the electrical field, and, depending on the species, one or two types of the individual fraction normally are present.

26.1 HYPERPROTEINEMIA

Hyperproteinemia can result from an elevation in the concentration of all plasma proteins (panhyperproteinemia) or an absolute increase in globulins (hyperglobulinemia) (Boxes 26-1 and 26-2).

26.1.1 Panhyperproteinemia

An increase in the concentration of all blood proteins most commonly results from loss of the fluid component of the blood. Dehydration (decreased fluid intake or excessive fluid loss or both) causes hyperproteinemia with an associated increase in packed cell volume (PCV); however, a dehydrated, anemic animal will have hyperproteinemia with a normal or subnormal PCV. The A/G ratio will be normal. In large animals a total plasma protein concentration above 8 g/dL can be expected with severe dehydration. Initially dehydration causes withdrawal of tissue fluid into the intravascular space as the body attempts to maintain adequate blood volume. As dehydration proceeds, intravascular fluid is lost; hemoconcentration results, with a relative increase in total protein and progressive peripheral circulatory failure. If renal function is adequate, urine concentration increases and output decreases in an attempt to compensate for the fluid loss; water is absorbed from the gastrointestinal (GI) tract, assuming that GI function is normal.

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Fig. 26-1 Immunoglobulin in foal serum during the first 15 weeks of life. From Tizard I: *Veterinary immunology*, ed 3, Philadelphia, 1987, Saunders.

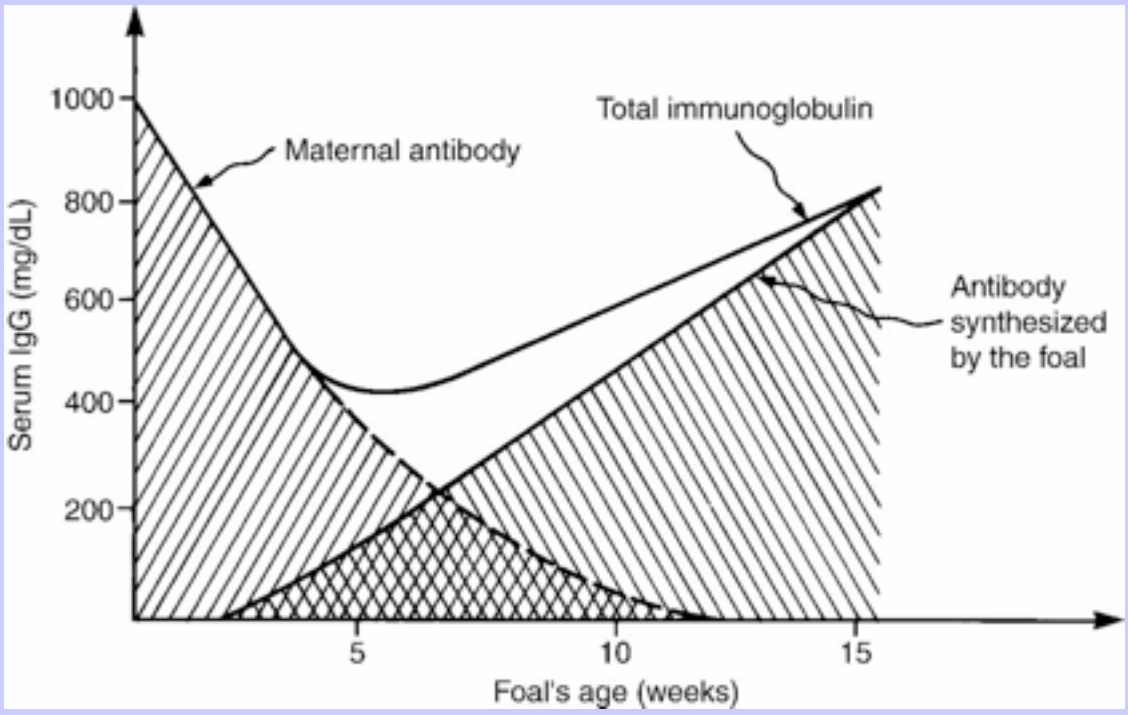

Table 26-1 Normal Serum Protein Values for Horses, Cows, Sheep, and Goats

	Value	Horse	Cow	Sheep	Goat
Total	g/dL	5.2-7.9	6.74-7.46	6-7.9	6.4-7
Albumin	g/dL	2.6-3.7	3.03-3.55	2.4-3	2.7-3.9
Globulin	g/dL	2.62-4.04	3-3.48	3.5-5.7	2.7-4.1
α_1	g/dL	0.06-0.7			
α	g/dL		0.75-0.88	0.3-0.6	0.5-0.7
α_2	g/dL	0.31-1.31			
β_1	g/dL	0.4-1.58	0.7-1.2		0.7-1.2
β	g/dL		0.8-1.12		
β_2	g/dL	0.29-0.89		0.4-1.4	
γ_1	g/dL		0.7-2.2		
γ	g/dL	0.55-1.9	1.69-2.23		0.9-3
γ_2	g/dL		0 .2-1.1		
A/G ratio		0.62-1.46	0.84-0.94		0.63-1.26
Fibrinogen	mg/dL	200-400	200-700	200-500	200-300

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A/G, Albumin to globulin ratio.

A decrease in fluid intake can result from unavailability of water, lack of thirst caused by depression or toxemia, or dysphagia.

In rare cases, polyuria with renal failure, exudation from extensive skin wounds, and excessive sweating can cause dehydration. Dehydration most commonly occurs after excessive fluid loss, especially from diarrhea. Other causes of increased fluid loss from the blood include fluid sequestration with an intestinal obstruction, vagal indigestion with internal vomiting, and grain engorgement.

Clinical signs of dehydration include tachycardia, an increase in the capillary refill time, and a decrease in pulse pressure, skin elasticity, and urine output. Improvement with appropriate fluid therapy is evidenced by improvement in clinical signs and a decrease in the PCV and the plasma protein concentrations. A decline in the plasma proteins while the PCV remains elevated often indicates protein loss into a third space (this occurs most commonly in horses with severe colitis) and is a poor prognostic sign. Massive plasma transfusions are indicated in such patients.

26.1.2 Hyperglobulinemia

Hyperproteinemia in a patient with apparently normal hydration usually is caused by hyperglobulinemia, because hyperalbuminemia is a result of dehydration. The most common cause of hyperglobulinemia is a generalized increase in γ-globulins (polyclonal gammopathy). This represents the activity of plasma cells in response to chronic antigenic stimulation. Chronic infection, abscess, amyloidosis, and neoplasia typically result in a generalized increase in γ-globulins. Some immunoglobulins (particularly IgM) migrate in the β-globulin region, and polyclonal increases in β-globulins usually are associated with an increase in γ-globulins. A concomitant decrease in albumin synthesis commonly occurs. Chronic hepatitis, hepatic abscess, and suppurative diseases are usually accompanied by an increase in the γ-globulin concentration. Immune-mediated disease processes (e.g., autoimmune hemolytic anemia and autoimmune thrombocytopenia), lymphosarcoma, and other tumors of the reticuloendothelial system typically demonstrate polyclonal increases in γ-globulin.

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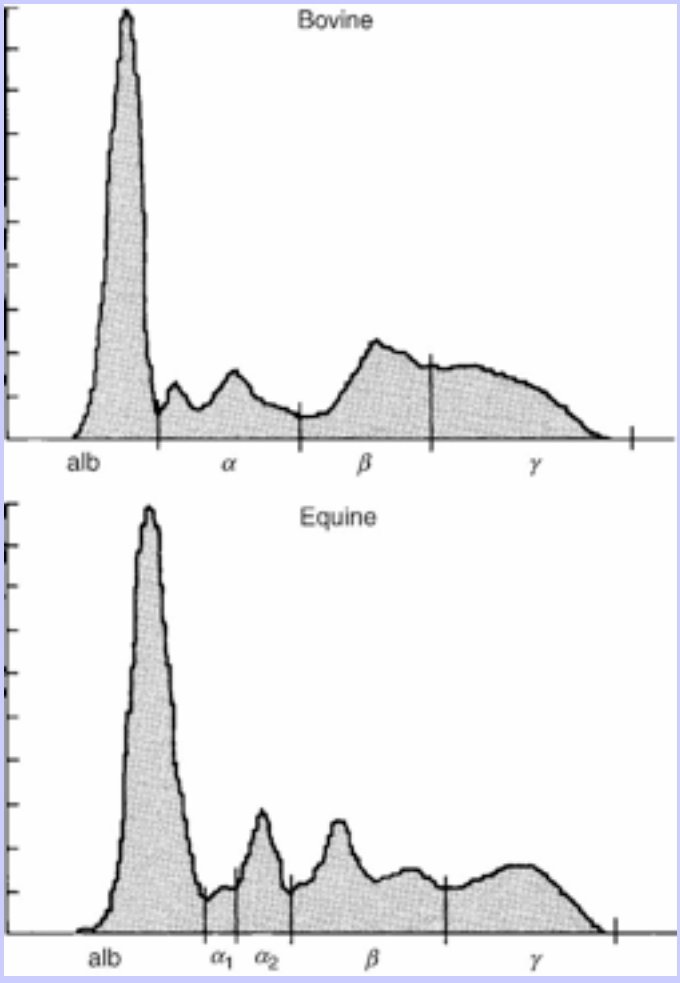
Fig. 26-2 Normal bovine and equine serum protein electrophoresis. *alb*, Albumin. Courtesy Dr. Dennis DiNicola, Purdue University, West Lafayette, Ind.



26.1.2.1

Box 26-1 Causes of Hyperproteinemia in Horses

26.1.2.1.1

PANHYPERPROTEINEMIA-DEHYDRATION

26.1.2.1.1.1

Common Causes

Acute toxic colitis of unknown cause

Acute salmonellosis

Potomac horse fever

Intestinal clostridiosis

Intestinal strangulating obstruction

Proximal enteritis

Gram-negative sepsis, endotoxemia

Botulism

Choking (esophageal obstruction)

26.1.2.1.1.2

Less Common Causes

Chronic renal failure

Chronic hepatic disease

Guttural pouch mycosis with dysphagia

Equine protozoal myelitis

Salt toxicity

Toxins, poisonous plants

Lead toxicity

Yellow star thistle poisoning (dysphagia)

Dysphagia of unknown cause

26.1.2.1.2 HYPERGLOBULINEMIA

26.1.2.1.2.1 Common Causes

Abdominal (mesenteric) abscess (including “bastard” strangles)

Pulmonary abscess

Chronic pleuritis

Purpura hemorrhagica

Equine infectious anemia

26.1.2.1.2.2 Less Common Causes

Chronic hepatic disease

Strongylosis

Lymphosarcoma

Immune-mediated cytopenia

26.1.2.2 Box 26-2 Causes of Hyperproteinemia in Ruminants

26.1.2.2.1 PANHYPERPROTEINEMIA-DEHYDRATION

26.1.2.2.1.1 Common Causes

Ruminal acidosis (grain overload)

Abomasal torsion

Acute salmonellosis

Peritonitis

Sepsis, toxemia (mastitis, metritis)

Intussusception

Vagal indigestion

Oral or pharyngeal foreign body with dysphagia

Coccidiosis

Diarrhea, undifferentiated

Salt toxicity

Toxins, poisonous plants

26.1.2.2.1.2 Less Common Causes

Renal amyloidosis

Lymphosarcoma

Johne's disease

Pregnancy toxemia

Rabies

26.1.2.2.2 HYPERGLOBULINEMIA

26.1.2.2.2.1 Common Causes

- Abdominal abscess (traumatic reticuloperitonitis, uterine tear, other)
- Chronic pneumonia
- Umbilical abscess
- Lymphosarcoma
- Caseous lymphadenitis (sheep and goats)
- Other abscess

26.1.2.2.2.2 Less Common Causes

- Parasitism
- Pregnancy

An abnormal increase in a single immunoglobulin class is known as *monoclonal gammopathy*. On SPE, the monoclonal peak is as sharp as or sharper than the albumin peak and is the result of a single clone of plasma cells producing an increased amount of immunoglobulin. Monoclonal gammopathies can be caused by multiple myeloma, lymphocytic leukemia, and other tumors of the reticuloendothelial system (e.g., lymphosarcoma). The clinical signs depend on the degree of organ involvement, plasma cell proliferation, and protein production. Increased susceptibility to infection can be expected as a result of decreased production of normal immunoglobulins, leukopenia, and/or impaired granulocyte function. Internal parasitism, especially strongylosis, may cause an associated β-globulin spike that does not usually cause hyperglobulinemia. An increase in both β- and γ-globulin fractions (β-bridging) can occur with intense antigenic stimulation, chronic active hepatitis, or lymphosarcoma.

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The α-globulins are divided into α_1 and α_2 fractions in most species except ruminants. α-Globulins are known as *acute-phase reactants* because their concentration rapidly increases after tissue injury or inflammation. α_2-Antiplasmin rapidly increases,[5] whereas ceruloplasmin[6] increases several days after the onset of inflammation.[7] An increase in C-reactive protein has been associated with pneumonitis, enteritis, and arthritis in horses.[8] The increase does not generally cause hyperglobulinemia.

26.2 HYPOPROTEINEMIA

26.2.1 Hypoalbuminemia

Hypoalbuminemia often exists despite normal total plasma protein levels. The three most common causes of hypoalbuminemia are a decrease in production, an increase in loss by the gut, and renal loss (Boxes 26-3 and 26-4).

Albumin is produced by the liver, has the lowest molecular weight, and is the most abundant of the plasma proteins, accounting for 75% of plasma osmotic activity. In addition to maintaining osmotic pressure, a major function of albumin is to bind and transport plasma components that do not have a specific transport protein. Hypoalbuminemia causes a decrease in the A/G ratio.

26.2.1.1 Box 26-3 Causes of Hypoproteinemia in Horses

26.2.1.1.1 HYPOALBUMINEMIA

26.2.1.1.1.1 Common Causes

Parasitism

Glomerulonephritis

Pyelonephritis

Idiopathic granulomatous enteritis

Intestinal lymphosarcoma

Parasitism

Salmonellosis

Equine ehrlichial enterocolitis (Potomac horse fever)

Colitis X

Clostridiosis

Nonsteroidal antiinflammatory drug toxicosis

26.2.1.1.1.2 Less Common Causes

Chronic hepatic fibrosis (pyrrolizidine alkaloid toxicity and other causes)

Hepatic neoplasia

Chronic hepatitis

Amyloidosis

Tuberculosis

Histoplasmosis

Chronic eosinophilic gastroenteritis

Starvation

26.2.1.1.2 PANHYPOPROTEINEMIA

26.2.1.1.2.1 Common Causes

Excessive fluid therapy or water intake

Acute blood loss

Gastrointestinal ulceration

Strangulating gastrointestinal obstruction, infarction

Protein-losing enteropathy (chronic granulomatous bowel disease)

Acute severe peritonitis

Nonsteroidal antiinflammatory drug toxicity

Glomerulonephritis

26.2.1.1.2.2 Less Common Causes

Blood-sucking gastrointestinal or external parasites

Intestinal lymphosarcoma

Urinary blood loss

Congenital vascular disorders:

Renal trauma

Renal calculi

Pyelonephritis

Neoplasia

Cystic calculi

Disseminated intravascular coagulation

Immune-mediated thrombocytopenia

Congestive heart failure

26.2.1.2 Box 26-4 Causes of Hypoproteinemia in Ruminants

26.2.1.2.1 HYPOALBUMINEMIA

26.2.1.2.1.1 Common Causes

Protein malnutrition, starvation

Amyloidosis

Pyelonephritis

Glomerulonephritis

Salmonellosis

Johne's disease

Trichostrongylus infection

26.2.1.2.2 LESS COMMON CAUSES

Chronic liver failure

Intestinal lymphangiectasia

Intestinal lymphosarcoma

26.2.1.2.3 PANHYPOPROTEINEMIA

26.2.1.2.3.1 Common Causes

Excessive intravenous fluid therapy or water intake

Acute blood loss

Abomasal ulceration

Blood-sucking gastrointestinal or external parasites

Gastrointestinal ulceration

26.2.1.2.3.2 Less Common Causes

Ingestion of caustic chemicals

Strangulation, infarction of intestine

Congestive heart failure

	Pyelonephritis
	Urinary tract blood loss

Starvation, malnutrition, and chronic GI disorders that interfere with digestion and absorption may lead to inadequate provision of amino acid substrate for general protein production. Hypoalbuminemia often precedes the development of panhypoproteinemia with dietary protein deficiencies. In certain cases, diets that appear to be well balanced and to provide adequate protein nutrition may actually be inadequate in demanding conditions.

Although albumin is produced by the liver, synthesis does not usually decrease in acute liver disease. Chronic, diffuse liver diseases such as chronic hepatitis, fibrosis, and hepatic neoplasia may cause hypoalbuminemia. Because the half-life of albumin is prolonged in horses and cattle compared with that in dogs and humans,[9] hypoalbuminemia rarely occurs with large animal hepatic disease.[10] If it does, it often is accompanied by increases in β- and γ-globulins. Because these changes occur late in the course of the disease, they may be of more prognostic than diagnostic value.

Increased metabolic demands such as occur with fever, trauma, surgery, and neoplasia can lead to a state of negative nitrogen balance with excessive albumin breakdown. Chronic antigenic stimulation can also result in increased albumin catabolism to provide necessary amino acids for immunoglobulin production; however, this increased albumin catabolism typically does not result in a change in the total plasma protein concentration.

Excessive protein loss usually occurs through the urinary and GI tracts. Normally urine contains little or no protein, but transient physiologic proteinuria occurs with exercise, stress, convulsions, and excessive protein intake, as well as in neonates; however, none of these factors causes hypoproteinemia.

Clinically significant proteinuria consists primarily of albumin, resulting in subsequent hypoalbuminemia. Because of its small size and low molecular weight, albumin is readily filtered through defects in the glomerular basement membrane. Glomerulonephritis, amyloidosis, and less commonly pyelonephritis cause albuminuria, which may lead to hypoproteinemia.[7]

Protein-losing enteropathy refers to the excessive loss of plasma proteins into the GI tract, with resultant hypoproteinemia. The diagnosis of protein-losing enteropathy usually is made after ruling out protein loss through other routes (urine), increased protein catabolism, and inability to produce protein (liver disease). The clinically important mechanisms of GI protein loss are defective lymphatic drainage, increased mucosal permeability, exudation as a result of inflammation, and ulceration. In a study of horses with diarrhea, albumin was lower in horses that died than in those that survived.[11] Panhypoproteinemia eventually develops, especially when inflammation is a cause.

The most common cause of protein-losing enteropathy in the horse is idiopathic granulomatous enteritis.[12] Tuberculosis and histoplasmosis also cause “granulomatous changes.” Lesions are most commonly located in the small intestine, and weight loss results. Other causes of chronic protein-losing enteropathy in the horse include eosinophilic gastroenteritis, intestinal lymphosarcoma, and strongyle larval migrans. Salmonellosis, nonsteroidal antiinflammatory drug (NSAID) toxicity, and other causes of acute colitis and enteritis may result in hypoalbuminemia and a general loss of all plasma proteins. A decreasing plasma protein level that occurs with an elevated PCV indicates acute protein loss from the gut.

The most common cause of chronic protein-losing enteropathy in ruminants is Johne's disease. Hypoalbuminemia causes hypoproteinemia. *Trichostrongylus* infection, intestinal lymphangiectasia, and intestinal lymphosarcoma can cause a primary hypoalbuminemic hypoproteinemia.

Clinical signs of hypoalbuminemia include edema of the distal extremities, ventral body wall, and face. The albumin level generally must be below 1.5 g/dL in horses and below 1 g/dL in ruminants before these clinical signs occur. Pharyngeal and laryngeal edema may result in upper airway obstruction, necessitating a tracheostomy.

26.2.2 Panhypoproteinemia

Vigorous fluid therapy or excess water intake can cause dilution of the plasma proteins, with subsequent panhypoproteinemia. Panhypoproteinemia occurs most often in animals that have acute protein-losing colitis or enteritis and that are receiving intravenous fluid therapy. Similarly, animals that lose large amounts of sodium through diarrhea and then drink fresh water may become hyponatremic as a result of a relative water excess.

Acute blood loss results in loss of plasma proteins and a dilution of the remaining protein by rapid movement of interstitial fluid into the intravascular space to help maintain intravascular volume. This dilutional effect is intensified by the excess water intake that commonly occurs after acute blood loss. Acute hemorrhage resulting from trauma, severe epistaxis, or internal vascular rupture should be ruled out in a hypoproteinemic, anemic animal.

GI blood loss can result from abomasal or gastric ulcers, blood-sucking parasites (particularly *Haemonchus contortus* in ruminants), viral or bacterial infection, azotemia, neoplastic invasion, or exposure to caustic chemicals. NSAID toxicosis and strangulating GI obstructions and infarctions can result in mucosal necrosis and leakage of plasma proteins into the gut lumen. Although protein-losing enteropathy initially results in hypoalbuminemia, it eventually results in panhypoproteinemia.

Blood loss from the urinary tract can result from congenital vascular disorders, renal trauma, renal calculi, pyelonephritis, neoplasia, or cystic calculi. Coagulation dysfunction, such as disseminated intravascular coagulation (DIC) or immune-mediated thrombocytopenia, may cause blood loss by way of the GI or urinary tract.

Congestive heart failure may cause hypoproteinemia by a number of mechanisms. Extracellular fluid is diluted by the retained sodium and water, and plasma protein is lost into interstitial spaces, ascitic fluid, and the GI tract. Hypoproteinemia also can occur as a result of acute severe peritonitis with massive protein exudation, as is seen with a ruptured GI viscus.

26.3 ALTERATIONS IN PLASMA FIBRINOGEN

Fibrinogen is a large—molecular-weight protein produced by the liver. Its primary function is to serve as substrate for thrombin in the formation of fibrin during hemostasis. Fibrinogen, as an acute-phase reactant protein, increases its concentration during active inflammatory disease and is a useful marker in assessment of the inflammatory response.

26.3.1

Hyperfibrinogenemia

Plasma fibrinogen is nearly always increased during severe inflammatory conditions and may increase with milder inflammation that is not associated with leukocytosis or neutrophilia (Boxes 26-5 and 26-6). After surgical treatment for subchondral bone cysts and osteochondrosis desiccans, horses still had hyperfibrinogenemia 15 days after surgery.[13] Hyperfibrinogenemia generally occurs with infectious, suppurative, traumatic, and neoplastic diseases and subsides as the condition improves. Chronic inflammation is associated with hyperfibrinogenemia, but the degree of hyperfibrinogenemia is not always directly correlated with the severity of the disease. Fibrinogen is an especially useful indicator of inflammation in cattle because of their greater capacity to produce fibrinogen,[14] which is a more sensitive indicator of inflammation than the leukocyte count (see Table 26-1).

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26.3.1.1

Box 26-5 Causes of Hyperfibrinogenemia in Horses

Abscess (abdominal or other)

Chronic peritonitis

Pleuritis

Pneumonia

Osteomyelitis

Septic arthritis

Cholelithiasis

Neoplasia with inflammatory response

Vasculitis (equine purpura hemorrhagica)

Cellulitis

Gastrointestinal inflammation

Salmonellosis

26.3.2

Hypofibrinogenemia

A decrease in the fibrinogen concentration may result from increased consumption of fibrinogen or decreased synthesis. Severe, diffuse liver damage, such as occurs with severe pyrrolizidine alkaloid toxicity, causes a decrease in the fibrinogen concentration, whereas mild to moderate inflammatory liver disease can result in an increase in plasma fibrinogen. With DIC and fibrinolysis a decrease in the fibrinogen concentration would be expected; however, hypofibrinogenemia is not common in horses with DIC. Inflammatory disorders often are the cause of DIC, and a compensatory increase in production masks the increased consumption. In rare cases, rapid removal of fibrinogen from the circulation may occur as a result of primary hyperfibrinolysis. An erroneous finding of hypofibrinogenemia may result if the fibrinogen concentration is quantitated from samples containing clotted blood.

26.3.2.1

Box 26-6 Causes of Hyperfibrinogenemia in Ruminants

Acute mastitis, especially coliform

Abscess

Traumatic reticuloperitonitis, pericarditis

Salmonellosis

Gastrointestinal inflammation

Pyelonephritis

Endocarditis

Pleuritis

Pneumonia

Chronic peritonitis

Necrotic rumenitis

Lymphosarcoma

Septic arthritis

Cellulitis

Omphalophlebitis

Osteomyelitis

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27 Chapter 27 Alterations in the Clotting Profile

Debra Deem Morris

The minimum laboratory data needed to evaluate hemostasis in large animals are platelet count, plasma fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), and serum fibrin and fibrinogen degradation products (FDPs). Proper collection and preparation of blood samples are paramount in obtaining accurate results (see Chapter 23). If the laboratory does not have normal values for the species in question, plasma from two or more healthy animals should be collected and assayed in a similar manner for comparison. Table 27-1 shows some normal values that have been published.

27.1 THROMBOCYTOPENIA

Thrombocytopenia (a platelet count below 100,000/µL) is caused by one of three basic mechanisms: a decrease in the production of platelets, platelet sequestration, or a shortened platelet lifespan (Boxes 27-1 and 27-2). Reduced production of platelets is the result of a bone marrow abnormality such as infiltration by neoplastic tissue (myelophthisic disease) or aplastic anemia. Occasionally immune-mediated destruction of megakaryocytes causes selectively reduced platelet production. Familial myelofibrosis occurs in some lines of pygmy goats.

Splenomegaly that may occur in acute and chronic infections and in noninfectious inflammatory disorders causes platelet sequestration, although this does not generally predispose the animal to hemorrhage. Congestive splenomegaly occurs when venous outflow is occluded by intestinal displacements or congestive heart failure.

Shortened platelet lifespan is the most common cause of thrombocytopenia in large animals. Excessive consumption of platelets occurs with disseminated intravascular coagulation (DIC), overwhelming septicemia or endotoxemia, and, in rare cases, systemic vasculitides. Platelet destruction by immune-mediated mechanisms is a common cause of thrombocytopenia in horses. Viral and rickettsial diseases may cause consumption or immune-mediated thrombocytopenia (IMTP).

Platelets form the initial hemostatic plug, provide phospholipid and a surface for clot formation, and maintain vascular integrity. Thrombocytopenia is characterized by petechial hemorrhages on the oral, nasal, and/or vaginal mucous membranes and the nictitans, sclerae, and pinnae. Epistaxis, melena, hyphema, or hematuria may occur, although spontaneous hemorrhage is rare unless the platelet count drops below 10,000/µL. Prolonged bleeding from injections or wounds and a propensity to form hematomas with minor trauma are quite common when the platelet count drops below 40,000/µL.

Anemia and mild hypoproteinemia accompany significant, chronic blood loss. Other components of the hemostatic system also should be evaluated (e.g., PT, aPTT, and FDPs), because thrombocytopenia may be only part of a disseminated coagulopathy. Evaluation of a bone marrow specimen (aspirate, core) is necessary to document adequate megakaryocyte numbers if thrombocytopenia is the only laboratory abnormality *or* if pancytopenia is present.

27.2 PROLONGED PROTHROMBIN TIME

The PT is a measure of the extrinsic and common pathways of coagulation (Fig. 27-1). It becomes prolonged when the fibrinogen level drops below 100 mg/dL or with a marked deficiency (less than 50% of normal concentration) of prothrombin and/or clotting factors V, VII, and X. In addition to deficiencies of these factors, functional

abnormalities or factor inhibitors may be reflected by changes in the PT. The most common mechanisms for prolonging the PT are increased consumption of the relevant clotting factors or failure of the liver to produce these factors. Congenital afibrinogenemia in goats may prolong the PT.[1]

Increased factor consumption usually is caused by DIC, which also causes prolonged aPTT and thrombocytopenia(Boxes 27-3 and 27-4). Reduced production occurs as a result of hepatocellular disease or vitamin K deficiency. Vitamin K is necessary for hepatic production of factors II, VII, IX, and X. The action of vitamin K is inhibited by coumarin compounds, which may be found in moldy sweet clover hay or rodenticides. Coumarin derivatives (warfarin) sometimes are used therapeutically in horses.

Clinical signs of clotting factor deficiencies relate to the tendency for spontaneous hemorrhage (e.g., epistaxis, melena, hematuria) or prolonged bleeding after trauma, diagnostic procedures, or surgery. Hematomas or hemarthroses are common after minor trauma or normal exercise. The clotting times are designed primarily for screening purposes and are very insensitive to minor abnormalities of one or more factors. Patients with mild bleeding tendencies may require more specialized diagnostic procedures.

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Table 27-1 Normal Values for Hemostatic Data in Ruminants and Horses

	Cattle	Sheep	Goats	Horses
Platelet count ($\times 10^{-3}$/L)	100–800	250–750	300–600	100–600
Fibrinogen (mg/dL)	200–500	100–500	100–400	200–400
Prothrombin time(s)	22–55	—*	9.5–12.5	7–9
Activated partial thromboplastin time(s)	44–64	—	28–52	37–54
Fibrin and fibrinogen degradation products (µg/mL)	<8	<8	—	<32

Modified from Duncan JR, Prasse KW, Mahaffey EA: *Veterinary laboratory medicine,* ed 3, Ames, 1994, Iowa State University Press; and Kaneko JJ: *Clinical biochemistry of domestic animals,* ed 4, San Diego, Calif, 1989, Academic.

* Insufficient data available

27.2.1

Box 27-1 Causes of Thrombocytopenia in Horses

27.2.1.1

COMMON CAUSES

Disseminated intravascular coagulation (DIC)

Immune-mediated thrombocytopenia (IMTP)

Endotoxemia, septicemia (e.g., acute toxic colitis, intestinal strangulating obstruction, neonatal septicemia)

Equine infectious anemia

Equine ehrlichiosis *(Ehrlichia equi)*

Lymphosarcoma

27.2.1.2 LESS COMMON CAUSES

Salmonellosis

Equine viral arteritis

Equine influenza

Myeloproliferative disease (myelogenous leukemia)

Plasma cell myeloma

Aplastic anemia

Stachybotryotoxicosis

27.2.2 Box 27-2 Causes of Thrombocytopenia in Ruminants

27.2.2.1 COMMON CAUSES

Disseminated intravascular coagulation (DIC)

Bracken fern *(Pteridium aquilinum)* toxicosis

Septic mastitis or metritis (endotoxemia)

27.2.2.2 LESS COMMON CAUSES

Salmonellosis

Gram-negative sepsis

Trichloroethylene-extracted soybean meal

Lymphosarcoma

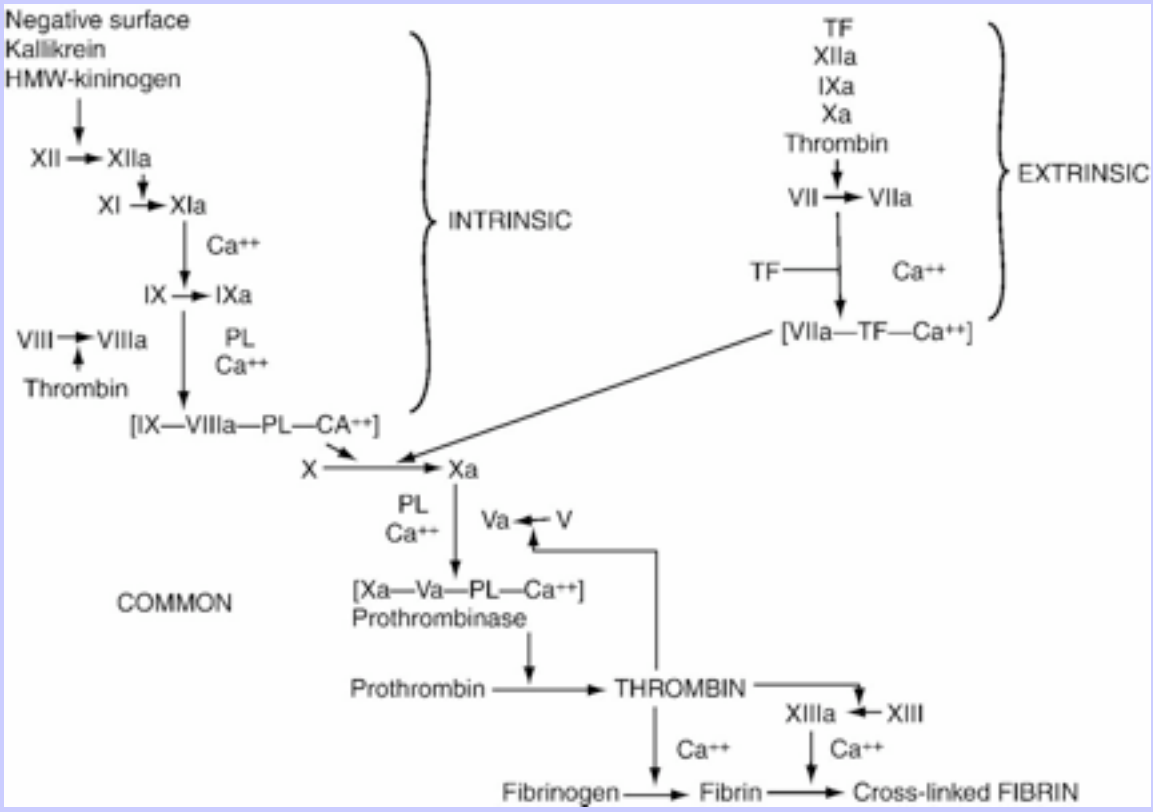
Plasma cell myeloma

Immune-mediated thrombocytopenia (IMTP)

Stachybotryotoxicosis

Myelofibrosis (pygmy goats)

Fig. 27-1 Coagulation pathways.



27.2.3 Box 27-3 Causes of Prolonged Prothrombin Time in Horses

27.2.3.1 COMMON CAUSES

Disseminated intravascular coagulation (DIC)

Rodenticide (warfarin) toxicosis

Acute hepatic necrosis

Pyrrolizidine alkaloid toxicosis

Aflatoxicosis

Chronic hepatic fibrosis

27.2.3.2 LESS COMMON CAUSES

Moldy sweet clover

27.2.4 Box 27-4 Causes of Prolonged Prothrombin Time in Ruminants

27.2.4.1 COMMON CAUSES

Moldy sweet clover (*Melilotus* species) toxicosis

Disseminated intravascular coagulation (DIC)

27.2.4.2 LESS COMMON CAUSES

Rodenticide (warfarin) toxicosis

Pyrrolizidine alkaloid toxicosis

Rubratoxicosis

Aflatoxicosis

Bitterweed *(Hymenoxys odorata)* toxicosis

Chronic hepatic fibrosis

27.3 PROLONGED ACTIVATED PARTIAL THROMBOPLASTIN TIME

The aPTT screens the function of the intrinsic coagulation pathway (see Fig. 27-1) and is sensitive to deficiencies or abnormal activity of factors VIII:coagulant (VIII:C), IX, XI, and XII. Insufficiencies of prekallikrein and high molecular weight kininogen may prolong the aPTT, depending on the thromboplastin reagent used in the assay. Thromboplastin in which ellagic acid is used as the activator will not demonstrate a prekallikrein deficiency because ellagic acid activates factor XII directly. Kaolin activates factor XII by means of prekallikrein. Of course, the aPTT is abnormal if deficiencies of factors in the common pathway exist. The activated coagulation time (ACT) is a simplified variation of the aPTT that can be tested by mixing whole blood with activator and calcium.

The most common cause of a prolonged aPTT is the increased consumption of clotting factors induced by DIC (Boxes 27-5 and 27-6). Liver failure and vitamin K deficiency prolong both the aPTT and PT, because factors II, IX, and X are tested by both. Inherited deficiencies of factors VIII,[2] IX, and XI[3] and prekallikrein[4] have been described in horses, and these are associated with prolonging the aPTT without affecting the PT. Congenital factor VIII deficiency is sex-linked, occurring only in males.[2,5] A mixed deficiency of intrinsic coagulation was reported in an aged horse with lymphosarcoma.[6] Inherited factor XI deficiency is transmitted in Holstein cattle by an autosomal recessive trait.[7]

27.3.1 Box 27-5 Causes of Prolonged Activated Partial Thromboplastin Time in Horses

27.3.1.1 COMMON CAUSES

Disseminated intravascular coagulation (DIC)

Warfarin toxicosis

Acute hepatic necrosis

27.3.1.2 LESS COMMON CAUSES

Moldy sweet clover toxicosis

Hemophilia A (deficient factor VIII:C)

Congenital deficiencies of factor IX, factor XI, prekallikrein, or high—molecular-weight kininogen

Hepatotoxins (pyrrolizidine alkaloids, rubratoxins, aflatoxins, bitterweed)

27.3.2 Box 27-6 Causes of Prolonged Activated Partial Thromboplastin Time in Ruminants

27.3.2.1 COMMON CAUSES

Moldy sweet clover toxicosis

Disseminated intravascular coagulation (DIC)

27.3.2.2 LESS COMMON CAUSES

Congenital deficiency of factor XI

Rodenticide (warfarin) toxicosis

Hepatotoxins (pyrrolizidine alkaloids, rubratoxins, aflatoxins, bitterweed)

Clinical signs of clotting factor deficiencies are those of hemorrhagic diathesis, as described in the previous section. Cattle deficient in factor XI seem to have complete in vivo coagulation competency. The level of factor VIII:C or factor IX must drop below 5% of normal before spontaneous bleeding occurs. Hemophilia A is a deficiency in factor VIII:C.

A disseminated coagulopathy should be manifested by several abnormalities in the coagulation profile, although variable use, synthetic rates, and the half-lives of clotting factors may result in abnormality of only one clotting time (PT *or* aPTT). Serial analyses should reveal a trend toward prolonged PT and aPTT, with dropping platelet numbers. When a persistently prolonged aPTT is the only laboratory abnormality, hereditary deficiency of one or more clotting factors should be suspected. Specific quantitative assays of intrinsic clotting factors usually are reserved for experienced coagulation laboratories.

27.4 ELEVATED FIBRIN AND FIBRINOGEN DEGRADATION PRODUCTS

Measurable levels of FDPs in the serum generally indicate increased fibrinolysis in response to excessive activation of coagulation (i.e., DIC) (Box 27-7). Severe inflammatory processes, hemorrhagic disorders, or postoperative states that cause extensive intravascular fibrin deposition may exceed the clearance capacity of the mononuclear phagocyte system (MPS) and elevate serum FDPs. Primary (spontaneous) hyperfibrinolysis has not been described in large animals.

Elevated serum FDPs contribute to the hemorrhagic manifestations of DIC by interfering with thrombin activity, fibrin monomer polymerization, and platelet function. Interpretation of this test depends on evaluation of the other components of the clotting profile (platelet count, PT, aPTT) in concert with the patient's clinical signs. A serum

FDP level above 40 µg/mL most often occurs secondary to DIC; however, values below 40 µg/mL do not exclude the diagnosis of DIC, because there may be considerable compensation by the MPS, degradation of FDPs, or both.

27.4.1

Box 27-7 Causes of Elevated Fibrin and Fibrinogen Degradation Products in Large Animals

27.4.1.1

COMMON CAUSES

Disseminated intravascular coagulation (DIC)

Thrombophlebitis

Postoperative state

Severe inflammation

Immune-mediated thrombocytopenia (IMTP)

27.4.1.2

UNCOMMON CAUSES

Massive internal hemorrhage

Primary hyperfibrinolysis

27.5

REDUCED PLASMA ANTITHROMBIN III

The physiologically most important inhibitor of coagulation is the α-globulin called *antithrombin III* (AT-III). This low—molecular-weight glycoprotein contributes up to 70% of the total procoagulant-inhibiting activity in plasma and can neutralize thrombin-activated factors IX, X, XI, and XII, kallikrein, and plasmin. Heparin is a necessary cofactor for the action of AT-III, causing a 200-fold acceleration of the interaction between the inhibitor and its substrates. Plasma AT-III may be reduced by failure of production in the liver, excessive use, loss from the intravascular compartment, or increased catabolism.

Chronic liver disease may result in failure to produce AT-III and a number of other important plasma proteins; however, horses with chronic liver disease were shown to have a higher than normal plasma AT-III level in addition to hyperfibrinogenemia.[8] These findings suggest that AT-III may behave as an acute-phase protein in horses, as has been shown in cats.[9]

In conditions such as DIC, AT-III is consumed as a result of irreversible binding to activated clotting factors. Any pathologic generation of thrombin and other activated clotting factors, such as can occur with trauma, neoplasia, or endotoxemia (all known initiators of DIC), would be expected to cause some reduction in plasma AT-III (Boxes 27-8 and 27-9).

27.5.1 Box 27-8 Causes of Reduced Antithrombin III in Horses

27.5.1.1 COMMON CAUSES

Disseminated intravascular coagulation (DIC)

Protein-losing enteropathy (e.g., granulomatous enteritis, intestinal lymphosarcoma, nonsteroidal antiinflammatory drug toxicosis)

Chronic glomerulonephritis

27.5.1.2 LESS COMMON CAUSES

Acute toxic enteritis

Acute hepatic necrosis

Starvation

Venous thrombosis

27.5.2 Box 27-9 Causes of Reduced Antithrombin III in Ruminants

27.5.2.1 COMMON CAUSES

Disseminated intravascular coagulation (DIC)

Renal amyloidosis

Johne's disease

27.5.2.2 LESS COMMON CAUSES

Starvation

Venous thrombosis

Hepatic failure

Diseases that cause massive proteinuria or protein-losing enteropathy result in reduced plasma AT-III, in addition to loss of other plasma proteins. Because of the small size of AT-III (molecular weight approximately 65,000), it is lost in approximately the same proportion as albumin. Starvation or sepsis resulting in massive protein catabolism may cause a reduction in plasma AT-III.

The major clinical sequela of AT-III deficiency is a tendency to develop venous thrombosis. A hypercoagulable state with nephrotic syndrome has been recognized in humans,[10] dogs,[11] and cattle.[12] Venous thrombosis is commonly recognized in horses with severe toxic colitis or endotoxemia; whether this involves AT-III is not known. The contribution of AT-III consumption in DIC to the clinical manifestations of this syndrome is difficult to evaluate; however, use of AT-III concentrates in human patients with acute DIC has improved survival in some circumstances.[8] As with all components of the hemostatic system, plasma AT-III must be evaluated in light of other clotting data.

27.6 HYPOFIBRINOGENEMIA

Hypofibrinogenemia may result from impaired hepatic synthesis, increased consumption with DIC, degradation during primary hyperfibrinolysis, or uncompensated loss during massive hemorrhage (Boxes 27-10 and 27-11). A reduction in plasma fibrinogen is rare under any circumstances in large animals. This protein is produced exclusively by the liver, and it functions as an acute-phase reactant, being rapidly released in response to a variety of inflammatory and procoagulant stimuli. The equine liver seems to have a remarkable reserve capacity to produce fibrinogen, because hypofibrinogenemia is a feature only of acute fulminant hepatic necrosis, which is attended by DIC. 420 421

27.6.1 Box 27-10 Causes of Hypofibrinogenemia in Horses

27.6.1.1 UNCOMMON CAUSES

Acute hepatic necrosis

Acute severe disseminated intravascular coagulation (DIC)

Severe hepatic fibrosis

27.6.2 Box 27-11 Causes of Hypofibrinogenemia in Ruminants

27.6.2.1 UNCOMMON CAUSES

Hereditary afibrinogenemia (goats)

Acute severe disseminated intravascular coagulation (DIC)

Hereditary afibrinogenemia has been recognized in a family of Saanen dairy goats.[1] This incompletely dominant trait causes a hemorrhagic diathesis in newborn kids that is characterized by umbilical bleeding, recurrent hemarthroses, and bleeding into the skin and mucous membranes. Heterozygotes have hypofibrinogenemia.

27.7 OTHER TESTS OF HEMOSTATIC FUNCTION

Other tests of hemostasis are performed less routinely in large animals because of lack of specificity or sensitivity, technical difficulty, or expense. Some of these tests may be useful in a particular disease situation.

27.7.1 Thrombin Time

The time required for a standard thrombin solution to clot plasma is a measure of the rate of fibrinogen to fibrin conversion. In large animals a prolonged thrombin time usually indicates the presence of FDPs that interfere with fibrin polymerization.

27.7.2 Factor Assays

(See previous discussion of prolonged aPTT.) For consumptive states such as DIC, factor analyses rarely provide significantly more information than the PT and aPTT. Factor VIII:C functions as an acute-phase reactant and may be increased by inflammatory disease. Specific factor analyses are indicated for the diagnosis of hereditary factor deficiencies.

27.7.3 Platelet Factor 3

The platelet factor 3 (PF_3) test is an indirect assay for the presence of serum antibodies directed against platelets. Because of its low sensitivity for the diagnosis of IMTP, it is no longer routinely available.

27.7.4 Plasminogen

The zymogen precursor of plasmin is reduced in the plasma during states that cause pathologic increased fibrinolysis such as DIC. Plasminogen levels have been explored in horses with colic.[13]

27.7.5 α_2-Antiplasmin

α_2-Antiplasmin (α_2-AP) a plasma glycoprotein, is the main physiologic inhibitor of fibrinolysis. In humans, α_2-AP is decreased by severe liver disease (reduced production) and with DIC (consumption). Limited experimental studies in ponies suggest that α_2-AP may be reduced significantly with chronic DIC.[14]

27.7.6 Fibronectin

The soluble form of fibronectin is a large glycoprotein that promotes clearance of plasma particulates by the MPS. Fibronectin initially is consumed by binding to fibrin breakdown products and platelet microaggregates; however, it is replenished rapidly in the acute-phase response. A persistently low fibronectin level is associated with a high mortality rate in humans with DIC.

27.7.7 Eicosanoids

During activation of coagulation, thromboxane A_2 (TxA_2) and prostacyclin are produced and released by platelets and endothelial cells, respectively. TxA_2 is a potent vasoconstrictor and aggregates platelets, whereas prostacyclin has the opposite effect. Plasma concentrations of thromboxane B_2 (TxB_2), the stable hydrolysis product of TxA_2, are elevated during acute, severe DIC in humans. Although not actually evaluated in DIC, both eicosanoids are increased in horses and cattle with endotoxemia.

27.7.8 Protein C

The protein C pathway provides the second major anticoagulant mechanism that regulates hemostasis. Protein C is activated by thrombin, then proteolytically destroys factors V and VIII. In humans, plasma protein C may be reduced by liver failure or by disseminated coagulopathy, inducing a tendency for thrombotic disease. The same may be true in horses.[13]

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28 Chapter 28 Collection and Analysis of Bone Marrow

Andrea A. Bohn

28.1 BACKGROUND

The hematopoietic system is composed of erythrocytes, leukocytes, and platelets, their precursor cells, and the tissues that support the continuous cycles of cell differentiation required for maintenance of oxygen delivery, protection from infectious agents, and hemostasis. A single pluripotent stem cell is the precursor for all hematopoietic cells. From this cell arise stem cells directed toward various cell lineages. Postnatally, hematopoiesis to replenish circulating erythrocytes, granulocytes, monocytes, and platelets predominantly occurs in the bone marrow. Although lymphocytic precursor cells continue to travel from the bone marrow to the thymic cortex and enteric mucosa for differentiation postnatally, most circulating lymphocytes are associated with the extramedullary lymphoid organs.

Constantly replenishing blood cells, the bone marrow is one of the most active tissues in the body. Blood cell turnover is rapid; for example, neutrophils have a circulatory half-life of approximately 10 hours. The lifespan of platelets, on average, is approximately 7 to 10 days, and the lifespan of large animal erythrocytes is approximately 5 months, with slightly shorter half-lives reported in some breeds.[1–3] Readers are referred to a veterinary hematology textbook for more in-depth information on the hematopoietic system.[4]

28.2 INDICATIONS FOR BONE MARROW ASPIRATION OR BIOPSY

Bone marrow evaluation provides important diagnostic information on the hematopoietic status of an animal; it is typically performed to evaluate hematopoiesis and to detect evidence of neoplastic or infectious disease (Box 28-1). The complete blood count (CBC) is the most common method used to evaluate the hematopoietic system, but a more comprehensive evaluation includes bone marrow aspiration and/or biopsy. Bone marrow aspiration is commonly used to evaluate the cause of cytopenia. Unexplained nonregenerative anemia, neutropenia, thrombocytopenia, and pancytopenia are indications for bone marrow aspiration. In these cases, bone marrow evaluation is used to determine if the cytopenia is more likely a result of lack of production or of consumption or destruction of the cell in question. If an animal's clinical presentation and other laboratory data provide a reasonable explanation for cytopenia, a decision to perform the procedure may not be justified. For example, if another disease process is present that could explain nonregenerative anemia, such as a chronic inflammatory disease or chronic renal failure, bone marrow aspiration is not indicated in most cases.

Another common reason for bone marrow aspiration is the observation of atypical cells, unexplained immature cells, or abnormal blood cell morphology on a peripheral blood film. In these cases bone marrow is evaluated for the diagnosis of leukemia, myelodysplastic syndromes, and infiltrative disease. Potential infiltrative disease is sometimes detected radiographically, and the presence of lytic or proliferative bone lesions can also be an indication for bone marrow aspiration. Because abnormalities within the bone marrow are not always reflected in the peripheral blood, it may be prudent to perform bone marrow aspiration if a neoplastic or infectious process is clinically suspected but cannot be found elsewhere. This suspicion may arise from detecting an unexplained hypercalcemia or monoclonal gammopathy, conditions that are often associated with neoplasia; identifying a fever of unknown origin; or recognizing the probability of an infectious agent that may have bone marrow involvement.

Even though complication rates are low, bone marrow aspiration should not be performed indiscriminately, and, as for all testing, the clinician should consider what question is being asked and if bone marrow evaluation is the appropriate diagnostic test for answering that question. Examination of a peripheral blood film often provides clues as to the necessity of bone marrow evaluation. In general, cytopenia should be persistent and confirmed before bone marrow evaluation is performed. Rechecking a low cell count by drawing a new blood sample, especially if initial results do not fit with the clinical presentation of the animal, is recommended. An ethylenediamine tetraacetic acid (EDTA)–associated pseudothrombocytopenia has been reported in horses,[5] which can be ruled out by drawing blood into a heparin or sodium citrate tube for platelet counts. A low platelet count can also be artifactual if platelet aggregation occurs during blood collection. The presence of clumped platelets on a peripheral blood film is an indication that platelet aggregation has occurred and that a low platelet count should be viewed with skepticism. Repeated CBCs can also be used to assess persistence of an abnormality. It can take up to 5 days for the bone marrow to respond to acute anemia and for regeneration to be evident in the peripheral blood. Bone marrow aspiration is typically not indicated when there is evidence of regeneration in the peripheral blood. Evidence of erythroid regeneration in the peripheral blood includes an increase in the number of reticulocytes or polychromatophilic cells, basophilic stippling, and macrocytosis. Because the changes typically associated with regenerative anemia are rarely seen in horses, bone marrow aspiration is often the only way to assess erythropoiesis in this species. Evidence of regeneration in granulocytes includes the presence of a left shift and toxic changes. 422

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28.2.1

Box 28-1 Indications for Bone Marrow Evaluation

To assess regeneration in anemic horses

To investigate cause of cytopenia

Unexplained nonregenerative anemia

Unexplained neutropenia

Unexplained thrombocytopenia

Pancytopenia

To investigate for neoplasia

Atypical cells in peripheral blood

Lytic or proliferative bone lesions

Hypercalcemia

Monoclonal gammopathy

To investigate for infectious disease

Fever of unknown origin

Lytic or proliferative bone lesions

Cytologic evaluation of a bone marrow aspirate is more commonly performed than core biopsy because results can be attained more quickly and the morphology of the cells is superior, allowing a more accurate assessment of cell types. The disadvantage of an aspirate versus biopsy is that architecture cannot be assessed with an aspirate and it can be impossible to confirm whether a poor cellular sample is a result of a pathologic process or an unsatisfactory sampling. The core biopsy provides a better assessment of bone marrow cellularity and is necessary for the confirmation of myelofibrosis, generalized bone marrow suppression, or necrosis. The core biopsy also provides a more accurate assessment of metastatic neoplasia because architecture can be assessed. When collecting a bone marrow sample for cytologic evaluation, some clinicians will also collect a core biopsy to store in formalin in the event that histologic evaluation is later recommended.

If a bone marrow sample is being submitted for evaluation, it is recommended to always submit a concurrent peripheral blood sample for a CBC because interpretation of the bone marrow is dependent on CBC results and changes can occur quickly in the blood.

28.3 BONE MARROW COLLECTION

28.3.1 Sites

Hematopoietically active bone marrow is most consistently found in the flat bones (sternum, ribs, pelvis, vertebrae) and proximal ends of long bones (humerus, femur). The most commonly described sites for bone marrow aspiration in large animals are the sternum, ribs, and iliac crest (Figs. 28-1 and 28-2). Which location is chosen may depend on species, age, and temperament of the animal as well as available facilities.

Fig. 28-1 Equine skeleton depicting sites for bone marrow aspiration: the sternum, iliac crest, vertebral ends of ribs *8* to *18*, and first lumbar vertebra.

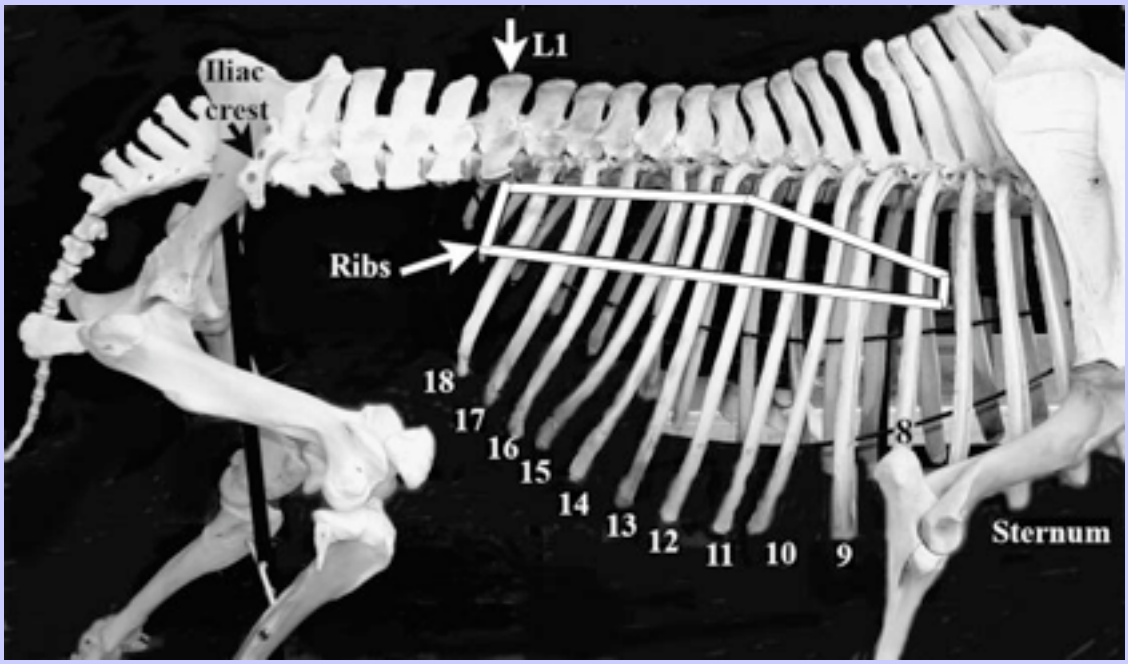


Fig. 28-2 Bovine skeleton depicting sites for bone marrow aspiration: the sternum and vertebral ends of ribs *8* to *11*.

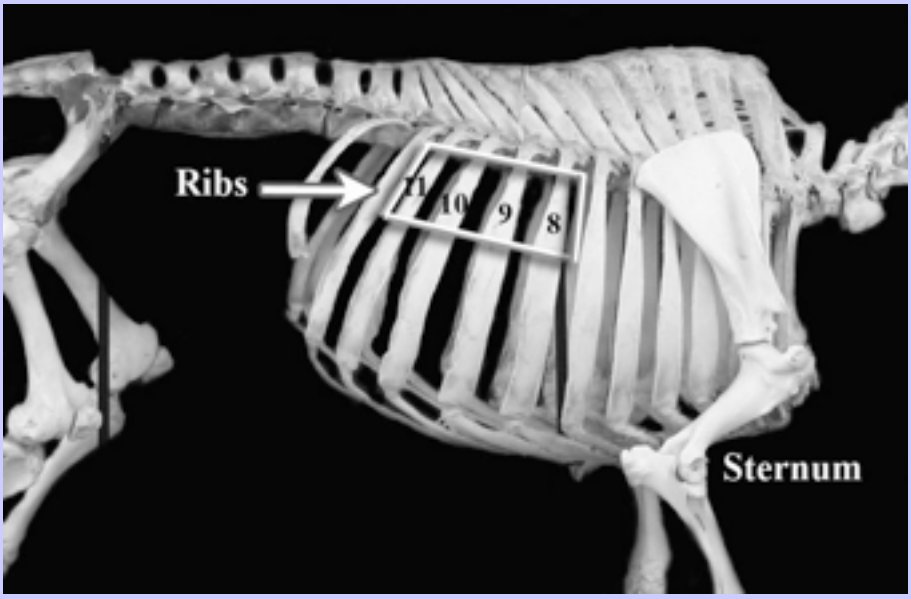
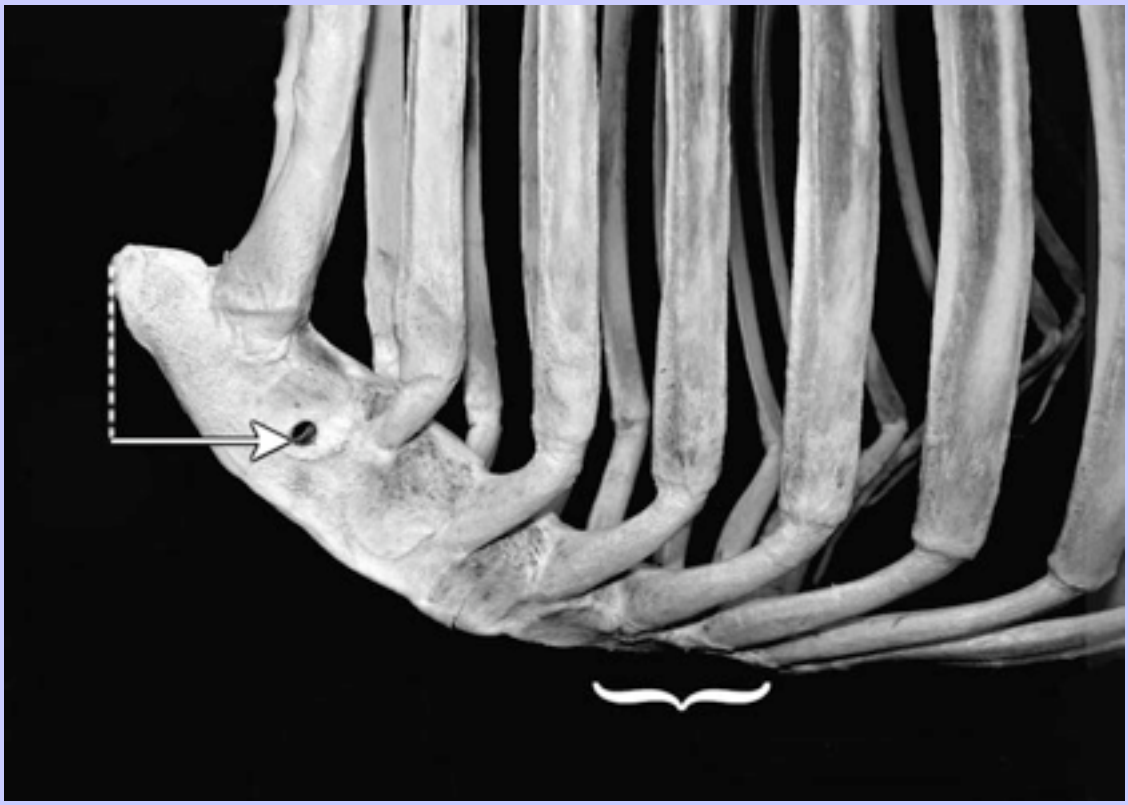


Fig. 28-3 Lateral view of equine sternum. The ventral sternum is the most popular site for sampling bone marrow in the adult horse *(bracket),* but the cranial sternum can also be used. The aspirate site of the cranial sternum is reached by going one hand width below *(dotted line)* and one hand width lateral to its cranial tip. From there, the needle is advanced in a horizontal plane at a 45-degree angle to the longitudinal axis of the horse *(arrow)*.



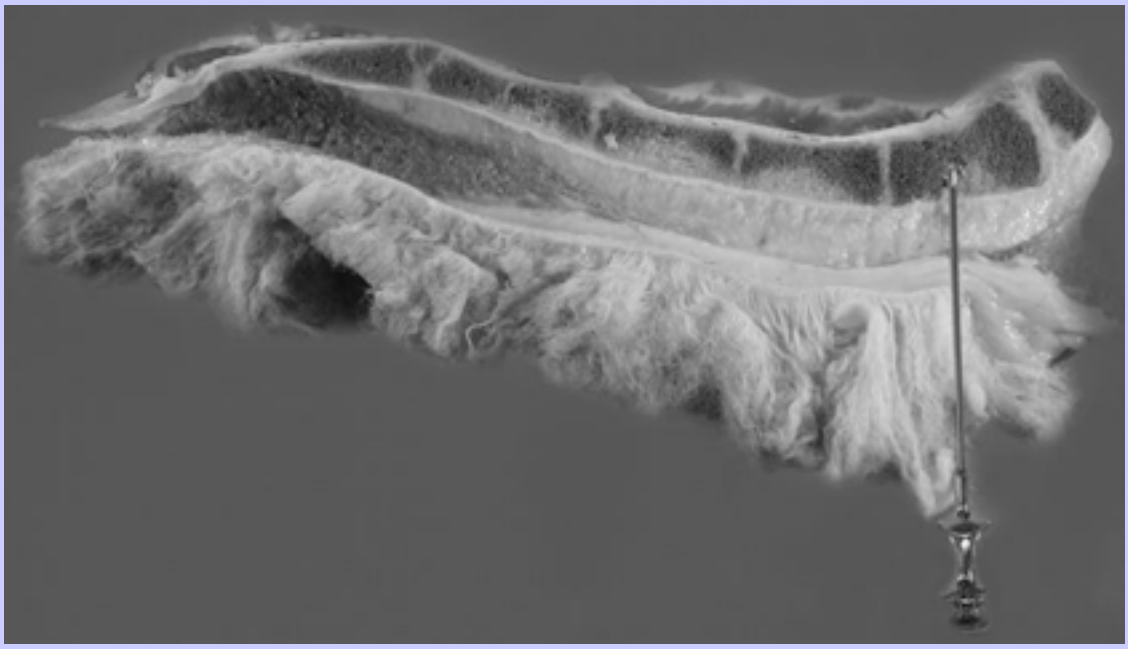
The ventral sternum is the preferred site in adult horses, small ruminants, and camelids (Figs. 28-3 to 28-6). It is one of the preferred sites in cattle (Fig. 28-7). The advantages of the sternum are that it is covered by only a thin layer of bone, it has areas not covered by thick muscles, and samples can be reliably obtained from the site. The disadvantages of the sternum are that it is near vital organs and that the operator is in an awkward position when working on a standing animal. A procedure for sampling the cranial aspect of the sternum has also been described in horses[6] (see Fig. 28-3). There is more muscle to go through with this approach.

The ribs are one of the preferred sites for bone marrow aspirates in cattle. The dorsal ends of ribs 8 to 11 can be accessed for sequential aspirations[7] (see Fig. 28-2). Ribs can also be used in the horse, but the needle slips off the bone more easily. In calves, sheep, and goats the marrow cavity of the rib is small and more difficult to hit,[8]

and in camelids the rib marrow is less consistent in location than the sternum.[9] Successful collection from ribs has been described in camels, with the fifth to eighth ribs as the best sites.[10] 423 424

Fig. 28-4 Ventral view of equine ribcage and sternum. *Arrows* depict optimal sites for sternal bone marrow aspiration or biopsy, on midline between the elbows of the horse.

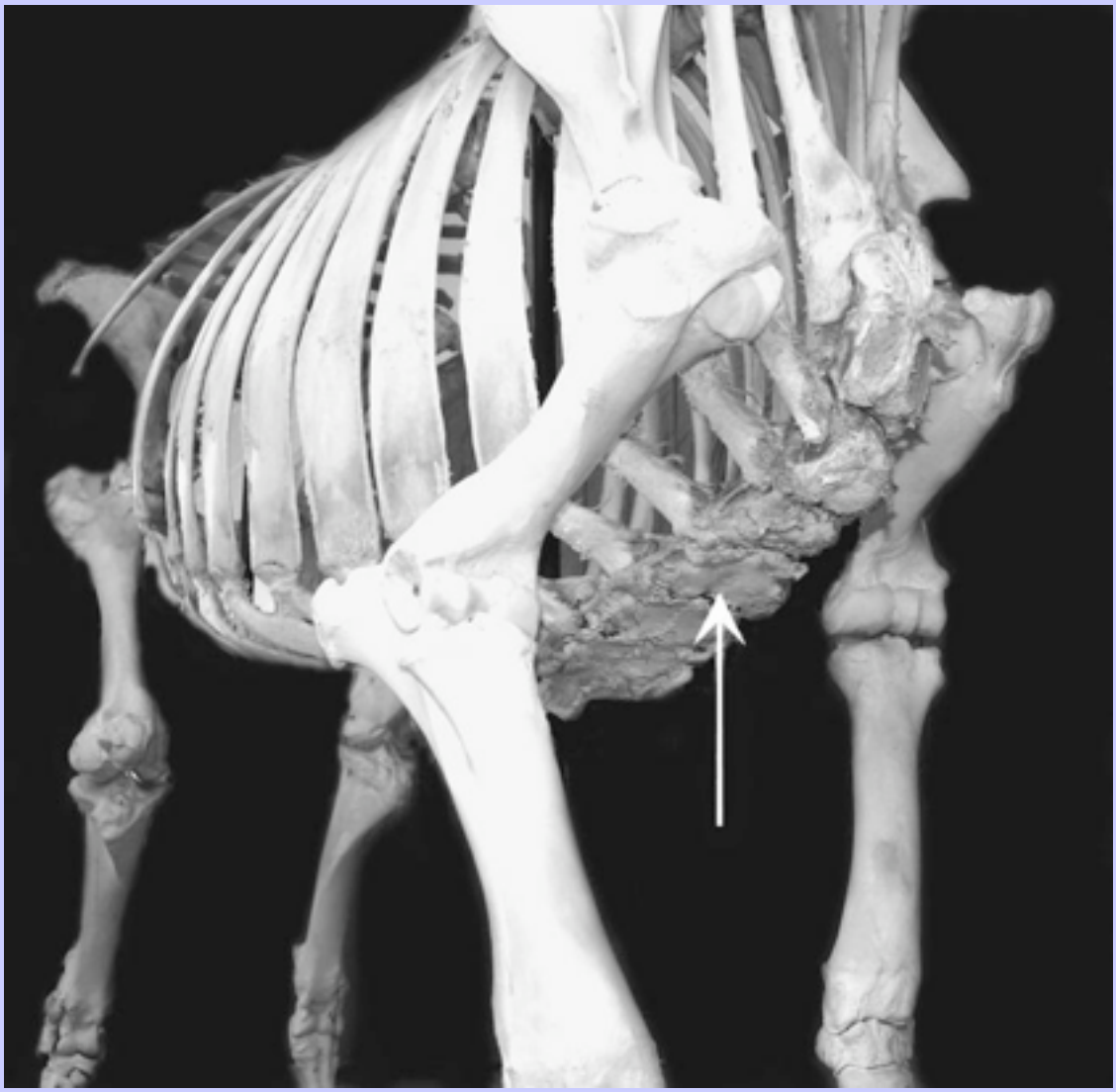
Fig. 28-5 Cross-section of sheep sternum. The needle is entering the second sternebra. The second through fourth sternebrae are recommended as optimal sites for bone marrow collection.



The iliac crest is the site often used in foals for bone marrow sampling and can also be used in young adult horses up to a couple of years in age[11] (Fig. 28-8). Samples can also be obtained from older horses at this site, but the needle must be inserted more deeply, needle placement is more critical, and it becomes difficult to obtain a successful sample in horses more than 9 years old.[12] The wing of the ilium is generally considered too thin for bone marrow aspiration in camelids,[9] although successful bone marrow aspiration from the iliac crest of a 2-year-old alpaca has been reported[13] (Fig. 28-9). The iliac crest can also be used in sheep (Fig. 28-10).

Fig. 28-6 Llama sternum. The llama sternum can be sampled at ventral midline, inserting the needle vertically through the callosity, or from a lateral approach, inserting the needle dorsal to the callosity.

Fig. 28-7 Bovine sternum. The third and fourth sternebrae are recommended for bone marrow collection. The *arrow* is pointing to the fourth sternebra.



Another site informally described for horses is the spinal process of the first lumbar vertebra (Fig. 28-11). It is usually vertical, whereas the adjacent processes tend to be more angled. The tip of the process is wider than the shaft and has a thin layer of bone. The needle is advanced straight down into the marrow cavity, which is narrow, but if the needle is close to correct placement, the walls of the process help guide the needle into the marrow cavity. The advantage of this site is that the operator is not working under the horse. The spinal process is reported to be a poor site to sample in the cow.[14]

Fig. 28-8 Equine pelvis. To obtain bone marrow, the needle should be placed near the center of the tuber coxae *(arrow)* and advanced toward the opposite coxofemoral joint *(dotted line)*.

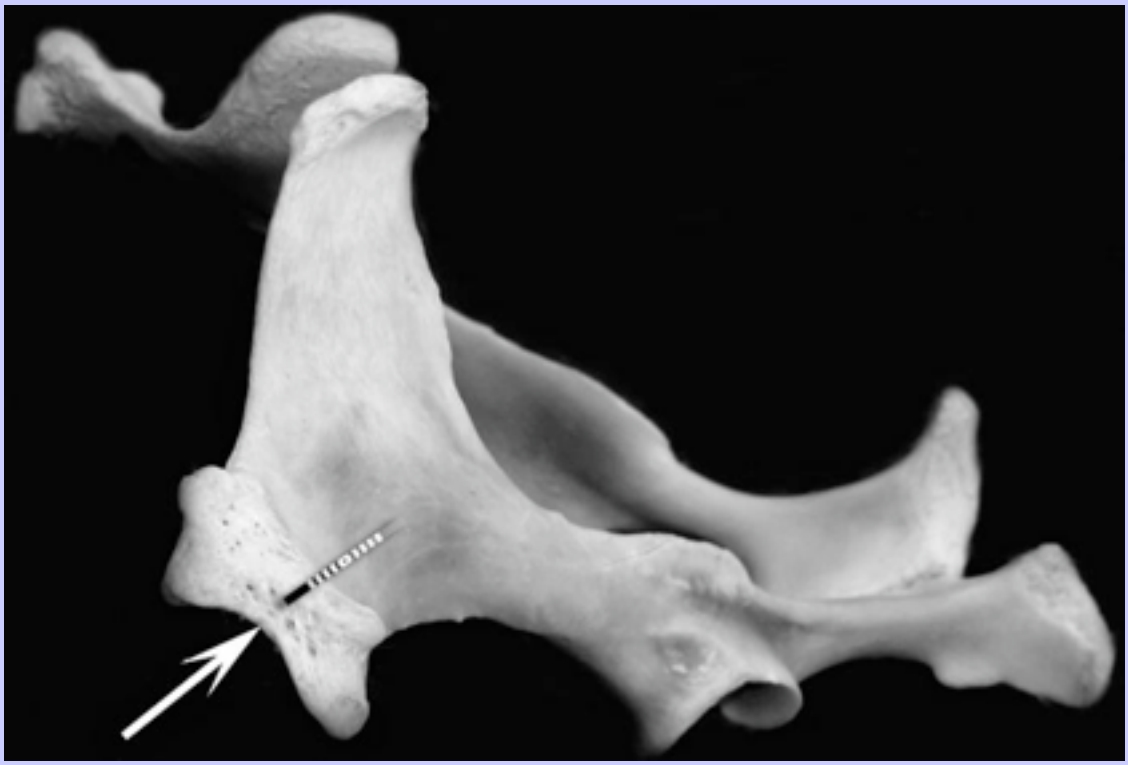


Fig. 28-9 Llama pelvis. The wing of the ilium *(arrows)* is generally considered too thin for easy bone marrow collection in camelids.

28.3.1.1

APPROACH TO THE STERNUM

In the horse, bone marrow aspiration is typically performed in the standing animal. Sedation or a twitch may be used if necessary. The preferred site is on the ventral midline in the cleavage between the deep pectoral muscles where a line connecting the points of the elbows would cross[15] (Figs. 28-4 and 28-12). The

manubrium of the sternum can also be sampled in horses by finding the cranial end of the sternum and going one hand width below and one hand width laterally from the end (see Fig. 28-3). From this spot the needle is advanced through the muscle in a horizontal plane at a 45-degree angle to the longitudinal axis of the horse.[6]

Sternal bone marrow can be sampled from adult cattle standing in stocks or a squeeze chute. It may be necessary to use techniques to prevent kicking, such as jacking the tail, or sedation. Unruly adult cattle and large calves can be cast and held in lateral recumbency. The upper front leg of the cast animal is held extended along the neck, exposing the sternum, after the other legs are secured with a rope.[16] Calves that weigh less than 300 lb can be placed in dorsal recumbency and secured by assistants or with ropes.[8] The needle should be placed on the midline and inserted perpendicular to the third or fourth sternebra. The appropriate sternebrae is located by palpating the third or fourth rib and following it to the sternum.

Fig. 28-10 Bone marrow aspirate from the ileum of a sheep. This sheep was undergoing necropsy, and the wing of the ileum has been dissected out.

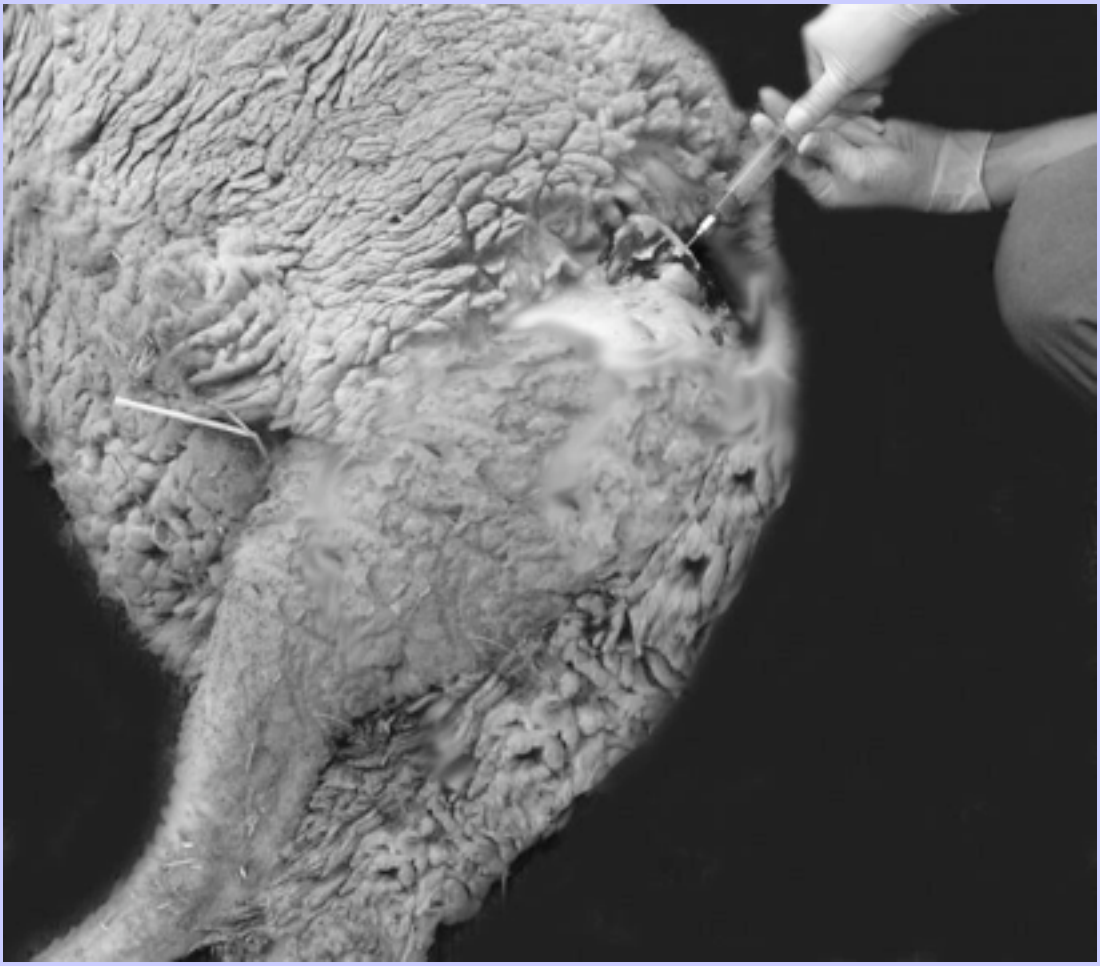
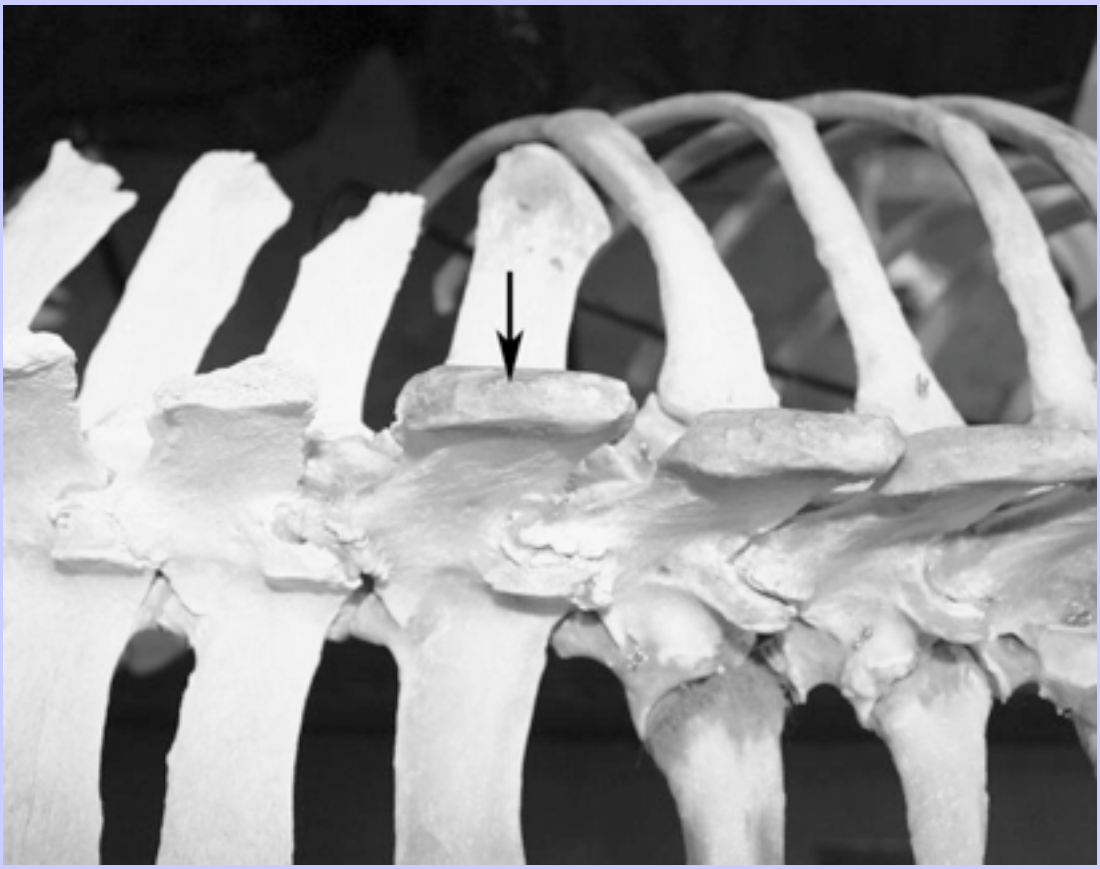


Fig. 28-11 First lumbar vertebra of a horse. Although not widely used, the spinal process of L1 *(arrow)* is another site from which bone marrow can be obtained in the horse.



For the sternum of a small ruminant to be sampled, the animal is placed in dorsal recumbency with legs secured, or it can be restrained in a sitting position with an assistant standing behind, supporting the animal and holding a foreleg in each hand.[8] The location of the appropriate site is midline, between the front legs. The second through fourth sternebrae can be used in sheep (see Fig. 28-5). A prominence may be felt between the first and second sternebrae. The appropriate sternebrae can also be located by palpating ribs and following them to their articulations.[17] In sheep, the needle will advance approximately 0.5 cm into the bone (2.5 to 3.8 cm from the skin) before entering the marrow cavity.[17]

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Fig. 28-12 Bone marrow aspiration in a horse. The animal was placed in a stock and sedated. **A,** The ventral sternum between the horse's elbows is clipped and surgically scrubbed. **B,** After local anesthetic, a stab incision is made on midline. **C,** A spinal needle is inserted to collect marrow.

The sternum of llamas can be sampled with the animal either standing in a chute or in left lateral recumbency, usually sedated[18] (see Fig. 28-6). The sample can be taken by inserting the needle vertically through the callosity on the ventrum of the sternum or with a lateral approach, approximately 3 to 4 cm dorsal to the callosity with the needle directed medially and slightly dorsally to engage bone.[9] Marrow will be approximately 2.5 cm deep in an adult. The sample is normally more dilute with blood than in other species.[9]

When the ventral sternum is sampled, unless a lateral approach is used, the needle should be placed on the midline, as near to the center of the bone as possible, and advanced perpendicular to the bone. A sudden reduction of resistance may be felt when the marrow cavity is entered, but because the sternal cortex is so thin, especially in horses, there may be no obvious change. Care needs to be taken to not enter the thoracic cavity. Because a change in resistance may not be felt, once the tip of the needle is firmly seated in the bone an aspiration attempt should be made.

28.3.1.2

APPROACH TO THE RIB

The vertebral end of the rib more consistently contains marrow than the sternal end of the bone[19,20] (Fig. 28-13). Palpation can be used to find the rib that has the least amount of fascia covering it. In the horse, the eighth to eighteenth ribs can be used, going as high as possible but below the latissimus dorsi and serratus posticus muscles[19] (see Fig. 28-1). In cattle, place the needle approximately 3 inches ventral to the ninth or

tenth costovertebral junction[14] (Figs. 28-2 and 28-14). The needle should be perpendicularly inserted at the middle of the rib, midway between the anterior and posterior borders (see Fig. 28-14, *A*). To help keep the needle from sliding off the bone, a scalpel can be first inserted until it touches the bone to be used as a guide.[11]

28.3.1.3 APPROACH TO THE ILIAC CREST

The iliac crest is often used in foals (see Fig. 28-8). The needle should be placed midway between the two tuberosities of the tuber coxae and somewhat toward its posterior border. With regard to angle, the needle should be pointing at the coxofemoral joint of the opposite side. Bone marrow will be hit when the needle is inserted approximately ⅛ inch for foals, whereas in adult horses bone marrow may be more than 2 inches deep. The main benefit of using this method is that there is no risk of inadvertently entering the thoracic cavity.[12]

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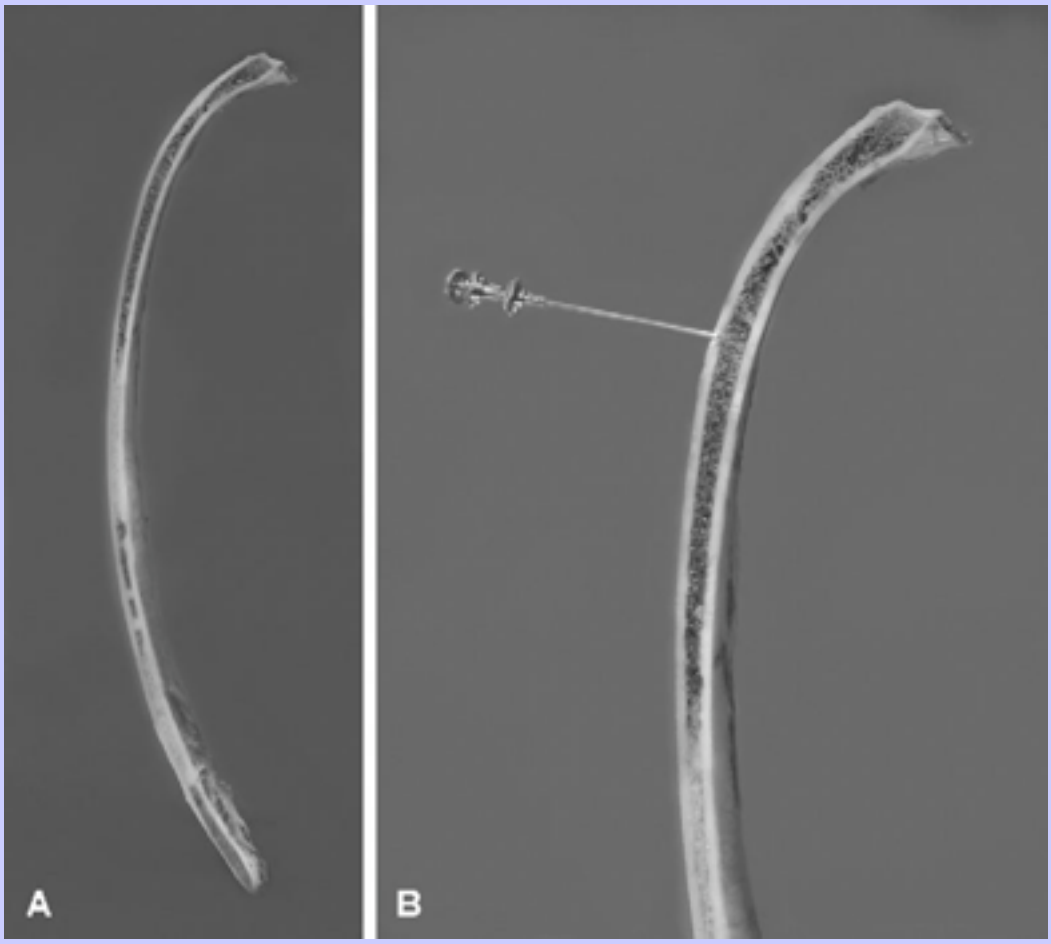
Fig. 28-13 Cross section of bovine rib 10. **A**, Bone marrow is more consistently present in the vertebral end. **B**, Rosenthal bone marrow needle is inserted into the rib approximately 3 inches below the costovertebral junction.



28.3.2 Preparation for Bone Marrow Aspiration or Biopsy

Bone marrow aspiration should be performed as a sterile procedure. After the animal has been restrained and the site of approach identified, hair should be clipped and the area surgically scrubbed (see Fig. 28-12, *A*). Local anesthetic is injected at the site where the needle will be inserted, from the skin to the periosteum (see Figs. 28-14, *B* and 28-15, *A*) A small stab incision is typically made with a scalpel to aid the needle's approach to the bone (see Fig. 28-12, *B*). If the rib is to be sampled, the scalpel blade can be held in place to act as a guide for the needle. It is important to be organized and have all supplies ready so that the procedure will flow smoothly and the sample will not clot before it can be processed (Box 28-2; Fig. 28-16).

How the sample will be ultimately handled will dictate some of the available supplies needed: glass slides, Petri dish, EDTA blood tubes, and/or anticoagulant. One option is to prime the syringe that will be used for aspirating the sample with anticoagulant. To prevent clotting, 1 to 2 mg of EDTA is recommended per milliliter of blood. One to two drops of a 3% to 15% EDTA solution should be adequate. The EDTA solution can be aspirated from a purple-topped blood tube. Priming the syringe with anticoagulant, although it adds a preparatory step, decreases the worry that the sample will coagulate and allows more time for processing the sample. If the syringe is not primed, as soon as the sample is seen in the syringe, the syringe needs to immediately be disconnected from the needle and the sample quickly processed before it has a chance to clot. If a reticulocyte count is to be performed to assess erythroid regeneration, supravital stains such as new methylene blue and brilliant cresyl blue, require mixing with a portion of anticoagulated, liquid sample before slides are made; therefore placing at least some of the bone marrow sample in an EDTA tube is recommended.

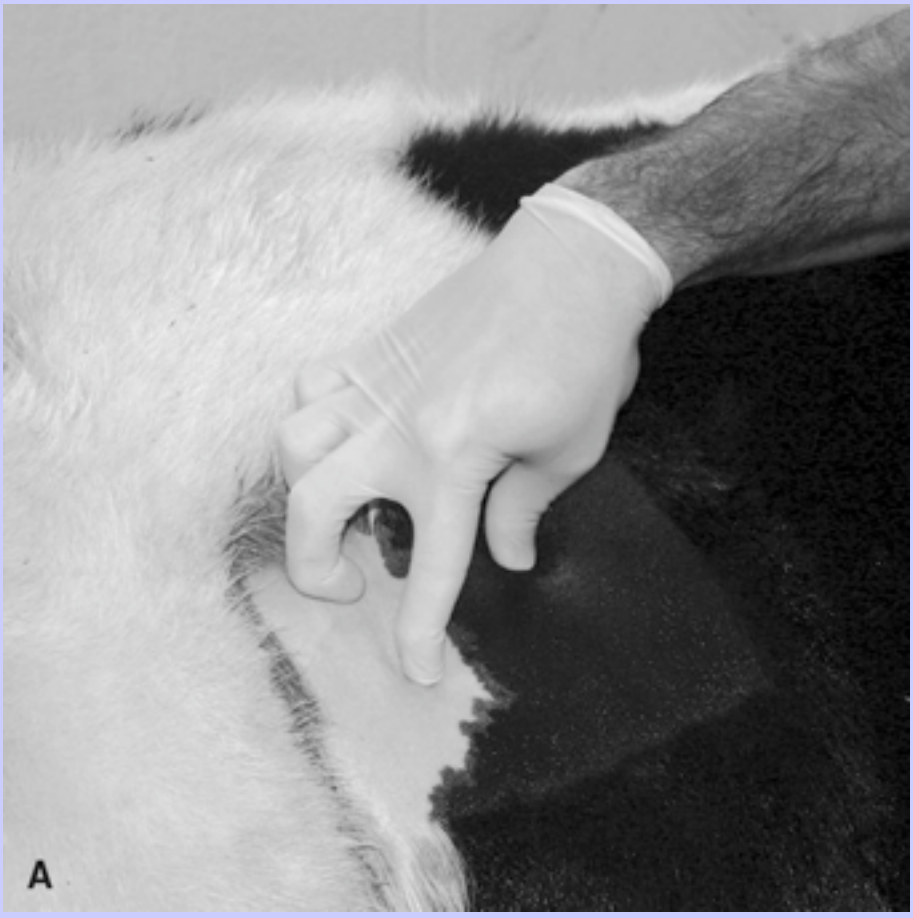
The sample in the syringe may be processed by expressing it directly onto several clean glass slides, into an EDTA blood tube, or into a Petri dish or watch glass. The Petri dish or watch glass must contain anticoagulant if no anticoagulant was used in the syringe. The anticoagulant commonly used is EDTA, which can be used in solution or as a salt, but other anticoagulants such as sodium citrate are also effective. Samples placed in an anticoagulant should be immediately gently mixed.

28.3.3 Collecting the Sample

The goal of bone marrow aspiration is to obtain a good sample of hematopoietic cells with minimal blood contamination. Anatomically, within the bone marrow, hematopoietic cells are extravascular and found in spaces dissected by venous sinuses and a central vein.[21] To collect the sample, a bone marrow or spinal needle with stylet should be used. Commonly used needles include Rosenthal, Illinois sternal-iliac, and Jamshidi bone marrow needles (Fig. 28-17). Some needles come with a guard that can be adjusted to prevent deeper penetration than desired. The needle used should be 16 gauge or larger and at least 1½ inches long. Larger needles may be needed, depending on the site of aspiration and the age and size of the animal.

After an animal has been properly prepared, the bone marrow needle is inserted through the skin, perpendicular to the bone (see Fig. 28-12, *C*). Once the needle contacts bone, it can be advanced using manual pressure and a clockwise-counterclockwise twisting motion (see Fig. 28-14, *C*). One hand can be used to stabilize the needle angle and placement while the other hand is on the needle hub pushing and turning the needle.[15] If the needle is going through dense bone, a wood mallet can also be used to advance it.

Fig. 28-14 Bone marrow aspirate of a cow. The animal was placed in a head-gate and sedated, and a tail jack was applied. **A,** The area over the vertebral end of rib 11 has been clipped and surgically scrubbed. The cranial and caudal edges of the rib are palpated approximately 3 inches down from the costovertebral junction, and the midpoint of the rib is identified for aspiration location. **B,** At the chosen aspiration site, lidocaine is injected from skin to periosteum. **C,** After a stab incision has been made and the Jamshidi-type bone marrow needle inserted through the skin, the needle is forcibly pushed forward through cortical bone as it is rotated in a clockwise-counterclockwise motion. **D,** After a decrease in resistance is felt, the stylet is removed. **E,** A syringe is attached to the needle, and a few sharp pulls on the plunger are needed before sample is noted in the hub of the syringe.



B

C

D

E

Fig. 28-15 Core bone marrow biopsy of a horse. The animal was placed in a stock and sedated; the ventral sternum between the elbows was clipped and surgically scrubbed. **A,** Lidocaine is injected from the skin to the periosteum. **B,** After a stab incision, the Jamshidi bone marrow biopsy needle is advanced into cortical bone. Here the stylet is about to be removed before the needle is advanced further. **C,** Core biopsy sample.

28.3.3.1

Box 28-2 Supply Check List for Bone Marrow Collection

Clippers

Surgical scrub

Lidocaine

Syringe and needle

Sterile gloves

Scalpel blade (No. 15 adequate)

Bone marrow needle

>16 gauge, 1½ inches

10- to 20-mL sterile syringe

Glass slides

Jar of formalin for core biopsy

Optional:

Anticoagulant

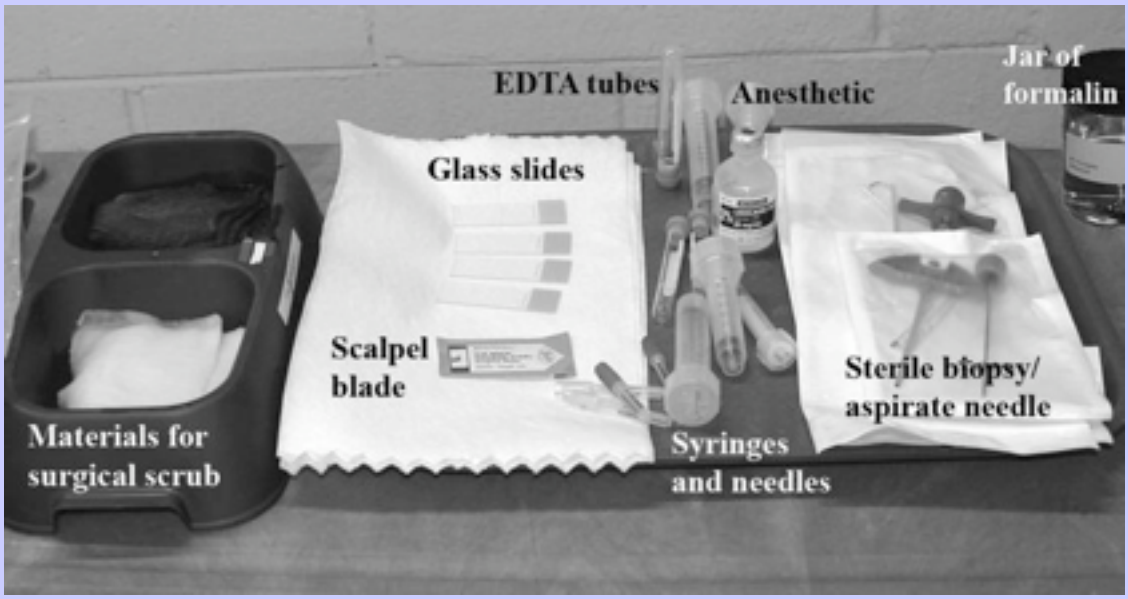
EDTA blood tubes

Petri dish or watch glass

EDTA, Ethylenediaminetetraacetic acid.

Once it is suspected that the needle has entered the marrow cavity, either because of detection of a sudden reduction in resistance or because of needle depth, the stylet should be removed and an aspiration attempted (see Fig. 28-14, *D*). In dense bone, pliers may be helpful in removing the stylet.[8] After the stylet is removed, a 10- to 20-mL sterile syringe is securely attached to the needle, and the plunger of the syringe is pulled back quickly and sharply, creating negative pressure in order to dislodge bone marrow particles (see Fig. 28-14, *E*). Suction can be repeated two or three times. As soon as blood is seen in the hub of the syringe, suction should be discontinued, the needle and syringe removed from the animal, and the sample processed promptly. Additional suction will likely only result in hemodilution of the sample. The first drop of blood is the most cellular, and further aspiration results in lower cellularity of the sample.[22]

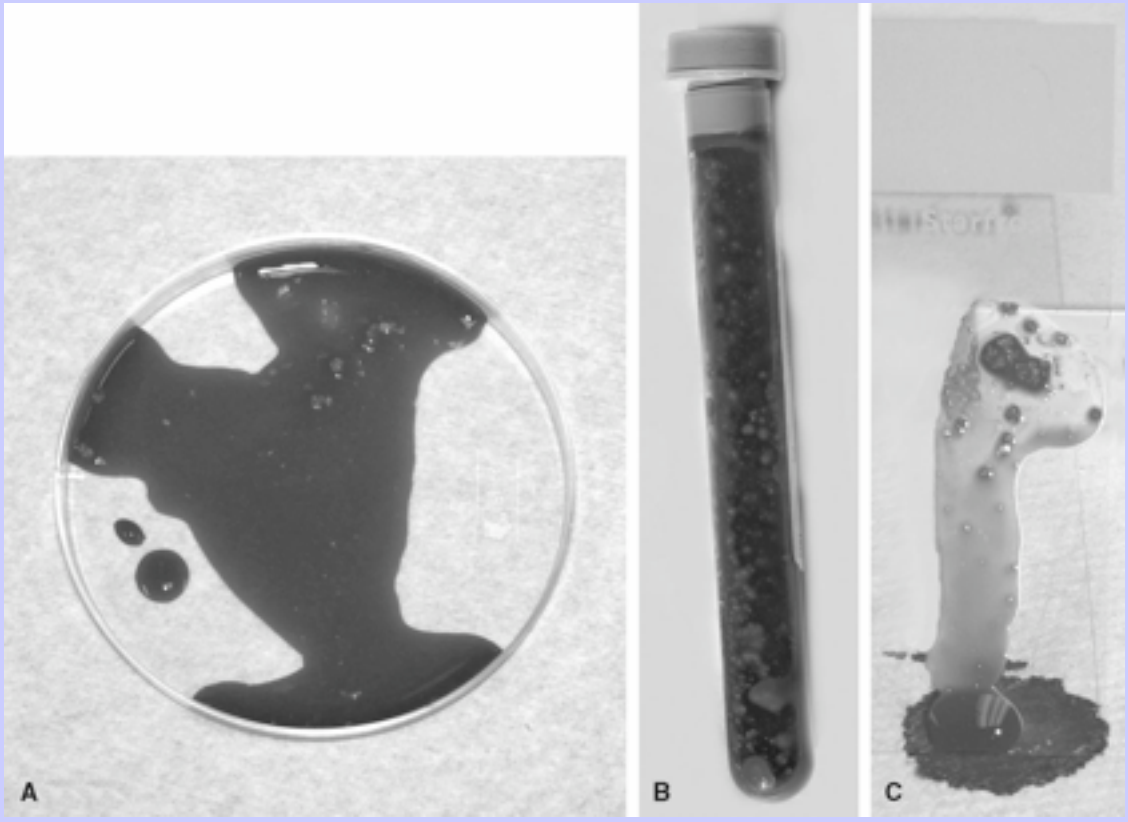
Fig. 28-16 Supply table is set up and ready for bone marrow aspiration. Sterile gloves were opened on an adjacent table.



If the initial aspiration does not obtain any material, remove the syringe, replace the stylet, and carefully advance the needle a little further. If still no sample is obtained after additional advancement of the needle and repeated suction, slowly withdraw the needle while applying suction to the syringe. Ultimately, repositioning the needle to a different site, such as moving a couple of centimeters cranially or caudally, may result in a successful aspiration.[9]

Fig. 28-17 Bone marrow needles with stylets separated. On the *left* is a 14-gauge, 2¾-inch Rosenthal needle. On the *right* is an 11-gauge, 4-inch Jamshidi needle.

Fig. 28-18 Bone marrow spicules (small grayish particles) should be seen in the aspirated sample. **A,** Particles can be picked out of background blood from a Petri dish. **B,** Particles can be seen adhering to the sides of an EDTA blood tube. **C,** Particles will adhere to a glass slide while excess blood runs off.



28.3.4 Processing the Sample

Whether the bone marrow sample is directly applied to glass slides or expressed into a Petri dish or watch glass, processing needs to proceed rapidly to prevent clotting or drying out of the sample. When on the slide, if the sample contains a lot of excess blood, the slide can be briefly tilted so that the fluid portion can run off into an absorbent surface, leaving behind adherent particles for spreading (Fig. 28-18, *C*; Fig. 28-19, *A*). If the sample is placed into an EDTA tube or Petri dish with anticoagulant, spicules (small grayish particles) can be transferred out of the bloody sample using a pipette and placed on a glass slide[23] (see Fig. 28-18).

To spread the sample on a slide, place a second glass slide flat on top of the sample, allowing the sample to form a thin layer between the slides (see Fig. 28-19, *B*). Without additional pressure other than the weight of the slide, gently pull the slides apart from each other horizontally and without vertical separation, which can create suction and rupture cells (see Fig. 28-19, *C*). This typically results in a nicely spread sample with intact particles and nice monocellular layers for evaluation. Several slides should be made. After slides are made, they should be

allowed to air dry, kept away from formalin fumes, and stored at room temperature until staining.

Some bone marrow slides are stained with a Romanovsky-type stain (Wright, Giemsa, Diff-Quick) for cytologic examination, and some should be left unstained in the event that special staining procedures are wanted. It is highly recommended to stain at least one slide right away for microscopic examination in order to determine sample quality and to make sure bone marrow elements are present while the animal is still available and prepped, in the event that the first aspiration is nondiagnostic and additional attempts will be needed (Fig. 28-20). If a hemodilute sample without spicules is obtained, it may be possible to acquire diagnostic information by centrifuging the sample in Wintrobe hematocrit tubes and making smears from the buffy coat. Staining for reticulocytes requires that an anticoagulated, liquid bone marrow sample be mixed and incubated with a supravital stain before slides are made.

Fig. 28-19 Making slides of a bone marrow sample. **A,** Excess blood is allowed to run off the slide onto an absorbent surface while the spicule stays adhered to the slide. **B,** A second slide is laid on top of the sample, causing the sample to spread out between the slides. **C,** The slides are horizontally pulled apart, then allowed to air-dry.

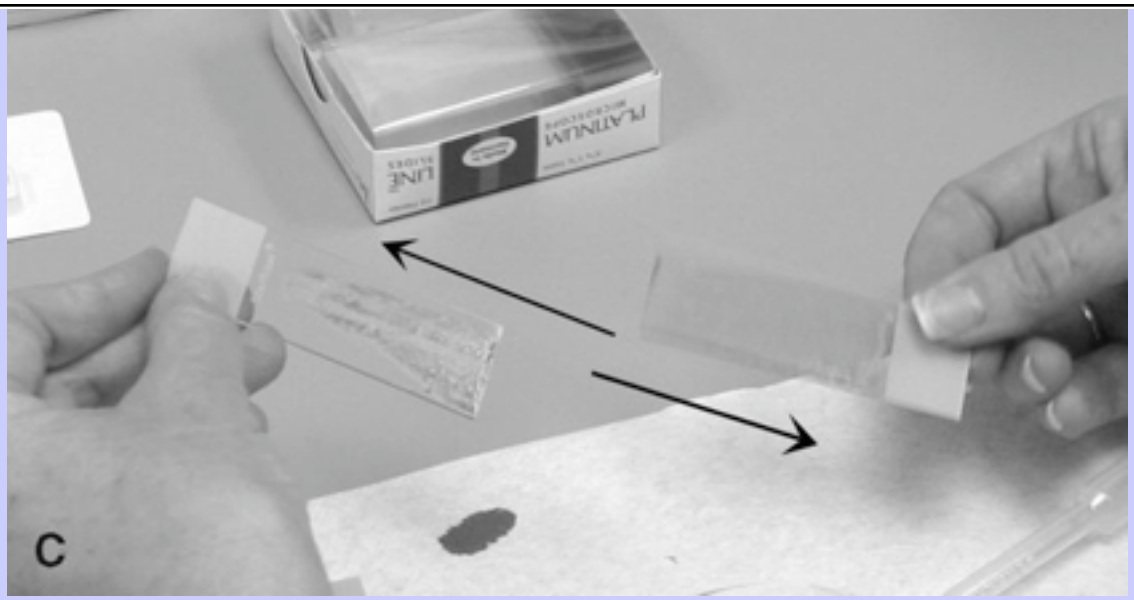
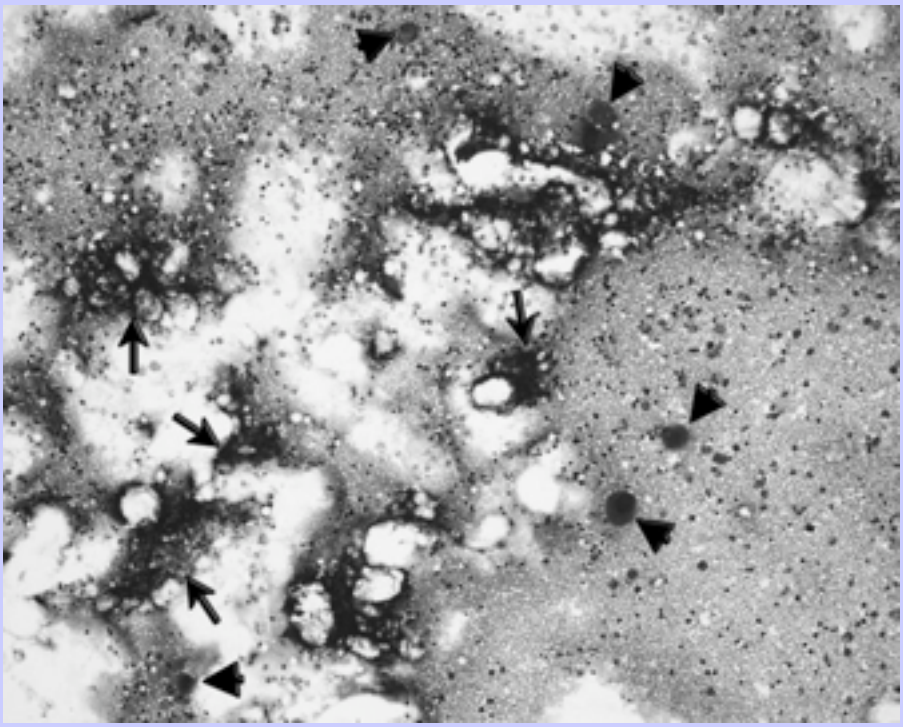


Fig. 28-20 Stained slide of adequate bone marrow aspirate sample. Megakaryocytes *(arrowheads)* and particles *(arrows)* are present. There is also increased cellularity compared with peripheral blood. (Wright-Giemsa stain, 10× objective.)



If a core biopsy sample is obtained, the tissue can be gently rolled on a slide to make an impression smear for

If a core biopsy sample is obtained, the tissue can be gently rolled on a slide to make an impression smear for cytologic evaluation. The biopsy tissue should then be placed in 10% neutral buffered formalin for preservation. A larger gauge needle (10 to 13 gauge) is generally recommended for core biopsy. The Jamshidi needle, designed so that the distal tip tapers to help retain the sample, is the most popular needle for biopsy. The needle and stylet are initially inserted as for aspiration. (see Fig. 28-15, *B*) Once the needle enters the bone marrow, the stylet is removed and the needle advanced further with the same twisting motion. Ideally, the needle is inserted at least an additional 1 to 2 cm, but this may be limited by location. After the needle is advanced to obtain the core, it is rotated and rocked forcibly to help break the core at its base for successful removal. Once the needle is removed from the animal, a probe is inserted into its lumen at the distal tip, pushing the sample out the hub end (see Fig. 28-15, *C*).

Often, bone marrow aspirates are placed into an EDTA blood tube for submission to an outside laboratory. In this case it is still recommended to make slides of the sample to submit along with the fluid sample. If the sample is left in the fluid phase, cells can deteriorate during transit, and it is always helpful for the cytologist to have a freshly prepared sample to examine (of both bone marrow and peripheral blood). In addition, a slide can be stained and evaluated for diagnostic quality before the sample is shipped.

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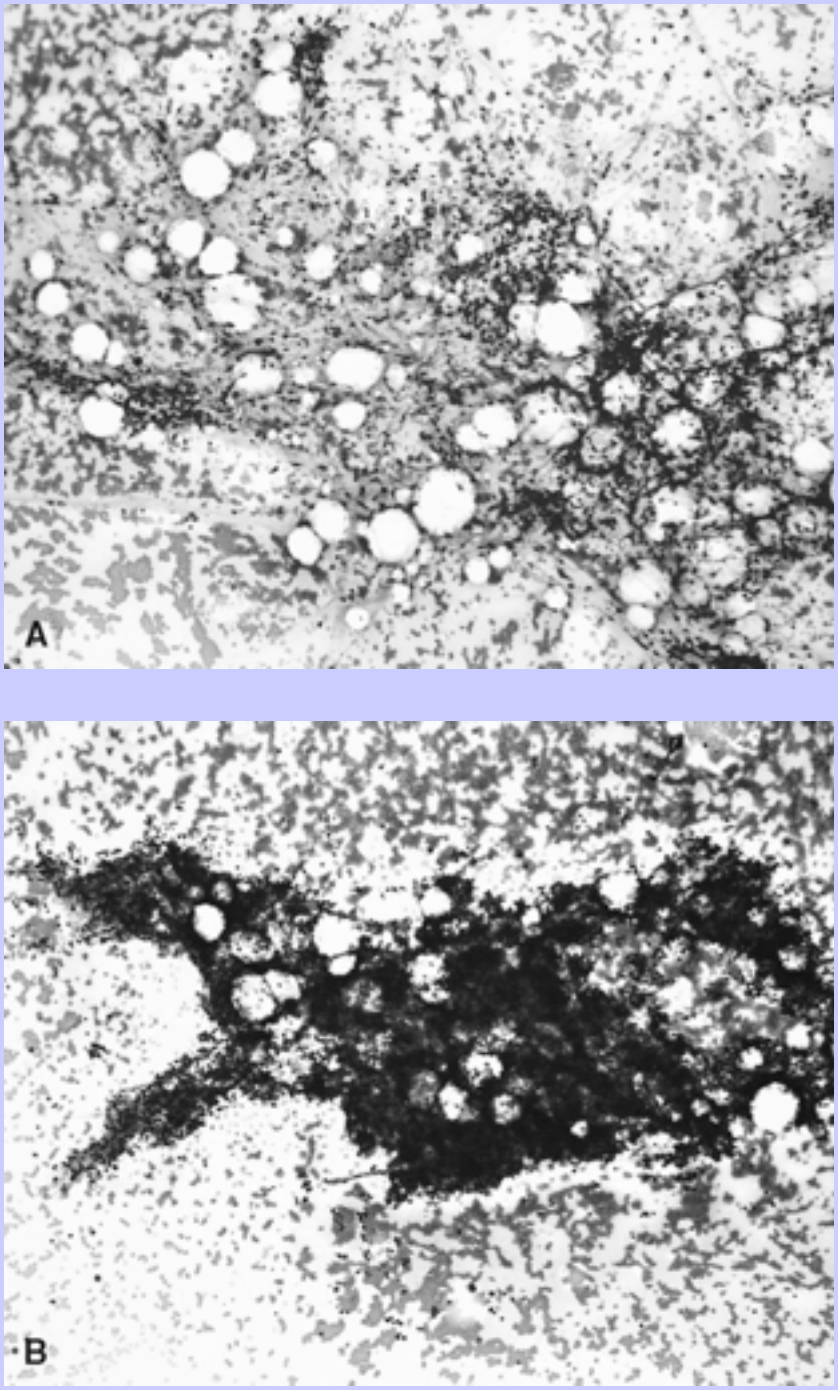
Fig. 28-21 Bone marrow particles. The particle in **A** is of low cellularity. Only a small proportion of the particle is composed of nucleated cells. The particle in **B** is of high cellularity. At least 75% of the particle is composed of nucleated cells. (Wright-Giemsa stain, 10× objective.)



If repeated aspirates all result in samples of low cellularity, a core biopsy may be indicated. Cytologically, it is

If repeated aspirates all result in samples of low cellularity, a core biopsy may be indicated. Cytologically, it is usually impossible to differentiate low cellularity caused by a pathologic process from that resulting from poor sampling; therefore, a biopsy may be needed for the evaluation of cellularity.

28.4 BONE MARROW EVALUATION

Bone marrow evaluation requires expertise (advanced training and experience), and in most cases it is anticipated that samples will be sent to a trained cytologist for evaluation. To obtain the most information from a bone marrow aspirate, it is important to have a good-quality sample. Even if not reading the sample oneself, it is recommended to stain a slide to confirm that a diagnostic sample was obtained (stain the worst slide; if it is acceptable, one can expect the others to be acceptable, too). Recent CBC results and freshly made blood films are also essential for full interpretation of a bone marrow sample. Relative changes among different cell lines are assessed in the evaluation of hematopoiesis because absolute cell counts are unreliable in bone marrow aspirates.[22] Knowledge of the peripheral blood picture is necessary to assess whether changes (or lack of changes) in the bone marrow are consistent with normal hematopoiesis. Freshly made blood films are important to have when comparing the morphology of cells in the bone marrow with the morphology of those in the peripheral blood. Results from cytologic evaluation of bone marrow should ultimately be correlated with history, clinical presentation, and other laboratory data.

28.4.1 Cytologic Examination

In general, the evaluation of bone marrow includes assessment of the following parameters. On low magnification the cellularity and quality of the sample as a whole are assessed, as well as the cellular density of bone marrow particles. Iron stores are evaluated within the particles. Megakaryocyte numbers are also best assessed at low magnification. On high magnification the sample is evaluated for the presence of myeloid and erythroid cell lines. The cell lines are evaluated for orderly maturation, and cell morphology is assessed for evidence of dysplastic changes. The relative proportion of myeloid to erythroid cells is determined by subjective assessment or by counting cells to derive a myeloid-to-erythroid (M:E) ratio. The sample is also evaluated for the presence of other cell types or infectious organisms. Results from the bone marrow evaluation are then interpreted in accordance with peripheral blood abnormalities.

Cellularity of bone marrow spicules is subjectively determined by assessing how much area of a particle is composed of cells versus fat. Cellularity of normal marrow can vary according to the age of an animal, with higher cellularity in younger animals and lower in older animals. Examples of differing cellularities are depicted in Fig. 28-21. Iron stores are assessed within spicules and typically described as *present, decreased,* or *increased* (Fig. 28-22).

Maturation of bone marrow cell lines follows somewhat of a pyramidal pattern, with cells dividing as they mature, resulting in higher numbers of cells in the more mature cell stages (Figs. 28-23 and 28-24). In bone marrow of healthy animals, rubriblasts and myeloblasts will typically comprise at most a small percentage of the total cell population. Twice as many prorubricytes and promyelocytes may be seen. Numbers of cells in each stage increase up to polychromatophilic rubricytes and metamyelocytes, after which there are relatively stable numbers between the subsequent maturational phases. In general, for each blast there are 16 mature granulocytes or erythrocytes. Mitotic figures are normally present in low numbers.

Fig. 28-22 Bone marrow aspirate. The blue-black granules visible extracellularly and within macrophages represent iron stores *(arrows)*. Iron stores can also be seen as brown crystalline material within particles. (Wright-Giemsa stain, 100× objective.)

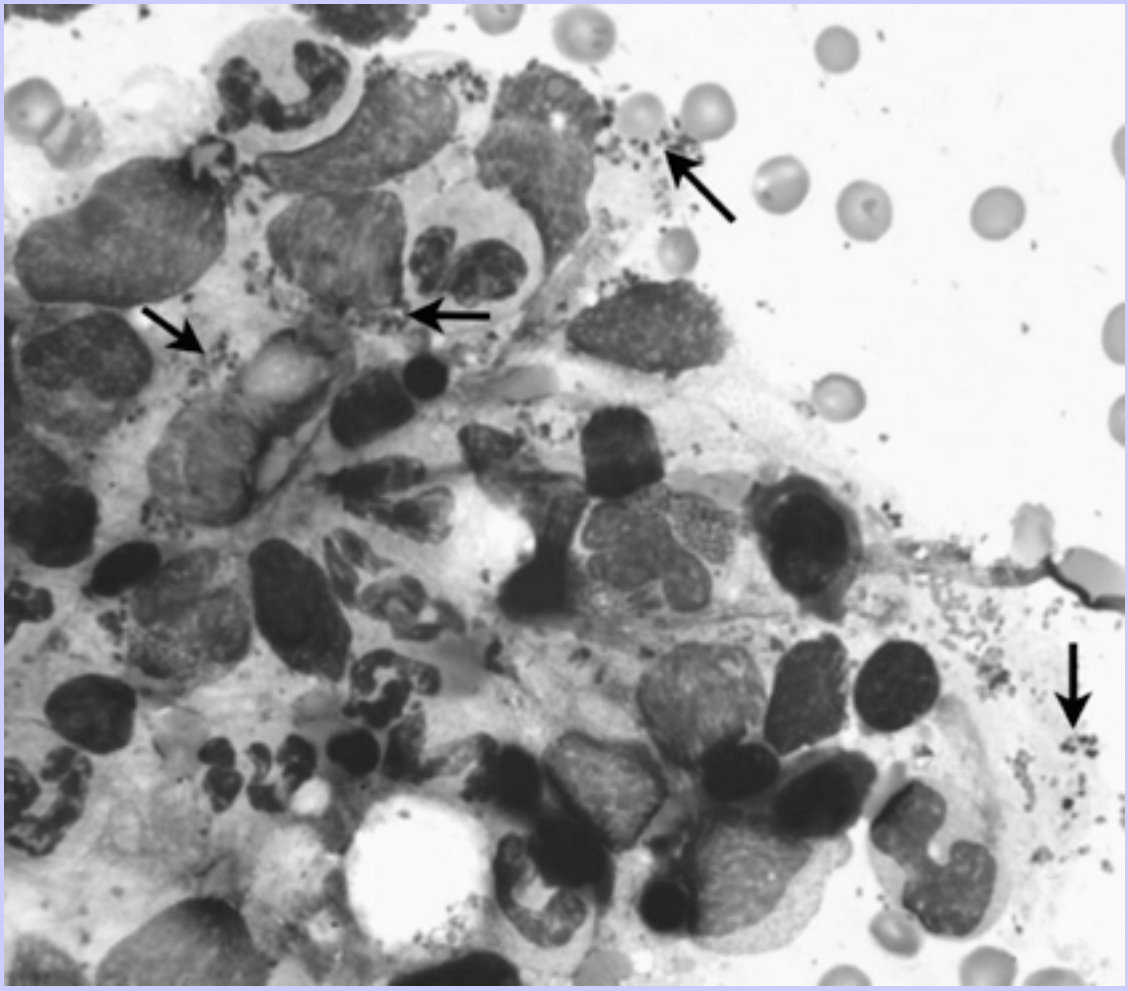
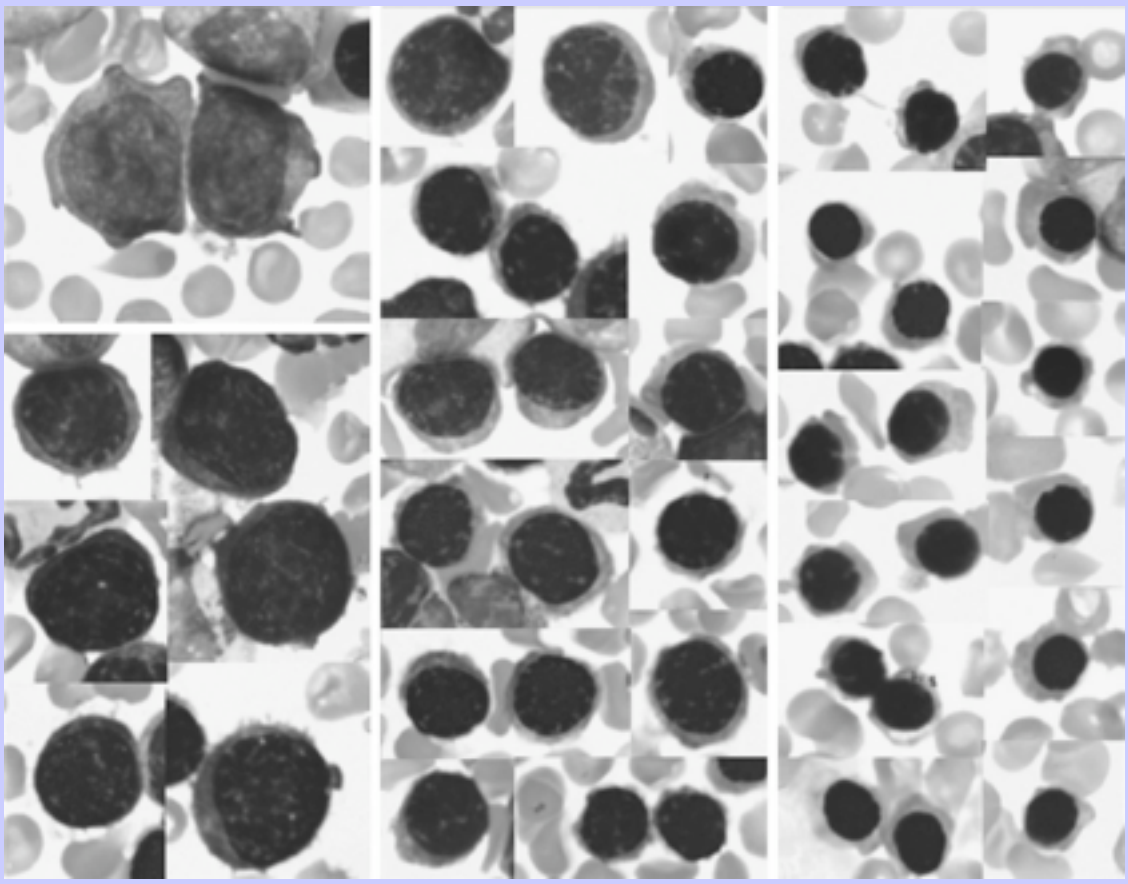


Fig. 28-23 Maturational stages of erythrocytes within the bone marrow. The *left panel* contains rubriblasts in the upper square with prorubricytes below. Rubriblasts are large cells with large nuclei containing coarse-grained chromatin and nucleoli; a perinuclear halo is present within scant deeply basophilic cytoplasm. Prorubricytes have a more mature nucleus; chromatin condensation begins, and no nucleoli are present. The *middle panel* contains basophilic and polychromatophilic rubricytes; chromatin condensation is distinct and the cytoplasm is paler, grayer, or polychromatic. The *right panel* contains metarubricytes with dark, intense chromatin condensation and pink cytoplasm. (Wright-Giemsa stain, 100× objective.)



The M:E ratio is most accurately determined by counting a minimum of 500 cells. Nucleated cells of all maturational stages are included in the count and categorized as myeloid or erythroid. The ratio is calculated by simply dividing the total number of myeloid cells by the total number of erythroid cells. It is important to include

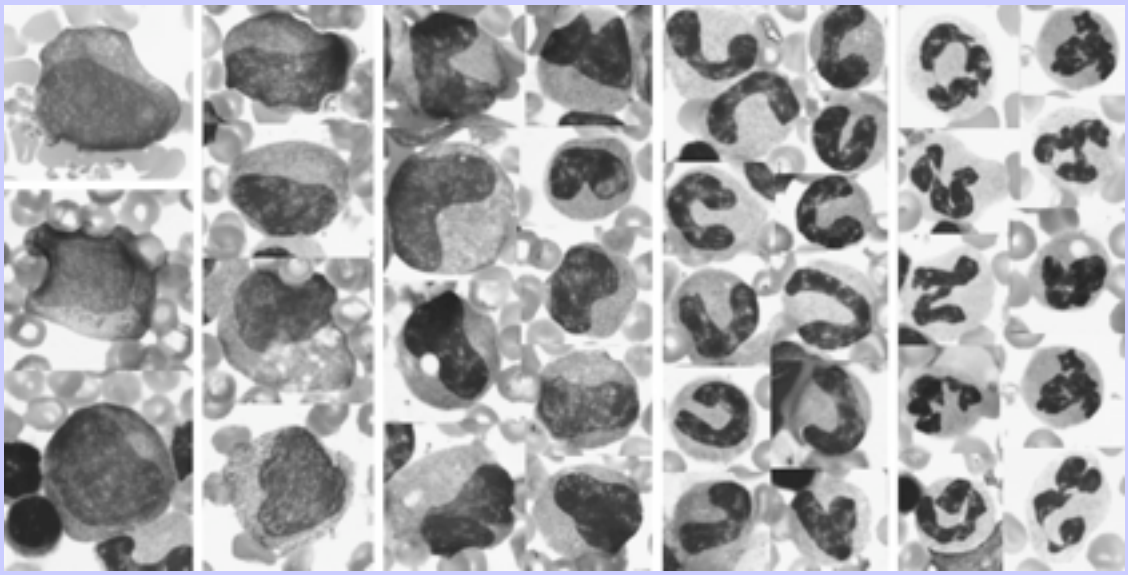
several different areas of the sample to make it as representative of the whole sample as possible. Blood contamination can also affect the M:E ratio, especially if leukocytosis is present. Reported M:E ratio ranges for healthy animals of different species have been variable. In some sources the M:E ratio in cattle is listed as <1, although ranges from 0.27 to 2.59 have been reported.[7,20,24–26] The range of M:E ratios in ten 3- to 6-year-old pregnant sheep was reported as 0.77 to 1.68.[17] The reported range for the M:E ratio in a low number of llamas is 0.9 to 2.9.[18] Llama, alpaca, and vicuna have a lower M:E ratio at high elevation (4200 m) versus low elevation.[2] M:E ratios in horses generally range from 0.5 to slightly greater than 1, with 1.5 sometimes reported as the upper value.[6,27–29]

Evidence of dysplastic changes in hematopoietic cells includes asynchronous maturation between the cytoplasm and nucleus, large cell forms, and abnormal nuclei, such as ring-shaped nuclei. Cell types other than hematopoietic cells should be evaluated as to their presence and proportion of the total cell population. Low numbers of macrophages (<1%), plasma cells (<2%), and small lymphocytes (<10%) are commonly seen in bone marrow samples.

28.4.2 Interpretation

It is easy to make a conclusion about bone marrow cellularity if the sample is highly cellular, but a poorly cellular sample is more difficult to interpret if adequate particles are not present. A core biopsy may be needed to differentiate between a poorly cellular marrow and a nonrepresentative sample. In general the bone marrow will become more cellular in a hyperplastic or regenerative response.

Fig. 28-24 Maturational stages of granulocytes within the bone marrow. The *left panel* contains a myeloblast in the upper square with promyelocytes below. Myeloblasts are large cells with large nuclei containing fine reticular chromatin and nucleoli; the cytoplasm is basophilic and agranular. Promyelocytes contain coarse cytoplasmic granulation; nuclear chromatin is beginning to condense, and nucleoli are present. *Subsequent panels, moving to the right*, contain myelocytes, metamyelocytes, band neutrophils, and segmented neutrophils. Myelocytes have a lower nuclear:cytoplasmic ratio and contain fewer and finer cytoplasmic granules; the nucleus is round to kidney-shaped and contains no nucleoli. As maturation progresses, the cells become smaller, the cytoplasm becomes more eosinophilic, the chromatin becomes more condensed, and the nucleus indents and segments.



In many cases it is adequate to describe iron stores as being present without quantification. When assessing the cause of anemia, an abnormality in iron stores may provide useful diagnostic information. Lack of iron stores would suggest iron deficiency, whereas abundant iron stores are associated with anemia of chronic inflammation. Perl's iron stain (Prussian blue reaction) can be used on bone marrow slides to confirm low iron stores. Llama bone marrows normally contain abundant iron.[18]

No definitive criteria for megakaryocyte numbers have been determined. If thrombocytopenia is not present, any number of megakaryocytes is acceptable. Many megakaryocytes are expected to be seen within individual particles when there is regeneration associated with thrombocytopenia. Higher numbers of immature

megakaryocytes may also be seen; these will be smaller cells (still larger than other bone marrow cells) with a higher nuclear-to-cytoplasmic ratio, deeper basophilic cytoplasm, and fewer lobes to the nucleus. If megakaryocytes are not frequently seen in the bone marrow from an animal with thrombocytopenia, this suggests hypoplasia or destruction of megakaryocytes.

When assessing bone marrow for normal, progressive maturation of cell lines, it is expected that all developmental stages will be present, with greater numbers of the more mature cells. Variation from normal can be seen for a variety of reasons, often reflected by a shift to the left or what appears to be a maturation arrest. A shift to the left is the situation in which all maturation stages are represented but there is a higher proportion of the less mature cells (the proliferating pool) than normal. *Apparent maturation arrest* is a term used maturation appears to terminate at a particular stage; the earlier maturation stages are present, but later stages are poorly represented. Suppression of hematopoiesis can result in abnormalities in maturation progression but often is reflected by a decrease in all stages of maturation. If the number of cells within a cell line is too low, progression of maturation can be difficult to evaluate. Destruction of cells, such as with immune-mediated disease, at a particular maturation stage will result in decreased numbers of cells of the affected type as well as cells at all later stages, which can appear as a maturational arrest. If a disease process results in large demand or rapid mobilization of cells out of the bone marrow, depletion of the more mature cell stages can appear as a maturational arrest. In such cases a left shift also is often associated with the increased demand. Acute leukemia is typically reflected as an apparent maturational arrest or left shift. Therefore it can be difficult to differentiate between hyperplastic marrow in which there has been rapid mobilization of mature cells out of the marrow and a myeloproliferative disorder on cytologic examination alone. In some instances sequential bone marrow aspirations can be useful in helping determine disease pathogenesis. Abnormalities in maturational progression may also be reflected by the presence of dysplastic changes.

The M:E ratio is used to help determine if the erythrocyte or myeloid cell lines are hypoplastic or hyperplastic. An equal number of nucleated erythroid and myeloid cells will result in an M:E ratio of 1. An M:E ratio greater than 1 (or greater than the reference interval) often indicates that granulocytic production exceeds erythroid production, but it could also indicate a decrease in erythropoiesis. Likewise, an M:E ratio less than 1 (or less than the reference interval) often indicates that erythropoiesis exceeds granulopoiesis, but it could also indicate suppression of the latter. Determining which interpretation is appropriate requires knowledge of concurrent CBC results. An increase in the M:E ratio would be appropriate in an animal with neutrophilia, but if the neutrophil count is normal and anemia is present, it would indicate erythroid hypoplasia. In the face of anemia, a decrease in the M:E ratio would indicate erythroid hyperplasia and regeneration, but a decrease in a neutropenic animal that is not anemic would indicate myeloid hypoplasia. In some disease states both the myeloid and erythroid series may be affected, which could potentially exacerbate or mask alterations.

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Whereas most species readily reflect an erythroid regenerative response in the peripheral blood, horses do not. Reticulocytes are rarely seen in equine peripheral blood, and in one investigation it took several days of severe anemia (PCV of 13% to 14%) in horses before a reticulocytosis of 1% to 2% was seen.[30] An increase in mean corpuscular volume (MCV) may be detected in the peripheral blood of horses with chronic anemia or acute, massive hemolytic or hemorrhagic anemias,[29–32] but the best way to assess erythropoiesis in horses is to examine the bone marrow. The number of reticulocytes significantly increases in the bone marrow of horses with regenerative anemia. In the study of acute blood loss in which only 1% to 2% of reticulocytes were seen in peripheral blood, bone marrow reticulocytes went from 4.1% (pre—blood loss) to as high as 66.5%.[30] Reticulocytes typically comprise <2% of erythrocytes in normal bone marrow, and a regenerative response is considered present if reticulocytes comprise <5%.[11] Determining the number of reticulocytes per 1000 erythrocytes after staining with a supravital stain such as new methylene blue is the most reliable method, but an

estimate can be made by counting the number of polychromatophils per 100× oil objective field in a Wright-stained smear (assuming the field of view includes approximately 100 cells; this can vary with the microscope). In the face of anemia, <5 polychromatophils/oil field is considered a good regenerative response and <2 is indicative of erythropoietic suppression.[33] Care should be taken not to dilute the sample with peripheral blood, as this will dilute the number of reticulocytes from the bone marrow.

Other bone marrow parameters that indicate erythrocyte regeneration in horses include a decreased M:E ratio (<0.5) and a left shift of erythroid precursors.[29,33] Depending on the type of blood loss, it could take several weeks to reduce the M:E ratio below the reference interval.[34] With regeneration, a doubling of the proliferating pool of erythrocyte precursors can occur within 3 days of an acute severe hemorrhage, with maximal response at 9 days.[35] The proportion of basophilic and polychromic rubricytes can reach 39% to 55% of all cells in the regenerative equine bone marrow.[29]

Atypical cell populations in the bone marrow can represent a myeloproliferative disorder, an infiltrative neoplastic process, inflammation, or antigenic stimulation. Atypical cell populations can be a result of significant increases in cell numbers of types normally seen in the marrow. Blast cells normally constitute only a small percentage of total cells in the bone marrow. A diagnosis of acute leukemia is typically associated with blast cells that constitute <30% of all cells in the bone marrow,[36] although human medicine has revised its criterion to <20% and some veterinarians are following suit. Cytologic results need to be correlated with other clinical data because granulopoiesis characterized by a marked left shift in bone marrow precursor cells with rapid mobilization of more mature cells from the bone marrow can resemble a myeloproliferative disorder.

Another cause of increased numbers of cells normally residing in the bone marrow is inflammation. Suppurative inflammation can be seen, typically associated with septicemia. Histiocytic or granulomatous inflammation is characterized by increased numbers of macrophages. Both suppurative and histiocytic inflammation can be associated with infectious or noninfectious disease processes. If inflammation is present, the sample should be thoroughly inspected for organisms, and culture may be indicated.

Increased numbers of lymphocytes and plasma cells can be seen with antigenic stimulation or with neoplasia. In general, it is rare to see the proportion of lymphocytes or plasma cells exceed 20% with antigenic stimulation. The morphology of lymphocytes and plasma cells should be well differentiated if they are associated with nonneoplastic processes. Cells associated with neoplasia can also appear well differentiated; therefore cell morphology alone may not be useful in establishing a diagnosis. Clinical presentation and ancillary testing (e.g., serum protein electrophoresis, flow cytometry) can be helpful in interpreting lymphocytoses and plasmacytoses.

The presence of cells not typically seen in the bone marrow or cells exhibiting a high degree of pleomorphism or other criteria of malignancy should raise suspicion of a neoplastic process. Neoplasia can arise from within the bone marrow or can metastasize to the bone marrow from other sites.

Degenerative cells or amorphous proteinaceous debris suggests bone marrow necrosis. This can occur secondary to infarction, neoplasia, or inflammation. Degenerative cells are often unidentifiable.

After cytologic evaluation of bone marrow and correlation with CBC results, a determination can be made as to whether any of the cell lines are hypoplastic or hyperplastic and whether there is evidence of maturational arrest, dysplasia, neoplasia, or inflammation. This information can then be correlated with the clinical information to determine appropriate differential diagnoses and likely disease pathogenesis.

28.5

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29 Chapter 29 Molecular Diagnostics in Large Animals

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29.1 MOLECULAR DIAGNOSTICS IN LARGE ANIMALS

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Of the four classes of organic molecules that compose the basic physical structure of all living beings, nucleic acids are the only molecules that carry replicable instructive information. Nucleic acids differentiate themselves from lipids, carbohydrates, and even proteins in their ability to organize the basic unit of life, the cell. Even minor alterations in DNA and RNA molecules can disrupt the fine balance between health and disease. The field of molecular diagnostics seeks to elucidate the variations and mutations in genetic material that can cause disorder in the otherwise intricately organized body.

The amplified era of molecular diagnostics for infectious diseases began in 1983 when Dr. Kary Mullis of Cetus Corporation first conceptualized the polymerase chain reaction (PCR). He went on to win the Nobel Price in Chemistry for this revolutionizing technology 10 years later.[1,2] Since the inception of PCR technology, infectious disease diagnostics has been at the forefront of molecular medicine, with the promise of detecting contagious pathogens in a safer and more sensitive way to aid in controlling their spread. Infectious disease testing is expected to continue to dominate the molecular diagnostic market for large animals in the foreseeable future. The use of amplified and nonamplified tests to assay the molecular makeup of the host rather than the pathogen is growing. Whereas cancer diagnostics is in its infancy for large animal testing, parentage and forensic testing together with single-nucleotide polymorphism (SNP) detection using in situ hybridization (ISH), fluorescent in situ hybridization (FISH), and sequencing technologies are gaining importance in assessing the presence and prognosis of genetic diseases.

The ability of molecular diagnostic assays to sensitively and specifically detect the primary cause of disease in a short time is unprecedented. Molecular tests are able to detect and sometimes to quantify a specific unknown. Such tests are binary by nature; they provide a yes-or-no answer. The clinically valuable information rests in determining the presence or absence of a specific pathogen in a biologic sample derived from an animal. Because detection of viral, bacterial, rickettsial, fungal, or parasitic nuclear material in a biologic sample gives clinically important information, molecular tests have clinical utility. Molecular probes are able to detect the presence of nuclear material from a given pathogen with an extraordinarily high level of sensitivity and specificity. The low relative complexity of a bacterial or viral genome allows for this type of detection. Comparatively, animals have a larger genome, with genotype associations linked to clinical pathologies. Determining the presence of a gene sequence does not necessarily correlate with a given clinical action, as diseases are generally multifactorial. In contrast, establishing the presence of the neuropathogenic form of equine herpesvirus (EHV) 1 in an equine patient's blood sample has direct association with EHV-1 infection, whether this translates into a symptomatic stage or not. The binary nature of molecular tests, which establishes the presence or absence of genetic material in a sample with a

high degree of accuracy, has high clinical value for infectious disease testing because of its high correlation with clinical signs.

Rapid results have tremendous clinical value in curtailing infection. Molecular methods can provide results in hours compared with days for culture-based or alternative technologies. The high sensitivity and specificity of molecular testing is particularly valuable in early determination of infection and makes it advantageous compared with antibody and antigen testing without amplification techniques. In most cases pathogens enter the host and replicate exponentially; early detection provided by the higher sensitivity allows for earlier clinical intervention. Molecular tests have been shown to produce fewer false-positive and false-negative results. Therefore molecular tests are becoming the gold standard in the laboratory in terms of sensitivity and specificity. Key features for the adoption of molecular diagnostics for infectious agents are as follows:

- Superior sensitivity and specificity compared with most immunoassays
- Automated platforms that significantly increase throughput
- Quantitative assessment of viral load, which is clinically useful
- Fast turnaround time that speeds detection and reduces overall costs
- Simultaneous analysis of multiple analytes

29.2 TECHNOLOGIC SUPERIORITY OF MOLECULAR TESTS

The relative technical superiority of molecular methods makes them likely to partially replace other types of more conventional methods such as culture-based tests or certain direct antigen and antibody tests to determine the presence of an infectious pathogen in a sick animal. Whereas antibody testing is more of a broad screening tool, molecular diagnostics allow accurate detection of the genome of a pathogen in a clinically sick animal. Culture-based tests have a turnaround time of days and are labor-intensive. In addition, certain infectious agents are difficult to culture or biohazardous for laboratory personnel (e.g., *Mycobacteria* species, fungi, *Mycoplasma* species, *Lawsonia intracellularis*). In such instances molecular detection of selected pathogens has already supplanted conventional culture.

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29.3 RAPID AND HIGH THROUGHPUT APPLICATIONS PROMOTE MOLECULAR TESTS

Rapid and specific detection of infectious disease agents is crucial for the prevention or containment of outbreaks. In the case of avian flu, the rapid detection of H5N1 strains of that virus is critical for containment. The avian flu pandemic concerns necessitate rapid and high throughput molecular tests to maintain well-being of animal and human community health. Similarly, West Nile virus (WNV) screening of mosquito pools and birds, and screening for exotic Newcastle disease are additional examples of high throughput applications with predominance for molecular tests.

29.4 INCREASING ADOPTION OF MOLECULAR TESTS BY UNIVERSITY AND COMMERCIAL LABORATORIES

Since the advent of molecular platforms in the diagnostic laboratory, most molecular tests in veterinary medicine are performed by several commercial and public laboratories (Table 29-1). Unlike the market in human molecular

diagnostics, which is dominated by four large players (Roche, Bayer, Gen-Probe, and Abbott), veterinary molecular diagnostics shows significant fragmentation.

29.5 SIMULTANEOUS TESTING OF MULTIPLE PATHOGENS

Parallel testing of multiple infectious agents in highly standardized platforms is a central component of molecular assays; it essentially allows several tests for both DNA and RNA pathogen targets to be performed simultaneously on one sample. This development is a noteworthy driver for molecular diagnostics as it allows acquisition of more meaningful data from a single sample. This so-called *panel strategy* allows an efficient workup of complex clinical syndromes with general symptomatology. These clinical situations do not involve easy diagnostic decision making for the veterinarian. In complex organ-related problems with general or unspecific symptomatology, multiple infectious agents can be responsible for a clinical picture. Even though veterinarians tend to make a single-pathogen diagnosis, it has become more evident in recent years that many syndromes are caused by co-infections. Panel testing on a large scale will uncover unknown dual or triple infections in animals, which can diffuse the clinical picture. It has long been speculated that seemingly clinically irrelevant EHV-2 infections in horses may underlie secondary infections, aggravating and diffusing the clinical picture. More characteristic examples include respiratory infections in companion animals, often initiated by subclinical viral infections that lead the way to secondary infections. In addition, many vector-borne pathogens have a high tendency to persist in infected animals and therefore may facilitate viral infections or aggravate preexisting conditions such as feline immunodeficiency virus or feline leukemia virus infection. Sepsis caused by infectious agents is expected to become an important segment for equine molecular diagnostics, especially in neonatal medicine. Molecular diagnostics enable fast turnaround time with rapid initiation of treatment. In the future, panel testing for the most important sepsis-inducing agents could be complemented by the addition of assays targeting antimicrobial resistance genes. This would allow the modification of treatment regimens in case antimicrobial resistance is detected.

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Table 29-1 Examples of Molecular Diagnostic Laboratories in the United States*

Laboratory	Website URL	PCR Platform		
		Conventional	Real-Time	Panels
Arizona Veterinary Diagnostic Laboratory	http://microvet.arizona.edu	X	X	
Arkansas Livestock and Poultry Commission Laboratory	www.arlpc.org/vetlab	X		
Auburn University VMTH	www.vetmed.auburn.edu/index.pl/molecular_diagnostics		X	
Biogenetics	www.biogeneticservices.com/contact.htm	X	X	
California Animal Health and Food Safety Laboratory	http://cahfs.ucdavis.edu	X	X	
Clemson University, Veterinary Diagnostic Lab	www.comptroller.clemson.edu	X		
Clongen	www.clongen.com	X		
Colorado State University	www.cvmbs.colostate.edu/dlab	X		
Colorado State University Veterinary Diagnostic Laboratory	www.dlab.colostate.edu/security2	X	X	Yes
Connecticut Veterinary Medical Diagnostic Laboratory	http://pathobiology.uconn.edu/cvmdl	X		
Cornell, Animal Health Diagnostic Lab	http://diaglab.vet.cornell.edu	X		
Diagnostic Vet Labs	http://dvl.datacorner.com	X		
Dynagenics	www.dynagenics.com	X		Yes
Florida Department of Agriculture-Kissimmee Vet Diag. Lab	www.doacs.state.fl.us/ai/labs	X	X	
Georgia University, Veterinary Diagnostic Laboratories	www.vet.uga.edu/dlab	X		Yes
Health Gene, Toronto, Canada	www.healthgene.com/vet	X		
Illinois Depart of Agriculture, Veterinary Diagnostic Lab	www.agr.state.il.us/AnimalHW/labs	X		
Illinois VMTH Diagnostic Lab	www.cvm.uiuc.edu/vdl	X	X	
Indiana Animal Disease Diagnostic Laboratory	www.addl.purdue.edu	X		
Iowa State University	www.vetmed.iastate.edule	X	X	

Kansas DMP Diagnostic Lab	www.vet.ksu.edu	X			
Kentucky Livestock Disease Diagnostic Center	http://ces.ca.uky.edu/lddc	X			
Louisiana State University Vet Medical Diagnostic Lab	http://laddl.lsu.edu	X			
Lucy Whittier Molecular & Diagnostic Core/ UC Davis	www.vetmed.ucdavis.edu/vme/taqmanservice/diag_home.html		X	Yes	
Michigan (Animal Health Diagnostic Laboratory)	www.animalhealth.msu.edu/Immunodiagnostics.htm	X			
Minnesota University, Veterinary Diagnostic Lab	www.vdl.umn.edu/vdl/ourservices/guidelinefiles/moleculardiagnostics/home.html	X			
Missouri (Veterinary Medical Diagnostic Laboratory)	www.cvm.missouri.edu/vmdl	X			
Montana Veterinary Diagnostic Laboratory	http://mt.gov/liv/lab	X			
Nebraska University, Vet Diagnostic	http://nvdls.unl.edu	X			
North Carolina Depart of Agriculture, Veterinary Diagnostic Laboratory	www.ncvdl.com/VetLabServicesMolecularDiagnostics.html	X	X	Yes	
Ohio State, Animal Disease Diagnostic Laboratory	www.ohioagriculture.gov	X			
Oklahoma Animal Disease Diagnostic Laboratory	www.cvm.okstate.edu/OADDL	X			
Oregon State University, Veterinary Diagnostic Lab	http://oregonstate.edu/vetmed	X	X		
South Dakota State, Animal Disease Research & Diagnostic Lab	http://vetsci.sdstate.edu	X			
Texas Vet Medical Diagnostic Laboratory	http://tvmdlweb.tamu.edu	X			
Texas A&M Gastrointestinal Laboratory	www.cvm.tamu.edu/gilab	X			
Vita-Tech	www.vita-tech.com/dnabasedtests.cfm	X			
Veterinary Molecular Diagnostics, Inc.	www.vmdlabs.com	X			
Washington Animal Disease Diagnostic Laboratory	www.vetmed.wsu.edu	X	X		

Wisconsin Vet Diagnostic Laboratory (emphasis in Avian)	www.wvdl.wisc.edu	X	
Wyoming State Vet Lab	http://wyovet.uwyo.edu	X	
Zoologix	www.zoologix.com/dogcat/Menu.htm	X	X
	STATISTICS		
	Percentage of labs that use conventional and real-time PCR	31%	
	Percentage of labs that use conventional PCR only	64%	
	Percentage of labs that use real-time PCR only	5%	

* American Association of Veterinary Laboratory Diagnosticians (AAVLD)–accredited laboratories are listed if they offer commercial molecular diagnostic services available to veterinarians.

29.6 INDICATIONS FOR USE OF POLYMERASE CHAIN REACTION ASSAYS FOR INFECTIOUS DISEASES

Diagnostic tests such as PCR assays offer the potential for fast and accurate determination of the presence of an infectious agent, which can lead to an improved clinical outcome because of the faster initiation of more etiologic-based treatment and the possibility for quantitative treatment monitoring. Even if molecular-based tests are more expensive than more traditional diagnostic assays, their overall impact will lead to reduction in treatment costs. 438 439

Key indications for use of a molecular test are the speed and accuracy of molecular assays. In comparison with traditional culture for bacteria, rickettsial organisms, fungi, and viruses, molecular testing offers direct detection of the target pathogen within a fraction of the time. Owing to its speed, PCR assays have the potential to replace traditional culture methods for infectious agents that are difficult to culture or not cultivable at all.

Compared with serology testing, molecular tests offer the advantage of detecting an infectious agent before an immune response occurs and a detectable antibody titer is developed. Immunoglobulin M (IgM) analysis in certain applications (such as WNV) can alleviate this problem; however, molecular testing methods are more reliable in picking up early virus replication and allow a faster epidemiologic assessment and earlier patient treatment.

In certain instances, for the discrimination of a clinically relevant EHV-4 infection from a latent infection, the detection of viral DNA is not informative. In such cases the quantitative assessment of viral loads is necessary.[3] Similarly, the choice of RNA or DNA affects the ability to distinguish disease (active virus replication and production of viral transcribed RNA) from nondisease (viral DNA of latently infected cells) status.

29.7 MOLECULAR BIOLOGY TECHNOLOGIES

The main methodologies used for molecular diagnostics include the following:

- Nucleic acid capture, probe hybridization
- ISH, FISH
- Isothermal amplification of nucleic acids[4]
- Transcription-based amplification methods

- Signal amplification by branched-chain DNA
- Qualitative pathogen identification using nucleic acid amplification
- Quantitative assays
- Genotyping assays
- Genotype sequencing assays
- Multianalyte testing panels

Genotyping assays are usually used to test for known mutations associated with inherited genetic conditions such as hyperkalemic periodic paralysis (HYPP) in horses, an autosomal dominant condition that causes potassium-induced attacks of skeletal muscle paralysis. Many of these assays depend on sequence-specific probes designed to hybridize with known genetic variations. For infectious agents, genotyping or speciation is achieved by using highly specific PCR-based or hybridization-based assays or by restriction enzyme fragment length polymorphism (RFLP) assays. In these assays, amplified material is digested with a certain restriction enzyme that characterizes the difference between two target sequences.

29.8 THE POLYMERASE CHAIN REACTION IN VETERINARY MOLECULAR DIAGNOSTICS

Because of its predominance in research and diagnostic applications, PCR assays will be discussed in more detail in later chapters. To give practitioners guidance about what to look for when PCR-based molecular diagnostic assays are offered, we will discuss some aspects such as design guidelines, differences between traditional and real-time PCR assays, sampling, controls, and interpretation of results in greater depth.

PCR testing in its pure form is a three temperature event: denaturation of double-stranded target (or in later cycles PCR products), annealing of target and primers, and extension of the DNA strand from the primer.

29.8.1 Comparing Real-Time Polymerase Chain Reaction with Traditional Polymerase Chain Reaction Testing for Diagnostic Applications

Real-time PCR testing was introduced into the marketplace in 1996 and replaced the tedious gel electrophoresis step to detect PCR products after amplification. In one survey, 98% of equine veterinarians knew about PCR testing and 79% of equine veterinarians at universities knew the difference between conventional and real-time PCR testing.[5] During gel electrophoresis, the PCR products are separated by size and visualized using a dye (ethidium bromide) which intercalates with the double stranded DNA. Real-time PCR detects the PCR products by using an internal probe that is labeled with two fluorescent dyes: a reporter dye and a quencher dye. The fluorescent activity of the reporter dye is absorbed (quenched) by the quencher dye. The probe binds to the PCR products between the two PCR primers. If the primers are extended by the DNA polymerase, the 5′ nuclease activity of the DNA polymerase digests the internal probe (hence hydrolysis probe) and releases the quenched fluorescence. Alternatively, hybridization probes can be used that are not digested during amplification and that allow melting curve analysis. This single change in the protocol regarding how to detect the PCR products revolutionized the use of PCR testing for both research and diagnostic applications. Most of the advantages resulting from this principle originate from the fact that the PCR tube does not have to be opened after a PCR assay for analysis. This principle is called *closed-tube detection*. The advantages are as follows:

1 Because of the closed-tube detection format, PCR products cannot escape from the PCR reaction containers. If escape occurs, it leads to the contamination of the PCR laboratory and subsequently the next PCR reactions. The consequence is false-positive PCR results. Real-time PCR efficiently eliminates this risk of PCR product carryover. There is also a second safety system called AmpErase UNG,[6] which eliminates contaminating PCR products.

2 Real-time PCR is a kinetic PCR principle, underlining the fact that PCR product accumulation is measured during every single PCR cycle in real time. Because of this fact, real-time PCR is a quantitative method.

3 The real-time PCR platform introduced in 1996 consisted of a laser-based thermocycler, software to design real-time PCR assays, reagents, disposables, and protocols. Because of its integrated design, PCR assays generated with the new system were highly standardized.

4 Data analysis is run on an attached computer that collects fluorescent data points. This principle eliminates all laboratory steps after the real-time PCR cycling is finished. Because of the computer-formatted end analysis, results can be fed directly into the information and management systems of diagnostic laboratories. Real-time PCR has also enabled rapid cycling to finish the PCR process in less than 1 hour. Real-time PCR results therefore can be turned around significantly faster than with traditional PCR testing (normally within a 24-hour period).

5 Because of the probe used to detect the PCR products, real-time PCR is also a more specific assay than single-round traditional PCR. Only specific PCR products are detected by the probe. Real-time PCR testing, essentially a liquid-based hybridization method, is considered as specific as Southern blotting, which is a solid-based hybridization method.

6 Because real-time PCR incorporates hot-start enzymes, the specificity is even greater than with regular non—hot-start DNA polymerases. Hot-start enzymes are inactive at ambient temperatures and have to be heated to 95 ° C for 20 seconds to 10 minutes in order for the DNA polymerase activity to begin. Because of the hot-start nature, nonspecific binding of primers does not lead to unspecific PCR products and results in an overall increased specificity of the assay. 439 440

7 In combination, real-time PCR is described to be as sensitive as or more sensitive than double-round (nested) traditional PCR. Analytic sensitivity and limit of detection using real-time PCR testing is normally in the single molecule range, whereas the limit of quantitation with traditional PCR testing is in the range of 10 to 20 molecules.

29.9 PREANALYTIC VARIABLES

In general, molecular diagnostic laboratories provide strict recommendations for sample collection, including shipping instructions. These instructions include specimen type, volume, anticoagulant, and specimen transport, storage, and handling. The sample type is largely influenced by the pathogenesis of the disease and plays a key role in the performance and interpretation of the test results. Veterinarians are advised to adhere to these recommendations, as the quality of the result is directly correlated to the quality of the sample and preservation of the nucleic acid content. Molecular assays often offer the convenience of using a small specimen acquired with a minimally invasive procedure. The diagnosis of herpesviruses is a classic example in which culture and neutralization assays have been largely replaced by PCR testing on a small volume of aspirate or swabs from mucosal surfaces. Molecular tests can detect the presence of small numbers of organisms, and the probability of

detection increases when a larger volume of specimen is added to the amplification reaction. Because molecular assays do not need viable organisms for testing, more flexibility in specimen transport is possible than with culture methods.

Appropriate specimen collection and transport conditions are important to ensure successful extraction of intact nucleic acid and to prevent cross-contamination. Specimen transport and storage conditions are likely to vary among specimen types and between RNA and DNA tests. RNA is more susceptible to degradation. Detailed storage and shipping instructions are crucial if RNA pathogens are part of the diagnostic workup. Practitioners should be aware of these recommendations and consider using appropriate cooling containers when samples are collected in the field. Such samples maintain stability if stored appropriately in a cooled environment. Freezing of fresh specimen often adversely affects the quality and should be avoided if not otherwise instructed by the laboratory.

Sampling errors are among the many preanalytic variables. It is therefore recommended to have the appropriate labeling material available for blood containers or other sample types. Blood or body liquid contamination on the outside of the containers is an obvious cause of sample cross-contamination before the samples are manipulated in the laboratory. Proper collection procedures are essential to prevent artifacts.

29.9.1 Nucleic Acid Extraction

Many commercially available manual and automated methods have been successfully applied to infectious disease testing of a variety of clinical materials. Especially in veterinary molecular diagnostics, the variety of sample types can be challenging for processing through a single platform. Automated or semiautomated platforms are rapid and usually require only a small volume of specimen. In general, these systems are total nucleic acid extraction systems and support the parallel analysis of DNA and RNA pathogens from the same sample. In addition, commercially available automated systems can reduce hands-on labor requirements. Most systems can accommodate sample volumes ranging from 100 µL to 500 µL and even 1 mL of specimen. Nucleic acid binding capacity varies and can be as high as 200 µg per individual extraction position. This maximizes nucleic acid extraction and ensures high consistency.

29.9.2 Interpretation of Results

Interpretation of results obtained with molecular assays for infectious diseases requires understanding of the pathogenesis and biology of the target organisms. Some challenges are unique to molecular tests and are different from considerations in interpreting other microbiologic tests. Such differences are related to the distinction of viable from nonviable organisms and the correlation of nucleic acid detection with presence of disease or disease association.

Interpretation of a negative result includes information about the sensitivity and nucleic acid extraction efficiency. A false-negative result may be caused by a degraded or instable sample. Insufficient or inappropriate sample type, inadequate sampling procedures, and transport problems are additional sources of false-negative results. Sample-specific internal positive controls targeting endogenous genes such as the universal 18S rRNA (ssrRNA) or glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene help to identify these problems. In addition, inhibition phenomena originating from difficult sample matrixes such as feces or environmental samples contaminated with soil (humic acid) have to be controlled with internal positive controls to assess the inhibitory effects.

The factors requiring consideration for the interpretation of positive results include assay specificity and contamination issues. PCR testing or any other target amplification method is subject to these considerations. Real-time PCR testing using closed-tube detection procedures reduces the risk of PCR product carryover as a source of false-positive results.

In general, molecular assays do not provide information about the viability of an infectious agent. Exceptions to this are DNA viruses, bacteria, and parasites analyzed for transcribed genes instead of their genomic DNA. Targeting spliced RNA occurring only if viral genes are actively transcribed provides a means for obtaining information about the replication activity of a virus. In other cases, targeting the ribosomal RNA of parasites such as *Toxoplasma* and *Cryptosporidium* is a means for obtaining viability information and also may increase the analytic sensitivity.[7]

Detection of nucleic acid of a pathogen does not necessarily ensure that the organism is the cause of the disease. A primary example is herpesvirus infections (EHV-1 and EHV-4), in which the detection of DNA may indicate the presence of lytic, nonreplicating, or latent virus. Studies indicated that high viral loads of EHV-4 DNA allow the formulation of a cutoff value to differentiate between lytic and nonreplicating virus.[8] In this particular case, high viral loads were associated with the presence of clinical symptoms and the presence of viral RNA transcripts. Therefore quantitative real-time PCR testing can provide a means to obtain better disease association.

29.9.3 Reporting of Molecular Results

Reporting results for qualitative assays in infectious disease monitoring is easy: a sample either does contain or does not contain nucleic acid of a target organism. Further relevant information includes the nucleic acid extraction efficiency, nucleic acid stability, and sample integrity. 440 441

Reporting results for quantitative molecular infections is more complex. For veterinary medicine, some quantitative applications have been established but are not yet offered as diagnostic assays. Eventually such assays will penetrate into the market with the more widespread adoption of quantitative PCR platforms and more standardized real-time PCR assays.

29.10 REGULATORY CONSIDERATIONS OF MOLECULAR LABORATORIES

Veterinary molecular diagnostics is an emerging market with little regulation. However, standards such as those defined by the American Association of Veterinary Laboratory Diagnosticians (AAVLD) or Molecular Diagnostic Methods for Infectious Diseases (NCCLS; www.nccls.org) are adopted by commercial laboratories aiming to provide a comprehensive diagnostic service. Other sources for guidelines are U.S. Food and Drug Administration (FDA) guidelines (www.fda.gov) for the detection of nucleic acids; ASTM guidelines (*Standard Guide for Detection of Nucleic Acid Sequences by the Polymerase Chain Reaction Technique;* www.astm.org); and Association for Molecular Pathology (AMP) *recommendations for in-house development and operation of molecular diagnostic tests* (www.ampweb.org).

29.11 GUIDELINES FOR CLINICIANS TO SELECT MOLECULAR DIAGNOSTIC LABORATORIES

Veterinarians can use a variety of guidelines to select laboratories for molecular diagnostics. However, there are questions worth asking before samples are submitted. First, it is worthwhile to obtain information about the nature

of the PCR test (traditional versus real-time). Second, questions addressing the quality control and quality assurance system within a particular laboratory should be asked. Third, turnaround time, pricing, and the level of guidance with result interpretation are additional factors worth investigating before samples are submitted.

29.12 SUMMARY

As with any methodologies, quantitative PCR is a work in continuous progress and development. Although all of the methods described in this review use the Nobel Prize—awarded PCR process, the advantages and disadvantages of subtle differences in assay format, accuracy, and reliability of quantitation have to be rigorously compared. The next generation of PCR quantitation will be increasingly automated, standardized, and miniaturized. The time for preparation and the time for amplification will be significantly reduced by using small microtiter-formatted microfluidic cards or silicon-based chip technology.[9–11] Amplification time has been brought down to several minutes by using an advanced nucleic acid analyzer (ANAA) consisting of a battery-powered array of silicon-based PCR microchips with thin-filmed resistive heaters enabling ultrafast amplification.[10]

How could these new systems be incorporated in routine veterinary diagnostics? Veterinary medicine will see a broad adoption of many assays for infectious agents and genetic abnormalities in the near future. The ability to standardize assays will allow high throughput applications that are not possible with traditional molecular methods. For this reason, applications for veterinary medicine may experience not only quantitative but also qualitative growth. These assays will help improve patient management and client satisfaction.

29.13 MOLECULAR TESTING FOR INFECTIOUS DISEASES IN HORSES

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The ready availability of a correct etiologic diagnosis, particularly in contagious infections, enables the veterinarian to make early decisions regarding the patient's care and management and to address appropriate treatment, and allows timely notification and discussion of management issues pertaining to the prevention of disease spread. The last two decades have seen a revolution in the understanding, management, diagnosis, control, and prevention of infectious diseases.[12,13] This period has encompassed the discovery of emerging equine agents, antimicrobials, and vaccines, as well as a wealth of improved diagnostic tests for equine practitioners. Despite these advances, infectious diseases remain a leading cause of equine morbidity and mortality, with resurgence of certain infections (e.g., WNV), an increasing population of elderly, more susceptible horses, and an increasing international equine commerce expanding the geographic distribution of pathogens.[14,15] The focus of rapid diagnosis of infectious diseases also has shifted during this time. The most obvious change has been the appearance and increasing importance of nucleic acid amplification—based techniques, primarily the PCR, at the expense of traditional methods of clinical microbiology.[16] The PCR has become an increasingly important tool in microbial diagnosis in recent years, mainly because of its rapidity, high sensitivity, and high specificity. These superior characteristics have propelled the field of PCR-based molecular diagnostics into the arena of applied diagnostics for infectious agents. Because the number of published and offered PCR assays is steadily rising, there is a need for critical evaluation, comparison of performance, and eventually also standardization of methods to enable equine practitioners to select the optimal method of testing.

29.14 SAMPLE SUBMISSION

Nucleic acid techniques to detect the presence of infectious agents in biologic specimens require stringent quality guidelines. These guidelines aim to ensure the stability of nucleic acids (both genomic DNA and total RNA), which are the target for molecular-based diagnostic methods. Whole blood samples are collected aseptically into evacuated blood tubes containing ethylenediaminetetraacetic acid (EDTA); body fluids (e.g., thoracic, abdominal, joint, cerebrospinal, tracheal wash [TW], bronchoalveolar, and guttural pouch lavage fluids) and tissues should be collected into serum tubes without additives; nasal or nasopharyngeal secretions should be collected with rayon or dacron swabs and are best kept in a sterile serum or conical tube (virus transport medium recommended for the detection of viruses); fecal material should be collected into small fecal cups or serum tubes (Table 29-2 and Fig. 29-1). All samples must be sent cooled on blue ice by express mail overnight to the laboratory. Freezing of samples should be avoided. Short-term storage for a period of 2 to 3 days before shipment (over a weekend) should be in a refrigerated compartment. Each sample should be properly labeled and accompanied by a submission form containing information on the animal, owner, veterinarian, sample, and pathogen(s) to be tested for (most submission forms can be downloaded from the respective laboratory's website). The laboratory should be notified in advance, and inquiry should be made about the availability of the offered tests as well as turnaround time and associated costs. Incoming samples normally are processed the same day, and PCR results usually are available within 24 to 48 hours if the nucleic acid passes quality control.

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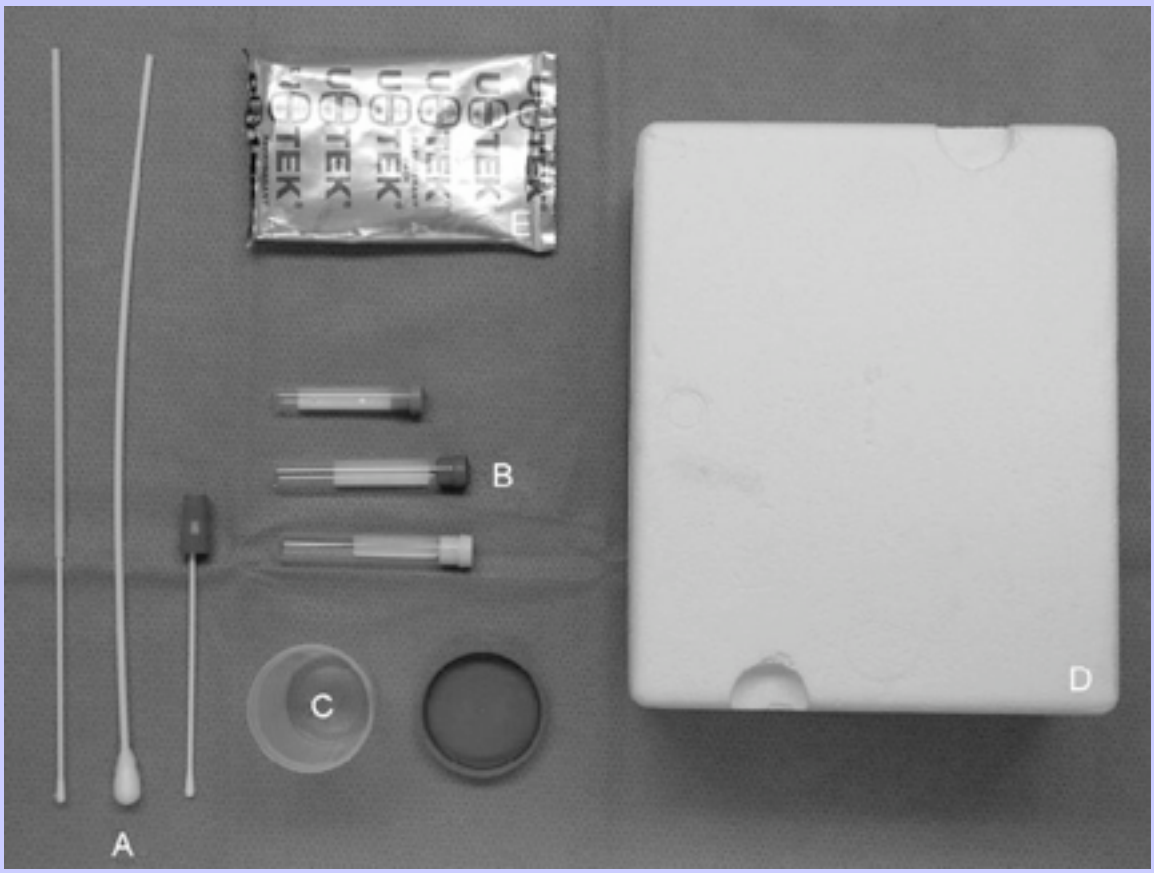
Table 29-2 Tissue Samples Commonly Used for the Molecular Detection of Common Equine Pathogens

Pathogen	Tissue Submission
Anaplasma phagocytophilum	Whole blood
Corynebacterium pseudotuberculosis	Aspirate from abscess, body fluid
Equine herpesvirus 1	NPS, whole blood, TW, BAL, CSF, CNS
Equine herpesvirus 4	NPS, whole blood, TW, BAL
Equine influenza virus	NPS, TW, BAL
Lawsonia intracellularis	Feces, intestinal biopsy
Neorickettsia risticii	Whole blood, feces
Neospora hughesi	CSF, CNS
Rhodococcus equi	TW, BAL, feces
Sarcocystis neurona	CSF, CNS
Streptococcus equi	NPS, NPL, GPL, lymph node aspirate
West Nile virus	Whole blood, CSF, CNS

BAL, Bronchoalveolar lavage fluid; *CNS,* cerebrospinal tissue; *CSF,* cerebrospinal fluid; *GPL,* guttural pouch lavage; *NPL,* nasopharyngeal lavage; *NPS,* nasal or nasopharyngeal swab; *TW,* tracheal wash fluid.

Fig. 29-1 Collection and shipping material routinely used to submit equine tissue samples for molecular detection. The picture shows **A,** three sterile swabs of different lengths; **B,** three sterile, evacuated tubes with and without additives; **C,** a sterile cup with lid; **D,** a Styrofoam shipping container; and **E,** and a cooling element to keep the samples cooled.



29.15 CLINICAL APPLICATIONS

An array of nucleic acid amplification techniques may be offered by laboratories in order to establish an etiologic diagnosis of equine infectious diseases. Several published studies have shown the benefit of nucleic acid amplification techniques compared with conventional microbiologic techniques. Current efforts are aimed at improving the diagnostic efficiency of molecular techniques, both for common and for less common infectious agents. To facilitate a decision about which pathogens should be evaluated for in a specific case, some laboratories offer panels covering specific organ systems (e.g., respiratory, gastrointestinal, neurologic). Such panels test for several common pathogens for each organ system. Some of the diagnostic PCR applications most relevant for equine practice are presented in the following sections, along with their advantages and potential pitfalls.

29.15.1 Respiratory Pathogens

Respiratory pathogens often are contagious, and infections must be diagnosed rapidly in order to prevent a disease outbreak and institute the appropriate management plan. The short turnaround time and reliability of PCR testing makes this molecular technology an ideal tool for the diagnosis of respiratory pathogens.

Equine influenza is commonly diagnosed by virus isolation or detection from nasopharyngeal swabs collected from horses during the early febrile stage of the disease. Virus can be grown from nasopharyngeal swabs by inoculation and incubation of embryonated chicken eggs or passage through Madin-Darby canine kidney cells. Although isolation of the virus is essential to allow antigenic and genetic characterization of the strain, this technology is time-consuming, and successful isolation is to be expected in at best 50% of cases. Furthermore, because mutations have been reported to occur during the process of viral culture, recovered isolates must be viewed critically. In recent years new methods for virus detection, such as antigen detection enzyme-linked immunosorbent assay (ELISA) and PCR assay, have been described; such methods allow a rapid diagnosis in the acute phase of infection. The commercially available Directigen Flu A assay* detects nucleoprotein, one of the type-specific antigens of type A influenza viruses, and was designed for use in cases of human influenza infection. Although this assay has the shortest turnaround time of all antigen tests (i.e., 15 minutes), its sensitivity decreases when low titers of virus are present (e.g., in a partially immune horse with subclinical signs or in a clinical case past the acute onset of disease). In recent years, PCR-based assays with higher sensitivity than virus isolation and antigen-capture ELISA have been described for the identification of equine influenza virus directly from clinical samples (Table 29-3).[17–19]

Amplification of the single-stranded RNA of equine influenza viruses is performed by reverse transcriptase–PCR (RT-PCR) technology, using a one-step, nested, or real-time approach. The hemagglutinin, nucleoprotein, and matrix gene are the commonly targeted genes for these molecular assays. Unfortunately, comparison of the different PCR assays is precluded by the use of different technologies, the lack of standardization among the assays, and variation in targeted genes. Nucleotide and deduced amino-acid sequences of portions of the hemagglutinin gene are now routinely used for phylogenetic characterization of outbreak strains. Furthermore, novel real-time assays can be used as a viable replacement for the more traditional methods of quantifying equine influenza virus in vaccine efficacy studies. Another advantage of assays such as antigen detection ELISA and PCR assay is their ability to detect nonviable virus, a situation that may occur when nasopharyngeal samples are frozen or not adequately stored and/or shipped to a diagnostic laboratory.

Table 29-3 Comparison of Different Viral Detection Methods Using Nasopharyngeal Secretions from Naturally and Experimentally Infected Horses with Equine Influenza Virus

			Detection Method (Mean Detection Days)			
Infection Type	**Number of Horses**	**Collection Type**	**VI**	**DFA**	**RT-PCR**	**Reference**
Experimental	4	Sequential postexposure	4/4 (5.5)	2/4 (3.5)	4/4 (6)	17
Natural	11	Single at peak of disease	5/11	7/11	9/11	18
Natural	171	Single at peak of disease	8/171	14/171	35/171	19

DFA, Directigen Flu A; *RT-PCR,* reverse-transcription polymerase chain reaction; *VI,* virus isolation.

EHV-1 and EHV-4 are important, ubiquitous equine viral pathogens that cause important economic losses in the equine industry. Both are double-stranded DNA alphaherpesviruses that affect the equine respiratory tract and can establish lifelong latent infection after primary exposure. Traditionally, virus isolation has been the gold standard for diagnosing EHV-1 and EHV-4 infections. The sample of choice is a nasal or nasopharyngeal swab, which should be taken early in the febrile phase of the disease. The swabs should be kept in viral transport medium and shipped on ice to a veterinary diagnostic laboratory. Because of the lymphotropism of EHV-1, virus isolation can also be attempted from citrated or heparinized whole blood. Virus isolation requires the maintenance of specific cell culture lines, making this process relatively expensive and time-consuming. EHV-1 can be propagated in a broad range of cell lines; however, EHV-4 grows only in cell lines of equine origin. Virus isolation is often hampered by the fragility of the virus, intermittent viral shedding, and the interference with local antibodies. PCR offers an alternative to virus isolation and has proven to be a sensitive method of detecting EHV-1 and EHV-4 in respiratory secretions, peripheral blood lymphocytes, and other tissues.[20–22] Many conventional PCR assays have been established to study the pathophysiology and improve the diagnosis of these viruses. Conventional one-step or nested PCR assays do have inherent risks of carry-over contamination resulting from postamplification steps required to detect the PCR products. Novel molecular platforms such as the real-time PCR assay have strongly reduced the risk of contamination. PCR assays used in routine diagnostics are based on the detection of viral genomic DNA and are therefore unable to distinguish among lytic, dead, or latent virus. Alternative molecular approaches have recently been established using the real-time PCR to allow discrimination among the different viral states in horses naturally infected with EHV.[23] Discrimination among the different viral states is now possible by (1) targeting several genes (e.g., glycoprotein, latency-associated transcripts); (2) detecting viral genomic DNA and transcriptional activity of the target genes at the messenger RNA (mRNA) level; and (3) using absolute quantification (Table 29-4). Viral threshold loads are used in selected human infectious diseases (e.g., human immunodeficiency virus [HIV], hepatitis C virus [HCV]) to determine disease stage and response to antiviral therapy. The concept of viral DNA threshold has been used diagnostically in EHV-4–infected horses to discriminate between lytic and nonreplicating virus.[23] A similar approach will likely be adopted in the near future for the molecular diagnosis of EHV-1 in order to differentiate

among viral states, as well as to evaluate the efficacy of antiviral therapy and determine the risk of exposure of a PCR-positive horse to other horses. Until such an approach is routinely instituted by veterinary laboratories, the random testing of normal horses for EHV-1 by PCR assay should be avoided, because practicing veterinarians and regulatory officials who receive positive PCR test results on samples they submit may be unaware of the complexities involved in test interpretation, leading them to make inappropriate decisions regarding quarantine of equine facilities or cancellation of competitions.

Table 29-4 Differentiation Among the Viral States of EHV-1 and EHV-4 by Targeting Several Genes and Detecting Either Viral Genomic DNA or Transcriptional Activity of the Target Genes at the Messenger RNA Level

	Viral State		
Target Gene and Nucleic Acid Type	**Nonreplicating Virus**	**Lytic or Replicating Virus**	**Latent Virus**
Glycoprotein B gene using gDNA	Yes	Yes	Yes
Glycoprotein B gene using mRNA	No	Yes	No
Latency-associated transcripts using mRNA	No	No	Yes

gDNA, Genomic DNA; *mRNA,* messenger RNA.

Streptococcus equi subsp. *equi* infection rarely is associated with detection difficulties when conventional cultures are used in clinically affected horses. Culture of nasal swabs, nasal or guttural pouch washes, or exudates aspirated from an abscess remains the gold standard for the detection of *S. equi*. Culture, however, may be unsuccessful during the incubation and early clinical phases of infection, and the presence of other beta-hemolytic streptococci, especially *Streptococcus equi* subsp. *zooepidemicus,* may complicate interpretation of cultures. Available PCR assays are designed to detect the DNA sequence of the *S. equi* M protein (SeM) gene, the gene for the antiphagocytic M protein of *S. equi*. This gene offers enough nucleotide variations between the two *S. equi* subspecies to allow full discrimination in clinical specimens. The test can be completed in a few hours, and results may be available on the same day samples are taken. One of the pitfalls of PCR testing has been its inability to distinguish between dead and live organisms; therefore, in the past, positive results have been considered presumptive until confirmed by culture. Nowadays the viability issue can be addressed by quantitation of the SeM gene or detection of transcriptional activity of the SeM gene at the RNA level. In several studies, PCR proved to be up to three times more sensitive than culture (Table 29-5).[24–26] PCR assay accompanying culture on a nasal swab or guttural pouch lavage may be used in a control program to select possible carrier animals, because PCR testing is capable of detecting *S. equi* DNA in guttural pouch lavages for weeks after disappearance of live organisms. Such is not the case for the nasopharynx, in which the efficient mucociliary apparatus removes organisms and DNA at the same time. PCR should be considered to detect asymptomatic carriers, establish the *S. equi* infection status of asymptomatic horses, and determine the success of elimination of *S. equi* from the guttural pouch. A particular problem in the management of strangles outbreaks is

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the lack of a suitable assay to differentiate between wild and vaccine *S. equi* strains. Recent studies have shown gene variations in the N-terminal region of the SeM gene of various field isolates, allowing epidemiologic analysis of disease transmission.[27] Furthermore, a deletion in the *aroA* gene of a live attenuated strangles vaccine[*] marketed in Europe has allowed the development of a PCR assay able to differentiate between wild and vaccine strains.[27] Such an assay has, however, not yet been developed to differentiate between the intranasally applied attenuated live vaccine[†] marketed in North America and field isolates.

Table 29-5 Comparison of Culture and PCR Assay for the Detection of ***Streptococcus equi*** in Equine Nasopharyngeal Secretions (Swab and Wash), Guttural Pouch Lavage Fluid, and Abscesses After Natural Outbreaks

		Detection Method		
Number of Specimens	**Sample Type**	**Culture**	**PCR**	**Reference**
117	Nasal swabs and washes	15/117	37/117	24
61	Nasopharyngeal swabs	18/61	34/61	25
70	Guttural pouch washes	41/70	53/70	
28	Nasal swabs	4/28	13/28	26
15	Abscesses	5/15	12/15	

PCR, Polymerase chain reaction.

Rhodococcus equi is an important cause of chronic suppurative bronchopneumonia with extensive abscessation in foals 3 weeks to 6 months of age. Culture of the organism from TW fluid currently is considered the gold standard for diagnosis.[28] However, it can be difficult to reliably grow *R. equi* from a single TW sample, possibly because of prior antimicrobial administration or overgrowth by multiple pathogenic bacterial species.[29,30] Hillidge[31] reported that only 62% of foals with positive *R. equi* cultures at necropsy and 64% of those with radiographic evidence of lung abscessation yielded *R. equi* on culture of TW fluid. PCR has been evaluated in order to increase the diagnostic sensitivity of TW fluid samples. Strains of *R. equi* isolated from sick foals uniformly contain an 85- to 90-kilobase (kb) plasmid that carries the gene responsible for expression of a 15- to 17-kDa antigen *(vapA)* of undetermined function.[32,33] Environmental strains of *R. equi* not associated with disease do not contain this plasmid. Therefore detection of the *vapA* gene of *R. equi* in a TW fluid sample from a foal with pneumonia can be considered diagnostic. Both culture and PCR, however, may detect environmental contaminants of *R. equi* in TW fluid, but PCR has the ability to distinguish between virulent and avirulent strains. Foals may have virulent or avirulent strains of *R. equi* present in their airways as contaminants that are not responsible for clinical signs of pneumonia. This situation may be more likely on farms where *R. equi* problems are endemic. In a recent study evaluating the sensitivity of conventional culture, PCR, and serology in 53 foals with pneumonia, PCR of TW fluid was found to be more sensitive and specific for the diagnosis of *R.*

equi pneumonia than the other two available diagnostic tests.[34] PCR should be used in conjunction with standard culture because of the probability of the presence of multiple bacterial pathogens and the inability of PCR to determine antimicrobial sensitivity of *R. equi*. PCR, with its higher sensitivity and specificity, may be useful to rule out *R. equi* pneumonia in culture-negative foals that have failed to improve with standard antimicrobial therapy and have clinical signs consistent with *R. equi* pneumonia. It also may be useful in monitoring response to therapy and deciding when to discontinue therapy in foals that are confirmed to have *R. equi* pneumonia. In clinical situations in which the severity of the respiratory signs of the patient prevents the collection of TW fluid, feces have been shown to be a sensitive surrogate specimen for the molecular detection of *R. equi*.[35] The study determined that fecal PCR assay had a diagnostic accuracy similar to that of culture of TW fluid samples and that false-negative fecal PCR results for *R. equi* were associated with prior use of antimicrobials.

* Directigen Flu A, Becton, Dickinson and Company, Franklin Lakes, NJ.

* Equilis StrepE, Intervet UK Limited, Walton Manor, Walton, Milton Keynes, United Kingdom.

† Pinnacle I.N., Fort Dodge Animal Health, Overland Park, KS.

29.15.2 Neurologic Pathogens

Although highly sensitive and specific PCR assays have been developed for detection of viral and protozoal genomes in the cerebrospinal fluid (CSF) of neurologic patients, these methods often are of limited value in the routine diagnosis of these diseases because viremia is often very short-lived or the pathogen has no affinity to the cells of the CSF. Consequently, pathogens are usually no longer detectable at the onset of systemic or CNS signs.

Equine protozoal myeloencephalitis (EPM), caused by the protozoal apicomplexan parasites *Sarcocystis neurona* and *Neospora hughesi,* represents one of the greatest diagnostic challenges for equine practitioners. Detection of the parasite at necropsy is considered the gold standard. Therefore clinical diagnosis is based on clinical findings, exclusion of other neurologic diseases, and the use of serologic assays (e.g., Western immunoblot, indirect immunofluorescent assay) on serum and CSF.[36–38] Molecular diagnostics has also been investigated, but sensitivity was found to be low.[39] Apparently, intact merozoites rarely enter CSF, and free parasite DNA is destroyed rapidly by enzymatic action.[40] Based on its low sensitivity, PCR testing of CSF should not be recommended for routine diagnosis of EPM. In contrast, PCR testing of neural tissue has been shown to be useful as a postmortem test.[41] Detection and isolation of *S. neurona* from peripheral blood has been reported only in experimental studies.[42,43] Therefore molecular detection of *S. neurona* in blood is very insensitive and should not be used in order to document or rule out EPM in a horse with neurologic signs.

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Diagnosis of WNV encephalitis in horses currently is based on observation of compatible clinical signs (e.g., ataxia, paresis, paralysis, hyperesthesia, muscle fasciculation, seizures, fever) and one or more of the following: isolation of WNV from blood, CSF, or tissue; a fourfold increase in plaque reduction neutralization test antibody titers on paired serum samples taken 2 weeks apart; or the detection of IgM antibody to WNV by IgM-capture ELISA.[44,45] Given the nonspecificity of the IgM ELISA (i.e., it does not differentiate between disease and exposure) and the time required to serologically confirm WNV infection, alternative tests able to rapidly detect WNV in clinical specimens are important. RT-PCR using a one-step, nested, or real-time approach has been evaluated to investigate antemortem cases of suspected WNV encephalitis in horses and humans using blood. The diagnostic sensitivity of WNV RT-PCR using either serum or whole blood was very low.[46–48] However, 57% to 70% of CSF samples from human beings with serologically confirmed WNV infection tested positive by real-time RT-PCR.[46,47] The reduced ability to detect WNV in CSF or serum from patients with serologically

confirmed WNV infection is likely a result of the short-lived viremia in dead-end hosts and emphasizes the fact that if WNV is to be detected in blood or CSF the sample should be collected early during the disease process. Investigation of the sensitivity of RT-PCR on CSF from horses with WNV encephalitis has not yet been reported. RT-PCR also has been shown to accurately identify WNV in field-collected mosquito pools, avian tissues, and human and equine brain tissue samples with a degree of sensitivity approaching that of virus isolation in Vero cells.[47–49]

Myeloencephalopathy is an uncommon presentation of EHV-1 infection and should always be considered as a differential diagnosis when a horse develops sudden neurologic signs (e.g., ataxia, paresis, urinary incontinence), especially if multiple horses on the premises are involved or when a recent history of fever, abortion, or viral respiratory disease in the affected horse or herdmates is reported.[50] Diagnosis often is based on history, clinical signs, and xanthochromia and elevated total protein concentration in CSF resulting from vasculopathy. Attempts to isolate virus from the blood or CSF of patients often are unsuccessful because the peak of viral shedding usually has passed by the time neurologic signs appear.[51] However, affected horses can shed the virus in nasal secretions and thus represent a risk of infection for unaffected in-contact horses. This outcome recently has been reported in a hospital setting in which horses developed neurologic disease after having been exposed to horses with EHV-1 myeloencephalopathy.[52] Therefore it is imperative to determine the risk of shedding in a suspected horse in order to initiate an appropriate infectious disease control protocol. PCR assay, as previously shown for viral respiratory diseases, is a fast and sensitive molecular diagnostic tool and should be performed on blood and nasal or nasopharyngeal swabs to document viremia and nasal shedding, respectively.[41,53,54] The dilemma as to whether the virus is in a lytic, nonreplicating or latent state can be addressed by using absolute quantitation or transcriptional activity of the target gene similar to the approach used for EHV-4.[23] Research groups have recently identified a region of variation in the genome of different EHV-1 strains that correlates directly with their ability to cause neurologic disease.[55] The sequence variation occurs in the DNA polymerase gene of the virus, which is involved in initial viral replication within infected cells and may also be involved in establishment of latency and reactivation. Rapid PCR assays have been established to allow differentiation between neuropathogenic and nonneuropathogenic strains.[56] However, such assays have moderate specificity, because 87% of neuropathogenic stains have been shown to harbor the mutation. Therefore such assays should be used judiciously, and the results should always be interpreted in the context of clinical presentation.

29.15.3 Gastrointestinal Pathogens

The detection of equine gastrointestinal pathogens using conventional or molecular tests often is very challenging because these pathogens either are difficult to grow in cell culture systems or can be present in pathogenic or nonpathogenic forms, making interpretation of positive results difficult. Furthermore, the use of fecal material for molecular diagnostics has been associated with false-negative results because of the presence of inhibitory substances in the feces that can interfere with nucleic acid extraction or amplification.[57] However, development and use of specific extraction kits* have improved the yield of nucleic acid from feces.[58]

Neorickettsia risticii (formerly *Ehrlichia risticii*) is the rickettsial agent responsible for Potomac horse fever (PHF), a serious enterocolitis of horses. Because of the nonspecific nature of the clinical signs, a provisional diagnosis of PHF is often based on the presence of typical clinical signs and the seasonal and geographic occurrence of the disease. A definitive diagnosis of PHF, however, should be based on isolation or detection of *N. risticii* from blood or feces of infected horses.[59] Isolation of the agent in cell culture, although possible, is time-consuming and not routinely available in many diagnostic laboratories. The recent development of *N.*

risticii–specific PCR assays has greatly facilitated the diagnosis of PHF.[60,61] These molecular assays have contributed to the investigation of the epidemiology of PHF, allowing the discovery of helminthic vectors and intermediate and definitive helminthic hosts as well as revealing the natural route of infection.[62–64] Nucleic acid of *N. risticii* can be detected in the blood and feces of naturally or experimentally infected horses, but the detection period does not necessarily coincide between the two sample types (Fig. 29-2). Based on these results, we recommend analyzing both blood and feces from suspected horses in order to enhance the chance of molecular detection of *N. risticii*. Another application of PCR has been recently described: the first equine cases of PHF from Nova Scotia using formalin-fixed and paraffin-embedded colon tissue.[65]

An emerging equine gastrointestinal pathogen, *L. intracellularis*, has been described in young horses.[66] This obligate intracellular bacterium is the causative agent of proliferative enteropathy (PE), a transmissible enteropathy known to affect a wide range of domestic and wild animal species.[67] This disease has a worldwide distribution and likely is underrecognized in horses. Antemortem diagnosis can be challenging and is based on interpreting clinical signs (e.g., lethargy, weight loss, subcutaneous edema, diarrhea, colic), clinicopathologic results (e.g., hypoproteinemia), and ultrasonographic findings (e.g., thickened small intestine) and excluding other causes of similar gastrointestinal findings.[68] Currently, culture of the organism is difficult and is not routinely offered by laboratories. Antemortem diagnosis relies on serology and PCR,[69–70] but these tests have not been systematically evaluated in horses. The combination of both tests as well as repeated fecal sampling from target animals for PCR assay will increase the chance of diagnosing the disease. Novel PCR assays, such as the real-time PCR, have increased the sensitivity of molecular detection, compared with initial conventional assays.[71] PCR testing has the advantage of being fast and can yield positive results in the early stage of disease, when antibodies are not yet measurable. Prior use of antimicrobials can negatively affect the molecular detection of *L. intracellularis* in feces. Therefore in a suspected case, fecal collection for PCR testing should be performed before institution of any antimicrobial treatment.

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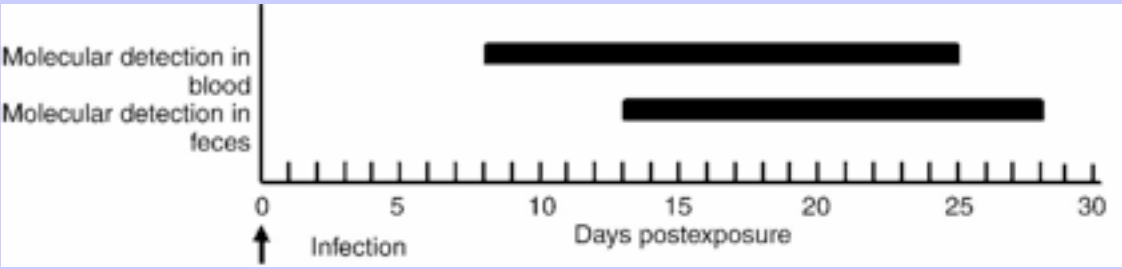
Fig. 29-2 Molecular detection period of *Neorickettsia risticii* in blood and feces of experimentally infected horses. From Pusterla N, Madigan JE, Leutenegger CM: Real-time polymerase chain reaction: a novel molecular diagnostic tool for equine infectious diseases. *J Vet Intern Med* 20:3, 2006. Reprinted with permission of the American College of Veterinary Internal Medicine.



* DNA Stool Mini Kit, QIAGEN, Valencia, CA.

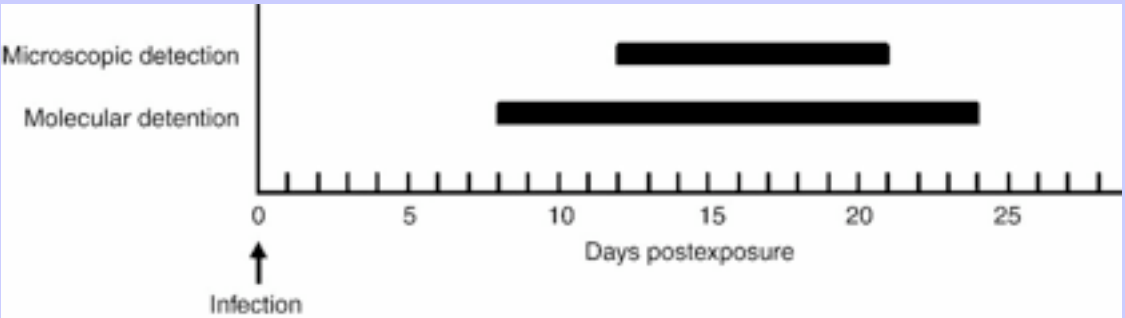
29.15.4 Miscellaneous Pathogens

Equine granulocytic ehrlichiosis (EGE) is caused by *Anaplasma phagocytophila* (formerly *Ehrlichia equi*), a rickettsial pathogen transmitted by *Ixodes* ticks. Diagnosis often is based on awareness of the geographic area for infection, presence of typical clinical signs, presence of abnormal laboratory findings, and identification of characteristic pathogen inclusions in the cytoplasm of neutrophils and eosinophils in a peripheral blood smear stained with Giemsa or Wright stain.[59] PCR has been used for many years to study several aspects of the epidemiology and pathophysiology of EGE.[72,73] For clinical purposes, the material of choice is whole blood. PCR has been shown to be a very sensitive and specific tool, helping with diagnosis especially during early and late stages, when the number of organisms is too small for diagnosis by microscopy (Fig. 29-3).[74]

Corynebacterium pseudotuberculosis is a common cause of external and internal abscesses in horses from arid regions of the western United States.[75] The epidemiology recently has been investigated with the help of PCR technology, and flies have been identified as potential vectors.[76,77] *C. pseudotuberculosis* is easy to grow on culture, and use of PCR testing on clinical samples is restricted to specific situations (e.g., culture-negative aspirates or body fluids).

In recent years PCR assays for the detection of *Salmonella* species in fecal samples from horses admitted to veterinary hospitals have been evaluated.[78–81] All the studies showed that significantly more fecal samples were positive according to PCR assay than according to microbiologic culture. The reasons why some fecal samples, from which *Salmonella* organisms cannot be isolated, are PCR positive need to be determined before PCR assays are routinely used in the hospital setting for the diagnosis of salmonellosis and surveillance programs.

Fig. 29-3 Microscopic and molecular detection period of *Anaplasma phagocytophila* in the blood of horses experimentally infected with *Ixodes scapularis*. From Pusterla N, Madigan JE, Leutenegger CM: Real-time polymerase chain reaction: a novel molecular diagnostic tool for equine infectious diseases, *J Vet Intern Med* 20:3, 2006. Reprinted with permission of the American College of Veterinary Internal Medicine.



Additional PCR assays for *Borrelia burgdorferi*, equine arteritis virus, *Leptospira* species, *Mycobacterium* species, *Clostridium difficile,* and methicillin-resistant *Staphylococcus aureus* have been developed and are being used in the research setting.[82–89] These assays likely will be offered for diagnostic purposes when additional clinical samples from horses have been analyzed.

29.16 MOLECULAR TESTING FOR INFECTIOUS DISEASES IN CATTLE, SHEEP, AND GOATS

Sharon K. Hietala

Beate M. Crossley

The availability of molecular-based diagnostic technologies designed to identify infection or genetic conditions by detecting specific genome targets in the host or agent DNA or RNA has expanded logarithmically in the past decade. Diseases and genetic conditions affecting cattle, sheep, and goats are now commonly studied and diagnosed using molecular techniques, and in particular PCR assays. PCR-based approaches, which by nature can be extremely sensitive for the detection of infectious agents, were once considered useful only in research laboratories based on concerns ranging from the risk of laboratory contamination and false-positive findings to high per-assay costs. With the commercial availability of specialized instrumentation, reagents, and technical training, 446
the criticisms have largely been overcome. Molecular technologies are now generally available for routine 447
diagnostic services provided by state and federal diagnostic laboratories and university laboratories, as well as commercial laboratories. The technical complexity of molecular-based diagnostics, paired with the wide range of assays available to diagnose genetic and infectious diseases of food animals, means that no single laboratory can feasibly provide comprehensive testing for all species and all diseases. Instead, laboratories tend to focus on the diseases or genetic conditions of primary significance to their allied industries and to use the technologies that provide the most rapid, reproducible and economical results for their particular group of clients. Largely based on this specialization within laboratories, molecular-based assays may be developed and put into use without significant effort toward assay standardization and validation. The list of PCR-based assays available for detection of infectious agents in particular has grown significantly in recent years, although with no guarantee that the assays have been suitably designed, tested in the field, or clearly advertised as to their “fitness for purpose.” For molecular-based assays the selection of the genetic sequence (DNA or RNA) used as the target of the diagnostic assay is heavily dependent on the proposed use of the test and on the availability of known genomic sequence(s) for development of the assay. All genomes accumulate mutations over time, with some genes being highly mutable to allow evolutionary advantage—for example, those genes that encode antimicrobial resistance or surface protein conformations used for evading the host immune system. Other genes (e.g., those encoding specific functions such as replication) tend to remain highly conserved and stabile to protect the survival of the organism. Assays used to detect a specific agent—for instance, bovine virus diarrhea (BVD) virus—can be designed to target a conserved region of the genome that is shared by all members of the species. Alternately, assays used to characterize or subtype particular strains or isolates—for example, BVD virus (BVDV) type 1b—can be designed to target regions with significantly more mutability or sequence variation. Assays designed as “fit” for surveillance testing must often sacrifice the ability to discriminate closely related pathogens, such as BVDV, from the genetically related border disease virus in order to have the needed surveillance sensitivity to detect the broad range of potential BVDV isolates. Similarly, assays designed for test and cull or related disease-control programs must have a high diagnostic specificity for detecting only the agent or trait of interest. These assays tend to sacrifice diagnostic sensitivity or detection level in order to minimize the risk of false-positive results. Although molecular diagnostics provides a powerful and rapidly advancing tool, the clinician is advised to use molecular-based assays with appropriate awareness of their individual strengths and weaknesses, including the designated use or “fitness for purpose.”

Unquestionably, molecular technologies will continue to be developed and implemented in veterinary medicine. Although it can be expected that some technologies will replace existing procedures, it should be expected that other molecular tools will be no more than a supplement to traditional diagnostic approaches.

29.17 SAMPLE SUBMISSION

As with any diagnostic technology, the specimen used must be appropriate for the disease or genetic condition, and consideration must be given to the timing and pathogenesis of the disease process and availability of the intact genetic material being targeted by the diagnostic assay. Among the important criteria in the selection and use of molecular-based assays are onset and duration of agent replication in the host, specific tissue(s) affected, and the relative abundance of target DNA or RNA over the course of the infection. In addition to tissues obtained from postmortem investigation or surgical sampling, antemortem diagnostic testing can target genetic material recovered from swabs of mucous membranes or from blood, urine, milk, skin scrapings, or fecal material as appropriate to the disease process.

Because all molecular-based diagnostic tests detect genomic material in one form or another, the isolation and purification of nucleic acids (DNA or RNA) from the diagnostic specimen is critical to the success of the assays. Depending on the tissue or specimen used for diagnostic testing, recovery of nucleic acid in sufficient quantity and quality can be problematic. Common sources of assay failure include substances in the sample that can interfere with the chemistries used in detection or PCR-based amplification steps. Examples include but are not limited to heparin, iron, peroxidases, hemoglobin, and myoglobin, as well as the relative abundance of total DNA or RNA associated with the different specimen types. Another common source of assay failure is destruction of target nucleic acids in the specimen before testing, commonly a result of enzymes associated with postmortem autolysis. Because of the complexities of nucleic acid recovery and target nucleic acid detection, assays developed for use with one matrix, for example whole blood, may not be suitable for use with other matrices, such as milk or feces. Appropriate sample collection buffers, storage temperatures, and shipping requirements are available from the laboratories performing the specific testing.

29.18 MOLECULAR-BASED DIAGNOSTIC TECHNOLOGIES

29.18.1 Hybridization Probes

Nucleic acid fragments, either DNA or RNA, can be detected by hybridizing to a complementary fragment of nucleic acid that has been marked with a reporter dye or enzyme. The short strands of DNA or RNA, generally chemically synthesized and referred to as *oligonucleotides,* are identified as hybridization probes when marked with a reporter dye or enzyme. Radioactively labeled probes, though once the standard, have largely been replaced by enzymatic tags, such as avidin-biotin, peroxidase, and chemiluminescent tags. Target nucleic acids can be detected directly in the diagnostic specimen when sufficiently abundant or may be detected after PCR-based amplification of the nucleic acid target.

29.18.2 Southern, Northern, and Dot-blots

Various techniques are used to immobilize genetic material before detection steps, with or without prior PCR amplification. As a group the techniques are referred to as *blots. Dot-blots* and *Southern blots* refer to DNA bound to nitrocellulose membranes, whereas *Northern blotting* is the terminology used when RNA is immobilized onto membranes. In Southern and Northern blots, nucleic acid fragments are first separated by size

through use of an electric current running through a semisolid gel, a technique referred to as *gel electrophoresis*. The nucleic acid detection step for DNA and RNA blots may include a specific hybridization probe or may simply use the molecular weight of the DNA or RNA fragment. Related terminology includes *Western blot,* which describes protein immobilized on a membrane, and *immunoblot*, referring to detection of the immobilized protein using specific antibody as an immunologic marker.

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29.18.3 In Situ Hybridization

The laboratory technique referred to as *in situ hybridization* allows for localization and observation of a DNA or RNA target within a histologic tissue section.[93,94,100,103] The hybridization probes are typically end-labeled with a radioactive or enzymatic reporter molecule. FISH is a relatively new staining approach that shows promise for future rapid diagnostic applications. ISH using RNA probes (riboprobes) is another rapidly advancing technology, with improved detection sensitivity compared with DNA probes, although it has been used primarily for studying viral infection and gene expression rather than for diagnostic applications. ISH technology can be applied to frozen or formalin-fixed tissues, with best results provided when the tissue is fixed as soon as possible postmortem to avoid loss of target nucleic acids during tissue autolysis. Nucleic acids from veterinary pathogens have been shown to be stabile in formalin-fixed, paraffin-embedded tissues for up to 15 years.[93,99] Because of technical complexity ISH is not yet widely applied to routine diagnostics but appears to be rapidly advancing in that direction.

29.18.4 Polymerase Chain Reaction

PCR is the most commonly applied of the molecular technologies and can be roughly grouped into standard PCR assays and the more rapid real-time or quantitative PCR assays. Both techniques amplify minute quantities of target DNA to levels that are detectable using laboratory instrumentation or special staining procedures. The principle difference in the two approaches is that standard PCR testing is divided into two major processes in the laboratory: the amplification of the DNA target, followed by the detection of the amplified target DNA. Real-time PCR testing combines the two steps so that target detection occurs during the DNA amplification process. The advantages of PCR assays over standard isolation and identification techniques is the significantly reduced time required to obtain a result, with PCR results generally provided in hours compared with days. PCR-based technologies are a particularly powerful tool when designed to detect the presence of organisms that are extremely slow-growing or difficult to culture, such as the *Mycobacterium avium* subsp. *paratuberculosis* (Johne's disease) bacterium, *Leptospira* species, and the bluetongue virus, among others. Because PCR-based assays detect nucleic acids, they do not require that the organism be viable in the sample. This is considered an advantage for those agents that may be easily destroyed during sample transport to the laboratory but a disadvantage where fragments of a pathogen's genome may persist for weeks or months after the animal has become noninfectious. An excellent example of this is the bluetongue virus; PCR can detect nonreplicating viral genome adherent to red blood cells for several weeks after live virus can be recovered from the blood.

29.18.4.1 STANDARD POLYMERASE CHAIN REACTION

Standard PCR testing is used for detection of DNA or RNA and can be applied to mammalian, microbial, or viral genomes. The PCR technique is based on the natural cross-linking of complementary (matching) nucleic acids to form double-stranded DNA. When DNA is sufficiently heated, double-stranded DNA separates into single strands, each of which can then be used as a template for chemically or biologically generating an exact copy. Specific heat-stabile polymerase enzymes are used in the laboratory for the process of DNA replication.

The PCR reaction amplifies DNA using multiple cycles of heating double-stranded DNA to generate a single-strand template and cooling sufficiently to allow the polymerase enzyme to generate a new double-stranded DNA made up of the original strand and its test-tube—synthesized copy. For diagnostic assay purposes, it is necessary to copy only a small but diagnostically characteristic fragment of any particular genome. This fragment is generally referred to as the *PCR target* or *target sequence*. PCR primers are short, chemically synthesized fragments, typically 10 to 30 nucleic acids in length, that are used to mark the beginning and end of the selected target sequence and, as their name implies, are used to prime or start the initial PCR amplification process. The choice of target sequence as well as appropriate primer design is critical to the accuracy and efficiency of PCR-based diagnostic assays. For detecting target RNA, as is needed for the PCR diagnosis of an RNA virus, the technique of RT-PCR is used. The reverse transcriptase enzyme converts target RNA into DNA, identified as cDNA or copy DNA, for use in the PCR steps. The PCR amplification process typically takes 2 to 6 hours to complete and is followed by detection steps that require additional hours to days to complete. Detection of the amplified DNA fragment, often referred to as an *amplicon,* uses techniques that identify the DNA fragment by molecular weight, by marking a specific target sequence in the amplified DNA with a hybridization probes, or by a combination of both (PCR and probe). PCR amplification followed by hybridization probe detection offers increased specificity and thus less chance of a false-positive finding and often provides a tenfold or greater increase in detection sensitivity. Depending on the stringency designed into the assay by balancing temperature, length of replication cycles, enzyme concentrations, and so on, false-negative results will occur when the sequence of the primers or probe does not precisely match the sequence of the target. In some cases PCR assays are very precise and designed to recognize a single nucleic acid polymorphism (SNP analysis) in the target sequence, and in other cases they are intentionally designed with lower stringency to allow some degree of variability among isolates or strains being detected by the assay. Because RNA viruses in general lack the proofreading enzymes found in DNA viruses, bacteria, and protozoa, they are at greater risk for appearance of random mutations at primer or probe sites. PCR false-negative results associated with primer or probe mismatches resulting from random genomic mutations at the primer or probe binding sites are of particular concern for RNA viruses and provide ample justification for a laboratory to investigate with alternate or additional technologies when negative PCR-assay results clearly do not match a clinical or epidemiologic pattern of disease.

29.18.4.2

NESTED POLYMERASE CHAIN REACTION

Nested PCR testing is a PCR technique modification generally used to increase the detection sensitivity of an assay.[92] During nested PCR testing, an initial PCR reaction amplifies a selected fragment of DNA, which is then used as template in a second round of PCR amplification. The second or nested PCR reaction targets one or more unique fragments of DNA within the initially amplified region. The two-step process has the advantages of increasing detection sensitivity and specificity and of diluting the impact of interference from potential PCR inhibitors found in some tissues and clinical materials. Nested PCR assays have been described for WNV, malignant catarrhal fever virus, and *Chlamydia* species, among others. The significant disadvantage of the two-step process comes from handling the first round of amplified DNA in the laboratory. With the high concentrations of target DNA available after PCR amplification, laboratories must take rigorous precautions to mediate the risk of contaminating laboratory workspaces, equipment, and reagents with the amplified DNA. The significant risk and associated costs of laboratory contamination and resulting false-positive results are used in many diagnostic laboratories as justification for charging additional fees or for not offering nested PCR techniques.

29.18.4.3 REAL-TIME POLYMERASE CHAIN REACTION AND REAL-TIME QUANTITATIVE POLYMERASE CHAIN REACTION

Diagnostic assays originally developed using standard PCR approaches are increasingly being converted to real-time PCR and real-time quantitative PCR (qPCR) technology to take advantage of the speed, technical efficiency, and cost reduction often associated with this approach.[96] Because real-time PCR technology completes both amplification and detection in the same reaction tube or well, there is no need for the laboratory to handle amplified DNA and risk workspace contamination. This noteworthy modification of PCR technology has been responsible for a significant expansion in use and general availability of PCR-based diagnostic assays. More important, the combination of amplification and detection in a single reaction vessel has allowed expansion of PCR-based assays into high-throughput, portable, and on-site formats as described for foot-and-mouth disease virus, anthrax detection, and others. Real-time PCR technology offers an additional advantage of supporting quantitative approaches to amplification and detection of the original target in the sample tested. Quantitative PCR testing answers a frequent criticism of standard PCR testing, specifically that detection limits, potentially as low as a single cell or viral particle, may produce a positive finding that is biologically irrelevant to clinical disease. Quantitative PCR technology allows the relative amount of target nucleic acid to be correlated with the associated clinical presentation.

29.18.4.4 MULTIPLEX POLYMERASE CHAIN REACTION

Multiplex PCR technology expands the use of PCR or real-time PCR-based detection from a single target to multiple targets simultaneously from a single specimen.[104,111,119] The ability to include multiple genome targets for a single virus or bacteria in a PCR assay minimizes the risk of a PCR false-negative result caused by genetic diversity within the agent of interest. Inclusion of targets for multiple closely related viruses has been used to differentially detect related pathogens, such as the closely related sheep- and wildebeest-associated forms of malignant catarrhal fever, to subtype BVD viruses, and to differentially detect virulent *Escherichia coli*. Multiplex PCR technology also has broad application in syndrome-based testing in which several pathogens may produce very similar or identical clinical pictures. A single diagnostic specimen could theoretically be used in a multiplex format to detect one or more agents associated with a particular clinical presentation, such as the multiple viral and bacterial agents in shipping fever complex. Prototypes of this approach have been developed but are not yet widely deployed, and there are technologic limits to the number of PCR assays that can be combined without significant loss of assay performance. In real-time PCR formats, three to five unique assays have been the practical limit, based on the technical limitations of commonly available equipment and detection dyes.

29.18.5 Isothermal Amplification

Isothermal amplification techniques use alternate chemistries to PCR technology and are carried out at a single temperature. Among the isothermal amplification technologies that have been used for the detection of veterinary pathogens are nucleic acid—based amplification (NASBA), loop-mediated isothermal amplification (LAMP), rolling circle amplification, and direct signal amplification systems.[102,112] None of these technologies has seen widespread diagnostic application, possibly because of the complexity of initial assay design, but they may offer future PCR alternatives that can be more automated, portable, or developed as fully integrated self-contained testing units.

29.18.6 Genechips and Microarrays

Arrays of DNA or RNA fragments, variously referred to as *genechips* and *microarrays,* consist of thousands of oligonucleotides attached in a specific pattern to a solid surface, typically a glass slide or silica chip.[97,98,101,108,120] The sample nucleic acids compete with fluorescently labeled competitor oligonucleotides for binding to the chip. A fluorescent detector and computer software are then used to analyze the patterns of fluorescence, indicating where nucleic acids have (or have not) been bound to the chip. Microarrays have been used primarily as research tools focused on detecting and understanding gene expression. The practical application to veterinary medicine includes studies such as the evaluation of genetic resistance to naturally occurring nematode infections, including *Haemonchus, Trichostrongylus,* and *Ostertagia* in sheep. Microarray technology has not seen wide use in veterinary diagnostic laboratories, largely because of the large initial investment required for equipment. However, examples of diagnostic microarrays have shown promise, and it is expected that, once established, the technology will be cost-effective on an individual-animal basis. In human diagnostic medicine, microarrays designed with genetically conserved sequences for all major groups of microorganisms have been used to identify or "mine" for unknown pathogens. This approach was used to detect and identify the severe acute respiratory syndrome (SARS) virus before it was initially recovered and characterized by virus isolation techniques. Alternately, genotyping arrays have been designed to target specific virulence-associated genes, allowing differentiation of disease-associated subtypes of organisms from other members of the same or closely-related species, for example enterotoxigenic *E. coli* and multidrug resistant *Salmonella* strains.

29.18.7 Liquid Array

An alternative to genechip technology is liquid array technology, in which the nucleic acids are captured by oligonucleotide probes bound to a microbead rather than to a flat surface. Bead sets are internally labeled with different colored dyes used to distinguish the specific agents being measured. Liquid array systems employ flow cytometry, laser technology, and signal processing to recognize the internal color of the beads and measure associated surface-binding of a target-specific fluorescent hybridization probe. The bead-based modification to microarray technology allows a laboratory to create a flexible diagnostic-test panel in a single assay by adding or removing target beads based on the unique clinical presentation, diseases suspected, or species specificity of interest. In theory, 100 different targets are detectable in a single assay. Liquid array technology was successfully demonstrated during a U.S. National Animal Health Laboratory Network pilot project in 2006, in which bovine oral swab samples were simultaneously screened for the presence of seven different bovine viral pathogens capable of producing vesicular-type lesions. Among the viruses included in the panel were foot-and-mouth disease viruses, bovine virus diarrhea viruses, bovine herpesvirus type-1, malignant catarrhal fever virus, bluetongue virus, and bovine papillar stomatitis virus.

29.18.8 Restriction Fragment Length Polymorphism, Random Amplified Polymorphic DNA, and 16s RNA Typing

Molecular techniques provide a valuable tool for genotypic characterization or subtyping of viral, bacterial, and parasitic agents. Subtype characterization[90,91,110,115] is essential for taxonomic classification, differential detection of virulent strains, identification of genetic sources of antimicrobic resistance or virulence factors, recognition of vaccine escape mutants, epidemiologic investigation of disease outbreaks, identification of interspecies transmission of specific pathogens, and so on. RFLP is a technique useful for subtyping of

pathogens based on genetic sequence variation within specific genes.[106] Target DNA, which may or may not previously have been PCR amplified, is digested using one or more well-characterized restriction enzymes. Characteristic profiles or patterns produced by the different sized DNA fragments remaining after enzyme digestion are detected by gel electrophoresis. RFLP has been used to investigate interspecies transmission of enterotoxigenic *S. aureus* associated with intramammary infections in cattle, sheep, and goats.[118] Random amplified polymorphic DNA (RAPD) analysis is a technique that has proven useful in detecting genetic variation and for strain typing.[107] Rather than amplifying a specific region of a genome, RAPD relies on random amplification of genomic DNA using short arbitrary sequences as PCR primers. RAPD does not require prior knowledge of an organism's DNA sequence for specific primer design and can be applied to very small amounts of template DNA. The RAPD technique has been applied, for example, to rapid differentiation of pathogenic from nonpathogenic coccidia of sheep, including *Toxoplasma gondii* and *Sarcocystis* species. Identification of nonculturable, slow-growing, and atypical bacterial species using sequence analysis of the 16s ribosomal RNA (rRNA) gene has become recognized as a valuable diagnostic tool in recent years. The basis of the 16s RNA typing technique is the highly conserved nature of the 16s rRNA gene within bacterial species as well among species of the same genus.[95,113,119] Automation developed to support 16s rRNA amplification, sequencing, and data analysis is available to and currently in place in selected veterinary diagnostic laboratories. Although the technique is not currently cost-effective for routine identification of all microbial isolates in a clinical setting, the technology is used for identification of atypical, slow-growing, and rarely encountered species. As 16s rRNA databases continue to be updated to include pathogens of veterinary and zoonotic interest, it is likely that the technology will see broader application.

29.18.9 Sequence Analysis

Nucleic acid sequence analysis is used to identify and compare the exact nucleic acid sequence of a gene fragment, gene, or possibly entire genome for forensic purposes, to investigate disease outbreaks, to track evolutionary changes in rapidly mutable microorganisms, or for precise phenotype or genotype analysis of animals or organisms. For example, nucleic acid sequencing of the sheep prion protein (PrP) gene allele has been used as a flock management tool associated with scrapie control.[109] Although at times controversial, rapid PCR-based genotyping of sheep has been used for selective breeding programs targeting the genetic alleles associated with “scrapie resistance.”

29.19 GENETIC DISEASES

Diseases that are linked to genetic mutations in specific breeds, such as bovine leukocyte deficiency (BLAD) and complex vertebral malformation (CVM) in Holstein cattle, β-mannosidosis in cattle or goats, and Spider Lamb Syndrome in sheep can be controlled by selective breeding using PCR-based testing to identify carriers of the defective gene. Similarly, susceptibility to certain diseases, such as scrapie in sheep, as noted previously has been linked to specific genetic haplotypes that can be detected by molecular analysis.[116] DNA testing for genetic selection, parentage confirmation, coat color, and related management purposes is also available for cattle, sheep, and goats. For genetic testing the appropriate sample is typically whole blood, from which genomic DNA is extracted; the gene of interest is amplified by PCR, then mutations are detected by sequence analysis, microsatellite target testing, and restriction enzyme analysis to identify the mutations in the gene of interest.[105,117]

29.20 SUMMARY

With molecular diagnostics, as with any new technologic advance, there was initial hesitation or mistrust of the techniques, followed by a rush to take advantage of new diagnostic tools. With routine implementation of PCR and associated molecular diagnostic techniques have come significant advantages in diagnostic sensitivity and specificity, in the speed with which a laboratory diagnosis can be reached, and in the potential for in-depth genome-level investigation of disease occurrences. At the same time, molecular techniques have introduced a new level of complexity to diagnostic medicine. The use and interpretation of molecular-based diagnostic results require sufficient understanding of the techniques used in order to judge the reliability and the relevance of the findings. Molecular techniques have become, and will continue to grow as, extremely valuable diagnostic tools, but like any tool in diagnostic medicine, they must be used with caution and with a clear understanding of their strengths, limitations, and appropriate application to specific clinical investigations.

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29.21 References

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30 Chapter 30 Diseases of the Cardiovascular System

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30.1 PERFORMING THE ELECTROCARDIOGRAM

No single electrocardiographic lead system has been universally accepted for use in large animals. Bipolar leads (I, II, III, base-apex, X, Y, and Z of the orthogonal lead system) and unipolar leads (aV_F, aV_R, aV_L, thoracic) have been described, but the amplitude, duration, and configuration of the different waveforms vary widely, depending on an animal's breed, size, body type, and sex. In addition, there is lability of certain waveforms within each animal depending on the level of exercise, excitement, or organic heart disease. Large animals have a deeply penetrating Purkinje system, and depolarization from ventricular endocardium to epicardium occurs explosively and in many directions at once. This period of ventricular activation is responsible for the electrocardiographic criteria indicative of ventricular enlargement in small animals but contributes little to the generation of the QRS complex of large animals. Thus establishing specific diagnostic criteria for chamber enlargement in large animal species has been difficult because changes in the QRS complex are not sensitive or specific for ventricular enlargement.

Therefore the electrocardiogram (ECG) is used primarily to detect cardiac arrhythmias. For this purpose a single-channel machine can be used, and the lead system chosen can be any that generates distinctive P, QRS, and T complexes. If an arrhythmia is detected, another lead can then be obtained to further characterize the QRS and T complexes and confirm their origin. The lead system should be easy to apply, and the tracing free of artifacts created by muscle tremors, skin movement, shifting of weight, and changes in limb position. Two such leads commonly used for the diagnosis of cardiac arrhythmias are the base-apex lead[1] and the Y lead of the orthogonal lead system.[2] The base-apex lead is attached by placing the positive electrode from one of three standard bipolar leads (lead I, II, or III) on the left thorax in the fifth intercostal space at the level of the elbow or at the location where the apex beat is most readily palpable. The negative electrode is attached to the skin of the right jugular furrow two thirds of the way from the ramus of the mandible to the thoracic inlet or at the top of the right scapular spine. The ground electrode can be attached to any site remote from the heart. Electrical contact is improved by clipping hair or wetting the skin with alcohol. The base-apex lead ECG is recorded by switching the machine to the bipolar lead that has been attached to the horse and recording the ECG (Table 30-1). Lead Y is attached by placing the positive electrode over the xiphoid and the negative electrode cranially to the front of the chest.

Continuous electrocardiographic recording over a 24-hour period (Holter monitoring) or with radiotelemetry is also useful for evaluating horses with arrhythmias. Continuous recording of the ECG can be performed with contact electrodes, electrode patches that are held against the skin with a surcingle, or electrode patches attached to shaved skin with a cyanoacrylate adhesive and protected underneath a surcingle.[3,4] The contact electrodes or electrode patches held against the skin with a tight surcingle appear to work best for obtaining a continuous ECG recording. With bipolar contact electrodes, the positive electrode is placed over the left cardiac silhouette or over the sternum and the negative electrode is placed over the dorsum to the left of the withers where the electrode will lie flat and remain in contact with the skin.[3] The electrodes are kept moist with alcohol. The electrodes are then covered with moist sponges to maintain contact and are held in position with a tight surcingle. With electrode patches the electrodes are taped to a small square of cardboard to provide them with some rigidity. The best recording is usually obtained with the left arm electrode placed on the sternum, the right leg electrode on the right side in the fifth intercostal space at the level of the point of the shoulder, and the right arm electrode placed on the left side in

the fifth intercostal space at the level of the point of the shoulder. These electrodes are then held in position with a tight surcingle after removal of the plastic that covers the conducting material overlying the electrode. The electrodes are connected to a recorder (reel-to-reel, cassette, or digital) that records the animal's heart rhythm for the entire monitoring period (Holter monitor) or a telemetry device that sends the ECG signal back to the receiver to be displayed on a monitor. The continuous 24-hour Holter monitor is useful for diagnosing arrhythmias that occur intermittently or for monitoring cardiac rhythm during exercise. Radiotelemetry electrocardiography is useful for monitoring cardiac rhythm during treatment or during exercise.

Table 30-1 Standard Bipolar Electrocardiographic Leads

Lead	Positive Electrode	Negative Electrode
I	Left arm	Right arm
II	Left leg	Right arm
III	Left leg	Left arm

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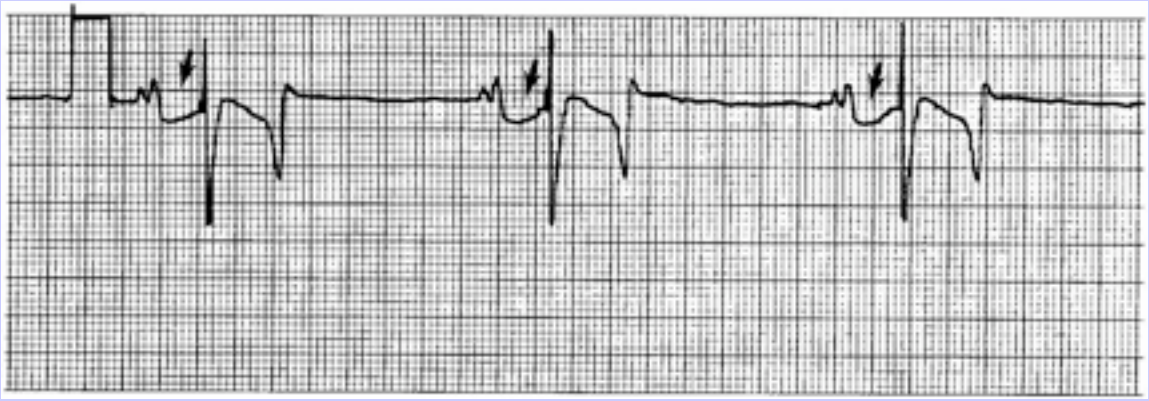
Fig. 30-1 Base-apex lead ECG recorded from a horse. *Arrows* point to the atrial repolarization wave (Ta) frequently seen in normal horses. It follows the notched P wave and precedes the QRS complex. Paper speed 25 mm/sec, calibration 1 cm/mV.



In the base-apex lead the P wave is positive in most horses and ruminants. The P wave is most frequently bifid in horses. In many horses a T_a wave, indicative of atrial repolarization, occurs as a negative deflection after the P wave (Fig. 30-1). The QRS complex begins with a small positive deflection (rS) and is followed by a large negative deflection, which terminates in the ST segment. The T wave is variable and can be positive, negative, or biphasic in horses and ruminants. Frequently the appearance of the T wave is variable within one recording. Fig. 30-2 illustrates a typical base-apex ECG recorded from a cow and a horse at a 25-mm/sec paper speed with the gain set at 10 mm/mV.

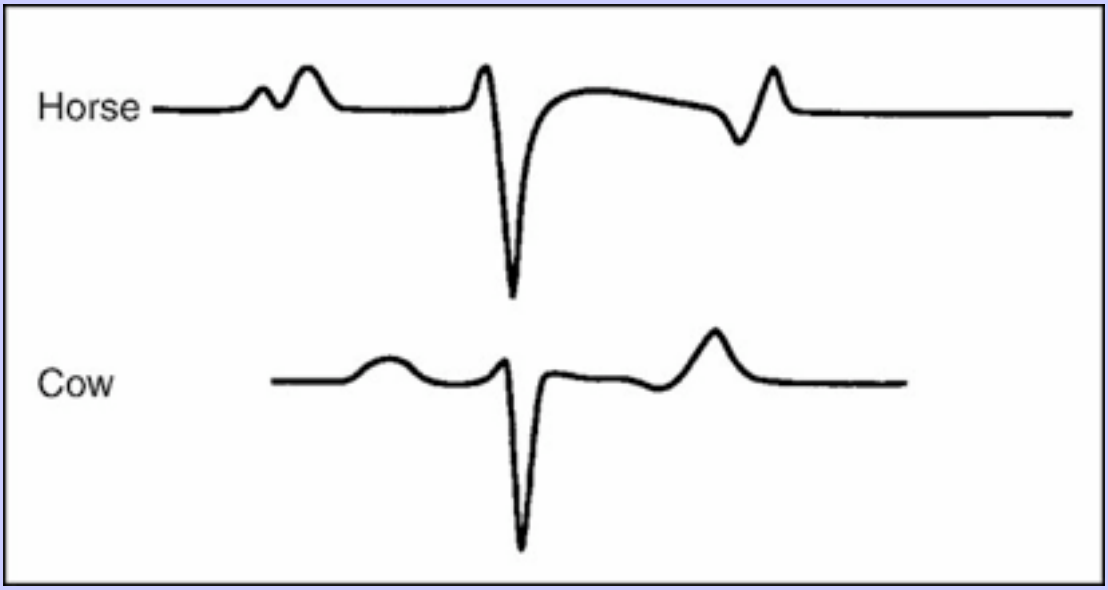
When a systematic approach is used to analyze the ECG, diagnosing arrhythmias is not difficult. The following step-by-step approach can be used:

1 Identify all the QRS complexes. Each QRS complex should be followed by a T wave, and the QT interval should be similar for all QRS configurations, unless there is a marked change in heart rate. Identify the remaining complexes. Are P waves, “F” (flutter) waves or “f” (fibrillation) waves present? Are there any artifacts?

2 Determine the atrial and ventricular rates. Are they identical? Is one too fast or too slow? This determines whether there is a tachycardia or bradycardia.

3 Are the P-P and R-R intervals regular? Determine whether an irregular rhythm has underlying regularity that is interrupted by irregular intervals or whether the rhythm is consistently irregular. Second-degree AV block and atrial and ventricular premature beats are arrhythmias with underlying regularity, whereas atrial fibrillation, sinus arrhythmia, and sinus arrest are truly irregular rhythms.

Fig. 30-2 Schematic representation of a typical base-apex lead ECG recorded from a cow and horse. In horses the P and T waves may be variable in appearance.



4 Are P waves present? If so, is there a P wave preceding every QRS complex? If not, there are premature depolarizations, escape beats, or atrial fibrillation. Are all P waves followed by QRS complexes? If not, second-degree AV block may be present. Is the resultant P-R interval constant? If not, there may be a wandering pacemaker or first-degree AV block.

5 Are all P waves and QRS complexes identical or normal in contour? If not, this signifies more than one pacemaker, premature depolarizations, or escape beats.

30.2 USE OF ECHOCARDIOGRAPHY IN LARGE ANIMALS

Echocardiography is a noninvasive diagnostic tool that uses sound waves in the range of 1.5 to 10 MHz to visualize the heart in motion, using either a single icepick (M-mode) or a two-dimensional (B-mode) image. Noninvasive evaluation of blood flow in the heart and great vessels is performed with pulsed wave, color flow, and continuous wave Doppler echocardiography. Precise localization of abnormal flow within the heart and great vessels is performed with pulsed wave and color flow Doppler echocardiography, whereas continuous wave Doppler echocardiography is used to determine the peak velocity of blood flow and to noninvasively estimate pressure gradients. In contrast to M-mode and two-dimensional echocardiography, in which the best image is obtained with the ultrasound beam perpendicular to the structures being imaged, optimal Doppler signals are obtained with the ultrasound beam parallel to the blood flow being evaluated. For accurate peak blood flow velocities to be recorded with continuous wave Doppler echocardiography, the ultrasound beam should be as close to parallel as possible (less than a 20-degree angle) to the direction of blood flow being measured. This alignment is difficult or impossible to achieve in most large animals with valvular heart disease; therefore accurate peak blood flow velocities often cannot be obtained from large animals with valvular heart disease. Noninvasive estimations of pressure gradients are inaccurate in these instances. Alignment of the ultrasound beam parallel to shunt flow is possible with most ventricular septal defects (VSDs) because of the typical location of the VSD in the membranous portion of the interventricular septum. A more extensive review of the theory and application of echocardiography in horses and cattle has been published.[5–11]

Echocardiography is particularly useful in evaluating large animals with cardiovascular disease because the examination is noninvasive and can be performed in most standing, unsedated animals in a timely fashion. Diagnostic criteria for valvular, myocardial, pericardial, and congenital lesions of the heart are well established, and the information obtained assists the practitioner in confirming a diagnosis, assessing the extent of the disease, determining the severity of cardiac dysfunction, monitoring the response to treatment, and providing an accurate prognosis. Large animal echocardiographic equipment should provide satisfactory resolution of images at depths of 26 cm or greater. Portable ultrasound machines are available that can display depths of up to 36 cm for equine and bovine cardiology. These machines are available with pulsed, continuous wave, and color flow Doppler. However, Doppler echocardiography is used mainly in specialty practices and referral institutions because performing and interpreting a complete echocardiogram, including Doppler, requires a significant amount of training and expertise and state-of-the-art color flow Doppler equipment remains fairly expensive, although it has decreased in price.

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Echocardiographic examination is performed in a systematic way, using standardized images to obtain information about chamber size, wall thickness, myocardial function, valve appearance, valve function, great vessels, blood flow, and presence of abnormal structures or echodensities. The standard equine or bovine echocardiogram is performed from the right parasternal window (the right fourth intercostal space in horses and third intercostal space in ruminants) with a 2.5-MHz transducer. Higher-frequency transducers should be used to examine younger animals, South American camelids, and small ruminants. Both long- and short-axis views of all cardiac structures should be evaluated. The cardiac valves should be carefully examined for any abnormalities of structure or function (thickening, prolapse, ruptured chordae tendineae, fenestrations, flail valve leaflet, vegetative lesion, or high-frequency vibrations). The relative size, shape, and relationship of the cardiac chambers and great vessels should be assessed, and an evaluation of myocardial function and blood flow performed. Standard measurements of left ventricular internal diameter, left ventricular free wall thickness, interventricular septal thickness, and right ventricular internal diameter should all be obtained at end diastole and peak systole from the M-mode echocardiogram. The diameter of the aortic root and left atrial appendage, the distance between the interventricular septum and the peak opening of the septal leaflet of the mitral valve (septal to E point separation), and the left ventricular ejection time (ET) should also be determined. End-diastolic measurements are obtained at the Q wave

of the ECG, whereas peak systolic measurements are made from the peak downward deflection of the interventricular septum. Calculations of fractional shortening (FS) and ejection fraction (EF) can then be performed to assess left ventricular function using the following formulas:

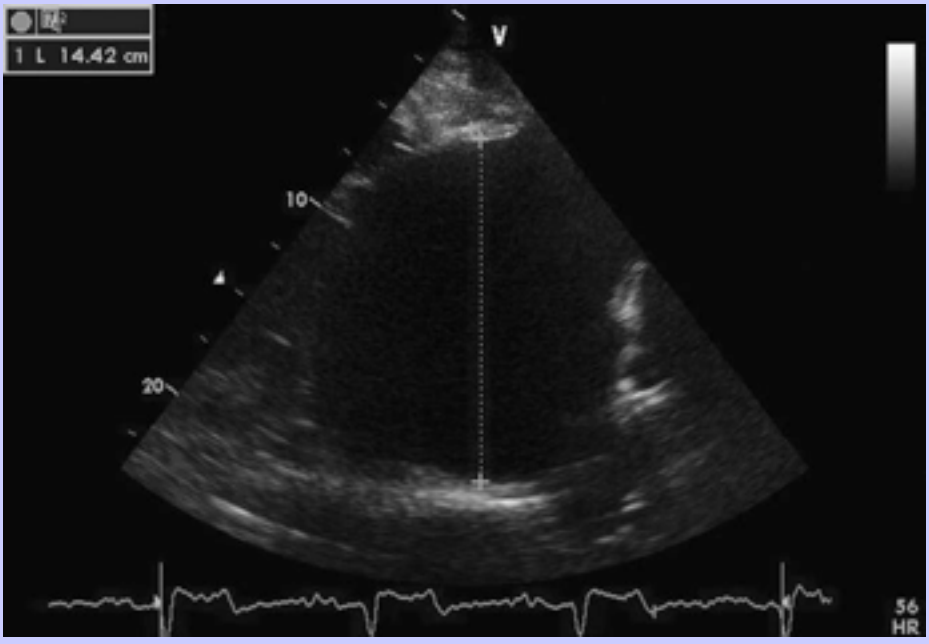
$$FS = \frac{LVID_d - LVID_s}{LVID_d} \times 100$$

$$EF = \frac{LVID_d - LVID_s}{LVID_d} \times ET \times 100$$

in which $LVID_d$ is the left ventricular internal diameter at end diastole (cm), $LVID_s$ is the left ventricular internal diameter in systole (cm), and ET is the left ventricular ejection time (sec).

Echocardiograms should also be performed from the left cardiac window when the entire heart cannot be successfully imaged from the right side; atrial fibrillation is present; abnormalities of the mitral valve, aortic valve, pulmonic valve, aorta, pulmonary artery, left atrium, left ventricle, or outflow portion of the interventricular septum are detected; or murmurs originating from the mitral, aortic, or pulmonic valves are detected or a pericardiocentesis is planned. The maximal diameter of the left atrium should be obtained from the left cardiac window at the level of the left coronary artery, parallel to the mitral valve (Fig. 30-3). The diameters of the aorta and pulmonary artery should be measured from similar locations in the vessel on the two-dimensional echocardiogram and compared. Echocardiography should be considered a useful diagnostic test to evaluate patients with the following complaints, physical examination findings, or tentative diagnoses:

Fig. 30-3 Two-dimensional echocardiographic image of the left atrial diameter obtained from the left parasternal long axis window in a horse with mild left atrial enlargement secondary to cardiomyopathy and mitral regurgitation.



1 Cardiac murmur, to determine whether the murmur is functional or pathologic

a Any grade 3/6 or louder holosystolic or pansystolic murmur on the right or left side of the thorax

b Any holodiastolic decrescendo murmur

c Any continuous machinery murmur

2 Congenital heart defects, especially atrial and VSDs

3 Acquired valvular heart disease

4 Cardiac enlargement

5 Cardiac arrhythmias not associated with high resting vagal tone

6 Unexplained exercise intolerance or intolerance attributed to cardiac causes

7 Muffled heart sounds, pericardial friction rubs, or pericardial effusion

8 Myocarditis or myocardial dysfunction

9 Congestive heart failure (CHF)

10 Pulmonary hypertension

11 Cardiovascular neoplasia

12 Prominent third heart sound

13 Aortic rupture or other abnormalities of the great vessels

14 Ionophore toxicity or exposure to other myocardial toxins

Color flow or pulsed wave Doppler echocardiography should be used to map the size and location of a turbulent jet associated with an intracardiac or extracardiac shunt, valvular regurgitation, or stenosis (rare) and to semiquantitate its severity. Continuous wave Doppler echocardiography can then be used to measure the peak velocity of blood flow in the jet, estimating (noninvasively) the pressure difference between cardiac chambers using the Bernoulli equation and assessing the hemodynamic significance of the lesion. This can be accurately performed in most patients with a VSD but is difficult to impossible to accurately perform in many patients with valvular insufficiencies because of the limited windows available for interrogating blood flow in large animals and the inability to align the ultrasound beam to within 20 degrees of the abnormal blood flow. Contrast echocardiography, a technique involving microbubble-laden injections of saline, carbon dioxide, or indocyanine green, can also be used to demonstrate valve dysfunction and the direction of intracardiac shunts (VSD and atrial septal defect [ASD]) and extracardiac shunts (patent ductus arteriosus [PDA], truncus arteriosus).

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30.3 CARDIAC CATHETERIZATION IN LARGE ANIMALS

Cardiac and great vessel catheterization can be performed in standing, unsedated large animals to determine the following data:

- Pressure and waveforms (shape of the pressure curve)
- Oxygen tension, oxygen saturation, oxygen content
- Cardiac output and other indicators of ventricular size and function

Cardiac catheterization is also used for special diagnostic studies such as angiocardiography, nuclear angiocardiography, and indicator dilution studies. These data are used to determine the direction and size of intracardiac and extracardiac shunts, chamber size and contractility, and valvular and myocardial function. Much of this same information can now be obtained noninvasively with echocardiography and can help the practitioner establish a diagnosis, more accurately assess the prognosis, and provide a direction for therapy.

Cardiac catheterization is usually reserved for specialty practices and referral institutions because of the equipment needed and the skills required for acquiring and interpreting accurate data. Results are not always specific, but catheterization can add quantitative measurements that increase the accuracy of the diagnosis and prognosis of certain cardiac conditions.

30.3.1 Blood Pressure Measurements

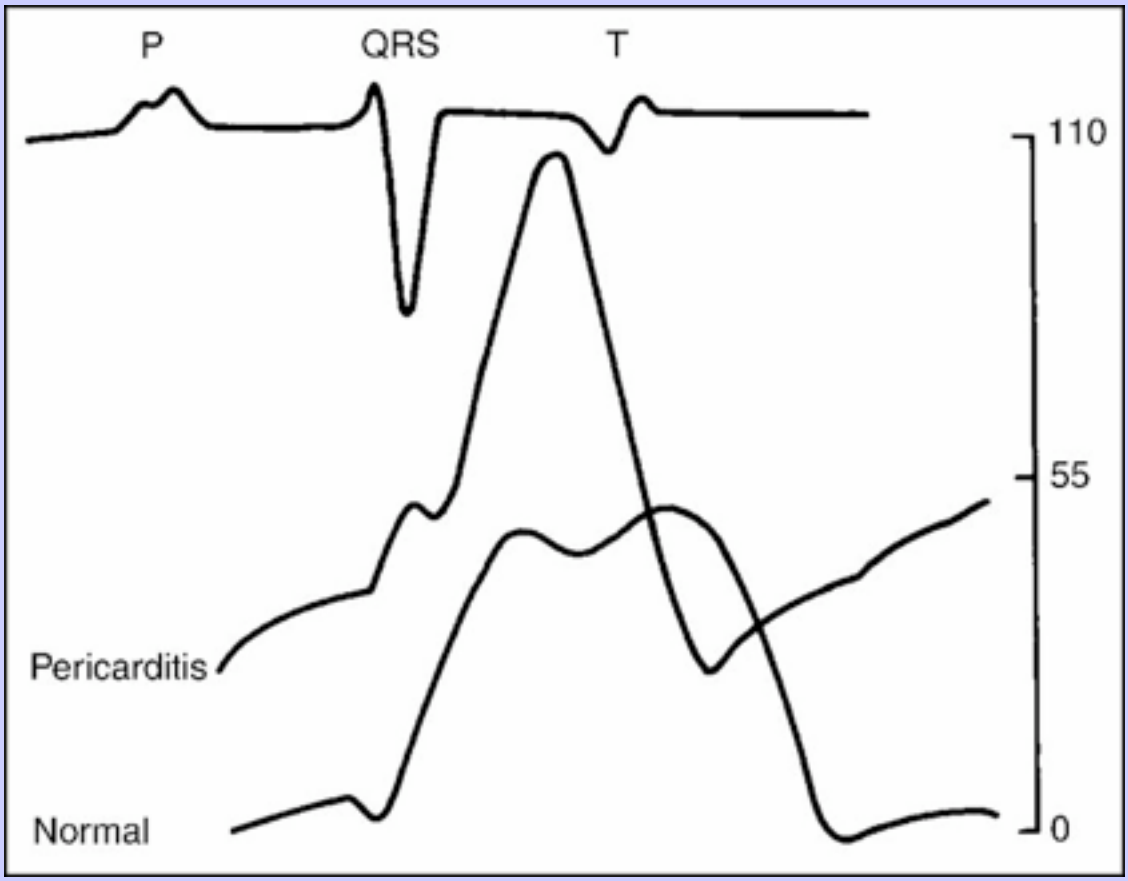
The normal pressures for cattle and horses are listed in Table 30-2.[12–15] The values for horses represent a summary of data from numerous authors as cited in the references given. The accuracy of pressure recordings is greatly influenced by the choice of catheter and the recording equipment used. The pulmonary arterial wedge pressure is an indicator of the left atrial mean pressure, as long as balloon inflation of the catheter occludes flow in the segment of the pulmonary artery that is catheterized. Pulmonary arterial wedge pressure is superior to central venous pressure as a monitor of left ventricular function and fluid therapy.

Table 30-2 Cardiac Pressure Measurements in Normal Horses and Cattle*

	Horses[12]	Cattle[13]
RA	12 to 28/22 to 5 (4 to 10)	(5)
RV	30 to 59/24 to 14 (9 to 25)	42 to 56/0 to 1 (19 to 28)
PA	34 to 48/14 to 22 (16 to 30)	33 to 46/19 to 21 (24 to 31)
PAW	13/3 (8)	(5 to 21)[11]
LV	140 to 148/15 to 17	(120 to 144)[12]
AO	131 to 144/86 to 100 (110 to 115)	
CA	142 to 157/98 to 119 (113 to 124)	160 to 208/110 to 147 (135 to 175)

* Pressure ranges are reported as systolic/diastolic (mean) in mm Hg unless otherwise designated. *AO,* Aorta; *CA*, carotid artery; *LV,* left ventricle; *PA,* pulmonary artery; *PAW,* pulmonary arterial wedge; *RA,* Right atrium; *RV,* right ventricle.

Fig. 30-4 Schematic representation of ventricular pressure curves recorded from a normal horse and a horse with pericarditis, showing the relationship between pressure changes and the ECG. With pericarditis, the ventricular end-diastolic and systolic pressures are elevated and pressure declines sharply in early diastole.



The shape of the pressure curve in the ventricles, aorta, or pulmonary artery may have diagnostic significance in conditions such as constrictive pericardial disease (Fig. 30-4); pulmonic stenosis (giant A wave), rare as an isolated defect in large animals; or tricuspid or mitral valve regurgitation (large V wave). These conditions are more commonly assessed by echocardiography. An abnormal rise in pressure going from one chamber to the next indicates a stenotic lesion (uncommon in large animals) at the level of the pressure gradient. The size of the pressure gradient can be used to determine the severity of the lesion.

30.3.2 Blood Oxygen Measurements

Blood oxygen measurements are taken from the chambers on the right side of the heart to detect abnormal elevations indicative of a left-to-right shunt (ASD, VSD, PDA). Criteria for oxygen step-ups have not been established for large animals, but human guidelines have been accepted for qualitative assessment of shunts.[16,17]

In humans, oxygen content step-ups of the following magnitude are considered abnormal and indicative of a left-to>right shunt[18]:

- ≥1.9 volume percent from the superior vena cava to the right atrium
- ≥0.9 volume percent from the right atrium to the right ventricle
- ≥0.5 volume percent from the right ventricle to the pulmonary artery

Oxygen content depends on the hemoglobin concentration; therefore oxygen saturation, which is independent of hemoglobin concentration, may be a more accurate indicator of shunts in anemic or polycythemic patients. Changes in the animal's physiologic status during sampling (cardiac output, ventilation, oxygen consumption), incomplete mixing of shunted blood, and variable time intervals between sampling can be potential sources of error. Several samples within a single chamber improve the reliability of results. Small shunts and shunts in animals with low systemic arterial oxygen tension may not be detected by this technique.

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Shunt calculations can be made once oxygen saturation or content has been measured in each of the right heart chambers, the pulmonary artery, and a systemic artery. For a left-to-right shunt, the pulmonary flow/systemic flow ratio (QP/QS) is determined as follows:

$$QP \Big/ QS = \frac{SAo_2 - MVo_2}{SAo_2 - PAo_2}$$

in which SAo_2 is the arterial blood oxygen content, MVo_2 is the mixed venous blood oxygen content, and PAo_2 is the pulmonary artery oxygen content. A 2:1 QP/QS represents a 50% left-to-right shunt, indicating that 50% of the pulmonary flow is from the left side of the heart. For a right-to-left shunt, the QP/QS is determined as follows:

$$QP \Big/ QS = \frac{SAo_2 - MVo_2}{PVo_2 - MVo_2}$$

in which PVo_2 is the pulmonary venous oxygen content (assumed to be 98% of oxygen capacity plus 0.3 mL of dissolved oxygen).[19]

30.3.3 Cardiac Output and Ventricular Function Assessment

Cardiac output is determined by indicator dilution methods (usually by dye dilution or thermodilution or, more recently, by lithium dilution), by the Fick method, or by using two-dimensional or Doppler echocardiography. The Fick method requires the use of a face mask and simultaneous determination of mixed venous and arterial blood samples. Dye dilution and thermodilution results are comparable when 30 to 40 mL of 5% dextrose are injected rapidly at 32° F (0° C).[17] Lithium dilution compares favorably with thermodilution in anesthetized horses and foals.[20,21] Volumetric echocardiography using the Bullet method achieves results similar to those obtained with the lithium-dilution method in anesthetized foals.[22] Transthoracic Doppler echocardiography was closely correlated with thermodilution in standing horses.[23] Cardiac output values in the resting horse range from 32 to 40 L/min.[24] Cardiac index is the cardiac output divided by a measure of body size (the body weight in kilograms) and is expressed in mL/kg/min.[24] The normal cardiac index for the adult horse ranges from 72 to 88

mL/kg/min.[24,25] Cardiac output values of 20.9 to 23.6 L/min have been reported in normal anesthetized horses.[20] In cattle a cardiac index of approximately 110 mL/kg/min has been reported.[15] Cardiac output measurements in clinical patients vary with heart rate, excitement, hydration, and many other factors and are best determined in the pulmonary artery. Electronic integration and computation of area under curve by means of battery-powered units that can display results instantly provide the most reliable results.[26]

Cardiac output results or indicator dilution curves can provide quantitative and qualitative assessment of cardiac shunts. Characteristic changes in the temperature-time curve (thermodilution methods) or dye concentration-time curve indicate the presence of a left-to-right, right-to-left, or bidirectional shunt. Calculation of the cardiac output in the chamber just proximal to the shunt and distal to it can give a quantitative estimate of the size of the shunt.[17]

30.3.4 Angiocardiography

Angiocardiography is used in neonates or animals small enough to have the entire cardiac silhouette visualized on a single radiograph cassette. The contrast medium must be injected rapidly, and in most cases this is done with a pressure injector. Specialized radiographic requirements include rapid film change capabilities, rapid image sequence acquisition, or cineradiography. Angiocardiography is used to confirm the presence of an intracardiac shunt (ASD, VSD) or extracardiac shunt (PDA, truncus arteriosus) or valve dysfunction, to visualize chamber size, or to estimate contractility. Angiocardiography is performed in anesthetized animals.

30.3.5 Nuclear Angiocardiography

In nuclear angiocardiography, specialized equipment captures sequential digitized images of the right side of the heart, lung, and left side of the heart after rapid injection of radiographic tracer into peripheral circulation. A more extensive review of this subject has been published.[27] Nuclear angiocardiography can be used to confirm valvular dysfunction, which is manifested by chamber enlargement or prolonged washout of affected vessels or cardiac chambers and is quantitated by the regurgitant fraction. It also can reveal enlargement of chambers and prolonged washout resulting from cardiac failure. The presence of intracardiac or extracardiac shunts can be demonstrated by the simultaneous visualization of left- and right-side cardiac chambers or slow washout downstream of the shunt. In addition, nuclear angiocardiography can be used to calculate cardiac output and EF and other indices of cardiac function.

30.4 CONGENITAL CARDIOVASCULAR DISEASE

The cause of congenital cardiac defects has not been established, although hereditary factors may be responsible for some defects. In humans, additional factors such as maternal infection, age, and nutritional status have been identified. Fetal anoxia from placental insufficiency, fetal infection or metabolic dysfunction, or other causes may contribute to the development of congenital cardiac defects. The same factors may apply in animals. Congenital cardiac defects in large animals can occur alone or in combination. The most commonly reported is VSD.[28–33] Multiple cardiac anomalies including PDA,[34,35] tetralogy of Fallot,[36,37] truncus arteriosus,[38,39] total anomalous pulmonary venous connection,[40] and Eisenmenger's complex in calves[41] have been reported. Congenital anomalies of the tricuspid,[38,42–44] mitral,[45] and pulmonic valves[38,46,47] are uncommon. Congenital abnormalities of the aorta are reported in calves and foals but are also uncommon.[33,48,49] ASD occurs more commonly in calves than in foals

and is frequently accompanied by other defects. [33,39,50,51] Hypoplasia of the left and right ventricles has been infrequently reported in calves and foals.[33,52,53]

Congenital cardiovascular disease should be suspected in a young patient if examination reveals a holosystolic (pansystolic), holodiastolic, or continuous murmur or a murmur with a palpable thrill or wide radiation over the thorax. Cyanosis at rest or with exercise in a patient with a cardiac murmur warrants consideration of a right-to-left cardiac shunt, obstructive pulmonary disease, or severe stenosis of the structures of the right side of the heart. The presence of any of these findings in a young animal with a history of lethargy, weakness, or failure to thrive constitutes grounds to suspect congenital cardiovascular disease.

30.4.1 Ventricular Septal Defect

30.4.1.1 Definition and Etiology

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A VSD is an opening in the interventricular septum that creates a communication between the left and right ventricles. In large animals most defects occur in the membranous septum and are imaged ventral to the septal leaflet of the tricuspid valve and the right and/or noncoronary leaflet of the aortic valve.[29–33] VSD can occur as a single defect or as part of a complex anomaly. Many cardiac malformations such as tetralogy and pentalogy of Fallot, truncus or pseudotruncus arteriosus, common atrioventricular canal defect, tricuspid atresia, and double outlet right ventricle include a VSD. The cause of VSD is unknown, although it has been documented to be a heritable defect in Limousine[33] and possibly Hereford[54] cattle. The defect is thought to result either from failure of fusion of a part of the endocardial cushion and the muscular ventricular septum or failure of fusion of the truncal and conal septa.[55]

30.4.1.2 Clinical Signs and Differential Diagnosis

The clinical signs of an isolated VSD vary and depend on the size of the defect, the direction of the shunted blood, and the presence of concurrent valvular or myocardial disease. In isolated VSD the blood flow is shunted from the left ventricle to the right ventricle through the defect in the interventricular septum. The size of the shunt depends on the size of the defect and the pressures in the left ventricle, right ventricle, and pulmonary artery.

VSD is suspected when there is a loud, harsh, plateau-shaped pansystolic murmur with its point of maximal intensity (PMI) in the tricuspid valve area and a slightly softer, more crescendo-decrescendo holosystolic murmur that is loudest in the pulmonic valve area. The murmur on the left side has its PMI in the pulmonic valve area, associated with a relative pulmonic stenosis (increased blood flow across a normal pulmonic valve). A palpable cardiac thrill usually is present over the tricuspid valve region, and occasionally there is splitting of the second heart sound. The murmur may be the only clinical sign identified if the defect is small. On the other hand, poor growth, lethargy, dyspnea, exercise intolerance, and signs of CHF can be exhibited by animals with a moderate to large VSD. This usually develops by the time the animal is 5 years old. Occasionally there is a diastolic murmur of aortic insufficiency associated with a large VSD, the location of which compromises the support of one of the aortic valve cusps.[31,32] Cardiac arrhythmias, particularly atrial fibrillation, may be associated with VSD when there is cardiac enlargement or failure.

If the systolic murmur is loudest on the left side of the thorax, a subpulmonic VSD or a complex anomaly with pulmonic stenosis (or some form of right ventricular outflow tract obstruction) should be suspected.[31,32,56]

The pulmonic murmur is usually louder than the tricuspid murmur in large animals with tetralogy of Fallot. Large animals with tetralogy of Fallot may have cyanosis at rest (uncommon in horses) or with exercise or exertion. Cyanosis is also a distinguishing feature of Eisenmenger's complex, a defect in which right-sided heart resistance to blood flow causes the shunt associated with VSD to become right to left. Congenital abnormalities of the mitral and tricuspid valves cause a loud systolic murmur audible on both sides of the thorax. The PMI of the left-sided systolic murmur is more caudally located (in the mitral to aortic valve area) than the relative pulmonic stenosis murmur. Usually, the murmur of mitral regurgitation is the loudest of the 2 murmurs. In addition, congenital mitral or tricuspid valve dysplasia is rare in large animals. An innocent flow murmur of neonates can usually be distinguished from VSD by its crescendo-decrescendo shape, PMI at the left heart base, lack of radiation, and low to moderate intensity.

30.4.1.3

Clinical Pathology

Echocardiography is the diagnostic technique of choice for identifying a VSD. With two-dimensional echocardiography the VSD can be imaged directly (Fig. 30-5) and the shunt size, location, and direction demonstrated with pulsed wave Doppler, continuous wave Doppler, color flow echocardiography, or the injection of microbubbles. Careful scanning of the interventricular septum should be performed with two-dimensional echocardiography to directly image the VSD and measure its maximal diameter in two mutually perpendicular planes.[31,32] The typical membranous VSD (≤2.5 cm in both planes) is missed if the long-axis view of the left ventricular outflow tract is not examined. The membranous VSD is located underneath the septal leaflet of the tricuspid valve and the right or noncoronary leaflet of the aortic valve. If a membranous defect is not found, the entire septum should be carefully scanned in all imaging planes to detect the VSD. The subpulmonic location, more common in calves, is easy to miss. This defect is usually best imaged in the short-axis view, scanning the interventricular septum between the left and right ventricular outflow tracts. With a left-to-right shunt a high-velocity turbulent jet is depicted from the right parasternal window, originating in the left ventricle, traversing through the hole in the interventricular septum into the right ventricle with color flow Doppler echocardiography (blood flow toward the transducer), whereas a negative contrast jet is imaged in the right ventricle with a right-sided injection of microbubbles.[31,32] A left ventricular injection of microbubbles is necessary to visualize echo-laden blood in the right ventricle with a typical VSD. M-mode echocardiography may show septal discontinuity when traversing the ventricular septum from the apex of the heart to the aortic root (septal dropout). Moderate to large VSDs show left atrial and left ventricular enlargement, right ventricular enlargement, and pulmonary artery dilation. The left atrial—to—aortic root ratio is increased. Aortic valve prolapse and aortic regurgitation may also be detected because of loss of support of the aortic root from the VSD. Myocardial dysfunction and subsequent CHF may occur with a large VSD. Continuous wave Doppler echocardiography can be used to noninvasively assess the hemodynamic significance of the shunt (see Fig. 30-5, *B*). A peak shunt flow velocity of greater than or equal to 4 m/sec indicates a restrictive VSD with normal or near normal right ventricular pressures. Nuclear angiocardiography can also be used to demonstrate simultaneous opacification of the left and right ventricles. The radiographic presence of cardiomegaly and increased vascularization of the lungs provides only nonspecific evidence of VSD. If polycythemia is found, a complicated VSD should be suspected.

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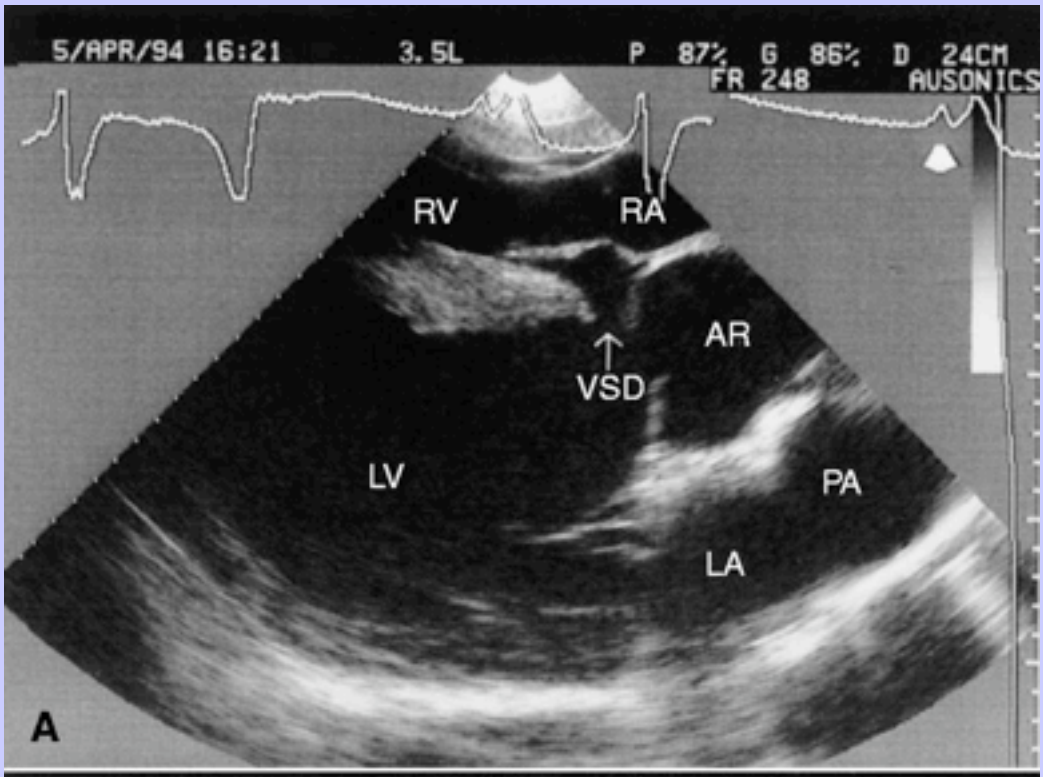
Fig. 30-5 Two-dimensional echocardiographic image **(A)** and continuous wave Doppler spectral tracing **(B)** of a ventricular septal defect *(arrow)* in a weanling colt. The ventricular septal defect *(VSD)* is located just underneath the septal leaflet of the tricuspid valve and right coronary cusp of the aortic valve. The VSD is best imaged in this left ventricular outflow tract view. There is significant left ventricular enlargement in this colt. The right atrium *(RA)*, right ventricle *(RV)*, left ventricle *(LV)*, left atrium *(LA)*, aortic root *(AR)*, and pulmonary artery *(PA)* are all visible in this view. The spectral tracing shows a peak shunt velocity of slightly under 4 m/sec in systole, with some turbulent flow (spectral broadening) also detected in diastole with a peak flow velocity of approximately 1.3 m/sec.


5/APR/94 16:21
3.5L
P 87% G 86% D 24CM
FR 248
AUSONICS
RV
RA
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VSD
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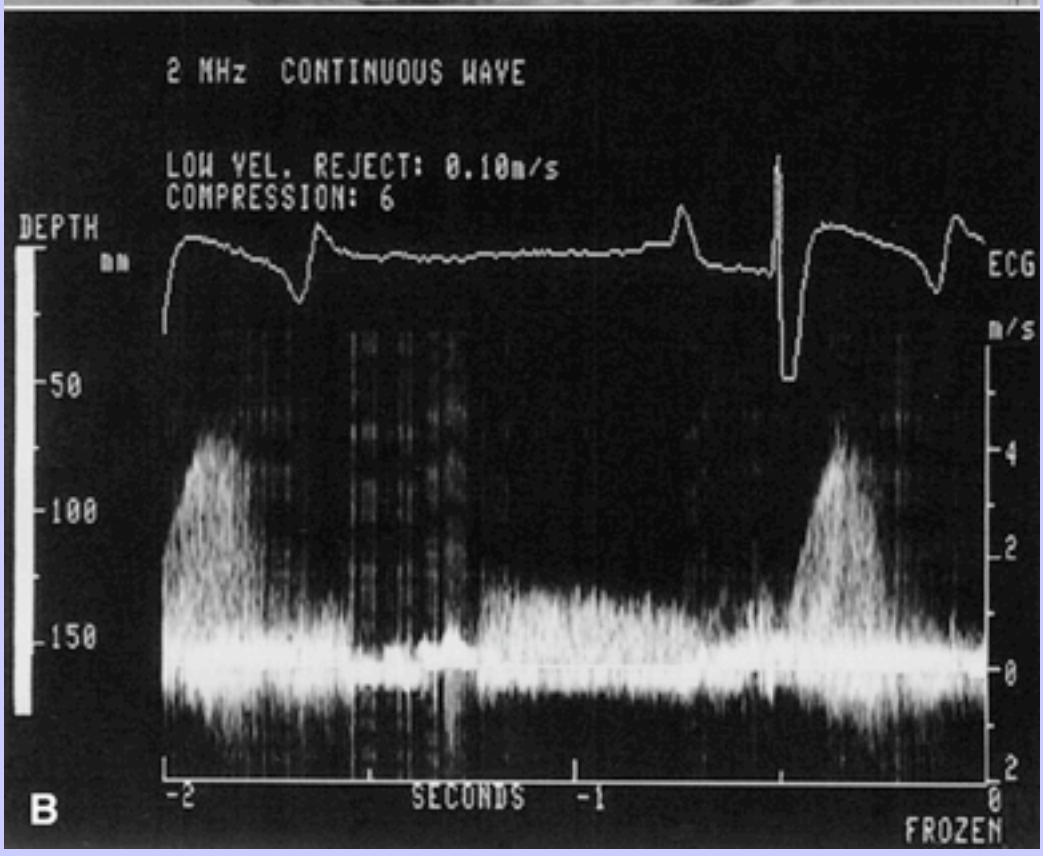
2 MHz CONTINUOUS WAVE
LOW VEL. REJECT: 0.10m/s
COMPRESSION: 6
DEPTH
mm
50
100
150
ECG
m/s
4
2
0
2
-2
SECONDS
-1
0
FROZEN
B

Cardiac catheterization can be used for qualitative and quantitative assessment of the VSD but has largely been supplanted by echocardiographic diagnosis. Elevated cardiac pressures provide qualitative evidence of a VSD. Right ventricular systolic pressure elevation is most common and may equal left ventricular pressure with a large VSD. Pulmonary artery pressure can be increased as a result of increased blood flow from the left-to-right shunt or increased pulmonary vascular resistance and decreased flow (restrictive pulmonary hypertension). Elevation of left or right ventricular diastolic pressure provides evidence of cardiac failure in the patient with VSD. Oximetric data (oxygen content or oxygen saturation) can be used to locate the shunt and provide some evidence of the size of the defect. A step-up in oxygen content or saturation between the right atrium and the pulmonary artery suggests a moderate or large VSD. Because most VSDs are located high in the right ventricular outflow tract, there may be inadequate mixing of shunted blood in the right ventricle to detect the shunt in this chamber unless the catheter is directed to the outflow tract for sampling. When the oxygen step-up is detected first in the pulmonary artery, a PDA cannot be ruled out. A small shunt may be missed by oximetry as described earlier under oxygen sampling.

Through the use of indicator dilution methods described previously, the shape of the concentration-time or temperature-time curve can be used to demonstrate the left-to-right shunt of a VSD. A comparison of the cardiac output measured in the right ventricle with the cardiac output measured in the pulmonary artery can give an estimation of the percent of pulmonary blood flow coming from shunted blood and therefore an estimation of the size of the defect.[57]

Angiocardiography can be performed in the anesthetized neonate and can definitively demonstrate VSD if there is simultaneous opacification of the left and right ventricles when dye is injected into the left ventricle.

30.4.1.4

Pathophysiology

A small VSD may provide enough resistance to flow that the left-to-right shunt is minimal and the patient remains asymptomatic. Horses can race successfully with small VSDs (≤2.5 cm in diameter with peak shunt velocities ≥4 m/sec), although they are not usually successful as elite racehorses.[32] VSDs produce a left-to-right shunt because the pressure in the left ventricle exceeds the pressure in the right ventricle. A peak shunt velocity of 3 to 4 m/sec indicates an increased right ventricular pressure and a less restrictive VSD; however, the defect is usually compatible with a normal life expectancy. A peak shunt velocity of less than 3 m/sec is indicative of a large shunt that is hemodynamically significant. These animals usually develop CHF by 5 years of age. Occasionally the VSD is so large that the pressure between the two chambers is equalized. The right ventricle, pulmonary circulation, left atrium, and left ventricle must compensate for this volume overload, which generally results in dilation of cardiac chambers and the development of pulmonary hypertension.

Pulmonary vascular resistance can increase because of simultaneous pulmonary disease or left-sided heart failure from chronic volume overload. In addition to volume overload, the right ventricle is subjected to a chronic pressure overload, which may be sufficient to reverse the direction of the shunt (Eisenmenger's complex, more common in cattle than horses). Because of the pressure and volume overload with moderate to large VSDs, patients with this condition run a greater risk of developing CHF.

Considerable turbulence associated with the left-to-right shunts and endocardial damage increase the risk of endocarditis in patients with VSD.[58] Because the VSD usually is located high in the left ventricular outflow tract, structural support of the aortic valve cusps may be lost, and aortic insufficiency may develop.[32] Significant aortic regurgitation adds to the left ventricular volume overload caused by the VSD.

30.4.1.5 Epidemiology

The true incidence of VSD in large animals is unknown, although it is recognized as the most common congenital cardiac defect. In one study, 36 calves had 78 congenital cardiac defects, of which 11 were VSDs.[33]

30.4.1.6 Necropsy Findings

VSD is usually located high in the interventricular septum just ventral to the right or noncoronary cusp of the aortic valve in the left ventricle and underneath the septal leaflet of the tricuspid valve or caudal or ventral to the crista terminalis in the right ventricle. It can be an isolated defect or can be accompanied by other cardiac or organ anomalies. If the defect is moderate or large, there is right ventricular, left atrial, and left ventricular enlargement and pulmonary artery dilation. The lungs may be congested because of increased pulmonary blood flow, and secondary pneumonia is not uncommon. If pulmonary vascular resistance was increased, right ventricular hypertrophy may be present. There may be secondary endocarditis (infrequent in large animals)[58] or endocardial lesions as a result of turbulent blood flow across the defect.

30.4.1.7 Treatment and Prognosis

There is no practical treatment for VSD in large animals. A complete echocardiographic examination is indicated to identify the presence and significance of a VSD. It is important to identify those animals with moderate to large defects, because the prognosis for normal production or function is poor. Horses with large defects (>3.5 cm) and peak shunt velocities through the defect of <3 m/sec should not be broken to ride as they will develop CHF early in life and have a shortened life expectancy. Animals with small defects may remain asymptomatic throughout life. It is important to recognize that small defects, which provide a large resistance to flow, can produce loud murmurs. Because of this, the intensity of the murmur is not a good predictor of the size of the defect.

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Currently there is limited evidence that VSD is inherited in cattle or horses. However, breeding animals with VSD is not advised because of the increased risk of heart failure and other cardiac complications. As a general rule, bull studs do not accept animals with this defect into a breeding program.

30.4.2 Patent Ductus Arteriosus

30.4.2.1 Definition and Etiology

A PDA is the persistent patency of a vessel (normally present in the fetus) that connects the pulmonary arterial system to the aorta. The ductus arteriosus fails to close at birth when breathing begins and placental circulation is removed. Closure of the ductus arteriosus occurs in response to decreasing pulmonary vascular resistance and increased systemic vascular resistance.

A PDA can occur as a single defect (rare in large animals) or with other cardiac anomalies. In large animals the most common other defects reported with PDA are tetralogy and pentalogy of Fallot and pseudotruncus arteriosus.

30.4.2.2

Clinical Signs and Differential Diagnosis

The clinical signs of PDA depend on the length and diameter of the ductus arteriosus, the direction of the shunted blood, and the presence of other cardiac defects. A PDA should be suspected when a continuous, high-pitched murmur, frequently referred to as a “machinery murmur” because of its alternating intensity, is auscultated. The murmur may be heard on the left and right sides of the thorax but is usually loudest in the left third or fourth intercostal space at the level of the shoulder. The intensity of the murmur increases with increased heart rate, exercise, or excitement. The arterial pulses are usually bounding because of the runoff of blood from the systemic to the pulmonary circulation. Occasionally the PDA is manifested by a holosystolic murmur[59] because the diastolic component is barely audible, except at the left heart base. Large PDAs can exist without producing a murmur. In the animal with increased pulmonary vascular resistance and reversal of the shunt, there may be cyanosis of the caudal parts of the body if the PDA enters the aorta caudal to the brachiocephalic trunk. Stunting of growth may also occur.

Other causes of a continuous murmur in large animals are extremely rare; however, the detection of a continuous machinery murmur should lead the veterinary clinician to suspect a complex congenital cardiac defect that includes a PDA, rather than an isolated defect. In older horses an aorticocardiac fistula should be suspected, particularly if the machinery murmur is of recent onset and is loudest on the right side of the chest. A systolic and diastolic murmur can be present in young animals with a large VSD causing aortic insufficiency. A similar murmur is possible with vegetative endocarditis of one of the atrioventricular or semilunar valves, producing insufficiency and stenosis of the affected valve. These latter conditions should not have the machinery murmur characteristic of the PDA. A loud systolic ejection murmur, which is confused with a PDA, frequently can be heard at the left heart base of foals shortly after closure of the PDA. This murmur may persist for 2 to 3 months.[34]

30.4.2.3

Clinical Pathology

No characteristic clinicopathologic changes are associated with a PDA. Radiography may show enlargement of the cardiac silhouette and pulmonary overcirculation in an uncomplicated PDA. Pulmonary venous congestion, interstitial pulmonary edema, and alveolar edema are evidence of a large PDA with left-sided heart failure. These signs are not specific for PDA and can be present with any congenital heart defect that results in a left-to-right shunt. No consistent electrocardiographic pattern has been identified with PDA. Echocardiographic evidence of a PDA is provided by the detection of an enlarged left atrium and left ventricle with a pattern of left ventricular volume overload and increased values for the ratio of the left atrial to aortic root dimension.[31,59–61] Direct visualization of the ductus arteriosus is difficult with echocardiography but is most successful when performed from the left cardiac window. A PDA arising from the pulmonary artery has been imaged echocardiographically in an 11-month-old Friesian-Holstein heifer.[35] High-velocity turbulent flow throughout the cardiac cycle in the pulmonary artery and ductus arteriosus is detected with pulsed wave, continuous wave, or color flow Doppler echocardiography.[60]

Cardiac angiocardiography and nuclear angiocardiography using a selective aortic angiogram provide definitive evidence of a PDA. Oximetric data show a step-up in oxygen content or saturation in the pulmonary artery that is proportional to the size of the shunt. Indicator dilution methods also provide evidence of a left-to-right shunt occurring in the pulmonary artery in cases of an uncomplicated PDA. Pulmonary arterial and right ventricular pressures may be increased with a large PDA.

30.4.2.4 Pathophysiology

Normally the ductus arteriosus narrows near term and constricts rapidly after birth in response to lowered pulmonary vascular resistance, increased systemic vascular resistance, increased blood volume, and increased left ventricular pressure when breathing begins and the placental circulation is removed. If the ductus arteriosus is large or the resistance to flow across the ductus is minimal, there is a significant left-to-right shunt, which produces a large left ventricular volume overload. The left ventricular response may be failure or, with time, dilation (primarily) and hypertrophy. Pulmonary hypertension and congestion result. The right ventricle can be affected by the pulmonary pressure load, and right ventricular hypertrophy can also develop. If the pulmonary resistance equals or exceeds the systemic vascular resistance, a right-to-left shunt occurs.

30.4.2.5 Epidemiology

Normal foals may have a PDA for a few days after birth, but closure of the ductus arteriosus is expected by 96 hours of age.[59] Normal ruminants rarely have a PDA after birth, and if one is present it is considered abnormal. Functional closure may precede anatomic closure of the PDA. This defect is uncommon in older animals. Currently there is no evidence to suggest that this is an inherited defect in horses or cattle.

30.4.2.6 Necropsy Findings

The ductus arteriosus can be of variable length and diameter but is patent between the aorta and the pulmonary artery. The PDA often enters the aorta caudal to the origin of the brachiocephalic trunk. Changes in the left and right ventricles and lung and pulmonary vasculature are variable and depend on the size of the shunt. When the PDA is large, there may be cardiomegaly with left atrial and left ventricular dilation, right ventricular hypertrophy, pulmonary congestion, and edema.

30.4.2.7 Treatment and Prognosis

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There is insufficient evidence on which to base a prognosis for animals with PDA. The condition can be corrected surgically in neonates, but future performance has not been documented. Animals with small defects may remain asymptomatic throughout life. The prognosis is poor if the defect is large, because the risk for left (primarily) and right ventricular failure is increased. Pharmacologic closure of the PDA using inhibitors of prostaglandin synthesis has been successful in humans but is not without risk of complications and recurrence. The efficacy of prostaglandin inhibitors has not been evaluated in large animals.

30.4.3 Tetralogy and Pentalogy of Fallot

30.4.3.1 Definition and Etiology

Tetralogy and pentalogy of Fallot are characterized by biventricular origin (overriding) of the aorta, VSD, right ventricular hypertrophy, and obstruction of pulmonary arterial flow. When there is an associated ASD, the anomaly is referred to as *pentalogy of Fallot*. The defect is caused by abnormal development of the conal septum in the embryonic heart, which leads to narrowing of the right ventricular infundibulum (pulmonic stenosis), an inability of the conal septum to participate in closure of the interventricular foramen (VSD), and

overriding of the aorta. Right ventricular hypertrophy develops as a result of the pulmonary outflow obstruction.

30.4.3.2

Clinical Signs and Differential Diagnosis

Tetralogy of Fallot is one of the more common congenital cardiac defects that cause cyanosis in large animals. Resting cyanosis is rare in horses, although it may be detectable after exercise. Cyanosis of the oral and nasal mucosa, the tongue, the vaginal mucous membranes, and occasionally the nose and skin of light-colored animals is noticed when more than 5 g/dL of hemoglobin are reduced (unoxygenated). Exercise intolerance is often marked and is characterized in most cases by dyspnea or collapse. Frequently the owner complains of slow growth or small size. A loud pansystolic murmur, which is associated with a palpable thrill, is loudest in the left third to fourth intercostal space. The murmur may be a crescendo-decrescendo murmur of pulmonic stenosis or the harsh, plateau-shaped murmur of a VSD; one of these usually predominates. A harsh band-shaped pansystolic murmur is also auscultated in the tricuspid valve area but is usually one or two grades softer than the pulmonic stenosis murmur. Excitement of the animal may result in auscultation of a gallop rhythm or an early systolic ejection click. A continuous machinery murmur can be auscultated in some patients, associated with continuous shunting through the PDA.

Tetralogy and pentalogy of Fallot must be distinguished from other causes of cyanosis in young animals. Respiratory distress syndrome of neonates can be distinguished by the presence of tachypnea, dyspnea, and abnormal lung sounds in the absence of a cardiac murmur. Cyanosis caused by central nervous system disease has other neurologic manifestations. Cyanosis from congenital cardiac disease may be caused by a right-to-left shunt or by heart failure with pulmonary edema. Cyanosis resulting from heart failure or respiratory disease improves with oxygen administration, whereas the patient with a right-to-left cardiac shunt fails to improve. Right-to-left cardiac shunting does or can occur with tetralogy and pentalogy of Fallot, reverse PDA or VSD, tricuspid valve or right ventricular atresia, left ventricular hypoplasia, persistent truncus arteriosus, pseudotruncus arteriosus, and other complex congenital cardiac disease, all of which may occur with cyanosis and a cardiac murmur. A complete echocardiographic examination using a segmental approach to cardiac anatomy is needed to accurately diagnose the correct congenital cardiac malformation and has widely supplanted other methods of diagnosing complex congenital cardiac disease in large animals. Radiography and cardiac catheterization provide supplemental information that may be helpful in distinguishing among the causes of right-to-left cardiac shunting.

30.4.3.3

Clinical Pathology

Increased packed cell volume (PCV), red blood cell count, and hemoglobin concentration (polycythemia) may be present in some animals with tetralogy and pentalogy of Fallot.[37] However, polycythemia is uncommon in foals with cyanotic congenital cardiac disease and is usually less than 45% in most calves. Electrocardiographic changes are usually nonspecific, but a right-axis deviation may be detected.[37] Radiographs of the lungs may show decreased vascularity. The four components of tetralogy of Fallot are easily visualized echocardiographically. The VSD and overriding aorta usually are clearly visible with two-dimensional echocardiography. The malalignment VSD is usually large and located just below the right cusp of the aortic valve, separated from the pulmonic valve by the crista supraventricularis. The aortic root is usually large and overrides the septal defect. Echocardiography shows increased thickness of the right ventricular wall, ventricular septal hypertrophy, paradoxic septal motion, and similar left and right ventricular internal dimensions. Narrowing of the right ventricular outflow tract, pulmonic stenosis, or a hypoplastic pulmonary artery (most common) may be imaged as the cause of the right ventricular outflow tract

obstruction. Pulsed wave and color flow Doppler echocardiography can be used to further characterize the abnormalities of blood flow associated with tetralogy of Fallot, in particular the severity of the right ventricular outflow tract obstruction. Contrast echocardiography also nicely demonstrates the path of blood flow with a peripheral venous injection. Contrast echoes are imaged entering the right ventricle from the right atrium, then simultaneous opacification of the pulmonary artery, left ventricle, and aorta occurs.

Cardiac catheterization can be used to demonstrate equalization of ventricular pressures and a pressure gradient between the right ventricle and pulmonary artery. Oximetry should demonstrate decreased oxygen content in the left ventricle compared with the pulmonary vein. Angiocardiography demonstrates simultaneous filling of the right ventricle, left ventricle, and overriding aorta with decreased pulmonary artery filling and increased right ventricular trabeculation (hypertrophy).

30.4.3.4 Pathophysiology

VSD is usually large, resulting in equalization of pressures in the two ventricles and the aorta. The degree of shunting is controlled by the resistance across the stenotic right ventricular outflow tract compared with the resistance across the aortic valve. If the right ventricular outflow tract is severely obstructed, the clinical signs of cyanosis are more marked. Excitement, drugs, or increased myocardial contractility from any cause decreases right ventricular volume and worsens clinical signs. Right ventricular failure usually is not a consequence of the pressure overload because of equalization of the ventricular pressures.

30.4.3.5 Epidemiology

The prevalence of tetralogy and pentalogy of Fallot in large animals has not been documented, but these defects seem to be more common in calves than in foals. There is no evidence that these disorders are inherited.

30.4.3.6 Necropsy Findings

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Examination of the heart reveals a rounded apex caused by right ventricular enlargement. A high, usually large 462
VSD, an overriding aorta that straddles the VSD and the left and right ventricle, right ventricular hypertrophy, and septal hypertrophy are present. There is usually right ventricular infundibular narrowing and a hypoplastic pulmonary artery, although there may be valvular pulmonic stenosis with a poststenotic dilation. The right and left atria may be enlarged.

30.4.3.7 Treatment and Prognosis

There is no practical treatment for tetralogy and pentalogy of Fallot in large animals. When cyanosis or exercise intolerance is present or growth is stunted (the latter two are common findings in affected animals), the prognosis for long-term survival, production, or performance is poor. Affected foals should not be used for performance or broken to ride if they live long enough. As with many congenital cardiac diseases, the intensity of the murmur is not a good predictor of the severity of the condition, and further diagnostic tests are indicated.

30.4.4 Other Congenital Cardiac Defects

30.4.4.1 ATRIAL SEPTAL DEFECT

ASD is a connection between the left and right atria at the septal level. The most common type of defect is the ostium secundum defect, of which patent foramen ovale is seen most frequently. Patent foramen ovale is relatively common in calves and is caused by the failure of the septum primum, the valve of the foramen ovale, to become adherent to the crista dividends after birth, when changes in left and right atrial pressures produce functional closure of the foramen ovale. Patent foramen ovale is frequently associated with PDA in calves.[33]

Animals frequently with an ASD are asymptomatic, but a holosystolic, crescendo-decrescendo murmur may be heard at the left heart base. The shunt is usually left to right, and the murmur is the result of increased volume being ejected across the pulmonic valve. If the defect is large, right atrial, right ventricular, and left atrial dilation may be present. Differential diagnostic considerations are a functional murmur, pulmonic stenosis, VSD, or PDA. A definitive diagnosis can be made by two-dimensional echocardiography in which an enlarged right atrium, right ventricle, and left atrium are imaged. Pulsed wave Doppler, color flow, or contrast echocardiography can be used to demonstrate the shunt through the ASD.

30.4.4.2 PULMONIC VALVE STENOSIS

Pulmonic valve stenosis is uncommon as a single defect but has been reported in a foal with VSD and as one of multiple defects in calves and foals.[33,47] Clinical signs of cardiac murmur, cyanosis, and polycythemia are variable and depend largely on the other cardiac defects present. Characterization of the severity of the pulmonic stenosis and other associated cardiac defects can be performed with a complete echocardiographic examination.

30.4.4.3 TRICUSPID VALVE ATRESIA

Tricuspid valve atresia has been reported in foals[38,42–44] in conjunction with other cardiac defects. The abnormalities associated with tricuspid atresia include patent foramen ovale, VSD, small right ventricle, large left ventricle, and large mitral valve orifice. The foals showed cyanosis and a crescendo-decrescendo or band-shaped holosystolic or pansystolic murmur audible over the left and right heart base. Tachycardia, tachypnea, and weak peripheral pulses also were present. Polycythemia was commonly reported. Echocardiographic diagnosis of tricuspid atresia in foals has been reported.[38,43] A thick echo in the region of the tricuspid valve that does not separate in diastole (absent tricuspid valve), an ASD (usually patent foramen ovale), a VSD, a small right ventricle, a large left ventricle, and a large mitral valve orifice are the echocardiographic findings in tricuspid atresia. Blood flow (right to left) through the patent foramen ovale into the left atrium and left ventricle followed by simultaneous opacification of the aorta and right ventricle is detected with contrast echocardiography. Necropsy showed tricuspid atresia, along with ASD, VSD, small right ventricle, and large left ventricle. Pulmonic valve stenosis and dextropositioning of the aorta have also been reported.

30.4.4.4

MITRAL VALVE DYSPLASIA

Mitral valve dysplasia is an early developmental anomaly that has been reported in the horse.[45] The affected foal had a grade 4-5/6 holosystolic decrescendo-type murmur loudest in the mitral to aortic valve area. The mitral valve leaflets appeared thickened, bright, and irregularly nodular echocardiographically. A cleft was imaged in the midportion of the free wall leaflet with small papillary muscles and shortened, unevenly thickened chordae tendineae.[45]

30.4.4.5

VENTRICULAR HYPOPLASIA

Ventricular hypoplasia has been reported in foals and calves.[33,52] The defect may be present with other cardiac defects and is usually associated with early death. The defect was present in three closely related Holstein calves, suggesting possible genetic factors.[33]

30.4.4.6

TRUNCUS OR PSEUDOTRUNCUS ARTERIOSUS

Persistent truncus arteriosus refers to the condition in which one arterial vessel leaves the heart above a VSD. The coronary and pulmonary arteries and aorta arise from this vessel. Persistent truncus arteriosus has been diagnosed in foals and calves.[39] Subclassifications of this condition have been applied to humans, depending on the origin of the pulmonary trunk or arteries. Pseudotruncus arteriosus has also been described in foals and a calf and is characterized by the presence of a remnant of an atretic pulmonary trunk.[38,62] With pseudotruncus arteriosus, the pulmonary blood supply comes from bronchial arteries or a PDA. Clinical manifestations of these conditions include tachycardia, exercise intolerance, and a cardiac murmur. The murmur may be a continuous machinery murmur if a PDA is also present, holosystolic and crescendo-decrescendo and loudest at the left heart base, or the coarse murmur of the VSD may be auscultated, although the relative pulmonic stenosis component is absent. Cyanosis, dyspnea, or syncope may be seen with exercise or excitement. CHF and stunted growth may be noticed. Polycythemia was detected in a calf with a pseudotruncus arteriosus.[62] The presence of cyanosis with the cardiac murmur helps differentiate this condition from a simple VSD or PDA. Definitive diagnosis may be made by echocardiography, angiocardiography, or nuclear angiocardiography.

30.4.4.7

AORTIC ANOMALIES

Dextropositioning or transposition of the aorta are the most common aortic anomalies of foals and calves and are seen most frequently with other defects. Other aortic anomalies of foals and calves are persistence of the right aortic arch and double aortic arch, which may cause esophageal compression. The clinical presentation is one of esophageal obstruction. Interruption of the aortic arch in two foals with VSD, ASD, and PDA has been reported.[49] The foals showed weakness, lethargy, cyanosis, and tachycardia. The murmur was pansystolic and plateau-shaped, with the PMI on the right side of the thorax. Radiology showed cardiomegaly and increased vascularization of the lungs. Cardiac catheterization showed left ventricular failure. Bicuspid and quadricuspid cusps of the aortic and pulmonic valves occur in large animals and usually result in both stenosis and valvular insufficiency. An aneurysm of the sinus of Valsalva was detected in a 3-year-old thoroughbred gelding as an incidental finding.[63] Occasionally a diastolic murmur may be associated with aortic insufficiency in horses with sinus of Valsalva aneurysms.[63,64] These sinus of Valsalva aneurysms usually rupture later in life, and the

horse develops acute distress, colic, and uniform ventricular tachycardia. A continuous machinery murmur is usually present on the right side of the thorax, associated with the presence of an aorticocardiac fistula.

30.4.4.8 EISENMENGER'S COMPLEX

Eisenmenger's complex has been described in a stunted, 24-month-old Holstein heifer that had a loud, crescendo-decrescendo, pansystolic murmur heard best over the pulmonic valve.[41] The heifer had a prominent gallop rhythm from a loud fourth heart sound and exercise intolerance without cyanosis. Polycythemia was present, however. Cardiac catheterization showed increased pressures in the right atria, right ventricle, and pulmonary artery, with normal left-sided pressures. The echocardiogram was characterized by a VSD, overriding aorta, and dilation of the pulmonary trunk, a feature that distinguished this from tetralogy of Fallot. Left ventricular function was decreased, and at necropsy the heart was enlarged and rounded with a dilated pulmonary trunk and small aorta. The right ventricle was dilated and hypertrophied, whereas the left atria and ventricle were only mildly dilated.

30.4.4.9 ECTOPIA CORDIS CERVICALIS

Ectopia cordis cervicalis is a relatively common defect of cattle.[33,48] Although this defect usually results in the heart being in the cervical region, a few animals may have the heart in the pectoral region (14%) or the abdomen (3%).[48] Various defects are associated with ectopia cordis cervicalis, including defects of the heart, great vessels, neck (torticollis), ribs, and sternebrae. The heart is usually contained within the pericardium under the muscles of the skin in the ventral cervical area, with the double apex of the heart pointing craniodorsally. The ligaments of the pericardium are most frequently attached to the mandibles and the parotid fascia cranially, the cervical fascia laterally, and the first rib or manubrium caudally. The lung may lack the cardiac notch and often protrudes to the base of the heart. Although the prognosis for a productive life is poor, some calves lived until approximately 1 year of age.

30.4.4.10 MISCELLANEOUS CARDIAC DEFECTS

Other cardiac defects can occur, but the significance of the lesion is questioned or the defect has been recorded infrequently. Complete atrioventricular canal defect has been reported in a foal.[51] Anomalous coronary artery development has been reported at postmortem examination, but the lesion was not necessarily the cause of death in a calf.[65] Anomalous origin of the coronary artery has been thought to be the cause of death in horses.[66] Congenital hematomas of the atrioventricular valves also have been noted, but the significance is unknown.[33] Endocardial fibroelastosis, an anomalous development of the endocardium associated with left ventricular hypertrophy, is usually a severe defect resulting in death of the animal. The frequency of this defect in large animals is not established.

30.4.4.11 VALVULAR HEART DISEASE

30.4.4.11.1 Definition and Etiology

In adult animals, disorders of the tricuspid, pulmonic, mitral, or aortic valves are usually acquired and most commonly result in insufficiency of the affected valve. These disorders may be the result of degenerative changes, infection (bacterial or viral endocarditis or myocarditis), inflammation (valvulitis), trauma, or

unknown causes (cardiomyopathy). They are usually manifested by a cardiac murmur, most frequently of valvular regurgitation, with the PMI at the location of the affected valve or in the direction of the regurgitant blood flow. The mitral and aortic valves are the most common location of degenerative valve disease in horses.[67] Predisposing causes such as microembolism or infarction have not been identified in large animals. Chronic active infection such as foot abscesses, rumenitis, reticular abscess, or other septic process may lead to sustained or recurrent bacteremia, predisposing the animal to the development of bacterial endocarditis, particularly in cattle, or a nonvegetative valvulitis, probably more common in horses. Experimentally, valvular vegetative endocarditis can be induced by intravenous administration of bacteria without preliminary damage to a valve.[68] Rupture of a valve leaflet or chordae tendineae can cause valvular heart disease, as can dilation of a cardiac chamber from any cause or rupture of the aortic root or of a sinus of Valsalva aneurysm.[69–71] In rare cases neoplasia, primarily lymphosarcoma of cattle, can cause valvular heart disease. Congenital valvular heart disease in adult animals is rare. The most common bacterial isolates from equine and bovine endocarditis cases are streptococci and *Pasturella* or *Actinobacillus* species and *Arcanobacterium (Actinomyces) pyogenes* in horses and cattle, respectively, although a wide variety of organisms has been isolated from large animals with endocarditis.[72,73,75–79]

30.4.4.11.2

Clinical Signs and Differential Diagnosis

Most animals with valvular heart disease have no clinical signs but have a cardiac murmur that is detected during a routine examination. The clinical signs vary depending on the severity of the lesion and its rate of development. Murmurs of valvular heart disease are frequently holosystolic (Fig. 30-6), pansystolic, or holodiastolic (Fig. 30-7). They radiate from the PMI in the direction of the abnormal blood flow; are coarse and band-shaped, crescendo or honking (if systolic), or decrescendo and blowing or musical (if diastolic); and are usually moderate to loud in intensity (≥grade 3/6) but may be softer if holodiastolic. All of these characteristics help distinguish these murmurs from functional or innocent murmurs, which generally occur early or late in systole or diastole but can be holosystolic; are soft and blowing or crescendo-decrescendo in quality; are localized to a small area; do not radiate; and are soft to moderate in intensity (≤3/6). The intensity of the murmur is not a reliable indicator of the severity of the lesion, except in horses with tricuspid regurgitation, in which the longer, louder murmurs are associated with a larger jet of tricuspid regurgitation.[80] In cattle, in particular, severely involved valves (usually in cattle with endocarditis) commonly have faint or no audible murmurs.

Fig. 30-6 Phonocardiogram obtained from a horse with a ruptured mitral valve chorda tendineae. A loud, plateau-shaped holosystolic murmur *(SM)*, which is variable in intensity, occurs when the free wall leaflet of the mitral valve is prolapsing into the left atrium.

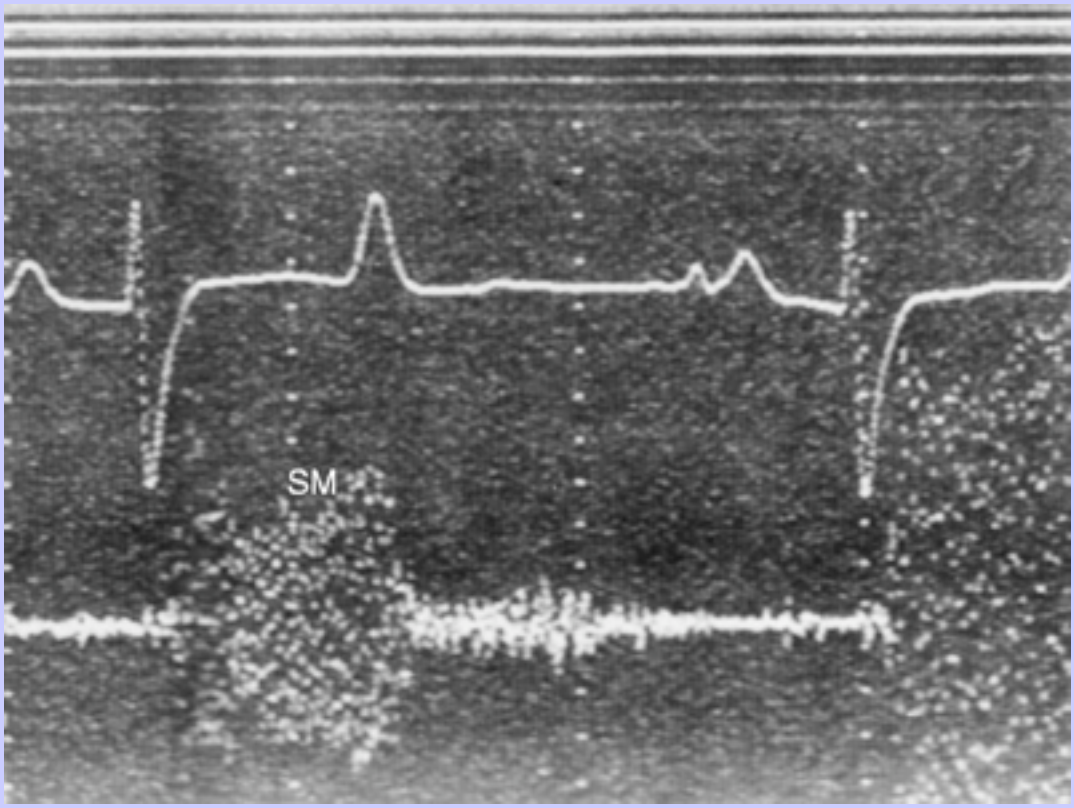
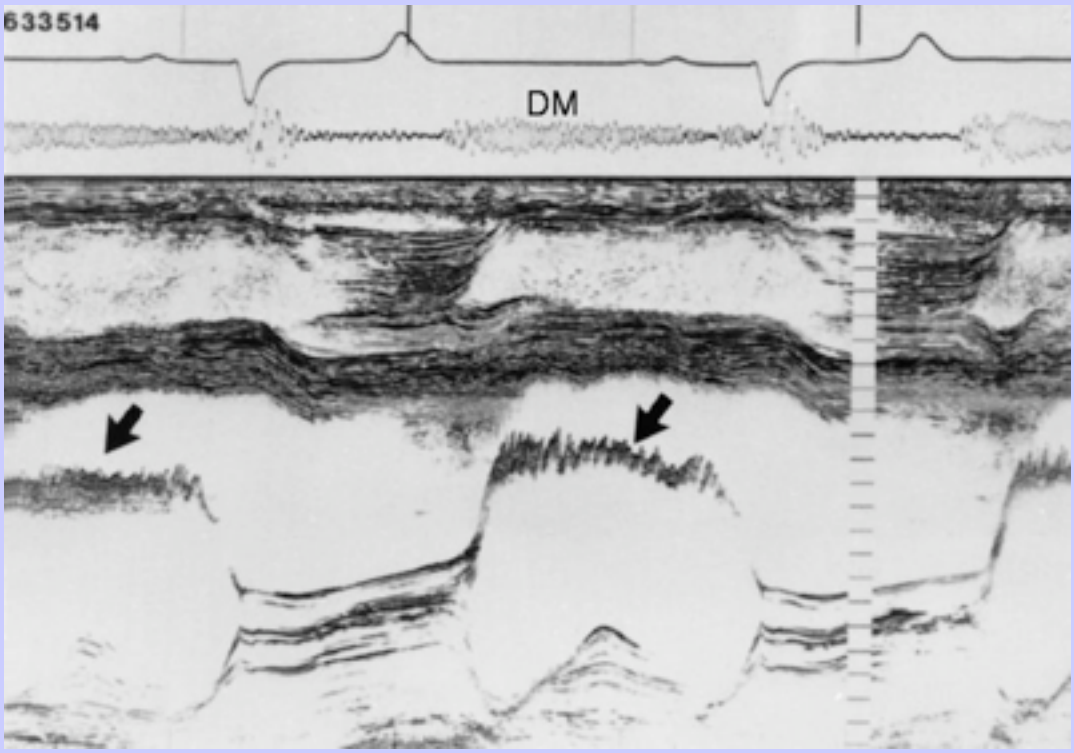


Fig. 30-7 Phonocardiogram and M-mode echocardiogram obtained from a horse with a holodiastolic murmur *(DM)* caused by aortic valve regurgitation. The M-mode echocardiogram shows diastolic flutter *(arrows)* of the septal mitral valve leaflet, characteristic of aortic valve insufficiency.



The location of the PMI of the murmur is helpful in distinguishing which valve is involved, although more than one valve can be affected in the same animal. The PMI for lesions of the mitral valve frequently is at the left apex of the heart, although murmurs of mitral regurgitation usually radiate dorsally and toward the left heart base and aortic valve area. Therefore loud systolic murmurs with the PMI in the aortic or mitral valve area in horses are usually mitral regurgitation murmurs. Disorders of the tricuspid valve commonly have the PMI on the right side of the thorax (third to fourth intercostal spaces [horses] or second to third intercostal spaces [cattle]). Infrequently, the murmur may also be heard on the left side of the thorax cranial to the pulmonic valve location in the second intercostal space. Aortic and pulmonic valve lesions produce murmurs with the PMI at the left heart base in the third or fourth intercostal space. Acquired valvular lesions of the mitral and tricuspid valves produce primarily systolic murmurs.[72,73,75,80–84] Diastolic tricuspid flow murmurs have been reported, however, and may be associated with right-sided mural or valvular masses in horses[85] or may be physiologic, associated with normal blood flow across the atrioventricular valves.[86,87] Lesions of the aortic and pulmonic valves may produce diastolic murmurs, systolic murmurs, or both.[72,88–90] However, diastolic murmurs of regurgitation are most common in large animals. Aortic regurgitation associated with degenerative valve disease is most common in horses, whereas

pulmonic regurgitation associated with bacterial endocarditis is more common in cattle. Aortic valve lesions in horses have primarily holodiastolic, decrescendo, musical murmurs (see Fig. 30-7) but can also be decrescendo, soft, and blowing. Aortic regurgitation murmurs are accompanied by a water-hammer or bounding arterial pulse if the aortic regurgitation is associated with a significant left ventricular volume overload.[72,91] The musical quality of the murmur (harmonic) indicates that some part of the aortic valve is vibrating during diastole. The arterial pulse quality becomes more bounding as the aortic regurgitation becomes more severe, and is a good clinical indicator of the degree of left ventricular volume overload. Ventricular premature beats and atrial fibrillation may also be detected in horses with significant aortic regurgitation.

Besides the cardiac murmur, animals with valvular heart disease may have exercise intolerance, weight loss, or signs of CHF evidenced by tachycardia, coughing, respiratory distress, jugular venous distention, subcutaneous edema, and ascites (uncommon in large animals). In adult cattle, mammary vein distention is another sign of CHF.[73] Cardiac enlargement may be noted as an increased area of auscultation and/or percussion or caudal dislocation of the apical impulse of the heart. Atrial fibrillation may be present. This development is usually an indicator of atrial enlargement in animals with valvular heart disease. If tricuspid valve regurgitation is present, there may be abnormal systolic jugular venous pulsations. If mitral regurgitation is present there may be tachycardia, tachypnea, poor recovery to resting respiratory rate after exercise, coughing, and frothy pulmonary edema. Lung sounds may be harsh at rest and on deep inspiration may include rare crackles or moist bubbly sounds. Most horses with pulmonary edema have only harsh breath sounds that are detected at rest and on deep inspiration.

One of the clinical signs of bacterial endocarditis is a cardiac murmur, the PMI and timing of which depend on the valve or valves affected. Other signs may include tachycardia, arrhythmias, auscultation of prominent heart sounds, tachypnea, coughing, recurring fever, anorexia, weight loss, or signs of CHF. Evidence of disseminated sepsis such as pneumonia, hematuria, or pyuria is usually present. Shifting leg lameness and swollen joints or tendon sheaths are common but usually have an immune-mediated cause, although a horse with bacterial endocarditis and septic tenosynovitis has been reported.[76] Mastitis and decreased milk production are common in cattle. The presence of weight loss, fever, and signs of recurring sepsis help distinguish bacterial endocarditis from other forms of acquired valvular disease.

The clinical signs of a major mitral valve chordal rupture (major chorda tendineae) or its characteristic murmur distinguish this disease from other mitral valve diseases. The murmur is usually a widely radiating murmur of mitral valve regurgitation (see Fig. 30-6) with a distinctive honking quality (again the honking quality is consistent with vibration of the mitral valve chorda tendineae or leaflet with blood flow in systole). However, the honking quality may be absent and replaced by a band-shaped pansystolic murmur. There may be evidence of acute hemodynamic collapse. Acute onset of respiratory distress with coughing and expectorating foamy pulmonary edema fluid (this fluid is also detected at the external nares) is a relatively consistent feature with rupture of a major chorda tendineae. Signs of right-sided heart failure (jugular venous distention, subcutaneous edema, and ascites) may develop rapidly. Atrial arrhythmias, most frequently atrial fibrillation, often develop secondary to atrial enlargement. Supraventricular arrhythmias have also been reported in foals with a ruptured mitral chorda tendineae.[83] The acute onset of respiratory distress, along with a honking systolic murmur, distinguishes mitral valve chordal rupture from other causes of mitral regurgitation. The honking systolic murmur of a ruptured mitral valve chorda tendineae can also be heard in the absence of any clinical signs in horses with a minor chordal rupture. The murmur of mitral valve prolapse is also a distinctive murmur and should be suspected in horses whenever a mid- to late-crescendo systolic murmur is auscultated with the PMI over the mitral valve area.[92] A similar murmur is

frequently auscultated in horses with tricuspid valve prolapse. Murmurs of mitral or tricuspid valve prolapse can be detected in horses with all degrees of valvular insufficiency. Most frequently, however, only small amounts of valvular regurgitation are associated with valvular prolapse. An increased prevalence of mitral and tricuspid regurgitation has been reported in young horses in training.[93]

30.4.4.11.3

Clinical Pathology

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Diagnosis of valvular disease is best performed with a complete echocardiographic examination including M-mode, two-dimensional, and Doppler echocardiography. Two-dimensional echocardiography is superior to M-mode for detection of valvular abnormalities (Figs. 30-8 and 30-9), measurement of valvular masses (Fig. 30-9, *B*), and the global assessment of ventricular function, but chamber enlargement, high-frequency vibrations of the valve leaflets, and shortening fraction (an indication of ventricular systolic function) can be determined by both. Pulsed wave, continuous wave, and color flow Doppler echocardiography can be used to semiquantitate the severity of valvular regurgitation.[92–97] The size of the regurgitant jet detected with pulsed wave or color flow echocardiography is one indicator of the severity of the valvular insufficiency.[98] The duration of the mitral regurgitation jet is also important in assessing severity. Clinically insignificant jets of regurgitation are detected only just behind the valve when it is closed. Valvular insufficiency is mild when the jet occupies one third or less of the receiving chamber, moderate when the jet occupies greater than one third but less than two thirds of the receiving chamber, and severe when the jet occupies greater than two thirds of the receiving chamber.

Fig. 30-8 Two-dimensional echocardiographic image obtained from the left parasternal window of a ruptured mitral chorda tendineae *(arrow)* in the left atrium of a gelding with mitral regurgitation and a honking pansystolic murmur.

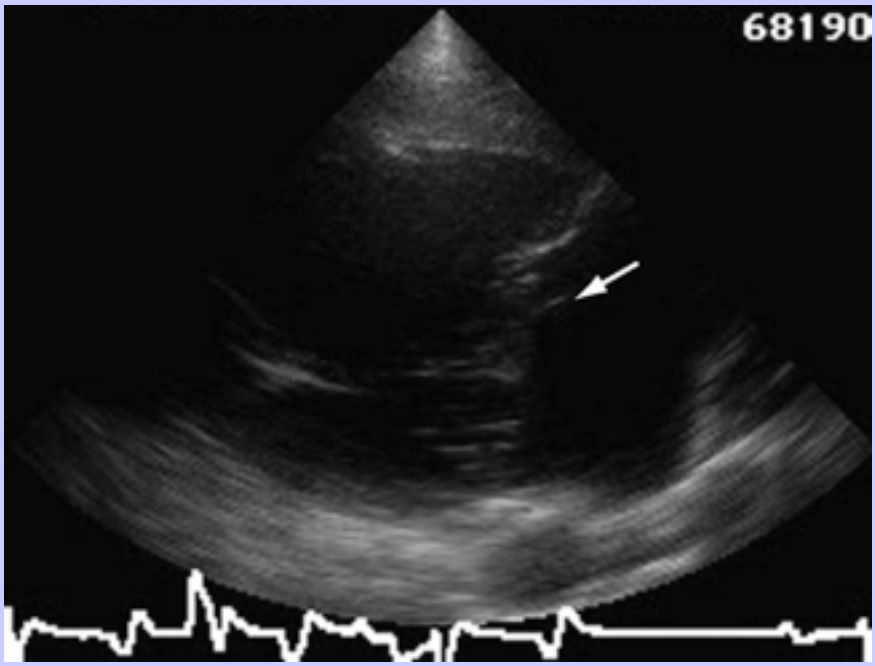
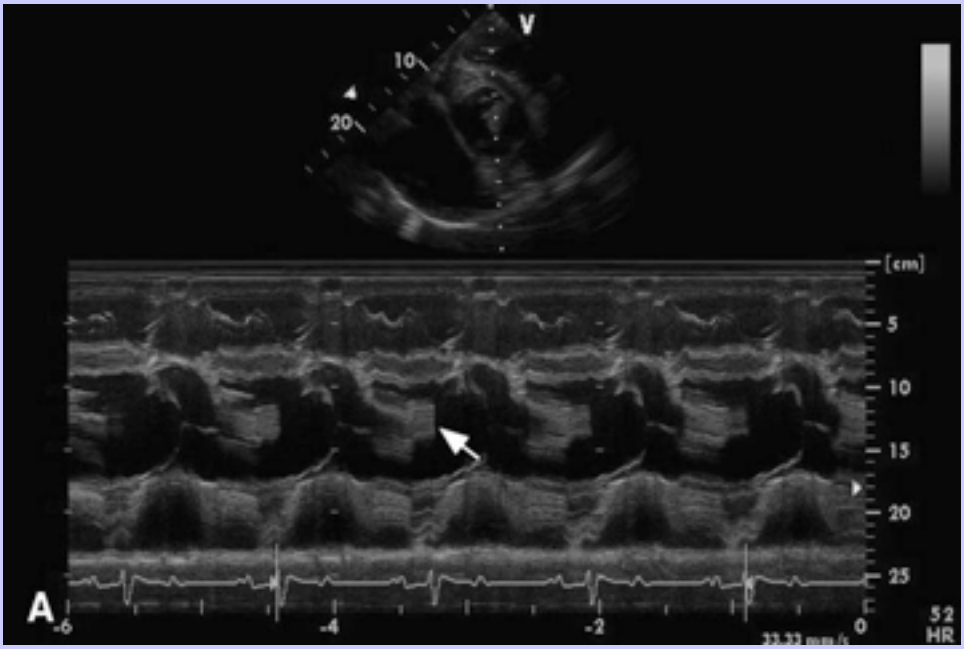
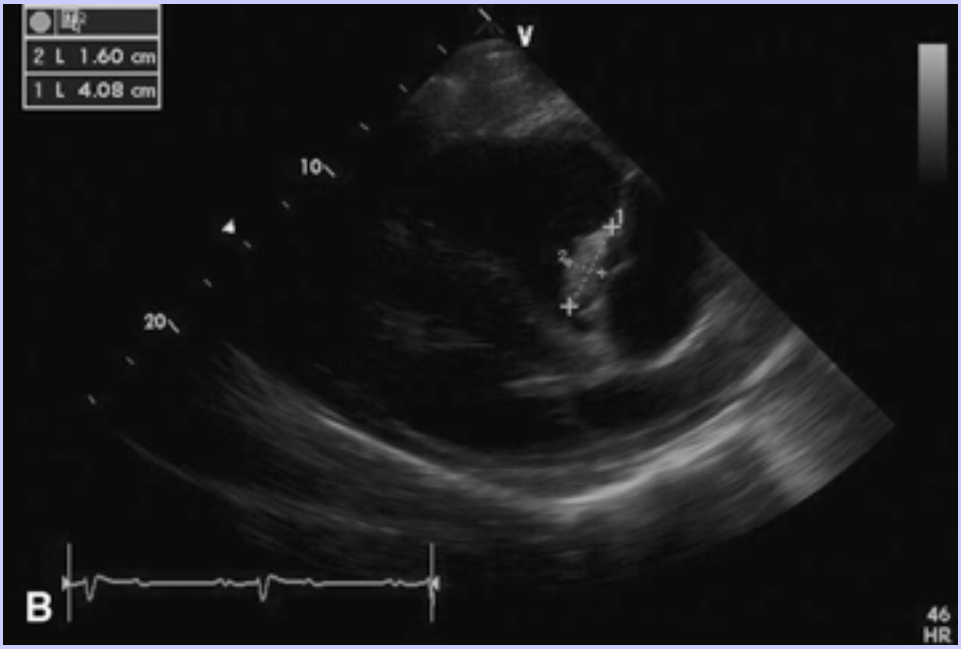


Fig. 30-9 Echocardiograms of a bacterial endocarditis lesion on the aortic valve of a horse. The lesion can be seen on the aortic valve M-mode **(A)** as a thick echoic band *(arrow)* and is measured in the two-dimensional echocardiographic image of the left parasternal long axis view **(B)**.





Echocardiographic signs of mitral regurgitation are increased left atrial (Fig. 30-10; see also Fig. 30-3) and left ventricular dimensions and a left-sided volume overload. The cause of the valvular regurgitation can often be determined. Endocarditis (see Fig. 30-9), ruptured mitral valve chordae tendineae (see Fig. 30-8), a flail valve leaflet, valvular prolapse, or thickening of the valve leaflet are readily imaged echocardiographically.[99] The regurgitant jet detected with pulsed wave or color flow Doppler echocardiography usually originates from the site of the valvular abnormalities detected with two-dimensional echocardiography. In some animals, the lesion responsible for the valvular insufficiency is not visualized with two-dimensional echocardiography but the regurgitant orifice is detected with pulsed wave or color flow Doppler echocardiography.[95–97,100] Left ventricular function may be normal (if the mitral regurgitation is mild) or the FS may be increased (if there is a significant left ventricular volume overload associated with moderate to severe mitral regurgitation), unless there is concomitant myocardial disease. A ruptured mitral valve chorda is diagnosed by finding a mobile linear echo everting into the left atrium or a flail leaflet that may prolapse into the left atrium during systole (see Fig. 30-8), systolic and chaotic diastolic mitral valve flutter, rapid mitral valve opening with increased excursion of the affected leaflet, and lack of coaptation of the mitral valve in systole. The asynchronous movement of any portion of the valve leaflet during any phase of the cardiac cycle indicates the presence of a flail valve leaflet.[81,99] A larger than normal pulmonary artery (larger than the aortic root) is compatible with severe pulmonary hypertension and left-sided heart failure. A smaller than normal aortic root is detected echocardiographically in horses in low-output left-sided heart failure.[83,98,99]

Tricuspid regurgitation may produce echocardiographic evidence of right atrial and right ventricular enlargement with paradoxic septal motion. Frequently the cause of tricuspid valve regurgitation in cattle is bacterial endocarditis, and the incompetent valve can be visualized. In cattle, neoplasia of the right atrium, tricuspid valve, or right ventricle can usually be visualized when present.[101] Tricuspid regurgitation is common in horses with no obvious valvular lesion.[87,93,102]

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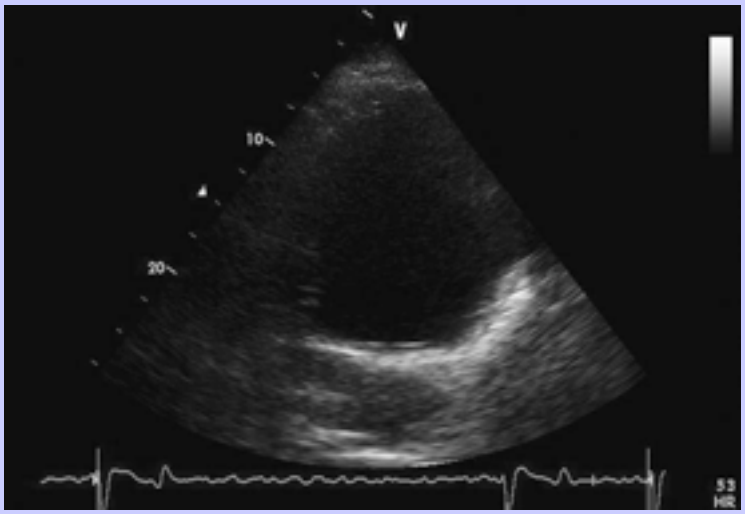
Fig. 30-10 Left parasternal echocardiographic image of the left atrium and mitral valve from a horse with left atrial enlargement (15.55 cm).



Aortic valve regurgitation is diagnosed echocardiographically by observing left ventricular dilation, increased aortic root diameter (Fig. 30-11), increased left ventricular FS (if the aortic regurgitation is moderate to severe and left ventricular function is normal), diastolic fluttering of the septal mitral valve leaflet (Fig. 30-12; see also Fig. 30-7), or, less frequently, by observing high-frequency vibrations of the interventricular septum or aortic valve in diastole.[89,91,96,98] Rarely, premature closure of the mitral valve is detected. Thickening of the left cusp of the aortic valve is frequently detected echocardiographically, but prolapse, fenestration, and tears of the aortic cusps also occur.

Acquired pulmonic valve lesions are uncommon in large animals and when present are usually associated with bacterial endocarditis.[83,90,103] Diagnosis is established by finding the mass associated with the pulmonic valve. Severe pulmonic regurgitation associated with pulmonic valve rupture has been reported in one horse.[104] Pulmonic regurgitation is most common in horses with pulmonary hypertension and CHF but is rarely detected clinically.

Fig. 30-11 Two-dimensional echocardiographic image of an enlarged aortic root (9.57 cm) obtained from an aged gelding with moderate aortic regurgitation that has been present for several years.

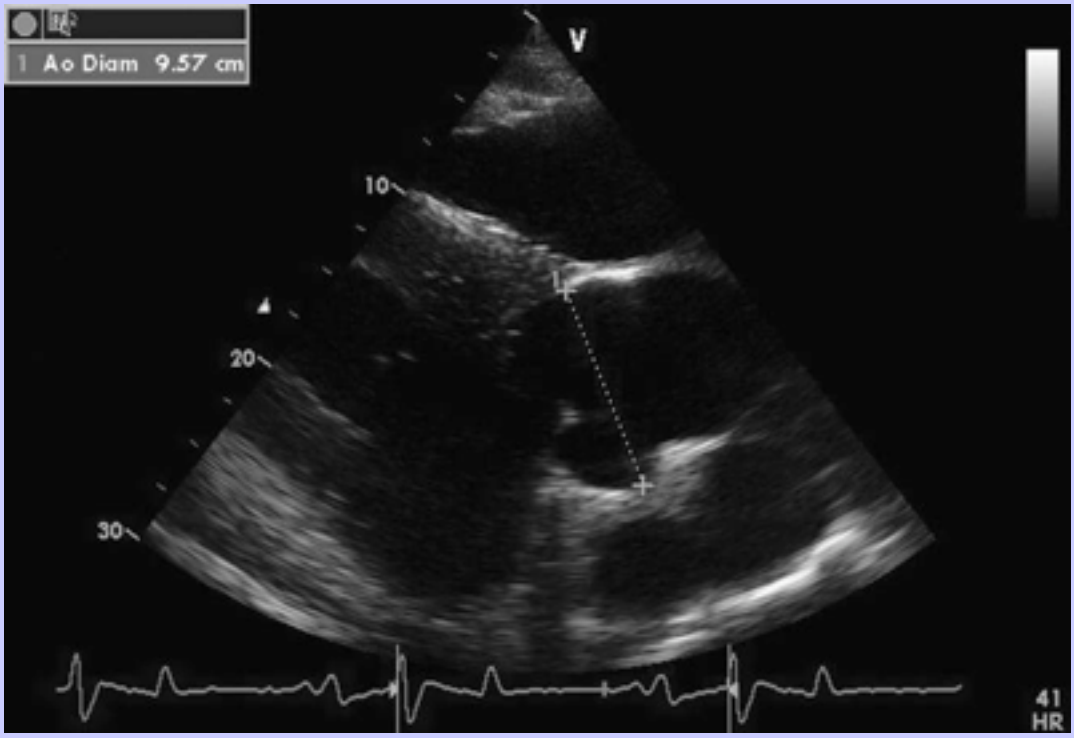
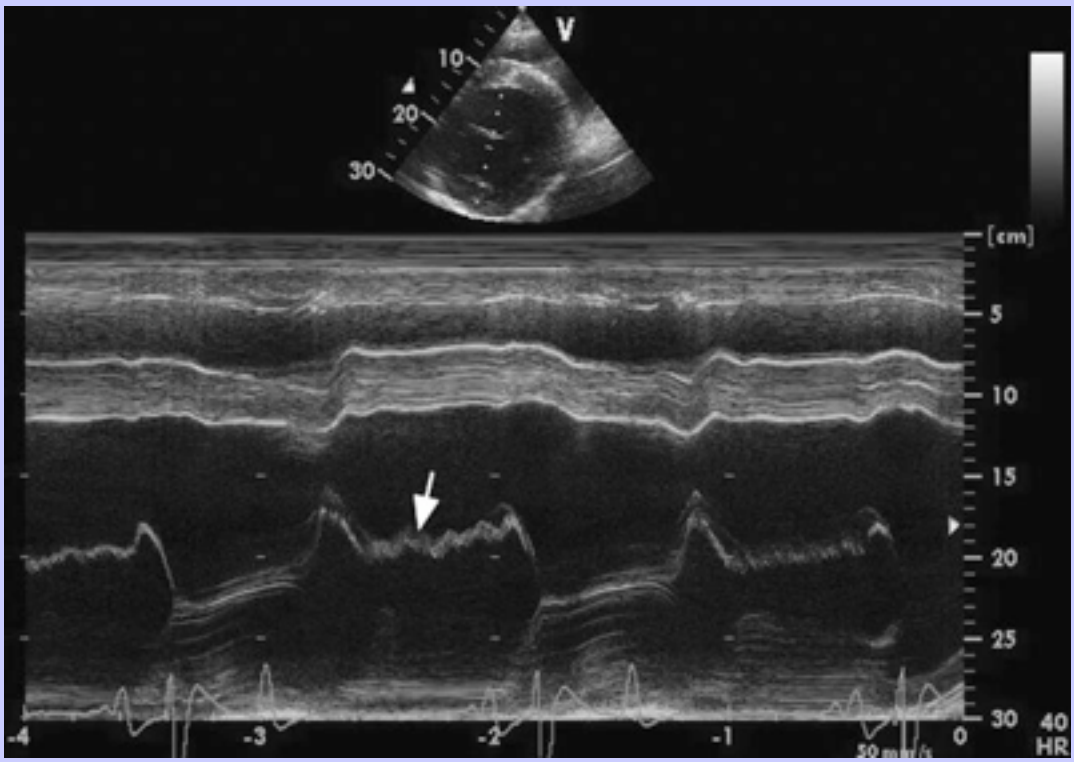


Fig. 30-12 M-mode echocardiogram obtained from a stallion with moderate chronic aortic regurgitation. Notice the high-frequency vibrations *(arrow)* on the septal leaflet of the mitral valve.



Lesions of bacterial endocarditis (see Fig. 30-9) may have a shaggy, ragged, or cystic appearance on two-dimensional echocardiography.* Occasionally the only abnormality noticed is valve thickening with ventricular hyperkinesis and enlargement of the chambers on the side of the affected valve. Acoustic reverberation and production of microbubbles have also been associated with valvular bacterial endocarditis.[83,86] Other laboratory evidence of bacterial endocarditis includes anemia, neutrophilia (a left shift may be present), an increased serum globulin concentration, and hyperfibrinogenemia. Liver enzymes are frequently mildly elevated, and a urinalysis sometimes shows hematuria or pyuria. Positive blood cultures taken during febrile episodes confirm the diagnosis when associated with the above findings. However, many times the culture results are negative in large animals with bacterial endocarditis. Other laboratory evidence of disseminated sepsis includes neutrophilic response in peritoneal, tracheal wash, or joint fluid. Ventricular arrhythmias are frequently detected electrocardiographically in individuals with mitral or aortic valve endocarditis. Radiographic or sonographic evidence of disseminated pneumonia also may be found with bacterial endocarditis, usually in large animals with a right-sided lesion.

Other laboratory evidence of valvular heart disease is nonspecific. The ECG is not reliable for detecting chamber enlargement associated with valvular incompetence. The ECG is valuable for documentation of cardiac arrhythmias occurring secondary to chamber enlargement or the underlying myocardial disease.

Radiographic findings of cardiac enlargement, increased pulmonary vascular pattern, or pulmonary edema are also nonspecific. Cardiac catheterization can be performed, and pressure measurements help determine the degree of cardiac dysfunction. Nuclear angiocardiography shows cardiac enlargement or prolonged washout of contrast material. Time-activity curves can be helpful in accurately documenting ventricular dysfunction and the valvular regurgitant fraction.[106]

* References 75, 77, 78, 83, 85, 89, 90, 105.

30.4.4.11.4

Pathophysiology

Acquired valvular heart disease that is slow in onset or gradually progressive may be asymptomatic at first, but cardiac changes occur that eventually may lead to CHF. Valvular incompetence from endocarditis, degenerative changes, chordal rupture, or other causes results in volume overload of the recipient chamber. Initially the output of the chamber is increased to maintain forward output, but the increased end-diastolic volume of the recipient chamber leads to compensatory dilation and a mild elevation in end-diastolic pressure. Compensatory hypertrophy may also result. In the later stages of valvular regurgitation, contractile function of the volume-overloaded chamber may diminish, leading to further elevation of end-diastolic pressure and decreased compliance. In the case of severe aortic and mitral regurgitation, this causes elevation of left atrial pressure and eventually pulmonary venous hypertension. Pulmonary artery wedge pressure is higher at rest and during exercise in horses with moderate mitral regurgitation.[107] With severe tricuspid regurgitation, right atrial or central venous pressure increases. Increased myocardial oxygen consumption is a natural sequela, and biventricular failure can ensue.

If valvular heart disease is acute in onset, as with major chordal rupture of the mitral valve, the regurgitation and volume overload are imposed on the left atrium, which cannot dilate and adapt acutely to the increased diastolic filling. The sudden hemodynamic change leads to pulmonary venous hypertension and acute pulmonary edema. However, most horses with mitral regurgitation do not have acute fulminant pulmonary edema. Instead, chronic pulmonary hypertension leading to subtle respiratory signs associated with interstitial pulmonary edema and the subsequent development of right-sided CHF are common in horses with severe mitral regurgitation.[99] In one study 12 of 14 horses with CHF had jugular distentions or pulsations, 10 had abnormal lung sounds (crackles), and nine had a cough.[108]

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Bacterial endocarditis of the mitral or tricuspid valve may lead to rupture of the chordae tendineae. Mitral chordal rupture has been reported in adult horses and foals with bacterial endocarditis, leading to acute left-sided CHF.[83] In addition to the hemodynamic load placed on the heart from an incompetent valve, bacterial endocarditis also results in disseminated sepsis. The vegetations are made up of layers of fibrin, blood cells, necrotic tissue, and bacteria and are relatively resistant to short-term antimicrobial therapy. The disseminated sepsis may be the cause of death or the reason for culling of the animal. Myocardial necrosis of a papillary muscle was associated with mitral chordal rupture in one foal.[83]

30.4.4.11.5

Epidemiology

Acquired valvular heart disease is common in large animals, involving 356 of 1557 horses (22.9%) in one abattoir survey.[67] Endocarditis, one form of valvular heart disease, was reported in 4% of cattle in another study.[109] Bacterial endocarditis most commonly affects the tricuspid valve in cattle but has been reported on the pulmonic, mitral, and aortic valves as well.[73,89,90,101] Most cases of tricuspid valve bacterial

endocarditis have been reported in horses with septic jugular vein thrombophlebitis.[72,75,110] Tricuspid valve endocarditis has also been reported in a horse with a VSD.[85] Aortic and mitral valve endocarditis are most common in horses, occurring with nearly equal frequency.[74,75] In the largest survey of acquired valvular heart disease in horses, the aortic valve was affected most commonly with degenerative valve changes, followed by the mitral valve, tricuspid valve, and, uncommonly, the pulmonic valve.[67] Not all valvular lesions are associated with incompetency of the valve. Degenerative valvular changes, particularly changes involving the aortic valve, are seen more commonly in older horses.

30.4.4.11.6

Necropsy Findings

Acquired valvular disease is associated with finding nodular thickening, fibrous bands, valve fenestrations, rupture of mitral valve chordae tendineae, fibrinous masses typical of endocarditis, and combinations of these lesions on postmortem examination. There may be associated or secondary changes varying from enlargement of a chamber or vessel to hematomas, degeneration, inflammation, and fibrosis. Enlargement (primarily dilation) of the chamber receiving the regurgitant flow, in addition to enlargement (primarily dilation) of the chamber or vessel from which the regurgitant flow arises, is commonly detected. Jet lesions, usually found in the receiving chamber, are associated with the high-velocity turbulent regurgitant blood flow.

Subcutaneous edema; increased pericardial, pleural, or peritoneal fluid; and congestion and mottling of the liver may be present and indicate CHF. Ascites associated with CHF is uncommon in large animals, particularly in horses. A primary source of chronic or active infection, along with evidence of bacterial embolization, may be seen in cattle with endocarditis but is rare in horses.

30.4.4.11.7

Treatment and Prognosis

The treatment and prognosis of acquired valvular heart disease depend on the cause, onset, duration, and severity of the lesion. In general, the prognosis is guarded to poor when evidence of valvular incompetence includes tachycardia, exercise intolerance, signs of CHF, or echocardiographic evidence of severe chamber enlargement. Degenerative valve disease may be asymptomatic except for a cardiac murmur, or it may be mild; but it generally is slowly progressive and therefore historically has been given a guarded prognosis. A more accurate prognosis for horses with murmurs can now be obtained from a complete echocardiographic examination, including Doppler echocardiography. The valve affected, the lesions detected on the valve leaflets, the degree of chamber enlargement and volume overload detected, the echocardiographic assessment of myocardial function, and the severity of the regurgitation determined with Doppler echocardiography, coupled with the animal's age and intended use, can be used to formulate a prognosis.[96,98] Valvular regurgitation associated with no detectable abnormalities, valvular prolapse, and mild valvular thickening usually has a fair to good prognosis if the amount of valvular regurgitation is small. Individuals with ruptured chordae tendineae, flail valve leaflets, and marked valvular thickening usually have moderate to severe regurgitation, which is likely to progress more rapidly and usually warrants a guarded to poor prognosis. Mitral regurgitation is the most likely valvular insufficiency to be associated with clinical signs of cardiovascular disease, whereas primary aortic regurgitation and tricuspid regurgitation infrequently result in the development of CHF or the death of the animal, except in horses with severe aortic regurgitation. Bacterial endocarditis has a guarded to grave prognosis, even with long-term antibiotic therapy, and frequently results in sudden death of the animal, although bacteriologic cures have been reported.

Despite the guarded long-term prognosis, palliative therapy can be applied for most forms of acquired valvular heart disease. Bacterial endocarditis is treated with long-term administration, ideally intravenously (IV), of bacteriocidal antimicrobials, the choice of which is based on blood culture and sensitivity results. Continuous intravenous infusion of antimicrobials is the ideal initial treatment, when feasible. In cattle and horses, initial therapy is directed at the likelihood of a gram-positive infection. Combination antibiotic therapy consisting of a penicillin and an aminoglycoside can be used for gram-negative organisms. Using rifampin at a dose of 5 mg/kg twice daily orally (PO) in combination with another antibiotic with appropriate spectrum has improved the short-term outlook for large animals with bacterial endocarditis. Aspirin (100 mg/kg/day, ruminants; 17 mg/kg every other day, horses) and low-dose heparin (30 U/kg subcutaneously [SC] twice daily, ruminants and horses) may be used in patients with valvular endocarditis in an attempt to prevent platelet adhesion and increased size of the valvular mass. Early diagnosis and aggressive treatment with the appropriate antimicrobials for a prolonged period are important for successful treatment of bacterial endocarditis. The long-term outcome for successfully treated cases is still poor because the scarring that results as the endocarditis lesion heals may lead to severe valvular regurgitation and the death of the animal, particularly with left-sided bacterial endocarditis lesions.[75,76,78,98,111] Compliance and economics are also major drawbacks in treating endocarditis.

The hemodynamic consequences of valvular heart disease (volume overload or CHF) may be improved by using diuretics. Furosemide has been used most commonly at a dose of 0.5 to 1 mg/kg as needed. With the low bioavailability of oral furosemide, intravenous administration is preferred to obtain the maximal diuretic effect.[112] Digoxin can be used to improve contractility when CHF has occurred. Conditions such as aortic valve or mitral valve regurgitation may show little or no long-term improvement, although many individuals improve for 2 to 6 months before the CHF becomes refractory to treatment. The administration of a maintenance dose of digoxin at 2.2 µg/kg IV twice daily or 11 µg/kg PO twice daily has resulted in therapeutic plasma digoxin concentrations and clinical improvement in horses with CHF with no significant adverse effects.[113] Loading doses are rarely used, because of problems with digoxin toxicity.[114] An intravenous loading dose of 12 to 14 µg/kg can be used in horses but must be divided into three administrations, followed by a maintenance dose of 6 to 7 µg/kg daily.[115] Digoxin can also be administered PO to horses at a dose of 34 to 70 µg/kg for loading and 17 to 35 µg/kg for maintenance.[115] Digoxin is administered IV to cattle at a loading dose of 22 µg/kg followed by a maintenance dosage of 11 µg/kg three times daily or, preferably, at an infusion rate of 0.86 µg/kg/hr.[116] The clinical impression is that horses, as do other species, benefit from the use of vasodilators. Clinical and echocardiographic improvement has been seen in several horses with moderate mitral or aortic regurgitation treated with angiotensin-converting enzyme (ACE) inhibitors. Quinapril at 120 mg/horse/day resulted in an increase in stroke volume and cardiac output that was statistically significant after 8 weeks of treatment in horses with mitral regurgitation.[117] Clinical and echocardiographic improvement has been seen in horses with CHF. Clinical improvement has been seen with hydralazine at 0.05 to 1.5 mg/kg PO twice daily. The ACE inhibitor enalapril has also appeared to be effective in horses with moderate to severe mitral or aortic regurgitation and in horses with CHF, at a dose of 0.5 mg/kg PO twice daily. Ramipril was beneficial in the treatment of one horse with CHF at 50 µg/kg daily PO.[118] Until recently the expense of these drugs limited the usefulness of enalapril and the other ACE inhibitors. However, a generic form of enalapril maleate is now available, making this treatment more affordable for most owners. Although the short-term outlook may be improved with use of cardiovascular drugs, the prognosis is guarded for long-term survival or production.

30.4.4.11.8 Prevention and Control

Many causes of acquired valvular heart disease cannot be controlled. Appropriate therapy for chronic active infections and careful attention to asepsis with intravenous medication and other invasive procedures may help prevent endocarditis and, possibly, nonvegetative valvulitis. Effective parasite control measures may eliminate some predisposing causes of valvular heart disease such as trauma to heart valves, microembolism, or infarction in horses.

30.4.5 BRISKET DISEASE: COR PULMONALE AND PULMONARY HYPERTENSION

30.4.5.1 Definition and Etiology

Cor pulmonale is a term used to refer to the effect of lung dysfunction on the heart and is therefore a secondary form of heart disease. Regardless of the cause, the underlying feature is pulmonary hypertension that leads to right ventricular hypertrophy, dilation, or failure. The primary cause of the disease (also called *high-mountain disease* or *high-altitude disease* in cattle) is hypoxic vasoconstriction from high-altitude dwelling. The disease is worsened by the ingestion of locoweed (*Oxytropis* and *Astragalus* species).[119,120] Chronic pulmonary disease such as bronchopneumonia or lungworm infection in cattle also can result in cor pulmonale.[121] In the horse, right-sided heart dysfunction (e.g., decreased cardiac output, increased right ventricular end-diastolic pressure, increased right atrial or central venous pressure, jugular venous distention, or subcutaneous edema) associated with chronic pulmonary disease is rare but may be more common than previously recognized. However, right-sided heart dysfunction associated with pulmonary hypertension and left-sided heart dysfunction is a common cause of CHF.

30.4.5.2 Clinical Signs and Differential Diagnosis

Frequently the primary presenting clinical sign of brisket disease is subcutaneous edema of the brisket, the ventral thorax, the submandibular area, and occasionally the limbs. Jugular venous distention or pulsations may be present. Dyspnea and tachypnea frequently are exhibited. Tachycardia is present, and a gallop rhythm may be auscultated. Splitting of the second heart sound (S_2) is a variable finding. Pulmonary hypertension may accentuate the separation of the aortic and pulmonic valve closures, producing audible splitting of S_2 that is most noticeable during inspiration. In some horses with moderate or severe recurrent airway obstruction (RAO) and increased vascular impedance; however, pulmonic valve closure occurs early, and only a single S_2 is audible.[122]

A cardiac murmur may be auscultated, caused either by tricuspid insufficiency or a pulmonic valve ejection murmur. The murmur of tricuspid insufficiency, which is secondary to right ventricular dilation, is regurgitant or plateau-shaped with the PMI over the right thorax or, less frequently, the left second intercostal space. The pulmonic valve ejection murmur, found less commonly, is audible as a crescendo-decrescendo murmur at the left heart base.[123] Pleural or pericardial effusion is not common with cor pulmonale.[124] In horses with RAO leading to cor pulmonale, tachypnea, labored breathing, coughing, and exercise intolerance are common complaints. Wheezes are usually auscultated bilaterally in the thorax of affected horses.

These clinical signs are not specific for brisket disease (cor pulmonale) and largely reflect right-sided heart failure. Other considerations when signs of right-sided heart failure are present should be bacterial

endocarditis or tricuspid insufficiency from any cause, cardiomyopathy, cardiac lymphosarcoma or other thoracic neoplasms, pericarditis, left-sided heart failure, pleuritis or pleural effusion, and congenital pulmonic valve stenosis (rare). With pericarditis, heart sounds may be muffled, or the characteristic “washing machine murmur” may be audible. Left-sided heart failure is frequently accompanied by pleural effusion, pulmonary edema, and weak peripheral pulses. In horses, however, expectoration of pulmonary edema fluid occurs only with sudden onset of severe left-sided heart failure. In horses with chronic left-sided heart failure, tachypnea, coughing, poor recovery after exercise, and harsh lung sounds may be all that is detected.

30.4.5.3

Clinical Pathology

A complete blood count may reveal a neutrophilia in cases of cor pulmonale caused by primary lung disease. Radiography of the thorax reveals primary pulmonary disease such as bronchopneumonia, bronchiectasis, or chronic bronchitis in cattle that have developed this disease at low altitudes. Radiographic findings in horses with RAO usually reveal an interstitial pattern. Arterial blood gases demonstrate the presence of hypoxia and may also show hypercapnia. Transtracheal wash fluid cytology and bacterial culture may provide evidence of the cause of the primary lung disease. Fecal sedimentation helps rule out parasitic bronchitis or pneumonia. Electrocardiographic findings are not specific. An echocardiogram may provide further evidence of pulmonary hypertension and right-sided heart dysfunction by showing right ventricular hypertrophy and dilation, increased septal thickness, and abnormal septal motion (Fig. 30-13).[125,126] Dilation of the pulmonary artery is also detected with two-dimensional echocardiography and is a sensitive indicator of pulmonary hypertension or increased flow through the pulmonary artery. A dilated pulmonary artery has been reported in horses with cor pulmonale and in horses with acute pulmonary obstruction from RAO.[126,127] Cardiac catheterization reveals elevated pressure in the pulmonary artery, right ventricle, and right atrium. Elevation of right ventricular end-diastolic pressure is a sign of right ventricular failure.

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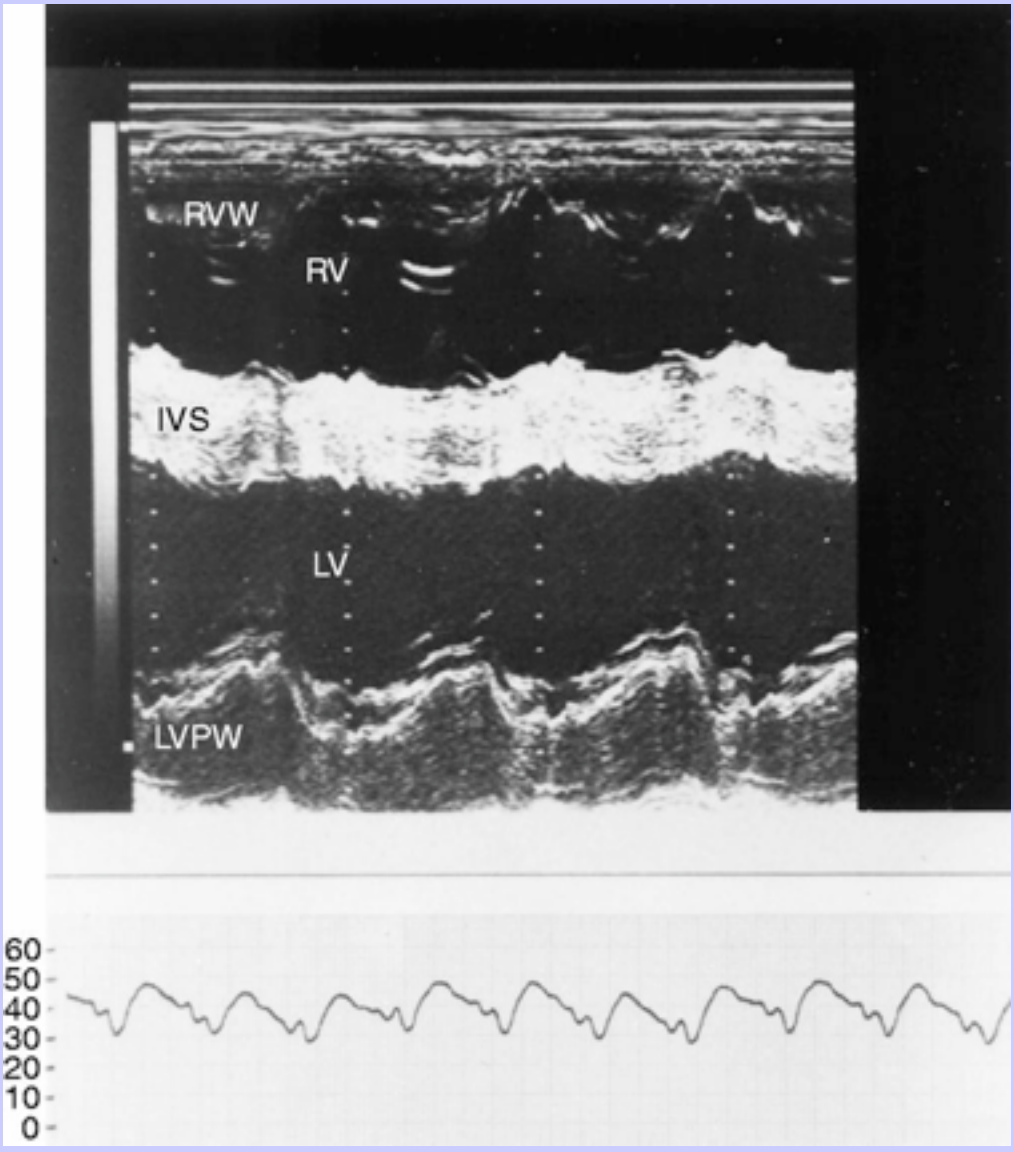
Fig. 30-13 M-mode echocardiogram and pulmonary artery pressure curve obtained from a cow with pulmonary hypertension and cor pulmonale. The echocardiogram shows mild thickening of the right ventricular wall *(RVW)* and interventricular septum *(IVS)*, dilation of the right ventricle *(RV)*, and abnormal septal motion. *LV*, Left ventricle; *LVPW*, left ventricular free wall. The pulmonary artery pressure curve demonstrates elevated systolic and diastolic pressures. (Pulmonary artery pressure curve in millimeters of mercury [mm Hg].)



30.4.5.4

Pathophysiology

Pulmonary arteriolar constriction is the response to hypoxia from high-altitude dwelling or pulmonary disease. The response to hypoxia varies, depending on the amount of smooth muscle in the pulmonary arteries. In cattle, increased pulmonary vascular resistance and pulmonary hypertension frequently develop. Chronic pulmonary artery hypertension causes a pressure overload on the right ventricle, which responds to the increased work load with hypertrophy, dilation, or failure, depending on the speed with which the condition develops. The disease is progressive, and at some stage the right ventricular myocardium is unable to compensate, dilates, and fails. With failure come the typical signs of jugular venous distention and development of subcutaneous edema. Chronic right-sided heart failure may result in diastolic dysfunction of the left ventricle.

30.4.5.5

Epidemiology

The disease is more common in cattle than in other animal species, especially when cattle are kept at altitudes over 6000 feet, in which cases the incidence has been estimated at 0.5% to 2%.[128] Mainly calves are affected, and some herds with a higher prevalence are thought to have a genetic predisposition to develop pulmonary arterial constriction when subjected to hypoxia at high altitude. Ingestion of locoweed (*Oxytropis* and *Astragalus* species) also predisposes cattle to right-sided heart failure at high altitudes by causing toxic myocardial damage.[119]

30.4.5.6

Necropsy Findings

There is evidence of right-sided heart failure such as subcutaneous edema in the submandibular area, brisket, and ventral abdomen. Findings include dilation and hypertrophy of the right ventricle, congestion of the liver, and ascites. The lung may have changes of pneumonia, bronchitis, bronchiectasis, or emphysema. Lesions of locoweed toxicity may be found in other organs in cattle.[119] Lesions of chronic interstitial pulmonary disease are found in horses with RAO.

30.4.5.7

Treatment and Prognosis

Removing the animal from high altitude, treating the primary lung disease, and administering oxygen may help eliminate the hypoxia and thus the pulmonary artery hypertension. Cor pulmonale from high altitude is potentially reversible when the animal is returned to a lower altitude. The heart failure can be treated with digoxin and diuretics. Beneficial effects of vasodilator therapy have not been documented. Once heart failure signs have developed, the prognosis is guarded even with appropriate treatment. Removing the horse from the environment inducing RAO is critical to the treatment of the horse with cor pulmonale. A more detailed discussion of the treatment and management of horses with RAO can be found in Chapter 31.

30.4.5.8

Prevention and Control

The selection of breeding stock with low or normal pulmonary arterial pressures at altitudes above 5000 feet (mean pulmonary artery pressure less than 35 mm Hg) helps to eliminate the predisposing genetic susceptibility to the effects of hypoxia of high altitude.[128] The disease can also be controlled by removing susceptible animals from high altitude and preventing locoweed ingestion. Herd health practices such as

avoiding crowding and poor ventilation and using appropriate vaccinations to reduce the incidence of pulmonary disease help to reduce the incidence of other causes of cor pulmonale.

30.4.6 MYOCARDIAL DISEASE: MYOCARDITIS AND CARDIOMYOPATHY

30.4.6.1 Definition and Etiology

Myocarditis is an inflammation in the myocardium caused by bacterial, viral, or parasitic organisms or thromboembolic disease caused by these organisms. In large animals, recognized bacterial causes include *Staphylococcus aureus, Streptococcus equi, Clostridium chauvoei,* and *Mycobacterium* species. Myocarditis also can occur after bacteremia, septicemia, pericarditis, or endocarditis, regardless of the causative agent. Known viral causes of myocarditis include foot-and-mouth disease, equine infectious anemia, equine viral arteritis, equine influenza, and African horse sickness. Parasitic causes of myocarditis may include strongylosis[129] or onchocerciasis in horses, and toxoplasmosis, cysticercosis, or sarcocystic infection in ruminants.[130,131] Currently it is thought that infection with the spirochete *Borrelia burgdorferi* may be a cause of myocarditis in domestic animals, as it is in human beings.[132] Cardiomyopathy is a subacute or chronic disease of the ventricular myocardium that occurs without anatomic valvular disease, congenital malformations of the heart or vessels, or pulmonary disease. In large animals, dilated cardiomyopathy is the only cardiomyopathy of known significance. Dilated cardiomyopathy is associated with ventricular dilation, increased ventricular mass, and decreased systolic function. Although the cause is frequently undetermined,[133–135] several conditions have been related to or identified with cardiomyopathy. The most common cause of cardiomyopathy in horses is probably myocarditis, although the inciting insult is usually difficult to identify. 469
An inherited cardiomyopathy, which is thought to be linked to the red Holstein gene, has been found in 470
Holstein-Friesian cattle in Canada, Japan, Australia, the Netherlands, and Switzerland.[136–139] There is also a cardiomyopathy associated with a curly hair coat in polled Herefords.[140] Cardiomyopathy has been associated with ingestion of monensin, lasalocid, salinomycin, gossypol, *Cassia occidentalis,* and *Phalaris* species. Vitamin E and selenium deficiency, copper deficiency, excessive molybdenum, or high sulfates (secondary copper deficiency) may cause cardiomyopathy.[141–150] Myocardial infiltration by neoplasia such as lymphosarcoma or fibrosarcoma also may cause cardiomyopathy. A fibrofatty infiltration of the right ventricle and interventricular septum that appears to be similar to arrhythmogenic right ventricular dysplasia has been reported in horses.[151]

30.4.6.2 Clinical Signs and Differential Diagnosis

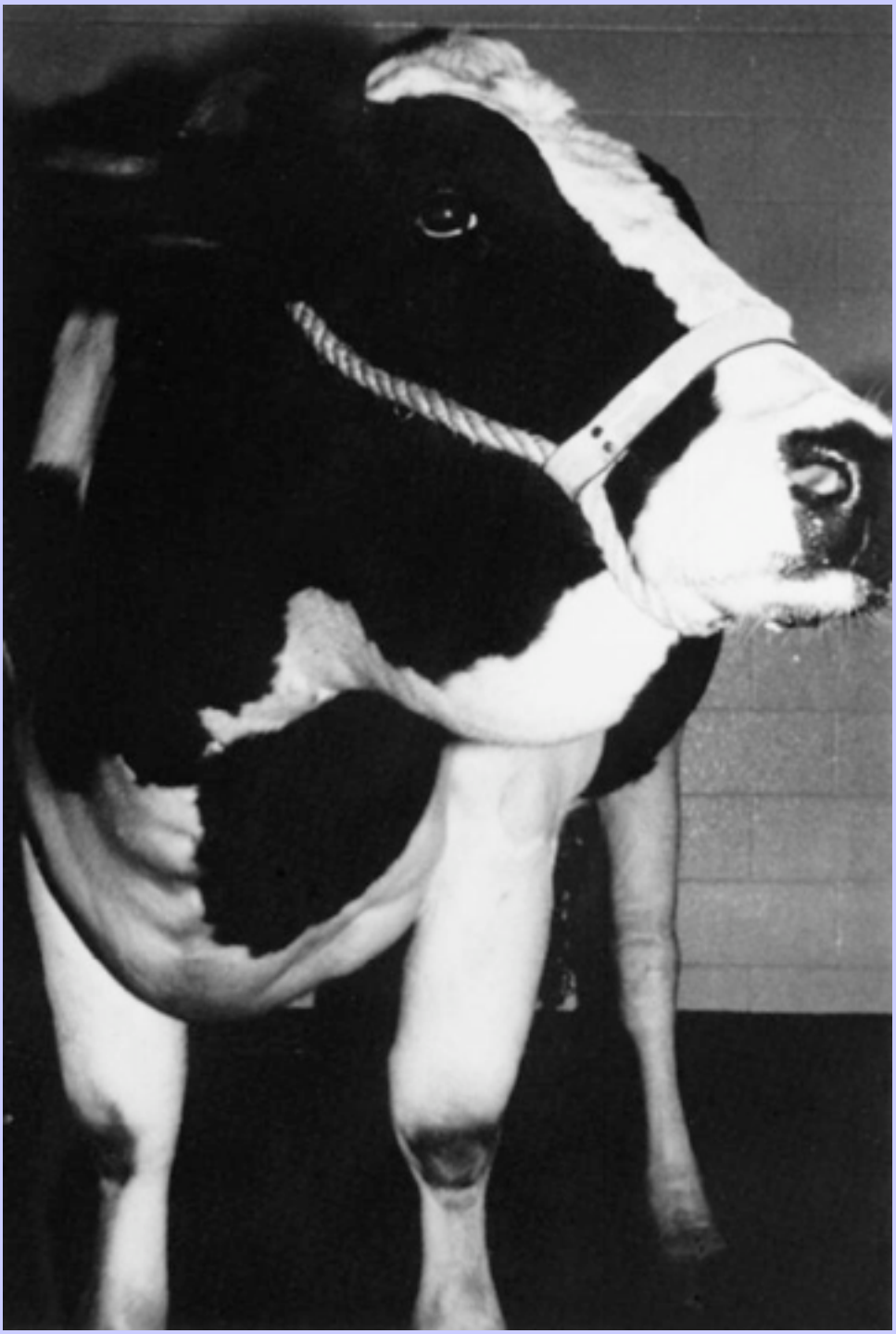
The manifestations of myocarditis are highly variable, depending on the extent of the disease, location of the inflammation within the myocardium, and associated systemic illness. Myocarditis can easily be missed because of the lack of specific cardiac signs or the predominance of signs related to the organ system with primary involvement (e.g., strangles in horses or mastitis in cattle). Animals with myocarditis are often febrile or have a recent history of fever and may have tachycardia. The elevated heart rate may be caused by sinus tachycardia or other paroxysmal or sustained supraventricular or ventricular arrhythmias, because cardiac arrhythmias are common. Premature beats are also commonly detected in large animals with myocarditis and may be present in animals with a normal or increased heart rate. Occasionally, acute myocarditis is associated with auscultation of a pronounced gallop rhythm or a cardiac murmur of either tricuspid or mitral valve insufficiency. Jugular venous distention, other signs of CHF such as peripheral edema, and signs of circulatory collapse may be present. Horses may show evidence of myalgia, reluctance to move, or exercise intolerance.

With these signs it may be difficult to distinguish myocarditis from colic, respiratory disease, lameness, or septicemia. If signs are more clearly cardiac (e.g., murmur, arrhythmia, jugular venous pulsations), the practitioner should rule out endocarditis, cardiomyopathy, cardiac neoplasia, and CHF from another cause.

The clinical signs associated with dilated cardiomyopathy can also be variable but are usually more clearly associated with heart disease. Most animals have signs of cardiac failure such as peripheral edema and jugular venous distention or pulsations (Fig. 30-14). Auscultation frequently reveals tachycardia, gallop rhythm, muffled heart sounds, or a cardiac arrhythmia. Cardiac murmurs of tricuspid or mitral valve insufficiency are usually present secondary to the ventricular dilation. The breath sounds are increased, tachypnea is present, and, frequently, percussion of the thorax reveals signs of pleural or pericardial fluid. Occasionally, respiratory distress is evident with hyperpnea, dyspnea, coughing, and the presence of a bloody froth at the nostril. Nonspecific signs of cardiomyopathy such as exercise intolerance, syncope, diarrhea, or anorexia may also be present. In cattle, decreased milk production and abomasal displacement have been associated with dilated cardiomyopathy.[136] Palpable liver enlargement has also been reported in cattle with cardiomyopathy.[137] Most affected cows develop clinical signs within 3 months of calving.[137]

Sudden death can be a feature of myocarditis or dilated cardiomyopathy, and it frequently follows stress or exercise. Recumbency, collapse, and sudden death are common presenting signs in animals with ionophore toxicosis.[141–147,149] In many animals with inherited cardiomyopathy, death occurs within 6 months of age.[138,140] In Holstein-Friesian cattle with suspected inherited cardiomyopathy, heart failure and death may not occur until cattle are 2 to 4 years old.[136,137] Other acquired causes of cardiomyopathy can occur at any age.

Fig. 30-14 Holstein cow with cardiomyopathy showing signs of CHF (submandibular and brisket edema, jugular venous distention, and pulsations).



When animals show clinical signs of dilated cardiomyopathy, many differential diagnoses should be considered. If the animal is young, other congenital heart defects, cor pulmonale, and nutritional myodegeneration should be considered. In adults, bacterial endocarditis, cardiac neoplasia, thoracic abscess, pericarditis, pleuritis, and diaphragmatic hernia may also have similar clinical manifestations. Although the cause of dilated cardiomyopathy may be difficult to determine, nutritional (vitamin E, selenium, or copper deficiency), toxic (monensin, gossypol, salinomycin, lasalocid, *Cassia* species, or *Phalaris*), infectious (viral, bacterial, or parasitic) or drug-induced causes should be investigated.

30.4.6.3

Clinical Pathology

Depending on the cause of the myocardial disease, the clinicopathologic findings may vary. Routine complete blood count may be normal, or a neutrophilic leukocytosis may be present. No consistent changes are expected in the serum chemistry profile, but serum albumin concentration may be slightly decreased and serum urea nitrogen, creatinine, γ-glutamyltranspeptidase (GGT), sorbitol dehydrogenase (SDH), and bilirubin concentrations may be increased because of congestive liver disease when signs of CHF are present. Serum concentrations of creatine kinase (CK) and lactic dehydrogenase (LDH) may be elevated, but hepatic and skeletal muscle contribution to these elevations cannot be ruled out. A better indication of myocardial disease may be the elevation of cardiac troponin I (cTnI) or the myocardial isoenzymes of CK (myocardial bound [MB]) and LDH (LDH_1). Large elevations of the myocardial isoenzymes of CK and LDH were detected in one outbreak of monensin toxicosis[144] and have been detected in other horses with myocardial necrosis of unknown etiology. Marked elevations of cTnI have also been reported in a horse with multiform ventricular tachycardia and myocardial necrosis of unknown cause.[152] and in a horse with ventricular tachycardia and aortic septal rupture.[153] Elevations of cTnI were detected in a recent herd exposure to lethal concentrations of monensin. Mild elevations of cTnI were also reported in two Belgian horses with atypical acute monensin toxicosis.[150] Analysis of pericardial or pleural fluid reveals a transudate with low protein concentration (less than 2.5 g/dL) and cellularity (white blood cell [WBC] count less than 2500/μL), with the predominant cell type being mononuclear cells, unless the myocarditis is an extension of pericarditis. Serum should be tested for serologic evidence of bovine leukosis (BLV) infection in adult cattle, α-tocopherol, glutathione peroxidase, and copper concentrations. Whole blood selenium levels should be determined. In infectious myocarditis or inherited cardiomyopathy, the results of these tests will most likely be normal. A negative BLV test result essentially eliminates lymphosarcoma as a cause of the myocardial disease; a positive test result does not confirm a causal relationship. In horses, serum should be tested for serologic evidence of a variety of equine viruses, particularly influenza, equine viral arteritis, and herpes virus. Hemoglobinuria, if present, suggests consideration of monensin, gossypol, or nutritional myodegeneration as the cause of myocardial disease. Arterial blood oxygen tension may be reduced below 80 mm Hg in animals with myocardial disease.

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An ECG may demonstrate sinus tachycardia or other cardiac arrhythmias; the frequency and severity of these arrhythmias are best demonstrated with continuous electrocardiographic monitoring. There may be some evidence of conduction abnormalities in the base-apex lead, but these findings are not specific for myocardial disease. Echocardiography may be normal in animals with myocarditis, or the abnormalities detected may be caused by the arrhythmias present. A small left ventricular internal diameter, thickened left ventricular free wall and interventricular septum, small aortic root diameter, and decreased FS may be detected in animals with sustained ventricular tachycardia and decreased cardiac output (Fig. 30-15). More frequently, however, there is increased ventricular chamber size, decreased thickness of the interventricular septum and left ventricular free wall, and decreased myocardial function (decreased FS, decreased EF, and myocardial dyskinesis), especially in more severe cases of myocarditis and in animals with dilated cardiomyopathy (Fig.

30-16). In humans with myocarditis there may be evidence of abnormal left ventricular wall motion, paradoxic motion of the interventricular septum, or an echo-free pericardial space.[154] Additional echocardiographic features of dilated cardiomyopathy are increased end-systolic and end-diastolic dimensions of the left and right ventricles (see Fig. 30-16), increased left atrial size, and an increased left atrial to aortic root dimension ratio. There may be abnormal mitral valve closure (increased EF slope) and increased separation of the septal mitral valve leaflet and the interventricular septum. A decreased aortic root diameter may be detected, along with a shortened ET, in animals with low-output left-sided heart failure. An enlarged pulmonary artery indicative of pulmonary hypertension (Fig. 30-17) may also be present.

Cardiac catheterization may reveal elevated intracardiac pressures (right atrial, right ventricular, pulmonary artery, pulmonary capillary wedge, and left ventricular end-diastolic) in animals with dilated cardiomyopathy. 471
Humans with acute infectious myocarditis may show hypotension and a narrow pulse pressure. Nuclear 472
angiocardiography may be used to show decreased EF[155] in animals with myocardial disease.

Fig. 30-15 M-mode echocardiogram of the left ventricle *(LV)* obtained from a mare with sustained uniform ventricular tachycardia. Note the small end-diastolic and end-systolic dimensions of the left ventricle and the little variation between systole and diastole in this dimension. *RV*, Right ventricle.

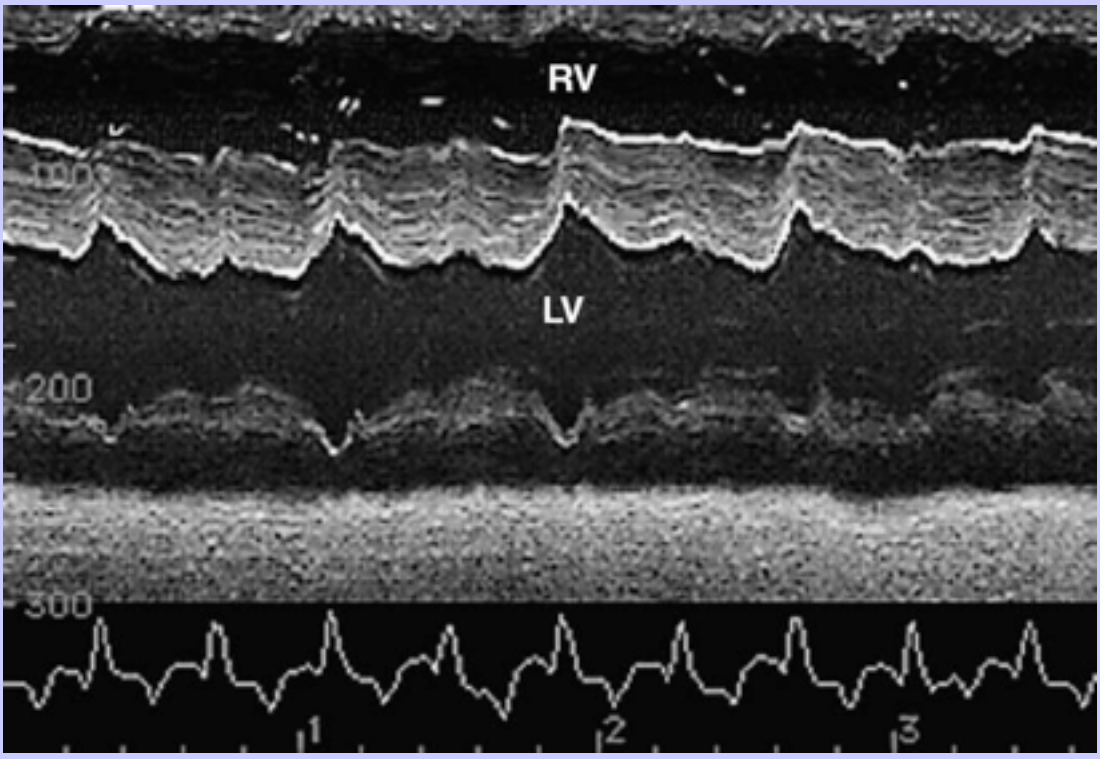


Fig. 30-16 M-mode echocardiogram of the left ventricle obtained from a mare with cardiomyopathy and severe left ventricular dysfunction. Note the large end-diastolic dimension of her left ventricle *(LV)*, the thin interventricular septum and left ventricular free wall, and the poor left ventricular contractility. The fractional shortening in this mare varied from 2% to 8%. *RV*, Right ventricle.

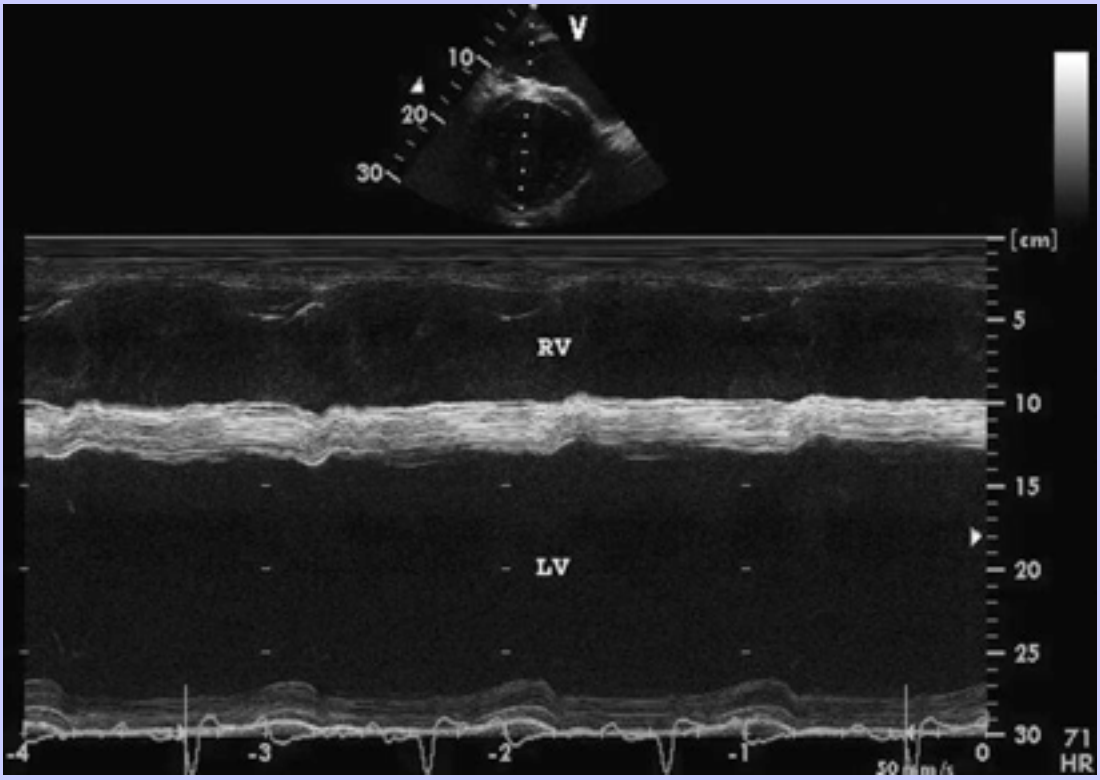
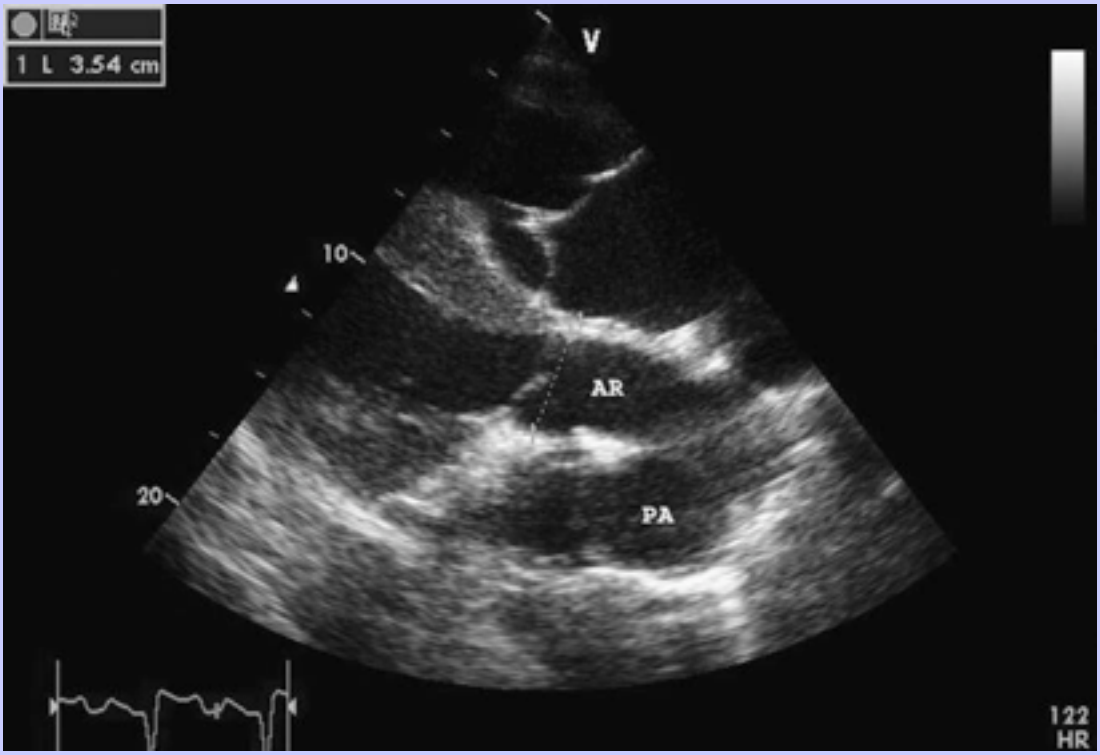


Fig. 30-17 Two-dimensional echocardiogram of the aorta *(AR)* and main pulmonary artery *(PA)* obtained from a foal with cardiomyopathy and severe mitral and tricuspid regurgitation. The pulmonary artery is larger than the aorta, indicative of pulmonary hypertension and impending left-sided CHF. The aorta measured 3.54 cm at its origin.



30.4.6.4

Pathophysiology

The pathophysiologic changes associated with myocardial disease depend on the specific nature and extent of the disease. Acute myocarditis or angiopathic myocardial lesions[129] may go on to develop into idiopathic dilated cardiomyopathy. It is speculated that changes in cellular metabolism occur with either acute myocarditis or dilated cardiomyopathy, resulting in ECG abnormalities and reduced myocardial performance (reduced cardiac output). In an attempt to compensate for reduced cardiac output, circulating fluid volume is increased by activation of the renin-angiotensin-aldosterone system, and arterial resistance is increased. These compensatory mechanisms frequently lead to only minor improvement in the cardiac output of the failing heart, and the increase in ventricular preload (venous return) and afterload (arterial resistance) may cause pulmonary edema and a further reduction in cardiac contractility. Ventricular dilation, further reduction in cardiac output, and signs of heart failure occur.

30.4.6.5

Epidemiology

The prevalence of acute myocarditis is difficult to estimate, because frequently the disease goes undiagnosed, is mild, or is masked by disease in another organ system or the animal recovers spontaneously. Similarly, it is difficult to assess the clinical significance of postmortem findings of myocardial inflammation and fibrosis. The morbidity of myocarditis in large animals probably is underestimated because it is rarely the cause of mortality and is associated with viral, bacterial, and parasitic infections that manifest themselves without specific signs of cardiovascular disease.

Inherited cardiomyopathy has been reported in cattle in Japan, Australia, the Netherlands, Canada, and Switzerland, with the incidence in inbred populations reaching 3% to 5%.[137] A familial form of dilated cardiomyopathy has also been reported in cattle in Sweden, Denmark, Australia, and the United Kingdom.[137] These cattle may be genetically linked by the presence of the red gene in Holstein-Friesian cattle.[136] Although in some cattle inherited cardiomyopathy resulted in death by 6 months of age,[138,140] other cattle failed to show clinical signs until 2 to 6 years of age.[134–135,137,139] No sex predilection is recognized in inherited cardiomyopathy of cattle.

The morbidity and mortality from cardiomyopathy stemming from other causes in cattle and horses is not known. From the number of clinical reports, inherited cardiomyopathy seems to be more prevalent in cattle than in horses. Idiopathic dilated cardiomyopathy or cardiomyopathy secondary to viral or bacterial infections may be more common in horses and is a common cause for the acute onset of CHF in horses of racing age.

30.4.6.6

Necropsy Findings

There may be no gross lesions associated with myocarditis. Depending on the relationship between death and the occurrence of myocarditis, microscopic examination of the myocardium may show no inflammatory cells but increased fibrous tissue in the interstitium, or there may be foci of inflammatory cells (typically mononuclear cells), variation in the cross-sectional area of the cardiac myocyte, degeneration of adjacent myocardial fibers, myocardial necrosis, and fibrosis. Focal interstitial nephritis and fibrosis were reported in eight of nine Holstein-Friesian cattle in Scotland with dilated cardiomyopathy.[137] Often the inciting cause of myocardial necrosis in horses is unknown.[152] Samples of gastric or ruminal contents should be obtained and submitted for analysis of ionophores if ionophore toxicosis is suspected. Feed samples should also be obtained and submitted for ionophore analysis in these cases.

The lesions of cardiomyopathy are recognized more easily grossly as enlargement of the heart, which may be rounded to globose. Biatrial, biventricular, and pulmonary artery dilation is usually present. Patchy or uniform streaks of myocardial pallor may be detected. In rare cases, one of the chambers or major vessels (usually pulmonary artery) may rupture. Generalized edema is frequently found as ascites (uncommon in horses), pericardial or pleural effusion, and edema of the mesentery and subcutaneous tissues. There may be evidence of vascular congestion of the liver, lungs, and spleen. The kidneys may be pale and swollen and have an irregular, granular, pitted surface.

Microscopically the lesions of cardiomyopathy are characterized as myocardial vacuolation and degeneration with necrosis and fibrosis. Calcification may be associated with these lesions. Occasionally there is increased vascularization with proliferative regeneration of myofibers. In some cases, no histopathologic abnormalities are found.

30.4.6.7

Treatment and Prognosis

The treatment of myocarditis includes treatment of the underlying causative agent if it is recognized and control of the complications such as arrhythmias, CHF, or shock. Thromboembolism is rarely a complication recognized in animals. Prompt administration of vitamin E may be beneficial to the survivors in cases of ionophore toxicosis. Performance animals should be rested. Corticosteroids may be beneficial in animals with severe toxemia, complicated arrhythmias, or intractable heart failure, but their use in early cases of myocarditis or in infections suspected of having a viral cause is controversial because viral recrudescence may occur. However, in many cases the corticosteroids appear to have a beneficial effect. Prognosis is good if there are no signs of heart failure and if cardiac arrhythmias are managed successfully. Prognosis is guarded to poor if signs of CHF are present.

Therapeutic strategies currently used for treatment of dilated cardiomyopathy include positive inotropic agents (digoxin), diuretics, vasodilators, rest, and in some cases removal of pleural or abdominal fluid. The advantages of vasodilators (venodilators to relieve pulmonary edema and arterial dilators to reduce preload and afterload and improve contractility) in the treatment of cardiomyopathy are recognized in humans and small animals,[156] but these drugs have not been widely used in large animals because of the lack of pharmacokinetic studies and clinical trials.

Digoxin is the positive inotropic agent used almost exclusively in large animals but is contraindicated in animals with acute monensin toxicosis. A priming or loading dose can be used in horses with acute severe CHF, followed with a maintenance dose, or, more frequently, the horse is started on a maintenance dose from the onset of therapy. In horses the drug can be administered PO or parenterally. In cattle, low bioavailability limits its use to the intravenous route of administration.[157] Guidelines for the use of digoxin are given in Box 30-1.[158–160] In general, maintenance dosages are used because of the lowered risk of adverse reactions. A peak and trough serum digoxin concentration should be obtained 3 to 5 days after digoxin therapy is begun, and the dosage should then be adjusted accordingly. Ideally the peak and trough digoxin concentration should be 1 to 2 ng/mL.

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30.4.6.7.1

Box 30-1 Guidelines for Digoxin Therapy in Horses and Cattle

HORSES	CATTLE
Priming dose IV: 12 to14 µg/kg	Priming dose IV: 22 µg/kg
Priming dose PO: 34 (elixir)to 70 (powdered tablets in suspension) µg/kg	Maintenance dosage IV: Infusion of 0.86 µg/kg/hr or give 11 µg/kg three times daily
Maintenance dosage IV: 2.2 µg/kg every 12 hours (most commonly used) or 6 to 7 µg/kg/24 hr	
Maintenance dosage PO: 11 µg/kg every 12 hours (most commonly used)	
or 17 (elixir) to 35 (powdered tablets in suspension) µg/kg/24 hr	

IV, Intravenous; *PO,* by mouth.

Dehydration, acid-base imbalance, and electrolyte abnormalities should be corrected before digoxin therapy. The dose of digoxin should be decreased in animals with elevated creatinine or blood urea nitrogen (BUN) until these values return to normal. In horses the intravenous loading dose of digoxin should be administered slowly or divided and given at a rate of one third of the loading dose hourly until completion.[158] Alternatively, therapy can be initiated with the maintenance dose. Close monitoring of body weight, appetite, electrolyte concentrations, creatinine or BUN concentration, and cardiac rhythm is essential during therapy. Therapeutic drug monitoring with digoxin plasma concentrations can be helpful during initial therapy, when the volume of distribution of the drug and the patient's body weight may be in a state of flux. Samples for determination of peak serum digoxin concentrations should be obtained 1 to 2 hours after digoxin administration and should not exceed 2.5 ng/mL.[160,161]

The diuretic used most commonly in large animals is furosemide. It is administered parenterally at the rate of 0.5 to 1 mg/kg twice daily or as needed to control edema. Oral absorption of furosemide is poor or variable in horses.[162] A continuous rate infusion of furosemide is recommended in horses when rapid profound diuresis is needed.[163] The half-life and diuretic effect of bumetanide, a sulfonamide diuretic, are shorter than those of furosemide in horses.[164] Electrolyte concentrations and water consumption should be monitored closely in patients receiving diuretics.

The vasodilators used most frequently in horses include hydralazine and enalapril, an ACE inhibitor. Both have resulted in clinical improvement in animals treated for CHF. Hydralazine is administered PO at a dose of 0.5 to 1.5 mg/kg twice daily. Enalapril has been used at a dose of 0.5 mg/kg PO twice daily in the management of horses with moderate to severe mitral or aortic regurgitation and in the treatment of horses with CHF. However, after a single 0.5-mg/kg oral dose of enalapril, neither enalapril or enalaprilat were detectable in the serum.[165] Ramipril was reported to result in clinical and echocardiographic improvement of a horse with CHF.[166] Quinipril at a dosage of 120 mg/horse/day has also been shown to increase stroke volume and cardiac output in horses with mitral regurgitation after 8 weeks of therapy.[167]

Control of cardiac arrhythmias should be attempted in animals that are hemodynamically unstable or threatened with the development of worsening arrhythmias. Quinidine is usually the drug of choice for control of atrial and ventricular arrhythmias in cattle and is one of the drugs of choice in horses. Procainamide, lidocaine and propafenone have also been successful in the treatment of ventricular arrhythmias in horses (Table 30-3). Although administration is limited to the intravenous route in cattle, oral or intravenous administration in horses results in adequate plasma concentrations to control arrhythmias. Quinidine is administered IV by infusion or by divided bolus injections as shown in Box 30-2.

When quinidine is used IV, concurrent intravenous administration of a balanced electrolyte solution at the rate of 3 to 4 mL/kg/hr is desirable to maintain blood pressure in animals with a severely compromised cardiovascular status.

Prognosis for animals with dilated cardiomyopathy is poor. Echocardiography is useful in determining the severity of the myocardial dysfunction and in formulating a prognosis. The results of the initial echocardiographic examination were the best prognostic indicator of survival in a recent outbreak of monensin toxicosis.[144] Recovery of animals with cardiomyopathy is unusual, constant therapy is required for maintenance of animals with CHF, and sudden death can occur at any time. Some animals may have significant myocardial dysfunction without CHF and are “cardiac cripples,” comfortable at pasture but not safe to use for performance. These animals may later develop CHF.

Table 30-3 Drug Therapy for Ventricular Tachycardia

Drug	Usual Dose
Bretylium tosylate	0.5 mg/kg IV for life-threatening ventricular tachycardia or ventricular fibrillation
Dexamethasone	0.05–0.22 mg/kg, IV or IM
Furosemide	1-2 mg/kg as needed for pulmonary edema
Lidocaine	Equine: 0.1-0.25 mg/kg as a bolus; repeat up to total of 0.5 mg/kg in 10–15 min
	Bovine: 0.5 mg/kg, slowly IV; can repeat in 15 min
Magnesium SO_4	IV infusion at 1 g/min, to effect, up to a maximum of 25 g
Procainamide	1 mg/kg/min, IV to a maximum of 20 mg/kg
Propafenone	2 mg/kg PO tid
	0.5-1 mg/kg in 5% dextrose slowly IV over 5-8 min for refractory sustained ventricular tachycardia (not available in United States)
Propranolol	0.03 mg/kg, IV
Quinidine gluconate (IV)	1-10 mg/kg, IV; total dose in 0.25- to 0.5-mg/kg boluses 5-10 min apart

IM, Intramuscular; *IV,* intravenous; *PO,* by mouth; *tid,* three times per day.

30.4.6.7.2

Box 30-2 Quinidine Administration in Horses and Cattle

HORSES	CATTLE
IV: 1.5 to 2 mg/kg every 10–20 min until conversion or desired effect but not to exceed a total dose of 12 mg/kg	IV: 48 mg/kg infused IV over a 4-hr period
PO: 22 mg/kg (1 g/100 lb of body weight) q2h until conversion or desired effect; not to exceed a total dose of 132 mg/kg q2h; if quinidine plasma concentrations cannot be obtained promptly, a total dose of 88 mg/kg q2h should not be exceeded	

IV, Intravenous; *PO,* by mouth.

30.4.6.8

Prevention and Control

Maintenance of a good vaccination program may limit the bacterial and viral causes of myocarditis. Parasite control may also reduce myocardial injury that predisposes to myocarditis or cardiomyopathy in horses. Toxic myocardial diseases are prevented by proper mixing of feeds containing monensin, salinomycin, or lasalocid

in feed mills in which horse feed is not made, by not shipping bulk horse feed in trucks in which medicated ionophore-containing feed has been transported, and by preventing horses from ingesting these medicated feeds. Gossypol toxicity can be prevented by feeding no cottonseed meal or cottonseed meal with low gossypol content, especially when feeding preruminants.[168] Feeding of cottonseed meal can be limited by providing more forage or additional protein sources in the diet of ruminants so that ingestion of gossypol is limited to concentrations of 1 to 2 g/kg or less of feed for adult cattle and 0.5 to 1 g/kg or less of feed for immature cattle.[169] Nutritional myocardial disease can be prevented by adequate feeding of vitamin E, selenium, and copper with supplementation as required. Inherited cardiomyopathy is controlled by avoiding breeding of known or suspected carriers of the polled Hereford and Holstein-Friesian breeds.

30.4.7 PERICARDITIS

30.4.7.1 Definition and Etiology

Pericarditis is inflammation of the pericardium that results in the accumulation of fluid or exudate between the visceral and parietal pericardium. Pericarditis in large animals can be caused by trauma from penetration of ingested foreign objects or external wounds, hematogenous spread (septicemia) of infection, extension of infection from the lung or pleura, viral infections such as equine viral arteritis or equine influenza, and neoplasia. Idiopathic pericarditis, characterized by an aseptic inflammatory exudate, is not uncommon in horses and has recently been reported in cattle.[170–176] Autoimmune, hereditary, and metabolic causes of pericarditis have not been documented in large animals.

30.4.7.2 Clinical Signs and Differential Diagnosis

The clinical presentation of pericarditis can vary, depending on the volume and rate of development of the pericardial effusion and the cause. Nonspecific clinical signs—fever, anorexia, depression, or weight loss—may be the chief complaints, but, more frequently, peripheral edema, jugular venous distention and pulsations, tachypnea, or dyspnea is the presenting clinical sign. Cattle may exhibit pain by an abnormal stance characterized by abducted elbows, a spontaneous or induced expiratory grunt, reluctance to move, or preference to stand with the forequarters elevated. Horses may show signs of colic or syncopal episodes.

The most consistent findings on auscultation are tachycardia, muffling of heart sounds, and absence of lung sounds in the ventral thorax. Dorsally the lung sounds are louder than normal. These findings are in contrast to pleuritis, an important diagnostic ruleout for pericarditis, in which the lung sounds are muffled ventrally but the heart sounds are not and radiation of the heart sounds occurs over a wider area than normal.[177] In cattle, splashing sounds frequently are audible in the cardiac auscultation area, a sound some refer to as a “washing machine murmur.” This is attributed to the accumulation of gas and fluid in the pericardium and is indicative of the presence of gas-forming (anaerobic) organisms and a grave prognosis. In cattle this murmur distinguishes pericarditis from cardiac neoplasia or other causes of CHF. The splashing sounds are absent in horses, and muffled heart sounds are the rule, but pericardial friction rubs may be auscultated, especially after pericardial fluid accumulation has been relieved.[172] A gallop rhythm may be auscultated in either horses or cattle.

Mucous membranes may be congested and have a prolonged capillary refill time. Jugular venous distention and pulsations usually are present. Arterial pulses are weak. The latter findings may help distinguish pericarditis from primary pleuritis. Percussion of the thorax reveals ventral dullness, and pleural effusion is

frequently present in horses with pericarditis. A concurrent pleuropneumonia or septic pleuritis is present in some horses.[174,178–181] Ascites is infrequently detected in horses with pericarditis, but concurrent peritonitis has been reported.[182]

30.4.7.3

Clinical Pathology

The changes shown in a complete blood count are not specific and depend on the cause of the pericarditis. There may be hemoconcentration if the animal is dehydrated or toxemic, or there may be a mild anemia associated with chronic infectious pericarditis. The WBC count may be normal or increased. There may be an absolute neutrophilia or a lymphopenia. Frequently the fibrinogen concentration is elevated. The serum chemistries are usually normal except for albumin concentration, which may be low[171–172] and accompanied by an elevation in globulin concentration. Liver enzyme, bilirubin, serum urea nitrogen, and creatinine concentrations are frequently mildly elevated, consistent with the development of CHF. Laboratory evidence of dehydration (increased PCV, total protein, serum urea nitrogen, and creatinine concentrations) may be exaggerated when diuretics have been administered previously. Although total serum LDH concentration may be elevated, more specific information may come from finding an increase in the cTnI or the myocardial isoenzymes CK and LDH. An elevated cTnI was reported in one cow with hemorrhagic pericarditis.[175] Electrolyte concentrations are frequently normal, but serum calcium and potassium concentrations may be low because of anorexia. Decreased sodium and chloride concentrations have been reported in horses with pericarditis.[172] No consistent abnormalities in arterial or venous blood gas concentrations have been reported in large animals with pericarditis.

Radiography is not a sensitive diagnostic test for pericarditis in horses, although an enlarged rounded cardiac silhouette is detected with large pericardial effusions. In cattle, traumatic pericarditis frequently results in fluid and gas accumulation in the pericardium that is detectable radiographically and is relatively specific for this disease. A metallic foreign body is usually detected radiographically in the cranial reticulum or caudal thorax in cattle with traumatic pericarditis (Fig. 30-18). Radiographic changes may not be detected in early or uncomplicated pericarditis and, if fluid accumulation is large and there is concurrent pleural effusion, are indistinguishable from those associated with pleuritis. An enlarged, rounded cardiac silhouette is not specific for pericarditis and can be seen with other causes of generalized cardiomegaly. An obscured cardiac silhouette, vena cava, and diaphragm with dorsal displacement of the trachea may be seen with pericarditis or pleuritis. The lungs, which may be aerated only dorsally, frequently have interstitial infiltrates.

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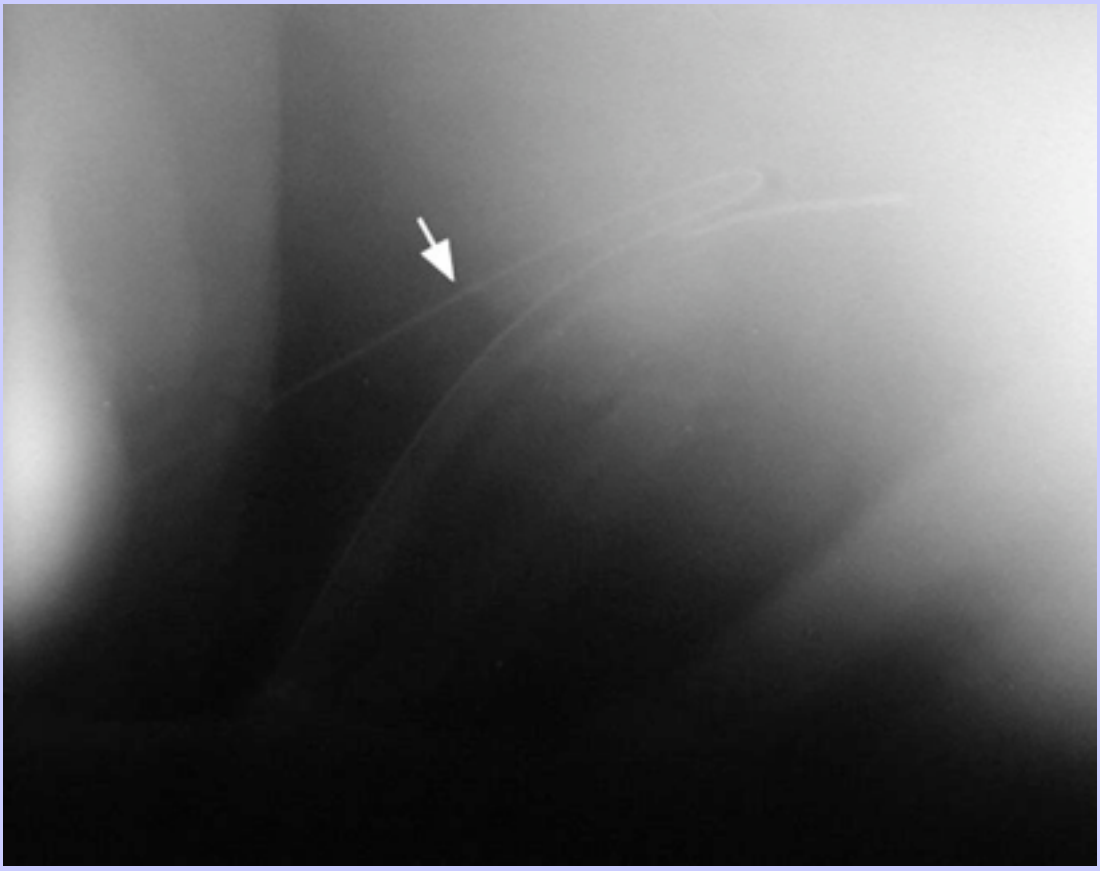
Fig. 30-18 Lateral radiograph of the caudal thorax and cranial reticulum showing a wire *(arrow)* in a cow with traumatic reticuloperitonitis.

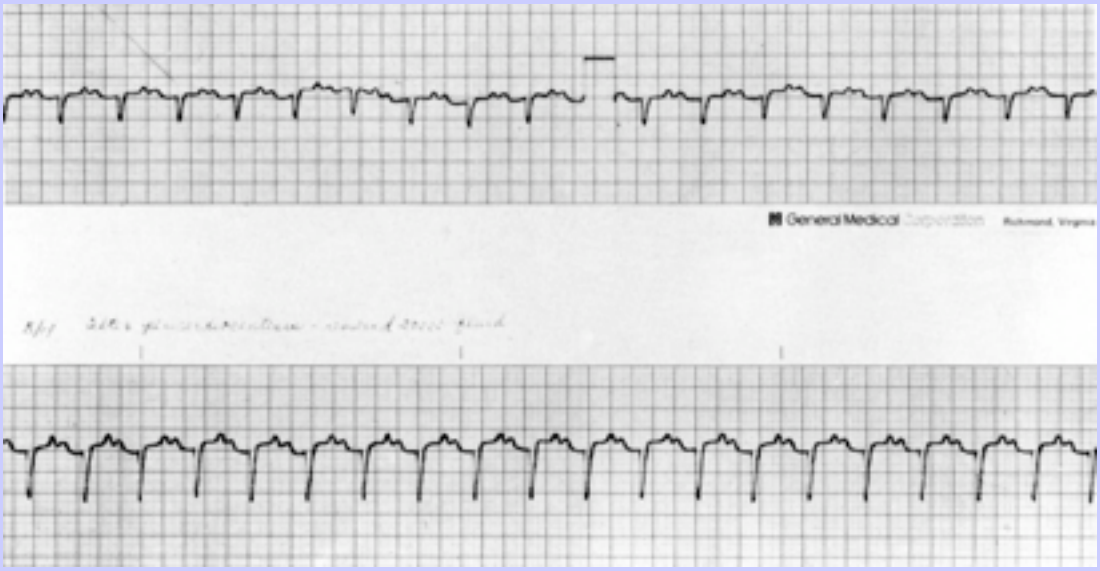


The ECG changes most commonly associated with pericarditis in large animals are decreased amplitude of the QRS complexes (less than 1.5 mV in the base-apex lead)[172,173,182] (Fig. 30-19), electrical alternans (altered configuration of the P, QRS, or T complexes on a regular basis), and ST-segment elevation or slurring.[171,172,178,182,183] A right-axis deviation in the standard limb leads may be apparent.[171,183] Cardiac arrhythmias (usually atrial or ventricular premature beats) may be detected in affected animals, suggesting a concurrent myocarditis (Fig. 30-20). In some animals, no ECG changes are evident.[184]

Echocardiography reveals findings specific for pericarditis and is used to confirm the diagnosis noninvasively. An echo-free space between the visceral and parietal pericardium is evident (Fig. 30-21) and apparent even with a minimum amount of fluid accumulation.[177,178] Frequently, hypoechoic to echoic strands that correspond to fibrin are imaged in the pericardial space with a hypoechoic to echoic layer covering the epicardial surface of the heart in large animals with pericarditis. The pericardial effusion is often anechoic to hypoechoic, but more echoic pericardial fluid is occasionally seen, consistent with a more exudative fluid. Bright hyperechoic pinpoint echoes representing free gas are often imaged in cattle with pericarditis. Gas in the pericardial sac of cattle with splashy heart sounds may limit the ability to obtain an echocardiographic

evaluation of all cardiac structures. The visualization of intrapericardial gas is a sensitive indicator of anaerobic pericarditis. Pericardial effusion is differentiated from pleural effusion by finding the echo-free space surrounding the right ventricle and left ventricular free wall, but pericardial effusion is rarely imaged behind the left atrium.[185,186] Right ventricular diastolic collapse and right atrial collapse are common findings with large pericardial effusions and are an indication of the development of cardiac tamponade and hemodynamically significant pericardial effusion.[173] Other echocardiographic findings consistent with pericarditis are decreased left ventricular chamber dimension, decreased left ventricular free wall motion, and decreased parietal pericardial motion.[173,174,178,187] Increased (see Fig. 30-21) or paradoxic motion (cranial motion beginning before the QRS complex) of the interventricular septum may be apparent.[186,187]

Fig. 30-19 Base-apex lead ECG taken from a cow before *(upper strip)* and after *(lower strip)* removal of 2 L of pericardial fluid. The markedly decreased amplitude (0.6 mV) of the QRS complexes is improved (1.2 mV) after pericardiocentesis.



The site for pericardiocentesis should be selected echocardiographically. Pericardial fluid is obtained most commonly from the left fifth intercostal space 2.5 to 10 cm dorsal to the olecranon, above the level of the lateral thoracic vein, the safest site for pericardiocentesis. When there is a large volume of pericardial effusion, pericardiocentesis can be productive from the right at approximately the same location. If at all possible, a pericardial catheter (large-bore Argyle tube) should be inserted into the pericardial space at the time the initial pericardiocentesis is performed to enable repeated drainage and lavage of the pericardial sac (Fig. 30-22). Fluid analysis and bacterial and viral culture results depend on the cause. In cattle with traumatic pericarditis, fluid analysis usually reveals elevated protein concentration (>3.5 g/dL) and an elevated WBC count (>2500/μL), composed primarily of neutrophils. The fluid is urine colored to slightly blood tinged and foamy, and it has a foul odor. A mixed population of gram-positive and gram-negative aerobic and anaerobic bacteria (gastrointestinal flora) usually are present. Protozoa may be found in unusual circumstances. Hemorrhagic effusion has been reported in several cows with idiopathic pericarditis that responded favorably to pericardial

drainage (usually with lavage) along with systemic antimicrobial therapy.[175] In horses, protein concentration of the pericardial fluid is elevated (≥2.5 g/dL) and the WBC count is normal or elevated with a population predominantly of neutrophils, although red blood cells, lymphocytes, eosinophils, mesothelial cells, and histiocytes have been observed.[171–173,178,182] Bacterial (aerobic and anaerobic) cultures and viral cultures may be negative. *Actinobacillus* organisms were frequently isolated from mares with pericarditis in association with the mare reproductive loss syndrome.[188] Paired serum may support a viral cause. Analysis of pleural and peritoneal fluid (when present) usually reveals fluid characterized as a modified transudate or that is mildly inflammatory.

Fig. 30-20 ECG (rhythm strip) obtained from a horse with pericarditis and junctional tachycardia. Note the P wave at the same place in the QT interval.

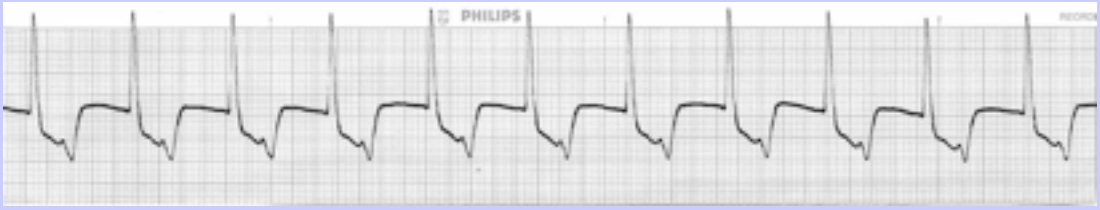


Fig. 30-21 M-mode echocardiogram obtained from a cow with traumatic pericarditis. There is a separation between the visceral and parietal pericardium cranial to the right ventricle *(RV)* and caudal to the left ventricle. The cranial pericardial effusion *(PE)* is echogenic, suggesting that fibrin or debris is present. The left ventricular *(LV)* dimension is reduced, and there is marked cranial motion of the interventricular septum *(IVS)* just before the QRS complex.

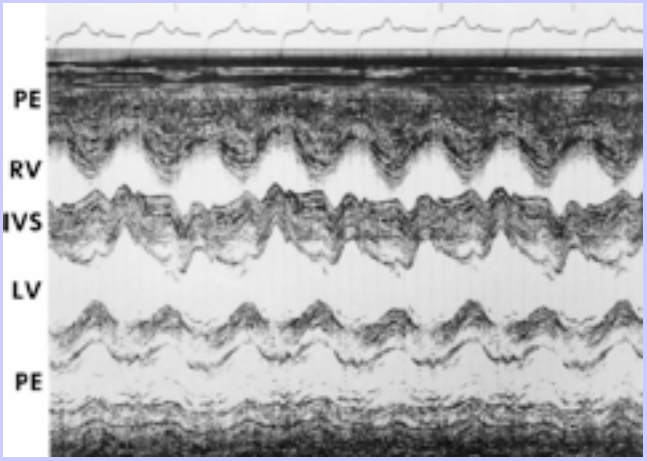


Fig. 30-22 Insertion of a pericardial chest tube into the left fifth intercostal space for drainage and lavage of the pericardial space. Note that the left foreleg is being pulled forward, the clinician is inserting the large-bore Argyle chest tube into the left fifth intercostal space above the lateral thoracic vein, and the cow is wearing a radiotelemetry ECG system underneath the surcingle.

Cardiac catheterization demonstrates an elevation in central venous or right atrial pressure, and the atrial and ventricular pressure curve may be abnormal in appearance. Right atrial, right ventricular, and pulmonary artery end-diastolic pressures may equilibrate.[183] In combination these findings are relatively specific for pericarditis.

30.4.7.4

Pathophysiology

The accumulation of fluid in the pericardium occurs as a result of inflammation. The rate of fluid accumulation and the degree to which the pericardial pressure increases determine the pathophysiologic consequences. Generally pericarditis results in decreased distensibility (increased ventricular end-diastolic pressure) of the heart, which impairs the ability of the heart to fill during diastole. The elevation in end-diastolic pressure and impairment of ventricular filling elevate atrial pressure and reduce venous flow or venous return to the heart and diastolic perfusion of the myocardium. The result is a depression of ventricular contractility, stroke volume, and consequently cardiac output. In addition, arterial pressure and renal blood

flow are decreased. Initially, compensatory mechanisms consisting of vasoconstriction, increased heart rate, and sodium retention (increased vascular volume) may maintain cardiac output. Failure to maintain cardiac output results in circulatory collapse.

Pericarditis can be classified as primarily effusive, constrictive, or a combination of both.[183] The hemodynamic consequences of effusive pericarditis are primarily caused by the physical presence of pericardial fluid, whereas constrictive pericarditis is classified as such because the reduction in ventricular compliance is caused by fibrinous or fibrotic involvement of the pericardium and epicardium. Removal of pericardial fluid results in improved cardiac performance in effusive pericarditis but is of limited usefulness in constrictive pericarditis.

30.4.7.5

Epidemiology

Pericarditis is uncommon in horses; when it does occur, it is most frequently idiopathic and can occur in a horse of any age. History of a recent respiratory tract infection is not uncommon. Exposure of horses to Eastern tent caterpillars was the greatest risk factor for the development of fibrinous pericarditis during the epidemic of mare reproductive loss syndrome.[189] Traumatic pericarditis has been reported in horses but is rare.[190] Traumatic pericarditis is not uncommon in cattle, but it occurs in less than 10% of cattle with traumatic reticuloperitonitis.[191] Most cattle are affected in late gestation or at parturition. Idiopathic pericarditis is rare in cattle.

30.4.7.6

Necropsy Findings

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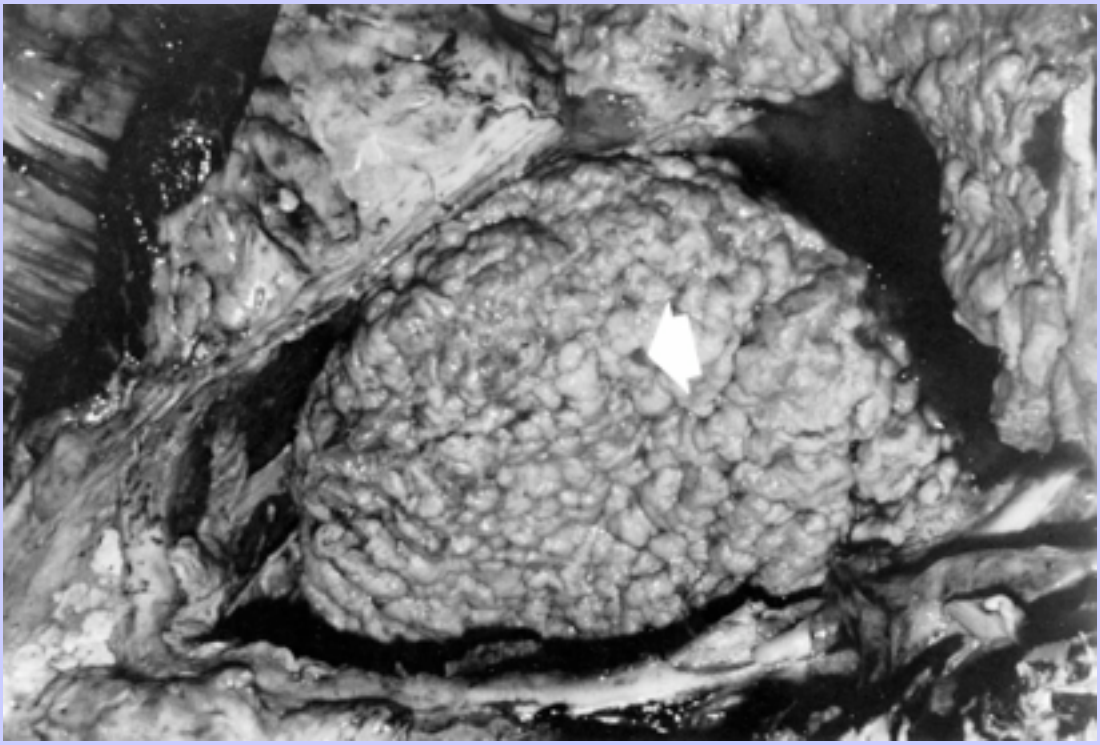
Gross postmortem examination shows distention of the pericardial sac with serosanguineous or urine-colored fluid that is foamy and may be malodorous (cattle). There may be organization of fibrinous exudate and fibrosis that is also evident on the epicardium (Fig. 30-23) and may infiltrate the myocardium. Pleural effusion may be present. Other signs of CHF such as pulmonary congestion, pulmonary edema, and chronic passive congestion of the liver may be present. If the cause is traumatic, the offending object may be well contained in a fibrous tract located between the reticulum and the pericardium.

Fig. 30-23 Postmortem photograph of a cow with constrictive pericarditis. The pericardium is opened and reflected, revealing the epicardium *(arrow)* covered in fibrinopurulent exudate.



Histopathologic examination reveals pericardial, epicardial, and occasionally myocardial fibrosis and inflammation with neutrophilic, lymphocytic, eosinophilic, or plasma cell infiltrates. Bacteria may be visible. The liver may show diffuse, centrilobular necrosis, fatty change, dilation and congestion of sinusoids, and perivenous fibrosis.

30.4.7.7

Treatment and Prognosis

Treatment of traumatic pericarditis in cattle is unrewarding and usually is addressed toward salvage or short-term survival to calving. Repeated pericardial drainage by means of pericardiocentesis or a fifth rib resection, lavage, or pericardiectomy may be useful for short-term survival, but the prognosis for return to normal function is poor, because CHF results from involvement not only of the pericardium but also of the epicardium and myocardium (see Fig. 30-23). Thoracotomy by a split-rib technique followed by pericardiectomy has been effective in treating some cattle with traumatic, restrictive pericarditis.[192]

Treatment of pericarditis not caused by trauma has been successful in horses, but the initial prognosis should be guarded. Aggressive treatment of horses with moderate to large pericardial effusions should include the placement of a large-bore indwelling chest tube into the pericardial sac under echocardiographic guidance and drainage and lavage of the pericardial sac, with local infusion of antibiotics, in addition to the initial broad spectrum antimicrobial therapy. Obtaining a sample for cytology and culture and sensitivity testing via a

pericardiocentesis should be postponed until an indwelling catheter can be safely inserted because it is difficult to insert the catheter once the pericardiocentesis has been performed. The pericardial drainage and lavage, performed once or twice daily as needed, has been very effective in treating idiopathic or septic pericarditis in horses.[173,174,178,182] The indwelling tube should remain in situ until the fluid recovered at the time of drainage is consistently less than or equal to the volume instilled in the pericardial sac with antimicrobials 12 to 24 hours earlier. The ECG should be monitored, because occasionally cardiac arrhythmias occur during the therapeutic procedure or during a routine pericardiocentesis. All horses with pericarditis should initially be treated for septic pericarditis with systemic broad-spectrum bacteriocidal antimicrobial drugs. The antimicrobial choice should be based on the most likely causative agents and modified as needed by the results of culture and sensitivity testing. Fibrinous pericarditis has been successfully treated in horses with broad-spectrum bacteriocidal antimicrobials when the amount of pericardial fluid detected echocardiographically was too small to safely obtain a sample for cytology and culture and sensitivity testing. Treatment of idiopathic pericarditis with corticosteroids should be initiated only after the results of the cytology and culture and sensitivity testing demonstrate no evidence of sepsis. Pericardiotomy or preferably pericardiectomy is the treatment of choice if signs of restrictive (constrictive) pericarditis are present. The surgical procedure is prolonged, expensive, and of considerable risk. A partial pericardiectomy was performed in one horse with constrictive pericarditis but was only transiently successful.[179]

In traumatic pericarditis the antibiotic selected must be capable of covering gram-positive and gram-negative aerobic and anaerobic bacteria. Nonsteroidal antiinflammatory drugs have been deemed useful as adjunctive therapy, as have corticosteroids if bacterial culture of the fluid is negative and if no evidence of sepsis is detected cytologically.

Although diuretics are effective in eliminating the severity of peripheral edema, they further reduce venous return and preload in animals with pericarditis. The result is further compromise of cardiac output and worsening of heart failure.

30.4.7.8 Prevention and Control

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Traumatic pericarditis in cattle can be prevented by routine administration of magnets to heifers at the time of 478 pregnancy diagnosis. At each subsequent pregnancy diagnosis, the cattle should be checked for the presence of the magnet in the reticulum. It is not beneficial to have more than one magnet present at one time.

Some types of infectious pericarditis in horses may be controlled by routine vaccination against the common respiratory pathogens.

30.4.8 CARDIAC TUMORS

30.4.8.1 Definition and Etiology

The heart may be the primary site of neoplastic disease, or it may be involved secondarily by tumors from adjacent structures such as the lungs, pleura, lymph nodes, or diaphragm. Cardiac neoplasia is uncommon in large animals. The most common primary cardiac tumor is lymphosarcoma. Mesotheliomas, fibrosarcoma, adenocarcinomas, and other carcinomas, especially squamous cell carcinomas in horses, may involve structures adjacent to the heart and may extend to the heart or heart base, producing signs of heart disease.[193,194] An infiltrative cardiac lipoma has been reported in a horse, but no signs of cardiac disease were attributed to it.[195] A metastatic anaplastic pulmonary carcinoma that did cause signs of CHF in a horse has

been reported.[194] Disseminated hemangiosarcoma with myocardial involvement was thought to be responsible for ventricular arrhythmias in one horse.[196] Primary pericardial hemangiosarcomas also have been reported in a horse.[197]

30.4.8.2

Clinical Signs and Differential Diagnosis

The clinical signs of cardiac neoplasia are not specific and depend on the cardiac site involved and on the other sites of tumor manifestation. Nonspecific signs of neoplasia are common and include anorexia, depression, weight loss, and fever. These signs can be produced by any site of chronic disease; and in large animals pneumonia, peritonitis, enteritis, and liver and kidney disease are considered differential diagnoses, among others. If the tumor involves the pericardium, signs of pericarditis or pericardial effusion such as tachycardia, pain, jugular venous distention, peripheral edema, and weak arterial pulses may be seen. Myocardial involvement of the neoplasia, as is most common with lymphosarcoma, may result in cardiac signs that include tachycardia, cardiac arrhythmias, and cardiac murmur (atrioventricular valve insufficiency) or signs of CHF such as peripheral edema, ascites, and diarrhea. Clinical signs attributable to tumor involvement of the endocardium (e.g., obliteration of a cardiac chamber, valvular obstruction or damage, embolic showering) are rare in large animals.

Tumor involvement of other organ systems and tissues can be manifested by lymphadenopathy, peripheral edema, diarrhea, melena, rectal palpation of abdominal masses, dysphagia, tachypnea, or pleural effusion.

30.4.8.3

Clinical Pathology

Cardiac tumors present no consistent clinicopathologic feature. The complete blood count from horses or cattle with lymphosarcoma may reveal neoplastic lymphocytes. The absence of leukemic changes does not rule out lymphosarcoma. Cattle with lymphosarcoma may test positive for fecal occult blood. A serum chemistry profile may reveal nonspecific changes such as hypoalbuminemia, hyperglobulinemia, or elevated liver enzyme concentrations, depending on the other organ systems affected by the tumor or the animal's debilitation. Diagnosis of the cardiac tumor is based on histopathology of tumor tissue. Tumor cells may be found in pericardial or pleural fluid or adjacent lymph nodes. Serologic evidence (agar gel immunodiffusion or radioimmunoassay) of BLV infection does not confirm a diagnosis of lymphosarcoma, but a negative test result virtually rules out the adult or enzootic form of lymphosarcoma in cattle. No evidence of BLV infection will be found in cattle or horses with the thymic form of lymphosarcoma.

If electrocardiographic evidence of cardiac tumors is present, it is nonspecific. Cardiac tumors may produce cardiac arrhythmias; reduce amplitude of the QRS complexes; or alter the normal appearance of the P, QRS, and T complexes. Two-dimensional echocardiography or an ultrasound examination of the lungs or pleura may show evidence of the cardiac tumor by providing direct evidence of abnormal echogenic masses involving the heart or surrounding tissue, abnormal fluid accumulation, or myocardial functional changes. The ultrasound findings can determine if there are any masses that can be safely biopsied to confirm the diagnosis.

Radiographs may provide evidence of cardiac tumors by showing abnormal soft-tissue densities in the thorax that obscure the cardiac silhouette or the ventral lung borders.

30.4.8.4

Pathophysiology

The most common cause of cardiac tumors in cattle, lymphosarcoma, has a predilection for the right atrial myocardium. Right ventricular myocardial involvement is not uncommon; left atrial or left ventricular involvement is rarer. Involvement of the right side of the heart may result in little or no evidence of heart disease. More commonly the myocardial involvement results in dilation of the chamber involved. As a consequence, the tricuspid valve ring may be dilated, and tricuspid valve insufficiency occurs. Either because of chamber enlargement or infiltration of the myocardial conduction system, cardiac arrhythmias may develop. Myocardial function may be impaired, so that signs of right-sided heart failure become apparent, including tachycardia, peripheral edema, jugular venous distention or pulsations, pericardial or pleural effusion, hepatic congestion, and ascites.

30.4.8.5

Epidemiology

Cardiac tumors are rare in large animals. The most common cause in cattle is lymphosarcoma. Although more than 50% of cattle in some parts of the United States are infected with BLV, less than 1% develop lymphosarcoma.[198,199] In herds with more than 50% of cattle infected with BLV, the incidence of lymphosarcoma may be higher. Cardiac involvement is common in cattle with the adult or enzootic form of BLV, a disease that occurs most commonly in cattle over 4 years old. Thymic lymphosarcoma, which is not associated with BLV infection, also involves the heart but is much less common, occurring in cattle under 30 months of age.

Lymphosarcoma, mesothelioma, and squamous cell carcinoma probably are the most common causes of neoplastic involvement of the equine heart, but the prevalence is not documented.

30.4.8.6

Necropsy Findings

Necropsy findings depend on the type of cardiac tumor. Direct involvement of the myocardium with lymphosarcoma is associated with finding diffuse infiltration by a pale, tan, homogenous tissue that frequently causes enlargement of the cardiac chamber. Involvement of the right atrium (Fig. 30-24) is the most common manifestation of adult enzootic BLV, but any area of the myocardium and pericardium may be involved. Intracavitary extension of the tumor may be evident (see Fig. 30-24). Histologic evaluation of the tumor shows diffuse infiltrates of lymphoblastic cells that obliterate the normal architecture of the myocardium.

Other tumors such as fibrosarcoma, squamous cell carcinoma, pulmonary carcinoma, thymic lymphosarcoma, and mesothelioma (Fig. 30-25) may involve the heart by extension or metastasis from other sites in the thorax.

Fig. 30-24 Postmortem photograph of a cow with lymphosarcoma demonstrating right atrial myocardial infiltration by a tumor and extension of the tumor into the atrial lumen.

Fig. 30-25 Postmortem photograph of a horse with pericardial mesothelioma. Notice the huge heart base tumor mass, along with several smaller masses.

30.4.8.7

Treatment and Prognosis

No definitive treatment exists for neoplasias involving the heart, and the prognosis for survival is poor. Death can be expected within 6 months with most cardiac tumors. Lymphosarcoma of the heart in cattle has a grave prognosis and is usually associated with death within a few months. Short-term improvement has been achieved in cattle with lymphosarcoma treated with a combination of corticosteroids, l-asparaginase, and cytotoxin. Thorascopic pericardiotomy has been used as a palliative treatment in a cow with pericardial lymphoma.[200]

30.4.8.8

Prevention and Control

The prevention and control of BLV can be accomplished by isolation of BLV-positive and BLV-negative animals; use of individual or sterilized supplies such as needles, rectal examination sleeves, tattooing, dehorning, and ear-tagging equipment on each animal; rigorous attention to a vector control program; and feeding colostrum from serologically negative cows only.[199,201] Frequent testing (at least every 6 months) and isolation of serologically positive animals over 6 months of age should be performed.

Prevention and control of other cardiac tumors is not possible.

30.4.9 VASCULAR DISEASE: ANEURYSMS, THROMBOSIS, EMBOLISM

30.4.9.1 Definition and Etiology

Aneurysms, which are vascular dilations, develop from weakening of the medial elastic coat of blood vessels. The medial weakness may be primary or caused by a progression of an intimal atherosclerotic lesion that has enlarged from hemorrhage, calcification, ulceration, and thrombus formation. The specific causes of aneurysms in large animals are unknown, but trauma (internal or external), sepsis, parasite migration, degenerative vascular disease, atherosclerosis, or aging changes (dilation, elongation, and loss of elasticity of blood vessels) may play a role.[202–204] Congenital aneurysms of the sinus of Valsalva have been reported in horses.[205–209] Hypertension can accelerate the degeneration of the wall.

Thrombosis is the formation of a clot that obstructs blood flow in the circulatory system. The causes of thrombosis are numerous and include trauma, venous stasis, and catheterization for administering medication or fluids. Needle penetration, indwelling catheters, thrombogenic solutions, or bacterial contamination can cause thrombosis associated with catheterization. Secondary thrombosis can result from perivascular inflammation caused by cellulitis, lymphangitis, or other sources of bacterial invasion around the blood vessel. Mural thrombi, which occur in cardiac chambers dilated from valvular regurgitation or chronic atrial fibrillation in humans and which are associated with low-flow states, also may occur in large animals, although they have been rarely diagnosed antemortem. Thrombosis usually occurs when intimal disease is present, but it may occur in arteries with no intimal disease when a hypercoagulable state exists such as with dehydration, endotoxemia, anemia, hypotension, stress, or stasis.[210,211] This type of thrombosis is frequently a complication of acute infectious disease (particularly acute toxic enteritis or colitis), neoplasia, or any chronic debilitating disease.

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An embolism is foreign material carried in the bloodstream. Emboli frequently arise from an arterial or venous thrombus, but unusual emboli include catheters and other foreign bodies inadvertently introduced into the circulatory system. In large animals, emboli occur most commonly in bacterial endocarditis, thrombophlebitis, omphalophlebitis, and parasitic arteritis. Emboli may also originate from detachment of mural thrombi in other forms of cardiac disease such as chronic atrial fibrillation and valvular heart disease. Aortoiliac thromboembolism has been reported as a complication of valvular endocarditis in a calf and mural endocarditis in a cow.[212–213]

30.4.9.2 Clinical Signs and Differential Diagnosis

Sites of thrombosis associated with thrombophlebitis are likely to have pain, swelling, redness, and palpable thickening of the involved vein. These signs frequently occur within 12 to 24 hours after catheter removal when the thrombus is associated with catheterization. If there is bilateral jugular venous thrombosis, sudden, marked swelling of the head may occur. If the thrombosis involves the terminal aorta and iliac arteries in horses, the signs are frequently a vague hindlimb lameness, exercise intolerance, or poor performance. These nonspecific signs make it necessary to rule out lameness from other causes, cardiac disease, or respiratory problems. Failure to ejaculate has been reported in breeding stallions with aortoiliac thrombosis.[214] Aortoiliac thrombosis in horses also is characterized by heavy sweating after exercise, except over the hindlimbs, which

are cool. With severe aortoiliac thrombosis the affected limb can be cool to the touch at rest or can be cold with no palpable femoral arterial pulse. Saphenous vein filling is slow or nonexistent in affected horses, and the metatarsal and other peripheral arterial pulses of the hindlimbs are weak. Rectal examination may be normal; or weak, absent, or asymmetric iliac pulses may be palpated. Fremitus of the iliac arteries or terminal part of the aorta may be palpated. The terminal part of the aorta may feel larger or firmer than normal, or an aneurysmal dilation may be detected. Similarly with verminous arteritis of the cranial mesenteric artery, a thickened, dilated cranial mesenteric artery or aorta may be palpated that may be firmer than normal and have a weak pulse, or fremitus may be palpated. In calves with aortic or aortoiliac thrombosis weakness, lameness, knuckling, paresis or paralysis of the hindlimbs, inability to rise, and cold hindlimbs lacking a femoral arterial pulse have been described.[212,215–217]

The signs attributable to embolism and thrombosis may be identical. Embolism usually is manifested by an acute episode of pain or fever, abnormal pulsation in a peripheral vessel, or a change in skin temperature. If there is peripheral vessel showering, superficial veins may be collapsed, and muscular weakness may be present. Embolic showering usually occurs in animals suspected of having or known to have thrombus formation.

Clinical signs associated with an aneurysm depend on the location of the aneurysm and may vary from being asymptomatic, to being a noticeable enlargement or mass associated with a blood vessel, to causing colic, syncope, seizures, or sudden death on rupture. In a peripheral artery a pulsatile, expansile mass may be visualized or palpated. Other considerations for this finding are a false aneurysm and an arteriovenous fistula. A false aneurysm is clinically indistinguishable from a true aneurysm but can be distinguished ultrasonographically. A false aneurysm is caused by a break in the continuity of all three coats of the arterial wall rather than in the tunica media alone. This results in extravascular accumulation of blood in adjacent tissues. Signs attributed to low blood flow such as lameness, colic, or edema may be present with arterial aneurysms. Aneurysms of the cranial mesenteric artery frequently are manifested as chronic episodes of colic. With involvement of major cardiac vessels there may be pain, an auscultable heart murmur, rapid tachycardia, signs of CHF, acute onset of pulmonary edema, or sudden death when the aneurysm ruptures. The latter signs make aneurysms difficult to distinguish from valvular heart disease or cardiomyopathy. One cause of an aorticocardiac fistula in horses is the result of rupture of an aneurysm of the sinus of Valsalva.[205–209]

30.4.9.3

Clinical Pathology

Aneurysms or pseudoaneurysms may be visualized radiographically as soft-tissue density masses continuous with a vessel wall (true aneurysm) or extending outward from a vessel wall (false aneurysm).[203,204] However, the majority of the aneurysms involving the aorta and aortic root are not visible radiographically. Echocardiography is useful in the diagnosis of aneurysms involving the aortic root (Fig. 30-26).[206–209] Angiography can be used in the diagnosis of peripheral vessel swelling or suspected thrombosis but is of little use in diagnosis of aneurysms of major vessels in adult animals. Ultrasonography may be used for the diagnosis of aneurysms or thrombosis of major arteries and peripheral vessels. In aortoiliac thrombosis of horses, ultrasound has been used to determine the origin of the thrombus and the extent of occlusion of the involved arteries (Fig. 30-27).[218] Abdominal ultrasonography of the upper left flank dorsal to the left kidney has been used to diagnose aortoiliac thrombosis in calves.[215] Diagnostic ultrasound has been used to detect thrombi in the caudal vena cava in cattle.[219,220] Although the occluding thrombus is not imaged, the detection of a distended oval or round caudal vena cava, rather than the normal triangular vessel, in the eleventh and twelfth intercostal spaces is consistent with this diagnosis in cattle. Thrombi have been detected

ultrasonographically in the hindlimb in both horses and cattle.[221–224] Jugular vein thrombophlebitis has also been diagnosed ultrasonographically in both horses and cattle (Fig. 30-28).[225,226] Similarly, diagnostic ultrasound has been used to image the cranial mesenteric artery, its branches, and the aorta in horses with verminous arteritis.[227] Aneurysms appear as dilated vascular structures or vascular outpouchings continuous with the vessel wall,[205] whereas a thrombus is apparent as a hypoechoic to echogenic mass within a blood vessel.[226] Cavitation of an occlusive thrombus is suggestive of septic thrombophlebitis (see Fig. 30-28), whereas a nonseptic thrombus usually has a homogeneously hypoechoic to echoic appearance.[226] Complete occlusion of the vessel can be determined ultrasonographically, or flow within an aneurysm or alongside a thrombus determined. Doppler ultrasound provides a more sophisticated method for determining blood flow and vessel patency. Computer-assisted radiographic techniques such as computed tomography and digital subtraction angiography may also be useful but have not yet been widely used in large animals. The latter methods may be limited in usefulness by the size of large animals and the cost of the equipment and procedures.

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Fig. 30-26 Two-dimensional echocardiogram of a horse with a ruptured sinus of Valsalva aneurysm. Not the defect in the right side of the aorta at the sinus of Valsalva *(vertical arrow)* extending into the right atrium *(horizontal arrow)*. The right atrium *(RA)*, right ventricle *(RV)*, left ventricle *(LV)*, left atrium *(LA)*, and aorta *(AO)* can be seen in this left ventricular outflow tract view.

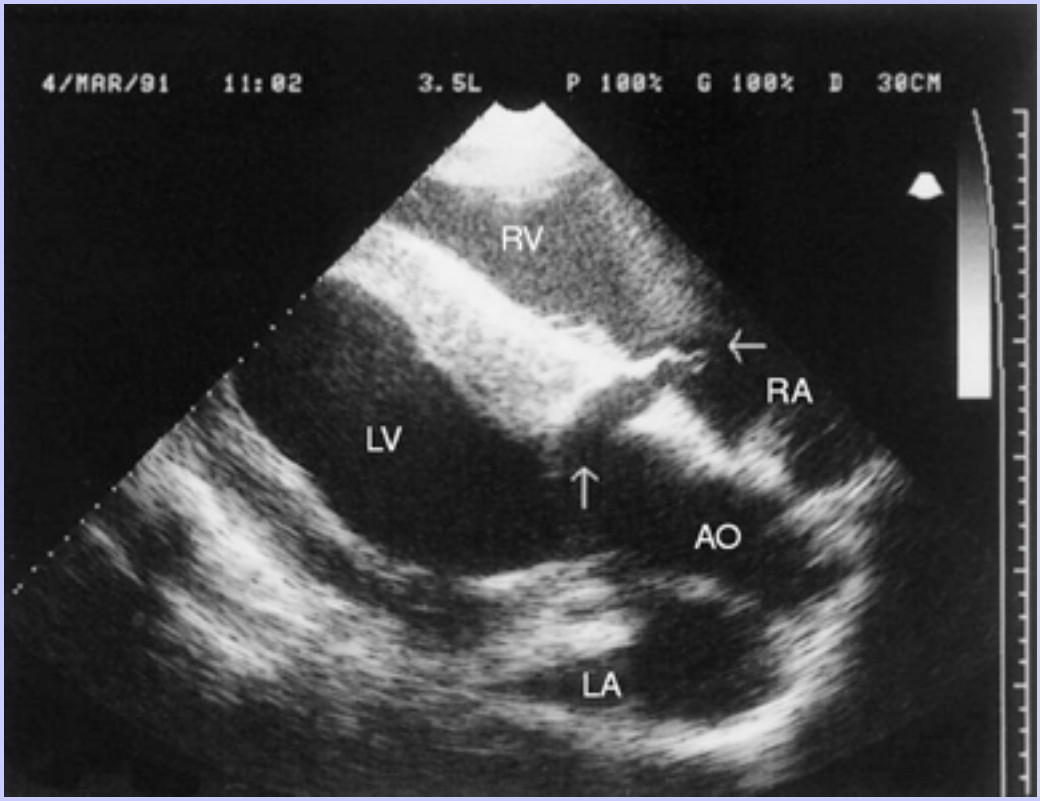
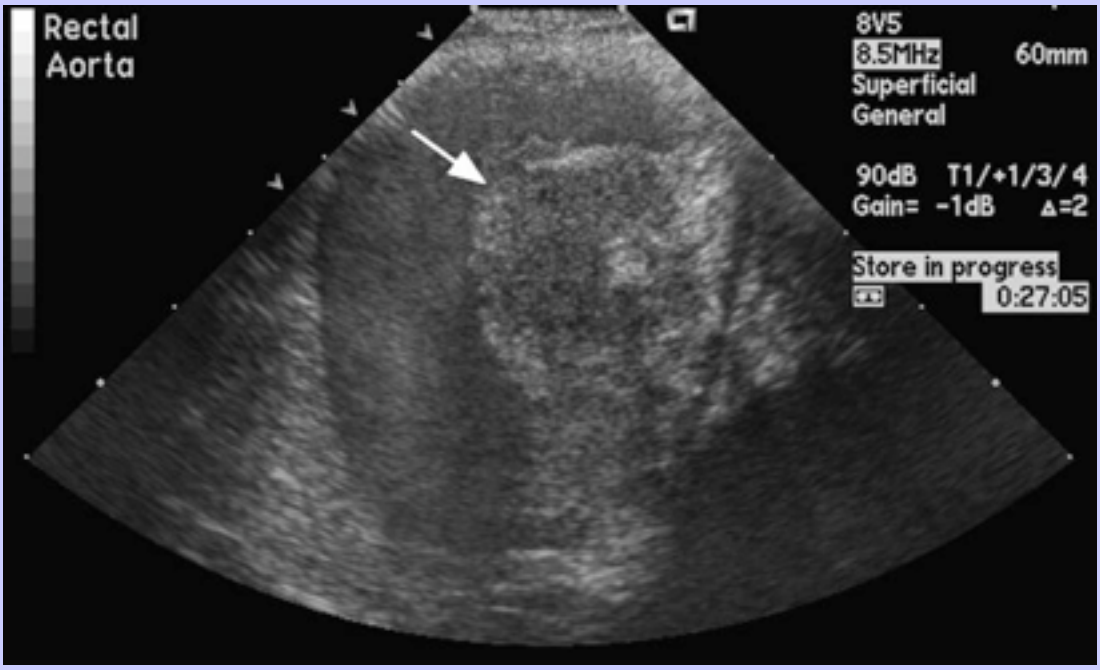
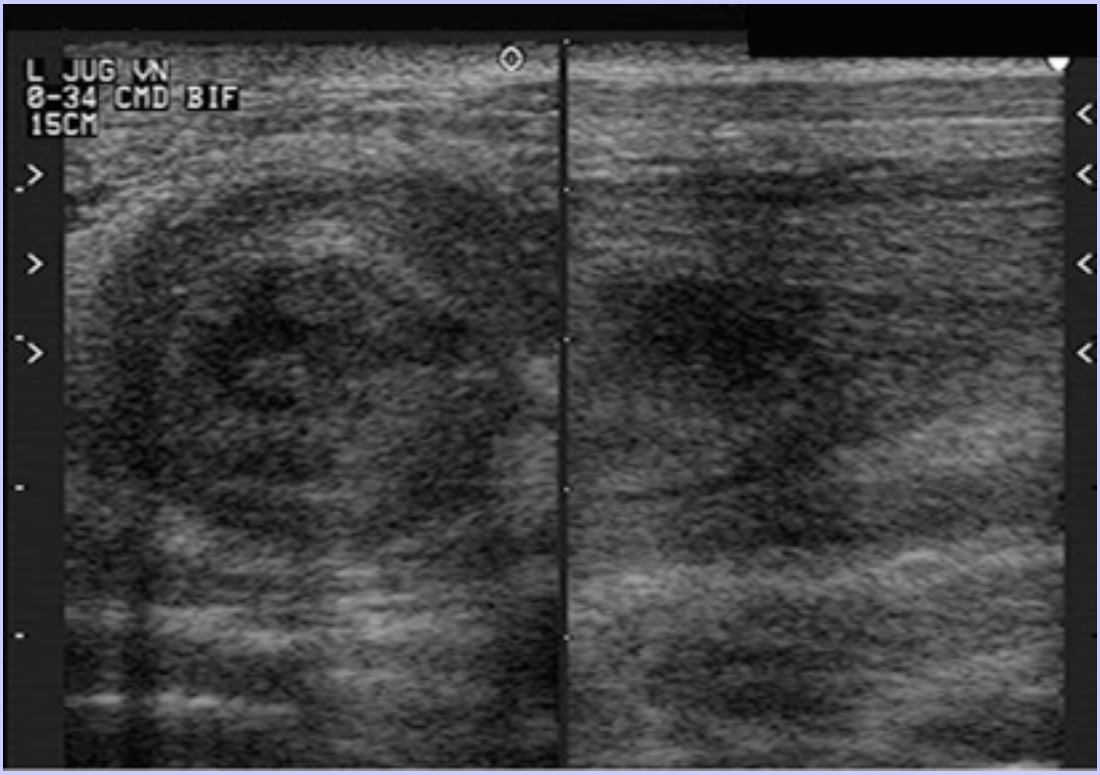


Fig. 30-27 Transverse sonogram of a large somewhat heterogeneous thrombus *(arrow)* in the terminal portion of the aorta extending into the right internal and external iliac arteries.



In the case of catheter-associated thrombosis, a positive catheter tip culture (>10^3 colony-forming units), along with a positive blood culture, provides evidence of septic thrombophlebitis.[228] An aseptic ultrasound-guided aspiration of the cavitary lesion within a heterogeneous thrombus can be performed, and the aspirate submitted for culture and sensitivity testing.[226] Septic thrombophlebitis from any cause or embolic showering of septic thrombi may be accompanied by neutrophilic leukocytosis and elevation in fibrinogen concentration.

Fig. 30-28 Sonogram of the left jugular vein from a horse with septic thrombophlebitis. Note the cavitary appearance in the center of the thrombus consistent with infection.



30.4.9.4

Pathophysiology

Irritation of the intimal lining of a blood vessel, stasis of blood flow, or the existence of a hypercoagulable state triggers the clotting cascade and sets the stage for the development of thrombosis. Further injury causes hemorrhage, more thrombosis, ulceration, and calcification. These in turn can compromise the media of the vessel, predisposing to aneurysm formation, and impinge on the lumen of the vessel, causing obstruction to blood flow. Either aneurysm or thrombosis can occlude blood flow to vital structures or organs, resulting in ischemia.

Thrombosis in any sizable vein causes venous hypertension, passive congestion, and subsequent edema and pain of the structure. As the thrombus matures, it adheres to the wall more, but with clot retraction and lysis, recanalization may occur. However, parts of the thrombus may protrude into the moving bloodstream and serve as the source of embolic showering, even during thrombus organization. The most common site for an embolus to lodge has not been established in large animals; the femoral and iliac arteries are common locations in humans. Emboli usually lodge at bifurcations, where the caliber of the artery is suddenly reduced.

The most common outcome of aneurysm of a major vessel is thought to be rupture. Rupture of sinus of Valsalva aneurysms into the right atrium, right ventricle, and interventricular septum has been reported in the

horse.[206–208] Ventricular tachycardia often occurs with rupture of an aortic sinus of Valsalva aneurysm and dissection into the interventricular septum.[207,208] Unruptured aneurysms may have other complications such as thrombosis or embolization of the thrombus. The frequency of rupture or embolic showering from thrombosis is unknown in animals.

30.4.9.5

Epidemiology

The significance of thromboembolism in large animals is poorly defined. Spontaneous thromboembolism is most commonly associated with parasitism in horses, and the aorta and cranial mesenteric arteries are the sites most frequently involved.[229] Aortoiliac thrombosis is also a recognized syndrome diagnosed most frequently in heavily exercised horses. Although parasitism has been associated with aortoiliac thrombosis in horses, other causes of this syndrome are probable but have not been elucidated. Thrombotic disease can occur in any animal having repeated intravenous injections or being catheterized for administration of medication or fluids but is particularly common in horses with acute toxic enteritis or colitis.

Arteriosclerosis is recognized in horses and in cattle. In cattle the lesion is most frequently caused by excessive vitamin D_3 supplementation or by ingestion of calcinogenic plants such as *Solanum malacoxylon, Cestrum diurnum,* or *Trisetum flavescens*.[230] In horses the arteriosclerotic lesions were caused by lesions induced by *Strongylus vulgaris*.[231]

Aneurysms are uncommon in large animals but have been documented as the cause of sudden death in breeding stallions and racing thoroughbred and standardbred horses.[208,231] Aneurysms of the sinus of Valsalva are probably a common cause of aortic rupture in older horses and are probably congenital in horses, as they are in humans.[205–208] Aortic root rupture also occurs with the presence of a preexisting aneurysm and has been associated with medial necrosis of the aorta.

30.4.9.6

Necropsy Findings

Aneurysms are detected grossly as dilations of the involved blood vessel. Aneurysms of the sinus of Valsalva are characterized by an absent tunica media in the wall of the aorta, causing the aneurysmal dilation.[205,208] 481
Rupture of a sinus of Valsalva aneurysm may occur into the right atrium, right ventricle (Fig. 30-29), or 482
interventricular septum, resulting in an aortic cardiac fistula and volume overload.[205–209] Rupture through the tricuspid valve or chordae tendineae may also occur. Subendocardial dissection of blood down the interventricular septum may occur, with subsequent rupture into the left ventricle and of the mitral chordae tendineae also reported. Aneurysms of the major vessels leaving the heart may involve more than one vessel by dissection and hemorrhage. Aneurysms may contain thrombi or parasites, and there may be evidence of embolic showering of thrombi into peripheral vessels or other organ systems, especially the lungs. Histologically there may be necrosis and inflammation at the site of the aneurysm with foci of mineralization.

Thrombosis and arteriosclerotic lesions are recognized as rounded, well-demarcated fibrous plaques frequently located in the thoracic and cranial abdominal aorta (Fig. 30-30). The plaques may contain a central calcified core or parasitic larvae. Microscopically there is a thin layer of fibrin, platelets, and inflammatory cells in early lesions, whereas older lesions have a greater fibrous component. Thrombotic lesions may be associated with proliferation of the underlying aortic intima. In horses, parasitic larvae may be found.

Fig. 30-29 Ruptured sinus of Valsalva aneurysm in a horse with acute onset of colic and right-sided congestive heart failure. The large aneurysm *(arrow)* ruptured through the tricuspid valve, creating an aortic-cardiac fistula.

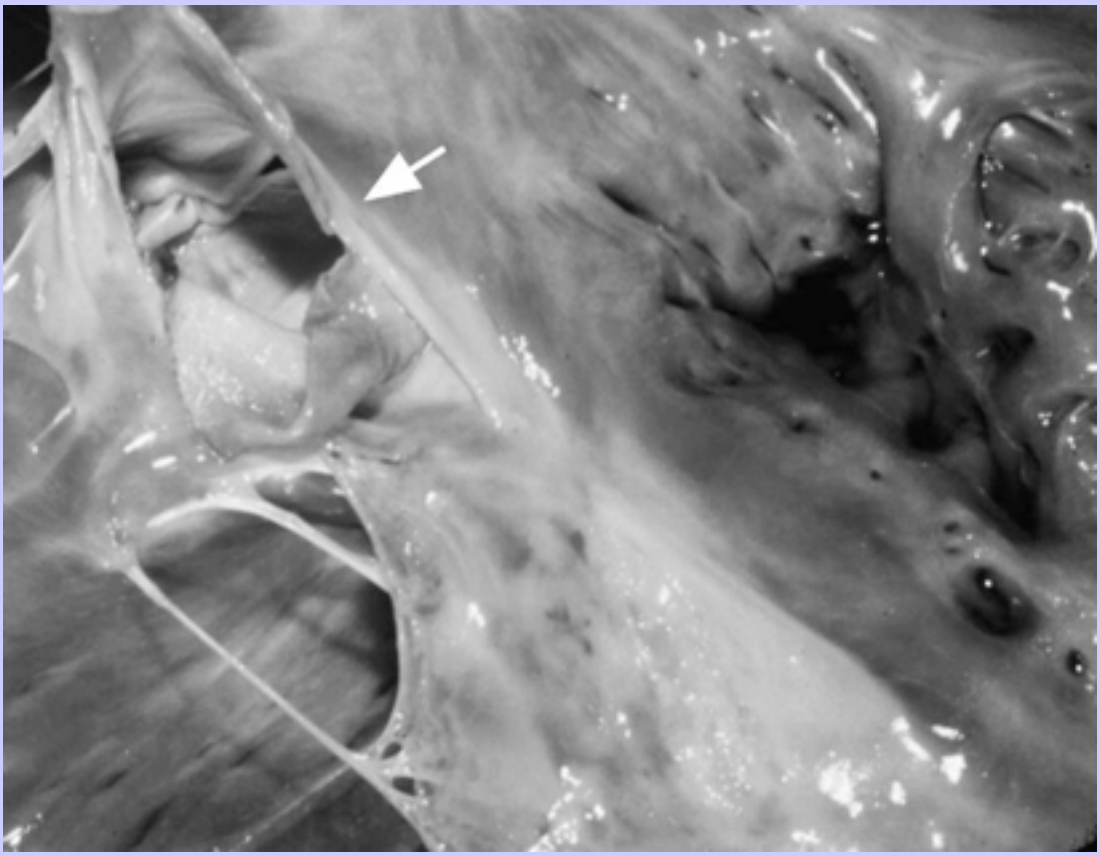


Fig. 30-30 Ascending aorta from a horse that experienced an acute onset of uniform ventricular tachycardia after exercise and died within 3 hours of onset. Notice the irregular calcified surface of the aorta, consistent with atherosclerosis.

30.4.9.7

Treatment and Prognosis

Aneurysms of major vessels carry a guarded to grave prognosis because surgical correction is rarely attempted and spontaneous rupture is thought to be relatively common. Intact aneurysms of the sinus of Valsalva can be detected echocardiographically, and once an aneurysm has been detected, the horse should be removed from all athletic competition because of the risk of rupture.[205]

Treatment of thrombosis consists of removal of the catheter, if present, and resting the affected vessel. Warm compresses or hydrotherapy may be helpful in some animals. Support wraps may be useful to control swelling. The effectiveness of anticoagulant therapy (aspirin at 100 mg/kg once daily PO or heparin at 30 U/kg SC twice daily) or antiinflammatory drugs for dissolving a thrombus is questionable. Anticoagulant therapy may be useful in preventing additional thrombus formation or propagation of the existing thrombus. Ultrasonographic guidance can be used to obtain a sterile aspirate of the cavitated area of the thrombus for culture and sensitivity testing when septic thrombophlebitis is suspected.[226] Broad-spectrum bactericidal antimicrobial therapy should be instituted for suspected septic thrombophlebitis or when a cavitated thrombus is detected ultrasonographically and modified, if necessary, based on the results of culture and sensitivity

testing.[226] Bacterial endocarditis, particularly involving the tricuspid valve, is a potential complication of septic jugular vein thrombophlebitis. With the exception of a jugular venous thrombus, surgical removal of an embolism or thrombus is rarely attempted in large animals. Surgical resection of a jugular vein with septic thrombophlebitis has been performed successfully when the surgeon could ligate the affected vein above and below the thrombus. Although the prognosis for complete resolution of the thrombophlebitis is guarded, especially if the thrombus is infected, many veins do recannulate with complete resolution of the thrombus and without vascular stricture. However, the time course is slow, and persistent local induration and obstruction to blood flow may persist.

30.4.9.8 Prevention and Control

Thrombosis and embolization from intravenous catheters can be prevented by aseptic insertion, stabilization of the catheter, use of topical antiseptics, application of a sterile dressing, daily inspection of the catheter and vein, and replacement of the catheter at another site (preferably in another vein) if phlebitis occurs. Attempts should be made to place long-term catheters in large peripheral or central veins, where contact between the endothelium and catheter is minimized and medications administered are diluted by the large volume of blood flow. Catheters left in place for prolonged periods should be of silicone rubber or polyurethane.[228] Aspirin (100 mg/kg PO once daily, ruminants; 17 mg/kg every other day, horses) and low-dose heparin (30 U/kg SC twice daily, ruminants and horses) therapy should be considered in maintaining a catheter without thrombus formation in septic or endotoxic patients. Horses are much more prone to jugular thrombosis than are ruminants.

Parasite control is important in the control of thromboembolic disease and aneurysm in horses. Aneurysms of the sinus of Valsalva may be detected by routine echocardiographic screening of horses. In cattle, arteriosclerotic lesions are prevented by proper calcium and vitamin D supplementation.

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30.4.10 ATRIAL FIBRILLATION

30.4.10.1 Definition and Etiology

Atrial fibrillation is a cardiac arrhythmia characterized by a lack of coordinated atrial electrical activity. It is caused by an abnormality of impulse conduction that results from unidirectional conduction block and random reentrant activation of the atria. High resting vagal tone, commonly found in horses, shortens the action potential duration in atrial myocardial cells, making atrial fibrillation more likely to occur. Atrial fibrillation can occur in the presence of atrial enlargement from atrial myocardial disease, atrioventricular valvular regurgitation, ventricular failure (organic atrial fibrillation), myocarditis, endocarditis, autonomic nervous system imbalance, electrolyte or acid-base disturbances, anesthetic drugs or tranquilizer administration, or unknown causes (functional or benign atrial fibrillation).

30.4.10.2 Clinical Signs and Differential Diagnosis

Large animals with atrial fibrillation may be asymptomatic at rest, and atrial fibrillation may be detected as an incidental finding in an otherwise normal horse. Horses that perform in rigorous athletic events usually have a history of exercise intolerance or poor performance. Other complaints may be exercise-induced epistaxis, respiratory disease, weakness, syncope, myopathy, colic, or CHF. Cattle with atrial fibrillation usually have gastrointestinal disease.[232,233] Atrial premature depolarizations have also been reported in cattle with

gastrointestinal disease and may be a prelude to the development of atrial fibrillation.[233] Foot rot, pneumonia, and endocarditis also have been associated with atrial fibrillation in cattle. Anorexia and decreased milk production are common in cattle with atrial fibrillation. Atrial fibrillation and the clinical signs associated with it in horses and in cattle can be paroxysmal. Paroxysmal atrial fibrillation usually lasts no more than 24 to 48 hours before spontaneous conversion to sinus rhythm occurs.[234] Spontaneous conversion usually occurs only in horses with small atria or in cattle with correction of the underlying problem. Transient potassium depletion associated with the administration of furosemide is a common cause of paroxysmal atrial fibrillation in horses. The administration of bicarbonate "milkshakes" has also been implicated in horses with paroxysmal atrial fibrillation.

Animals with atrial fibrillation have an irregularly irregular cardiac rhythm. In horses with atrial fibrillation, there is a high degree of underlying periodicity.[235] The heart sounds vary in intensity, and no fourth heart sound is audible. The heart rate may be slow, normal, or elevated. In cattle with severe abdominal disease, the heart rate usually reflects the severity of the underlying disease. In horses the resting heart rate is usually normal to slightly elevated and is rarely above 50 beats/min, unless there is underlying myocardial or valvular disease. During exercise, horses with atrial fibrillation develop abnormally high heart rates that are usually 40 to 60 beats/min higher than expected for each level of exercise, far exceeding the peak heart rate of 240 beats/min at maximal exercise.[236,237] The arterial pulse varies in intensity. A pulse deficit occurs when two beats occur in rapid succession and is infrequent unless the heart rate is elevated. Cardiac murmurs of grade 3/6 or louder are present in less than 50% of the horses and in even fewer cattle with atrial fibrillation.[238–240] Signs of CHF (peripheral edema, jugular venous distention) may be present in some animals, but they are not caused by the arrhythmia. In these cases the atrial fibrillation occurs secondary to the atrial enlargement that occurs with the underlying valvular or myocardial disease.

The lack of an auscultable fourth heart sound in the presence of an irregular cardiac rhythm with no underlying regularity distinguishes atrial fibrillation from other cardiac arrhythmias. Sinus arrhythmia, which is also an irregular rhythm, has an audible fourth heart sound. Ventricular and atrial ectopic beats usually occur with a relatively regular underlying rhythm. A complicated ventricular rhythm with more than one focus of activation may have characteristics similar to those of atrial fibrillation and must be distinguished from it by an ECG. Atrial tachycardia with varying degrees of atrioventricular block has similar characteristics, and the underlying fourth heart sounds may be missed if the animal is auscultated in a noisy environment.

30.4.10.3

Clinical Pathology

In cattle with atrial fibrillation, acid-base and electrolyte disturbances occur frequently and are most likely attributable to the underlying primary disease. Most cattle with atrial fibrillation have gastrointestinal disease, and the most consistent acid-base disturbance is metabolic alkalosis.[240] Hypocalcemia, hypokalemia, and hypochloremia may also be seen in cattle with atrial fibrillation. Experimental induction of metabolic alkalosis with hypokalemia in cattle has been associated with the development of atrial fibrillation.[241] Most horses with atrial fibrillation have normal electrolytes, although the fractional excretion of potassium may be low, particularly in horses that sweat excessively or are routinely receiving furosemide for exercise-induced pulmonary hemorrhage.

The diagnosis of atrial fibrillation is made by ECG. The arrhythmia is characterized by an irregular R-R interval. The ventricular response rate is low, normal, or high, depending on the presence of heart disease or the severity of the primary disease. The ventricular complexes have normal polarity and amplitude but vary slightly in appearance from beat to beat. Similarly, the QT interval and the appearance of the T wave vary. P

waves are absent, replaced by fine undulations of the baseline called *fibrillation* or *f waves*. In some leads the f waves are barely visible, particularly in cattle (Fig. 30-31).

The echocardiogram is used to determine whether cardiac disease is present. The most significant change associated with the arrhythmia is a mild reduction in shortening fraction (24% to 32%) that occurs, in part, secondary to the loss of the atrial contribution to ventricular filling.[242] Absence of the second (atrial) opening of the mitral valve, corresponding to atrial contractions, is also detected with atrial fibrillation.[243] Conversion to sinus rhythm usually results in these echocardiographic findings returning to normal within several days, if there is no underlying myocardial disease.[242,244] Similar findings were reported in horses with mitral and aortic regurgitation after conversion to normal sinus rhythm.[244] In many large animals with atrial fibrillation, no evidence of heart disease can be detected echocardiographically; these animals are often considered to have "lone" atrial fibrillation. Abnormal echocardiographic dimensions, if detected, indicated that underlying heart disease is present. Measurement of the maximal left atrial dimension in the two-chambered view of the left atrium and left ventricle from the left cardiac window should be performed to determine whether there is left atrial enlargement. This measurement is a more sensitive indicator of left atrial enlargement than the left atrium—to—aortic root ratio. In normal horses the left atrial diameter in this view should be less than or equal to 13.5 cm.

Cardiac catheterization reveals normal cardiac output and blood pressure measurements in most conscious horses with atrial fibrillation, but conversion to normal sinus rhythm may induce a reduction in mean right atrial, pulmonary arterial, and aortic pressures.[245] Similar studies have not been reported in cattle.

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Fig. 30-31 ECGs showing atrial fibrillation in a horse **(A)** and cow **(B).** The irregular QT intervals and absence of P waves are apparent. *Arrows* point to fibrillation waves, which are apparent only in **A.**

30.4.10.4

Pathophysiology

Experimentally rapid stimulation of the atrium can initiate atrial fibrillation, which can be sustained if the animal has a large heart and sufficient vagal tone.[233,246–249] In horses and cattle the normal atria may be large enough to support atrial fibrillation once it is established. In addition, both species have a high vagal tone at rest. This combination of factors may be responsible for the large number of benign or functional cases of

atrial fibrillation in large animals. The ventricular response during atrial fibrillation results from rate-dependant concealment of atrial fibrillation wavelets bombarding the AV node.[235] Cardiac diseases such as endocarditis, atrioventricular valvular regurgitation, and CHF that result in atrial enlargement and rapid stimulation of the atria provide a setting in which atrial fibrillation can develop and can be sustained naturally. Microscopic cardiac pathology might also create the proper setting for the development of conduction block and reentry.

During atrial fibrillation there is no coordinated contraction of the atria; thus ventricular filling is passive. Although this might be expected to reduce cardiac output, there is no evidence that this occurs in resting horses without concurrent mitral or aortic regurgitation.[245] In horses with aortic regurgitation (n = 2) or aortic and mitral regurgitation (n = 3), a decreased cardiac output was detected compared with horses without valvular insufficiencies before conversion.[244] The cardiac output increased significantly in warmblood horses with valvular regurgitation after conversion. During exercise, however, the heart rate of horses with atrial fibrillation exceeds normal limits, often by 40 to 60 beats/min for each level of exercise. This results in a decreased cardiac output and the resultant exercise intolerance that occurs in horses performing high-intensity athletic work.[236] Blood flow to other organs and viscera, although not studied, may be altered in large animals with atrial fibrillation, resulting in reduced gastrointestinal motility, colic, reduced muscle blood flow, and poor milk production.

Atrial pressures are elevated in horses with atrial fibrillation.[245,250] Sustained high pressure is likely to produce dilation of the atria. With progressive dilation, secondary atrioventricular valve regurgitation may occur. During atrial fibrillation blood flow to the atrial myocardium is reduced, and progressive fibrosis can also be a consequence of chronic atrial fibrillation. Sustained atrial fibrillation may result in progressive cardiac disease, although it is usually well tolerated in the horse.

30.4.10.5

Epidemiology

Standardbred, thoroughbred, and draft horses have been reported to have the highest incidence of atrial fibrillation.[237–239] Racehorses have been diagnosed most frequently, but atrial fibrillation has been found in all types of horses.[238,239,244] Horses of all ages are susceptible to atrial fibrillation; however, atrial fibrillation occurs infrequently in ponies, foals, weanlings, and yearlings. Older horses, ponies, foals, weanlings, and yearlings with atrial fibrillation more frequently have underlying heart disease associated with the arrhythmia.

In cattle, atrial fibrillation is diagnosed more frequently in dairy cattle than in beef cattle, but there is no apparent breed predilection.[232,240] It is commonly associated with gastrointestinal disease or abdominal pain in cattle.[232,233,240] Foot rot and pneumonia can also be associated with the development of atrial fibrillation in cattle.

30.4.10.6

Necropsy Findings

Many cattle and horses have “lone” atrial fibrillation without apparent underlying heart disease, so the necropsy findings reflect the primary disease. Microscopic cardiac pathology has been found in horses with atrial fibrillation that consists of focal atrial myocardial fibrosis, microvascular alterations, and cardiac nerve abnormalities.[251–253] Multifocal or large areas of myocardial fibrosis were detected in dairy cows with idiopathic atrial fibrillation.[254] Whether these changes predisposed to the development of atrial fibrillation, were a consequence of atrial fibrillation, or are aging changes has not been established. A minority of horses

and cattle have endocarditis, CHF, or valvular lesions; and the necropsy findings reflect these conditions. In horses with atrial fibrillation, mitral valve disease was the most common valvular lesion.[239] Pharmacologic and transvenous electrical cardioversion are both options for conversion of atrial fibrillation to normal sinus rhythm in horses.[239,255–262]

30.4.10.7

Treatment and Prognosis

Quinidine is the drug of choice to convert atrial fibrillation to normal sinus rhythm in horses and cattle. The drug is a negative inotrope at high dosages, causes systemic hypotension, increases the ventricular response rate, and can produce undesirable side effects and toxicity; thus it must be used with caution. In animals with CHF, quinidine therapy has considerable risk.[239] Because most large animals have little or no underlying cardiac pathology, treatment with quinidine is successful in restoring normal sinus rhythm. Treated animals should be monitored frequently by physical examination, with careful auscultation and ECG recording. Continuous ECG recording using radiotelemetry should be performed throughout treatment, if possible.[258] Animals should have normal acid-base balance and electrolyte concentrations before treatment. They should be adequately hydrated, allowed to drink and eat, or given additional oral fluids (horses) or intravenous fluids (cattle) during therapy. The intravenous administration of quinidine gluconate is successful in converting horses with recent-onset atrial fibrillation to sinus rhythm.[259] Quinidine gluconate is most successful when administered to horses with atrial fibrillation of 2 weeks or less. However, quinidine gluconate had been successful in converting horses with atrial fibrillation of 2 to 4 weeks duration. Horses with longer durations of atrial fibrillation should be treated PO with quinidine sulfate. Quinidine is poorly absorbed after oral administration to cattle and so must be given by intravenous infusion to obtain therapeutic concentrations. Cattle should be given intravenous fluids during quinidine infusion. Quinidine therapy should always be discontinued when conversion to normal sinus rhythm occurs.

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Quinidine sulfate is the preparation most economically used in large animals, although quinidine gluconate has resulted in successful conversion of a cow with atrial fibrillation.[263] Before therapy, a baseline ECG is recorded. Horses are given a dose of 22 mg/kg (1 g/100 lb) of body weight in a suspension of water via nasogastric tube. At 2 hours (time by which blood concentration of quinidine should have peaked), horses are evaluated closely for idiosyncratic or toxic reactions such as nasal edema, cutaneous reactions (urticaria or wheals), laminitis, colic, diarrhea, or ataxia. If no abnormalities are noticed, an ECG is recorded. If conversion to normal sinus rhythm has not occurred and the QRS duration is not greater than 25% of the pretreatment QRS duration, an additional dose is administered. Two hours after each dose administered via nasogastric intubation, an ECG is recorded. If there has been no conversion to normal sinus rhythm, another dose is administered, up to a maximum of four doses. A plasma quinidine concentration should be obtained 1 hour after the fourth dose administered every 2 hours to be sure that the horse will be able to tolerate another dose without experiencing toxicity. If the QRS complex is prolonged by more than 25% of the pretreatment value or if a fast (more than 80 to 100 beats/min) supraventricular arrhythmia, ventricular rhythm, colic, diarrhea, ataxia, nasal edema or laminitis develops, therapy should be discontinued. Although laminitis is a frequently reported complication of quinidine sulfate therapy, the actual incidence of laminitis associated with the administration of quinidine is rare.[258] Nasal mucosal edema, neurologic signs, and prolongation of the QRS duration to greater than 25% of the pretreatment value are all signs of quinidine toxicity that, if detected, should prompt discontinuation of the drug. Colic, associated with high dosages of quinidine, should also prompt discontinuation of treatment (at least for this attempt at conversion). If conversion has not occurred after a total of four to six doses (one every 2 hours) or after a cumulative dose of 88 to 132 mg/kg of quinidine sulfate has been administered, treatment intervals should be prolonged to every 6 hours (half-life of

quinidine).[258] The every-6-hour treatment can be continued until the horse converts or shows toxic or adverse side effects or the owner elects to discontinue treatment. The advantage of this treatment regimen is that steady-state plasma and myocardial concentrations of the drug are achieved. There is less quinidine toxicity, a lower total dose of quinidine sulfate is used, and horses that did not convert after the standard every-2-hour administration may convert with this treatment regimen. Digoxin at 0.011 mg/kg PO twice daily can then be added to the therapeutic regimen if conversion has not occurred in 24 to 48 hours and appears to be helpful in some horses. The concurrent administration of digoxin and quinidine will result in increased plasma digoxin concentration. Therefore, digoxin concentrations should be monitored beginning the second day of combined quinidine and digoxin therapy to prevent digoxin toxicity. If this is not possible, the horse should not receive more than 2 days of combined digoxin and quinidine therapy. Transvenous electrical cardioversion has been very successful in converting horses to normal sinus rhythm and is particularly useful in horses in which adverse or toxic reactions to quinidine prompted discontinuation of antiarrhythmic therapy with the result that conversion to normal sinus rhythm was not achieved.

Quinidine sulfate at a dose of 48 mg/kg is suspended in 4 L of saline or lactated Ringer's solution when cattle are treated for atrial fibrillation. This dose is administered at a rate of 1 L/hr. Intravenous fluids are administered simultaneously in the opposite jugular vein. Cattle should be monitored continuously during the infusion. Cattle frequently become depressed and develop diarrhea during the infusion of quinidine. These signs are side effects, and therapy can be continued. The infusion rate should be slowed if the ventricular response rate exceeds 100 beats/min. If the QRS complex is visibly prolonged or a fast (more than 120 beats/min) supraventricular arrhythmia or ventricular rhythm develops, therapy is temporarily discontinued. Just before conversion, some cattle have blepharospasm and are ataxic. The infusion should be discontinued as soon as conversion occurs. Therapy should be discontinued after the 4 L infusion, even if conversion to normal sinus rhythm has not occurred.

During quinidine therapy the ECG shows predictable changes. The fibrillation waves become coarser and less frequent. The R-R interval becomes more regular as the heart rate increases. Before conversion there may be a rapid regular atrial rate with more than one P wave for each QRS complex (atrial tachycardia with atrioventricular block). At the time of conversion, a single P wave is present for each QRS complex. Frequently a large T_a wave is present and the ST segment is elevated. The ECG should be normal within 12 hours of conversion. A continuous 24-hour ECG is recommended in horses with atrial fibrillation after conversion to determine if frequent atrial premature depolarizations are present. If the continuous ECG is normal during the 24 hours after conversion and myocardial function has returned to normal, the horse can be returned to training. If frequent supraventricular premature extrasystoles are detected, the horse should be rested and treatment with corticosteroids may be considered for a possible myocarditis. The horse should not be returned to work until the atrial premature depolarizations have resolved. Intravenous amiodarone and flecainide have been used to convert horses with atrial fibrillation.[261,262] However, ventricular arrhythmias were common in horses given flecainide, limiting its usefulness as a treatment for atrial fibrillation in horses.[262]

Digoxin is used before quinidine therapy in horses and cattle with fast heart rates. The ventricular response rate should be less than 60 beats/min in horses and 100 beats/min in cattle before quinidine therapy. One or two doses of digoxin are administered before initiation of quinidine therapy in horses with only mild tachycardia. In horses with very labile heart rates or problems with supraventricular tachycardia during a previous conversion, digoxin is administered for up to 5 to 7 days before initiation of quinidine therapy. Digoxin should be administered at a dose of 11 µg/kg twice daily PO to horses. Cattle are given digoxin IV by infusion of 0.86 µg/kg/hr or 11 µg/kg three times daily. The side effects of quinidine treatment such as rapid supraventricular tachycardia may be decreased in animals pretreated with digoxin. Digoxin is also indicated as

a pretreatment in horses with atrial fibrillation and very low FS (<24%), indicative of underlying myocardial disease. Transvenous electrical cardioversion should be considered in horses with high heart rate responses to stimulation or during prior quinidine therapy.

Cattle with primary gastrointestinal disease that is treated successfully frequently convert to normal sinus rhythm spontaneously. Spontaneous conversion usually occurs within 5 days of resolution of the primary problem; therefore treatment is delayed for this period.[240] Cattle that do not convert spontaneously in 5 days, have chronic gastrointestinal problems, or have atrial fibrillation with adverse hemodynamic effects (poor peripheral perfusion, weak arterial pulses, pulse deficit) are selected for quinidine therapy. The prognosis for cattle with atrial fibrillation is good if the primary problem has been resolved and conversion to normal sinus rhythm occurs. Prognosis for cattle with chronic gastrointestinal disease is guarded, but many show improved appetite and milk production when atrial fibrillation is resolved. Unless heart disease is present, few cattle experience a recurrence of atrial fibrillation. A small percentage of cattle fail to respond to quinidine therapy, and their prognosis is guarded to poor because milk production and appetite are intermittently poor and heart disease can be progressive.

Horses with paroxysmal atrial fibrillation have a good prognosis for return to performance, and few have a recurrence of the arrhythmia. Predisposing factors such as transient potassium depletion should be removed, if possible, by discontinuing the furosemide administration or adding oral KCl to the diet. Oral bicarbonate milkshakes should be avoided. Horses with “lone” sustained atrial fibrillation have a good prognosis for conversion to normal sinus rhythm and a return to previous performance level.[238,239] Horses with sustained atrial fibrillation associated with mild to moderate valvular regurgitation and atrial enlargement often have a recurrence of atrial fibrillation but can usually be successfully converted when indicated. Horses with heart rates greater than 60 beats/min or with signs of CHF have a guarded to grave prognosis, and conversion to sinus rhythm is rarely warranted. Treatment of the underlying cardiac disease, if possible, is warranted, and the horse should be treated for CHF with digoxin, diuretics, and vasodilators as needed. Recurrence of atrial fibrillation and side effects of quinidine therapy are more frequent in horses that have had atrial fibrillation for longer than 4 months before treatment.[239] The recurrence rate for horses with atrial fibrillation of greater than 4 months’ duration increases to 60% from 25%. This may be the result of microscopic cardiac lesions that developed with chronic atrial fibrillation.

30.4.11 VENTRICULAR TACHYCARDIA

30.4.11.1 Definition and Etiology

Ventricular tachycardia is a cardiac arrhythmia characterized by a rapid rhythm originating in the ventricle. This rhythm originates below the bundle of His in the specialized conduction system, the surrounding ventricular myocardium, or both.[264] Ventricular tachycardia may be caused by disorders in impulse formation or impulse conduction or a combination of these two mechanisms.[264] Ventricular reentry is an important mechanism in the genesis of sustained ventricular tachycardia, whereas abnormal automaticity is probably responsible for idioventricular rhythms and parasystole. Changes in autonomic tone may also be important in the genesis of ventricular tachycardia. Early afterdepolarizations are thought to be the mechanism responsible for ventricular tachyarrhythmias associated with sympathetic stimulation. Late coupled ventricular complexes or a very premature ventricular depolarization are usually required to initiate ventricular tachycardia. Ventricular tachycardia can occur when there is myocarditis, myocardial necrosis, fibrosis or neoplasia, bacterial endocarditis (especially involving the aortic or mitral valve), autonomic nervous system imbalance,

hypoxia, ischemia, electrolyte or metabolic disturbances, anesthesia, drug administration, sepsis, endotoxemia, toxic myocardial injury, or aortic root rupture; or it may be associated with other, unknown causes.[265–269]

30.4.11.2 Clinical Signs and Differential Diagnosis

The clinical signs detected depend on the ventricular rate, the type of ventricular tachycardia (uniform or multiform), the duration of ventricular tachycardia, and the severity of the underlying cardiac disease.[266] Large animals with ventricular tachycardia may be asymptomatic at rest, if the rhythm is relatively slow and uniform, or may have severe CHF with rapid uniform or multiform ventricular tachycardia.[266] Exercise intolerance is common and may be so severe that the animal has frequent syncope. Other complaints include depression, weakness, colic, respiratory distress, coughing, ventral edema, and pulmonary edema. Acute viral or bacterial respiratory disease with high fever may precede the development of ventricular tachycardia in horses or may occur concurrently with it.[270] Gastrointestinal disease and primary myocardial disease are common in horses with ventricular tachycardia.[265] In cattle, ventricular tachycardia occurs most frequently secondary to sepsis and toxemia. Anorexia and decreased milk production are common in affected cows.

Animals with sustained ventricular tachycardia have a rapid heart rate with a regular (uniform) or irregular (multiform) rhythm.[271–274] Heart rates as high as 300 beats/min have been detected in horses with ventricular tachycardia. Heart sounds vary in intensity, with some very loud booming sounds (“bruit de cannon”). Arterial pulse may be variable or uniform, with normal (slower rate) or weak (rapid rate) intensity pulses. Pulse deficits frequently occur, particularly with rapid or multiform ventricular tachycardia. Jugular pulses are frequently detected in large animals with ventricular tachycardia. The large pulse waves seen in the jugular vein are cannon “a” waves that occur when the right atrium and ventricle contract simultaneously. Cardiac murmurs are not commonly detected. Signs of CHF are usually present when ventricular tachycardia is rapid and sustained but are uncommon in animals with slower or paroxysmal ventricular tachycardia.[271–273] Signs of right-sided CHF (ventral edema, venous distention) usually predominate with sustained uniform ventricular tachycardia and increase in severity the longer the duration and more rapid the rate of the arrhythmia. Signs of left-sided CHF (coughing, expectoration of foamy fluid, respiratory distress) usually predominate with multiform ventricular tachycardia.[270]

The presence of jugular pulses and “bruit de cannon” in an animal with a rapid regular rhythm helps distinguish ventricular tachycardia from sinus or supraventricular tachycardia. Multiform ventricular tachycardia can be difficult to distinguish from atrial fibrillation, because both arrhythmias have an irregular rhythm with heart sounds that vary in intensity. Jugular pulses may also be detected in large animals with atrial fibrillation but are usually less prominent than in animals with ventricular tachycardia. Although large animals with multiform ventricular arrhythmias usually have more severe clinical signs, an ECG is necessary to distinguish these arrhythmias.

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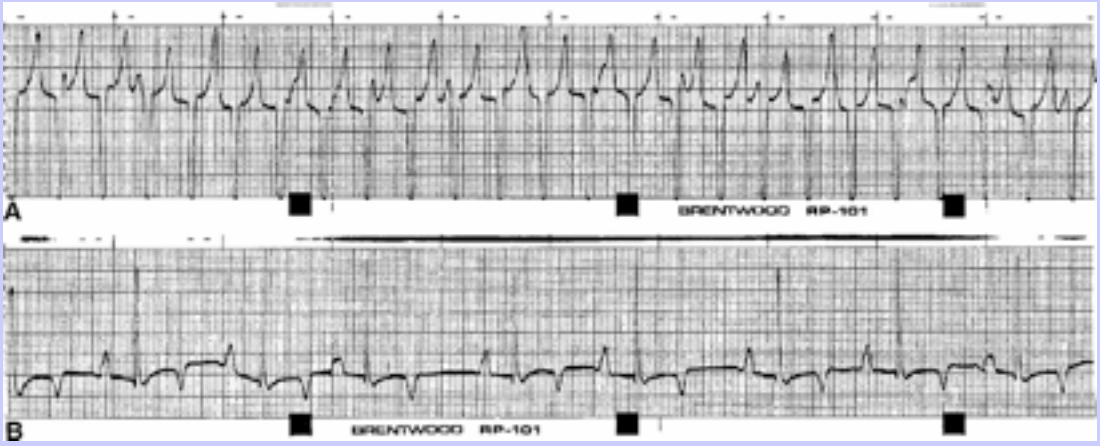
30.4.11.3 Clinical Pathology

Electrolyte, metabolic, or toxic causes of ventricular tachycardia may be present in large animals with primary gastrointestinal disease. Hypomagnesemia and hypokalemia has also been associated with the development of ventricular tachycardia.[274] Serum creatinine and BUN may be elevated in horses and cattle in CHF associated with prerenal azotemia. Serum osmolality, BUN, and creatinine increase and urine osmolality decreases acutely in horses with experimental monensin toxicosis.[270,275] Initial decreases in serum potassium and serum calcium have also been reported in these animals. Marked elevations of cTnI have been seen in horses with

ventricular tachycardia.[276,277] cTnI is a more sensitive indicator of myocardial injury in human beings and appears to have a similar sensitivity in the horse. Cardiac isoenzymes of CK and LDH are often elevated if there is recent myocardial injury associated with the ventricular tachycardia. Elevation of the myocardial fraction of CK (CK-MB) in excess of 5% of the total CK is compatible with myocardial injury in horses.[270,275] A neutrophilic leukocytosis and hyperfibrinogenemia may be detected in animals with an infectious myocarditis or bacterial endocarditis or may be elevated associated with the primary underlying disease. In most large animals with ventricular tachycardia, however, the hematology is normal.

The diagnosis of ventricular tachycardia is made from the ECG. A series of four or more ventricular premature depolarizations is diagnostic of ventricular tachycardia.[265,278] The electrocardiographic appearance of the ventricular premature depolarizations may be widened and bizarre, or the QRS duration and appearance of the QRS and T may be near normal, especially in horses (Fig. 30-32).[265,266] Although the duration of QRS complexes that are ventricular in origin is usually within the normal range reported for horses, it is usually longer than the QRS duration of the horse's normal sinus beats.[265] The major direction of the QRS complex is usually oriented opposite to that of the T wave. The R-R intervals may be regular or irregular. The morphology of the QRS complexes may be similar (uniform) or may vary widely (multiform). Atrioventricular dissociation is usually present, with an atrial rate slower than the ventricular rate. Fusion beats and capture beats may be detected (Fig. 30-33). Ventricular tachycardia can be sustained or paroxysmal.

Fig. 30-32 Lead II ECG obtained from a horse with sustained uniform ventricular tachycardia and CHF before **(A)** and after **(B)** conversion to sinus rhythm. Note the abnormal QRS and T configuration and slower atrial rate during the sustained ventricular tachycardia.



The echocardiogram is used to determine whether cardiac disease is present. The echocardiogram is usually abnormal in large animals with primary myocardial disease and normal in large animals with secondary ventricular tachycardia, except for the changes associated with the ventricular tachycardia itself. Abnormal echocardiographic findings that may be detected in large animals with primary myocardial disease include myocardial dyskinesis, hypokinesis, and akinesis; abnormal myocardial echogenicity; decreased FS, ET, and EF; loss of the normal systolic and diastolic undulations of the aortic root; and detection of spontaneous

contrast, small aortic root, and large pulmonary artery (see Fig. 30-15). Occasionally the echocardiographic abnormalities created by ventricular tachycardia may be difficult to distinguish from those of primary myocardial disease. Rupture of the aortic root at the right sinus of Valsalva may be detected in horses with acute onset of uniform ventricular tachycardia and colic.

Cardiac catheterization may reveal severe hypotension and low cardiac output. In healthy ponies with pacing-induced ventricular tachycardia, stroke volume decreased significantly when the ventricle was paced at 150, 200, and 250 beats/min.[279] Mean left atrial pressure, mean pulmonary arterial pressure, and right ventricular systolic pressure increased significantly when the ventricle was paced at 220 and 250 beats/min. Aortic pressure and cardiac output decreased in these ponies at 250 beats/min, but the decrease from resting values was not statistically significant. Myocardial perfusion in the papillary muscles and subendocardium decreased significantly with pacing-induced ventricular tachycardia at a rate of 250 beats/min. Decreases in cardiac output, arterial blood pressure, and myocardial perfusion are even more marked in animals with underlying myocardial disease or multiform ventricular tachycardia, as are the changes in left atrial, pulmonary arterial, and right ventricular pressure.

30.4.11.4 Pathophysiology

Ventricular tachycardia is probably initiated spontaneously by late coupled ventricular complexes, whereas one very early ventricular premature depolarization can often initiate ventricular tachycardia electrically.[264] Sympathetic stimulation may also provoke ventricular tachycardia by increasing the amplitude of the early afterdepolarizations, culminating in a run of ventricular tachycardia.[264] This may be the mechanism of some of the exercise-induced ventricular tachycardia in horses. Reentry in the ventricle is an important cause of sustained ventricular tachycardia, particularly in human patients with dilated cardiomyopathy and ischemic heart disease. The area of reentry is reportedly small, less than 1.4 cm^2.[2,264] Reentry is also thought to be an important mechanism in horses with sustained ventricular tachycardia.[273,280,281] Delayed afterdepolarizations may trigger ventricular tachycardia in humans and dogs and may be the mechanism for digitalis-induced ventricular tachycardia.[264] Abnormal action potentials have also been demonstrated in ventricular myocardium resected from human beings with recurrent ventricular tachycardia.[264] Depressed automaticity and afterdepolarizations have been associated with acute myocardial ischemia, whereas automaticity and afterdepolarizations are enhanced in Purkinje fibers surviving myocardial infarction. Idioventricular rhythms and parasystole may be caused by abnormal automaticity.

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Fig. 30-33 Lead II ECG obtained from a horse with multiform ventricular tachycardia and acute onset of pulmonary edema. Notice the multiple different QRS and T configurations and the elevated ventricular rate.

Cardiac diseases such as endocarditis may result in septic myocardial emboli and myocardial ischemia. Aortic root rupture and the dissection of blood into the interventricular septum disrupts conduction and usually results in a uniform ventricular tachycardia. Myocarditis, myocardial necrosis, and fibrosis also may result in abnormalities of impulse formation and conduction, leading to ventricular tachycardia.[282] The excitement of the high-performance situation and the decreased myocardial perfusion that may occur at peak exercise may make exercise-induced ventricular tachycardia more common in racehorses and other types of high-performance horses.

30.4.11.5

Epidemiology

Ventricular tachycardia has been reported in all large animals, although horses may have the highest incidence. Ventricular tachycardia leading to ventricular fibrillation is thought to be one of the leading causes of sudden death in horses when other causes of death cannot be found on postmortem examination.[281] Male horses are at increased risk for aortic root and sinus of Valsalva rupture and are usually at least 10 years old at the time of rupture. Ventricular tachycardia is also more likely in large animals of any age with primary gastrointestinal disease.

30.4.11.6

Necropsy Findings

If the ventricular tachycardia is not associated with primary myocardial disease, the necropsy findings reflect the underlying disease. Gross and microscopic cardiac pathology has been found in horses with ventricular tachycardia, although in some horses no cardiac pathology is found. Areas of myocardial necrosis, inflammatory cell infiltrate, fibrosis, infarction, microvascular alterations, and cardiac nerve abnormalities have been reported in horses with ventricular tachycardia.[273,280–282] CHF is most likely in large animal patients with multiform ventricular tachycardia and heart rates in excess of 180 beats/min. A minority of large animal patients have bacterial endocarditis with septic emboli disseminated through the coronary arteries associated with ventricular tachycardia. Aortic root rupture and rupture of a sinus of Valsalva aneurysm with dissection of blood into the interventricular septum are infrequently detected in horses.

30.4.11.7

Treatment and Prognosis

The treatment and prognosis for ventricular tachycardia depends on the suspected cause of the arrhythmia, the severity of the animal's clinical signs, and the electrocardiographic abnormalities detected.[265,266] Relatively slow uniform ventricular tachycardia often resolves or improves significantly with the correction of the underlying electrolyte or metabolic imbalances, without requiring antiarrhythmic therapy. These animals usually have an excellent prognosis for conversion with correction of the underlying problem. Similarly, in large animals with sepsis or toxemia, hemodynamically and electrically stable ventricular tachycardia often resolves with treatment of the underlying disease. Uniform, hemodynamically stable ventricular tachycardia in animals with myocarditis may resolve with rest and/or corticosteroid therapy. A minimum of 4 to 8 weeks of rest is indicated in these patients before returning to work, once the ventricular tachycardia has resolved.

Treatment with antiarrhythmics is indicated in any animal with hemodynamically unstable or life-threatening ventricular tachycardia. Treatment with antiarrhythmics is indicated if clinical signs of CHF or cardiovascular collapse are present or if the rate of sustained ventricular tachycardia is extremely high. In horses with sustained uniform ventricular tachycardia, a heart rate in excess of 120 beats/min usually warrants

antiarrhythmic therapy, whereas in cattle, antiarrhythmic therapy may not be indicated until the heart rate exceeds 140 beats/min or greater. Horses with rapid sustained uniform ventricular tachycardia (120 beats/min or faster) need antiarrhythmic therapy because signs of CHF will develop after several days or weeks with this arrhythmia, if not already present. The rapidity of onset of CHF is related to the heart rate and type of primary myocardial disease, if present. These horses usually have a good prognosis for conversion and return to their previous performance level, with appropriate antiarrhythmic therapy (many times three or more antiarrhythmic drugs must be tried before conversion occurs) and rest before the horse is returned to work.

The electrocardiographic findings associated with life-threatening ventricular tachycardia include a multifocal origin for the ventricular premature depolarizations, torsades de pointes (wide ventricular tachycardia), and the presence of an R wave superimposed on the preceding T wave ("R on T"). Large animal patients with clinical signs of CHF and hemodynamic collapse with rapid (heart rate <120 beats/min) multiform ventricular tachycardia (±R on T) should be treated as a cardiovascular emergency, because sudden death from ventricular fibrillation is likely without antiarrhythmic therapy. Large animals with multiform ventricular tachycardia (±R on T) must be given a guarded to grave prognosis for survival, because most have severe underlying myocardial disease. Often conversion to sinus rhythm may not be successful before the animal develops ventricular fibrillation and dies. If successfully converted to sinus rhythm, many of these animals die or are euthanized because of the severity of the underlying cardiac disease.

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Several antiarrhythmic choices are available to the large animal practitioner for the correction of life-threatening ventricular tachycardia (see Table 30-3). Lidocaine hydrochloride is the most readily available drug for most large animal practitioners, is rapidly acting, is administered IV, and has a short duration of action and minimal hemodynamic effects. Lidocaine hydrochloride does, however, have central nervous system side effects in horses (hyperexcitability and seizures) and must be used at a lower dosage than in cattle. Quinidine gluconate (or quinidine sulfate in cattle) is very effective in large animals but is less rapidly acting, has negative inotropic effects at large doses or if primary myocardial disease is present, causes hypotension, and can produce undesirable adverse or toxic reactions. Magnesium sulfate can cause hypotension but has no other recognized adverse cardiovascular effects. Magnesium sulfate is less rapidly acting than lidocaine but may be effective when other antiarrhythmics fail, in both normomagnesemic and hypomagnesemic patients. Intravenous procainamide, intravenous and oral propafenone and intravenous flecainide have also been used successfully in horses with ventricular tachycardia. Intravenous propafenone is indicated for refractory ventricular tachycardia and has been used successfully in several horses that did not respond to lidocaine, quinidine, procainamide, or magnesium sulfate. However, it is not available at this time in the United States. Other antiarrhythmics such as propranolol have been used with less success but have converted large animals with sustained ventricular tachycardia.

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31 Chapter 31 Diseases of the Respiratory System

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31.1 DIAGNOSTIC PROCEDURES FOR THE RESPIRATORY SYSTEM

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* Based on chapters from previous editions authored by Angeline Warner.

31.2 GENERAL EVALUATION OF THE PATIENT WITH RESPIRATORY DISEASE

31.2.1 History

As with any disease process, acquisition of an accurate and appropriate history is the first step undertaken in evaluating the patient with a complaint thought to be related to the respiratory tract. Animals with respiratory disease may have widely varied histories, and it is important to gather as much information as possible. Age and breed may play a role in the development of respiratory disease such as congenital defects, neoplastic disease, or inherited or acquired immuno-deficiency syndromes seen in certain breeds. The environment in which the animal is maintained can contribute to the development or severity of respiratory disease—heaves in horses for example—and respiratory disease may become manifest after a change to new environment. In horses the work they are expected to perform can lead to important diagnostic clues, and recent events, such as long-distance transport, can predispose to diseases such as pleuropneumonia. It is important to know if certain diseases are either endemic or epidemic where the horse is kept or has recently moved from; diseases such as strangles and *Rhodococcus equi* bronchopneumonia of foals come to mind. Any recent traumatic or potentially traumatic event should be noted. If possible, a thorough vaccination history should be obtained, as should an accurate history of any administered treatments or supplements and the patient's response to those treatments.

31.2.2 Presenting Signs or Chief Complaints

Many presenting signs or chief complaints should lead to more thorough evaluation of the respiratory system; some are more directly associated with either the upper or the lower respiratory tract. Findings or complaints associated with respiratory disease include nasal discharge, either bilateral or unilateral. Respiratory noise at rest or during exercise is commonly associated with abnormalities of the upper airway, as may be inequalities of airflow present at the nares. Normal animals may periodically cough or sneeze, but an increase in either activity may indicate involvement of the respiratory tract. Exercise intolerance or apparent decrease in the ability of the animal to exercise should prompt evaluation of the respiratory system. Other clinical signs that indicate thorough evaluation of the respiratory tract include but are not limited to abnormal breathing patterns (tachypnea, hyperpnea, dyspnea), cyanosis, hemoptysis, epistaxis, unusual swellings (facial, pharyngeal, cervical), lymphadenopathy, ataxia or reluctance to move, foul smell to the breath, weight loss and ventral abdominal, and sternal or limb edema.

31.2.3 Physical Examination

The initial physical examination occurs at some distance from the patient and involves evaluation of the demeanor, posture, mental status, and way of movement of the patient. It is important to note whether the patient has an abnormal stance, such as standing with the head and neck extended; is unwilling to move; or is standing with elbows abducted, suggesting pleural pain. Ideally the respiratory rate can be determined by observation, as can the respiratory pattern. Although some respiratory diseases are not manifested at rest, important clues can be gained from observation of the patient at rest in many others. The normal resting respiratory rate of an adult horse is between 8 and 16 breaths/min; for adult cattle, 15 to 35 breaths/min; and for sheep and goats, 12 to 20 breaths/min. There is some small abdominal component during the expiratory phase, which is, along with inspiration, an active process for horses. The normal rate for neonates is up to 60 breaths/min at birth and less than 30 breaths/min by 1 month of age; respiratory rate decreases toward the adult rate with age. High ambient temperature, fever, and excitement can all increase respiratory rate. Normal breathing is quiet, is apparently effortless, and is termed *eupnea*. The term *dyspnea* refers to a breathing pattern that is inferred by the observer to reflect difficulty in breathing; the animal will appear distressed, and the work of breathing is obviously increased, although the actual rate may be within normal limits. Other terms used to describe breathing patterns include *tachypnea* (characterized by rapid rate and shallow depth or low tidal volume), *hyperpnea* (increased frequency and depth of breathing [e.g., postexercise recovery]), and *apnea* (no discernable breathing). Two additional terms are *hypoventilation* and *hyperventilation*, both of which require a change in arterial carbon dioxide partial pressure as a component of their definitions. Hyperventilation is a pattern that increases alveolar ventilation and causes arterial hypocapnia, whereas hypoventilation alters gas exchange in such a way as to cause arterial hypercapnia, or retention of carbon dioxide.

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Closer examination can reveal some of the physical manifestations of the presenting complaints listed earlier. Beginning with the head, the clinician should determine that airflow is even from both nostrils, as differences can indicate either congenital or acquired abnormalities ranging from choanal atresia to the presence of upper airway masses. Abnormal respiratory sounds can sometimes be present at rest and may be heard at the nares; abnormal breath odors may be particularly prominent at the nares. The frontal and maxillary sinuses should be percussed; identification of abnormal resonance, usually dullness, may be made easier by performing this with the patient's mouth held open. Palpation of the submandibular regions, larynx, and pharyngeal and cervical regions should be performed to identify any abnormal lymph node enlargement, masses, or areas of muscular atrophy. Both jugular veins should be checked for both patency and the presence of any evidence of injection sites or infections that may contribute to abnormal upper airway function by interfering with normal recurrent laryngeal nerve or vagosympathetic trunk function.

Coughing represents a nonspecific irritation of receptors in the airway and can be induced by many mechanisms. It can be, and usually is, a normal protective reflex that allows the animal to clear material from the airway. Cough can be associated with increased mucus production, production of other respiratory secretions, or decreased mucociliary clearance. In older horses cough is most commonly associated with heaves; in younger horses an association has been made both with infectious diseases and small airway inflammatory disease. Normal animals should not cough when the larynx or trachea is palpated.

Nasal discharge can be unilateral or bilateral, scant or copious, clear, mucoid, mucopurulent, or even bloody. The nature and character of nasal discharge can provide some information about a possible source of the discharge but should not be overinterpreted. Horses, for example, have a tendency to swallow excess airway secretions, and the volume of secretions may be underestimated. Although unilateral nasal discharge seems to suggest a source in front of the larynx, bilateral nasal discharge can be of either upper or lower airway origin. Skin

depigmentation of the ventral nares or presence of mucoid material in feed or water containers is a clue to presence of a nasal discharge.

Hemoptysis is the coughing up of blood from the airways or lungs. It is important to determine conclusively that the blood has come from the respiratory system. Epistaxis is defined as blood seen at the nares and often originates in the nasal passages, sinuses, turbinates, nasopharynx, or equine guttural pouches, although the lung can be, and is, a source on occasion, as in exercise-induced pulmonary hemorrhage (EIPH) or after lung biopsy. Bilateral epistaxis generally indicates bleeding caudal to the choanae. Because animals tend to swallow excessive respiratory secretions, bleeding can be occult and may not be seen unless the animal drops its head toward the ground. Significant blood loss can occur in this manner, unseen by owners.

Examination of the oral mucous membranes may reveal cyanosis—bluish discoloration of the oral, nasal, or vulvar mucous membranes. Cyanosis does not become apparent until a level of 5 mg/100 mL of deoxygenated hemoglobin, about one third of the total normal hemoglobin, is present, reflecting a profound decrease in oxygen saturation of hemoglobin and suggestive of severe hypoxemia. As it is the total quantity of deoxygenated hemoglobin that lends the mucous membranes the bluish color, very anemic patients may lack sufficient deoxygenated hemoglobin to appear blue, making appreciation of cyanosis impossible in these patients. One caveat is that all newborns are cyanotic for the first few breaths and become pink only when they have established neonatal, as opposed to fetal, cardiorespiratory circulation and opened their lungs to allow for gas exchange.

It is important that auscultation of the thorax take place in as quiet an environment as possible. In addition, auscultation of the lung fields should be performed under two breathing conditions: eupnea and hyperpnea, with hyperpnea induced by the use of a rebreathing bag. Some common misconceptions regarding the use of a rebreathing bag exist. Simply occluding the animal's nostrils or using a rectal sleeve as a rebreathing bag are both inadequate methods of fully examining the patient. The purpose is to cause the animal to rebreathe its own expired carbon dioxide, not to necessarily deprive it of oxygen. Rebreathing expired carbon dioxide results in increased $Paco_2$, which stimulates deeper and more frequent breathing efforts, making recognition of abnormal lung sounds simpler. The bag used should be large enough to accommodate two to three times the normal tidal volume of the animal and should be held in such a manner as to prevent the bag from occluding the patient's nostrils. Once the bag is removed, the animal will usually take several very deep breaths and the examiner should take advantage of these very large breaths to reexamine areas where suspicious sounds were heard during rebreathing. Animals with significant lung pathology will not tolerate the bag well, may cough when the bag is removed, and may require more time to return to baseline respiratory patterns when the bag is removed.

Normal breath sounds are those produced by turbulence within the tracheobronchial tree and may vary considerably depending on location within the lung, breathing pattern, and condition of the animal.[1] Only airways from the larynx to segmental bronchi contribute to sound generation; bronchial and vesicular sounds both represent larger airway flow events. Vesicular sounds are the quietest sounds, heard over the middle and diaphragmatic lung regions, correlate best with regional ventilation, and mainly represent segmental bronchial sounds; they do not represent air flow in terminal conducting airways and alveoli, which is silent because of the nature of its flow. Bronchial sounds are louder and are heard best over the trachea and base of the lung. Common abnormalities found during auscultation include ventral areas of dullness if pleural effusion is significant, dorsal areas of dullness or hyperresonance with pneumothorax, and dorsal harsh lung sounds. The degree of variation in normal regarding lung sounds is large, and auscultatory findings do not always correlate well with the degree of lung abnormality. That said, abnormal lung sounds are always potentially clinically important.

Adventitious lung sounds are divided into short discontinuous sounds called *crackles* and longer continuous sounds called *wheezes*, replacing the older terms *rales* and *rhonchi*, respectively. Crackles are most commonly generated by sudden pressure equalization when collapsed airway segments open. Although an air-fluid interface is required, crackles do not necessarily imply excessive secretions or pulmonary edema. They are often end-inspiratory and associated with reinflation of atelectatic lung. Crackles may be normal when ausculted in the previously down lung of a laterally recumbent neonate. Disease processes that generate crackles include pneumonia, interstitial fibrosis, chronic obstructive lung disease, congestive heart failure, and atelectasis.[2]

Wheezes commonly represent oscillation of airway walls before complete closing (expiratory) or opening (inspiratory). Intrathoracic airways are usually involved in expiratory wheezes and include the lower trachea and main, lobar, and segmental bronchi. Disappearance of a wheeze after coughing indicates secretory rather than tissue-component origin. Disease processes responsible for wheezes include airway stenosis or external compression; airway luminal compromise by foreign body, purulent material, cyst, or neoplasm; airway wall thickening as in chronic bronchitis; and bronchoconstriction. Expiratory wheezes are a hallmark of obstructive lung diseases such as heaves. Crackles and wheezes may be variably present. A final category of adventitious sounds includes the “rubbing” or “creaking” sounds generated by sliding or stretching of inflamed pleural surfaces, commonly termed *pleural friction rubs*.

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Percussion of the thorax is performed by methodic tapping over the intercostal spaces of the thorax using a variety of instruments, including plexors, pleximeters, spoons, fingers, neurologic hammers, and hands. It is an inexpensive and useful component of the physical examination and should be performed in all patients in which the respiratory system is suspect. Percussion of the thorax can reveal hyporesonance (dullness) ventrally when pleural effusion is present and hyperresonance dorsally in pneumothorax and can cause some patients to exhibit pleurodynia during the examination. Other conditions that can alter resonance of the thorax include but are not limited to diaphragmatic hernia with intrathoracic intestine, pericardial effusion, pulmonary and pleural abscessation, and consolidated lung. The point at which a change occurs from resonant to dull can be marked with adhesive tape. Thus the outline of aerated lung immediately beneath the chest wall is delineated. It is usually impossible to fully delineate the lung field cranially because of body fat and triceps musculature. There is a distinct region of cardiac dullness for all species on the left side.

Percussion allows delineation of pleural effusion and intrathoracic masses or consolidated lung up to 7 cm beneath the pleural surface but cannot distinguish between them. The procedure should be performed whenever pleural effusion is suspected on the basis of auscultatory findings and in all ruminants as part of the physical examination to uncover occult pneumonia.

31.3 ADDITIONAL DIAGNOSTIC EVALUATION OF THE RESPIRATORY TRACT

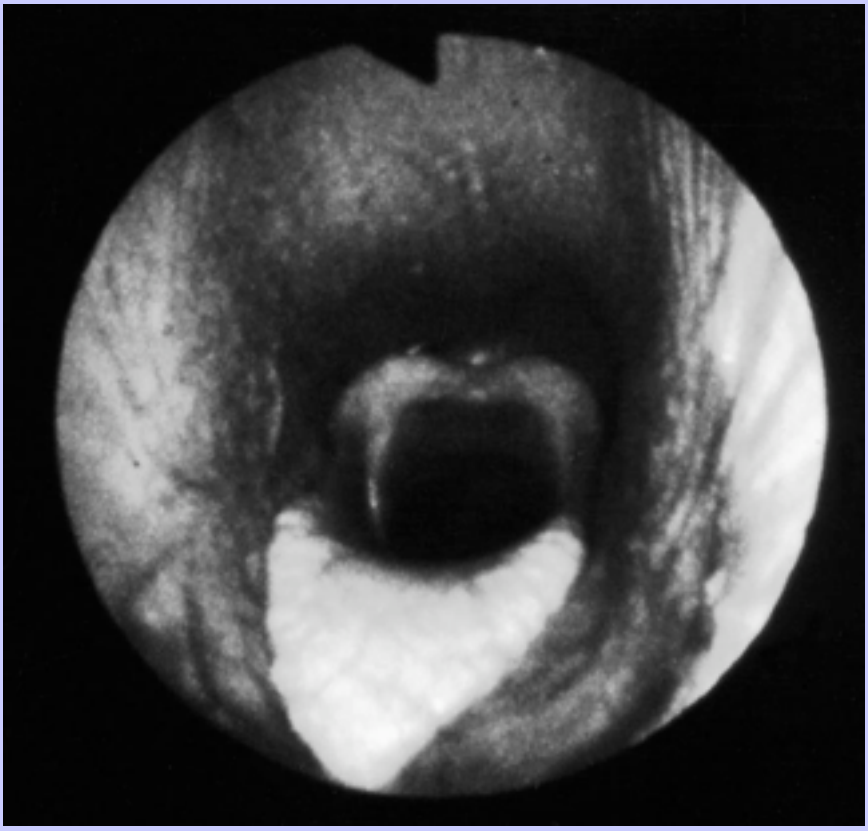
31.3.1 Endoscopy

The upper airway can be directly examined with the aid of an endoscope, the only limitations being the size of the patient, the patency of the airway, and the size of the available equipment. Standard flexible fiberoptic endoscopes, available to most practitioners and present now in virtually all referral hospitals, allow direct examination of the nasal passages, ethmoid turbinates, nasal maxillary opening of the sinuses, pharynx, guttural pouch openings, larynx, and cranial trachea (Fig. 31-1). Smaller (8- to 10-mm-diameter) endoscopes can be readily introduced into the equine guttural pouches with the aid of a biopsy instrument, and longer endoscopes (more than 150 cm long with diameters greater than 10 mm) are commonly employed to examine mainstem

bronchi and their initial branches in large animals.[3] Small brushes, used for collecting exfoliated cells for cytologic study, and a variety of biopsy instruments can be used for sampling the airway. The use of airway endoscopy has evolved to include videoendoscopy of the equine upper airway during treadmill exercise at high speed (12 to 14 m/sec) to evaluate dynamic respiratory function and make objective measurements by use of freeze-frame features.[4]

Sedation or tranquilization will facilitate many endoscopic examinations, but examinations aimed at evaluating pharyngeal and/or laryngeal function are best performed without any form of chemical restraint that might alter function. Most horses will allow standing examination of the upper airway with only physical restraint, such as judicious use of a nose twitch. Introduction of the endoscope into the trachea may elicit coughing, particularly in horses but less so in cattle. Small ruminants, such as sheep and goats, may require local tracheal anesthetic administration in the form of 2% lidocaine administered through small tubing passed through the biopsy channel of the endoscope. If used, care must be taken that lidocaine is diluted and does not reach a toxic dose in small ruminants. Diluted topical 2% lidocaine can similarly be used in horses and cattle if needed for evaluation of the distal trachea, main stem bronchi, and larger bronchial tree branches. Horses are more sensitive to tracheal and bronchial stimulation and are more likely to require topical anesthesia than cattle.

Fig. 31-1 Normal equine larynx. The larynx is directly visualized by endoscopy, with both structure and symmetry evaluated. Courtesy Dr. Corinne Sweeney, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.



Airway abnormalities such as pharyngeal lymphoid hyperplasia, laryngeal hemiplegia, epiglottic entrapment by arytenoepiglottic folds, dorsal displacement of the soft palate, pharyngeal cysts, retropharyngeal masses, and epiglottic deformities are all best diagnosed by endoscopic examination. Guttural pouch diseases and EIPH are also best evaluated using this technique. The degree and nature of airway secretions accumulating in the trachea can be easily assessed using an endoscope, and accumulated secretions may be sampled by aspirating the secretions through small tubing introduced into the trachea via the biopsy channel. Because the endoscope has passed through the nonsterile upper airway, these samples are best suited for cytologic, not microbiogic, evaluation but may be fully compatible with evaluation using newer molecular diagnostic techniques.[5–8] Endoscopy has also been used to facilitate removal of foreign bodies from the airway, generally aided by the biopsy instrument.

31.3.2 Radiography

Radiographs are indicated when the clinician suspects a congenital anomaly involving any thoracic structure; infectious disease of the pleura, pulmonary parenchyma, racheobronchial tree, or mediastinum; pneumothorax or pneumomediastinum; thoracic neoplasia of any origin; or trauma. Radiographs are frequently coupled with thoracic ultrasonographic evaluation. If significant accumulation of pleural fluid is suspected based on physical examination findings, the ultrasonographic portion of the examination should be performed first and radiographs obtained after drainage of excess fluid, as fluid may obscure potentially important parenchymal disease. The equipment needed to perform radiographic evaluation of the upper airway is available in most private practices, and most large referral and university practices have the equipment needed to perform thoracic radiography in larger patients such as adult horses and cattle. Digital radiography is becoming more commonplace and may replace more convention radiography in many practices and referral clinics over the next few years. Because of its configuration, the thorax in adult horses and cattle is filmed in the standing lateral position, generally requiring a series of three or four separate but overlapping images; thus the benefit of the ventrodorsal view in which the two lungs may be compared is lost. Neonates and small ruminants can be more readily handled and retained in recumbent positions, allowing for multiple recumbent views.

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Skull and cervical radiographs offer diagnostic information for evaluation of the upper respiratory tract. For large animal species, standing lateral skull films are easily obtained, and, with practice and adequate sedation, ventrodorsal and oblique projections can also be obtained in most patients. Certain difficult patients may require general anesthesia in order to obtain radiographs of diagnostic quality. In these cases other imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) might also be considered if available. Skull radiographs image the sinuses, pharynx, and larynx, allowing for assessment of anatomic dimensions of the pharyngeal and laryngeal structures. Sinuses affected by neoplasia or inflammation may show abnormal tissue density, a horizontal fluid line on a standing lateral film, bone lysis around the affected sinus, or alveolar periostitis. Thorough evaluation of the sinuses and nasal passages requires lateral, dorsoventral, and oblique views. Foreign bodies can be assessed in many cases. The equine guttural pouches are evident on lateral skull projection, and abnormal fluid accumulation, distortion by enlarged retropharyngeal lymph nodes, or emphysema can be radiographically apparent.

Radiographic assessment of the thorax of large animals remains preferable to ultrasonographic examination for detection of diffuse parenchymal diseases such as interstitial pneumonia, pulmonary edema, equine multinodular pulmonary fibrosis (EMPF), fungal pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), chronic disorders, and deep parenchymal or mediastinal abscesses. Unfortunately, many radiographic changes in equine respiratory disorders tend to be nonspecific or, in certain disease such as EIPH, inflammatory airway disease (IAD), or heaves, minimal to nonexistent.

Four types of radiographic patterns are described for the thorax: alveolar (airspace), interstitial, bronchiolar, and vascular. Opaque areas coalesce and fully obliterate vessels and bronchi in the alveolar pattern; air bronchograms may be prominent. This pattern is common in pulmonary edema, pulmonary hemorrhage, EMPF, ALI, ARDS, lung consolidation, and neoplasia. Interstitial patterns are the most common patterns noted in equine thoracic radiographs and are characterized by a blurring of the edges of pulmonary vessels, a diffuse increase in lung density, and variable reticular, linear, and nodular opacities. The reticular pattern is most commonly associated with more diffuse infectious lung diseases, pulmonary edema, interstitial pneumonia, and pulmonary fibrosis, whereas the irregular linear pattern is seen most commonly with resolving bronchopneumonia. A nodular pattern is seen with abscesses, granulomata, and neoplasms. It is rare to see a pure bronchial pattern in a horse, and it usually seen in association with an interstitial pattern. An exception is paired linear opacities or numerous small circular opacities (donuts) representing thickening of large or medium airways in equine bronchitis and bronchiolitis. The vascular pattern is seen in horses radiographed immediately postexercise or in animals with left-to-right cardiac shunts. Finally, extraparenchymal problems such as pleural effusions or free gas may be seen on thoracic radiographs of large animals. Thoracic radiology may be used for evaluation of potential rib fracture but is far less sensitive than thoracic ultrasonography in this regard.

31.3.3 Ultrasonography

Thoracic ultrasonography, a companion to thoracic radiography, is useful for diagnostic, therapeutic, and prognostic evaluation of the extraparenchymal thorax, the pleural space, and the peripheral (superficial) parenchyma of the lung. Unlike thoracic radiography, in which specialized equipment is needed to image the adult large animal, thoracic ultrasonography is an imaging technique readily available to most practitioners. In many instances it is superior to thoracic radiography as an imaging method; examples include evaluation of pleural effusions, assessment of thoracic trauma, evaluation of neoplasms or granulomata, detection of mediastinal masses or abscesses, and guidance of transthoracic lung biopsy.[9,10] Ultrasonography is considered greatly superior to thoracic radiography in the detection of rib fractures.[11] This imaging technique should be considered for complete evaluation of any large animal with suspected or diagnosed pulmonary disease.

Ultrasonography is generally performed with the patient standing, although in neonates lateral recumbency may be preferred or even necessary, and sound waves are generated by piezoelectric crystals and transmitted to the area of interest through a skin coupling gel, with subsequently reflected echoes detected by the same crystal. Echo signals from all tissue interfaces are displayed on a screen; the image can be photographed for a permanent record or stored digitally. Air trapped beneath the haired skin can interfere with the process, as can excessive skin dirt, so preparation of the acoustic window usually involves hair removal and cleansing in order to get the best image possible.

Although ultrasound waves will not penetrate the aerated portion of the lung, limiting the examination to extraparenchymal surfaces in normal horses, ultrasonography is superior to thoracic radiography in evaluation of these areas of the chest. Small amounts of pleural fluid that would be missed on auscultation, percussion, or thoracic radiographs can be detected, and the amount and character of pleural effusion in each hemithorax can be separately evaluated.[9] Clear fluid is anechoic, but inflammatory cells, gas, and fibrin are echogenic, causing opacities that can be seen floating in pleural fluid and altering the general echogenicity of the fluid. Because of this, ultrasound is the method of choice for diagnosis and monitoring of pleural space disease. Ultrasonography should be used to guide catheter placement for drainage of accumulated fluid in the pleural space. The pleural surfaces are imaged well by ultrasound, with thickened or roughened areas easily detected. Lack of normal

independent movement of the visceral and parietal pleural surfaces during the respiratory cycle, suggestive of adhesion formation, can be readily monitored.[9,10]

Consolidated lung is a better acoustic medium than aerated parenchyma and can be well visualized. If there is pleuropneumonia with consolidation or atelectasis caused by compression of the ventral lung by pleural effusion, it will be evident. Pulmonary abscesses or masses extending to the lung surface can be imaged, and ultrasound can be used for guidance for transthoracic biopsy.[9,10] Thoracic radiography remains superior to ultrasound in diagnosis of pulmonary parenchymal disease and pneumothorax, but combined the two techniques will improve patient management diagnostically and therapeutically.

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31.3.4 Nuclear Medicine Imaging

Nuclear medicine imaging is a very specialized technique available at a few university and private specialty referral practices. Gamma-emitting radioisotopes such as krypton-81 m or technetium-99 m can be used with an external detector (gamma camera) to assess regional pulmonary ventilation and perfusion in the horse. The procedure is safe and painless. Anesthesia is not needed, and the only requirement is that the patient stands quietly in front of the gamma camera. After the study the patient must be kept in an isolated area to allow decay and excretion of the radiopharmaceutical (normally no more than 48 hours), and, of course, all pertinent radiation regulations must be strictly adhered to.

The radioisotope is bound to albumin aggregates of 10 to 15 μm diameter. When injected into a peripheral vein (e.g., for a perfusion scan), the aggregates become trapped in the pulmonary arterial vasculature. Given even and thorough mixing in the right ventricle, the resulting image illustrates the perfusion distribution of the pulmonary arterial system. The ventilation scan is generated when the horse inhales aerosolized radioisotope particles through a close circuit system.[12] The particles have a small enough diameter to be deposited in the alveoli and small conducting airways with the gamma camera recording the sites of deposition. Together, the ventilation and perfusion scans allow for evaluation of the ventilation/perfusion ($\dot{V}/\dot{Q}$) ratio, important in evaluation of certain respiratory problems such as EIPH (high $\dot{V}/\dot{Q}$ areas), pulmonary thromboembolism (high $\dot{V}/\dot{Q}$ areas), and heaves (low $\dot{V}/\dot{Q}$ areas).[13] One final use is in the evaluation of mucociliary clearance or tracheal mucous transport. The time a bolus of radioisotope requires to cover a given tracheal distance is recorded in millimeters per minute and compared with normal ranges.[14]

This technology is specialized, expensive, and not readily available as of this writing. It has greatest potential application in the equine athlete or the valuable equine patient.

31.3.5 Arterial Blood Gas Analysis

Arterial blood gas determinations are the most sensitive indicator of respiratory function readily available to the clinician. The most accessed arteries for sampling are the metatarsal, temporal, facial, and brachial arteries (Fig. 31-2). In cattle the coccygeal artery on the ventral aspect of the tail head is easily accessible. Heparin is the only acceptable anticoagulant for blood gas samples, and all gas bubbles must be removed and the syringe capped to prevent equilibration of the sample with room air. Use a short (1-inch), small-gauge (25-gauge generally) needle and a 1- to 3-mL syringe for most samples. The syringe and needle can be purchased preheparinized especially for arterial blood gas sampling, or regular syringes and needles may be heparinized by aspirating a small volume of heparin into the syringe via the needle and then forcefully expelling the air and heparin from the syringe three times. This minimizes the effect heparin might have on any reported values from the blood gas analyzer. Pulsation of blood from the needle, spontaneous filling of the syringe, and bright color of the blood all confirm a

successful arterial puncture. If successful arterial puncture is questionable, then a comparison sample may be drawn from the jugular vein. Once the sample has been drawn, the vessel should be manually compressed for 2 to 5 minutes to prevent hematoma formation. If the sample will not be analyzed within 10 minutes, it should be placed on ice to slow metabolism of blood cells. The patient's body temperature at the time of sampling should also be recorded, as results are frequently reported at both 37° C and at the actual temperature of the patient, called *temperature-corrected values*, for pH, P_{O_2}, and P_{CO_2}, as these values are known to be temperature variable.

Fig. 31-2 Arterial blood sample drawn from temporal artery for arterial blood gas analysis. Courtesy Dr. Eric Birks, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.

Portable arterial and venous blood gas analyzers are now making arterial blood gas analysis more practical for use in the field, and the technique is no longer reserved for large institutions or referral practices.[15] It is virtually impossible to manage severe respiratory disease without knowledge of arterial blood gas parameters. Pulse oximetry is also being more commonly employed in some institutions and referral centers, but these monitors measure only oxygen saturation of hemoglobin, useful for severe hypoxemia but giving no measurement of actual arterial oxygen and carbon dioxide partial pressures. The most common abnormalities recognized with arterial blood gas analysis in animals breathing room air are hypoxemia with normocapnia or hypocapnia and hypoxemia with hypercapnia. There are five primary means by which hypoxemia develops in any animal with a

heart and lungs. For our purposes, *hypoxemia* is defined as decreased oxygen tension of the arterial blood (decreased Pa_{O_2}) and *hypoxia* is defined as decreased oxygen concentration at the level of the tissue, with or without hypoxemia. Hypoxia results from hypoxemia, decreased perfusion of the tissue bed in question, or decreased oxygen-carrying capacity of the blood as a result of anemia or hemoglobin alteration.

Hypoxemia develops from (1) low content or concentration of oxygen in the inspired air (Fi_{O_2}) such as seen in high altitude or when an error is made during the mixing of ventilator gas; (2) hypoventilation; (3) ventilation-perfusion mismatch; (4) diffusion limitation; or (5) intrapulmonary or intracardiac right-to-left shunting of blood. Mild to moderate hypoxemia is not an uncommon finding in neonates but must be evaluated in terms of the current age of the foal and its position. The difficulty encountered obtaining the sample must also be considered, as severe struggling can variably affect the arterial blood gas results. If the lung is significantly involved in the underlying pathology, such as with severe pneumonia, ALI, or ARDS, increased Pa_{CO_2} may very well be present, representing respiratory failure.

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Hypoxemia is usually treated with intranasal humidified oxygen insufflation at 4 to 10 L/min in neonates and 10 to 15 L/min in adults. Hypercapnia is not a simple matter to treat. It is important to try to distinguish between acute and chronic hypercapnia. Acute hypercapnia is usually accompanied by a relatively dramatic decrease in blood pH of 0.008 pH units for each 1-mm Hg increase in Pa_{CO_2}. This respiratory acidosis can promote circulatory collapse, particularly in the concurrently hypoxemic and/or hypovolemic patient. The effects of more chronic CO_2 retention are less obvious, as the time course allows for adaptation. The pH change is less, about 0.003 pH units per 1-mm Hg increase in Pa_{CO_2}, as it is balanced by enhanced renal absorption of bicarbonate by the proximal renal tubule. Most patients in acute respiratory distress are in the acute stages of respiratory failure, but chronic adaptation will begin to occur within 6 to 12 hours and will be maximal in 3 to 5 days. An increase in bicarbonate will be noted, particularly if the acidosis is primarily respiratory in origin.

Alveolar gas exchange is readily estimated by determining the alveolar-arterial (A-a) gradient for oxygen, computed by subtracting the Pa_{O_2} measured by the arterial blood gas from the calculated alveolar oxygen partial pressure (PA_{O_2}). The PA_{O_2} is effectively estimated using the partial pressure of inspired oxygen (Pi_{O_2}) as follows[16]:

$$PAo_2 = \frac{Pio_2 - Paco_2}{0.8}$$

The Pi_{O_2} equals the total barometric pressure (760 mm Hg) minus the partial pressure of water vapor (42 mm Hg) multiplied by the fraction of room air that is oxygen (0.21), and thus equals 150 mm Hg for room air. For patients on supplemental inspired oxygen, the practitioner must remember to recalculate the Pi_{O_2} with the new oxygen fraction (Fi_{O_2}) in the inspired gas, possible only in patients receiving inspiratory gas through a closed system. The Pa_{CO_2} is obtained from the arterial blood gas measurement. The A-a gradient is normally only 4 to 10 mm Hg; an increase beyond this indicates impaired gas exchange within the lungs, most often the result of ventilation-perfusion mismatching. The A-a gradient can be estimated only in patients receiving intranasal insufflation of oxygen.

A second useful measure is the Pa_{O_2}/Fi_{O_2} ratio, a component of most definitions of both ALI and ARDS.[17] The Pa_{O_2}/Fi_{O_2} ratio equals the Pa_{O_2} obtained from the arterial blood gas divided by the Fi_{O_2}, the oxygen fraction in the inspired gases. The normal Pa_{O_2}/Fi_{O_2} ratio is >300 mm Hg; a ratio <300 mm Hg is consistent with a

potential diagnosis of ALI, and a ratio <200 mm Hg suggests ARDS, a more severe form of ALI. The ranges of normal arterial blood gas values for various species are listed in Table 31-1.

Table 31-1 Normal Arterial pH and P_{CO_2} Values for Various Species (Nonneonate)

Species	Blood pH	P_{CO_2} (mm Hg)
Bovine	7.32–7.45	35–53
Ovine	7.32–7.54	37–46
Equine	7.32–7.44	38–46
Caprine	7.42–7.46	33–38

31.3.6 Respiratory Function Testing

The major functions of the lungs are to transport gas from the periphery to the site of gas exchange (i.e., the "bellows" function) and to provide gas exchange with the blood, facilitating gas transport to the tissues. The first of these is assessed by means of pulmonary function tests, and the second by arterial blood gas evaluation, discussed earlier.

Pulmonary function tests have historically primarily been used in horses and in most cases as a research tool in veterinary teaching hospitals. However, newer, portable technologies are beginning to allow use of some of the less invasive techniques in the field, and practitioners are becoming aware of the potential utility of these testing techniques.[18] Pulmonary function testing (PFT) involves measurement of pressure, flow, and volume during breathing to allow computation of ventilatory functional values. They are valuable in assessment of equine athletes, especially those suspected of inflammatory obstructive airway disease, and a portion of this section is dedicated to this subject. Baseline measurements can be compared, and airway hyperreactivity (AHR) can be evaluated using histamine or methacholine bronchoprovocation protocols.[19] Responses to environmental changes or therapy can be noninvasively evaluated.[20–22]

31.3.7 Collection and Evaluation of Respiratory Secretions

31.3.7.1 TRACHEAL ASPIRATES AND BRONCHOALVEOLAR LAVAGE

Various spaces in the respiratory system can undergo aspiration or lavage for diagnostic or therapeutic purposes. The most commonly performed procedure is the tracheobronchial aspiration. By aspirating from the airways caudal to the larynx, a sample without pharyngeal contamination is obtained.

In both the horse and the ruminant the procedure is performed with the animal standing. Sedation or restraint may be needed. A small area over the trachea in the middle third of the neck is clipped and routinely sterilely prepared. The skin is anesthetized using a local block of 2% lidocaine, generally less than 3 mL is given as a "bleb" subcutaneously, and a small stab incision is made. A trocar or angiocatheter needle is introduced on the midline between muscle bundles, with the beveled edge facing ventrally to decrease the opportunity for inadvertent cutting of the tubing when the needle is introduced or manipulated, and the ventral tracheal wall is

punctured between two cartilaginous rings. The distal end of the trocar or needle is then advanced distally in the trachea, taking care not to lacerate the dorsal tracheal mucosa. Sterile polyethylene tubing or the catheter from the angiocatheter is introduced through the trocar or needle for about 30 cm. A needle or sharp trocar should be withdrawn to prevent severing the tubing or catheter, but a cannula with rounded edges may be left in place. Approximately 20 to 30 mL of nonbacteriostatic sterile saline solution is introduced quickly. Intermittent aspiration is performed as the tubing is gradually withdrawn. The tubing can be advanced again if a guarding cannula has been left in place to prevent introduction of skin contamination. Additional saline solution aliquots can also be introduced. Once an adequate sample has been obtained, the tubing is completely withdrawn. Injectable antimicrobial solution or suspension can be infiltrated at the skin incision site if a septic sample is suspected, and in horses and small ruminants a sterile dressing can be applied for 24 hours if desired. Possible complications include subcutaneous (SC) emphysema (usually peritracheal but may extend into the mediastinum), local cellulitis, or cutting of the catheter at the needle and loss into the airway. The latter is usually resolved because the catheter is rapidly coughed up, but good technique should prevent this complication. The sample should be cultured for aerobic bacteria. Anaerobic colonization is possible, and appropriate cultures should be made if these organisms are suspected (evidence of pleural effusion, consolidation, abscessation, history of aspiration fetid breath). For patients with prior antimicrobial therapy, it is advised to discontinue antibiotics for 72 to 96 hours before culture, although a recent study has shown reliable recovery of bacteria using bronchoalveolar lavage (BAL) fluid from foals receiving therapy.[6]

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Airway aspiration can also be performed during routine endoscopy of the trachea using an aspiration catheter advanced through the endoscope biopsy channel, but there is potential for pharyngeal contamination. Results comparing culture from a protected aspiration catheter passed through an endoscope compared favorably with culture from traditional percutaneous tracheobronchial aspiration (TBA).[5]

A direct smear and Gram stain can be used as an initial guide for antimicrobial therapy pending culture results. Cytologic evaluation can be extremely valuable in differentiating among infectious, allergic, parasitic, and neoplastic processes. Transtracheal aspirates (TTAs) from clinically normal horses contain columnar ciliated epithelial cells, a few neutrophils, and multiple mononuclear cells. Increased percentages of neutrophils and the presence of mast cells, eosinophils, giant cells, and hemosiderophages have been demonstrated in aspirates from normally performing thoroughbred racehorses, indicating some airway inflammation in “normal” equine athletes.[8] Mucus, large spores, and fungal hyphae may be found in the absence of airway disease and must not be overinterpreted. Heaves, or recurrent airway obstruction (RAO), is characterized by increased numbers of nondegenerate neutrophils and occasional eosinophils. In cases of pneumonia, neutrophils may constitute 40% to 90% of the cellular sample. Bacterial pneumonia causes a more degenerate appearance of neutrophils, and intracellular bacteria may be found. Equine lungworm is characterized by finding large numbers of eosinophils and occasionally a larva. In ruminants the most important information gathered in patients with bronchopneumonia is usually the result of culture and antimicrobial sensitivity testing.

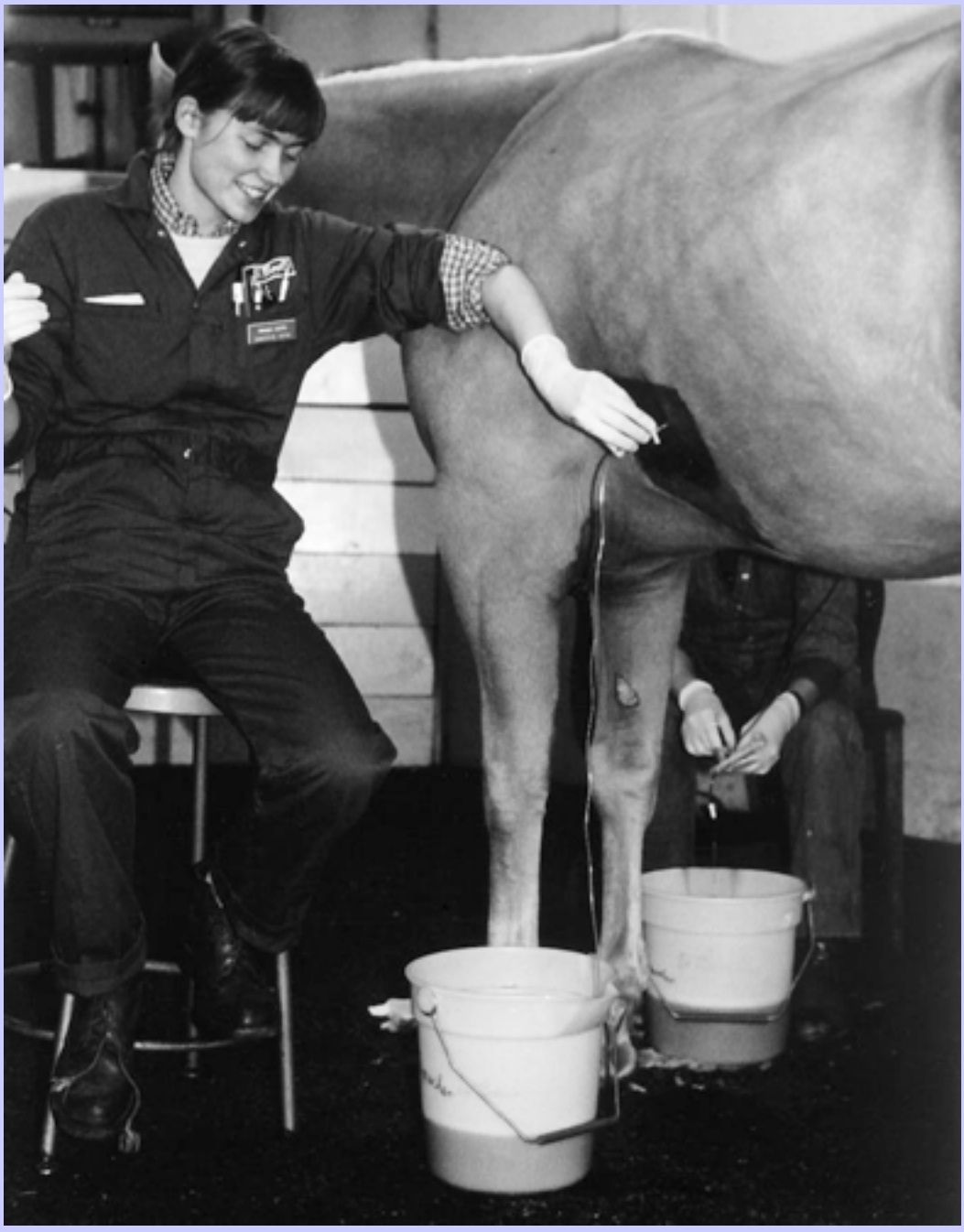
BAL involves obtaining a sample from the terminal airways and alveolar region. It is performed using a long endoscope or double-lumen tube introduced through the nares. Endoscopic BAL allows for more exact placement of the end of the endoscope, so a clear understanding of the anatomic location of the distal airway lavage is available. Use of the double-lumen tube is essentially a blind technique, but most frequently the dorsal lung of one hemithorax is sampled. The outer tube or the endoscope is wedged in a bronchus, and the smaller tube advanced. Saline solution aliquots of 60 to 300 mL are introduced, followed by continuous aspiration using low suction pressure. The procedure has the advantage of sampling the airways nearest the parenchymal region, but only a limited area of the lung is sampled instead of the pooled secretions from a tracheobronchial aspirate. Thus BAL may be superior to tracheobronchial aspiration in evaluation of horses with chronic lung diseases, but false-negative results can be obtained from horses with pneumonia or

pleuropneumonia. BAL cytology is valuable in evaluation of fungal infections and IAD and assessment of therapeutic response.

31.3.8 Thoracocentesis

Aspiration from the pleural space is a simple, easily performed, inexpensive procedure that can be both diagnostic and therapeutic. In the horse with septic or neoplastic effusions, sedation is often unnecessary because the procedure causes only minimal additional discomfort. After ultrasonographic evaluation of the thorax, a point is chosen at which drainage or fluid sampling would seem most appropriate—frequently in the sixth or seventh intercostal space 10 cm dorsal to the olecranon and above the lateral thoracic vein. The area should be clipped, if it was not clipped for the thoracic ultrasound examination, and surgically prepared. Multiple sites may be needed in horses with loculated pockets of fluid in the pleural cavity, and these sites should also be chosen using ultrasonography. The skin and intercostal tissue down to the pleura are anesthetized with lidocaine, and a stab incision is made. A sterile 2- to 3-inch teat cannula or bitch catheter is introduced immediately cranial to the rib border to avoid the intercostal nerve and vessel along the caudal aspect of the ribs. The cannula should be attached to sterile intravenous (IV) extension tubing and a three-way stopcock. When the cannula is advanced bluntly through the parietal pleura, a sudden loss of the force required to advance is felt. Aspiration should be attempted at this point. The orientation of the cannula can be varied to reach as much fluid as possible. Normally only a few milliliters of straw-colored fluid are obtained. In cases of pleural effusion, as much as 30 L may be removed from each side of the chest (Fig. 31-3). If fluid is excessive, the tubing can be extended over a bucket for gravity drainage, or a vacuum pump with fluid trap can be attached. Once the procedure is complete, a purse-string suture is placed around the stab incision, and the cannula is withdrawn while the suture is tightened. In 496
cases in which the effusion is large and expected to continue forming for several days, the initial drainage can be 497
performed by placing a chest tube instead of puncturing the pleural space with a teat cannula. If a chest tube is to be left in place it should be secured with a Chinese finger trap suture and the end covered by a Heimlich valve to prevent aspiration of air into the thorax through the tube. If the thorax is being drained rapidly, the patient should be watched carefully for signs of distress, as draining of large volumes can alter cardiovascular parameters significantly.

Fig. 31-3 Thoracocentesis and therapeutic drainage in the horse. Pleural effusion can be large and bilateral. Samples should be obtained for culture and cytologic examination at the time the chest is drained. Courtesy Dr. Corinne Sweeney, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.



Increasing opacity, presence of fibrin clumps, and malodor of pleural fluid all suggest relative progression from transudate to septic exudate containing inflammatory cells and debris. A putrid odor suggests the presence of anaerobic bacteria. Samples should be cultured for aerobic and anaerobic organisms. A white blood cell (WBC) count of 10,000/μL or less is considered normal; fewer than 60% are normally neutrophils, the remainder being lymphocytes and macrophages. The proportion and total number of neutrophils increase with pleuritis. Erythrocytes are normally not present in the absence of a traumatic tap. The protein concentration is normally less than 3.5 g/dL, and pH should be approximately 7.4. Additional metabolic values that give early indication of sepsis can be obtained on pleural fluid samples collected after filtration through a blood administration set to remove fibrin and debris potentially detrimental to analytic equipment. Pleural fluid pH, P_{CO_2}, and concentration of glucose, lactate, and bicarbonate can be directly compared with similar analysis of venous blood from the patient. A septic pleural exudate is acidic, with decreased glucose and bicarbonate but increased lactate and P_{CO_2} compared with venous blood concentrations or tensions, apparently reflecting metabolic activity of phagocytic cells and bacteria and development of an anaerobic environment.[23] Of these values, low pleural fluid glucose concentration (<40 mg/dL) has the best correlation with sepsis.[24]

Neoplastic cells may be found in cases of lymphosarcoma, adenocarcinoma, or other neoplasms. Equine gastric squamous cell carcinoma occasionally manifests with neoplastic pleural effusion. If neoplastic effusion is suspected but diagnostic cells do not exfoliate into the pleural fluid, pleuroscopy with the patient under sedation and local anesthesia can be used directly to visualize and obtain biopsy samples of intrathoracic lesions. The technique of pleuroscopy is beyond the scope of this chapter.

Mediastinal fenestrations may be occluded by fibrin and cell debris; therefore each side of the thorax should be evaluated separately. In the horse a transtracheal aspiration for culture should also be performed because of the common association of pleuritis with bacterial pneumonia and pulmonary abscessation. Although identical organisms are generally isolated from both samples, this is sometimes not the case.

31.3.9 Sinus Trephination

Sinus trephination is performed with some frequency in horses and ruminants. Clinical signs indicating a need for sinus trephination include foul-smelling purulent nasal discharge (the most consistent sign with dental disease or invasive tumors), facial malformation, exophthalmos, stertorous breathing, and epistaxis. Sinus cysts, neoplasms, and hematomas occasionally occur and result in serosanguineous discharge. When the physical examination, especially percussion, and radiographic findings indicate, the sinus should be trephined for diagnostic aspiration, drainage, and flushing, if necessary. In some cases sinoscopy may be indicated, particularly when the true extent of the disease process is difficult to determine or if biopsy samples are needed.

In the horse the frontal, sphenopalatine, and ethmoidal sinuses all communicate with the posterior chamber of the maxillary sinus and drain through the nasal maxillary opening into the middle meatus. The anterior chamber of the maxillary sinus is separated by an osseous septum that often breaks down with infection, making the posterior chamber of the maxillary sinus the most productive site for diagnostic aspiration. A line is drawn from the medial canthus of the eye perpendicularly to the facial crest. After tranquilization and local anesthesia, the sinus is approached with a Steinmann pin midway on this line. Once the sinus has been entered, aspiration should be performed by using a sterile 16-gauge needle or canine urinary catheter. One skin suture will suffice for closure. If purulent material or fluid within the sinus is under pressure, some leakage into the SC space may occur, with resulting cellulitis. The sample should be cultured for aerobic and anaerobic bacteria and examined cytologically for signs of septic inflammation or neoplastic cells.

The frontal sinus is trephined more often for flushing in chronic cases than for diagnostic purposes. The approach is 2.5 cm lateral to the midline of the face and 2.5 cm caudal to the point at which the nasal bones begin to diverge.

In cattle the frontal sinus is most often affected with septic inflammation as a consequence of dehorning. Purulent material frequently accumulates in the postorbital diverticulum of the sinus. This site is approached for trephination 4 cm from the edge of the orbital cavity just dorsal to the temporal (lateral) canthus of the eye.

Postdehorning sinusitis in goats can be a severe condition, especially in animals dehorned when mature. The frontal sinus contains numerous septa, creating poor drainage; the bony plate protecting the brain is thin, so that septic necrosis of bone leading to meningitis may occur. Therefore, in mature goats with sinusitis, appropriate systemic antimicrobial therapy and vigorous curettage of the affected areas should be used. A bone flap similar to the technique used in chronic maxillary sinusitis may be required to expose the frontal sinuses to curettage adequately.

31.3.10 Guttural Pouch Catheterization

When indicated by radiography and/or endoscopy, equine guttural pouches are easily catheterized for diagnostic sampling and flushing. Sampling can also be achieved by placing thin tubing through the biopsy channel and directly aspirating or aspirating after introduction of sterile saline, as TBA and lavage are performed through the biopsy channel. The patient should be tranquilized so that the head drops, facilitating drainage of the secretions by gravity. A Chambers mare catheter can be passed through the ventral meatus into the pharynx if the endoscope is not to be used for the sampling or lavage. The curved end is directed beneath the flap of the medial lamina of the pouch ipsilateral to the nostril used for passage. Successful passage is indicated by lack of resistance while the catheter is inserted deeper than if it were in the pharynx. The position of the catheter tip in the pharynx can be observed through an endoscope placed up the opposite nasal passage. Once the catheter is within the pouch, it can be used to obtain a sample, to drain excessive secretions, or to act as a conduit for flushing. A self-retaining uterine catheter can be left in place for repeated flushing, but the Chambers catheter can be passed repeatedly with no complications.

31.3.11 Lung Biopsy

Lung biopsy is most often done in the horse and should be used in conjunction with other, less invasive diagnostic techniques such as ultrasonography, radiography, and transtracheal aspiration. Lung biopsy is indicated to obtain a histologic diagnosis or prognostic information primarily in cases of diffuse lung disease, because the sample obtained is generally very small. A more useful parenchymal sample is obtained by means of percutaneous rather than endobronchial biopsy; complications of percutaneous biopsy are uncommon but do occur. A large gauge (14-gauge) 15-cm or longer biopsy needle, with a sample “slot” length of 22 mm, provides an excellent sample. Lung biopsy is easier with newer spring-loaded biopsy instruments than with older hand-operated biopsy instruments. Discomfort is minimal, and sedation may or may not be needed. The site for biopsy should be determined after ultrasonographic evaluation of the thorax, and the procedure should be performed away from common locations of major pulmonary vessels. Caudal and dorsal locations are generally chosen. The site should be widely clipped, surgically prepared, and infiltrated with local anesthetic down to the pleura. The biopsy needle is inserted through a stab incision just cranial to the rib, similar to catheter placement for pleural fluid sampling and drainage, and directed medially through the intercostal muscles and parietal pleura. The needle should be advanced the distance indicated by ultrasonographic measurement and then sharply advanced <1 cm to enter the lung parenchyma. The biopsy is obtained by “firing” the spring-loaded instrument, and the

biopsy instrument is then withdrawn. If no specimen is obtained, the procedure can be repeated. After sufficient biopsy specimens have been obtained and the biopsy instrument withdrawn, a single skin suture can be placed at the incision site, but no additional aftercare is needed. The specimen should be placed directly in 10% formalin or glutaraldehyde for fixation. If additional samples can be safely obtained, they should be submitted for bacterial and fungal culture and potentially for more advanced molecular diagnostic techniques and handled appropriately for the desired test. Complications of lung biopsy have been reported to range from transient epistaxis or hemoptysis, which is to be expected, to more severe pleural and parenchymal hemorrhage. Lung biopsy is not indicated for pleuropneumonia cases but is generally required to differentiate among EMPF, discrete fungal lesions, and potential neoplasia, when accurate diagnosis is required for therapeutic and prognostic purposes.

31.3.12 Molecular Techniques

Infectious pulmonary disease represents a diagnostic challenge for the equine practitioner. A presumptive diagnosis can often be made based on the history, physical examination, clinical impression, complete blood cell count, radiography, and endoscopy. Definitive identification of the causative agent(s) is necessary to ensure that the appropriate therapeutic and prophylactic protocols are instituted.

Culture of infectious pathogens is an indispensable diagnostic technique and should be attempted in all cases of pulmonary disease. However, cultivating infectious pulmonary pathogens from clinical specimens is time-consuming and may require from days to months before an organism is identified, potentially delaying appropriate management. Molecular recognition systems that can be used for rapid identification can improve response time and reduce the number of susceptible animals exposed to the infectious pathogen.

Several technologic innovations have improved the rapidity and sensitivity with which microorganisms are identified.[25] Immunologic assays and nucleic acid—based methods for the identification of bacterial, viral, and fungal pathogens have found clinical application in the diagnosis of pulmonary disease.

31.3.12.1 IMMUNOLOGIC TECHNIQUES

Immunologic detection of bacterial, viral, and fungal pulmonary pathogens have been developed. Immunoassays rely on interaction between the bacterial, viral, and fungal antigens and enzyme- or fluorescent-labeled antibody. The use of polyclonal antibodies tends to increase the sensitivity of the assay, as the preparation may contain antibodies to multiple epitopes on the target antigen, thus increasing the chance of antigen detection, but tends to decrease assay specificity because of their heterogenous nature. Test specificity can be improved by the use of monoclonal antibodies, as these antibodies interact with only a single well-defined epitope or very similar epitopes.

Immunohistochemistry (IHC) is rapidly becoming a standard diagnostic tool for the identification of viral, bacterial, and protozoal pathogens in tissue sections. This technique depends on polyclonal or monoclonal antibodies binding to a target antigen and the demonstration of this interaction by colored histochemical reactions visible by light microscopy or by emittance of fluorescence detectable after ultraviolet light illumination. IHC is highly versatile, and assays have been developed to detect a variety of equine pulmonary pathogens including, but not limited to, equine herpesviruses (EHVs), equine viral arteritis (EVA) virus, Hendra virus (HeV), *R. equi*, and *Pneumocystis carinii*, in tissue sections. Recent advancements in methodology have increased the ability to detect antigens in formalin-fixed tissues.

31.3.12.2 NUCLEIC ACID-BASED TECHNIQUES

Nucleic acid—based techniques for the diagnosis of equine pulmonary disease are becoming widely accepted because of the sensitivity, specificity, and speed with which results can be obtained. These assays can detect nucleic acid of both live and dead pathogens at very low concentrations, often less than 100 copies per microliter. Bacterial, viral, and fungal pulmonary pathogens can be discriminated based on nucleic acid sequences unique to those particular organisms. Polymerase chain reaction (PCR) testing is the most widely used molecular diagnostic technique in both research and clinical laboratories. PCR testing involves the enzymatic replication of a target region of deoxyribonucleic acid (DNA) as defined by a set of oligonucleotide primers. DNA polymerase synthesizes each complementary strand of the target region in the 5' to 3' direction, and the amount of DNA that is synthesized increases exponentially. For viruses whose genome is composed of ribonucleic acid (RNA), an initial reverse transcriptase (RT) step is required to generate a complementary strand of nucleic acid because the DNA polymerase requires a double-stranded template to amplify the target sequence.

Real-time PCR combines PCR amplification with detection of the amplified products, allowing quantification of PCR products. In real-time PCR the PCR reaction is carried out in a reaction tube to which an optical device is attached to read the fluorescent signal generated during each cycle of PCR reaction. Increases in the reporter fluorescence are proportional to the increase in PCR product. By monitoring the changes in degree of fluorescence, the time in which a transition from exponential to log phase amplification occurs can be determined and compared with that of a standard control to determine the initial template concentration.

Hydrolysis probes, such a TaqMan (Applied Biosystems, Foster City, Calif.), are commercially available and can be tailored for use in diagnostic tests to detect specific pathogens. In the TaqMan assay a probe is labeled with fluorescence and binds to a nucleic acid sequence within the target region. During amplification the *Thermus aqaticus* (Taq) polymerase hydrolyses the probe that separates the fluorescein from a quenching dye and allows the emission of fluorescence. The amount of fluorescence emitted is proportional to the accumulation of specific PCR product. TaqMan assays reduce the risk of contamination, as there is less sample handling compared with traditional PCR techniques, and the results are produced rapidly.

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With the increased use of PCR assays as diagnostic tests, there is increased demand for standardized techniques and internal control measures. PCR is a highly sensitive test and may produce false-positive results, commonly attributed to contamination. False-negative results may occur as a result of the presence of enzyme inhibitors in the sample that suppress DNA amplification. Control plasmids, which contain a DNA sequence that is amplified at the same time as the target DNA but is sufficiently mutated that it can be distinguished from the target DNA sequence after PCR testing, are increasingly being used to identify the presence of inhibitory molecules within the assay either resulting from tissue or sample handling problems or associated with collected tissues.

These assays do not substitute for careful clinical evaluation but can shorten the time to confirmed, accurate diagnosis and thus allow for early initiation of therapeutic strategies and prevention protocols. With further understanding of the molecular biology and immunology of pulmonary disease, diagnostic and management techniques will become further refined.

31.4 PULMONARY FUNCTION TESTING

DANIELA BEDENICE

PFT has emerged as an essential tool in equine referral practice and is largely aimed at describing the severity, anatomic pattern, stability (reactivity), and reversibility of bronchoconstriction caused by noninfectious airway obstruction and inflammation, such as is seen in heaves and airway inflammatory disease.[26] Clinical indications for noninvasive PFT include assessment of horses with intermittent cough, exercise intolerance, abnormal breathing pattern, and excess mucus, as well as early detection of subclinical disease, evaluation of treatment response, intensive care monitoring, and prediction of outcome. PFT is generally divided into the assessment of respiratory mechanics (mechanical properties of the respiratory system) and gas exchange. Analysis of gas exchange investigates ventilation-perfusion matching, shunt, diffusion capacity, and dead space—to—tidal volume ratio (V_D/V_T). Lung mechanics, on the other hand, determines the static and dynamic properties of the lung, including resistance, compliance, functional residual capacity (FRC), and ventilatory parameters.[26]

31.4.1 Mechanics of Breathing

The mechanical function of the lung is essentially defined by static and dynamic properties. Tests that are performed with the respiratory system at equilibrium and zero flow are referred to as *static tests*. Examples include measurement of lung volume subdivisions (e.g., FRC) and compliance of the lung and chest wall.[26]

FRC is a measure of the amount of gas that remains in the lungs at end-expiration (end-expiratory volume). FRC is lower in patients with increased "lung stiffness" (reduced elastic recoil of the lung) as well as airway inflammation, whereas FRC increases in patients with expiratory airway obstruction and gas trapping.[27] This test can be easily performed in awake clinical patients via a helium dilution technique.[28] In short, the patient is connected to a reservoir bag at end-expiration to rebreathe a standard, commercial breathable gas mixture of 10% helium (He), 20% oxygen, and the remainder nitrogen for 90 seconds. The dilution of He (a nonexchangeable gas) gives a measure of end-expiratory lung volume.[28]

Measurements of static compliance or "elastic recoil of the lung" require breath holds and have applications only to the anesthetized patient. So-called *pressure-volume curves* are generated in the relaxed patient during lung deflation from total lung capacity (TLC), using an esophageal balloon technique. Compliance is defined as the lung volume change per unit of pressure change[27]:

$$\text{Compliance} = \Delta V / \Delta P$$

Reduced lung compliance (i.e., increased lung stiffness) may be associated with increased fibrous tissue (pulmonary fibrosis), atelectasis (e.g., underventilated lung), or an increased pulmonary venous pressure, in which the lung becomes engorged with blood. Emphysema and normal aging of the lung, which leads to alteration in elastic tissue, are causes of increased lung compliance.[27]

In contrast to static tests, tests that are performed with the respiratory system in motion (e.g., during quiet breathing) are referred to as *dynamic*. An example of a dynamic measurement is resistance, a measurement that requires flow. Resistance arises from friction of air molecules against airway walls (see formula[26]).

$$\text{Resistance} = \frac{\text{Change in pressure } (\Delta P)}{\text{Change in flow } (\Delta V)}$$

The measurement of pulmonary resistance (R_L) using a flow meter attached to a face mask and an esophageal balloon catheter to measure transpulmonary pressure changes is conventional in the horse but is rarely used in

the clinical setting.[26] This technique allows computation of both R_L and dynamic compliance (C_{dyn}) at spontaneous breathing frequencies. Maximal transpulmonary pressure change ($\Delta P_{PL_{max}}$) and R_L both increase in cases of obstructive airway disease, whereas C_{dyn} decreases. However, this classic technique is fairly insensitive in detecting subclinical disease[29,30] and has greater utility in the diagnosis of IAD if coupled with a challenge test (i.e., histamine bronchoprovocation [see later]).[31,32]

31.4.2 Forced Oscillation Techniques

In contrast to the conventional methods, noninvasive measurements of total respiratory system resistance via forced oscillation techniques (FOT) are used in the diagnosis of IAD in horses. In short, oscillometry is the study of lung mechanical function via the application of external forces to the respiratory system.[33] Either a loudspeaker (e.g., Impulse Oscillometry System [IOS]) or air pressure (e.g., Monofrequency Forced Oscillatory Mechanics [FOM]) is used to superimpose pulses of flow (4 to 5 L/sec peak) through a face mask on the horse's respiratory system during spontaneous breathing. The generated reciprocal pressure waves are subsequently recorded at the airway opening (i.e., face mask). The magnitude and phase relationship between the input of flow and output of pressure are then used to perform the calculations of impedance (total opposition to airflow) and its components, resistance and reactance, at a variety of oscillatory frequencies (generally 1 to 7 Hz).[26] In most horses with IAD there is a frequency dependence of resistance, with higher values for resistance recorded at the lower oscillatory frequencies (1 to 2 Hz), indicative of bronchoconstriction.[34–36] Higher frequencies (≥2 Hz) provide information concerning central airway resistance (R_{aw}). Baseline respiratory resistance measurements using FOT are commonly combined with bronchoprovocation tests for the early diagnosis of IAD (see later).

31.4.3 Histamine Bronchoprovocation

Bronchoprovocation is a challenge test that assesses the response of the respiratory system to a bronchoconstrictor agonist (e.g., inhaled histamine).[26] The provocatory concentration necessary to cause a 100% increase in baseline respiratory system resistance is commonly termed $PC100_{RRS}$. Horses with a low $PC100_{RRS}$ (e.g., less than 6 mg/mL of histamine) are designated as having hyperreactive airways. Airway hyperreactivity (AHR) is an exaggerated narrowing response to a bronchoconstrictive stimulus, was first found in horses with heaves,[37] and is considered a hallmark of IAD. There is a correlation between airway reactivity and mast cell percentage in BAL fluid (BALF) in horses with a history of exercise intolerance.[38] The clinical symptoms associated with AHR are thought to include coughing (increased sensitivity) and exercise intolerance, whereas bronchoconstriction causes uneven ventilation and hypoxemia.[39]

31.4.4 Respiratory Inductive Plethysmography

The objective assessment of respiratory function and breathing pattern may also be obtained through the concurrent application of respiratory inductive plethysmography (RIP) and pneumotachography, which has been validated for the use in humans,[40,41] horses,[42] and sheep.[43] In summary, two elastic bands, each containing a single sinusoidal conducting wire, are temporarily placed around the animal's thorax and abdomen (Fig. 31-4). Stretch and contraction of the bands resulting from normal respiratory movements are measured as voltage changes, which are proportional to the change in circumference and volume of the thorax and abdomen.[44] Simultaneous measurements of nasal flow are obtained at the airway opening (face mask). This technique rapidly assesses the synchronicity of breathing pattern (e.g., thoracoabdominal asynchrony due to diaphragmatic

paralysis)[44] and the individual contribution of the thorax and abdomen to respiration. It further quantifies changes in flow resulting from airway obstruction.

31.4.5 Forced Maneuvers

Forced expiratory maneuvers are commonly performed in humans with suspected asthma. Simplistically, the patient is asked to blow out hard from TLC until the lung is empty. The volume of air expelled in 1 sec (FEV_1) corrected for vital capacity (FVC) is used as a measure of lower airway obstruction.[26] Couetil adapted the method of forced maneuvers for routine clinical application in heavily sedated, nasotracheally intubated horses.[45] He further demonstrated flow limitation in horses with early signs of obstructive airway disease (IAD) that was worse in animals with heaves. Remission from heaves showed improvement in flow limitation.[26]

Fig. 31-4 Inductance plethysmography being performed in a horse. Courtesy Dr. Andrew Van Eps, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.

PFT is considered instrumental in the understanding of the pathogenesis, pathophysiology, epidemiology, diagnosis, and treatment of lung disease in the horse.[26] The described tests are aimed at quantifying airway obstruction, airway reactivity, and lung stiffness in the clinical setting. PFT will thus facilitate the diagnosis of

subclinical disease and improve the clinician's assessment with regard to aggressive management of lung disease, decisions for ventilation, intensity of monitoring, and assessment of treatment response and prognosis.

31.5 EQUINE RESPIRATORY SYSTEM

PAMELA A. WILKINS, Consulting Editor

31.6 DISORDERS OF THE LUNGS

31.6.1 BACTERIAL PNEUMONIA AND PLEUROPNEUMONIA IN ADULT HORSES

STEEVE GIGUÈRE

Bacterial infections of the lower respiratory tract are common in adult horses. Lower respiratory tract infections may be localized to the lumen of the airways (termed *bacterial bronchitis* or *septic inflammatory airway disease*) or may involve the pulmonary parenchyma (termed *pneumonia*). In equine medicine the term *bronchopneumonia* is often used to refer to lower respiratory tract infection regardless of whether the infection is localized to the bronchi or involves both the bronchi and the lung parenchyma. When there is subsequent extension of the infection from the pulmonary parenchyma to the visceral pleura and pleural space, the disease is referred to as *pleuropneumonia*. The spectrum of clinical signs shown by horses with bronchopneumonia is broad and reflects the severity of the disease process. Early identification of affected animals and immediate initiation of appropriate therapy are essential to prevent mortality and functional impairment of the respiratory system. Expenses incurred by owners of affected horses include cost of medical care, loss of income during the illness and the recovery period, cost of training after a prolonged period of inactivity, and financial loss resulting from death of some animals or diminished performance of others after recovery.

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31.6.2 Infectious Agents Involved

Adult horses most commonly acquire bacterial pneumonia by aspiration of microorganisms that normally inhabit their nasopharynx or oral cavity.[46,47] β-hemolytic streptococci, particularly *Streptococcus equi* subsp. *zooepidemicus*, are by far the most common bacterial pathogens isolated from adult horses with bronchopneumonia.[48] Nonenteric gram-negative bacteria such as *Pasteurella* species and *Actinobacillus* species are also frequently isolated, either alone or in combination with *S. zooepidemicus*. Enteric gram-negative bacteria such as *Klebsiella* species*, Escherichia coli, Enterobacter* species, and *Salmonella enterica* may also be isolated. Other aerobic gram-positive organisms such as *Staphylococcus* species and *R. equi* or gram-negative organisms such as *Pseudomonas* species and *Bordetella bronchiseptica* are occasionally isolated. *Pseudomonas* species are rarely a primary cause of pneumonia in horses, and their presence often reflects contamination of equipment used for taking airway samples (such as endoscopes). *Streptococcus pneumoniae*, a common pathogen of humans, has been positively correlated with lower airway inflammation in young thoroughbred racehorses in the United Kingdom.[49] The microorganism can also induce pneumonia in ponies after heavy intrabronchial challenge.[50] However, *S. pneumoniae* is rarely isolated from pneumonic horses in the United States.

Anaerobic bacteria are isolated from approximately one third of adult horses with severe bronchopneumonia, pleuropneumonia, or pulmonary abscessation. The most common anaerobes isolated are *Bacteroides* species., particularly *Bacteroides fragilis, Clostridium* species, and *Peptostreptococcus* species; *Fusobacterium* and *Eubacterium* species may also be isolated.[48,51] Isolation of anaerobes from horses with pneumonia or

pleuropneumonia has been associated with a less favorable prognosis in some studies. In one study the survival rate for 221 pneumonic horses with strictly aerobic isolates from tracheobronchial aspirates was 81.4% compared with 38.3% for the 81 horses in which anaerobes were cultured.[48] Mixed bacterial infections are very common and may represent synergy between aerobic or facultative aerobic and anaerobic bacteria.

The importance of *Mycoplasma* species in the development of equine bronchopneumonia and pleuropneumonia is controversial. Several *Mycoplasma* species have been isolated from the respiratory tract of both diseased and healthy horses, with *Mycoplasma felis* and *Mycoplasma equirhinis* being the most common isolates. In one study, isolation of *M. equirhinis* was positively correlated with lower airway inflammation in a group of young thoroughbred racehorses in the United Kingdom,[52] whereas isolation of *Mycoplasma* species was not significantly associated with disease in a similar population in Australia.[53] An outbreak of lower respiratory tract disease caused by *M. felis* infection has been described.[54] *M. felis* has also been isolated from horses with pleuropneumonia, and at least in one instance experimental infection with *M. felis* has resulted in pleuropneumonia.[55,56]

31.6.3 Epidemiology

Bacterial bronchopneumonia may affect horses of any age and breed. In one retrospective study of 327 horses with pneumonia or pleuropneumonia, there was no sex predilection but 82% of the horses were less than 5 years of age.[48] In a retrospective case-control study of risk factors for development of pleuropneumonia, thoroughbreds were at greater risk whereas standardbreds were at lower risk for developing the disease.[57] In the same study the most significant risk factor for development of pleuropneumonia was long-distance transport within the week before the onset of clinical signs.[57] In another study, 24.4% of 90 horses with pleuropneumonia had recently been transported over long distances, and 12.2% had recently undergone general anesthesia.[58] Five of the postsurgical cases had undergone upper airway surgery.[58] Whether these horses had preexisting lung disease or whether they developed aspiration pneumonia as a result of surgery and general anesthesia could not be ascertained.

Other factors significantly associated with increased risk of developing pleuropneumonia include recent viral respiratory tract infection or exposure to horses with viral infections and racing within 48 hours before developing clinical signs.[57] One study in the United Kingdom identified a higher incidence of pneumonia and pleuropneumonia in show jumpers, presumably reflecting the greater distance over which these horses are transported compared with racehorses in that country.[59]

31.6.4 Pathophysiology

Colonization of the lungs by opportunistic bacteria occurs when the pulmonary defense mechanisms are compromised or are overwhelmed by massive numbers of bacteria. Several factors can contribute to causing increased numbers of bacteria in the lower airways. Dysphagia or esophageal obstruction will lead to aspiration of large numbers of pharyngeal bacteria, and these disease processes often result in pneumonia. However, the vast majority of horses with bacterial pneumonia or pleuropneumonia do not have a history of dysphagia or esophageal obstruction. Other factors that have been shown to significantly increase bacterial contamination of the lower respiratory tract include confinement with the head elevated, transportation, and high-intensity exercise.[60–62] In one study, confinement of horses with the head elevated resulted in a significant increase in bacterial numbers as well as neutrophilic inflammation in the lower respiratory tract as early as 6 hours after

initiation of confinement.[61] *Actinobacillus* species, *Pasteurella* species, and β-hemolytic streptococci were the predominant bacterial isolates. Lowering the head for 30 minutes every 6 hours to facilitate postural drainage during a 24-hour confinement did not prevent multiplication of bacteria.[61] Clearance of accumulated secretions and bacteria occurred within 8 to 12 hours after release from confinement.[61] In similar confinement experiments, pretreatment with penicillin considerably reduced the number of β-hemolytic streptococci but did not reliably reduce total bacterial numbers.[63] Cilia of many other species such as dogs and humans can transport mucus effectively against gravity, and posture has no effect on tracheal mucociliary transport in these species.[64,65] In contrast, periods of lowered head posture are absolutely essential for normal mucociliary clearance in horses.[66]

In one study, long-distance transport by road over 12 hours resulted in increased bacterial contamination and neutrophilic inflammation in tracheal aspirate fluid when the horses' head were restrained in an elevated position.[67] This is in contrast to another study in which there was no significant cytologic or bacteriologic change in BALF from mares whose heads not restrained in an elevated position during transportation for 12 hours.[68] Collectively, these findings suggest that duration of time with a raised head position is more important than the stress of transport alone in development of airway colonization. Finally, the last factor shown to increase bacterial contamination of the large airways of horses is exercise. In one study a single bout of high-intensity exercise resulted in a tenfold increase in aerobic and a hundredfold increase in anaerobic bacterial counts in tracheal aspirate samples compared with preexercise values.[60]

Pulmonary defense mechanisms can be compromised by numerous factors. These include stress (e.g., transport and intense exercise), viral infections, malnutrition, exposure to dust or noxious gases, immunosuppressive therapy, immunodeficiency disorders, and general anesthesia. Infections with influenza virus and EHV-4 have been shown to significantly decrease mucociliary clearance for up to approximately 30 days after infection in horses.[69] In one study, long-distance transportation resulted in a significant reduction in phagocytosis by peripheral blood neutrophils for approximately 36 hours after transportation.[67] The effect of long-distance transport on number, viability, and function of cells in BALF has given conflicting results with no clear pattern emerging.[68,70–72] Similarly, the effects of exercise on the immune system are complex and depend on a multitude of factors including the intensity or duration of exercise, the specific immune function being analyzed, and the timing of the measurement in relation to exercise. In general, moderate exercise enhances immune function whereas strenuous exercise tends to be detrimental to immune function.[73] High-intensity exercise in horses leads to a significant decrease in blood neutrophil and bronchoalveolar macrophage phagocytic activity, which may lead to decreased bacterial clearance from the lungs.[74–76] Exercise also affects the adaptive immune system, as lymphocyte proliferation responses and interferon (IFN)-γ production are decreased after high-intensity exercise.[77–79] Strenuous exercise has also been shown to increase susceptibility to experimental influenza virus infection in ponies compared with rested animals, indicating that alterations of the immune function after exercise is a real phenomenon and not just an in vitro artifact.[77]

Regardless of the exact mechanism predisposing to bacterial colonization, the inflammatory response induced by bacterial invasion results in infiltration of neutrophils and other inflammatory cells into the airways and pulmonary parenchyma. Inflammatory cells and their mediators cause damage to the airway epithelium and capillary endothelium, leading to flooding of the terminal airways with inflammatory cells, serum cellular debris, and fibrin. This process is generally more severe in the ventral portions of the lung. In early stages the lungs may be simply edematous, reflecting inflammation and early exudation, whereas in chronic severe cases the airways may be filled with purulent material and necrotic debris. Affected areas may show various degrees of consolidation, although in some cases focal abscesses may develop. These lesions interfere with gas exchange,

and if the condition is severe enough the resulting ventilation-perfusion mismatch leads to hypoxemia and clinical signs of respiratory disease.

In severely affected animals, inflammation extends to the pleural space. The first stage of bacterial pleuropneumonia is an exudative stage, which is characterized by rapid outpouring of sterile pleural fluid into the pleural space in response to inflammation of the pleura. The associated pneumonic process is usually contiguous with the visceral pleura and results in increased permeability of the capillaries in the visceral pleura. If appropriate antimicrobial therapy is initiated at this stage, the pleural effusion may not become septic and may resolve. With progression, the bacteria invade the pleural fluid from the contiguous pneumonic process and the second, fibropurulent, stage evolves. This stage is characterized by the accumulation of large amounts of pleural fluid with many degenerate neutrophils, bacteria, and cellular debris. Fibrin is deposited in a continuous sheet covering both the visceral and parietal pleura adjacent to affected areas. As this stage progresses, there is often loculation and formation of limiting membranes. These loculations prevent dissemination of the infection but make drainage of the pleural space with chest tubes increasingly difficult. The last stage is the organization stage, in which fibroblasts grow into the exudate from both the visceral and parietal pleura surfaces and produce the membrane called the *pleural peel*. This inelastic pleural peel encases the lung and renders it virtually functionless. At this stage the exudate is generally thick.

31.6.5 Clinical Signs and Physical Examination

The spectrum of clinical signs shown by horses with bacterial lung infection is broad and usually reflects the severity of the disease process. Horses with septic IAD and no or minimal involvement of the lung parenchyma may be completely normal at rest. Clinical signs may be limited to exercise intolerance and poor performance, or affected horses may cough or have bilateral nasal discharge during or immediately after exercise. Even in cases of early bronchopneumonia, clinical signs may not be obvious. As the disease progresses clinical signs may include any combination of fever, anorexia, depression, bilateral nasal discharge, cough, weight loss, tachypnea, and respiratory distress. Nasal discharge is usually mucopurulent but may be hemorrhagic in some cases with pulmonary infarction and necrotizing pneumonia.[80] Halitosis and a foul-smelling nasal discharge may be present and has been associated with infection by anaerobic bacteria. However, the absence of a putrid odor does not rule out anaerobic infections.

Because the parietal pleura are highly innervated and painful when inflamed, horses with acute pleuropneumonia often exhibit pleurodynia (pleural pain). Pleurodynia can often be detected by applying digital pressure to the intercostal space, resulting in grunts, intercostal muscle spasm, or even escape maneuvers by the patient when pain is present. Pleurodynia may also be manifested as pawing, stiff forelimb gait, abducted elbows, and reluctance to move. The condition may easily be mistaken for colic, exertional rhabdomyolysis, or laminitis. As more fluid accumulates in the pleural space and the disease becomes chronic, pain is less evident. A plaque of sternal edema is a common clinical finding in horses with pleuropneumonia. This is not a specific finding, as it can occur with many other disease processes.

Careful auscultation after application of a rebreathing bag (if not precluded by respiratory distress) is extremely valuable in defining the presence and sometimes extent of lung involvement. Horses with a large amount of secretions in the trachea often have an audible tracheal rattle. Most horses with bronchopneumonia cough when the rebreathing bag is applied, whereas normal horses do not. Occasional inspiratory or expiratory crackles and/or wheezes may be heard over affected areas, which are more commonly located ventrally. Because consolidated lung parenchyma is a good acoustic medium, mild consolidation sometimes results in only increased bronchial sounds. In contrast, the lung sounds may be diminished in areas of severe consolidation, extensive abscess formation, or pleural effusion.

Auscultation of horses with pleuropneumonia reveals normal lung sounds in the dorsal lung fields with no or considerably decreased lung sounds ventrally. Pleural friction rubs are often not heard because they are present only in the acute stage of the disease. If they are heard, friction rubs are present predominantly at the end of inspiration and the early part of expiration. They disappear as inflammation decreases or as pleural fluids accumulate. Cardiac sounds are often heard over a wider area of the chest than normal, probably as a result of enhanced conduction of sound through the pleural fluid. Thoracic percussion is useful to detect and delineate pleural effusion with resonant sounds dorsal and dull sounds ventral to the horizontal line of effusion.

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31.6.6 Differential Diagnosis

When physical examination and auscultation indicate pulmonary disease, the major clinical task is differentiating infectious from noninfectious causes. Among infectious causes, bacterial pneumonia is most common. Viral infections are usually confined to the upper respiratory tract. Pulmonary aspergillosis most often follows severe gastrointestinal (GI) disease that resulted in mucosal compromise. Severe respiratory disease unresponsive to antimicrobial therapy should arouse suspicion of fungal pneumonia.[81] Parasitic pneumonitis is rare in adult horses but may be seen in horses pastured with donkeys or mules. The two major noninfectious causes of pulmonary disease that may be confused with bacterial pneumonia include heaves and nonseptic IAD. Other uncommon causes of noninfectious pulmonary disease that may result in similar clinical signs include pneumothorax, pulmonary edema, smoke inhalation, neoplasia, and idiopathic interstitial pneumonia. The diagnostic tests described in the following sections aid in the differentiation between infectious and noninfectious causes of lower respiratory tract disease.

When pleural effusion is present, several differential diagnoses should be considered. Bacterial pleuropneumonia is by far the most common cause of pleural effusion in horses. In one study, 90 of 122 horses (73.8%) with pleural effusion had pleuritis secondary to bacterial pneumonia or lung abscessation.[58] Other, less common causes of pleural effusion in horses include hemothorax, penetrating chest wounds, esophageal ulceration or rupture, neoplasia, fungal pneumonia, pericarditis, congestive heart failure, diaphragmatic hernia, hypoproteinemia, and chylothorax.

31.6.7 Diagnostic Approach

Presumptive diagnosis of lower respiratory tract infection is generally based on clinical signs and careful auscultation of the lungs with a rebreathing bag. The need for additional diagnostic procedures is determined by the severity and duration of clinical signs, the number of affected animals, and the value of the affected animal(s), as well as prior treatment used and response to such therapy. Bacterial pneumonia or pleuropneumonia most commonly affects an individual horse on a given farm. In horses suspected of having bacterial pneumonia, the goal of diagnostic evaluation is to rule out diseases of the upper respiratory tract and to determine the cause and severity of lung involvement.

31.6.7.1 HEMATOLOGY AND BIOCHEMISTRY

Horses with bacterial bronchopneumonia commonly have an inflammatory hematologic profile. Leukocytosis and absolute neutrophilia with or without a left shift are supportive of a diagnosis of bacterial infection. Neutropenia with a toxic left shift may also be evident in the acute stages in severely affected animals. Increased fibrinogen concentrations, hyperglobulinemia, and mild hypoalbuminemia are common. Anemia of chronic inflammation may develop in chronically affected animals. There does not seem to be a good

correlation between the severity of clinical signs and the presence or the magnitude of hematologic changes. When plasma fibrinogen concentrations are elevated, their sequential measurement provides a useful means of monitoring response to treatment and is a useful guide in the decision to discontinue treatment. It must be remembered that a normal hematologic profile does not rule out bacterial bronchopneumonia.

31.6.7.2 ENDOSCOPY

Endoscopy may be useful to rule out upper airway infection when physical examination and auscultation of the lungs are not conclusive. Presence of mucopurulent secretions in the trachea and bronchi confirms lower respiratory tract disease. However, the presence of mucopurulent secretions does not necessarily indicate a bacterial infection, as this is also a common finding in horses with heaves and horses with nonseptic IAD. Bronchoscopy may also be useful in locating the affected lung segment in horses with focal pneumonia or draining pulmonary abscesses. It should be noted that exploration of the trachea and lower airways via bronchoscopy may contaminate subsequent samples taken for culture.

31.6.7.3 TRACHEOBRONCHIAL ASPIRATION FOR CYTOLOGY AND CULTURE

TBA for cytologic examination and bacterial culture is one of the most helpful diagnostic procedures available when bronchopneumonia is suspected. BAL is not as useful as tracheobronchial aspiration in cases of bronchopneumonia, because with BAL only a small portion of a lung is sampled. In contrast to BAL, TBA yields a pooled sample of secretions from all portions of the lung, thus increasing chances of culturing the pathogen of interest. In one study involving 22 horses diagnosed with pneumonia or pleuropneumonia based on thoracic radiographs or ultrasonography, cytology of BAL was abnormal in only 10 horses despite attempts at selectively sampling the affected area.[82] In contrast, all horses had evidence of septic inflammation based on tracheobronchial aspirate cytology.[82] Whenever possible, antimicrobial therapy should be discontinued at least 24 hours before tracheobronchial aspiration is performed. Tracheobronchial aspirate is preferably obtained by sterile percutaneous transtracheal aspiration to avoid contamination from the upper airway. Alternatively, the sample can be collected with a sterile guarded aspiration catheter passed through the biopsy channel of a flexible endoscope.[83,84] Endoscopy has the advantage of allowing selective aspiration of exudate when it is present, which may therefore enhance recovery of bacteria. However, bacterial contamination of nasal or pharyngeal origin more commonly occurs in tracheobronchial aspirate samples collected via endoscopy. Airway fluid specimens should be submitted for cytology and Gram stain, as well as for aerobic and anaerobic bacterial culture. The fluid used for anaerobic cultures should be transferred to the laboratory immediately after collection in a manner that prevents or minimizes exposure to air. Anaerobic transport media are commercially available and should be routinely used. Specimens submitted for isolation of anaerobes should not be refrigerated, because many anaerobes are intolerant to cold. In horses with pleural effusion, a tracheobronchial aspirate should be obtained even if pleural fluid is available for bacterial culture. In one study, culture of the pleural fluid was negative in 43% of 111 horses with pleuropneumonia, whereas tracheobronchial fluid yielded growth in all cases.[48] Only approximately 5% of cases had growth from the pleural fluid but not from the tracheobronchial aspirate.[48]

Macrophages and columnar ciliated epithelial cells predominate in tracheobronchial aspirates from healthy horses. The percentage of neutrophils in tracheobronchial aspirates from apparently healthy horses can be quite variable. In one study approximately 75% of apparently healthy thoroughbred racehorses in training had less than 20% well-preserved neutrophils.[85] Occasionally plant spores and fungal hyphae may be present, either free or in large mononuclear cells. Their presence does not necessarily indicate fungal infection and

probably reflects the horse's environment. Degenerated neutrophils displaying karyolysis and cytoplasmic vacuolization are the predominant cell type in horses with bacterial lower respiratory tract infections. Bacteria may be found intracellularly or extracellularly. Presence of squamous epithelial cells indicates contamination with the upper respiratory tract or pharynx and is more common in samples obtained via the endoscope. The trachea is not a perfectly sterile site, and potentially pathogenic bacteria can be isolated from the trachea of normal horses.[83] Therefore culture results should always be interpreted in the context of clinical signs and cytologic examination. If small numbers of bacteria are cultured in the absence of cytologic evidence of sepsis, it is unlikely that they are the cause of the respiratory problem. Similarly, growth of various molds is common in tracheobronchial aspirate cultures, and the clinical signs and cytologic findings should be considered before treatment with antifungal agents is initiated.

31.6.7.4

THORACIC ULTRASONOGRAPHY

Thoracic ultrasonography can be performed using a range of transducers and machine types. The normal aerated lung parenchyma is not penetrated by the ultrasound beam, rendering only the pleural space and superficial lung surface available for study. Ultrasonography is a helpful diagnostic tool when lung involvement includes peripheral areas but may not be as useful as radiography to evaluate the full extent of lung lesions because lesions with overlying aerated lung will not be detected. However, in most horses with bronchopneumonia the periphery of the lung is affected, enabling the clinician to successfully image some of the lesions. Early ultrasonographic lesions are nonspecific and may include only irregularities of the pleural surface. These lesions may progress to form focal areas of consolidation of various sizes. Consolidated lung varies in appearance from dimples of the pleural surface to large wedge-shaped areas of sonolucent lungs (Fig. 31-5).

Ultrasonography offers a considerable advantage over radiographs in the study of the pleural surfaces and space. Small amount of pleural effusion that would otherwise be missed clinically or by radiography can be easily detected by ultrasonography. Ultrasonography can also be used to assess the nature and approximate volume of fluid, to select the optimal site and depth for thoracocentesis, and to detect sequelae such as fibrin deposition, pleural adhesion, abscess formation, and pneumothorax. Pleural effusion appears as hypoechoic to anechoic fluid between the parietal pleural surface and the lungs (Fig. 31-6). The echogenicity of the fluid typically reflects the degree of cellularity. Fibrin appears as filamentous strands floating in the effusion (Fig. 31-7). The presence of small (<1 mm) bright echoes (gas echoes) often indicates anaerobic infections (see Fig. 31-7).[86] Gas echoes may also be seen with gangrenous pneumonia or bronchopleural fistulas, or they may result from leakage of air during thoracocentesis.

Fig. 31-5 Sonogram of the left thorax obtained from a 3-year-old thoroughbred gelding. The ventral aspect of the lung is completely consolidated. Note the liver-like appearance of the wedge-shaped area of the lung. Fluid bronchograms are indicated by an *arrow*.

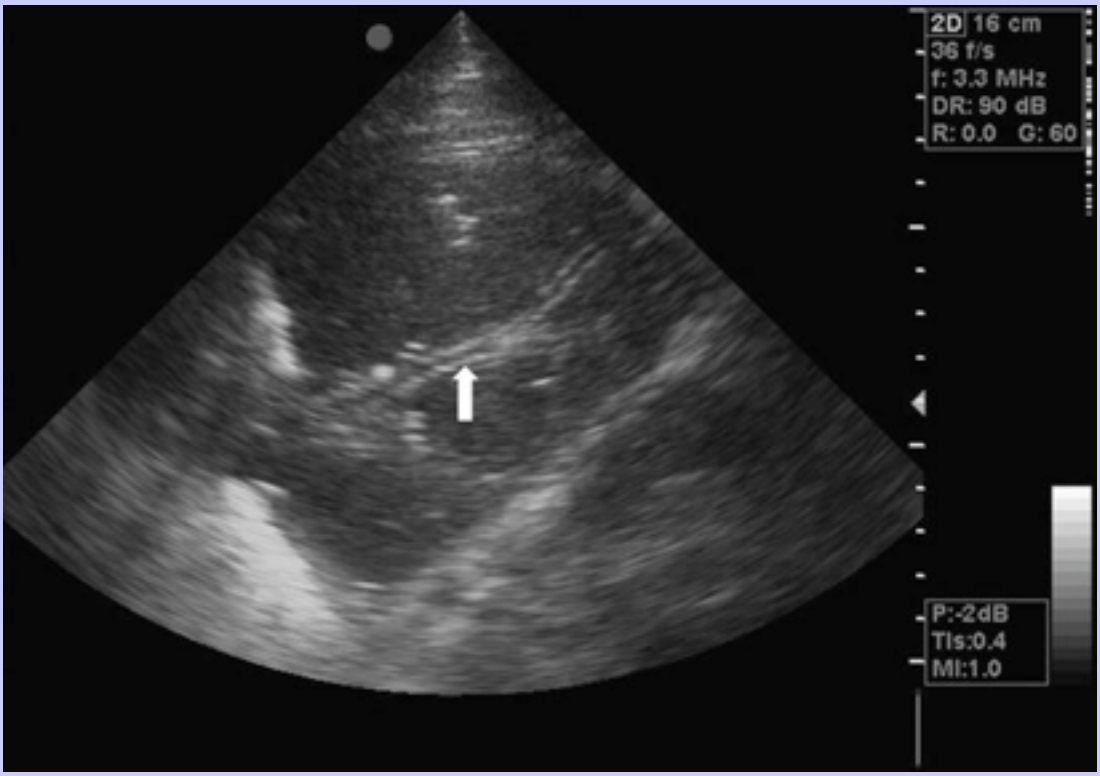


Fig. 31-6 Sonogram of the thorax obtained from a 4-year-old horse with pleuropneumonia. The ventral tip of the lung is atelectatic and covered with fibrin. There are adhesions between the tip of the lung and the diaphragm and chest wall *(arrows)*.

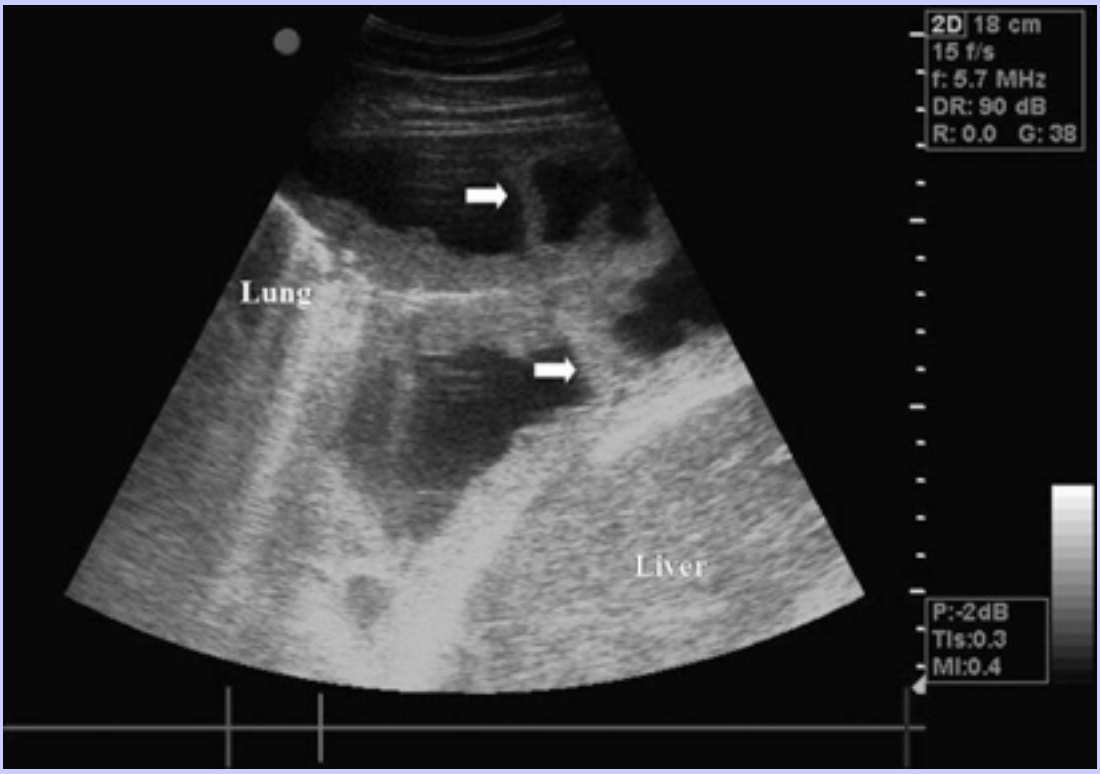
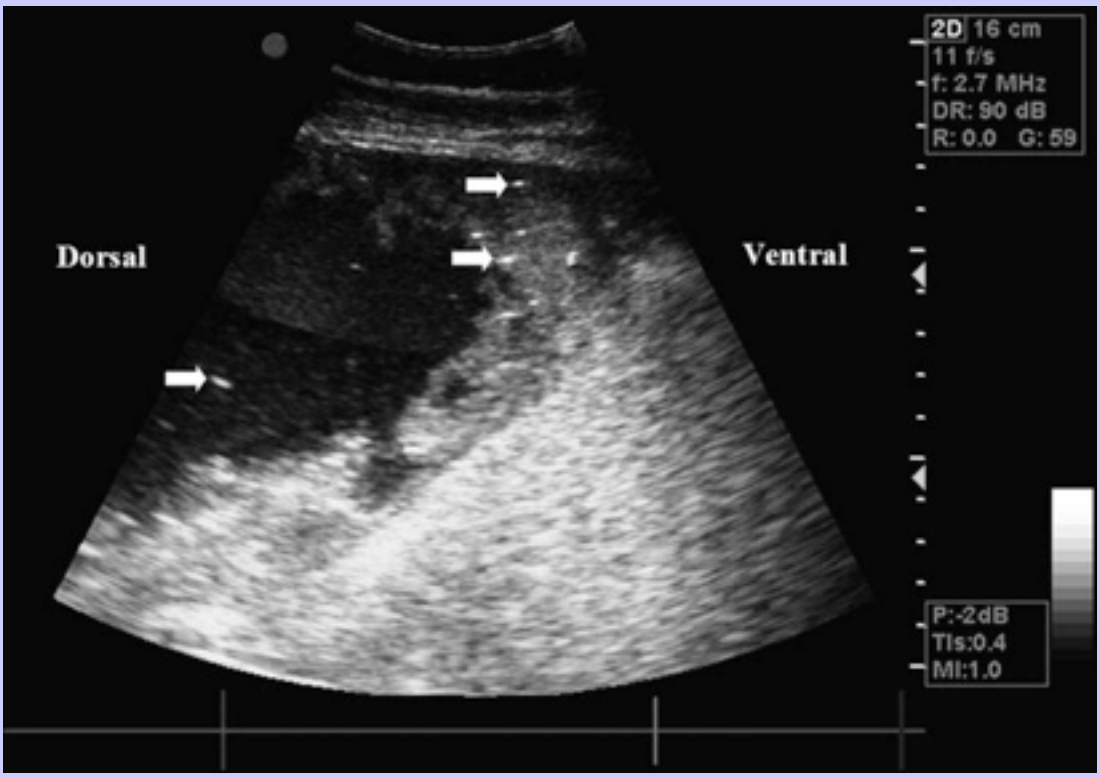


Fig. 31-7 Sonogram of the ventral thorax obtained from a horse being treated for pleuropneumonia. The sonogram shows a pleural abscess filled with fluid dorsally and with hyperechoic material ventrally. There are multiple gas echoes (some indicated by *arrows*). Multiple anaerobes were obtained on culture of an aspirate.



31.6.7.5

RADIOGRAPHY

In horses with mild septic IAD, thoracic radiographs may be normal or may reveal only mild bronchial or bronchointerstitial patterns. In more severely affected animals, radiographs demonstrate irregular opacities in the ventral thorax that may obscure the normal vasculature and cardiac silhouette (Fig. 31-8). Air bronchograms are sometimes visible. Abscesses are often present as circular soft-tissue opacities of varying sizes. In some cases they may be cavitated with thick walls and a distinct horizontal line representing fluid-gas interface (Fig. 31-9). Pleural effusion appears as a horizontal line demarcating a ventral soft-tissue opacity that obscures the heart and ventral lung fields (Fig. 31-10). When severe pleural effusion is present, it is most efficient to perform thoracic radiographs after the pleural fluid has been drained. Although ultrasonography is superior to radiographs in horses with pleuropneumonia, radiography should still be performed when possible to detect and monitor resolution of deep pulmonary abscesses that may be missed during ultrasonography.

31.6.7.6

THORACOCENTESIS FOR CYTOLOGY AND CULTURE

Thoracocentesis should be considered in horses with pleural effusion. The procedure can be of diagnostic value by allowing differentiation of septic pleuritis from effusion caused by other disease processes. It can also be of therapeutic value via removal of excessive chest fluid, which allows pulmonary reexpansion and a reduction in respiratory distress. Thoracocentesis is best performed using ultrasound guidance to determine the most appropriate site. A blunt teat cannula is typically used if a small volume of effusion is being sampled strictly for diagnostic purposes. Depending on the volume of effusion, a 16-, 24-, or 32-French chest tube is used when pleural drainage is also indicated (see later). An aliquot of pleural fluid is placed into tubes containing anticoagulant solution (ethylenediaminetetraacetic acid [EDTA]) so that cytologic evaluation may be performed. Part of the fluid should be saved in sterile containers with appropriate transport media for subsequent Gram stain and aerobic as well as anaerobic bacterial culture.

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Fig. 31-8 Lateral thoracic radiograph of the caudoventral lung field from a 4-year-old thoroughbred mare showing a pronounced alveolar pattern with air bronchograms. The caudal silhouette of the heart is almost completely obscured.

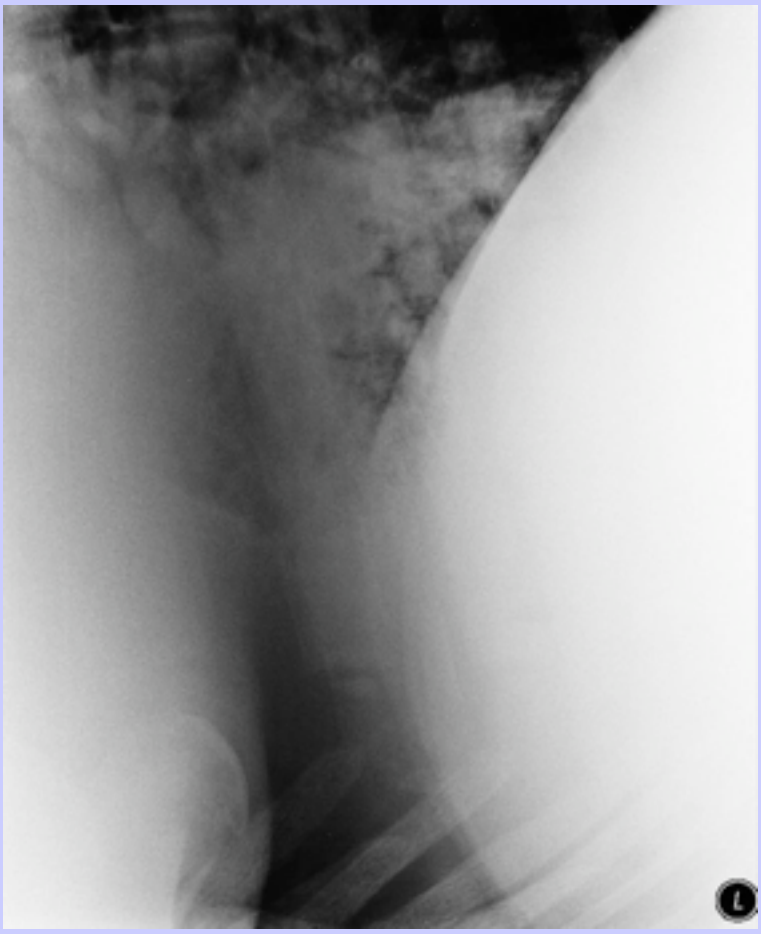


Fig. 31-9 Lateral thoracic radiograph of the caudodorsal lung field from a 3-year-old thoroughbred filly showing two cavitary abscesses with distinct horizontal lines representing fluid-gas interface.

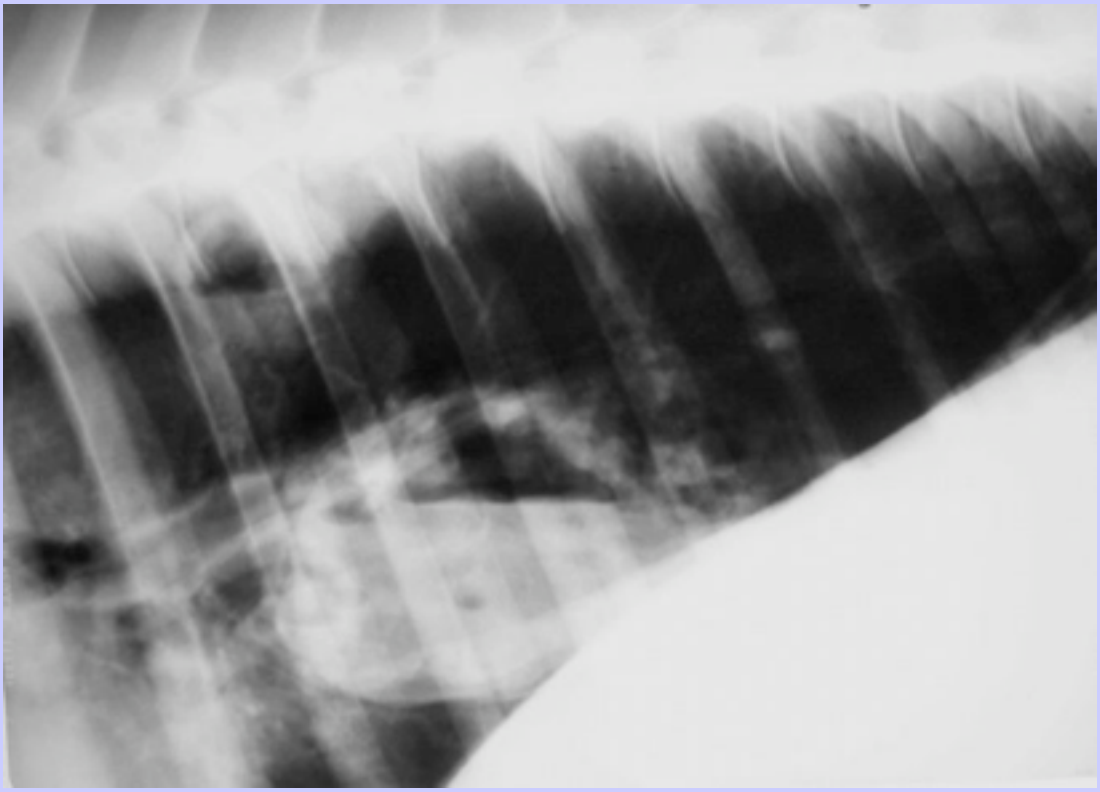
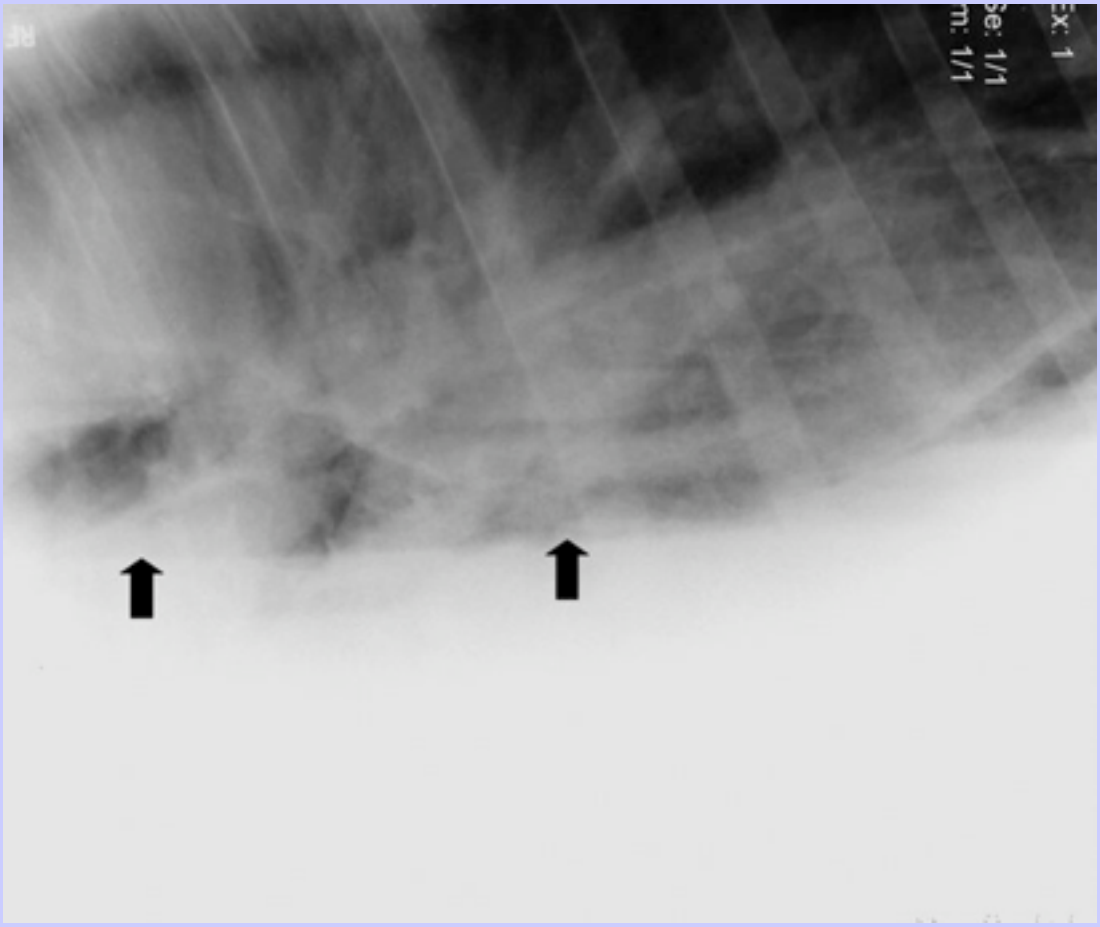


Fig. 31-10 Lateral thoracic radiographs from a four-year-old thoroughbred gelding with pleuropneumonia. There is a large amount of pleural effusion obscuring the ventral lung fields. The dorsal aspect of the fluid line is indicated by *arrows*. An interstitial pattern is noted in the caudodorsal lung fields.



Normal equine pleural fluid is clear to light yellow and odorless. Protein concentration is <3.4 g/dL (range 0.2 to 4.7 g/dL), and nucleated cell count is <8000/µL (range 800 to 12,100/µL) in approximately 95% of apparently healthy horses.[87] In horses with bacterial pleuropneumonia the effusion is typically exudative, cloudy, and yellow to red, with increased nucleated cell count and protein concentration. Such effusion usually contains greater than 90% neutrophils, most of which exhibit degenerative changes. Putrid-smelling pleural fluid is a hallmark of anaerobic infection; however, the absence of odor does not exclude anaerobic infection. There is no association between the WBC count or protein concentration in pleural fluid and survival.

Biochemical analysis of the pleural fluid may also provide a rapid assessment of the likelihood of sepsis, hence the need for pleural drainage. Values for pH, P_{O_2}, P_{CO_2}, bicarbonate, lactate, and glucose in pleural

fluid from horses with nonseptic pleural effusion are similar to those in concurrent venous blood samples.[88] Horses with septic pleural effusion have significantly lower pH, bicarbonate, and glucose in their pleural fluid compared with paired venous blood samples. In contrast, their pleural fluid has a significantly higher P_{CO_2} and lactate concentration.[88] Pleural fluid pH <7.1 and glucose concentration <40 mg/dL are suggestive of septic effusion in horses.[89]

31.6.7.7 THORACOSCOPY

Thoracoscopy is rarely necessary in the initial evaluation of horses with pleuropneumonia. However, the technique may be of diagnostic and therapeutic value in more chronic cases in which pleural abscesses or pleural adhesions develop (see section on treatment).[90]

31.6.8 Treatment

31.6.8.1 SYSTEMIC ANTIMICROBIAL THERAPY

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Administration of appropriate antimicrobial agents is the most important part of the therapeutic plan. The choice of the antimicrobial agent depends on the severity of the clinical signs, cost, ease of administration, and, when available, results of bacteriologic culture and susceptibility testing of a tracheobronchial aspirate. Doses for commonly used antimicrobial agents are presented in Table 31-2. In early cases of mild bronchopneumonia, the practitioner is justified in suspecting *S. zooepidemicus* as the causative organism and treating accordingly. *S. zooepidemicus* is almost invariably susceptible to penicillin, ampicillin, and cephalosporins such as ceftiofur (Table 31-3). The possibility of a mixed infection, especially involving gram-negative organisms, must be kept in mind when such empiric therapy is unsuccessful. Ceftiofur offers the advantage of having a good spectrum of activity against common nonenteric gram-negative pathogens such as *Pasteurella* species and *Actinobacillus* species. Therapy of horses with mild lower respiratory tract infections should be continued for a minimum of 10 days or until clinical signs resolve. In some cases the duration needed may preclude continuous intramuscular (IM) therapy because of muscle soreness. Trimethoprim-sulfonamide (TMS) combinations offer the advantage of oral administration. Unfortunately, the usefulness of TMS combinations for the treatment of bacterial respiratory tract infections in horses is limited by their lack of in vivo activity against *S. zooepidemicus*. In contrast to penicillin, TMS is ineffective in eradicating *S. equi* subsp. *zooepidemicus* in a tissue chamber model of infection in horses.[91,92] This failure of in vivo response was observed despite in vitro susceptibility of the isolate and high concentrations of TMS in the tissue chamber fluid.[91,92]

Table 31-2 Antimicrobial Agents Commonly Used to Treat Bacterial Bronchopneumonia in Adult Horses

Antimicrobial Agents*	Dose	Frequency (h)	Route
β-LACTAMS			
Benzyl Penicillins			
Penicillin G (Na, K)	25,000 IU/kg	6	IV
Penicillin G (procaine)	25,000 IU/kg	12	IM
Aminobenzyl Penicillins			
Ampicillin sodium	20 mg/kg	8	IV
Ampicillin trihydrate	20 mg/kg	12–24	IM
Cephalosporins			
Cefazolin	10–20 mg/kg	6	IV
Ceftiofur	2.2–4.4 mg/kg	12–24	IV or IM
AMINOGLYCOSIDES			
Amikacin	10 mg/kg	24	IV or IM
Gentamicin	6.6 mg/kg	24	IV or IM
FLUOROQUINOLONES			
Ciprofloxacin†	5.5 mg/kg	24	IV
Enrofloxacin†	5.5 mg/kg	24	IV
	7.5 mg/kg	24	PO
TETRACYCLINES			
Oxytetracycline‡	6.6 mg/kg	12	IV
Doxycycline§	10 mg/kg	12	PO
OTHERS			
Chloramphenicol	50 mg/kg	6	PO
Metronidazole	25 mg/kg	12	PO
	35 mg/kg	12	Per rectum
Rifampin	5 mg/kg	12	PO
Trimethoprim-sulfonamide	30 mg/kg (combined)	12	PO

IM, Intramuscular; *IV*, intravenous; *PO*, by mouth.

* Pharmacokinetics data are available for horses, but in most cases safety studies have not been performed in the equine species.

† Should not be used in young growing horses because of the risk of arthropathy.

‡ Dilute and give by slow IV infusion.

§ Administer orally only. IV doxycycline has resulted in severe cardiovascular effects including collapse and death in some horses.

In more severe cases of bronchopneumonia and in all cases of pleuropneumonia, antimicrobial therapy should ultimately be selected based on results of culture and in vitro susceptibility testing. Before these results are obtained, selection should be based on knowledge of the prevalence and susceptibility pattern of bacteria commonly isolated from affected horses (see Table 31-2). Polymicrobial and mixed aerobic and anaerobic infections are common; thus broad-spectrum antimicrobial therapy is initially required. A combination of gentamicin for gram-negative coverage and penicillin for gram-positive and anaerobic coverage is commonly used as initial broad-spectrum therapy for moderate to severe bronchopneumonia. Enrofloxacin can be used as a substitute for gentamicin for gram-negative coverage in adult horses. Advantages of enrofloxacin over gentamicin include greater activity against Enterobacteraceae, better penetration in phagocytic cells and tissues, and better activity in purulent material. However, enrofloxacin should never be used as standalone initial therapy in horses with bronchopneumonia because of its lack of activity against anaerobes and against streptococci such as *S. zooepidemicus*. Ampicillin or cefazolin can replace penicillin for gram-positive coverage and offers the supplementary advantage of providing additional gram-negative coverage.

Treatment of anaerobic pleuropneumonia is usually empiric, because antimicrobial susceptibility testing of anaerobes is difficult owing to their fastidious nutritive and atmospheric requirements. Thus familiarity with antimicrobial susceptibility patterns is helpful in formulating the treatment regimen when an anaerobe is suspected. The majority of anaerobic isolates are susceptible to relatively low concentrations of penicillin. However, *B. fragilis*, a frequently encountered anaerobe in horses with pleuropneumonia, is routinely resistant to penicillin. Other members of the *Bacteroides* family are known to produce β-lactamases and are potentially penicillin resistant. Metronidazole has excellent in vitro activity against a variety of obligate anaerobes including *B. fragilis*. Oral administration rapidly results in adequate serum levels and thus is an acceptable route of administration for horses with pleuropneumonia. Therefore, if anaerobic infection is suspected, oral metronidazole is usually added to the combinations mentioned previously. Malodorous nasal discharge, halitosis, or the presence of gas echo in pleural effusion on ultrasonographic examination suggests the presence of an anaerobic infection. However, the absence of these findings does not rule out anaerobic bacterial infection. Horses with extensive lung consolidation and horses with pleuropneumonia may benefit from adding metronidazole to the treatment regimen. Metronidazole is not effective against aerobes and therefore should always be used in combination therapy. Chloramphenicol is active against most aerobes and anaerobes cultured from horses with bronchopneumonia or pleuropneumonia. However, because of human health concerns, its use should be limited to the treatment of horses with severe anaerobic bacterial infections refractory to metronidazole therapy in countries where its use is allowed. 506 507 Rifampin is bactericidal and active against streptococci and most species of *Bacteroides* and *Clostridium*. It penetrates well into abscesses and may be helpful in anaerobic infections with walled-off abscesses. Rifampin should always be used in combination with another antimicrobial agent to decrease the likelihood of emergence of resistant mutants.

Table 31-3 In Vitro Antimicrobial Susceptibility of Aerobic Bacterial Isolates That Are Commonly Isolated from Horses with Bronchopneumonia or Pleuropneumonia*

Microorganisms (n)	Antimicrobial Agents†														
	GM	AMI	CHL	TMS	TE	RIF	P	AM	TIM	CFZ	CFT	XNL	CPE	ENR	CIP
GRAM-POSITIVE															
Streptococcus zooepidemicus (192)	19	0	100	62	43	98	100	100	100	100	100	98	—	69	—
Staphylococcus aureus (43)	70	86	100	95	78	89	41	41	79	68	68	67‡	68	79	81
Other staphylococci (48)	91	100	97	85	71	97	30	30	—	65	65	85‡	65	94	97
GRAM-NEGATIVE															
Escherichia coli (127)	62	90	72	43	51	—	—	51	73	70	87	69	97	82	83
Klebsiella pneumoniae (52)	88	96	94	79	96	—	—	6	88	90	98	69	98	88	100
Enterobacter species (32)	40	83	41	40	57	—	—	3	43	10	53	34	80	78	80
Pseudomonas aeruginosa (48)	70	97	—	—	—	—	—	—	94	—	15	6	91	65	97
Pasteurella species (40)	94	94	100	91	100	—	—	100	100	94	100	95	100	100	100
Actinobacillus species (31)	100	87	100	93	90	—	—	95	100	100	100	97	100	100	100

AM, Ampicillin; *AMI*, amikacin; *CFT*, cefotaxime; *CFZ*, cefazolin; *CHL*, chloramphenicol; *CIP*, ciprofloxacin; *CPE*, cefepime; *ENR*, enrofloxacin; *GM*, gentamicin; *P*, penicillin; *RIF*, rifampin; *TE*, tetracycline; *TIM*, ticarcillin-clavulanic acid (Timentin); *TMS*, trimethoprim-sulfonamide; *XNL*, ceftiofur.

* Data from the clinical microbiology laboratory, University of Florida (2003–2005). Isolates were obtained from multiple equine clinical specimens including but not restricted to tracheobronchial aspirates and pleural fluid.

† Percent of susceptible isolates (number of susceptible isolates/number of isolates tested × 100).

‡ In vivo, ceftiofur is rapidly metabolized to desfuroylceftiofur. Desfuroylceftiofur is as effective as ceftiofur against most bacterial pathogens but most coagulase positive *Staphylococcus* species are resistant. Therefore, despite in vitro susceptibility, ceftiofur is not the ideal choice for the treatment staphylococcal infections.

—Not tested or testing not warranted.

In cases of severe bronchopneumonia, lung abscesses, or pleuropneumonia, long-term antimicrobial therapy ranging from 3 weeks to sometimes several months may be required. In the initial stages of therapy IV antimicrobials are preferred to achieve higher serum concentrations. Oral antimicrobial agents can be used later in the course of the disease if appropriate based on susceptibility testing. Clinical signs, lung auscultation, fibrinogen concentrations, and repeated ultrasonographic and radiographic examination are useful in assessing response to therapy and deciding when to discontinue antimicrobial therapy. Stall rest must be enforced during therapy of pneumonia, and return to exercise should be gradual and permitted only after the horse is clinically normal and antibiotic therapy has been completed.

31.6.8.2

AEROSOLIZED ANTIMICROBIAL AGENTS

Aerosolized antimicrobial agents may be a useful adjunct to oral or systemic administration, particularly in horses with chronic septic IAD and no or minimal involvement of the lung parenchyma. The rate and extent of penetration of a drug into most sites outside the vascular space such as lung tissue are determined by the drug's concentration in plasma, molecular charge and size, extent of plasma protein binding, and blood flow.[93] In other tissues such as the central nervous system (CNS) and the eye, a lipid membrane provides a barrier to drug diffusion.[93] There is a similar barrier between blood and the bronchial epithelium, restricting penetration of some drugs into bronchial secretions and epithelial lining fluid of the lower airways.[94] Aerosol administration of antimicrobial agents can result in high drug concentrations in the respiratory tract while minimizing systemic concentrations and their resulting toxicity.

Antimicrobial delivery by inhalation is greatly influenced by the product formulation and type of nebulizer. Aerosol use of IV formulations can lead to exposure to potentially irritant or toxic additives and inappropriate pH or osmolality ranges. In one study the particle size distribution and particle density of gentamicin sulfate and ceftiofur sodium aerosols were affected by the antimicrobial concentration of the solution.[95] Gentamicin concentrations of 50 mg/mL or ceftiofur concentrations of 25 mg/mL produced the optimal combinations of particle size and aerosol density with the use of a medical ultrasonic nebulizer.[95] In healthy horses, aerosolization of 20 mL of the commercially available IV gentamicin sulfate solution (diluted to 50 mg/mL) using an ultrasonic nebulizer resulted in bronchial lavage fluid concentrations approximately 12 times higher than concentrations achieved by IV administration at a dose of 6.6 mg/kg.[96] In the same study, serum concentrations after aerosol administration were below 1 μg/mL at all times.[96] Once-daily aerosol administration of gentamicin to healthy horses for 7 consecutive days did not result in pulmonary inflammation or drug accumulation in the respiratory tract.[97] The major limitation to the use of aerosolized gentamicin in horses is its lack of activity against *S. zooepidemicus*, the most common bacterial pathogen of the equine respiratory tract. Additional studies are required to assess the efficacy of aerosolized antimicrobial agents for the treatment of bacterial respiratory tract infections in horses.

31.6.8.3

ANCILLARY TREATMENTS

The need for ancillary treatments depends on the severity of the disease and is most often necessary in horses with pleuropneumonia. Nonsteroidal antiinflammatory drugs (NSAIDs) such as flunixin meglumine (1 mg/kg IV or by mouth [PO] once or twice daily) or phenylbutazone (2.2 mg/kg IV or PO once or twice daily) may be beneficial to minimize inflammation, provide analgesia, and control high fevers. Additional analgesia may be

necessary in horses with severe pleurodynia. Adequate hydration should be maintained in patients receiving these agents for extended periods, especially if aminoglycosides are used concurrently. IV fluid therapy may be necessary to correct hypovolemia in acute stages, but it is rarely required in chronic cases. Intrapharyngeal insufflation of oxygen is indicated in horses that remain severely hypoxemic despite adequate drainage of the pleural cavity. Adequate parenteral or preferably enteral nutritional support via a nasogastric tube (NGT) is beneficial in horses that remain anorectic for several days. In horses presented with severe systemic illness, additional therapies aimed at treating endotoxemia may be beneficial (see section on endotoxemia).

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31.6.8.4

PLEURAL DRAINAGE

Small amounts of pleural effusion may be resorbed quite readily with appropriate antimicrobial therapy. Therefore although a small sample of pleural fluid is diagnostically useful, pleural drainage is not necessarily indicated in all cases of pleuropneumonia. Drainage of pleural effusion results in removal of exudate and debris and allows for reexpansion of the lungs. Indications for drainage include a poor response to conservative therapy or the presence of pleural fluid with at least one of the following characteristics: sufficient volume to cause respiratory distress, empyematous character, fetid odor, or cytologic or biochemical evidence of sepsis. If indicated, the procedure should be attempted as early as possible before deposition of fibrin results in loculations and impairs drainage. The ventral mediastinum is perforated in normal horses in such a way that the left and right pleural spaces communicate. During severe inflammation the small perforations in the ventral mediastinum may be become obstructed by fibrin. Therefore, depending on the severity of the inflammatory response present, draining one side of the thorax may or may not be sufficient to resolve bilateral pleural effusion. Repeat ultrasonography of the opposite hemithorax should always be performed before the placement of a chest tube to determine if draining one side has actually emptied both sides of the thorax. Pleural drainage is best performed using ultrasound guidance to determine the most appropriate site. Pleural drainage can be accomplished either with intermittent thoracocentesis or indwelling chest tubes. Thoracocentesis is easily accomplished in the field and may not need to be repeated unless considerable pleural effusion reaccumulates. Indwelling chest tubes are indicated when continued pleural fluid accumulation makes intermittent thoracocentesis impractical. If properly placed and managed, indwelling tubes provide a method for frequent fluid removal and do not exacerbate the underlying pleuropneumonia or increase the production of pleural effusion. A one-way valve may be attached to allow for continuous drainage without leakage of air into the thorax. A Heimlich valve or an unlubricated condom with the tip cut off may be used for that purpose. As an alternative to continuous drainage, the tube can be temporarily occluded and periodically attached to a one-way valve for intermittent drainage. Heparinization of tubing after drainage may help maintain patency. The chest entry site and end of the drainage tube must be maintained aseptically. If a chest tube is placed aseptically and managed correctly, it can be maintained for several days to weeks. Local cellulitis may occur at the site of entry into the chest but is considered a minor complication. Pneumothorax is another potential complication of indwelling chest tubes. It should be removed as soon as it is no longer functional. A purse-string suture must be preplaced and tied as the tube is removed to prevent pneumothorax.

31.6.8.5

PLEURAL LAVAGE

Pleural lavage may be helpful to dilute thick viscous pleural fluid and remove fibrin, debris, and necrotic tissue. Pleural lavage is most helpful in subacute stages before loculated pockets of pleural fluid develop. However, pleural lavage may help break down fibrous adhesions and establish communication between loculae. Pleural lavage is typically performed by using the same chest tube for infusion and drainage of lavage fluid. Alternatively, lavage can be performed by infusing fluid through a dorsally positioned tube and draining it through a ventrally positioned tube. Five to 10 liters of sterile, warm isotonic fluid solution is infused by

gravity flow. After infusion, the chest tube is reconnected to the unidirectional valve for drainage. Allowing the horse to walk once the continuous flow stops will often result in drainage of additional fluid. Pleural lavage is probably contraindicated in horses with bronchopleural communications because it may result in spread of septic debris up the airways and into normal areas of the lungs.[98] Coughing and drainage of lavage fluid from the nose during infusion suggest the presence of a bronchopleural fistula (see discussion of complications, later).

31.6.8.6

THORACOSCOPY

Thoracoscopy allows direct evaluation of the lungs and pleural cavity. In selected cases thoracoscopy may be a useful tool to facilitate placement of thoracic drains in abscesses, transect pleural adhesions, and disrupt loculations.[90] The technique can also be used to perform biopsy or aspiration of specific lesions affecting the periphery of the lungs. The procedure can be performed in the standing sedated horse with local anesthesia and is usually very well tolerated.[99]

Adhesions between the lung and the diaphragm or body wall may prevent complete collapse of the lung, making insertion of the instruments more difficult and sometimes limiting the view of the pleural cavity. Adhesions are easier to disrupt during the first week after formation when the tissue is fibrinous rather than fibrous. Transection of mature adhesion is more difficult and can result in severe hemorrhage. Creation of a pneumothorax is a necessary feature of thoracoscopy, and horses should be monitored carefully throughout the procedure. Transient exacerbation of clinical signs of pulmonary disease caused by pneumothorax can be alleviated by reinflation of the lungs.

31.6.8.7

THORACOTOMY

Surgical intervention in horses with pleuropneumonia is not a substitute for adequate medical management, but in carefully selected cases it can save the lives of horses that would have to be euthanized otherwise. The criteria for surgical intervention include: (1) failure to respond to antimicrobial therapy, pleural drainage, and pleural lavage; (2) stable systemic medical condition; (3) presence of a large amount of fibrin, debris, or pus in the pleural space; and (4) presence of either a walled-off lesion or a complete mediastinum to avoid creation of a bilateral pneumothorax. Surgical intervention is most beneficial in chronic cases with large unilateral localized pockets of thick debris, especially if there is resolution or at least a significant improvement of the disease in the opposite hemithorax. Before surgical exploration, the nature and location of the lesion must be thoroughly characterized by ultrasonography or thoracoscopy to determine the ideal surgical site. When there is bilateral disease, thoracotomy is performed on the most severely affected side. If necessary a second thoracotomy can be performed on the opposite side at a later time. Thoracotomy is typically performed with the horse standing. It is common practice to place a large chest tube into the targeted cavity and leave it open to atmospheric air for at least 2 hours before thoracotomy.[98] The onset of respiratory distress indicates development of bilateral pneumothorax, in which case standing thoracotomy is contraindicated and pneumothorax must be corrected. Unilateral pneumothorax is usually well tolerated.

The standing surgical procedures most commonly performed include thoracotomy via an intercostal approach and thoracotomy and rib resection. For the intercostal approach the surgical site is prepared and infiltrated with local anesthetic. The lateral thoracic vein must be identified to avoid inadvertent incision. A vertical incision is made through the skin, intercostal musculature, and pleura. The length of the incision is dictated by the size of the pleural abscess and consistency of its content. When necessary, partial excision of the intercostal muscles will facilitate manual exploration of the cavity and removal of fibrin and necrotic debris

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(Fig. 31-11). The major advantage of the intercostal approach over rib resection is preservation of thoracic wall integrity and compliance. Thoracotomy with rib resection is elected when the cavity is very large and it is anticipated that extensive manual debridement of fibrin and necrotic debris will be necessary. The advantage of the thoracotomy with rib resection over the intercostal approach is improved access to the thorax, allowing manual removal of large fibrin clumps and necrotic debris (Fig. 31-12). With both rib resection and intercostal approaches, the incision is left open and irrigated once or twice daily with a sterile isotonic fluid solution. The cavity is periodically debrided via gentle massage, taking care not to disrupt mature adhesions. After adequate formation of granulation tissue, tap water may be used. Depending on the size of the incision, it may take a few weeks to 2 to 3 months for complete closure by second intention. Complications during thoracotomy may include bilateral pneumothorax (if the cavity is not walled off and the mediastinum is not complete) and cardiac arrhythmias (if the lesion is in close proximity to the heart). The most common long-term complication is the formation of a chronic draining fistula, but by itself, this complication does not prevent the horse from returning to its usual occupation.

Fig. 31-11 Intercostal thoracotomy with partial excision of the intercostal muscles in a 7-year-old horse with a large pleural abscess. The image was obtained 3 weeks after surgery.

31.6.9 Complications of Pleuropneumonia

Several complications may occur during medical therapy of severe pneumonia and pleuropneumonia. These complications include jugular vein phlebitis or thrombosis from catheter placement, diarrhea resulting from antimicrobial therapy, pneumothorax or cellulitis secondary to thoracocentesis, endotoxemia, coagulopathies, and laminitis. In a retrospective study of 153 horses with pleuropneumonia presented to a referral hospital, complications included pleural abscesses (21.6%), cranial thoracic masses (7.2%), bronchopleural fistulas (6.5%), pericarditis (2.6%), and laminitis (1.3%).

Pleural abscesses refractory to antimicrobial therapy are treated by thoracocentesis or thoracotomy (see earlier). In some cases of pleuropneumonia, the heart may act as a valve to trap effusion and inflammatory debris in the cranial thorax. Small cranial thoracic masses may result in nonspecific clinical signs such as fever, tachycardia, and sternal edema. Larger abscesses may result in jugular vein distention, forelimb extension (pointing), and caudal displacement of the heart. Diagnosis is made by ultrasonography (Fig. 31-13). It is necessary to pull a forelimb forward to successfully image the cranial thorax. Most horses with cranial thoracic masses will respond to conservative therapy with antimicrobial agents.[100] Drainage of the abscess should be performed in cases refractory to medical therapy or when the mass interferes with normal cardiac function. Cranial thoracic abscesses may be sampled in the standing horse with a front limb pulled forward. However, when drainage and lavage are required, the procedure is best performed under short-term general anesthesia to avoid damage to the heart and major blood vessels present in the cranial thorax. It is not recommended to leave an indwelling tube because the triceps musculature often causes the tube to kink. Repeated drainage and lavage may be necessary in some cases.

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Fig. 31-12 Thoracotomy and rib resection in a thoroughbred filly with a large pleural abscess in the right hemithorax communicating with another abscess cranial to the heart. In this case a rib resection was performed to facilitate manual removal of purulent material and necrotic debris from both abscesses.

Fig. 31-13 Sonogram of the cranial thorax obtained from the third intercostal space of a 2-year-old thoroughbred filly with distended jugular veins and pitting edema of the ventral thorax. A large fluid-filled loculated abscess was imaged.

Bronchopleural fistulas develop when necrosis of lung tissue leads to direct communication between the airways and the pleural cavity. Diagnosis may be confirmed by thoracoscopy or by injecting sterile fluorescein dye into the pleural fluid and looking for the presence of dye at the nostrils or within the trachea by endoscopy. Horses with bronchopleural fistula often cough during pleural lavage, and lavage fluid may be noted at the nostrils. Most bronchopleural fistulas spontaneously seal as a result of adhesions to the chest wall or fibrin deposition on the visceral pleura. Sealing may take several weeks to months. In one case partial pneumonectomy was successful in resolving a chronic bronchopleural fistula and pulmonary abscess.[101]

31.6.10 Prognosis

The prognosis for survival and return to normal athletic function depends on the severity and duration of clinical signs before therapy. Horses with septic IAD or mild to moderate bronchopneumonia have a very good prognosis for a return to previous athletic performance. The prognosis for horses with pulmonary abscesses and without concurrent pleuritis is also good. In one study, 45 of 50 (90%) adult horses with pulmonary abscesses survived.[102] In the same study, 92% of standardbreds and 52% of thoroughbreds raced after treatment of

pulmonary abscesses.[102] For horses that returned to racing, performance after successful treatment of lung abscesses was not significantly different from that before the illness.[102]

In a retrospective study of 327 horses with pneumonia or pleuropneumonia, the overall survival rate was 75%.[93] In the same study, the survival rate for 81 horses from which anaerobic bacteria were cultured was only 4.3%.[93] However, another study failed to identify an association between the presence of anaerobic bacteria and decreased survival.[103] In cases of pleuropneumonia, retrospective studies have shown survival rates ranging from 43.3 to 87.6%.[103,104] Differences in survival rates among studies may reflect differences in referral populations as well as advances in therapy in more recent years. Many horses that would have been euthanized owing to chronicity and lack of response to medical therapy several years ago are now successfully treated with the surgical approaches described earlier. This is evidenced by a retrospective of 153 horses with pleuropneumonia in which the survival rate was 95.7% when horses electively euthanized were excluded.[104]

The effect of pleuropneumonia on subsequent racing performance has not been examined extensively. In one retrospective study, 43 of 70 (61%) horses that had recovered from pleuropneumonia returned to racing, and 24 of the 43 (56%) won at least one race.[104] In the same study, horses that required placement of an indwelling thoracic drain did not have a worse prognosis for return to performance compared with horses that did not require placement of a drain.[104] In contrast, horses that developed complications such as pulmonary abscesses, cranial thoracic masses, or bronchopleural fistulas were significantly less likely to return to racing.[104]

31.7 *RHODOCOCCUS EQUI* INFECTIONS

STEEVE GIGUÈRE

R. equi, a gram-positive facultative intracellular pathogen, is one of the most common causes of pneumonia in foals between 3 weeks and 5 months of age. *R. equi* has also emerged as a significant opportunistic pathogen in immunosuppressed people, especially those infected with the human immunodeficiency virus.[105,106] Although *R. equi* can be cultured from the environment of virtually all horse farms, the clinical disease in foals is endemic and devastating on some farms, sporadic on others, and unrecognized on most. On farms where the disease is endemic, costs associated with veterinary care, long-term therapy, and mortality of some foals may be very high. This section reviews the clinical manifestations, pathogenesis, epidemiology, diagnosis, treatment, and prevention of *R. equi* infections in foals.

31.7.1 Clinical Manifestations

The most common manifestation of *R. equi* infections in foals is a chronic suppurative bronchopneumonia with extensive abscessation (Fig. 31-14). The slow spread of the lung infection combined with the remarkable ability of foals to compensate for the progressive loss of functional lung make early clinical diagnosis difficult. Early clinical signs often consist of only a mild fever or a slight increase in respiratory rate that may not be apparent unless foals are exercised or stressed by handling. As the pneumonia progresses, clinical signs may include decreased appetite, lethargy, fever, tachypnea, and labored breathing characterized by nostril flaring and increased abdominal effort. Cough and bilateral nasal discharge are inconsistent findings. A smaller percentage of affected foals may have a more devastating subacute form. These foals may be found dead or more commonly are presented in acute respiratory distress with a high fever and no previous history of clinical respiratory disease. Foals with the subacute form of the disease have a poor prognosis despite appropriate therapy.

Extrapulmonary manifestations of rhodococcal infections may also occur. Intestinal lesions are present in approximately 50% of foals with *R. equi* pneumonia presented for necropsy.[107] However, the majority of foals with *R. equi* pneumonia do not show clinical signs of intestinal disease. In the same study, only 4% of the foals had intestinal lesions without pneumonia.[107] The intestinal form of *R. equi* infection is characterized by a multifocal ulcerative enterocolitis and typhlitis over the area of the Peyer's patches, with granulomatous or suppurative inflammation of the mesenteric and/or colonic lymph nodes.[107] In some cases, the only abdominal lesion noted may be a single large abscess (usually in a mesenteric lymph node) that often adheres to the large or small bowel. Clinical signs associated with the abdominal form of the disease may include fever, depression, anorexia, weight loss, colic, and diarrhea.[108] Marked GI lymphatic obstruction associated with increased protein concentration in the peritoneal fluid and hypoproteinemia may lead to ascites, giving affected foals a pot-bellied appearance. Such foals have a poor prognosis because of the extensive granulomatous inflammation of the colonic mucosa and submucosa and mesenteric lymph nodes.

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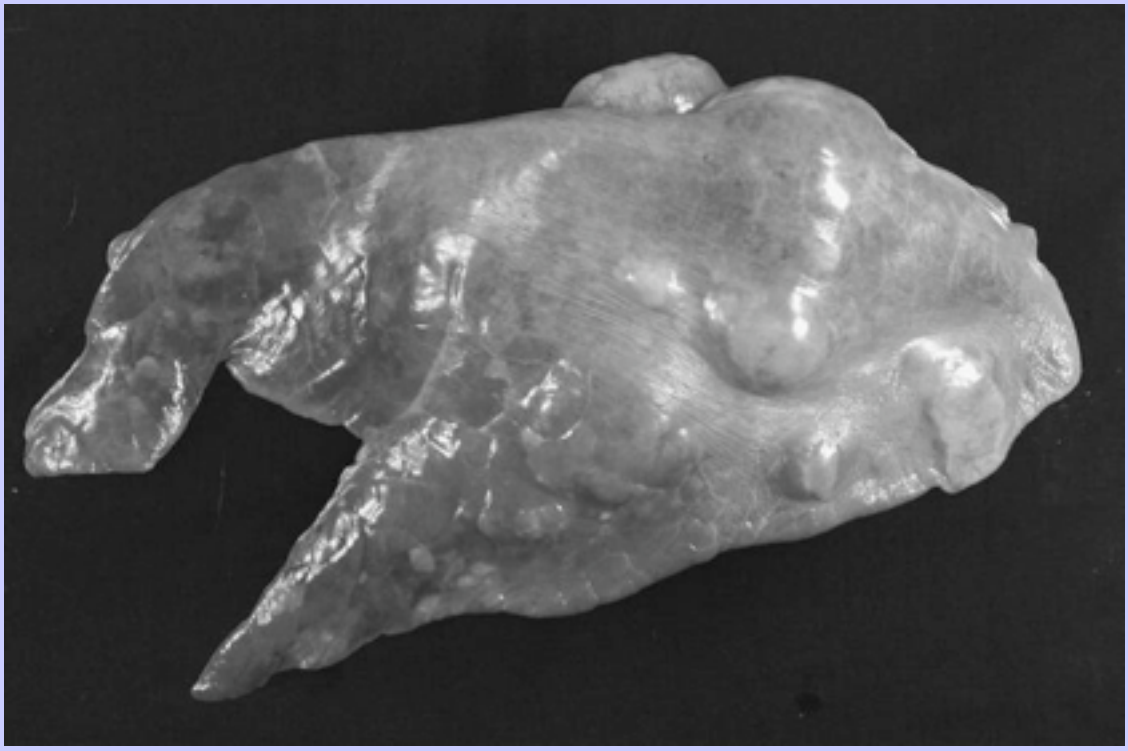
Fig. 31-14 Left lung from a foal with severe pneumonia caused by *R. equi*. There is marked consolidation of the cranial portion of the lung, and multiple abscesses are present caudodorsally. Courtesy Dr. William Castleman.



Polysynovitis is present in approximately one third of cases of *R. equi* infection; in some cases effusion of multiple joints may even be the presenting complaint.[109,110] The tibiotarsal and stifle joints are most commonly affected. Occasionally all joints are affected. The degree of joint effusion is variable, and in most cases lameness

is not apparent or is limited to a stiff gait. Cytologic examination of the synovial fluid usually reveals a nonseptic mononuclear pleocytosis, and bacteriologic culture of the synovial fluid is negative.[110] Histologic examination of the synovial membrane of a few affected foals revealed lymphoplasmacytic synovitis.[109,111] Fluorescein-labeled antiequine immunoglobulin G (IgG) staining of the synovial membrane of three affected foals revealed evidence of immunoglobulin within the synovial membrane, and rheumatoid factors (i.e., antibodies directed against autologous or heterologous Fc portion of immunoglobulin) were identified in the synovial fluid of a foal with nonseptic joint effusion and *R. equi* pneumonia.[109,111] These findings are suggestive of an immune-mediated process. However, experimental infection with a heavy intrabronchial inoculum of virulent *R. equi* consistently results in polysynovitis without associated lameness.[112] Culture of the synovial fluid within a few days of the onset of synovial effusion in these foals often yields *R. equi*, and histologic examination of the synovial membrane reveals suppurative inflammation.[112] Therefore it is possible that the synovitis is septic in origin but that the infection is rapidly cleared from the synovial structures, resulting in chronic nonseptic inflammation at the time of diagnosis. Regardless of the inciting cause, local therapy of the affected joints in clinical cases of *R. equi*–associated polysynovitis is usually not indicated because the effusion resolves without any apparent consequences as the primary infection responds to appropriate antimicrobial therapy. The presence of a nonseptic polysynovitis in a foal between 3 weeks and 6 months of age is highly suggestive of *R. equi* infection and deserves further investigation (see section on diagnosis). Immune-mediated processes may also contribute to the development of uveitis, anemia, and thrombocytopenia in some foals infected with *R. equi*.[113]

Bacteremic spread of the organism from the lungs or GI tract may occasionally result in septic arthritis and, more commonly, osteomyelitis. However, foals can occasionally develop *R. equi* septic arthritis or osteomyelitis without apparent lung or other source of infection. The degree of lameness of foals with septic arthritis distinguishes them from foals with nonseptic polysynovitis. In equivocal cases bacterial culture and cytologic examination of the synovial fluid should be performed. In addition to appropriate antimicrobial therapy (see treatment), foals with *R. equi* septic arthritis and osteomyelitis often require aggressive local therapy. *R. equi* vertebral osteomyelitis or diskospondylitis resulting in spinal cord compression has also been reported.[114–116]

Other rare extrapulmonary manifestations of *R. equi* infections in foals include panophthalmitis, guttural pouch empyema, sinusitis, pericarditis, nephritis, and hepatic, renal, and intracranial abscessation.[113,117] Ulcerative lymphangitis, cellulitis, and SC abscesses have also been reported. Disease caused by *R. equi* is rare in adult horses. Sporadic reports of infection involving primarily lungs or abdominal lymph nodes (similar to infection observed in foals), or rarely of wound infection, exist. In one adult horse, acquired combined immunodeficiency of unknown origin led to *R. equi* septicemia and lung abscessation.[118] Rarely the organism has also been isolated from infertile mares and aborted fetuses.[107,119,120]

R. equi has been isolated from many species other than humans and horses. *R. equi* is frequently cultured from the submaxillary lymph nodes of pigs with granulomatous lymphadenitis. However, *R. equi* can also be isolated from the submaxillary lymph nodes of 3% to 5% of apparently healthy pigs, and experimental infection studies in pigs have failed to reproduce the lesions.[121,122] The causative role of *R. equi* in granulomatous lymphadenitis in pigs thus remains unproven. Isolation of *R. equi* from other domestic animal species is rare. *R. equi* can be isolated from lymph node granulomas in 0.008% of cattle at abattoir postmortem inspection.[123] *R. equi* has also been cultured in rare cases of bronchopneumonia, mastitis, metritis, ulcerative lymphangitis, and septic arthritis in cattle. In goats *R. equi* has a tendency to cause liver abscesses with concurrent bronchopneumonia or pulmonary abscessation.[124] *R. equi* has been isolated from cases of pneumonia as well as from wound infections, SC abscesses, vaginitis, hepatitis, osteomyelitis, myositis, and joint infections in dogs and cats.[125]

31.7.2 Virulence

The ability of *R. equi* to induce disease in foals likely depends on both host and microbial factors. *R. equi* is a facultative intracellular pathogen, and its ability to persist in and eventually destroy alveolar macrophages seems to be the basis of its pathogenicity. Knowledge of the virulence mechanisms of *R. equi* were largely speculative until the discovery of a virulence plasmid.[126,127] Unlike most environmental *R. equi*, isolates from pneumonic foals typically contain an 80- to 90-kb plasmid. Plasmid-cured derivatives of virulent *R. equi* strains lose their ability to replicate and survive in macrophages.[112] Plasmid-cured derivatives also fail to induce pneumonia and are completely cleared from the lungs of foals within 2 weeks after heavy intrabronchial challenge, confirming the absolute necessity of the large plasmid for the virulence of *R. equi*.[112,128]

Nucleotide sequencing of the large plasmid of two foal isolates revealed the presence of 69 open reading frames (ORFs).[129] Comparisons of the plasmid sequence with genes previously identified in other microorganisms has identified three functional regions. Two of these regions contain genes encoding proteins involved in conjugation, plasmid replication stability, and segregation.[129] The third region of 27.5 kb bears the hallmark of a pathogenicity island and contains the genes for a family of eight closely related virulence-associated proteins designated VapA and VapC to VapI.[127,129–133] With the exception of *vapF* and *vapI*, which are not functional, all *vap* genes encode proteins with a clear signal sequence, indicating that they are extracellular proteins.[129,133,134] VapA is expressed on the bacterial surface, and its expression is temperature regulated, occurring between 34° C and 41° C.[135] VapC, VapD, and VapE are secreted proteins concomitantly regulated by temperature with VapA.[136] In a recent study, an *R. equi* mutant lacking a 7.9-kb DNA region spanning six *vap* genes *(vapA, vapC, vapD, vapE, vapF, vapI)* was attenuated for virulence in mice and failed to replicate in macrophages.[137] Complementation with *vapA* alone could restore full virulence, whereas complementation with *vapC, vapD*, or *vapE* could not. Conversely, a recombinant plasmid-cured derivative expressing wild-type levels of VapA failed to survive and replicate in macrophages and remained avirulent in foals, showing that expression of VapA alone is not sufficient to restore the virulence phenotype.[112] These findings show that although VapA is essential for virulence, other plasmid-encoded products also contribute to the ability of *R. equi* to cause disease. Consistent with these findings, it was recently demonstrated that two *R. equi* mutants lacking expression of pathogenicity island genes (ORF4 and ORF8) were fully attenuated despite enhanced transcription of *vapA*.[138] All *vap* genes as well as five other ORFs within the pathogenicity island are upregulated when *R. equi* is grown in macrophage monolayers.[139] Regulation of expression of the genes of the pathogenicity island is complex and depends on at least five environmental signal including temperature, pH, oxidative stress, magnesium, and iron.[135,139,140] The precise role of each of these genes in the pathogenesis of *R. equi* infections remains to be determined.

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R. equi isolates are often classified as virulent, avirulent, or intermediately virulent based on their ability to induce disease or death in mice. Virulent *R. equi* isolates contain the large plasmid described previously and express VapA. Intermediately virulent *R. equi* isolates contain one of four distinct large plasmids encoding a 20-kDa antigen (VapB) that is related to, but distinct from, VapA. In contrast, avirulent *R. equi* isolates do not express Vap antigens. All three categories of *R. equi* have the ability to cause disease in immunosuppressed humans. Analysis of *R. equi* isolates from immunocompromised human patients with and without acquired immunodeficiency syndrome (AIDS) reveals that only approximately 20% of isolates contain an 80- to 90-kb plasmid and express VapA.[141,142] Therefore the pathogenesis of *R. equi* infection in immunocompromised human patients appears to be different from the pathogenesis in foals, in which the virulence plasmid is always

found. To my knowledge, intermediately virulent isolates (expressing VapB) have never been isolated from foals with naturally acquired *R. equi* infections. Experimentally, heavy intrabronchial challenge of foals with intermediately virulent *R. equi* results in pneumonia but at a dose much higher than that required for induction of pneumonia with VapA-expressing strains.[143] Almost all isolates from the submaxillary lymph nodes of pigs produce VapB and are intermediately virulent to mice, suggesting that pigs or their environment may be the source of infection for some human cases.[144] Most isolates from cattle, goats, and dogs are avirulent and do not contain plasmids encoding *vapA* or *vapB*.[123–125] In contrast, most isolates from cats contain a large plasmid and express VapA.[125]

Although it has been firmly established that the virulence plasmid is essential for infection of foals, it is also clear that chromosomally encoded factors, such as regulatory genes and metabolic pathways are also important for allowing the pathogen to thrive within the host.[145–148] *R. equi* is closely related to *Mycobacterium tuberculosis* as evidenced by a partial genome sequence of *R. equi*, which showed that the majority of *R. equi* genes have most homology with *M. tuberculosis*.[149] The unique cell wall of *R. equi* and other mycolata such as *Mycobacterium, Corynebacterium*, and *Nocardia* species is completely different from those of gram-negative and other gram-positive bacteria. Mycolata are characterized by a unique cell envelope that consists of mycolic acid anchored to an arabinogalactan wall polysaccharide.[150] The mycolic acid—containing cell wall is likely to be of importance for survival of *R. equi* under harsh environmental conditions such as those that occur within macrophages. Consistent with this theory, *R. equi* isolates with a longer carbon chain and mycolic acid are more virulent than those with shorter chains as determined by lethality and granuloma formation in mice.[151]

31.7.3 Epidemiology and Pathogenesis

R. equi is a soil organism with simple growth requirements. The highest numbers of *R. equi* are found in surface soil, whereas the organism cannot be found at depths exceeding 30 cm.[152] *R. equi* can be isolated from the feces of most adult horses at concentrations ranging between 10 and 10^3 colony-forming units (CFUs) per gram of feces. The number of *R. equi* in the feces of mares on endemic farms does not increase in the weeks before or after foaling.[153] In the same study, *R. equi* could be isolated from the feces of only 19% of the foals at 1 week of age and from all foals by 4 weeks of age.[153] In another study, virulent *R. equi* could be isolated from the feces of all sampled mares during at least one sampling period, indicating that mares can be an important source of virulent *R. equi* for their surrounding environment.[154] However, dams of affected foals did not shed more *R. equi* in feces than did dams of unaffected foals, indicating that heavier shedding by particular mares does not explain infection in their foals.[154]

Intestinal carriage in adult herbivores is mainly passive, as the organism cannot replicate in the anaerobic environment of the adult large intestine. However, the organism multiplies in the intestine of the foal up to about 3 months of age, reaching numbers up to 10^5 CFUs per gram of feces.[155] Virulent *R.* equi present in the sputum of pneumonic foals will be swallowed and thus can multiply in the intestine. Therefore the manure of *R. equi*–affected foals is likely a major source of progressive contamination of the environment with virulent organisms. Under suitable conditions of high summer temperatures, *R. equi* can multiply in the environment by 10,000-fold in only 2 weeks.[156] A single gram of soil contaminated with foal manure may therefore, under favorable conditions, contain millions of virulent *R. equi* organisms. *R. equi* can also be cultured from the air in the stalls on endemic farms, particularly on dry and windy days.[153] In a recent study, the odds of detecting airborne

virulent *R. equi* in stables were approximately 17 times greater than in paddocks of a given farm, and concentrations of virulent *R. equi* were also significantly higher in stables than in paddocks.[157]

Inhalation of virulent *R. equi* is the major route of pneumonic infection. The incubation period after experimental intrabronchial challenge varies from approximately 9 days after administration of a heavy inoculum to approximately 2 to 4 weeks when a lower inoculum is administered.[112,158] Lung consolidation can be detected as early as 3 days after heavy intrabronchial challenge.[112] The incubation period under field conditions likely depends on the number of virulent bacteria in the environment as well. Ingestion of the organism is a significant route of exposure, and likely also of immunization, but rarely leads to hematogenously acquired pneumonia unless the foal has multiple exposures to large numbers of bacteria.[159] Indeed, oral administration of live virulent *R. equi* to foals on day 2 and day 7 of life is highly effective in preventing development of pneumonia after subsequent heavy intrabronchial challenge.[160] Clearly, oral vaccination with live *R. equi* would not be an acceptable way to immunize foals because it would lead to progressive contamination of the environment with virulent bacteria. However, it undoubtedly shows that newborn foals have the ability to mount protective immune responses against *R. equi* (see section on immunity).

Epidemiologic evidence suggests that most foals on endemic farms become infected early in life.[161] The median age at the time of diagnosis is approximately 37 days on endemic farms with a screening program to promote early diagnosis.[162] Given the fairly long incubation period of the disease, this finding would also support the fact that many foals become infected within the first few weeks of life. In one study, foals aged 3 to 13 days (mean 6.4 days) were more susceptible to experimentally induced *R. equi* pneumonia than foals aged 14 to 36 days (mean 25 days). Collectively these findings indicate that many foals on endemic farms become infected at a young age and that younger foals may be more susceptible to infection caused by *R. equi*. However, these findings do not indicate that foals are susceptible to *R. equi* only during the neonatal period. Much older foals are still highly susceptible to infection by *R. equi*, particularly if they have never been exposed to *R. equi*. In one study, intatracheal administration of *R. equi* to 10 foals aged 27 to 67 days (mean 49 days) resulted in disease in all foals, including those receiving a low-dose challenge.[128] In addition, some foals are diagnosed with *R. equi* pneumonia at 3 or 4 months of age. There is no evidence to support a 90- to 120-day incubation period, which would be required if all foals were infected shortly after birth.

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Although *R. equi* can be cultured from the environment of virtually all horse farms, the clinical disease in foals is endemic and devastating on some farms, sporadic on others, and unrecognized on most. This probably reflects differences in environmental and management conditions, as well as differences in the virulence of isolates, but the exact basis for the difference in the prevalence of the disease among farms remain unknown. Breeding farms with a large acreage, a large number of mares and foals, a high foal density, and a population of transient mares and foals have greater odds of being affected by *R. equi* pneumonia.[163,164] In contrast, *R. equi* pneumonia does not appear to be associated with lack of attention to routine preventative health practices.[165] Although the total numbers of *R. equi* isolates in the environment may be similar in farms with and without a history of *R. equi* infections, farms with endemic disease may be more heavily infected with virulent *R. equi*.[166] In a survey of the prevalence of *R. equi* at horse-breeding farms in Japan, the organism was isolated from almost all soil samples, at numbers of 10^2 to 10^5 CFUs per gram of soil. The vast majority of these isolates did not contain plasmids and were avirulent. Virulent *R. equi* isolates containing 80- to 90-kb plasmids and expressing VapA were cultured from 24 of the 31 farms examined. On those farms, virulent *R. equi* represented 1.7% to 23.3% of all isolates.[167] However, quantification of virulent *R. equi* from a single soil sample cannot be used to determine whether foals on a given farm are at increased risk for developing disease caused by *R. equi*.[168] There is considerable

chromosomal variability among isolates of *R. equi* obtained from the same farm and among isolates from various continents.[169] However, a small number of strains on a given farm are often responsible for the majority of clinical cases.[170] It is interesting to note that multiple *R. equi* strains were isolated in five of the six cases in which more than one isolate from a single foal was examined, indicating that disease is commonly caused by simultaneous infection with multiple strains.[170] Differences in disease prevalence among farms cannot be explained by soil geochemistry factors, as there is no association between soil pH, salinity, nitrate, phosphorus, potassium, calcium, magnesium, sodium, sulfur, zinc, iron, manganese, and copper and *R. equi* disease status on a given farm.[171]

R. equi can also be cultured from the soil of areas not inhabited by horses. In one study, *R. equi* was isolated from approximately 73.9% of soil samples collected from 115 parks and 49 household yards in Japan. The number of *R. equi* in those samples ranged from 10 to 10^5 CFUs per gram of soil. None of the 1294 isolates from those samples expressed VapA or VapB, suggesting that the human environment is not a significant route of exposure to virulent or intermediately virulent *R. equi*.[122]

31.7.4 Rhodococcus equi-*Phagocytic Cell Interactions*

The infectivity of *R. equi* in vitro is largely limited to cells of the monocyte-macrophage lineage.[172] Optimal binding of *R. equi* to mouse macrophages in vitro requires complement and is mediated by MAC-1, a leukocyte complement receptor type 3 (CR3, CD11b/CD18).[172] After entry through Mac-1, virulent *R. equi* can survive and even replicate in macrophages.[173] In contrast, opsonization of *R. equi* with specific antibody significantly enhances killing of *R. equi* by equine macrophages.[174] These findings suggest that cellular entry by non-Fc receptors may allow *R. equi* to avoid antibody-associated killing pathways. Entry of several microorganisms into macrophages after adherence to complement receptors, rather than Fc receptors, has been shown to allow them to avoid the toxic consequences of the oxidative burst.[175] The lipoarabinomannan, an important component of the cell envelope of *R. equi*, has the ability to bind to mannose-binding protein.[176] Binding of mannose-binding protein by lipoarabinomannan in vivo may activate complement C3b deposition onto *R. equi* via the lectin pathway, thereby promoting Mac-1 mediated uptake into macrophages. Alternatively the lipoarabinomannan of *R. equi*, like that of *M. tuberculosis*, may mediate bacterial entry through the macrophage mannose receptors. Recent studies have shown that *R. equi* can also activate macrophages through Toll-like receptor 2 (TLR2), leading to the release a variety of proinflammatory mediators.[177] In the same study VapA was identified as one of the bacterial components leading TLR2-mediated macrophage activation.[177] However, plasmid-cured derivatives of *R. equi* induced cytokine release by macrophages to the same degree as the parent strain, indicating that the presence of VapA is not necessary for activation of the innate immune response.[178] Consistent with these findings, the lipoarabinomannan of *R. equi* has been shown to be a potent inducer of cytokine induction by equine macrophages.[176]

During phagocytosis, bacteria are wrapped in a portion of the plasma membrane and taken up into macrophages, forming a new organelle called a *phagosome*. The phagosome matures over time by consecutive interactions with early endocytic, late endocytic, and lysosomal vesicles, leading to the formation of a phagolysosome. During phagosome maturation, bacteria are exposed to a number of microbicidal products, such as acid, reactive oxygen and nitrogen intermediates, and lysosomal hydrolases, that all contribute to killing and degradation of ingested bacteria. Intracellular persistence of *R. equi* in equine macrophages is associated with absent or decreased phagosome-lysosome fusion, and phagocytosis of *R. equi* is not associated with a functional

respiratory burst.[174,179,180] Recent studies in mouse macrophages have shown that *R. equi* has the ability to block maturation of endocytic organelles after completion of the early endosome stage but before a fully mature late endosome compartment is reached.[181] After ingestion by macrophages both virulent strains of *R. equi* and their avirulent plasmid-cured derivatives replicate in single membrane vacuoles for approximately 6 hours. Thereafter, virulent *R. equi* suppresses acidification of the vacuole and replicates intracellularly. In contrast, the vacuoles containing plasmid-cured derivatives progressively acidify, leading to complete eradication of the bacteria.[181,182] These findings indicate the importance of plasmid-encoded products in preventing acidification of *R. equi*–containing vacuoles within macrophages. Similarly, necrotic death of *R. equi*–infected macrophages is also regulated by plasmid-encoded products.[183]

As stated earlier, *R. equi* can survive and even replicate in resident or nonactivated macrophages. Killing of *R. equi* by mouse macrophages is dependent on the presence of IFN-γ, which activates macrophages to produce both reactive oxygen and reactive nitrogen intermediates. These two radicals combine to form peroxynitrite, which efficiently kills *R. equi*.[184] Neither reactive oxygen nor reactive nitrogen intermediates alone are sufficient to mediate killing of *R. equi*.[184] Additional cytokines such as TNF-α may have a similar effect on macrophages, as both IFN-γ and tumor necrosis factor (TNF)-α are both required for clearance of virulent *R. equi* in mice.[185]

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Neutrophils play an important role in early host defense against virulent *R. equi*.[186] As opposed to macrophages, neutrophils from foals and adult horses are fully able to kill *R equi*.[187–189] As seen with macrophages, killing of *R. equi* by neutrophils is considerably enhanced by specific opsonizing antibody.[187–191]

31.7.5 Immunity

31.7.5.1 ANTIBODY-MEDIATED IMMUNITY

Immunity to *R. equi* pneumonia in foals likely depends on both the antibody and cell-mediated components of the immune system, but its exact basis remains to be determined. The strongest evidence for a role of antibody in protection against *R. equi* is the partially protective effect of passively transferred anti—*R. equi* hyperimmune (HI) equine plasma (see section on prevention). The mechanisms by which HI plasma confers protection are not completely understood. The list of possible effector molecules includes antibody and nonspecific factors such as fibronectin, complement components, collectins, cytokines, and acute phase proteins. Opsonization of *R. equi* with specific antibody has been shown to promote phagocytosis and killing of *R. equi* by alveolar macrophages, identifying antibody as a critical component of HI plasma.[174] In most studies evaluating the protective effect of HI plasma, plasma donors were immunized with whole cell vaccines or a mixture of several soluble antigens, making it impossible to determine the role of antibody against defined antigens of *R. equi*.

Recent studies have focused more specifically against the role of antibody against plasmid-encoded virulence-associated proteins (Vap). First, a monoclonal antibody to VapA and serum from horses immunized with partially purified VapA have opsonizing activity.[192] Moreover, purified immunoglobulins obtained from horses vaccinated with partially purified VapA protected mice against intraperitoneal challenge with virulent *R. equi* compared with mice administered immunoglobulins from nonimmunized horses.[193] More recently, IV administration of purified immunoglobulins obtained from horses immunized with recombinant VapA and VapC to foals was found to reduce the severity of pneumonia after heavy experimental challenge with *R. equi*.

[194] In the same study the degree of protection conferred by purified anti-VapA and anti-VapC immunoglobulins was similar to that provided by commercially available HI plasma.[194]

In adult horses the concentrations of *R. equi*-specific and VapA-specific IgGa and IgGb antibodies (the IgG isotypes that preferentially opsonize and fix complement in horses) are dramatically enhanced after intrabronchial administration with virulent *R. equi*. This occurs in conjunction with clearance of the bacteria from the lungs.[195] In foals, production of antibody to VapA and VapC but not to other Vap proteins, increases after natural exposure to *R. equi*.[194] Characterization of the subisotype response in naturally infected foals revealed mainly an increase in IgGa, IgGb, and IgG(T).[194,196]

31.7.5.2

CELL-MEDIATED IMMUNITY

Because of the facultative intracellular nature of *R. equi*, cell-mediated immune mechanisms are thought to be of major importance in resistance to infection. A large part of the knowledge of cell-mediated immunity to *R. equi* infections comes from infection of mice. Deficiencies in the complement component C5 and natural killer (NK) cells in mice do not impair the pulmonary clearance of virulent *R. equi*.[197] In contrast, functional T lymphocytes are absolutely required for the clearance of virulent (plasmid and VapA positive) *R. equi* in mice.[198–200] However, athymic nude mice (lacking functional T lymphocytes) clear plasmid-cured derivatives from their lungs within 1 week of infection, suggesting that, as opposed to virulent organisms, clearance of avirulent plasmid-negative strains in mice does not require functional lymphocytes and depends mainly on innate defense mechanisms.[198]

The two major mechanisms by which T lymphocytes mediate clearance of intracellular pathogens are secretion of cytokines and direct cytotoxicity. Although both $CD4^+$ (helper) and $CD8^+$ (cytotoxic) T cells contribute to host defense against *R. equi* in mice, $CD4^+$ T lymphocytes play the major role and are absolutely required for complete pulmonary clearance.[199,201,202] The mouse $CD4^+$ Th cells can be divided into two subsets based on the cytokines they produce. The Th1 subset produces primarily IFN-γ and IL-2 and is mainly responsible for macrophage activation and cell-mediated immunity. The Th2 subset produces mainly IL-4, IL-5, and IL-10, which primarily promotes humoral immunity. Studies in mice have clearly shown that a Th1 response is sufficient to effect pulmonary clearance of *R. equi*, whereas a Th2 response is detrimental.[200,203]

Clearance of virulent *R. equi* in adult horses is associated with a significant increase in BALF $CD4^+$ and $CD8^+$ lymphocytes, lymphoproliferative responses to *R. equi* antigens, development of *R. equi*–specific cytotoxic $CD8^+$ T lymphocytes, and IFN-γ but not IL-4 induction by $CD4^+$ and $CD8^+$ lymphocytes.[195,204–206] How these findings in mice and adult horses relate to the foal is currently being elucidated. Even on endemic farms on which exposure to virulent *R. equi* is high, most foals do not develop clinical signs of respiratory disease, suggesting that most foals develop protective immune responses that continue to operate throughout adult life. Age-related deficiencies in *R. equi*—specific cytotoxic T lymphocyte activity have been documented in 3-week-old foals.[206] Cytotoxic T lymphocyte activity was improved by 6 weeks of age and was similar to that in adult horses by 8 weeks.[206] In another study, foals with a peripheral blood CD4:CD8 T lymphocyte ratio <3 between 2 and 4 weeks of age were more likely to develop *R. equi* pneumonia than foals with a higher ratio.[207] These findings may represent important immunologic mechanisms associated with increased susceptibility of individual foals to *R. equi* infections.

The fact that young foals are deficient in their ability to produce IFN-γ in response to mitogens has led to the hypothesis that IFN-γ deficiency may be at the basis of their peculiar susceptibility to *R. equi* infections.[208] A comparison between cell-mediated immune responses of foals and adult horses after intrabronchial challenge with virulent *R. equi* has recently been completed. The results indicate that foals can mount an appropriate IFN-γ response to a low inoculum of virulent *R. equi* but that their immune system is naive compared with that of adult horses.[209] A heavy intrabronchial challenge overwhelms their immune system, leading to a significant increase in IL-4 induction.[209]

In another study, foals infected intrabronchially with a heavy inoculum of a virulence plasmid—containing strain of *R. equi* had significantly lower IFN-γ mRNA expression by bronchial lymph node $CD4^+$ T lymphocytes than foals infected with an avirulent plasmid-cured derivative of the same strain.[210] In addition, IL-10 (a cytokine known to downregulate Th1 responses in other species) and many inflammatory cytokines (IL-1β, TNF-α) were expressed at significantly higher levels in the lungs of foals infected with the virulent strain.[210] The cytokine response in the lungs of foal infected with virulent *R. equi* is at least partially mediated by NF-κB activation.[211] Taken together, these findings suggest that plasmid-encoded products of *R. equi* may have an immunomodulating effect in the respiratory system of foals.

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31.7.6 Diagnosis

The distinction between lower respiratory tract infections caused by *R. equi* and those caused by other pathogens is problematic, especially on farms with no previous history of *R. equi* infections. Many diagnostic tests including complete blood count (CBC), measurement of fibrinogen concentrations, ultrasonography, radiographs, and serology may help distinguish *R. equi* pneumonia from that caused by other pathogens. However, bacteriologic culture and/or PCR amplification combined with cytologic examination of a tracheobronchial aspirate are necessary to make a definitive diagnosis of *R. equi* pneumonia.

31.7.6.1 CLINICAL LABORATORY TESTS

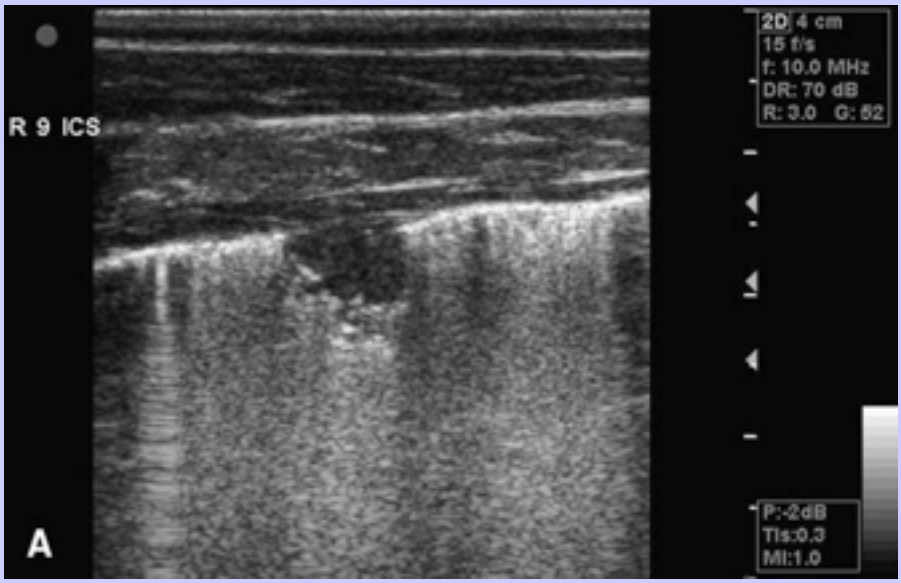
Hyperfibrinogenemia is the most consistent laboratory finding in foals with *R. equi* pneumonia, although in rare cases patients may have normal fibrinogen concentrations. Neutrophilic leukocytosis with or without monocytosis is also common. One study showed significantly higher fibrinogen concentrations and WBC counts in nonsurvivors than in survivors,[212] whereas other studies showed no difference between the two groups.[213,214] In a review of 40 cases of lung abscesses, there was a trend toward higher fibrinogen concentrations and WBC counts for the foals from which *R. equi* was isolated from a tracheobronchial aspirate as opposed to foals from which another pathogen was isolated.[214] However, in all these studies there was a considerable overlap in ranges, which precludes the use of fibrinogen concentrations and WBC as diagnostic tests or prognostic indicators for an individual animal.

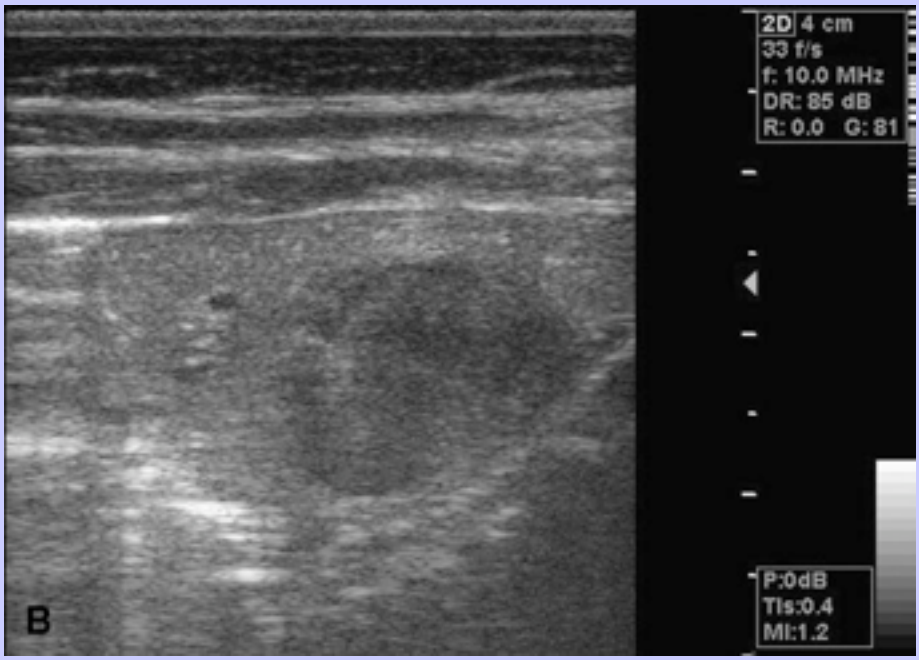
31.7.6.2 IMAGING TECHNIQUES

Thoracic radiography is useful in evaluating the severity of pneumonia and in assessing response to therapy. A prominent alveolar pattern characterized by ill-defined regional consolidation is the most common radiographic abnormality.[212] The consolidated lesions are often seen as more discrete nodular and cavitary lesions consistent with pulmonary abscessation. Although in one study nonsurvivors tended to have more

severe radiographic lesions than survivors, many survivors have very severe radiographic lesions; thus radiographs should not be used as the sole criterion for prognostication and euthanasia.[110,212,213] In foals less than 4 months of age radiographic evidence of nodular lung lesions and tracheobronchial lymphadenopathy is highly suggestive of *R. equi* infections. However, in foals of 4 months and older *S. zooepidemicus* is another common cause of lung abscesses.[214] Ultrasonography is a helpful diagnostic tool when lung involvement includes peripheral areas but may not be as useful as radiography to evaluate the full extent of lung lesions because abscesses with overlying aerated lung will not be detected. However, in most horses and foals with pulmonary abscessation the periphery of the lung is affected, enabling the ultrasonographer to successfully image some of the abscesses.[215] Early ultrasonographic lesions are nonspecific and may include only irregularities of the pleural surface. These lesions may progress to form focal areas of consolidation of various sizes (Fig. 31-15, *A*). In more chronic cases, well-circumscribed, encapsulated abscesses can be detected (Fig. 31-15, *B*). Ultrasonography is very useful in evaluating the severity of pneumonia and in assessing response to therapy, especially for equine practitioners who do not have access to thoracic radiography. Ultrasonography is also a useful tool for detection of some abdominal abscesses (Fig. 31-16) and for screening for *R. equi*–infected foals on farms where the disease is endemic (see section on control).

Fig. 31-15 **A**, Sonogram of the right thorax in a foal with mild pneumonia caused by *R. equi*. There is an approximately 1 cm^2 area of focal consolidation. **B**, Sonogram of the left thorax in a foal with severe pneumonia caused by *R. equi*. There is consolidation of the ventral aspect of the lung surrounding a large encapsulated abscess.





31.7.6.3

SEROLOGY

A number of workers have investigated serologic approaches to diagnose *R. equi* infections in foals. The two most commonly used types of assays are agar gel immunodiffusion (AGID) and the enzyme-linked immunosorbent assay (ELISA). Serologic diagnosis of *R. equi* infections is problematic because the widespread exposure of foals to this organism at a young age leads to antibody production without necessarily producing clinical disease. In addition, maternally derived antibody causes positive reactions with sensitive ELISA assays, which further confound the interpretation of the test. Several independent studies have recently evaluated the performance of available serologic tests for diagnosis of infection caused by *R. equi* on endemic farms.[186,216–218] The serologic tests evaluated were found to have low sensitivity, low specificity, or both. Improving either sensitivity or specificity of ELISA by changing the cutoff value of the tests could be done only at the detriment of the other. The performance of each assay was not improved by sequential sampling of each foal at 2-week intervals over time.[186] Reliance on serology as the sole diagnostic test for *R. equi* infections results in overdiagnosis of the disease and in missing infections in the early stages. Serologic tests may be more useful at the farm level to detect overall exposure, but they have little value in establishing or excluding a diagnosis of *R. equi* pneumonia.

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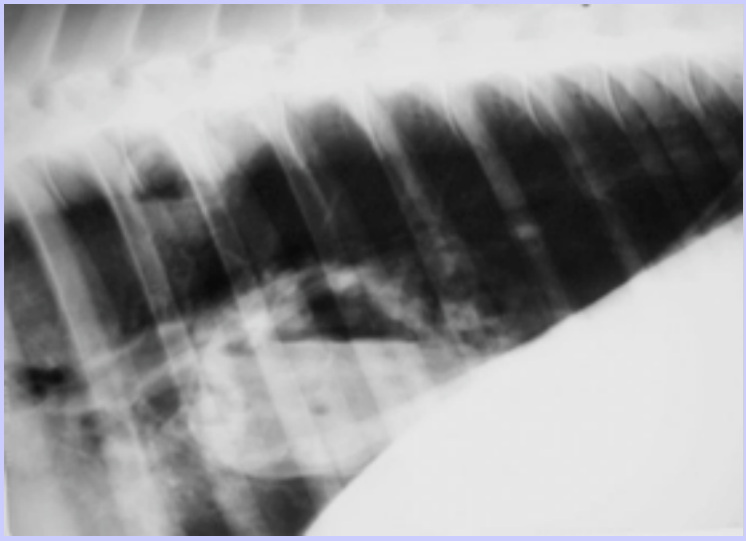
Fig. 31-16 Radiograph of the caudodorsal lung of a foal with severe *Rhodococcus equi* pneumonia demonstrating the classically described “Easter Basket” abscess. The appearance of the abscess results from the thick capsule, the fluid within the abscess, and the gas cap above the fluid, creating the gas-fluid interface line contained within the capsule. This radiographic appearance is not as common as a more usual radiographic appearance of bronchointerstitial pneumonia with associated variably sized abscesses.



31.7.6.4 CYTOLOGY, CULTURE, AND POLYMERASE CHAIN REACTION AMPLIFICATION

Bacteriologic culture or PCR amplification combined with cytologic examination of a tracheobronchial aspirate is the only acceptable way of making a definitive diagnosis of *R. equi* pneumonia. In one study only 7 of 11 foals (64%) with positive *R. equi* culture at necropsy and 57 of 89 foals (64%) with radiographic evidence of lung abscessation yielded *R. equi* on culture of a tracheobronchial aspirate.[219] However, in two other studies all 17 foals in which *R. equi* was isolated from the lung parenchyma at necropsy had previously undergone culture of a tracheobronchial aspirate that had yielded the organism, suggesting that culture of a tracheobronchial aspirate is a consistent and reliable method of diagnosing *R. equi* pneumonia.[214,220] Larger case series are required to determine the exact sensitivity of tracheobronchial aspirate culture for the diagnosis of *R. equi* pneumonia in foals. Multiple other pathogens are often isolated along with *R. equi*. Foals without clinical disease exposed to contaminated environments may have *R. equi* in the trachea as a result of inhalation of contaminated dust. In one study conducted on a farm with endemic *R. equi* pneumonia, 77 of 216 foals sampled (36%) had positive tracheobronchial aspirate cultures but no signs of respiratory disease.[221] For this reason, bacteriologic culture of a tracheobronchial aspirate should be interpreted in the context of cytologic evaluation, physical examination, and laboratory results. A light growth of *R. equi* from a foal with no clinical signs of respiratory disease, normal fibrinogen concentrations and WBC count, and no cytologic evidence of airway inflammation is likely an incidental finding. The use of PCR amplification based on the VapA gene sequence is a more sensitive mean of identifying *R. equi* in tracheobronchial aspirate samples than bacterial culture, especially if the foal sampled is concurrently being treated with antimicrobial agents.[222] However, increased sensitivity may also result in a higher incidence of false-positive results owing to the detection of very small numbers of *R. equi* present as environmental contaminants. Several conventional and real-time PCR assays have been developed for the detection of virulent *R. equi*.[222–225] PCR amplification may be done in association with, but should not replace, bacterial culture because it does not permit identification of concurrent bacterial pathogens and in vitro antimicrobial susceptibility testing of *R. equi* isolates.

Positive *R. equi* culture from nasal or fecal swabs cannot be taken as evidence of infection. *R. equi* can be cultured from the feces of normal horses even if they live on farms with no history of *R. equi* pneumonia.[155,226,227] The quantitative culture of the feces of foals at weekly intervals has been advocated as an aid in early diagnosis of *R. equi* infections in foals because the bacterial count per gram of feces increased at the same time as clinical signs appeared.[226] However, a single fecal sample from a foal has no diagnostic value because of individual as well as farm-to-farm variation in the number of *R. equi* in the feces.[155,226,227] Furthermore, a negative fecal culture may not be helpful in ruling out *R. equi* infection; in one study only 5 of 30 foals (17%) with confirmed *R. equi* pneumonia had positive fecal cultures.[221] Similarly, bacterial culture and PCR amplification of nasal swabs are poorly sensitive for the diagnosis of *R. equi* pneumonia.[222,228]

31.7.7 Treatment

A wide variety of antimicrobial agents are active against *R. equi* in vitro. However, because *R. equi* is a facultative intracellular pathogen surviving and replicating in macrophages and therefore causes granulomatous lesions with thick caseous material, many of these drugs are ineffective in vivo. For example, in one study all 17 foals with *R. equi* pneumonia treated with the combination of penicillin and gentamicin died despite the fact that all isolates were sensitive to gentamicin.[214] The combination of rifampin and erythromycin became the treatment of choice in the 1980s and has dramatically reduced foal mortality since its introduction.[110,219] In recent years

clarithromycin or azithromycin, two newer generation macrolides, often replaces erythromycin in the combination with rifampin.[229] Macrolides and rifampin are highly active against *R. equi* in vitro but exert only bacteriostatic activity.[230] As a result, macrolides exert time-dependent activity against *R. equi* in vitro. Of the three macrolides listed previously, clarithromycin is the most active against *R. equi* in vitro. The minimum inhibitory concentrations at which 90% of *R. equi* isolates are inhibited (MIC_{90}) are 0.12, 0.25, and 1 μg/mL for clarithromycin, erythromycin, and azithromycin, respectively.[231] The combination of a macrolide and rifampin is synergistic both in vitro and in vivo, and the use of the two classes of drugs in combination reduces the likelihood of *R. equi* resistance to either drug.[230,232] Rifampin and macrolides are lipid soluble, allowing them to penetrate cell membranes and caseous material.

The recommended doses are listed in Table 31-4. Several formulations of erythromycin are commercially available. Although they all show slight differences in bioavailability and elimination, they all result in therapeutic concentrations at recommended doses. Advantages of azithromycin and clarithromycin over erythromycin in foals include enhanced oral bioavailability, prolonged half-lives, and much higher concentrations in bronchoalveolar cells and pulmonary epithelial lining fluid.[233–235] These properties of the newer generation macrolides contribute to their lower doses and longer dosing intervals. Concentrations of clarithromycin in pulmonary epithelial lining fluid and bronchoalveolar cells of foals at steady state are considerably higher than concentrations reported after daily administration of azithromycin to foals.[234,235] However, clarithromycin concentrations at these sites decrease rapidly, whereas the release of azithromycin from cells is much slower, resulting in sustained concentrations of azithromycin in tissues for days after discontinuation of therapy.[233–235] In a retrospective study, the combination clarithromycin and rifampin was significantly more effective than erythromycin-rifampin or azithromycin-rifampin, especially in foals with severe radiographic lesions.[229]

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Table 31-4 Recommended Doses, Oral Bioavailability, and Serum Half-Lives of Antimicrobial Agents Commonly Used for the Treatment of *R. equi* Infections in Foals

Class	Drug	Dose (mg/kg)	Route	Frequency (h)	Oral Bioavailability (%)	Serum $t_{1/2}$ (h)	References
Macrolides	Erythromycin*	25	PO	6–8	18	1	163c, 163d
		5	IV	6	NA	1	163c, 163d
	Clarithromycin	7.5	PO	12	57	5.4	131, 163e
	Azithromycin	10	PO	24–48†	56	18	129, 130
		5	IV	24–48†	NA	16	129, 130
Rifamycins	Rifampin	5	PO	12	49	15	163a, 163b, 163f

IV, Intravenous; *PO*, by mouth; *NA*, not applicable.

* Erythromycin base, stearate, phosphate, estolate, or ethylsuccinate.

† Administration q24h for 5 days and q48h thereafter.

Because polymicrobial infections are common, a third antimicrobial agent may be necessary if another pathogen resistant to macrolides and rifampin is isolated in significant number along with *R. equi*. The combination of gentamicin or amikacin with erythromycin or rifampin in vitro gives significant antagonistic activity against *R. equi* compared with either drug alone.[230,232] However, the clinical significance of this in vitro finding has not been established. Resolution of clinical signs, normalization of plasma fibrinogen concentrations, and radiographic or ultrasonographic resolution of lung lesions are commonly used to guide the duration of therapy, which generally ranges between 2 and 12 weeks depending on the severity of the initial lesions.

Although well tolerated by most foals, macrolides commonly cause diarrhea. Most of the time the diarrhea is self-limiting and does not necessitate cessation of therapy, but affected foals should be monitored carefully because some may develop severe diarrhea, leading to dehydration and electrolyte loss that necessitate intensive fluid therapy and cessation of oral macrolides. The incidence of diarrhea in foals treated with erythromycin-rifampin has ranged from 17% to 36%.[229,236] In one study, foals treated with clarithromycin had a higher incidence of diarrhea (28%) than those treated with azithromycin (8%).[229] In most cases diarrhea was mild and self-limiting. In the same study the incidence of severe diarrhea necessitating administration of IV fluids was not significantly different among groups of foals treated with azithromycin-rifampin, clarithromycin-rifampin, or erythromycin-rifampin.[229] During surges of very hot weather an idiosyncratic reaction characterized by severe hyperthermia and tachypnea has been described in foals treated with erythromycin.[236] Anecdotal reports suggest that these reactions may occasionally occur with newer macrolides as well. Administration of antipyretic drugs and placement of the foal in a cool environment will treat this problem. Severe enterocolitis has also been reported in mares whose foals are being treated with erythromycin, presumably resulting from disruption of the mare's normal colonic microflora after ingestion of small amounts of active drug during coprophagia or after contamination of feeders or water buckets with drug present on the foal's muzzle.[237]

Even though the vast majority of *R. equi* isolates from foals are highly susceptible to macrolides and rifampin, strains resistant to each have been encountered. The percentage of *R. equi* isolates resistant to either macrolides or rifampin has ranged between 0% and 4% depending on the studies.[231,238] Rifampin should not be used in monotherapy because this increases the chance of resistance developing.[230,239] Rifampin resistance is conferred by mutations in the RNA polymerase β subunit encoded by the *rpoB* gene.[240,241] Progressive development of resistance to both erythromycin and rifampin during treatment is extremely rare, but it has been reported.[215] The molecular mechanisms of macrolide resistance in *R. equi* isolates have not been determined, but *R. equi* isolates resistant to one of the three macrolides listed previously are almost invariably resistant to the other two as well. Therapy of foals developing severe diarrhea during macrolide therapy or therapy of foals infected with resistant isolates is problematic because of the limited range of alternative effective drugs.

Oral doxycycline in combination with rifampin has been used successfully for the treatment of foals with pneumonia caused by *R. equi*. The recommended dose of doxycycline in foals is 10 mg/kg q12h PO. This dose results in serum, pulmonary epithelial lining fluid, and bronchoalveolar cell concentrations above the MIC_{90} of *R. equi* isolates (1 μg/mL) for the entire dosing interval. Doxycyline is bacteriostatic against *R. equi*, but the drug is highly synergistic with rifampin and with macrolides in vitro. Therefore doxycycline could also be combined with a macrolide for the treatment of rifampin-resistant isolates. Chloramphenicol can be administered orally and achieves high concentrations within phagocytic cells in other species. The recommended dosage regimen is 50 mg/kg q6h PO. However, the fact that only 70% of *R. equi* isolates are susceptible to this drug and the potential human health risk make this drug a less attractive alternative. High doses of a TMS combination (30 mg/kg of combination every 8 or 12 hours orally) have been used alone or in combination with rifampin in foals with mild

or early *R. equi* pneumonia or for continued therapy in foals responding well to other antimicrobials.[110] However, TMS is not nearly as effective as the combination macrolide-rifampin.

In an experimental model of *R. equi* infection in immunosuppressed mice, the most effective drugs in monotherapy were found to be, in order of effectiveness, vancomycin, imipenem, and rifampin.[242] Amikacin, erythromycin, ciprofloxacin, or minocycline in monotherapy did not lead to a significant decrease in bacterial counts. The most active drugs in combination were those including vancomycin or rifampin, but these combinations were not significantly different from vancomycin monotherapy.[242] Vancomycin and imipenem should be used in foals only for the treatment of life-threatening *R. equi* infections caused by isolates confirmed to be resistant to all other possible alternatives.

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Nursing care, provision of adequate nutrition and hydration, and maintenance of the foal in a cool and well-ventilated environment are important. Oxygen therapy using humidified oxygen by pharyngeal insufflation in moderately hypoxemic foals, or by percutaneous transtracheal oxygenation in severely hypoxemic animals, is indicated.[243] Judicious use of NSAIDs is of value in reducing fever and improving attitude and appetite in febrile depressed anorectic foals. Nebulization may be helpful in selected animals with tenacious secretions and nonproductive cough. However, most foals with *R. equi* pneumonia do not benefit from nebulization, and the procedure is stressful to some. Similarly, bronchodilators are rarely helpful clinically in foals with pneumonia caused by *R. equi*. In addition to appropriate systemic antimicrobial therapy, foals with *R. equi* septic arthritis or osteomyelitis often require aggressive local therapy such as joint lavage, surgical debridement, and IV or intraosseous regional limb perfusion with antimicrobial agents. The prognosis of foals with abdominal abscesses is poor, although rare patients will respond to long-term antimicrobial therapy. Surgical removal or marsupialization has been attempted in some foals, but abdominal adhesions usually result in the inability to resect the lesion or in chronic intermittent episodes of colic.

31.7.8 Prognosis

Before the introduction of the combination of erythromycin and rifampin as the treatment of choice in the early 1980s, the prognosis of *R. equi*–infected foals was poor, with reported survival rates as low as 20%.[244] Using erythromycin and rifampin, Hillidge reported a successful outcome (as assessed by survival) in 50 of 57 foals (88%) with confirmed *R. equi* pneumonia.[219] Studies in referral centers, more likely to see the most severely affected cases, have revealed survival rates ranging from 59% to 72%.[9,213,229] Recent studies have shed light on the impact of *R. equi* infections on future athletic performance. Ainsworth and colleagues[245] performed radiography, hematologic and BAL analysis, and pulmonary function tests in five horses (6 to 18 months) with prior *R. equi* pneumonia and compared the results with age-matched controls with no history of respiratory disease. There was no significant difference between the two groups. In another study the gas exchange of seven standardbred horses previously diagnosed with *R. equi* pneumonia as foals was not compromised during intense treadmill exercise compared with reference values for healthy fit standardbreds.[246] Bernard and co-workers[247] evaluated the influence of *R. equi* pneumonia on future racing performance. Thirty horses that previously had *R. equi* pneumonia were compared with the affected foals' dams' progeny. There were no significant differences in total earnings, average earning index, and age at the first race between horses that previously had *R. equi* pneumonia and controls or the North American average. These results suggest that horses with previous *R. equi* pneumonia are likely to perform as well as expected if they race, but because only foals registered with the Jockey Club were considered, it does not indicate if they are as likely to race as a control population. More recently, the records of 219 foals diagnosed with *R. equi* pneumonia and treated with erythromycin and rifampin were reviewed.[213] The survival rate was 72%. Of the survivors 54% had at least one racing start, as opposed to

65% for the control population, suggesting that horses contracting *R. equi* pneumonia as foals may be slightly less likely to race as adults. However, as also shown by Bernard and colleagues,[247] the racing performance of foals that raced was not significantly different from that of the U.S. racing population.[213]

31.7.9 Control of *Rhodococcus Equi* Infections on Farms where the Disease Is Endemic

Current approaches for the control of *R. equi* infections on endemic farms depend on (1) decreasing the size of infective challenge, (2) screening for earlier recognition and therapy of affected foals, and (3) passive immunization. Recent advances in the area of chemoprophylaxis and immunoprophylaxis are also discussed.

31.7.9.1 DECREASING THE SIZE OF INFECTIVE CHALLENGE

There seems to be a progressive buildup of infection on horse farms with prolonged use. Thus, endemic farms are often those used for breeding horses for many years, those with heavy concentrations of mares and foals, and those located where summer temperatures are high, where the soil type is sandy, and where dust is extensive. Large numbers of foals kept on bare, dusty, manure-containing paddocks may result in heavy environmental challenge, with clinical disease maintaining the population of environmental virulent bacteria. General recommendations that would be expected to decrease dust formation and inhalation of virulent *R. equi* may help in reducing the incidence of the disease. However, solid evidence demonstrating the efficacy of the following general recommendations in decreasing clinical disease is lacking. Common sense dictates that foals should be housed in well-ventilated, dust-free areas and that dirt paddocks should be avoided. Pneumonic foals should be isolated, because they may contribute the most to contamination of the environment with virulent organisms. When possible, pasture could be rotated to decrease grass destruction, dust formation, and consequent inhalation of *R. equi*. Any sandy or dirt areas should ideally be planted with grass or made “off limits” to foals, or, alternatively, irrigation may be useful in decreasing dust formation and encouraging grass propagation. Because mares and foals tend to congregate around water sources and under shade in hot summers, reduction in the size of mare-foal bands or mobile troughs and shade may reduce the destruction of grass and exposure to barren soil. Dispersal of foals onto grass paddocks will reduce dust formation and therefore the number of inhaled bacteria. Ingestion of low numbers of organisms via grazing on contaminated grass may actually have the beneficial effect of immunizing foals orally.[160,248] Manure should be regularly removed from stalls, pens, and paddocks and composted. The fact that the concentrations of airborne virulent *R. equi* are higher in stables than in paddocks[157] suggests that frequent cleaning and disinfection of stalls may help to decrease contamination and opportunity for infection. Avoiding dirt-floored foaling stalls should be considered, because *R. equi* is a soil saprophyte and epidemiologic evidence suggests that dirt floors may increase the risk of development of *R. equi* pneumonia.[163]

31.7.9.2 SCREENING FOR EARLIER DETECTION OF AFFECTED FOALS

R. equi pneumonia is often not recognized until it is well advanced and therefore difficult to treat. Even severely affected foals may appear to suckle and behave normally to a casual observer. Screening for early recognition of *R. equi*–induced pneumonia before development of clinical signs and appropriately treating infected foals reduce losses and limit the costs associated with long-term therapy of severely affected animals. It is important to emphasize that screening methods are not diagnostic tests. A useful screening test is one in which the probability of disease is high with a positive test result (high positive predictive value) and very low with a negative test result (high negative predictive value). The higher the prevalence of disease at a given farm, the higher the positive predictive value of a given test will be. Therefore, depending on the prevalence of

R. equi infections on a given farm, a positive result of a screening test could be a basis to perform a diagnostic test (low to moderate prevalence) or to initiate therapy (high prevalence). Screening methods can be divided into three categories: physical examination findings, imaging techniques, and laboratory tests (Box 31-1). In one study on a large breeding farm with endemic *R. equi* problems, use of twice-weekly complete physical examinations with auscultation of the lungs was apparently successful in promoting early diagnosis and preventing mortality.[249] However, thoracic auscultation is a fairly insensitive tool, and many foals will not show clinical signs of respiratory disease or develop a fever until lung lesions are well established.

Imaging techniques such as radiography and ultrasonography are relatively specific because they detect lung lesions. As stated in the diagnosis section earlier, radiography offers the advantage of detecting either central or peripheral lesions. However, radiography has several disadvantages that limit its use as a practical screening test. Disadvantages of radiography include cost, need for special equipment, need for more personnel, and exposure of personnel to radiation. In addition, early radiographic lesions can be subtle and less typical of *R. equi* pneumonia than more advanced cases. Ultrasonography of the chest offers several advantages over radiography as a screening test. The entire chest can be scanned in just a few minutes, and when the periphery of the lung is affected ultrasonography is more sensitive than radiography. Biweekly ultrasonographic examination of the chest of all the foals on endemic farms (starting at 3 to 4 weeks of age) has been extremely useful in preventing mortality by promoting early identification of pneumonic foals before development of clinical signs.[250] Using this approach, as many as 50% of foals on a farm were found to have subclinical lung lesions.[250] Many foals with mild lung lesions may recover without therapy. However, it is impossible to discriminate between foals in which the infection will successfully resolve without treatment and foals that will eventually develop clinical signs. Foals with no clinical signs and ultrasonographic lesions consisting of only irregularities of the pleural surface (comet tail artifact) do not require therapy.[250] However, foals with focal areas of consolidation ≥1 cm in diameter or in depth (see Fig. 31-15, *A*) and foals with clinical signs of respiratory disease are usually treated.[251] Ultrasonography also offers the advantage of allowing evaluation of the severity of lung involvement, and follow-up examinations permit a more objective assessment of response to therapy. The duration of therapy is proportional to the initial severity of the lesions.[250]

31.7.9.2.1

Box 31-1 Screening Methods for Earlier Detection of Foals Infected with *R. equi* on Endemic Farms

31.7.9.2.1.1

PHYSICAL EXAMINATION

Daily visual inspection of foals for attitude and respiratory effort

Measuring rectal temperature of each foal twice daily

Biweekly thoracic auscultation by a veterinarian

31.7.9.2.1.2

IMAGING TECHNIQUES

Biweekly thoracic radiography

Biweekly ultrasonography*

31.7.9.2.1.3

LABORATORY TESTS

Biweekly measurement of white blood cell count

Biweekly measurement of fibrinogen concentrations

* Preferred method when the resources or expertise required are available.

Many farms do not have access to the resources or expertise required for periodic ultrasonographic evaluation. Laboratory tests may be more practical on farms where blood can be collected by farm workers. Recent studies have shown that currently available serologic assays and measurement of serum amyloid A are not useful screening tests.[252,253] In contrast, combination of careful daily observation and measurement of WBC counts and plasma fibrinogen concentrations in all foals at 2- to 4-week intervals, although labor intensive, may be a useful alternative to ultrasonography for early identification of *R. equi*–infected foals on endemic farms. In one study 165 foals were monitored during the entire breeding season, and diagnosis of *R. equi* pneumonia was confirmed in pneumonic foals by culture of a tracheobronchial aspirate. Total WBC count was found to be a significantly better screening method than measurement of fibrinogen concentrations.[216] Using a cutoff value of 14,000 cells/μL, sensitivity and specificity for early identification of foals with *R. equi* pneumonia were 88% and 81%, respectively.[216] On a farm where the disease prevalence is 40%, the predictive value of a positive test result (WBC >14,000 cells/μL) would be 75% and the predictive value of a negative test result (WBC <14,000 cells/μL) would be 91%. In contrast, the same cutoff value used on a farm with a disease prevalence of 5% would result in a predictive value of a positive test result of only 20%. This example underscores the fact that such screening methods are valid only when the prevalence of the disease is high. Because increases in WBC counts and fibrinogen concentrations are nonspecific findings, it is advisable to subject foals identified by such screening methods to additional diagnostics (e.g., ultrasonography or TBA) before initiation of therapy to reduce the rate of false-positive results. However, some farms where the prevalence of the disease is particularly high and well documented may elect to initiate therapy based on these screening methods alone.

31.7.9.3

PASSIVE IMMUNIZATION

IV administration of HI plasma obtained from horses vaccinated against *R. equi* using various antigens has consistently proved effective in significantly reducing the severity of *R. equi* pneumonia in foals after experimental challenge.[192,254] However, studies evaluating the efficacy of various HI plasma preparations under field conditions have given equivocal results, with only two of five controlled clinical trials demonstrating a statistically significant reduction in the incidence of *R. equi* pneumonia.[162,220,255–257] In one randomized controlled prospective study involving 165 foals on an endemic farm, the incidence of pneumonia caused by *R. equi* was 19% in the group that had received plasma versus 30% in the control group. Although the decrease in incidence did not quite reach significance ($P = .09$), such a decrease would be relevant to many farm managers.

The ideal time for administration of HI plasma and the minimal effective dose require further research. Administration of HI plasma before infection with *R. equi* is important.[258] However, early administration may result in the decline of passively transferred antibody to a nonprotective level at a time when foals are still susceptible to *R. equi* and environmental challenge is high.[256] Therefore IV administration of 1 L of HI plasma within the first few days of life followed by a second administration at approximately 25 days of age, although expensive, may be the best approach on farms with high morbidity rates. U.S. Department of Agriculture (USDA)–licensed *R. equi* antibody (HI plasma) for the prevention of *R. equi* pneumonia is commercially available in North America (Lake Immunogenics Inc., Ontario, NY; Plasvacc USA, Templeton, Calif.). HI plasma is expected to slightly decrease the incidence of the disease (by 30% to 40%) but will not prevent infection in all foals and should not lull farm owners into a false sense of security and reduce the need for continued vigilance. Whether this strategy is cost-effective will vary from farm to farm. When used for the control of *R. equi* infections on endemic farms, administration of HI plasma should always be combined with screening techniques aimed at early identification and treatment of infected foals (see earlier).

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31.7.9.4

CHEMOPROPHYLAXIS

Another suggested approach for the prevention of *R. equi* infections on endemic farms is the prophylactic administration of antimicrobial agents to all the foals during the time period when they are most susceptible to infection. Azithromycin is an attractive choice for prophylactic administration because of good oral bioavailability, long half-life, and high and sustained concentrations in pulmonary epithelial lining fluid, bronchoalveolar cells, and neutrophils. In a prospective randomized clinical trial, azithromycin was administered at a dose of 10 mg/kg q48h for the first 2 weeks of life. Preliminary data analysis suggests an overall significant benefit, although protection was not absolute.[259] However, there are several potential problems with the mass administration of azithromycin or other antimicrobial agents for the prevention of *R. equi* infections. First, the period of susceptibility to *R. equi* is much longer than 2 weeks. As a result, the ideal time period for antimicrobial prophylaxis remains unknown. Second, administration of azithromycin to foals has occasionally resulted in life-threatening adverse effects such as enterocolitis and possibly hyperthermia. Prophylactic administration to all the foals on a farm will increase the likelihood of occurrence of adverse effects. Finally and most importantly, the long-term effects of this practice on selection of resistant bacterial isolates are unknown. Given the fact that *R. equi* isolates resistant to azithromycin are usually resistant to erythromycin and clarithromycin also, development of resistance could have devastating consequences for the foal crop.

A novel approach that may prove beneficial in the prevention of *R. equi* pneumonia is the administration of gallium maltolate. Gallium is a trivalent semimetal that shares many similarities with ferric iron. Most bacteria require iron for survival. Recent studies have shown that iron acquisition is essential for the survival of *R. equi* and that the organism can acquire and use iron bound to transferrin and lactoferrin.[260] Gallium readily binds to plasma transferrin and lactoferrin.[261] Bacteria acquire gallium and incorporate it into essential iron-dependant enzyme systems, which leads to inactivation of those systems and bacterial death. A recent study has shown that gallium inhibits in vitro growth of *R. equi* and that oral treatment of mice with gallium maltolate may decrease the number of *R. equi* in tissues after experimental infection.[262] Recent pharmacokinetic and safety studies in neonatal foals have indicated that gallium maltolate at a dose of 20 mg/kg results in adequate serum concentrations and that no adverse clinical or clinicopathologic effects were apparent when gallium was administered for 5 days.[263] Larger numbers of foals treated over longer periods of time will be needed to more

fully characterize safety issues. Clinical trials to critically evaluate the prophylactic effectiveness of gallium in foals on endemic farms are awaited.

31.7.9.5 ACTIVE IMMUNIZATION

It would be considerably more convenient to control *R. equi* pneumonia on endemic farms by the active immunization of mares or foals with a protective antigen. Such attempts have so far been unrewarding in foals. The role of antibody in partial protection against *R. equi* infection would suggest that vaccination of mares would be effective at conferring at least some degree of protection. However, in both a field study and an experimental challenge, vaccination of mares did not provide protection against *R. equi* pneumonia despite a significant increase in colostral specific *R. equi* antibody and transfer of passive immunity to foals.[257,264] More recently, a vaccination of a small number of mares with VapA protein antigen associated with a water-based nanoparticle adjuvant led to high anti-VapA IgG concentrations in mares and foals and may have conferred protection against natural challenge compared with nonvaccinated controls.[265] However, a more extensive study on an endemic farm will be necessary to confirm these preliminary findings before widespread vaccination of mares can be recommended.

Because cell-mediated immunity is of paramount importance in protection against *R. equi*, active immunization of foals will likely be required for complete protection. Recent studies in mice indicated that DNA immunization against *vapA* protects against *R. equi* infection and that the IgG subisotype response is consistent with a Th1-based immune response.[266] A similar DNA vaccine containing the *vapA* gene has been shown to induce strong cell-mediated immune responses in adult horses, but responses were poor in foals.[267] Immunization in foals will need to be initiated very early in life, and an effective vaccine will have to overcome the relative immaturity and possible inherent bias of the naive neonatal immune system. The fact that oral administration of live virulent *R. equi* confers almost complete protection against heavy intrabronchial challenge[248,264] and the fact that most foals on endemic farms do not develop disease or develop subclinical disease and eventually clear the infection provide the proof of concept regarding the potential for active immunization in foals. Further work is needed to examine active immunization strategies based on a better understanding of the antigens of importance and the method of administration or adjuvant required to produce the effective Th1 immune response required for protection against *R. equi* pneumonia in neonatal foals.

31.8 PNEUMONIA IN FOALS

DANIELA BEDENICE

Equine pneumonia is a significant cause of morbidity and mortality in both the newborn and the older foal.[268–271] Although the causative agents and the mode of lung infection are generally different for each age-group, foal pneumonia is commonly associated with a compromise in the immunologic protection of the host. The exact immunologic basis of the foal's inherent susceptibility to opportunistic respiratory pathogens needs to be further elucidated.

Failure of passive transfer of immunity (FPT) is a well known risk factor of neonatal infection, including respiratory disease,[271] because not only are affected foals deprived of specific maternal antibody protection, but their neutrophil function is also seriously impaired.[272] Although foals can respond immunologically in utero to bacterial or viral infections, their ability to do so is less than that of adults. Reduced complement values and

defective chemotaxis (directed migration of neutrophils or macrophages) and killing capacity of the neonatal neutrophil contribute to a relatively decreased defense against invading bacteria. Furthermore, an immature ciliary apparatus and the presence of fewer alveolar macrophages in neonates in comparison with adult horses lead to decreased bacterial clearance from the lungs.[273] The number and distribution of the bronchoalveolar cells approach adult levels only at approximately 3 to 6 weeks of age.[274]

It has been suggested that a natural cellular immunodeficiency may also occur in foals at 2 to 4 months of age.[275] Although the exact association between age-related cellular immunodeficiency and the defense against intracellular pathogens such as *P. carinii (Pneumocystis jiroveci)* and *R. equi* of foals still needs to be clarified, $CD4^+$ and $CD8^+$ T lymphocytopenia was documented in a filly with *P. carinii* pneumonia.[276]

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31.8.1 Etiology

31.8.1.1 NEONATAL PNEUMONIA (<1 MONTH OF AGE)

In contrast to the older foal, infectious lung disease in the neonate is usually part of a multiple-organ, systemic infection or sepsis, which may be acquired via the placenta in utero or perinatally through environmental bacteria leading to hematogenous (ascending) infection (e.g., omphalophlebitis). *E. coli, Klebsiella* species, *Actinobacillus equuli, Salmonella* species, and *Streptococcus* species are some of the more common bacteria involved in neonatal foal pneumonia.[277]

Descending lung infections may be caused by inhalation of viral, bacterial, or opportunistic fungal agents. Furthermore, iatrogenic aspiration (oil, medication, oral supplements) or aspiration of gastric reflux, milk, meconium, and contaminated amniotic fluid after placental infection may seed the foal's lung. Meconium aspiration occurs in utero in foals that experience fetal distress (perinatal asphyxia). Although the meconium is commonly sterile at this time, it creates mechanical airway obstruction, surfactant inactivation, and pulmonary inflammation (caused by vasoactive mediators and chemotactic and inflammatory cytokines, including TNF-α, interleukin [IL]-1β, and IL-8).[278] The resulting edema and vasoconstriction may lead to hypoperfusion of the pulmonary parenchyma, with damage to type II pneumocytes and decreased production of surfactant.[279] This type of “secondary surfactant deficiency” may also be induced by other forms of generalized pulmonary inflammation, including diffuse bacterial pneumonia. Neurologic dysfunction, severe inflammation, or structural abnormalities of the upper airways (congenital cysts, dorsal displacement of the soft palate, laryngeal paralysis, pharyngeal weakness, etc.) may predispose to aspiration pneumonia postpartum.

EVA and herpes viral infections (EHV-1 and EHV-4) have been implicated in in utero viral infections leading to lung disase.[280] Although involvement of adenovirus in the pathogenesis of pneumonia has also been reported in a thoroughbred foal, fatal adenoviral pneumonia is primarily associated with combined immunodeficiency (SCID) in Arabian foals.[281,282] In addition, a recent report documents the isolation of influenza A virus from a seven-day-old foal with bronchointerstitial pneumonia.[282]

31.8.1.2 PNEUMONIA IN OLDER FOALS (1 TO 6 MONTHS OF AGE)

S. zooepidemicus and *R. equi* are the most important pathogens associated with pneumonia in older foals, although plurimicrobial infections *(Actinobacillus* species, *B. bronchiseptica, E. coli, Klebsiella pneumoniae, Pasteurella* species, *Pseudomonas* species, *Salmonella* species, and *Staphylococcus* species) are not

uncommon.[283,284] *S. zooepidemicus* was isolated from 87% of uncomplicated lower respiratory tract infections in foals (1 to 8 months old) on selected farms[285] and was documented as the most common cause of pulmonary abscesses in a second study.[286] In contrast, anaerobes appear to be infrequently involved in primary pneumonia of foals.[285] *Corynebacterium pneumonia* due to aerosol infection is a rare cause of diffusely increased interstitial and peribronchial radiographic densities, indicative of pulmonary abscesses in foals.[287]

Although respiratory viruses are often believed to be primary offending agents that lead to secondary bacterial lung invasion, they have limited importance in nursing foals.[285,288] Equine adenoviruses (EAdVs) and EHV-2 are ubiquitous in the general equine population, with little pathogenicity in immunocompetent foals. Although adenoviruses are the most common respiratory pathogens in Arabian foals with severe combined immunodeficiency (SCID), the role of EHV-2 in the respiratory disease complex of foals remains unclear. The latter has been implicated as a predisposing factor for *R. equi* pneumonia.

Because of the complexity of the disease, in-depth discussions of *Rhodococcus* pneumonia and ALI and ARDS are presented elsewhere in Chapter 31.

31.8.1.3

INTERSTITIAL PNEUMONIA

Acute, severe interstitial or bronchointerstitial pneumonia is a sporadic, rapidly progressive disease of foals of 1 to 6 months of age that is characterized by a sudden onset of respiratory distress, tachypnea, fever, high mortality, and histopathologic evidence of severe, diffuse, necrotizing bronchiolitis, alveolar septal necrosis, and neutrophilic alveolitis on necropsy.[289–291] Although no definitive causative agent(s) or factor(s) of this disease have yet been identified, suspected causes include viruses, *P. carinii*, heat stroke, environmental toxins, and bacteria.[289–292] Enteric gram-negative organisms, *R. equi, Pseudomonas aeruginosa*, and *P. carinii* have all been cultured from the lungs of affected foals.

The reported cases are usually sporadic, affecting a single foal within a herd,[289] although rare clusters of cases have also been described.[291] The disease is generally rapidly progressive and may lead to sudden death as a result of fulminant respiratory failure. Severe respiratory distress, hypoxemia, hypercapnia, and respiratory acidosis are the most striking clinicopathologic signs. The hypoxemia of bronchointerstitial pneumonia is relatively resistant to supplemental oxygen therapy, indicating a pulmonary shunt. Thoracic radiographs commonly demonstrate caudodorsally distributed interstitial and bronchointerstitial pulmonary opacities. With advanced disease, the radiographic pattern progresses to include patches of a coalescing alveolar nodular pattern with air bronchograms.[293] As with bacterial pneumonia, many foals demonstrate hyperfibrinogenemia and neutrophilic leukocytosis on hematology.

Therapy is symptomatic, including antiinflammatory therapy, broad-spectrum antibiotics, thermoregulatory control, bronchodilation, and supplemental oxygen. Surviving foals may develop a proliferative epithelial and interstitial response including bronchiolar and alveolar epithelial hyperplasia, type II cell hyperplasia, and hyaline membrane formation.[293]

Chronic pulmonary disease (1 to 3 months' duration) with marked radiographic interstitial opacities was reported in 12 foals, age 3 to 9 months, that were examined at a veterinary teaching hospital.[294] Evaluation failed to yield a consistent pathogen from tracheobronchial aspirates. The authors proposed that chronic

interstitial pneumonia occurring in foals is associated with a good prognosis and considered corticosteroid therapy as a potentially useful treatment.

31.8.1.4 *PNEUMOCYSTIS JIROVECI (CARINII)* INFECTION

Rare opportunistic fungal pathogens of the lung may include *P. carinii* (renamed *P. jiroveci* in humans), *Aspergillus, Candida*, and *Mucor* species. *P. carinii* is a unicellular eukaryote that has been classified as a fungus after DNA studies.[295] It is most commonly seen in humans and animals that suffer from a concurrent immunodeficiency. It was first recovered in Arabian foals with SCID.[296] It has since been recovered from foals of other breeds with no specific history of immunodeficiency, although for the most part no direct testing for immunocompetence was performed in the reported cases. However, one more recently documented case demonstrated a low number of circulating $CD4^+$ and $CD8^+$ lymphocytes in a filly with *P. carinii*.[276]

In several reports the onset of clinical signs in affected foals ranged from a 3-week history of weakness, weight loss, and nasal discharge to acute dyspnea. Half of the reported non-Arabian cases had concurrent infections with *R. equi, Enterobacter cloaca, E. coli*, or *S. zooepidemicus*. A severe interstitial, sometimes miliary and alveolar pattern was seen on radiographs of the lungs. The majority of the reported foals died, and the diagnosis of *P. carinii* was obtained at necropsy.[276,292,296–299] On postmortem examination the lungs were uniformly heavy and consolidated, and a diffuse interstitial pneumonia was found. Trophozoites and cysts were observed in the alveolar epithelial cells, and macrophages within the alveoli. Silver staining and streptavidin-biotin immunolabeling of histologic sections provide a better visualization of the organisms in the pulmonary tissue.[297] A few foals were diagnosed by visualization of the organism on a BAL sample. Two surviving foals responded to trimethoprim-sulfamethoxazole (TMS) therapy.

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31.8.2 Clinical Presentation and Diagnosis of Foal Pneumonia

The clinical manifestation of pneumonia in the newborn foal can be variable and depends on the disease severity and underlying or associated problems. Early in life, localizing clinical signs of respiratory infection may be absent even in the presence of extensive disease. Dyspnea may be seen in severely affected foals and may manifest as an increase in respiratory rate, effort, or thoracoabdominal asynchrony (paradoxic breathing). However, signs of respiratory distress and hypoxemia are frequently vague. Even some severely hypoxemic foals may show only restlessness, considerable resistance, and struggling when being handled or restrained. Abnormal respiratory sounds (crackles or wheezes) may be heard on auscultation of ill foals. However, even normal foals may show crackles on the down lung after having remained in lateral recumbency for a prolonged period of time. Furthermore, foals with no auscultable abnormalities may still have extensive pulmonary disease.[300,301] Similar to other species, cyanosis is a sign of severe hypoxemia in foals. The arterial Pa_{O_2} (partial pressure of oxygen), however, must reach very low levels (35 to 45 mm Hg) before clinical cyanosis is observed. Approximately 5 g/dL of unoxygenated hemoglobin in the capillaries generates the dark-blue color that is appreciated as cyanosis in humans. Therefore severely anemic foals may never appear cyanotic even in the face of profound hypoxemia. Weakness, depression, anorexia, weak or absent suckle reflex, dehydration, and fever may also be noted in newborn foals with respiratory disease. Cough and nasal discharge are usually absent in the early stages of neonatal pulmonary disorders.[277] The older foal, on the other hand, will generally exhibit clinical signs that focus on the respiratory tract, such as abnormal auscultation of the lungs, nasal discharge, cough, fever, tachypnea, and increased respiratory effort.

Thoracic radiographs and arterial blood gas analysis are important in confirming the presence and evaluating the extent and distribution of foal pneumonia. Because radiographic findings may precede or lag behind alteration of respiratory function, repeated diagnostic imaging is recommended. A recent study documented that radiographic abnormalities involving the caudodorsal lung region were most common in neonatal foals admitted to a referral center.[302] Bedenice and colleagues showed that the presence of dyspnea, tachypnea, a fibrinogen concentration >400 mg/dL, systemic inflammatory response syndromes (SIRS), hypoxemia, or FPT in neonatal foals may be a predictor of underlying respiratory disease and should prompt an early radiographic evaluation of the thorax, even in the absence of other localizing clinical signs.[271,302] Thoracic ultrasonography has become a popular diagnostic tool for the assessment of equine lung and pleural disease and is particularly useful in determining the side(s) of the thorax affected, as well as the precise location of the lesion in most cases.[271]

Diagnostic sampling of the respiratory tract is less commonly performed in neonatal foals compared with older foals and adult horses. However, TBA, BAL, protected catheter brush (PCB), or protected aspiration catheter sampling (PAC) is important in stabilized patients, irrespective of age, to direct antimicrobial therapy and evaluate therapeutic efficacy. Lung biopsies are rarely performed and are limited to patients with chronic disease or suspected fungal pneumonia.[301]

31.8.3 Treatment

The treatment goals in dealing with bacterial pneumonia in either age-group are similar and directed at maintaining adequate gas exchange to ensure patient survival, limit progressive pulmonary damage, and ultimately eradicate infection. Long-term goals should aim to maintain optimal pulmonary function and conserve adult athletic performance. Specific treatment strategies for septic pneumonia may include goal-directed antimicrobial therapy, treatment of inflammation independent of antimicrobial therapy, respiratory therapy (oxygen therapy, ventilation, bronchodilation), and cardiovascular support.[300]

Broad-spectrum antimicrobial treatment, with consideration of the drugs' anticipated sensitivity and lung penetration, should be initiated before culture results are available. Third- or fourth-generation cephalosporins (ceftiofur and cefepime, respectively) show good penetration into lung tissues.[303] Alveolar delivery of antibiotics typically occurs via diffusion of a free, nonprotein-bound drug and is usually satisfactory if plasma concentrations and alveolar perfusion are adequate.[304] Aminoglycosides penetrate lung tissue at 10% to 45% of serum levels. However, the acidic environment of infected airways may reduce the drug's activity below levels sufficient to eradicate the offending bacteria in some cases.[305,306] Antibiotic therapy should not be discontinued prematurely in neonatal foals, because pulmonary infection is commonly well established before its diagnosis.[307]

31.8.4 Outcome

The survival of neonatal foals with septic pneumonia is contingent on the underlying disease conditions, a prompt diagnosis, and the cause and severity of lung dysfunction. Few studies have objectively evaluated the outcome of foal pneumonia.[300] One report documented that 65% of foals with radiographic evidence of pulmonary disease were discharged alive from the hospital, in contrast to 86% survival of foals without respiratory illness. The presence of diffuse radiographic infiltrates (caudodorsal, caudoventral, and cranioventral lung involvement) or concurrent alveolar patterns within the caudodorsal and caudoventral lung indicated lower

survival rates.[271] Pneumonia is also one of the greatest causes of morbidity and mortality in foals greater than 1 month of age.[269]

The long-term effect on athletic performance has thus far been evaluated only in older foals that survived *rhodococcus* pneumonia. *R. equi* infection in foals was associated with a decreased chance of racing as adults. However, the performance of foals that went on to race was not significantly different from that of the general U.S. racing population.[308] It remains speculative whether severe equine neonatal pneumonia will most likely limit future peak athletic performance. Human studies have shown that many hosts develop long-lasting or permanent lung changes after recovery from neonatal pneumonia, which may significantly affect the quality of life and susceptibility to later infections. Case-based evaluations in horses have demonstrated that functional and structural pulmonary abnormalities may occur in survivors of severe neonatal pneumonia. However, the clinical significance of this finding currently remains unclear.

31.9 FUNGAL INFECTIONS OF THE EQUINE RESPIRATORY TRACT

ALLISON J. STEWART

31.9.1 Definition and Etiology

Fungi are eukaryotic organisms with a definitive cell wall made up of chitins, glucans, and mannans. Within the fungal cell wall, the plasma membrane contains ergosterol, a cell membrane sterol that is frequently targeted by antifungal agents. There are over 70,000 species of fungi, but only 50 species are known to cause disease in people or animals. Pathogenic fungi can be divided into three groups: multinucleate septate filamentous fungi, nonseptate filamentous fungi, and yeasts. Dimorphic fungi are able to interchange between forms depending on environmental conditions. Examples of dimorphic organisms include *Blastomyces dermatitidis, Histoplasma capsulatum*, and *Coccidioides immitis*, which exist in yeast form in vertebrate host tissue and in hyphal or mycelial form in vitro. In soil and decaying matter, the mycelial form usually is present and is composed of a collection of hyphae. The mycelia produce infective spores that are capable of inoculating vertebrate tissue.

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Fungal infections in horses are relatively uncommon, although geographic prevalence is highly variable. Fungi are ubiquitous, and their constant aerosol exposure to respiratory tissue is inevitable. Upper respiratory and pulmonary disease caused by fungi is frequently acquired by the inhalation route, with the sporular diameter small enough to allow penetration into the distal airways and alveoli. In most samples of stable air, more than 90% of particles visible under a light microscope are spores of fungi or actinomycetes.[309] One study found that if a horse stood quietly in its stable without access to hay, the mean concentration of dust was very low (approximately 12 particles per cubic centimeter [of particles less than 5 mm in diameter]). When the bedding was disturbed during the normal "bedding down" operation, the concentration of respirable dust increased sixfold.[310] Systemic fungal infections and some cases of fungal pneumonia are thought to arise through a compromised GI tract, by inhalation, or via open wounds.

Tissue invasion of pulmonary tissue usually occurs in the immunocompromised host, although on occasion the normal individual may be affected. Important predisposing factors for fungal pneumonia include (1) qualitative and especially quantitative granulocyte abnormalities and (2) the presence of devitalized tissue. In most cases of upper respiratory tract fungal granuloma, there are no obvious predisposing causes.

Primary pathogenic fungi such as *B. dermatitidis, H. capsulatum, C. immitis, Cryptococcus neoformans*, and *Conidiobolus coronatus* usually infect immunologically normal horses. However, in a report of cryptococcosis in

seven horses, five had a history of illness that may have predisposed them to cryptococcosis.[311] A separate group of fungal pathogens tend to infect only those equine patients with abnormal host defenses. Opportunistic fungi including *Aspergillus* species, *Candida* species, *Fusarium* species, *Emmonsia crescens*, and *P. carinii* have caused fungal disease in horses that are immunocompromised or neutropenic; have neoplasia, colitis, enteritis, or bacterial pneumonia; or have been treated with corticosteroids.[312–323] In vitro studies support the critical role of phagocytic cells in host defense against opportunistic fungi.

31.9.2 Clinical Signs

Mycotic granulomas have been found in the nasal passages, paranasal sinuses, nasopharynx, guttural pouch, trachea, bronchioles, lungs, and mediastinum of infected horses. The most common clinical signs of upper respiratory fungal infection include unilateral or bilateral serosanguineous or mucopurulent nasal discharge, as well as inspiratory or expiratory noise. Other clinical signs include coughing, facial deformation, and dyspnea caused by partial blockage of nasal passages by granulomatous masses. Differential diagnoses for fungal granulomas of the respiratory tract include ethmoidal hematoma, squamous cell carcinoma, amyloidosis, and exuberant granulation tissue.

Fungal plaques in the guttural pouch often are located over the arterial blood supply. Horses with guttural pouch mycosis usually have episodic serosanguineous nasal discharge that may progress to potentially fatal epistaxis if there is erosion into an artery. The duration of clinical signs can vary from days to many months. Guttural pouch mycosis is discussed in detail elsewhere.

Pulmonary fungal infections causing granulomas, diffuse pneumonia, or pleuropneumonia can manifest with signs similar to those of bacterial infection. There may be cough, nasal discharge, tachypnea, respiratory distress, hemoptysis, and, if chronic, weight loss. Radiographic appearance of fungal pneumonia may reveal virtually any infiltrative pattern. Although miliary patterns are occasionally seen, the most common initial finding is a patchy bronchopneumonia. Multiple focal sites are common, and lesions tend to be peripheral in distribution. Differential diagnoses include bacterial pneumonia, recurrent airway obstructive disease, silicosis, granulomatous disease complex, or neoplasia.

Systemic infections can have variable clinical signs dependent on the location and extent of the infection. Fungal infections can affect multiple organ systems and body cavities. Weight loss, colic, or diarrhea can often occur with infection within the abdominal cavity.

31.9.3 Diagnostic Sampling

Lesions in the nasal passages, nasopharynx, guttural pouch, trachea, and bronchioles usually can be observed directly during endoscopic examination. Masses in lungs and paranasal sinuses may be observed radiographically. CT or MRI provides detailed imaging of the equine skull and can be used to determine the extent of lesions and bony invasion. An 8- to 20-mm trephine* can be drilled into the nasal or maxillary sinus; a sterile rigid arthroscope or flexible endoscope can then be passed through the trephine to directly view some lesions within the paranasal sinuses.

For nasal and nasopharyngeal lesions, specimens for cytology, histopathology, and culture can be obtained by use of endoscopically guided biopsy instruments; however, these samples tend to be small, superficial, and often nondiagnostic. Mucosal contaminants may overgrow the organism of interest. Larger biopsy samples from the nasal passages or nasopharynx often can be obtained by use of a uterine biopsy instrument† passed nasally with

visual guidance from a flexible endoscope. Excisional biopsy or surgical debulking may be performed through a sinus flap or via laryngotomy.

Fungal pneumonia may be diagnosed from samples obtained by tracheal wash or BAL or via a lung biopsy (Fig. 31-17). Lung biopsy is associated with significant risk if a pulmonary vessel is accidentally biopsied. The biopsy should be performed ideally after radiographic evaluation or with concurrent ultrasound guidance, and the sample should be obtained from the periphery of the lung; however, some horses have experienced fatal hemorrhage associated with biopsy of a vessel only 2 cm from the periphery. The lung is rich in plasminogen, so bleeding complications may be severe. Spring-loaded biopsy needles‡ are safer for lung biopsy than Tru-Cut biopsy instruments.[324] Ultrasound evaluation can be used to monitor for bleeding after the procedure.

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Fig. 31-17 Percutaneous lung biopsy from caudal periphery of lung of a weanling foal.

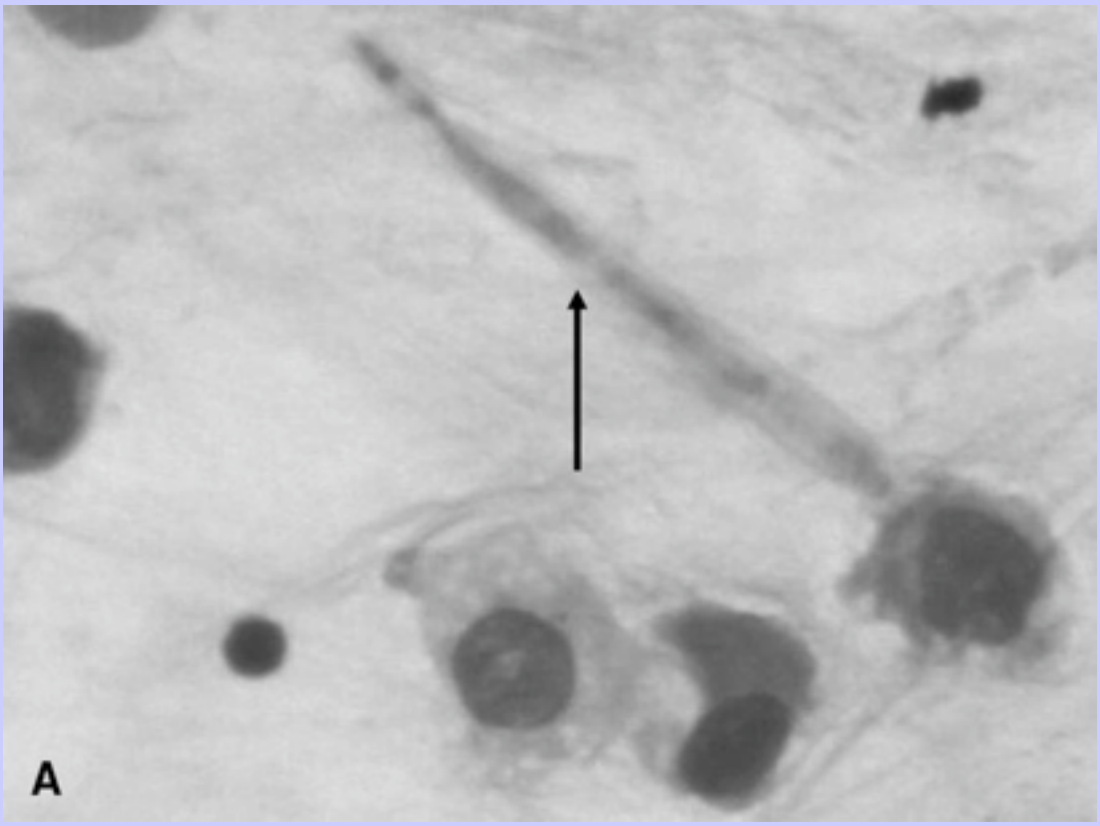
31.9.3.1

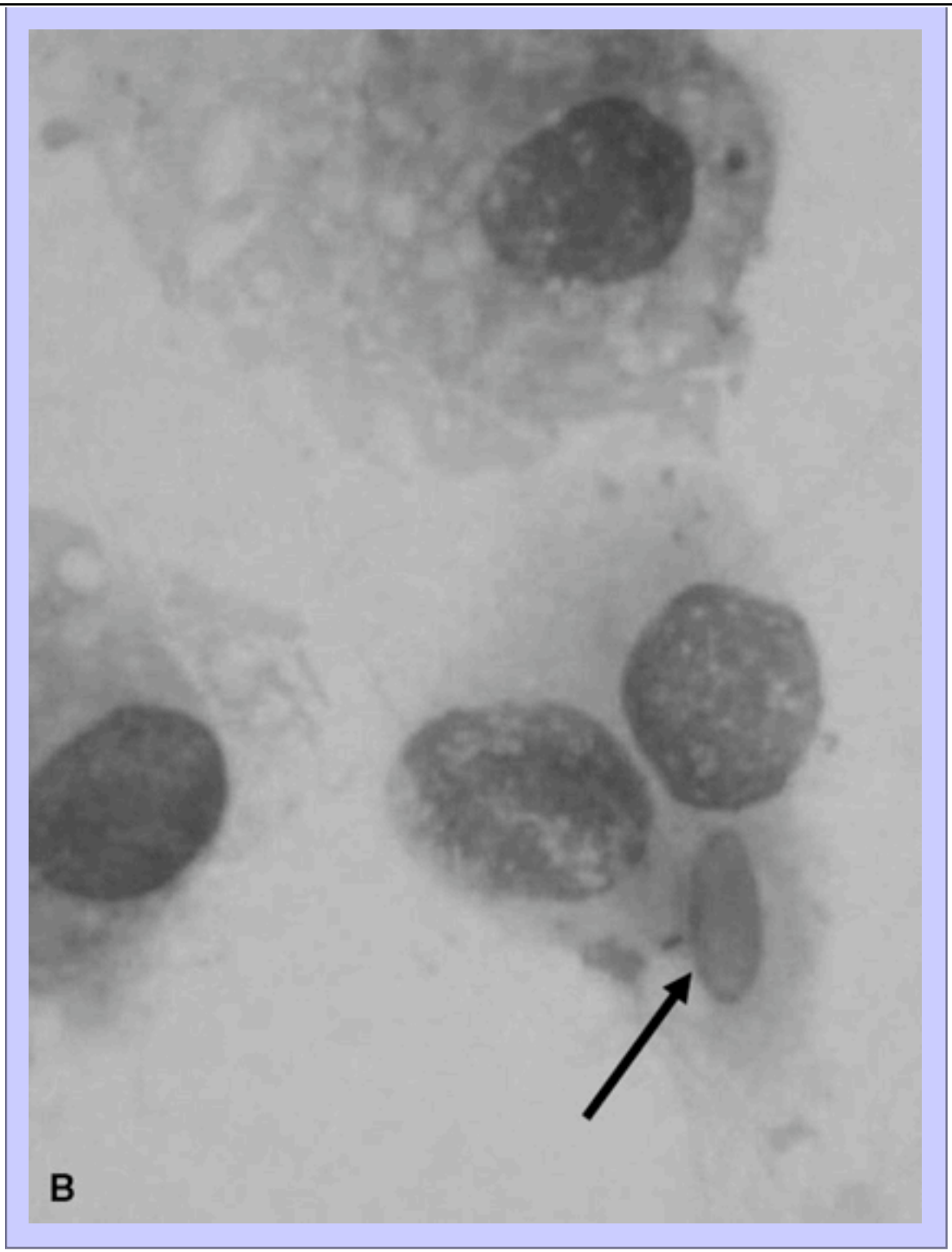
CYTOLOGY

Fungal hyphae may be identified in airway fluid or in impression smears obtained from biopsied masses. Clinicians must be careful in attributing significance to the presence of fungal elements in a TTA. Fungal hyphae are often present either free or in large mononuclear cells in tracheal aspirates from healthy horses.[90] A study of healthy thoroughbred racehorses showed that 70% had fungal elements detected in their tracheal

aspirates.[92] None of the horses from either study had other evidence of fungal pneumonia. Barn fungus such as *Alternaria* species are nonpathogenic and rarely incite an inflammatory response in the host. The organisms often have a blocklike appearance and may be colored (Fig. 31-18, *A* and *B*). A normal predominance of macrophages, lymphocytes, and nondegenerate neutrophils (<5% to 10%) would be expected.

Fig. 31-18 *Alternaria* species from transtracheal wash specimens obtained from healthy horses. **A**, An extracellular spore *(arrow)* with several macrophages, squamous cell (indicative of pharyngeal contamination. **B**, Intracellular spores *(arrow)* within binucleated macrophage. Courtesy Elizabeth Welles, Auburn University, Ala.





To be significant cytologically, large numbers of fungi should be involved in the inflammatory process within the lung. With fungal pneumonia, aspirates may contain predominately neutrophils that often are degenerate and may contain intracellular fungal hyphae. If processing of the sample is delayed, extracellular fungi may be

phagocytized, which confuses the interpretation. Some fungi have characteristic morphologic features that can permit an early presumptive identification (Table 31-5).

* Michelle 8-mm trephine or 14- to 20-mm Galt trephine, Jorgensen Laboratories, Inc., Loveland, Colo.

† Jorgensen Laboratories, Inc., Loveland, Colo.

‡ 4-g × 20-cm biopsy needle, Temno Products Group International, Lyons, Colo., or Magnum biopsy needle.

31.9.3.2

HISTOPATHOLOGY

Hyphae of certain fungi may be poorly visualized when routine hemotoxylin and eosin (H&E) stains are used; therefore special stains such as periodic acid Schiff (PAS), Gridley's fungus, and Grocott-Gomori methenamine-silver nitrate (GMS) can be useful to stain histopathologic specimens. With chronicity, there is often evidence of extensive fibrosis.

31.9.3.3

MICROBIOLOGIC CULTURE

Fungi can be found in tracheal aspirates from healthy horses. Sixteen percent of healthy horses are reported to have fungal growth on the tracheal aspirate bacterial culture plates; therefore results of fungal culture must be interpreted with caution.[91] Some fungi have fastidious growth requirements. They may be outcompeted by contaminant bacteria and may take up to several weeks to grow on culture media. For transport of tissue for microbiologic culture, the sample should be placed in a prepared culture medium* and transported at room temperature. Specific culture media such as Sabouraud's dextrose agar,† inhibitory mold agar, and Mycobiotic agar containing cycloheximide and chloramphenicol are useful.

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Table 31-5 Characteristic Morphologic Features and Availability of Serologic Tests for Fungal Organisms Reported to Cause Fungal Granulomas in Horses (September 2006)

	Cytologic Appearance	Serologic Test	
Agent	**Tissue Form**	**Method**	**Veterinary Laboratory***
Cryptococcus neoformans	Round, thin-walled, yeastlike fungus (51–10 µm) with a large heteropolysaccharide capsule (1–30 µm in diameter) that does not take up common cytologic stains. Capsule is best stained using Mayer's mucicarmine stain. Organisms show narrow-based budding and lack endospores.	Capsular antigen ELISA (antigen) Latex agglutination (antigen)[331]	$30.00 UT $12.50 CU $20.00 CSU $16.00 UGA $18.00 NMDA
Conidiobolus coronatus	Broad, thin-walled highly septate, irregularly branched hyphae (5–13 µm in diameter).[356] Often surrounded by acidophilic staining glycoprotein antigen-antibody complex known as Splendore-Hoeppli material.	Immunodiffusion is highly sensitive and specific; decreasing titer correlated to disease resolution in horses[354,358]	Serologic testing not widely available
Pseudallescheria boydii	Hyaline, nonpigmented, septate, randomly branched hyphae (2–5 µm in diameter) with regular hyphal contours. Asexual form has nonbranching conidiophores with terminal conidia. Sexual form in culture has cleistothecium (large round body) and ascospores.[347]		
Coccidioides immitis	Spherules have a double-contoured wall, are variable in size, but can be large (20–80 µm, up to 200 µm). The mature spherules (sporangia) contain endospores (sporangiospores) 2–5 µm in diameter. In the environment, mycelium are thick-walled with barrel shaped arthroconidia.	AGID (antibody) for IgM and IgG[332,375] CF (antibody)[375,379,385] May have some false-positive results[378]	$15.00 UT $12.00 CSU $8.00 NMDA $12.00 NMDA $12.50 CU

Aspergillus species	Broad (2–4 µm diameter) septate hyphae with parallel sides and acute right angled branching.	*Aspergillus* galactomannan EIA (sandwich immunoassay) Some reactivity to *Penicillium*, *Alternaria*, and *Paecilomyces* AGID (antibody) *Aspergillus fumigatus* only	Platelia *Aspergillus* antigen EIA by MDL $15.00 UT $12.50 CU
Blastomyces dermatitidis	Yeasts are spherical (15–17µm in diameter) with basophilic protoplasm and unstained, uniformly shaped refractile walls. Unilateral, broad-based budding is characteristic. Yeasts are often located within multinucleated giant cells.	AGID (Antibody)[328]	$15.00 UT $12.50 CU
Histoplasma capsulatum	Yeasts (2–4 µm in diameter) have a thin clear halo surrounding a round or crescent- shaped basophilic cytoplasm.	AGID (Antibody)[374]	$15.00 UT $12.00 CSU $12.50 CU
Acremonium strictum	Mononuclear cells contain single, spherical, intracytoplasmic encapsulated spores 3–5 µm in diameter[313]		
Candida species	Ovoid budding yeast cells (2–4 µm in diameter) with thin walls or can occur in chains that produce septate pseudohyphae when blastospores remain attached after budding division. Filamentous, regular, true hyphae also may be visible.		
Pneumocystis carinii	Trophozoite (yeast form), ameboid (2–5 µm in diameter) with filopodia that attach to the surface of type I pneumocytes. Sporangia (cystic form) are encapsulated spores (4–6 µm in diameter) containing eight uninuclete spores (intracytic bodies).[322,323,325,383]		

AGID, Agar gel immunodiffusion; *CF*, complement fixation; *EIA*, enzyme immunoassay; *ELISA*, enzyme linked immunosorbent assay.

* CSU = Colorado State University, (970) 297-1281, fax (970) 297-0320, www.dlab.colostate.edu/security2/testprice.cfm.

CU = Cornell University, Animal Health Diagnostic Center, (607) 253-3900, fax (607) 253-3943, www.diagcenter.vet.cornell.edu.MDL = Miravista Diagnostics Laboratory, Indianapolis, IN, (317) 856-2681, www.miravistalabs.com.

NMDA = New Mexico Department of Agriculture Veterinary Diagnostic Services, (505) 841-2576, www.nmda.nmsu.edu/DIVISIONS/vds.html.

UT = University of Tennessee, College of Veterinary Medicine, (856) 974-5639, fax (865) 974-5564, www.vet.utk.edu/diagnostic/bacteriology.shtml.

UGA = University of Georgia, College of Veterinary Medicine, (706) 542-5812, fax (706) 542-5233.

* BBL Port-A-Cul Vial, Becton, Dickinson and Company, Sparks, Md.

† Remel, Inc., Lenexa, Kans.

31.9.3.4 MOLECULAR TECHNIQUES

Serologic tests that use immunodiffusion, radioimmunoassays, complement fixation, and ELISA are available to detect circulating antibodies against several fungal organisms (Table 31-6). These titers often decrease with resolution of disease; therefore repeated measurements can be used to help monitor response to treatment. IHC,[318,325–327] fluorescent in situ hybridization,[326] and DNA probes[328] can be used to positively diagnose fungal organisms in histopathogy sections. A panfungal real-time PCR assay‡ can be used to detect a variety of fungal organisms in body fluids and fungal isolates, followed by species-specific real-time PCR assay to positively identify the organism.[313]

‡ University of California Davis, Calif.

31.9.3.5 IMMUNE FUNCTION TESTING

Several fungal infections have been associated with host immunosuppression caused by severe malnutrition, congenital immunodeficiency, or acquired immunodeficiency.[321–323] Blood can be tested for immunoglobulin quantification by radial immunodiffusion§ and lymphocyte subpopulation phenotyping via flow cytometry.‖,[323,329]

§ Cornell University, Ithaca, NY.

‖ Kansas State University, Manhattan, Kans.

31.9.4 Treatment

Treatment of fungal granulomas of the upper respiratory tract may involve surgical options (debulking, laser therapy, or cryotherapy) and/or medical therapy (systemic, topical, or intralesional). Treatment of *Aspergillis* species pneumonia is usually frustrating, as diagnosis is often made late in the course of disease and the horse frequently has severe underlying illness. Successful therapy has been reported for fungal pneumonia with other causes.[313,330–333] Several pharmacokinetic studies on antifungal drugs have been recently performed,[334–337] and as these medications become more affordable, the success rate of therapy is likely to increase. The drug of choice depends on the site of infection, the fungus involved, and the financial resources of the owner. Specific antifungal agents used in horses have been recently reviewed.[338] Therapy may not be attempted because of the severity of the primary disease, expense, or poor prognosis.

Prevention of invasive fungal pneumonia is difficult. It is impossible for the horse to avoid large inhaled inocula, given its environmental conditions. Improving ventilation and minimizing exposure to inspired spores are most beneficial in immunocompromised patients. At present the most important methods of disease prevention are treating predisposing illnesses promptly and effectively and judiciously avoiding overuse of corticosteroids and broad-spectrum antibiotics.

Table 31-6 Pharmacokinetic Studies of Antifungal Drugs Performed in Horses

Drug and Relative Cost	Dosage	Source	Susceptible Organisms, Equine Reports, Comments
Ketoconazole $ = Moderate	30 mg/kg q12h mixed with 0.2 NHCl via nasogastric intubation[333]	LW Tablets (200 mg) (Nizoral, Janssen)	*Scopulariopsis*,[334] *Coccidioides, Cryptococcus, Candida, Malassezia, Histoplasma, Sporthrix, Microsporum, Trichophyton*.
Itraconazole $ = Very expensive	5 mg/kg/day solution PO[336] (bioavailability 60%, compared with 12% for capsules)	Sporonox solution (10 mg/mL oral or injectable solution) Sporanox capsules (100 mg) (Janssen)	*Aspergillus*,[348,369] *Histoplasma, Bastomyces, Coccidioides*,[381] *Cryptococcus, Candida*, Paracoccidia, *Paecilomyces, Scopulariopsis, Sporothrix, Alternaria, Sporotrichum, Prototheca*. Not active against *Fusarium, Mucor, Rhizopus*. Very unstable and lipophilic, therefore compounded substances are not recommended.
Fluconazole $ = Moderate	14 mg/kg PO loading dose followed by 5 mg/kg/day PO[335]	LW Injectable solution (2 mg/mL) (Pfizer, Bedford Labs) Tablets (200 mg) (Pfizer) Generic available Powder (100 g) (Spectrum Chemicals)	*Histoplasma, Bastomyces, Coccidioides*,[332] *Cryptococcus, Mucor, Rhizopus, Candida*,[320] *Conidiobolomycosis*,[360] *Parracoccidia, Paecilomyces, Scopulariopsis, Sporothrix, Alternaria, Sporotrichum, Prototheca*. Minimal activity against *Aspergillus* and *Fusarium*.
Voriconazole $ = Very expensive	4 mg/kg/day PO[336]	Vfend (Pfizer, Bedford Labs) Tablets (200 mg)	Drug of choice for invasive *Aspergillus, Candida, Cryptococcus, Scedosporium apiospermum*, and *Fusarium* species in human patients who are unable to tolerate or are refractory to other therapeutic agents.

LW, Local wholesaler; *PO*, by mouth.

31.9.5 ANTIFUNGAL THERAPEUTICS (Table 31-7)

31.9.5.1 Amphotericin B

Amphotericin B deoxycholate is a polyene antibiotic that combines with ergosterol in the fungal cell membrane, resulting in an increase in cell permeability. IV amphotericin B can cause nephrotoxicity and phlebitis. Other possible side effects include anorexia, anemia, cardiac arrhythmias, hepatic and renal dysfunction, and hypersensitivity reactions.[339] Amphotericin B also been used successfully to treat histoplasmosis and pulmonary aspergillosis and cryptococcosis.[330,331,340] A high dose of oral amphotericin B successfully treated mucormycosis caused by *Absidia corymbifera*.[341] Topical amphotericin B has been successful in treatment of nasopharyngeal *C. coronatus*.[342–345]

31.9.5.2

Azoles

Benzimidazole derivatives in the class azoles, such as miconazole, enilconazole, ketoconazole, itraconazole, fluconazole, and voriconazole, destroy fungi by inhibition of ergosterol biosynthesis in the fungal cell membrane. Azole antifungals inhibit cytochrome P450-dependent 14α–sterol demethylase, which is essential for the formation of ergosterol. Topical 2% miconazole was used in the resolution of four cases of guttural pouch mycosis[346] and as part of successful multimodal therapy against nasopharyngeal *Pseudallescheria boydii*.[347] Enilconazole is not commercially available in the United States but has been used topically in the successful treatment of guttural pouch mycosis.[348–350] Aerosolization of 1.2 mg of enilconazole per kilogram q12h in 125 mL of saline resolved *Scopulariopsis* pneumonia.[333] Ketoconazole is absorbed poorly in the nonacidified form[334] but can be acidified for better absorption (30 mg/kg via NGT q12h mixed with 0.2 NHCl).[333]

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Table 31-7 Treatment of Common Fungal Infections in Humans and Horses

Infection	Recommended Treatment in Humans[386]	Treatments Tried in Horses	Comments
Cryptococcosis	Induction with amphotericin B 0.7–1 mg/kg, plus 5-fluorocytosine 100 mg/kg/day for 2 weeks then consolidation with fluconazole 400 mg/day for >10 weeks.	Daily infusions of amphotericin B (initially 0.35 mg/kg, increasing over 8 days to 0.5 mg/kg in 1 L 5% dextrose in water over 1 hr IV for 1 month) successfully used to treat pulmonary cryptococcosis. Flunixin meglumine (0.25 mg/kg IV) was administered before each treatment.[331]	Reported doses range from 0.3–0.9 mg/kg in saline IV over 1 hr.
Histoplasmosis	Amphotericin B 0.7–1 mg/kg/day for 2 weeks, then itraconazole 200 mg-400 mg/day for 4–18 months.	Successful treatment of histoplasmosis in a filly using amphotericin B (0.3–0.6 mg/kg eod IV infused over 1 hr) with a total cumulative dose of 6.75 mg/kg administered over a 1 month period. After each treatment the filly became lethargic for 18–24 hr. Polyuria and polydipsia occurred during the fourth week, but urine concentrating ability was maintained and azotemia did not occur.[330]	In vitro susceptibility to fluconazole is poor.
Blastomycosis	Amphotericin B 0.7–1 mg/kg/day to 1.5–2.5 g total or to 0.5 g total, then itraconazole 200–400 mg/day		
Aspergillosis(invasive pulmonary)	1. Voriconazole 200–400 mg PO q12h, 3–6 mg/kg IV q12h 2. Amphotericin B 1–1.5 mg/kg/day until desired response, then itraconazole 400 mg/day when disease progression slows		Fluconazole has limited efficacy.

Candidiasis	1. Amphotericin B 0.7–1 mg/kg/day for 2 weeks 2. Fluconazole 6 mg/kg for 2 weeks 3. Caspofungin 70 mg once, then 50 mg/day for 2 weeks 4. Voriconazole	Two foals were treated with intravenous amphotericin B for 8 days (total dose, 2.6 mg/kg) and 29 days (total dose, 10.3 mg/kg), respectively. Fluconazole 5.5 mg/kg PO q24h for 6 weeks and 4 mg/kg PO q24h for 28 days was used to treat two other foals.[320]	Fluconazole is generally considered the drug of choice against *Candida* species, although *Candida krusei* is resistant to fluconazole.
Pneumocystis	1. Trimethoprim-sulfamethoxazole 2. Pentamidine isethionate 3. Trimetrexate	Trimethoprim-sulfamethoxazole (TMS) (25–30 mg/kg POq12h) is the treatment of choice.[384] Dapsone*(3 mg/kg PO daily for 2 months) was used to successfully treat a foal with *Pneumocystis carinii* that developed *Salmonella* enterocolitis after treatment with TMS.[329]	Lacks ergosterol, therefore antifungals are not effective.

eod, Every other day; *IV*, intravenously; *PO*, by mouth.

* Jacobus Pharmaceutical Company, Inc., Princeton, NJ.

Itraconazole (Sporanox solution) is absorbed well orally (bioavailability 60%). A dose of 5 mg/kg PO q24h maintains concentrations above MIC for susceptible yeasts (*Histoplasma* and *Blastomyces* species) and *Aspergillus* species, with no detectable side effects.[336] The use of compounded itraconazole is not recommended. It is very unstable (requires low pH), and owing to its lipophilic nature it is difficult to formulate in aqueous solution.

Oral fluconazole at a loading dose of 14 mg/kg followed by 5 mg/kg every 24 hours yields concentrations in plasma, cerebrospinal fluid (CSF), synovial fluid, aqueous humor, and urine above the MIC reported for several equine fungal pathogens.[335] Fluconazole, however, reportedly has minimal activity against filamentous fungi (*Aspergillus* and *Fusarium* species). Low-dose oral fluconazole (1 mg/kg PO q24h) for at least 10 to 15 days anecdotally has been successful in treatment of fungal keratitis. Compounded fluconazole formulations are very stable. The cost of fluconazole has been markedly reduced since generic products became available.

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Voriconazole, a new broad-spectrum triazole antifungal agent, was approved for use in human medicine in 2002. It is now considered the drug of choice for initial treatment of invasive aspergillosis, candidiasis, cryptococcosis, and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species in patients that are unable to tolerate or are refractory to other therapeutic agents.[351,352] An initial single-dose pharmacokinetic study in horses recommended a dose of 4 mg/kg PO q24h.[337] Multiple dosing studies are still required owing to the potential for drug accumulation.

31.9.6 SYSTEMIC IODIDE THERAPY

The exact mode of action of iodides is unknown; however, they seem to have a beneficial effect on the granulomatous inflammatory process. Iodides have very little, if any, direct in vitro antibiotic effect.[353] Although several successful cases in which iodides were used as primary or adjunctive therapy have been reported, overall efficacy is considered limited at best. Treatment is inexpensive, but toxicity and resistance can occur. Iodide toxicity is characterized by excessive lacrimation, nonproductive cough, increased respiratory secretions, and dermatitis.[354] The recommended dose of 20% sodium iodide is 20 to 40 mg/kg/day IV for 7 to 10 days.[342,345,354,355] Orally administered iodine is available in two forms. Inorganic potassium iodide (10 to 40 mg/kg/day) is available only as a chemical grade and is unstable in the presence of light, heat, and excessive humidity.[345,355] Organic ethylenediamine dihydriodide (EDDI) (0.86 to 1.72 mg of EDDI per kilogram, equivalent to 20 to 40 mg/kg/day of the 4.57% dextrose powdered form*) is commercially available.[355] Administration of iodine in the diet of pregnant mares may cause congenital hypothyroidism in foals and should be avoided.

* The Butler Company, Columbus, Ohio.

31.9.7 ETIOLOGIC AGENTS

31.9.7.1 Conidiobolomycosis

C. coronatus is a saprophytic fungus that causes granulomatous lesions of the upper respiratory tract in horses. Single to multiple granulomatous lesions in the nasal passages, trachea, or soft palate can be observed endoscopically (Fig. 31-19). Histologic appearance of conidiobolomycosis is similar to that of pythiosis and basidiobolomycosis. Hyphae of *C. coronatus* are thin-walled, highly septate, and irregularly branched (see Table 31-5).[356] The lesions typically have large numbers of eosinophils and fewer macrophages, neutrophils, plasma cells, and lymphocytes surrounding hyphae. Definitive diagnosis is based on microbiologic culture, immunodiffusion, or PCR.[357] Detection of serum antibodies by immunodiffusion is considered highly sensitive and specific[354,358] and can be used to monitor response to treatment.[358] A nested PCR *Pythium* assay has also been used to identify *C. coronatus*.[359]

Conidiobolomycosis lesions can be treated with surgical excision, laser therapy, cryotherapy, or long-term administration of iodides or antifungals.[342,354,357] Amphotericin B has been administered intralesionally or topically in combination with dimethyl sulfoxide (DMSO) to treat *C. coronatus*.[342–345] It is important to remember that long-term therapy and reevaluation are essential, as recurrence can occur.[345] Oral fluconazole was successful in treating two pregnant mares with nasal conidiobolomycosis.[360] A vaccine using *C. coronatus* antigen from broth cultures was unsuccessful in treating seven horses with conidiobolomycosis.[357]

31.9.7.2 Cryptococcosis

Cryptococcosis is caused by *C. neoformans* (var. *neoformans* and var. *gattii*) and is a ubiquitous, saprophytic, round, basidiomycetous yeastlike fungus with a large heteropolysaccharide capsule that does not take up common cytologic stains (see Table 31-5, Fig. 31-20). The capsule forms a clear halo when stained with India ink. The capsule is immunosuppressive and antiphagocytic. A relatively high frequency of equine

cryptococcosis occurs in Western Australia.[311] There is an epidemiologic relationship between *C. neoformans* var. *gattii* and the Australian river redgum tree *(Eucalyptus camaldulensis)*, whereas *C. neoformans* var. *neoformans* has historically been associated with bird (particularly pigeon) excreta.[311] Cytologic or histopathologic identification is very reliable for diagnosis because of the characteristic morphology.[361] Serologic testing with latex agglutination to identify cryptococcal capsular antigen is useful with resolution of lesions correlated with declining serum titers.[331]

Fig. 31-19 Endoscopic image of mycotic granulomas caused by *Conidiobolus coronatus* in the nasopharynx of a horse.

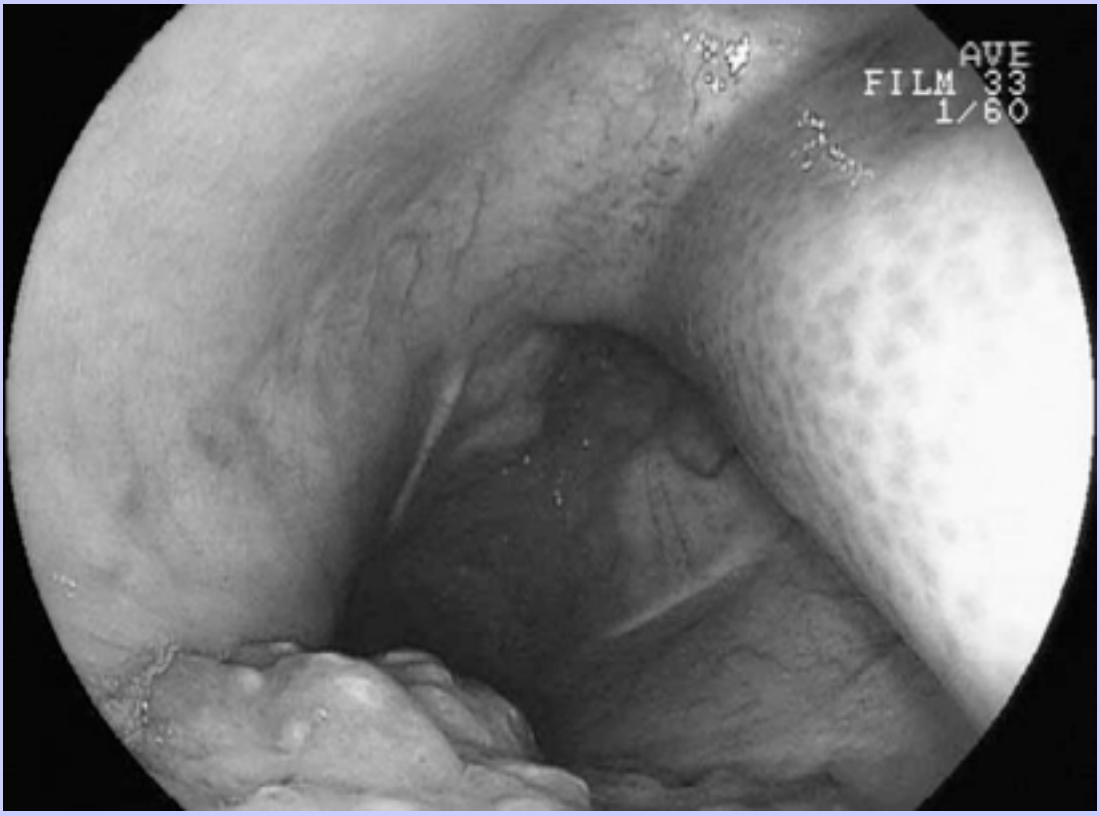
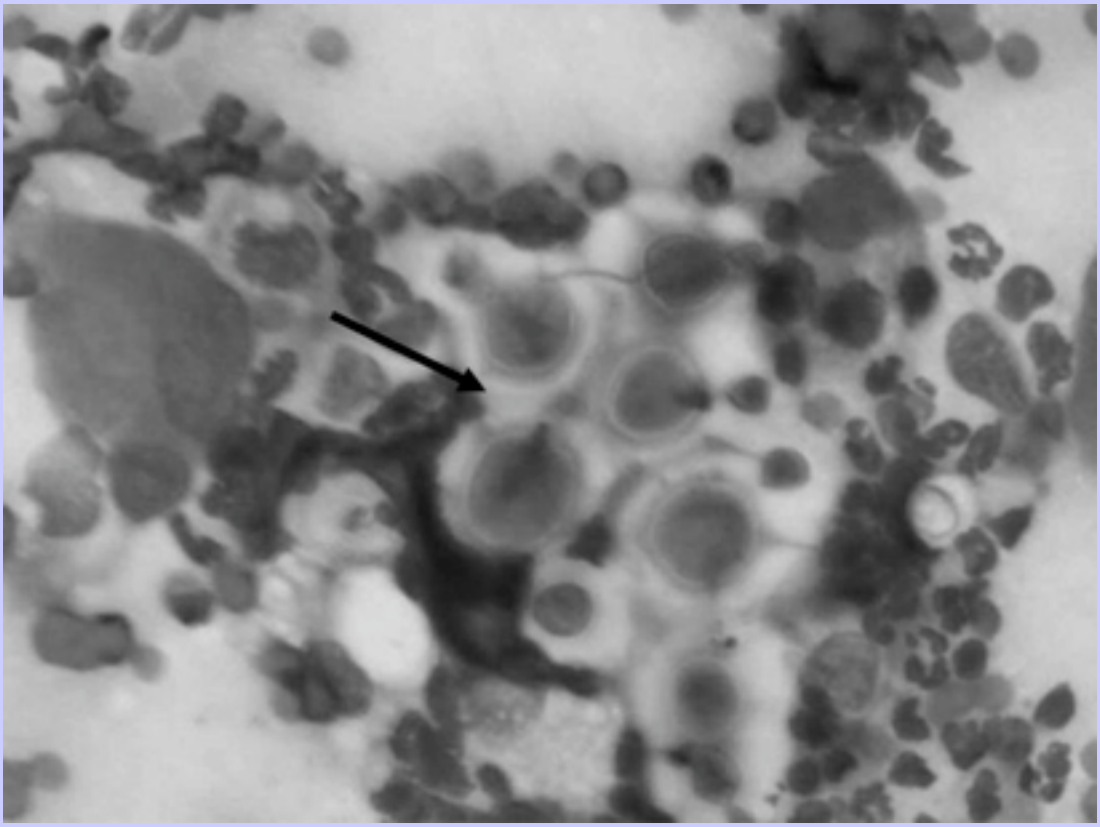


Fig. 31-20 Photomicrographs of an impression smear from a biopsy of a mass in the nasal passage of a horse. The smear is extremely cellular, with abundant neutrophils and macrophages. Round yeast cells with large nonstaining capsules and occasional narrow-based budding consistent with cryptococcal organisms *(arrow)* are shown. (Modified Wright stain ×100.) Courtesy Elizabeth Welles, Auburn University, Auburn, Ala.



Cryptococcosis in horses is associated primarily with pneumonia, rhinitis (Fig. 31-21), meningitis, and abortion. Successful medical treatment, however, has been reported rarely. Surgical removal of a localized jejunal lesion was successful in one horse.[362] A pony with multiple pulmonary cryptococcomas, from which *Cryptococcus gattii* was cultured from both transtracheal washings and lung mass aspirates, was treated successfully with daily infusions of amphotericin B over 1 month. One year after cessation of treatment, clinical signs had resolved and the cryptococcal antigen titer had decreased from 4096 to 256.[331]

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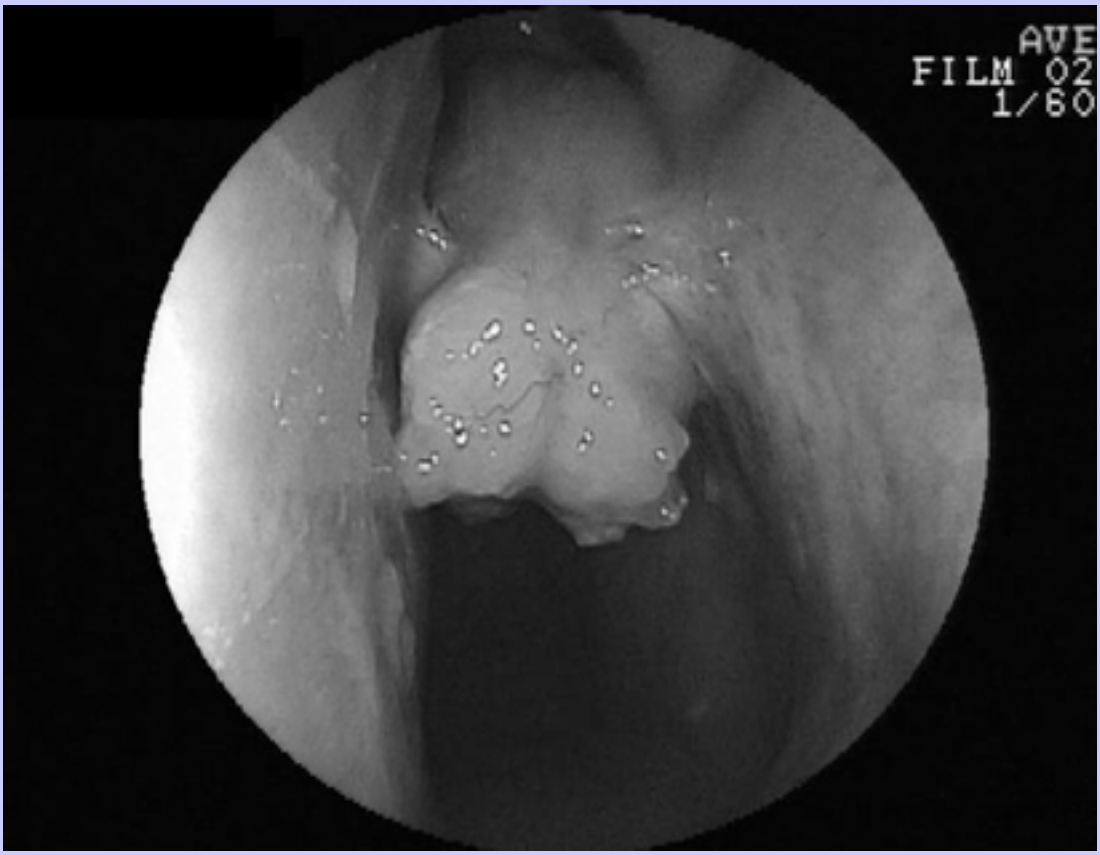
Fig. 31-21 Endoscopic image of a cryptococcus granuloma in the nasal passages of a horse.



Cryptococcus should be treated with amphotericin B, fluconazole, or voriconazole (see Table 31-7).

31.9.7.3

Pseudallescheriosis

P. boydii is a saprophytic ascomycete. Infection most commonly involves the extremities, and in human patients it is known as Madura foot. Hyphae within tissue cannot be differentiated from *Fusarium* or *Aspergillus* species unless cultured. *P. boydii* cultured from the nasal cavity and sinus of a horse with chronic, malodorous nasal discharge was susceptible in vitro to miconazole, ketoconazole, natamycin, and clotrimazole. After debridement and flushing of the plaque, miconazole cream was infused twice daily for 4 weeks through lavage tubing that had been passed into the nasal passage through a hole drilled in the frontal bone and sinuses. Adjunctive iodide therapy was also administered, and the lesions resolved (Fig. 31-22).[347]

Nasal mycosis caused by *P. boydii* has been reported in two other horses, both of which were euthanized.[363,364] *P. boydii* has also been isolated from the pharynx of 2 of 60 normal donkeys and from horses with chronic uterine infection.[365,366]

31.9.7.4

Aspergillosis

Aspergillus species have broad septate hyphae with parallel sides and acute right-angled branching (see Table 31-5). They have a propensity for vascular invasion. Definitive diagnosis is by culture or staining by IHC or immunofluorescence. *Aspergillus* species are very common in the environment, especially in moldy feed and bedding.[340] They are opportunistic pathogens and often cause disease in horses that are immunosuppressed from debilitating disease such as enterocolitis, septicemia, neoplasia, Cushing's disease, or equine protozoal myeloencephalitis or because of surgery or that have been treated with immunosuppressive drugs[312,314,316–318] (Fig. 31-23).

Infection is by inhalation of an overwhelming number of spores resulting in fungal proliferation and invasion of the small airways, or by translocation of organisms across an inflamed GI tract leading to lesions centered around large blood vessels as a result of hematogenous spread. In two retrospective studies of invasive pulmonary aspergillosis, 41 of 49 cases were associated with enterocolitis.[312,314] *Aspergillus* species pneumonia is almost uniformly fatal, often with no or mild respiratory signs. Antemortem diagnosis of pulmonary aspergillosis is made rarely. In a retrospective study of 30 cases of *Aspergillus* species pneumonia, only two cases were diagnosed or suspected antemortem.[314] TTA or BAL may not be helpful because hyphae and spores are often present extracellularly or within macrophages in aspirates and lavages from healthy animals.[312] False-negative results also can occur. Cytologic examination of a transtracheal wash specimen obtained from the foal shown in Fig. 31-23, *A*, 2 days before euthanasia failed to identify *Aspergillus* species hyphae. Serologic diagnosis occasionally has been useful[367] but is often unreliable because many horses have titers to *Aspergillus* species. Development of a commercially available ELISA is promising.[316,340]

In human medicine 50% to 90% of patients with invasive aspergillosis die despite treatment. Amphotericin B has been the mainstay of treatment for invasive aspergillus for decades but is associated with nephrotoxicity in about 50% of human patients. Nephrotoxicity is reduced using liposomal amphotericin B. Voriconazole, a new azole antifungal, is now considered the drug of choice against human aspergillosis, whereas caspofungin (in the new class of echinocandin antifungals) shows promising results in patients with refractory infections.[368] Oral itraconazole is currently the treatment of choice for aspergillosis in horses owing to a lack of pharmacokinetic analysis and safety testing and the costs associated with the newer antifungal agents.[336] In human medicine itraconazole has shown comparable response rates to amphotericin B.[368] There are limited reports of horses surviving pulmonary aspergillosis.[340]

Treatment of mycotic *aspergillus* rhinitis and sinusitis in horses has been more successful. It is, however, important to rule out concomitant invasive pulmonary aspergillosis. Oral itraconazole,[369] topical natamycin (flushed via an endoscope or indwelling catheter placed into the sinus), and nystatin powder (insufflated up the nostril) have been curative.[370]

31.9.7.5

Blastomycosis

Blastomycosis is caused by inhalation of conidiae of the thermally dimorphic saprophytic fungus *B. dermatitidis. Blastomyces* yeasts can be identified on cytologic examination, often within multinucleated giant cells. They are spheric, with basophilic protoplasm and unstained, uniformly shaped refractile walls. Unilateral, broad-based budding is characteristic (see Table 31-5).

Blastomycosis was reported to cause pyogranulomatous pleuropneumonia, pulmonary abscessation, peritonitis, and abscesses in a 5-year-old horse.[328] *B. dermatitidis* was positively identified from transtracheal wash fluid by use of a DNA probe, and serology was strongly positive. The horse was euthanized without treatment.[328] Disseminated blastomycosis was diagnosed in a miniature horse with SC infections associated with a chronic pectoral wound. The pony had pulmonary consolidation and pleural effusion. Yeasts were observed histologically in many tissues, and *B. dermatitidis* was cultured after 6 weeks.[371]

Treatment with amphotericin B, itraconazole, or fluconazole is recommended (see Table 31-7).

31.9.7.6

Histoplasmosis

Histoplasmosis is caused by the saprophytic, dimorphic fungus *H. capsulatum*, which is most prevalent in moist soil containing bird or bat waste. Yeast organisms are 2 to 4 µm in diameter, with a thin clear halo surrounding a round or crescent-shaped basophilic cytoplasm (Fig. 31-24). Histoplasmosis has been reported in less than 10 equine cases,[330] and thus horses are considered to be relatively resistant to disease. *H. capsulatum* may occur in an enteric, pulmonary, or disseminated form.[330] *H. capsulatum* was identified in pulmonary granulomas in a horse dying of chronic *Yersinia* colitis[372] and in another horse with intestinal salmonellosis.[373] It has also been associated with abortions and severe granulomatous pneumonia in neonatal foals (Fig. 31-25) and a yearling.[374] Successful treatment with amphotericin B was reported in a filly with pulmonary histoplasmosis diagnosed by cytologic identification of the organism on a tracheal wash smear and from a lung aspirate.[330]

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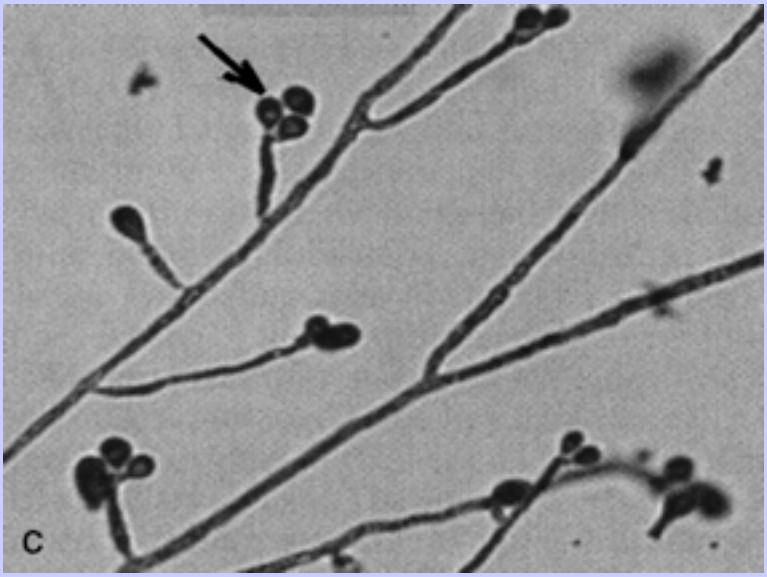
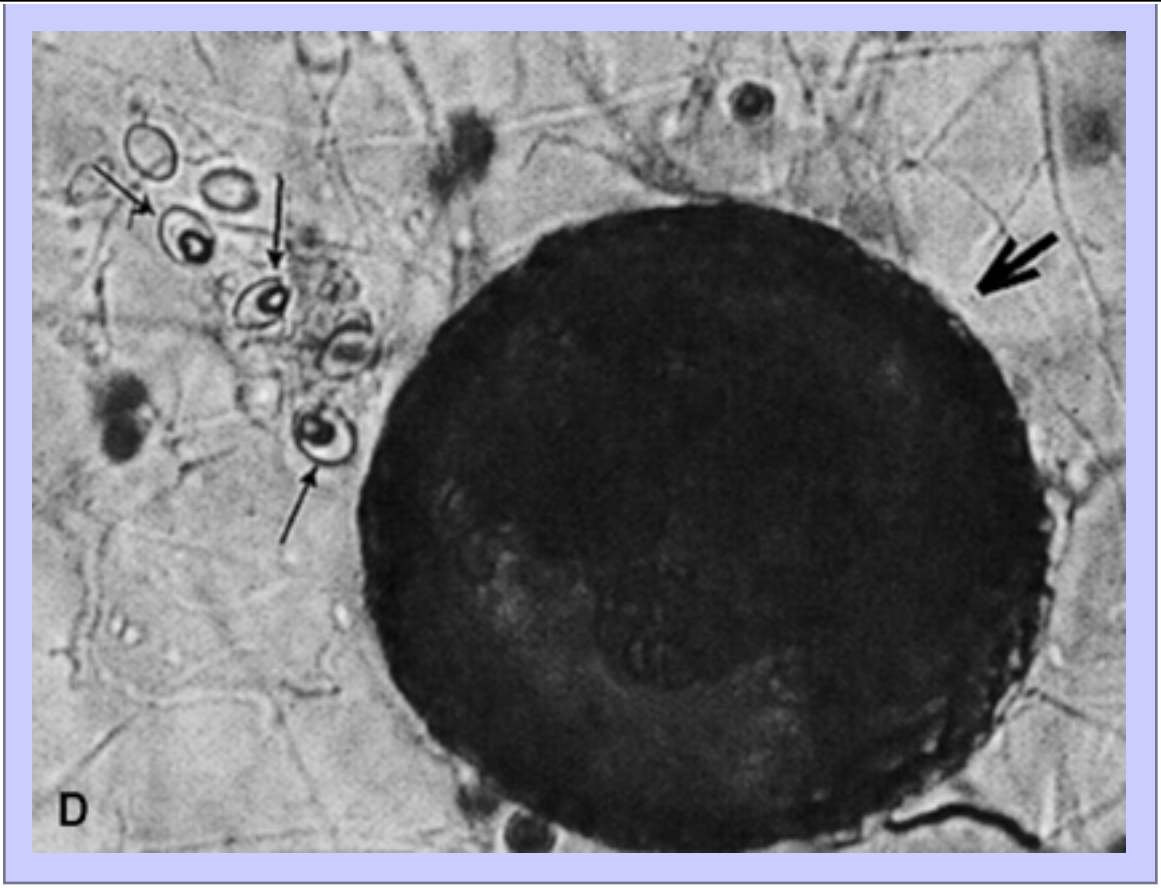
Fig. 31-22 Nasal and nasopharyngeal masses caused by *Pseudallescheria boydii* in a quarter horse gelding with chronic, malodorous nasal discharge. **A**, Mucosanguineous nasal discharge. **B**, Mass visible within the external nares. **C**, Asexual form of *P. boydii* in culture showing nonbranching conidiophores with terminal conidia *(arrow)*. **D**, Sexual form of *P. boydii* in culture with the cleistothecium *(thick arrow)* and ascospores *(thin arrow)*. Courtesy R. Reid Hanson, Auburn University, Auburn, Ala.





Treatment with amphotericin B or itraconazole is recommended (see Table 31-7).

31.9.7.7 Coccidiomycosis

C. immitis is a soil saprophyte that grows in semiarid areas with sandy, alkaline soils.[375] Inhaled arthroconidia enlarge to form nonbudding spherules, which incite an inflammatory reaction in the lungs and lymph nodes.[375] Horses have weight loss, fever, abdominal pain, and signs of respiratory disease (Fig. 31-26). Localized, recurring nasal granulomas also have been reported.[376] Diffuse infections with granulomas in the lungs, liver, kidney, or spleen carry a grave prognosis.[375] Przewalskii horses may be more susceptible.[377]

C. immitis is difficult to culture, and spherules may not be observed histologically from antemortem lung biopsies. However, serology is very useful to diagnose infection, and decreasing titers are associated with clinical improvement.[332,375] Serum antibodies are detected rarely in healthy horses.[378] Antifungal agents successful in treatment of infected horses include itraconazole and fluconazole.[332,379]

31.9.7.8 Scopulariopsis

Scopulariopsis pneumonia was diagnosed by culture of BALF in a 2-year-old quarter horse filly with pleuropneumonia. The infection resolved after multimodal therapy with ketoconazole and aerosolization of enilconazole.[333]

31.9.7.9

Adiaspiromycosis

Adiaspiromycotic miliary fungal pneumonia caused by the saprophytic soil mold *E. crescens* was diagnosed in a horse by percutaneous lung biopsy. Euthanasia was performed without treatment.[319]

Fig. 31-23 One-month-old foal with *Escherichia coli* septicemia and secondary *Aspergillus* pneumonia. **A**, Dyspneic foal being supported with intranasal oxygen. The foal had eight septic joints and severe pneumonia and was subsequently euthanized owing to the guarded prognosis. **B**, Photomicrograph of the pleural surface of the lung *(black arrows)* with extensive superficial and deep fungal growth. *Aspergillus* species characteristically have parallel-sided, regular septate hyphae with acute-angled dichotomous branching. They are seen reasonably well with hemotoxylin and eosin stain. **C**,*Aspergillus* species hyphae within pulmonary parenchyma stained metachromatic with specific fungal stain (Gridley stain). Courtesy Calvin Johnson, Auburn University, Auburn, Ala.

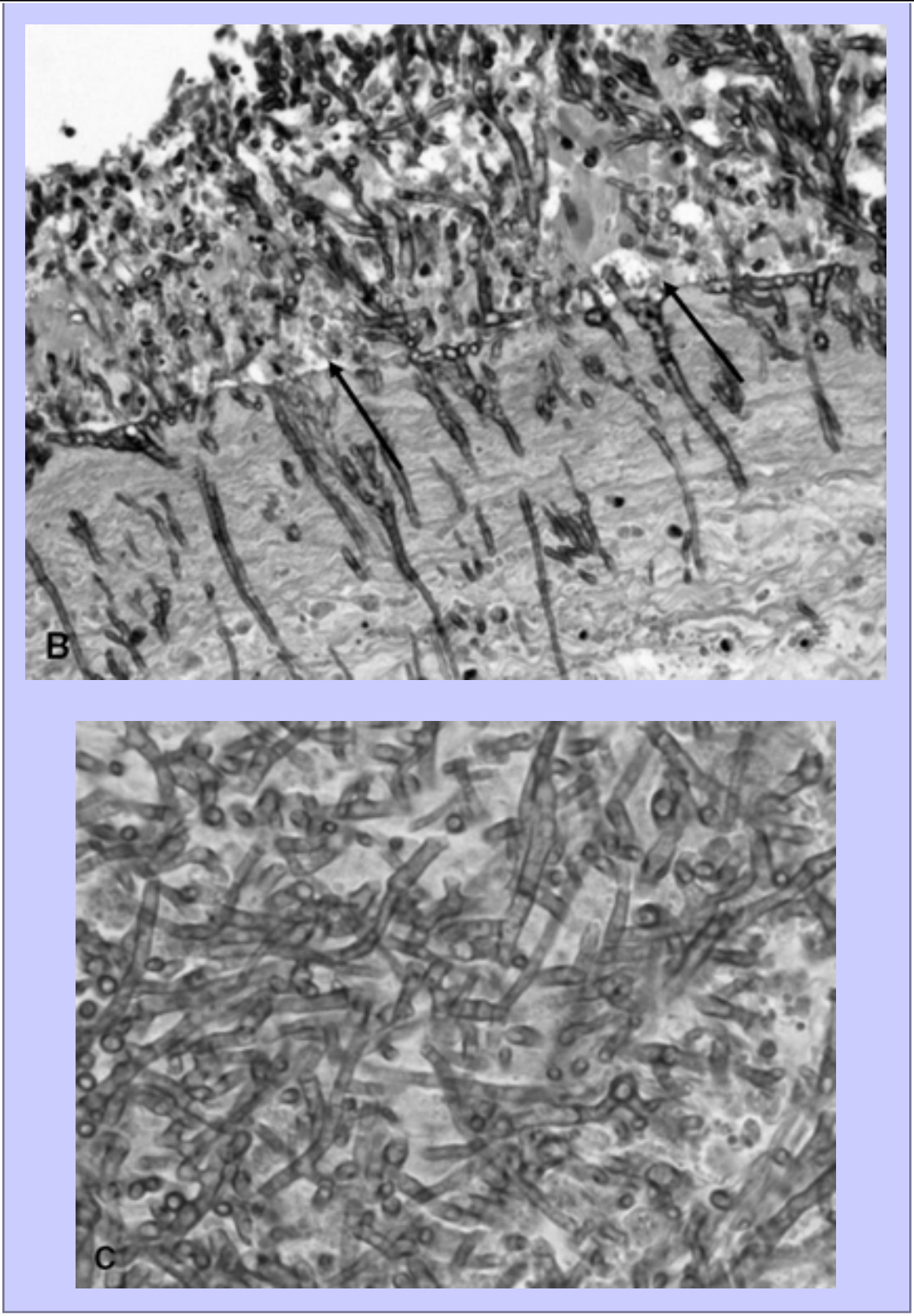

B
C

Fig. 31-24 Photomicrograph of tissue infiltrated by activated macrophages containing usually multiple yeasts of *Histoplasma* species. These yeasts characteristically measure approximately 2 to 4 µm and appear as structures with a basophilic center and clear halo. (Hemotoxylin and eosin stain, ×40.) Courtesy Arno Wünschmann, University of Minnesota, St. Paul, Minn.

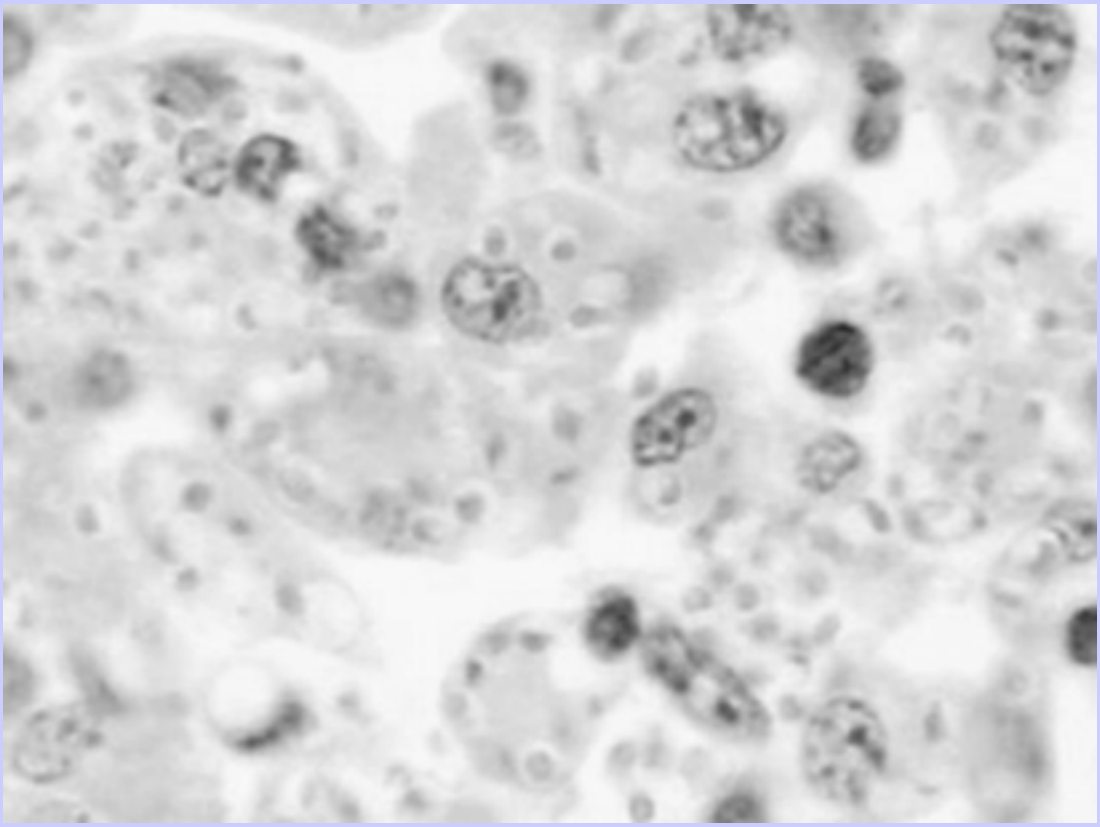


Fig. 31-25 Lateral thoracic radiographs from a foal with *Histoplasma* pneumonia. Courtesy Carol Clark, Peterson and Smith Equine Hospital, Ocala, Fla.

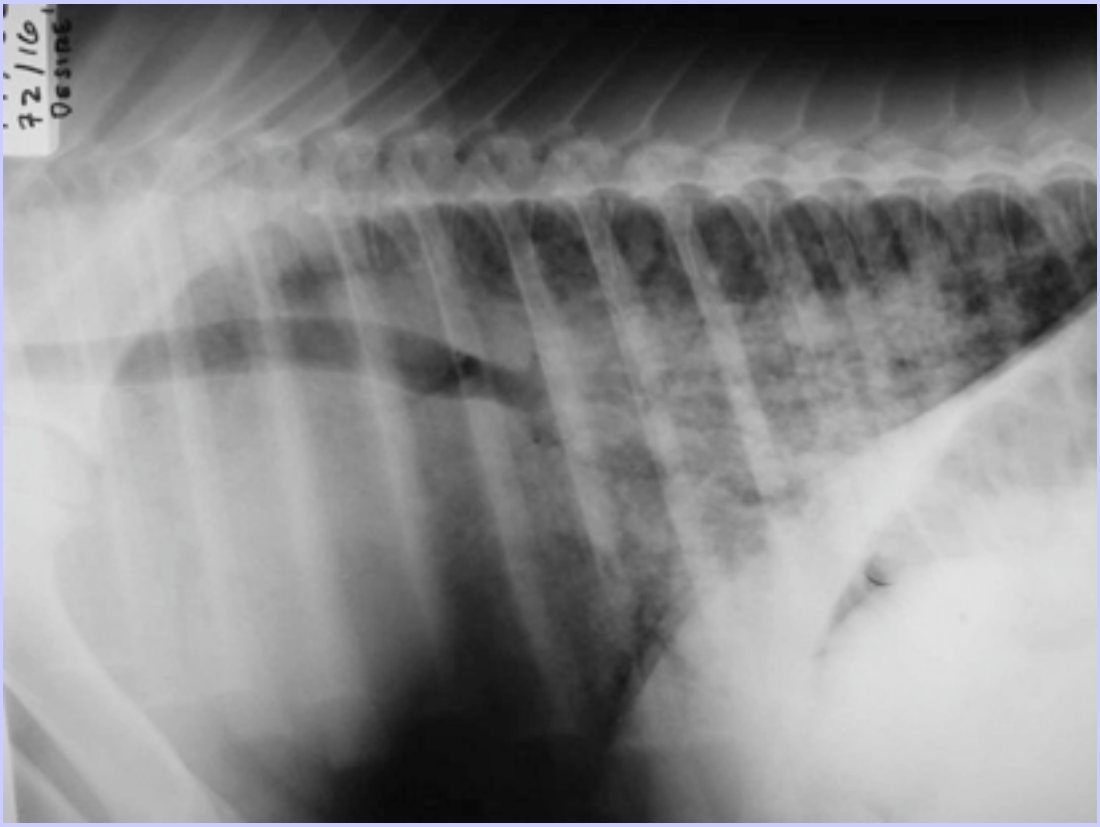


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Fig. 31-26 **A**, Coccidiomycosis in a quarter horse mare with severe weight loss after a 3-month period in Arizona and Colorado. Ultrasound image of free **(B)** pleural fluid and **(C)** abdominal fluid. Courtesy Jamie Murphy, Califon, NJ.

31.9.7.10

Acremonium Strictum

A diagnosis of interstitial fungal pneumonia caused by *Acremonium strictum* was made based on cytologic evaluation, culture, and PCR testing of BALF in a 10-year-old horse. The horse made an uneventful recovery with supportive treatment, which included 1 month of fluconazole.[313] In general, fluconazole has been shown to have poor activity against *A. strictum* in vitro.[380] The isolate cultured from the horse was found to be resistant to fluconazole based on in vitro sensitivity testing that was performed after the course of treatment. It is therefore uncertain if the fluconazole assisted in disease resolution.[313]

31.9.7.11

Candidiasis

In human medicine, candidemia is the most common fungal infection in burn patients, neutropenic patients with malignancies, patients undergoing complex abdominal surgery, and patients receiving total parenteral nutrition and long-term corticosteroid therapy.[368] In humans, *Candida* species account for 8% to 10% of all

blood culture isolates and rank fourth in the list of most frequently isolated pathogens from blood cultures.[368] The mortality in patients with candidemia is 40% to 75%.[368] Over 60% of isolates are *Candida albicans*.[368] Fluconazole is generally considered the drug of choice against *Candida* species, although *Candida krusei* is resistant to fluconazole. Itraconazole, amphotericin B, caspofungin, and voraconazole are alternative antifungal agents (see Table 31-7).[368]

Systemic candidiasis was diagnosed and successfully treated in four neonatal foals. Each foal had prior sepsis attributable to gram-negative bacteria that had been aggressively treated with numerous antibiotics and parenteral nutrition. *C. albicans* was cultured from a transtracheal wash from one of the foals. Three of the foals had *Candida* glossitis, and one had panophthalmitis and fungal keratitis. Two of the foals were treated with IV amphotericin B, and oral fluconazole was used on the other two foals.[320]

Superficial *Candida* species infections of the mucous membranes (thrush)[381] can occur in isolation or as part of a systemic infection, and further microbiologic culturing of the blood, tracheal wash, urine, or joint fluid may be indicated to rule out systemic infection.[320] *Candida* species glossitis can be treated by rinsing the mouth either with potassium permanganate (0.025% q24h) or nystatin (0.3 g in 10 mL of water q8h).

31.9.7.12 Pneumocystosis

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P. carinii has been reclassified from a protozoan to a saprophytic fungus based on the DNA sequence of its 16S-like RNA subunit, but some researchers even consider it to be a plant because it lacks ergosterol, the major fungal sterol.[382] It exists as an ameboid yeast or as a cystic sporangia. *P. carinii* cannot be cultured, and diagnosis is based on the cytologic identification of characteristic morphologic features using specimens obtained by BAL rather than tracheal wash. A fluorescent in situ hybridization method with an oligonucleotide probe that targets the 18S ribosomal RNA has been developed recently to detect *P. carinii* in histologic sections.[326] IHC also can be used.[325]

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Three quarters of human AIDS patients are infected with *P. carinii*, and people undergoing immunosuppressive therapy after organ transplantation are predisposed. *P. carinii* causes diffuse interstitial pneumonia, especially in immunocompromised patients such as Arabian foals with SCID.[321] It also has been diagnosed in immunocompromised adult horses,[322,323] as well as an immunocompetent foal.[325] TMS (25 to 30 mg/kg PO q12h) is the treatment of choice (see Table 31-5).[383,384] Dapsone* (3 mg/kg PO daily for 2 months) was used to successfully treat a foal that developed *Salmonella* enterocolitis after treatment with TMS.[329]

* Jacobus Pharmaceutical Company, Inc., Princeton, NJ.

31.10 *STREPTOCOCCUS EQUI* INFECTION (STRANGLES)

Corinne R. Sweeney

S. equi infections in horses, commonly referred to as *strangles*, was described in early veterinary science literature. Since described by Jordanus Ruffus in 1251, much has been learned about the disease and the organism that causes it.[387,388]

31.10.1 Clinical Signs

Strangles is characterized by sudden onset of fever followed by upper respiratory tract catarrh, as evidenced by mucopurulent nasal discharge (Fig. 31-27) and acute swelling with subsequent abscess formation in submandibular and retropharyngeal lymph nodes. The name *strangles* was coined because affected horses sometimes suffocated as the lymph nodes became enlarged and obstructed the airway. Clinical severity varies greatly depending on the immune status of the animal.

Fever is the first clinical sign and is maintained as lymphadenopathy develops and abscesses mature. Pharyngitis makes swallowing painful, and affected animals may become anorectic or reluctant to eat and stand with the neck extended.

Lymphadenopathy is a major clinical sign. The submandibular and retropharyngeal lymph nodes are about equally involved in *S. equi* infections. They usually become swollen and painful approximately 1 week after infection. Other lymph nodes of the head region (parotid, cranial cervical, and retropharyngeal) are also frequently involved and may abscess (Fig. 31-28). Retropharyngeal lymph nodes may drain into and cause empyema of the guttural pouch (Fig. 31-29). Periorbital abscesses can cause marked swelling of the eyelids. Abscesses of the lymph nodes at the thoracic inlet can cause severe tracheal compression, asphyxia, and death.

31.10.2 Pathogenesis

S. equi enters via the mouth or nose and attaches to cells in the crypt of the lingual and palatine tonsils and to the follicular associated epithelium of the pharyngeal and tubal tonsils. There is no evidence of colonization before penetration. After a few hours the organism is difficult to detect on the mucosal surface but is visible within cells of the epithelium and subepithelial follicles. Translocation occurs in a few hours to the mandibular and suprapharyngeal lymph nodes that drain the pharyngeal and tonsillar region.

Fig. 31-27 Horse with bilateral thick purulent nasal discharge typical of strangles.

Fig. 31-28 Draining submandibular lymph node in a standardbred mare with strangles.

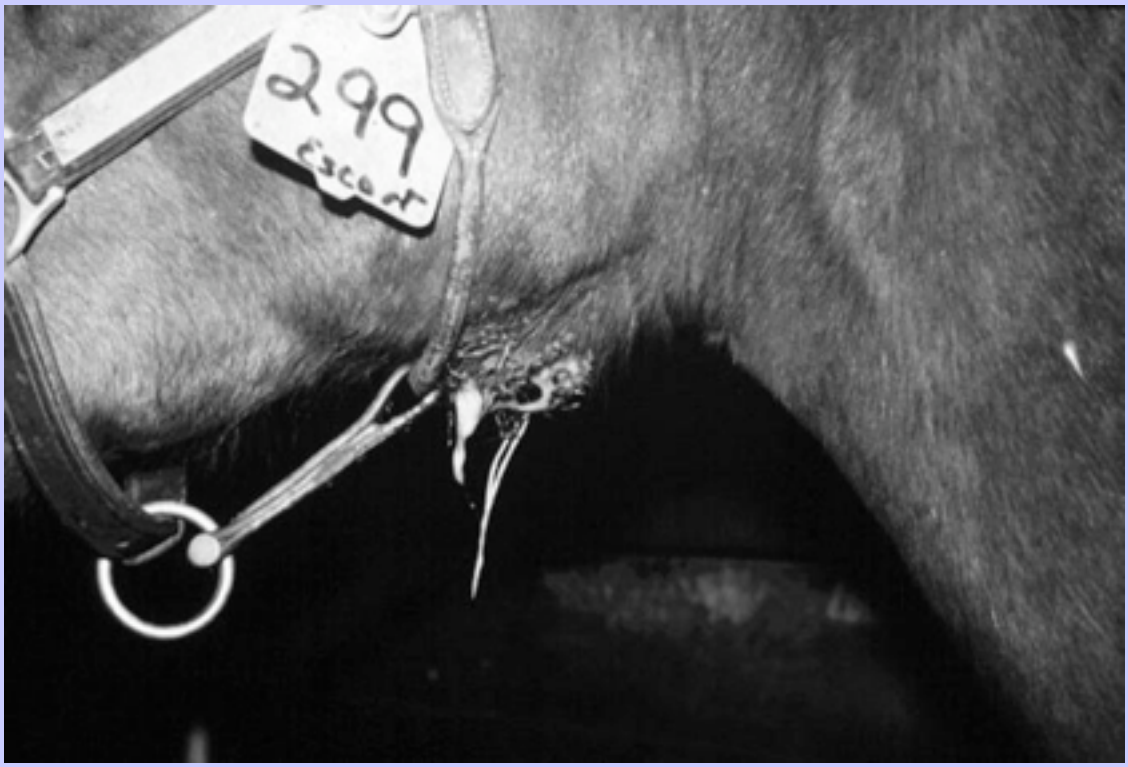


Fig. 31-29 Guttural pouch empyema with marked distention of the guttural pouch in a foal with strangles infection.

Complement-derived chemotactic factors attract large numbers of polymorphonuclear neutrophils (PMNs), although gross evidence of abscessation is not visible for 3 to 5 days after *S. equi* enters the lymph node. Failure of neutrophils to phagocytose and kill the streptococci appears to be a result of a combination of the hyaluronic acid capsule, antiphagocytic SeM protein, Mac protein, and other undetermined antiphagocytic factors released by the organism. 533 534

Although strangles predominantly involves the upper airways including the guttural pouches and associated lymph nodes, metastasis to other locations occasionally occurs. Spread may be hematogenous or via lymphatic channels, which results in abscesses in lymph nodes and other organs of the thorax and abdomen (Fig. 31-30). This form of the disease is known as *bastard strangles*.

Nasal shedding of *S. equi* usually begins 2 to 3 days after onset of fever and persists for 2 to 3 weeks in most animals. Some animals never shed. In others, shedding may persist much longer, should infection persist in the guttural pouch.[389,390] Systemic and mucosal immune responses are evident 2 to 3 weeks after infection and coincide with mucosal clearance.

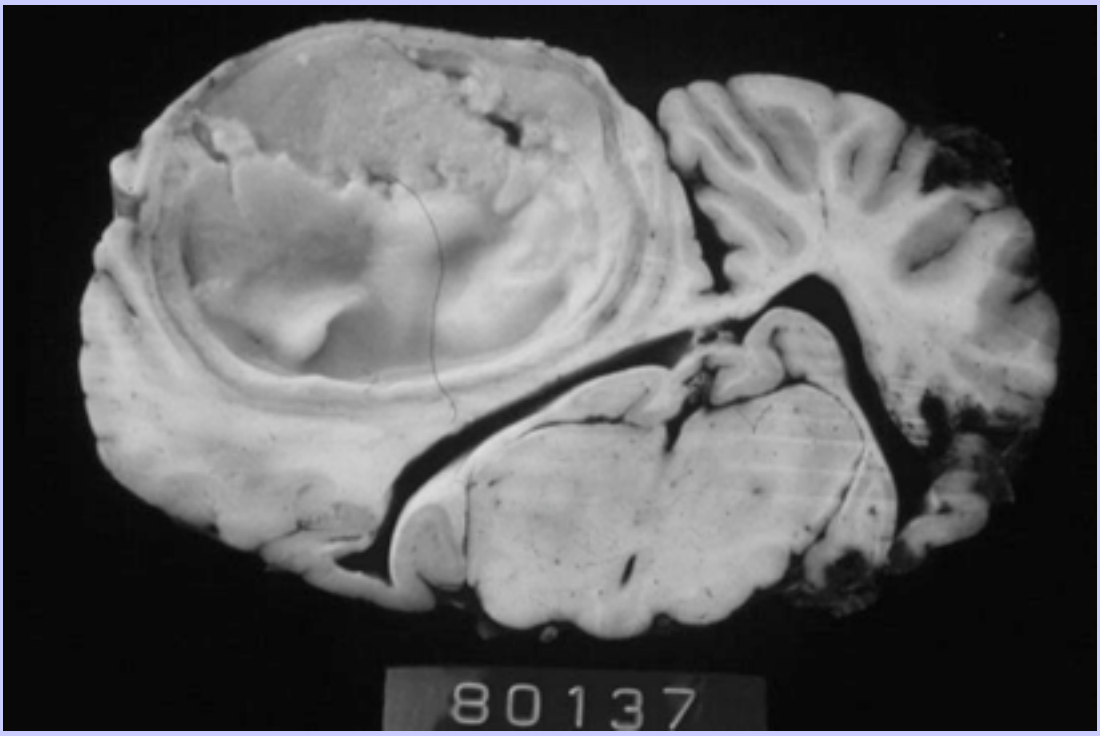
Approximately 75% of horses develop a solid enduring immunity to strangles after recovery from the disease. A small percentage of these horses become susceptible to a second attack of the disease within months, which probably represents a failure to produce or maintain an adequate level of the appropriate mucosal and systemic antibodies. Older horses with residual immunity have limited susceptibility and develop a mild form of strangles often termed *catarrhal strangles*. These animals shed virulent *S. equi* that will produce severe disease in more susceptible, often younger horses. Colostral antibodies ingested during the first 24 hours of life have also been shown to recirculate to the nasopharyngeal mucosa, thus providing an additional source of protection to the foal during its first weeks. Foals that suckle immune mares are usually resistant to *S. equi* infection until weaning.

31.10.3 Epidemiology

31.10.3.1 TRANSMISSION

Purulent discharges from horses with active strangles and those that are recovering are an important and easily recognizable source of new *S. equi* infections among susceptible horses. Transmission of infection occurs when there is either direct or indirect transfer of *S. equi* within these purulent discharges between affected and susceptible horses. Direct transmission refers to horse-to-horse contacts, particularly through normal equine social behavior involving mutual head contact. Indirect transmission occurs through the sharing of contaminated housing, water sources, feed or feeding utensils, twitches, tack, and other less obvious fomites such as the clothing and equipment of handlers, caretakers, farriers, and veterinarians unless appropriate barrier precautions are undertaken to prevent spread of *S. equi*.

Fig. 31-30 "Bastard strangles": brain abscess caused by *Streptococcus equi* in a yearling Arabian colt.



It is increasingly recognized that there may be transmission that originates from outwardly healthy-appearing animals, and in this situation the source of infection may not be readily recognized and clinical signs may appear in in-contact animals without warning. *S. equi* may originate from outwardly healthy horses as follows:

- Horses that are incubating the disease and go on to develop signs themselves
- Horses that are recovering from recent disease but that continue to harbor the organism after full clinical recovery for some weeks
- Horses that are fully recovered from the disease but continue to be potentially infectious for prolonged periods through periodic shedding of *S. equi*

31.10.3.2

ENVIRONMENTAL PERSISTENCE OF *STREPTOCOCCUS EQUI*

Currently there is a lack of definitive field-based proof for prolonged environmental persistence of *S. equi. S. equi* is known to be sensitive to bacteriocins from environmental bacteria and does not readily survive in the presence of other soil-borne flora.

31.10.4 Diagnosis

31.10.4.1 CULTURE

Culture of nasal swabs, nasal washes, or pus aspirated from abscesses remains the gold standard for detection of *S. equi*. Nasal washes are more effective than swabs in detection of small numbers of *S. equi* because a greater surface area within the internal nares is sampled. Culture may, however, be unsuccessful during the incubation and early clinical phases. *S. equi* is normally not present on the mucosa until 24 to 48 hours after the onset of fever, so infection in horses monitored by daily measuring of rectal temperatures during an outbreak may be recognized early and isolated to limit transmission of *S. equi*.

31.10.4.2 POLYMERASE CHAIN REACTION

The PCR is designed to detect DNA sequence of *SeM*, the gene for the antiphagocytic M protein of *S. equi*. However, PCR does not distinguish between dead and live organisms, so a positive test result must be considered presumptive until confirmed by culture. In addition, clinical samples that contain polymerase inhibitors or abundant *S. equi* may give negative PCR results although culture of the same sample confirms the presence of *S. equi*. PCR accompanying culture on a nasal swab or wash may be used in a control program to select animals for guttural pouch endoscopy.[389,391]

31.10.4.3 SEROLOGY

Fifteen or more surface exposed or secreted proteins of *S. equi* elicit strong serum antibody responses during infection and convalescence. The most reactive and best studied of these is SeM, a major virulence factor and protective immunogen. A proprietary ELISA for measuring SeM specific antibody is commercially available (EB1, IDEXX, Lexington, Ky.) and is useful for diagnosing recent (but not necessarily current) *S. equi* infection, determining the need for booster vaccination, and aiding in the diagnosis of purpura hemorrhagica and metastatic abscesses. It does not distinguish between vaccine and infection response. That considerable variation exists in the responses of individual horses should be kept in mind when interpreting results.

31.10.5 Vaccination

Most horses develop a solid immunity during recovery from strangles, which persists in over 75% of animals for 5 years or longer. This indicates that stimulation of a high level of immunity is biologically feasible given appropriate presentation of protective immunogen(s). There is evidence that immunity in horses resistant to reinfection is mediated at the mucosal level and functions to block entry of *S. equi*. However, systemic immunity after parenteral inoculation of avirulent live *S. equi* is also protective. Together, these findings indicate that optimum immunity may require both systemic and mucosal responses.

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It is likely that more effective and safer vaccines will eventually be developed based on genomic sequence information from *S. equi* and *S. zooepidemicus*. Protective immunogens must be identified for systemic and mucosal responses, and the appropriate modes of presentation elucidated by experiment. Because it is likely that different immunogens function at the tonsillar and lymphatic levels, the appropriate combination of these components will also have to be identified in multiple experiments with ponies and horses.

31.10.5.1

USE OF EXTRACT VACCINES

Extract vaccines are given intramuscularly or subcutaneously and elicit serum antibody responses 7 to 10 days later. Naïve horses and foals require a schedule of two or three doses at an interval of 2 weeks. Booster doses are given once annually. Pregnant mares may be boostered a month before expected date of foaling. Horses known to have had strangles within the previous year should not be vaccinated. Horses with signs of strangles should not be vaccinated. During an outbreak, only horses with no known contact with animals with strangles should be promptly vaccinated.

Table 31-8 Aims and Measures Used To Control Transmission of *S. equi* on Affected Premises

Aim		Measure
1.	To prevent the spread of *S. equi* infection to horses on other premises and to new arrivals on the affected premises	Stop all movement of horses on and off the affected premises immediately and until further notice. Horses with strangles and their contacts should be maintained in well-demarcated "dirty" (i.e., *S. equi* positive) quarantine areas. Clustering of cases in groups should allow parts of the premises to be easily allocated as "dirty" and "clean" areas.
2.	To establish whether convalescing horses are infectious *after* clinical recovery	At least three nasopharyngeal swabs or lavages are performed at approximately weekly intervals in all recovered horses and their contacts, and the samples are tested for *S. equi* by culture and PCR assay. Horses that are consistently negative are returned to the "clean" area.
3.	To investigate all outwardly healthy horses in which *S. equi* is detected by either culture or PCR assay	Perform endoscopy of the upper respiratory tract and guttural pouches.
4.	To eliminate *S. equi* infection from the guttural pouches	Remove pathology through a combination of flushing and aspiration with saline, and remove chondroids using endoscopically guided instruments. Perform topical and systemic administration of antimicrobials to eliminate *S. equi* infection.
5.	To prevent indirect cross-infection by *S. equi* from horses in the "dirty" area to those in the "clean" area of the premises	Personnel should use dedicated protective clothing when dealing with infectious animals and should not deal simultaneously with susceptible animals. If this is unavoidable, infectious horses should be dealt with *after* susceptible animals. Strict hygiene measures are introduced, including provision of dedicated clothing and equipment for each area and disinfection facilities for personnel and use of thorough stable cleaning and disinfection methods. When cost is not a factor, consideration should be given to destruction of the dedicated equipment after eradication of the infection. After removal of organic material from stables, all surfaces should be thoroughly soaked in an appropriate liquid disinfectant or steam-treated and allowed to dry. This should be repeated if possible. Manure and waste feed from infectious animals should be composted (disinfected by heat) in an isolated location. Pastures used to hold infectious animals should be rested for 4 weeks. Care should be taken to disinfect water troughs at least once daily during an outbreak. Horse vans should be hosed clean and disinfected after each use.

PCR, Polymerase chain reaction.

31.10.5.2 USE OF ATTENUATED LIVE INTRANASAL VACCINE

Live vaccine should be administered only to healthy nonfebrile animals free of nasal discharges. Vaccine is given in a schedule of two doses at 2- to 3-week intervals. Annual booster doses are recommended. Live vaccine should not be used during an outbreak, except in horses with no known contact with infected or exposed animals. The mode of application should be such that an adequate amount of vaccine reaches the pharyngeal and lingual tonsils.

31.10.6 Control of Outbreaks

A practical disease-control strategy should then be agreed on and implemented. The general aims and measures for such a strategy are outlined in Table 31-8.[387]

31.10.7 Treatment

Appropriate treatment of horses with strangles usually depends on the stage and severity of the disease, and veterinary opinion as to whether or not to use antibiotic treatment remains markedly divided. However, the majority of strangles patients require no treatment other than proper rest, a dry, warm stall, and soft, moist, and palatable food of good quality while the disease is allowed to run its course. Food and water should be easily accessible to the horse.

31.10.7.1 HORSES WITH EARLY CLINICAL SIGNS

During an outbreak, immediate antibiotic therapy for new cases in the early acute phase with fever and depression may be curative and may prevent focal abscessation. Because abscesses have not developed at this early stage, the antibiotics have adequate access to the bacteria. Immediate treatment of horses that show the earliest clinical sign, fever, could be an effective way of controlling strangles outbreaks in racing stables or riding barns, although the disadvantages of treatment should be weighed.

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31.10.7.2 HORSES WITH LYMPH NODE ABSCESSATION

Once an external lymphadenopathy is detected in an otherwise alert and healthy horse, antibiotic therapy is probably contraindicated. Although it provides temporary clinical improvement in fever and lethargy, it only prolongs the inevitable enlargement and eventual rupture of lymph node abscess. Therapy should be directed toward enhancing maturation and drainage of the abscesses. Topical treatments such as Ichthammol or a hot pack may be applied to promote maturation of the lymph node abscess, although objective controlled data supporting the use of these techniques are lacking. Surgical drainage of lymphadenopathies is sometimes indicated if abscesses do not rupture spontaneously; however, it is critical to wait until the abscess has matured and thinned out ventrally. The use of NSAIDs such as phenylbutazone may improve the horse's demeanor by reducing fever, pain, and inflammatory swelling at the site of the abscesses. This may in turn encourage eating and drinking.

Even in the face of detectable lymphadenopathy, if the horse is febrile, depressed, anorectic, and especially manifesting dyspnea as result of partial upper airway obstruction, antibiotic therapy is indicated to decrease abscess size and prevent complete airway obstruction. Rarely, affected horses may require intensive

supportive therapy, including IV fluids, feeding by nasogastric tube, and tracheostomy. An animal requiring a tracheostomy should be given systemic antimicrobial drugs to prevent secondary bacterial infections of the lower respiratory tract.

31.10.7.3 DRUGS OF CHOICE FOR THERAPY

Penicillin is generally considered the drug of choice for the treatment of nonpneumococcal streptococcal disease, with alternative drugs used depending on ease of administration or the site of infection. Other agents for therapy include cephalosporins and macrolides. Although there is evidence that trimethoprim-sulfadiazine did not eliminate *S. zooepidemicus* infection in tissue chambers implanted subcutaneously in ponies, the study did not determine its effectiveness against *S. equi*. Anecdotally, many veterinarians believe that trimethoprim-sulfadiazine is effective in treating horses with strangles.

31.10.8 Complications

The overall complication rate associated with *S. equi* infection is approximately 20%. The occurrence of complications can significantly increase the mortality rate.

A variety of complications can occur as a result of strangles. These can be generally grouped as:

- Those associated with the spread of infection to other locations (bastard strangles)
- Immune-mediated processes, including purpura hemorrhagica and myopathies
- Other complications

31.10.8.1 COMPLICATIONS ASSOCIATED WITH METASTATIC SPREAD OF INFECTION

S. equi may potentially infect any site. The term *bastard strangles* is often used to describe metastatic abscessation. Spread of the organism may occur through several routes, including hematogenous spread, lymphatic migration, or spread via close association with a septic focus or direct aspiration of purulent material.

Common sites of infection include the lung, mesentery, liver, spleen, kidneys, and brain. Respiratory distress may occur owing to tracheal compression resulting from enlargement of the cranial mediastinal lymph nodes. Suppurative bronchopneumonia is one important sequela of strangles.

Another important complication of strangles is extension of infection to the sinuses or guttural pouches. Infection of the guttural pouch is of particular importance, as the guttural pouch is the most common site for prolonged carriage of the organism.[389] Other reported conditions associated with *S. equi* infection include myocarditis, endocarditis, panophthalmitis, periorbital abscesses, ulcerative keratitis, paravertebral abscesses, septic arthritis, and tenosynovitis.

31.10.8.2 IMMUNE-MEDIATED COMPLICATIONS

31.10.8.2.1 Purpura Hemorrhagica

Purpura hemorrhagica is an aseptic necrotizing vasculitis characterized primarily by edema and petechial or ecchymotic hemorrhage. Although the exact pathogenesis of purpura hemorrhagica is not fully understood, it appears to a vasculitis caused by the deposition of immune complexes in blood vessel walls. The risk of developing purpura hemorrhagica after exposure to *S. equi* through infection or vaccination is not known. A preexisting high serum antibody titer to *S. equi* antigens may predispose horses to the development of purpura hemorrhagica.

31.10.8.2.2 Myositis

Both muscle infarctions and rhabdomyolysis with progressive atrophy have been documented in horses after exposure to *S. equi*.

- Muscle infarctions: This syndrome is most likely a manifestation of purpura hemorrhagica. On histopathology, there is acute coagulative necrosis of muscle with infarctions.
- Rhabdomyolysis with progressive atrophy: Significant rhabdomyolysis has been identified in some quarter horses after exposure to *S. equi*.

31.10.8.3 OTHER COMPLICATIONS

Streptococcal antigens have been suggested as a trigger for development of myocarditis and proliferative glomerulonephritis. Agalactia has been reported in broodmares with strangles. Although infection of the mammary glands is possible, the mammary glands are usually normal and the agalactia is thought to be secondary to the fever, anorexia, and lethargy associated with infection.

31.11 ACUTE RESPIRATORY DISTRESS SYNDROME AND ACUTE LUNG INJURY (ACUTE BRONCHOINTERSTITIAL PNEUMONIA)

BETTINA DUNKEL

PAMELA A. WILKINS

31.11.1 Definition and Pathophysiology

ALI and ARDS comprise a syndrome of severe pulmonary dysfunction and respiratory failure caused by physical or chemical injury or an exaggerated pulmonary immune response. In human medicine ALI and ARDS are defined by an acute onset, bilateral pulmonary infiltrates, a ratio of pulmonary arterial oxygen pressure (Pa_{O_2}) to fraction of inspired oxygen (Fi_{O_2}) of <300 for the less severe form, ALI, and <200 for ARDS, and no clinical evidence of left atrial hypertension or a pulmonary arterial occlusion pressure of <18 mm Hg.[392] The definition acknowledges ALI and ARDS as clinically recognized conditions, regardless of the inciting cause of

the respiratory failure.[393] No consensus with regard to a uniformly accepted definition in veterinary medicine has been published as of this writing.

ALI or ARDS arises as a complication after major infectious or noninfectious bodily injury. During infections, such as pneumonia, inflammatory cells and mediators localize and destroy the infectious agent while fibrin generated by a locally confined procoagulant state immobilizes the source of infection and minimizes spread of the pathogens.[394] In ALI and ARDS an imbalance of proinflammatory and antiinflammatory factors combined with activation of the pulmonary endothelium and derangement of the coagulation cascade favors the development of a fulminant, uncontrolled pulmonary inflammatory response and a widespread procoagulant environment in alveoli and the pulmonary microcirculation.[393] The triggering event may be an intrapulmonary (viral or bacterial pneumonia, smoke inhalation, near drowning, or food aspiration) or extrapulmonary (trauma, multiple transfusions, systemic inflammatory response, or sepsis) insult.[393,395]

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Although not temporally distinct and largely overlapping, the pathophysiologic events can be divided into an initial exudative phase, a fibroproliferative phase, and, if the patient survives, a recovery phase.[396] The exudative phase is characterized by uncontrolled released of inflammatory mediators such as IL-1, IL-6, IL-8, and TNF-α and influx of inflammatory cells into the pulmonary tissue. Activated neutrophils and alveolar macrophages marginate in the microcirculation and extravasate into the pulmonary tissue, where they release oxidants, reactive oxygen species, proteases, and cytokines. These in turn attract and activate further inflammatory cells, thereby amplifying and perpetuating the inflammatory cascade. The inflammatory process ultimately damages or destroys the alveolar endothelial and epithelial barrier, causing flooding of the alveoli once the edema safety factors are exhausted. The barrier tends to collapse suddenly, resulting in rapid filling of the alveoli with proteinaceous exudate, leukocytes, and red blood cells and destruction of the surfactant layer.[393] The fast onset of pulmonary edema may correspond with the clinically observed acute onset of respiratory distress. Endotoxin and inflammatory cytokines such as TNF, IL-1, and IL-6 activate the coagulation cascade by tissue factor release while fibrinolysis is inhibited by increased plasminogen activator inhibitor (PAI)–1 activity. The result is formation of thrombi in the pulmonary microvasculature and deposition of intraalveolar fibrin-rich hyaline membranes.[394,396] The fibroproliferative response, which can begin within 24 hours of the onset of ALI and ARDS, is characterized by type I pneumocyte necrosis and proliferation of the more resistant type II pneumocytes in an attempt to restore the epithelial surface.[393,396] Fibroblasts invade pulmonary interstitium, alveolar walls, and deposited collagen. The resultant fibrosis reduces pulmonary compliance and increases the work of breathing, and alveolar obliteration and interstitial thickening lead to poor gas exchange.[396]

The effect on the patient is severe hypoxemia with hypocapnia or hypercapnia caused by ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch and decreased pulmonary compliance. Alveolar edema causes hypoxemia by creating areas of a low $\dot{V}/\dot{Q}$ ratio (adequate perfusion but no ventilation), whereas areas with deceased perfusion generate hypoxemia and eventually hypercapnia by increasing dead space ventilation (high $\dot{V}/\dot{Q}$ ratio; adequate ventilation with minimal perfusion).[393] The coexistence of areas with high and low $\dot{V}/\dot{Q}$ ratios adjacent to normal lung tissue makes mechanical ventilation of patients with ALI and ARDS extremely challenging.

The resolution of ALI and ARDS depends on a functional distal lung epithelium. For edema to resolve, endothelial and epithelial leaks must be sealed before active salt and water transport can clear the edema fluid followed by cellular protein clearance.[393] Sodium and chloride ions are actively transported via ion channels (epithelial sodium channel ENaC and cystic fibrosis transmembrane conductance regulator CFTR, a chloride transporter) on the apical surface and Na/K-ATPase on the basolateral membrane of alveolar epithelial cells. Water follows the created osmotic gradient through aquaporin-5 channels located on type I epithelial cells.[393,397]

If damage to the pulmonary epithelium is minor, pulmonary edema can be cleared swiftly, pulmonary function improves rapidly, and chances of survival increase. If large areas of alveolar epithelium are destroyed, repair must occur before the edema can be cleared.[393] Severe damage to the epithelium corresponds with prolonged respiratory failure, slow recovery by gradual regeneration of the respiratory epithelium, and high mortality.[397] Although the mortality of human patients with ALI and ARDS is still high, less than 5% of patients die of refractory hypoxemia. Most patients succumb to their primary disease process and multiorgan failure.[396] Recovering patients may have complete resolution of pulmonary compromise, whereas others suffer from residual functional impairment such as muscle weakness, decreased pulmonary function, restrictive or obstructive changes, and low diffusion capacities.[396]

An ALI-ARDS-like syndrome has been described in 1- to 7-month-old foals and occasionally in neonatal foals.[398–400] In earlier reports the condition was named *acute interstitial* or *bronchointerstitial pneumonia*. Extensive searches for a common pathogen were conducted until with increasing understanding of the pathophysiology it became evident that multiple infectious and noninfectious agents are able to initiate the inflammatory response.[398,400–402] In foals the most common underlying condition appears to be bacterial pneumonia, and in rare cases the underlying condition is viral pneumonia.[398–402] There are no reports of ALI or ARDS in adult horses, although based on few clinical case reports and small studies one can suspect that a similar form of acute pulmonary injury exists. Buergelt and colleagues[398] reported not only on 14 foals with acute respiratory distress, but also on six adult horses. However, the onset of respiratory disease in the adults was more prolonged (11 days to 2 months), and the description better fit the heterogenous group of interstitial pneumonia than ALI and ARDS. Two adult horses with respiratory distress after near drowning met the criteria for ALI,[403,404] and two horses affected by smoke inhalation experienced fulminant pulmonary inflammation and most likely ALI.[405] Acute respiratory distress in ponies after experimentally induced gram-negative sepsis has been reported, and although some of the ponies may have suffered from ALI and ARDS, most animals were agonal, making interpretation of the observed pulmonary changes difficult.[406]

31.11.2 Clinical, Diagnostic, and Postmortem Findings

Clinically it is almost impossible to differentiate foals with ALI and ARDS from foals with severe bacterial, particularly advanced *R. equi*, pneumonia, and in a number of cases ALI or ARDS has been triggered by an underlying bacterial infection. Clinical signs include profound depression, fever, and respiratory distress with tachycardia, tachypnea, nostril flare, and cyanotic mucous membranes. Auscultation of the lungs can reveal a variety of abnormal sounds or even complete silence over nonventilated areas. Laboratory findings include severe hypoxemia with hypocapnia or hypercapnia and, depending on the underlying disease process, leukocytosis or leukopenia and hyperfibrinogenemia. Signs of disseminated intravascular coagulation were present in two foals with ALI and ARDS in one report,[401] and an abnormal coagulation panel may be observed. Transtracheal lavage fluid demonstrates neutrophilic inflammation with or without signs of infection, depending on the underlying cause. Thoracic radiographs demonstrate a diffuse, dense bronchointerstitial pattern often coalescing to a focal or diffuse alveolar pattern with prominent airbronchograms. The initial radiographic appearance of the lungs may worsen dramatically within hours because of rapid progression of pulmonary edema. On the other hand, absorption of the alveolar fluid may result in impressive improvement of the radiographic appearance within days.[401,402] A thoracic sonogram is useful in foals that cannot be safely transported to a radiography unit and reveals multiple coalescing comet-tail artifacts predominately in the caudodorsal lung field.

On gross pathologic examination, the affected lungs are wet and firm and fail to collapse, and airways contain variable amounts of pink, foamy liquid. Histologically necrosis of alveolar and terminal bronchial epithelium is observed, with extensive filling of the alveolar spaces with neutrophils, macrophages, hemorrhage, protein-rich edema fluid, or hyaline membranes. Occasionally, microthrombi can be detected in interstitial capillaries. In more chronic cases diffuse proliferation of cuboidal pneumocytes and fibroblasts and beginning fibrosis may be present.[398,400–402]

31.11.3 Diagnosis

The diagnosis can be established if the onset of the respiratory distress is acute, Pao_2/Fio_2 is <300 (Pao_2 of <63 mm Hg on room air) with little response to O_2 supplementation, the correspondent radiographic or ultrasonographic changes are observed, clinical signs of cardiac disease are absent, and the extent of the respiratory distress cannot solely be attributed to a primary disease process (e.g., almost complete destruction of the pulmonary parenchyma by *R. equi* abscesses). Presence of a primary disease process such as bacterial or viral pneumonia does not rule out the concurrent presence of ALI or ARDS.

31.11.4 Treatment and Prognosis

In human medicine, mechanical ventilation using low tidal volumes (6 mL/kg) and some form of positive end-expiratory pressure is the treatment of choice.[407] Because mechanical ventilation, with the exception of rare circumstances,[408] is possible only in neonatal equine patients, the most important treatment remains intranasal insufflation of humidified oxygen via unilateral or bilateral intranasal cannulas at high flow rates (10 to 30 L/min). Large-bore tubing systems minimize the resistance to airflow, and Fio_2 as high as 70% has been measured at the carina in adult horses using bilateral flow rates of 15 L/min (combined 30 L/min).[409] Alternatively, use of intratracheal O_2 insufflation has been described, achieving results similar to high bilateral intranasal flow rates.[410] Antiinflammatory treatment is also essential; although the use of corticosteroids in human ALI and ARDS is controversial; a recent small study reported reduced mortality and decreased need for ventilation in the group treated with low doses of corticosteroids (2 mg of methylprednisolone per kilogram IV loading dose followed by 2 mg/kg/day IV divided in four treatments).[411] Considering that ventilation is rarely an option and that in two reports all but two foal surviving ALI and ARDS received corticosteroids, anecdotal evidence is in favor of steroid administration. IV prednisolone sodium succinate or methylprednisolone at 1 to 2 mg/kg/day divided in two to four doses may be useful. Antimicrobial treatment, if required, should be directed against the underlying disease process. Bronchoconstriction is not a prominent feature of ALI and ARDS, and bronchodilators are therefore of limited use but may be beneficial in individual cases. As described earlier, clearance of edema fluid from the lungs depends on active transepithelial ion transport, a process that can be stimulated by β_2-agonists such as salmeterol, terbutaline, and epinephrine. There is some evidence in experimental models of ALI that β_2-agonists delivered into the airways reduce pulmonary edema by attenuating pulmonary vascular injury and upregulating fluid clearance from the air spaces.[412] Care should be taken when administering bronchodilators as they can induce sudden worsening of ventilation-perfusion mismatch and can lead to acute decompensation of the severely hypoxic patient. Judicious IV fluid therapy may be necessary in dehydrated patients. The increased permeability of the pulmonary capillaries makes capillary hydrostatic pressure the main determinant of pulmonary edema formation, and overhydration or rapid changes in circulating blood volume should be avoided. On the other hand, suboptimal hydration status decreases cardiac output and worsens oxygen delivery to the

peripheral tissue. Measurement of central venous pressure may aid in determination of the patient's hydration status. If foals are too depressed to nurse or eat, nutritional support is essential.

Several other treatments have been suggested in human medicine, including vasodilators such as inhaled nitric oxide or prostacycline, surfactant to reduce surface tension, and scavengers of reactive oxygen species (tocopherol, ascorbic acid); however, none has been proven to increase survival despite the fact that individual treatments improved pulmonary function.[396] Considering that, in contrast to human medicine, most equine patients die as a direct result of respiratory failure and severe hypoxemia, some of those therapeutic options may benefit the equine patient.

Based on the limited information available, the prognosis for survival and future athletic performance is guarded, with survival rates ranging from 60% to 69% in two clinical reports.[401,402] Nevertheless, survival and successful careers as racehorses have been reported even in severely affected animals.[402]

31.12 INTERSTITIAL PNEUMONIA

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KURT WILLIAMS

FABIO DEL PIERO

Interstitial pneumonia is an uncommon cause of acute or chronic disorders of the lower respiratory tract of horses.[413–419] However, because of the severity of the process, it becomes important to recognize and definitively diagnose this entity as early as possible in its clinical course. The term *interstitial pneumonia* defines a number of diseases that are chronic and progress to pulmonary fibrosis. The course is insidious and morphologically characterized by alveolar structural derangements that lead to loss of functional gas exchange units of the lung and altered mechanical properties of the lung, characterizing the pneumonia as a restrictive lung problem.

31.12.1 Etiology

Multiple agents have been implicated in the genesis of interstitial pneumonia in animals, but fewer than 20 have been confirmed in horses (Box 31-2). Chief among these are infectious agents and ingested toxins. Frequently the causative agent cannot be identified, because of the insidious nature of the process, and the final diagnosis is idiopathic interstitial pneumonia. The lung responds in a rather stereotypic manner to injury, and our limited ability to identify infectious, toxic, and immunologic causes frequently hinders our current ability to make an accurate identification of a specific cause. All efforts should be made to identify a causative agent early in the course of the disease, but the practitioner needs to be aware that treatment frequently will be nonspecific and supportive.

31.12.1.1 Box 31-2 Causes of Interstitial Pneumonia in Horses

31.12.1.1.1 ACUTE

Infections (systemic viral, bacterial, parasitic)

Inhaled chemicals

Oxygen (FiO_2 > 50%)

Smoke

Ingested toxins or precursors

Perilla mint *(Perilla frutescens)*, crofton weed *(Eupatorium adenophorum), Crotalaria* species, *Senecio* species

Adverse drug reactions

Uncertain

Hypersensitivity

Acute hypersensitivity pneumonitis

Endogenous metabolic or toxic conditions

Shock—particularly endotoxic (ARDS)

Disseminated intravascular coagulation (DIC)

Uremia

Idiopathic or cryptogenic

31.12.1.1.2 CHRONIC

Infections (systemic viral, bacterial, parasitic)

Inhaled inorganic dust (pneumonoconioses)

Silicosis

Hypersensitivity

Hypersensitivity pneumonitis

Ingested toxins or precursors

Perilla mint *(Perilla frutescens)*, crofton weed *(Eupatorium adenophorum), Crotalaria* species, *Senecio* species

Collagen-vascular disorders

Uncertain

Idiopathic or cryptogenic

31.12.2 INFECTIOUS AGENTS

Infectious causes of interstitial pneumonia in horses and foals include viral, bacterial, parasitic, protozoal, and fungal agents. Typically the pneumonia is acute and severe, characterized by severe damage to the lung parenchyma (alveolar region).

Viral agents are frequently implicated or suspected but rarely identified by the usual serologic, histopathologic, and virus isolation methods. The advent of more sensitive and specific techniques, such as in situ PCR and monoclonal antibody IHC, may partially resolve the current diagnostic challenge. Most recently, a novel gamma-EHV, EHV type 5 (EHV-5), has been found associated with a nodular form of interstitial pneumonia of horses characterized by pulmonary interstitial fibrosis, suggesting that these rather unusual cases may have an underlying infectious cause.[420] This disease has been termed *equine multinodular pulmonary fibrosis* by the authors describing the pathology of the disease. Horses affected generally have a history of fever, cough, and weight loss, accompanied by exercise intolerance and finally respiratory distress. They can be acutely affected or have a more chronic progressive problem. Typical radiographs reveal multiple discreet to coalescing nodular densities overlying a diffuse interstitial pattern (Figs. 31-31 and 31-32). Histologic appearance is diagnostic of this disease (Figs. 31-33 and 31-34). EHV-5 has been identified in both BALF and lung biopsy samples from affected patients by both PCR assay and IHC.

In some horses with bronchointerstitial pneumonia of unknown cause, bacterial agents have been isolated from the lung. The usual distribution of bacterial bronchopneumonia in the horse is cranioventral, whereas the distribution in interstitial pneumonia is diffuse. In the latter cases the bacteria are most likely opportunistic pathogens and do not represent the primary causative agent. An exception is *R. equi* pneumonia of foals, which can cause an ARDS in older foals. *R. equi* has been cultured from foals with severe, acute bronchointerstitial pneumonia with a diffuse pulmonary distribution.[416] Interstitial pneumonia associated with *P. carinii* has been described in the foal, and *Mycoplasma* species has been isolated from the respiratory tract of adult horses.[421] The significance of the *Mycoplasma* isolates remains a matter of debate. *P. carinii* pneumonia is thought to occur

primarily in immunocompromised foals as a complication of some other serious disease, such as infectious pneumonia or SCID. It is characterized by plasmacytic lymphocytic interstitial pneumonia with flooding of alveoli with foamy acidophilic material.

Fig. 31-31 Radiographic appearance of caudodorsal lung field in a horse with equine multinodular pulmonary fibrosis. Note increased interstitial pattern and nodular alveolar pattern. Courtesy Dr. David Wong, Iowa State University, Ames, Ia.

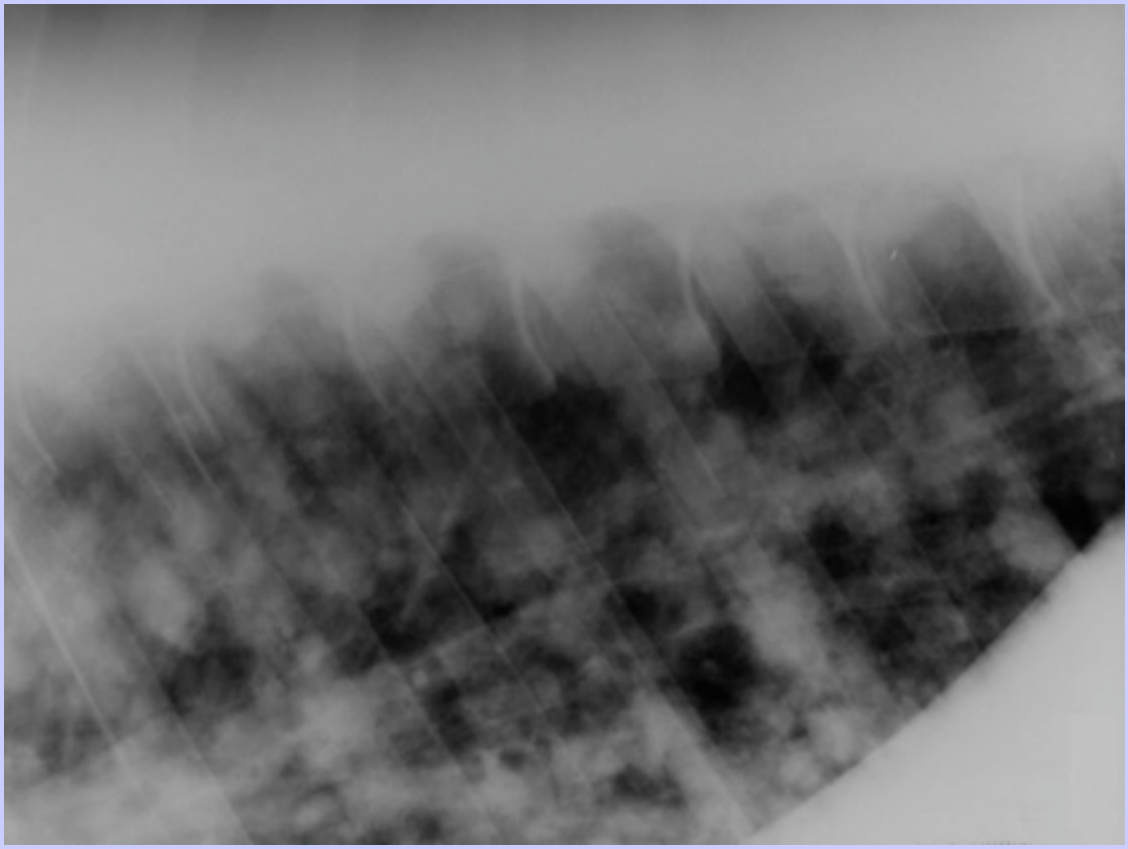


Fig. 31-32 Cut section of lung from horse with equine multinodular pulmonary fibrosis. Note large areas of apparent fibrosis within the pulmonary parenchyma. Courtesy Dr. Perry Habecker, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.

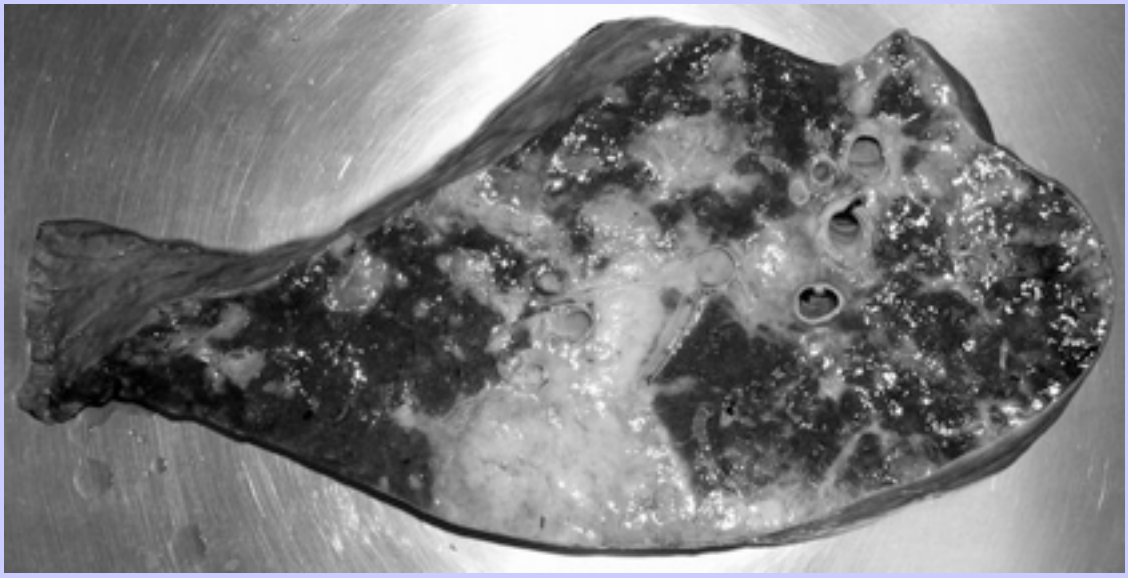


Fig. 31-33 Postmortem histopathologic specimen from a horse with severe equine multinodular pulmonary fibrosis. This is the histologic appearance of one of the fibrotic nodules. The alveoli are constricted within dense neoformed fibrotic tissue. Alveoli have an abnormal cuboidal epithelium (type 2 pneumocytes), and the lumen contains macrophages, sloughed epithelial cells, and neutrophils. Denser and diffuse fibrotic areas present. Courtesy Dr. Fabio Del Piero, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.

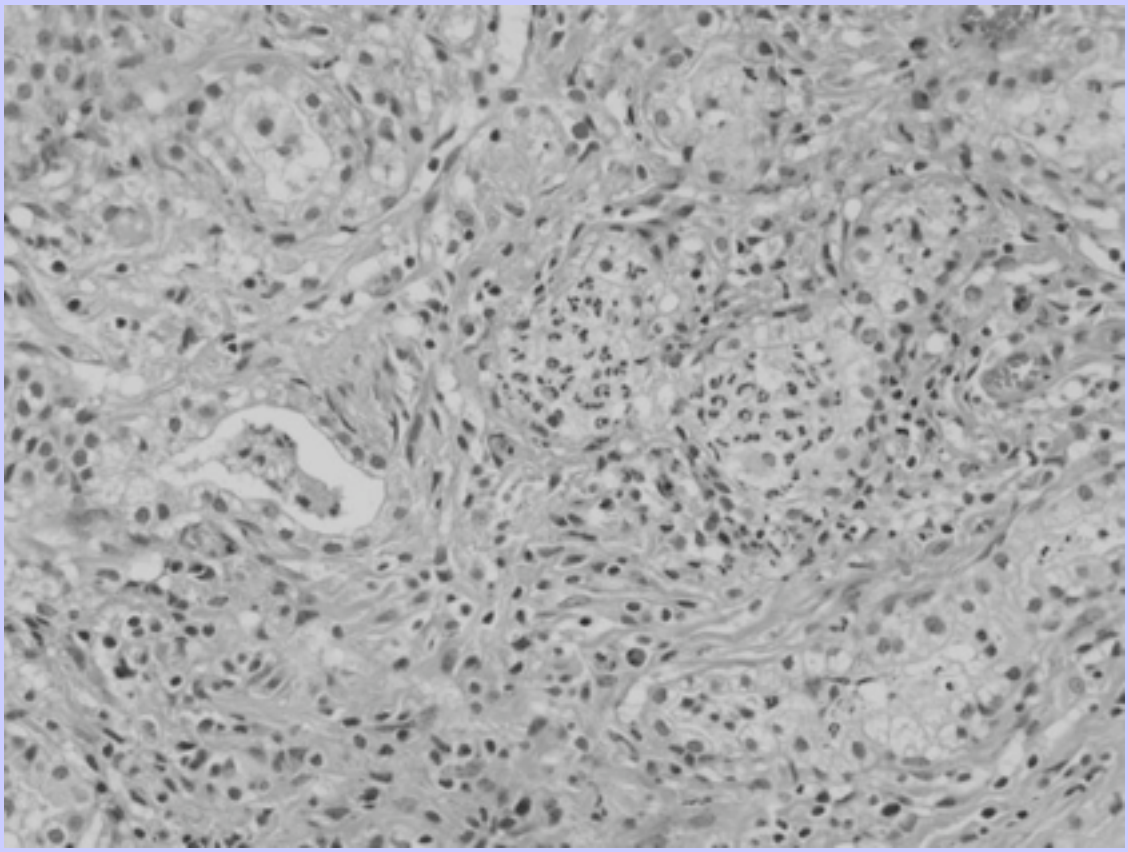
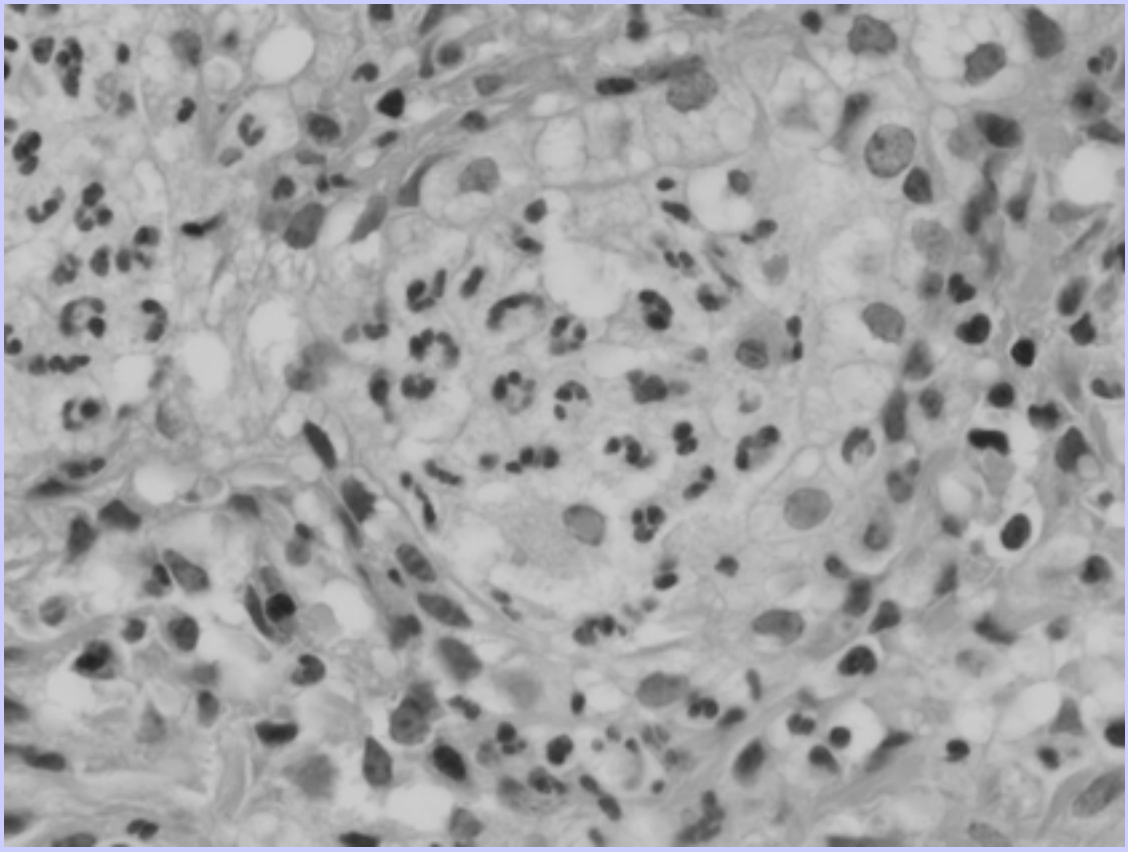


Fig. 31-34 Postmortem histopathologic specimen from a horse with severe equine multinodular pulmonary fibrosis. Note abnormal alveolar cuboidal epithelium, and within the lumen neutrophils and intranuclear amphophilic viral inclusion with chromatic margination within a sloughed epithelial cell or perhaps a macrophage. Courtesy Dr. Fabio Del Piero, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.



Parasitic pneumonia, an uncommon cause of chronic bronchointerstitial pneumonia, usually occurs in young foals secondary to migration of *Parascaris equorum* larvae through the pulmonary parenchyma.

31.12.3 INGESTED CHEMICALS

Ingested chemicals rank second only to infectious agents as potential causes of interstitial pneumonia in horses. Ingestion of pyrrolizidine alkaloids from a variety of plants (mostly genera *Crotalaria, Trichodesma*, and *Senecio*) can cause interstitial pneumonia in horses.[422] This toxicity is associated with production of a toxic metabolite that is activated in the liver then circulates to the lung. The toxic alkylating agents damage capillary endothelial cells, although the amount of alkaloid required to damage the lung is generally less than that required

for hepatotoxicity. Crofton weed *(Eupatorium adenophorum)*, a poisonous plant found primarily in Australia and Hawaii, produces interstitial pneumonia in horses. Toxicity is associated with ingestion of the flowering plant, but the nature of the toxin is not known. Perilla ketone, derived from the plant *Perilla fructans*, produces acute respiratory distress with a week of ingestion in ponies. The lesions include diffuse alveolitis and type II pneumocyte proliferation with sparing of the bronchioles. Toxicity depends on additional metabolism of the 3-substituted furan by the mixed function oxidase system, which occurs directly in the lung of the horse.

31.12.4 INHALED CHEMICALS

Direct pulmonary injury by inhaled chemicals is an uncommon cause of interstitial pneumonia in horses. In people this type of pneumonia is primarily related to occupational exposure. Smoke inhalation causes acute, diffuse interstitial pneumonia in horses, frequently followed within a few days by opportunistic bacterial pneumonia. Oxygen toxicity can theoretically produce interstitial pneumonia and alveolar type II cell proliferation. This problem is more likely to be seen in neonatal foals mechanically ventilated with increased levels of oxygen ($Fio_2 > 50\%$) for several days, although this may in fact be a form of ventilator-associated lung injury (VALI) associated with mechanical stretch of the airspaces. Damage is thought to be due to production of reactive oxygen metabolites, which attack a lung that may already have been injured by barotrauma resulting from a ventilator-driven increase in airway pressure. Agrichemicals or herbicides, such as paraquat, may cause acute interstitial pneumonia (AIP) in horses and should be considered in horses with a history of possible exposure. Silicosis is a specific chronic granulomatous pneumonia of horses associated with inhalation of silicon dioxide crystals. This syndrome has been described in horses originating from the Carmel Valley region of California. The inhaled particles are ingested by alveolar macrophages and result in lysis of the macrophage, chronic alveolitis, and fibrosis. Multiple granulomas are present, and submicron intracytoplasmic crystalline particles can be identified in macrophages.

31.12.5 HYPERSENSITIVITY REACTIONS

In the most specific sense, *hypersensitivity pneumonitis* refers to pulmonary disease caused by inhalation of organic antigens. Lymphocytic, plasmacytic bronchitis and bronchiolitis, combined with lymphocytic interstitial pneumonia, characterize the disease in horse lung. Granuloma formation and fibrosis can be observed. Chicken dust and fungi have been implicated as causes of severe, chronic bronchointerstitial pneumonia, but the syndrome itself is quite rare.

31.13 ENDOGENOUS METABOLIC AND TOXIC CONDITIONS

Various conditions cause acute pulmonary injury with inflammatory edema or severe alveolar wall damage and serofibrinous exudation similar to that described for AIP. Acute uremia, shock, burns, and trauma can produce an acute pulmonary injury termed *acute lung injury* or *acute respiratory distress syndrome*, depending on severity. Although endotoxin does not directly injure the lung, endotoxemia in the horse initiates inflammatory and metabolic cascades that can lead to pulmonary injury. Activation of these pathways produces vasoactive and chemoattractant molecules that increase vascular permeability, activate complement, produce proinflammatory cytokines, and release neutrophil enzymes that can adversely affect the lungs of horses. Horses as a species are quite sensitive to the negative effects of endotoxemia, and their lungs are particularly sensitive, perhaps because of the presence of intravascular macrophages, which further amplify the inflammatory cascade. Both ALI and ARDS have recently been defined for veterinary patients, although the definition has not been published as of the date of this writing.

31.13.1 Pathophysiology

Interstitial pneumonia progresses through four phases. During the first, the initial insult causes parenchymal injury and alveolitis. This is followed by a proliferative phase characterized by cellular and parenchymal alterations in tissues of the lung. Chronic cases progress to the development of interstitial fibrosis, and the final stage results in end-stage irreparable fibrosis of the lung.

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The structural changes that occur in the lung reduce the number of functional alveoli, adversely affecting ventilatory function of the lung and altering ventilation-perfusion relationships. Reduced lung compliance is associated with the loss of distensible alveoli, the presence of pulmonary edema, and fibrosis. Total and vital lung capacity are decreased in association with the loss of functional gas exchange units and reduced lung compliance. The work of breathing is increased, resulting in exercise intolerance and difficulty in breathing. Pulmonary hypertension and cor pulmonale may be complications of interstitial pneumonia and fibrosis. Although the origin of pulmonary hypertension is unclear, hypoxic vasoconstriction and generation of vasoactive compounds (such as endothelin-1) that alter pulmonary vascular resistance acutely, and vessel anatomy chronically, may play a role.

31.13.2 Clinical Signs

Horses affected with interstitial pneumonia frequently have fever, cough, weight loss, nasal discharge, exercise intolerance, severe dyspnea, cyanosis, and a restrictive breathing pattern. A “heave line” is frequently present; nostril flare and an anxious expression are usual. The history can be acute or chronic. Although affected foals are frequently depressed and anorectic, adults may be bright and alert with a variable appetite. The disease proceeds toward death in many cases, with progressive respiratory compromise, although some patients may also slowly improve with time. More than one foal at a farm may be affected.

31.13.3 Diagnosis

In older horses the primary differential diagnosis of heaves may be excluded by the leukocytosis and hyperfibrinogenemia that commonly occur in horses with interstitial pneumonia and fibrosis but do not occur in horses with heaves. However, these abnormal features are common in horses with infectious bronchopneumonia, and thoracic radiography is of paramount importance in the establishment of a definitive diagnosis. Typically, thoracic radiographs reveal extensive interstitial and bronchointerstitial pulmonary patterns.[423] Nodular infiltrates may be present, either large or miliary, but always diffusely distributed.

Culture of transtracheal or BAL aspirates often yields no significant growth of bacterial or fungal pathogens. Cytologic evaluation of tracheal or BALF shows increased numbers of neutrophils and macrophages. If *P. carinii* is involved, BALF may reveal trophozoites or intracystic bodies with special stains, such as toluidine blue or methenamine silver. Using PCR, EHV-5 has been found in BALF from horses with EMPF.

Histologic examination of a transthoracic lung biopsy specimen is the definitive diagnostic test for chronic interstitial pneumonia and fibrosis and for EMPF. Care must be taken to ensure the biopsy is obtained from a representative area, and we have found ultrasound guidance useful. Clinically important complications from this technique are uncommon but can occur. Biopsy can both define the causative agent and confirm the clinical diagnosis in EMPF when the sample is evaluated for EHV-5.

Additional diagnostic procedures could include arterial blood gas analysis, abdominocentesis and thoracocentesis to rule out metastatic neoplastic disease, PFT, viral isolation, serologic testing for antibody to fungi and chicken serum if hypersensitivity pneumonitis is suspected, and immunohistochemical evaluation of lung tissue for suspected infectious agents. A complete cardiac evaluation should also be conducted, as pulmonary hypertension and cor pulmonale are not uncommon sequelae.

31.13.4 Treatment

Treatment of these cases is often unrewarding. Therapeutic goals are treatment of any underlying or secondary infection; suppression of inflammation; maintenance of tissue oxygen delivery within appropriate limits; relief of any associated bronchoconstriction; and prevention or treatment of complications. Environmental control, with appropriate temperature and humidity control and good ventilation, is beneficial.

Parenteral corticosteroid therapy is the mainstay of treatment, with early and aggressive therapy providing the best long-term outcome, particularly in foals. In one report of 23 foals affected with acute bronchointerstitial pneumonia, 9 of 10 treated with corticosteroids survived, but none of those not receiving steroid treatment lived.

Broad-spectrum antimicrobial treatment should be instituted initially, particularly in foals, as described for the treatment of infectious bronchopneumonia. The choice of antimicrobial agent and duration of therapy should be dictated finally by the culture and sensitivity results from the TTA and by the patient's clinical course. Anecdotally, horses with EMPF have responded to treatment with acyclovir and corticosteroids. The course of therapy is generally prolonged (6 to 12 weeks); clinical and radiographic improvement has been noted in a few cases to date.

Foals, in particular, and adults with severe respiratory distress may benefit from nasal insufflation of humidified oxygen, with flow rates of 10 L/min for foals and 15 L/min in adults. If necessary, as determined by persistent hypoxemia in the face of intranasal insufflation at the rates given, a second nasal canula can be placed in the opposite nostril to increase the Fio_2. Care must be taken to avoid obstruction of the nasal passages. Alternatively, intratracheal or transtracheal insufflation can be considered to further increase Fio_2 and improve oxygenation.

Systemic bronchodilator therapy may or may not be indicated in these cases. If used, bronchodilators may worsen ventilation-perfusion inequalities. Therefore bronchodilator therapy should be accompanied by supplemental oxygen, and the effects should be monitored with serial blood gas measurements and discontinued if hypoxemia worsens. Nebulized or aerosolized bronchodilator therapy may be more judicious, and beneficial effects are evident in some foals with respiratory distress. Aminophylline and theophylline should not be used, owing to their narrow therapeutic range. Furosemide may be appropriate for its bronchodilator effect and its effect on reducing pulmonary artery pressure, particularly if cor pulmonale develops.

31.13.5 Prognosis

The prognosis for horses with interstitial pneumonia is uniformly poor to guarded. Affected foals, treated early and aggressively with corticosteroid and antimicrobial therapy, have the best outlook for life. The disease is usually progressive in adults and eventually results in the demise of the horse, although the occasional horse recovers sufficiently to return to previous performance levels. A fair number of adult horses, with continuous intense management, will live for a period of time but will be severely compromised, which limits their usefulness. Exceptions to the poor prognosis may be seen in cases of *P. carinii* pneumonia in foals if they are treated early and aggressively and possibly also in cases of idiopathic interstitial pneumonia or EMPF in adult

horses that are treated early with corticosteroids and antiviral drugs. A trial of treatment for peracute interstitial disease for 48 hours is warranted, and patients with chronic interstitial pneumonia should be treated for a minimum of 6 weeks before the possibility of recovery is discarded.

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31.14 EQUINE RESPIRATORY VIRUSES

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D. Paul Lunn

Viral respiratory infections in horses are major causes of respiratory disease, resulting in impaired pulmonary function and reduced performance. Although vaccines are available for many of the causative agents, the respiratory viruses have remained a major concern in the horse industry. Infection with equine respiratory viruses can lead to serious respiratory illness with potentially fatal consequences. Yet the incidence and severity of viral respiratory disease may vary from year to year and are dependent on the attack rate, virulence of the circulating virus, infectious dose, management and environmental conditions, and degree of immunity of individual animals in the population.

With the exception of HEV infection, in a group of susceptible horses equine viral respiratory infection generally is characterized by the rapid spread of an acute, febrile respiratory disease accompanied by a dry cough and nasal discharge. Therefore a presumptive diagnosis of viral respiratory disease can often be made based on history and clinical signs. However, to confirm and differentiate among the potential causative agents, laboratory diagnosis is required.

31.14.1 Diagnosis of Equine Respiratory Viruses

The basic approaches for the laboratory diagnosis of equine viral respiratory disease are the isolation of the causative agent (virus isolation), demonstration of the virus or viral product in clinical specimens (detection of virus particles by electron microscopy; detection of viral antigens by immunofluorescence, ELISA, or immunoperoxidase; detection of the viral genome), and the detection of virus-specific antibodies (serology). Because each of these methods has its merits as well as disadvantages (e.g., lack of sensitivity, long turnaround time, high costs), it may be necessary to combine several of them to identify the causative agent accurately and rapidly. The World Organisation for Animal Health (OIE, www.oie.int) publishes the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*, which provides an in-depth review of current diagnostic testing strategies.

31.14.1.1 VIRUS ISOLATION

Virus isolation from clinical samples is crucial for epidemiologic investigation and for vaccine production and generally is carried out in cell culture. The notable exception is equine influenza virus, for which embryonated chicken eggs have remained the culture system of choice. As virus shedding in secretions of the respiratory tract is greatest within the first few days after infection, the best results for virus isolation are often achieved by culturing nasopharyngeal swabs collected in the first 24 to 48 hours after onset of clinical disease. The duration of nasal virus shedding is often brief in partially immune animals, so it may prove useful to sample immunologically less protected individuals in a group (e.g., younger horses, poorly vaccinated or unvaccinated animals) to increase the likelihood of demonstrating infectious virus. Nasopharyngeal or nasal passage samples are best collected using polyester-tipped swabs instead of cotton swabs because certain

viruses (e.g., influenza A virus) have been found to adhere to the cotton fibers. The swabs should be placed in a sterile viral transport medium and kept on ice until further analysis.

31.14.1.2 ANTIGEN DETECTION

The most important advantages of diagnostic tests aimed at the detection of viral antigen over traditional virus isolation are the faster turnaround time as well as the ability to detect virions that have lost their infectivity. Immunofluorescence (fluorescent antibody [FA] test) is based on the detection of virus-infected cells employing virus-specific fluorochrome-labeled antibodies. The technique is used to detect viral antigen in a broad range of clinical samples (e.g., frozen sections of tissues, 132 tissue imprints, cells obtained from nasal scrapings or tracheal washes) and has been shown to be highly sensitive. A number of antigen-capture ELISA-based assays have been developed for the detection of equine respiratory viruses.[424–428] Frequently a solid-phase system is used for virus detection. Specific antibody is first adsorbed to the surface of a microtiter plate, and the sample containing the suspected virus is then added. If the virus is present, it binds to the adsorbed antibody. After washing, specific enzyme-labeled antibodies are added. Detection of virus in the sample is achieved by addition of the enzyme substrate, which results in a color reaction. Commercially available ELISA-based test kits (e.g., Flu OIA assay, Biostar, Boulder, Colo.; Directigen Flu-A assay, Becton Dickinson Microbiology Systems, Cockeysville, Md.) have been validated for the rapid, stallside detection of equine influenza virus. Many investigators have found these commercial diagnostic kits to be highly specific and rapid, and their sensitivity approaches that of egg isolation.[429–433] Since the discovery of the PCR the technique has found wide application in diagnostic laboratories. Through the choice of appropriate oligonucleotide primers, a selected region of the viral genome can be amplified. PCR-based assays are extremely sensitive and theoretically can detect a single copy of the target nucleic acid in a sample.[434–436] Yet, owing to the assay's high sensitivity, the greatest challenge facing the diagnostic application of PCR is the production of false-positive results. Nevertheless, PCR-based techniques offer a more sensitive tool for the diagnosis of equine respiratory viruses than conventional techniques such as culture or immunoassays. To increase the diagnostic capacity of PCR, multiplex PCR assays have been developed. By including more than one pair of primers in the reaction mixture, these assays are designed to simultaneously detect a panel of respiratory pathogens. For example, multiplex PCR assays designed to detect nucleic acid of influenza A and B viruses, respiratory syncytial virus (RSV), adenovirus, and parainfluenza virus have been developed for screening of human clinical samples.[437–440] In equine diagnostics, assays capable of simultaneously detecting and differentiating EHV-1 and EHV-4[441–443] as well as EHV-2 and EHV-5[444] have been published. More recently, real-time PCR–based assays have been used for the detection and quantification of equine respiratory pathogens.[445–447] By employing a target-specific fluorescent probe, real-time PCR–based assays eliminate the need to distinguish the target by PCR fragment size on electrophoresis or hybridization with probes post-PCR. The advantages of real-time PCR include high specificity, sensitivity, and a rapid turnaround time.

31.14.1.3 ANTIBODY DETECTION

Detection of virus-specific antibodies has been and continues to be a cornerstone in the diagnosis of equine viral respiratory disease. Detection of specific antibody can provide support that an animal has been exposed to a given antigen. Often, this is used as circumstantial evidence of infectious disease. Commonly used techniques for antibody detection include ELISAs, serum neutralization tests, single radial hemolysis, and hemagglutination inhibition assays. Because most serologic assays are fairly easy to perform and cost-effective and because large numbers of samples can be collected and tested simultaneously, serologic testing is particularly useful for large-scale herd surveillance. Although useful, there are limitations to serologic testing.

For example, the presence of antibody indicates exposure to antigen but does not necessarily indicate active infection or disease. If horses have been vaccinated, a diagnosis of acute infection can often be made only by testing paired samples (acute and convalescent) and by demonstrating at least a fourfold rise in antibody titers over a period of several weeks (seroconversion). Because of the inherent variability of immunoassays, paired samples always should be run by the same laboratory. In addition, antibody is not always detected in the presence of active infection. The most common reason for a negative result despite infection is that insufficient time has passed between infection and measurement of an antibody response. Alternatively, immunocompromised horses may fail to produce a detectable antibody response despite active infection.

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31.14.2 Treatment

The treatment of horses with viral respiratory disease is primarily symptomatic. It is important to ensure that sick animals are kept in a clean, well-ventilated, and stress-free environment. Morbidity caused by pyrexia and myalgia may be reduced by administering NSAIDs. It is important to monitor affected horses for development of complications such as pneumonia and myocarditis, and animals exhibiting signs of respiratory disease after 10 days should be reevaluated to rule out secondary bacterial infections.

Antiviral drugs, such as amantadine, rimantadine, and acyclovir, have been used for prophylaxis and treatment of horses during outbreaks of equine influenza and EHV-1, respectively. Clinical trials with the influenza virus M2 ion channel blockers amantadine and rimantadine have shown that both drugs appear to be equally effective in reducing the severity and duration of clinical illness.[448,449] In addition, oral administration of rimantadine (30 mg/kg q12h) was shown to reduce the virus load in nasal secretion, although the duration of nasal virus shedding was similar to that in the untreated controls.[448] However, the therapeutic and prophylactic benefits of M2 ion blocker antiviral therapy during outbreaks of equine influenza may be limited owing to the potential for the rapid development of drug resistance. In vivo and in vitro studies have demonstrated that drug-resistant influenza virus mutants can develop as early as 1 day after the start of treatment.[450] Subsequent isolation of the drug-resistant virus from susceptible contacts showing signs of clinical disease indicates that acquisition of drug resistance is not associated with attenuation of the virus.[451,452] Finally, treatment of horses with amantadine has also been associated with adverse effects and poor oral bioavailablity.[453]

Acyclovir (9-[2-hydroxyethoxymethyl]guanine), a chain-terminating nucleoside analog, has been shown to be highly efficacious against herpes simples virus and, to some extent, varicella-zoster virus. EHV-1 was also found to be sensitive to inhibition by acyclovir in vitro and in animal models.[454,455] Although there have been no controlled studies reporting on the efficacy of acyclovir in the treatment and prevention of EHV-1 infection in horses, anecdotal reports suggest a potential benefit of acyclovir administration (10 mg/kg PO five times daily) in horses with clinical signs of EHV-1 infection (e.g., myelitis, neonatal infection).[456–458] In humans, acyclovir can be administered by injection, as a topical cream, or as an ingestible capsule. It is interesting to note that evaluation of the pharmacokinetics of a single PO or IV dose of acyclovir in adult horses revealed that intragastric administration of the drug was associated with high variability in serum drug concentrations as well as poor bioavailability.[459]

31.15 EQUINE INFLUENZA VIRUS

Equine influenza is the most frequently diagnosed cause of viral respiratory disease of the horse.[460,461] It is a highly infectious disease that affects horses, donkeys, mules, and zebras. Outbreaks of a disease resembling influenza were reported as early as 1751; however, the causative agent was not isolated until 1956.[462,463]

31.15.1 Etiology

Equine influenza viruses are members of the family Orthomyxoviridae, which contains enveloped viruses with segmented, single-stranded, negative-sense RNA genomes.[464] The Orthomyxoviridae include five genera: influenza A, B, and C viruses, thogotoviruses, and isaviruses.[464] Equine influenza viruses are influenza A viruses. In contrast to influenza B and C viruses, which appear to have a fairly narrow host range, influenza A viruses can infect a wide variety of species (e.g., horses, humans, wild and domestic birds, pigs, sea mammals, dogs, and cats). It has long been recognized that influenza A viruses exhibit partial restriction of their host range,[463] indicating that viruses from one host species occasionally can transmit to infect another host. Undoubtedly, the most prominent examples for direct transmission of influenza A viruses among species are the recent infections of humans and cats with the highly pathogenic avian H5N1 viruses.[465–468] Although horses have often been regarded as isolated or "dead-end" hosts for influenza,[463] events of recent years clearly indicate that the species barrier for viruses jumping either to or from horses is not absolute. For example, the severe influenza epidemic in horses occurring in 1989 in the Jilin and Heilongjiang provinces in the northeast of the People's Republic of China was caused by a virus with avian-like genetic features, suggesting that the virus had spread directly to horses from birds.[469] Another more recent example is the transmission of an equine-lineage virus to dogs in the United States.[470] First isolated from greyhound dogs at a racing kennel in Florida in 2004, the equine-lineage virus spread quickly though a substantial portion of the dog population in the United States over the course of 2 years.

Although the viral and host factors that determine the host range of influenza viruses, and the mechanisms by which species barriers are overcome, are not completely understood, a large body of research highlights the importance of the viral hemagglutinin (HA) glycoprotein in determining host specificity.[463,471,472] HA serves as the viral receptor-binding protein and is embedded, along with the neuraminidase (NA) and the ion channel M2 protein, in a host cell—derived lipid envelope. Mediated by binding of the HA to sialic acid residues on the host cells, the virion envelope and the host cell membrane fuse. This interaction subsequently promotes the release of the viral genome into the cytoplasm of the host cell. NA is responsible for the cleavage of the α-ketosidic linkage between a sialic acid molecule and an adjacent sugar D-galactose or D-galactosamine. Biologically, NA facilitates the mobility of the influenza virus virion by assisting in the release of the budding virus particle from the host cells.[473,474] Both HA and NA are major surface antigens of the influenza virus virion. Partly because of the host immune pressure, these proteins can undergo substantial antigenic variation (antigenic drift), which allows the mutant viruses to escape neutralizing antibodies.

Based on antigenic properties of HA and NA, influenza A viruses are divided into subtypes. To date, 16 HA subtypes (H1 to H16) and nine NA subtypes (N1 to N9) have been described. Although viruses of all 16 HA and nine NA subtypes of influenza A viruses have been isolated from wild waterfowl,[475–477] only a limited number of subtypes have been associated with infection of mammals. For example, in humans, only viruses of H1, N2, H3, N1, and N2 subtypes have circulated widely in the population,[463,478] and only H1, H3, N1, and N2 subtypes have been consistently isolated from pigs.[479–481] In horses, apart from isolated reports of infection with viruses of H1N1, H2N2, and H3N2 viruses (usually associated with human infections),[482] equine influenza infections have been caused by viruses of H7N7 (A/equine/1) and H3N8 (A/equine/2) subtypes.[462,483,484] Although large-scale serologic surveillance indicates that H7N7 viruses may still be circulating at low levels in the equine population of Central Asia[463] and Eastern Europe,[462,485] these viruses have not been isolated from horses since the late 1970s.[433,475,486] In contrast, despite intensive vaccination programs, equine H3N8 viruses continue to

circulate in large parts of the world. Since the 1980s a number of severe, widespread influenza outbreaks in horses have occurred in South Africa,[487] India,[488] the People's Republic of China,[469,489] and most recently the United Kingdom.[490] The causative agent of the South African outbreak was identified as an H3N8 virus, which was most likely introduced by importation of infected horses from the United States or Europe.[433,491]

Since the early to mid 1980s the equine lineage H3N8 viruses have diverged into two distinct evolutionary lineages: European and American. Although the circulation of both lineages initially centered largely on their geographic origin,[492] both lineages now appear to be cocirculating in Europe and, to a considerably lesser extent, in the United States.[433,493,494] Continued genetic divergence appears to have resulted in the formation of three American-like lineages with distinct antigenic characteristics (a South American lineage, a Kentucky lineage, and a Florida lineage).[493] The rate of genetic diversion of equine viruses is small compared with human and swine influenza viruses, but the sustained genetic evolution continues to have considerable impact in terms of immunization.

31.15.2 Epidemiology

Experimentally, horses of all age-groups are susceptible to infection.[495] However, although sporadic infection in foals has been described, there exists only one published report of a widespread outbreak in foals less than 6 months of age.[496] The lower incidence of disease in young foals is most likely a result of the presence of maternally derived antibodies. Influenza-specific serum antibody concentration is a highly accurate correlate to protection against infection and disease, and animals with high concentrations of homologous antibody are almost always protected against experimental challenge.[497,498] After natural infection, ponies were reported to be protected from infection for 8 months, with partial protection persisting for more than 1 year.[499] Although vaccination does not always provide full protection against clinical disease, immunization of horses against influenza has reduced the frequency of disease outbreaks and the frequency and severity of clinical signs when epizootic disease occurs among vaccinated animals.[495,500,501]

Outbreaks of equine influenza occur most often when susceptible animals are congregated and housed in close contact with one another (e.g., horse shows, racetracks, sale barns). Virus transmission occurs through direct contact with infected animals or via droplet or airborne transmission.[502] The virus has been shown to be able to remain infectious for up to 48 hours on dry surfaces (equipment, countertops), but it is capable of surviving for as long as 72 hours in wet environments.[503] Anecdotal evidence suggests that the disease can spread in a matter of hours to days among immunologically naïve animals that are kept in close confinement. Such effective spread is enhanced by a short incubation period (approximately 2 days), high concentrations of virus shed in nasal secretions, an explosive cough, and the practice of housing horses in confined spaces.[503] In partially immune animals, the spread of disease is often considerably slower and outbreaks may last as long as 3 to 4 weeks.[504] After experimental infection, horses typically shed virus for 6 to 7 days.[505–508]

31.15.3 Pathogenesis

Influenza A viruses replicate and induce pathologic changes throughout the entire respiratory tract, with the most significant lesions occurring in the lower airways. After inhalation of the virus, the virion attaches to and enters the respiratory epithelial cells. After replication and release from the host cell, the virus spreads quickly throughout the respiratory tract. Largely through apoptosis,[509–511] influenza virus replication leads to cell death

and subsequent loss of the ciliated respiratory epithelium in the trachea and bronchial tree.[512] Consequently, tracheal mucociliary clearance is impaired, predisposing affected horses to the development of secondary bacterial infections.[483,513,514] In addition, the disruption of the superficial cell layers allows opportunistic bacteria to invade the respiratory epithelium of both the upper and the lower respiratory tract. The combination of reduced airway clearance and erosion of the respiratory epithelium can result in bacterial bronchopneumonia and other complications.[512,515] In uncomplicated cases, regeneration of the respiratory epithelium begins approximately 3 to 5 days after onset of illness,[515] but resolution of the epithelial damage takes a minimum of 3 weeks.[514,516]

31.15.4 Clinical Presentation

Clinical signs of influenza virus infection in horses are often seen 48 hours after exposure to the virus. In vaccinated animals the disease is rarely fatal, but deaths have been reported during some epidemics, particularly in donkeys and rarely in neonatal foals.[462,517] The typical clinical presentation of equine influenza consists of pyrexia, anorexia, lethargy, nasal discharge, and cough. Pyrexia is often the first symptom present, with body temperatures peaking somewhere between 48 to 96 hours after infection. In some cases a second peak of pyrexia may occur around 7 days after infection. Nasal discharge is often serous in the first few days of illness but may become mucopurulent by 72 to 96 hours after infection. Concurrently a dry, hacking cough develops. Coughing typically persists long after pyrexia and nasal discharge have resolved and may still be present 3 weeks postinfection. Most affected animals are anorectic during the initial pyrexia, and weight loss has consistently been documented in experimental infections. In severe infections, lung sounds may become increased in amplitude and adventitial sounds may sometimes be detected. Uncomplicated cases of equine influenza typically resolve within 7 to 14 days postinfection, but complications of equine influenza virus infections can be severe and include secondary bacterial pneumonia, myositis, myocarditis, and limb edema.[484,513,514] It has also been speculated that influenza infection may predispose horses to the development of IAD, RAO, and EIPH.[484,512,513] Furthermore, the effects of influenza virus infection can be significantly exacerbated by even moderate exercise, resulting in increased weight loss and other clinical signs.[518]

Hemographic abnormalities associated with equine influenza infection can include moderate normocytic, normochromic anemia and leukopenia, which may result from both neutropenia and lymphopenia. Monocytosis during early convalescences is a variable finding.

31.15.5 Control

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Vaccination against equine influenza virus infection is the foundation of influenza control. Although a wide variety of vaccine formulations, including modified live and recombinant vaccines, are commercially available, inactivated vaccines are the most common type of vaccine used. Many challenge studies have demonstrated the ability of inactivated vaccines to protect against homologous virus challenge.[497,498,519,520] However, the value of inactivated vaccines is critically dependent on the quality, quantity, and strain of virus used for vaccine preparation.[521]

Based on the finding that the H7N7 viruses have not been isolated from horses since the late 1070s,[486] the inclusion of A/equine/1 virus is no longer thought to be necessary for equine influenza vaccines. In contrast, the divergence of the H3N8 equine viruses in two distinct lineages has made the inclusion of strains representative of both the American and European lineages a desirable feature of vaccines.[433] Sustained genetic evolution of

the A/equine/2 viruses will continue to result in failure of killed vaccines, and therefore inclusion of viral antigens representative of contemporary circulating viruses has to remain a priority.

An intranasal, cold-adapted, modified live virus vaccine (FluAvert I.N., Intervet, Millsboro, Del.) has become available in North America. Whereas studies have demonstrated that the vaccine was able to confer protection for up to 12 months after a single administration, only a 6-month claim is made on the product data sheet.[508,522] Despite the fact that the vaccine contains only one modified live virus strain, which is based on the H3N8 A/Eq/KY/91 isolate, the vaccine appears to protect against both the European and the American lineages.[523] A recombinant canary pox vector-based vaccine (ProteqFlu, Merial) is also available on the veterinary market and has shown excellent performance against recent influenza virus strains.[524]

Because of the presence of maternal antibodies, recommendations for vaccination generally state not to vaccinate foals younger than 6 months of age.[525–527] For inactivated vaccines, initial vaccination should include three doses (even when the data sheet recommends only two initial doses). The timing of the first three doses is critical. The recommended interval between the first and second dose is 3 to 4 weeks. The third dose should be administered when the antibody response to the second dose has waned, which is thought to occur at 3 to 4 months after the administration of the second dose. Regardless of the recommendations provided by the manufacturer, this vaccination regimen is preferred, and contemporary inactivated vaccines are likely to perform well if this approach is taken. After the initial vaccination series, subsequent booster vaccinations should be given at 6-month intervals in high-risk populations. The modified live cold-adapted intranasal vaccine requires only a single initial dose, followed by booster doses at 6-month intervals. If a higher risk of infection is anticipated (e.g., horse show), booster doses may be administered even to well-vaccinated horses 1 to 2 weeks before potential exposure.

31.16 EQUINE HERPES VIRUSES

EHV infection is a common infection of equids throughout the world, with at least nine herpesviruses identified to date and with more likely to be identified in future.[528,529] The most important EHVs are the Alphaherpesvirinae EHV-1 and EHV-4, which both cause respiratory disease. EHV-1 commonly infects horses, donkeys, and mules and occasionally infects domestic cattle, captive camelids, cervids, and zebras; EHV-4 is restricted to horses.[528] Both EHV-2 and EHV-5, which are Gammaherpesvirinae, can be associated with respiratory disease, although their pathogenicity is low.[530] EHV-2 is distributed throughout the world and is a ubiquitous infection of the horse; this increasingly appears to be also the case for EHV-5,[531–533] which previously had been identified only in Australia and New Zealand.[530]

31.16.1 Etiology

Both EHV-1 and EHV-4 are members of the Alphaherpesvirinae subfamily of herpesviruses, in the genus Varicellovirus. These two viruses have very similar antigenic, genetic, and pathogenetic characteristics, although they are quite distinct from the major equine gammaherpesviruses (EHV-2, EHV-3, and EHV-5).[528] Both viruses are easily destroyed by solvents, detergents, disinfectants, and other common veterinary means of decontamination, but under favorable conditions they can persist in the environment for as long as a month, and in refrigerated liquids for much longer.

Both EHV-1 and EHV-4 have a linear double-stranded DNA genome of 145 and 150 kbp encoding 79 and 80 ORFs, respectively,[534–536] which can code for 77 proteins. Amino acid homology of EHV-1 and EHV-4 is 55% to 96%.[534] The gene products of EHV-1 and EHV-4 are classified as immediate early, early, or late (which include the major glycoproteins).[537–540] One genetic factor that has been identified as being associated with the occurrence of EHV myeloencephalopathy (EHM) is a mutation in the DNApol gene.[541] This mutation is present in the large majority, but not all, of the EHM isolates of EHV-1. Infection with viruses with this mutation generated higher levels of viremia in experimental infection,[542] but beyond this there is still a limited understanding of the relationship between the mutation and the pathology that results in EHM.

31.16.2 Epidemiology

EHV-1 infection causes significant suffering in horses and extensive economic losses through frequent outbreaks of a range of diseases including outbreaks of respiratory disease, abortion, neonatal foal death, myeloencephalopathy, and chorioretinopathy.[528] EHV-4 can cause respiratory disease outbreaks, but only sporadic cases of abortion rather than abortion storms. Infections caused by EHV-1 and EHV-4 are particularly common in young performance horses and typically result in establishment of latent infection within the first weeks or months of life,[543] with subsequent viral reactivation causing clinical disease and viral shedding during periods of stress.[528] As more sophisticated methods of detecting latent infection with EHV-1 and EHV-4 are developed,[544] the detectable prevalence of infection continues to rise, with the implication that EHV-free horses are very rare.

31.16.3 Pathogenesis

The pathogenesis of EHV-1 infection has been comprehensively reviewed.[528,545,546] Primary EHV-1 infection occurs at the respiratory epithelium, resulting in erosion of the upper respiratory mucosal surface and viral shedding for 4 to 7 days postinfection; shedding can occur for longer at lower levels, and possibly beyond 14 days. Cell-to-cell spread results in the presence of virus in respiratory tract lymph nodes within 12 to 24 hours postinfection. A lymphocyte-associated viremia is then established and is responsible for the delivery of EHV-1 to the pregnant uterus and other tissues. This viremia can persist for up to 21 days and is a prerequisite for abortion and EHM. In pregnant horses, EHV-1 infection can result in abortion, typically in the last 4 months of pregnancy. There are usually no signs of impending abortion, and the foal is typically expelled in the amniotic membrane having just died from asphyxia owing to placental separation. Some fetuses survive initially but then die as a result of respiratory failure caused by infection of the lungs. The pathology is of infection of endothelial cells of the pregnant uterus causing a vasculitis affecting the small arteriolar branches of the glandular layer of the endometrium at the base of microcotyledons.[528] EHV-1 myeloencephalitis results from widespread vascular injury after damage to the vascular endothelium of the blood-brain barrier resulting from viral infection of the endothelium. Vasculitis develops, with or without local hemorrhage and thromboischemic necrosis, in the brain and spinal cord. It is possible that the immunopathologic response to EHV-1 infection of the vascular endothelium of the CNS may play a part in the cause of the thromboischemic necrosis, thereby contributing to the disease process.

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Latency is established in both the lymphoreticular system and in the trigeminal ganglion,[528] although lymphoid tissues are likely to be the primary home of latent virus.[544] Reactivation of latent virus frequently results in reinfection of the upper respiratory tract and further shedding of virus. Latency and reactivation are critical

features of the epidemiology of EHV-1 infection, allowing the virus to persist for lengthy periods, and in all likelihood as a life-long infection, in the majority of previously infected horses before reactivating and infecting new susceptible horses or resulting in disease in the latently infected horse itself.

Immunity to EHV-1 and EHV-4 has been extensively reviewed.[546] The protective immune response after infection is short lived (3 to 6 months), although this may increase with age and repeated exposure. High titers of virus-neutralizing (VN) antibody before infection can reduce the amount and duration of virus shed from the nasopharynx[547] but fail to prevent infection.[548] The underlying reason for this failure to prevent infection is likely to be related to the rapid intracellular location of EHV-1,[549,550] which permits escape from the effects of VN antibody. However, intracellular virus is susceptible to cytotoxic T lymphocytes (CTLs), which can lyse virus-infected cells. This CTL activity is major histocompatibility complex (MHC) class I restricted and mediated by $CD8^+$ lymphocytes.[551] Ponies with high frequencies of $CD8^+$ CTLs show a reduction in the clinical and virologic outcome of infection[552] and are protected against abortion.[553] Control of EHV-1 infection requires an immune response that not only limits primary infection but also controls reactivation of latent infections.[548] Although circulating and mucosal antibodies each play some role in protection,[547,554] the most important component of a protective immune response to EHV-1 is the CTL response.[553,555,556]

An important aspect of EHV-1 pathogenesis and immunity is the capacity of the virus to evade the immune response.[557] This may be mediated by downregulation of expression of viral proteins in infected cells[558,559] or by downregulation of host MHC-1 expression, thereby reducing antigen presentation to the critical CTL population.[560]

31.16.4 Clinical Presentation

Both EHV-1 and EHV-4 cause respiratory signs, but signs are more severe for EHV-1, as is the likelihood of viremia. Clinical respiratory disease in susceptible horses has an incubation period of 1 to 3 days. Signs include pyrexia, which is typically biphasic, with a first peak at 24 to 48 hours associated with upper respiratory tract infection and a second peak at 4 to 8 days associated with the development of viremia. Depression and anorexia are often mild, and progressive nasal discharge becomes mucopurulent by day 5 to 7. Conjunctivitis, lymphadenopathy of the submandibular lymph nodes, and edema or vasculitis of the distal limbs are variable findings. Respiratory disease, particularly as an outbreak, is uncommon in horses over 2 years of age, presumably because of recurrent exposure to the virus and development of sufficient immunity to suppress clinical signs of disease.

In neonatal foals infected with EHV-1 in utero, foals may be normal at birth but quickly become affected by weakness, lethargy, and profound respiratory distress. Prognosis is poor for survival. The abortion and EHM forms of EHV-1 are discussed elsewhere under the appropriate system.

The clinical signs resulting from infection with EHV-2 remain poorly described and established, although it may be a cause of keratoconjunctivitis and possibly upper respiratory tract disease in foals and weanlings.[530]

31.16.5 Prevention

Because of the ubiquitous nature of EHV-1 and EHV-4 infection, elimination of these pathogens from the population is impossible. Strategies must be used to prevent dissemination of the virus from horses undergoing an active infection. Vaccines are an attractive tool for this, but currently there are no products that can provide

comprehensive protection against infection and its sequelae. Inactivated EHV-1 vaccines are capable of eliciting circulating VN antibody responses, which can limit respiratory disease and nasal viral shedding, and the use of some of these vaccines has been associated with a reduction in the incidence of abortion storms.[546–548,561] Vaccines containing higher antigen loads, and typically those licensed for control of abortion, can generate high titered VN antibody responses and even EHV-1-specific IFN-γ responses.[561] Such vaccines are likely to outperform other inactivated products with lower antigen loads. The one commercially available modified live EHV-1 vaccine (MLV) generates limited EHV-specific cellular immunity[562] and has been demonstrated to reduce respiratory disease and viral shedding.[563] The use of current commercial vaccines of proven efficacy is recommended at 6-month intervals for control of respiratory disease and shedding of EHV-1 and EHV-4. Generally, vaccines effective against EHV-1 will cross-protect against EHV-4. There is no evidence that any commercial or experimental vaccine can prevent the occurrence of EHM.

No attempts are made to control infection caused by EHV-2 or EHV-5 with vaccination. However, the proposal that concurrent EHV-2 infection may play a role in the cause of *R. equi* pneumonia has led some clinicians to attempt vaccination of foals with killed EHV-2 vaccines.[564]

Biosecurity measures after detection of outbreaks of EHV-1 and EHV-4 should include isolation of affected and in-contact horses for 21 to 28 days. The virus is thought to spread primarily through contact, with a limited aerosol spread compared with influenza virus. Extensive codes of practice have been described for control of spread of EHV-1 in breeding facilities, both in publications[528] and in online resources (www.hblb.org.uk).

31.17 EQUINE ARTERITIS VIRUS

EVA is a contagious disease of horses caused by equine arteritis virus (EAV).[565] The disease was probably recognized for two centuries before the isolation of EAV in 1953.[565] Although the vast majority of EAV infections are inapparent or subclinical, occasional outbreaks occur that result in respiratory disease in adults, abortion, and fatal pneumonia in foals. These disease outbreaks have significant costs in terms of animal suffering and economic loss, and the virus now appears to occur worldwide, infecting horses, donkeys, and mules.

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31.17.1 Etiology

EAV is an enveloped RNA virus and is the prototype virus of the genus Arterivirus, family Arteriviridae, order Nidovirales.[566] The genome has only nine ORFs, encoding five structural proteins, a viral replicase, and two known nonstructural membrane glycoproteins. The GL envelope glycoprotein expresses the major neutralization determinants of the virus.[567] Only one serotype has been identified, which is the Bucyrus strain derived from the 1953 disease outbreak of abortion and respiratory disease in standardbreds that first led to the definition of EVA as a clinical viral disease of horses and the identification of EAV as the causative agent.[565] Although there is only one serotype, there are extensive variations in antigenic and pathogenic properties in different isolates of the virus, which are accompanied by differences in structural protein genes. The virus is readily inactivated by lipid solvents and disinfectants, although it can survive for years at subfreezing temperatures.

31.17.2 Epidemiology

EAV is spread by the respiratory and venereal routes, and the persistently infected carrier stallion is central to its persistence and epidemiology.[565] Outbreaks of EVA frequently follow the importation of carrier stallions, and

this has been identified as an increasingly important factor in the spread of this infection throughout the world in recent years. Similarly, virus can be transported and transmitted through infected semen.

Stallions infected by the respiratory route can become carriers in 30% to 50% of cases, shedding for months to years, although some of these horses do spontaneously clear the infection. The carrier state is testosterone dependent, as castration resolves infection. In the carrier stallion the virus spontaneously generates diverse populations of viral variants, which are found in the semen of infected stallions.[568] When one of these variants is transmitted to a mare through breeding, or occasionally through semen-contaminated fomites, a new outbreak can occur if the population is susceptible.[565] Transmission by the venereal route is associated with infection rates in mares as high as 85% to 100%.[566] In this circumstance subsequent spread of the virus is by aerosol and the respiratory route, with large quantities of virus shed for 7 to 16 days.[566] During these outbreaks the EAV strain remains stable with minimal genetic change.[565] Seroprevalence varies among breeds and among countries and geographic regions; up to 85% of standardbreds but <5% of thoroughbreds are infected in the United States.[569] Because there is no variation in breed susceptibility to EVA, this difference is probably a consequence of the number of actively shedding carrier stallions in different breeds. The virulence of strains in specific breeds can vary, however, and the strains shed by standardbreds are typically highly attenuated, causing minimal disease.[565]

The immune response to infection is strong, leading to protective immunity with a duration of several years.[566] Foals born to immunized mares are protected by colostral antibodies for 2 to 6 months.

31.17.3 Pathogenesis

Both venereal and inhalation transmission of the virus occurs in EVA. After respiratory infection the virus invades the respiratory epithelium and infects bronchial and alveolar macrophages, reaching bronchial and other regional lymph nodes by 48 hours postinfection.[566] A leukocyte-associated viremia then leads to general distribution of the virus and further replication in the adrenals, thyroid, liver, and testes. The virus localizes to the endothelium and medial myocytes of blood vessels by 6 to 8 days postinfection, with endothelial damage, lymphocytic infiltration, and damage to the elastica interna of arterioles in the respiratory tract and throughout the body. This results in both hemorrhage and edema in affected organs and tissues, which is most severe approximately 10 days postinfection. Virus is eliminated by 28 days postinfection, except in carrier stallions, in which it persists particularly in the ampulla of the vas deferens.[566]

31.17.4 Clinical Presentation

The great majority of infected horses are asymptomatic. When disease does occur, the clinical signs of EVA can vary from fever and leukopenia to severe disease and death. The incubation period is 3 to 7 days. Each individual may show some of the following signs. Typically the affected animals are pyrexic, with temperatures reaching 40.5° C (105° F) for 1 to 5 days. Anorexia, depression, serous nasal discharge, lacrimation, and coughing may also occur. Edema of the limbs, palpebra, and scrotum has been reported.[566]

Abortion occurs in the acute or early convalescent phases of infection and can be the only sign of infection. Abortion can occur at 2 to 10 months of gestation, with abortion rates of 10% to 70%. Comingling of mares recently bred by an infected stallion with pregnant mares is a common scenario leading to abortion.

Neonatal foals infected with EAV show severe respiratory signs and high mortality. In foals that survive more than 24 hours, a fever and leukopenia or thrombocytopenia are present. Interstitial pneumonia, lymphocytic

arteritis or periarteritis, renal tubular necrosis, and fibrinoid necrosis of the tunic media are seen on pathologic examination. Old, debilitated, or immunosuppressed horse can be similarly predisposed to severe EVA.[565]

31.17.5 Prevention

Both a modified live and a killed vaccine against EVA have been developed in recent years.[565,566] The modified live vaccine provides complete or partial protection against the clinical signs of EVA, but viral replication still occurs after challenge. The duration of vaccinal protection appears to be as long as 2 years, although annual revaccination of breeding stallions is recommended before the start of the breeding season. The modified live vaccine has been used successfully to limit outbreaks of infe ction in race courses after initial diagnosis.[566]

The most important steps in EVA control are the identification of carrier stallions, the prevention of the development of the carrier status in future stallions through vaccination of all colts with breeding potential in the first year of life, and annual revaccination thereafter.[566] Mares being bred to carrier stallions should be vaccinated against EVA. Fresh and frozen semen from carrier stallions is also infective, and EAV-negative mares receiving infected semen should be vaccinated. Extensive codes of practice have been produced by both the USDA (www.aphis.usda.gov) and the Horserace Betting Levy Board (www.hblb.org.uk) to assist in control of EVA.

31.18 EQUINE RHINITIS VIRUS

31.18.1 Etiology

Equine rhinitis viruses (formerly equine rhinoviruses) are a known cause of clinical and subclinical respiratory infections in horses worldwide. The viruses are classified as members of the family Picornaviridae, which includes small (“pico”), nonenveloped, single-stranded RNA viruses. Among the equine rhinitis viruses, at least two serotypes have been isolated from horses: equine rhinitis A virus (ERAV) (formerly equine rhinovirus 1 [ERV-1]) and equine rhinitis B virus (ERBV) (formerly equine rhinovirus 2 [ERV-2]).[570,571]

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Considerable uncertainty has surrounded the classification of the equine rhinitis viruses. Because the illness caused by these viruses resembles the common cold brought about by rhinoviruses in humans, they initially were included in the genus Rhinovirus. However, subsequent studies demonstrated that ERAV differed from other members of the Rhinovirus genus as well as from ERBV.[571–574] For example, whereas rhinoviruses generally demonstrate a narrow host cell range in vitro and in vivo, ERAV is able to infect and replicate in a broad range of cell types and host species. For instance, intranasal inoculation of a human volunteer with ERAV resulted in pharyngitis, lymphadenitis, fever, and viremia.[575] Furthermore, the presence of systemic signs and viremia during ERAV infection, the occurrence of persistent infections, and the physical properties of the virus are all more reminiscent of foot-and-mouth disease virus (FMDV). Based on these characteristics, along with similarities in protein sequences, ERAV was placed alongside FMDV in the Aphthovirus genus of the picornavirus family. Subsequently, ERBV has been reclassified as the sole member of the new genus Erbovirus.

31.18.1.1 EPIDEMIOLOGY

First isolated from horses in the United Kingdom,[576] ERAV infection occurs worldwide and is a recognized cause of acute respiratory disease.[570,577–579] The incidence of neutralizing antibody to ERAV varies

according to the age of the horses, and most horses appear to become infected during their second year of life. In a study by Studdert and Gleeson, only 16% of horses between the ages of 6 and 12 months were seropositive.[573] However, studies conducted in older horses found that a high percentage of 5-year-old horses have antibodies to equine rhinitis virus.[577,580] As with many other respiratory pathogens, young horses entering a large population and in frequent contact with other horses are most susceptible to infection.[577] In addition, there appears to be a seasonal distribution, with most of the ERAV infections occurring in late winter and spring.[581,582] Stress (e.g., transportation and training) and concurrent disease resulting in immunosuppression may predispose to infection.[583] The virus is fairly resistant to inactivation and is thought to survive in the environment for a considerable amount of time. As for human rhinoviruses, virus spread occurs most likely through direct and indirect contact (fomites).[584]

In contrast to ERAV, the prevalence and clinical significance of ERBV are less defined. A recent study found that 24% of 258 horse sera tested were seropositive for ERBV, indicating that this virus may also be prevalent in the horse population.[585] In fact, the results of a recent study suggest that ERBV may play an important role as a causative agent of clinical respiratory disease.[586] However, although ERBV was recovered from a large number of horses with acute respiratory disease, only a small percentage of animals demonstrated a concurrent rise in antibody titers for paired sera.

31.18.2 Clinical Presentation

Although ERAV is generally considered a respiratory pathogen, the clinical signs associated with infection may be quite variable. After experimental infection with ERAV, horses may develop pyrexia, anorexia, nasal discharge, pharyngitis, and lymphadenitis involving at least the submandibular and pharyngeal lymph nodes.[587] On rare occasions laryngitis or mild bronchitis can develop.[580] Based on serologic studies, subclinical ERAV infection may also occur and may be important in the dissemination of the disease.[573,581,584,587,588]

An important distinction of ERAV compared with other members of the genus Rhinovirus (e.g., human or bovine rhinoviruses) is the finding that horses infected with ERAV may develop viremia. On average, viremia lasts 4 to 5 days and the disappearance of virus from the blood coincides with the appearance of neutralizing antibodies.[587] Although the relationship between antibody levels and protection against disease has not been established, immunity is thought to be solid, and antibodies persist for a long time.[584]

Infection with ERAV may be accompanied by long-term urinary and fecal shedding as well as viral persistence.[587] The recognition of the potential for ERAV persistence has important implications for disease diagnosis. Highly sensitive diagnostic methods (e.g., IFA or RT-PCR) may be able to detect persistent ERAV in horses suffering from respiratory disease, which may not be associated with the observed illness. This notion is underlined by the recent finding that the ERAV genome was detected by RT-PCR in nasopharyngeal swab samples obtained from two clinically healthy horses 1 year after acute ERAV infection.[571]

31.18.3 Control

There is currently no vaccine available to control ERAV infection. A recent study by Warner and co-workers demonstrated that the capsid protein VP1 participates directly in viral receptor binding.[589] VP1 is a major surface antigen and therefore may serve as a potential target for vaccines.

31.19 EQUINE ADENOVIRUS

31.19.1 Etiology

Adenoviruses (family Adenoviridae) are a group of nonenveloped, icosahedral DNA viruses. Whereas most vertebrate species harbor an adenovirus, the viruses are highly species-specific. In humans, adenoviruses are extremely prevalent and represent a significant cause of acute respiratory, ocular, and GI disease. Infections of immunocompetent individuals usually stay localized and often take a mild or subclinical course.[590] Similarly, equine adenoviruses have been isolated from clinically healthy adult horses[591] and foals.[592,593] Equine adenovirus (EAdV)–1 has been implicated as the cause of acute respiratory tract disease[594,595] and conjunctivitis, as well as a progressive, fatal pneumonia in Arabian foals with SCID.[596–598] A second serotype, EAdV-2, has been incriminated as a cause of intestinal infection[599,600] and diarrhea in immunocompetent foals.[601,602]

31.19.2 Epidemiology

First isolated in 1969 from a foal with respiratory disease,[603] EAdVs have a worldwide distribution.[604] Although serologic evidence from Australia, the United Kingdom, the United States, the Netherlands, and Nigeria indicates that adenovirus infection occurs at a high frequency in the general horse population,[605–608] the role of EadV in respiratory disease in adult horses remains unclear. In this regard it is interesting that a number of studies found no apparent association between clinically apparent respiratory disease in young adult horses and infection with adenovirus, as diagnosed by subsequent seroconverison.[588,609,610]

In contrast, fatal and nonfatal adenovirus pneumonia has been well documented in foals, particularly of the Arabian breed. Fatal respiratory disease is predominantly seen in foals with SCID. Other foals may develop respiratory disease but usually do not succumb to it.

In general, adenovirus transmission is thought to occur via direct contact with secretions from infected animals or indirectly via fomites or infected premises. In adult horses the virus can persist in the upper respiratory tract, and these animals can act as a reservoir host for the virus. Adenoviruses are highly stable and have been found to remain infectious at 4° C for up to 1 year.

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31.19.3 Clinical Presentation

The clinical signs recorded after experimental intranasal infection of a thoroughbred yearling were confined to a serous nasal discharge that lasted from 4 to 12 days postinoculation. Peak levels of serum antibodies were found at 13 days after inoculation and dropped by approximately 2 months after experimental infection.[611]

In foals, clinical signs generally occur at 10 to 35 days of age.[612] After experimental inoculation at 24 hours of age, clinical signs appeared 3 to 5 days after infection and consisted of intermittent pyrexia, nasal and ocular discharge, tachypnea, and cough. All foals recovered by day 10 postinoculation. The majority of foals developed a mild and transient lymphopenia that was followed by lymphocytosis. Typically, about 25% of infected foals also develop diarrhea.[612] Gross pulmonary lesions found in animals euthanized at 14 to 21 days postinoculation included atelectasis involving up to 25% of the pulmonary parenchyma and suppurative bronchopneumonia.

Histologically, swelling and hyperplasia of the airway epithelium, as well as intranuclear inclusion bodies in the respiratory epithelial cells, were consistent findings up to 11 days postinfection.[613]

Foals with SCID show a progressive decline in health despite intensive therapy. At necropsy, conjunctivitis, rhinitis, tracheitis, and bronchopneumonia are present. Intranuclear inclusion bodies are readily demonstrated in the respiratory epithelial cells. Areas of interstitial pneumonia surround affected bronchi. Acute pancreatitis characterized by inclusion bodies in acinus and ductal cells, as well as adenoviral sialoadenitis involving the labial and parotid salivary gland, can often be demonstrated.[600,614]

31.19.4 Control

No vaccine is available to control adenovirus infection in horses. However, except in immunocompromised animals, the virus appears to be of little clinical importance.

31.20 HENDRA VIRUS

In August 1994, two horses died suddenly on a property in Mackay, Queensland, Australia. Ten days after the death of the second horse, the owner was admitted to the hospital with meningitis. One month after the incident in Mackay, 13 horses housed at a stable in Hendra, Queensland, died or were euthanized owing to severe respiratory illness. Subsequently the trainer and one of the stable workers developed an influenza-like illness, to which the trainer succumbed 6 days later. Potential diagnoses included African horse sickness and equine influenza, although they were exotic to Australia. Yet, during postmortem examination, a novel paramyxo-like virus was isolated from tissues of the affected horses and the trainer.[615] The virus, first referred to as *equine morbillivirus*, was subsequently named *Hendra virus*.

31.20.1 Etiology

HeV is a member of the genus Henipavirus (which also contains Nipah and Menangle viruses) within the Paramyxoviridae virus family. Paramyxoviruses, like orthomyxoviruses (see discussion of equine influenza), are enveloped viruses that contain a negative-sense, single-stranded RNA genome. HeV has unique morphologic characteristics that are useful for diagnostic purposes.[616] Electron microscopy reveals pleomorphic enveloped particles that contain a helical nucleocapsid that is characteristic for paramyxoviruses. The envelope is covered with spikes of 10 and 18 nm length, which gives the particle a unique “double-fringed” appearance.[617] Owing to the fact that HeV contains a host cell—derived lipid envelope, inactivation of the virus is possible using compounds that disrupt the lipid envelope (e.g., lysol, sodium dodecyl sulphate [SDS], acetone, methanol).[618]

31.20.2 Epidemiology

HeV is able to cause natural disease in humans and horses[615] and experimentally induced disease in cats, guinea pigs, and mice.[619,620] The virus naturally infects bats of the suborder Megachiroptera, in which infection does not seem to cause clinical disease.[621,622] These bats are considered to be the natural reservoir of HeV, yet the method of transmission from bats to horses is unknown. Although the virus transmits readily between bats, it does not appear to spread easily between horses or from horses to humans. This notion is highlighted by the finding that no disease spread occurred to other nearby stables during the outbreaks in 1994.[623] In addition, not all horses on the premises became infected, and horses placed in uncleaned stalls that previously contained

animals that succumbed to the disease did not become infected. Under experimental conditions, transmission did not occur between infected and in-contact horses.[624] However, natural transmission among mammalian species can occur but seems to require very close contact.[619] Despite the fact that intermammalian transmission of HeV appears to be relatively rare, the virus has the potential to cause lethal zoonotic infection and therefore poses a serious public health and occupational safety risk for veterinarians.

31.20.3 Pathogenesis

Experimentally, horses can be infected after parenteral and oronasal challenge.[615,624] Infection is characterized by the systemic distribution of the agent. After experimental infection of horses and cats, virus was isolated from the buccal cavity, blood, brain, spleen, lungs, bronchial lymph nodes, kidneys, and urine.[619,620,624] Based on the finding that virus is shed in the urine of experimentally infected animals, it has been speculated that consumption of food contaminated by urine of infected horses may serve as a method of transmission under natural conditions. However, although virus was present in the urine of horses that had died of natural HeV infection, investigators failed to recover HeV from the floors of the stalls in which the animals had been housed.[624]

31.20.4 Clinical Presentation

In horses, HeV infection is characterized by an acute, febrile respiratory illness that is sometimes accompanied by facial swelling, ataxia, head pressing, and recumbency. Frothy nasal discharge and tachycardia are considered to be indicators of imminent death. The course of disease in infected horses is short, with animals dying within 36 hours after onset of clinical signs. Experimentally the incubation period is 6 to 12 days. Although only one of eight experimentally infected horses recovered, seven infected horses survived during the field outbreak at Hendra. However, two of these horses subsequently developed neurologic signs, which consisted of tonic spasms of the muscles of the neck and hind limbs.[625]

At necropsy the most significant lesions are the severely congested, firm, and fluid-filled lungs. In some cases fibrin tags are present on the pleural surface. Histologically, HeV infection is associated with interstitial pneumonia with proteinaceous alveolar edema and hemorrhage. Possibly the most remarkable histologic finding is the presence of syncytial giant cells in the endothelium of pulmonary blood vessels. If examined under the electron microscope, these giant cells contain cytoplasmic inclusion bodies containing the characteristic nucleocapsid structure of paramyxoviruses.[618]

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As only three cases of human HeV infection have been reported, the disease syndrome associated with infection is poorly defined. One patient developed severe, fatal respiratory illness, and a second patient developed a self-limiting influenza-like illness.[626] The third patient succumbed to severe HeV encephalitis more than a year after initial infection.[627]

31.20.5 Control

To date, no vaccine or antiviral therapy is available to control HeV infection. The outbreak in Australia was controlled by a stamping-out program involving slaughter of all known infected horses, quarantine of premises, control of animal movement in defined zones, and serologic surveillance.

31.21 EQUINE LUNGWORM

JULIE ROSS

The nematode *Dictyocaulus arnfieldi* can affect donkeys, horses, ponies, and zebras and is found throughout the world.[628] Donkeys are believed to be the natural hosts of *D. arnfieldi*, with a reported prevalence of infection of 51% to 73%.[629,630] Clinical signs of *D. arnfieldi* infection are rarely seen in donkeys, and individual animals have been found to maintain patent, nonclinical infection for over 5 years in the absence of effective anthelmintic treatment.[631] Horses (and ponies) are abnormal *D. arnfieldi* hosts. The prevalence of *D. arnfieldi* infection in horses is difficult to establish, as infection is usually nonpatent owing to retardation of larval maturation in the lungs.[632] Clayton and colleagues[629] found that 5.88% of horses living in contact with donkeys had patent *D. arnfieldi* infection. A study of thoroughbred horses in Kentucky by Lyons and co-workers[633] found *D. arnfieldi* to be present in the lungs of 11% of horses at postmortem examination (on individual farms, a prevalence of up to 83% was found). In horses with documented parasite infection, only 30% had patent *D. arnfieldi* infection (documented via a modified Baermann's technique). Most parasites identified in the pulmonary tissues were larval stage 5 (L5), with few sexually mature adults being found. A study of 5437 live equids revealed a prevalence of patent *D. arnfieldi* infection of 2% and 0% in horses and ponies, respectively.[634] In contrast, patent *D. arnfieldi* infection was identified in 68% of donkeys and 30% of mules. These studies highlight the difficulty of identifying *D. arnfieldi* infection in horses and ponies. Patent *D. arnfieldi* infection can be more easily established in pony foals than in adults. Necropsy examination of these foals revealed no evidence of retardation of larval development, with sexually mature adult parasites frequently being identified.[629]

D. arnfieldi has a direct life-cycle. L1 hatches shortly after eggs are passed in the feces, and the larvae undergo two molts before they enter a free-living, infective stage (L3). The development of L3 can occur in 4 days. *Pilobolus* fungi may play a role in the dissemination of *D. arnfieldi* larvae from feces.[635] L3 is ingested by the host and penetrates the intestinal mucosa before passing to the mesenteric lymph nodes, where molting occurs. L4 organisms travel, via lymph and blood, to the lungs and break out of the capillaries into the alveoli. Molting from L4 to L5 occurs in the bronchioles, and maturation to the adult form occurs in the small bronchi.[628] Eggs are laid in the bronchi and then transported via the mucociliary clearance apparatus to the pharynx, where they are swallowed and eventually passed in the manure. The prepatent period of *D. arnfieldi* is 2 to 4 months.[635] Clinical disease can be seen as early as 12 days after ingestion of infective larvae.[628] The parasite has a limited survival time in the environment (49 days in warm soil) and cannot overwinter on pasture.[632] Fecal larval production in donkeys increases through the spring and summer months,[636] and environmental conditions favor development of patent infections in late summer and autumn.

Transmission from donkeys to horses is thought to be the main source of infection in horses, but horse-to-horse transmission does occur, thus clinical disease cannot be ruled out based on lack of contact with donkeys.[634,629] In one study 67% of farms on which horses with patent *D. arnfieldi* infection were stabled had no history of occupancy by donkeys.[634]

Clinical disease associated with *D. arnfieldi* was identified in 2.6% of horses presented to a referral clinic for evaluation of suspected pulmonary disease.[637] The average age of the population identified as being infected with *D. arnfieldi* was 5 years. Clinical signs of *D. arnfieldi* infection in horses have been described. One study identified coughing in 100% of cases, with nasal discharge (42.9%), abnormal tracheal auscultation (42.9%), dyspnea

(33.3%), and abnormal thoracic auscultation (28.5%) being identified less frequently.[637] Other clinical signs that have been described include paroxysmal coughing, increased expiratory effort, and audible wheezes and crackles on auscultation.[632] Many reports of lungworm infection describe a chronic disease process; however, in a study involving seven *D. arnfieldi* cases, three cases were of acute onset. It is possible that these animals had concomitant bacterial or viral disease or that the initial lungworm challenge resulted in acute clinical signs.[637] Although clinical disease is rare in donkeys, *D. arnfieldi* infection has been associated with increased susceptibility to respiratory viruses (e.g., influenza).[637]

As discussed earlier, identification of *D. arnfieldi* infection using a modified Baermann's technique frequently results in false-negative results.[629] Clinical signs of nonpyrexic, chronic respiratory disease, possibly with a history of contact with donkeys, may be suggestive of *D. arnfieldi* infection if other causes of respiratory disease have been ruled out. Dixon and colleagues[637] associated a marked increased in eosinophil ratio in BALF and tracheal secretions with *D. arnfieldi* infection if there was concurrent evidence of lungworm larvae in the airways or respiratory secretions or if the eosinophilic nature of the respiratory secretions resolved with appropriate anthelmintic treatment. Respiratory secretion eosinophilia may be a useful indicator of lungworm infection; however, this finding can also be seen in eosinophilic pulmonary disease[637,638] and during transient migration of *P. equorum*.[628] Clinical disease with *P. equorum* is most commonly seen in young horses and ponies. Tracheobronchial aspirates and BALF obtained from normal horses are expected to contain few (<3%) eosinophils[639]; however, significant respiratory secretion eosinophilia has been identified in horses with no apparent respiratory disease.[640] Eosinophilia in respiratory secretions is therefore suggestive of but not pathognomic for *D. arnfieldi* infection. Repeat evaluation of respiratory secretions after *D. arnfieldi* treatment should reveal a marked improvement in eosinophilia ratio in lungworm cases.[640] *D. arnfieldi* larvae have been identified during microscopic examination of centrifugated respiratory mucus before fixing and staining have been performed, and it is suggested that such evaluation is an important diagnostic tool.[632] Peripheral eosinophilia has not been definitively correlated with lungworm infection.[641] At necropsy, a modified Baermann's technique can be applied to diced lung tissue to aid in the identification of larvae.

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Treatment for *D. arnfieldi* infection includes effective anthelmintic treatment, removal from contact with donkeys, and moving horses and ponies to a pasture not grazed by donkeys since the previous autumn. Effective anthelmintics include moxidectin,[642] ivermectin (active against mature and immature parasite stages),[629,643] and mebendazole (16–20 mg/kg for 5 days).[644] Fenbendazole has been shown to improve clinical signs of presumed *D. arnfieldi* infection; however, suppression of fecal shedding was maintained for less than 4 weeks with doses up to 30 mg/kg.[641] Treatment with 200 µg of ivermectin per kilogram, along with a pasture change after treatment, resulted in complete improvement in six of seven *D. arnfieldi* cases and partial improvement in one case.[645] Treatment of donkeys should be instituted to decrease transmission to horses and ponies and potentially to decrease the donkey's susceptibility to other respiratory diseases.[636]

Necropsy findings in donkeys and horses with *D. arnfieldi* infection are similar.[646,647] Gross findings include circumscribed areas of raised pulmonary tissue (3 to 5 cm), more commonly found in the caudal lung lobes. Sectioning of these areas reveals overinflated pulmonary tissue surrounding small bronchi that are packed with mature *D. arnfieldi*. Small airways in these areas tend to be occluded with exudate. Histologic examination of the pulmonary tissue reveals diffuse eosinophilia throughout the pulmonary tissues, especially around the airways. A marked inflammatory reaction is found around parasitized bronchi, with heavy lymphoid cell infiltration of epithelium, lamina propria, and peribronchial tissue. Epithelium becomes hyperplastic, and mucus-secreting cells

increase in size and number. Little cellular or mucoid reaction is seen in bronchial lumen around adult parasites; however, free larvae in bronchial lumen result in intense mucopurulent reaction. Bronchioles in affected areas of the lung usually show evidence of bronchiolitis, with free mucus present in the lumen of bronchioles and hyperplastic, columnar epithelium. Bronchioles are most commonly surrounded by discrete lymphoid nodules. Pulmonary pathology in donkeys tends to be very localized with much of the lung appearing normal on histologic examination.[646]

Prevention of *D. arnfieldi* infection in horses and ponies involves effective anthelmintic treatment and pasturing horses and ponies separately from donkeys or treating donkeys with appropriate anthelmintic treatment to avoid patent infection. Anthelmintic treatment is especially important in the spring. Regular removal of manure from pasture can also help to decrease the parasite load in the environment.

31.22 THORACIC TRAUMA

JANE E. AXON

Thoracic trauma results from blunt or penetrating injuries to the chest wall. Trauma can result in thoracic wounds, hemothorax, pneumothorax, fractured ribs, and diaphragmatic hernia, and a combination can occur in the same horse. Prompt assessment and implementation of emergency procedures in the injured horse with respiratory distress in the field is vital to optimize the horse's chances for survival.[648]

Clinical signs associated with injury to the thorax can vary from mild musculoskeletal pain and a stiff gait to severe respiratory distress and hypovolemic shock. Signs of respiratory distress include anxiety, tachypnea, nostril flaring, cyanotic mucous membranes, tachycardia, and an altered respiratory pattern. Auscultation and percussion of the thorax may assist with locating and identifying the lesions. Percussion and palpation will need to be performed carefully in horses in pain. Palpation of SC emphysema in the absence of an external wound may be associated with a lacerated lung or tracheal trauma and in a dyspneic horse should raise the suspicion of a concurrent pneumothorax.[649] The injured horse may also have weak pulses, pale mucous membranes, and tachycardia resulting from acute hemorrhage from lacerated intercostal or pulmonary parenchymal vessels. Evaluation of the abdomen should also be undertaken. On expiration the cranial portion of the diaphragm extends to the sixth rib; therefore an abdominocentesis should be performed on a horse with a wound caudal to the sixth rib or with a deep penetrating wound to assess abdominal involvement.[648] Further evaluation of the injured horse will include thoracic radiographs, ultrasonographic examination, and exploration of the wound. Arterial blood gas analysis will assist in determining the extent of hypoventilation.

Open thoracic wounds should be covered immediately to prevent additional air from entering the chest cavity.[649] Plastic food wrap wrapped around the thorax or a gauze roll or towel sutured in place can be used. A tension pneumothorax, which may occur with sucking thoracic or axillary wounds, can be alleviated by inserting a trocar into the dorsal pleural space so pleural and atmospheric pressures can equilibrate and a less compromising pneumothorax is created.[648] Intranasal oxygen therapy and removal of air from the thorax may be necessary to improve alveolar ventilation and oxygenation in a horse with pneumothorax before further evaluation. Circulatory support may be necessary until hemorrhage has stabilized.[648] Sedatives and tranquilizers should be used judiciously because most cause respiratory depression; however, they may have to be used if the horse's anxiety precludes instituting treatment.

31.22.1 Hemothorax

Thoracic trauma resulting from lacerations to pleural or pulmonary vessels or rupture of large thoracic vessels may result in hemothorax. Other causes of hemothorax include rupture of lung parenchymal bullae, vessel erosion by severe lung abscessation or neoplasia, hemangiosarcoma, spontaneous hemorrhage at maximal excursion, and coagulopathy.[650,651] Iatrogenic causes include tube thoracostomy and lung biopsy. Hemothorax can be unilateral or bilateral depending on the cause and whether the mediastinum is complete.

Diagnosis is based on clinical signs, radiographic and ultrasonographic findings, and laboratory evaluation of the fluid obtained from thoracocentesis.[650] The horse may be dyspneic and tachycardic, depending on the volume of blood loss into the pleural cavity. On auscultation there is a decrease in normal breath sounds ventrally, and heart sounds are often muffled and radiate over a wider area.[650] Percussion reveals a change from the normal resonance of aerated lung to dullness over the hemothorax.[650] Thoracic radiographs show opacity of ventral lung fields, with an associated horizontal fluid line and a loss of diaphragmatic and cardiac silhouettes.[652] Ultrasonography shows fluid within the pleural cavity with a characteristic hypoechoic to echogenic smoke swirling pattern.[653] Fluid collected by thoracocentesis should be submitted for cell count, packed cell volume, and total protein. A cytologic evaluation should also be performed to determine whether there is evidence of infection or neoplasia, and the sample should be cultured if an infection is suspected. A clotting profile and platelet count should be performed if a coagulopathy is suspected. Hematology and biochemistry should also be performed, as the horse may develop anemia and hypoproteinemia associated with the blood loss.

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Treatment is aimed at stabilizing cardiopulmonary function and treating the underlying cause. Horses with hemothorax from nonpenetrating thoracic trauma or a noninfectious cause can be managed conservatively with intranasal oxygen insufflation, analgesics, IV fluids, or whole blood transfusion if the blood loss is severe. If the horse is not hypoxemic or in respiratory distress, rest alone and close monitoring may suffice. Even if respiratory distress is evident, a tube thoracostomy and drainage of blood may not be necessary.[651] Drainage of the thorax is not recommended in horses with a coagulopathy unless severe respiratory distress is present.[651] If there is a penetrating wound or evidence of infection, drainage should be attempted by ultrasound-guided ventral placement of chest drains. This, however, should not be undertaken until the hemorrhage has stopped and the circulating blood volume has been restored.[654] All horses, even without evidence of infection, should have broad-spectrum antimicrobial coverage, as blood is an excellent medium for bacterial growth.[650]

The prognosis for horses with uncomplicated trauma and hemothorax is good. If the hemothorax is the result of a penetrating wound, the prognosis is poor.

31.22.2 Pneumothorax

Traumatic causes of pneumothorax include puncture or laceration of the trachea, ruptured esophagus, penetration of foreign objects into the thoracic cavity, external wounds resulting in SC emphysema and pneumomediastinum, and direct penetrating or blunt trauma to the lung parenchyma.[650,655–657] Pleuropneumonia is also an important cause of pneumothorax; in one study 17 of 40 horses had pneumothorax resulting from pleuropneumonia.[655] Air can escape into the pleural cavity through slow leaks from necrotic lung or through formation of bronchopleural fistulas. Additional causes of pneumothorax include ruptured

emphysematous lung bullae, maximal exercise, and iatrogenic causes such as tube thoracostomy, lung biopsy, mechanical ventilation, and transtracheal aspiration.[650,651]

Pneumothorax can be described as *closed*, in which air from the lung is trapped in the pleural space, or *open*, in which there is free communication between the pleural space and external environment and air is sucked into the pleural space with inspiration. A tension pneumothorax occurs when air accumulates in the thorax until intrapleural pressure exceeds atmospheric pressure. This is often seen with a sucking pleurocutaneous wound as air moves into the chest cavity with inspiration and, owing to a valve effect of the wound, cannot escape during expiration.[649] Intrapleural pressure may increase to such an extent that the thorax becomes fixed in maximal extension. This leads to severe cardiopulmonary effects with decreased venous return to the heart because of vena cava compression and hypoxemia.[658,658a] Pneumothorax is usually bilateral because of the incomplete mediastinum of horses; however, it may be unilateral if the fenestrations in the mediastinum are blocked as a result of inflammation or a collapsed lung.

Diagnosis is based on clinical signs, aspiration of air from the pleural cavity, and radiographic and ultrasonographic findings.[650] Clinical signs that can be associated with pneumothorax are dyspnea, tachypnea, cyanosis, and evidence of trauma.[650] Characteristic findings on auscultation are a decrease or lack of normal breath sounds dorsally and tympany and hyperresonance on percussion; however, these clinical signs can vary and are not reliable.[655] Concurrent SC emphysema may complicate interpretation. However, if a horse with SC emphysema is dyspneic or distressed, pneumothorax should be suspected unless the emphysema is causing airway compression.[650] Thoracic radiographs show lack of pulmonary vasculature in the dorsal aspect of the caudal lung fields and ventral displacement of the dorsal lung margin (Fig. 31-35). On ultrasonographic examination there are parallel horizontal lines of air artifact reverberation without the pattern of pleura and "comet tail" artifacts. The dorsal air image also moves ventrally with inspiration over underlying collapsed lung or pleural fluid, creating a "curtain" image.[653] SC emphysema in tissue and fascial planes may prevent accurate sonographic imaging. Aspiration of air from the thorax is also diagnostic, as is the associated improvement in clinical signs.

Treatment is aimed at improving alveolar ventilation by correcting the pneumothorax, if the horse is showing signs of respiratory distress, and treating the underlying cause. Treatment of simple pneumothorax requires rest and close observation while gradual reabsorption of air occurs. If hypoxemia (Pa_{O_2} < 80 mm Hg, percent oxygen saturation [$\%O_2$sat] < 90%) or dyspnea is present, nasal insufflation of oxygen (15 L/min) should be administered.[654] An open sucking wound should be occluded. Air is removed from the pleural space by inserting a teat cannula or thoracostomy tube, with a suction device attached, into the dorsal thoracic cavity. If a suction machine is not available, repeated aspiration with a 60-ml syringe through a three-way stopcock valve and or tubing attached to the teat cannula and run into a container of water can be used.[649] The latter acts as a simple water trap, allowing air to be expelled during inspiration while preventing air movement back into the chest with expiration.[649] If the pneumothorax reoccurs or continues, tubes should be left in place to allow constant air removal. A Heimlich chest drainage valve* provides continual drainage and if correctly placed is effective for long periods. In long-standing cases, gradual reexpansion of the lungs is recommended to avoid reexpansion pulmonary edema.[650] Prophylactic broad-spectrum antimicrobial therapy is recommended as long as the tube is in place. If the cause of pneumothorax requires correction under general anesthesia, ventilation should be improved before induction by removing air from the pleural cavity and correcting lung atelectasis.

The prognosis for horses with pneumothorax is good, providing infections can be successfully treated and air leaks are sealed. Pneumothorax associated with pleuropneumonia and parenchymal lesions resulting in air leakage carry a poor prognosis and with an esophageal rupture carry a very poor prognosis.[650,655]

* Heimlich chest drainage valve, Bard-Parker, Division of Becton-Dickson Co., Rutherford, NJ.

31.22.3 Rib Fractures

Fractured ribs are most often a result of an accident or kick; however, in neonates fractured ribs are commonly associated with birth trauma.

31.22.3.1 ADULTS

Fractured ribs can be detected either through exploration of the wound or by eliciting a pain reaction on palpation over the affected area. Crepitus associated with a closed fracture is often not detected. Shallow breaths and guarded thoracic movements may be seen as a result of pain from the fracture. Soft-tissue swelling and SC emphysema may also be present. Fractured ribs in adults usually heal without fixation; however, if pain and excessive movement of rib ends are present, surgical correction may be warranted. Stabilization of a flail thorax is usually not necessary unless there is respiratory compromise.[649] NSAIDs, circumferential bandaging, and intercostal nerve blocks assist with providing pain relief. Open fractures should be explored and debrided, and soft tissue repaired.[649] The horse should be closely monitored for respiratory distress or hemorrhage, as a closed pneumothorax or hemothorax may result if a fractured rib end lacerates underlying lung parenchyma or vessels.[648]

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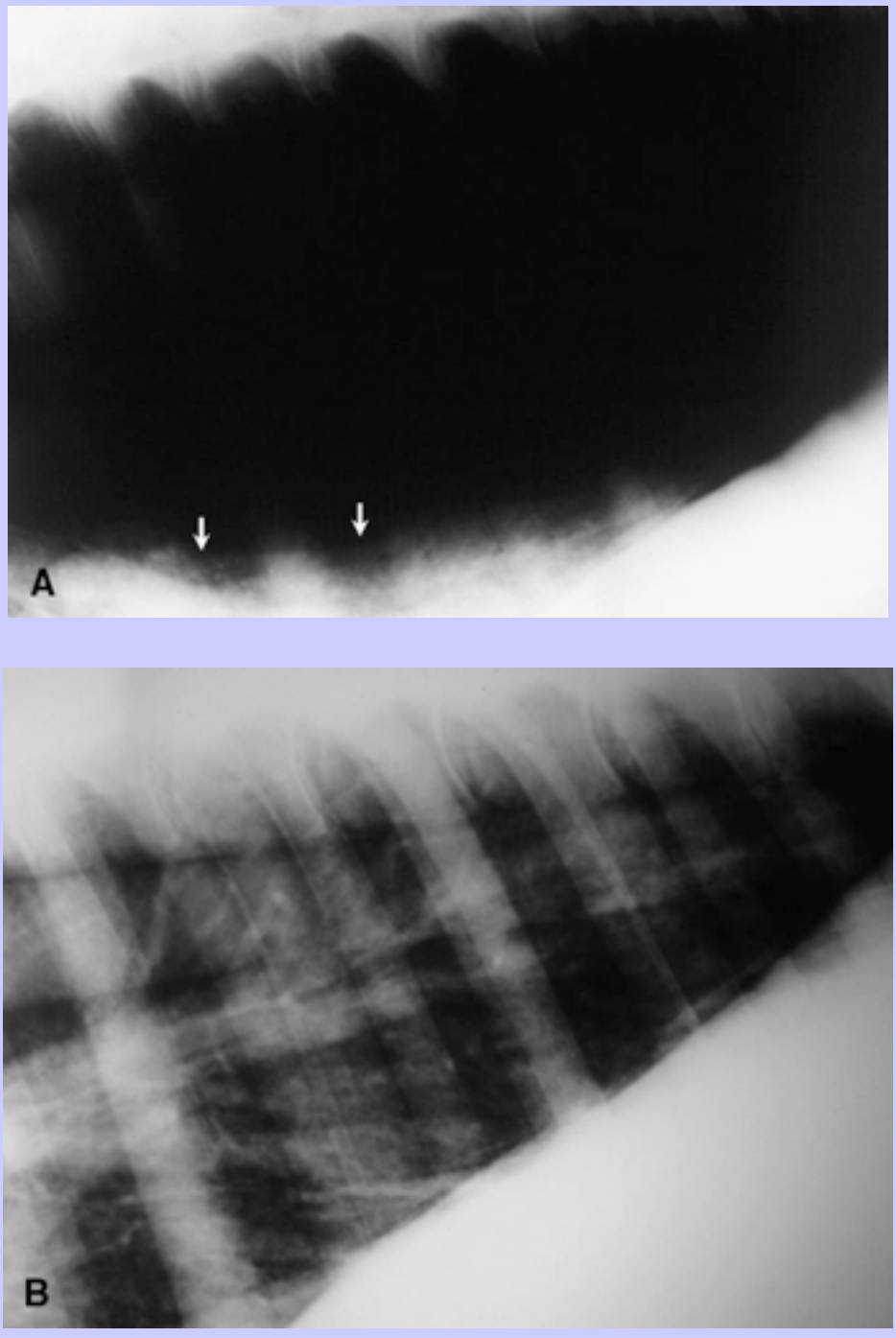
Fig. 31-35 **A**, Lateral radiographic view of the caudal dorsal portion of the thorax of a horse with bilateral pneumothorax. The dorsal borders of the lung margin are *arrowed*. **B**, Same view after thoracocentesis and resolution of the pneumothorax.



31.22.3.2 FOALS

Blunt thoracic trauma during parturition resulting in costochondral dislocation or rib fracture is more common in foals from primiparous mares and dystocias.[658a] The majority of fractures are subclinical; however, sudden death, hemothorax, hemopericardium, lacerated myocardium, pneumothorax, diaphragmatic hernia, and severe respiratory distress can occur.[658a,659] The incidence of fractured ribs in newborn foals on one farm was 21% (55 of 263), and none had clinical signs associated with the fracture after a 6-month period.[658a] However, in other reports rib fractures accounted for 13% of life-threatening fractures in foals less than 7 days of age, and in a necropsy study 19 of 67 foals with fractured ribs (28%) died as a direct result of rib fracture.[659,660] The most common site of injury is the cranioventral half of the thorax at the costochondral junction or adjacent dorsal area.[659] Clinical signs are variable and include pain on rib palpation, “clicking” or crepitation on auscultation, edema localized over or ventral to the fractured ribs, and signs of pain including grunting or groaning when the patient is manipulated or lying on the affected side. Palpation of crepitus over the fractured site is not a consistent finding. If the foal is systemically stable, asymmetry of the thoracic cage can be evaluated if the foal is positioned in dorsal recumbency.[658a] In severe cases involving multiple consecutive ribs, the foal can be in respiratory distress with a flail thorax. Foals may also exhibit respiratory distress with pneumothorax. Pale mucous membranes can be indicative of internal hemorrhage and abdominal hemorrhage, and diaphragmatic hernia should be considered if the diaphragm has been lacerated. Radiographs for detection of fractured ribs in neonates is not reliable.[659,661] Ultrasonographic examination is more reliable and also assists in evaluating the adjacent structures and presence of hemothorax or pneumothorax (Fig. 31-36). Conservative treatment with box rest and supportive care is successful in the majority of uncomplicated rib fractures; however, surgical repair has been performed in patients with multiple rib fractures or those with potential for severe internal injury.[661,662] Specific treatments based on the internal injuries should also be implemented.

31.22.4 Diaphragmatic Hernia

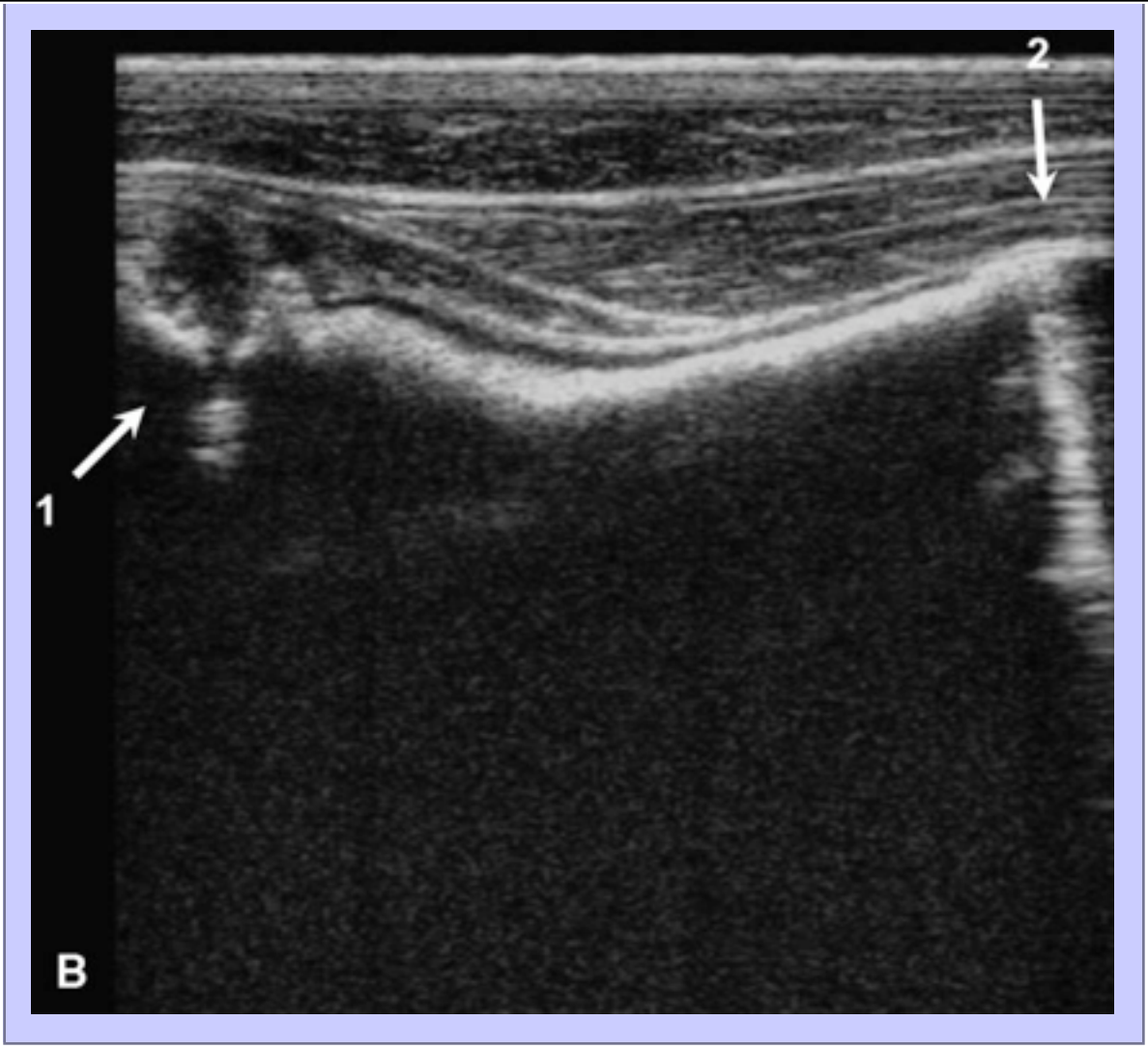
Diaphragmatic hernias occur sporadically in horses.[663,664] Occurrence is usually associated with a history of trauma or sudden increase in abdominal pressure and exertion, as may be experienced by stallions during breeding or mares during parturition.[664] In one study, 48% of 50 horses diagnosed with diaphragmatic hernia had a history of recent trauma.[663] In some cases no history of injury or predisposing cause can be identified.[664] Congenital diaphragmatic hernia can occur owing to incomplete fusion of any of the four embryonic components of the diaphragm or as a result of abdominal compression during parturition.[665] A congenital peritoneopericardial hernia has been reported.[666] Congenital hernias are typically located in the most ventral portion of the diaphragm, whereas diaphragmatic defects from trauma are usually located at the junction of muscular and tendinous portions of the diaphragm.[665] The size and position of the defect are important in determining whether herniation of abdominal viscera occurs.[664,667] Any segment of intestine can be involved, although small intestine is the most frequent.[665]

Clinical signs usually relate to intestinal obstruction or respiratory compromise; however, less specific signs of exercise intolerance and weight loss have been reported.[664] A diaphragmatic hernia may also initially be clinically silent if there is minimal pulmonary or bowel compromise. GI-related clinical signs are variable and depend on the segment and amount of intestine herniated and whether it is simply displaced, incarcerated, or

strangulated.[664] Frequently reported clinical signs are colic, moderate to severe tachypnea, and endotoxic shock. Respiratory signs of tachypnea can be attributed to pain at the site of injury or GI tract, shock, and lung compression and decreased ventilation.[664,667,668] Acute tearing of the diaphragm may be associated with hemorrhage into both thoracic and abdominal cavities.

Diagnosis can be challenging, and thoracic radiographs showing abdominal organs within the thoracic cavity are considered most diagnostic.[664,667] Ultrasonographic examination may show abdominal organs in the thoracic cavity; however, viscera may not be seen if covered by aerated lung or located away from the thoracic wall.[653] Rectal examination often suggests a relative lack of normal abdominal viscera. Auscultation of the thorax may reveal GI sounds, but it is usually not possible to differentiate from sounds referred from the abdomen. There may also be an absence of breath sounds ventrally and associated dullness on percussion, although these findings are not reliable. Abdominal paracentesis is usually normal and can be misleading because the compromised intestine is in the thorax, and therefore thoracocentesis may be more representative.[664] Thoracoscopy may also assist visualization of the hernia; however, partial deflation of the lungs is necessary to visualize the diaphragm, which may further compromise the patient.[658,667]

Fig. 31-36 **A**, Fractured rib *(arrow)*. Sagittal view. Left is dorsal. **B**, Healing fractured rib *(1)* and costochondral junction *(2)*. Sagittal view. Left is dorsal.



Surgical repair of diaphragmatic hernias has been reported but is fraught with complications associated with anesthesia, resection of devitalized bowel, anatomic location, and repair of the defect and possible fractured rib repair.[664] In chronic cases with few or no clinical signs, repair does not appear to be necessary, although complications associated with herniated viscera may eventually occur.[665,669]

31.23 PULMONARY EDEMA

PAMELA A. WILKINS

Pulmonary edema rarely occurs as a primary event in the horse and, when present, is usually secondary to some other pathologic process. Extravascular fluid accumulates within the lung after events that alter hydrostatic and colloid osmotic interstitial and vascular forces, change the surface area and pore size of the blood gas barrier, or diminish lymphatics drainage.[670] Pulmonary edema can be classified as cardiogenic or noncardiogenic. Pulmonary capillary pressure can be increased by any increase in left atrial or pulmonary artery pressure. In the horse this can occur secondary to acute renal failure, left ventricular failure, or very high cardiac output conditions, such as

extreme exercise. Increases in microvascular permeability may occur with sepsis, disseminated intravascular coagulation, hypoxic acidosis, or primary pulmonary pathology, resulting in the release of mediators of inflammation that increase vascular endothelial or alveolar epithelial permeability. Pulmonary edema associated with airway obstruction has been termed *negative-pressure pulmonary edema* (NPPE) and has been reported in horses.[671,672] NPPE occurs secondary to inspiratory efforts against a closed glottis that result in a precipitous fall in intrathoracic pressure. The large decrease in intrathoracic pressure increases the transmural pressure gradient for all intrathoracic vascular structures, favoring movement of water into the extravascular space.

Diagnosis is based on clinical examination, a history of predisposing causes, and radiographs. Horses have a shallow rapid respiratory pattern and may be dyspneic. Arterial blood gas analysis may reveal hypoxemia and hypercapnia. Fine crackles or wheezes may be audible on auscultation. Patients with volume overload (associated with renal failure or, rarely, too-rapid fluid administration) or primary cardiac problems may have an increased central venous pressure with pronounced venous distention. Fluid (clear or slightly yellow or pink-tinged) may drip from the nostrils and can increase in volume without necessarily becoming frothy. Progression to this stage warrants a very grave prognosis. Radiographic findings are nonspecific but include peribronchial and perivascular cuffing, increased prominence of vessels, and a hazy reticular interstitial pattern. Underlying pulmonary disease may obscure signs of edema, and radiographs of sufficiently high quality to show relatively subtle changes may not be obtainable in mature horses. Noncardiogenic pulmonary edema (capillary leak) is a component of the definition for ALI and ARDS.

31.23.1 Treatment

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Treatment consists of correcting the cause, reversing hypoxemia, decreasing plasma volume and left atrial pressure, and increasing plasma colloid osmotic pressure. Intranasal oxygen and even mechanical ventilation may be needed in severe cases. Improvement in oxygenation can be monitored by sequential arterial blood gas analysis or by using transcutaneous oxygen saturation monitoring equipment applied to the nasal mucosa, tongue, or other available nonpigmented mucous membrane. In cases of NPPE, maintaining an adequate, low-resistance airway is very important to prevent further damage, and tracheostomy may be necessary. IV fluid therapy should be guided by the patient's needs and monitored by serial measurement of central venous pressure if necessary. Furosemide may be given intravenously or intramuscularly at a dose of 1 to 2 mg/kg and repeated in 1 hour. If helpful, the dose can be titrated for each patient. At a dose of 1 mg/kg, approximately 8 L of urine is produced in approximately 1 hour.[673] A few studies have been conducted on the effects of furosemide on pulmonary hemodynamics in the horse.[674–677] The effects in horses with pulmonary edema have not been reported. Colloid solutions should be administered cautiously or in conjunction with use of diuretics because they can initially increase vascular pressure. Plasma may be safer than other colloid preparations such as dextrans or hetastarch. Colloid solutions may be of little benefit in raising intravascular osmotic pressure in patients with increased microvascular permeability.

Antiprostaglandin drugs (flunixin meglumine, phenylbutazone) and antihistamines may help. Bronchodilators may be of benefit. The use of corticosteroids remains controversial; if they are used, antimicrobial coverage is advisable because pulmonary edema has been shown to impair pulmonary bacterial defense mechanisms.

31.24 SMOKE INHALATION

PEGGY S. MARSH

Smoke inhalation injury is typically associated with exposure to fires, and there are often concurrent problems in other body systems from thermal injury. Extensive or severe burns can magnify the severity of the injuries. Thermal injury along with smoke inhalation leads to both local and diffuse lesions. Massive tissue edema may occur; it can be a challenge to manage and can create organ dysfunction. To further complicate the problem, severely affected patients may develop a wide variety of problems including life-threatening sepsis and/or hypermetabolism. Depending on the severity of the lesions, smoke and fire injuries often lead to systemic inflammatory response syndrome and in some cases multiple organ system failure.

Insult to the respiratory system by smoke inhalation depends on the fuels that burned, the completeness of combustion, and the generated heat intensity. In general, lesions are initiated by three mechanisms. The first is direct thermal injury, which can be limited to the upper respiratory tract by laryngeal reflexes and efficient heat exchange within the nasal passages. Toxic chemicals in the smoke can cause damage, both directly and indirectly, through inflammatory mediators. Carbon monoxide intoxication is commonly associated with human injuries from smoke and is a product of incomplete combustion.[678] Finally, with combustion there is consumption of oxygen, and the resulting low PAO_2 can lead to pulmonary vasoconstriction as well as generalized hypoxia.

Three phases of pulmonary dysfunction have been described in the horse.[679,680] The first stage is acute pulmonary insufficiency caused by several mechanisms. Carbon monoxide may be present in sufficiently high concentration to cause toxicity within a short time after exposure. Carbon monoxide combines with hemoglobin to form carboxyhemoglobin. Hemoglobin has a 200- to 250-times greater affinity for carbon monoxide as compared with its affinity for oxygen.[678] High levels of circulating carboxyhemoglobin result in a shift of the oxyhemoglobin dissociation curve to the left, thereby decreasing oxygen release at the tissue level and leading to tissue hypoxia. Other processes occurring during this acute phase include progressive edema and necrosis in the upper respiratory tract, leading to airway obstruction, bronchoconstriction in the lower respiratory tract from the irritating effects of noxious products, and altered pulmonary blood flow.[681]

These insults produce the second stage: formation of pulmonary edema, lower airway obstruction, and pulmonary parenchymal lesions. Within 48 to 72 hours after exposure, driven by pulmonary macrophages, neutrophils are called into the area of insult. They release cytokines, proteolytic enzymes, and oxygen-derived free radicals. Expression of the inflammatory cascade in excess of balance causes microvascular damage, leading to increased extravascular lung water. Local insult also results in the release of tissue factor initiating the coagulation cascade to produce fibrin. Debris from the inflammatory cascade along with fibrin and material directly deposited from smoke inhalation create pseudomembranous casts, which may obstruct the small airways. Widespread plugging of the airways may significantly increase airway pressure, causing barotrauma and alveolar damage.[681] Bronchopneumonia is the last stage and occurs as a result of the impaired host immune system, both locally and systemically. This phase may occur up to 1 to 2 weeks after the initial injury.

As the saying goes, “Where there's smoke, there's fire”; commonly horses with smoke inhalation injury will also have burn injury. A complete description of this process in horses has been reported.[682] Thermal injury causes a local response that includes microvascular insult and direct tissue coagulation leading to inflammation, local edema, and finally necrosis. Extensive local injuries will drive a systemic response. Initially there is a decrease in systemic organ blood flow. This is followed by the formation of generalized edema. The pathophysiology of edema formation is complex and involves protein shifts, endothelial damage, and alteration of the interstitial architecture, all leading to a net accumulation of fluid in the interstitial spaces.[683] Over time major thermal injury is characterized by high cardiac output, increased oxygen consumption, and protein and fat wasting, all of which may create a hypermetabolic state.[684,685] Loss of skin as a barrier, release of inflammatory mediators, and

hypermetabolism play a role in the development of immunosuppression. Other features noted with burn injury in the horse include acute hemolysis, renal failure, laminitis, and myositis.[686]

Horses exposed to fire with smoke will have a variety of clinical signs depending on the duration and type of exposure and the length of time from the insult. The extent of damage to the skin may be very difficult to ascertain initially. Acutely, within the first 6 hours, signs of carbon monoxide toxicity and shock may occur. The patient shows signs of severe hypoxemia and may be depressed, disoriented, irritable, ataxic, or even moribund and comatose. As edema and necrosis progress in the upper respiratory tract, dyspnea and stridor may develop. Auscultation of the thorax may reveal decreased air movement, crackles, or wheezes, but these may not become apparent for 12 to 24 hours. If edema of the airways is sufficiently severe, airflow may be severely restricted. Edema fluid may be visible at the nostrils and, later, may be replaced by inflammatory exudate. Concurrent edema formation may be occurring systemically. Hypoxia and generalized edema may lead to dysfunction of distant organs such as the kidneys and muscles. Signs of infection may be difficult to ascertain from other signs. All that may be noticed is a fever and a worsening of respiratory signs after initial improvement.

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Diagnosis is typically based on history and physical examination. A normal initial examination does not rule out exposure because the onset of clinical signs may be delayed several days. Within a short time after exposure, carboxyhemoglobin concentration in venous blood can be measured. A level above 10% is consistent with carbon monoxide toxicity.[679] Various diagnostic tests are useful in determining the extent of respiratory injury. These include endoscopy of the upper respiratory tract and tracheobronchial tree, thoracic radiographs, blood gas analysis, hematology, and cytologic evaluation of tracheal aspirates. Any or all of these tests can be performed on a serial basis as prognostic aids. Diagnostic tools for other organ injury include blood pressure monitoring, measurement of central venous pressure, serial hematologic and serum chemistry analyses, and monitoring of urine production.

Treatment depends on stage of injury. Initially, oxygen support is of benefit. It is a treatment for CO toxicity and helps reduce hypoxemia.[687] Humidified oxygen can be supplied by nasal insufflation or via transtracheal catheter. Upper respiratory tract obstruction may necessitate a tracheostomy. Attention should be paid to keeping the airways clear, and nebulization may be useful, especially when pseudomembranous casts are suspected. Bronchodilators may be useful in counteracting reflex bronchoconstriction. Decreasing inflammation and pulmonary edema may necessitate the use of diuretics and NSAIDs. Use of corticosteroids is controversial because of potential for immunosuppression and laminitis.[679] Novel therapies may include use of hyperbaric oxygen chambers and inhalation treatment with medication to inhibit inflammatory mediators, coagulation factors, or oxidative stress.[688]

Secondary complications require attention. Cardiovascular compromise and burn-induced edema may necessitate the judicious use of IV fluids. To prevent infection, strict hygiene, meticulous nursing care, and optimal nutritional support should be provided.[682,688] Prophylactic antimicrobial use is not recommended in human patients. Documented infection should be treated with appropriate antimicrobial agents based on results of culture and sensitivity patterns.[682]

31.25 RECURRENT AIRWAY OBSTRUCTION

DOROTHY M. AINSWORTH

31.25.1 Definition and Etiology

RAO is an inflammatory condition of the lower respiratory tract of mature horses that is characterized by excessive mucus production, neutrophil accumulation, bronchial hyperreactivity, and (in most cases) reversible

bronchospasm. Because the equine disease differs substantially in its etiopathogenesis from chronic obstructive pulmonary disease (COPD) of humans, it is recommended that the equine disorder no longer be called COPD. The preferred name is RAO or "heaves."[689]

RAO typically develops in adult horses residing in the northern hemisphere, for example in the Northeast and Midwest regions of the United States as well as in Great Britain and Switzerland, where the climate is wet and cool and horses are stabled and fed hay. RAO rarely occurs in horses maintained in warm dry climates such as those found in California or in Australia.[690] In North America the prevalence of RAO diagnosed at veterinary teaching hospitals has been positively correlated with rainfall, minimum temperatures, and total pollen and mold counts occurring 1 to 3 months previously.[691] These findings suggest that environmental conditions are integral to the development of the disease in susceptible horses.

RAO is considered to be a hypersensitivity to inhaled molds and organic dusts contained in the feeds hay and straw. In this regard, RAO is similar to occupational asthma that develops in human workers exposed to organic dusts.[692] Identifying the *specific* causative agents within the hay dust that induce the disease has been a challenge, as stable dust contains over 50 species of molds, large numbers of forage mites, endotoxin, and other inorganic components.[693] Inhalation of aqueous extracts of *Aspergillus fumigatus, Faenia rectivirgula (Micropolyspora faeni)*, or *Thermoactinomyces vulgaris* partially but not fully induces RAO in susceptible horses.[694–696] Similarly, inhalation of endotoxin, a component of hay dust, has been found to produce airway neutrophilia but not all of the changes in pulmonary function that are characteristic of RAO.[697,698] To fully induce RAO in susceptible horses requires inhalation of hay dust particulates either by natural challenge (stabling and feeding hay) or by nebulization of a hay dust solution.[699–702]

31.25.1.1 ROLE OF THE INNATE IMMUNE SYSTEM

After inhalation of the organic dust, it appears that both adaptive and innate immunologic responses contribute to the pulmonary inflammation. Within hours of hay dust exposure, neutrophilia and excessive mucus production are evident endoscopically and cytologically.[703,704] Pulmonary macrophages isolated from affected horses at this time exhibit an upregulation in the gene expression of TNF-α, IL-1β and IL-8.[705] The transcription of these proinflammatory genes may reflect involvement of TLR2 and/or TLR4 signaling pathways (stimulated by fungal wall components and endotoxin) with subsequent nuclear factor (NF)–κB activation and gene transcription.[706–708] However, the importance of these pathways needs to be confirmed because many different mediators activate NF-κB and enhance gene expression. The initial upregulation of these proinflammatory genes is transient, with mRNA levels returning to preexposure levels 24 hours after hay dust challenge.[705] With continuous hay dust exposure, both the protein and the gene expression levels of IL-8 in the airway cells and bronchial epithelium, as well as the gene expression levels of IL-1β and TNF-α in the bronchoalveolar lavage fluid (BALF) cells are upregulated in chronically affected horses.[709–712] However, this gene upregulation may reflect contributions from both macrophages and extravasated neutrophils accumulating in the airways. In addition to IL-8, IL-1β, and TNF-α, another chemokine that has the potential to propagate the airway neutrophilia is IL-17.[712,713] Secreted by lymphocytes and neutrophils, IL-17 promotes maturation, chemotaxis, and activation of neutrophils. In horses continuously exposed to hay dust for periods exceeding 2 weeks, IL-17 also upregulates the gene expression of IL-8 in the airway epithelium.[712]

31.25.1.2

ROLE OF THE ADAPTIVE IMMUNE SYSTEM

The role of the adaptive immune system in the development of RAO is currently controversial. Data that support the hypothesis that RAO is an IgE-mediated (T-helper 2 [Th2]) disorder include the findings of elevated allergen-specific IgE concentrations in the serum[714] and in the BALF of RAO-susceptible or affected horses[715,716] and increased *numbers* of IL-4 and IL-5 (mRNA positive) BALF cells—detected by in situ hybridization techniques—in RAO-affected horses.[717,718] Although Th2 disorders are typically characterized by eosinophilic infiltrates, it has been hypothesized that IL-4 activates its receptor on neutrophils to inhibit neutrophil apoptosis, to increase protein synthesis, and to upregulate the expression of the IL-9 receptor.[719] It has been further hypothesized that activation of the IL-9 neutrophil receptor then enhances IL-8 production and neutrophil influx.[719,720] Although the gene expressions of IL-4 and IL-9 receptors are indeed upregulated in peripheral blood neutrophils isolated from RAO-prone and RAO-affected horses, the existence of this pathway, linking the Th2 limb with the development of neutrophilia, requires additional investigation and confirmation.

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In contrast, other data suggest that RAO is not simply a Th2 immune response. For example, Van der Haegen and colleagues were unable to demonstrate a significant difference in IgE-protein—positive cells in the lung tissue samples of RAO-affected as compared with control horses.[721] Second, cytokine profiles of BAL cells[710,711] or of pulmonary $CD4^+$ and $CD8^+$ cells[722] isolated from RAO-affected horses during the first 24 or 48 hours after hay dust exposure fail to demonstrate an upregulation of IL-4, IL-5, or IL-13. Furthermore, chronic (3 week) hay dust exposure is associated with an increase in the gene expression of IFN-γ in the BALF cells,[710,711] although in one trial but not in the second trial of the same chronically affected horses the gene expression of IL-4 was upregulated.[710] Fourth, GATA-3, the transcription factor required for IL-4 gene expression, is not upregulated in the bronchial cells of RAO-affected horses.[723] Nevertheless, in evaluation of these studies caution should be exercised in categorizing RAO as a Th1 immune disorder. This is because (1) concomitant increases in the gene expression of t-bet, the transcriptional factor for IFN-γ expression in $CD4^+$ cells, is not upregulated concurrently with IFN-γ,[711] and (2) multiple signaling pathways may stimulate the production of IFN-γ. In other species, TLR stimulation leads to the production of proinflammatory factors including IL-12 and subsequent IFN-γ synthesis.[724,725]

31.25.1.3

OTHER INFLAMMATORY MEDIATORS

With the accumulation of intraluminal neutrophils and peribronchiolar lymphocytes and with the activation of alveolar macrophages, it is not surprising that numerous other inflammatory mediators are released and may contribute to the inflammatory response of RAO. For example, histamine that is released by degranulated mast cells increases vascular permeability and produces bronchoconstriction. Although histamine concentrations in the BALF increase in RAO-susceptible horses after exposure to dusty hay, histamine-1 receptor antagonists provide little therapeutic relief for affected horses. This finding suggests that histamine may not be the predominant mediator responsible for the airway inflammatory response.[726] The potential role of prostaglandins, with their bronchoconstrictive ($PGF_{2\alpha}$, PGD_2, TXA_2) and/or bronchodilatory capabilities (PGE_2, PGI_2), have also been examined. In RAO-affected horses, increases in BALF PGE_2 and PGF[727,728] and in serum TXB_2 (a metabolite of TXA_2) are found.[729] However, although administration of a cyclooxygenase inhibitor prevents the increase in the serum TXB_2 in RAO-affected horses, it does not inhibit

the development of airway hyperresponsiveness or bronchospasm in susceptible horses. This finding suggests that the eicosanoids are not the major contributor to the disease.[729] The contribution of lipoxygenase metabolites to the airway disease has also been investigated in RAO-affected horses. In humans, leukotrienes have multiple actions: LTB_4, LTC_4, and LTD_4 are bronchoconstrictors; LTC_4 and LTD_4 are mucus secretagogues; and LTB_4 (through its action on NF-κB) is a chemotactin, promoting the upregulation of adhesion molecules and cytokines that facilitate neutrophil extravasation.[730] In horses, inhalation of LTB_4 or LTD_4 induces airway neutrophilia and bronchoconstriction, respectively, in normal and RAO-affected horses.[731] BALF cells isolated from RAO-affected horses during the first 48 hours of hay dust exposure and stimulated ex vivo produce increased concentrations of LTB_4 and LTC_4.[730] However, actual BALF concentrations of LTB_4 and LTC_4 are not elevated in chronically affected horses.[728] Furthermore, pretreatment of RAO-susceptible horses with either a 5-lipoxygenase inhibitor or a leukotriene receptor antagonist before hay dust exposure does not prevent the development of airway neutrophilia or alterations in lung mechanics.[732,733] Treatment of clinically affected horses with a leukotriene receptor antagonist also fails to improve pulmonary function test results, clinical scores, or arterial blood gas tensions.[734]

There is some evidence that reactive oxygen species, derived from pulmonary macrophages and granulocytes, contribute to the inflammatory process of RAO.[735] An "oxidant stress" has been proposed to develop, based on the findings of increased levels of oxidized glutathione; increased glutathione redox ratios (the ratio of oxidized glutathione to total glutathione); and decreased ascorbic acid concentrations in the pulmonary epithelial lining fluid of RAO-affected horses.[735,736] Changes in these indices of oxidant stress are also correlated with lung dysfunction parameters—total lung resistance, dynamic lung compliance, and arterial oxygen tensions—in RAO-susceptible and affected horses.[737] Reactive oxygen species are well recognized for their microbicidal activities. They also function as messengers in intracellular signaling pathways, upregulating proinflammatory gene expression by activating NF-κB.[738] Thus it is possible that reactive oxygen species generated during the inflammatory process of RAO also contribute to the NF-κB activation that has been detected in bronchial epithelial cells and in BALF cells of RAO-affected horses.[739,740]

Proteases derived from airway phagocytes, lymphocytes, and epithelial cells may also propagate the inflammatory reaction of RAO. Although many matrix metalloproteinases (MMPs) with gelatinolytic and collagenolytic activities have been identified in the respiratory tract secretions of RAO-affected horses,[741,742] the gelatinase MMP-9 is markedly increased in BALF and in tracheal epithelial lining fluid of diseased horses.[743] It has been suggested that the degradative effect of MMP-9 on the basement membrane and on the extracellular matrix components facilitates the extravascular movement of neutrophils into the airways. In vitro, tetracycline derivates effectively inhibit MMP activity detected in tracheal epithelial lining fluid,[744] but the efficacy of these compounds in ameliorating or preventing the inflammatory response of RAO-susceptible horses exposed to hay dust remains to be determined.

31.26 SUMMER PASTURE–ASSOCIATED OBSTRUCTIVE PULMONARY DISEASE

31.26.1 Definition and Etiology

In the southeastern United States a condition clinically similar to RAO called *summer pasture–associated obstructive pulmonary disease* (SPAOPD) develops in mature horses that are kept outdoors. Clinical signs

typically manifest during the late spring, summer, and early autumn.[745] It is interesting to note that this disorder has also been reported to occur in horses in the United Kingdom.[746,747] Horses with SPAOPD exhibit airway neutrophilia, excessive mucus production, and accentuated breathing efforts,[748] although the inciting environmental factors and the immunopathogenesis of this disorder have yet to be determined.

Because of its similarity to RAO, investigators have sought to determine if SPAOPD reflects a Th2 or Th1 immune response to inhaled molds or antigens by examining BALF antibody isotypes and BAL cell cytokine profiles. Seaborn and colleagues found that neither the total nor the antigen-specific IgE and IgG titers to *Aspergillus* species, *Cladosporium herbarum, Penicillium* species, *F. rectivirgula, Saccharomonospora viridis, Thermoactinomyces thalpophilus*, and the forage mite *Lepidoglyphus destructor* in the tracheal lavage fluid were increased in SPAOPD-affected horses relative to controls.[749] During the winter months, when the horses are free of clinical signs, *A. fumigatus*–specific IgG titers in the SPAOPD group exceeded those in controls, but it could not be determined if this increase reflected ongoing production or decreased consumption.

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Cytokine profiles of BALF cells isolated from SPAOPD-susceptible and affected horses have also been examined. When horses are symptomatic, the mRNA copy numbers of *both* IL-4 and IFN-γ in BALF cells are increased relative to controls.[750] This difference is not apparent when horses are asymptomatic, although the copy number of IL-4 in the SPAOPD-prone horses does not decrease during the asymptomatic periods either.[750]

31.26.2 Epidemiology

RAO occurs in both ponies and horses, but no gender or breed predisposition has been identified.[751,752] The prevalence of RAO is dependent on the geographic region examined. Bracher reported that 60% to 80% of Swiss horses older than 8 years of age suffer from some degree of this disease. In North America and in Europe the prevalence of RAO is estimated to range from 12% to 50%.[751]

To assess the genetics of RAO, Marti and colleagues examined families of horses affected with the disease. In one family 67% of the offspring born to an affected dam and an affected sire developed RAO in contrast to the 17% of affected offspring born to unaffected parents.[753] In an analysis of half-siblings, Marti also showed that stallions with chronic airway disease produced more affected offspring than did healthy stallions. Marti concluded that the clinical manifestations of RAO are the result of the interactions of genetic and environmental factors. There are currently no genetic markers that can be used to identify horses or ponies that are prone to developing RAO.

Although it has been clearly demonstrated that hay particulates are integral to the development of the disease, the role of a prior viral (or bacterial) infection in inducing susceptibility to hay dust hypersensitivity has not been established. Furthermore, even though horses with IAD share many of the clinical features of RAO,[754] the relationship of IAD to the development of RAO is unknown.[689]

31.26.3 Clinical Signs and Differential Diagnosis

The severity of clinical signs in RAO-affected horses is variable and is exacerbated by stabling; exposure to dusts, hay, and ammonia fumes; and hot humid weather. In a study of 148 cases of RAO presented for evaluation to a veterinary referral hospital in the United Kingdom, the chief complaints (median duration of which was 7 months) included coughing (84% of cases), bilateral nasal discharge (54%), exercise intolerance (51%), and postexercise breathing difficulty (23%).[755] In a review of 16 cases presented to a veterinary teaching hospital in

western Canada, the most common historical complaint (88% of the cases) was coughing,[756] whereas the predominant clinical complaints in 65 cases presented to a veterinary teaching hospital in the northeastern United States were abnormal breathing effort (68%), nasal discharge (50%), and a spontaneous cough (46%).[757]

On physical examination, mildly affected horses are typically afebrile and exhibit a bright demeanor. In such cases horses exhibit a normal or slightly accentuated (abdominal) breathing effort, respiratory rate, and heart rate. A nasal discharge may not be evident in all cases, but the horse may be observed to swallow excessively because of expectorated exudate. When the horse is exercised, a thick white nasal discharge and a cough become apparent. The frequency of coughing also increases when horses are stabled, and it often exceeds 10 to 15 coughs per hour.[758] Physical examination of more severely affected horses reveals tachypnea (respiratory rates exceed 40 breaths/min), nostril flaring, and a markedly accentuated expiratory effort (heave). The thoracic expiratory component may precede that of the abdominal compartment, producing a "double effort."[759] Abdominal pressure swings may be large enough to cause the anus to protrude with expiration. Paroxysmal coughing, bilateral nasal discharge, anxious facial expression, flatulence during coughing, reluctance to move, inappetence, and weight loss occur in severely affected horses.[760]

Although RAO is a diffuse lung disease, auscultation of mild cases may not reveal abnormal lung sounds unless a rebreathing bag is used to induce a hyperpnea. In one survey thoracic auscultation was abnormal in 47% of the cases, whereas tracheal auscultation was abnormal in 63% of the cases (755). In the latter, abnormal lung sounds and "mucous clicks" (tracheal exudate) were detected by tracheal auscultation. In mildly affected horses, only regional areas of adventitious lung sounds—crackles or high-pitched expiratory wheezes—may be detected. In contrast, in severely affected horses wheezes and mucous clicks may be heard at the horse's nostrils without the use of a stethoscope. Depending on the severity of the disease, thoracic percussion may be normal or may reveal expansion of the caudal lung fields beyond the normal line of pleural reflection.

Researchers have developed a clinical scoring system to categorize the severity of RAO. In one system the total clinical score is based on the magnitude of nostril flaring, ranging from 1 to 4, and the abdominal breathing effort, ranging from 1 to 4.[761] RAO in horses with a clinical score of 3 or 4, 5 or 6, or 7 or 8 was diagnosed as mild, moderate, or severe, respectively. In moderately to severely affected horses, there is a very good correlation between the clinical signs and alterations in pulmonary resistance or dynamic compliance.[762] For mildly affected horses (total scores of 3 or 4), the physical examination findings underestimate the severity of changes in the pulmonary function test results. Naylor and colleagues also developed a clinical scoring system based on the respiratory rate (graded 0 to 2), the respiratory effort (0 to 2), and lung auscultation findings (0 to 2) in affected horses. Although those investigators did not measure pulmonary function test results, they found that the clinical score was more closely correlated with histopathologic changes obtained by lung biopsy (and in particular the presence of peribronchiolar neutrophil and/or mast cell infiltration) than with the degree of BALF neutrophilia.[756]

Rarely, horses with longstanding RAO develop cor pulmonale. Clinically these horses have jugular distention, pulsation, ventral edema, and tachycardia in addition to the clinical signs of RAO.[760–763]

31.26.4 Laboratory Aids and Diagnostic Tests

The diagnosis of RAO is based on the history, the clinical signs, and the response to therapy. It may be difficult to arrive at a definitive diagnosis in asymptomatic horses or in horses that are exhibiting mild signs at the time of the examination, thus necessitating the use of additional diagnostic tests such as cytologic analysis of lower

respiratory tract secretions. During periods of clinical remission, BALF cell populations obtained from RAO-susceptible horses consist predominantly of mononuclear cells (90% macrophages and lymphocytes), and the cell differential counts do not differ from those found in healthy horses.[764] However, when horses develop RAO, aspirates of tracheal and bronchoalveolar fluid contain increased numbers of nondegenerative neutrophils (>25%). For example, in the BALF the percentage of neutrophils may be as great as 90%, far exceeding the normal 5% to 15% found in healthy horses that are stabled and fed hay. In most cases the percentage of eosinophils or mast cells is not increased in affected horses. Therefore cytologic analysis of respiratory secretions in RAO-affected horses reflects a suppurative nonseptic inflammation, distinguishing this disorder from lungworm infections (pulmonary eosinophilia) or pneumonia (degenerative neutrophils, intracellular bacteria). Rarely an infectious bronchitis may complicate a case of RAO; microbial cultures yield low growth of the bacterial isolate, but the predominant cell type in the tracheal secretions is a nondegenerative neutrophil.

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Endoscopic examination of the respiratory tract of RAO-affected horses demonstrates excessive amounts of tracheobronchial secretions that originate from most of the bronchial segments. Distal airways are edematous and inflamed, and airways easily collapse during expiration. Expectorated secretions from the lower respiratory tract coat the pharynx, larynx, and other structures of the upper respiratory tract.

In general, the CBC, serum biochemistry profile, and serum fibrinogen concentrations are normal in RAO-affected horses.[757] In severely stressed horses, a mature neutrophilia and lymphopenia may be evident on the leukogram. Arterial blood gas analyses are normal in approximately 25% of the cases,[765] but others demonstrate hypoxemia (Pa_{O_2} < 85 mm Hg) in the absence of arterial hypercapnia. In affected horses that are exercised, at a given work effort the arterial oxygen tensions are reduced compared with blood gas values obtained from the same horses during clinical remission.[766] Prognostic value of arterial blood gases in RAO-affected horses has not been examined.

Radiographs are usually of limited value in diagnosing RAO because the accentuated bronchointerstitial pattern typically found in the diseased horses can be detected in healthy aged horses. Radiographs can be helpful in ruling out thoracic neoplastic or infectious disorders in horses that have clinical signs resembling RAO (cough, nasal discharge, abnormal breathing effort). In severely affected horses with RAO that repeatedly fail to respond to bronchodilators and glucocorticoids, radiographs should be taken to determine if bronchiectasis (dilation or deformation of the bronchi or bronchioles) exists.[767] Bronchiectasis is a relatively uncommon complication of RAO but causes irreversible airway obstruction as a result of collapse of the affected airways.

Ultrasound evaluation of RAO-affected horses confirms a shift of the caudal lung border caused by alveolar hyperinflation.[768] However, gas in the large colon (left side) or in the cecum (right side) may preclude complete imaging of the most caudal extent of the lung fields at the sixteenth intercostal space. Thoracic ultrasonography of RAO-affected horses may demonstrate small hypoechoic areas of irregularity on the lung surface, but, in general, ultrasonography is not useful in detecting airway inflammation. In horses with cor pulmonale, ultrasonography confirms the presence of pulmonary hypertension and right ventricular hypertrophy.[769]

Lung biopsies, although not typically performed to diagnose RAO-affected horses, demonstrate bronchiolar goblet cell metaplasia, bronchiolar luminal exudate, peribronchiolar lymphoplasmacytic cell infiltration, and accumulations of neutrophils within the airways.[756] The potential disadvantages of performing a lung biopsy include the risk of inducing hemorrhage (hemothorax, epistaxis) and the chance of obtaining a nonrepresentative (nonaffected) tissue sample.

Intradermal skin testing of RAO-affected horses has been performed by many investigators, but unfortunately the results (and conclusions) are variable. Evans and colleagues found that in RAO-affected horses the total number of positive intradermal skin tests evaluated at 0.5, 4 to 6, and 24 hours after allergen injection exceeded that in control horses. Positive responses were detected for two pollens (English plantain, goldenrod), three molds (*Rhizopus* species, *Monilia* species, and *Alternaria tenuis*), and one insect extract (*Tabanus* species). However, this difference in skin reactivity, which involved only 3% of the possible extract reactions, did not permit discrimination between a diseased horse and a healthy horse.[770] Similarly, in a retrospective study of cases examined at a veterinary teaching hospital over a 10-year period, Jose-Cunilleras and colleagues found that the percentage of RAO-affected horses that had positive skin reactions exceeded that of the control horses at all time points examined (0.5, 4, and 24 hours).[771] In contrast, others have failed to find a significant difference between RAO-affected and control horses in either the number of positive skin responses or in the titers developed at the early (0.5, 4 hours) or late (24 hours) phases to a variety of molds.[772–774] Recently Wong and colleagues evaluated the skin responses of RAO-prone (asymptomatic) and control horses to intradermal injections of histamine and a mixture of *Aspergillus* species. They found that compared with the controls the RAO-affected horses had a heightened response to histamine (evaluated at 0.5 hours postinjection) and a delayed resolution of the skin wheal (after 24 hours) to the *Aspergillus* antigens.[775] Thus, positive skin tests and serum precipitins to fungal and thermophilic actinomycete antigens are found in many normal as well as RAO-affected horses, reflecting a level of exposure of the horse rather than a susceptibility to heaves. In general, skin testing does not allow identification of RAO-affected horses or the specific inhaled particulate that is inciting the pulmonary inflammation.[776]

Similarly, serum allergy tests such as the radioallergosorbent test (RAST) or the IgE-based ELISA, which aim to identify the allergen that is inciting the hypersensitivity, are also of limited value in the diagnosis of RAO. Lorch and colleagues compared the results of two different ELISAs (one based on the human FcεRIα chain, the other based on a polyclonal antiserum to equine IgE) and a RAST test with intradermal skin test responses in RAO-affected horses. They concluded that based on the poor performance of all three tests, none should be used as a screening test for allergen hypersensitivity.[777]

Conventional pulmonary function tests, which require measurements of pleural pressure (obtained via an intrathoracic esophageal balloon catheter system) and airflow (detected by a flow meter attached to a sealed face mask worn by the horse) are typically reserved for experimental investigations and are not routinely performed on clinical patients. The characteristic alterations in the pulmonary function test results of horses with RAO are a decrease in dynamic lung compliance or lung distensibility (C_{dyn}); an increase in pulmonary resistance (R_L); an increase in maximum pleural pressure changes (ΔP_{plmax}); and an increase in peak inspiratory and expiratory flow rates.[778] (In general, C_{dyn} reflects peripheral airway function, whereas R_L reflects central airway function.) RAO-affected horses also exhibit bronchial hyperreactivity. The dose of aerosolized histamine required to reduce C_{dyn} to 65% of its baseline value is much less in diseased horses than in controls.[779] These alterations in lung function that develop in affected horses are repeatable on reexposure to hay dust.[780,781] During periods of clinical remission the pulmonary function test results return to normal and are not significantly different from those of healthy age-matched horses. However, an inability to detect a difference in R_L or C_{dyn} between healthy horses and RAO-susceptible horses during periods of disease remission may reflect a relative lack of sensitivity of these tests.[782] For example, some researchers have found that in RAO-susceptible horses during periods of clinical remission, some degree of bronchial hyperreactivity and airflow obstruction remains.[783,784]

31.26.5 Pathophysiology

The changes in respiratory mechanics and the development of clinical signs are consequences of the influx of inflammatory cells (mechanisms discussed earlier), the contraction of smooth muscle in the airways, and the production and accumulation of mucus. Bronchoconstriction probably results from the cumulative effects of (1) released inflammatory mediators—histamine, serotonin, eicosanoids, leukotrienes—and (2) activation of muscarinic receptors on the smooth muscle by released acetylcholine.[785] In addition to their direct effects on smooth muscle tension, histamine and serotonin also augment the release of acetylcholine from parasympathetic nerves.[786] Based on in vitro muscle bath studies, there is also evidence that RAO-affected horses lack inhibitory nonadrenergic-noncholinergic innervation (iNANC) of the peripheral (but not central) airways, further contributing to the development of bronchospasm.[787] The magnitude of airway narrowing that occurs in response to smooth muscle contraction is a function not only of the thickness of the smooth muscle layer but also of the width of the mucosal layer between the muscle and airway lumen. Thus thickening of the airway by peribronchial infiltrates and by epithelial metaplasia amplifies the airway narrowing induced by bronchospasm.[788]

As noted earlier, excessive mucus is evident endoscopically and cytologically in RAO-affected horses. Mucus consists of a liquid sol layer, which surrounds the ciliated epithelium, and an overlying viscous gel layer, which contains water, electrolytes, lysozymes, cells, and the mucin glycoproteins. In RAO-affected horses the excessive mucus formation may be the result of an upregulation of a mucin-producing gene, MUC5AC, responding to released elastases, reactive oxygen species, and other inflammatory mediators.[789] Increased viscosity of the mucus[790] may be a consequence of alterations in the side chain glycoproteins[791] and/or formation of mucin aggregates from DNA and actin released by airway neutrophils. Delayed clearance of the mucus from the lower respiratory tract contributes to the accumulation of the exudate and may reflect an impairment of the mucociliary apparatus as a result of epithelial cell destruction.[792,793]

Narrowed and/or obstructed airways increase R_L and fail to participate in efficient gas exchange.[778] Low ventilation-perfusion lung regions contribute to a widening of the aveolar arterial oxygen-difference ($AaDO_2$) gradient and the development of arterial hypoxemia.[794,795] High ventilation-perfusion regions (dead space) also increase in affected horses, but normal arterial $PaCO_2$ levels are maintained by increases in the total minute ventilation.[796] Changes in minute ventilation are due to an increase in breathing frequency, as tidal volume changes little with the disease. In general, there are no significant changes in cardiac output, heart rate, and mean systemic arterial pressure, but pulmonary artery systolic and mean pressures and pulmonary vascular resistances are significantly increased in diseased horses.[796] The combination of airway inflammation and hypoxemia, if severe enough, stimulates the respiratory controller in the ventral medulla to increase the respiratory drive and to activate inspiratory and expiratory muscles (abdominal heave). Recruitment of respiratory muscles increases the maximum pleural pressure excursion (ΔP_{plmax}), the work of breathing, and the total body oxygen consumption.[797] However, much of the increased expiratory effort (and increased intrathoracic pressures) serves to collapse the noncartilaginous airways, further compounding gas trapping and impairing gas exchange.

31.26.6 Pathology

The lungs obtained from RAO-prone horses that are asymptomatic at the time of death macroscopically appear normal.[794] In symptomatic horses, the lungs are pink, soft, hyperinflated, and imprinted with rib impressions.

Lungs fail to collapse when the chest is opened because of gas trapping distal to occluded airways.[772] Emphysematous bullae are lacking, but accumulations of mucus and cellular debris occlude the small airways, forming "spiral-shaped casts" known as *Curschmann's spirals*. Light and electron microscopic examinations of lung segments from diseased horses demonstrate that the peripheral airways are the most severely affected, although pathologic alterations do occur in the central airways.[792,793] Histologic changes include goblet cell hyperplasia, epithelial cell damage, bronchial and bronchiolar epithelial cell hyperplasia, smooth muscle hypertrophy and hyperplasia, collagen deposition, and overinflation of the alveoli.[798–800] It is interesting to note that the extent of the bronchiolar epithelial cell hyperplasia is correlated with the increase in dead space ventilation that occurs in RAO-affected horses.[796] Peribronchiolar infiltrates consist of lymphocytes and plasma cells, along with collagen deposition.[801] Eosinophils are rarely observed either within the airways or in the lung parenchyma.

Despite these pathologic changes, the clinical signs are usually considered to be reversible. However, in rare instances bronchiectasis may develop in RAO-affected horses. In a single case study of one such affected horse, histopathologic alterations of the affected airway demonstrated separation of the cartilaginous plates of the dilated bronchus, disorganization of the chondrocytes, reduction in the elastic fibers surrounding the perichondrium and lamina propria, and a lymphoplasmacytic infiltrate.[767]

In RAO-affected horses with cor pulmonale, reductions in the circumferential ratio of the aorta to the pulmonary artery and in the mass ratio of the left ventricle and septum to the right ventricle are found.[769,802]

31.26.7 Treatment and Prognosis

31.26.7.1 ENVIRONMENTAL MANAGEMENT

Environmental management changes are the single most important aspect of the treatment protocol to be implemented. Whenever possible, RAO-prone and RAO-affected horses should be kept outside at all times, blanketed during inclement weather as needed, and provided access to a well-ventilated three-sided shelter from which manure and urine are frequently removed. Horses should be allowed pasture access (except for those with SPAOPD, which improve with stabling) and fed pellets or hay cubes when pasture is unavailable. Some horses will tolerate hay that has been soaked in water, but this practice reduces the nutrient value of the hay and is often forsaken when the weather becomes cold. Reducing dust exposure is critical, as inhaling organic dusts for as little as 1.5 hours causes a significant increase in R_L. By 5 hours, horses exhibit significant decreases in C_{dyn} and Pao_2 and evidence of pulmonary neutrophilia.[703,803] The ensuing inflammation from a single 5 hour dust exposure takes approximately 4 days to resolve.[804] For chronically affected horses that have been turned out to pasture, clinical remission and normalization of pulmonary function test results take 4 to 8 weeks depending on weather conditions.[690,805]

Horses for which optimal management changes cannot be implemented should be fed pellets and/or hay cubes and kept in well-ventilated stalls that are bedded with a material that has a low respirable dust particle count and mold concentration. Cardboard bedding has a significantly lower particulate concentration (dust, *A. fumigatus, F. rectivirgula*, and *T. vulgaris*) than wood shavings, wheat, or flax straw, although cardboard may be difficult to obtain and store.[805,806] Typically, when affected horses are bedded on shaving and fed pelleted rations, significant improvements in the pulmonary function test results occur within 3 days.[807] When RAO-susceptible horses that are in clinical remission are fed low dust—containing forages and bedded on low dust

—containing materials, they can remain clinically normal for months. However, even though BALF neutrophil percentages, pulmonary function test results, and indices of airway inflammation such as exhaled ethane are normal, bronchial hyperreactivity of RAO-prone horses remains increased in these horses.[783,806,808,809] Therefore these horses will always be more susceptible to disease development than healthy horses when dust levels increase in the environment.

Environmental management considerations should also be implemented when horses are transported. Their heads should not be tied in close proximity to the hay net, as this practice places their breathing zone near a concentrated source of organic dusts and molds and restricts their head position so as to further decrease mucociliary clearance of respiratory secretions.[760,810]

31.26.7.2

BRONCHODILATORS

During acute exacerbations of RAO, bronchodilators can be very effective in improving lung mechanics. Three main classes of bronchodilators have been examined in RAO-affected horses and include the anticholinergics (muscarinic antagonists), the β_2-agonists, and the phosphodiesterase (PDE) inhibitors.

The muscarinic antagonists, of which atropine and ipratropium are examples, block the smooth muscle constricting effects of acetylcholine. These actions have the greatest effects in the central as opposed to the peripheral airways. Murphy and colleagues reported on the efficacy of atropine sulfate used in 25 clinical cases of RAO. IV administration (0.02 mg/kg) decreased ΔP_{Plmax}, respiratory rate, and Pa_{O_2} (2 to 3 torr) within 30 minutes of administration.[811] In another clinical study of 18 RAO-affected horses, Pearson and Riebold found that atropine (0.01 mg/kg IV) decreased ΔP_{Plmax} 83% and produced clinical improvement in 87% of the cases. Despite its bronchodilating effects, atropine's short duration of action (2 hours) and undesirable side effects of mydriasis, ileus, tachycardia, dry airway secretions preclude its routine use in the treatment of RAO.[813] In contrast, ipratropium bromide is poorly absorbed from either the respiratory or GI tract, minimizing the development of systemic effects. The onset of action of inhaled ipratropium is 30 minutes, and the duration of effect ranges from 4 to 6 hours.[814] The powder form may be nebulized (dose of 2 to 3 µg/kg), or the dry powder inhaler may be attached to a specially constructed mask that allows the generation of a sufficiently negative inspiratory pressure to dispense the inhalant.[815] When given to RAO-affected horses before an incremental exercise test, ipratropium reduces R_L and ΔP_{plmax} and increases C_{dyn} in resting horses. However, during exercise the drug produces no significant improvement in lung mechanics, blood gas tensions, or oxygen consumption. It also does not prolong the time to fatigue (or prevent exercise intolerance) in treated horses when compared with diseased horses that received a placebo.[816] During exercise the pulmonary resistance values of the treated RAO-affected horses is twice that of healthy controls, suggesting that despite bronchodilation, mucosal thickening and accumulations of intraluminal secretions and cellular debris probably continue to obstruct airflow.[816]

The β_2-adrenergic agonists—clenbuterol, albuterol, fenoterol, pirbuterol, and salmeterol—produced relaxation of smooth muscle by increasing the intracellular levels of cAMP. Clenbuterol is one of the earliest drugs to be evaluated for use in RAO-affected horses. Because its bioavailability is greater than 90%, clenbuterol can be given orally. When the drug is administered at a dose of 1.6 µg/kg of body weight twice per day (bid), there is a significant improvement in the clinical signs of horses with RAO.[817] However, the effective dose of clenbuterol may vary among horses: Traub-Dargatz and colleagues[818] found that 400 µg of oral clenbuterol hydrochloride administered twice daily failed to improve the severity of clinical signs, the BALF or tracheal

cytologies, or the arterial blood gases in affected horses. During the treatment, horses were maintained outside but still fed hay. It is likely that 1 µg/kg was too low a dose for horses continuously exposed to hay dust. Based on the study of Erichsen and colleagues,[817] it has been recommended to increase the dose of clenbuterol if clinical improvement is not observed with 3 days of initiating treatment (e.g., 2.4 µg/kg for 3 days, 3.2 µg/kg for 3 days). Adverse side effects—anxiety, shivering, sweating, and tachycardia—occur at higher dosages but appear to be minimized when clenbuterol is increased in a stepwise manner. Erichsen reported that side effects developed in <7% of the cases when clenbuterol was administered at 3.2 µg/kg using an incremental approach. In addition to its bronchodilatory effect, clenbuterol also exerts an antiinflammatory effect. When administered intravenously (0.75 µg/kg bid) to RAO-susceptible horses before hay dust exposure, there is a significant attenuation of the BALF neutrophilia, the ΔP_{Plmax}, and the transcription of the proinflammatory genes, TNF-α and IL-1.[819]

Other β_2-agonists have been administered as aerosolized drugs to RAO-affected horses. Inhalation therapy has increased in popularity for the treatment of these cases because it allows direct delivery of the drug to the respiratory tract, minimizing the total amount of drug needed to be delivered as well as the prevalence of unfavorable systemic effects. In most instances, inhalation therapy can be performed by the client. Aerosolized drug is delivered by attaching the metered dose inhaler (MDI) to a mask (Aeromask, Trudell Medical, Inc.) or other drug delivery system (Equine haler, Equine Health Care, Inc.). Both systems contain spacers to optimize the drug particle size that is inhaled (larger sized particles drop out) and deposited in the lower respiratory tract. The inhaled rapidly acting β_2-agonists pirbuterol, albuterol sulfate, and fenoterol improve pulmonary function by 60% to 70% in RAO-affected horses for approximately 1 to 3 hours, necessitating frequent administration of the drugs.[820–822] They are poorly absorbed, so systemic effects are uncommon. The recommended dose of albuterol is 600 to 720 µg q4-6h, that of pirbuterol is 16 µg/kg q4-6h, and that of fenoterol is 2 mg q4-8h. More frequent administration may be necessary in some horses. Recently the efficacy of a longer-acting β_2-agonist, salmeterol, was evaluated in RAO-affected horses.[823] Clinical improvement developed within 2 hours of administration, but significant changes in pulmonary resistance lasted for only 6 hours, necessitating repeated administration every 6 to 8 hours.[823]

The PDE inhibitors are the third class of bronchodilators that have been used in horses. These drugs inhibit the breakdown of intracellular cAMP, thus maintaining smooth muscle relaxation. Because cAMP facilitates the proinflammatory effects of certain cytokines, the PDE inhibitors exert antiinflammatory properties.[824] Examples of PDE inhibitors are aminophylline, pentoxifylline, and the recently studied PDE-4 inhibitor L-826, 141. The clinical efficacy of aminophylline (the soluble salt of theophylline) was evaluated by Pearson and Riebold in their study of 18 clinical cases of RAO. They found that when the drug was administered at 12 mg/kg IV in 1 L of 5% dextrose to achieve blood levels of 10 µg/mL, there was an improvement in the clinical signs in 50% of the cases and a 41% reduction in the ΔP_{Plmax}. Horses also became hyperesthetic and hyperexcitable and trembled.[812] Because of the narrow therapeutic range—pharmacologic benefits are achieved at serum concentrations of 10 µg/mL, and toxicities develop at 15 µg/mL—and because of erratic drug absorption after oral administration, aminophylline is not routinely used for the treatment of RAO. However, pentoxifylline, another methylxanthine derivative and PDE inhibitor, is well absorbed after oral administration (16 g bid). Pentoxifylline improves pulmonary function test results (effects are similar to those produced with atropine) and lacks adverse side effects. However, at a dose of 16 g PO bid it lacks discernible antiinflammatory effects: BALF neutrophilia is not improved.[825] Another PDE inhibitor (L-826,141) that was evaluated in RAO-affected horses failed to improve either lung mechanics or airway inflammation.[826]

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31.26.7.3 ANTIINFLAMMATORY DRUGS

Corticosteroids are efficacious in the treatment of RAO, whereas NSAIDs have not proven to be beneficial.[729] Yet, oral prednisone also does not improve the clinical signs, the BALF cytologic alterations, or the pulmonary function test results in RAO-affected horses.[807,817,827] Its therapeutic failure is attributed to its poor absorption and the lack of conversion to the active metabolite, prednisolone.[828] In contrast, both the liquid and tablet forms of prednisolone are rapidly absorbed from the equine GI tract. The bioavailability is approximately 50%, peak concentrations of prednisolone are detected 45 minutes postadministration, and the pharmacologic effects (based on changes in serum cortisol levels) last for 8 hours.[828] Nevertheless, although oral prednisolone (2.2 mg/kg PO once per day [sid]) is routinely prescribed for the treatment of RAO, its efficacy and its duration of effect in improving pulmonary function test results and in resolving airway inflammation have not been demonstrated.

In contrast, the beneficial effects of dexamethasone in the treatment of RAO-affected horses have been investigated by several different research groups.[828–831] Within 2 hours of its IV administration to RAO-affected horses (0.1 mg/kg) there is a 37% decrease in ΔP_{plmax} that is further reduced 59% by 4 hours posttreatment.[828] Oral administration of the IV formulation of dexamethasone (0.164 mg/kg sid) produces a significant improvement in lung function parameters within 6 hours of treatment, with peak effects occurring 24 hours later.[828] For horses that are maintained in dusty environments during a 10-day treatment period, IV dexamethasone (0.1 mg/kg sid) or dexamethasone isonicotinate (0.04 mg/kg IM every 3 days for three treatments) improves pulmonary function within 3 days of initiating therapy[827] and reduces airway inflammation (BALF neutrophilia) within 10 days of treatment.[830] As might be predicted, a single dose of dexamethasone isonicotinate (0.06 mg/kg IM) administered to RAO-affected horses maintained in a dusty environment fails to provide discernible improvements in the clinical score, the pulmonary function test, the BALF cytologies, or the activities of the transcription factors NF-κB or AP-1 evaluated 10 days posttreatment.[831]

The therapeutic efficacy of two other parenteral glucocorticoids, triamcinolone acetonide and isoflupredone, has also been evaluated in RAO-affected horses maintained in a dusty environment.[832,833] A single IM dose of triamcinolone acetonide (0.09 mg/kg) markedly improved lung mechanics evaluated 7 and 14 days posttreatment, and this effect lasted for 4 weeks. Cytologic changes were also evaluated 14 days posttreatment and demonstrated a reduction in airway neutrophilia (neutrophil percentages decreased from 62% to 32%), but this improvement was not statistically significant.[832] Adverse effects of triamcinolone administration were not reported. In another study, RAO-affected horses received isoflupredone acetate for 14 days (0.03 mg/kg IM sid) while being maintained in a dusty environment. Significant increases in C_{dyn} and reductions in R_L and P_{plmax} occurred within 3 days of initiation of the treatment,[833] and the beneficial effects continued 7 days beyond the cessation of drug therapy. The only adverse effect noted was the development of hypokalemia.

The effectiveness of a prolonged course of inhaled fluticasone on pulmonary function, BALF cytologies, and BAL cell gene expression was examined by Giguère and colleagues.[710] RAO-affected horses that received 2 mg of fluticasone propionate bid for 21 days while still being fed hay demonstrated marked (and significant) improvements in P_{plmax}, C_{dyn}, and R_L by day 21 of the treatment period. Furthermore, BALF neutrophil counts became normal and IL-8 copy numbers in the BALF cell were reduced to levels equivalent to those found during remission.[710] Fluticasone is approximately 18 times more potent than beclomethasone

dipropionate (which is no longer available in the United States). Nasal or oral administration of fluticasone has no effect on circulating glucocorticoids levels, suggesting that the bioavailability across nasal and intestinal epithelium is poor.[834]

Inhaled steroids are often used in conjunction with inhaled bronchodilators for maximal therapeutic effects. When separate formulations are used, it is recommended that the bronchodilator be administered first so as to improve subsequent glucocorticoid deposition in the peripheral airways.[835] When treating horses with glucocorticoids, adrenal gland atrophy, immunosuppression, and precipitation of laminitis remain the main concerns of many clinicians. All of the previously discussed parenteral and inhaled glucocorticoids reduce endogenous serum cortisol levels. However, despite prolonged treatment protocols with glucocorticoids, adrenal gland responsiveness to adrenocorticotropic hormone (ACTH) administration remains.[832,833,836] It is interesting to note that none of the studies cited examined the development of laminitis, secondary infections, or gastritis or gastric ulcers. In my clinical and research experience, gastric ulceration is a problem in RAO-affected horses that are receiving long-term dexamethasone therapy while being fed pelleted rations. Affected horses respond to gastroprotectants.

31.26.7.4 OTHER THERAPIES

In horses that develop respiratory distress because of the bronchospasm and airway inflammation, additional therapies are required. Administering nasal oxygen at flow rates as low as 5 L/min improves arterial oxygen tensions by as much as 30 mm Hg in some severely affected horses.[837] As the total nasal oxygen flow increases, so too will the mean arterial oxygen tension, although not to the same degree that occurs in healthy horses. Flow rates of 30 L/min (delivered by 2 nasal cannulae at 15 L/min) are associated with coughing and gagging in the horse. Nasal oxygen supplementation does not reduce breathing frequency, suggesting that stimulation of vagally mediated afferents—perhaps responding to inflammatory mediators—is responsible for the tachypnea.

Furosemide (1 mg/kg IV or nebulized) provides beneficial effects to RAO-affected horses within 20 minutes of its administration, decreasing R_L and increasing C_{dyn} without affecting PaO_2.[838] The beneficial effects appear to be mediated by prostaglandin E_2, derived from either the renal or airway epithelium, which promotes smooth muscle relaxation. Prior treatment with the cyclooxygenase inhibitor flunixin meglumine prevents the furosemide-induced bronchoconstriction.[839]

Other therapies that have been evaluated and found not to be efficacious in the treatment of RAO-affected horses include a single acupuncture treatment,[840] the oral administration of an herbal preparation containing thyme and primula,[841] and the rapid IV administration of 30 L of isotonic saline.[842]

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31.26.8 Prognosis

RAO-prone horses are likely to develop acute exacerbations of the disease when husbandry practices lapse or when weather conditions become adverse. Horses do not “outgrow” the disorder, and, in fact, some clinicians believe that the inflammation becomes more difficult to manage as the horse ages. The basis for the lack of clinical response is unknown but may be the result of lung remodeling—development of fibromuscular hyperplasia in the alveolar septa,[769] excessive smooth muscle hyperplasia,[800] bronchiectasis,[767] or potential downregulation of the glucocorticoid receptor.

If proper environmental management changes are implemented and if the appropriate therapy is initiated, then clinical remission occurs in most cases. In a follow-up survey conducted by Naylor of RAO-affected horses that had been examined and treated at a referral center 2 to 4 years previously, it was found that 20% of the original cases (3 of 15) had been euthanized, that 33% were still receiving bronchodilators on an as-needed basis, and that the athleticism had not decreased in 92% of the horses.[756] Similarly, in a follow-up survey conducted by Aviza and colleagues,[757] 13% of the horses that had been diagnosed with RAO 3 to 4 years earlier had been euthanized. However, in contrast to Naylor's findings, Aviza noted that more than 50% of the respondents in that survey stated that the athletic performance of the horse had been compromised by the disease. Perhaps this difference between the two surveys simply reflected a failure of the owners to comply with environmental management recommendations. When queried about the husbandry practices, 77% of the respondents still stabled the horse for part of the day, and 84% still fed dry hay.[757]

Because the effects of repetitive episodes on the development of irreversible changes in lung structure have yet to be determined, clients should be encouraged to implement effective husbandry changes that minimize the recurrences of RAO.

31.27 INFLAMMATORY AIRWAY DISEASE IN THE HORSE

MELISSA MAZAN

31.27.1 What Is Inflammatory Airway Disease?

IAD, small airway inflammatory disease, small airway disease, allergic airway disease—these names are often used interchangeably, but the once-fluid definition of IAD is slowly taking form. Although low-grade inflammation of the small airways is recognized as a common cause of poor performance in young to middle-aged, athletic horses, it is only recently that the clear distinction has been made between heaves, or RAO, and IAD. Workers in the field continue to debate whether IAD is a discrete disease entity[843] or whether it is merely a part of the continuum of airway inflammation that if left untreated will progress inexorably to the more well-characterized syndrome of RAO.[844] Horses with IAD are generally young, although middle-aged horses may also be affected[845]; have impaired performance that may go unnoticed at rest or during light work[846–848]; have mild to moderate airway inflammation that may involve neutrophils,[848,849] mast cells,[846,850,851] eosinophils,[844] or lymphocytes[848]; have variable clinical signs, including cough, nasal discharge, and abnormal lung sounds[844,851,852]; may have endoscopic evidence of tracheobronchial mucus accumulation[844,851,853]; and may have normal lung function at rest but show evidence of airway hyperresponsiveness on exposure to nonspecific agents such as histamine[855] or evidence of low limitations on forced expiratory maneuvers.[856] These observations were confirmed by a consensus agreed on in October 2002,[857] which also stated that the clinical picture of horses with IAD includes poor performance or exercise intolerance, coughing, and excessive tracheal mucus—although not all of these need be present—and nonseptic inflammation as detected by bronchoalveolar lavage cytology. In addition, these horses may have lung dysfunction as evidenced by airway obstruction, airway hyperresponsiveness, or abnormal blood gas exchange. This definition specifically excludes horses that appear systemically sick or that have overt evidence of respiratory dysfunction, such as flaring nostrils or excessive thoracic or obvious abdominal breathing efforts.

The prevalence of IAD is somewhat of a guessing game. One study involving 965 standardbreds in active racing founding that 22% had evidence of mucopus at the trachea or bronchial bifurcation when examined

endoscopically, although these were diagnosed as horses with COPD; undoubtedly these horses properly belong in the IAD group.[854] Similarly, 27% of actively racing thoroughbreds in one study had IAD.[858] A remarkable 55% of 2-year-old thoroughbreds in training could be classified as having lower airway disease on the basis of finding mucus in the trachea on endoscopy and inflammation on examination of tracheal aspirate fluid,[859] and abattoir studies have shown up to 37% of horses with histopathologic evidence of airway inflammation.[860] Because a standard definition of IAD has only recently been agreed on, the prevalence of IAD has varied according to the individual researcher's case definition. Nonseptic airway inflammation, regardless of whether it causes overt signs of respiratory disease, appears to be very common in performance horses. For the purpose of this discussion, we will adhere to the definitions of IAD and RAO as developed by the International Workshop on Equine Chronic Airway Disease,[843] the Havemeyer Workshop,[857] and the recent American College of Veterinary Internal Medicine (ACVIM) consensus statement on IAD. With RAO, horses have demonstrable lower airway obstruction, characterized by peak pleural pressures of at least 15 cm H_2O, induced by an environmental challenge of moldy hay, largely reversible by use of a bronchodilator or return to nonchallenge environment, and accompanied by an increase in BALF neutrophils during challenge. In contrast, IAD refers to a nonseptic airway disease in athletic horses that does not have a clearly defined allergic cause. When we look at the data, we find that many studies involving horses with what was traditionally known as COPD and is now more properly referred to as RAO, or heaves, did not conform with these guidelines, and many of the horses would more properly be characterized as having IAD.

31.27.2 Clinical Findings

Although most investigators agree that IAD is a disease of younger horses expected to do athletic work, and as such is distinct from the picture of the dyspneic horses with overt RAO, there remains a plethora of clinical signs and case definitions for IAD. One of the most common findings in IAD is exercise intolerance, with or without overt signs of respiratory disease. Of 25 horses referred either for routine physical examination or poor performance, and without any clinical signs or history of respiratory disease, 76% had evidence of airway inflammation according to an inflammation scoring system based on endoscopy and tracheal wash findings.[861] Subclinical airway disease may result simply in mild abnormalities on auscultation and endoscopy, and occasional in coughing.[862] Signs such as nostril flaring and excessive abdominal effort at rest, however mild, are usually associated with the true RAO horses, as clinical signs that can be reliably detected using clinical scoring systems usually are accompanied by significant mechanical dysfunction of the respiratory system.[863] The prevalence of cough in IAD horses is hard to estimate, as many studies use the presence of cough as an inclusion criterion.[851,856,864] Other studies have shown that cough may be seen less than 16% to 50% of the time.[848,864,865] On endoscopic examination, excessive airway mucus is often seen, ranging from multiple specks to streams of mucus.[866] Other clinical signs that are frequently noticed include prolonged respiratory recovery,[845] respiratory embarrassment at exercise,[867] worsening of signs during hot, humid weather, and inability to perform work during collection. Racehorses with IAD are typically described as fading during the last quarter of the race (personal observation).

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How does IAD affect performance? The answer depends on the use of the horse and the expectations of the owner. A practitioner with a primarily pleasure-horse practice or with show-hunter clientele might report a very low incidence of IAD in younger horses, primarily because the level of exercise in these horses is not likely to force a diagnosis through signs of exercise intolerance. A racetrack practitioner, on the other hand, would be far more likely to detect exercise intolerance resulting from lower airway disease in young horses because the level of expected athletic output is much higher and the horses have a greater likelihood of being examined

endoscopically. As might be expected, cough is more common in sport horses than in racehorses, as is an elevated respiratory rate, reflecting the generally earlier diagnosis in racehorses.[865] Indeed, racehorses with excessive tracheal mucus performed at a lower level than those with no mucus found on endoscopy.[854,867] Persson, looking at standardbred trotters and saddle horses, found that low-grade nonseptic airway inflammation does have a negative impact on ventilatory capacity, but that this is more pronounced in racehorses.[868] Moreover, using bronchiolar biopsy, this group also demonstrated that oxygen uptake and pulmonary ventilation correlated inversely with the morphologic grade of small airway disease and the height of the bronchiolar epithelium—the last finding suggesting that the extent of obstruction may determine the extent of exercise impairment. Racehorses with IAD have impaired gas exchange during exercise.[847,869] However, other studies have found that horses with obvious evidence of airway inflammation do not necessarily have a history of exercise intolerance.[858,870] This may reflect the difficulty of diagnosing low-grade respiratory impairment and the trainer's failure to recognize poorer performance than nature intended, however, rather than the benign nature of the underlying disease.

31.27.3 Diagnosis

31.27.3.1 BRONCHOALVEOLAR LAVAGE

Varying levels of specificity are used when documenting the presence of airway inflammation. The least specific is the documentation of mucus in the trachea; however, it is the method that best lends itself to large studies in the field.[854,867] Visualization of mucus in the trachea gives little information, however, as to the nature and the exact origin of the inflammation. Many workers have used and continue to use tracheal aspirate cytology to describe the nature of inflammation in IAD. Although tracheal aspiration can be used to explore the presence of inflammation and has been used to document neutrophilia, mastocytosis, and eosinophilia in young performance horses,[858,871] the question of the nature and exact origin again presents itself. Studies have shown poor correlation between tracheal aspiration and BAL cytology in horses,[872,873] with tracheal aspiration harvesting primarily neutrophils and epithelial cells, whereas BAL yields primarily alveolar macrophages and lymphocytes in normal horses. Moreover, there is no evidence of correlation between tracheal wash findings and performance. Consequently, to avoid the problem of neutrophil count sensitivity to the collection method, the recent International Workshop on Equine Chronic Airway Disease[843] recommended use of BAL to characterize horses with chronic airway disease; this recommendation was seconded by the Havemeyer Workshop on IAD.[857]

Different pictures of inflammation emerge from various BAL studies, leading to speculation that different genetic predispositions and environmental exposures are important to the inflammatory phenotype. In comparison with healthy horses, BAL cytology in horses with IAD has shown, variably, both neutrophilia and lymphocytosis,[848,856] neutrophilia and lymphopenia,[874] neutrophilia and mastocytosis,[845,846,851] and eosinophilia.[845] In general, horses with IAD have airway inflammation that may involve increases in nucleated cells or may also involve lymphocytosis. This is distinguished from RAO by the relatively low percentage of abnormal cells in IAD; whereas horses with RAO may exhibit almost entirely neutrophils in the BALF, horses with IAD seldom have greater than 2–15% neutrophils. The Havemeyer consensus has established that horses with IAD will have airway inflammation characterized by BAL cytology with any one of the following: mast cells >2%; PMNs >5%; or eosinophils >1%.

31.27.3.2

HISTOPATHOLOGY

Histopathologic studies of IAD are sparse, but useful information can be teased from COPD studies that on inspection included horses with what we would more appropriately term IAD. Bronchiolar biopsies of athletic young horses with lower airway inflammation have shown inflammatory mucosal cellular infiltrates and luminal exudates, bronchiolar hyperplasia, and goblet cell metaplasia.[868] It is interesting to note that 80% of supposedly normal horses had minimal evidence of peribronchiolitis—raising the question, of course, of what constitutes normal. O'Callaghan, while directing his concern to EIPH, nevertheless found plentiful evidence of multifocal, small airway—centered disease on postmortem examination of young racehorses. These findings included thickened walls caused by increased quantities of mucosal and peribronchiolar connective tissue, mononuclear bronchiolar cuffs, and extension of nonciliated bronchiolar epithelial cells into alveolar ducts.[875] Lakritz,[876] looking at lung tissue of clinically normal, young thoroughbred horses in training, found evidence of increased collagen, disruption of the epithelial basement membrane, and duplication of the epithelial basement membranes, suggesting previous airway inflammation and epithelial injury, which correlate with an increased interstitial pattern on radiographs. An ultrastructural study of young horses with “mild COPD” in one study found a decreased number of typical Clara cell granules and goblet cell metaplasia before the bronchioles began to show signs of inflammation typical of RAO.[877] Although the authors state that there was good correlation between histopathology and the results of a battery of pulmonary function tests, auscultation, bronchoscopy, blood gas analysis, and BAL in these horses, it is a lasting disappointment that the results of the ancillary testing remain unpublished. These data in sum certainly suggest that the histopathologic lesion of IAD is not only local bronchiolar inflammation, but also remodeling and thickening of the bronchioles themselves, which lends itself to at least low-grade airway obstruction.

31.27.3.3

LUNG FUNCTION TESTING

The esophageal balloon and pneumotach method for measuring lung function tends not to detect airway obstruction even in horses with RAO in remission.[878] However, use of the forced oscillatory technique[879] and forced expiratory maneuvers[856] has shown the existence of low-grade obstruction of the small airways of some horses with IAD. The mechanical behavior of the respiratory system has been shown to differ with sampling frequencies in asthmatic humans,[880] and a pattern of decreasing respiratory system resistance (RSR) with increasing frequency has been termed *negative frequency dependence of resistance* and has been interpreted as evidence of underlying small airway obstruction despite baseline measurements within the expected range. Similarly, horses with IAD as a group have significantly higher values for respiratory system resistance at the lower frequencies (1 to 3 Hz) and mild frequency dependence of resistance compared with controls,[879] although the baseline measurement of RSR may still frequently fall within the normal range. A study finding that lower oxygen uptake capacity and tidal volume correlated to a reduced diameter of the bronchiolar lumen owing to epithelial hyperplasia is strongly supportive of the existence of airway obstruction in IAD.[868] Consequently, without dynamic, frequency-dependent tests of lung function, forced maneuvers, or bronchoprovocation, it seems that we are simply failing to document a common feature of small airway obstruction in horse with IAD because our testing devices are not sufficiently sensitive to these changes.

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31.27.3.4 AIRWAY RESPONSIVENESS

Horses with clinical signs compatible with IAD also exhibit signs of airway hyperresponsiveness when they are exposed to nonspecific agents such as histamine aerosol.[845,855,881,882] The basis for airway hyperresponsiveness remains hotly debated among pulmonary physiologists. It is likely a multifactorial phenomenon that has been associated with airway wall thickening undetectable by conventional lung function testing,[883] airway inflammation, and autonomic nervous system dysfunction.[843] There is a paucity of information concerning the mediators of airway hyperresponsiveness in horses with IAD, although the presence of elevated levels of leukotriene C4 levels has been documented.[881] In our laboratory, horses with a clinical history and signs compatible with IAD have significantly greater airway reactivity than controls, although some control horses display airway hyperresponsiveness as well.[879] This nonspecific airway hyperresponsiveness has been seen in humans and is associated with a greater risk of eventual development of asthma.[884] Although nonspecific airway hyperresponsiveness has been noted both in adult horses without signs of respiratory disease and in foals,[885] the significance of this finding remains unclear.

31.27.3.5 RADIOGRAPHY

Although radiography can be useful in helping to exclude septic causes of lower respiratory disease, such as pneumonia, lung abscess, or pleuropneumonia, its sensitivity in IAD is too low for it to be useful for identification of this disease. Moreover, no correlation exists among thoracic radiographs, airway hyperresponsiveness, and BAL cytology.[886] However, the more frequent finding of a bronchial pattern on thoracic radiographs supports the existence of airway obstruction in these horses.

31.27.4 Etiology

No single cause of IAD has been identified, although there has been plentiful speculation about the role of environment, viral disease, bacterial infection, air pollution, and genetic predisposition. Although horses with IAD do not seem to experience bouts of overt airway obstruction on exposure to an allergenic environment, organic dust associated with stabling likely contributes to the initial inflammation. Sweeney noted that the racehorses in her study lived in conditions of poor ventilation, and speculated that covert IAD may be instigated by the organic dusts, especially mold, in hay.[858] Others have noted that there is more mucopus in the tracheas of horses kept in poorly ventilated conditions,[887] and in one study thoroughbred racehorses in training, housed on straw, were found to be twice as likely to suffer from lower airway disease as those kept on shredded paper.[866] More recently, Holcombe and co-workers[887] showed that yearlings had a significantly higher number and percentage of neutrophils (PMNs as high as 18%) in BALF when they were stabled versus when they were at pasture. Although none of these horses had any clinical signs of respiratory disease or evidence of exercise intolerance, they were not in work, and subtle signs of performance impairment could easily have gone undetected. Dust levels in the horse's breathing zone can be as high as 25 mg/m^3—a level that would be considered unacceptable in any human workplace[888]—which can go far to explain the development of airway neutrophilia as a nonspecific response to high levels of particulates.[889] It is also likely that increased levels of endotoxin in hay and grain dust contribute to the development of airway neutrophilia.[890–892]

Although previous viral disease is commonly invoked as a predisposing factor in the development of IAD, little evidence exists to implicate viral disease. As in human asthmatics, viral respiratory disease has been shown to cause airway hyperresponsiveness for a period of time after infection,[885] perhaps due to denuding of the respiratory epithelium. However, no known virus was associated with poor performance and respiratory disease in 68% of cases in the United Kingdom.[893]

Recently there has been considerable speculation as to the role of bacterial infection in IAD, particularly in young racehorses. In several studies there was a strong relationship between inflammation of the lower respiratory tract and the presence of streptococcal species; horses with greater evidence of airway inflammation on tracheal aspiration and endoscopy had higher mean bacterial counts in tracheal aspirate,[866] and horses with bacteria found in the tracheal aspirate had a greater tendency to cough.[859] However, it is important to remember that association is not necessarily causation, and increased numbers of bacteria may reflect impaired airway clearance rather than a causative role for bacteria. The role of bacterial and viral infection in IAD remains unclear at this time.

Horses sample the ambient air on a continual basis: it seems logical that air pollution might contribute to the development of IAD. In one study clinically normal horses exposed to ozone had a significant increase in the glutathione redox ratio as well as total iron levels in the pulmonary epithelial lining fluid—both markers of exposure to oxidizing agents—and there was a strong correlation between airway inflammation score and the glutathione redox ratio in horses examined for poor performance but without overt airway disease.[861] In contrast, horses living in urban environments have been shown to have less airway reactivity, although greater levels of iron in the BALF, than do horses living in rural environments.[894]

Although heaves has been shown to be at least partially allergen mediated, in which horses manifest a Th2-type cytokine response,[895] and although environmental challenge can produce a consistent exacerbation of disease,[891] there is no such convincing evidence of an allergic response in horses with IAD. However, the presence of elevated numbers of mast cells in BALF of horses with poor performance,[850] the association of BAL mastocytosis with airway hyperresponsiveness,[846,896] and IHC studies showing more IgA-containing cells and occasionally increased numbers of IgM- and IgG-containing cells are suggestive of a degree of allergic response and a heightened immune response. It is most likely that multiple factors contribute to the development of IAD in individual horses; a critical level of risk factors or exposure is probably necessary for the disease to manifest itself.

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31.27.5 Differential Diagnoses

The diagnosis of IAD often requires the exclusion of other diseases that may have a similar clinical picture. Whereas horses with RAO (heaves) or summer pasture—associated RAO (SPARAO) in remission may be very difficult to distinguish from horses with IAD, horses with RAO or SPRAO have a history of episodes of obvious breathing difficulty associated with exposure to either moldy hay or summer pasture. Upper airway disease, such as sinus infection or guttural pouch infection, may cause cough and nasal discharge, and both static and dynamic upper airway obstructions may cause poor performance and poor recovery from exercise. These may be largely ruled out by endoscopy. Horses with pneumonia, bronchopneumonia, or lung abscess commonly have abnormalities suggesting systemic disease, such as abnormal findings on CBC, recent history of fever, weight loss, or inappetence. In these cases tracheal wash can be very helpful in determining a septic cause of disease. Thoracic radiographs or ultrasound will also aid in the detection of these septic respiratory diseases. EIPH may

be seen in conjunction with IAD, but the presence of epistaxis, blood on endoscopy of the trachea, or red cells or hemosiderophages on BAL confirm the diagnosis of EIPH. Overt viral respiratory disease is difficult to confuse with IAD, as it usually manifests with fever and malaise, but horses with viral respiratory disease may exhibit prolonged cough and airway hyperresponsiveness for weeks to months after resolution of primary disease.

31.27.6 Therapy

There is remarkably little evidence-based support for any particular therapy in treating IAD. However, the mainstay of treatment has become a combination of environmental remediation, corticosteroid therapy, and bronchodilators.

31.27.6.1 ENVIRONMENTAL REMEDIATION

The barn environment is a hotbed of particulate matter, respirable endotoxin, molds, and volatile gases such as ammonia. The worst offenders appear to be hay and straw. A study looking at different management systems showed that when hay and straw bedding were replaced by pelleted feed and wood shavings, the respirable particulate levels were remarkably reduced.[888] Further improvements can be made by using cardboard bedding to reduce dust and mold levels.[897] Indoor arenas present another high dust challenge to the horse, with respirable particulate levels 20 times the level recognized to cause respiratory dysfunction in humans.[898] Other fairly commonsense strategies can be used. I make the following recommendations to owners in addition to the suggestion to change to low-dust feeds and beddings:

- Sprinkle aisles with water before sweeping.
- Avoid storing hay overhead. If unavoidable, lay a tarp under the hay to avoid dust raining down on the horses.
- Use a humectant or hygroscopic agent to reduce dust in the indoor and outdoor arenas.
- Remove horses from the barn while cleaning stalls or moving hay.
- Do not use blowers to clean aisles.
- Wet hay before feeding or use Dengie or other baked hay products.
- Remove cobwebs and other dust collectors routinely.

It is important to note that a recent study demonstrated that environmental control was by far the most important means of treating airway inflammation and dysfunction in horses with heaves, a more severe disease than IAD.[899] It is logical, therefore, to suppose that environmental management is equally important in the treatment of IAD.

31.27.6.2 CORTICOSTEROID THERAPY

Either parenteral or inhaled corticosteroids form the mainstay of drug therapy for IAD. Although the utility of corticosteroids for preventing or ameliorating airway remodeling in human asthma is debated,[900] corticosteroids have recently been demonstrated to prevent airway smooth muscle thickening in mice with

experimental asthma.[901] The degree of efficacy in decreasing BAL neutrophilia is not completely known, with some studies showing obvious benefit for dexamethasone in improving clinical signs and lung function and reducing BAL neutrophilia,[902] whereas others show primarily improvement in lung function with little effect on BAL cytology.[899,903] Corticosteroid treatment certainly causes adrenocortical dysfunction, but this is less pronounced with inhaled therapy versus systemic.[902] Although concerns about precipitating laminitis with corticosteroid therapy are frequently expressed, the actual risk of laminitis with corticosteroid therapy is completely unknown. Prednisone has been used in the past, but studies have shown lack of effect in horses with RAO.[904] In our clinic we frequently treat with an initial course of parenteral corticosteroids, typically a 4-week decreasing course of prednisolone followed by inhaled corticosteroids.

31.27.6.3 BRONCHODILATOR THERAPY

Bronchodilators, especially the inhaled form, appear to be efficacious in treating IAD in conjunction with corticosteroids. The most commonly used bronchodilators in IAD include aerosolized β-adrenergics, such as albuterol, and aerosolized parasympatholytics, such as ipratropium. Despite very legitimate concerns about development of tolerance to β-adrenergic drugs, a small study has shown that a chronic (2-week) course of aerosolized albuterol did not increase airway responsiveness to histamine in horses with preexistent airway hyperresponsiveness.[905] β-Adrenergic drugs such as albuterol also increase mucociliary transport. The use of systemic β-adrenergics such as clenbuterol is not advised, as the extent of bronchoconstriction in IAD does not warrant risking the adverse effect of cardiovascular remodeling, which has been shown to occur in horses.[906]

31.27.6.4 MAST CELL INHIBITORS

Sodium cromoglycate can be efficacious in treating known mast cell—mediated IAD[850] but will not be of use for treating the majority of horses with neutrophil-mediated disease. However, it requires considerable owner compliance, as the maximum response to this drug occurs at 1 to 2 weeks after beginning treatment.

31.27.6.5 AEROSOLIZED THERAPY

Aerosolized therapy using a combination of inhaled corticosteroids and bronchodilators is well established clinically in the treatment of IAD; however, there are no clinical trials establishing the efficacy of these drugs. When using inhaled drugs, we use a spacer and mask in order to improve delivery of the drug. Regardless of the type of mask and spacer device used, actual delivery of particles to the lower airways is poor in horses, as indeed it is even in humans, and the least efficacious means of delivering aerosolized drugs is by nebulization.[907–910] Unfortunately, strategies that we know improve lung deposition of aerosolized drugs in humans, such as slow deep breathing and breath holding, are not practical in horses. Devices currently on the market include the Aeromask and the Equine Haler. Individual horse and owner preference determines which device should be used. Inhaled corticosteroids commonly used in the treatment of IAD include beclomethasone and fluticasone.

Although there are no reported clinical trials using corticosteroids in horses with IAD, horses with RAO treated with 3750 μg of beclomethasone dipropionate twice daily using the Aeromask had improvement in both clinical signs and in lung function.[911] Smaller doses (500 to 1500 μg twice daily) administered with a device that is no longer on the market were shown to be efficacious in horses with heaves.[902] I commonly use small doses (500 to 1000 μg twice daily) using the Aeromask with good clinical effect in horses with IAD.

Fluticasone is a more potent corticosteroid than beclomethasone and has been shown to be efficacious when administered in conjunction with the Aeromask in treating horses with heaves, as well, using doses of 2000 µg twice daily. Unlike beclomethasone, in this study fluticasone did not cause adrenocortical dysfunction.[912] I use a decreasing-dose regimen, starting at 1500 to 2000 µg twice daily, working down to 1000 µg once daily or every other day. The lowest dose is arrived at over a 3- to 4-week period. Use of a short-acting bronchodilator, such as inhaled albuterol, 5 to 15 minutes before treatment with inhaled corticosteroid may help to increase deposition of the latter by fully opening the small airways. It is important that the owner understand that even with the higher doses of inhaled corticosteroid it may require 1 to 2 months for the best therapeutic effects to be achieved.

The most commonly used inhaled bronchodilator is albuterol, a β_2-specific adrenergic drug. The onset of effect with albuterol is quite rapid, with maximum bronchodilation being seen within 15 minutes. However, it is important to note that the maximum effect lasts in some horses for only an hour, and there are side effects with higher doses of drug, even in the inhaled form, such as anxiety, nervousness, trembling, and tachycardia. There is no evidence to suggest that the oral form of albuterol is even absorbed in the horse, and it is not suggested as appropriate therapy. Longer-acting β_2-adrenergic agonists, such as salmeterol and formoterol, can also be used, with bronchodilation lasting 6 to 8 hours. Parasympatholytic drugs such as ipratropium have a slower onset of action but longer duration than albuterol—at least 6 hours—and lack the severe side effects of parenteral use of drugs such as atropine. It is important to remember that these bronchodilators are symptomatic drugs only; they do not treat the underlying inflammation and therefore are unsuitable for single-drug therapy.

Mast cell inhibitors that can be administered by MDI include Intal (cromolyn) and Tilade (nedocromil sodium). They are discussed in earlier sections.

In summary, IAD is a disease characterized by nonseptic inflammation, visible on BAL cytology as excessive neutrophils, mast cells, or eosinophils, and involving low-grade airway obstruction and airway hyperresponsiveness. Clinical signs include variable cough, nasal discharge, and poor performance. Excessive amounts of mucus may also be visualized in the trachea using endoscopy. The cause of IAD is unknown, but the disease is probably best avoided by achieving a low-dust and low-endotoxin environment. Treatment logically begins with environmental remediation and is supplemented by antiinflammatory drug therapy using systemic or inhaled corticosteroids and inhaled bronchodilators. IAD that involves an excess of mast cells in the airways can be further treated with inhaled mast cell inhibitors.

31.28 TUBERCULOSIS

PEGGY S. MARSH

Tuberculosis refers to any infectious disease caused by *Mycobacterium* species and associated with the formation of focal granulomatous lesions with caseous necrosis. In humans many forms of the disease exist, with the primary site of infection most commonly being the lungs. *M. tuberculosis* is the typical causative agent in humans, whereas *Mycobacterium avium* or *Mycobacterium bovis* is usually implicated in animal cases. Tuberculosis is extremely rare in horses, especially in the United States. Most cases in horses have reported isolation of *M. avium*[913–916]; however, there are more recent reports of infection with *Mycobacterium bovis*.[917] In equine cases the organism is usually ingested, although primary respiratory infection may occur. Spread is hematogenous, and the organism frequently settles in lymph nodes and the spleen.

The most frequent presenting complaint is chronic weight loss with ensuing weakness and lethargy. Terminally ill horses with the pulmonary form are febrile and dyspneic and have a cough. Radiographic or sonographic evaluation of the thorax may be helpful in defining the pattern and distribution of lesions. Other clinical signs may be noted depending on the organ systems affected and include intestinal tract signs, hepatitis, and osteomyelitis of the cervical vertebrae, as well as guttural pouch and ocular infections.[913–917]

Diagnosis is based on presence of tubercles and isolation of the organism and probably most frequently is made after the horse's death. The intradermal skin test is not reliable in the horse because a majority of clinically normal horses may have positive test results.[918] Cytologic or histologic evaluation of a wash or aspirate of a lesion may reveal acid-fast bacilli. Biopsy of the lesion(s) is necessary for a definitive diagnosis. When tuberculosis is suspected, culture of an appropriate sample, such as a tracheal aspirate with primary pulmonary involvement, is advisable. However, this is a very slow-growing organism, and isolation may take multiple weeks. More recently PCR technology has proven a useful tool.[917]

Treatment is not usually attempted, because of public health concerns. I am unaware of any published report on treating horses with tuberculosis. If treatment is undertaken, the horse should be isolated, with precautions taken to prevent spread of disease and in consultation with the handler's physician and/or public health officials. Tuberculosis is a reportable disease in other species. Drugs used in other species (rifampin, isoniazid, and streptomycin) could be considered, but there are no guidelines for their use in horses with this condition. Isoniazid has been used in horses for other conditions at a dose of 5 to 15 mg/kg PO twice daily.[919] Although a study on rifampin pharmacokinetics in horses recommended using 10 to 25 mg/kg PO twice daily,[920] clinical results in foals with *R. equi* pneumonia suggest that 5 to 10 mg/kg PO twice daily is adequate. In humans, treatment periods are very prolonged, frequently a year or more. Because treatment is usually not a viable option in horses, prognosis is very poor.

Bacillus Calmette-Guérin (BCG) vaccine has been used in humans with potential exposure, but the benefit of its use in horses to providing increased resistance after exposure to a tuberculosis infection is unknown.

31.29 PNEUMOCONIOSIS (SILICOSIS)

PEGGY S. MARSH

Pneumoconiosis refers to lower respiratory tract disease associated with deposition of small particles (dust) within the lungs. In human medicine the majority of cases are occupation related and include coalworker's lung, silicosis, and asbestosis.[921] There are two related reports of horses with silicosis.[922,923] The majority of the horses originated from the Monterey-Carmel Peninsula in California. Silicosis is a disease caused by inhalation of crystalline silica. There are several clinical forms of silicosis in humans, including simple and complicated chronic forms as well as acute silicosis (silicoproteinosis). Silicosis has also been associated with immune system deficits, in particular alteration of cell-mediated immunity. Freshly fractured silica is more toxic to alveolar macrophages than aged silica. Crushing silica leads to the formation of reactive radials.[924] The small (0.5 to 5 mm) particles are deposited in small airways and alveoli and subsequently phagocytosed, initiating a cycle of granulomatous inflammation, oxidative stress, and apoptosis leading to chronic fibrotic interstitial disease.[921,924]

The clinical signs reported in the horses were similar to those of COPD and included weight loss, cough, exercise intolerance, and, sometimes, exercise-induced respiratory distress (sweating, nostril flaring, abducted elbows, reluctance to move, and shaking). Resting respiratory rates are often increased. Physical examination revealed a

restrictive pattern of breathing. Auscultation revealed harsh breath sounds and some wheezing, which was exacerbated by exercise.

Diagnosis was based on the presence of birefringent crystalline inclusions within pulmonary macrophages.[923] Samples were obtained via tracheal aspiration, BAL, or lung biopsy or at necropsy. In some cases repeated tracheal sampling was required. Radiographs of the thorax revealed a variety of findings including most commonly an interstitial pattern (miliary, reticulonodular, and linear) that was most severe in the caudodorsal lung fields. Other radiographic abnormalities noted were lymphadenopathy, pleural effusion or thickening, hyperinflation, and pulmonary consolidation.[923]

Gross pathologic analysis revealed interstitial granulomatous pneumonia and fibrosis. Histologic examination with both light and electron microscopy revealed peribronchitis, perivasculitis, and cellular infiltrates consisting of mostly macrophages and giant cells, with refractile inorganic dust particles noted both intracellularly and extracellularly.[922,923]

In general the horses reported to have silicosis had a poor prognosis. The original study discussed postmortem findings of nine horses.[922] In the other related paper a total of 19 horses were identified.[923] Short-term (2 to 12 months) follow-up evaluation was available in eight of these individuals, with a progressive loss of respiratory function noted in four of the cases, leading to euthanasia. Treatment consisted of environmental change and glucocorticoid therapy. Novel forms of therapy, including inhibition of inflammatory mediators as well as inhibition of apoptosis, may be seen in the future.[924]

There are no recent reports of silicosis or other forms of pneumoconiosis in the horse. However, there are reports in other domestic species in areas of environmental contamination.[925] Also, new forms of pneumoconiosis are being investigated in humans, such as World Trade Center Cough.[926] It may be prudent to keep environmental contamination in mind when investigating chronic noninfectious forms of lower respiratory tract disease in the horse.

31.30 MYCOPLASMA

PEGGY S. MARSH

Mycoplasma species are a group of bacteria that differ from other bacteria because they lack a cell wall, are much smaller than most bacteria, and need cholesterol to survive. These organisms are proven to cause respiratory disease in humans, cattle, and pigs. *M. felis* has been isolated as a pathogen causing pleuritis and pericarditis in the horse.[927–929] Experimental infection with *M. felis* in ponies induced pleuritis.[929] The relative importance of *Mycoplasma* species as a pathogen in acute respiratory disease of the horse has been debated. Several species of mycoplasma can be isolated from the respiratory tract of healthy and diseased animals, both adults and foals. A report from Australia did not yield growth of mycoplasmas in any of the samples from young racing horses with coughs.[930] However, a similar case control type study from the United Kingdom showed an association between *M. felis* and IAD in young racehorses.[931] Also, a Canadian report demonstrated growth of *M. equirhinis* and *M. felis*, along with other bacteria commonly thought of as respiratory pathogens, in horses with acute lung disease.[932] *M. felis* has been reported as a potential cause of an outbreak of acute respiratory disease in a stable of young racehorse, as well as of respiratory disease in foals.[933,934]

Clinical signs of pleuritis caused by mycoplasma infection, including fever, depression, and pleurodynia, mimic other bacterial pleural pneumonia cases. Auscultation of the thorax may reveal pleural friction rubs and dull lung sounds over the cranioventral thorax. Sonographic examination of the thorax reveals pleural effusion, often bilateral. Thoracocentesis should be performed for both diagnostic and, if necessary, therapeutic purposes. The fluid is most often an exudate, lacking any odor. Cytologic examination reveals large numbers of neutrophils within the pleural fluid.

Crucial to diagnosis of mycoplasma infection is the elimination of more common pathogens, such as streptococcal infections. Thus routine cultures for aerobic and anaerobic bacteria should be performed in any case of pleuritis. Culture for the presence of mycoplasma is difficult. Immediate centrifugation of pleural fluid is ideal, because supernatants are the preferred culture samples.[935] These samples should then be placed in mycoplasma-specific media. Seroconversion can also be an aid in diagnosis, with seroconversion occurring in a large number of the reported cases of *M. felis* infection.[927,928,933] Experimental infection revealed that once seroconversion has occurred, the organism can no longer be isolated from culture samples.[929] Seroprevalence in this country is not known.

Experimentally infected ponies recovered without treatment in one study, so the requirements of treatment specific for mycoplasma are unclear.[929] Although sensitivity testing should be performed on any isolate, *Mycoplasma* species have been found to be sensitive to gentamicin, tetracyclines, and erythromycin.[936] The role these organisms play in equine respiratory disease is still unclear, and investigation continues.

31.31 EXERCISE-INDUCED PULMONARY HEMORRHAGE

K. W. HINCHCLIFF

EIPH is a pervasive disorder of horses that perform strenuous exercise and is best recognized in thoroughbred and standardbred racehorses. The disorder is associated with reduced performance of thoroughbred racehorses, and probably in other breeds, and costs the thoroughbred and standardbred racing industries in the United States and Canada between $100,000,000 and $225,000,000 (U.S. dollars [USD]) annually.[937] The disease occurs commonly in horses but less commonly in camels, greyhounds, and, rarely, human athletes.[938–940]

31.31.1 Etiology

Epistaxis and hemorrhage into airways can occur as a result of a number of diseases, including disorders of the upper airways and lungs. Hemorrhage into trachea or bronchi can be a result of EIPH, pulmonary abscess, fungal granuloma, trauma, pneumonia, pulmonary foreign body, or hemangiosarcoma or other pulmonary neoplasia. 568
Epistaxis can be associated with all of these causes of hemorrhage into the lower airway and, in addition, 569
diseases of the upper airway including guttural pouch mycosis, ethmoidal hematoma, trauma, and neoplasia of the upper airways and associated structures. Thrombocytopenia can cause epistaxis.

The likely proximate cause of hemorrhage in horses with EIPH is rupture of alveolar capillary membranes with subsequent extravasation of blood into interstitial and alveolar spaces.[941] The source of blood in such instances is the pulmonary circulation. Bleeding from bronchial circulation during exercise has been suggested based on histologic evidence of bronchial angiogenesis in horses that have experienced previous episodes of EIPH,[942] but contribution of the bronchial circulation to EIPH has not been demonstrated. Regardless of the contribution of

bronchial circulation to blood in the airways, the likely initial lesion is in capillaries associated with the pulmonary circulation. Hemorrhage into the interstitial space and alveoli, with subsequent rostral movement of blood in the airways, results in blood in the trachea and bronchi, which in rare instances results in epistaxis.

31.31.2 Clinical Signs and Differential Diagnosis

31.31.2.1 HISTORY AND PRESENTING COMPLAINT

Poor athletic performance and epistaxis (Fig. 31-37) are the most common presenting complaints for horses with EIPH. Although poor performance may be attributable to any of a large number of causes, epistaxis associated with exercise is almost always secondary to EIPH.

Epistaxis due to EIPH occurs during or shortly after exercise and is usually first noticed at the end of a race, particularly when the horse is returned to the paddock or winner's circle and is allowed to lower its head. It is usually bilateral and resolves within hours of the end of the race. Epistaxis can occur on more than one occasion in the same horse.

Fig. 31-37 Horse with exercised-induced pulmonary hemorrhage and epistaxis.

31.31.3 EXERCISE-INDUCED PULMONARY HEMORRHAGE AND PERFORMANCE

Failure of racehorses to perform to the expected standard (poor performance) is often, accurately or not, attributed to EIPH. Many horses with poor performance have cytologic evidence of EIPH on microscopic examination of tracheobronchial aspirates or BALF or have blood evident on endoscopic examination of the tracheobronchial tree performed 30 to 90 minutes after strenuous exercise or racing.[943,944] However, it is important to recognize that EIPH is very common in racehorses and it should be considered the cause of poor performance only after other causes have been eliminated. Severe EIPH undoubtedly results in poor performance and, on rare occasions, death of thoroughbred racehorses.[945–948] A relationship between finishing position and incidence of EIPH, diagnosed by bronchoscopic examination, was not detected for 191 thoroughbred racehorses that finished in first, second, or third place.[946] Furthermore, there was no relationship between the proportion of horses with EIPH and placing (first, second, or third versus other) in another 98 horses.[947] Similarly, there was no relationship between finishing position and proportion of horses with EIPH in 191 thoroughbreds examined after racing.[948] There was no relationship between severity of EIPH, assessed on tracheobronchoscopic examination, and race performance in 258 thoroughbreds or 296 standardbred racehorses.[949] Together, these studies do not demonstrate a clear relationship between the presence of EIPH, or its severity, and race performance.

In contrast to the studies just discussed, among 452 thoroughbred horses examined after racing in Hong Kong, those finishing in the first three positions had less severe EIPH than did horses finishing in lower positions.[950] Of horses finishing in the first three places, 43.9% had evidence of EIPH on tracheobronchoscopic examination after racing, whereas 55.9% of horses finishing in fourth to fourteenth place had evidence of EIPH.

A recent study demonstrated that thoroughbred horses with EIPH racing in Victoria, Australia have impaired performance compared with unaffected horses. Horses were assessed as having no EIPH or grades 1 to 4 EIPH on the basis of endoscopic examination performed within 2 hours of racing. After statistical correction of other factors that could influence performance, there was a clear association between EIPH of >grade 1 (i.e., grades 2 to 4) and impaired performance.[951] Horses with EIPH ≤1 were 4 times more likely to win, 1.8 time more likely to finish in the top three positions, and 3 times as likely to be in the 90th percentile for earning as horses with EIPH ≥grade 2. Horses with EIPH finished further behind the winner than did horses that did not have EIPH.[951]

Results of studies in standardbred racehorses indicate either a lack of effect of EIPH on performance or an association between EIPH and superior performance. There was not a relationship between presence of EIPH and finishing position in 29 standardbred racehorses with intermittent EIPH examined on at least two occasions,[952] nor in 92 standardbred racehorses examined on one occasion.[953] However, of 965 standardbred racehorses examined after racing, those finishing first or second were 1.4 times more likely (95%, confidence interval 0.9 to 2.2) to have evidence of EIPH on tracheobronchoscopic examination than were horses that finished in the seventh or eighth position.[954]

31.31.4 Physical Examination

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Apart from epistaxis in a small proportion of affected horses, there are few abnormalities detectable on routine physical examination of horses with EIPH. Rectal temperature and heart and breathing rates may be elevated as a consequence of exercise in horses examined soon after exercise, but values of these variables in horses with EIPH at rest are not noticeably different from those in horses with no evidence of EIPH. Affected horses may

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swallow more frequently during recovery from exercise than do unaffected horses, probably as a result of blood in the larynx and pharynx. Coughing is common in horses recovering from strenuous exercise, and after recovery from exercise horses with EIPH are no more likely to cough than are unaffected horses.[955] Other clinical signs related to respiratory abnormalities are uncommon in horses with EIPH. Respiratory distress is rare in horses with EIPH and when present indicates severe hemorrhage or other serious lung disease such as pneumonia, pneumothorax, or rupture of a pulmonary abscess. Lung sounds are abnormal in a small number of EIPH-affected horses and when present are characterized by increased intensity of normal breath sounds during rebreathing examination.[956] Tracheal rales may be present in horses with EIPH but are also heard in unaffected horses.[957]

Horses that have experienced one episode of epistaxis are more likely to have a second episode. For this reason most racing jurisdictions do not permit horses with epistaxis to race for a period of weeks to months after the initial instance, with more prolonged enforced rest after a subsequent episode of epistaxis and retirement from racing after a third bout. The recurrence rate after one episode of epistaxis in thoroughbred horses is approximately 13.5% despite affected horses not being permitted to race for 1 month after the initial episode of epistaxis.[958] This high rate of recurrence suggests that the inciting pulmonary lesions have not healed.

31.31.5 Diagnostic Approach

31.31.5.1 DIAGNOSTIC TESTS

Various techniques are available for determining the presence and severity of EIPH, including direct examination of the airways through a flexible endoscope or examination of bronchial lavage fluid or tracheal aspirates for evidence of hemorrhage. The utility of these diagnostic tests varies, and choice of examination technique depends on the time between the racing of the horse and the examination and on the desired sensitivity of the test. For instance, tracheobronchoscopic examination is most appropriate if a horse is examined within 1 to 2 hours of exercise, whereas examination of airway washings is most appropriate if the examination is days to a week after strenuous exercise. Radiography, pulmonary scintigraphic examination, and lung function tests are useful in eliminating other respiratory diseases as causes of poor performance but are minimally useful in confirming a diagnosis of EIPH or in determining the severity of hemorrhage.

31.31.5.2 TRACHEOBRONCHOSCOPY

Observation of blood in the trachea or large bronchi of horses 30 to 120 minutes after racing or strenuous exercise provides a definitive diagnosis of EIPH. The amount of blood in the large airways varies from a few small specks on the airway walls to a stream of blood occupying the ventral third of the trachea (Fig. 31-38). Blood may also be present in the larynx and nasopharynx. If there is a strong suspicion of EIPH and blood is not present on a single examination conducted soon after exercise, the examination should be repeated in 60 to 90 minutes. Some horses with EIPH do not have blood in the rostral airways immediately after exercise, but do so when examined 1 to 2 hours later. Blood is detectable by tracheobronchoscopic examination for 1 to 3 days in most horses, with some horses having blood detectable for up to 7 days.

Bronchoscopic examination can be used to estimate the severity of EIPH through use of a grading system.[946,959] The interobserver repeatability of tracheobronchoscopic assessment of severity of EIPH using a 0 to 4 grading scale has been demonstrated[959] (see Fig. 31-38).

- Grade 0: No blood detected in the pharynx, larynx, trachea or mainstem bronchi.
- Grade 1: Presence of one or more flecks of blood or ≤2 short (<¼ length of the trachea) narrow (<10% of the tracheal surface area) streams of blood in the trachea or main stem bronchi visible from the tracheal bifurcation.
- Grade 2: One long stream of blood (>half the length of the trachea) or >2 short streams occupying less than ⅓ of the tracheal circumference.
- Grade 3: Multiple, distinct streams of blood covering more than ⅓ of the tracheal circumference. No blood pooling at the thoracic inlet.
- Grade 4: Multiple, coalescing streams of blood covering >90% of the tracheal surface with pooling of blood at the thoracic inlet.

It is assumed that a higher score represents more severe hemorrhage, but although the repeatability of this scoring system has been established, the relationship between the amount of blood in the large airways and the actual amount of hemorrhage has not been established.

31.31.5.3 TRACHEAL ASPIRATION AND BRONCHOALVEOLAR LAVAGE

The presence of red cells or macrophages containing either effete red cells or the breakdown products of hemoglobin (hemosiderophages) in tracheal fluid or BALF provides evidence of EIPH. Detection of red cells or hemosiderophages in tracheal aspirates or BALF is believed to be both sensitive and specific in the diagnosis of EIPH.[944,960] Examination of airway fluids indicates the presence of EIPH in a greater proportion of horses than does tracheobronchoscopic examination after strenuous exercise or racing. The greater sensitivity of examination of airway fluid is likely attributable to the ability of this examination to detect the presence of small amounts of blood or its residual products and the longevity of these products in the airways. Whereas endoscopic examination may detect blood in occasional horses up to 7 days after an episode of EIPH, cellular evidence of pulmonary hemorrhage persists for weeks after a single episode.[944,960,961] Red blood cells and macrophages containing red cells are present in BALF or tracheal aspirates for at least 1 week after strenuous exercise or instillation of autologous blood into airways, and hemosiderophages are present for at least 21 days and possibly longer.[944,961]

Recent studies have reported on the use of red cell numbers in BALF as a quantitative indicator of EIPH.[962–965] However, this indicator of EIPH severity has not been validated or demonstrated to be more reliable or repeatable than tracheobronchoscopic examination and visual scoring. Furthermore, considerable concern exists over the suitability of red cell counts in BALF for assessment of severity of EIPH given that an unknown area, although presumably small, of the lung is examined by lavage and there is a risk that this area of lung may not be representative of the lung as a whole, similar to the situation of examination of BALF of horses with pneumonia.[966] BAL of sections of both lungs, achieved using an endoscope, may obviate some of these concerns.

Tracheal aspirates may be obtained any time after exercise by either aspiration during tracheobronchoscopic examination or aspiration through a percutaneous intratracheal needle. Aspirates obtained through an endoscope may not be sterile, depending on the collection technique. BALF can be obtained through either an endoscope wedged in the distal airway or a cuffed tube inserted blindly into a distal airway. Collection of fluid

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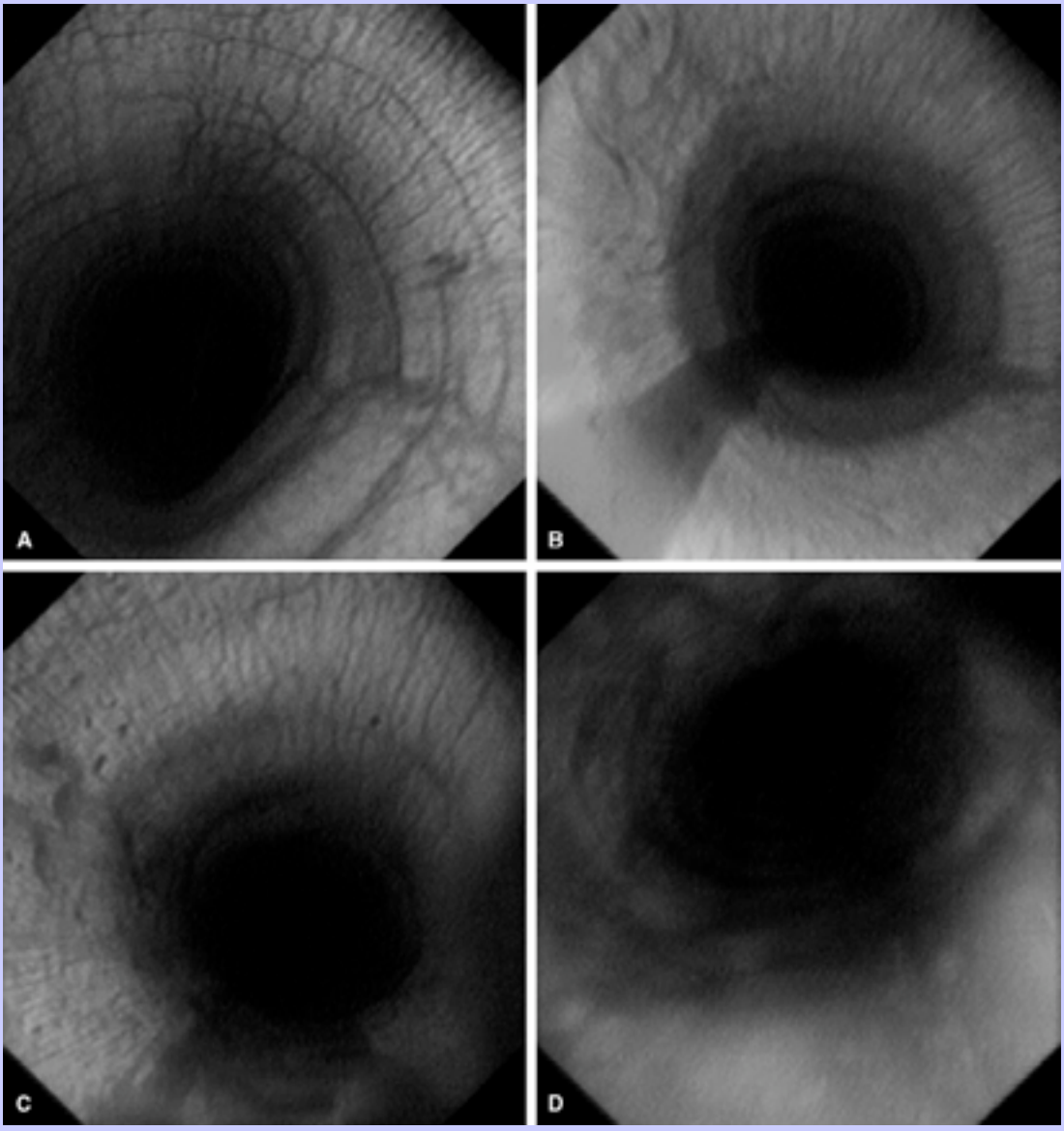
through an endoscope has the advantage of permitting examination of the distal airways and selection of the area of lung to be lavaged. However, it does require the use of an endoscope that is longer (2 m) than those readily available in most equine practices. Use of a commercial BAL catheter does not require use of an endoscope and can be readily performed in field situations.

Fig. 31-38 Tracheobronchoscopic findings in horses with exercise-induced pulmonary hemorrhage. **A** is from a horse with grade 1 hemorrhage. **B** is from a horse with grade 2 hemorrhage. **C** is from a horse with grade 3 hemorrhage. **D** is from a horse with grade 4 hemorrhage.



31.31.5.4 RADIOGRAPHY

Thoracic radiography is of limited use in detecting horses with EIPH. Radiographs may demonstrate the presence of densities in the caudodorsal lung fields of some horses, but many affected horses have minimal to undetectable radiographic abnormalities.[967] Examination of thoracic radiographs of horses with EIPH may be useful in ruling out the presence of another disease process, such as a pulmonary abscess, that is contributing to the horse's pulmonary hemorrhage or poor athletic performance.

31.31.6 Pathophysiology

Rupture of alveolar capillaries occurs secondary to an exercise-induced increase in transmural pressure (pressure difference between the inside of the capillary and the alveolar lumen). If the transmural stress exceeds the tensile strength of the capillary wall, the capillary ruptures.[968] The proximate cause of alveolar capillary rupture is the high transmural pressure generated by positive intracapillary pressures that are largely attributable to capillary blood pressure and the lower intraalveolar pressure generated by the negative pleural pressures associated with inspiration.

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During exercise the absolute magnitudes of both pulmonary capillary pressure and alveolar pressure increase, with a consequent increase in transmural pressure. Strenuous exercise is associated with marked increases in pulmonary artery pressure in horses.[963,969,970] Values for mean pulmonary arterial pressure at rest of 20 to 25 mm Hg increase to greater than 90 mm Hg during intense exercise because of the large cardiac output achieved by exercising horses. The increases in pulmonary artery pressure, combined with an increase in left atrial pressure during exercise, likely result in an increase in pulmonary capillary pressure. Combined with the increase in pulmonary capillary pressure is a marked decrease (more negative) in pleural, and therefore alveolar, pressures during exercise. Pleural pressures of normal horses during inspiration decrease from approximately −0.7 kPa (−5.3 mm Hg) at rest to as low as −8.5 kPa (−64 mm Hg) during strenuous exercise.[971] Together, the increases in pulmonary capillary pressure and decrease (more negative) in intrapleural (alveolar) pressure contribute to a marked increase in stress in the alveolar wall. Although the alveolar wall and pulmonary capillary of horses are stronger than those of other species, rupture may occur because the wall stress in the alveolus exceeds the mechanical strength of the capillary.[972]

Other theories of the pathogenesis of EIPH include small airway disease, upper airway obstruction, hemostatic abnormalities, changes in blood viscosity and erythrocyte shape, intrathoracic sheer forces associated with gait, and bronchial artery angiogenesis.[942,973] It is likely that the pathogenesis of EIPH involves several processes, including pulmonary hypertension, lower alveolar pressure, and changes in lung structure, that summate to induce stress failure of pulmonary capillaries.

Obstruction of either the upper or lower airways has been proposed as a cause of EIPH.[974] Inspiratory airway obstruction results in more negative intrapleural and therefore alveolar pressures. This effect is exacerbated by exercise, with the result that alveolar transmural pressure is greater in horses with airway obstruction.[975,976] The higher transmural pressure in such horses may increase the severity of EIPH, although this has not been demonstrated. Moreover, although inspiratory airway obstruction may predispose to EIPH, the prevalence of this condition is much less than that of EIPH, indicating that it is not the sole factor inducing EIPH in most horses.

Horses with moderate to severe EIPH have histologic evidence of inflammation of the small airways,[977,978] and there is a clear association between presence of EIPH and inflammatory changes in bronchoalveolar or tracheal aspirate fluid.[979] However, instillation of autologous blood into the airways induces a marked inflammatory response in normal horses,[980] and it is therefore unclear if inflammation alone induces or predisposes to EIPH or if the inflammation is a result of EIPH. Theoretically, small airway inflammation and bronchoconstriction have the potential to produce intrathoracic airway obstruction and therefore a more negative alveolar pressure. Given that small airway disease is common in horses, there is the potential for an important effect of factors, such as viral infections, air pollution, and allergic airway disease, to contribute to the initiation or propagation of EIPH.[981]

Exercise is accompanied by marked changes in blood flow characteristics attributable to an increase in hematocrit and decrease in red cell deformability.[982,983] These changes cause an increase in microvascular shear stress and thus could conceivably contribute to capillary rupture. However, there is at present no direct evidence that indicates that this is an important feature of development of EIPH.

The characteristic location of lesions of EIPH in the caudodorsal lung fields has lead to the proposal that hemorrhage is a result of tissue damage occurring when waves of stress, generated by forelimb foot strike, are focused and amplified by the narrowing cross-sectional area of the caudal lung lobes.[973] According to the theory, the locomotory impact of the forelimbs results in transmission of forces through the scapula to the body wall; from there they pass into the lungs and caudally and dorsally. As the wave of pressure passes into the narrower caudodorsal regions of the lungs, it generates progressively greater shearing forces that disrupt tissue and cause EIPH. However, studies of intrapleural pressures have not demonstrated the presence of a systemic pressure wave passing through the lung and do not provide support for this hypothesis.[984] The observation that horses competing in hurdles or steeplechase events on hard ground have increased incidence of epistaxis lends support to the suggestion that locomotory impact might influence the development of EIPH.[985]

Horses with EIPH have been suspected of having defects in either hemostasis or fibrinolysis. However, although exercise induces substantial changes in blood coagulation and fibrinolysis,[986] there is no evidence that horses with EIPH have defective coagulation or increased fibrinolysis.[987,988]

Regardless of the cause, rupture of pulmonary capillaries and subsequent hemorrhage into airways and interstitium causes inflammation of both airways and interstitium, with subsequent development of fibrosis and alteration of tissue compliance. Heterogeneity of compliance within the lungs, and particularly at the junction of normal and diseased tissue, results in development of abnormal shear stress with subsequent tissue damage. These changes are exacerbated by inflammation and obstruction of small airways with resulting uneven inflation of the lungs.[989] The structural abnormalities, combined with pulmonary hypertension and the large intrathoracic forces associated with respiration during strenuous exercise, cause repetitive damage at the boundary of normal and diseased tissue with further hemorrhage and inflammation. The process, once started, is life-long and continues for as long as the horse continues to perform strenuous exercise.[942]

31.31.7 Epidemiology

EIPH occurs in horses throughout the world. It is a disorder of horses that run at high speed, such as thoroughbred or standardbred racehorses, quarter horses (racehorses and barrel racing horses), and polo ponies. The disorder is apparently uncommon in endurance horses and is very uncommon in draft breeds, such as

Clydesdales, Percherons, or Belgians, after participation in weight-pulling competition.[990] As a general rule, the more intense the exercise or the higher the speed attained, the greater the proportion of horses with EIPH.

The prevalence of EIPH varies with the method used to detect it and the frequency with which horses are examined, as discussed later in this section. Almost all thoroughbred racehorses in active training have hemosiderophages in BALF, indicating that all have some degree of EIPH.[944] The prevalence of EIPH decreases when diagnosis is based on endoscopic examination of horses after exercise or racing.

31.31.8 Risk Factors

31.31.8.1 BREED

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EIPH is very common in thoroughbred racehorses, with estimates of prevalence, based on a single endoscopic examination of the trachea and bronchi, of 43% to 75%.[948,950,991] The prevalence increases with the frequency of examination, with over 80% of horses having evidence of EIPH on at least one occasion after examination after each of three consecutive races.[992] The prevalence of EIPH in standardbred racehorses is assumed to be lower, with 26% to 34% of horses reported to have blood in the trachea after racing.[953,993] However, these studies were based on a single examination, and one study [993] reported as positive only those horses with blood covering more than one half of the tracheobronchial tree. When examined after each of three races, 87% of standardbred racehorses have evidence of EIPH on at least one occasion,[952] suggesting that EIPH is as common in standardbred racehorses as it is in thoroughbred racehorses.

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EIPH occurs in approximately 62% of racing quarter horses and has been observed in quarter horses used for barrel racing.[994] The disorder occurs in racing Appaloosa horses.[995] Approximately 11% of polo ponies are affected with EIPH[996] and the disorder occurs in Chilean Criollo horses.[997]

31.31.8.2 AGE

Age is considered an important risk factor for EIPH, with the prevalence of the disorder being higher in older horses.[946,947,998,999] There is no consistent effect of sex on prevalence of EIPH.[948,950,953,991]

Among thoroughbred racehorses the prevalence of EIPH increases with increasing speed,[948,977] being greater in thoroughbreds after racing than after breezing (galloping). Lesions of EIPH are not detected in young thoroughbred racehorses that have trained at speeds less than 7 m/sec.[948,977]

Epistaxis associated with exercise is almost always attributable to pulmonary hemorrhage but occurs only in a small proportion of racehorses.[958,1000,1001] The prevalence of epistaxis in racehorses varies between 0.1% and 9%, with the frequency depending on the breed, age, and sex of horses selected for study, the type of racing, and the timing and frequency of observation of horses after racing. Epistaxis is more common in older horses.[958,1000] There are conflicting reports of a sex predisposition, although epistaxis may be more common in female thoroughbreds.[958,1000] Epistaxis is more common after races <1600 m than in longer races,[958] although not all sources agree on this point.[1000] However, horses in steeplechase races, which are typically longer than 2000 m, are at greater risk of epistaxis than are horses in flat races.[958,985] In addition, horses racing in hurdle or steeplechase races over hard ground in Britain are more likely to have epistaxis.[985]

The effect of genetics on the incidence of EIPH has been examined only minimally, with one study of horses with epistaxis, which is characteristically associated with severe EIPH, suggesting a hereditary predisposition among thoroughbred racehorses in South Africa.[1002] The heritability of the predisposition to epistaxis was considered low.[1002]

31.31.9 Necropsy

EIPH is a cause of sudden death of horses during racing and training[1003–1005] and in most studies is secondary to musculoskeletal injury as the cause of death. Necropsy examination reveals that approximately 60% of horses that die during racing or training or are euthanized because of acute injury during racing or training have evidence of EIPH.[1005] Necropsy examination of affected horses is usually but not always incidental to examination for another cause of death.

Pertinent abnormalities detected on necropsy of horses with EIPH are restricted to the respiratory tract. Grossly, horses examined within hours of strenuous exercise, such as horses examined because of catastrophic musculoskeletal injuries incurred during racing, often have severe petechiation in the caudodorsal lung fields. Horses that die of EIPH also have pulmonary congestion and edema.[1005] Horses with chronic disease have blue-gray or blue-brown discoloration of the visceral pleural surfaces of the caudodorsal lung fields that is often sharply demarcated, especially on the diaphragmatic surface.[1005,1006] The discoloration affects both lungs equally, with 30% to 50% of the lung fields being discolored in severe cases. Affected areas do not collapse to the same extent as unaffected areas and, in the deflated lung, have a spleenlike consistency. On the cut surface the discolored areas of lung are predominantly contiguous with the dorsal pleural surface and extend ventrally into the lung parenchyma. Areas of affected lung may be separated by normal lung. There is proliferation of bronchial vessels, predominantly arteries and arterioles, in affected areas.[1007] Histologically, affected areas exhibit bronchiolitis, hemosiderophages in the alveolar lumen and interstitial spaces, and fibrosis of interlobular septa and pleura and around vessels and bronchioles.[978]

31.31.10 Therapy, Prevention, and Control

Therapy for EIPH is usually a combination of attempts to reduce the severity of subsequent hemorrhage and efforts to minimize the effect of recent hemorrhage. Treatment of EIPH is problematic for a number of reasons. First, the pathogenesis of EIPH has not been determined, although the available evidence supports a role for stress failure of pulmonary capillaries secondary to exercise-induced pulmonary hypertension (see later). Second, there is a lack of information using large numbers of horses under field conditions that demonstrates an effect of any medication or management practice (with the exception of bedding) on EIPH. There are numerous studies of small numbers of horses (less than approximately 40) under experimental conditions, but these studies often lack the statistical power to detect treatment effects, and, furthermore, the relevance of studies conducted on a treadmill to horses racing competitively is questionable. Treatments for EIPH are usually intended to address a specific aspect of the pathogenesis of the disease and will be discussed in that context.

31.31.10.1 PREVENTION OF STRESS FAILURE OF THE PULMONARY CAPILLARIES

There is interest in reducing the pressure difference across the pulmonary capillary membrane in an effort to reduce EIPH. Theoretically, this can be achieved by reducing the pressure within the capillary or increasing (making less negative) the pressure within the intrathoracic airways and alveolus.

Furosemide apparently reduces pulmonary capillary pressure in exercising horses. Furosemide administration as prophylaxis against EIPH is permitted in a number of racing jurisdictions worldwide, most notably Canada, the United States, Mexico, and most of the South American countries.[1008] Within the United States and Canada, almost all thoroughbred, standardbred, and quarter horse racing jurisdictions permit administration of furosemide before racing. The vast majority (>90%) of thoroughbred horses racing in the United States receive furosemide before racing, at an estimated annual cost of between $6,000,000 and $20,000,000.[937] Although accurate numbers are not available, it appears that a smaller proportion of standardbred and quarter horse racehorses receive furosemide before racing. Furosemide is administered to 22% to 32% of standardbred racehorses and 19% of racing quarter horses in two racing jurisdictions.[1009–1011]

The efficacy of furosemide in treatment of EIPH is uncertain. Although field studies of large numbers of horses do not demonstrate an effect of furosemide on the prevalence of EIPH,[992] studies of thoroughbred horses running on a treadmill provide evidence that furosemide reduces the severity of EIPH.[964,965,1012] Under field conditions, based on tracheobronchoscopic evaluation of the severity of bleeding, furosemide has been reported to reduce or have no influence on the severity of bleeding.[1013] This apparent inconsistency may be attributable to measurement of red blood cell counts in BALF of horses that have run on a treadmill not being representative of effects of furosemide under field conditions. The weight of evidence, albeit unconvincing, from field studies does not support a role for furosemide in preventing or reducing the severity of EIPH.

The mechanism by which furosemide may reduce the severity of EIPH is unknown, although it is speculated that furosemide, by attenuating the exercise-induced increase in pulmonary artery and pulmonary capillary pressure of horses, reduces the frequency or severity of pulmonary capillary rupture.[970,1014,1015]

Furosemide is associated with superior performance in both thoroughbred and standardbred racehorses.[1009,1016] Thoroughbred horses treated with furosemide are 1.4 times as likely to win the race, earn more money, and have a standardized 6-furlong race time 0.56 to 1.09 seconds less than that of untreated horses.[1016] Similarly, furosemide reduces 1-mile race times of standardbred pacers by 0.31 to 0.74 seconds.[1009]

Enalapril inhibits angiotensin-converting enzyme (ACE) activity in horses but does not affect pulmonary artery pressure of exercising horses.[1017] Similarly, the efficacy of enalapril in preventing EIPH has not been demonstrated.

Nitric oxide is a potent vasodilator in many vascular beds. Administration of nitroglycerin (a nitric oxide donor) reduces pulmonary artery pressure of standing horses but does not affect pulmonary artery pressure of horses during intense exercise.[1018] L-Arginine is a nitric oxide donor with no demonstrated efficacy in reducing pulmonary capillary pressure or EIPH in horses. The effect of L-NAME, an inhibitor of nitric oxide synthetase, on pulmonary artery pressure during maximal exercise is controversial, with either no effect or a decrease in pulmonary artery pressure reported.[1019,1020] It is interesting to note that L-NAME administration has been reported to cause an increase in severity of EIPH.[1019] Sildenafil, a PDE inhibitor that accentuates the effect of nitric oxide and is used in the treatment of erectile dysfunction in men, has been administered to horses in an apparent attempt to reduce EIPH. However, its efficacy in preventing EIPH or reducing pulmonary capillary pressure has not been demonstrated.

An increase in pulmonary capillary pressure secondary to altered rheostatic properties of blood during exercise has been suggested as a possible contributing factor for EIPH.[982] Furosemide increases blood viscosity, whereas pentoxifylline increases red blood cell deformability and may attenuate the increase in blood viscosity that occurs during exercise.[1021–1023] However, pentoxifylline does not affect pulmonary capillary pressure of exercising horses and did not affect the prevalence of EIPH in a small experimental study.[1024]

Airway obstruction, either intrathoracic or extrathoracic, increases airway resistance and results in a more negative intrathoracic (pleural) pressure during inspiration to maintain tidal volume and alveolar ventilation. Causes of extrathoracic airway obstruction include laryngeal hemiplegia and other abnormalities of the upper airway, whereas intrathoracic obstruction is usually a result of bronchoconstriction and IAD. Horses with partial extrathoracic inspiratory obstruction or bronchoconstriction and airway inflammation associated with recurrent airway obstructive disease (heaves) have pleural (and hence alveolar) pressures that are lower (more negative) than those in unaffected horses or in horses after effective treatment.

Partial inspiratory obstruction, such as produced by laryngeal hemiplegia, exacerbates the exercise-induced decrease in intrapleural pressures, with a consequent increase in transmural capillary pressures.[975,976,1025] These changes may exacerbate the severity of EIPH, although an association between upper airway obstructive disease and EIPH has not been demonstrated. Surgical correction of airway obstruction is expected to resolve the more negative intrapleural pressure, but its effect on EIPH is unknown.

Recently the role of the nares in contributing to upper airway resistance, and therefore lowering inspiratory intrapleural pressure, during intense exercise has attracted the attention of some investigators. Application of nasal dilator bands (Flair strips) reduces nasal resistance by dilating the nasal valve[1026] and reduces red cell count of BALF collected from horses after intense exercise on a treadmill.[964,965] Furthermore, application of the nasal dilator strips to horses in simulated races reduces red cell count in BALF of some, but not all, horses.[1027]

The role of small airway inflammation and bronchoconstriction in the pathogenesis of EIPH is unclear. However, horses with EIPH are often treated with drugs intended to decrease lower airway inflammation and relieve bronchoconstriction. β-Adrenergic bronchodilatory drugs such as clenbuterol and albuterol are effective in inducing bronchodilation in horses with bronchoconstriction, but their efficacy in preventing EIPH is either unknown or, in very small studies, is not evident. Clenbuterol does not alter the hemodynamic responses of horses to exertion nor attenuate exercise-induced arterial hypoxemia in normal horses.[1028,1029] Ipratropium, a parasympatholytic drug administered by inhalation, showed promised in a very small study (two horses) of preventing EIPH.[1030] Corticosteroids, including dexamethasone, fluticasone, and beclomethasone administered by inhalation, parenterally, or enterally reduce airway inflammation and obstruction but have no demonstrated efficacy in preventing EIPH. Cromolyn sodium (sodium cromoglycate) has no efficacy in preventing EIPH.[1031]

Water vapor treatment (inhalation of water-saturated air) has been proposed as a treatment for EIPH because of its putative effect on small airway disease. However, water vapor treatment has no effect on EIPH.[1032]

The use of bedding of low allergenic potential (shredded paper) to prevent EIPH has no apparent effect on prevalence of the condition.[1033] Although it is suggested that preventing or minimizing small airway disease may reduce the severity of EIPH, studies to demonstrate such an effect have not been reported. However,

optimizing the air quality in barns and stables and preventing infectious respiratory disease appear to be sensible precautions.

31.31.11 INTERSTITIAL INFLAMMATION AND BRONCHIAL ANGIOGENESIS

Hemorrhage into interstitial tissues induces inflammation with subsequent development of fibrosis and bronchial artery angiogenesis.[980,1007,1034] The role of these changes in perpetuating EIPH in horses is unclear but likely is of some importance. Treatments to reduce inflammation and promote healing with minimal fibrosis have been proposed. Rest is an obvious recommendation, and many racing jurisdictions have rules regarding enforced rest for horses with epistaxis. Although the value of rest is intuitive, there is no information that rest reduces the severity or incidence of EIPH in horses with prior evidence of this disorder.

Similarly, corticosteroids are often administered by inhalation, enterally, or parenterally in an attempt to reduce pulmonary inflammation and minimize fibrosis. Again, the efficacy of this intervention in preventing or minimizing severity of EIPH has not been documented.

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31.31.12 EXCESSIVE BLEEDING

Exercise induces substantial changes in blood coagulation and fibrinolysis.[986] However, there is no evidence that horses with EIPH have defective coagulation or increased fibrinolysis.[987,988,1035] Regardless, aminocaproic acid, a potent inhibitor of fibrin degradation, has been administered to horses to prevent EIPH. Although appropriate doses of aminocaproic acid do inhibit fibrinolysis in stationary horses,[1035] the efficacy of aminocaproic acid in preventing EIPH has not been demonstrated. Tranhexamic acid is similarly administered to horses in the hope of preventing or mitigating EIPH. Estrogens are given to horses with the expectation of improving hemostasis, although the effect of estrogens on coagulation in any species is unclear. There is no evidence that estrogens prevent EIPH in horses.

Vitamin K is administered to horses with EIPH, presumably with the expectation that it will decrease coagulation times. However, because EIPH is not associated with prolonged bleeding times, it is unlikely that this intervention will affect the prevalence or severity of EIPH.

Herbal preparations are marketed for treatment of EIPH. The only scientific study of these products examined the efficacy of Yunnan Paiyao or Single Immortal on red cell count in BALF of horses that had run on a treadmill. Neither product affected red cell count or coagulation variables.[1036]

Aspirin inhibits platelet aggregation in horses and increases bleeding time.[1037] Seemingly paradoxically, aspirin is sometimes administered to horses with EIPH because of concerns that increased platelet aggregation contributes to EIPH.[1038] There is no evidence that aspirin exacerbates or prevents EIPH.

31.31.13 CAPILLARY INTEGRITY

Capillary fragility increases the risk of hemorrhage in many species. Various bioflavinoids have been suggested to increase capillary integrity and prevent bleeding. However, hesperidin and citrus bioflavinoids have no efficacy in prevention of EIPH in horses.[1039] Similarly, vitamin C is administered to horses with EIPH without scientific evidence of any beneficial effect.

31.31.14 SUMMARY OF TREATMENT OPTIONS

Selection of therapy for horses with EIPH is problematic. Given that most horses have some degree of pulmonary hemorrhage during most bouts of intense exercise, the decision must be made not only as to which type of treatment to use and its timing, but also which horses to treat. Moreover, the apparent progressive nature of the disease with continued work highlights the importance of early and effective prophylaxis and emphasizes the need for studies of factors such as air quality and respiratory infections in inciting the disorder.

The currently favored treatment for EIPH is administration of furosemide before intense exercise. Its use is permitted in racehorses in a number of countries. Increasingly persuasive laboratory evidence of an effect of furosemide to reduce red cell count in BALF collected from horses soon after intense exercise supports the contention that furosemide is effective in reducing the severity of EIPH in racehorses. However, it should be borne in mind that neither the relationship between severity of EIPH and red cell count in BALF nor the efficacy of furosemide in reducing severity of EIPH in racehorses in the field has been demonstrated. In fact, there is evidence that furosemide does not reduce the prevalence of EIPH and other evidence that it does not reduce the severity of EIPH under field conditions. The association between furosemide administration and superior performance in standardbred and thoroughbred racehorses should be borne in mind when recommending use of this drug.

Rest is an obvious recommendation for horses with EIPH, but the hemorrhage is likely to recur when the horse is next strenuously exercised. The duration of rest and the optimal exercise program to return horses to racing after EIPH is unknown, although some jurisdictions require exercise no more intense than trotting for 2 months. Firm recommendations cannot be made on duration of rest because of a lack of objective information.

Although a role for lower airway disease (either infectious or allergic) in the genesis of EIPH has not been demonstrated, control of infectious diseases and minimization of noninfectious lower airway inflammation appear prudent.

31.31.15 Prognosis

The prognosis for racing for horses with clinically significant EIPH is guarded because of the progressive nature of the disease. Horses that have experienced severe EIPH on one occasion are likely to do so again regardless of treatment. However, the risk of horses experiencing a repeated bout of severe hemorrhage and the effect of EIPH on career longevity are unknown.

31.31.16 Cost

The cost to the industry of treating horses for EIPH has not been determined. The costs of administration of furosemide are readily estimated (see later) but not so the costs of other treatments, absences from racing because of EIPH, shortened racing careers, and impaired performance. Conservatively estimated, this cost could easily exceed $400 per horse per year (and could be as high as $500 to $1000 per year). For example, costs associated with endoscopic examination (two or three examinations annually at $50 to $75 each) and alternative, herbal, and hormonal treatments ($1 to $5 per day) easily amount to more than $400 annually, without including costs associated with furosemide administration or the opportunity costs of lost racing days, poor performance, and shortened racing career. Spread over the 250,000 standardbred and thoroughbred racehorses starting annually in the United States, the total cost of EIPH to the thoroughbred and standardbred racing industries may well exceed $100,000,000 per year.

The high incidence of EIPH in racehorses and recognition of the adverse effect of EIPH on performance results in the widespread use of furosemide in racehorses in the United States. Ninety percent of thoroughbred and 50% to 70% of standardbred racehorses receive the drug before racing. Administration of furosemide to thoroughbred and standardbred horses racing in the United States costs the racing industry $17,000,000 to $35,000,000 annually. Costs associated with use of furosemide are incurred not just for injection of the drug into horses before racing (direct costs), but also for diagnosis of EIPH to determine eligibility for furosemide administration; clerical and administrative costs associated with enforcing policies governing use of furosemide, such as supervision of drug administration and documentation in race records and programs; and drug testing before or after racing to ensure appropriate dosing.

The direct cost for administration of furosemide, which includes the veterinary fee and cost of drug and supplies, varies geographically but is between $20 and $30 per administration per horse.[1040] Costs associated with enforcement of rules governing use of furosemide, including documentation and drug testing, are estimated at an additional $25 to $35 per head. The estimated total cost of furosemide administration is therefore approximately $50 but may be as high as $65 per dose. These estimates of the total cost of furosemide use in racehorses are the same as an estimate of the cost made in 1995 and therefore are conservative estimates.[1041]

There were 444,586 starts by 107,437 horses in thoroughbred racing in the United States in 2003. Assuming that furosemide is administered to 90% of these starters and that there is no cost for horses not administered furosemide, the direct cost of furosemide administration is $10,003,150 annually (444,586 × 0.9 × $25). However, if the total costs associated with furosemide administration are considered, the annual cost for administration of furosemide in thoroughbred racing is $20,006,300 (444,586 × 0.9 × $50) and could be as high as $28,000,000.

Similarly, there were 635,292 standardbred starts in the United States in 2003 (United States Trotting Association, October, 2004). If 50% of these horses were administered furosemide (a conservative estimate of the prevalence of furosemide administration) at a direct cost of $25 per dose, the cost to the industry would be $7,941,000. The total cost, assuming $50 per dose, is $15,882,000 per annum.

The cost to the racing industry of furosemide administration is therefore over $35,800,000 annually, and EIPH costs the racing industry over $100,000,000 annually.

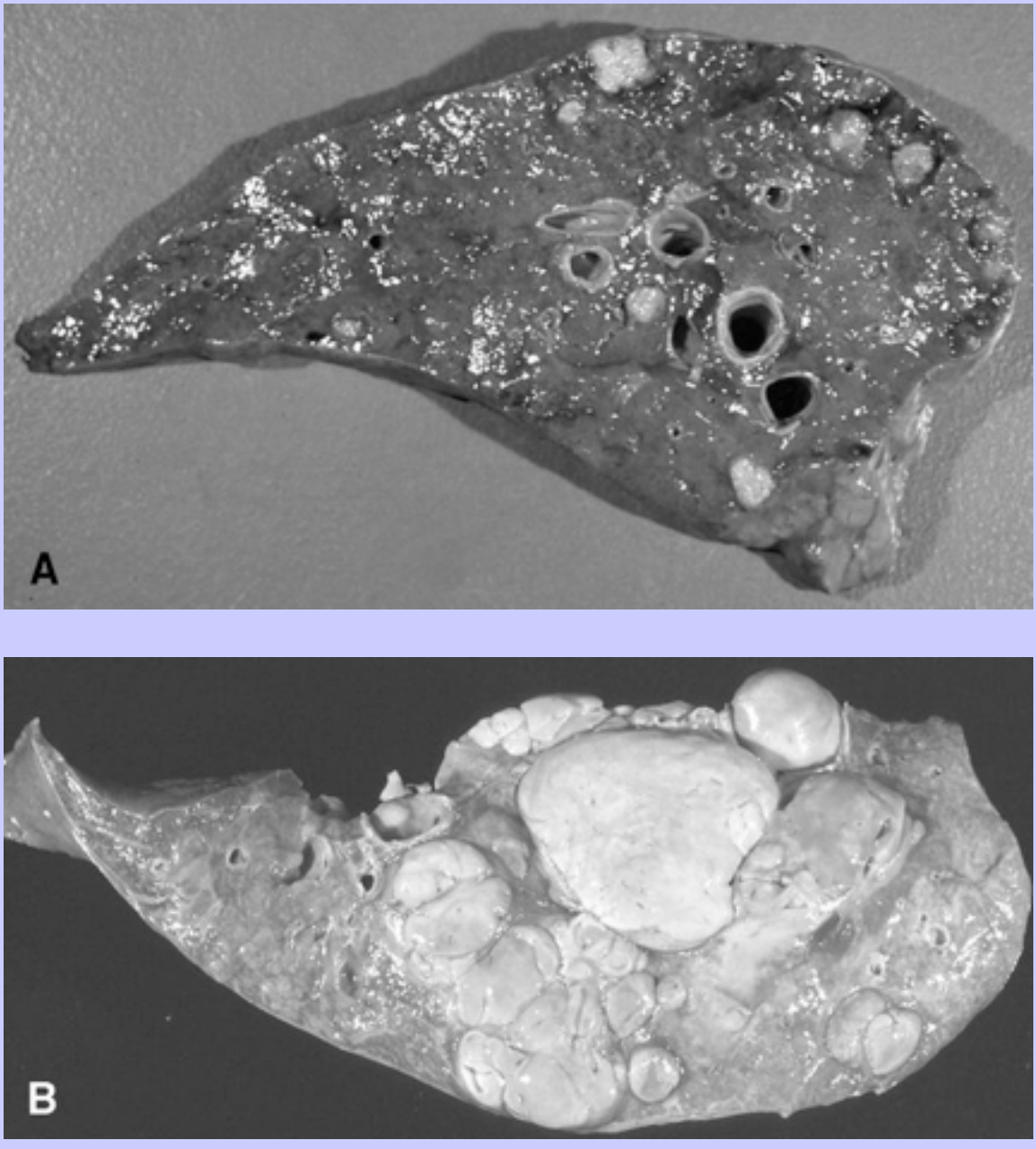
31.32 EQUINE THORACIC NEOPLASIA

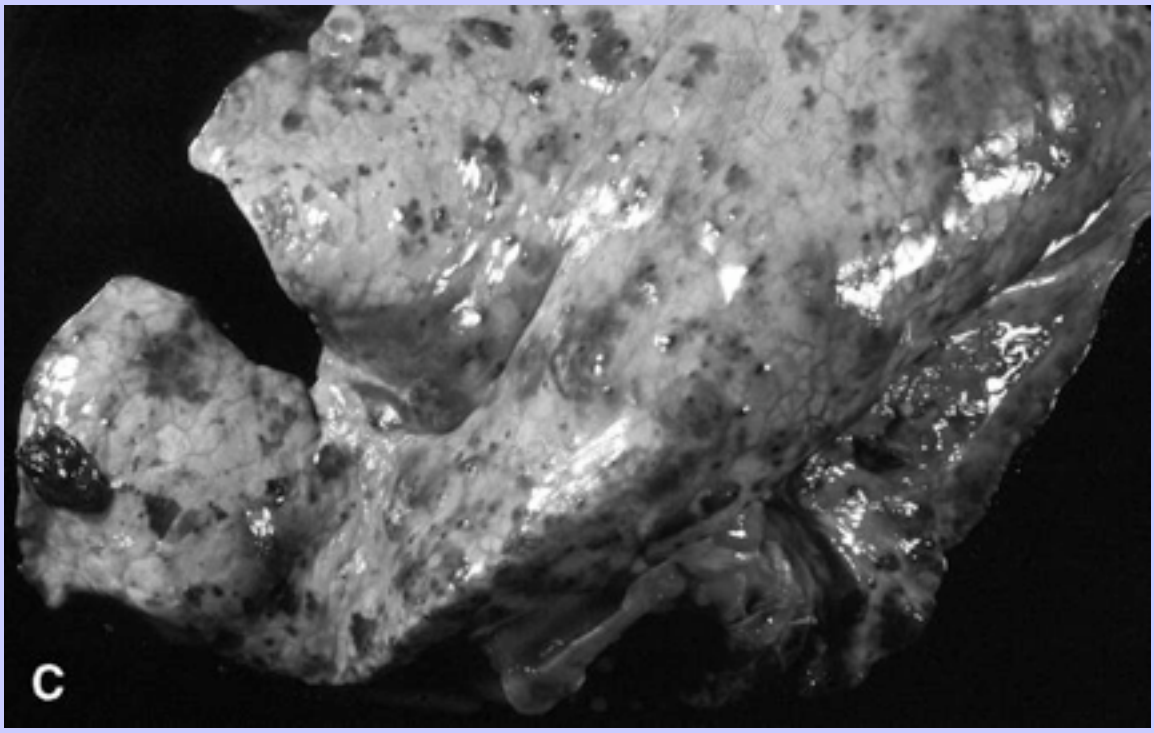
FABIO DEL PIERO

PAMELA A. WILKINS

Surveys of equine neoplasms indicate a low incidence of thoracic neoplasia in the horse (Fig. 31-39). In an abattoir survey in London of 1308 horses, two horses had pulmonary tumors, one granular cell tumor, and one bronchiolar adenoma.[1042] Two other necropsy surveys of 155 and 687 equines reported no thoracic neoplasms.[1043,1044] A report on chronic pulmonary disease in the horse states that the practical importance of lung tumors is negligible.[1044] University of Pennsylvania researchers examined 5629 horses between 1968 and 1987. Thirty-five horses had neoplasia involving the thoracic cavity, for an incidence of 0.62%.[1045]

Fig. 31-39 **A**, Metastatic undifferentiated sarcoma. **B**, Granulosa cell tumor. **C**, Metastatic hemangiosarcoma. **D**, Metastatic squamous cell carcinoma.

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Primary pulmonary tumors are rare in the horse. The incidence of primary lung tumors of any type is reported to be less than 1% of all reported tumors in domestic animals.[1046] The lungs are susceptible to tumor emboli because of the filter action of the capillary bed associated with small capillary diameter and, perhaps, specific adhesion factors. It can sometimes be difficult or impossible to distinguish gross and microscopic patterns of metastatic disease from those of primary lung neoplasia; thus an important part of the diagnosis is exclusion of possible primary sites elsewhere in the body. Primary pulmonary tumors reported in the horse include granular cell tumor, bronchial myxoma, adenoma, adenocarcinoma, anaplastic bronchogenic carcinoma, and pulmonary carcinoma and perhaps undifferentiated sarcoma. Other primary thoracic tumors reported in the horse include pulmonary chondrosarcoma, plural mesothelioma, thymoma, and malignant lymphoma. All these neoplasms generally occur in the mature or aged horse. The exception is malignant lymphoma, which may also be observed in young animals.

Antemortem diagnosis of thoracic neoplasia depends first on recognition of thoracic disease. Most of the reported cases of thoracic neoplasia involve metastatic disease. The horses' clinical signs are generally related to the primary site of the neoplasm; therefore the clinician often has no reason to suspect thoracic involvement. When respiratory signs, such as dyspnea, tachypnea, hemoptysis, cough, cyanosis, nasal discharge, and epistaxis, are present, relevant diagnostic tests are more likely to be performed. Ultrasonography and bronchoscopy increase the frequency of antemortem diagnosis of thoracic neoplasia.

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Granular cell tumor is the most frequently reported primary pulmonary tumor of the horse, with at least 15 articles in the literature. Granular cell tumors in horses are usually confined to the lungs. The neoplasia usually has consisted of single to multiple well-defined whitish compact nodules associated with a major bronchus, often protruding into the bronchial lumen or more distally within the parenchyma. Most granular cell tumors have been diagnosed only at postmortem examination, often as incidental findings. In a population of 350 mature and elderly horses examined in an abattoir by one of us (Fabio Del Piero), two pulmonary granular cell tumors were observed. These homogeneous growths of granular eosinophilic cells expressed S-100 and occasionally neuron-specific enolase, as previously observed.[1047] The ultrastructural morphology of this tumor may suggest a neural origin, leading to the definition of granular cell schwannoma.

Primary pulmonary chondrosarcoma has been reported in a horse.[1048] In this horse, cytologic examination of pleural fluid and an antemortem needle aspirate of the pulmonary mass revealed neoplastic chondrocytes. Another report describes metastatic chondrosarcoma in the lungs of a horse with a primary tumor in a rib.[1049] A primary bronchial myxoma, characterized by loose spindloid mesenchymal cells, was reported in a 25-year-old Arabian mare with a history of intermittent coughing, hyperpnea, and respiratory disease of 2 years' duration.[1050]

Primary pleural tumors are also rare. The specific type reported in the horse is pleural mesothelioma. The tumor frequently is associated with a large volume of pleural effusion. Cytologic examination of the pleural effusion revealing numerous pleomorphic mesothelial cells may aid in the antemortem diagnosis.

Thymomas are neoplasms of thymic epithelial cells, regardless of the presence or absence of lymphocytes. They are infrequently reported in the horse.[1051–1053] Equine malignant lymphoma occurs in mediastinal, alimentary, multicentric, cutaneous, and generalized forms; combinations of one or more of these are not infrequent.[1054,1055] In a 1973 review of 54 cases of equine malignant lymphoma,[1044] the lung was involved in 16.6% of the cases, whereas the thoracic lymph nodes were involved in 35.2%.[1056] In the University of Pennsylvania survey, thoracic malignant lymphoma was the single most common neoplasia of the thorax and was present in 19 (54%) of the cases.[1044] Pleural fluid cytologic evaluation was diagnostic in six (75%) of the eight horses. Diagnosis was made by biopsy of a peripheral lymph node in several cases. In a report from the University of Bristol, thoracic malignant

lymphoma accounted for 74% of the cases of thoracic neoplasia.[1056] Metastatic adenocarcinoma accounted for 20% of the cases in the University of Pennsylvania study[1045] and 11% of the cases in the University of Bristol study.[1056] The primary sites of the tumor were thought to be kidney, uterus, thyroid, and ovary.

Gastric squamous cell carcinomas commonly metastasize to the thoracic cavity. Cytology of pleural fluid with identification of neoplastic epithelial pleomorphic and squamous cells has allowed for antemortem diagnosis of the carcinoma in several cases. Metastatic squamous cell carcinoma of the thorax was found in 14% and 5% of the cases in the University of Pennsylvania[1045] and University of Bristol[1056] surveys, respectively. Neoplastic epithelial cells may also be identified in biopsy specimens using “cocktails” of primary antisera containing antibodies recognizing cytokeratins of various molecular weights.

Hemangiosarcoma with pulmonary involvement has been previously reported and was found in 9% of the horses in the University of Pennsylvania survey.[1045] Hemothorax, anemia, and dyspnea were commonly seen with pulmonary hemangiosarcoma. Tentative antemortem diagnosis of the hemangiosarcoma has been made by transcutaneous direct thoracoscopy and observation of the hemorrhages distributed over the visceral and parietal pleural surfaces and biopsy of these sites. Identification of neoplastic endothelial cells demarcating variously irregular, sometimes blood-filled cavities allows diagnosis from the biopsy specimen. Neoplastic endothelium still expresses a variable amount of immunohistochemically identifiable factor VIII.

Malignant melanoma in a 20-year-old gelding had widespread infiltration of many organs including the lungs and pleura.[1056] This pattern of distribution is not uncommon in malignant, less pigmented melanomas. Amelanotic melanomas are very rare in the horse, and microscopic identification of melanin simplifies the diagnosis of these tumors. Melanocytes express S-100 protein and may demonstrate cross- reactivity to melanoma cell markers of other species.

Other pulmonary metastatic tumors reported are mammary carcinoma,[1057] seminoma,[1058] and malignant pheochromocytoma.[1059] Metastatic pulmonary tumors have been so far examined only morphologically. The use of IHC for the detection of specific cell markers and other sophisticated molecular studies may lead to different diagnoses.

Occasionally, a myxomatous multifocal to coalescing infiltrative neoplastic-like growth can be observed within the lung of mature and aged horses generally as an incidental finding. This infiltration is composed of loosely arranged mesenchymal cells with moderate collagen deposition.

Pulmonary hamartomas are occasionally observed in the newborn foal. Although they are nonneoplastic growths, they appear as tumorlike masses that can compress the surrounding parenchyma and cause systemic passive congestion and hydrops of the amnion in the fetus. Histologically they may be characterized by an organized proliferation of bronchiolar-like structures lined by cuboidal epithelium with lack of alveolar development or by normal alveoli, bronchi, and blood vessels but with alveolus:artery ratio greater than normal. Generally they are not compatible with a long period of extrauterine life.

An unusual progressive idiopathic multifocal granulomatous pneumonia of adult horses may resemble neoplasia behaviorally and morphologically during clinical examination.[1060,1061] Pulmonary biopsy may allow the identification of EMPF, pulmonary fibrosis associated with EHV-5 infection[1061] (Fig. 31-40).

Clinical signs of thoracic neoplasia are often inapparent or nonspecific—for example, depression, inappetence, weight loss, and pyrexia. More specific signs include cough, epistaxis, and dyspnea. Cytologic examination of a

tracheobronchial aspirate, bronchoalveolar lavage fluid, or pleural fluid or histologic examination of a thoracic mass biopsy with ancillary histochemistry and IHC may allow for antemortem diagnosis of the tumor. Occasionally, electron microscopy may provide additional information. In equine patients with respiratory signs, all causes of infectious or allergic lung disease should be eliminated before neoplasia is considered in the differential diagnosis.

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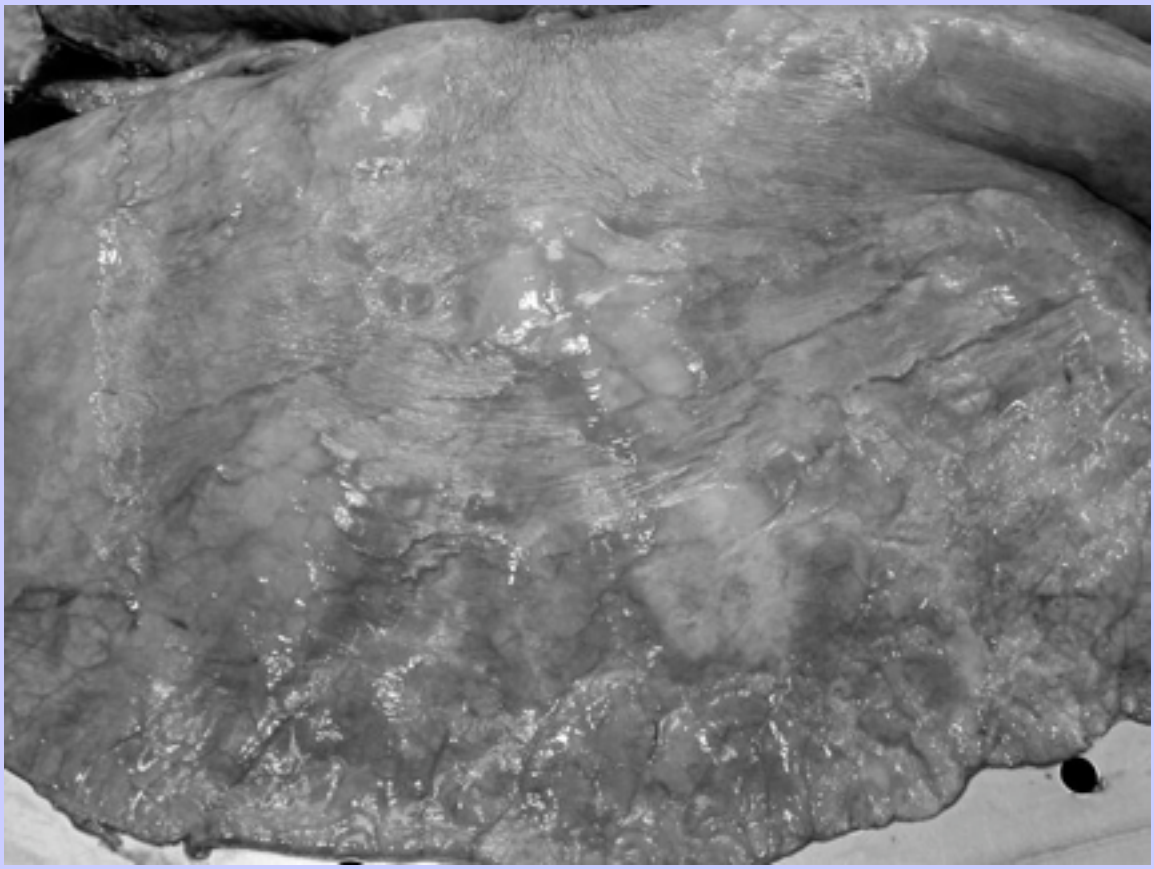
Fig. 31-40 Equine multinodular pulmonary fibrosis.



31.33 DISEASES OF LYMPH NODES, VASCULATURE, AND PHARYNX

31.33.1 RETROPHARYNGEAL LYMPH NODE ABSCESSATION

JOHN R. PASCOE

31.33.2 Definition and Etiology

In horses the retropharyngeal lymph nodes consist of medial and lateral lymphoid chains. The lateral chain (8 to 15 nodes) is located ventral to the atlas and along the lateral sides of the guttural pouches. These lymph nodes are covered by the parotid gland and are not clearly distinguishable from the medial retropharyngeal lymph

nodes (20 to 30 nodes). The medial retropharyngeal lymph nodes are located ventral to the lateral chain on the dorsolateral aspect of the pharynx and the caudoventral aspect of the guttural pouches.[1062]

Retropharyngeal lymph node abscesses in horses are generally caused by *S. equi* subsp. *equi* infection (see Strangles, p. 533) or are secondary to trauma.[1063,1064] Other bacterial isolates have included *S. equi* subspecies, *Streptococcus zooepidemicus, Corynebacterium pseudotuberculosis*, and *Actinobacillus* species. An unusual case of granulomatous infection of the guttural pouch caused by *M. avium* complex was believed to have originated from the retropharyngeal lymph nodes.[1065] Extension of guttural pouch infections into the retropharyngeal space has been suggested as another source of infection.[1066] Lymphadenopathy of the retropharyngeal nodes may also occur during viral respiratory infections, including EHV, influenza, and viral arteritis.[1067] Retropharyngeal abscesses not associated with regional lymph nodes can result from perforation of the oropharynx or nasopharynx by ingested foreign bodies,[1068] passage of an NGT,[1069] or use of a balling gun.

In ruminants the medial retropharyngeal lymph nodes are located on the dorsolateral aspect of the pharynx, one on each side of the midline. One to three lymph nodes may be present in cattle. The lateral retropharyngeal lymph nodes are located caudal to the medial retropharyngeal lymph nodes in the cranial neck region and are caudal to the retropharyngeal space.[1062]

Abscessation of the medial retropharyngeal lymph nodes in cattle may result from pharyngeal actinobacillosis, foreign body penetration, or traumatic perforations by balling guns or dose syringes.[1070,1071] Frequently *Arcanobacterium (Actinomyces) pyogenes* or *Actinobacillus* species can be isolated.[1072] Cattle with abscessed pharyngeal lymph nodes often have a small ulcer in the mouth, most frequently at the junction of the base and shaft of the tongue. This is more likely to occur when cattle are eating dry scabrous roughage. In addition to traumatic perforations and foreign bodies, caseous lymphadenitis (CLA) caused by *C. pseudotuberculosis* frequently results in abscessation of these lymph nodes in sheep and goats.[1067]

31.33.3 Clinical Signs and Differential Diagnosis

The clinical signs associated with retropharyngeal lymph node infection or abscessation in horses include dysphagia, odynophagia (painful swallowing), nasal or oral regurgitation, excess salivation, difficult and often noisy breathing, painful throatlatch swelling, mucoid to mucopurulent nasal discharge, extension of the head and neck, and weight loss.[1062] In a retrospective study of 46 horses referred because of retropharyngeal lymph node abscessation, the frequency of abnormal clinical signs was as follows: fever and increased heart and respiratory rates, 80%; unilateral or bilateral throatlatch swelling, 65%; respiratory stertor or distress, 35%; purulent nasal discharge, 20%; inappetence and signs of depression, 15%; and dysphagia, 9%.[1073] Other clinical signs observed endoscopically include reduction in size or collapse of the pharyngeal lumen, asymmetry of the dorsal pharyngeal wall, and deviation of the laryngeal aperture away from the retropharyngeal mass.[1063,1073] The differential diagnosis for a retropharyngeal mass should include abscess, cellulitis, guttural pouch empyema or tympany, parotiditis, lymphadenopathy, neoplasia, and hematoma.

Clinical signs observed in cattle with infection or abscessation of the medial retropharyngeal lymph nodes include difficult breathing, excessive salivation, extension of the head and neck, anorexia, enlarged submandibular lymph nodes, nasal discharge, and swelling in the retropharyngeal space.[1070] Other disease conditions that affect the oropharynx and surrounding lymph nodes should be considered in the differential

diagnosis. These include actinobacillosis, lymphosarcoma, sialolithiasis, and necrotic laryngitis, laryngeal edema, or severe tracheitis caused by infectious bovine rhinotracheitis (IBR) virus.[1067,1070]

Affected sheep and goats may exhibit excessive salivation, increased respiratory rate, stertorous breathing, mucopurulent nasal discharge, regurgitation, gagging, depression, SC crepitation, weakness, and fetid breath. A false carotid aneurysm in the retropharyngeal space has been reported; on external examination it may be confused with abscessation of the medial retropharyngeal lymph nodes.[1074] Enlarged retropharyngeal lymph nodes are usually easily palpated and identified in sheep and goats. CLA (see Chapter 37) is the most frequent cause of enlarged retropharyngeal lymph nodes in these species.

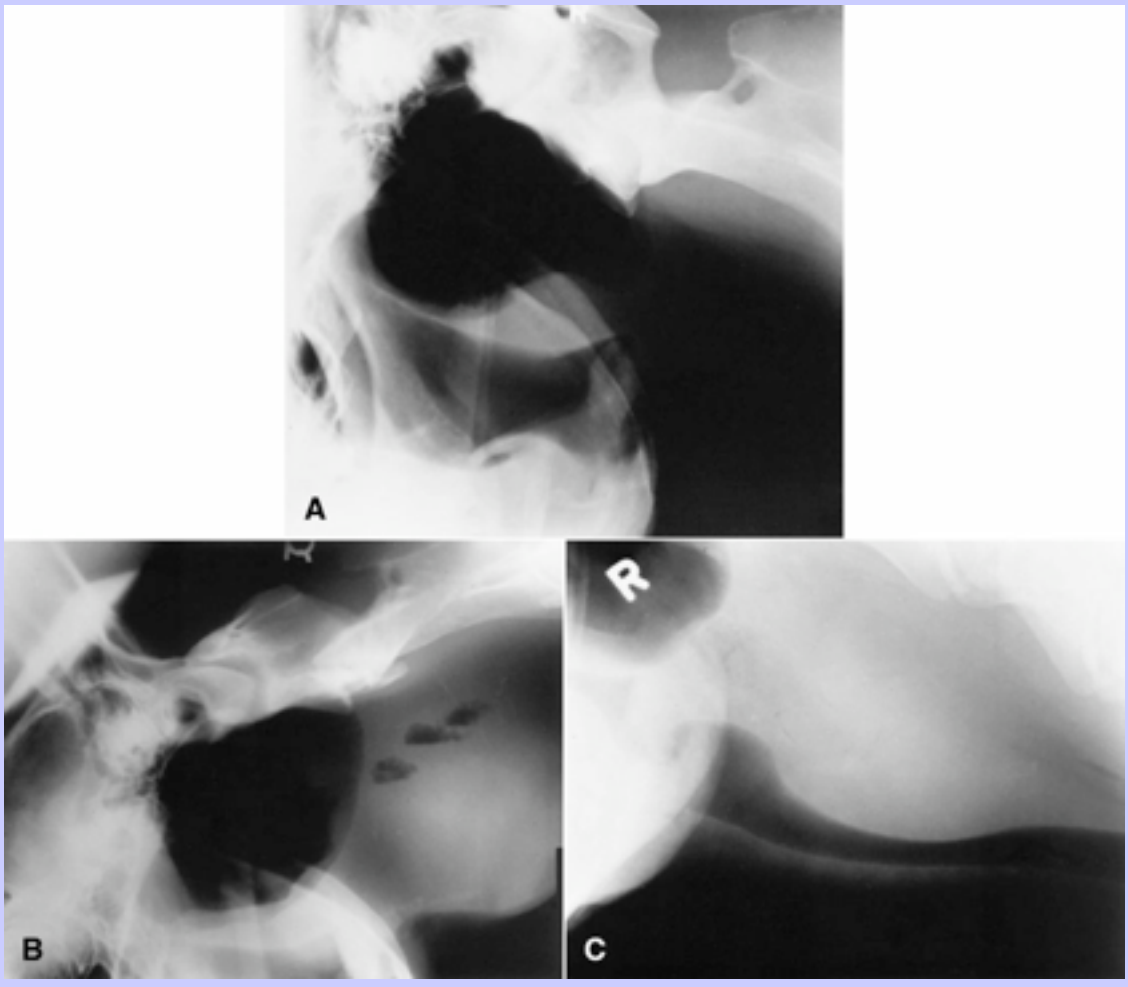
31.33.4 Clinical Pathology

Collection of purulent material from abscessed lymph nodes may assist in identification of the causal agent. Leukocytosis may be evident on the hemogram, with neutrophilia peaking as the lymph nodes abscess.

31.33.5 Laboratory Aids and Definitive Diagnostic Tests

Lateral radiographs of the pharynx, diagnostic ultrasound, and endoscopy aid in the diagnosis of retropharyngeal infections or abscesses. In horses, radiography may reveal a large soft-tissue mass impinging on the guttural pouch from a caudoventral direction (Fig. 31-41, *A*), as well as thickening of the pharyngeal roof. The soft-tissue swelling may contain gas (Fig. 31-41, *B*). Compression of the larynx and trachea with ventral displacement may also be evident (Fig. 31-41, *C*).[1063] Observation of a gas-fluid interface on radiographs of the pharynx generally indicates abscessation, but care should be taken to distinguish a retropharyngeal abscess from guttural pouch empyema.[1065] Foreign bodies associated with pharyngeal trauma are not usually radiopaque and therefore are not visible radiographically unless outlined by contrast medium. Exceptions include small wire foreign bodies likely ingested from baled hay that can perforate the tongue or oropharynx causing cellulitis and dysphagia[1068] and, in cattle, magnets that have been inadvertently placed retropharyngeally.

Fig. 31-41 **A**, Lateral radiograph. A soft-tissue density (retropharyngeal abscess) is distorting the floor of the guttural pouch. **B**, Lateral radiograph. There is increased soft-tissue density with gas shadows ventral to the cervical vertebrae. These changes are consistent with abscessation of the retropharyngeal lymph nodes. **C**, Lateral radiograph. There is increased soft-tissue density ventral to the cervical vertebrae, with compression of the dorsal border of the trachea. These changes were caused by cellulitis and abscessation of the retropharyngeal lymph nodes.



On endoscopy, asymmetry or collapse of the pharyngeal lumen or both signs suggests a retropharyngeal space-occupying mass. Recognition of drainage from the guttural pouch openings or examination of the guttural pouches may be necessary to differentiate between guttural pouch empyema and retropharyngeal lymphadenopathy or pharyngeal neoplasia. Occasionally the pharyngeal wall ruptures, allowing endoscopic

observation of retropharyngeal drainage into the pharynx, usually near the esophageal entrance.[1063] Percutaneous needle aspiration may yield a definitive diagnosis if purulent material is obtained. Ultrasonography improves diagnostic precision by permitting more accurate identification of the abscess and highlighting its anatomic relationships as an aid to surgical drainage.[1075]

Clinical examination, radiography, ultrasonography, endoscopy, and percutaneous centesis may all prove helpful in making a diagnosis of medial retropharyngeal lymph node infection or abscessation in ruminants. In cattle, localized swelling cranial to the larynx may be detected by digital palpation of the oropharynx.[1070] Oropharyngeal examination must be performed carefully in animals with respiratory distress to prevent further airway compromise.

31.33.6 Pathophysiology

Upper respiratory disease, trauma, and foreign body penetration with resulting infection and drainage to local lymph nodes result in clinically apparent infection and abscessation of the retropharyngeal lymph nodes. In horses the retropharyngeal space is occupied primarily by the guttural pouches. Because the vagus, glossopharyngeal, hypoglossal, spinal accessory, and sympathetic nerves traverse this area, their function can be affected by infectious or inflammatory processes involving the retropharyngeal space.[1063] If such infections are contained within the lymph nodes or are confined within the fibrous capsule of the abscess, cranial nerve dysfunction is not usually evident.[1063] Clinical evidence of dysphagia or odynophagia such as the presence of feed and saliva at the external nares may result from inflammation or injury of the glossopharyngeal nerve or pharyngeal branch of the vagus nerve,[1063] compression, or obstruction of pharynx or esophagus and from angina. It has been suggested that retropharyngeal lymphadenitis may result in neuritis of the pharyngeal branch of the vagus nerve in young horses and contribute to the pathogenesis of dorsal displacement of the soft palate.[1076]

Respiratory distress may result when enlargement of the retropharyngeal lymph nodes compresses or obstructs the nasopharyngeal, laryngeal, or tracheal lumen,[1063,1070] and the disease caused by *S. equi* subsp. *equi* in horses is appropriately named *strangles*.

The most common cause of pharyngeal inflammation and infection in cattle is pharyngeal trauma associated with balling guns, dose syringes, paste wormer guns, esophageal feeders, or stomach tubes. A careful history to determine whether any of these devices were used is important in ascertaining the source of pharyngeal abscessation. Such infections usually involve mixed bacterial flora, because they are directly connected with the oral pharynx.

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31.33.7 Epidemiology

Infection with *S. equi* usually results from contact (inhalation or ingestion) with pasture, feed, or water contaminated with nasal discharge from infected horses. Asymptomatic carrier horses have also been implicated as source of infection.[1077] The likely bacterial reservoir in carrier horses is the guttural pouch, particularly if chondroids are present in one or both pouches[1077–1079] or if swollen or discharging lymph nodes are present in the floor of the medial compartment of the guttural pouch. Infection of the pharyngeal and nasal mucosa results in an acute pharyngitis and rhinitis, and drainage to regional lymph nodes results in lymphadenopathy and possibly abscessation.[1067]

CLA is spread through the discharges from ruptured lymph nodes. The causal agent *C. pseudotuberculosis* may persist in the environment for long periods, and infection results from contact of shearing, docking, or castration wounds with contaminated soil, equipment, or freshly ruptured abscesses. Sheep dips have been reported as another important source of infection.[1067] Spread of infection from skin wounds often leads to involvement of local nodes and abscess formation. The mode of spread in goats is still not well understood, but the disease usually spreads in a low-grade contagious manner, often involving most of the herd over a period of years.

31.33.8 Necropsy Findings

Fatalities are rare and most likely result from respiratory compromise or septicemia. Postmortem lesions include cellulitis with compression and ventral displacement of the larynx and cranial cervical trachea. Abscesses are variable in size and may contain either caseous *(C. pseudotuberculosis)* or liquid material *(S. equi* subsp. *equi)*. A thick, fibrous capsule may occur in response to the infectious process and may account for the surrounding tissue compression. Occasionally, draining tracts may connect the abscess to the pharynx, guttural pouch, or skin.[1069,1080]

31.33.9 Treatment and Prognosis

Treatment goals are relief of respiratory distress and control of infection. Temporary tracheotomy may be needed for relief of respiratory distress and may be prudent, especially in foals with singular, large, or multiple abscesses, before percutaneous drainage is attempted. After surgical drainage, appropriate systemic antibiotics are administered and supportive therapy to further reduce swelling may be beneficial.

Surgical approaches include percutaneous drainage, intraoral drainage, and marsupialization.[1063,1070] In horses an intraoral approach is very difficult because of the long narrow oral cavity, and for this reason percutaneous drainage is commonly used. For abscesses visible through the mucosal lining of the guttural pouch, endoscopically assisted drainage into the pouch can also be considered. Surgical access to the retropharyngeal space has been described, including dorsal and ventral approaches, an approach through Viborg's triangle, and a lateral approach.[1073,1081] A ventral surgical approach is recommended because of the relative lack of vital structures encountered and the excellent ventral drainage achieved. A less invasive drainage technique can be accomplished in standing sedated horses, by ultrasound-guided percutaneous needle placement into abscessed lymph nodes. Affected nodes can have a wall thickness of 1 to 2 cm and a diameter of 5 to 11 cm.[1075] Aspiration of purulent matter and cavity lavage with antiseptic solutions and concurrent administration of parenteral antibiotics may be sufficient for resolution. If aspiration is not possible because the purulent material is too viscous, incision directly along the needle shaft, after careful consideration of regional anatomy, provides adequate exterior drainage and access for cavity lavage with antiseptic solutions or use of a seton or gauze packing. If the abscess is endoscopically visible beneath the guttural pouch mucosa, drainage into the guttural pouch and subsequent lavage of the purulent material can be accomplished. Before or at the time of abscess drainage or excision, the horse should be started on broad-spectrum antimicrobials, followed by the appropriate specific antimicrobial drug when results of the culture and susceptibility test are known.

Occasionally, medical management alone may resolve infection; however, this is less likely if abscessation has occurred. Because the most common bacterial isolate in the horse is *S. equi*, parenteral antimicrobial therapy with procaine penicillin G (22,000 IU/kg IM twice daily) or potassium penicillin (20,000 IU/kg IV four times daily) is recommended. Systemic NSAIDs are useful to reduce inflammation and swelling, and fluid and

electrolyte therapy may be necessary if there is odynophagia or dysphagia. Aspiration pneumonia can occur with dysphagia or if there is oral or nasal regurgitation associated with painful swallowing.

In cattle with pharyngeal trauma, an existing wound is often draining from the retropharyngeal area to the oropharynx, making surgical drainage unnecessary. Such animals tend to respond well to parenteral broad-spectrum antimicrobial therapy.[1082] Parenteral antimicrobial therapy alone has been ineffective in treating retropharyngeal abscesses when there is no draining tract.[1070,1071] Intraoral or percutaneous drainage has been used successfully in conjunction with broad-spectrum, parenteral antimicrobial therapy.[1071] After drainage, the abscess cavity is flushed daily with an antiseptic or antibiotic solution.[1070] Surgical drainage into the oral cavity must be handled with caution. The patient's head should be lowered so that exudate or flush solution is not aspirated; inspection of the granulating abscess cavity is necessary if feed impaction is suspected.[1063,1070] Aspiration pneumonia may be a serious complication when dysphagia is present.

In sheep and goats, walled-off *C. pseudotuberculosis* abscesses may often be most safely drained by suturing the skin to the heavy abscess capsule (a procedure known as *marsupialization*) before opening the capsule. Marsupialization prevents contamination of other retropharyngeal structures with infected material and markedly reduces postsurgical cellulitis. Although *C. pseudotuberculosis* is susceptible in vitro to a number of antimicrobial agents, abscesses associated with the condition have not been well controlled by antimicrobial therapy. Walled-off *C. pseudotuberculosis* abscesses are difficult to eliminate solely with antimicrobial therapy, and drainage or removal of the entire lymph node gives the best results.

31.33.10 Prevention and Control

Preventive measures to limit infection and abscessation of retropharyngeal lymph nodes include proper administration of therapeutic agents with balling guns and dose syringes, isolation of horses affected with viral or bacterial upper respiratory disease, vaccination against strangles, and vigorous treatment in the early stages of streptococcal infection. Preventing contamination of shearing equipment and dipping vats with *C. pseudotuberculosis* is important in limiting the spread of this organism in sheep. Culling affected sheep and goats may also help to reduce the incidence of CLA.

31.34 PHARYNGITIS

JOHN R. PASCOE

31.34.1 Definition and Etiology

Pharyngitis is inflammation of the pharyngeal tissues. It is not generally considered to be a specific disease entity but rather a response to other diseases, particularly viral and bacterial respiratory disease, and to a lesser extent to local physical, chemical, or allergic causes. Acute and chronic forms of pharyngitis are recognized.

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Although physical and chemical causes of pharyngitis may be identified with certainty, the role and specificity of microbial pathogens as causative agents remain controversial. In horses, *Streptococcus* species, picornavirus, rhinovirus 1 and 2, herpesvirus (EHV-1, EHV-2), myxovirus (influenza A/equi 1, A/equi 2), and paramyxovirus (parainfluenza 3) have been incriminated as specific causes of pharyngitis.[1083–1087] In cattle, *Arcanobacterium (Actinomyces) pyogenes, Actinobacillus* species, and *Fusiformis necrophorus* are frequently isolated.[1088]

In horses, synonyms for chronic pharyngitis include pharyngeal lymphoid hyperplasia (also PLH), chronic pharyngitis, chronic lymphoid follicular hyperplasia, follicular pharyngitis, and follikelkatarrh.[1089–1091]

31.34.2 Clinical Signs and Differential Diagnosis

In acute pharyngitis, signs are associated with pharyngeal pain (odynophagia, dysphagia), nasal discharge (serous, seromucous, mucopurulent, purulent, feed-contaminated), regional lymphadenopathy (submandibular, retropharyngeal nodes), ptyalism (especially in cattle), respiratory noise (often inspiratory), pharyngeal swelling, and cough. Mouth breathing may occur in cattle when there is increased resistance to breathing associated with excessive exudate, diphtherous membranes, and lymphadenopathy or lymph node abscess. Pharyngitis from local pharyngeal trauma or incarcerated foreign bodies may also be associated with odor of either the breath or nasal discharge. Calves with necrotic laryngitis, pharyngitis, and stomatitis also have a characteristic malodorous breath. Acute laryngeal inflammation and edema of unknown cause can occur in horses and ruminants and is characterized by marked inspiratory difficulty and stertor without malodorous breath. Treatment of acute edema with dexamethasone (0.05 mg/kg IM) and broad-spectrum antimicrobials or penicillin has produced rapid clinical improvement.

Signs observed on endoscopic or oropharyngeal examination in cattle include pharyngeal hyperemia and edema, lymphonodular swelling, and either a moist appearance of the pharyngeal surface or the presence of exudate or a diphtherous membrane adhering to the pharyngeal surface. Focal necrosis or ulceration of the mucous membrane and tonsillar tissue may occur; signs associated with rhinitis and laryngitis may also be evident. Signs of chronic pharyngitis are similar. In horses there may be endoscopic evidence of more marked hyperplasia of the lymphonodular follicles within the pharyngeal mucosa, and single or multiple lymphonodular masses may be within, or protrude from, the pharyngeal mucosa. Biopsy and cytologic evaluation are recommended to rule out neoplasia, particularly squamous cell carcinoma, lymphoma, and lymphosarcoma. Differential diagnostic possibilities include rhinitis and laryngitis, and in cattle rabies should be strongly considered before oropharyngeal examination. If the predominant sign is dysphagia (see Chapter 7), other diagnostic ruleouts include tongue foreign bodies, fractures of the hyoid apparatus or jaws, and, in the horse, diseases of the guttural pouches. If exercise intolerance is the primary complaint in a horse, pharyngitis should be considered only after all other possible causes of impaired performance have been eliminated (see Chapter 5).[1092–1096] Pharyngitis has not been shown to be a risk factor for poor racing performance.[1097]

Upper airway inspiratory pressures recorded during strenuous exercise in horses with grade IV lymphoid hyperplasia do not appear to be different from those recorded in normal horses under the same exercise conditions.[1095] If the assumption is made that airflow in both groups of horses is comparable, then severe lymphoid hyperplasia does not appear to cause functional upper airway obstruction. It is conceivable that pharyngeal pain associated with lymphoid hyperplasia may contribute to bronchoconstriction and impaired performance; however, this effect remains unproven.

31.34.3 Clinical Pathology

Changes in the hemogram and biochemical profiles are likely to result from concurrent respiratory disease (increases or decreases in absolute or differential leukocyte counts, hyperfibrinogenemia, anemia) or to reflect abscess formation (neutrophilia, hyperfibrinogenemia) or dehydration and fasting associated with dysphagia.

31.34.4 Laboratory Aids and Definitive Diagnostic Tests

Although a presumptive diagnosis can be made from the clinical signs, definitive diagnosis requires observation of the pharynx (Fig. 31-42) and, more important, exclusion of other conditions that might have similar signs. Radiography of the pharynx can provide information on pharyngeal anatomy, radiodense foreign bodies, soft-tissue masses, fractures, and, in horses, guttural pouch disorders. Ultrasonography of the pharyngeal region and, if indicated by the clinical examination, both radiographic and ultrasound examination of the thorax may help define the extent of concurrent pulmonary disease.

Microbial culture of pharyngeal secretions can be considered, but interpretation is difficult because (1) the pharynx normally has resident microflora with considerable individual variation, and (2) many of the microorganisms isolated are capable of opportunistic infection. In horses with grades III and IV pharyngeal lymphoid hyperplasia, the number of bacteria recovered per gram of pharyngeal secretion was almost 100-fold greater than in normal horses.[1096] The pattern of microbial isolation was not consistent among horses, suggesting that these organisms were not the source of the pharyngitis but rather other factors had made conditions for colonization more favorable.

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Fig. 31-42 Endoscopic view showing the nodular appearance of pharyngeal lymphoid hyperplasia.

Biopsy and cytologic examination are indicated in refractory cases and when abnormal masses are present to rule out neoplasia.

31.34.5 Pathophysiology

Acute pharyngitis occurs as a sequela to inflammation of regional lymphoid tissue (see Kumar and colleagues[1098] for a description of the morphologic and histochemical features of the normal equine nasopharyngeal tonsil).[1099] In horses the pharyngeal tonsil consists of discrete lymphoid follicles diffusely distributed in the dorsal and lateral walls of the pharynx. In ruminants the pharyngeal tonsil is located caudal to the pharyngeal septum in the caudodorsal wall of the pharynx and is bounded by long ridges and grooves into which mucous glands open. In response to local or lymphogenous spread of infection, the tonsillar tissue becomes inflamed and the tonsillar crypts become filled with desquamated epithelium, leukocytes, and bacteria. Clinically this is seen as hyperemia and edema of the pharyngeal tonsil with diffuse white or yellow tips to the lymph nodules. The edematous appearance is associated with hyperplasia of the lymph nodules and sequestration of perinodular inflammatory fluid.

If extensive destruction of the lymphoid cells or subsequent invasion of the nodules or supporting soft tissue is evident, the result is focal or diffuse necrosis, which may be seen as pinpoint areas of follicular necrosis or diffuse necrosis with associated purulent or fibrinonecrotic exudate. With resolution, atrophy of some follicles and increased fibrosis are present. Follicular atrophy also occurs with aging.

31.34.6 Epidemiology

No specific epidemiologic data are available on pharyngitis. When pharyngitis occurs as a sequela to respiratory tract infection, the population demographics should be similar to those known for the specific respiratory disease. For example, grade II pharyngeal lymphoid hyperplasia was identified in 60% of foals with distal respiratory tract infection and in only 13% of control foals.[1100] Because physical and chemical injury to the pharynx occur sporadically, no universal epidemiologic characteristics would be anticipated.

Pharyngeal lymphoid hyperplasia has been reported to be particularly prevalent in horses younger than 5 or 6 years of age.[1089,1093,1097,1101–1103] In an endoscopic survey of 479 horses, primarily thoroughbreds in race training, 141 (29%) had pharyngeal lymphoid hyperplasia. Of the 2-year-olds, 63% were affected, and the prevalence decreased with age; less than 20% of horses older than 5 years were affected.[1093] In a subsequent survey of 678 thoroughbred horses in training, the prevalence of pharyngeal lymphoid hyperplasia was 34%; the prevalence was again age-related, and severe grades of pharyngeal lymphoid hyperplasia were observed more often in younger horses.[1101] Grade II pharyngeal lymphoid hyperplasia was observed in 45% of 2-year-old horses, whereas only 16%, 15%, and 12% of 3-, 4-, and 5-year-old horses were classified as grade II. Similar results were reported from Japan for racing thoroughbreds with a history of cough or abnormal respiratory noise.[1102]

31.34.7 Treatment and Prognosis

The approach to treatment is largely symptomatic and directed to palliation of pharyngeal pain and maintenance of unobstructed breathing until the initiating disease process has abated. In many instances the signs are sufficiently mild that treatment is unnecessary. When pharyngeal angina is causing inappetence or dysphagia,

administration of NSAIDs should be considered. Dehydration should be corrected by either parenteral or enteral fluid administration. Enteral fluid therapy may be difficult because passage of an NGT may elicit too much pain. If the animal has been inappetent for several days, nutritional support may be necessary until pharyngeal pain subsides sufficiently to allow normal eating to resume. Soft feeds, especially green grass, should be offered when available to encourage animals with pharyngeal discomfort to eat.

Although routine antimicrobial therapy is probably not indicated, it is often given to limit development of secondary bacterial infection. Infections caused by foreign body injuries should be treated with antibiotics that have broad aerobic and anaerobic sensitivity. Daily lavage of any cavitary wounds, debridement, and removal of feed material may be necessary to prevent additional abscess formation and hasten healing.

Custom topical preparations, usually containing an antibiotic, an antiinflammatory drug, and a hygroscopic agent (glycerine) or DMSO, are often used for palliation of clinical signs, especially in horses with pharyngeal lymphoid hyperplasia.[1103,1104] These preparations are usually administered two or three times daily through a transnasal catheter and sprayed onto the pharyngeal surface. Despite their frequent use, it is not known whether this form of therapy is effective or whether the response merely reflects natural resolution of the predisposing cause.

Treatment of pharyngeal lymphoid hyperplasia is also empiric and generally palliative. Rest from training for 4 to 8 weeks is commonly advocated, and, although some horses experience recurrence when training resumes, this enforced rest is beneficial as a convalescent period for any concurrent subclinical respiratory disease. Horses that are kept in training are often initially treated empirically with sulfa compounds and topical throat preparations. With continued clinical signs, penicillin or broad-spectrum antibiotics are often given. If the pharyngeal lymphoid hyperplasia does not improve or resolve after this therapy, pharyngeal cautery is often used. Techniques for pharyngeal cautery include topical application of trichloroacetic acid, electrocautery, freezing with liquid nitrogen or Freon, and photoablation by neodymium: yttrium aluminum garnet (Nd:YAG) laser with either contact or noncontact technique.[1103–1106] Cauterization techniques have received considerable testimonial support, but it should be realized that cautery does not really effect a cure but rather obliterates the reactive tissue so that it is no longer clinically evident.

Routine immunization at frequent intervals for known viral respiratory pathogens is also advocated for both the treatment and the prevention of pharyngeal lymphoid hyperplasia.[1103,1107]

31.34.8 Prevention and Control

Methods used to control and prevent most of the common viral and bacterial respiratory diseases (see Chapter 48) should limit herd problems with acute pharyngitis. Non—respiratory disease—related causes such as trauma from balling guns, NGTs and dose syringes, foreign objects, and chemical burns can be minimized by improvement of husbandry practices.

Although preventing pharyngeal lymphoid hyperplasia in horses by prophylactic immunization against common equine viral respiratory agents at regular intervals has been discussed at length, there are no substantive data to support this practice. Nevertheless, racetrack veterinarians maintain that frequent immunization (60-day intervals) against influenza and rhinopneumonitis markedly reduces the severity of pharyngeal lymphoid hyperplasia and improves exercise tolerance.[1107] Considering the mobility of racing and show horse populations, this approach should at least be beneficial for limiting outbreaks of viral respiratory disease and consequently perhaps limiting chronic pharyngeal lymphoid hyperplasia. Until more is understood about the clinical appearance of the pharyngeal tonsil in horses, along with normal variations that occur with aging in exercised

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and nonexercised horses, and these findings can be correlated with immunopathologic events and indexes of performance, it will remain difficult to treat, control, and prevent pharyngitis in a systematic manner.[1108]

31.35 GUTTURAL POUCH DISEASES

JOHN R. PASCOE

31.35.1 Definition and Etiology

The guttural pouches are paired air-filled diverticula of the eustachian tubes that communicate between the middle ear and the pharynx. They are located ventral to the atlas, dorsocaudal to the pharynx, and rostrodorsal to the retropharyngeal lymph nodes and occupy a large part of the retropharyngeal space. Each pouch is divided into medial and lateral compartments by a stylohyoid bone that courses through the caudolateral aspect of each pouch. The medial compartments appose each other on the midline. The lateral walls of each guttural pouch contain cranial nerves VII (facial), IX (glossopharyngeal), X (vagus), XI (spinal accessory), and XII (hypoglossal); the cranial sympathetic trunk; the internal carotid artery; and branches of the external carotid artery.[1109] The intimate relationship of these vessels and nerves with the mucous membrane lining the guttural pouches explains why epistaxis and nerve dysfunction frequently accompany guttural pouch disease. Each pouch has a capacity of approximately 300 mL, with the medial compartment accounting for approximately two thirds of this volume. Communication with the pharynx occurs through a slitlike opening situated rostral and ventral to the pharyngeal recess. The pharyngeal opening of the guttural pouch is funnel shaped and wider rostrally than caudally. The plica salpingopharyngea is a fold of mucous membrane that contributes to the caudal narrowing of the pharyngeal opening and makes catheterization of the guttural pouch difficult. Redundancy of this fold of tissue may contribute to guttural pouch tympany.[1109]

The guttural pouch is not a sterile environment; as an extension of the pharynx, it normally contains bacteria. In one report of 30 normal horses, 59% of percutaneous guttural pouch lavage aspirates had bacterial growth, although only 7% were considered to have bacteria considered to be pathogenic; no fungi were isolated.[1110] Inflammatory cell counts and distribution were correlated with recovery of bacteria. Aspirates were considered normal if there were less than 5% neutrophils; typical cell distribution was primarily ciliated columnar epithelial cells, a few nonciliated cuboidal epithelial cells, and less than 1% monocytes, lymphocytes, and macrophages.[1110] Horses exercised strenuously on a regular basis had lower total cell counts, lower neutrophil counts, and fewer bacteria isolated.[1110] Preventing horses from head lowering for 12 to 24 hours increases the frequency of bacterial isolation, especially at 24 hours, including an increase in neutrophil counts, and likely indicates reduced ability to clear guttural pouch secretions.[1111] Interpretation of microbial isolates from guttural pouches requires correlation with cytologic characteristics of guttural pouch fluid and clinical signs.[1112]

Three disease conditions commonly affect the guttural pouches: tympanitis, empyema, and mycosis.[1109] Less common conditions include neoplasia,[1113] fractures of the hyoid bone, foreign bodies,[1109,1114] and cystic structures.[1115]

31.36 GUTTURAL POUCH TYMPANY

Tympany of the guttural pouch occurs infrequently and is recognized in foals after birth up to 1½ years of age[1109,1116–1118]; affected foals are usually identified within the first 2 weeks of life. Fillies are more commonly

affected, with the ratio of females to males ranging from 2:1 to 4:1. Arabian foals may have a higher risk for tympany, which may be an inherited trait.[1119] Tympany is characterized by unilateral or bilateral distention of the guttural pouch with air. The exact cause is unknown, but numerous reports have implicated a congenital redundancy of the plica salpingopharyngea, which acts as a one-way valve that apparently permits airflow into but not out of the pouch.[1116] It has also been postulated that upper airway infections and inflammation may result in enlargement of this fold of tissue, with subsequent air trapping in the pouch.[1120]

31.36.1 Clinical Signs and Differential Diagnosis

Affected foals usually have a nonpainful, soft, fluctuant swelling in the retropharyngeal space (Fig. 31-43, *A*) with variable respiratory distress, extension of the head and neck, and signs of dysphagia.[1116,1117] Mild tympany may not result in signs other than swelling of the throatlatch region.[1120] Respiratory distress occurs when continued distention of the pouch compresses the pharyngeal area. The differential diagnosis should include guttural pouch empyema and retropharyngeal abscesses or cellulitis.

31.36.2 Clinical Pathology

Stress leukocytosis may occur if there is marked respiratory distress.

31.36.3 Diagnostic Aids

Diagnosis of guttural pouch tympany is based on recognition of characteristic swelling in the retropharyngeal space and confirmation by physical examination. Although the distention is most often unilateral, extreme distortion of a single pouch may give the impression of bilateral involvement.[1121] Differentiation between unilateral and bilateral involvement can be difficult and may require deflation of the affected guttural pouch by catheterization or percutaneous needle aspiration combined with external compression. Other adjunctive diagnostic procedures include radiographic demonstration of gas distention of one or both pouches (see Fig. 31-43, *B*) and endoscopic observation of pouch distention and pharyngeal distortion.

31.36.4 Treatment and Prognosis

Guttural pouch tympany and respiratory distress can be alleviated temporarily by aspiration of air from the affected pouch by means of either percutaneous decompression at the point of greatest distention through Viborg's triangle or introduction of a catheter through the pharyngeal opening of the guttural pouch.[1109] These measures are palliative, and the pouch rapidly refills when decompression is discontinued. Treatment methods of choice include surgical excision or photoablation of the redundant plica salpingopharyngea; fenestration of the medium septum between the two pouches by excision, electrosurgery, or photoablation; and creation of a salpingopharyngeal fistula by photoablation and temporary stenting of the fistula.[1116–1118,1122–1124] The latter technique is similar to an older, successful approach that involved incising the floor of the guttural pouch into the pharynx.[1125] If the condition is bilateral, fenestration of the median septum alone does not successfully resolve the condition, and either excision of one or both plica salpingopharyngea in combination with septal fenestration or septal fenestration and salpingopharyngeal fistula formation must be performed. After surgery the prognosis for resolution of guttural pouch tympany is generally considered favorable[1118] unless complicating factors such as aspiration pneumonia exist.[1117] Early recurrence after surgery can range from 15% to 30%, but further

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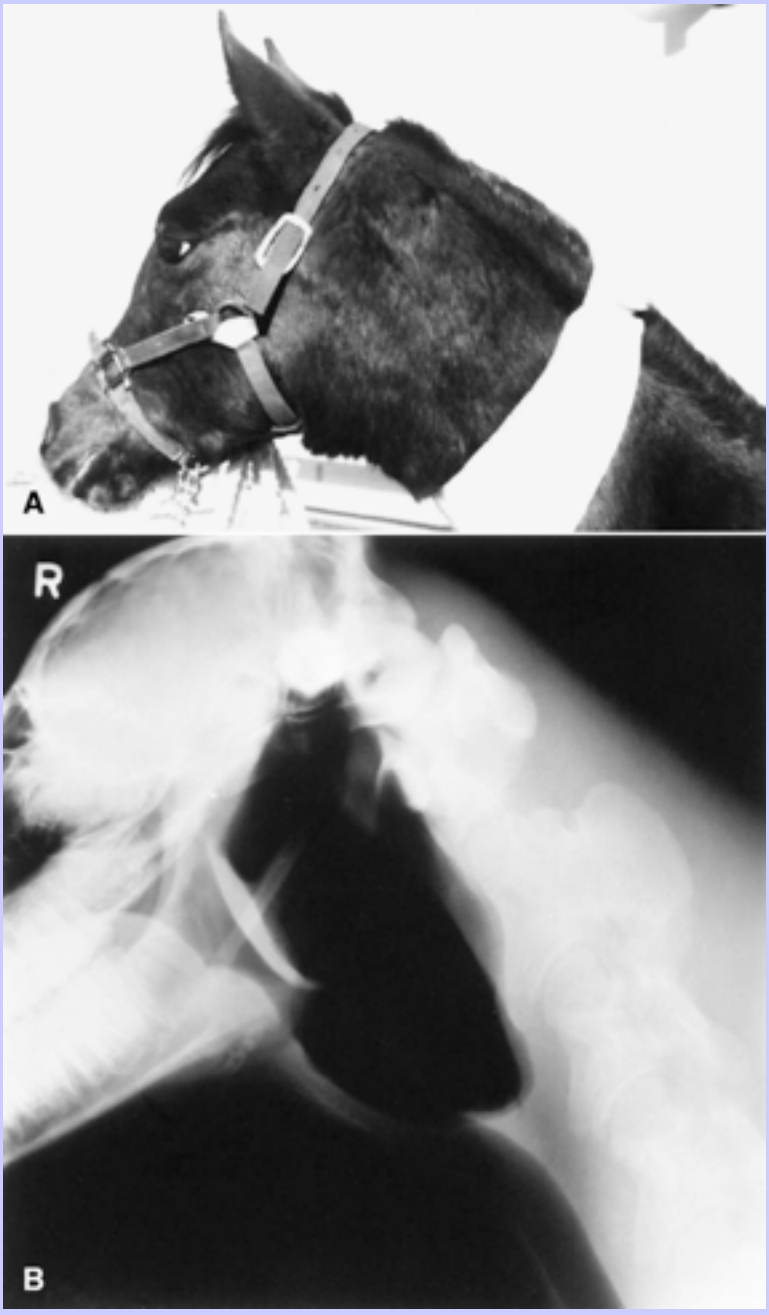
resection of the plica salpingopharyngea or refenestration of the mesial septum or enlargement of the fenestration typically results in resolution of signs.[1117,1118]

Fig. 31-43 **A**, Foal with guttural pouch tympanitis. Note the protrusion of the soft tissues over the lateral and ventral aspects of the throatlatch. **B**, Lateral radiograph of a foal with tympanites of both guttural pouches.



31.37 GUTTURAL POUCH EMPYEMA

Guttural pouch infections are introduced either directly through the pharyngeal opening or by lymphatic spread.[1126] Accumulation of purulent material (empyema) is considered to be a secondary, chronic, localized manifestation of a more generalized ascending respiratory infection. Empyema is usually unilateral and is often a sequela to an infectious respiratory disease, especially infection by *S. equi* subsp. *equi*.[1127–1130] Typically a horse with guttural pouch empyema displays continued nasal discharge after recovery from streptococcal infection.[1121,1130] In a case control study of foals with distal respiratory tract infection, 21% had concurrent mucopurulent drainage from the pharyngeal openings of the guttural pouches.[1131] *S. equi* subsp. *zooepidemicus* was isolated from respiratory secretions of the majority of infected foals and from exudate collected from guttural pouches.[1132] Rupture of retropharyngeal abscesses into the guttural pouch has also been associated with empyema, suggesting that strangles or other upper respiratory tract infections may have an important role in the development of guttural pouch infection in horses.[1128,1130,1133]

31.37.1 Clinical Signs and Differential Diagnosis

The clinical signs of guttural pouch empyema include intermittent nasal discharge that may worsen when the head is lowered, retropharyngeal swelling, cough, fever, parotid swelling and pain, dysphagia, difficult breathing, dysphagia, and pneumonia.[1134] Nasal discharge can be unilateral or bilateral, even if only one pouch is affected, because the pharyngeal openings of the guttural pouches are located caudal to the nasal septum. The nasal discharge is generally nonodorous, white, and opaque. Signs of dysphagia may be observed secondary to pharyngeal compression or paresis. Labored breathing may result from gradual collapse of the pharynx as the guttural pouch distends. Inspissation of the purulent material results in chondroids, which are hard concretions of inspissated pus.[1135] The differential diagnosis of guttural pouch empyema should include those diseases with chronic mucopurulent nasal discharge such as pneumonia, sinusitis, upper respiratory tract infections, and guttural pouch tympany.

31.37.2 Clinical Pathology

Leukocytosis is often present. Plasma fibrinogen levels are often increased, [1134] and these changes generally parallel the development of leukocytosis, pyrexia, and clinical signs of strangles or primary guttural pouch empyema. Analysis of fluid obtained by catheterization of the guttural pouch often reveals a beta-hemolytic *Streptococcus* species,[1128,1135] although other bacterial species have been isolated.[1134]

31.37.3 Diagnostic Aids

Guttural pouch empyema should be considered in any patient with a chronic, nonresponsive nasal discharge.[1121] Diagnostic aids include radiography, endoscopy, percutaneous centesis, and aspiration of material from the pouch through the pharyngeal opening.[1109] Recognition of fluid (Fig. 31-44) or radiodense masses (chondroids) within the pouch on standing lateral radiographs supports a diagnosis of empyema. Physical and endoscopic examination or oblique radiographic projections may be necessary to identify which pouch is involved. Endoscopic examination permits identification of the affected pouch and evaluation of the character of the fluid. Endoscopic examination of the lateral compartment is important to avoid missing sequestered fluid or

chondroids.[1136] Absence of fluid at the pharyngeal ostium does not preclude the possibility of guttural pouch empyema, especially if the fluid has become inspissated[1121] or the ostium is sealed closed.[1137] Fluid identified on radiographs should be characterized by endoscopic examination of the pouches or aspiration of the fluid with appropriate cytologic and microbial analysis. Fluid samples can be aspirated through the pharyngeal ostium with a sterile artificial insemination (AI) pipette, a Chambers catheter, or tubing advanced through the biopsy channel of an endoscope. Alternately, fluid can be aspirated percutaneously, but this may lead to cellulitis along the needle tract if pathogenic bacteria are tracked through tissues on needle withdrawal.

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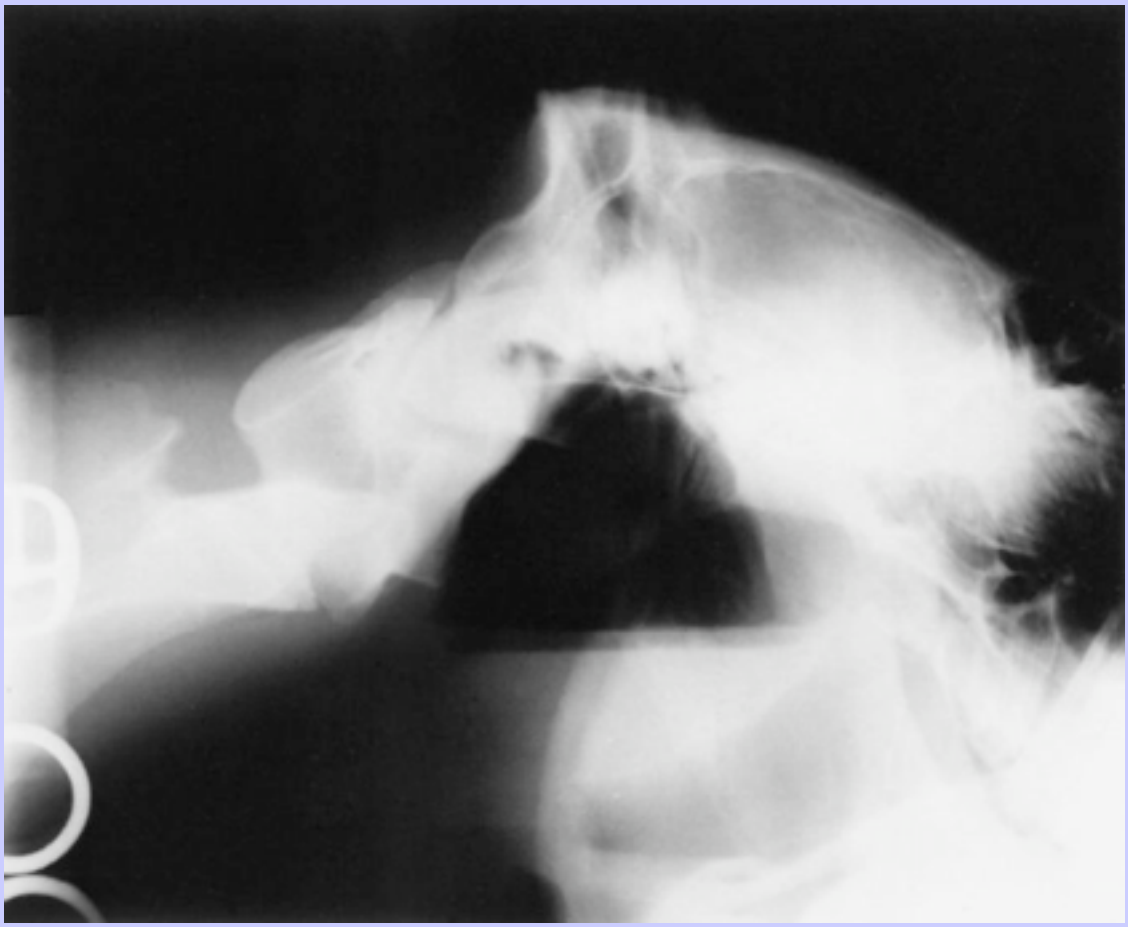
Fig. 31-44 Lateral radiograph demonstrating distinct fluid lines in both guttural pouches.



31.37.4 Pathophysiology

Strangles is a common upper respiratory disease affecting young horses. Primary clinical signs of strangles usually develop after a short incubation period of 2 to 6 days and include depression, pyrexia, coughing, and ocular and nasal discharges that become mucopurulent as the disease progresses. Lymph nodes of the head and neck become enlarged and painful, often forming abscesses. Guttural pouch empyema may result from extension of the upper respiratory infection with *S. equi* (strangles) to the guttural pouches or from rupture of

retropharyngeal lymph node abscesses into the guttural pouch.[1127,1128] Commonly isolated bacteria from guttural pouch empyema include *S. equi, S. zooepidemicus, E. coli*, and *Klebsiella* species.[1134] Not all horses with empyema have a history of strangles or previous respiratory infection, and empyema seemingly can occur by many of the same mechanisms as middle ear infection: that is, fluid accumulates in the area, and uncontrolled growth of bacteria normally present results in inflammation and exudation. Most streptococcal isolates are resistant to potentiated sulphonamides and sulfadimethoxine.[1134]

31.37.5 Treatment and Prognosis

Treatment of guttural pouch empyema is complicated by poor drainage from the affected pouch.[1109] In the normal horse the pharyngeal opening of the guttural pouch is located rostrodorsal to the floor of the guttural pouch, and drainage can be achieved only by lowering the horse's head.[1109,1122,1126] However, in horses with empyema, lowering the head may not achieve adequate drainage if there is ventral distortion of the pouch.[1109] Inflammation of the lining mucosa may result in swelling of the tissue surrounding the pharyngeal opening, further compromising normal drainage.[1109]

Choice of medical or surgical treatment depends on the duration and nature of the empyema. Parenteral antimicrobial therapy may reduce the quantity of the nasal discharge, but relapse often follows cessation of treatment.[1121,1134] The early stages of empyema may respond to daily lavage of the affected guttural pouch with physiologic solutions or saline antibiotic solutions injected through a catheter. A volume of 500 mL should be flushed into the involved pouch under moderate pressure to create contact with as much of the interior of the guttural pouch as possible.[1138] During lavage the head should be lowered to prevent aspiration of fluid. Purulent fluid from the affected guttural pouch should be aspirated on initial catheterization and submitted for bacterial culture and antimicrobial susceptibility testing. This can be accomplished with most flexible uterine culturettes under direct endoscopic observation. Parenteral antimicrobial drugs should be administered on the basis of susceptibility testing results; although medication may be of benefit in treating empyema, adequate drainage and local therapy are of primary therapeutic importance.

Irrigating the guttural pouch with an indwelling catheter may result in the development of severe inflammatory changes in the guttural pouch.[1139] Indwelling catheters placed in horses with normal guttural pouches have caused increasing purulent discharge with time; nasal discharge diminished after catheter removal and was absent after 3 days. Povidone iodine (1% available iodine) diluted to a 10% solution (0.1% available iodine) for lavage of the guttural pouch caused considerable reaction, including inflammatory infiltrates, hemorrhage, necrosis, and lymphoid reaction. Therefore, if possible, other means should be used to achieve antiseptic or antimicrobial therapeutic goals.[1139] Consideration should be given to using nonirritating solutions to prevent initiating cranial nerve neuritis. Although indwelling catheters are convenient, it may be well to suggest daily catheterization and irrigation with an AI pipette or Chambers catheter to diminish the inflammatory response associated with indwelling catheters in an already inflamed guttural pouch. Consideration of daily catheterization must be weighed against stress, possible tissue trauma, and time requirements for intermittent catheterization.[1139]

Treatment with parenteral antimicrobials and local lavage is successful and requires a patent opening for adequate drainage, but the course of treatment may be protracted. Acetylcysteine, a mucolytic, has been used successfully to resolve inspissated empyema.[1140] If response to lavage is poor or if secretions reaccumulate and empyema returns, surgical drainage of the guttural pouch should be considered.[1109]

Surgery is generally indicated when purulent material becomes inspissated or chondroids have formed,[1109,1141] although resolution has been reported in one horse after prolonged lavage (14 days) through an indwelling catheter.[1142] Surgical approaches include percutaneous drainage through standard approaches to the guttural pouches in anesthetized recumbent or standing sedated horses and creation of a nasopharyngeal fistula by use of an Nd:YAG laser.[1143] Other approaches when chondroids are present include removal by retrieval snares passed endoscopically, standing removal through a modified Whitehouse approach,[1144] and removal from the contralateral pouch after fenestration of the mesial septum when the ipsilateral ostium is closed.[1137]

The prognosis for guttural pouch empyema is generally favorable if it is recognized promptly and treated appropriately.[1134] Likewise, removal of chondroids typically carries a good prognosis.[1134]

31.38 GUTTURAL POUCH MYCOSIS

Guttural pouch mycosis is a fungal disease of the guttural pouch that typically affects the dorsocaudal region of the medial compartment, although lesions affecting larger areas, including the lateral compartment, have been seen.[1121,1145–1148] Fungal invasion of neurovascular structures coursing through the walls of the guttural pouches results in clinically apparent disease. Although the exact cause of guttural pouch mycosis is not known, a number of fungi, especially *Aspergillus (Emericella) nidulans* and *A. fumigatus*, have been isolated from the lesions.[1109,1148–1154]

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31.38.1 Clinical Signs and Differential Diagnosis

Lesions are usually unilateral and occasionally bilateral. The wide spectrum of clinical signs that can occur in association with guttural pouch mycosis reflects the degree of fungal invasion and subsequent inflammation of vascular structures or nerves beneath the mucous membrane lining the guttural pouch. Common clinical signs include intermittent spontaneous epistaxis and dysphagia.[1109,1145] Epistaxis generally results from fungal erosion of the wall of the internal carotid artery in the roof of the medial compartment and, less commonly, from erosion of the external carotid artery and maxillary artery in the lateral compartment.[1109,1145] Epistaxis is usually unilateral, occurring from the ipsilateral nostril, but can also be bilateral because the pharyngeal openings of the guttural pouches are located caudal to the caudal border of the nasal septum.[1147] Episodes of epistaxis generally occur while the horse is at rest and can vary from mild to severe, with several premonitory bleeds that generally culminate in a fatal episode of epistaxis.[1146,1147] Occasionally a horse dies of a single episode of epistaxis without previous clinical signs. Epistaxis may recur at intervals varying from 24 hours to 3 weeks.[1147]

Dysphagia, the second most common clinical sign, likely results from damage to the pharyngeal branches of the vagus and glossopharyngeal nerves and generally occurs later than epistaxis in the course of the disease.[1147] Horses with dysphagia cough during attempts to eat solid food, and, in addition to the presence of food material in nasal discharge, a considerable quantity of food is coughed out the mouth. Recovery from dysphagia may occur,[1147] but in general the prognosis for full recovery is poor.

Other clinical signs include parotid pain, abnormal head posture, unilateral or bilateral nasal discharge, head shyness, abnormal respiratory noise, sweating and shivering, Horner's syndrome, visual disturbances, colic, and facial paralysis.[1146,1147,1152–1155] These signs are the result of angina and dysfunction of cranial nerves and the sympathetic nervous system.

The differential diagnosis for the horse with epistaxis should include EIPH, ethmoid hematoma, guttural pouch or pharyngeal neoplasia, tracheobronchial foreign bodies, and guttural pouch mycosis.[1147] Differentiation of these diseases is aided by a thorough history and endoscopic examination. Differential diagnosis for dysphagia should include fractures of the hyoid apparatus; pharyngeal and guttural pouch fistula; cleft palate; esophagitis; pharyngeal paralysis; foreign body entrapment in the mouth or esophagus; pharyngeal neoplasia; lead poisoning; bacterial, viral, and mycotic CNS infections; and guttural pouch mycosis.[1147,1153]

31.38.2 Clinical Pathology

If epistaxis is the presenting complaint, there may be moderate to severe anemia with accompanying hypoproteinemia. Differential white cell distributions may be normal or may indicate a stress response. If dysphagia becomes a dominant clinical sign, other hematologic changes indicative of infection secondary to aspiration pneumonia may be evident.

31.38.3 Diagnostic Aids

Clinical signs of epistaxis or cranial nerve dysfunction are suggestive of a diagnosis of guttural pouch mycosis. A thorough physical examination may reveal abnormal sensitivity on digital palpation of the parotid area on the affected side.[1146] A definitive diagnosis of guttural pouch mycosis requires endoscopic observation of the characteristic diphtheritic lesion in the dorsocaudal aspect of the medial compartment or elsewhere within the guttural pouch.[1147] A healed lesion may be identified by the presence of scar tissue within the mucous membrane.[1147] Lesions may vary in color (brown, yellow, black, or white) and in size (from discrete nodules to diffuse irregular patches covering the roof of both the medial and lateral compartments)[1148,1155]; erosion with fistula formation can occur into the opposite guttural pouch or pharynx. Occasionally the characteristic lesion is obscured by clotted blood, so that the diagnosis is based on the clinical signs of epistaxis correlated with blood present in the guttural pouch. Because hemorrhage may originate from the internal carotid, external carotid, or maxillary arteries, it is important to identify the source of bleeding before therapy, particularly if surgical intervention is being considered.[1145] Care should be taken not to dislodge a thrombus and produce further hemorrhage. If dysphagia is apparent, food and saliva may be identified during endoscopy of the pharynx and nasal passages.[1109]

In guttural pouch mycotic infections, radiographs are of limited value because only minimum suppuration is associated with mycotic infections[1153]; however, the lateral view may allow assessment of the degree of fibrous reaction and loss of normal air space.[1153] Radiography may also aid in diagnosing some of the long-term sequelae such as fibrous deposits in the pouch and associated bony changes.[1156]

Serum titers to *A. fumigatus* are not diagnostic; however, reactivity to 22-kd and 26-kd serum antigens measured by immunoblot analysis may be diagnostic for guttural pouch mycosis.[1157]

31.38.4 Pathophysiology

The pathogenesis and predisposing factors leading to guttural pouch mycosis and arterial erosion are unknown, but it is believed that the disease is initiated by some stress to the soft tissues where the mycotic plaques are generally found.[1148] Potential stresses include inflammation, trauma, and vascular insult.[1133] Aneurysm

formation is not well correlated with the severity of the plaque formation. Although the nature of the initiating lesion remains unclear, it is generally agreed that the later stages are associated with deep fungal infections.[1148] *A. nidulans* and other *Aspergillus* species have been isolated and may be the causative agents.[1148–1156] *A. nidulans* is rarely pathogenic, but in the warm humid environment of the guttural pouch it may grow as an opportunist under certain circumstances.[1148] The mycotic lesions show no predilection for either the right or the left guttural pouch.[1147] Fungal infection of the pouch, erosion of major blood vessels, and involvement of nerves (IX, X, XI, XII, cranial cervical ganglion, and postganglionic sympathetic fibers) that traverse the area explain the epistaxis, local pain, and neurologic signs associated with guttural pouch mycosis.[1147,1148]

31.38.5 Epidemiology

No apparent age, sex, breed, or geographic predispositions have been observed. Guttural pouch mycosis is a sporadic disease that tends to arise during the warmer months of the year and rarely affects more than one horse in a particular stable.[1147] Affected horses are afebrile; infection is diagnosed when clinical signs such as epistaxis and dysphagia occur.[1147]

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31.38.6 Necropsy Findings

At postmortem examination, lesions are confined to the pharyngeal muscles, guttural pouch, and bones of the skull.[1146] Gross findings may include large blood clots in the nasal passages and at the pharyngeal opening of the guttural pouch.[1156] Unilateral denervation atrophy of the ipsilateral pharyngeal or laryngeal muscles may occur if there is involvement of the pharyngeal and recurrent laryngeal branches of the vagus.[1146] Examination of the guttural pouch generally reveals clotted blood and a diphtheritic plaque in the dorsocaudal aspect of the medial compartment that is firmly adherent to the underlying tissue and is clearly demarcated from surrounding tissue.[1148,1156] The lesion may be localized or may affect the entire roof of the pouch. If hemorrhage has occurred, the lesion may be obscured by clotted blood, pus, or mucus.[1148] An intense inflammatory reaction may be evident in response to acute fungal infection, whereas the inflammation may subside with chronic healing lesions so that scar tissue is evident.[1148,1153] Active inflammation may also predispose to osseous lesions of the petrous temporal and stylohyoid bones.[1146,1148,1152] Some cases of guttural pouch mycosis may remain asymptomatic and may be diagnosed only at routine postmortem examination.[1147]

31.38.7 Treatment and Prognosis

Without treatment a poor prognosis is warranted, because horses affected with guttural pouch mycosis are at risk for a fatal episode of epistaxis. Both medical and surgical treatments have been advocated for horses affected with guttural pouch mycosis with variable results; however, surgical treatment by an intraarterial occlusion technique is generally considered to provide the best prognosis.[1158–1161] Spontaneous regression of guttural pouch mycosis may occur, and this must be considered when evaluating the various medical or surgical treatments for this disease.[1109,1147]

Medical treatment is generally aimed at topical therapy of the mycotic lesion through the pharyngeal opening of the guttural pouch by means of a catheter.[1109] Bathing of the lesion may be facilitated by anesthetizing the horse and placing it in dorsal recumbency.[1146] Instilling fungicidal and fungistatic drugs, topical enzymes, and organic

iodine compounds into the guttural pouch has been attempted with variable success.[1162,1163] The necessity and efficacy of these treatments are unknown, and systematic treatment is hampered by a lack of knowledge of the pathogenesis of guttural pouch mycosis.[1164] Parenteral administration of antibiotics, corticosteroids, thiabendazole, ketoconazole, and iodine compounds also has questionable efficacy.[1156,1158,1164] The response of guttural pouch mycosis to local and parenteral treatment is protracted; thus the risk of fatal hemorrhage exists long after treatment has commenced.[1165,1166]

Surgical treatment of guttural pouch mycosis appears to offer the best prognosis for eventual cure. The internal carotid artery is not an end artery, and blood may enter this vessel from the bifurcation of the common carotid or may return from the cerebral arterial circle. Various surgical techniques have been described, and use of a balloon-tipped catheter inserted into the distal internal carotid artery combined with proximal ligation of the internal carotid artery [1156,1165–1167] or transarterial coil embolization[1160,1168] induces thrombus formation and prevents hemorrhage from normal and retrograde blood flow. Thrombosis sufficient to prevent hemorrhage may develop in the distal internal carotid artery within 10 days of catheter placement.[1167] Mucosal healing and complete regression of the fungal plaque have been reported to occur as early as 5 weeks after arterial catheterization[1165] and as early as 15 days after coil embolization.[1160] In a series of 13 cases the insertion of the balloon-tipped catheter successfully prevented fatal epistaxis in all horses.[1165] Topical or systemic treatment of the mycotic plaque is believed to be unnecessary after arterial catheterization.[1165] Intraarterial insertion of latex balloons or embolization coils also results in lesion resolution,[1169–1171] although progression of a mycotic plaque after coil embolization and subsequent development of neurologic signs has been reported in one horse.[1172]

31.39 DISEASES OF THE PARANASAL SINUSES

31.39.1 SINUSITIS

JOHN R. PASCOE

31.39.1.1 Definition and Etiology

Sinusitis refers to inflammation of the paranasal sinuses, from primary microbial infection or secondary bacterial infection associated with dental disease or other sinus disease. Lined by respiratory mucosa, the paranasal sinuses are at risk for developing diseases affecting the respiratory tract.[1173] Sinus empyema, accumulation of pus within a sinus cavity, may result from bacterial or viral infection.

Incidence of sinusitis is relatively low, likely less than 0.5% of disease in equine practice.[1174] In 256 horses with sinonasal disease, primary sinusitis (24%) and dental disease—associated sinusitis (22%) occurred with similar frequency and were the most common cause of sinusitis, whereas sinus cysts (13%), sinonasal neoplasia (8%), ethmoid hematoma (8%), sinonasal trauma (6%), mycosis (5%), and rostral maxillary tooth infection (4%) were the other more common causes.[1175] The frontal and maxillary sinuses are more commonly involved, with the corresponding conchal sinuses and the sphenopalatine sinus affected less often. Median age of horses affected with sinonasal disease is 7 to 11 years.[1175]

Acute or chronic upper respiratory tract infections of viral or bacterial origin can result in primary sinusitis; *Streptococcus* species infection is the most common. Maxillary sinusitis caused by disease of the third (caudal

roots) through sixth cheek teeth (modified Triadian numbers 109 to 111, 209 to 211) often results from alveolar periostitis, patent infundibula, or fractured or split teeth.[1173] Dental defects permit access of food material or bacteria to the tooth root and sinus cavity, with extension to the frontal sinus likely through the frontomaxillary opening. Reported neoplasms include osteoma, osteosarcoma, adenocarcinoma, lymphosarcoma, squamous cell carcinoma, and fibroma.[1176–1179]

31.39.1.2 Clinical Signs and Differential Diagnosis

Signs vary depending on cause, location, and extent of sinus involvement, with unilateral nasal discharge (serous, mucoid, mucopurulent, purulent) being the most frequent sign.[1175,1180] Physical examination of a horse with sinusitis should include observation for epiphora, facial asymmetry, altered nasal airflow, abnormal breath odor, mandibular lymphadenopathy, and sinocutaneous fistula.

Nasal discharge is typically unilateral because the nasomaxillary opening is located rostral to the caudal edge of the nasal septum. Intermittent or continuous, nasal discharge need not be related to a previous upper respiratory infection. Malodorous discharge is commonly associated with dental sinusitis and sinonasal mycosis, whereas mucopurulent discharge is more commonly associated with sinus cysts.[1175] Sanguineous discharge is common with ethmoid hematoma and sinonasal trauma; however, guttural pouch mycosis, pulmonary hemorrhage, nasal turbinate necrosis, and neoplastic or granulomatous lesions should also be considered. Other differential diagnoses of nasal discharge should include guttural pouch empyema or mycosis; acute pharyngitis (strangles, rhinopneumonitis, and influenza); neoplasia or necrosis of the turbinates; ethmoid hematoma; and pulmonary disease.

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After nasal discharge, submandibular lymphadenopathy is the most common sign, particularly when microbial infection is a component of sinusitis. Facial swelling occurs with frequency similar to that of lymphadenopathy, typically when sinus drainage is obstructed or there is an expansile mass within the sinus, or as an acute sign after facial trauma. Occasionally exophthalmos can occur with marked sinus distortion.

Patency of the nasomaxillary opening generally precludes facial distortion. Loss of patency occurs when inspissated exudate accumulates or mucosal lining tissue reaction obstructs the opening. Expansion of the sinus may result in reduced nasal airflow, particularly ipsilaterally, caused by distortion of the architecture of the nasal passages, and in such instances abnormal respiratory noise rather than nasal discharge may be the primary presenting sign.[1178]

Epiphora occurs if there is nasolacrimal duct involvement from trauma, or compression or destruction of the duct from underlying sinus disease. Approximately one third to one half of horses with dental sinusitis, sinus cyst, and sinonasal trauma have epiphora as a presenting sign.[1175]

Percussion of the affected sinus may reveal dullness or pain, although normal resonance does not preclude the possibility of sinusitis. If there is bone thinning over gas above a fluid line (as can occur with some maxillary sinus cysts), percussion may elicit increased resonance.

Careful examination of the oral cavity for signs of dental or periodontal disease should be performed when any of these signs are present. Particular attention should be paid to examination of the occlusal surface of the teeth with a very fine dental pick (e.g., 22-gauge needle); however, it should be recognized that periapical abscess formation can occur without defects in the occlusal surface. Accuracy of diagnosis of dental disease is substantially enhanced by use of intraoral endoscopy and CT.

31.39.1.3

Clinical Pathology

The hemogram in animals with sinusitis generally remains within the normal range, although acute sinusitis of infectious origin may be associated with neutrophilia. With chronic sinusitis there may be concurrent hyperfibrinogenemia. Sinus fluid obtained by percutaneous centesis should be examined cytologically (including a Gram stain) and submitted for microbial culture and susceptibility testing to differentiate among bacterial, fungal, and neoplastic disease. Flecks of feed material indicate sinusitis secondary to dental abnormalities.

31.39.1.4

Laboratory Aids and Definitive Diagnostic Tests

A presumptive diagnosis of sinusitis can be made from the physical examination and associated clinical signs.[1175,1181] Procedures most helpful in establishing a diagnosis of sinus disease in 85 horses were radiography (92%), endoscopy (38%), percutaneous centesis (21%), and examination of the oral cavity (20%).[1177]

Endoscopic examination of the nasal cavity may permit identification of exudate draining from the nasomaxillary opening or in advanced cases may reveal distortion of the nasal cavity secondary to sinus enlargement. Middle meatus examination is an important component of endoscopic examination. Diagnosis beyond recognition of the potential source of the nasal discharge is limited unless there is an obvious mass or abnormal tissue is observed. Sinoscopy can be accomplished by using an arthroscope[1182] or flexible endoscope[1183] inserted through small trephine holes in either the maxillary or the frontal sinus. Examination of the rostral compartment of the maxillary sinus requires a separate portal unless the bony septum between the rostral and caudal compartments has been destroyed. Observation may be limited by fluid or tissue especially in the rostral compartment of the maxillary sinus but can potentially be enhanced after sinus lavage and aspiration.

Standard radiographic projections include the standing lateral, dorsoventral, and right and left oblique views.[1184,1185] Radiographic findings include fluid lines within the sinus, space-occupying soft-tissue densities, areas of decreased bone density, fractures, or dental abnormalities. Dental root disease is identified radiographically by a loss of continuity of the lamina dura and lysis of the tooth root or surrounding bone, combined with new bone formation and cement deposition.[1184] Anatomy of normal equine skulls as demonstrated by CT and MRI has been described.[1186–1188] Diagnostic accuracy, especially determination of the extent of involvement of structures within the skull, can be enhanced by CT.[1189,1190] CT imaging enhances diagnostic accuracy of tooth involvement.[1190] Findings associated with dental caries include hypoattenuation of cementum, destruction of enamel, and filling of the infundibular cavity with gas, whereas with dental decay there is gas accumulation in the root area or fragmentation of the root, and sinus mucosal thickening. Additional changes with sinusitis typically involve the maxilla with endosteal sclerosis, thickening, periosteal reaction, and deformation, especially involving the facial crest.[1190] Scintigraphic examination may improve specificity in identification of dental involvement in sinusitis.[1191,1192]

Percutaneous sinus centesis may provide a definitive diagnosis and allow an avenue for subsequent therapy. Cytologic evaluation, with concurrent microbial culture and antibiotic susceptibility testing, may elucidate the cause of the sinusitis.[1177] Isolation of a single organism such as *Streptococcus* species generally indicates a primary sinusitis, whereas polymicrobial infection is more compatible with sinusitis of dental origin. Visual

examination of the oral cavity, especially intraoral endoscopy, and careful probing of the occlusal surfaces with a dental pick may identify dental abnormalities.

31.39.1.5 Necropsy Findings

Affected sinuses contain fluid or tissue of variable color and consistency. Fluid character ranges from clear and odorless with cystic sinus disease to white, yellow, or green purulent fluid with a variable, but often putrid, odor in sinusitis resulting from other causes. Sinusitis of dental origin has a characteristically pungent and unpleasant odor. Granulomatous lesions have been reported to appear as large lobular gelatinous masses filling the sinus cavity. The gross appearance of neoplastic lesions within the sinus cavity depends on the type of neoplasm. Neoplasia may cause surrounding soft-tissue and bony destruction, whereas large, benign space-occupying lesions may result in distortion of the nasal turbinates and nasal septum, as well as external facial bone distortion.

31.39.1.6 Treatment and Prognosis

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Not infrequently, horses with a chronic mucopurulent nasal discharge from sinusitis have a history of response 589 to antimicrobial therapy, followed by recurrence of the discharge after antibiotic therapy ceases. Definitive diagnosis of sinusitis can be accomplished using the techniques described earlier. Sinoscopy permits examination of the paranasal sinuses and in some instances facilitates treatment.[1184,1193]

Suggested treatment for primary sinusitis or empyema involves daily lavage of the sinus through a percutaneous centesis site with 1 L of saline, to which a broad-spectrum antibiotic or antiseptic has been added. Once the results of culture and susceptibility testing are available, the appropriate antibiotic should be administered locally in the flush solution, as well as systemically, for 14 days. Resolution or reduction in the volume of nasal discharge is an indication of successful therapy. If little progress is made after 10 to 14 days or if drainage recurs, sinusotomy (trephination or bone flap technique, standing or recumbent anesthetized) may be required to resolve the condition.[1194] The prognosis is generally favorable if primary sinusitis is not chronic and if the mucous membrane is not markedly thickened.[1195] Chronic sinus disease (longer than 6 months) carries a poor prognosis, and, for resolution to occur, surgical removal of the thickened, infected mucous membrane is required; creation of sinonasal drainage by sinus fenestration is also recommended. Isolation of *Pseudomonas* species from a sinus aspirate generally indicates an unfavorable prognosis.[1180]

Sinusitis that results from secondary factors is generally not responsive to medical management. Such conditions include diseased teeth, granulomas, or neoplasia; surgical removal of the inciting cause is required, and adjunctive treatment may be required. The prognosis for sinusitis associated with dental abnormalities is usually favorable once the diseased tooth has been removed.[1195,1196] If the periodontal ligament is intact, endodontic therapy can be used to save the tooth. This is accomplished by surgical apicoectomy and retrograde occlusion of the root canal after debridement of the pulp. In geriatric horses with dental-associated sinusitis, when economic constraints limit surgical options, sinusotomy and periodic sinus lavage and antibiotic therapy have been used successfully to manage nasal discharge.

The prognosis for resolution of granulomatous lesions is generally guarded and depends on surgical access and extent of the lesion. Neoplastic lesions are often well established and have metastasized, either locally or regionally, by the time they become clinically apparent; the prognosis for resolution is generally guarded to poor.[1176] In a series of 16 horses with sinus neoplasia, 11 were euthanized because of the extent of the lesion,

four lesions recurred after surgical removal, and one horse with squamous cell carcinoma was successfully treated and had no recurrence at a 2-year follow-up evaluation.[1177]

31.39.1.7 Prevention and Control

Prevention of sinusitis in horses is difficult because of the variety of causes. Isolation of horses from those with upper respiratory bacterial or viral diseases may be of benefit in preventing primary sinusitis. Regular dental care and a proper diet may help circumvent sinusitis caused by dental abnormalities, although many cases most likely result from a variety of causes not yet defined or over which the owner or veterinarian has no control.

31.39.2 ETHMOID HEMATOMA

JOHN R. PASCOE

31.39.2.1 Definition and Etiology

Also termed *progressive ethmoidal hematoma*[1197] and *hemorrhagic nasal polyps*,[1198] ethmoid hematomas are slowly expanding angiomatous masses that appear to originate principally from the mucosal lining of the ethmoid conchae. Smaller hemangiomas arising from the mucosal lining of the frontal, maxillary, and sphenopalatine sinuses have been recognized, but the relationship between these benign endothelial tumors and ethmoid hematoma is uncertain. A relationship between paranasal sinus cysts and ethmoid hematoma has been suggested,[1199] but distinctly different histologic features characterize each disorder,[1200] seemingly arguing against a common cause and the likelihood that these lesions are variants of each other. The cause of ethmoid hematoma is unknown, and it remains a relatively uncommon condition.[1201–1205] Although reported in a 4-week-old foal and in 3-year-old horses, most affected horses are older than 8 years—generally thoroughbred, Arabian, or warmblood horses.[1201–1207]

31.39.2.2 Clinical Signs

A blood-tinged nasal discharge with intermittent epistaxis from one or both nostrils is the most common clinical sign.[1208] Unilateral or bilateral, epistaxis varies from blood-tinged mucoid or mucopurulent discharge to blood spots or a trickle of blood. Fulminant or fatal epistaxis as can occur with guttural pouch mycosis is uncommon. If the hematoma occupies the choana(e) or nasal cavity, a mucopurulent, occasionally malodorous nasal discharge with some blood discoloration is more commonly seen. Typically these horses have a history of abnormal respiratory noise, both inspiratory and expiratory, especially during exercise. With nasal cavity involvement, airflow is usually reduced or may be absent on the affected side. Facial distortion or asymmetry is uncommon and is more likely to occur when the hematoma occupies the frontal and maxillary sinuses. Less commonly there may be an associated history of coughing, choking, ptyalism, increased respiratory effort during resting breathing, and either head shyness or head shaking.[1197] If the hematoma has expanded into the paranasal sinuses, percussion yields a dull sound.

31.39.2.3 Laboratory Aids and Definitive Diagnostic Tests

Confirmation requires endoscopy of the ethmoid conchae and skull radiography (Figs. 31-45 and 31-46); however, the origin and extent of the mass can be delineated more accurately by computed tomographic examination of the skull. Sinoscopy may be of diagnostic value in horses with ethmoid hematoma involving the paranasal sinuses without protrusion into the nasal cavity. Rarely, ethmoid hematoma infiltrates the nasal conchae; these lesions, identifiable by CT, may be missed by sinoscopy. Because ethmoid hematoma is bilateral in approximately 30% of affected horses, it is prudent to examine both the left and right ethmoidal conchae. The ethmoidal labyrinth is visible approximately 25 cm from the nares, with the endoscope positioned in the ventral nasal meatus and the viewing tip deflected dorsally. The rostral surface of the ethmoidal concha does not protrude beyond the caudal nasal cavity and has a bulbous shape and a moist pink to pale red mucosal covering.

Beyond the rostral surface the numerous pillars that form the ethmoidal conchae and separate the ethmoidal spaces (cellulae ethmoidales) are visible. Ethmoidal hematomas that project into the ventral meatus or through the choana into the nasopharynx often obscure the ethmoidal concha. Occasionally, unilateral ethmoid hematomas that have expanded into the nasopharynx may protrude into the contralateral ventral meatus, obscuring the view of the ethmoidal labyrinth on that side. The origin of hematomas that expand dorsally into the frontal sinus may not be visible on endoscopy, but hemorrhage that originates deep to the visible portion of the ethmoidal conchae may be evident or may be noticed from the region of the nasomaxillary opening in the middle meatus. Visible ethmoid hematomas can vary in color from deep red to red-purple or may have a yellow-brown or yellow-green-brown to bronze color. The surface is irregularly rounded, with small punctate hemorrhages or erosions, and may be partially covered in yellow-white mucopurulent material that may be admixed with blood. Often the floor of the ventral meatus and the regions of contact with the nasal cavity have pooled exudate of blood and mucopurulent matter. Manipulation of the visible surface of the hematoma with the tip of the endoscope may elicit bleeding or oozing.

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Fig. 31-45 Endoscopic view of left ethmoturbinate. **A**, Normal appearance. **B**, Ethmoturbinate obscured by an ethmoid hematoma.

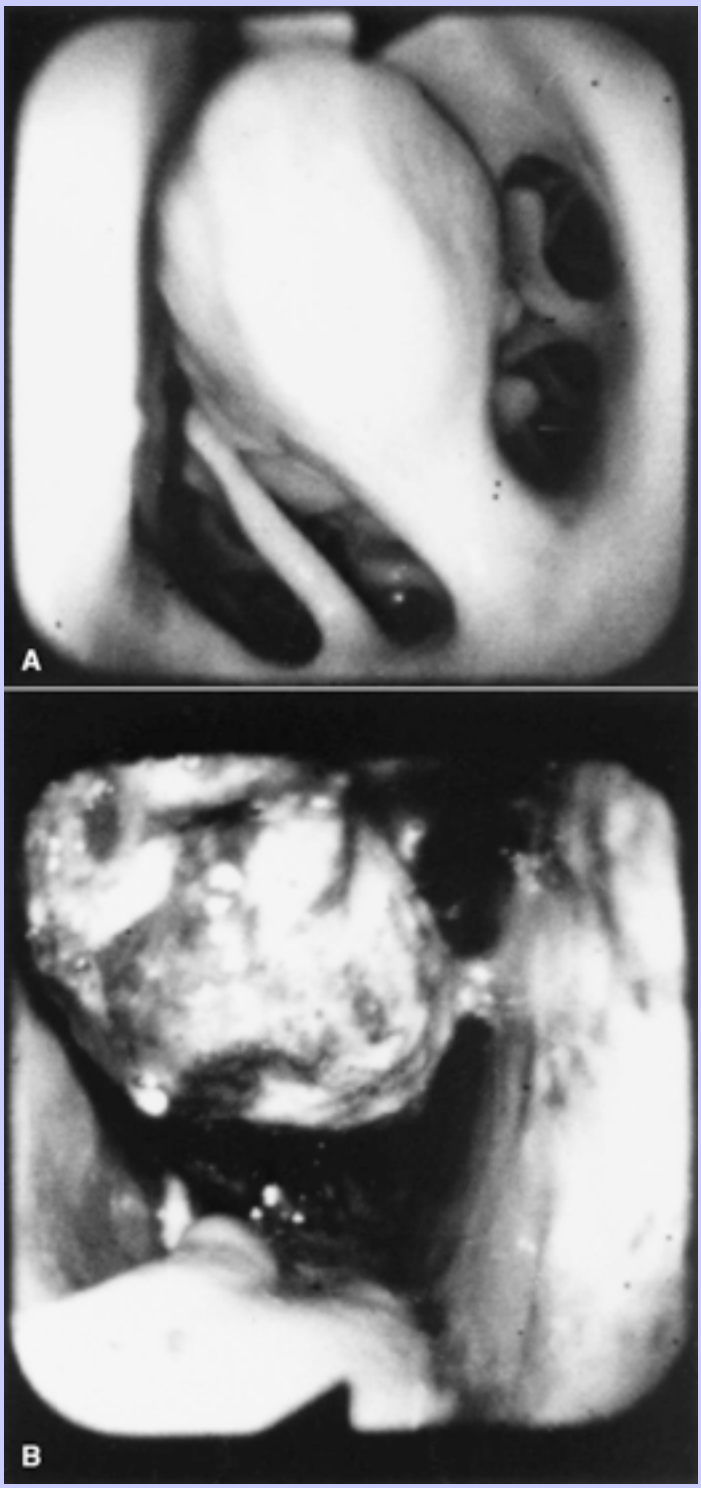
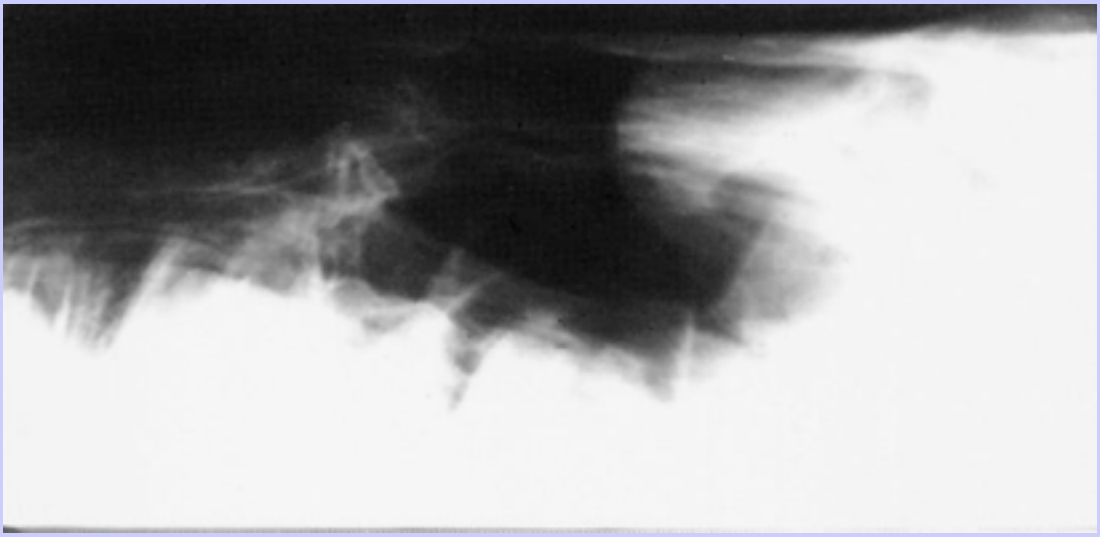


Fig. 31-46 Lateral radiograph demonstrating an ethmoid hematoma.



Recognition of a discrete, often smooth-surfaced homogeneous radiodensity originating from the ethmoidal conchae and extending into the frontal, maxillary, or sphenopalatine sinuses or into the pharynx or nasal cavity is suggestive of an ethmoid hematoma. Radiography is beneficial in determining the extent of the hematoma and in identifying suspected ethmoid hematomas that are not visible by endoscopy; however, precise definition of the origin of any hematoma is difficult from radiographic projections. Small hematomas contained within the ethmoid labyrinth may not be visible on radiographs. Computed tomographic examination of the skull allows more accurate assessment of the origin of the ethmoid hematoma,[1207,1209] allows determination of the extent of involvement of the paranasal sinuses and conchae, and facilitates surgical planning.

31.39.2.4

Necropsy Findings

Most of the morphologic features have been described from surgical specimens; few skulls with intact ethmoid hematomas have been examined.[1198] Except in regions with necrosis or secondary infection associated with contact with the sinus or nasal cavity walls, the hematoma is a smooth-surfaced saclike structure containing blood in various stages of organization. The sac lining is generally healthy respiratory mucosa originating from a pedunculated region of the mucosal covering of the ethmoturbinal or sinus wall. On section the contents are amorphous red-black to chocolate brown, and in larger masses some evidence of irregular compartmentalization by fibrous tissue exists, especially on the inner surface of the sac.

Morphologic features include an outer covering of respiratory epithelium (flattened columnar or cuboidal ciliated epithelium containing glands, and occasionally stratified squamous epithelium[1200]) overlying an irregular zone of submucosal fibrous tissue, containing hemosiderophages, occasional plasma cells, and lymphocytes, less commonly neutrophils, that forms a pseudocapsule around hemorrhage in varying states of organization. There is typically variable organization of the fibrous tissue components. Endothelial cells do not show evidence of neoplasia. Thin endothelium-lined sinuses are often present within the myxomatous stroma. The respiratory epithelium is sometimes focally ulcerated and infiltrated with neutrophils, and

occasionally there are squamous metaplastic changes. Ethmoid adenocarcinoma with a similar gross appearance to ethmoid hematoma has been reported in one horse.[1210]

31.39.2.5 Treatment and Prognosis

Because these masses slowly and progressively increase in size and can cause distortion of skull architecture if the paranasal sinuses are involved, removal is recommended. Treatment method depends on the location and size. Surgical ablation has been the preferred method; however, destruction of the hematoma by intralesional injection of formaldehyde solution is associated with less morbidity, although recurrence rates are similar to those with other methods.[1204–1212] Surgical access is usually achieved by sinusotomy and then hematoma ablation by curettage, cryosurgery, or use of an Nd:YAG laser[1213–1215]; photoablation can also be accomplished through the biopsy channel of an endoscope. After sinusotomy, the pedunculated origin of the hematoma is identified by digital palpation and then dissected, frozen, or photoablated, and the hematoma removed. If the hematoma is friable, intact removal may not be possible, and hemorrhage may make observation of the origin of the mass difficult. After removal the paranasal sinuses and nasal cavity are packed with gauze to control postoperative hemorrhage.

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Surgical curettage can have the disadvantage of being associated with marked intraoperative blood loss typically from the turbinates or sinus mucosa rather than the hematoma. Temporary occlusion of both carotid arteries[1214] can substantially decrease blood loss until the sinus cavity is packed with gauze. Blood loss is minimized by cryosurgical extirpation and photoablation techniques, but these approaches are not always practical when initially dealing with large hematomas. There is also minimum blood loss with transnasal photoablation; however, this technique requires multiple procedures to destroy large masses but can be performed in the standing sedated horse. Photoablation (Nd:YAG laser, 100 W in noncontact technique) is effective in controlling remnants after surgical extirpation or subsequent regrowth.[1215,1216]

Destruction of ethmoid hematomas by endoscopically guided intralesional injection of formalin in standing sedated horses may reduce the need for surgical ablation in many horses.[1211,1217] A catheter passed through the endoscope biopsy channel is advanced through the rostral surface of the mass toward its origin, then 10% formalin (4% formaldehyde solution) is injected intralesionally. Commercially available catheters with a beveled needle tip have been used, but relatively stiff plastic tubing that will slide through the biopsy channel works will penetrate the capsule of the ethmoid hematoma. Sufficient volume (from 10 to 100 mL) is injected until fluid leaks back alongside the catheter or leaks from the mass. For visibly pedunculated masses, it is best to inject the formalin at the origin or neck of the mass. Tissue necrosis and slough occur in 5 to 10 days and may be associated with nasal discharge. Repeat injections, typically at no longer than 10- to 14-day intervals may be necessary to destroy the mass. Removal of necrotic tissue can be facilitated by use of long grasping forceps and hydropulsion. Mycotic plaques may cover the treated site during healing but typically resolve without treatment; endoscopically delivered topical natamycin has been used if mycotic plaque is extensive and associated with malodorous, purulent discharge.[1218]

Occasionally progression of the ethmoid hematoma may result in weakening or loss of the cribriform plate or roof of the sphenopalatine sinus.[1218] During mass removal, loss of this protective bony covering may result in intraoperative or postoperative neurologic complications. Recognition of loss of the integrity of these bony plates may not occur until sinus lavage. In a rare complication death occurred after intralesional formalin injection in a horse where the cribriform plate had been eroded by the ethmoid hematoma.[1219] Erosion of

calvarial bone is rare, but careful computed tomographic evaluation of these regions in horses with extensive hematoma formation involving the frontal or sphenopalatine sinuses is warranted.

Irrespective of treatment method, recurrence of the hematoma occurs in 30% to 50% of cases from several months to years after the initial surgery.[1198,1203–1206,1211,1212]

31.39.3 RUMINANT RESPIRATORY SYSTEM

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31.39.4 UPPER RESPIRATORY TRACT DISEASES

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31.39.5 DISEASES OF THE NASAL CAVITY

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31.39.5.1 Mycotic or Bacterial Nasal Granuloma

Infectious granulomas in the nasal cavity of ruminants are not common. Documented causes include the fungal organisms *Rhinosporidium seeberi* and other *Rhinosporidium* species (which cause rhinosporidiosis), *Helminthosporium* species (which cause maduromycosis), *Drechslera rostrata, Aspergillus* species, *Phycomycetes* species, *Stachybotrys* species, and *Bipolaris* species. Phycomycosis is discussed in the dermatology section in Chapter 40. Nasal granuloma caused by *Nocardia* species bacteria has also been reported.[1] There is no apparent age, breed, or seasonal predilection, and cases are sporadic. The major clinical signs are upper respiratory noise (stridor), dyspnea, and mucopurulent nasal discharge, sometimes with epistaxis. Affected animals may rub the nose, suggesting pruritus or irritation.[2–3] Nasal airflow may be reduced, and open-mouth breathing may occur in advanced cases. Hot or dusty weather may accentuate the signs, giving the appearance of seasonal exacerbation, but the lesions are progressive. The granulomas may be single or multiple, unilateral or bilateral, and located anywhere in the nasal cavity. They consist of 0.5- to 5-cm yellow to yellow-green or red nodules or polyps, which may be sessile or pedunculated. Rhinosporidiosis tends to be a single unilateral polyp in the posterior nasal cavity, and maduromycosis tends to occur in the anterior cavity, but these distinctions are not consistent. Red and black spots (spores) may occur on the masses, and some may become secondarily infected with bacteria and ulcerate. Differential diagnoses include allergic rhinitis, foreign bodies, tumors, nasal actinobacillosis, nasal actinomycosis, and *Oestrus ovis* infection in small ruminants.

Endoscopy, biopsy, and culture of the lesions aid in the diagnosis. Histopathologic analysis reveals granulation tissue containing eosinophils, mononuclear cells, round sporangia, and sometimes hyphae or filamentous bacteria.[1,2] The pathogenesis of the disease involves inoculation of eroded nasal mucosa with fungal spores or filamentous bacteria from the environment. The infectious agent causes a chronic delayed (type IV) hypersensitivity reaction, which eventually leads to the formation of a granuloma. Fungal granulomas can be more common in warm, wet climates. The granulomas can be difficult to treat, and although rarely fatal the disease is chronically debilitating, with salvage often being the most practical solution.

Recommended treatments include surgical removal of the granulomas when possible and long-term sodium iodide (NaI) therapy. NaI can be administered at a dose of 66 mg/kg IV as a 20% solution, repeated at 10- to 14-day intervals until remission or iodism occurs. Iodism is characterized by lacrimation, cough, and scaling of the skin. The use of antifungal drugs to treat this condition in ruminants has not been reported.

31.39.5.2 Allergic Rhinitis and Enzootic Nasal Granuloma

Allergic rhinitis occurs in cattle and in its chronic stages may lead to the formation of granulomas. A similar condition may occur in sheep.[4] The inciting antigen is frequently a plant pollen or more likely a fungal spore.[5] Once homocytotropic antibody (immunoglobulin E or possibly other classes in cattle) to the allergen has developed, subsequent exposure results in a localized, ongoing, immediate (type I) hypersensitivity reaction.[5–7] If recurrent exposure to the allergen occurs, repeated tissue damage by mast cell factors results in chronic epithelial, duct, and goblet cell hyperplasia and metaplasia, as well as mucous hypersecretion and granulomatous inflammation, suggesting that a type IV hypersensitivity reaction contributes to the chronic lesion.[5,6,8]

Any breed may be affected, but Channel Island breeds and Friesians seem most susceptible.[5] The disease occurs sporadically in the United States. A familial predisposition has been reported.[9] Most affected animals are between 6 months and 2 years of age. The signs are initially seasonal, usually occurring in warm, moist conditions; they include rhinorrhea, sneezing, nasal pruritus, a sudden onset of dyspnea, and stertorous inspiration.[9,10] There is a profuse bilateral nasal discharge. Intense pruritus is characteristic and associated with sneezing, head shaking, and nose rubbing.[10] In severe cases facial swelling, tachypnea, hyperpnea, and ulceration of the nasal mucosa may occur.[6,10] Nasal foreign objects may result from the animal's attempts to scratch the nasal mucosa. Lacrimation, chemosis, and blepharitis may also be present. In the chronic stages (the “enzootic nasal granuloma”), the signs are more constant, with seasonal exacerbations.[6,8,10] The granulomas tend to be multiple, firm, white, raised nodules 1 to 2 mm in diameter with an intact mucosa, or pale pink flat plaques scattered throughout the nasal cavity. Differential diagnoses include fungal granulomas, foreign bodies, respiratory viruses, nasal actinomycosis or actinobacillosis, tumors, *O. ovis* infection (small ruminants), and irritation caused by inhalation of hot or irritant gases.

Endoscopy, biopsies, cultures, antigen detection tests for viruses, bacteria, or fungi, and serologic analysis can be used to rule out these differential diagnoses. Eosinophil counts in nasal secretions correlate with the susceptibility of the animal and activity of the disease, but no absolute level is diagnostic.[5] Intradermal allergen testing has been suggested to aid in diagnosis, but interpretation of results needs to be done in conjunction with historical and clinical findings.[7] This condition should be differentiated from fungal or bacterial granuloma because the therapy is different.

Treatment and control entail removal of the allergen, or removal of the animal from the allergen, and therapy to block the hypersensitivity reaction. Recommended drugs include various antihistamines, meclofenamic acid, and corticosteroids at standard antiinflammatory doses (0.05 to 0.2 mg of dexamethasone per kilogram IM or IV or 1 to 2.2 mg of prednisolone per kilogram IM or IV daily). Topical corticosteroid therapy can be considered in severe, acute occurrences of the disease. The adverse effects of corticosteroids on milk production and their potential to induce abortion or parturition should be considered before their use. Antihistamine therapy has had equivocal results.[7]

31.39.5.3 Nasal Foreign Bodies

Cattle are more prone than small ruminants to the acquisition of nasal foreign bodies. Foreign objects may be acquired as a result of attempts to scratch the nose in cases of allergic rhinitis, or because of the cow's aggressive eating habits. Depending on the size and duration of residence of the object, signs may include head shaking, stridor, sneezing, snorting, frequent nose licking, unilateral decreases in airflow, foul odors, and serous, mucopurulent, or hemorrhagic discharges. Differential diagnoses include fungal granulomas, allergic rhinitis, tumors, nasal actinomycosis or actinobacillosis, and *O. ovis* (small ruminants). Many objects can be visualized on careful examination of the nasal cavity with an adequate light source, whereas some may require endoscopy for diagnosis and removal.

31.39.5.4 Nasal Trauma and Fractures

Trauma to the facial bones, sinuses, and turbinates may result from fighting, accidents caused by improper restraint, farm machinery accidents, human maliciousness, and passage of excessively large NGTs. Severe fractures can lead to facial swelling, SC emphysema, obstruction of airflow, stertor, and epistaxis. Secondary infection causes foul odors and mucopurulent nasal discharge. Differential diagnoses for the acute external swelling of the head with stertor include snakebite, actinobacillosis, actinomycosis, and phlegmon (*Fusobacterium, Clostridium* species). Unless the development of severe depression fractures, formation of sequestra, or severe obstruction of airflow occurs, surgery is usually not indicated. Radiographs confirm the diagnosis and help determine the need for surgical removal of potential sequestra or elevation and fixation of large displaced segments. Prophylactic antibiotics (typically penicillin, 22,000 U/kg IM or SC q12-24h) are recommended to prevent fracture infection and sinusitis, and NSAIDs (aspirin, 100 mg/kg PO twice; flunixin meglumine, 1.1 to 2.2 mg/kg IV daily or divided twice daily) may help relieve pain, swelling, and stridor. The prognosis is usually good.

31.39.5.5 Nasal Tumors and Polyps

Tumors and polyps of the nasal cavity and sinuses are rare in ruminants. Nasal tumors reported in cattle include osteomas and osteosarcomas of the sinuses, squamous cell carcinomas,[11] neuroblastomas, and adenocarcinomas of the ethmoid mucosa. Ethmoid adenocarcinomas are speculated to be caused by viruses on the basis of an endemic pattern in some cases.[12] They tend to occur in cattle 6 to 9 years of age and are frequently unilateral. Metastasis occurs to the lymph nodes and lungs. There is a report of a hemangiosarcoma involving the external naris of a cow.[13] Signs common to all nasal tumors include mixed or inspiratory dyspnea, stridor, nasal discharge, epistaxis, foul breath odors, unilateral decreases in airflow, open-mouth breathing, and distortion of the facial bones. Differential diagnoses include fungal granulomas, atopic

granulomas, foreign bodies, sinusitis, fractures, and nasal actinobacillosis and actinomycosis. Treatment has not been investigated.

The majority of nasal neoplasms in sheep and goats are adenopapillomas, adenomas, or adenocarcinomas.[14] Squamous cell carcinoma[15] and osteoma[16] have also been reported. Nasal adenocarcinomas have also been described in goats.[17]

An enzootic form of nasal adenocarcinoma occurs in both sheep and goats and is associated with ovine nasal adenocarcinoma virus (ONAV)[18,19] or caprine nasal adenocarcinoma virus (CNAV),[20] respectively. These agents are β retroviruses that are closely related to, but distinct from, jaagsiekte sheep retrovirus (JSRV), the cause of ovine pulmonary adenocarcinoma (OPA).[20,21] Although nasal adenocarcinoma has been difficult to consistently reproduce experimentally, inoculation of kids with concentrated cell-free and bacteria-free filtrate containing virus from naturally infected goats has resulted in disease.[22] Neoplastic transformation is limited to secretory epithelial cells of the nasal turbinates, but CNAV appears to have a wider tissue tropism than ONAV; in one study viral provirus incorporated into host DNA was found in many tissues of infected goats but was largely confined to tumor tissue of infected sheep.[20] There is no breed or sex predisposition for enzootic nasal adenocarcinoma; affected animals are most commonly young adults, but the tumor has been identified as early as 4 months of age.[18] Signs include progressive inspiratory dyspnea; stridor; exercise intolerance; mouth breathing; serous, mucoid, or mucopurulent nasal discharge, which is typically profuse; tachypnea; decreased airflow; head shaking; sneezing; exophthalmos; and facial asymmetry.[14,17,18,21] The lesions may be unilateral or bilateral, originating in the olfactory region of the ethmoid turbinates. The neoplasia arises either from Bowman's glands[18] or serous glands of the nasal mucosa.[17] The tumor begins as a small nodule that can grossly resemble the mucoid polyps that occur in animals with chronic rhinitis. Over time the adenocarcinoma grows into a soft, gray to grayish pink, mucoid, nodular, cystic mass. The tumor is benign but locally expansive, often entering the sinuses and eroding overlying bone.[17] Histologically the tumor is typically classified as a low-grade adenocarcinoma, but it may also be identified as an adenopapilloma or adenoma.[17] Initially affected animals eat and drink normally and maintain body condition, but as the tumor expands the animal begins to lose condition, and death eventually occurs as a result of inanition, asphyxia, or aspiration pneumonia. Necrosis or secondary bacterial infection of the tumor can occur and may lead to the production of foul-smelling, purulent discharge and systemic signs related to bacterial infection, such as fever, depression, and hyperemic mucous membranes.

Differential diagnoses for nasal neoplasia in small ruminants include nasal fungal or bacterial granuloma, actinobacillosis, actinomycosis, *O. ovis* infection, and sinusitis. Endoscopy and radiology are helpful in establishing an initial diagnosis of a nasal mass. Preoperative or antemortem pinch biopsies and exfoliative cytologic analysis frequently are nondiagnostic, and findings may be misleading.[14,15] Identification of tumors in multiple animals in a herd or flock supports a diagnosis of enzootic nasal adenocarcinoma. Definitive identification of infection with ONAV or CNAV can be difficult. Serologic tests are not reliable because animals do not consistently produce antibody to the viruses,[23] possibly because of the presence of endogenous retroviruses[24] that share epitopes with ONAV and CNAV and induce the development of immunologic tolerance. Recently PCR has been used to specifically identify and differentiate ONAV, CNAV, and JSRV in tissues of affected animals.[25] Surgical management of nasal adenocarcinoma in sheep has been described.[26]

31.39.6 *OESTRUS OVIS* INFESTATION

AMELIA R. WOOLUMS

31.39.6.1 Definition and Etiology

O. ovis is parasite of the nasal passages and sinuses of sheep and, less commonly, goats. Goats are relatively resistant to infection and, even when housed with sheep, tend to have a lower prevalence of infection.[27] Occasionally humans and other animals are accidentally infected, with conjunctival infection the most common form of disease in humans.[28,29] The pathogenic stage of the parasite is the larval stage. The first instar larvae are deposited near the nostrils of sheep by the adult female fly and migrate into the nasal and ethmoid turbinates; in the ethmoids the larvae molt to second instars, which migrate to the sinuses before molting again and becoming third instar larvae. Third instar larvae, which are yellow-white in color and have a dark dorsal stripe with rows of spines on the ventrum of each segment, return to the nasal passages and are sneezed out onto the ground, where they pupate and eventually develop into adult flies.[30,31] The adult is active during warm months, and the parasite may overwinter either as a first instar larva in the host or as a pupa in the ground. Larvae can persist in the upper airways for weeks to months, and appear to be able to arrest development for a period of time if necessary to avoid climate extremes.[32] Adult flies have a rudimentary mouthpiece and are not able to feed; thus the larvae must ingest adequate nutrients while in the host to support the life of the adult fly.[33]

31.39.6.2 Clinical Signs

The larvae cause irritation of the nasal passages and sinuses, leading to mucoid to mucopurulent and sometimes blood-tinged nasal discharge, sneezing, nose rubbing, and inspiratory stridor. Adults flies cause annoyance by flying around the heads of animals; thus both stages can lead to decreased productivity by decreasing the time spent grazing by affected animals. Occasionally the larvae may cause sinusitis or pneumonia owing to secondary bacterial infection associated with irritation caused by the larval infestation. Differential diagnoses to consider include nasal foreign bodies, allergic rhinitis, nasal adenocarcinoma, fungal rhinitis, trauma, sinusitis, actinobacillosis, or actinomycosis.

31.39.6.3 Pathogenesis

The larvae cause direct irritation to the nasal passages and sinuses, and this irritation may predispose animals to the development of secondary bacterial rhinitis, sinusitis, and/or pneumonia. Interstitial pneumonia has also been seen on occasion in affected sheep, presumably induced by inhalation of parasite antigens and inflammatory mediators from the upper respiratory tract.[34]

31.39.6.4 Epidemiology

Infection is more common in warm climates. Recent European surveys have identified *O. ovis* in 35% to 91% of sheep surveyed,[35,36] with seroprevalences of 46% to 69%.[27,36,37] A majority of flocks surveyed had at least one infected animal.[27,35] No North American reports describing the prevalence of *O. ovis* infestation have been published in recent decades.

31.39.6.5 Diagnosis

Diagnosis is usually presumptive, based on typical clinical signs. The larvae can also be identified via radiographs of the head or by endoscopy, but these tests may not be practical for field use. Serologic diagnosis has been used for research studies of the epidemiology of *O. ovis* infection, but these tests are unlikely to be available at most diagnostic laboratories.

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31.39.6.6 Treatment and Prevention

The larvae are susceptible to ivermectin at 200 µg/kg PO.[38] Moxidectin at 0.2 mg/kg as a 0.1% oral drench was not effective against *O. ovis*[39]; these investigators found that the same dose given as a 1% injectable solution was effective, but this route is not approved in the United States. Pour-on eprinomectin at 0.5 mg/kg (applied immediately after shearing)[40] and injectable doramectin at 200 µg/kg IM[41] have also been shown to be effective in sheep, but these treatments are also not approved for use in sheep or goats in the United States. Because the adult fly should be killed by freezing weather, in areas with a season of freezing weather it is logical to treat after the first hard freeze, when sheep will no longer be susceptible to infection until warm weather returns. Prevention is aimed at regular strategic treatment with effective anthelmintics to prevent long-term infection with the larvae.

31.39.7 CONGENITAL CYSTIC NASAL TURBINATES IN CATTLE

An apparently developmental anomaly that results in signs of nasal obstruction has been reported in cattle.[42] The nasal conchae lack the normal communication with the nasal cavity and become filled with a thick white fluid, which may account for the enlargement. Signs are evident at or near birth and include progressive stridor, tachypnea, decreased airflow, exercise intolerance, mouth breathing, and short, convex nasal bones. Digital, radiographic, and endoscopic examinations of the nasal cavity reveal large, smooth, bilateral cystic ventral nasal conchae, often bilobate. Differential diagnoses include foreign bodies, trauma, and tumors. Surgical removal of the conchae with bilateral dorsolateral nasal bone flaps relieves the obstruction. Transnasal removal using obstetric wire has been described.[43]

31.39.8 DISEASES OF THE SINUSES

JOHN R. PASCOE

31.39.9 SINUSITIS

31.39.9.1 Definition and Etiology

Inflammation of the paranasal sinuses is most common in cattle and occurs infrequently in sheep and goats. Typically the frontal or maxillary sinuses are involved, and a variety of bacteria may be isolated. The proximate cause for infection is usually dehorning (frontal sinusitis) or infected teeth (maxillary sinusitis). Other causes include extension of actinomycosis or nasal neoplasia into the sinus, injuries to the horn, facial fractures, respiratory viruses (including malignant catarrhal fever [MCF], IBR, and parainfluenza viruses), sinus cysts,[44,45] lymphosarcoma,[46] and *O. ovis* (in sheep).[47–50]

31.39.9.2

Clinical Signs and Differential Diagnosis

Sinusitis associated with dehorning may be acute or may occur weeks to months later; typically only one sinus is affected. Nonspecific clinical signs include anorexia, lethargy, reluctance to move, and fever. When sinusitis occurs acutely after dehorning, the portal of entry is frequently open and discharging pus, and the animal is often febrile (39.5° C to 40.5° C). In chronic sinusitis, signs may include unilateral or bilateral nasal discharge, mild stridor, changes in airflow, and foul breath odors that are frequently unilateral; fever is not common. The animal may hold its head at an odd angle (extended up or down, tilted) and may squint the eyelids as if in pain. [49,51] With chronicity, frontal bone distortion, exophthalmos, and neurologic signs may occur.[51,52] In one report of 12 cattle with frontal sinusitis, four cattle had abnormal posture, with an extended head and neck, partially closed eyes, and a tendency to head-press or to rest the head on a stationary object; the other 8 cattle were apprehensive and intolerant of head manipulation.[51] Extension of infection may involve the CNS.

Occasionally sinusitis irritates the animal sufficiently that it may rub its head on the ground, driving more debris into the sinus.[50] Maxillary sinus cysts have been observed in cattle.[44] Typical signs included unilateral facial swelling over the affected sinus; mucopurulent, nonfetid nasal discharge; and radiographic evidence of septal deviation. One cow had stertorous respiration with diminished airflow. Differential diagnoses for sinusitis include facial fractures, nasal tumors, actinomycosis, actinobacillosis, retrobulbar abscess, and lymphosarcoma.

31.39.9.3

Diagnosis

Diagnosis can usually be made based on clinical signs. Diagnostic aids may be useful in selected cases, particularly when there is no recent history of dehorning, or in cases of maxillary sinusitis. The hemogram is quite variable and is of little assistance in diagnosis. Percussion of the sinus may reveal a dull, full sound and may elicit pain. If the bone has been greatly thinned and has gas underlying it, percussion may produce a hyperresonant sound. Fractures, soft-tissue masses, dental disease, fluid in the frontal sinus, or lysis of bony septa may be evident on radiographs.[51] Sinus centesis may yield purulent material, which should be cultured and examined cytologically. A small area over the affected sinus is clipped and surgically prepared, and local anesthetic is infiltrated subcutaneously. Then a small stab incision is made through the skin and periosteum, and a Steinmann pin is used to drill a small hole. Polyethylene tubing is inserted, and attempts are made to aspirate material. A small amount of sterile isotonic fluid can be injected and aspirated to obtain a washing. The stab incision is closed unless sinusitis is confirmed.

31.39.9.4

Treatment and Prognosis

Trephine sites for sinusotomy (Fig. 31-47) are as follows:

1 Dorsal frontal sinus

2 Postorbital diverticulum

3 Rostral frontal sinus

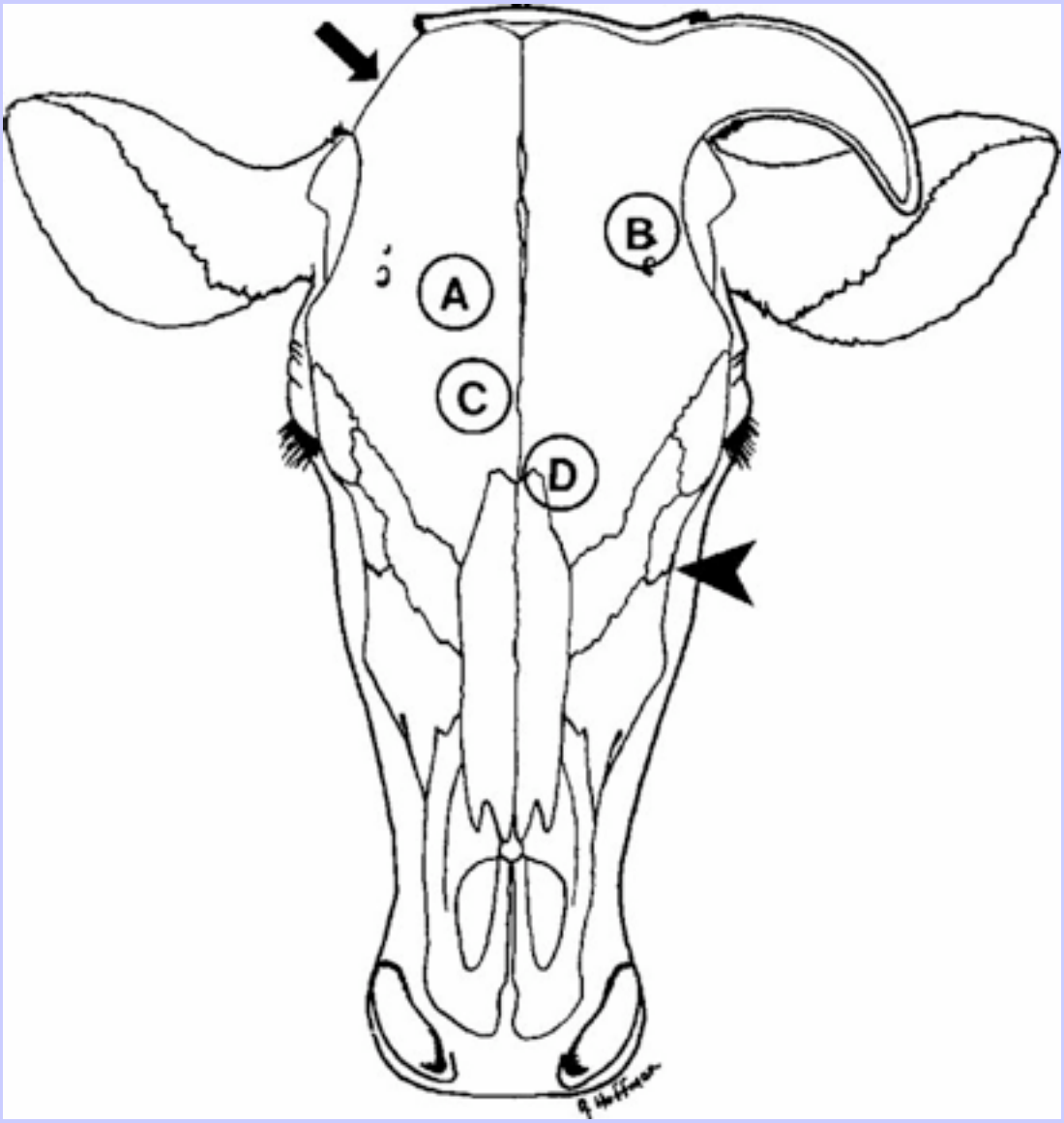
4 Turbinate portion of the frontal sinus

5 Maxillary sinus

Cattle that have frontal sinusitis after dehorning should be treated by sinusotomy and drainage of the sinus.[53] Sinusotomy sites should be based on anatomic landmarks[51] and modified as needed to accommodate any frontal bone distortion or wounds related to dehorning.[51] Sinusotomy should be performed 3 to 4 cm from midline, intersecting a line drawn between the caudal aspect of the orbits. If draining tracts are present at the poll, an additional sinusotomy can be made in the cornual portion of the frontal sinus.[51] Sinusotomy is performed after sedation and local anesthetic infiltration of the centesis site(s). A 2-cm—diameter circular piece of skin is excised, and a 19-mm (¾-inch) trephine used to create an opening into the sinus, through which purulent fluid should be evacuated and the sinus lavaged.

Additional trephine sites that permit access to other regions of the frontal sinus include the postorbital diverticulum, which is trephined approximately 4 cm caudal to the dorsal rim of the orbit, just above the temporal crest of the frontal bone; the rostral frontal sinus, which is trephined just caudal to a line between the centers of the orbits and to either side of the midline; and the turbinate portion of the frontal sinus, which is trephined just rostral to the line described and to either side of the midline.

Fig. 31-47 Trephine sites for sinusotomy. *A*, Dorsal frontal sinus. *B*, Postorbital diverticulum. *C*, Rostral frontal sinus. *D*, Turbinate portion of frontal sinus. The maxillary sinus is trephined ventral to a line from the infraorbital foramen to the medial canthus *(arrowhead)*. If draining tracts are present at the poll, an additional sinusotomy can be made in the cornual portion of the frontal sinus *(arrowhead)*.



Access to the maxillary sinus is achieved by trephining ventral to a line from the infraorbital foramen to the medial canthus. If an infected tooth is the cause of maxillary sinusitis, a sinusotomy is created with a trephine over the affected tooth to repel it; otherwise, the hole is usually made just dorsal and caudal to the facial tuberosity. The trephine site should be higher in the sinus of younger animals because the tooth roots are longer.

If the frontomaxillary and nasomaxillary openings are still patent, one trephine site may be sufficient, with the natural opening providing ventral drainage. In more chronic cases, two trephine sites (for ingress and egress) are needed. Another alternative in chronic sinusitis is the use of a curved steel sinus probe (1 cm diameter × 55 cm long), which is forcefully driven through the septal plates of the frontal sinus into the nasal meatus for ventral drainage.[54] The frontal sinus is very compartmentalized in mature sheep and goats, and effective drainage is difficult. Therapy should therefore be aggressive in these species, even in early cases, and double trephination or bone flaps for exposure and curettage should be considered.

If a tooth has been repelled, a roll of gauze or dental impression material should be used to occlude the alveolar socket to prevent feed material from entering the sinus. A strip of umbilical tape tied around the gauze roll or a wire in the dental material is passed through socket, sinus, and trephine hole and secured to the face by tying around another roll of gauze as a stent. These gauze packs are replaced each time the sinus is flushed. The sinus is lavaged daily with dilute antiseptic solutions such as 0.1% povidone iodine or chlorhexidine in saline, or 1:1000 potassium permanganate. Lavage is continued until infection is resolved. Enzymes (papain or 200,000 U of streptokinase and 50,000 U of streptodornase in at least 10 mL of normal saline solution) may help remove thick exudate.

Parenteral antibiotics and NSAIDs (aspirin, 100 mg/kg PO twice daily or flunixin meglumine, 1.1 to 2.2 mg/kg IV daily or divided twice daily) are indicated if systemic signs are present. In the absence of microbial culture and susceptibility results, penicillin (22,000 U/kg IM or SC q12-24h) is recommended as the antibiotic of choice because *Arcanobacterium (Actinomyces) pyogenes* is the most common organism isolated from cattle with chronic frontal sinusitis resulting from dehorning. *Pasteurella multocida* is the most common organism isolated from infections of the frontal sinus not associated with dehorning.[51] Penicillin may be effective against some isolates of *P. multocida;* alternatively, oxytetracycline can be administered if *P. multocida* is suspected (11 mg/kg IV or SC q24h, or 20 mg of long-acting oxytetracycline per kilogram SC q72h). If bacterial culture and susceptibility results are available, antimicrobial therapy should be modified accordingly. Early cases often resolve in 10 to 14 days, with a good prognosis. Long-term therapy (weeks) is frequently needed in chronic cases; the prognosis is more guarded, and salvage is often the best option.

31.39.9.5

Prevention and Control

Dehorning ruminants as neonates, particularly if a “closed” method such as a dehorning iron is used, is the most effective way to prevent frontal sinusitis. In larger cattle surgical dehorning with primary skin closure achieved under aseptic conditions minimizes the likelihood of sinusitis.[55] When this is not practical, dehorning should be avoided in rainy, windy, or dusty conditions, and fly control must be used. The dehorning of mature sheep or goats leaves massive wounds that typically take 4 to 6 weeks to close by second intention and so are susceptible to infection; special care, such as bandaging for the initial 7 to 10 days, must be taken.[56] Sinusitis did not occur in goats aged 2 to 24 months dehorned with a technique in which primary skin closure was achieved.[57]

31.40 DISEASES OF THE PHARYNX, LARYNX, AND TRACHEA

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31.41 PHARYNGEAL TRAUMA, ABSCESSES, CELLULITIS, AND GRANULOMAS

31.41.1 Definition and Etiology

Pharyngeal trauma may result in hematomas, foreign body granulomas, cellulitis, or abscesses. Trauma usually results from careless use of balling guns, dose syringes, paste-type anthelmintics or calcium preparations, specula, and stomach tubes. Rough, stemmy feeds (especially when chopped), grass awns, briars, and foreign objects (e.g., nails, baling wire) may also cause punctures. Migrating foreign objects or medications (e.g., mineral oil, anthelmintics) may cause pharyngeal granulomas. Hematomas and puncture wounds often result in abscess formation. Diffuse cellulitis may also result. Common bacteria involved include *Arcanobacterium (Actinomyces) pyogenes, Actinobacillus* species, *Pasteurella* species, *Bordetella* species, *Fusobacterium necrophorum*, and *Streptococcus* species. In cases of particularly virulent bacterial invasion, the condition can become rapidly fatal. *C. pseudotuberculosis* (CLA) may localize in the pharyngeal nodes of sheep and especially goats. CLA is discussed further on p. 658 and also in relation to the hemolymphatic system in Chapter 37.

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31.41.2 Clinical Signs and Differential Diagnosis

Signs of pharyngeal trauma vary with the severity of the resulting reaction (e.g., peracute cellulitis vs. chronic abscess or granuloma). Prominent signs include inspiratory dyspnea with stertorous inspiratory sounds and a prolonged inspiratory phase; extended head and neck; ptyalism, which is often profuse; quidding; evident pain on swallowing or reluctance to swallow solid feed but willingness to drink liquids; prolonged chewing of boluses; regurgitation of food or saliva through the nostrils caused by pharyngeal paresis; mucopurulent to bloody nasal discharge and fetid odors, usually bilateral; cough; bloat; and visible or palpable swelling in the pharyngeal area.[58,59] Megaesophagus has been reported subsequent to pharyngeal trauma.[60] Palpation of the pharynx may increase the stertor and cause pain. In severe cases, systemic signs of fever, anorexia, depression, dehydration, and forestomach stasis may be present. Aspiration pneumonia may be a secondary complication.

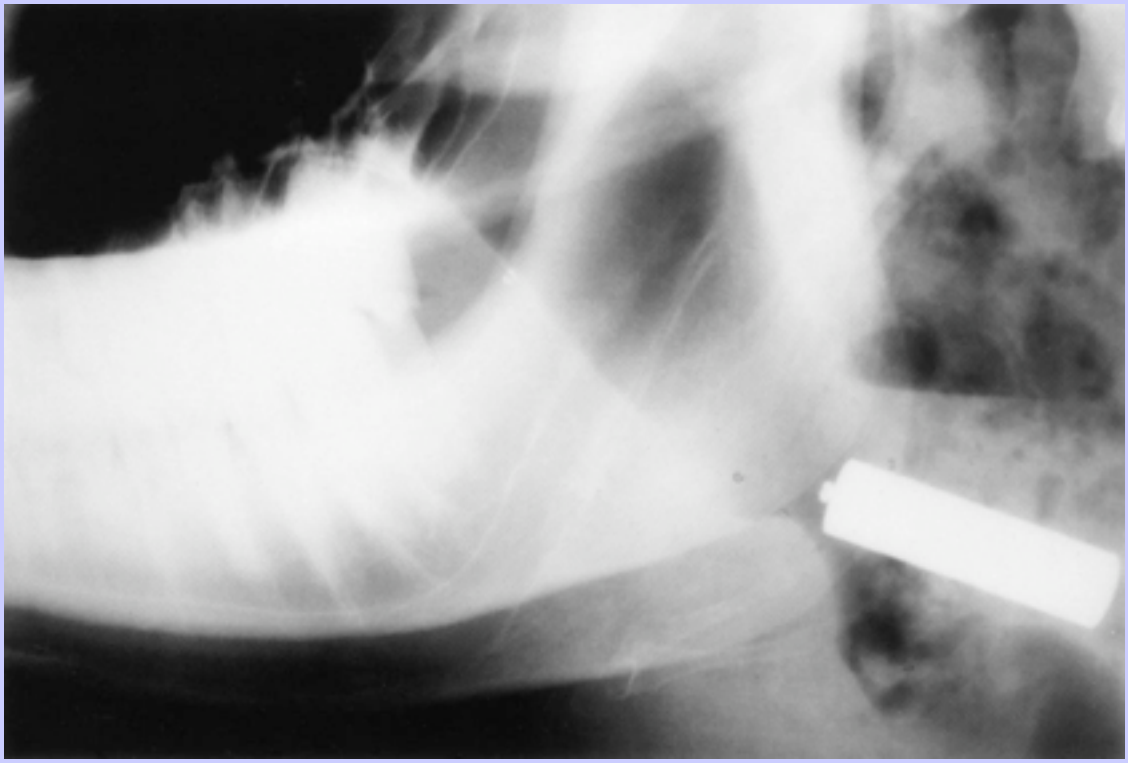
Differential diagnoses include pharyngeal tumors; lymphosarcoma; sialoliths; rabies; botulism; actinobacillosis; necrotic laryngitis; laryngeal abscesses, trauma, edema, or paralysis; and laryngeal tumors.

31.41.3 Diagnosis

A thorough manual examination of the oropharynx or a visual examination with an adequate speculum and light source usually confirms the diagnosis of a pharyngeal swelling and often reveals a puncture that is discharging pus. Cases in which the infection is diffuse can be more difficult to recognize, and endoscopy or radiography can be particularly helpful.[58] Restraining the jaws with a McAllum speculum allows a guarded needle attached to a length of tubing and a syringe to be inserted into the swelling for aspiration of any swelling identified. This helps

to differentiate localized abscesses from granulomas, hematomas, cellulitis, and tumors; allows culture and sensitivity determinations on abscesses; and may aid in cytologic diagnosis of granulomas or tumors. Radiographs may reveal foreign bodies (Fig. 31-48) or air densities (Fig. 31-49) in the pharyngeal tissues. The CBC usually reflects a chronic inflammatory process, with a neutrophilic leukocytosis and a left shift, or a neutrophil-lymphocyte reversal. Dehydration is frequently evident. If the animal is unable to swallow, large amounts of bicarbonate may be lost through the saliva, which may lead to evidence of metabolic acidosis on blood gas analysis or serum biochemical profile.

Fig. 31-48 Radiograph of the pharyngeal area of a cow. Note magnet located in the retropharyngeal tissue.



31.41.4 Treatment and Prognosis

Discrete pharyngeal abscesses are usually best drained into the pharynx. Whenever possible the procedure should be done on the standing animal without sedation to preserve the cough reflex and prevent aspiration. A good oral speculum and excellent restraint are needed. The head should be kept lowered. A guarded blade such as a hook blade from a fetotomy set is introduced into the pharynx, and the abscess is lanced. The cavity is flushed with a mild antiseptic such as 0.2% povidone iodine in saline solution, again taking care to prevent aspiration. Other options include drainage to the exterior, drainage and flushing with a large-gauge needle and tubing, and extirpation.[59] Removal of a bacterial granuloma from the pharynx of a cow via electrocautery has been described.[61] Systemic antibiotics are administered in accordance with culture and sensitivity results, or, in their absence, procaine penicillin G (22,000 U/kg IM or SC q12-24h), tetracyclines (11 mg/kg IV or SC daily, or 20 mg/kg of long-acting oxytetracycline SC q72h), or sulfadimethoxine (55 mg/kg IV loading dose followed by

27.5 mg/kg IV q24h) are used. NSAIDs (aspirin, 100 mg/kg PO twice daily, or flunixin, 1.1 to 2.2 mg/kg IV daily or divided twice daily) help relieve pain, swelling, and stertor. In animals with severe persistent dyspnea, tracheostomy may be necessary. Granulomas and diffuse cellulitis are likewise treated medically with appropriate antimicrobials and antiinflammatory drugs. Supportive therapy such as IV fluids or feeding through a rumenostomy site may be necessary if the animal refuses to eat or drink. The prognosis for most pharyngeal abscesses, hematomas, cellulitis, and granulomas is usually good with appropriate therapy.

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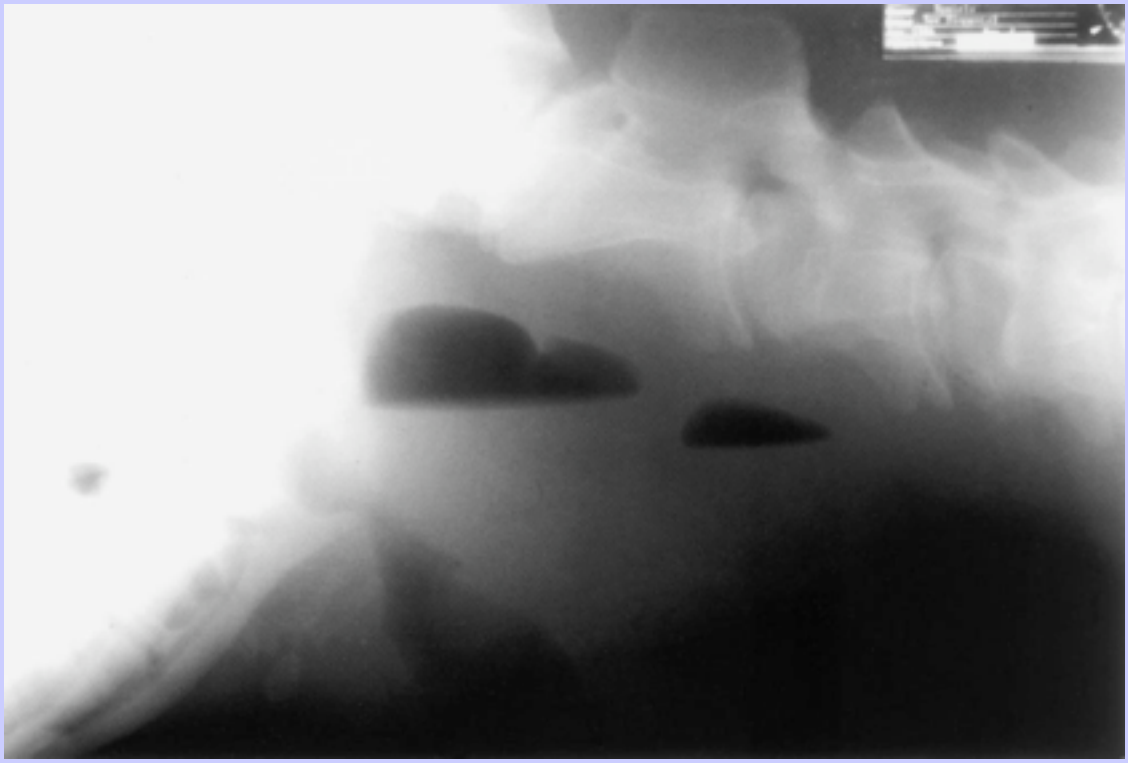
Fig. 31-49 Radiograph of the pharyngeal area of a cow. Note air densities in the tissue, suggestive of abscess formation.



31.42 DORSAL DISPLACEMENT OF THE SOFT PALATE

Although rare, dorsal displacement of the soft palate has been reported in cattle.[62] Respiratory noise is apparent on inspiration and expiration but is loudest on inspiration. Diagnosis can be made by endoscopic examination. Treatment is similar to that used in horses and can include conservative therapy, which consists of antiinflammatory drug therapy and rest, or the condition can be surgically corrected.

31.43 SUBEPIGLOTTIC CYST

Although rare, a subepiglottic pharyngeal cyst causing upper airway obstruction has been reported in cattle.[63] Surgical removal by a peroral approach has been described.[63]

31.44 NECROTIC LARYNGITIS (CALF DIPHTHERIA, LARYNGEAL NECROBACILLOSIS)

31.44.1 Definition, Etiology and Epidemiology

Acute to chronic infection of the laryngeal mucosa and cartilage of young cattle is very common, particularly in feedlots. Laryngeal contact ulcers[64] probably provide a damaged mucosal surface, which then allows invasion of the cartilage by *F. necrophorum*, which is the proximate cause of the lesions. It has also been suggested that *Histophilus somni* is the primary agent inducing a perilaryngeal vasculitis and that *F. necrophorum* represents a secondary bacterial invader.

The disease is most common where cattle are housed in dirty or crowded conditions and in feedlots. Most feedlot cases occur in animals on feed for longer than 30 days. The incidence is sporadic. Cases occur year round, but there appears to be a higher incidence in fall and winter. The disease has a worldwide distribution.

31.44.2 Clinical Signs and Differential Diagnosis

The problem occurs most commonly in calves from 3 to 18 months of age, up to about 24 months. It is characterized by an acute onset of a moist, painful cough, which the animal may attempt to suppress because of pain. Frequently a severe inspiratory dyspnea with a loud guttural stertor and open-mouth breathing with the head and neck extended are observed. The animal may salivate, make frequent painful swallowing movements, and stand and sip water continually. Signs of systemic disease including anorexia, depression, fever (as high as 106° F [41.1° C]), and hyperemic mucous membranes are present. There is often a bilateral nasal discharge and a fetid odor to the breath. The larynx may be visibly or palpably swollen, and palpation may elicit a cough, cause pain, and markedly increase the dyspnea and stertor. If untreated, many calves will die in 2 to 7 days as a result of systemic effects of bacterial toxins and upper airway obstruction. Recovered cases may have a chronic roaring respiration and a harsh, dry cough because of the misshapen larynx. Aspiration pneumonia and chronic “poor doers” are common sequelae. Differential diagnoses include pharyngeal trauma (abscess, cellulitis), severe viral laryngitis (e.g., IBR), actinobacillosis, and laryngeal edema, abscesses, trauma, paralysis, and tumors.

31.44.3 Diagnosis

The diagnosis is usually made presumptively based on clinical signs alone. A laryngoscopic or endoscopic examination can help confirm the diagnosis, but care must be taken to prevent further stress and respiratory embarrassment. Acute cases show changes in the CBC consistent with any acute septic condition: leukopenia caused by neutropenia with a left shift. In chronic or ongoing cases, leukocytosis with neutrophilia, monocytosis, and hyperfibrinogenemia may be present.

31.44.4 Pathophysiology

F. necrophorum normally does not penetrate intact mucous membranes. Laryngeal contact ulcers are thought to provide the portal of entry for *F. necrophorum*, which is ubiquitous. Laryngeal contact ulcers are also very common in slaughter cattle and are speculated to be caused by the following combination of factors: (1) an acute mucositis from mixed upper respiratory infections (such as IBR virus, bovine respiratory syncytial virus [BRSV], parainfluenza virus 3 [PI3], mycoplasma, and bacteria, including *Mannheimia, Pasteurella*, and *Histophilus* species); (2) reflex coughing and swallowing, which accelerate the rate of laryngeal closure; and (3)

resulting erosion of the swollen membranes over the vocal processes and medial angles of the arytenoid cartilages.[65] It has also been proposed that necrotic laryngitis results from a perilaryngeal vasculitis initiated by *H. somni* with secondary invasion by *F. necrophorum*.[66] Necrotic laryngitis can alter pulmonary function such that the growth rate is impeded, and also predisposes to secondary bacterial pneumonia.[67]

31.44.5 Necropsy Lesions

The lesions are typically located over the vocal processes and medial angles of the arytenoid cartilages. Acute lesions consist of marked edema, hyperemia, and swelling of the mucous membrane around a necrotic ulcer, with accumulated exudate. The lesions spread along the vocal processes and vocal folds and may extend into the cricoarytenoideus dorsalis muscles. In chronic cases the lesions consist of a focus of necrotic cartilage surrounded by purulent exudate, with a tract extending to the mucosal surface (Fig. 31-50). The tract opening is surrounded by granulation tissue and may drain pus. The arytenoid cartilage may be rotated into the lumen or may contain mucosal cavities lined with thin, hyperemic epithelium.[65]

31.44.6 Treatment, Prognosis, Prevention, and Control

Oxytetracycline (11 mg/kg IV or SC q24h, or 20 mg/kg of long-acting oxytetracycline SC q72h) or procaine penicillin G (22,000 U/kg IM or SC q12-24h) is appropriate; a sulfonamide, streptomycin, or tylosin is also usually effective. NSAIDs (aspirin, 100 mg/kg PO twice daily, or flunixin, 1.1 to 2.2 mg/kg IV once daily or divided twice daily) reduce swelling, inflammation, and fever. Cases with severe respiratory distress may benefit from one or two doses of steroids (dexamethasone 0.5 to 0.2 mg/kg IV or IM once or twice), but repeated doses of steroids are not recommended. A tracheostomy may be necessary in severe cases to relieve dyspnea and rest the larynx. Good nursing and supportive care are also important, including shelter, adequate ventilation, easy access to feed and water, and oral or IV fluids if needed. The prognosis is good when the condition is detected very early and treated vigorously; when extensive cartilage necrosis occurs, a fatal outcome or chronic ill-thrift with stertorous breathing is expected. There are no specific control measures. The proposed pathogenesis would suggest that measures to control other respiratory diseases may reduce the incidence of necrotic laryngitis.

Fig. 31-50 Postmortem photograph of necrotic laryngitis. Note the purulent material medial to the arytenoid cartilages. Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.

31.45 LARYNGEAL GRANULOMAS

Laryngeal granulomas have been described in cattle.[68] They may originate from laryngeal contact ulcers that have been described in feedlot cattle at slaughter (see the previous section on necrotic laryngitis for more information).[64]

31.46 LARYNGEAL PAPILLOMATOSIS

Papillomas of the larynx are common in feedlot cattle. They are caused by a papovavirus, which is thought to enter laryngeal contact ulcers (see the previous section on necrotic laryngitis).[64] Characteristic signs of laryngeal papillomatosis are stertorous respiration and cough. Differential diagnoses include necrotic laryngitis, pharyngeal trauma, abscess, or granuloma; actinobacillosis; and laryngeal abscesses, trauma, edema, paralysis, and tumors. The lesions are sessile to pedunculated, yellow, frondlike, 1- to 10-mm growths over the vocal processes of the arytenoid cartilages.[69] Treatment usually is not indicated but involves surgical removal. Measures to decrease other respiratory infections and thereby decrease contact ulcers may lower the incidence of papillomas.

31.47 LARYNGEAL ABSCESSES

Abscessation of the arytenoid cartilages caused by *Arcanobacterium (Actinomyces) pyogenes* has been reported in calves[70] and sheep.[71] Clinical signs include tachypnea, extension of the head and neck, cyanosis, and a severe progressive dyspnea with marked stertor that can be localized to the larynx. Many affected animals remain alert and afebrile and continue to eat until the terminal stages of severe dyspnea. Endoscopy reveals generalized edema and hyperemia of the laryngeal mucosa and obstruction of the rima glottidis by swelling of one or both arytenoids. Radiographs may demonstrate soft-tissue swelling of the larynx. The condition has been speculated to be initiated by grass awns, trauma, hereditary predisposition, or congenital cavitations in the cartilages. In sheep, rams appear to be more commonly affected than ewes, and two reports found a breed predisposition in Texels and Southdowns, although other reports have indicated that various breeds are affected.[71] The necropsy lesions consist of encapsulated abscesses containing pus and necrotic debris in the arytenoid cartilage, usually in the vicinity of the vocal cord. A tract from the abscess typically opens in an area of granulation tissue in the laryngeal mucosa. Treatment consists of tracheostomy, antibiotics (usually penicillin at 22,000 U/kg IM or SC q12-24h), and antiinflammatory drugs (aspirin, 100 mg/kg PO twice daily, or flunixin, 1.1 to 2.2 mg/kg IV daily or divided twice daily). The prognosis for recovery is considered guarded unless the condition is detected in the earliest stages and treated vigorously; however, one affected heifer lived for at least 1 year and was bred successfully after permanent surgical tracheostomy for chronic arytenoid abscessation.[72]

31.48 OTHER LARYNGEAL OBSTRUCTIONS (LARYNGEAL TRAUMA, EDEMA, PARALYSIS, AND FOREIGN OBJECTS)

Other laryngeal obstructions are all sporadic and may manifest with similar signs. Trauma to the larynx may result from roping or injury in restraint devices. Inappropriate placement of an endotracheal tube can potentially damage the larynx. The respiratory system is the main target organ for anaphylaxis in ruminants, and laryngeal edema can be a prominent component of this syndrome, which is discussed fully in this chapter on p. 652. Inhalation of smoke or other noxious gases also may cause laryngeal edema. Paralysis of the larynx was reported in a sheep with a false carotid aneurysm[73]; presumably other lesions of the neck or anterior mediastinum could cause laryngeal paralysis through involvement of the recurrent laryngeal nerves. Laryngeal hemiplegia has been reported in association with *Sarcocystis* species infection of the muscles of the larynx and pharynx in a ram.[74] Foreign objects more commonly lodge in the pharynx, but sharp objects and food materials may be aspirated and lodge in the larynx. Signs common to these laryngeal obstructions include inspiratory dyspnea, prolongation of the inspiratory phase, mouth breathing, stertor, cyanosis, salivation, and extension of the head and neck. Palpation of the larynx may reveal swelling and may exaggerate the dyspnea and stertor. Differential diagnoses include necrotic laryngitis, laryngeal abscesses, severe viral laryngitis, actinobacillosis, and tumors. Endoscopy and radiology are required in most cases to differentiate these conditions. Hematologic analysis may give some indication of the presence of bacterial infection; a stress leukogram may also be seen. Tracheostomy is indicated in all severe cases. Surgical correction of laryngeal obstruction by tracheolaryngostomy has been described in cattle.[75]

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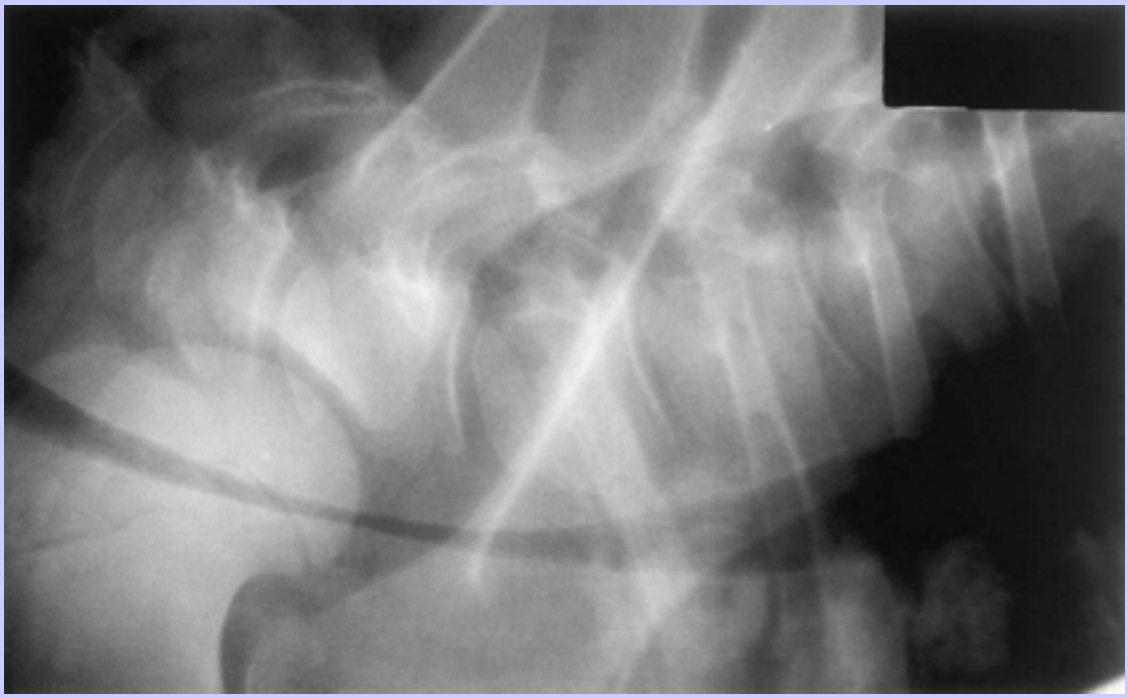
Laryngeal trauma and paralysis may resolve spontaneously or may require reconstructive surgery. The therapy of anaphylaxis is discussed on p. 652. Foreign objects should be removed surgically or endoscopically. NSAIDs (aspirin, 100 mg/kg PO twice daily, or flunixin, 1.1 to 2.2 mg/kg IV daily or divided twice daily) may help reduce swelling, edema, and respiratory embarrassment in all forms of obstruction.

31.49 TRACHEAL COLLAPSE AND STENOSIS

31.49.1 Definition and Etiology

Tracheal collapse or stenosis is infrequently reported in cattle and goats.[76–81] The cause is usually unknown, but the problem may result from cranial thoracic trauma, roping, tracheostomies, or possibly congenital defects. In cattle the majority of reports have described tracheal collapse in calves in which signs were usually first evident at several weeks of age.[76–79] The majority of these cases also involved the thoracic trachea (Fig. 31-51), suggesting a congenital lesion. However, in most calves with tracheal collapse the condition has been a result of dystocia at birth, especially breech presentations, which suggests a traumatic cause.[82] In contrast to reports in cattle, tracheal collapse has been reported in a mature goat that showed no previous signs of respiratory abnormality.[81]

Fig. 31-51 Radiograph demonstrating collapse of the thoracic trachea in a calf.



Tracheal collapse has also been reported in Texel-cross lambs with inherited chondrodysplasia[83]; affected lambs were normal at birth but developed exercise intolerance as early as 1 week of age. Severely affected lambs developed fatal respiratory compromise when exercised. Tracheal stenosis can also occur in lambs born to ewes that ingest *Veratrum californicum* root and rhizome material at days 31 through 33 of gestation.[84]

31.49.2 Clinical Signs and Differential Diagnosis

Clinical signs of tracheal collapse may include fever, tachycardia, tachypnea, cyanosis, and mucosal hyperemia with vessel engorgement, but affected animals may have normal vital signs and are otherwise alert and in good condition. Dyspnea is usually induced or exacerbated by excitement or exercise or may be severe at rest. Stertorous respiration is usually evident, is frequently worse on inspiration, and can often be localized to the trachea on auscultation. The inspiratory phase is prolonged, and a "honking" cough is characteristic, especially with intrathoracic collapse. Palpation may reveal or induce the collapse when the cervical trachea is involved. Tracheal palpation or elevation of the head may increase the stertor or induce the honking cough. In some cases there may be other evidence of trauma (fractured ribs, sternebrae), and in some animals pneumonia may be present. There is no response to antibiotics, steroids, or tracheostomy.

Texel-cross lambs with tracheal collapse resulting from inherited chondrodysplasia also exhibited retarded growth, forelimb varus, and reluctance to walk. Severity of signs varied among affected individuals; some died or were euthanized within weeks because of respiratory compromise, whereas others survived to breeding age.[83] Animals that survived for several months often developed arthritis characterized by severe erosive lesions of the articular cartilage of major joints including the shoulder, hip, and stifle. Lambs with congenital tracheal stenosis resulting from maternal ingestion of *V. californicum* died within 5 minutes of birth after signs of severe respiratory distress.

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Other possible disorders with signs similar to those seen in animals with tracheal collapse or stenosis are tracheal foreign bodies, tracheal actinobacillosis, neoplasms, bronchopneumonia, necrotic laryngitis, and extratracheal compressive lesions (e.g., abscesses, tuberculosis, hematomas).

31.49.3 Diagnosis

Any deviation of the hemogram from normal is probably a reflection of associated pneumonia or stress. Endoscopy and radiography are the most helpful ancillary aids. Care must be taken when restraining, sedating, and passing the endoscope in these animals; oxygen should be available. In cattle with idiopathic tracheal collapse, radiography (see Fig. 31-51) and endoscopy usually reveal a dorsoventral flattening, most typically in the caudal cervical and cranial thoracic trachea, although lateral collapse and collapse in other locations (cranial cervical, intrathoracic) are occasionally encountered.

31.49.4 Pathophysiology

Proposed causes of tracheal collapse in other species include congenital malformations, genetic or nutritionally induced weakness of cartilage, deficient innervation of the trachealis muscles, trauma, ischemic lesions from endotracheal tube cuffs, and primary pulmonary disease. No histologic differences were noted in tracheal rings from collapsed and normal segments in calves in one report.[76]

As previously mentioned, most calves with tracheal collapse have a history of dystocia at birth. During delivery, compression of the chest wall with fracture of the first pair of ribs may cause injury at the thoracic inlet.[85] However, signs of tracheal collapse are not immediately evident at birth, but develop over time.

Lambs with tracheal collapse associated with inherited chondrodysplasia had clinical signs most similar to a condition in humans that results from a mutation in the diastrophic dysplasia sulphate transporter gene,[86] but the

causative mutation in sheep has not yet been reported. Preliminary data indicated that the chondrodysplasia was inherited via a recessive mode of inheritance.[83] Tracheal stenosis in lambs born to ewes fed *V. californicum* was presumed to be caused by cyclopamine, a steroidal alkaloid which is the toxic principle in highest concentration in *V. californicum*. It was notable that lambs developed tracheal stenosis when ewes were fed *V. californicum* at 31 to 33 days of gestation, whereas craniofacial defects typically recognized in lambs born to exposed dams are seen when the ewe ingests the toxic plant by day 14 of gestation.[84]

31.49.5 Necropsy Lesions

At necropsy, affected animals may have either a laterally[78] or dorsally[77,81] compressed trachea; typically several centimeters of the trachea are affected. Necropsy of sheep with inherited chondrodysplasia reveals a trachea that is flaccid, flattened, and sometimes irregularly kinked. Tracheal rings are markedly thickened, and the lumen is narrow, possibly extremely so. Diffuse pulmonary congestion and edema, with epidcardial ecchymoses, may occur as a result of terminal anoxia and respiratory distress. Other lesions include exaggerated convex curvature of the ribs, anglular limb deformities, and erosive arthritis with exposure of the subchondral bone in one or more joints. Histologically, hyaline cartilage in affected organs is hypercellular and disorganized, with foci of apparent chondrolysis. Chondrocytes are larger than normal, although shrunken, apparently necrotic chondrocytes are also seen.[83] Necropsy of lambs with congenital tracheal stenosis resulting from maternal ingestion of *V. californicum* reveals pronounced lateral flattening of the trachea. Tracheal rings are reduced in number, with abnormal size and shape and irregular spacing. Histologically the cartilage rings in affected lambs were flattened and thin and had a thinner zone of proliferating chondrocytes on their outer surface compared with normal age-matched controls.[84]

31.49.6 Treatment and Prognosis

Mild cases may respond to confinement sufficiently to be fed out for slaughter. A number of surgical treatments have been proposed in other species, including anastomosis, bisection of tracheal rings, internal and external prostheses, and plication of the dorsal membrane.[76] External prostheses have been used successfully in calves,[76,82,85] adult cattle,[80] and a goat.[87] A favorable prognosis for surgical correction is estimated at approximately 30%.[82] A detailed description of surgical repair in calves by external prostheses has been published.[82] Successful management of lambs with congenital tracheal collapse or stenosis has not been reported, although mildly affected lambs with congenital chondrodysplasia survived into adulthood. Because of the apparent genetic basis for the disease, breeding of affected animals should not be recommended.

31.50 TRACHEAL FOREIGN BODIES AND MASSES

Ruminants may occasionally inhale foreign objects that lodge in the trachea. There are also two reports of tracheal actinomycosis that resulted in signs of tracheal obstruction.[88] Signs include a chronic cough, inspiratory dyspnea, audible stridor that can be localized to the trachea, extension of the head and neck, open-mouth breathing, and salivation. Differential diagnoses should include pharyngeal trauma, necrotic laryngitis, laryngeal abscesses, trauma, edema, or paralysis, tracheal collapse, and extratracheal compressive lesions. Endoscopy and radiology are important aids to diagnosis. Care must be exercised in restraint and in passage of the endoscope. Some small objects may be retrieved by a snare passed through an endoscope; others may require tracheostomy. When possible, the tracheostomy should be performed below the object. The actinomycotic masses are soft, pedunculated lesions with a granular surface containing small yellow foci. Of the two reported cases of tracheal actinomycosis, one died

of asphyxiation and the other responded initially to partial surgical removal of the masses, tracheostomy, and therapy with sodium iodide, penicillin, and streptomycin but relapsed some months later.[88a]

31.51 TRACHEAL EDEMA SYNDROME OF FEEDLOT CATTLE

Tracheal edema syndrome has also been referred to as *tracheal stenosis* in feedlot cattle. In this condition extensive edema and hemorrhage in the dorsal wall of the trachea result in coughing, dyspnea, and stertor, which has given rise to the term "honker cattle."[89] Tracheal edema syndrome occurs in two forms, characterized by either acute dyspnea or a chronic cough. It is not known whether the two forms are related. Although the syndrome has been recognized for years, no controlled research has been undertaken to determine the cause or risk factors of this syndrome, and the cause is unknown. Theories regarding possible causes include infections with upper respiratory viruses or bacteria such as *P. multocida* or *H. somni*, trauma to the trachea from feedbunks, passive congestion and edema from excessive fat accumulation in the thoracic inlet, hypersensitivity reactions, and mycotoxins.[90]

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The acute dyspnea syndrome occurs mainly in heavy feedlot cattle in the latter two thirds of the feeding period and is most common in southern plains feedlots. It is sporadic and more common in summer, possibly because of exacerbation by hot weather. At one extreme, sudden deaths without the onset of noticeable clinical signs have been reported, and at the other extreme subclinical disease was evidenced by lesions in animals at slaughter that did not have clinical signs. Other factors that increase respirations also may cause signs to appear. Signs include an acute onset of dyspnea and loud guttural inspiratory sounds that can be localized to the lower trachea. Open-mouth breathing, extension of the head and neck, and cyanosis, leading to recumbency and death by asphyxiation, are present. Differential diagnoses for this form include pharyngeal trauma or abscess; necrotic laryngitis; IBR; laryngeal abscess, tumor, foreign object, edema, or paralysis; tracheal foreign object, mass, or collapse; and AIP.

The chronic form occurs in lighter cattle (135 to 400 kg [300 to 900 lb]) and is more common in western plains feedlots. It is also sporadic but less seasonal. Affected animals may have a history of IBR or pneumonia. The main sign is a continuous, frequent, deep, hacking, nonproductive cough. The animal may be unthrifty but is otherwise normal in appearance. The main differential diagnoses are necrotic laryngitis or mild, chronic suppurative pneumonia. Endoscopy and visualization of the lesions subsequently described aid in the diagnosis. Necropsy of the acute form reveals an edematous thickening of the submucosa and mucosa of the dorsal trachea (Fig. 31-52), as much as 5 cm thick and extending 20 to 30 cm from the midcervical area to the thoracic inlet or tracheal bifurcation. There is also extensive mucosal, submucosal, and peritracheal edema and/or hemorrhage, possibly related at least in part to agonal breathing. There may be no other lesions of the airway or lungs,[90] or abnormalities (e.g., pulmonary edema, bronchitis, interlobular edema and emphysema, alveolar hemorrhage) may be seen.[89] Lesions in the chronic form consist of hyperemia of the mucosa of the caudal third of the trachea, with a thin layer of mucopurulent exudate. The mucosa may have a cobblestone appearance or even large, fiber-like projections and polyps. No effective treatment exists for the chronic form. Corticosteroids (dexamethasone, 0.05 to 0.2 mg/kg IM or IV; prednisolone, 1 to 2.2 mg/kg IM or IV daily) are recommended for the acute form, as well as such practices as preventing stress, providing shade, and cooling with water sprays and fans. Broad-spectrum antibiotics have been recommended by some,[89,90] whereas others have not found them to be necessary.[91] However, because animals with tracheal edema syndrome may be difficult to distinguish clinically from animals with conditions that could respond to antimicrobials (such as necrotic laryngitis), antimicrobials are often administered. Because withdrawal times associated with antimicrobial administration could delay shipment of affected animals to slaughter, drugs with a short withdrawal time should be used if salvage is an option. Tracheostomy may not be helpful if placed proximal to the obstruction, and relief of dyspnea via tracheostomy may require insertion of an endotracheal tube to the tracheal bifurcation. Oxygen administration could be beneficial if available. Recovered patients tend to relapse and should be salvaged.

Fig. 31-52 Postmortem photograph of tracheal edema syndrome. Note severe mucosal and submucosal thickening, which has obstructed the trachea by approximately 50%. Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.

31.52 LOWER RESPIRATORY TRACT DISEASES

AMELIA R. WOOLUMS

TREVOR R. AMES

JOHN C. BAKER

31.53 CLINICAL CLASSIFICATION OF PNEUMONIA

AMELIA R. WOOLUMS

TREVOR R. AMES

JOHN C. BAKER

In an effort to simplify the differential diagnosis of the bewildering array of lower respiratory diseases of cattle, a classification system based on pathophysiology and clinical signs has been suggested.[92] Three classifications were proposed:

1 Bronchial pneumonia is characterized pathophysiologically by invasion of pathogenic organisms that gain access to the lung through the pulmonary tree. It is characterized clinically by depression, fever, and other signs of sepsis such as hyperemic mucous membranes or scleral injection, and an anterior-ventral distribution of abnormal lung sounds and lesions (see the following section). Bronchial pneumonia is the final outcome of the respiratory disease complex of ruminants, and because viruses play an important role in this disease complex, viral causes of respiratory tract disease in ruminants are placed in this category.

2 The interstitial pneumonias are a very diverse group of (usually) noninfectious diseases. Although it is difficult to make generalizations, these diseases are characterized pathophysiologically by an interstitial reaction that usually results from ingestion or inhalation of toxins or allergens. Clinically affected animals tend not to be as depressed and septic, the abnormal lung sounds and lesions are diffusely distributed, and there is little or no response to antibiotic therapy.

3 Metastatic pneumonia is characterized pathophysiologically by septic embolization of the lungs from other foci in the body, classically liver abscesses and postcaval thrombi. Clinically, cases of metastatic pneumonia exhibit signs of sepsis as with bronchopneumonia, but with widespread pulmonary lesions and abnormal lung sounds, and the eventual development of hemoptysis (see descriptions of vena caval thrombosis and metastatic pneumonia in this chapter).

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31.54 THE BRONCHOPNEUMONIAS (RESPIRATORY DISEASE COMPLEX OF CATTLE, SHEEP, AND GOATS)

AMELIA R. WOOLUMS

TREVOR R. AMES

JOHN C. BAKER

The respiratory disease complex of ruminants consists of the single clinical entity of bronchopneumonia but is caused by numerous combinations of infectious agents, compromised host defenses, and environmental conditions. Bronchopneumonia causes greater economic losses than any other disease of feedlot cattle or lambs and is one of the most common causes of dairy calf mortality.

In dairy calves, bronchopneumonia, often called *enzootic pneumonia*, is most common in housed calves. It is called *shipping fever* in beef calves because the greatest incidence of bronchopneumonia occurs after shipment to stocker operations or feedlots; the term *bovine respiratory disease* (BRD) is also used to describe feedlot bronchopneumonia. Bronchopneumonia also occurs in nursing beef calves and in mature beef or dairy cows, sometimes in outbreaks that can have significant morbidity or mortality. Little is known about which factors are specifically the most important for putting these populations at risk for bronchopneumonia, but they are likely similar to risk factors described for housed dairy calves or feedlot cattle. The infectious agents and risk factors of bronchopneumonia of sheep and goats are very similar to those of calves.

Bronchopneumonia of ruminants is a disease of multifactorial causation that occurs when a certain combination of host, environment, and infectious agent characteristics (risk factors) is active. The numerous infectious agents (Boxes 31-3 and 31-4) that are associated with bronchopneumonia are ubiquitous in ruminant populations, and the bacteria most often associated with pneumonic lesions are part of the normal resident flora of the ruminant nasopharynx. In addition to recognition of the microbial agents that contribute to the development of bronchopneumonia in ruminants, understanding of the management practices that also play a role is necessary for developing successful programs of prevention.

31.54.1 Box 31-3 Viral Agents Associated with Respiratory Tract Diseases in Ruminants

31.54.1.1 BOVINE

31.54.1.1.1 Viruses of Major Importance (Commonly Isolated or Generally Accepted to be Important Contributors to Ruminant Respiratory Disease)

Bovine herpesvirus type 1 (IBR)

Bovine respiratory syncytial virus (BRSV)

Bovine viral diarrhea virus (BVDV)

Bovine parainfluenza virus type 3 (PI3)

Bovine respiratory coronavirus

Alcelaphine herpesvirus 1 and 2/ovine herpesvirus 2 (malignant catarrhal fever)

31.54.1.1.2 Viruses of Minor Importance (Uncommonly Isolated or of Uncertain Importance in Ruminant Respiratory Disease)

Bovine herpesvirus type 4 (DN-599, Movar 33/63, FTC-2)

Bovine adenovirus

Bovine rhinovirus

Bovine reovirus

Bovine enterovirus

Calicivirus

Influenza virus

31.54.1.2 OVINE AND CAPRINE

Ovine or bovine respiratory syncytial virus (ORSV, BRSV)

Parainfluenza virus type 3 (PI3)

Adenovirus

Bluetongue virus

Ovine progressive pneumonia (maedi-visna) virus of sheep*

Pulmonary carcinoma of sheep*

* Progressive pneumonias, capable of causing severe chronic respiratory disease.

31.54.2 Box 31-4 Bacteria, *Mycoplasma, Ureaplasma*, and *Chlamydia* Species Associated with Bronchopneumonia of Cattle, Sheep, and Goats

31.54.2.1 Bacteria of Major Importance (Commonly Isolated or Generally Accepted to be Important Contributors to Ruminant Respiratory Disease)

Mannheimia haemolytica

Pasteurella multocida

Histophilus somni

Mycoplasma bovis

Mycoplasma dispar

Ureaplasma species

Mycoplasma ovipneumonia (sheep and goats only)

Mycoplasma mycoides subsp. *mycoides*, large colony variant (goats)

Arcanobacterium (Actinomyces) pyogenes (secondary opportunistic pathogen)

31.54.2.2 Bacteria of Minor Importance (Uncommonly Isolated or of Uncertain Importance in Ruminant Respiratory Disease)

Pseudomonas aeruginosa

Escherichia coli

Streptococcus species

Staphylococcus species

Moraxella species

Salmonella species

Bacteroides species (anaerobe)

Peptococcus indolicus (anaerobe)

Fusobacterium species (anaerobe)

Chlamydia species

31.55 INFECTIOUS AGENTS ASSOCIATED WITH THE RESPIRATORY COMPLEX OF CATTLE, SHEEP, AND GOATS

31.55.1 Etiology

Numerous infectious agents have been isolated from cases of bronchopneumonia in ruminants (see Boxes 31-3 and 31-4). Although infectious bronchopneumonia of ruminants is usually caused by two or more infectious agents acting together, some agents can also cause significant disease alone. Therefore the clinical and epidemiologic characteristics, means of diagnosis, and treatment and prevention of the infectious agents will be

first considered individually. A description of epidemiology, diagnosis, and treatment of "undifferentiated" bronchopneumonia (bronchopneumonia with no specific causative diagnosis attempted) will then follow. The clinical signs, gross pathologic lesions, and recommended methods of diagnosis for the major infectious causes of ruminant respiratory disease are listed in Table 31-9.

31.56 VIRAL AGENTS

31.56.1 Bovine Herpesvirus Type 1 (Infectious Bovine Rhinotracheitis Virus)

31.56.1.1 Definition and Etiology

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Bovine herpesvirus 1 (BHV-1) is an enveloped DNA virus that is classified as an alphaherpesvirus in the family Herpesviridae. It is associated with multiple, distinct disease syndromes of cattle that include IBR, conjunctivitis (see Chapter 39), infectious pustular vulvovaginitis (IPV), balanoposthitis, abortion (see Chapter 43, encephalomyelitis (see Chapter 35), and mastitis.[93,94] Although only a single serotype of BHV-1 is currently recognized, three subtypes have been identified on the basis of restriction endonuclease cleavage patterns. These subtypes are referred to as BHV-1.1 (respiratory infections), BHV-1.2 (respiratory and genital infections), and BHV-1.3 (neurologic infections). BHV-1.3 has been reclassified as a distinct herpesvirus and is designated as BHV type 5.[93] Only the respiratory manifestations of infection with BHV-1 are discussed here. The respiratory form is characterized by rhinitis, tracheitis, and pyrexia and is referred to as IBR. BHV-1 can also cause pneumonia as part of a severe generalized infection in newborn calves.[95] The virus is also of great importance in the bovine respiratory disease complex because of its role in enhancing secondary bacterial bronchopneumonia by causing respiratory injury and immunosuppression,[96] as discussed later.

Table 31-9 Clinical and Gross Pathologic Characteristics of Common Infectious Agents That Cause Respiratory Disease in Ruminants

Agent	Species	Clinical Signs*	Gross Pathology*	Diagnosis
VIRUSES				
BHV-1 (IBR)	Cattle	Fever, depression, anorexia, serous to mucopurulent nasal discharge, muzzle hyperemia, nasal plaques, coughing, inspiratory stridor (conjunctivitis ± keratitis, abortion)	Congestion; fibrinopurulent exudate of nasal passages, larynx, trachea; in young calves, pneumonia and involvement with other organs	VI or IFA nasal swabs, conjunctival scrapings PS VI, IFA, or IHC of tissue from upper airways or lungs collected at necropsy
BRSV†	Cattle, sheep, goats	Fever, depression, anorexia, tachypnea, nasal discharge (±), coughing, expiratory dyspnea, harsh bronchovesicular sounds over cranioventral lung, crackles and wheezes rarely, quiet lung sounds caused by pneumothorax, subcutaneous emphysema	Lobules in cranioventral lung collapsed, firm, dark red; caudodorsal lung fails to collapse, rubbery texture (suggestive of acute interstitial pneumonia); dorsocaudal emphysema	IFA or RT-PCR of nasal swabs (VI unreliable) PS IFA or IHC of lung at necropsy (most reliable in acute stage of disease)
PI3	Cattle, sheep, goats	Like BRSV but more mild, commonly asymptomatic; contributes with other agents to enzootic calf pneumonia or shipping fever	Scattered lobules of cranioventral lung collapsed, firm, dark red	VI or IFA of nasal swabs PS VI, IFA, or IHC of lung at necropsy

BVDV	Cattle	Fever, depression, anorexia, nasal discharge, tachypnea, coughing (±); contributes with other agents to enzootic calf pneumonia or shipping fever (diarrhea, abortion, congenital defects, PI calves, hemorrhagic syndrome)	Scattered lobules of cranioventral lung collapsed, firm, dark red	VI, ELISA or PCR of peripheral blood buffy coat PS VI, IFA, or IHC of lung at necropsy
Respiratory coronavirus[†]	Cattle	Contributes with other agents to enzootic calf pneumonia or shipping fever	Not yet well characterized, probably as for PI3	VI (need special cells) or RT-PCR of nasal swabs PS VI or IFA of lung at necropsy
BACTERIA				
Mannheimia haemolytica	Cattle, sheep, goats	Fever, depression, anorexia, signs of endotoxemia, tachypnea, evidence of pleural pain, mucoid to mucopurulent nasal discharge, harsh bronchovesicular sounds over cranioventral lung ± crackles (coughing not prominent)	Cranioventral lung lobes firm, dark red to gray-brown; fibrin on pleura; yellow pleural fluid that may be gelatinous; infarct-like (wedge-shaped) lesions sometimes seen	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret) Culture from characteristic lesions at necropsy
Pasteurella multocida	Cattle, sheep, goats	Fever, tachypnea, cough, depression, mucoid to mucopurulent nasal discharge, harsh bronchovesicular sounds over cranioventral lung ± crackles	Cranioventral lobules (sometimes lobes) firm, dark red to purple; purulent exudate in airways; fibrin on pleura not expected	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret) Culture from characteristic lesions at necropsy

Histophilus somni†	Cattle, (uncommon in sheep, goats)	As for *P. multocida*; possibly also evidence of pleural pain (joint effusion, infertility or abortion, otitis, conjunctivitis, neurologic signs)	As for *M. haemolytica*, although fibrinous pleuritis not as consistent; fibrinopurulent arthritis, myocarditis often seen in respiratory cases	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret) culture from characteristic lesions at necropsy
Mycoplasma bovis‡	Cattle	Fever, anorexia, tachypnea, cough, nasal discharge; chronic or ongoing pneumonia that fails to respond as expected to therapy (joint or tendon sheath effusion, otitis, conjunctivitis)	Cranioventral lobules collapsed, firm, dark red; multiple grossly visible raised nodules filled with caseous material (abscesses or caseous necrosis); (fibrinopurulent arthritis, tenosynovitis, or otitis common in respiratory cases; myocarditis or pericarditis)	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret; more meaningful if several in group have positive culture from characteristic lesions at necropsy)

BVDV, Bovine viral diarrhea virus; *BHV-1*, bovine herpesvirus type 1; *ELISA*, enzyme-linked immunosorbent assay; *IBR*, infectious bovine rhinotracheitis; *IFA*, immunofluorescent assay; *IHC*, immunohistochemistry, most commonly used on formalin fixed lung tissue collected at necropsy; *PCR*, polymerase chain reaction; *PI3*, parainfluenza type 3; *PS*, paired serology; *RT-PCR*, reverse transcriptase—PCR; *TTA*, transtracheal aspirate; *VI*, virus isolation.

* Clinical signs not related to the respiratory system but possibly also prevalent are listed in parentheses. Note that respiratory disease is often caused by two or more agents, so clinical signs and gross pathology in an individual or herd may be any combination of those listed for individual agents.

† Agent does not survive transport well or can be difficult to isolate; requires special handling or culture techniques to maximize likelihood of isolation.

‡ Usually need to specifically request tests to isolate mycoplasmas and to specifically identify the species *M. bovis*.

31.56.2 Clinical Signs

Clinical signs vary and range from mild to severe. Genetic factors also appear to be an important determinant of the severity of BHV-1 infection, specifically the type-I interferon genotype.[97] Clinical signs include pyrexia, anorexia, dramatic drop in milk production in dairy cattle, increased respiratory rate, a slight degree of hyperexcitability, ptyalism, coughing, and nasal discharge that progresses from serous to mucopurulent. Dyspnea characterized by open-mouth breathing may appear if the larynx or trachea becomes partially blocked with mucopurulent material. Auscultation of the lungs reveals harsh bronchovesicular sounds and referred tracheal

sounds. Clinical signs of lower respiratory tract infection may be exacerbated by secondary bacterial pneumonia, which is a common sequela to BHV-1 infection. Severe hyperemia and reddening of the muzzle can occur, which is the reason for the common name of "red nose" to describe BHV-1 infection. Pustules may develop on the nasal mucosa and later form diphtheritic plaques. Conjunctivitis with excessive ocular discharge may be present. Conjunctivitis with corneal opacity can also occur as the principal manifestation of BHV-1 infection and may be misdiagnosed as infectious bovine keratoconjunctivitis (pinkeye). Abortions may occur concurrently with respiratory disease, but they can also occur as late as 100 days after infection.[93,94] Abortions may also occur in cattle that escape serious respiratory disease.

On rare occasions, neonatal calves may suffer from both an acute respiratory and a systemic form of BHV-1 infection. The infection is characterized by rhinitis, marked lacrimation, inflammation and necrosis of the soft palate, laryngotracheitis, and ulceration of the GI tract.[95] Vaccination of calves within 3 days of age with modified live viral vaccines has also been associated with severe fatal systemic BHV-1 infection.[98] The severity of disease in vaccinated calves was suspected to be caused by lack of maternal antibody and resultant widespread multiplication of the vaccine virus.

31.56.3 Pathogenesis

The route of infection is by direct contact with infected cattle or aerosol; apparent transmission by aerosol has been recognized among calves separated by as little as 4 m.[99] At least three of the surface glycoproteins of BHV-1, gC, gD, and gB, mediate host cell attachment and entry through interaction with heparan sulfate proteoglycans and other host cell proteins.[100,101] Epithelial cells of the respiratory tract are the initial target of infection after respiratory exposure, and after initial infection the virus can spread intracellularly to neighboring epithelial cells via intracellular bridges. Lymphocytes and monocytes are also susceptible to infection; although infection with these cells produces little virus, they appear to be a means by which the virus reaches extrarespiratory sites after respiratory infection. In severe field cases of BHV-1 infection the virus can be found in multiple organs including the esophagus, spleen, and liver.[102,103]

Respiratory disease caused by BHV-1 is mediated by two major mechanisms: (1) direct injury and destruction of infected epithelial cells in the upper respiratory tract and bronchi, with resultant inflammation and increased susceptibility to infection with secondary opportunistic pathogens; and (2) immunosuppression resulting from dysfunction of neutrophils, lymphocytes, and macrophages. Immunosuppressive actions of BHV-1 include decreased neutrophil chemotaxis and mitogen-induced blastogenesis of lymphocytes,[104] decreased expression of MHC class I molecules,[105] and induction of apoptotic death of lymphocytes and monocytes.[106] BHV-1 infection modifies expression and activity of cell surface receptors in ways that can be harmful; binding of the adhesion molecule ICAM-1 (CD18/CD11a) on bovine leukocytes to *Mannheimia haemolytica* leukotoxin was increased after BHV-1 infection of cattle, leading to enhanced leukocyte death.[107]

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Another important mechanism of pathogenesis of BHV-1 is the ability to establish latent infection in neural tissue.[101] After acute infection, BHV-1 can be found in a latent state in the trigeminal ganglia; recent research indicates that the virus may also persist latently in the tonsil.[108] During latent BHV-1 infection, virus is not actively produced in infected cells; thus latently infected cattle do not shed virus. However, an RNA molecule termed the *latency related transcript* (LRT) is abundantly produced in latently infected cells. Research indicates that the LRT prevents apoptosis in cells receiving signals that should trigger apoptosis, suggesting that the LRT functions at least in part to promote survival of infected cells.[101] One or more proteins encoded by the LRT

appear to be required for the virus to reactivate from latency.[109] Stress or administration of glucocorticoids causes reactivation of the latent virus, leading to shedding of virus and the possibility of infection of in-contact susceptible animals. Latency appears to occur in effectively all cattle that are infected with BHV-1, thus ensuring that the virus can be spread during times of stress by animals that have been free of clinical disease from BHV-1 infection for months to years. Calves that are exposed to BHV-1 when they have moderate levels of circulating maternal antibody can develop latent infection while never showing signs of clinical disease.[110] Latency of BHV-1 is thus an important mechanism by which the virus can persist and spread in a group of cattle.

31.56.4 Epidemiology

Studies of antibody prevalence to BHV-1 indicate that infection is widely distributed in the cattle population.[93,94] Adult cattle are thought to be the principal reservoirs of infection.[93,94] Infections of the respiratory tract by BHV-1 are prevalent when large concentrations of beef or dairy cattle are assembled, although BHV-1 does not appear to have an important role in enzootic pneumonia of calves.[111–113] Feedlot cattle appear to have higher attack rates, more severe disease, and higher case fatality rates than do range or dairy cattle. This is likely because of the stressful conditions experienced by feeder calves at the time of entry into feedlots. Entry into feedlots may also coincide with decline of passive immunity. The case fatality rate is generally low unless complicated with secondary bacterial pneumonia. Historically, disease caused by BHV-1 infection was most commonly recognized within the first few weeks after feedlot entry. However, since the 1990s, disease resulting from BHV-1 has sporadically been recognized in cattle that have been in feedlots for several months; these “late breaks” of disease are noteworthy in that they often occur in cattle that have been previously vaccinated against BHV-1.[114,115] Although BHV-1 is a relatively genetically stable virus, there is evidence that mutations are occurring in BHV-1 isolates currently circulating in cattle populations, which may help the virus escape host immunity.[115] Studies have shown that, although commercially available vaccines can still prevent disease resulting from experimental challenge with modern BHV-1 isolates, viral shedding is increased relative to cattle challenged with older BHV-1 isolates that are more similar to the strains of virus included in vaccines.[115,116] Repeat vaccination later in the feeding period has been recommended to decrease risk of late BHV-1 breaks,[114] although the efficacy of this practice has not been confirmed in clinical trials.

The fact that BHV-1 is capable of establishing latent infections in neural tissue is undoubtedly important in the epidemiology of disease caused by the virus. Under periods of stress, latent infections can become reactivated, resulting in viral shedding. Modified live BHV-1 vaccines are also capable of causing latent infections.[93,117]

Fig. 31-53 Postmortem photograph of opened trachea from animal infected with BHV-1. Note multiple white fibrinonecrotic plaques and, distal to plaques, yellow fibrinopurulent material on tracheal mucosa. Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.

31.56.5

Necropsy Findings

IBR is rarely fatal in mature cattle unless it occurs during periods of severe stress or is complicated by secondary bacterial infection of the lung. Lesions caused by BHV-1 infection include rhinitis, laryngitis, and tracheobronchitis. The mucosa of the nasal passages and trachea can be congested or hemorrhagic. Pustular lesions (sometimes referred to as *plaques*) may be observed, and these lesions may coalesce to form adherent necrotic material on respiratory (Fig. 31-53), ocular, and reproductive mucosa.[103] Usually the inflammatory lesions induced by BHV-1 do not extend into airways contained within the lung, but secondary bacterial bronchopneumonia with the expected pathology is common. Conjunctivitis and, less commonly, keratitis may be present. Esophageal erosions have been identified in severe natural outbreaks.[102] Perinatal infection of calves can lead to fatal systemic disease, with necrotic foci found in the liver, adrenal glands, kidneys, and other organs.[98] Although intranuclear inclusion bodies are a feature of herpesvirus infections, they are not a common histologic feature of BHV-1.

31.56.6 Diagnosis

BHV-1 can be diagnosed by virus isolation or immunofluorescent antibody (IFA) testing to identify virus in nasal swabs or conjunctival scrapings antemortem, or from samples collected postmortem. Infection can also be diagnosed by paired serology, with tests for serum neutralizing antibody (SN) most commonly done.

31.56.7 Treatment and Prevention

Cattle infected with BHV-1 should receive supportive care. Administration of antimicrobials appropriate to prevent infection with bacteria likely to cause secondary bronchopneumonia is appropriate (Table 31-10). Good-quality feed and water should be made easily available, and additional stressors such as movement or mixing should be avoided or postponed. NSAIDs such as aspirin or flunixin meglumine (1.1 to 2.2 mg/kg IV daily or divided twice daily) may help severely affected individuals maintain water and feed consumption. Steroids should not be administered. Because protective immunity develops rapidly after either intranasal or IM vaccination (see later), BHV-1 vaccination in the face of an outbreak may help limit disease, although the efficacy of this practice has not been tested in a controlled study.

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Table 31-10 Antimicrobials Approved by the FDA for Treatment of Bronchopneumonia of Beef Cattle

Antimicrobial	Label Dose	Route of Administration	Treatment Interval (hr)	Slaughter/MilkWithdrawal	Approved for Sheep and Goats?
STANDARD PREPARATIONS					
Amoxicillin	11 mg/kg	IM, SC	24	25 days/96 hours	No
Ampicillin	2–5 mg/kg (22 mg/kg)*	IM	24	6 days/48 hours	No
Ceftiofur (sodium)	1.1–2.2 mg/kg	IM, SC (cattle) IM (sheep and goats)	24	4 days/0 days	Sheep and goats
Ceftiofur (HCl)	1.1 mg/kg	IM, SC	24	3 days/0 days	No
Enrofloxacin†	2.5–5.5 mg/kg multiday therapy	SC	24 or once	28 days/not approved	No
Erythromycin	1.1–2.2 mg/kg (11–22 mg/kg)*	IM	24	14 days/72 hours	Sheep
Oxytetracycline	11 mg/kg	IV‡, IM‡, SC‡	24	15–22 days‡/not approved	Not for injection§
Procaine penicillin G	6600 U/kg (22,000 U/kg)*	IM	24	10 days (cattle), 9 days (sheep) /48 hours	Sheep
Spectinomycin	10–15 mg/kg	SC	24	11 days/not approved	No
Sulfadimethoxine	55 mg/kg, initial treatment 27.5 mg/kg thereafter	IV, PO	24	7 days/60 hours	No
Tylosin	17 mg/kg	IM	24	21 days/not approved	No
LONG-ACTING PREPARATIONS					
Ceftiofur crystalline free acid (Excede)	6.6 mg ceftiofur equivalent per kg (1.5 mL/45 kg)	SC in the ear	Once (7-day duration)	13 days/0 days	No
Danofloxacin†	6 mg/kg	SC	48	4 days/not approved	No
Enrofloxacin†	7.5–12.5 mg/kg	SC	Once	28 days/not approved	No
Florfenicol	20 mg/kg	IM	48	28 days/not approved	No
	40 mg/kg	SC	Once (4-day duration)	38 days/not approved	No
Oxytetracycline	20 mg/kg	IM, IV, SC	48–72	28 days/96 hours	No

Oxytetracycline (Tetradure)	30 mg/kg	IM, SC	Once (7-day duration)	28 days/not approved	No
Sulfadimethoxine (sustained release bolus)	138 mg/kg	PO	7 days	21 days/not approved	No
Tilmicosin	10 mg/kg	SC	72	28 days/not approved	Sheep Toxic to goats
Tulathromycin	2.5 mg/kg	SC	Once (7- to 14-day duration)	18 days/not approved	No

IM, Intramuscular; *IV*, intravenous; *PO*, oral; *SC*, subcutaneous.

* Author-suggested dose that has been shown to be more effective than label-approved dose. Higher dose can be given by the same route of administration and with the same treatment interval, but use of extralabel dosages must comply with the Animal Medicinal Drug Use Clarification Act (AMDUCA), and withdrawal times must be significantly extended.

† Extralabel use in food animals prohibited by law.

‡ Varies with preparation.

§ Oxytetracycline is labeled for administration to sheep in feed; not a recommended route for treatment of respiratory disease.

Note: Many of the drugs listed in this table are not approved for use in veal calves.

Efforts to prevent BHV-1 infection should include practices that optimize host immunity and avoiding management practices that put cattle at risk, such as mixing newly introduced cattle with established populations. Many brands of inactivated and attenuated BHV-1 vaccines for SC or IM administration are commercially available; products are available that contain BHV-1 alone or in combination with other pathogens. Temperature-sensitive, modified live vaccines are also available for intranasal administration; intranasal vaccines also include parainfluenza type 3 (PI3). Numerous reports confirm that either parenteral or intranasal BHV-1 vaccines can protect cattle from disease after experimental challenge with virulent BHV-1[118–122] or BHV-1 followed by *M. haemolytica*[123]; only a few are referenced here. Unfortunately there are few studies of BHV-1 vaccine efficacy in field trials, which better reflect the impact of vaccination in the "real-life" setting. In one older trial, vaccinated feedlot cattle were actually more likely to develop respiratory disease than unvaccinated cattle[124]; in a more recent trial there was no difference in respiratory disease between vaccinated and unvaccinated cattle, but vaccinated cattle had improved feed efficiency over the first 28 days after entering the feedlot.[125] The lack of field trials confirming vaccine efficacy may result in part from reluctance on the part of veterinarians or producers who perceive the vaccines to be useful to allow the inclusion of control groups of animals that are not vaccinated; researchers have admitted to being thwarted by this obstacle when organizing a field trial of BHV-1 vaccine efficacy.[126] In spite of the lack of published field trials supporting efficacy of BHV-1 vaccines to prevent respiratory disease, they are widely used; over 90% of feedlot cattle are reported to receive BHV-1 vaccines.[127] Historically it was thought that vaccination with modified live BHV-1 leads to protective immunity for years, or perhaps even the life of the animal, but recent evidence of infection and disease in feedlot animals within months of vaccination[114,115] indicates that this is not the case.

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While both modified live and inactivated BHV-1 vaccines are available, modified live vaccines are preferable when it is safe to use them because they are more likely to stimulate a cell-mediated immune response similar to that induced by infection.[128] Few studies to date have compared modified live to inactivated vaccines in the same trial. When this comparison has been made it has been to compare protection against experimental BHV-1 infection, with modified live vaccines providing superior protection in some[129] but not other[130] studies. Improved efficacy of inactivated vaccines in more recent studies[130] may be a result of inclusion of more advanced adjuvants, which can greatly improve the immune response to inactivated vaccines. Modified live BHV-1 vaccines are capable of causing latent infections, which could theoretically lead to shedding and spread of the vaccine strain of virus to in-contact naïve animals.[94,117] Because modified live BHV-1 vaccines can induce abortion, the manufacturer's recommendations regarding administration should be closely followed. Modified live vaccines may also lead to severe disease if administered to calves within a few days of birth[98]; intranasal modified live BHV-1 vaccines may be safer than parenterally administered modified live virus vaccines in very young calves.[131]

If a modified live vaccine is to be used, the veterinarian must then decide whether to use a product for intranasal or for parenteral administration. Both have been shown to provide protection rapidly; in one study, intranasal vaccination protected calves challenged within 48 hours of vaccination,[118] whereas other studies have shown that intramuscularly or subcutaneously administered modified live vaccine can protect cattle challenged 72 hours after vaccination.[119,122] Both types of vaccines can induce protection in cattle before serum neutralizing antibodies are evident,[121,122] indicating that cell-mediated rather then humoral immunity is responsible for protection soon after vaccination. In one trial that compared the protection afforded by intranasal versus parenteral BHV-1 vaccine, feedlot cattle that received intranasal vaccine had improved feed efficiency over cattle that received parenteral vaccine, but there was no difference in morbidity or mortality attributable to respiratory disease between the two groups.[125] Intranasally administered BHV-1/PI3 vaccines are theoretically preferable to parenteral vaccines because they induce a better mucosal immune response; they may also have an advantage when calves are vaccinated in the presence of passive immunity.[120,132] It appears that intranasal modified live vaccines are more likely to be spread to in-contact animals than are parenteral modified live vaccines; two studies confirmed BHV-1 shedding by nonvaccinated cattle in contact with cattle vaccinated intranasally with modified live BHV-1,[133,134] although two different studies could not identify evidence that modified live virus vaccine given intramuscularly spread to nonvaccinated cattle.[135,136]

Vaccines that have gene deletions have been developed and used in Europe.[137] These vaccines allow serologic differentiation of vaccinated from naturally infected animals and have application for BHV-1 control or eradication programs.

31.56.8 Herpesviruses in Sheep and Goats

Herpesviruses have been isolated from sheep and goats. It remains undetermined whether herpesviruses have a role, and if so, to what extent, in respiratory disease of small ruminants.

31.56.9 Respiratory Syncytial Viruses of Cattle, Sheep, and Goats

31.56.9.1 Definition and Etiology

BRSV is an enveloped RNA virus that is classified as a nonhemagglutinating pneumovirus of the family Paramyxoviridae. This virus was named for the characteristic cytopathic effect it produces in vitro and in vivo, which is the formation of syncytial cells. BRSV shares many similarities in its biology and epidemiology with the human respiratory syncytial virus (HRSV). HRSV is considered to be the most important respiratory tract pathogen of infancy and early childhood. Although BRSV and HRSV are closely related, they are distinct viruses.[138] RSV has also been isolated from sheep and goats with respiratory disease. Studies using RNAse mismatch cleavage analysis indicate that ovine RSV may be distinct from HRSV and BRSV, whereas caprine RSV may be more closely related to BRSV.[139,140] The possibility of interspecies transmission has not been well defined. However, a European serologic survey undertaken to determine whether nonbovine species were likely to harbor BRSV infection found that only goats, in addition to cattle, were commonly seropositive.[141] These results indicate either that goats are commonly infected with BRSV or that antigenic similarities between caprine RSV and BRSV led to production of cross-reactive antibodies in many goats. Although two major antigenic subtypes, A and B, of human RSV have been clearly defined, research has shown that BRSV is less variable than human RSV at the genetic level, as indicated by evaluation of nucleotide sequences in genes for viral proteins or by digestion of viral RNA with restriction enzymes.[142] However, in spite of minimal to moderate differences among BRSV isolates at the genetic level, isolates can differ notably in their reactivity with monoclonal antibodies directed against individual BRSV proteins[143,144]; this indicates that apparently minor genetic differences could lead to changes that allow the virus to evade host immunity. Differences in molecular weights of viral proteins also divide isolates into two major groups.[145] A study of genetic variability in BRSV isolates collected over several decades showed that genetic change occurred over time[146,147] and that BRSV isolates commonly included in commercial vaccines differed a relatively large amount from some isolates collected from recent natural outbreaks.[146] Studies have also shown that genetic differences in BRSV isolates can be grouped by geographical origin, with some European isolates differing to a notable degree from isolates from the United States or Japan.[146,147] Most important, European research identified genetic changes in a region of the BRSV G glycoprotein (the viral attachment protein) that was previously thought to be highly conserved and difficult or impossible for the virus to change.[146] These changes appear to be driven by vaccination, indicating that antigenic pressure induced in cattle by vaccination can lead BRSV to change in unexpected ways. These data indicate that commercial vaccines may need to be reformulated periodically to include isolates of the virus that are similar to isolates currently circulating in natural populations.

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31.56.9.2 Clinical Signs

Clinical signs of BRSV infection can vary from inapparent to severe in an infected group of cattle.[148–151] Signs of disease are limited to the respiratory system. Infected animals may display elevated rectal temperature of 40° C to 42.2° C (104° F to 108° F), depression, decreased feed intake, elevated respiratory rates, ptyalism, cough, and nasal and lacrimal discharges. Signs of disease may progress rapidly, and early signs may be missed. Thoracic auscultation may reveal increased bronchial and bronchovesicular sounds; fine crackles or wheezes may be heard, particularly in the middle or dorsocaudal lung fields. Absence of

bronchovesicular sounds may be noticed in the dorsal or dorsocaudal lung fields if an emphysematous bulla is present, or if a bulla has ruptured, leading to pneumothorax. In later stages of the disease, dyspnea can become pronounced and is characterized by increased expiratory effort and mouth breathing. SC emphysema and intermandibular edema are sometimes noted. Dramatic reduction in milk production has been reported in dairy cattle. Duration of disease is variable (1 to 2 weeks). A biphasic clinical course has been described but does not appear to be a consistent finding. Experimental infections of lambs with ovine RSV caused a mild primary pneumonia and was also capable of causing lower respiratory tract lesions in calves and deer.[152]

31.56.9.3

Pathogenesis

The means of transmission appears to be contact with infected cattle and aerosols. The incubation period is 3 to 5 days. Infection with BRSV can cause bronchitis, bronchiolitis, alveolitis, and interstitial pneumonia.[148–151] After experimental infection, BRSV is found in cells of the nasal, tracheal, and bronchial epithelium by 2 days postinfection and in bronchiolar and alveolar epithelial cells by day 4 postinfection.[153] The virus causes epithelial cells to fuse, resulting in the characteristic multinucleated cells, or syncytia, which are seen in airways and alveoli. Epithelial cells, which may undergo apoptosis after BRSV infection,[153] slough into the lumen of airways and are phagocytized by neutrophils or alveolar macrophages.[153] Infection of alveolar macrophages and circulating peripheral blood mononuclear cells occasionally occurs,[154,155] and BRSV infection of macrophages decreases important functions of these cells including Fc receptor expression, phagocytosis, phagosome-lysosome fusion, and production of factors that induce neutrophil chemotaxis.[156,157] Infection leads to bronchitis, bronchiolitis, alveolitis, and sometimes AIP; these changes lead to clinical signs referable to small airway and alveolar disease (expiratory dyspnea, auscultable wheezing) and hypoxemia as evidenced by arterial blood gas analysis.[158]

The severity of disease after BRSV infection is related to host immunity. Both humoral and cell-mediated immunity contribute to protection. Clinical signs of infection are less severe in animals with moderate to high levels of serum antibody against BRSV,[159,160] and more extensive pathology is seen in calves depleted of $CD8^+$ T cells before infection.[161] Protection after intranasal vaccination is related to the rapidity in onset of nasal BRSV-specific IgA production,[162] indicating that mucosal immunity is likely also important in protection against naturally occurring disease. Host immunity after exposure to BRSV can minimize disease, and clinical signs are usually the most noticeable in calves under 6 months of age.[149,163] However, ruminants appear to be susceptible to reinfection with BRSV throughout their lives, and adult cattle can develop severe disease after BRSV infection.[149,150] Because genetic variability among BRSV isolates is not great, reinfection does not seem to be solely a result of viral strain variation. Although data investigating the duration of BRSV immunity after natural infection are limited, it appears that natural infection does not confer lifelong immunity, and some cattle may be reinfected annually,[164] although clinical signs are not always apparent.

While host immunity can protect ruminants from severe disease after BRSV infection, the host immune response can also contribute to disease. Evidence for BRSV immunopathogenesis comes from both natural outbreaks and experimental challenge studies. Cattle with severe disease after natural infection have a higher proportion of degranulated mast cells in their lungs than less severely affected cattle,[165,166] indicating that mast cell mediators contribute to physiologic and pathologic changes seen in severe cases. Serum tryptase, a preformed enzyme present in mast cell granules, was significantly increased in the serum of cattle experiencing severe naturally occurring BRSV infection,[166] also supporting a contribution of mast cells in

severe BRSV-induced disease. In experimentally challenged cattle, BRSV-specific IgE has sometimes been associated with disease severity.[167,168] Exposure to the fungus *Saccharopolyspora rectivirgula* (formerly *M. faeni*), the spores of which induce pulmonary hypersensitivity in cattle and other species, enhanced BRSV-specific IgE production in calves, indicating that environmental allergens can also affect the nature of the immune response to BRSV infection.[168] Recent research showed that calves infected with BRSV before infection with *Histophilus somni* developed higher levels of *H. somni*–specific serum IgE than did calves infected with *H. somni* alone.[169] Thus BRSV infection can lead to production of virus-specific IgE, which may be enhanced by coexposure to allergens, and BRSV infection may also increase IgE production in response to infection with other agents. In these cases, cross-linking of IgE bound to mast cells by binding of BRSV or other specific antigen is expected to lead to bronchoconstriction, pulmonary edema, and other signs of mast cell mediator release and immediate hypersensitivity.

Perhaps the most convincing evidence that BRSV can trigger immunopathogenesis is the fact that certain BRSV vaccines have on rare occasion been shown to cause enhanced disease when vaccinated animals are subsequently infected with BRSV. Vaccine-enhanced disease has been seen after both natural[170,171] and experimental[172,173] infection. Vaccine-enhanced disease has also occurred in human infants vaccinated with a formalin-inactivated RSV vaccine,[174] and formalin-inactivated BRSV vaccines have caused enhanced disease in some[172,174] but not all[158] studies. Inactivated BRSV vaccines have also been shown to prevent disease after infection[175,176]; therefore not all inactivated BRSV vaccines enhance disease. It appears that the dose of BRSV protein, the adjuvant included in the vaccine, and probably also other factors related to the formulation of the vaccine affect whether enhanced disease is likely after infection of cattle given a particular BRSV vaccine.[177] Apparent vaccine-enhanced disease has also been reported in cattle that received a modified live vaccine in the early stage of a natural BRSV outbreak.[170] It is important to note that BRSV vaccines are used very commonly, and vaccine-enhanced disease is very rare; thus vaccination is still recommended as part of any plan to control disease caused by BRSV. Many gaps exist in our understanding of what aspects of the immune response contribute to disease severity after BRSV infection or vaccination. Most research completed to date has focused on enhanced disease in calves that received formalin-inactivated BRSV. The data suggest that when enhanced disease occurs in calves vaccinated with formalin-inactivated BRSV, it is related to a relatively strong response by T helper type 2 (Th2) cells, as evidenced by decreased production of the Th1 prototype cytokine interferon gamma,[178] increased production of BRSV-specific IgE,[179] and pulmonary eosinophil infiltration.[173] The association of BRSV-specific IgE production with disease severity in some experimental studies indicates that at least some individual ruminants will produce IgE after BRSV vaccination or infection, which may contribute to severe disease in these individuals.

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The presence of co-infection with other pathogens such as *M. haemolytica*[180] or bovine virus diarrhea (BVD) virus (BVDV)[181] can also increase the severity of disease after BRSV infection. Although genetic variation among BRSV isolates is not extensive, experimental challenge with certain isolates of BRSV can lead to serious disease,[158,182] whereas challenge with other isolates leads to only minimal disease.[183,184] This indicates that, in spite of limited differences among viral isolates at the genetic level, variation among BRSV isolates may still contribute to variations in disease severity.

31.56.9.4

Epidemiology

Prevalence of antibodies to BRSV in the cattle population of the United States ranges from approximately 60% to 80%.[151] The virus has been recognized in association with respiratory tract disease in nursing beef

calves, in dairy calves, and in cattle entering into feedlots. BRSV was demonstrated to be involved in 14% to 71% of respiratory disease outbreaks in North American and European studies of calf pneumonia outbreaks involving several farms.[185] Seroconversion to BRSV has been significantly associated with treatment for respiratory disease in feedlot cattle,[186,187] and cattle with low antibody titers to BRSV at feedlot entry have increased risk of developing disease.[186] Although feedlot cattle are commonly infected with BRSV after arrival, a recent survey of necropsy findings at 72 Canadian feedlots found BRSV at postmortem of only 11% of the cattle that died or were euthanized because of pneumonia.[188] The low rate of isolation at necropsy suggests that if the virus contributes to the development of pneumonia in feedlot cattle, it is often no longer present by the time the animal dies or is euthanized.

BRSV therefore represents an important virus in the bovine respiratory disease complex on the basis of its frequency of occurrence and predilection for causing infection of the lower respiratory tract. In general, morbidity rate tends to be high in outbreaks of BRSV, whereas case fatality rate is variable, ranging from none to as high as 20%.[185]

Cattle are most likely the principal reservoirs of infection, although a European serologic survey of different species found that goats were also often seropositive,[141] indicating that goats may be a source of BRSV infection for cattle, and vice versa. The mechanism by which BRSV persists in the cattle population is not known. Possibly a similar epidemiologic pattern to the one that has been described for HRSV also exists for BRSV. HRSV is capable of reinfecting the host throughout his or her life; however, severe lower respiratory tract disease occurs only in association with the initial exposure. Subsequent exposure results in mild upper respiratory tract disease. Similarly, adult cattle may periodically undergo subclinical to mild infections and serve as a source of infection for susceptible young stock. However, a recent study concluded that transmission among seropositive cattle was not a plausible mechanism of BRSV persistence in a dairy herd.[189] These authors suggested that persistent BRSV infection in individuals is a more plausible explanation of population persistence of BRSV. BRSV has been identified in B lymphocytes in tracheobronchial and mediastinal lymph nodes of calves 71 days after experimental infection,[190] so it may be that individual cattle harbor the virus long term and periodically begin shedding it, allowing it to periodically reappear in herds even if they are closed to new introductions. However, more research is needed before persistent infection is clearly proven to be a means by which BRSV remains established in herds.

31.56.9.5 Necropsy Findings

Grossly, BRSV infection can cause signs of AIP; therefore differential diagnoses for the typical gross lesions include other causes of AIP (see later discussion). Signs of AIP are most evident in the dorsocaudal lung; affected lung is heavy, with a rubbery texture, and fails to collapse when the thorax is opened. Individual lobules may appear dark, and interstitial or bullous emphysema is often present in the dorsocaudal lung in severe cases (Fig. 31-54). Pathologic emphysema must be differentiated from that sometimes caused by agonal breathing of cattle. Cranioventral lobes or lobules are often dark and collapsed because of atelectasis or consolidation (Fig. 31-55). Histologic lesions depend on the stage of infection. Neutrophilic and later mononuclear bronchitis, bronchiolitis, and alveolitis are present in infected animals. Syncytial cells may be seen in the airways or alveoli; intracytoplasmic inclusion bodies are rarely present.[149,160,182] Signs of AIP including alveolar epithelial hyperplasia, hyaline membrane formation, and interstitial inflammatory cell infiltrate, hemorrhage, and edema are seen in severe cases. Later, evidence of chronic bronchitis and bronchiolitis obliterans can be found.[149]

31.56.9.6

Diagnosis

Infection is diagnosed by identification of the virus in nasal secretions, tracheal aspirates, or lung lavage fluid from live calves or in lung tissue collected postmortem. BRSV is difficult to isolate as it does not survive transport well; thus methods of identification that do not require the virus to be alive (such as immunofluorescence, IHC, and RT-PCR) are preferable to virus isolation for the identification of BRSV. IHC of formalin-fixed tissue is convenient because the virus can be identified in tissue processed for histopathologic evaluation. If virus isolation is to be attempted from samples collected in the field, it is recommended that that veterinarian contact his or her diagnostic laboratory before collecting samples so that samples are collected and transported in ways that optimize likelihood of success. Although virus is readily identifiable in lung tissue of cattle early in the course of disease (within approximately 8 days of infection), virus is less likely to be found in lung tissue by 10 to 15 days postinfection, even when IHC is used.[153,172,182]

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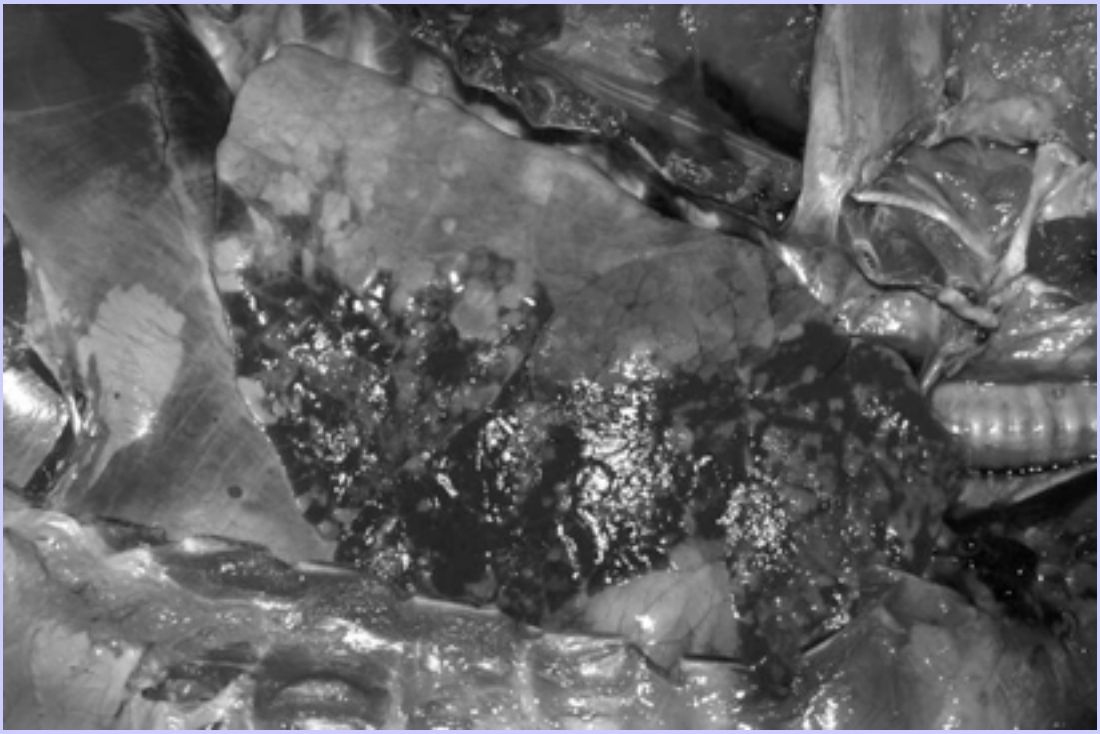
Fig. 31-54 Postmortem photograph of bovine lung with interstitial emphysema often seen in severe BRSV infection, as well as other causes of acute interstitial pneumonia. Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.

Fig. 31-55 Postmortem photograph of lungs from calf with severe BRSV infection. Photograph contributed by Dr. Laurel Gershwin, University of California, Davis, Calif.



Seroconversion as evidenced by paired serology also supports a diagnosis; virus neutralizing or ELISA assays are most commonly used to identify BRSV-specific antibody. Identification of BRSV-specific IgM in a single acute sample is also diagnostic,[191] but testing for BRSV-specific IgM may not be available at most diagnostic laboratories.

31.56.9.7

Treatment and Prevention

Treatment of BRSV is supportive and aimed at preventing secondary bacterial infection and limiting the inflammatory response in bronchioles and alveoli. Antimicrobial therapy appropriate for common secondary bacterial pathogens (see Table 31-10) is appropriate. Antiinflammatory therapy with NSAIDs (flunixin meglumine at 1.1 to 2.2 mg/kg IV daily or divided twice daily) is considered appropriate, but controlled studies of these drugs in animals with disease caused by BRSV are limited. Administration of one or two doses of steroid therapy (dexamethasone 0.05 to 0.2 mg/kg IV or IM once or twice) is appropriate in animals with severe respiratory distress or evidence of AIP. Intranasal oxygen insufflation is appropriate if available. Diuretic therapy with furosemide (0.5 to 1 mg/kg IM or IV once or twice daily) is warranted in animals suspected of having AIP. Although the prognosis for animals with uncomplicated BRSV infection is good, the prognosis for animals with AIP is guarded. Animals with severe respiratory distress should be handled with care, as even careful manipulation to administer treatment can lead to rapid respiratory decompensation and death.

Both modified live and inactivated BRSV vaccines for IM or SC administration are commercially available. Certain commercially available vaccines have been shown to protect calves against virulent experimental challenge.[175,176,192] Results of some well-designed trials of BRSV vaccine efficacy have also been published.[193–196] In some studies the effect of BRSV vaccination on all clinical respiratory disease (i.e., not only disease caused specifically by BRSV) was evaluated,[193,195,196] whereas in other studies protection against disease caused by BRSV was specifically evaluated by identification of clinical respiratory disease and simultaneous seroconversion to BRSV in vaccinated cattle.[194] Vaccination decreased all respiratory morbidity in some[195] but not other[193,195,196] groups of cattle evaluated. Vaccination decreased disease specifically caused by BRSV in large groups of calves if all calves in the group were vaccinated, but not if half of the calves in the group were vaccinated.[194] A recent large clinical trial evaluating the effect of vaccination of feedlot cattle with a modified live vaccine containing BHV-1, PI3, and BVDV, with or without BRSV, found that pens of cattle that received the vaccine including BRSV had lower overall morbidity and mortality and lower numbers of respiratory deaths than pens of cattle that received the vaccine that did not include BRSV.[196] There is no RSV vaccine licensed for use in small ruminants, and no controlled studies of the effects of extralabel administration of BRSV vaccines licensed for cattle on respiratory disease in sheep or goats have been published.

31.56.10 Bovine Virus Diarrhea Virus

BVDV is an enveloped RNA virus of the genus Pestivirus in the family Flaviviridae. A wide spectrum of disease has been associated with BVDV infection, including subclinical infection, bovine virus diarrhea and mucosal disease (see Chapter 32), immunosuppression, repeat breeding problems, abortion, fetal mummification (see Chapter 43), congenital defects, immunotolerance, and persistent infections. Only the contribution of this virus to respiratory disease is discussed here.

Historically the role of BVDV in the bovine respiratory disease complex has been controversial,[197–199] but more recent research provides good evidence that the virus contributes to bovine respiratory disease and related decreased productivity of cattle in the field in at least some cases.[200,201] Experimental challenge of cattle with BVDV alone leads to mild pneumonia,[202,203] and occasionally herd outbreaks of BVDV are first identified by the presence solely of signs that are likely to be interpreted as evidence of respiratory disease, such as fever, tachypnea, and loud bronchovesicular sounds.[204] Experimental infection studies have also shown that respiratory disease caused by *M. haemolytica*,[202] BHV-1,[205] or BRSV[181] is significantly more serious when cattle are co-infected with BVDV. This synergistic effect of BVDV with other respiratory pathogens is believed to be a result of immunosuppression caused by BVDV, which is discussed in detail in Chapter 32. The ability of BVDV to cause respiratory disease appears to depend in part on the strain of infecting virus.[203,206]

Although the results of experimental challenge studies show that BVDV can cause mild respiratory disease alone and can contribute to the development of more serious disease in combination with other pathogens, data from field cases of respiratory disease are generally considered of greatest relevance. Studies of naturally occurring bovine respiratory disease have shown that in some situations BVDV can be isolated from a majority of cattle affected with shipping fever pneumonia, particularly in association with *M. haemolytica*,[188,207] or in association with *Mycoplasma bovis* in animals with chronic pneumonia.[208,209] Seroepidemiologic studies have indicated an association of BVDV with respiratory disease in some but not all cases.[198,210] The most convincing data linking BVDV to respiratory disease has come from studies of calves purchased and assembled at sale barns for

shipment to feedyards across several states.[201] In 2 consecutive years BVDV was significantly more likely to be isolated from calves that were treated for respiratory disease than calves in the same group that were not treated; calves treated for respiratory disease were also significantly more likely to seroconvert to BVDV than penmates who were not treated for respiratory disease. The majority of BVDV isolates collected from calves in this study were BVDV type 1b. If this finding is representative of the BVDV isolates circulating in cattle throughout the United States, it could have important implications for the ability of vaccines to adequately protect cattle, as commercially available vaccines currently contain BVDV type 1a almost exclusively.[211] More research will be necessary to determine how frequently viral strains in BVDV vaccines will need to be updated so that they provide adequate protection from currently circulating strains.

In addition to contributing directly to bovine respiratory disease by infecting the respiratory tract and enhancing the pathogenicity of co-infecting bacteria or viruses, BVDV may also contribute to respiratory disease by impairing the ability of cattle to respond properly to vaccination against other respiratory pathogens. Calves infected with BVDV before BHV-1 vaccination shed BHV-1 longer after subsequent BHV-1 infection than calves that were not co-infected with BVDV.[212] In another study, calves persistently infected with BVDV failed to develop a serologic response to a *M. haemolytica* vaccine, in contrast to control animals not infected with BVDV.[213]

In summary, although the importance of BVDV in the bovine respiratory disease complex has previously been debated, recent research indicates that BVDV is significantly associated with the development of bovine respiratory disease in at least some cases. Whereas experimental challenge studies indicate that BVDV can cause at least mild respiratory disease when acting alone, the virus appears to contribute most importantly by impairing the host's ability to resist infection and limit disease caused by other pathogens that infect the animal at the same time or soon after BVDV infection occurs.

31.56.11 Parainfluenza Virus Type 3 of Cattle, Sheep, and Goats

31.56.11.1 Definition and Etiology

Parainfluenza virus type 3 (PI3) is an enveloped RNA virus classified in the family *Paramyxoviridae*. The virus has been associated with respiratory tract disease in cattle, sheep, and goats. It hemagglutinates and hemadsorbs red blood cells of certain species, which means that serum antibodies can be identified by hemagglutination inhibition assays. Variation in virulence among strains of PI3 has been reported.[214] Significant similarities between bovine PI3 and human PI3 have led to efforts to use bovine PI3 as a modified live intranasal vaccine for humans; bovine PI3 was found to be safe and immunogenic in a clinical trial in human infants.[215]

31.56.11.2 Clinical Signs

Uncomplicated PI3 infections result in subclinical to mild signs. Clinical signs, if present, may include fever, cough, nasal and ocular discharge, increased respiratory rate, increased bronchovesicular sounds, and wheezes.[216–218] The most important role of PI3 is in predisposing the respiratory tract to subsequent infection by other viruses and bacteria such as *Mannheimia (Pasteurella) haemolytica*.[219] Severity of signs increases with the development of secondary bacterial pneumonia, and if death occurs it is usually the result of secondary bacterial infection. Infection with PI3 is widespread in sheep and goats.[220–221] Only one serotype of ovine PI3

has been identified, and it is related to but distinct from the bovine strain. Most infections are inapparent to mild.

31.56.11.3 Pathogenesis

Infection with PI3 can lead to signs referable to both upper and lower respiratory tract infection. After experimental infection of calves, clinical signs are evident by 2 days postinfection, and signs peak 4 days postinfection. Virus is found in the nasal passages, trachea, and bronchiolar and alveolar epithelial cells. The virus damages the pulmonary mucociliary apparatus[222] and depresses several important functions of alveolar macrophages such as Fc receptor expression, phagocytosis, and microbicidal activity,[223] which are important in predisposing infected animals to secondary bacterial pneumonia.

31.56.11.4 Epidemiology

The widespread prevalence of antibodies to this virus indicates that it commonly circulates in ruminant populations.[191,221,224] This finding suggests the possibility of repeat infections or at least the persistence of antibodies after infection. Inapparent or subclinical infections with PI3 are common; in one report, 28 groups of calves seroconverted to PI3 over 8 months, but respiratory disease was seen in association with PI3 infection in only four of these groups.[225] Although infection can often be inapparent, if environmental and managerial practices are suboptimal, PI3 may become an important initiator of respiratory tract disease. Infection appears to spread rapidly in susceptible cattle housed at high population densities and in close contact. In seroepidemiologic surveys evaluating groups of calves in herds experiencing outbreaks of respiratory disease, seroconversion to PI3 has been associated with 14% to 38% of outbreaks evaluated.[111,112,226] In some surveys PI3 is the virus most commonly isolated from the lungs of calves that die or are euthanized because of pneumonia.[227] Feedlot cattle commonly seroconvert to PI3 soon after feedlot arrival, and seroconversion has been associated with treatment for respiratory disease in some[186] but not all[187] cases. In spite of the fact that feedlot cattle frequently become infected with PI3 after feedlot entry, a recent survey of necropsy findings at 72 Canadian feedlots found PI3 at postmortem examination of only 4% of the cases with pneumonia.[188] The low rate of isolation at necropsy suggests that if the virus contributes to the development of pneumonia, it may no longer be present by the time the animal dies or is euthanized.

31.56.11.5 Necropsy Findings

Lesions of PI3 infection alone are rarely seen during postmortem examination. Experimental PI3 infection results in congestion of the respiratory mucosa, swelling of lymph nodes associated with the respiratory tract, and lobular consolidation concentrated in the cranioventral lung.[218,219] Bronchiolitis and alveolitis are seen histologically with both proliferative and degenerative changes in the epithelial cells of the bronchioles and alveoli. Syncytia and intranuclear and intracytoplasmic inclusion bodies may be seen.[218,219] In many respects, pathologic features of PI3 infection are similar to those caused by BRSV, although the lesions produced by the latter are generally more extensive.

31.56.11.6 Diagnosis

PI3 can be isolated from nasal swabs of infected animals. Unlike BRSV, which is also in the paramyxovirus family, PI3 is not particularly difficult to isolate. Diagnosis can also be confirmed with paired serology, with hemagglutination inhibition or virus neutralizing assays most commonly used.

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31.56.11.7 Treatment and Prevention

There is no specific treatment for infection with PI3; as for other respiratory viruses of ruminants, administration of appropriate antibiotics to prevent secondary infection with likely bacteria is recommended. As for any viral respiratory tract infection, supportive care is indicated, such as providing readily available good-quality feed and water and avoiding or postponing additional stressors such as movement or mixing of animals. Both inactivated and modified live PI3 vaccines are available for parenteral administration, and modified live PI3 vaccines are available in combination with BHV-1 for intranasal administration; these vaccines are labeled for use in cattle but not in sheep or goats. A univalent modified live intranasal PI3 vaccine is available in Europe.[218] Experimental challenge studies have shown that both parenteral and intranasal vaccines can decrease viral shedding and clinical signs after challenge.[216–218,228] No field trials have specifically evaluated the effect of PI3 vaccines to decrease respiratory disease. One study reported that a modified live BHV-1/PI3 vaccine licensed for use in cattle decreased clinical signs and viral shedding when administered before experimental challenge of sheep, but the vaccinated sheep also appeared to become latently infected with BHV-1.[228] The investigators noted that induction of latent BHV-1 infection could be an important negative side effect of vaccination, as sheep could theoretically spread BHV-1 to other in-contact ruminants, such as cattle. Although the practice appears to occur commonly, administration of BHV-1/PI3 vaccines to sheep or goats constitutes an extralabel use of these products.

31.56.12 Bovine Coronavirus

Coronaviruses are enveloped, single-stranded positive sense RNA viruses of the family Coronaviridae. Bovine coronavirus is a major cause of calf diarrhea and has also been implicated as a cause of winter dysentery in cattle. Although it has been known for some time that bovine coronavirus can infect the respiratory tract of calves,[229] the practical relevance of this agent as a respiratory pathogen has been debated. However, evidence is accumulating that bovine coronavirus may be an important contributor to outbreaks of respiratory disease in some cases.

One reason for the lack of awareness regarding a role for coronavirus in respiratory disease may be the fact that standard cell lines used for isolation of other respiratory viruses are often not permissive to bovine respiratory coronavirus infection. Thus, coronavirus may not be isolated if only standard cell lines are used to attempt to isolate viruses from cattle experiencing respiratory disease. Bovine respiratory coronavirus can readily be recovered by using human rectal tumor-18G cell lines.[230] An antigen-capture ELISA and a sensitive RT-PCR assay have also been developed for identification of the virus.[231] It is not yet clear whether the coronaviruses that have been associated with respiratory disease in cattle are different in important ways from the coronaviruses that cause enteric disease; studies comparing biologic and antigenic properties of enteric and respiratory isolates have yielded mixed results.[232,233]

An association of coronavirus with two naturally occurring outbreaks of shipping fever was described in a well-detailed report.[234] In these outbreaks, which were characterized by high morbidity and mortality, coronavirus was isolated from the nasal passages of over 80% of the cattle in the early stages of the outbreaks. No other respiratory viruses were identified in most of the cattle, but *M. haemolytica* was also isolated from a majority of cattle as the two epizootics progressed. A few cattle with high serum antibody titers against coronavirus at feedlot arrival did not shed the virus. However, a clear causative role for coronavirus was difficult to identify because so few cattle remained healthy that it was apparently not possible to find a difference in viral shedding or seroconversion in animals that had respiratory disease versus those that did not. In a separate report the researchers used Evans's criteria of causation, which have been suggested as more appropriate than Koch's postulates for evaluation of causative factors in complex diseases such as the bovine respiratory disease complex, to support a causative role for coronavirus in the outbreaks they studied.[235] Other researchers attempting to confirm or refute an important causative role for coronavirus in bovine respiratory disease have nearly always found the virus when calves are sampled soon after feedlot entry.[231,236,237] Moreover, it is very common for a majority of cattle to have antibody titers to the virus at feedlot arrival or to seroconvert soon after feedlot entry; therefore it is clear that cattle are often infected with the virus at times when respiratory disease is likely to occur.[231,236,238] However, the importance of the virus in causing respiratory disease has still been debated[238] because seroconversion has not been significantly associated with treatment for respiratory disease or with decreased weight gain during the feeding period.[238–240] One group did find that cattle shedding coronavirus from the respiratory tract soon after feedlot entry were significantly more likely to have pneumonia at slaughter as compared with cattle not shedding the virus.[240] Another group found that vaccinating calves intranasally with a modified live coronavirus and rotavirus vaccine commercially marketed to decrease diarrhea caused by these viruses (i.e., an extralabel use of the vaccine) significantly decreased the subsequent rate of treatment for respiratory disease in cattle that had relatively low serum antibody titers against coronavirus at arrival.[237] These studies provided direct or indirect evidence that coronavirus caused respiratory disease in the cattle under study.

In summary, some of the currently available data support an important role for coronavirus in contributing to the bovine respiratory disease complex, but other data do not. In this regard coronavirus is similar to other infectious agents, which can be identified as important players in some outbreaks studied but not identified at all in others. More research would be useful to better characterize the relevance of bovine respiratory coronavirus as a respiratory pathogen. Currently no vaccines are commercially marketed for the prevention or control of respiratory disease caused by bovine respiratory coronavirus infection.

31.56.13 Malignant Catarrhal Fever Virus

The African (wildebeest-associated) form of malignant catarrhal fever (MCF) is caused by alcelaphine herpesvirus types 1 and 2. A causative agent for the American (sheep-associated) form is believed to be ovine herpesvirus type 2. The occurrence of MCF in the cattle population is sporadic. There is multisystemic involvement, including involvement of the respiratory tract. MCF is discussed in detail in Chapter 32.

31.56.14 Bovine Herpesvirus Type 4

The bovine type 4 herpesviruses are serologically distinct from other herpes viruses such as BHV-1 and BHV-2 (bovine mammillitis).[94] Although the level of antibody prevalence to BHV type 4 (BHV-4) is high in the cattle population of the United States, the pathogenic role of this virus remains unclear. It has been implicated in several disease conditions of cattle, including respiratory tract disease, reproductive disorders (abortions and

metritis), mammillitis, and enteric disease.[241] It has also been isolated from apparently healthy cattle. Several of these viruses (DN-599, Movar 33/36, FTC-2) have been isolated from cattle with respiratory tract disease. Intranasal inoculation of DN-599 into calves produced respiratory disease, but the importance of this group of viruses in the bovine respiratory disease complex is poorly defined. Currently they are not thought to be important enough to warrant vaccine development.

31.56.15 Adenoviruses of Cattle, Sheep, and Goats

Adenoviruses are nonenveloped double-stranded DNA viruses of the family Adenoviridae. Ten serotypes of bovine adenovirus (BAV) are currently recognized.[242] BAV infection is widespread and is frequently subclinical[243,244]; adenoviruses are also often isolated in association with other viruses and bacteria,[94,243] making it difficult to assign causation in naturally occurring disease outbreaks. Adenoviruses have been associated with pneumonia, enteritis, conjunctivitis, keratoconjunctivitis, and "weak calf syndrome."[245] When calves develop pneumonia and enteritis at the same time ("pneumoenteritis"), adenoviral infection should particularly be considered as a possible cause.[94]

Six antigenic types of ovine adenovirus and two types of caprine adenovirus have been identified.[246] Little information concerning the incidence and distribution of adenovirus infection in the sheep and goat population is available; however, it appears likely that this virus causes widespread infection.[247] A study in Iowa reported that adenovirus infections were widespread in the sheep population and that the prevalence of active infection based on seroconversion rates was approximately 45%.[247] The majority of isolations of this virus have been from young lambs, and it has been isolated in association with respiratory and enteric disease. Experimental infections result in mild disease with anorexia, pyrexia, increased respiratory rates, coughing, and diarrhea. Gross lesions observed include atelectasis, edema, and consolidation of the lungs.[248] Ovine adenovirus serotype 6 has been shown under experimental conditions to act synergistically with *Mannheimia (Pasteurella) haemolytica* in the production of pneumonia in lambs.[249]

31.56.16 Bovine Rhinovirus

Bovine rhinovirus is a nonenveloped single-stranded RNA virus in the family Picornaviridae. Two serotypes of bovine rhinovirus are officially recognized.[94] Infection with this virus appears to be widespread in the cattle population. By 10 to 12 months of age virtually 100% of beef and dairy cattle in Missouri are seropositive to rhinovirus.[250] Clinical signs of rhinovirus infections range from inapparent signs to fever, depression, decreased appetite, increased respiratory rate, lacrimation, conjunctivitis, salivation, coughing, and nasal discharge. Little research is available that characterizes the relative importance of rhinovirus in the bovine respiratory disease complex.

31.56.17 Bovine Reovirus

Bovine reovirus is a nonenveloped, double-stranded segmented RNA virus in the family Reoviridae. Three mammalian serotypes are recognized. Reoviruses have been isolated from the respiratory and digestive tracts of apparently healthy cattle. Infections appear to be common in cattle, and bovine isolates are antigenically identical to human serotypes. The importance of reovirus infections in bovine respiratory tract disease is unclear. Subclinical infections appear to predominate under field conditions.

31.56.18 Bovine Enterovirus

Enteroviruses are nonenveloped single-stranded positive sense RNA viruses in the family Picornaviridae. Over 60 strains of bovine enterovirus have been isolated from the respiratory, reproductive, and digestive tracts of cattle. The majority of these isolates have been obtained from healthy animals, although isolations have been made from cattle in association with abortions, enteritis, and respiratory disease. In general, infections with enteroviruses are common and transient and usually not considered to be pathogenic.

31.56.19 Calicivirus

A calicivirus has been isolated from dairy calves from a herd with a persistent respiratory disease problem.[251] This virus caused only minimal disease in experimentally infected calves, but a persistent infection was produced.

31.56.20 Influenza

Influenza virus has not historically been considered to cause naturally occurring respiratory disease in ruminants in North America. However, it is possible to experimentally infect cattle with influenza,[252] and a report from England describes several cattle that seroconverted to human influenza A virus during outbreaks of clinical respiratory disease and decreased milk production in dairy cattle.[253] Antibodies from the cattle reacted most strongly with a human H1N1 virus (A/England/33/80) and a human H3N2 virus (A/England/427/88). Retrospective analysis of banked serum samples also identified measurable antibody titers to human influenza in 49% to 59% of samples tested, with several sets of paired sera taken from animals during respiratory disease outbreaks showing evidence of seroconversion, with relatively high virus neutralizing antibody titers.[253,254] Attempts were made to isolate influenza virus from cattle with signs of respiratory disease but were not successful.[254] It was not possible to rule out other more recognized causes of bovine respiratory disease in the outbreaks in which cattle seroconverted to influenza, so it has not been proven conclusively that influenza is a significant contributor to naturally occurring bovine respiratory disease. However, the relatively high rate of seropositivity seen in cattle in England suggests that the virus may commonly circulate among cattle in at least a subclinical form, and thus cattle may be a significant reservoir of virus that could infect other species. More research is necessary to determine the significance of influenza infection in cattle and other ruminants. More information about influenza virus is presented in the section on equine influenza on p. 543.

31.57 BACTERIAL AND CHLAMYDIAL AGENTS

31.57.1 Mannheimia Haemolytica

31.57.1.1 Definition and Etiology

M. haemolytica (formerly *Pasteurella haemolytica*) is a gram-negative aerobic bacteria of the family *Pasteurellaceae*. There are at least 12 serotypes of *M. haemolytica*, and some ruminant isolates are untypable with currently available laboratory tools. Five serovars previously classified as *M. haemolytica* have been determined to be separate species and have been reclassified as *Pasteurella trehalosi* or *Mannheimia*

glucosida.[255,256] *P. trehalosi* causes pneumonia or systemic disease with multiorgan infection in sheep,[257] whereas *M. glucosida* is a low virulence opportunistic pathogen of sheep.[258] Some serotypes of *M. haemolytica* are pathogenic, whereas others are nonpathogenic commensals of the ruminant nasopharynx, and the serotypes that are pathogenic for cattle are not the same as those that are pathogenic for sheep or goats.[259–261] Serotype A1 is the most common isolate from pneumonic lungs of cattle, and serotype A6 is the next most common[262,263]; serotype A2 is the most common isolate from the nasopharynx of normal cattle.[264] Serotype is also relevant to pathogenicity of isolates from sheep and goats; both *M. haemolytica* and *P. trehalosi* can be isolated from the nasopharynx of normal small ruminants,[265] but *M. haemolytica* serotype A2 is the most common isolate from sheep and goats with pneumonia, and serotypes A7, A9, and several others have also been associated with disease.[259,261,266]

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31.57.1.2

Clinical Signs

Cattle, sheep, or goats infected with *M. haemolytica* display a dull or depressed attitude and lose interest in eating. Fever, tachypnea, and depression are often the only abnormal signs early in the course of infection[267–269]; coughing is not a prominent sign in the acute stage of disease[268,269] unless co-infection with another agent such as BHV-1 or BRSV is present. Animals may display evidence of thoracic pain, such as standing with elbows abducted or catching the breath before expiration; these signs are a result of the painful fibrinous pleuritis caused by *M. haemolytica*. Because *M. haemolytica* is a gram-negative organism, endotoxin (lipopolysaccharide) is produced by the agent, and thus cattle with mannheimiosis may show signs of endotoxemia, including fever, tachycardia, tachypnea, salivation, respiratory distress, pale or dark mucous membranes with prolonged capillary refill time, and cool extremities. Thoracic auscultation may reveal harsh or loud bronchovesicular sounds consistent with pulmonary consolidation,[268] particularly over the cranioventral lung. Disease after *M. haemolytica* infection can be fatal, particularly if it is not treated; it can also lead to chronic pneumonia associated with secondary invasion with agents such as *P. multocida, Mycoplasma bovis*, or *Arcanobacterium (Actinomyces) pyogenes*.

It is important to remember that naturally occurring disease caused by *M. haemolytica* is commonly preceded by infection with a viral agent such as BHV-1, BRSV, or BVD; therefore the clinical signs described previously for these and other respiratory viruses may also be present in animals infected with *M. haemolytica*.

31.57.1.3

Pathogenesis

M. haemolytica is a normal inhabitant of the nasal pharyngeal mucosa,[96,265] but not the lung, and is considered an opportunistic pathogens. Calves and lambs become infected at an early age and carry *Pasteurella* as a minor part of the upper respiratory tract flora. Only a small percentage of nasal swabs yields positive results for *M. haemolytica* serotype A1 in healthy, unstressed calves,[270] but if several areas of the nasal mucosa are cultured at necropsy, it is often possible to isolate *M. haemolytica* from animals that previously had negative findings on nasal swabs.[271] The stress of transportation or viral infection causes a breakdown of the defense mechanisms that hold the nasal mucosa infections in check, resulting in a rapid proliferation of virulent *M. haemolytica* serotype A1. A greater number of calves will yield positive nasal mucosa swab *M. haemolytica* results during and after transport, and there is a large increase in the numbers of *M. haemolytica* in positive samples.[270,272] BHV-1 and PI3 viruses have been shown to have the same effect as transportation on *Pasteurella* populations of the nasal mucosa. *M. haemolytica* has been demonstrated in the tracheal air of stressed, healthy calves harboring the organism on their nasal mucosa. Some of these inhaled

organisms are deposited deep within the lung and normally are cleared within hours. But under conditions of impaired pulmonary defenses caused by stress, nutritional deficiencies, or preexisting viral infection, *M. haemolytica* is able to proliferate rapidly within the lung and with the aid of its virulence factors and toxins to produce a severe lobar necrotizing fibrinous pleuropneumonia. Calves infected with respiratory viruses, including BHV-1, PI3, BVDV, and BRSV, or *Mycoplasma* species have increased susceptibility to severe bronchopneumonia when exposed to *M. haemolytica*.[96] Similarly, infection of lambs with PI3 or adenovirus followed in several days by *M. haemolytica* causes severe pneumonia.[220,273]

Once *M. haemolytica* becomes established in the lungs, interactions between the bacteria and the host defenses result in tissue damage and elimination of the invader. A major virulence factor of *M. haemolytica* is an exotoxin that is lethal to ruminant leukocytes, the leukotoxin. Leukotoxin, which is produced by *M. haemolytica* during the logarithmic phase of growth, causes cytolysis of ruminant platelets, lymphocytes, macrophages, and neutrophils.[274] There is diversity in the gene encoding the leukotoxin molecule among *M. haemolytica* serotypes, and genetic diversity is related to differences in toxicity. For example, the leukotoxin encoded by some pathogenic bovine serotype A1 strains differs from the leukotoxin encoded by ovine A1 strains by only one amino acid but is substantially more toxic for bovine leukocytes than for ovine leukocytes.[260] Leukotoxin binds to cells via CD18, the beta subunit of the β_2 integrins CD11a/CD18 (LFA-1), CD11b/CD18 (Mac-1), and CD11c/CD18 (CR-4)[275,276]; although leukotoxin can bind to cells from nonruminant species, only ruminant cells are killed by the toxin.[274] Contact with leukotoxin increases expression of LFA-1 on ruminant leukocytes, making the cells even more sensitive to injury by leukotoxin.[277] At low concentrations, leukotoxin induces leukocyte death by apoptosis, whereas at higher concentrations the toxin causes cell lysis.[278] *M. haemolytica* expressing a mutant nontoxic leukotoxin induced less lung pathology in calves as compared with *M. haemolytica* producing functional toxin, but clinical signs were not different between the two groups of calves, indicating that leukotoxin is not the only virulence factor of importance in causing disease.[279]

Another virulence factor that certainly contributes to disease resulting from *M. haemolytica* is lipopolysaccharide, or endotoxin. As in all species, exposure of ruminants to endotoxin from gram-negative bacteria induces a multitude of responses leading to inflammation, including initiation of the complement and coagulation cascades, activation of endothelial cells and recruitment of neutrophils, and activation of neutrophils and alveolar macrophages, leading to their production of proinflammatory cytokines, which further amplify the inflammatory response. The proinflammatory cytokines TNF-α, IL-1β, and IL-8 are expressed in the lungs of cattle within 48 hours of *M. haemolytica* infection.[280] Calves exposed to a preparation containing *M. haemolytica* endotoxin develop leukopenia, fever, tachypnea, diarrhea, and dyspnea as early as 2 hours after exposure.[281] Endotoxin potentiates the effects of leukotoxin by inducing increased expression of β_2-integrins on leukocytes, which contain CD18, the receptor for leukotoxin.[277,282] Bovine alveolar macrophages first exposed to endotoxin were susceptible to death induced by concentrations of leukotoxin too low to cause cell death alone; and macrophages exposed to both endotoxin and leukotoxin produced more of the proinflammatory cytokines IL-8 and TNF-α than did macrophages exposed only to leukotoxin.[282] These data indicate that leukotoxin and endotoxin work in synergy to cause disease in ruminants. The production of IL-8 is of particular importance, because IL-8 is a major inducer of neutrophil chemotaxis.[283] The massive influx of neutrophils induced by IL-8 and other inflammatory mediators is a key factor in lung tissue destruction caused by *M. haemolytica*. Calves experimentally depleted of neutrophils are completely protected from gross and microscopic lesions of the severe fibrinonecrotic bronchopneumonia that is induced by intratracheal inoculation of *M. haemolytica* in calves with normal neutrophil levels.[284] Lysis of

neutrophils results in the release of lysosomal products, including elastase, collagenase, and reactive oxygen intermediates. These chemicals are bactericidal but also capable of destroying the neutrophils themselves and surrounding tissues. Neutrophil-mediated damage to the endothelial cells results in exudation and thrombosis, which produce the classic lesions of necrosis and fibrinous exudation.[285]

In addition to leukotoxin and endotoxin, *M. haemolytica* possesses other factors that contribute to its virulence. The bacteria have a polysaccharide capsule that aids in attachment and prevents phagocytosis by neutrophils,[286] and iron-regulated outer membrane proteins (IROMPs) that bind transferrin and alter the function of neutrophils.[287,288] The bacteria produce adhesions that mediate attachment to host cells,[289] and neuraminidase produced by the bacteria may aid in host colonization by decreasing the viscosity of respiratory mucus[290] and decreasing the repellant negative charge on host cells by cleaving sialic acid residues.[291]

31.57.1.4

Epidemiology

In many studies over several decades, *M. haemolytica* has been found to be the most common bacterial isolate from feedlot cattle with fatal fibrinous bronchopneumonia.[188,292–296] *M. haemolytica* was isolated postmortem from 25% to 30% of cattle that died or were euthanized because of pneumonia in two studies evaluating causes of mortality in feedlot cattle.[188,296] Seroconversion to *M. haemolytica* or *M. haemolytica* leukotoxin has been significantly associated with treatment for respiratory disease or "undifferentiated fever" in feedlot cattle in some[186,297] although not all[298] studies. Booker and colleagues found that the odds of developing undifferentiated fever (case definition similar to that usually used for undifferentiated respiratory disease) was 2.8 times greater for cattle that developed a fourfold rise in antibody titer to *M. haemolytica* leukotoxin, as compared with cattle that did not seroconvert to leukotoxin.[297] And whereas O'Connor and co-workers found no association between seroconversion to *M. haemolytica* and treatment for undifferentiated respiratory disease, they did find that vaccination against *M. haemolytica* was significantly associated with protection against the development of undifferentiated respiratory disease in feedlot cattle in their study, which indirectly indicated a role for *M. haemolytica* in the development of respiratory disease.[298] Although *M. haemolytica* is recognized as the bacteria most commonly contributing to fibrinous pneumonia in feedlot cattle, one study that used BAL to identify bacteria present in the lungs of feedlot cattle before antimicrobial treatment for acute pneumonia found that *M. haemolytica* was not identified more frequently in the lungs of cattle with pneumonia than normal controls, whereas *P. multocida* was significantly associated with bronchopneumonia.[299] In the study by Allen and colleagues, none of the calves died or were euthanized because of the naturally occurring disease, indicating that disease was not severe. Because *M. haemolytica* is relatively more likely to cause acute fatal pneumonia than other bacterial pathogens of the ruminant lung, it may be overrepresented in necropsy surveys in which only fatal cases of disease are sampled.

In contrast to the situation in feedlot cattle, *M. haemolytica* is not commonly associated with outbreaks of pneumonia in calves. At postmortem examination of 43 calves from 34 outbreaks of respiratory disease, *M. haemolytica* was isolated from only two calves[111]; in another study, *M. haemolytica* was isolated from calves in 4 of 14 outbreaks of respiratory disease.[112] Although *M. haemolytica* is not as commonly isolated from calves as are other bacterial pathogens, it can be a cause of fatal disease; in one study, only *M. haemolytica* was significantly more often isolated from calves with fatal pneumonia as compared with calves with subclinical pneumonia.[300]

31.57.1.5

Necropsy Findings

Infection with *M. haemolytica* causes fibrinopurulent bronchopneumonia (Fig. 31-56). The infection is aerogenous, so disease occurs primarily in the cranioventral lung, but in severe cases, a majority of the lung may be affected. Affected areas of lung are dark red to purple or gray-brown (Fig. 31-57), firm, and heavy; discolored areas may be wedge-shaped owing to thrombosis of a vessel supplying the affected region during the severe inflammatory response (Fig. 31-58). The interlobular septa are expanded by clear to yellow gelatinous material that represents proteinaceous fluid that has leaked from blood vessels in the lung. The inflamed areas of lung are covered with yellow fibrin that may adhere to the pleura of the thoracic wall, and the pleural cavity usually contains straw-colored fluid, which may be voluminous.[267–269] In cases that have been ongoing for a few days, firm, gritty lumps that are dry and crumbly on sectioning may be identified; these represent areas of necrotic tissue.[269] Bronchial lymph nodes may be swollen, wet, and dark red. Histologically, alveoli are filled with edema and fibrin, and there is massive infiltration of neutrophils and macrophages. “Oat cells” can be seen, which are necrotic leukocytes with streaming of the chromatin.[188] Foci of coagulative necrosis are often found rimmed by a basophilic border of leukocytes; coagulative necrosis may expand to fill entire lobules. Hemorrhage is often present both within and between alveoli, and an occasional vessel may be found to contain a thrombus. Interlobular septa and lymphatics can be found dilated with edema and fibrin. Bronchioles are filled with leukocytes and may have foci of epithelial necrosis.[188,268,269] *M. haemolytica* may also produce pneumonia characterized by firm, dark red pulmonary consolidation without fibrinous pleuritis; this is especially common in dairy calves or sheep and goats. Animals that survive the acute stage of pneumonia caused by *M. haemolytica* may have multiple abscesses and pleural adhesions; in these cases other bacteria such as *P. multocida, Mycoplasma bovis*, or *Arcanobacterium (Actinomyces) pyogenes* may be contributing to pathology.

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Fig. 31-56 Postmortem photograph of fibrinopurulent bronchopneumonia caused by *Mannheimia haemolytica*. Note extensive dark red consolidated cranioventral lung and fibrin on pleural surface. Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.

Fig. 31-57 Postmortem photograph of necrotizing bronchopneumonia caused by *Mannheimia haemolytica*. Abnormal lung is dark red to gray-brown in color. Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.

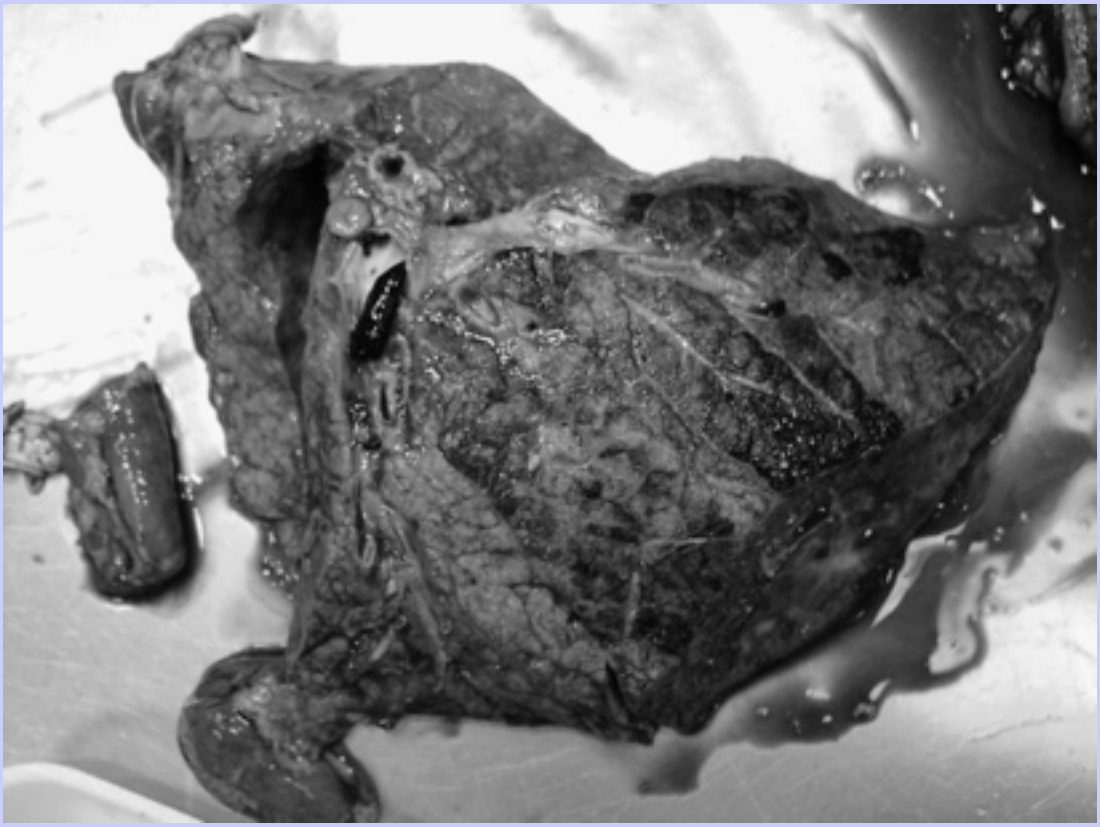
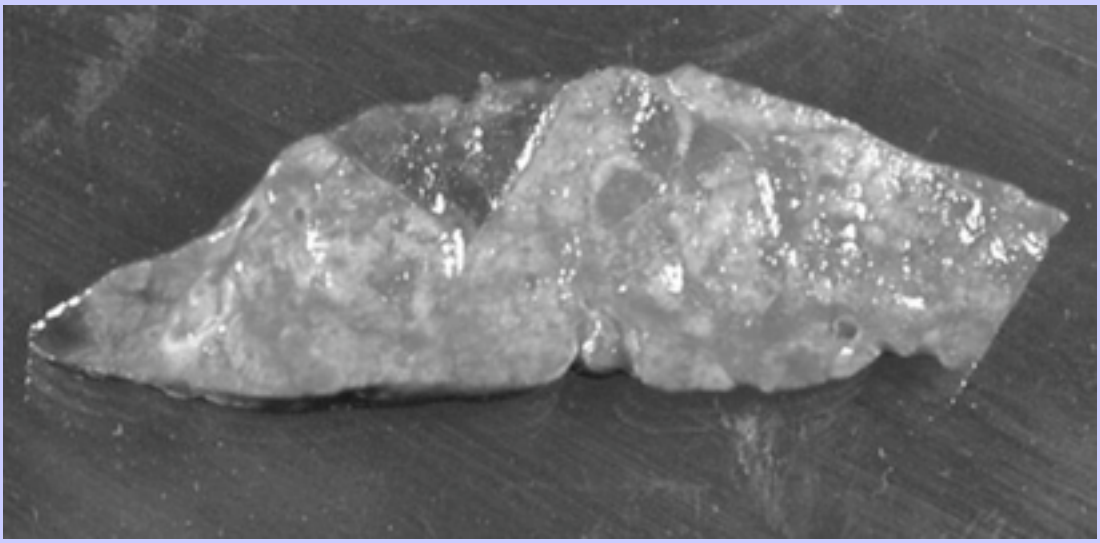


Fig. 31-58 Postmortem photograph of infarct *(dark red triangular lesion at uppermost edge of tissue)* in lung of calf with necrotizing bronchopneumonia caused by *Mannheimia haemolytica*. Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.



31.57.1.6

Diagnosis

Diagnosis of pneumonia due to *M. haemolytica* is most reliably made by culture of lungs with typical gross pathology at postmortem evaluation of animals that die or are euthanized as representative cases in outbreaks. Antemortem diagnosis in individual animals can be made by collecting fluid by transtracheal aspiration (TTA) or BAL and submitting the fluid for aerobic bacterial culture. These methods are not practical for widespread use in the field, but they may be warranted for valuable individual animals or to identify the cause of an outbreak of respiratory disease in several animals. Cytologic evaluation of TTA or BAL samples would be expected to reveal septic purulent inflammation characterized by large numbers of neutrophils that may be degenerate, exhibiting toxic change, and possibly containing intracellular bacteria. Thoracocentesis can be a useful diagnostic procedure to identify fluid accumulation in the thorax; fluid collected shows a high percentage of neutrophils with a high (>3 g/dL) total protein content if bacterial pleuropneumonia is the cause of fluid accumulation. Pleural fluid collected by thoracocentesis can also be submitted for aerobic bacterial culture to confirm infection with *M. haemolytica*. In a hospital with the necessary equipment, transthoracic ultrasound evaluation can be used to confirm the presence of consolidated lung tissue and pleural effusion with fibrin.[301] Thoracic radiography, if possible, is expected to show evidence of consolidation of the cranial lung and possibly pleural fluid accumulation.[302] Evidence of pneumonia identified by either radiography or transthoracic ultrasound evaluation has been shown to correlate strongly with findings on postmortem examination of calves with bacterial bronchopneumonia.[301,302]

Collecting bacteria by nasal swabs could be a reliable means of diagnosis if *M. haemolytica* isolated from swabs can be serotyped,[303] but because nonpathogenic *M. haemolytica* can be present in nasal passages of normal animals and can be distinguished only by serotyping, simple identification of the bacteria in nasal swabs as identified by culture is not diagnostic.

Serologic tests can be used to identify serum antibodies to *M. haemolytica*, and seroconversion identified by paired serologic testing could be used to confirm infection with *M. haemolytica* in one or more ruminants. However, these tests are most commonly used for research applications, and they may not be available at all diagnostic laboratories.

31.57.1.7

Treatment and Prevention

Treatment of *M. haemolytica* requires administration of an antimicrobial effective against the organism. Many antimicrobials are currently labeled for the treatment of *M. haemolytica* (see Table 31-10). The decision to choose any one of the many approved products is based on multiple factors including regional susceptibility of *M. haemolytica* isolates, the number of times it is possible to treat animals, withdrawal times, and cost. See the discussion on pp. 630–633 for further information on treatment of bacterial bronchopneumonia.

In addition to appropriate antimicrobial therapy, treatment to prevent the adverse effects of endotoxin should be considered for ruminants suspected or confirmed to have pneumonia caused by *M. haemolytica*. The NSAID flunixin meglumine can ameliorate the inflammatory response to endotoxin, and treatment with flunixin meglumine has been shown to improve outcome in individual animals infected with *M. haemolytica*. However, administration of NSAID drugs such as flunixin meglumine has not been shown to be reliably cost-effective in the treatment of large numbers of feedlot cattle with respiratory disease. Thus a consideration of the value of the animals treated may be necessary before NSAID therapy can be justified in an entire group of calves.

Prevention of infection and disease caused by *M. haemolytica* is approached by three avenues: administering antimicrobials prophylactically to animals at high risk of disease; increasing host immunity by ensuring adequate passive transfer and administering vaccines against *M. haemolytica*; and minimizing factors such as viral respiratory tract infection, mixing of animals from various sources, and long-distance shipment, which increase the susceptibility of animals to infection and disease caused by pathogenic serotypes of *M. haemolytica*.

Prophylactic or metaphylactic administration of antimicrobials effective against *M. haemolytica* is a reliable means of decreasing morbidity and mortality associated with respiratory disease in calves at high risk for disease because of recent weaning, uncertain immune status, mixing with cattle from a variety of sources, and long-distance shipment. Administration of tilmicosin to groups of such high-risk calves either before shipment or on arrival at feedlots decreased the proliferation of *M. haemolytica* serotype A1 in the nasopharynx of calves and was associated with decreased treatment for respiratory disease as compared with calves not treated with tilmicoson.[304] In a later study, administration of florfenicol at arrival decreased colonization of the nasopharynx with *M. haemolytica* A1 and delayed treatment for respiratory disease.[270] Further discussion of the role of metaphylactic administration of antimicrobials to control bovine respiratory disease can be found on p. 639.

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Mixing recently weaned calves from multiple sources and shipping them long distances is a well-known precursor to outbreaks of fibrinous pneumonia[305]; and because *M. haemolytica* is the species of bacteria most

commonly associated with fatal fibrinous pneumonia, it follows that efforts to minimize stresses and improve immunity for calves moving through the marketing chain should lessen disease caused by *M. haemolytica*. Recent studies have indicated that preconditioning, wherein vaccination and stressful procedures such as weaning and castration are carried out well in advance of mixing and shipment, can decrease costs associated with fibrinous pneumonia in feedlot cattle.[306] However, preconditioning should not be considered a guarantee against all respiratory disease; disease that is sometimes severe can occur in preconditioned calves. Further discussion of the role of preconditioning to prevent bovine respiratory disease is continued on p. 638.

Vaccination can be used as part of a plan to decrease disease caused by *M. haemolytica*. Many experimental and commercially marketed vaccines have been tested for efficacy in preventing either disease resulting from experimental infection with *M. haemolytica* or naturally occurring respiratory disease, and the published literature is too extensive to describe in detail here. In summary, some research indicates that vaccination can lessen disease, other research shows that vaccination has no effect, and a few older reports show that *M. haemolytica* vaccination can enhance disease after infection.[307] Although commercially marketed vaccines are tested for safety, and no published reports exist that describe enhanced disease caused by currently available products, the fact that *M. haemolytica* bacterins historically caused enhanced disease is a reason to avoid the use of autogenous products that are not thoroughly tested for safety before administration. To induce protective immunity, a vaccine against *M. haemolytica* must contain leukotoxin; additional benefit may be gained by including other antigens associated with the bacterial cell wall.

Experimental challenge studies have shown that currently available commercial vaccines can lessen disease caused by infection with *M. haemolytica*.[308–310] However, data from well-designed field trials, which are a more relevant measure of the value of vaccination in the field, have reported mixed results. Most of the published field trials that have evaluated currently available (as of 2007) vaccines have evaluated a leukotoxin-rich bacterial culture supernatant vaccine (Presponse, Fort Dodge Animal Health, Fort Dodge, Ia). Of four trials carried out by different investigators in different regions, vaccinated calves had decreased respiratory morbidity (treatment for respiratory disease) in two trials,[311,312] but not in the other two trials.[313,314] Mortality resulting from respiratory disease was lower in vaccinated calves in two trials[312,313] but not in the other two trials.[311,314] Fewer vaccinated calves required a second treatment for respiratory disease (repulls) in three trials[312–314]; this variable was not examined in the fourth trial. Two trials found an economic advantage to vaccinating calves with this vaccine[312,313]; the other two trials did not measure costs related to vaccination. In all of these trials calves were vaccinated at feedlot arrival; in some cases subsets of calves also received a vaccination before arrival.[312,314]

Another recent trial evaluated a commercially available vaccine containing leukotoxin and cell-associated antigens (Pulmo-Guard, Boehringer Ingelheim, St. Joseph, Mo.), and found that vaccination of calves at feedlot arrival had no effect on respiratory morbidity or mortality or on the number of calves that required a second treatment for respiratory disease.[315] A trial testing an *M. haemolytica* vaccine currently available in Canada (Pneumo-Star, Biostar Inc., Saskatoon, Saskatchewan) found that vaccination at arrival was associated with decreased respiratory morbidity.[298]

This short summary of clinical trials testing the efficacy of *M. haemolytica* vaccines yields a clue to the reason for the ongoing debate regarding whether these vaccines are useful: about half the time field trials indicate that the vaccines decrease illness or death related to respiratory disease, and about half the time they do not. Therefore there is support for using *M. haemolytica* vaccines, and there is support for not using them. Note also that no large-scale clinical trial has compared two different *M. haemolytica* vaccines, so it is not possible

to give an evidence-based recommendation in favor of any vaccine over another. It must be remembered that in none of these clinical trials was the actual cause of respiratory disease determined, which is typical of large-scale field trials. Therefore vaccination was expected to decrease all respiratory disease, not just respiratory disease caused by *M. haemolytica*. This may be an unreasonable expectation for a vaccine from an immunologic perspective, but from a practical perspective, this is what producers expect. In general, if vaccination against *M. haemolytica* is used, evidence best supports its use in "lightweight" (300 to 600 lb) calves at high risk for disease. In one trial, vaccination decreased disease in calves with relatively high morbidity, but no effect was seen in a group of calves with low respiratory morbidity.[311] *M. haemolytica* vaccination is also recommended as part of many preconditioning programs, particularly if calves are to be sent directly to the feedlot without any backgrounding period.[316]

Vaccination of sheep or goats using commercially available vaccines labeled for use in cattle is not likely to provide reliable protection against disease, as serotypes of *M. haemolytica* that most commonly cause disease in sheep and goats are not included in vaccines for cattle. Moreover, although vaccination with sheep-associated serotypes can provide protection against infection, cross protection among different serotypes is not reliable,[261] indicating that an effective vaccine will likely need to contain antigens from multiple serotypes. There is a vaccine labeled for use in sheep and goats in the United States (*M. haemolytica–P. multocida* Bacterin, Colorado Serum Co., Denver, Colo.), but published clinical trials testing the efficacy of this product are lacking.

31.57.2 Pasteurella Multocida

31.57.2.1 Definition and Etiology

P. multocida is a gram-negative aerobic bacteria of the family Pasteurellaceae. Like *M. haemolytica, P. multocida* can be found in the nasopharynx of healthy ruminants. Although *P. multocida* is regularly isolated from the lungs of ruminants with bronchopneumonia, there has been debate over the years as to whether this species is a primary pathogen—that is, capable of causing disease alone—or whether some other primary stressor or insult is required to occur before this agent can participate in disease. As with *M. haemolytica*, experimental challenge of calves with *P. multocida* alone does cause clinical signs and pathologic change in the lung similar to that seen in natural outbreaks of disease (described later),[268,317,318] but large numbers of the bacteria must be administered in a way that bypasses the upper respiratory tract (most commonly by intratracheal instillation). Alternatively, prior administration of a viral respiratory pathogen makes animals more susceptible to disease caused by experimental *P. multocida* infection. These findings indicate that some insult that weakens the ability of the respiratory tract to resist advancement of these bacteria into the lower airways is necessary for most if not all cases of naturally occurring disease to occur. However, because *P. multocida* can cause lung lesions that can be severe,[317] and because the bacteria can exacerbate disease caused by primary viral infection, it is logical to consider this agent when planning strategies to treat and control ruminant respiratory disease.

P. multocida is a diverse species of bacteria that is classified into five serogroups (A, B, D, E, and F) based on antigenic differences in the bacterial capsule. Serogroups B and E cause hemorrhagic septicemia, a disease predominantly seen in Asia and Africa[319]; these serogroups are rarely isolated in the United States. Serogroup A is by far the predominant serogroup associated with ruminant respiratory disease,[263,320] although serogroups D and F may be common in some regions, particularly in sheep.[321] In addition to the alphabetic serogroup designation, isolates may also receive a numeric designation based on cell wall antigen types (for

example, *P. multocida* A3 has been commonly isolated from cases of bovine pneumonia).[318] A recent study characterized 153 *P. multocida* isolates from cases of pneumonia and mastitis in cattle in England and Wales based on the outer membrane proteins expressed by the bacteria. This research indicated that relatively few strains of *P. multocida* cause the majority of disease in cattle. Moreover, although a few strains isolated from cattle had also been associated with disease in swine and poultry, the majority of strains were uniquely associated with their host species of origin.[320] Other research indicated that certain strains of *P. multocida* had a predilection for the respiratory tract of sheep, whereas other strains were associated with the reproductive tract.[321] Taken together, these data suggest that differences among strains of *P. multocida* are related to the type of disease caused and the host likely to be affected. Therefore merely isolating *P. multocida* without further characterizing the isolate could make it difficult to know with confidence whether the type of bacteria isolated was actually contributing to disease. It has been suggested that strain variation is related to differences in severity of respiratory disease occurring in ruminants infected with *P. multocida*.[317]

31.57.2.2

Clinical Signs

Calves infected with *P. multocida* alone display clinical signs of fever, increased respiratory rate, and sometimes depression, coughing, and mucoid to mucopurulent nasal discharge.[268,317,318] Loud or harsh bronchovesicular sounds may be heard over the cranioventral lung fields owing to pulmonary consolidation, and coarse crackles may be heard as a result of air moving through exudate in large airways. Because *P. multocida* is a gram-negative organism that produces endotoxin, signs of endotoxemia (tachypnea, tachycardia, fever) may also contribute to signs that accompany infection with the organism. Compared with calves infected with *M. haemolytica*, calves infected with *P. multocida* tend to have less severe signs, and signs of disease last for a shorter time.[268,317]*P. multocida* is more commonly isolated from young calves with pneumonia[111,112] than with other bacterial respiratory pathogens such as *M. haemolytica*, but it is less commonly isolated from feedlot cattle with acute bronchopneumonia.[188] Thus *P. multocida* is considered to be of relatively greatest importance in contributing to calf pneumonia. *P. multocida* has been found to overgrow *M. haemolytica* in the lungs of calves experimentally challenged only with *M. haemolytica*[268]; therefore *P. multocida* may also be an important contributor to cases of subacute to chronic pneumonia in feedlot cattle initiated by other organisms.

31.57.2.3

Pathogenesis

Little is known regarding the pathogenesis of *P. multocida* in ruminant respiratory disease. In addition to lipopolysaccharide (LPS), the organism also has a capsule that allows it to resist phagocytosis. Outer membrane proteins, particularly iron-regulated outer membrane proteins, are likely to contribute to the ability of the bacteria to establish and proliferate within the host.[322,323] The prominent role of *P. multocida* in enzootic calf pneumonia (ECP) and rather minor role in acute bronchopneumonia of feedlot cattle suggests that prolonged impairment of the respiratory defense mechanisms is necessary for this organism to establish in the lungs in sufficient numbers to create bronchopneumonia. It is likely that the organism is chronically inhaled in small numbers into the lungs of calves with persistent damage to the respiratory defenses from infectious agents such as viruses or mycoplasmas and environmental damage from inadequate housing and ventilation, allowing it to colonize and produce an expanding lesion. This proposed pathogenesis agrees with the insidious onset that is commonly observed with ECP, and would also fit the association of *P. multocida* with chronic or ongoing pneumonia in feedlot cattle. It is important to remember that culture of *P. multocida* from pneumonic lung does not exclude the possibility of other bacteria such as *M. haemolytica* being the

primary pathogen, because *P. multocida* has been shown to overgrow *M. haemolytica* in challenge studies using large doses of pure cultures of *M. haemolytica*.[268]

31.57.2.4 Epidemiology

P. multocida is commonly isolated from the lungs of calves that die or are euthanized because of bronchopneumonia, with mycoplasmas being the only bacteria isolated more often in surveys involving multiple farms experiencing outbreaks of calf pneumonia.[111,112] In contrast, *M. haemolytica* is more frequently isolated postmortem from feedlot cattle with fibrinous pneumonia than is *P. multocida*.[188,296] However, one study of bacterial isolates from BAL of feedlot cattle found that *P. multocida* was the only species isolated more frequently from cattle with clinical signs attributed to acute pneumonia as compared with normal cattle.[299] A notable aspect of this study was that animals were sampled before treatment with antimicrobials; in surveys of bacteria identified postmortem, animals have usually received antimicrobial treatment before death, which may bias the microbiologic findings.

31.57.2.5 Necropsy Findings

P. multocida produces a purulent bronchopneumonia with plum-colored cranioventral consolidation and purulent exudate on cut section within the airways; when calves are experimentally infected with *P. multocida* alone, the lesion is usually not extensive and is typically confined to the cranioventral lung lobes.[268,317,318] Histologically, bronchopneumonia characterized by infiltration of neutrophils and macrophages into alveoli and airways is seen. Microscopic evidence of abscesses may be present. Fibrin deposition with expansion of lymphatics and interlobular septa with edema, and focal areas of coagulative necrosis, has been reported in calves infected with *P. multocida*,[317,318] but this lesion is more typical of infection with *M. haemolytica*.[268]

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31.57.2.6 Diagnosis

Bronchopneumonia caused by *P. multocida* is diagnosed as described for *M. haemolytica*. The species is most commonly identified by culture of lung lesions identified at postmortem examination of affected animals. Because of the association of *P. multocida* with chronic or ongoing pneumonia, identification of this agent may indicate that the animal has been affected with bronchopneumonia for several days to weeks.

31.57.2.7 Treatment and Prevention

Treatment of *P. multocida* is as described for *M. haemolytica*. Several antimicrobials are labeled specifically for the treatment of *P. multocida*, and products labeled for the treatment of *M. haemolytica* are also likely to be effective against this organism (see Table 31-10). Because *P. multocida* seems to be associated with chronic or ongoing pneumonia, effective treatment of infection with this species may require longer therapy than the 3 to 5 days historically recommended for ruminants with bronchopneumonia, but this recommendation has not been tested in controlled studies and would be an extralabel use of some antimicrobials.

Because prior insult to respiratory defense mechanisms appears necessary for infection with *P. multocida* to cause disease, prevention of disease is likely to be aided by undertaking efforts to prevent other primary respiratory injury. This would include efforts to prevent infection with viral respiratory pathogens and to establish management practices that help minimize respiratory tract disease.

As compared with *M. haemolytica*, relatively little is known about protective immunity to *P. multocida*. Modified live vaccines can protect calves from disease caused by experimental challenge.[324,325] Antibody responses to several outer membrane proteins were associated with protection in one study, and these were induced by live but not killed vaccine.[325] Several commercial vaccines are marketed that contain *P. multocida* in combination with *M. haemolytica*; one such vaccine is approved for use in sheep and goats as well as cattle (*M. haemolytica–P. multocida* Bacterin, Colorado Serum, Denver, Colo.). There are currently no vaccines marketed that contain only *P. multocida*. No published large-scale trials have specifically evaluated the effect of vaccination against *P. multocida* on respiratory disease in the field.

31.57.3 Histophilus somni (Formerly Haemophilus somnus)

31.57.3.1 Definition and Etiology

H. somni is a gram-negative aerobic bacteria of the family *Pasteurellaceae*. The name of this organism was recently changed form the previous name, *Haemophilus somnus*.[326] *H. somni* can be found on the genital and upper respiratory mucosa of normal ruminants,[327–330] but it can also cause a variety of diseases, including septicemia, thrombotic meningoencephalitis (TEME), endometritis, abortion and infertility, pneumonia, pleuritis, laryngitis, otitis, conjunctivitis, myocarditis, mastitis, and polyarthritis.[331] Only pneumonia and pleuritis resulting from this organism are considered here. Two bacteria very similar to *H. somni, Haemophilus agni* and *Haemophilus ovis*, have been isolated from sheep with septicemia, meningitis, mastitis, and reproductive abnormalities; DNA hybridization studies have indicated that these three organisms should all be classified as *H. somni*.[332] Although specific serotypes of *H. somni* have not been associated with disease as is the case for *M. haemolytica* and *P. multocida*, differences in virulence among different strains have been demonstrated in experimental challenge studies.[333] Moreover, differences in expression of molecules considered to be virulence factors have been demonstrated when strains from healthy animals are compared with strains from diseased animals.[334] Thus it appears that some isolates of *H. somni* are more likely to cause disease than others, but more research is needed to confirm the characteristics that define a pathogenic isolate.

31.57.3.2 Clinical Signs

As mentioned earlier, *H. somni* can cause disease in a variety of organ systems, and the clinical signs of infection will depend on the organ system affected. The possibility of concurrent infection of multiple systems should be considered in patients suspected to have disease caused by *H. somnus*. In a Canadian retrospective study from the early 1990s, the majority of animals presented to a regional diagnostic laboratory for necropsy as a result of haemophilosis had disease in more than one organ system.[335] Signs of respiratory tract infection can range from mild to severe and can include fever, tachypnea, cough, nasal discharge, and depression. Severe cases of disease can be fatal.[333,336] Harsh or loud bronchovesicular sounds may be heard on thoracic auscultation because of pulmonary consolidation, particularly over the cranioventral lung fields. Affected animals may have signs of pain owing to fibrinous pleuritis,[336] including reluctance to move, standing with elbows abducted, and catching the breath before expiration. The cell wall of *H. somni* contains lipooligosaccharide (LOS), which induces inflammatory responses identical to those induced by LPS from *E. coli*[337]; therefore animals with pleuritis or pneumonia caused by *H. somni* could also have clinical signs referable to endotoxemia, including tachypnea, tachycardia, dark or pale mucous membranes with prolonged capillary refill time, salivation, or dyspnea.

31.57.3.3 Pathogenesis

H. somni can live on respiratory or genital mucous membranes without causing disease, and it is not entirely clear what factors related to the pathogen or host must change for disease to occur. The physical and immunologic barriers presented by the upper respiratory tract are apparently of major significance; calves exposed to *H. somni* by aerosol did not develop disease,[338] whereas instillation of the bacteria directly into the trachea or bronchi led to disease that could be severe.[333,336] As has been shown for *M. haemolytica* and *P. multocida*, primary infection by a viral respiratory pathogen is likely a predisposing factor that allows *H. somni* to advance and establish in the lower respiratory tract in many cases. Calves infected with BRSV before infection with *H. somni* had disease of greater severity than that seen in calves infected with either BRSV or *H. somni* alone.[169,336]

H. somni has many features that help the bacteria escape the immune response. The bacteria have outer membrane proteins that bind to the Fc region of antibody, allowing them to escape opsonization.[334] When the bacteria are ingested by neutrophils or macrophages, they are able to resist being killed.[339] The bacterial LOS induces inflammatory responses similar to the LPS of other gram-negative bacteria,[337] and *H. somni* is able to periodically change the structure and antigenicity of its LOS, which is likely to be important in evading the host immune response.[340]

An important aspect of the pathology caused by *H. somni* is the formation of vasculitis and vascular thrombi; this was first recognized in the context of the neurologic lesion caused by the bacteria, which is known as *thrombotic meningoencephalomyelitis* (TME), but vascular thrombi are also identified histologically in the lungs of animals with pneumonia caused by *H. somni*.[336] For some time the exact cause of the vascular thrombosis typical of *H. somni* infection was not known, but recent research indicates that the bacteria cause death of vascular endothelial cells by inducing apoptosis (programmed cell death).[341] Apoptotic death of endothelial cells is mediated in part through the bacterial LOS, which interacts with the P2X7 purinergic receptor on endothelial cells, inducing activation of certain caspases, enzymes that activate the apoptotic pathway and initiate a cell suicide program.[328] Although the entire pathway leading to vasculitis and thrombosis has not been completely elucidated, thrombosis is no doubt mediated in part by exposure of the vascular basement membrane on endothelial cell death, which leads to exposure of the basement membrane, activation of platelets and the coagulation cascade, and thrombosis.

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Another important aspect of *H. somni* is the propensity of infection to induce IgE production by the host.[169,342] Infection with BRSV before infection with *H. somni* led to production of high levels of *H. somni*–specific IgE, which was associated with disease of increased severity as compared with control calves.[169] Cattle vaccinated with four different *H. somni* bacterins were all found to develop serum levels of *H. somni*—specific IgE that were significantly higher than levels seen in control unvaccinated cattle.[342] Because IgE mediates type I (immediate) hypersensitivity, animals that produce IgE against *H. somni* after vaccination or primary infection could have signs of an allergic or anaphylactic response on subsequent revaccination or reinfection. Such IgE-mediated hypersensitivity reactions have been proposed to contribute to the adverse reactions sometimes seen in cattle after vaccination for *H. somni*.[342] In addition to inducing IgE production, *H. somni* directly produces histamine,[343] which could further contribute to the development of hypersensitivity-like signs during *H. somni* infection. Among other actions, histamine increases permeability of bronchial epithelium; this may aid the bacteria in moving out of the airway and into the lung parenchyma.

31.57.3.4

Epidemiology

Exposure to *H. somni* is common, with 25% to 100% of cattle in various populations having serum antibodies.[344] A retrospective study of bovine carcasses submitted to a regional diagnostic laboratory in western Canada from 1970 to 1990 indicated that cases affected with the neurologic form of haemophilosis were decreasing, whereas cases with respiratory and/or myocardial disease caused by the organism were increasing.[335] The reason for the apparent shift in type of disease caused in cattle could not be determined from the study, and a similar study has not been repeated to see if the trend is continuing.

It is common for feedlot cattle to have measurable antibody titers to *H. somni* at feedlot entry,[187,297] indicating that cattle are commonly exposed on the farm of origin or in transit to the feedlot. Seroconversion is also common in the first few weeks after feedlot entry,[297,298] indicating that cattle also continue to be exposed to *H. somni* in the feedlot. Several Canadian reports have indicated that *H. somni* can be a significant contributor to the development of respiratory disease or undifferentiated fever in feedlot cattle,[297,345,346] although studies of feedlot respiratory disease do not always find the bacteria involved. A causative association is typically inferred either by the association of seroconversion with respiratory morbidity and mortality during the period of study or by the association of *H. somni* vaccination with decreased respiratory morbidity and mortality. By these measures it appears that most disease resulting from *H. somni* occurs within the first 2 months of the feeding period,[346] and perhaps even within the first 2 weeks.[298] In some cases the association of seroconversion or vaccination with all morbidity and mortality is also evaluated, but one study found that when causes of mortality were separated into those in which it was biologically plausible for *H. somni* to be involved and those in which it was not (e.g., cattle with musculoskeletal injuries), vaccination was associated with decreased mortality attributable to *H. somni* but not with a decrease in all causes of mortality.[346] A causative association for *H. somni* (or any respiratory pathogen) is sometimes assumed when animals with high antibody titers to the organism at feedlot entry ultimately have lower respiratory morbidity and mortality,[297] although the case has been made that this is not a reliable marker of causation.[298] A *decreasing* antibody titer to *H. somni* was associated with decreased likelihood of disease in one study[297] and increased likelihood of disease in another[187]; this demonstrates that it is not always easy to develop a unified theory regarding the role of infectious agents and the immune response from the available data. It is also noteworthy that high-quality field research on the role of *H. somni* in feedlot respiratory disease in recent years has come almost entirely from Canada; it is not clear whether this indicates that *H. somni* is a less significant contributor to disease in the United States or whether the research has just not been done.

H. somni is uncommonly isolated in surveys of the causes of pneumonia in young calves,[112,300] but it can cause bronchopneumonia that is significant; one necropsy survey found pneumonia in 12 of 15 calves under 8 weeks of age submitted because of disease resulting from *H. somni*, and in 8 of the 15 calves, pneumonia was the only lesion found.[335]

31.57.3.5

Necropsy Findings

H. somni produces lesions similar to that of *P. multocida*, and it may rarely produce lesions that resemble *M. haemolytica*, creating a fibrinous pleuropneumonia.[331,333,336] Grossly, plum or red to brown consolidated lobules are seen in the cranioventral lung (Fig. 31-59), sometimes with abscesses containing brown-red fluid material. Interlobular septa can be distended with edema and fibrin, and hemorrhage may be grossly visible.

333 Purulent material is seen within airways on the cut surface of lung. The surface of the pleura may be flecked with fibrin, or in some cases fibrin deposition may be extensive, with varying amounts of straw-colored fluid in the pleural cavity. Bronchial lymph nodes may be enlarged, with ecchymotic hemorrhages on the cut surface.

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Fig. 31-59 Postmortem photograph of lungs from feedlot steer with bronchopneumonia caused by *Haemophilus somni*. Note extensive dark red, consolidated cranioventral lung. Laceration of caudoventral lung is iatrogenic and not relevant to the lesion. Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.

Histologically, inflammatory cells predominately made up of neutrophils infiltrate the alveoli and airways. Edema, hemorrhage, and fibrin can be seen in alveoli and interstitial spaces, and areas of coagulation necrosis

surrounded by inflammatory cells may be found. Interlobular septa are expanded with fibrin, and thrombi are seen in blood vessels.[333,336]

A massive fibrinous pleuritis with pleural effusion sometimes results from septicemic spread of *H. somni*. This condition can be differentiated from the fibrinous necrotizing lobar pleuropneumonia of shipping fever caused by *M. haemolytica* because the *H. somni* lesion involves only the pleural surface, not the lung.

31.57.3.6

Diagnosis

Bronchopneumonia or pleuropneumonia caused by *H. somni* is diagnosed as described for *M. haemolytica*. The bacteria can be difficult to isolate, so samples collected for culture should be transported to the diagnostic laboratory without delay, and the diagnostic bacteriology laboratory should be specifically requested to attempt to isolate *H. somni* if involvement of the agent is suspected. Samples are ideally taken from animals before antimicrobial treatment, as *H. somni* is susceptible to a wide variety of antimicrobials, and treatment makes it difficult to isolate the bacteria.[331] Serologic tests have been used to identify antibodies to *H. somni* for studies of the epidemiology of *H. somni* infection,[297,298] and seroconversion as measured via paired serology could be used to confirm infection in a group of cattle, but these assays may not be available at all diagnostic laboratories. IHC has been used to identify *H. somni* in association with lesions in formalin-fixed tissues,[347] and this may be an additional test available at some diagnostic laboratories.

31.57.3.7

Treatment and Prevention

H. somni is susceptible to a variety of antimicrobials, including tetracycline, penicillin, sulfonamides, and erythromycin, as well as more recently developed antimicrobials, many of which are labeled for use in the treatment of *H. somni* (see Table 31-10). In a feedlot with unusually high morbidity and mortality because of haemophilosis, prophylactic treatment with oxytetracycline was administered at different time points within the first 2 weeks of the feeding period in an effort to decrease haemophilosis morbidity or mortality, to no avail (although morbidity from all causes of respiratory disease was decreased).[348]

Several *H. somni* vaccines are commercially available; all are killed whole bacteria preparations (bacterins). Vaccination can prevent disease caused by experimental challenge; in one study, vaccination of 10-week-old calves with a commercial bacterin significantly decreased clinical signs and pulmonary pathology resulting from *H. somni* challenge.[333] Clinical trials of *H. somni* bacterins in the 1980s gave mixed results, with evidence that vaccination decreased respiratory morbidity and/or mortality in some trials but not in others[346,349,350]; and very little research has provided more information since then. In a cow-calf herd with a high incidence of calf pneumonia, vaccination of calves at 3 and 5 weeks of age with an *M. haemolytica* and *H. somni* bacterin in combination with a modified live BRSV vaccine led to decreased treatment rates as compared with calves not vaccinated or calves vaccinated with either the bacterin or the BRSV vaccine alone.[351] The decrease in treatment rates only tended toward statistical significance; this may have been because small numbers of calves were enrolled in the study. The specific influence of *H. somni* vaccination in this trial could not be determined. The same authors found that vaccination of cows with *M. haemolytica* and *H. somni* bacterin 4 weeks and/or 7 weeks prepartum increased antibody titers to both pathogens in the serum of their calves at 3 days and 1 month of age. Furthermore, calves vaccinated at 1 and 2 months in the face of maternal antibody had significantly higher titers at 4 and 6 months of age than unvaccinated calves.[352] The effect of

antibody titers on disease in the calves was not examined. A recent trial of the effect of vaccination on respiratory morbidity in feedlot cattle showed no effect of *H. somni* vaccination.[298]

The fact that *H. somni* vaccines induce cattle to produce IgE against the bacteria[342] indicates that vaccinated cattle may be at increased risk for a hypersensitivity reaction after a booster vaccine or infection. Although some older clinical trials showed a benefit associated with vaccination in terms of decreased respiratory morbidity and/or mortality, *H. somni* vaccination may also put cattle at risk for adverse reactions. Therefore it may be most prudent to recommend vaccination only for groups of cattle on operations in which significant morbidity or mortality caused by infection with *H. somni* has been confirmed.

As described for *M. haemolytica* and *P. multocida*, preventing primary injury to the respiratory tract by viral infection and limiting other causes of stress that suppress the host immune response are expected to help animals resist disease caused by *H. somni*.

31.57.4 Mycoplasma Bovis

31.57.4.1 Definition and Etiology

Mycoplasma bovis is a member of the genus *Mycoplasma* of the class Mollicutes, and as such it is among the smallest free living organisms. The first known mycoplasma, identified in 1898, was the causative agent of contagious bovine pleuropneumonia, *Mycoplasma mycoides* subsp. *mycoides*, small colony variant.[353] Mycoplasmas have since been recognized to cause disease in humans and a wide variety of animal and plant hosts. Mycoplasmas are small (approximately 200 nm) and pleomorphic, with a genome of only approximately 500 to 1000 kD.[354] They are bounded by a single membrane, and because they lack a cell wall they are naturally resistant to antimicrobials such as penicillins and cephalosporins that work by impairing cell wall synthesis. *Mycoplasma bovis* was first identified in 1961 in the United States, where it was isolated from a case of mastitis.[355] It has since spread worldwide. The bacterium was originally considered a subspecies of *Mycoplasma agalactiae*, and the two agents can be difficult to distinguish.[356] However, *M agalactiae* is a pathogen of sheep and goats and is rarely isolated in the United States, whereas *Mycoplasma bovis* is regularly isolated in cases of pneumonia, respiratory disease, arthritis, tenosynovitis, and other disorders of cattle. *Mycoplasma bovis* can cause disease in sheep, goats, and other species, but this is a rare occurrence.

31.57.4.2 Clinical Signs

Respiratory infection with *Mycoplasma bovis* causes fever, tachypnea, inappetence, and sometimes respiratory distress.[357] Coughing and nasal discharge are reported in some outbreaks.[358,359] Respiratory disease caused by *Mycoplasma bovis* can occur in outbreaks; in young dairy calves, a subset of calves affected often develops otitis, characterized by unilateral or bilateral drooping of ears with purulent aural discharge, possibly with facial paralysis caused by cranial nerve VII involvement, and vestibular signs such as head tilt, nystagmus, and ataxia.[358–361] In weaned beef calves and cattle entering feedlots, a subset of affected animals may develop arthritis and tenosynovitis[361–363]; this syndrome is sometimes referred to as *chronic pneumonia and polyarthritis syndrome* (CPPS).[363,364] Young dairy calves can also develop arthritis or tenosynovitis.[359] A typical complaint by the producer experiencing a respiratory disease outbreak involving *Mycoplasma bovis* is that cattle do not respond to therapy as expected, and a significant proportion of affected animals remain chronically ill and unthrifty for weeks after the onset of disease.[361,362,365] In addition to respiratory disease,

Mycoplasma bovis can also cause mastitis, arthritis and tenosynovitis, conjunctivitis, otitis, sinusitis, and myocarditis and/or pericarditis. The bacteria can also be isolated from aborted fetuses and from semen, linking the agent to reproductive failure.

The ability of *Mycoplasma bovis* to act as a primary respiratory pathogen has been debated. Classically the agent has been understood to be an opportunist, establishing itself after primary infection with viral pathogens or other bacteria. However, experimental challenge of gnotobiotic calves with *Mycoplasma bovis* alone induced respiratory disease with clinical signs of fever, tachypnea, and inappetence in four of seven calves and grossly evident lung lesions in all seven.[357] These findings indicate that *Mycoplasma bovis* can cause disease while acting alone, but, as for other bacterial respiratory pathogens described earlier, it is likely that natural disease often follows other primary insult. A recent survey of causes of death in cattle in Ontario feedlots identified caseonecrotic pneumonia caused by *Mycoplasma bovis* as a cause of more fatalities within the first 60 days of the feeding period than acute fibrinosuppurative pneumonia typical of disease caused by *M. haemolytica* or *H. somnus*.[188] This study indicates that *Mycoplasma bovis* is an important contributor to mortality in some feedlots, but more research is needed to determine whether the factors that predispose cattle to fatal disease resulting from *Mycoplasma bovis* are different from the factors known to predispose cattle to fibrinous bronchopneumonia caused by *M. haemolytica*.

31.57.4.3

Pathogenesis

Although *Mycoplasma bovis* has been recognized to cause respiratory disease in cattle for some time, very little is known about the mechanisms by which the agent causes disease. In disease caused by other mycoplasmas, attachment has been shown to be a key factor in pathogenesis. In vitro studies of *Mycoplasma bovis* suggest that pathogenicity is likewise associated with the ability to attach, as isolates from cases of clinical disease were better able to attach to embryonic bovine lung cells than were isolates from asymptomatic animals or high passage laboratory isolates.[366] Antibodies against several of the variable surface proteins (Vsps) expressed by *Mycoplasma bovis* were able to partially but not completely block attachment, indicating that the Vsps play a role in attachment.[366] Invasiveness is another pathogenic mechanism of *Mycoplasma bovis; Mycoplasma bovis* was found to be capable of migration between ciliated respiratory epithelial cells, whereas *Mycoplasma dispar*, another mycoplasma commonly isolated from cases of bovine pneumonia, remained attached to the surface of ciliated epithelial cells.[367] The ability of *Mycoplasma bovis* to invade allows the organism to cause disease in organs outside the respiratory tract, such as joints and tendon sheaths. *Mycoplasma bovis* produces a toxin that increases vascular permeability.[368] Certain strains of the agent have also been shown to be cytotoxic to mammalian cells[369]; it is not known whether this effect is related to the vascular toxin reported by Geary and colleagues.

Available data indicate that *Mycoplasma bovis* may cause disease in part through evading or impairing host immune function. Although not yet well characterized, a feature of *Mycoplasma bovis* that is likely important in enabling the bacteria to escape the host immune response is the expression of Vsps. The ability to vary surface protein expression has been shown to be an important pathogenic mechanism in certain mycoplasmas.[354] *Mycoplasma bovis* expresses at least three Vsps—VspA, VspB, and VspC—and isolates have been found that express some or all of these proteins.[370] A study of 50 *Mycoplasma bovis* isolates, including many field isolates, showed extensive variability in Vsps at both the genetic and antigenic level.

Evidence indicates that *Mycoplasma bovis* can directly impair the activity of neutrophils. In one study *Mycoplasma bovis* was found to adhere to bovine neutrophils, but adherence did not elicit an expected

activation response. Moreover, adherent *Mycoplasma bovis* inhibited normal neutrophil microbicidal activity.[371] The bacteria is also able to kill lymphocytes by inducing them to undergo apoptosis (programmed cell death).[372] Induction of proinflammatory cytokine production by the host may also contribute to disease caused by *Mycoplasma bovis*; an isolate of *Mycoplasma bovis* induced production of the proinflammatory cytokine TNF-α by bovine alveolar macrophages to a degree similar to that induced by *M. mycoides* subsp. *mycoides* (the cause of contagious bovine pleuropneumonia, a serious disease exotic to the United States) but in contrast to nonpathogenic mycoplasmas tested.[373]

Other research suggests that *Mycoplasma bovis* may induce an immune response that is not optimally protective. Vanden Bush and Rosenbusch showed that in calves experimentally infected with *Mycoplasma bovis*, serum titers of *Mycoplasma bovis*-specific IgG1 increased significantly after infection, whereas titers of antigen-specific IgG2 did not increase as markedly.[374] Because IgG2 is considered superior in opsonizing ability as compared with IgG1, the authors speculated that preferential induction of IgG1 by *Mycoplasma bovis* infection may be related to the apparent inability of the immune response to rapidly clear the organism, as evidenced by the common association of chronic pneumonia with *Mycoplasma bovis* infection.

31.57.4.4

Epidemiology

Mycoplasma bovis can be isolated from the respiratory tracts of normal cattle[188,375,376] and from cattle with respiratory disease.[208,365,377–380] Surveys of nasopharyngeal swabs taken from dairy calves with no clinical signs of respiratory disease found *Mycoplasma bovis* in 0% to 34% of the animals sampled.[376,380,381] A recent survey of multiple source weaned beef calves sampled soon after arrival at nine different backgrounding or stocker operations identified nasal shedding of *Mycoplasma bovis* in 0% to 6% of animals at each operation.[382] *Mycoplasma bovis* can also be found in bovine lungs without evidence of disease at postmortem examination.[188] The fact that *Mycoplasma bovis* can be isolated from animals with no clinical or pathologic signs of pneumonia has led some to question whether the agent is a true respiratory pathogen. However, a consistent association of *Mycoplasma bovis* with a clinical syndrome of chronic nonresponsive pneumonia with or without otitis, arthritis, or tenosynovitis,* and a pathologic syndrome of bronchopneumonia with multifocal caseous necrosis visible histologically and/or grossly,[362,364] has led to general acceptance that *Mycoplasma bovis* can contribute to significant morbidity and mortality in some situations.

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Although more research is needed, currently available data support the concept that *Mycoplasma bovis* can spread from a few animals carrying the bacteria to others until a large proportion of a group is infected; transmission in these cases is most likely via respiratory infection by direct contact or short-distance aerosol.[361,362,375] Feeding milk infected with *Mycoplasma bovis* appears to be another important source of infection for dairy calves.[359–361] The fact that *Mycoplasma bovis* infection can be widespread in some populations was illustrated by a case-control study of cattle in the first 4 weeks after feedlot entry. Researchers used a protected BAL catheter to collect samples from the lower airways with minimal contamination from the nasal passages. Soon after arrival, these investigators found *Mycoplasma bovis* in the BALF of 52% of controls that were not treated for respiratory disease in the first 28 days, versus 61% of cases that were treated for respiratory disease within 28 days.[299] Two weeks later *Mycoplasma bovis* was found in BALF from over 80% of the controls and in 100% of animals who ultimately were treated for respiratory diseases by 28 days, indicating that colonization of the respiratory tract of all cattle sampled was widespread within a short period after feedlot entry.[375] Genetic characterization by arbitrarily primed PCR (AP-PCR) has been used to characterize *M. bovis* isolates associated with herd outbreaks of disease, with a single genetic lineage associated with disease in a

closed herd, and multiple genetic lineages associated with disease in a calf ranch where animals were frequently brought on site from multiple sources.[384]

Mycoplasma bovis has been isolated from both dairy calves and feedlot cattle with respiratory disease in multiple studies,* with particularly high prevalence occurring in animals with chronic pneumonia nonresponsive to antimicrobial therapy.[208,209,365,377] In a recent survey of cattle subjected to necropsy within 60 days of arrival at 72 feedlots, lung lesions were categorized as either fibrinosuppurative (typical lesion caused by *M. haemolytica* or *H. somni*) or caseonecrotic, which were characterized grossly by the presence of multiple foci of dry caseous material and histologically by areas of eosinophilic necrotic cellular debris (caseous necrosis) surrounded by inflammatory cells and fibrous tissue. *Mycoplasma bovis* was isolated in 53 of 54 cases (98%) with caseonecrotic lesions and in 52 of 58 of cases (89%) with fibrinosuppurative lesions; it was also isolated from 6 of 13 animals (46%) with normal lungs in this study.[188] In 49 chronically sick cattle from a single feedlot that were subjected to necropsy in 1 month, *Mycoplasma bovis* was identified in the lungs of 82% of the cases, and in the joints of 45% of the cases.[209] BVDV was also present in 39% of the cases from which *Mycoplasma bovis* was isolated. A later retrospective study by the same authors found BVDV in the lungs of 44% of cattle subjected to necropsy with a final diagnosis of pneumonia caused by *Mycoplasma bovis*; these data lead the authors to suggest that immunosuppression resulting from BVDV may predispose a subset of animals to chronic pneumonia and/or arthritis caused by *Mycoplasma bovis*. In contrast, Gagea and colleagues found that although BVDV infection was more common in feedlot cattle with bacterial pneumonia than in those with other diseases, it was not more common in cattle with caseonecrotic lesions typical of *Mycoplasma bovis* infection.[379]

* References 208, 209, 358, 359, 365, 377, 383.

* References 208, 262, 365, 377–379, 384.

31.57.4.5

Necropsy Findings

Grossly, lungs of cattle with pneumonia caused by *Mycoplasma bovis* have dark red, firm consolidated lobules of the cranioventral lung. Raised white to yellow, firm nodules that range from 0.5 to several centimeters in diameter are often but not invariably seen clustering in the cranioventral lung (Figs. 31-60 and 31-61).[357,364,379,385] These nodules may appear to be abscesses, but in most cases they are actually foci of coagulation necrosis.[357,379] Differential diagnoses for gross lesions of abscessing pneumonia in cattle include infection with *Arcanobacterium (Actinomyces) pyogenes* and *F. necrophorum* (both of which are more likely to cause a foul odor than *Mycoplasma bovis*) and *Mycobacterium bovis* (tuberculosis).[364] Other gross lesions include enlargement of interlobular septa by edema and fibrin; fibrinous or fibrous pleural adhesions are unusual but could be present if the animal is or has been co-infected with *M. haemolytica* or *H. somnus*. Animals with pneumonia typical of *Mycoplasma bovis* may also have arthritis in one or more joints characterized by abundant yellow fluid with fibrin and sometimes purulent material, and tenosynovitis characterized by extensive caseous exudate and pyogranuloma formation in the tendon sheaths.[362,364] Fibrin, purulent material, and caseous material may be present in the tympanic bullae.

Fig. 31-60 Postmortem photograph of lung from calf with bronchopneumonia caused by *Mycoplasma bovis*. Note extensive nodular abscessation of cranioventral lung. Photograph contributed by Dr. Tom Mullaney, Michigan State University, East Lansing Mich.

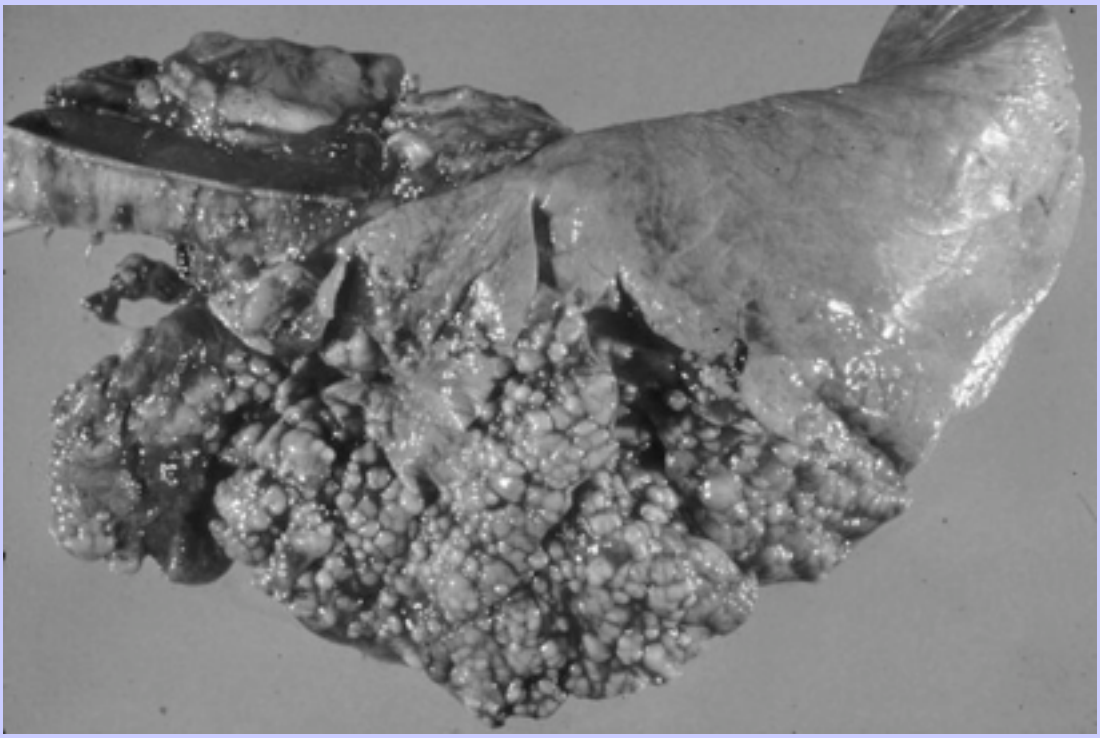

Fig. 31-61 Postmortem photograph of lung from calf with bronchopneumonia caused by *Mycoplasma bovis*. Note dark red consolidated cranioventral lung and white caseous material visible on cut surface. Photograph contributed by Dr. Ricardo Rosenbusch, Iowa State University, Ames Iowa.

Histologically there is purulent pneumonia and bronchiolitis, with extensive infiltration of neutrophils in airways, and peribronchiolar cuffing with lymphocytes and mononuclear cells. Foci of eosinophilic coagulation necrosis are surrounded by a rim of dark pyknotic inflammatory cells and, farther out, a region of primarily macrophages and some plasma cells.[357,364] Areas of coagulation necrosis may extensive, and ghostlike outlines of cells, alveolar walls, and alveoli may be seen.[357,364] Immunohistochemical staining for the organism often shows large numbers surrounding the periphery of areas of coagulation necrosis, as well as in association with bronchiolar and alveolar epithelial cells.[364,385] Histologic evaluation of joints, tendon sheaths, and the tympanic bullae and petrous temporal bone will reveal changes consistent with the gross lesions. Close inspection may also reveal foci of mononuclear cell accumulation with positive staining for *Mycoplasma bovis* by IHC in the liver and kidney[385] or in the pericardium.[347]

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31.57.4.6

Diagnosis

Confirmation of disease caused by *Mycoplasma bovis* is best made by identification of the agent by culture or IHC in conjunction with gross and histopathologic lesions typical of disease attributed to the agent. Thus, in

order to reliably confirm a role for *Mycoplasma bovis* in an outbreak of bovine respiratory disease, postmortem of representative affected cases is necessary. It is important to request that the diagnostic laboratory specifically identify *Mycoplasma bovis*; in many cases diagnostic laboratories characterize agents only to the level of the genus by identification of typical organisms in culture. Because other mycoplasma such as *Mycoplasma bovirhinis, M. dispar*, and *Mycoplasma alkalescens* can also be isolated from the respiratory tract of cattle with pneumonia, a report of "*Mycoplasma* sp." is not equivalent to a diagnosis of disease caused by *Mycoplasma bovis*. Species-specific identification of *Mycoplasma bovis* can be made by antibody-based tests such as IHC or immunofluorescence (available at the Iowa State University Veterinary Diagnostic Laboratory, and possibly others) or PCR (available at many laboratories including the University of Georgia Athens Veterinary Diagnostic Laboratory).

Although available data suggest that *Mycoplasma bovis* is less commonly isolated from healthy cattle than other mycoplasmas are, because the organism can be found in nasal swabs and lung tissue of apparently normal animals, an isolation of the bacteria in the absence of evidence of disease is of uncertain significance. Nasal shedding has not been confirmed to be a reliable antemortem measure of the presence of pneumonia caused by *Mycoplasma bovis*; the agreement between the results of nasal swab culture and the presence of lung disease caused by *Mycoplasma bovis* was good in one study[378] and only moderate to poor in two other studies.[299,386] Serologic assays have been used to characterize seroconversion in epidemiologic studies, but the tests are not widely available, and their results have not been shown to reliably indicate active infection.[369] A recent report evaluated the agreement between the measurement of serum antibodies using a blocking ELISA and shedding of *Mycoplasma bovis* in the milk in a small number of cows; agreement was significant but only moderate ($\kappa = 0.44$).[387] If serology is attempted, paired serology with evidence of rising titers in association with outbreaks of respiratory and/or joint disease is likely to be more useful than measurement of titers on a single occasion.

31.57.4.7

Treatment and Prevention

Multiple authors report that cattle with pneumonia or arthritis caused by *Mycoplasma bovis* respond poorly to antimicrobial therapy.[209,362,363,369] Early studies indicated that tilmicosin had good effect against experimentally induced[388] disease caused by *Mycoplasma bovis* in cattle; however, recent studies of in vitro susceptibility profiles of panels of *Mycoplasma bovis* isolates reveal evidence of widespread evidence of resistance to tilmicosin, as well as erythromycin, ampicillin, and ceftiofur.[389,390] Susceptibility to oxytetracycline, chlortetracycline, and spectinomycin has been variable, although most isolates have been susceptible to fluoroquinolones such as enrofloxacin or danofloxacin.[390–392] However, no fluoroquinolone marketed in the United States is specifically labeled for treatment of cattle for disease caused by *Mycoplasma bovis*, and extralabel use of fluoroquinolones is illegal. A relatively new antimicrobial, tulathromycin, has shown good efficacy against experimentally induced *Mycoplasma bovis* infection; it is interesting to note that the response did not correlate with in vitro MIC data for the challenge isolate, which was high and predicted that the antimicrobial would not likely be effective.[393] Tulathromycin (Draxxin, Pfizer Animal Health) has recently been approved for treatment in the United States of respiratory disease caused by *Mycoplasma bovis*.

Although clinical trials and data from well-controlled experimental studies under conditions typical of U.S. cattle operations are lacking, reports suggest that in vitro MIC data may not always predict antimicrobial efficacy in the field.[369,394] If in vitro susceptibility tests do indeed fail to predict clinical efficacy, the reason for this failure is not certain. Because *Mycoplasma bovis* can be seen in association with foci of coagulation necrosis in lungs of affected cattle,[364,379,385] it may be that antimicrobials are not maximally effective in this

environment, or it may be that insufficient duration of treatment is carried out in at least some cases. Controlled trials indicating the duration of antimicrobial therapy needed for effective treatment of pneumonia caused by *Mycoplasma bovis* are lacking, but anecdotal reports suggest that early treatment is critical for success,[359,395] and that treatment should be continued for at least 7 to 10 days.[359] The high concentrations of tulathromycin found in bovine lung for 7 to 15 days after SC injection[393] make this a logical choice for prolonged treatment; a form of oxytetracycline that provides therapeutic blood levels for 7 days (Tetradure, Merial) may also be a good choice for treatment of some cases of disease caused by *Mycoplasma bovis*. Failure of antimicrobials that are predicted to be efficacious against *Mycoplasma bovis* may also be related to inability of the immune response to effectively clear the organism by mechanisms described previously. Some veterinarians report that outbreaks of *Mycoplasma bovis* cannot be stopped with any treatment, but that outbreaks are eventually terminated when chronically affected animals die or are shipped to slaughter.

Research indicates that vaccination can afford some protection against experimental challenge with *Mycoplasma bovis*.[396,397] Autogenous vaccines have been used for years, but no reports with large numbers of animals and appropriate controls are available to provide information about efficacy. Recently two *Mycoplasma bovis* vaccines have been licensed for sale in the United States. To my knowledge no studies have yet been reported in a peer-reviewed forum to provide unbiased evidence of efficacy for either product. Therefore, although small experimental studies suggest that vaccination might be an effective means of minimizing disease caused by *Mycoplasma bovis*, research in the clinical setting with currently available commercial vaccines is sorely needed to indicate whether vaccination can be recommended as an efficacious and cost-effective means of preventing morbidity associated with *Mycoplasma bovis*.

It is not yet clear why some animals develop chronic disease typical of *Mycoplasma bovis* and others do not when it can be found in the respiratory tracts of animals in both populations. Certainly the primary insults known to put ruminants at increased risk for infection with other bacterial respiratory pathogens, such as primary viral infection, mixing of animals from multiple sources, inadequate host immunity, and environmental stressors, may all play a role, but the relative importance of these and other factors in predisposing animals to disease caused by *Mycoplasma bovis* are not yet known. One group presented data suggesting that disease resulting from *Mycoplasma bovis* has increased in severity since the early 1980s,[379] so it may be that factors such as increasing virulence of currently circulating isolates or changes in certain management practices are involved. Because of the chronic nature of disease often associated with *Mycoplasma bovis*, the syndromes described warrant control from both a financial and an animal welfare perspective. Anecdotal reports indicate that some producers with at-risk cattle have more problems with chronic nonresponsive disease caused by *Mycoplasma bovis* than other producers with similarly at-risk cattle,[363] so it is hoped that future research will clarify the factors that put animals at specific risk for chronic disease associated with *Mycoplasma bovis* infection.

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31.57.5 Mycoplasma Pneumonia of Goats

31.57.5.1 Definition and Etiology

Caprine pneumonias that are not contagious among adults are caused by several species of *Mycoplasma*. *Mycoplasma capricolum* has not been associated with disease in the United States since 1955, and *M. mycoides* subsp. *capri* has not been identified in the United States.[398] However, large colony type *M. mycoides* subsp. *mycoides* (Mmm) can be a very serious cause of mortality among goat kids and does in North America.[399,400]

31.57.5.2

Clinical Signs and Differential Diagnosis

In herds with Mmm infections, goat kids usually appear clinically normal until 2 to 8 weeks of age, when the following three clinical syndromes occur[399,400]:

1 A peracute illness characterized by high fevers (41.1° C to 42.2° C [105.8° F to 107.9° F]) and death within 12 to 24 hours

2 A CNS syndrome with opisthotonos and death within 24 to 72 hours

3 An acute to subacute syndrome with high fevers, multiple hot swollen joints, and pneumonia

The most common manifestations are swollen joints, lameness, and recumbency. About one half of affected kids have increased lung sounds on expiration and elevated respiratory rates. During an outbreak, 80% to 90% of kids die or are euthanized because of permanent recumbency. Mmm infection in adult does is also life-threatening. Forty-six does died in 1 week on a 600-goat dairy during an acute outbreak of arthritis and polyarthritis, mastitis, and interstitial pneumonia caused by Mmm infection.[401]

In the United States the main differential diagnosis of Mmm infection in goats is caprine arthritis-encephalitis (CAE), which is a chronic, sporadic disease. Animals with CAE are generally alert and nonfebrile and continue to eat well. Affected kids exhibit a CNS syndrome at 8 to 16 weeks of age characterized by ataxia and posterior paresis progressing to tetraparesis in 2 weeks to 2 months. They also have a progressive interstitial pneumonia that is usually inapparent. The arthritic form of CAE usually occurs in goats 1 to 2 years of age. In addition, the joints of animals with acute Mmm contain fibrinopurulent exudate, whereas mononuclear cells are present in the joint fluid of CAE cases.

31.57.5.3

Diagnosis

The definitive diagnosis of Mmm infection in individuals requires isolation of the agent from milk, joint fluid, blood, urine, or tissue. Infected goat herds can be readily identified by culturing bulk tank milk because infected does shed up to 10^{10} Mmm organisms per milliliter of milk.[399] Inapparent carriers can be identified by milk culturing, but false-negative results are a risk because organisms are shed intermittently. An ELISA to detect specific antibodies against Mmm has been developed but has not been evaluated for detection of carrier animals.[402]

31.57.5.4

Pathophysiology

Field cases of Mmm infection show evidence of widespread thrombosis, suggesting disseminated intravascular coagulation. A coagulopathy, indicated by increases in prothrombin and partial thromboplastin times and a decrease in number of platelets, has been demonstrated in experimental infections.[403] Mmm has been shown to cause direct damage to cultured endothelial cells and to activate complement.[404]

31.57.5.5

Epidemiology

Localization of Mmm in the udder with no overt signs of mastitis is a key feature of transmission of the disease. In other does, udder infections develop through contact with the organisms during milking, and their

kids become infected by ingestion of colostrum.[405] The localization of Mmm, often associated with mites in the external ear canal of asymptomatic goats, may also play a role in the epidemiologic process of Mmm infections.[406]

31.57.5.6

Necropsy Findings

The most common necropsy finding in goat kids that die of Mmm infections is a fibrinopurulent polyarthritis.[399,400] Approximately one half of field cases have pneumonia. One or more lung lobes have areas of patchy to diffuse red consolidation that is sometimes covered with a fibrinous exudate. Clear, golden yellow to serosanguineous fluid is found in the thorax in half of the cases. In some patients there are fibrinous adhesions between the lungs and thoracic wall. Affected lungs have microscopic evidence of bronchopneumonia or interstitial pneumonia. Other common lesions include pericarditis, peritonitis, and enlargement of the kidneys, liver, and spleen.

31.57.5.7

Treatment and Prognosis

Conventional antibiotic therapy for goats with Mmm infections is almost always unsuccessful.[399,400] Tylosin or tetracyclines are commonly used. A low percentage of kids make a clinical recovery from the septicemic illness but often have arthritis by the time they freshen. Does that recover from mastitis become chronic carriers.

31.57.5.8

Prevention and Control

Prevention is based on maintaining herds free of Mmm infection. Purchased does should originate only from herds that have no history of mortality in kids from arthritis and pneumonia and that have negative bulk tank cultures for Mmm. Purchased individuals should be held separate from the milking herd until they have an Mmm-negative milk culture result; treatment for ear mites may also be prudent. A vaccine is not commercially available; however, an experimental formalin-killed vaccine has been shown to be protective.[407]

Control of Mmm outbreaks is centered on prevention of the systemic infection in kids and mastitis in milking does. Rapid prevention of new cases in kids can be expected from a program of feeding heat-treated goat colostrum (56° C [132.4° F] for 1 hour) or cow colostrum at birth, pasteurized milk up to 1 month of age, and pasteurized milk or a high-quality milk replacer from 1 month to weaning.[399] All kids with swollen joints should be culled. Milking hygiene should be improved to prevent transmission of infection during milking. Udders should be dried with individual cloths or paper towels, teats should be dipped with an organic iodine base preparation, and teat cups should be backflushed. Milk samples from all does in the milking herd should be cultured to identify carrier does. Infected does should be kept in a separate string and milked last or culled, depending on production. Colostrum of dry does should be cultured as they freshen, and the does should be hand-milked separately until their milk is found to be free of Mmm. Monthly cultures of the bulk tank milk from the noninfected string should be performed to ensure that it is free of Mmm infection. The goal of control procedures is eradication of Mmm from the herd.

31.57.6 Other Mycoplasmas

Mycoplasmas are isolated, usually in combination with other pathogens, from 50% to 90% of beef and dairy cattle pneumonias.[111,112,408,409] Mycoplasmas have been associated with peribronchial and peribronchiolar lymphoid hyperplasia, which is sometimes referred to as a "cuffing pneumonia," a common lesion in calves that die or are euthanized because of ECP.[410,411] Mycoplasmas have also been recovered from lesions of acute and chronic bronchopneumonia in which a cuffing pneumonia was not apparent.

Other than *Mycoplasma bovis*, the species of mycoplasmas (see Box 31-4) prevalent in North America are generally considered to be mild respiratory pathogens, mainly causing subclinical infections unless coupled with environmental stresses or infections by other pathogens.[409] Tracheal bronchial aspiration performed on dairy calves at random found that calves with both *Mycoplasma* species and *Pasteurella* species present in the aspirate were at significantly greater risk of developing ECP than calves with only one organism or no organisms. A recent study of feedlot cattle found seroconversion to *M. alkalescens* to be significantly associated with undifferentiated fever, a clinical definition similar to undifferentiated respiratory disease.[297] Effects such as immunosuppression[412] and inhibition of the mucociliary transport mechanism,[413] which can be mediated by mycoplasmas, suggest that they may play an important contributory role in the pathogenesis of bovine pneumonia. *Mycoplasma ovipneumonia* is often isolated from pneumonic lungs of sheep and goats, usually accompanied by *M. haemolytica*. On its own, *M. ovipneumonia* is capable of causing mild, subacute to chronic bronchiolitis or bronchopneumonia that probably predisposes to *M. haemolytica* infections.

31.57.7 Arcanobacterium Pyogenes

Arcanobacterium pyogenes (formerly *Actinomyces pyogenes*, and before that, *Corynebacterium pyogenes*) is a gram-positive rod-shaped species of bacteria that is a common cause of internal or SC abscesses in ruminants. *Arcanobacterium pyogenes* is occasionally isolated from the lungs of ruminants with pneumonia, typically from animals that have chronic pneumonia, possibly from grossly visible abscesses.[111,410,414] This species is viewed as an opportunist that contributes to respiratory disease as a secondary or possibly "tertiary" invader after viral pathogens and other bacterial respiratory pathogens have become established. *Arcanobacterium pyogenes* has a variety of virulence factors including a cytolytic toxin termed *pyolysin*, as well as several molecules that aid in adherence to host cells.[415] Diagnosis of this pathogen is usually made as an incidental finding at necropsy of an animal with significant respiratory disease from other primary causes. Finding *Arcanobacterium pyogenes* during a respiratory necropsy should not induce efforts to directly treat or prevent this pathogen, but rather should induce efforts to prevent other primary or secondary causes of pneumonia and to treat animals in a timely manner with appropriate therapy for an adequate duration in order to prevent chronic pneumonia.

31.57.8 Other Bacteria Associated with Respiratory Disease in Ruminants

Bacteroides melaninogenicus and other anaerobic bacteria are considered opportunistic pathogens that become established after other primary or secondary respiratory pathogens induce lesions. Anaerobic bacteria are isolated from approximately one third of the lungs of cattle that die of bronchopneumonia.[416] These opportunists are believed to be inhaled with eructated ruminal gases. Other bacteria infrequently isolated from pneumonic bovine lungs are listed in Box 31-4. Isolation of these uncommon pathogens during a respiratory necropsy should signal a search for other underlying disease that put animals at risk for pneumonia caused by opportunistic pathogens; it

may also indicate a need for increase efforts to prevent and effectively treat other primary and secondary respiratory pathogens, which may have been present earlier and set the stage for these opportunists.

31.57.9 Chlamydial Agents (*Chlamydophila* Species)

Chlamydial agents are occasionally isolated from pneumonic ruminant lungs. These organisms are thought to produce only mild respiratory infections by themselves but may enhance the pathogenicity of concurrent infections. Research indicates that calves are infected with chlamydial agents relatively early in life and that crowding enhances the likelihood of a high proportion of animals being infected.[417] Experimental challenge of calves with a combination of chlamydia and *M. haemolytica* results in clinical disease more severe than either agent produces alone.[418]

31.58 APPROACH TO DIAGNOSIS AND TREATMENT OF RESPIRATORY DISEASE OF UNDETERMINED CAUSE (UNDIFFERENTIATED RESPIRATORY DISEASE OF RUMINANTS)

Information regarding diagnosis and treatment of individual infectious agents that can cause ruminant respiratory disease was described earlier. However, it is most common for one or more of these agents to be involved when a group of cattle, sheep, or goats has an outbreak of respiratory disease. Moreover, when a veterinarian is called to make an initial evaluation of a group of ruminants with respiratory disease, the exact causative diagnosis is not known. The term *undifferentiated respiratory disease* has been applied to respiratory disease of uncertain cause.[419] Thinking of an outbreak as “undifferentiated respiratory disease” before a causative diagnosis is confirmed is helpful to ensure that the veterinarian considers all possible infectious agents and management factors that may be contributing to disease in the animals in question, rather than immediately focusing on one agent or factor that is guessed to be of importance. A plan to diagnose and treat the current problem and prevent future respiratory disease can then be made by administering treatments and instituting management changes appropriate for any of the agents likely to affect the class of animals involved.

31.58.1 Clinical Signs

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Successful intervention with an outbreak of undifferentiated respiratory disease is based on identification and alteration of the risk factors associated with the outbreak. An investigation begins with collection of a thorough history of the problem and is followed by examination of affected animals and the environment. The history questions are directed to management practices that predispose to pneumonia (see later). It is important to observe personally as many management practices as possible to ensure that what is described is actually implemented. Examination of the environment includes evaluation of the nutrition program to determine whether any of the dietary factors that predispose to pneumonia are present.

Once a thorough history is collected, several animals involved in the outbreak should be examined. Because infectious respiratory disease is so common in ruminants, producers may assume that any illness not obviously occurring in another body system is a result of respiratory disease. However, to ensure rational use of antimicrobials and vaccines and to make properly focused management changes, confirmation of the clinical diagnosis of respiratory disease is necessary.

Ruminants affected by bronchopneumonia exhibit signs of respiratory tract inflammation and, sometimes, toxemia. In early stages, animals stand off by themselves and do not approach feed. They hold their heads and

ears low, appear depressed, and move slowly. Respirations become rapid and shallow, there is frequent licking of the muzzle, and a moist cough is often present. Animals may have a fever of 40° C to 41° C (104° F to 105.8° F) and as the disease progresses they appear gaunt, have deep labored respirations, and may hold the head extended. Dyspnea may be both inspiratory and expiratory. Ocular and nasal discharges progress from serous to mucopurulent. Normal lung sounds are difficult to hear except in calves, goats, and sheep. Sheep normally have harsh inspiratory sounds. The heavy chest wall of larger cattle makes it difficult to hear normal airway sounds. The first auscultable lung changes are increased harshness of inspiratory sounds. By the time expiratory sounds are as loud as or louder than inspiratory sounds, severe bronchopneumonia exists. In the most severe cases, auscultation of the anterior ventral lung fields reveals crackles and wheezes and an increase in bronchial sounds, especially on inspiration. When ventral consolidation occurs, harsh tracheal breathing is still audible ventrally, but percussion reveals ventral dullness. Percussion is best accomplished on young calves and goats of any age. Recently shorn sheep can be readily percussed, but heavy wool makes percussion difficult. Animals in which a fibrinous pleuritis develops are reluctant to move because of pain, have shallow respirations, and sometimes have pleural friction rubs detectable on auscultation. Nasal discharge, dyspnea, abnormal lung sounds, cough, and high fevers are cardinal signs of bronchopneumonia. Other respiratory tract conditions that must be considered as differential diagnoses include acute bovine pulmonary edema and emphysema (ABPEE), interstitial pneumonia, pulmonary edema, pleuritis, laryngitis, tracheitis, and lungworms. Rare conditions include thoracic neoplasia and diaphragmatic hernia. Systemic conditions that result in respiratory signs include septicemia, heart failure, acid-base imbalances, and poisonings such as nitrate toxicity. An important feature that separates systemic conditions from bronchopneumonia is that, in addition to signs of pulmonary dysfunction, systemic conditions often are manifested by clinical signs of damage to other organ systems. In sheep and goats, ovine progressive pneumonia (OPP), CAE, and lung or mediastinal abscesses caused by *C. pseudotuberculosis* or other bacterial invaders are additional differential diagnoses.

Clinical signs associated with specific viral infections of the respiratory tract have previously been presented. In general the clinical signs observed are dependent on the stage of the disease and particularly on whether secondary bacterial pneumonia has been superimposed. In the early stages of viral pneumonia common clinical features include mild depression and anorexia, often marked elevation in body temperature, serous to mucopurulent lacrimal and nasal discharges, cough, and elevated respiratory rates. On auscultation of the lungs there may be an increase in breath sounds. In the presence of secondary bacterial pneumonia, the severity of clinical signs becomes more pronounced.

31.58.2 Diagnostic Workup of Undifferentiated Ruminant Respiratory Disease

If clinical examination of a group of cattle, sheep, or goats indicates that respiratory disease is present, it is not always necessary to immediately submit diagnostic tests. Occasional outbreaks of respiratory disease occur in groups of ruminants, and such occasional outbreaks can often be managed successfully with administrative symptomatic therapy alone (described later). However, if recurrent outbreaks occur, or if animals do not respond appropriately to symptomatic therapy, then diagnostic tests are warranted so that more information is available to better characterize the nature of the problem. In such situations a careful evaluation of management practices and facility design is also warranted to ensure that all practices possible are maximizing the ability of animals to resist respiratory infection. Management practices important to minimizing respiratory infection are described later (p. 638).

31.58.3 Clinical Pathology and Assessment of Immune Status

CBCs or serum biochemical analyses are rarely of much value in diagnosis of respiratory disease in ruminants. Some viruses, such as BVDV, may cause leukopenia, but when bacterial pneumonia is superimposed the WBC count is most often in the high-normal range to mildly elevated with a left shift. Animals with bacterial pneumonia may have an inflammatory leukogram characterized by a leukocytosis with a mature neutrophilia, possibly with a left shift; hyperfibrinogenemia is likely to occur. Animals with chronic pneumonia may have a normal WBC count even when there is significant pulmonary pathology.

Failure of passive transfer is a major risk factor for pneumonia in calves, so investigation of outbreaks in calves should include an evaluation of passive transfer status by measurement of immunoglobulins in the serum of calves 1 to 7 days of age. The zinc sulfate turbidity test, sodium sulfite test, and measurement of total serum protein with a refractometer are practical, satisfactory procedures for estimation of serum immunoglobulin concentrations.

31.58.4 Necropsy Findings

The value of necropsy findings to confirm the cause of death, particularly in animals that die unexpectedly, cannot be overemphasized. If producers can be encouraged to allow all animals that die to be subjected to necropsy, much valuable information may be gained before a disease outbreak causes excessive mortality. It is unfortunately common for veterinarians to be contacted only after several animals have died without any having been subjected to necropsy, and thus much valuable information that could have helped prevent further disease and death has been lost. Establishing a practice of subjecting all animals that die to at least gross necropsy can aid greatly in maintaining management practices that limit animal disease and death; this is because the actual cause of death identified at necropsy can sometimes be unexpected. For example, if an animal is assumed to have died of pneumonia, but it actually died of acute enterocolitis, then control measures may be undertaken that are inappropriate for the true problem.

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The cost of having animals sent to the local diagnostic laboratory for full necropsy may dissuade some owners from allowing necropsies. However, much useful information can be gained simply by gross necropsy evaluation performed on the farm by the local veterinarian. With some practice veterinarians can develop confidence in identifying the major differentiating gross features of common diseases, and they can thus ensure that management is aimed at control of disease of the correct organ system. Moreover, there are some identifiable characteristics typical of the major infectious causes of bronchopneumonia. Gross necropsy can help the veterinarian make a more accurate list of differential diagnoses for outbreaks of bronchopneumonia, allowing the development of a more logical plan for treatment and prevention.

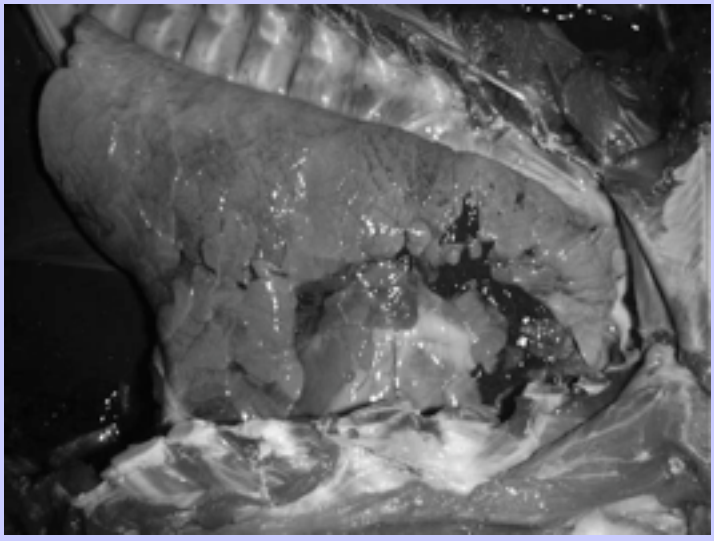
A respiratory necropsy should include assessment of the upper airways and trachea. Fibrinopurulent material in the larynx is evident in cattle with necrotic laryngitis (see Fig. 31-50). Infection with BHV-1 (IBR) causes generalized reddening (congestion) and small raised, red or pale plaques on the mucosa of the nasal passages and trachea; more severe cases have dark red, hemorrhagic changes, possibly with yellow-brown exudate adherent to the mucosa (fibrinopurulent tracheitis) (see Fig. 31-53).

Bronchopneumonia in recently transported cattle (shipping fever pneumonia) is most commonly a fibrinopurulent bronchopneumonia. The infection is aerogenous; it begins in the bronchioles and extends through their walls into the surrounding parenchyma. The cranioventral areas of affected lungs are swollen, dark red to gray-brown in color, firm, and heavy. Bronchial lymph nodes are swollen, wet, and dark red. The inflamed lung

and parietal pleura are sometimes covered with variable amounts of yellow fibrin, and the pleural cavity may contain straw-colored fluid (see Fig. 31-56). Fibrinous pleuritis usually indicates the presence of *M. haemolytica* or *H. somnus*. These species can also cause necrosis of lung, which will be firm and brown to gray (see Fig. 31-57), or dark red wedge-shaped lesions (infarcts) that are caused by thrombosis of an artery supplying the region (see Fig. 31-58). The dorsal regions of the caudal lobes often are mottled by interspersed patches of inflammation and normal parenchyma. In up to one third of bronchopneumonia cases, forced respirations result in vesicular to bullous pockets of emphysema in the dorsal areas of the caudal lobe (see Fig. 31-54). These changes can also be seen with primary BRSV infections or with AIP. Focal or multifocal areas of firm white to yellow material that look like abscesses may actually be caseous necrosis caused by *Mycoplasma bovis* (see Figs. 31-60 and 31-61); the chronic phase of pneumonia resulting from *M. haemolytica* may also cause similar lesions. Abscesses containing caseous or liquid purulent material may also be caused by *Arcanobacterium (Actinomyces) pyogenes* or anaerobic bacteria. Lambs that die of bronchopneumonia caused by *M. haemolytica* have swollen lungs with reddish purple anterior ventral consolidation. An extensive fibrinous pleuritis with large amounts of straw-colored exudate is often present. Chronic cases have multiple abscesses and pleural adhesions. As much as 60% to 80% of the lung tissue is usually involved in fatal cases of severe bacterial pneumonia.

Bronchopneumonia in housed dairy calves (ECP) is less often fibrinous, but rather is characterized by the presence of firm, collapsed, dark red lobules in the cranioventral or caudal ventral lung (Fig. 31-62); in severe cases whole lobes of the lung may be affected. Firm dark red lobules without fibrin on the pleura are common in pneumonia caused by *P. multocida, Mycoplasma bovis*, or other mycoplasmas. Infection with BRSV and PI3 can also cause lobular consolidation of the ventral lung (see Fig. 31-55). Less commonly *M. haemolytica* or *H. somnus* organisms are isolated from such lesions without fibrinous pleuritis.

Fig. 31-62 Postmortem photograph of lung lesions typical of enzootic calf pneumonia. Note scattered collapsed, dark red lobules in the cranioventral lung. This type of lesion could be caused by BRSV, PI3, *Pasteurella multocida*, or various mycoplasmas. Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.



Animals that die after chronic persistent coughing, dyspnea, and weight loss exhibit lesions of chronic suppurative pneumonia. Bronchi and bronchioles are filled with purulent exudate, there are multiple mature lung abscesses, and greatly dilated bronchioles contain malodorous exudate. When bronchiectasis is severe, the lung lobes have a nodular appearance. Pulmonary abscesses and bronchiectasis are common findings in cases of chronic pneumonia and explain poor weight gains.[414]

Although gross necropsy alone can be very helpful in generating an accurate list of differential diagnoses, histopathologic and microbiologic findings often add critical information. Gross necropsy findings are not always definitive; for example, in one study of AIP in feedlot cattle, only 67% of the cases that were diagnosed with AIP based on clinical and gross pathologic findings were confirmed by histopathology.[420] Therefore in outbreaks with relatively high mortality or in cases in which long-term and possibly expensive therapy is not yielding expected results, the cost of full necropsy of two or three typical cases is likely to be well worth the expense.

If full necropsy at a local diagnostic laboratory is to be undertaken, two or more animals showing signs that are typical of the early stages of the disease outbreak should be selected for euthanasia and necropsy. Although the producer may be reluctant to euthanize animals that may recover, and would rather send animals with chronic, nonresponsive disease, the chronic cases are unlikely to yield information relevant to the primary problem.

31.59 MICROBIOLOGIC TESTS

If samples are collected from a necropsy on the farm for testing for viral or bacterial pathogens, proper handling and transport of the specimens is critical to maximize the chance of an accurate diagnosis. The veterinarian is encouraged to contact the diagnostic laboratory if uncertain about proper methods of sample collection and transport; most laboratories now post this information on their websites, making it easy to find for those with Internet access.

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31.59.1 Viruses

A specific viral diagnosis requires laboratory confirmation. Most laboratories direct their diagnostic efforts toward the viruses for which vaccines are available. Diagnosis of other respiratory viruses may require the assistance of specialized laboratories. Because of the time and expense that specific viral diagnosis entails, care must be taken in the collection, storage, and transport of appropriate specimens to a diagnostic facility. The veterinarian is encouraged to contact the diagnostic laboratory if uncertain about the proper methods for collecting and transporting specimens for microbiologic diagnosis.

31.59.1.1 VIRUS ISOLATION

Virus isolation is time-consuming and expensive, but it is a sensitive method for identifying viruses. Virus isolation is performed in cell culture. A variety of specimens can be tested, including nasopharyngeal, conjunctival, and tracheal swabs, TTAs, BALFs, and a variety of respiratory tract tissues that can be obtained at postmortem examination. Fluids, tissues, and swabs may be frozen; alternatively, swabs and tissue specimens may be placed in a viral transport medium and kept refrigerated until arrival at the diagnostic laboratory, preferably within 24 hours. BRSV does not appear to survive freezing or transport well, and it is important that specimens be inoculated onto cell cultures as soon as possible. In general, better success at virus isolation is obtained when specimens are collected in the acute phase of disease. Chances of successful

isolation may be improved by sampling asymptomatic animals that are in close contact with affected animals. These animals may be in an incubation phase of infection. Some viruses appear to be more difficult to isolate than others. For example, BRSV is very difficult to isolate by routine procedures, and other diagnostic procedures (discussed later) should be performed in conjunction with attempts at virus isolation. During isolation procedures, viruses are detected by production of cytopathic changes in cell monolayers. Viral identification is accomplished by a variety of procedures such as neutralization with specific antiserum, FA staining, immunoperoxidase staining, and examination by electron microscopy and immunoelectron microscopy. An immunoperoxidase monolayer assay has been developed for detection of BVDV and is in routine use for screening serum samples for detection of cattle persistently infected with BVDV.

31.59.1.2

DETECTION OF VIRAL ANTIGENS

Immunofluorescence is a rapid method for identification of specific respiratory viruses. Antemortem identification can be made from conjunctival or nasal smears and from cells obtained by tracheal lavage or BAL. Postmortem identification can be made from frozen tissue sections prepared from a variety of respiratory tract tissues.

Another technique that is used to detect viral antigen in tissues is immunoperoxidase staining, which is most often carried out using formalin-fixed tissue. This is a very useful procedure that allows histologic examination of tissues in conjunction with immunologic identification of the causative agent.

Antigen capture enzyme immunoassay (EIA) provides a rapid means for detection of respiratory viruses. These tests can be performed on fluids obtained from the respiratory tract. Commercially available antigen capture EIAs are available for diagnosis of human RSV infections in infants and young children that are also capable of detecting BRSV,[421] and these are in use in some veterinary diagnostic laboratories. The same technique has been developed for the detection of BVDV and is in use for screening serum samples to detect cattle persistently infected with BVDV.

31.59.1.3

DETECTION OF VIRAL NUCLEIC ACIDS

The nucleotide sequence has been determined for the genome or partial genome for many of the ruminant respiratory viruses. Testing for viral nucleic acid by PCR (for DNA viruses) or RT-PCR (for RNA viruses) is increasingly more widely available at veterinary diagnostic laboratories. Although they are not currently in routine use, the possibility exists of using nucleotide probes for the detection of these viruses in tissue samples. One benefit of using nucleic acid detection to identify pathogens is that the pathogen does not have to be alive to be identified; this can be a particular benefit for relatively fragile viruses such as BRSV.

31.59.1.4

SEROLOGIC DIAGNOSIS

Retrospective diagnosis of viral infections can be made by determination of antibody titers in paired sera from individual animals. The first sample is collected in the acute phase of the disease, and the second is collected 2 to 4 weeks later (“convalescent sample”). In a respiratory disease outbreak multiple animals should be tested to achieve a serologic diagnosis; it is typical for seroconversion to be identified in only a subset of animals tested in any outbreak. Serologic diagnosis is made by demonstrating a fourfold increase in antibody titer in the convalescent sample as compared with the acute sample; a fourfold fall in titer also indicates recent infection. Because day-to-day variation in results of tests used for serologic diagnosis is typical, the acute and

convalescent samples should be run by the laboratory on the same day. Thus the acute samples can be stored in the freezer by the local veterinarian and shipped together with the convalescent samples.

Because infections in young ruminants can occur in the presence of passively derived antibodies, seroconversion might not always occur during outbreaks of bronchopneumonia involving young animals.[422] This problem may be overcome by inclusion of older individuals in contact with the younger animals in the population sampled, which are likely to have lost passively derived antibody to these viruses and will be more likely to seroconvert. Also, BRSV antibody levels appear in some instances to peak at the onset of severe disease, and a decreasing antibody level is seen on paired serologic analysis rather than a rising level. Serologic testing of normal appearing, in-contact cattle that may be in early stages of infection may be helpful in demonstrating seroconversion to BRSV. A wide variety of serologic procedures is available for antibody determinations, but most laboratories use a microtiter serum neutralization test (also known as *virus neutralization test*) for IBRV, BVDV, PI3, and BRSV. It is important to remember that serum neutralization tests take several days to run. Some laboratories are beginning to use more rapid procedures such as ELISA for determination of serum antibody titers. Through use of an isotype-specific ELISA, diagnosis of BRSV can be achieved with a single serum sample by measurement of IgM levels[423]; similar tests could be developed for other pathogens, but these are unlikely to be widely available. A hemagglutination-inhibition test can also be used for PI3 and respiratory coronavirus.

31.59.2 Bacteria

A wide variety of bacteria have been isolated from the respiratory tract of ruminants in association with respiratory disease. However, the most frequent and most important isolates are *M. haemolytica, P. multocida, H. somni*, and *M. bovis*. The isolation of *A. pyogenes*, coliforms, or anaerobic bacteria often is indicative of chronic pneumonia or aspiration pneumonia and may be associated with lung abscessation. 629 630

Before bacterial culture is attempted, the status of any recent antibacterial therapy should be determined, and, if possible, specimens from untreated cattle should be collected. It is important to remember that *M. haemolytica, P. multocida, H. somni*, and mycoplasmas are normal inhabitants of the nasal passages of cattle and may be cultured in the absence of respiratory disease. It is important to note that not all laboratories will identify the species of mycoplasmas cultured; thus an isolate may be identified only as "*Mycoplasma* sp." If involvement with *Mycoplasma bovis* is suspected, the laboratory may need to be specifically asked to identify the species of any mycoplasmas they isolate. Specific identification of *M. bovis* is most often done by immunofluorescent assay (available at the diagnostic laboratory at Iowa State University, and possibly others), IHC (available at Iowa State University, the University of Saskatchewan, and possibly others), or PCR (available at the diagnostic laboratory at the University of Georgia in Athens, and possibly others). Some mycoplasmas are more hardy or easier to grow than others; for example, it is not unusual for *Mycoplasma bovis* to overgrow *M. dispar* when both are present in the same sample. Culture of mycoplasmas typically takes at least 1 week, and laboratories often call a sample negative only after the sample has been subcultured at least once.

Although isolates obtained from nasal swabs may reflect the organisms causing pneumonia on a group level, specificity can be increased by obtaining specimens from the lower respiratory tract.[299] Specimens appropriate for bacterial culture are similar to those discussed for viruses, such as nasopharyngeal and tracheal swabs, TTAs, and BAL or lung aspirates. Swabs are acceptable for transferring samples directly to culture medium, but if transport is necessary, the swab must be placed in a transport chamber such as a Culturette (Marion Scientific, Kansas City, Mo.) to ensure adequate moisture for the sample during transport. Contamination of the sample with environmental agents can best be prevented by first searing the lung surface, then making an incision with a

sterile scalpel, followed by sampling with a swab through the incision; but it may not be practical to sear the surface of the lung in the field setting. Specimens of respiratory tract tissues such as lung and bronchial lymph nodes can be placed in sterile containers such as Petri dishes or self-sealing plastic bags and transported to the laboratory on ice.

Chlamydial organisms may be demonstrated by staining smears and sections of lesions with a Gimenez stain or by immunofluorescence techniques. Isolation attempts are done by inoculation of yolk sacs of embryonated chicks. Serologic tests such as complement fixation are also available.

31.59.2.1 DETECTION OF BACTERIAL ANTIGENS OR NUCLEIC ACIDS

It is increasingly common for diagnostic laboratories to use IHC for identification of bacteria in formalin-fixed tissues. This technique offers many advantages, including correlation of the pathogenic organism with the lesion and detection of pathogens not found on bacterial culture because of overgrowth of other organisms such as *A. pyogenes* or *P. multocida*. The use of PCR for identification of bacterial agents in a variety of samples is also increasingly available. The veterinarian is encouraged to contact the diagnostic bacteriologist at the local diagnostic laboratory or check the laboratory website for information regarding which tests are available.

31.59.2.2 SEROLOGIC TESTING FOR BACTERIAL PATHOGENS

Diagnosis of infection with bacterial pathogens can be attempted as described earlier for viral pathogens. However, the use of serologic tests for identification of infection by bacterial respiratory pathogens has mostly been limited to use in research. Thus these tests are not likely to be widely available for clinical use.

31.59.3 Treatment of Undifferentiated Bronchopneumonia

31.59.3.1 ANTIMICROBIAL THERAPY

The basic foundations of antimicrobial therapy for bacterial bronchopneumonia are treat early enough, treat long enough, and treat with the appropriate antimicrobial agent. Because there are currently many effective products marketed for the treatment of important bacterial respiratory pathogens in cattle, treating early enough is perhaps more important than what is used for therapy. It should be remembered that a major reason for treatment failure is the presence of a lesion that is too far advanced for successful therapy. If lesions becomes too far advanced, the antimicrobial agents will have difficulty reaching walled-off areas of necrosis and suppuration; moreover, the regenerative response will not be able to return this tissue to normal lung parenchyma.

Although antibacterial agents for the treatment of bacterial bronchopneumonia may reduce losses caused by fatality and retarded growth, they do not serve as a substitute for preventive management practices. Cattle requiring treatment do not perform as well as those that have not needed treatment. However, cattle requiring only one treatment perform better than those that require two or more treatments[424]; this further emphasizes the need for treating early enough with an effective antimicrobial, because animals with treatment failure will have suboptimal performance.

The precise temperature used to determine whether animals need treatment depends on the balance between the costs of overtreatment (drugs and labor) and undertreatment (treatment failures and mortality.) This

temperature may vary depending on the animal type. The cutoff commonly used for feedlot cattle is 104° F to 104.5° F (40° C to 40.3° C), but 103.5° F (39.7° C) may be more appropriate for calves. This recommendation is based on the long-term effects that ECP has been shown to have on growth rate, age at first calving, culling before calving, and culling after calving, indicating that ECP can have long-lasting effects if not properly treated with early antibiotic therapy. When outbreaks of respiratory disease occur, surveillance of the affected group must be increased to ensure early detection of diseased animals.

Treatment of sufficient duration can be achieved only if the response to therapy is monitored. Therapy should be continued for at least 48 hours after clinical signs of fever, dyspnea, and toxemia have abated. Many of the antimicrobial drugs labeled for use in the treatment of pneumonia in cattle provide multiple days of therapeutic drug concentrations in lung tissue after only a single injection. These products decrease the time and stress associated with daily treatment; they also make it easier for feedlots to return animals to home pens rather than keeping them in hospital pens, which seems to be associated with poorer responses by treated animals.[425] Frequently, antibiotics are evaluated over a 3-day treatment period, with cases failing to demonstrate a normal body temperature after 3 days being classified as nonresponders; a different class of antimicrobial should be administered to nonresponders.

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Although a 3-day course of antimicrobial therapy for bronchopneumonia was for many years standard operating practice, particularly in the treatment of feedlot cattle, the view is increasingly held that treatment for a longer duration may be more appropriate. This is particularly true for pneumonia caused by *Mycoplasma bovis* in dairy calves or feedlot cattle, which seem to respond better to treatment for at least 7 to 10 days.[359,395] Although treatment for 7 to 10 days would be extralabel for many antibiotics, at least three products currently marketed have been shown to provide therapeutic drug levels for at least 7 days when used at dosages recommended on the label (see Table 31-10). Unfortunately there is little research evaluating the effect of treatment duration on long-term outcome in ruminants with bacterial bronchopneumonia, so it is difficult to make evidence-based recommendations regarding exactly how long antibiotics should be administered. Determination of therapeutic response by evaluation of general appearance without regard to restoration of normal body temperature has been shown to result in high relapse rates. A typical decision tree for treating feedlot cattle with antibiotics is shown in Fig. 31-63, but protocols such as these may be modified as more information about the use of long-acting antimicrobials is obtained from field research.

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Selection of the appropriate antibiotic tends to be what most veterinarians focus on when treating respiratory disease because this is the aspect of therapy over which they have the greatest control. Factors such as cost, route of administration, treatment interval, drug labeling, necessity of extralabel doses, and withholding times quickly cull a number of antibiotics, leaving a short list of suitable alternatives for use as first-line antimicrobial agents. Antibiotics that are associated with severe injection site reactions such as erythromycin or those associated with complications of administration such as balling gun injuries with oral boluses are often avoided. Only antibiotics that are licensed and effective at label doses should be considered for routine use in food animals. Table 31-10 lists the approved antimicrobials for treating respiratory disease in cattle. If data regarding the MIC of bacteria isolated from animals before treatment with antimicrobials are available, the dose or duration of therapy can be rationally modified, but it is imperative that proper withdrawal times be observed when antimicrobials are used in an extralabel fashion. At the time of this writing, the Food Animal Residue Avoidance Databank (FARAD; www.farad.org or 1–888-USFARAD) is an invaluable resource for veterinarians who need to identify withdrawal times for drugs administered to food animals at extralabel dosages. The use of MIC data requires some understanding of the pharmacokinetics of the drugs in question; published information is available regarding interpretation of MIC data, or veterinarians can contact FARAD or the diagnostic bacteriologist at their local diagnostic laboratory for assistance.

Determining the antimicrobial sensitivity patterns or MIC data for causative agents such as *M. haemolytica* in the case of bacterial bronchopneumonia can be difficult. The best information is that gained from bacterial culture and susceptibility testing of animals subjected to necropsy before receiving any antimicrobial therapy; however, producers may be reluctant to allow necropsy of animals that have never been treated. Once an animal has been treated, any antimicrobials administered can bias the results of susceptibility testing of bacteria later cultured from the animal. Many bacteria, including *M. haemolytica*, can develop plasmid-mediated multiple antimicrobial resistance by bacterial conjugation so that, for example, exposure to oxytetracycline may induce resistance not only to oxytetracycline, but also to penicillin. Therefore, *M. haemolytica* recovered from cattle treated with antibiotics will have a different sensitivity pattern than *M. haemolytica* cultured from untreated cattle. This is especially important when reviewing publications reporting antimicrobial susceptibility of *M. haemolytica* isolates cultured at diagnostic laboratories, because these results will most often be from cases that have been treated with antimicrobial agents before death. The findings of these studies may be looked at as a worst-case scenario demonstrating antimicrobial agents for which acquired resistance is rarely or never a problem, versus those for which acquired antimicrobial resistance occurs commonly. In general, resistance to many drugs used for the treatment of bovine pneumonia has been identified when *M. haemolytica* isolates from cattle treated with antibiotics before death are evaluated.

Sensitivity testing using isolates from clinical cases raises questions regarding the best site for sample collection. Antibacterial sensitivities of isolates cultured from nasal swabs may not represent sensitivities of organisms causing pneumonia. This is surprising, because pneumonia usually is preceded by multiplication of bacteria such as *M. haemolytica* in the upper respiratory tract, and the nasopharynx serves as the source of bacteria colonizing the lungs. Nevertheless, there are discrepancies between antimicrobial sensitivities of bacteria isolated from nasal swabs and clinical outcome. Specimens for sensitivity testing should be collected from pneumonic lung, tracheal swabs, or TTAs collected from cattle before treatment whenever possible.

The choice of which drug to use can also be based on records of efficacy for animals treated in the past. Producers who keep accurate records of drugs used, with results of treatment responses, relapses, and chronic cases, may select first-line antibiotics based on historical performance of a drug. This may be the best approach to antimicrobial selection. A final method of choosing a first-line antimicrobial drug is reliance on published treatment trials. Published trials give comparisons between among responses for various antibiotics in cattle with naturally occurring bacterial bronchopneumonia. The outcomes for these trials are often expressed as both health and production values. When evaluating published treatment trials that use cases of naturally occurring bacterial bronchopneumonia, it is important to realize that the results may not be applicable to the cattle and pathogens outside the operation where the trial was carried out, but if the trial was well designed, it should provide useful comparisons. The characteristics of a well-designed field trial are discussed later in the section on vaccination (p. 641).

Mass medication with antibiotics at full therapeutic doses during an outbreak of feedlot cattle pneumonia dramatically curtails the daily number of new cases and improves feed consumption. In the acute stages of an outbreak, whatever drug is chosen should be given by injection; therapeutic levels cannot be reliably maintained by administering drugs in feed or water. Bronchopneumonia cases that occur after administration of mass medication have an increased possibility of being resistant to therapy with the antimicrobial used in mass treatment and have a greater than usual resistance to other antimicrobials. Thus mass medication should not be a standard practice but is warranted to control severe outbreaks of pneumonia. It is important to base a decision to mass medicate on measurable criteria. Some feedlot veterinarians implement mass medication when the pull rate of sick animals is 10% on any 1 day or is 25% over a 3- to 5-day period. A sudden drop in feed consumption, especially in high-risk cattle, is another situation in which mass antibiotic medication

should be cost-effective. Long-acting antibiotics have extended withdrawal times to slaughter. It is of critical importance that animals that receive them are properly identified and that the withdrawal times are observed. 631

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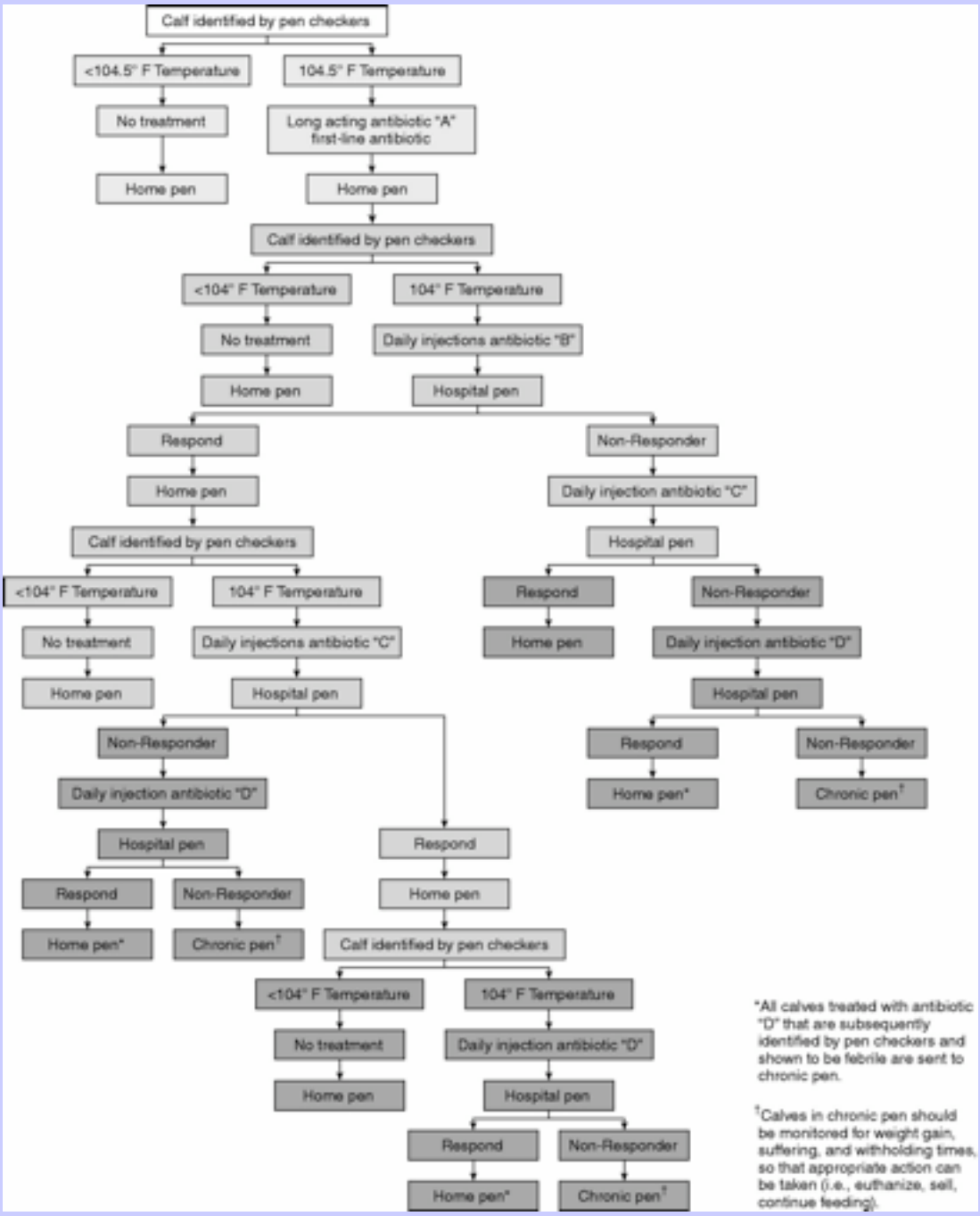
Fig. 31-63 Decision tree for antibiotic treatment of feedlot cattle.



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The same principles of therapy described previously apply to the treatment of sheep and goats.[220] Unfortunately, fewer drugs are labeled for the treatment of sheep and goats as compared with products used

for cattle. Drugs labeled for use in sheep and goats are listed in Table 31-10. Note that whereas tilmicosin (Micotil 300, Elanco Animal Health) is labeled for use in sheep, fatal reactions to tilmicosin have occurred in goats treated with this drug. Goats should not be treated with tilmicosin. Long-acting tetracycline at 10 mg/kg is very effective against experimental *M. haemolytica* infections in sheep. Administration of tetracycline subcutaneously is effective and less painful than IM injection. It is imperative to ensure that producers are given an appropriate meat and milk withdrawal time when antimicrobials are administered to sheep and goats at extralabel dosages; this is a particular concern in feedlot lambs or goats and in lactating dairy sheep or goats, from which products may enter the food chain in a relatively short time after treatment.

31.59.3.2

ANTIINFLAMMATORY THERAPY

Favorable responses to treatment with corticosteroids and antihistamines have been reported from field outbreaks of BRSV infection. However, corticosteroids should not be used indiscriminately in the treatment of respiratory disease because of the potential for immunosuppression. Corticosteroids may have a place in treatment of respiratory diseases such as necrotic laryngitis or tracheal edema syndrome of feedlot cattle.[90] It is unlikely that a single administration of a glucocorticoid will have a detrimental effect on the immune system of cattle. The dose for dexamethasone in cattle is 0.05 to 0.2 mg/kg IM or IV, and the dose for isoflupredone acetate is 10 to 20 mg IM. Treatment with corticosteroids may cause recrudescence of BHV-1 infections.

NSAIDs such as acetylsalicylic acid (aspirin), flunixin meglumine, and ibuprofen have been reported to be beneficial in the treatment of respiratory disease in ruminants. Aspirin (100 mg/kg every 12 hours) is approved for use in cattle, as is flunixen meglumine (1.1 to 2.2 mg/kg IV either as a single dose or divided into two doses at 12-hour intervals). Flunixin meglumine administered intravenously at 2.2 mg/kg to calves with pneumonia induced by PI3 virus results in a marked improvement in clinical signs and reduction in lung consolidation.[426] However, the use of flunixin meglumine may not be cost-effective in large numbers of animals. It is important to remember that flunixin meglumine is approved only for IV use; administration via the IM or SC route can result in violative residues in tissues if longer withdrawal times are not observed. Phenylbutazone, which has been used in the past for antiinflammatory effect in ruminants, is now illegal to use in lactating dairy cattle, and because of prolonged tissue levels found in treated cattle its use is discouraged in all food animals.

Unlike corticosteroids, NSAIDs do not impair immune function. The clinical responses of calves with either experimental or naturally occurring pneumonic pasteurellosis are markedly improved by adding flunixin meglumine to tetracycline therapy. In contrast, supplementation of antibiotic therapy with corticosteroids usually results in poorer responses, more relapses, and prolonged illness, although there is still some controversy over the use of corticosteroids for treatment of pneumonia. Because of the potential for renal toxicity with NSAIDs, dehydrated animals should be rehydrated before administration of these drugs. Care should also be taken not to overdose with NSAIDs or use them for prolonged periods, because they may also result in abomasal ulceration.

There has been little work done to evaluate the use of antihistamines as an ancillary treatment for bovine respiratory disease. Tripelennamine HCl is labeled for cattle at a dose of 1.1 mg/kg, which can be repeated in 6 to 12 hours if needed.

Tilmicosin has been suggested to have antiinflammatory effects in cattle because of the effect of the drug to induce apoptosis in leukocytes, which could theoretically decrease inflammatory responses in treated animals.[427] However, the concentrations of tilmicosin used in this study were quite high relative to concentrations

obtained in treated animals, and a later study of the effect of tilmicosin on the function of leukocytes taken from treated cattle showed no effect.[428]

31.59.3.3 ANTIVIRAL AND IMMUNOMODULATING THERAPY

Because viral respiratory infections predispose to development of secondary bacterial infections, antibiotic therapy is indicated to prevent or limit the development of bacterial pneumonia in animals with viral respiratory tract disease. Few antiviral drugs are available in human medicine, and none of these is in routine use in veterinary medicine for the treatment of viral respiratory disease in ruminants. Interferon has potential as an immunomodulating and antiviral drug in the prevention and treatment of viral respiratory disease. Human leukocyte interferon has been shown to decrease morbidity associated with shipping fever, but the therapy has not become widely used. Levamisole and isoprinosine have been used in attempts to stimulate the bovine immune system with equivocal success and cannot yet be recommended as supportive treatments.[426] It is important to recognize that the immunostimulatory benefits of levamisole occur at doses in the 2- to 3-mg/kg range, compared with the anthelmintic dose of 6 mg/kg. A decreased immune response has been observed after an 8-mg/kg dose of levamisole. High doses of vitamin C (1 g/45 kg; 1 g/100 lb) have been shown to enhance the activity of bovine neutrophils and reverse dexamethasone-induced suppression of neutrophil activity.[429] Isoprinosine has been evaluated as an immunomodulating drug for treatment of bovine respiratory disease and has shown some potential on the cellular level.[426]

31.59.3.4 SUPPORTIVE THERAPY

Supportive treatment of any kind will relieve stress, thus fostering the resistance of the patient, a very important component of the successful therapy of pneumonia cases. Sick animals should be provided shelter that protects them from rain, cold, wind, and hot sun. They should not be crowded, and the best-quality feed and clean water should be easily accessible. Mineral and vitamin deficiencies should be corrected with the use of injections or oral preparations if necessary. An IM vitamin A injection is considered useful adjunctive therapy by some veterinarians treating ruminants with bronchopneumonia.

31.59.4 Epidemiology of Ruminant Respiratory Disease

31.59.4.1 ENZOOTIC CALF PNEUMONIA

ECP has traditionally been described as affecting calves from 2 to 6 months of age; however, prospective studies examining cohorts of calves have found calves may be affected with ECP as early as 2 weeks of age.[430] Slaughter surveys of dairy calves 4 to 14 days of age have found ECP to be the second most common cause of slaughter condemnation.[431] Virtala and colleagues[430] found that veterinarian-diagnosed ECP occurred at a younger age than did caretaker-diagnosed ECP. As a whole, these studies suggest that ECP may start much earlier than previously recognized.

Pneumonia of dairy calves occurs both as endemic disease and as outbreaks (epizootics) of respiratory disease. Chronic endemic disease is the most common manifestation of this disease, and as a result pneumonia of dairy calves is commonly called *enzootic calf pneumonia*. The distinction between enzootic and epizootic calf pneumonia is important in reference to etiology because different causes are more important in each form of the disease.

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Waltner-Toews, Martin, and Meek[432] determined from producer diagnosis that 15% of Ontario Holstein dairy calves were treated for pneumonia before weaning. Curtis, Erb, and White[433] reported that Holstein calves in New York had a crude incidence risk of 7.4% for respiratory tract illness, as diagnosed by the farmer. Sivula and colleagues[434] found that 7.6% of 845 Minnesota dairy calves were diagnosed by producers as having pneumonia. Van Donkersgoed and colleagues[435] found that the risk of pneumonia in Saskatchewan dairy calves was 39% as diagnosed by the farmer and 29% when the pneumonia was veterinarian diagnosed. Virtala and colleagues[430] found that the risk of pneumonia was 11% in New York dairy calves when diagnosed by producers and 25.6% when diagnosed by a veterinarian.

Mortality rates reported for ECP vary from 1.8%[434,435] to 4.2%.[430] Case fatality rates reported for calves with ECP range from 2.2% to 9.4% and vary with the sensitivity of the initial detection method (veterinarian versus producer).[430]

Pneumonia accounts for a significant proportion of the mortality (proportionate mortality) in dairy calves raised on dairy farms. Pneumonia accounted for 24% of deaths in New York calves[430] and 30% in Minnesota calves.[434] In one study examining Ontario veal calves raised in veal barns, pneumonia accounted for 52% of mortality in 4863 calves on six farms.[436] Producer accuracy in diagnosing causes of mortality was examined by Sivula and colleagues.[434] Producers were found to be moderately accurate but often listed the cause of death as unknown. This emphasizes the importance of laboratory confirmation of cause of death over producer diagnosis.

31.59.4.2

SHIPPING FEVER

Despite the undisputed economic importance of the disease, surprisingly little has been established regarding the behavior of pneumonic mannheimiosis or shipping fever at the population level, and even the question of whether the disease is truly contagious has yet to be answered from the epidemiologic perspective. Reviews of the literature from North American feedlot studies before 1985 found that published measures of morbidity in calves ranged from 0% to 69%, whereas measures of population mortality ranged from 0% to 15%. Incidence of disease was found to peak within 3 weeks of calves arriving at the feedlot. In view of the lack of uniformity in methods used to define cases of respiratory disease and calculate disease incidence, however, these data may not be reliable. In most of the studies the crude measures of total morbidity and total mortality were used as outcomes, and case definitions for these were often highly variable or absent. This lack of uniformity with respect to case definition and nomenclature, along with the inherently subjective nature of morbidity assessment, makes it difficult to draw legitimate comparisons among reports. One observational study specifically addressing epidemiology of fibrinous pneumonia (the classic lesion of shipping fever caused by *M. haemolytica*) was conducted by Ribble and colleagues.[305] Because of the difficulty and expense inherent in making definitive diagnoses of the causes of illness and death among feedlot cattle, most epidemiologic studies have used crude (total) mortality as an estimate of death losses caused by shipping fever, and treatment rate as a measure of respiratory morbidity. The results of several necropsy surveys and the previously cited epidemiologic study, however, indicate that crude mortality is unreliable as a surrogate measure of fibrinous pneumonia mortality and may lead to erroneous conclusions regarding risk factors contributing to this important disease.

In the observational study of fatal fibrinous pneumonia conducted by Ribble and colleagues in 1995,[305] risk factors specifically associated with shipping fever mortality in western Canadian feedlot calves were

investigated. Data were collected on all 58,885 spring-born calves entering a single feedlot in southwestern Alberta between September 1 and December 31 over a 4-year period (1985 to 1988). The vast majority of calves were purchased from auction marts throughout western Canada and transported to the feedlot by truck. A complete necropsy was performed on all dead cattle within 24 hours of death, and a gross diagnosis recorded. Cases were assigned a diagnosis of fatal fibrinous pneumonia on the basis of pathologic evidence of acute fulminating lobar bronchopneumonia with fibrinous exudate, and data from each year were analyzed separately. Crude mortality ranged from 2.44% to 4.78%, whereas the mortality caused specifically by fibrinous pneumonia varied more than tenfold (0.25% to 2.73%) between years. Proportionate mortality caused by fibrinous pneumonia ranged from 10% to 57%, and this large annual variation was interpreted as evidence that crude mortality should not be used as a measure of fibrinous pneumonia mortality in epidemiologic studies. Epidemic curves constructed for each of the 4 years showed that peak mortality occurred approximately 16 days after arrival at the feedlot and that at least 50% of fibrinous pneumonia mortalities occurred within 3 weeks of arrival. Epidemic curves using the time of first treatment for all cases that eventually died of fibrinous pneumonia revealed that peak fatal disease onset occurred within 8 days of arrival and that 75% of fibrinous pneumonia mortalities were already sick within 2 weeks of arrival. The consistent onset of fatal disease in calves within days of their arrival at the feedlot indicates that the disease process may have been well underway in affected calves before their installation in a home pen, and that preventive measures should be implemented at the time of arrival, or possibly even before. In one of the study's most important findings Ribble and colleagues[305] demonstrated that when the incidence of fatal shipping fever was high (greater than 2%), the disease clustered within truckload groups of calves and also, in 1 year, within pens. This was contrary to the conclusions of other studies and lends credence to anecdotal reports from feedlot owners that shipping fever mortality is not randomly distributed in calves throughout the feedlot, but may often be abnormally high in individual truckloads or pens, indicating a contagious nature to the disease.

Although *H. somni* can also cause fibrinous bronchopneumonia in feedlot cattle, epidemiologic curves evaluating the day of first treatment of calves ultimately dying of disease caused by *H. somni* are distinct from epidemic curves of cattle dying of fibrinous pneumonia caused by *M. haemolytica*. The median days after arrival for the onset of fatal disease caused by *H. somni* is 28, as opposed to 8 days after arrival for fatal fibrinous pneumonia.[345,346]

31.59.4.3

BRONCHOPNEUMONIA OF ADULT CATTLE

Although anecdotal reports indicate that adult beef or dairy cows can experience outbreaks of bronchopneumonia that can have high morbidity and an important impact on milk production (in dairy herds), very little is published in the veterinary research literature regarding the problem. Outbreaks of significant respiratory disease with notable mortality caused by BRSV infection have been described in individual herds of adult dairy cattle.[149,150] Respiratory disease and decreased milk production in adult dairy cows was associated with seroconversion to influenza virus and BRSV,[253] but the authors could not confirm that influenza was contributing to clinical disease in the affected cows. The lack of research on respiratory disease in adult cows is likely a result of the fact that other diseases that affect reproductive performance and milk yield are of greater economic significance in this class of cattle, but the few published descriptions of respiratory disease outbreaks confirm that the problem can on occasion be of major importance to individual herds. Little research has investigated the effects of infectious respiratory disease in adult cattle on productivity.

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31.59.4.4 BRONCHOPNEUMONIA OF SHEEP AND GOATS

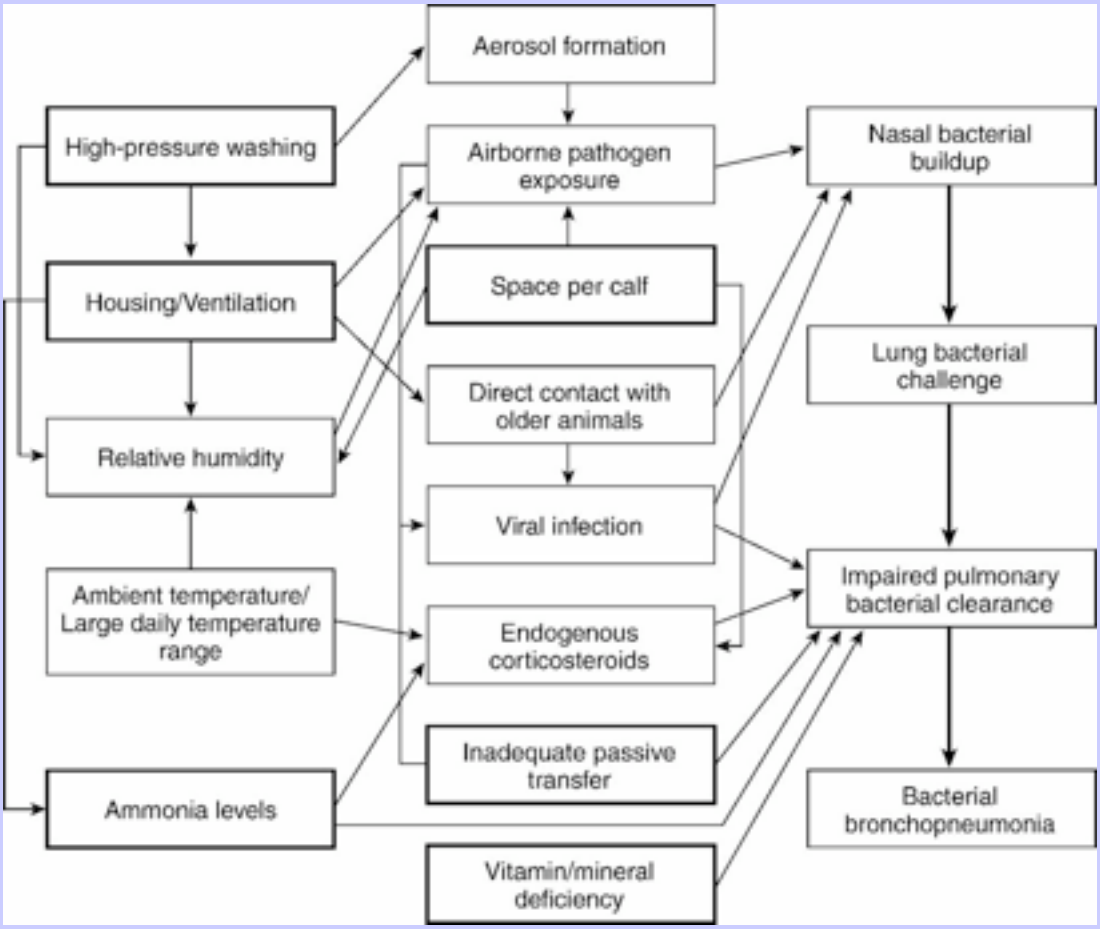
Little information has been published regarding the epidemiology of bronchopneumonia in sheep and goats. The 2001 National Animal Health Monitoring System (NAHMS) survey of producers indicated that 7% of death in adult sheep were due to respiratory disease, whereas 12% of lamb deaths were due to respiratory disease.[437] Feedlots reported that shipping fever pneumonia accounted for 13% of feedlot lamb deaths, and other respiratory disorders accounted for 29% of lamb deaths.[438]

31.59.5 Host and Environmental Risk Factors for Respiratory Disease

31.59.5.1 ENZOOTIC CALF PNEUMONIA

The documented host and environmental risk factors of dairy and veal calf bronchopneumonia involve inadequate passive transfer of immunoglobulins, nutritional deficiencies, and adverse environmental conditions (Fig. 31-64). Calves are generally affected at less than 2 months of age. Successful passive transfer is the foundation of protection against pneumonia at this age and older and is effective except in situations in which the other risk factors are so severe that even calves with high concentrations of passively acquired immunoglobulins are at high risk. Successful passive transfer requires good-quality colostrum and adequate volume (4 L in the first 12 hours for 45-kg calves). In addition, regular herd vaccination, especially in dry cows, should increase the levels of specific antibody in calves, provided passive transfer is accomplished. Vaccination of calves may produce a protective immune response in calves that prevents or limits the severity of ECP from certain infectious agents. Historically it has been recommended that vaccination be delayed until maternal immunity has waned, but recent research indicates that calves can be primed for a protective immune response by vaccination in the face of maternal antibodies in at least some cases (see further discussion on p. 640).

Fig. 31-64 Path model for risk factors for enzootic calf pneumonia. *Note:* Risk factors in bold-faced rectangles indicate those that may be altered by management.



Nutritional problems that predispose to calf pneumonia include deficiencies of energy, protein, vitamins, or the minerals necessary for the immune response. Deficiencies of copper, selenium, zinc, manganese, iron, and vitamins A and E are of special concern. Dairy managers sometimes create energy and protein deficiencies by feeding calves a low volume of milk during the first few weeks of life to minimize the incidence of neonatal diarrhea.

The calf's immediate environment affects the calf in a number of ways. Ambient temperature is an important factor affecting dairy calf health.[439] Cold weather is especially detrimental to young calves, which have little body insulation. Increased humidity or precipitation in the calf's environment worsens the calf's ability to maintain thermal neutrality. Warm weather can also be undesirable, because young calves are capable of greater perspiration per pound of body weight than adults, and warm weather may predispose young calves to dehydration.[439]

The bacterial content of air in cattle barns can be as high as 10^6 organisms per cubic meter.[440] Disease incidence can be affected by length of pathogen survival time as an aerosol and the concentration of the pathogen in the air space. Humidity is an important limiting factor affecting pathogen survival. The optimum zone for limiting survival time of bovine pathogens is 55% to 75% relative humidity. Adequate fresh airflow into the calf's environment is important in limiting humidity and reducing the concentration of noxious gases and pathogens. The flow of air should be from younger, more susceptible cattle to older, less susceptible cattle to limit moving pathogens from older cattle to younger cattle. Adequate fresh airflow and proper directional movement of air are important goals of ventilation.

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Calf housing with overcrowding of calves or excessive stocking densities results in increased transmission of pathogens, especially if there is mixing of age-groups. Overcrowding also puts additional stress on the building ventilation through buildup of noxious gases and pathogens. Cleaning of calf crates with high-pressure water sprayers is associated with new cases of pneumonia several days later. Bates and Anderson[441] have recommended standards for ventilation, including building location, fan capacity and location, intake location and design, temperature regulation, air space needed and airflow directions, and acceptable humidity levels. Individual calf hutches that are properly located provide the calf with adequate fresh air free of pathogens and noxious gases and overcome many of the problems found with calf barns. Calves moved out of hutches can then be put into small groups (seven or eight calves) separated from older cattle through use of super hutches. Like the calf hutch the super hutch also serves to limit pathogen transmission and buildup of noxious gases in this susceptible group of calves. Alternatively, calves can be moved out of hutches and placed in pens in pole sheds provided groups are small (7 to 10 calves), air quality is good, and proper segregation from older age-groups is maintained. Standards of housing for calves are shown in Table 31-11.

Sivula and colleagues[434] found that 80% of calf barns provided housing that failed to meet adequate standards of ventilation and housing[441] regardless of whether calves were housed individually or in groups. In addition, calf housing in which calves shared the same air space as adults never met the adequate standards of ventilation and housing.[434] A much higher percentage of calf housing that used calf hutches met these adequate standards of ventilation and housing, and virtually 100% would have been adequate housing if the hutches had been positioned correctly.[434] Calves raised in inadequate housing have significantly poorer growth rates than do calves raised in housing that is considered adequate,[434] which emphasizes the importance of adequate housing. The percentage of producers who use calf hutches continues to increase, as the benefits of their use are documented and published.

Table 31-11 Standards for Adequacy of Ventilation of CalfHousing[434,441]

Housing Type	Ventilation Standards
Calf hutch	One calf per hutch
	Minimum of 4 ft between hutches
	Hutches further than 50 ft from exhaust outlets of other buildings
	Hutches 10 ft from fenced enclosure with older cattle
Mechanically ventilated calf barn	200 ft^3 of air space per calf Barrier walls to separate age-groups of cattle housed in building
	Fan capacity to achieve four air changes per hour in winter, 15 air changes per hour in spring and fall, and 40 air changes per hour in summer
	Humidity levels between 50% and 80%
	Ammonia levels less than 10 ppm
	Intake velocity for fresh air intakes of 200 to 800 feet/sec
Naturally ventilated calf housing	Adjustable opening on sidewalls Open ridge for dual slope (2 in/10 ft of building width)
	Eve opening for monoslope buildings (2 in/10 ft of width)
	Barrier walls between age-groups (especially first postweaning age-group and older animals)
	Separate waterer for first postweaning age-group

Veal calves are at greatest risk because they are reared in rooms that are filled to high stocking density with calves from multiple dairies that put minimal effort into ensuring that the calves are fed adequate amounts of high-quality colostrum. Similar problems occur on “calf ranches,” where hundreds to thousands of very young dairy calves are raised to the point at which they are old enough to be returned to dairies or sent on to feedlots. A high proportion of calves that enter calf ranches have FPT. Also, the accumulation of a large number of calves with a variety of histories and from a variety of sources causes problems similar to those encountered with older animals in feedlots. The respiratory defenses of the calf lung include aerodynamic filtration, particle removal, adhesion resistance, secretory defenses, and cellular defenses. The physical respiratory defenses (filtration, removal, adhesion resistance) can be compromised by inhaled noxious gases, temperature extremes, dehydration, and viral infections causing impairment through damage to the mucosal lining of the upper respiratory tract, or by increased viscosity of respiratory secretions. Noxious gases, such as ammonia, methane, hydrogen sulfide, and carbon dioxide, which become increased from inadequate manure handling or poor ventilation, can also impair secretory defenses via damage to the mucosal lining and impair cellular defenses by direct effect on alveolar macrophages. Viral infection may also damage the mucosal lining and impair production of secretory defenses, such as lysozymes, lactoferrin, complement, or secretory immunoglobulin. Viral infections can also have a direct effect on cellular defenses, including alveolar macrophages, and for some viruses, the neutrophils. Stress caused by overcrowding, temperature extremes,

commingling, surgical procedures, or vaccination may impair cellular defenses and immunoglobulin production and enhance bacterial adherence.

Calves that have neonatal diarrhea are at greater risk of pneumonia.[435] Thus risk factors that are unique to neonatal diarrhea, such as poor sanitation in the calving area, must be added to those outlined in Fig. 31-64 as possible risk factors for dairy calf bronchopneumonia. Calves born in loose housing have a higher risk of illness than those born in individual maternity pens. Treatments at birth can affect subsequent calf health. All dairy calves should have the navel treated. Injections of vitamin A and iron at birth may increase the disease resistance of dairy calves, which can be deficient in these nutrients at birth.

Other risk factors associated with ECP include large herd size, weather extremes (hot and cold), birth to a heifer, and low antibody titers to certain respiratory pathogens.[430,435] Pneumonia of beef calves on the farm has the greatest incidence after weaning. The occasional outbreaks of pneumonia in suckling beef calves may be associated with adverse weather, parasitism, or nutritional deficiencies.

31.59.5.2 SHIPPING FEVER PNEUMONIA

Risk factors of feedlot calf bronchopneumonia are active in three areas: (1) at the farm of origin, (2) during transit, and (3) in the feedlot[305,442,443] (Fig. 31-65).

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Fig. 31-65 Path model for risk factors of feedlot cattle pneumonia. *Note:* Risk factors in *bold-faced rectangles* indicate those that may be altered by management.

Several on-farm management practices have a large impact on feedlot cattle pneumonia. Weaning, creep feeding, and performance of routine surgeries at least 3 weeks before shipment have been shown to reduce morbidity rate 20% to 25%.[443] Vaccination on the farm against respiratory pathogens would be expected to reduce the incidence of feedlot cattle pneumonia but has not always been beneficial. Other farm factors are deficiencies of nutrients necessary for normal immune responses. Pneumonia has a higher incidence in young calves, and severe outbreaks sometimes occur in early weaned calves that enter feedlots.

Risk factors that are active during transport from the farm to the feedlot include sale through auctions, feeding of low-energy diets before shipping, and prolonged time in market channels (sales barns, transport vehicles). Excessive dehydration or "shrink" from transport has been shown to account for significant morbidity and mortality in the feedlot. Movement through multiple auctions greatly increases the risk of pneumonia.

Feedlot risk factors that influence morbidity and mortality rates include processing procedures, numbers of calves and number of different origins of calves per pen, diet, on-arrival surgeries (e.g., dehorning), and environmental conditions. Calves that arrive in the feedlot with moderate levels of antibodies against the respiratory viruses have been shown to have a decreased incidence of pneumonia, indicating that natural exposure or vaccination at the ranch, rather than the feedlot, is protective. Mixing of calves from different origins and filling of feedlot pens with calves over a prolonged period increase mortality and morbidity rates because infectious agents spread more readily in large populations. Starting calves on diets containing 75% concentrate or greater or feeding corn silage as a major dietary component during the first month is associated with higher mortality and morbidity rates, probably because of an inhibition of alveolar macrophage function caused by acidosis. Nonprotein nitrogen, such as urea, fed to stocker calves at any time or to feedlot calves on arrival is associated with increased levels of pneumonia. The addition of antibiotics to the drinking water of newly arrived feedlot cattle has been shown to be detrimental to their health, possibly because of decreased water consumption.

As mentioned in the earlier discussion of respiratory defenses of dairy calves, endogenous corticosteroid release caused by physical stressors (overcrowding, mixing of calves, surgical procedures, starvation, dehydration), environmental stressors (weather extremes), and damage to respiratory defenses (vehicle exhaust, environmental dust, noxious fumes, acidosis, dehydration, and viral infections) may also weaken or overwhelm the respiratory defenses of feedlot calves.

31.59.5.3 BRONCHOPNEUMONIA OF ADULT CATTLE

Studies confirming risk factors for bronchopneumonia of adult cattle in modern North American production systems are lacking, but it is assumed that factors are similar to those described previously for calves and for cattle entering feedlots.

31.59.5.4 BRONCHOPNEUMONIA OF SHEEP AND GOATS

Many of the risk factors that have been found to predispose to bronchopneumonias of sheep and goats are similar to those affecting cattle.[220] Pneumonia is more common in younger animals, after shipping or storms, and under crowded conditions. In addition, cold stress is an important risk factor for pneumonia in young lambs and recently shorn adult sheep and goats. In contrast, heat stress may predispose to pneumonia in unshorn sheep that do not have access to shade. Pneumonia also is associated with semiconfinement or total confinement of sheep in poorly ventilated barns.

31.59.6 Prevention and Control of Ruminant Respiratory Disease

31.59.6.1 MANAGEMENT PRACTICES TO MINIMIZE ENZOOTIC CALF PNEUMONIA

Bronchopneumonia of dairy and veal calves is prevented by eliminating or altering as many predisposing risk factors as possible. Control is based on healthy, well-vaccinated dams giving birth in maternity facilities that limit pathogen exposure. Good colostral management is needed to ensure adequate passive transfer. The calves must have their navels disinfected and be moved to calf housing that limits pathogen exposure by overcrowding and direct contact, provides good-quality air, and protects the calf from environmental extremes.

Evaluation of the microclimate of housed calves is of critical importance in the control and prevention of pneumonia. Equipment useful for evaluating mechanically ventilated buildings includes a smoke generator to visualize airflow patterns, an anemometer to measure air velocity, a psychrometer to determine air temperature and relative humidity, and a gas detector kit to measure ammonia concentrations in the air. Agricultural engineers from animal science departments at regional universities can be often be contacted for guidance in the use of these tools. Naturally ventilated buildings should also be evaluated for adequate sidewall and ridge openings, adequate segregation of age-groups, and stocking densities. Calf hutches that are managed properly provide most, if not all, housing needs required to minimize calf pneumonia. Hutches should be evaluated for proper placement in relation to other hutches, other buildings, prevailing winds, exposure to sun, bedding and draining, and ventilation of the hutch.

After weaning, calves need to move to housing that allows small groups to be segregated from older age-groups. Sharing air space or having direct contact with older calves or adult cattle is an important risk factor for calf respiratory disease. Super hutches or pens in pole sheds separated by barrier walls can effectively provide this postweaning housing. Calves should be fed proper nutrition for protein, energy, minerals, and vitamins and should be vaccinated appropriately. Vaccination programs are often used in dairy calves beginning at 1 to 2 months of age in situations where housing or mixing of calves results in a high incidence of ECP. More information regarding the use of vaccines for preventing infectious respiratory disease is presented in the following sections.

31.59.6.2 MANAGEMENT PRACTICES TO MINIMIZE FEEDLOT PNEUMONIA

31.59.6.2.1 Preconditioning

Preconditioning of calves is an attempt to eliminate certain risk factors that influence the occurrence of feedlot cattle pneumonia. Preconditioned calves are weaned well in advance of shipment to feedlots. They are trained to eat some grain from feed bunks and drink water from tanks (this is especially important for calves raised on rangeland where feed bunks or water tank may not be seen). Calves are castrated and dehorned, treated for internal and external parasites, and vaccinated against respiratory pathogens, with one dose of vaccine administered before weaning and the second dose administered 2 to 4 weeks after weaning. The exact details of a preconditioning program can be tailored to the needs and characteristics of the individual herd of cattle. A variety of preconditioning protocols have been described, and most of the major companies that sell vaccines have recommended standardized preconditioning programs. Also, in many areas of the United States and Canada, state, provincial, or regional groups have become established that offer a standardized preconditioning program for local cattle producers. Typically some sort of validation

that calves have received preconditioning is available through these organizations. Some of these groups also help the participating producers market the preconditioned calves in large, relatively uniform groups, which helps the calves bring better prices. In some cases, producers can retain ownership of their cattle after they enter the feedlot, and they receive data regarding health and performance of their animals throughout the feeding period and at slaughter. Information about local preconditioning programs can usually be obtained from agricultural extension agents or from faculty who specialize in beef cattle management and health at colleges of animal science or veterinary medicine.

The value of preconditioning has been debated over the decades. A summary of eight studies comparing the health of preconditioned calves with that of control calves indicated that, on average, preconditioning reduced morbidity rate by 23% and mortality rate by 50% in the feedlot.[443] However, preconditioned cattle do not always escape disease once they enter feedlots, and they sometimes experience outbreaks of high morbidity and mortality not unlike those seen in high-risk calves that are not preconditioned. Moreover, even when preconditioned calves experience less disease, their performance in the feedlot is not always better than that of nonpreconditioned calves,[444] or they may not always perform well enough that a profit is returned that is greater than the cost of preconditioning.[445] An evaluation of data collected over 8 years by the Texas A&M Ranch to Rail program showed that preconditioned cattle returned on average $90 more per head than nonpreconditioned cattle. However, in some years the return was better for preconditioned cattle than in other years.[306] These data emphasize that preconditioning is likely to pay in the long run, but it may not always pay for individual groups of cattle in a single given year. Because of year-to-year uncertainty in the economic advantage of preconditioned cattle, producers who sell preconditioned calves may not always be able to sell calves at a price that provides a profit over the cost of preconditioning. Marketing preconditioned calves through state or provincial organizations that have gained the respect of cattle buyers and that allow the marketing of large numbers of uniform cattle may be the best way for the producer to realize a profit from preconditioned calves. Retaining ownership of calves sent to feedlots may also allow the producer to realize better profits, but this requires a relationship with a feedlot that will manage the calves in ways that will continue to optimize health once the calves enter the feedlot.

31.59.6.2.2

Backgrounding

Another practice similar to preconditioning is the practice of backgrounding. In backgrounding, weaned beef calves from a variety of sources (often purchased from multiple sale barns) are accumulated and processed in a manner similar to that carried out for high-risk calves at feedlot entry (Box 31-5). Calves are then sorted by size and type and sold to feedlots, usually within a few days of arriving at the backgrounding operations. A variation of the backgrounding operation is the stocker operation; in stocker operations calves are processed and then “stocked” onto pastures, often with supplemental concentrate feeding, to graze and grow for a few weeks to months before shipment to feedlots. The difference between preconditioning and backgrounding is that preconditioning occurs on the farm where the calf is born, or at least before the calf is mixed with other calves from different sources, with some aspects of treatment such as the first dose of vaccines ideally being administered before weaning. Calves that enter backgrounding or stocker operations often have uncertain health histories and have often been weaned immediately before purchase. Because of this, disease outbreaks of high morbidity and mortality are not uncommon on some backgrounding operations. The backgrounder or stocker operator is thus taking on some of the risk of high-risk calves and is theoretically providing the feedlot with animals more likely to grow well with minimal disease than if they entered the feedlot straight from the auction market.

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31.59.6.2.2.1

Box 31-5 Examples of Processing Protocols for High- and Low-Risk Cattle Entering Feedlots

31.59.6.2.2.1.1

PROCESSING PROTOCOL FOR HIGH-RISK, FALL-WEANED, AUCTION MARKET CALVES

1. Modified live IBR, BVD, BRSV, and PI3 vaccines
2. Eight-way clostridial bacterin
3. Ivermectin type "pour-on" antiparasitical
4. *Mannheimia haemolytica* ± *Pasteurella multocida* vaccine
5. *Haemophilus somnus* vaccine (if significant problem in past)
6. Implant
7. Ear tag identification
8. Bulls castrated (if needed)
9. Tip dehorning (if needed)
10. "Temp" all incoming cattle and sort by temperature (e.g., >105° F (40.5° C)—treat with tilmicosin; all others treat with long-acting oxytetracycline)

31.59.6.2.2.1.2

PROCESSING PROTOCOL FOR HEALTHY YEARLINGS PREVIOUSLY FED IN BACKGROUNDING OPERATIONS

1. Modified live IBR, BVD, BRSV, and PI3 vaccines
2. Eight-way clostridial vaccine
3. Ear tag identification
4. Implant
5. Ivermectin type "pour-on" if days on feed will allow for withholding times needed

BRSV, Bovine respiratory syncytial virus; *BVD*, bovine virus diarrhea; *IBR*, infectious bovine rhinotracheitis; *PI3*, bovine parainfluenza virus type 3.

31.59.6.2.3

Management at Feedlot Entry

It is not surprising that preconditioning does not always influence the occurrence of pneumonia in cattle after they enter the feedlot, because it has no effect on many risk factors active during transit and in the feedlot. Therefore optimal control of feedlot pneumonia should begin with preconditioning and continue

with avoidance of auction yards, minimization of transport time to the feedlot, limited mixing of calves from different sources, limited number of calves per pen, control of dust, and careful diet management in the feedlot. Correction of vitamin and/or mineral deficiencies if known or detected, using vitamin injections in entering calves, may be a very important aspect of prevention of feedlot pneumonias that are associated with immunodeficiencies of nutritional origin.

Processing procedures on arrival at the feedlot affect the incidence of pneumonia. General recommendations for handling incoming cattle can be made that are appropriate for any category of animals. In a receiving program, rest, rehydration, and ruminal restoration need to be addressed because cattle are physically and psychologically stressed by the marketing and transportation processes. It is useful for these cattle to be rested for 12 to 24 hours before processing to allow the immune system to overcome the effects of stress. Prolonged holding before processing is associated with increased illness, and holding times over 48 hours should be avoided. Holding pens should be clean and dry or have dry bedding (if pens are wet from excessive precipitation), because this allows all cattle to lie down and rest. Shelter from wind, sun, rain, and dust should also be present in the receiving pen.

Holding pens should have 150 to 200 square feet of pen space per animal and 12 to 16 inches of bunk space per animal and should be located close to the processing facility. Excess mixing of cattle in the receiving pens should also be avoided.

It is important that incoming cattle have access to clean, fresh water. Raised spigots have been suggested as a way to teach incoming cattle to drink out of automatic watering devices because cattle will be attracted to the sound of splashing water. Incoming cattle should also be offered good-quality, long grass hay on arrival. This is the most similar to what cattle are used to on range. Hay is the best foodstuff for restoring or refilling the rumen. Hay can be put in the feed bunks as well as in feeders in the pen as a way of teaching cattle to eat out of bunks. Hay feeders may also be put along the pen perimeter to decrease walking the fence line and encourage eating. The starter ration is an important source of energy and should be highly palatable. The proportion of the starter ration dry matter that is forage is not usually less than 50% to prevent problems of acidosis. Starter rations often contain a coccidiostat, because coccidiosis can occur in calves after commingling.

Processing protocols may be tailored to the category of the incoming cattle. Pharmaceutical processing options include vaccination (respiratory and nonrespiratory), vitamin injections, implanting, deworming for internal parasites and acaricides for external parasites (may be the same product for both), long-acting antibiotic therapy, drugs for aborting pregnant heifers, and probiotic administration. Management procedures for processing include ear tagging, branding, tail trimming, castration, tip dehorning, and temperature sorting. Some management procedures such as castration and dehorning could be left for a later time—for example, at reimplanting at 70 to 90 days on feed (if cattle are expected to be on feed for more than 150 days). “Temping” on arrival can be very useful, because even cattle that look bright can have very high temperatures and thus can be identified as “sick” by this procedure. Examples of processing protocols for high- and low-risk cattle are shown in Box 31-5.

31.59.6.2.4

Metaphylactic Antimicrobial Therapy

The term *metaphylaxis* refers to the administration of an antimicrobial to a group of animals that may be in the early stages of bacterial pneumonia or that are at significant risk of developing bacterial pneumonia. Thus the antimicrobial drug administered may have either therapeutic or prophylactic effect, depending on the state of each animal treated. Metaphylactic administration of antibiotics to feedlot cattle on arrival in

order to prevent bacterial bronchopneumonia in feedlot cattle has been shown in many studies to decrease morbidity and mortality in groups of high risk cattle.[446,447] It is useful to consider the theoretic mechanisms by which metaphylactic administration of antimicrobials may limit disease. Soon after cattle are shipped, *M. haemolytica* A1 can proliferate in large numbers in the upper respiratory tract. This period of replication is a crucial phase because large numbers of bacteria can be inhaled into the lung, allowing colonization, proliferation, and production of virulence factors. There appears to be a short time after arrival in the feedlot when cattle that will subsequently develop bacterial bronchopneumonia have large numbers of *M. haemolytica* A1 present in their upper respiratory tract. Antimicrobial therapy timed to coincide with this pathologic event and designed to provide therapeutic levels in respiratory tissues is aimed at reducing the number of *M. haemolytica* A1 present in the upper respiratory tract of calves, which should also limit colonization of the lung and prevent horizontal transmission of *M. haemolytica* from calf to calf. Long-acting antibiotics have been reported to significantly alter the number of calves from which *M. haemolytica* can be cultured.[270,448] An additional rationale for metaphylaxis on arrival is based on the epidemic curve of fatal disease onset for bacterial bronchopneumonia, which shows that feedlot calves dying from fatal fibrinous pneumonia are already sick on arrival or become ill within days of arrival. Although metaphylaxis through feed and water was used in the past, it is currently recommended that metaphylaxis be administered by use of injectable antimicrobial agents. The ability of these drugs to reach therapeutic levels quickly in all animals gives them a clear advantage given the previously discussed rationale for bacterial bronchopneumonia metaphylaxis.

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A number of trials have been published that examine various antimicrobial agents and their effectiveness for bacterial bronchopneumonia metaphylaxis. Most of these studies have examined both health and production values, and a variety of products have been shown to be efficacious in decreasing respiratory morbidity and mortality and sometimes in improving production parameters.[449–451] Tilmicosin or long acting oxytetracycline, both of which provide therapeutic levels of drug for 3 days, are most commonly used for metaphylaxis in feedlot cattle.

Similar use of long-acting antimicrobials in dairy calves may also be of value. The disease process does not have the same narrow windows of therapeutic intervention that occur in calves entering the feedlot. Dairy calves properly managed in maternity facilities and raised in hutches rarely experience any respiratory disease until they are moved to postweaning housing. Injectable mass medication is often used at the time calves are moved and then again at some time later (7 to 10 days after entering the postweaning housing) as a means of controlling postweaning ECP.

31.59.6.3

MANAGEMENT PRACTICES FOR PREVENTING SHEEP AND GOAT PNEUMONIA

Prevention of pneumonia in sheep and goats is also based on altering the risk factors that predispose to pneumonia. Minimizing cold and heat stress, providing properly ventilated housing, avoiding overcrowding, and avoiding long transports in adverse weather aid in prevention. Mass medication can be used to control outbreaks of pneumonia in flocks. Injectable long-acting oxytetracycline is often used subcutaneously at 10 mg/kg. Tilmicosin can also be used for mass medication therapy for sheep, but tilmicosin should never be administered to goats, as it can result in fatal reactions. Feedlot lambs are sometimes administered metaphylactic therapy (long-acting oxytetracycline) on arrival.

31.59.6.3.1

Vaccination To Prevent Respiratory Disease

31.59.6.3.1.1

Factors That Affect Success of Vaccination

Many factors can affect the success of vaccination. For a vaccine to successfully prevent disease, the vaccine must induce a protective immune response against a pathogen to which the host will be exposed. Apparent vaccine failure is often blamed on the product or the manufacturer, but in many cases other factors may have led to vaccine failure. Possible causes of apparent vaccine failure that must be also be considered when vaccinated animals contract disease are related to the administration of the vaccine, the ability of the host to respond to vaccination, and to the nature of pathogen exposure. Examples are listed in Box 31-6. Although the points listed may be obvious, it is important to carefully consider and rule out these problems when a vaccine has failed to prevent respiratory disease before making a quick switch to another brand or type of vaccine.

In addition to the factors just discussed, vaccine characteristics can also affect the success of a vaccination program. Once the decision has been made regarding choice of pathogens to be included in the vaccine, the use of a live versus killed vaccine must be considered. Much research has evaluated the immune response of animals to modified live versus killed (inactivated) vaccines, and the subject has been the focus of much discussion. To summarize:

31.59.6.3.1.1.1

Box 31-6 Reasons for Apparent Vaccine Failure

31.59.6.3.1.1.1.1

FACTORS RELATED TO ADMINISTRATION OF THE VACCINE

Improper storage of live vaccines

Residual chemical disinfectant in reusable syringes

Using live vaccine reconstituted days or weeks previously

Administration into wrong anatomic location

Administration of antibiotics with live bacterial vaccines

Incorrect timing of vaccine administration

Animals already incubating disease

Failure to allow time for immune response to occur

Administering booster too early, too late, or not at all

31.59.6.3.1.1.1.2

FACTORS RELATED TO ABILITY OF HOST TO RESPOND TO VACCINATION

Age (very young or very old animals)

High levels of maternal antibody

Immunocompromise resulting from concurrent disease or stress

Genetic factors

Poor air quality or other environmental insults

31.59.6.3.1.1.1.3

FACTORS RELATED TO PATHOGEN EXPOSURE

Disease caused by pathogens not included in vaccines

Antigenic variation (strain variation) of naturally occurring pathogens

Overwhelming pathogen exposure

- Modified live virus (MLV) vaccines in general stimulate cell-mediated immunity, important for an effective immune response to most viral pathogens, as well as effective humoral immunity.
- Live vaccines can sometimes elicit protective immunity with only a single dose of vaccine.
- Live vaccines contain a smaller dose of organisms, because the organisms in the vaccine are expected to replicate at least minimally.
- Live vaccines generally do not require adjuvants, which are often a major cause of adverse reactions after vaccination (however, some MLV vaccines do contain adjuvants to improve the immune response).
- Live vaccines are generally cheaper.
- Disadvantages of live vaccines include the possibility of causing abortion in pregnant animals, transmission to nonvaccinated animals, exacerbation of morbidity in sick or immunocompromised animals, and reversion to a more virulent form with disease possibly occurring.
- Another disadvantage of live vaccines is that they can be inactivated in a short time by exposure to heat or light.

- In contrast, inactivated vaccines do not generally stimulate effective cell-mediated immunity, although certain adjuvants can overcome this.
- Inactivated vaccines often stimulate high levels of antibody.
- Inactivated viral vaccines require at least two doses at a 14–28 day interval to induce an effective anamnestic response to subsequent challenge.
- Adjuvants in killed vaccines can cause adverse reactions.
- Inactivated vaccines are safe in pregnant or immunocompromised animals, and storage requirements are not as rigorous for inactivated vaccines as for MLV vaccines.

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Much of the above has been determined using viral vaccines; the situation with bacterial vaccines is less well characterized. Modified live bacterial vaccines may stimulate both humoral and cell-mediated arms of the immune response better than inactivated products (bacterins). However, for extracellular bacterial pathogens such as *M. haemolytica*, humoral immunity is the most critical component of an effective immune response. Past evidence has suggested that live *M. haemolytica* vaccines are superior to inactivated products; however, recent comparisons have shown some nonliving products to provide superior resistance to experimental challenge. Live bacterial vaccines can be inactivated if animals are given antibiotics at or near vaccination.

It is important to note that all vaccines for a given disease are not necessarily equal. If a vaccine is inactivated, the means by which it is inactivated can influence antigenicity. Moreover, a wide variety of adjuvants exist, and the adjuvant included in a vaccine can greatly influence the type and duration of immune response elicited. Adjuvants are included in inactivated and some modified live products. The choice of adjuvant to include in a vaccine is the subject of much creative thinking and research effort by manufacturers; this is emphasized by the fact that it is often very difficult to obtain detailed information about the adjuvant contained in a vaccine.

31.59.6.3.1.2

Impact of Maternal Antibody on the Response to Vaccination

For many decades veterinarians have been taught that young animals cannot be effectively vaccinated when they have moderate levels of maternal antibodies obtained through passive transfer after birth. This was based on numerous research studies that showed that vaccination of young animals with maternal antibodies did not lead to the expected increase in serum antibodies to the agent in the vaccine. However, an important finding is that some vaccines appear to prime calves for an improved response to subsequent challenge, even when vaccination occurs in the presence of maternal antibodies. In such cases vaccination does not induce an increase in serum antibody titer within 2 weeks of vaccination, but when calves are vaccinated or challenged at a later date, they respond with what appears to be an anamnestic response as measured by increased serum antibodies, or protection against disease resulting from experimental or natural challenge, as compared with unvaccinated calves.[351,352,452,453] In general, a response was induced most reliably when modified live vaccines were administered and when the calves received at least two doses of vaccine at an appropriate (2- to 4-week) interval. Similarly, calves exposed to live pathogens in the face of maternal antibody can develop a protective immune response, even though they do not seroconvert after exposure.[454,455] It has been shown that a cell-mediated immune response can be measured even when there is no evidence of humoral response in calves infected in the

face of maternal antibodies.[455] Although multiple studies show that calves can be primed for an anamnestic immune response in the face of maternal antibodies, if very high titers of maternal antibody are present, priming by the vaccine can be blocked, as traditionally understood.[453]

This information suggests that at least in some cases a protective immune response can be initiated in calves when the first dose of vaccine is given in the face of maternal antibodies; a cell-mediated response may occur even if calves do not have an increase in serum antibody titer after vaccination. This is particularly useful in the context of pneumonia in nursing dairy or beef calves, as it supports the concept that vaccination can improve the immune response to challenge even if calves have some level of maternal antibodies at the time of vaccination. More research is needed to confirm which vaccines have this effect and to determine how this information should be used to guide vaccination recommendations for calves. It is also not known if this information can be extrapolated to sheep and goats.

31.59.6.3.1.3

Efficacy of Vaccines for Preventing Ruminant Respiratory Disease

Information regarding the use of vaccines for individual agents that cause ruminant respiratory disease was presented earlier in the section describing the individual infectious agents. There has been considerable debate over the years regarding whether vaccines have any impact on ruminant respiratory disease.[456] The literature on the subject is extensive, and interpretation of the data is complicated by the fact that there is much variation among research studies in the type and number of animals studied, the nature of animal management, and the outcomes measured as evidence of efficacy. There are three major types of research studies by which vaccine efficacy can be measured: studies that measure production of antibodies or in vitro cell-mediated immune responses in vaccinated animals; studies that measure the resistance of vaccinated animals to experimental challenge with viral or bacterial pathogens; and studies that measure the impact of vaccination on health and productivity of animals in a conventional field setting (field trials). Of the three methods, field trials are the most meaningful, but they are also the most expensive and difficult to undertake. When they are undertaken, it is often in small numbers of animals under management practices that may not be representative of practices in other regions. Moreover, they rely on the natural occurrence of the disease in question in the animals under study. A well-designed field trial can be very expensive and time-consuming, and the results can be useless if no animals in the study contract the disease naturally.

In spite of these limitations the results of some field trials testing the efficacy of respiratory disease vaccines have been published. For some important pathogens (e.g., BVDV), there are still no large-scale field trials published that show evidence of efficacy in preventing respiratory disease. One trial showed an economic advantage to administering a modified live vaccine containing BHV-1, BVDV, PI3, and BRSV over the use of a modified live vaccine containing only BHV-1 in feedlot cattle,[457] but it was not possible to determine which component of the multivalent vaccine was responsible for efficacy. Multiple field trials have been published that tested currently available vaccines against *M. haemolytica*[311–314] and BRSV[193–196]; these are discussed further in the earlier sections on these specific pathogens. In general, some of these studies found that vaccination could prevent disease and sometimes improve productivity, and some of these studies could not find a beneficial effect of vaccination. It is important to remember that in nearly all of these field trials, the effect of vaccination to decrease *all* respiratory disease was measured. That is, in most cases, no effort was made to determine whether disease specifically caused by the agent included in the vaccine was affected by vaccination. Therefore the apparent lack of efficacy of

vaccines in some studies may have been because animals developed disease caused by other respiratory pathogens.

Occasionally, in addition to evaluating the impact of vaccination on morbidity, mortality, and measures of productivity, investigators calculate the economic advantage or disadvantage of vaccination. When such calculations are made, it is important that the reader assess the assumptions made and determine whether they are appropriate. It has been noted that when the economic advantage of using a given vaccine is calculated, various scenarios should be considered that may prove the vaccine to be economically advantageous in some situations and disadvantageous in others.[458]

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The mixed results of clinical trials published to date indicate that vaccines decrease respiratory disease, improve animal productivity, and save money for the producer in some cases, and in some cases they do not. This should not be a surprise when the multitude of factors that can converge to cause an outbreak of respiratory disease is considered. Vaccination should be seen as one component of a multifactorial approach to minimize animal disease; it should not be seen as a guarantee against all disease, all the time. Thus, the value of vaccination will depend on the risk of disease in the population in question, and the risk of disease will depend on the likelihood of pathogen exposure and the likelihood that other host and management factors can be modified to maximize the ability of the host to respond to vaccination and resist disease.

No single, simple recommendation for vaccination of ruminants for the control of respiratory disease can be made. The veterinarian must individualize each vaccination program to the situation at hand. Many factors need to be considered in formulating recommendations for vaccination, including type of production unit, age of animals, system of management, housing facilities, amount of stress imposed on animals, open or closed herd, type of ration, and level of sanitation. In addition, some infectious agents such as BHV-1, BVDV, and *H. somni* can cause other disease problems not associated with the respiratory tract. Thus the complete spectrum of disease caused by these agents must be considered in formulation of a vaccination program. Examples of respiratory vaccination protocols that could be used in a cow-calf operation and in a dairy are presented in Boxes 31-7 and 31-8.

31.59.6.3.1.4

Evaluating Reports of Vaccine Efficacy

Vaccines approved for sale in the United States must be proven by the manufacturer to be safe, potent, stable, and efficacious. Duration of immunity is an additional parameter that manufacturers are beginning to be required to address. Efficacy is usually determined by experimental challenge, using defined methods or methods approved on a case-by-case basis. For many bovine respiratory pathogens (e.g., BHV-1, *M. haemolytica*), experimental challenge protocols have been developed that can induce disease of reasonable severity. To be approved for sale, vaccines need to prevent to a significant degree clinical signs associated with such experimental challenge. However, whereas protection against experimental challenge is a useful indication of the possible efficacy of a vaccine under field conditions, few experimental challenge protocols closely model the field situation in terms of simultaneous occurrence of other stresses and concurrent infection with other pathogens. Thus, it is ideal to evaluate vaccine efficacy through evaluation of an appropriately designed field trial. The design of field trials has generally improved greatly in recent years, but in the case of many vaccines, no high-quality published field trials evaluating the efficacy of vaccination for prevention of BRD exist.

31.59.6.3.1.4.1

Box 31-7 One Example of a Respiratory Vaccination Protocol for Use in a Cow-Calf Herd

31.59.6.3.1.4.1.1

REPLACEMENT HEIFERS

Modified live BHV-1/PI3/BRSV/BVD with boost 2–4 weeks later, prior to breeding

31.59.6.3.1.4.1.2

COWS

Modified live BHV-1/PI3/BRSV/BVD prior to breeding

Boost with killed **or approved modified live*** BHV-1/PI3/BRSV/BVD at pregnancy check

Consider *M. haemolytica/P. multocida* vaccine at pregnancy check with boost one month prior to calving in herds with history of problems with pneumonia in nursing calves

31.59.6.3.1.4.1.3

CALVES

In herds with significant pneumonia in nursing calves, consider killed or **approved modified live***(preferable) BHV-1/PI3/BRSV/BVD and *M. haemolytica/P. multocida* vaccine at 1–4 months of age with boost 2–4 weeks later, timed so that boost occurs 2–4 weeks prior to expected onset of calf pneumonia.

31.59.6.3.1.4.1.3.1

To Minimize Pneumonia in Calves Postweaning;

Killed or **approved modified-live***(preferable) BHV-1/PI3/BRSV/BVD one month prior to weaning with boost at weaning

Consider *M. haemolytica/P. multocida* vaccine preweaning with boost at weaning in herds with a history of post weaning pneumonia, or if required for participants in defined preconditioning programs

* Certain modified live BHV-1/PI3/BRSV/BVD vaccines are approved for use in pregnant cattle and in calves nursing pregnant cattle when administered in accordance with label directions.

31.59.6.3.1.4.2

Box 31-8 One Example of a Respiratory Vaccination Protocol for Use in a Dairy

31.59.6.3.1.4.2.1

REPLACEMENT HEIFERS

Modified live BHV-1/PI3/BRSV/BVD with boost 2–4 weeks later, prior to breeding

31.59.6.3.1.4.2.2

COWS

Modified live BHV-1/PI3/BRSV/BVD prior to breeding

Consider boost with killed **or approved modified live*** BHV-1/PI3/BRSV/BVD at dry off

Consider *M. haemolytica/P. multocida* vaccine at 2 months prior to calving, with boost one month later, in herds with history of problems with pneumonia in nursing calves

31.59.6.3.1.4.2.3

CALVES

In herds with significant calf pneumonia prior to weaning, consider modified live† BHV-1/PI3/BRSV/BVD and *M. haemolytica/P. multocida* vaccine at 1–4 months of age with boost 2–4 weeks later, timed so that boost occurs 2–4 weeks prior to expected onset of calf pneumonia.

31.59.6.3.1.4.2.3.1

To Minimize Pneumonia In Calves Postweaning

Modified live BHV-1/PI3/BRSV/BVD one month prior to weaning with boost at weaning

Consider *M. haemolytica/P. multocida* vaccine one month prior to weaning with boost at weaning in herds with a history of post weaning pneumonia, or if required for participants in defined preconditioning programs

* Certain modified live BHV-1/PI3/BRSV/BVD vaccines are approved for use in pregnant cattle **when administered in accordance with label directions**.

† Modified live BHV-1 and BVD vaccines can induce disease in very young (<1 month of age) or debilitated calves. In such calves, intranasal MLV BHV-1 vaccines or inactivated vaccines may be safer.

Veterinarians can arm themselves with useful information by evaluating published studies of vaccine efficacy in a critical manner. In some studies animals are vaccinated but never exposed to the pathogen. Serum and/or mucosal antibody levels may be measured, and markers of cell-mediated activity, such as

lymphocyte blastogenesis, cytokine production, or cytotoxic T cell activity, may be assayed. Such studies can indicate the antigenicity of a vaccine, but one must consider whether the parameters measured are known to correlate strongly with protection against disease. More information can be gained when measurements of immune function are evaluated in light of natural or experimental challenge. In experimental challenge studies, relatively small groups of animals are vaccinated and later challenged with the pathogen contained in the vaccine. Although experimental challenge studies are rather artificial compared with the situation animals experience in the field, a high-quality experimental study has certain characteristics. Some questions to ask include the following: Was a nonvaccinated control group, identical to the vaccine group in all ways except vaccination status, included? Were control animals tested at the same time as vaccinated animals? If factors that could affect vaccination were present (e.g., maternal antibody), were affected animals divided equally between control and vaccine groups? Did experimental challenge result in disease in the control group? If not, it is impossible to say if vaccination had an effect on challenge. Were investigators who evaluated clinical or pathologic signs of disease blinded to the treatment status of the animals? This removes an important source of bias that otherwise can make data, particularly subjective data such as "depression" or "dyspnea," suspect. Were statistical tests used to compare results of vaccine and control groups, and was the *P* value given to indicate likelihood that differences were due to chance alone? Other questions that can help determine the relevance of the experimental study to the field situation include the following: Was disease resulting from challenge clinically and/or pathologically similar to that seen in field cases? Was the vaccination regimen similar to that used in the field? How soon after vaccination were animals challenged? Did the time between vaccination and exposure mimic the field situation?

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Field trials are characterized by allocation of animals in a natural "field" situation to either vaccine or control groups. Animals are treated accordingly and then followed for variable periods of time to determine whether disease occurs in vaccinated animals and, if so, whether vaccinated animals have disease less often, have disease that is less severe, or have improved production characteristics (e.g., average daily gain) after vaccination. When evaluating a field trial, consider the following questions to determine the value of the study: Were animals randomly allocated to control or treatment groups? This is critical; if there is no mention of randomization, it is difficult to gain useful information from the study because of the many types of bias that can affect the outcome. Were concurrent controls used, as opposed to historical controls? Historical controls are of much less value in determining vaccine efficacy, as many factors can affect disease outcome in a group of animals from year to year. How many animals were included in the study, and for how long did the study run? In general, trials with larger numbers of animals are more likely to reveal differences between vaccine and control groups. Were evaluators of disease blinded to the treatment groups to remove their bias in interpreting outcomes? Did disease occur in the control animals? One weakness of field trials is that natural disease must occur in the animals under study to determine the effect of vaccination on disease; the investigators have no control over this aspect of the study. If disease did not occur in at least the control animals, the vaccine cannot be evaluated for protection against the disease. Also, ask what outcomes were measured as evidence of protection against disease. In most cases of feedlot trials, fibrinous pneumonia morbidity and mortality are measured. If this was the case, identify how cases were identified, and determine if the definition is accurate. In many trials, total morbidity and mortality is also measured as an outcome. This may be considered a less reasonable outcome; for example, it may not be reasonable to expect BHV-1 vaccination to decrease deaths caused by ruminal acidosis. Production characteristics, such as rate of gain or feed efficiency, are also often evaluated, and net cost of vaccination, including estimated losses due to disease or loss of production, may be calculated. In these cases, evaluate how costs were estimated, and determine if estimates appear to be accurate and reasonable. Finally, veterinarians may want to consider

whether the field trial was conducted under conditions similar to that seen in their practice; if so, the results may be more relevant to the needs of their clients (adapted in part from Ribble).[459]

31.60 THE INTERSTITIAL PNEUMONIAS

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Understanding of the interstitial pneumonias of ruminants has undergone considerable evolution in the past 30 years. Unfortunately, confusion still exists, particularly with regard to terminology. Terms such as *acute bovine pulmonary emphysema, atypical interstitial pneumonia* or AIP, *fog fever, pulmonary adenomatosis, farmer's lung*, and *ARDS* have been used interchangeably for all of the conditions that follow. This text uses a classification presented by Breeze,[460] which places the interstitial pneumonias into four groups: (1) ARDS, (2) hypersensitivity diseases, (3) chronic conditions that may be sequelae of ARDS or hypersensitivity diseases, and (4) parasitic diseases. BRSV infection can also cause AIP; this disease was discussed in relation to the respiratory disease complex of cattle, sheep, and goats earlier in this chapter.

31.61 ACUTE RESPIRATORY DISTRESS SYNDROMES

ARDS is any respiratory condition characterized clinically by a sudden onset of (usually severe) dyspnea (Fig. 31-66) with gross and histopathologic findings consistent with AIP. The characteristic gross findings of AIP are lungs that fail to collapse when the thorax is opened (Fig. 31-67) and that are heavy and have a firm, rubbery texture on palpation. Interlobular or bullous emphysema is usually present (see Fig. 31-54), and sometimes the cut surface of the lung has a shiny or wet appearance because of edema. In some cases affected lobules, which are dark red to purple, or sometimes grayish, are interspersed with normal-looking lobules, giving the lung a “patchwork” appearance. Although the gross findings are suggestive and often characteristic, other lung diseases can cause similar changes, so a diagnosis of AIP can be confirmed only by histopathologic evaluation. The histopathologic changes that confirm a diagnosis of AIP include alveolar hyaline membrane formation and fibrin deposition, alveolar and interstitial edema, and type 2 pneumocyte proliferation. Hemorrhage, emphysema, and interstitial inflammatory cell infiltrate can also be seen.

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Fig. 31-66 Heifer exhibiting respiratory distress typical of ARDS. Note extended head, frothing at mouth, and wide-set front legs. Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.

Fig. 31-67 Postmortem photograph of lung from heifer with ARDS caused by feedlot acute interstitial pneumonia (AIP). Note expanded dorsocaudal lung, and dark, collapsed lobules interspersed with pale, hyperinflated lobules. Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.

The term *atypical interstitial pneumonia* has often been applied to describe the changes characteristic of AIP, but it has been pointed out that the clinical and pathologic changes in affected cattle are not "atypical" but are rather "typical" of ALI.[460,461] Use of the term "acute interstitial pneumonia" to describe the characteristic pathologic changes, and the term *acute respiratory distress syndrome* to describe the clinical picture in an animal with AIP of as-yet undetermined cause, is both accurate and all-encompassing. A diagnosis of AIP should be understood as a pathologic diagnosis rather than an etiologic diagnosis, because a variety of insults can lead to the same lung lesion of AIP.[460,461]

31.61.1 Acute Bovine Pulmonary Edema and Emphysema

31.61.1.1 Definition and Etiology

Acute bovine pulmonary edema and emphysema (ABPEE), classically known as *fog fever*, is an ARDS of adult (over 2 years old) cattle that are changed from dry, sparse forages to lush green pastures. It is caused by the conversion of L-tryptophan ingested in the lush forages to a pneumotoxic compound (3-methylindole [3-MI]), which leads to the development of pulmonary edema, alveolar epithelial hyperplasia, hyaline membranes, and emphysema.[460]

31.61.1.2 Clinical Signs

Adult brood cows are most commonly affected because this is the type of animal most likely to be subjected to the abrupt pasture change required to produce the condition. No breed is resistant.[460] The type of pasture appears to be unimportant, as long as it is lush; ABPEE has been reported on a wide variety of grasses, alfalfa, rape, kale, and turnip tops.[462] Signs usually occur within 2 weeks of the pasture change.[460] In severe cases there is an acute onset of very severe dyspnea with a loud expiratory grunt, frothing at the mouth, mouth breathing, and tachypnea (35 to 75 breaths/min).[462] The animals are obviously distressed (as opposed to exhibiting the typical depression that occurs with infectious diseases) and stand with the head and neck extended and elevated and the nostrils dilated.[463] Temperature and heart rate may be elevated secondary to the severe dyspnea and hypoxia.[463] On auscultation the breath sounds are usually surprisingly soft in view of the gross dyspnea and tachypnea; a few crackles may be heard.[462] Even mild exercise increases the dyspnea and may precipitate collapse and death. As many as 30% of severely affected patients may die, usually within 2 days.[462] Those that survive typically show a dramatic improvement after 3 days.[462] Recovering patients and those that are less severely affected exhibit tachypnea (50 to 80 breaths/min), hyperpnea, harsh breath sounds, and crackles and wheezes, particularly in the caudal lung fields.[462] SC emphysema may develop. The demeanor of the entire group tends to become more tranquil.[462] In cattle that have repeated episodes of nonfatal ABPEE, a chronic respiratory condition characterized by diffuse pulmonary fibrosis and alveolitis may develop.[464] For purposes of differential diagnosis, it is important to note that coughing is not prominent in the individual or the group.[462] The main differential diagnoses are those diseases that cause ARDS in pastured adult cattle, usually in outbreak form. The association of ABPEE with typical management conditions (e.g., changes of pasture) and the absence of coughing, signs of sepsis, and adventitious lung sounds in early cases are also very important features. Primary considerations should include the other plant toxicities (moldy sweet potatoes, perilla mint, and possibly others) that can be differentiated only by identifying the source. An outbreak of BRSV infection or parasitic bronchitis could cause similar clinical signs and pathology, but these are characterized by more coughing, signs of depression, and more prominent adventitious sounds; fever is common in animals with acute BRSV infection.

31.61.1.3 Pathophysiology

L-Tryptophan in lush forages is converted by ruminal microorganisms to indole acetic acid and eventually to 3-MI, which is rapidly absorbed from the rumen into the blood. Metabolism of 3-MI by the cytochrome P-450 mixed function oxidase system in the nonciliated bronchiolar epithelial (Clara) cells and type 1 pneumocytes

results in one or more highly reactive intermediates that bind to intracellular proteins or other macromolecules. It is thought that these intermediates produce the damage to these cells. These intermediates are detoxified by conjugation with glutathione.[465] Cellular damage results in degeneration, necrosis, exfoliation of type 1 pneumocytes and Clara cells, and edema. These lesions in turn cause hyaline membrane formation, proliferation of type 2 pneumocytes, and, to a lesser extent, proliferation of Clara cells.[465] The proliferation of type 2 cells is also known as *adenomatosis*. Emphysema is probably secondary to the severe dyspnea.[465]

31.61.1.4 Epidemiology

As indicated, ABPEE is consistently related to management practices in which hungry adult cattle are suddenly moved from sparse, dry grazing to lush green pastures. The British name "fog fever" arose from the association of the disease with "fog" pastures, which are the lush green regrowth pastures after hay or silage has been cut. The problem usually occurs in the fall. In the typical pattern in the western United States, cattle are moved from dry summer range onto irrigated or fertilized aftermath pastures.[460] The disease usually appears as a herd outbreak, but individuals may be affected to widely varying degrees; morbidity rate commonly approaches 50%, with a case fatality rate as high as 30%.[466,467] Nursing calves are apparently not at risk, and yearlings are less susceptible than adults.[468]

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31.61.1.5 Necropsy Findings

In animals that die of ABPEE, ecchymotic to petechial hemorrhages occur in the larynx, trachea, and bronchi, and frothy fluid is present in the airways. The gross and histopathologic lung lesions are consistent with AIP. Congestion, edema, and hyaline membranes cause deep red-to-purple coloration of the cranial lung lobes and a smooth, glistening appearance to the cut surface. Interstitial emphysema with large bullae and gelatinous yellow interlobular edema is common. Histologically, eosinophilic hyaline membranes line alveoli and alveolar ducts, and there edema and proliferation of type 2 alveolar epithelial cells are present.[460] In animals that are killed after 3 to 4 days, emphysema and edema are less obvious, and the lungs tend to be light brown, firm, heavy, and rubbery. There is severe diffuse alveolar epithelial hyperplasia ("adenomatosis"), and large mononuclear cells, multinucleated giant cells, and hyaline membranes are present in alveolar spaces. Edema, eosinophils, and inflammatory cells occupy the septa.[460]

31.61.1.6 Diagnosis

Diagnosis is made based on the history of recent exposure to lush green forage and typical clinical signs and pathology in fatal cases. Thoracic radiographs could be used to identify changes consistent with interstitial pneumonia in valuable individual animals. The results of TTA or BAL cytology have not been reported for cattle with ABPEE, but a nonseptic mixed inflammatory cell response would be expected. There are no unique hematologic or biochemical changes.[463] A stress leukogram is often seen.

31.61.1.7 Treatment and Prevention

The stress of handling cattle can precipitate further losses. Some authors maintain that most cases in an outbreak occur within 4 days, that removing the herd from the pasture does not prevent additional cases, and that leaving the herd on the pasture does not result in additional cases; consequently the recommendation has been to handle severely affected cattle only if necessary to remove them to shade or to slaughter.[467]

Others[460,468] recommend careful removal from the offending pasture. Antihistamines, corticosteroids, epinephrine, atropine, diethylcarbamazine, and diuretics are alleged to be of palliative value,[460,470] but none of these has been properly tested.[460] Pretreatment with antagonists to postulated mediators of inflammation, including acetylsalicylic acid, mepyramine, sodium meclofenamate, diethylcarbamazine citrate, and betamethasone, did not influence the clinical course or lesions of experimental 3-MI toxicity. Likewise, pretreatment with chloramphenicol or disodium cromoglycate failed to alter signs or lesions.[469] However, in one small trial, flunixin meglumine at 1.1 mg/kg IV daily given after the onset of 3-MI–induced disease in calves was effective in lessening signs and lesions.[470] Recovery often occurs without therapy in the less severe cases. In view of the dangers of handling affected cattle, the questionable efficacy of medical treatment, the probable irreversible nature of severe lesions, and the probability of spontaneous recovery in less severe cases, the best treatment may be no treatment. If treatment must be attempted, affected cattle should be handled very cautiously, and furosemide (0.5 to 1 mg/kg IM or IV once or twice daily)[463] and flunixin meglumine (1.1 to 2.2 mg/kg IV daily or divided twice daily) or steroids (dexamethasone at 0.05 to 0.2 mg/kg IM or IV once daily) may be given. Most fatalities occur in the first 2 days. Severely affected animals that survive may develop chronic emphysema or heart failure secondary to cor pulmonale.[467] Moderate to mild cases often show marked improvement after day 3, with recovery over about 10 days; relapses do not occur.

Prevention is based on management and prophylactic drugs. Management strategies that prevent the exposure of susceptible cattle to potentially toxic pastures include the following:

1 Place the cattle in a drylot, feed palatable hay for several days, and turn them onto the lush pasture for 2 hours the first day. Gradually decrease the amount of hay fed and increase the time on pasture over a period of 10 to 12 days.[467]

2 Delay use of lush pastures until after a hard frost.[468]

3 Cut and windrow the pasture before turning cattle out.[469]

4 Use the pasture for young stock (less than 15 months old) or sheep or other livestock[468]; turn adult cattle out only after the pasture has been thoroughly grazed over.

5 Use the pasture before it becomes particularly lush.[465]

6 Use continuous strip-grazing.[467]

Because such management changes are frequently not feasible, prophylactic medication is a promising alternative. Monensin or lasalocid at 200 mg/head/day PO reduces the conversion of tryptophan to 3-MI.[462] Treatment with monensin should be started at least 1 day before pasture change and should be continued an additional 10 days, whereas lasalocid requires a longer pretreatment period of 6 days.[471] For example, 1 kg/head/day of a protein or energy supplement containing 0.15% Rumensin 60 supplies 200 mg of monensin.[460] Monensin or lasalocid is not expected to be beneficial after the onset of signs. Future possibilities include blockers of the mixed function oxidase system and enhancers of intracellular glutathione levels.

31.61.2 Feedlot Acute Interstitial Pneumonia

31.61.2.1 Definition and Etiology

In feedlot cattle an ARDS occurs that is commonly referred to as *feedlot AIP*. The exact cause of this syndrome is unknown, and it is probably multifactorial. Feedlot management practices typically do not include exposure of cattle to lush forages similar to those that cause ABPEE, and the feeding of moldy sweet potatoes has not been associated with feedlot AIP.[472] A variety of causes have been proposed[473,474]; unfortunately, the amount of research to confirm or refute the various hypotheses ranges from small to nonexistent. The most commonly suggested possible causes or predisposing factors are (1) feed-associated pneumotoxins such as 3-MI[475–477] or dietary factors related to protein metabolism[478]; (2) chronic bacterial pneumonia[479–481]; (3) gender[475,476] and hormonal influences[482,483]; (4) chronic small airway injury[480,481,484]; (5) BRSV infection[481,485]; (6) heat or dust exposure[484,486]; and (7) hypersensitivity reactions.[484,487,488] These possible causes could also work together in various combinations to cause feedlot AIP.[477,481]

Support for 3-MI as a cause of feedlot AIP comes from research that showed that levels of a stable metabolite of 3-MI, 3-methyleneindolenine (3-MEIN), were significantly higher in the blood of cattle with AIP than in control cattle.[475,476] Increased levels of 3-MEIN may be a result of decreased clearance of the toxin.[475] Loneragan and colleagues also found that 3-MEIN levels were higher in lung tissue of AIP cases as compared with animals without lung disease, but they were not higher than 3-MEIN levels in the lung tissue of cattle with bronchopneumonia; this suggested that 3-MI may contribute to the pathogenesis of both AIP and bronchopneumonia.[476] The mechanism by which 3-MI is generated and leads to lung damage was discussed earlier in the section describing ABPEE. If 3-MI does contribute to the pathogenesis of feedlot AIP, it is not clear what about the feedlot diet predisposes cattle to produce high levels of 3-MI. Normal cattle produce some 3-MI through metabolism of dietary proteins. It may be that the protein composition (e.g., the tryptophan concentration) of feedstuffs sometimes added to feedlot rations can lead to spikes in 3-MI production. Cattle with feedlot AIP have been found to have higher ruminal pH values than expected for cattle adapted to a high concentrated diet. Ruminal pH in AIP cases ranged from 5.6 to 7.2 in one study[481] and from 4.9 to 7.4 in another,[489] whereas the ruminal pH of cattle adapted to a high concentrate diet is typically about 5.5 to 5.6.[490] Many proteins are relatively basic; therefore the high ruminal pH could be related to abnormal protein metabolism. However, the relatively high ruminal pH could also be caused by anorexia. The concept that abnormal ruminal protein metabolism could contribute to feedlot AIP was also supported by a small study that found increased ammonia levels in the ruminal gas cap of cattle with AIP.[491] An interaction between digestive health and AIP was also suggested by the finding that in feedlot pens in which at least one animal had died from digestive disease, the incidence of AIP was approximately 70% greater than in pens in which digestive disease deaths did not occur.[478]

The hypothesis that bacterial bronchopneumonia contributes to feedlot AIP is supported by the finding by multiple authors that cattle with AIP frequently have superimposed gross and histopathologic lesions consistent with bacterial bronchopneumonia.[479–481] In a study evaluating the bacteria isolated from the lungs of cattle with feedlot AIP that had not received antimicrobial therapy, *P. multocida* and *Mycoplasma* species were significantly more likely to be isolated from the lungs of cattle with AIP than from the lungs of normal penmates.[481] An earlier study found that bacterial respiratory pathogens were not more likely to be isolated from cases of AIP as compared with controls, but the samples in this study were collected at necropsy of

animals that received antimicrobial treatment before death in at least some cases.[492] It should be noted that no study has yet been able to confirm whether in cases with both lesions the bacterial bronchopneumonia was present before AIP occurred or the bacterial bronchopneumonia developed after the animals had AIP. If bacterial bronchopneumonia leads to the development of AIP, it is not clear how this happens. In humans with ARDS, bacterial infection is often a predisposing factor that appears to lead to ARDS through the induction of high local or systemic levels of proinflammatory cytokines.[493,494] The role of proinflammatory cytokines in cattle with feedlot AIP has not been investigated.

A role for gender and/or hormonal influences in the pathogenesis of feedlot AIP is related to the frequent (although not inevitable)[480] finding that the majority of affected animals are heifers.[475,478,481,495] Feeding of melengestrol acetate (MGA), which is fed to heifers to control estrus, has been suggested to contribute to AIP by some authors,[473,482] but others have not found evidence of any association between MGA and AIP.[478,495] Although one research study indicated that MGA could exacerbate experimentally induced AIP in sheep,[482] a well-controlled experimental study to determine the effect of MGA on AIP in cattle in the field is needed to clarify the involvement of MGA with AIP. It has also been suggested that growth hormone implants may contribute to development of feedlot AIP, although a survey of feedlot managers did not find data to support this.[495]

Infection with BRSV was linked to feedlot AIP in an early study.[485] Because BRSV infection can sometimes cause AIP, the possibility that a ruminant with lesions of AIP is simply a case of BRSV infection must always be considered. However, cattle with feedlot AIP do not always have a fever,[481] which is expected in animals with acute BRSV infection. Moreover, feedlot AIP can occur in outbreaks, but cases often occur sporadically, which would be less consistent with BRSV infection. Neither Sorden and colleagues nor Loneragan and colleagues found BRSV significantly more often in animals with feedlot AIP than in controls.[480,492] In another study the difference in frequency of identification of BRSV in feedlot AIP cases as compared with normal penmates approached significance ($P = .07$).[481] It is interesting to note that in this study BRSV antigen was not found in airway epithelial cells, as is characteristic of acute BRSV infection,[496] but rather was found in cells, possibly macrophages, that were surrounding airways. The significance of this was not clear; perhaps the BRSV antigen found in these cases was residual antigen in phagocytic cells that was engulfed during BRSV infection in the recent past.

Although AIP is by definition “acute,” it is interesting that several authors have reported histopathologic evidence of chronic airway injury (particularly, bronchiolitis fibrosa obliterans) in the lungs of animals with AIP.[480,481,484] In one study, the presence of bronchiolitis fibrosa obliterans was identified significantly more often in cattle with AIP than in penmates with no history of treatment for respiratory disease; this was in spite of the fact that AIP cases in the study also had no history of previous treatment for respiratory disease.[481] It is not known how past airway injury is related to the development of AIP, although chronic airway injury could be linked to the occurrence of chronic bacterial pneumonia, which has also been associated with feedlot AIP, as described previously. It may be that the chronic airway injury is related to dust exposure, although it is not clear why animals with AIP would be more likely to have airway injury caused by dust exposure than other penmates. Dust exposure has been anecdotally related to AIP,[484,486] and feedlot managers often report that efforts to control dust, such as spraying water lightly onto the surface of pens, decreases AIP occurrence when the disease is a problem. However, repeated exposure to feedlot dust or to fungal organisms from feedlot dust did not induce AIP in sheep or goats in experimental studies.[497,498] One study of the effect of dust on feedlot respiratory disease found only a weak association between airborne dust particles and respiratory disease.[499]

High ambient temperatures are thought to contribute to feedlot AIP because several investigators have found that the majority of cases occur in the summer,[478,484] but no mechanism by which hot weather might exacerbate AIP has been researched. Hypersensitivity reactions are often suggested to cause AIP.[502,503] It is true that anaphylaxis can cause pulmonary edema, hemorrhage, and emphysema, with microscopic evidence of hyaline membrane formation.[500] However, animals that survive longer than a few hours after an episode of anaphylaxis do not have lung changes consistent with AIP, such as type 2 pneumocytic proliferation and interstitial inflammatory cell infiltrate.[501] Therefore an anaphylactic reaction may cause an occasional case of sudden death with lung changes typical of AIP, but anaphylaxis does not explain the majority of feedlot AIP cases. Other types of hypersensitivity-mediated lung disease have pathology that is unlike that seen in feedlot AIP, also making other types of hypersensitivity an unlikely cause of the majority of feedlot AIP cases.[460,473]

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In summary, the cause of feedlot AIP is unknown, but the strongest support currently exists for some role for (1) factors related to feed, or ruminal metabolism, including 3-MI; (2) infectious respiratory disease, especially chronic bacterial pneumonia, and possibly BRSV; (3) gender and/or other hormonal influences; and (4) chronic airway injury, which may be related to infectious respiratory disease. It seems likely that multiple factors can contribute to the development of feedlot AIP, and the factors may act in some as-yet unidentified combination in at least some cases. It is also possible that some causes predominate in some feedlots or individual cases, whereas other causes predominate in other feedlots or individual cases. A study evaluating the occurrence of bacterial respiratory pathogens in cattle with feedlot AIP found bacterial respiratory pathogens in the lungs of the majority of cases in one feedlot, and in almost none of the cases in a second feedlot,[481] suggesting that bacterial infection played a role in the development of AIP cases in the first feedlot but not the second.

31.61.2.2 Clinical Signs

Feedlot cattle with AIP may be found dead in the pen.[504] Clinical presentation includes rapid onset of expiratory dyspnea and tachypnea, although if the respiratory effort is great, the actual respiratory rate may not be greatly elevated. Cattle typically stand with their heads extended and front legs spread apart, and exhibit open-mouth breathing (see Fig. 31-66). Frothing from the mouth may also be observed. Rectal temperatures are variable, ranging from normal to elevated.[481] Physical examination may reveal cyanosis, tachycardia, and SC emphysema that extends from the cervical to dorsal thoracic area.[505] Auscultation of lungs reveals dull areas throughout the lungs, along with some crackles. Differential diagnoses of bronchopneumonia, tracheal edema, tracheal obstruction, and hypersensitivity pneumonitis should be considered.

31.61.2.3 Pathogenesis

Because the cause of feedlot AIP is unknown, the pathogenesis is also uncertain. If feed-related pneumotoxins cause at least a subset of cases with AIP, the pathogenesis will be similar to that described for ABPEE, 4-ipomeanol toxicity, and perilla ketone toxicity. If bacterial infection is a cause of some cases of feedlot AIP, as is true for some human cases of ARDS, then proinflammatory cytokine production and the resultant inflammatory cascades they initiate are likely involved. More research is necessary to determine the cause and the pathogenesis of feedlot AIP.

31.61.2.4

Epidemiology

In the 1999 NAHMS survey of feedlots, AIP was identified as the second leading cause of feedlot mortality, behind bronchopneumonia (shipping fever).[502] Mortality rates resulting from AIP of 0.03% to 0.15% have been reported.[478,479,484,495] An important feature of AIP is the tendency of the disease to occur most often in cattle on feed more than 60 days,[475,481,484,492,495] as opposed to shipping fever, in which mortality peaks by 45 days after feedlot entry.[506] This means that losses due to AIP deaths are amplified by the fact that relatively more resources in feed and labor have been invested in cattle that die of AIP, as compared with cattle that die of shipping fever. Most cases of feedlot AIP occur in the summer,[478,484,495] but the disease can occur in any season of the year; and most studies report that heifers are disproportionately affected.[475,476,495] One survey found the odds of an animal with AIP being a heifer were 3.1 times greater than the odds of the animal being a steer.[476] In feedlot pens in which an animal died from a digestive disorder, the relative risk of AIP occurring was about 1.7, indicating that pens with a digestive disorder death were about 70% more likely to also have an AIP death, as compared with pens with no digestive disorder deaths.[478]

A survey of feedlot managers was undertaken to determine risk factors for feedlot AIP.[495,503] Although the response rate was relatively poor (12%), the responding managers oversaw just under 2.5 million cattle, which represented about 10% of the U.S. feedlot inventory the year the survey was undertaken.[503] Feedlots in northern states were significantly less likely to recognize AIP as a cause of morbidity or mortality as compared with feedlots elsewhere, whereas larger feedlots and feedlots placing a higher proportion of yearlings were more likely to recognize AIP as a cause of morbidity or mortality. Feedlots that vaccinated less than 95% of placements for *M. haemolytica* ± *P. multocida* were more likely to recognize AIP as a cause of disease, and these feedlots recognized AIP as a cause of a larger proportion of deaths, as compared with feedlots that vaccinated more than 95% of cattle for these pathogens.[495] If the data reported by the feedlot managers are representative of a true association between *Mannheimia* and *Pasteurella* vaccination and AIP, the reason for the link is not clear. It may simply be related to the association between placement of a high proportion of yearling cattle and AIP, as yearlings are less likely to be vaccinated for *Mannheimia* and *Pasteurella* than younger cattle. It may also be related to the finding that AIP cases have increased likelihood of having concurrent bacterial pneumonia in some feedlots, but more research is necessary before any definite conclusions can be made.

31.61.2.5

Necropsy Findings

The gross pathology of feedlot AIP is essentially the same as that described for ABPEE. If there is concurrent bacterial bronchopneumonia, there may be cranioventral consolidation, with fibrin deposition on the pleura, but in cases with no concurrent bacterial pneumonia, the pleura is free of fibrin. Grossly it is common to see a “patchwork” appearance of dark and light colored lobules interspersed, and the lobules are freely movable[473,481] (see Fig. 31-67). Histologically, the most acute cases will have only hyaline membrane formation and alveolar edema, possibly with hemorrhage in the alveoli or interstitium; cases that have been going on longer will have proliferation of type 2 alveolar epithelial cells and inflammatory cell infiltrate into the interstitial space (septa). It is not unusual to find evidence of chronic airway injury, such as peribronchiolar lymphoid cuffing, peribronchiolar vascular fibrosis, and bronchiolitis fibrosa obliterans.[480,481] Whether the chronic airway injury is related to the pathogenesis of AIP or whether it is an incidental finding is unknown,

but in one study bronchiolitis fibrosa obliterans was significantly more common in AIP cases than in penmates with no history of lung disease.[481]

31.61.2.6 Diagnosis

Diagnosis of feedlot AIP can be confirmed only by histopathologic evaluation of lung from animals that die or are euthanized because of the disease. Clinical signs and even gross pathology are not definitive; only 65% to 80% of cases identified based on clinical signs were confirmed by histopathologic evaluation to have AIP in two studies.[475,481]

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31.61.2.7 Treatment and Prevention

Treatments recommended are similar to those recommended for ABPEE. However, feeding monensin does not preclude development of feedlot AIP, as cattle that die of AIP are often consuming feed including monensin when they contract AIP.[481] Treatment is supportive and typically includes administration of antiinflammatory drugs such as steroids (dexamethasone at 0.05 to 0.2 mg/kg once or twice) or flunixin meglumine (1.1 to 2.2 mg/kg IV q24h), and diuretics such as furosemide (1 mg/kg IM or IV q12-24h). Antimicrobial drugs are appropriate given the fact that cases often have superimposed bacterial pneumonia (see Table 31-10). There are no studies evaluating the response of cattle with AIP to any treatment, and such studies would be difficult because there is no perfect method of making an antemortem diagnosis of the disease. However, anecdotal reports indicate that the prognosis is guarded even with treatment. It is important to note that simply moving cattle out of the pen could lead to death from severe respiratory compromise. Because of the risks and uncertainties of treatment and the expected high case fatality rate, immediate salvage slaughter may be the most economic course to take[507]; if salvage slaughter is attempted, remember to observe proper drug withdrawal times.

Because the cause of feedlot AIP is unknown, it is difficult to recommend control measures. Administration of aspirin and of vitamin E have been suggested as rational preventative strategies to counteract inflammatory pathways suspected to be involved in feedlot AIP; however, two trials showed no clear effect of these therapies on levels of 3-MI in treated cattle.[508,509] No cattle in these trials developed AIP, so an effect on disease could not be identified. The risk factors identified suggest that management strategies to minimize abrupt dietary changes and to control infectious respiratory disease may be helpful; anecdotal reports also suggest that efforts to control feedlot dust may be helpful.

31.61.3 4-Ipomeanol (Moldy Sweet Potato) Toxicity

31.61.3.1 Definition and Etiology

Moldy sweet potato toxicity is caused by the ingestion of a furanoterpenoid toxin produced by sweet potatoes *(Ipomoea batatas)* in response to infestation with the fungus *Fusarium solani (javanicum)*. It should be emphasized that this disease is an intoxication and not an allergic response to the fungus.[460]

31.61.3.2 Clinical Signs

There is an acute onset of tachypnea, tachycardia, hyperpnea, and dyspnea, with loud expiratory grunting, frothing at the mouth, extension of the head and neck, flaring of the nostrils, and frequent deep coughing. Crackles and harsh bronchial sounds are heard on auscultation.[510] Signs usually occur within 1 day of exposure, and deaths may occur 2 to 5 days later.[460] Differential diagnoses are as for ABPEE (see earlier discussion), which this condition closely resembles, except for the history of exposure and the more prominent cough and adventitious lung sounds.

31.61.3.3 Pathogenesis

When *F. solani* (or closely related species) grows on sweet potatoes, the potato produces several 3-substituted furans, including 4-hydroxymyoporone, which is hepatotoxic. This is converted by the fungus to a series of pneumotoxins, the most abundant of which is 4-ipomeanol. When ingested by cattle in sufficient amounts, this toxin is absorbed, carried to the lungs in the blood, and converted to a highly reactive metabolite by a cytochrome P-450–dependent mixed function oxidase system.[460] From this point the pathogenesis is similar to that of ABPEE—that is, the toxin binds to intracellular macromolecules in the cell, causing cellular damage, particularly in Clara cells, type I pneumocytes, and endothelium; edema, hemorrhage, cellular necrosis, hyaline membrane formation, and proliferation of cuboidal epithelium result, with secondary emphysema.

31.61.3.4 Epidemiology

The disease usually occurs in outbreak form when groups of cattle are fed damaged sweet potatoes. Morbidity and case fatality rates are high. Calves nursing affected cows are unaffected.[511]

31.61.3.5 Necropsy Findings

The lungs are wet, firm, and large and fail to collapse. Hemorrhages, yellow gelatinous edema fluid, and emphysema with bullae occur throughout. Lobules are dark red and firm.[510,511] Microscopic lesions include edema, emphysema, hyaline membranes, hemorrhage, mixed interstitial infiltrates, alveolar epithelial hyperplasia, peribronchiolar fibrosis, and bronchiolitis obliterans.[511]

31.61.3.6 Diagnosis

Diagnosis is made based on history of feeding sweet potatoes and identification of clinical signs and pathology consistent with AIP. Other diagnostic tests as described for ABPEE could also be attempted in valuable individual animals.

31.61.3.7 Treatment and Prevention

Treatment has not been investigated. Because the pathophysiologic mechanisms are similar to those of ABPEE, similar recommendations are offered here: handle affected animals with extreme care; if treatment is attempted, furosemide (0.5 to 1 mg/kg IM or IV q12-24h) and flunixin meglumine (1.1 to 2.2 mg/kg IV daily or divided twice daily) or dexamethasone (0.05 to 0.2 mg/kg IV or IM q24h) may be given. The prognosis for

moderate to severe cases is grave, regardless of management. Because toxicity is difficult to predict and is usually severe and irreversible when it occurs, the feeding of mold-damaged sweet potatoes should be strictly prevented.

31.61.4 Perilla (*Perilla Frutescens*) Ketone Toxicity

31.61.4.1 Definition and Etiology

Perilla ketone toxicity is an ARDS caused by ingestion of a pneumotoxin found in the leaves and seeds of *Perilla frutescens*, a common weed in the southeastern United States. This plant is also known as purple mint, perilla mint, wild coleus, and beefsteak plant.[512] It is an erect herbaceous annual about 2 m high, with characteristic square stems, an aromatic odor, and opposite, coarsely serrated ovate leaves 5 to 10 cm long and 4 to 8 cm wide, with a purplish tint at maturity. The seed and flower stage, which occurs in August to October, appears to be most toxic.[512] The flowers are small, white to purple blooms on a long raceme.[512] The plant prefers semishade, such as damp, open wooded areas.

31.61.4.2 Clinical Signs

Animals are often found dead.[512] Signs observed include a sudden onset of moderate to severe dyspnea, wheezing, frothing at the mouth, and an expiratory heave or grunt.[512,513] In less severe cases the cow may pant.[513] Exertion worsens the signs and may precipitate death. Mature cows are most often affected, but deaths have been reported in yearlings and calves.[512] Death occurs in 3 to 7 days in experimental toxicity.[512] Differential diagnoses are as for ABPEE (see earlier discussion), which this condition closely resembles and from which it can be differentiated only by history of exposure.

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31.61.4.3 Pathogenesis

The volatile oils of *P. frutescens* contain a number of 3-substituted furans that are chemically similar to 4-ipomeanol, the moldy sweet potato toxin. One of these, perilla ketone, predominates in the later growing season (when most toxicities occur) and has been shown to be pneumotoxic when given parenterally to mice, hamsters, goats, calves, and sheep.[512] The toxin is absorbed from the rumen, carried to the lungs through the blood, and probably metabolized to the toxic form by the mixed function oxidase system, as for 4-ipomeanol and 3-MI (see earlier). The pathogenesis from this point parallels that of ABPEE or moldy sweet potato toxicity.

31.61.4.4 Epidemiology

P. frutescens seems to thrive in late summer, when pastures in the southeastern United States are frequently dry and dormant.[513] This also corresponds with the more toxic stage of the plant.[512] Cattle normally avoid the plant when other pasture is available but may be forced to consume it during this critical period.[513] However, under experimental conditions calves were noted to prefer the mint.[512] The preseed stage appears to be of relatively low toxicity; the green seed-stage plant is most toxic, especially the seed parts; dried hay from seed-stage plants is less toxic than green plants but is still potentially lethal; and frosted plants appear to have

relatively low toxicity.[512] The exact toxic dose is unknown, but 2.3 kg of green seed-stage plant and 11.2 kg of hay were lethal for cattle in one trial.[512]

31.61.4.5 Necropsy Findings

The lungs are distended (often bearing the impressions of the ribs), fail to collapse, and are moist, heavy, edematous, and emphysematous. There are often bullae, pleural effusions, and froth in the airways. Histologic characteristics are edema, extensive alveolar epithelial hyperplasia, emphysema, and congestion.

31.61.4.6 Diagnosis

Diagnosis is based on history of exposure to perilla mint and characteristic clinical signs and lung pathology. Other diagnostic tests as described for ABPEE could also be attempted in valuable individual animals.

31.61.4.7 Treatment and Control

Treatment has not been investigated. On the basis of the similar pathophysiologic mechanisms, the recommendations for ABPEE should be followed (see earlier discussion). The prognosis for severe cases is grave, regardless of management. Cattle should be provided sufficient forage that they do not seek out perilla mint; once they have begun to eat it, they should be fenced away from stands of the plant, and other forage should be provided.

31.61.5 Other Toxic Plants

Zieria arborescens (stinkwood) leaves cause a fatal ARDS in Tasmanian and Eastern Australian cattle after ingestion of 15 to 30 kg over 2 to 4 weeks. An oil isolated from the leaves has produced the same lung lesion in rabbits. The signs are as for the other ARDS: acute tachypnea, grunting, extension of the head, mouth breathing, abdominal respiration, tachycardia, and fever secondary to the respiratory effort. Death occurs in 1 to 21 days; some animals survive. Lesions include massive pulmonary edema and emphysema.[514] Treatment has not been investigated, and recommendations as for ABPEE (see earlier discussion) are suggested. As mentioned in relation to ABPEE, *Brassica* species (rape, kale, turnip tops) are currently regarded as one of the types of pasture that can precipitate the 3-MI–associated disease. The possibility that other specific toxins may be identified in these species has not been excluded. Morbidity and mortality rates appear to be much higher on *Brassica* species pastures than on other lush forages.[460] The hepatotoxic effects of pyrrolizine alkaloids are well known, but they also cause lung lesions. Lung lesions develop only in animals with chronic liver lesions, and the minimum dose necessary to produce lung lesions is never less than that which is hepatotoxic; therefore signs of liver disease usually predominate. *Crotalaria* and *Trichoderma* species are the most common offenders; to a lesser extent, *Senecio* species are a cause. Horses, sheep, cattle, and pigs have been affected. Pulmonary lesions include edema, congestion, hemorrhage, proliferation of bronchiolar and alveolar epithelial cells with megalocytosis, and interstitial fibrosis and cellular infiltration. As with 3-MI, 4-ipomeanol, and perilla ketone, the toxicity of the pyrrolizine alkaloids depends on activation by the mixed function oxidase system; in this case, however, the toxin is probably formed in the liver and spills over into the blood to reach the lungs. Vascular endothelium is probably the primary target for injury (vs. the Clara cells and type 1 pneumocytes in the other ARDS).[515]

31.61.6 Toxic Gases

Food animals may be exposed to a variety of toxic gases in the environment. The most important are ammonia, hydrogen sulfide, carbon dioxide, and methane from excreta and respiration; these can be especially important when excreta is collected in pits or tanks. Other gases include nitrogen dioxide from silos; carbon monoxide from machinery exhausts and heaters; zinc oxide from welding of galvanized metal in barns; chlorine, formaldehyde, insecticides, and other fumes from agricultural chemicals and cleaners; and smoke from fires. In most cases concentrations usually remain below overtly toxic levels, and effects are very subtle. Such chronic low-level exposure may result in decreased disease resistance and depression of growth rates.[516] Slightly higher levels of chronic exposure may cause clinically vague syndromes of lethargy, mild dyspnea, anorexia, depressed growth, excessive lacrimation and salivation, low incidence of sudden deaths over weeks or months, and stillbirths.[516] Acute, severe outbreaks usually occur in tightly enclosed facilities and are related to accidents, power outages, agitation or pumping of manure pits, or other combinations of unusual circumstances. Such outbreaks are characterized by an ARDS of variable morbidity and frequently a high case fatality rate.

31.61.6.1 NITROGEN DIOXIDE

Nitrogen dioxide (NO_2) is a yellow-orange to brown gas with an acrid odor that is produced by anaerobic fermentation of green plant material. It is a major component of “silo gas.” Acute exposure of farm workers to high concentrations of NO_2 causes a respiratory condition known as “silo-filler's disease,” characterized by severe acute edema and congestion and followed by bronchiolitis obliterans and progressive interstitial pulmonary fibrosis. A similar condition has been induced experimentally in cattle,[517] and apparent (although unproved) spontaneous field cases have been reported.[518,519] Clinical signs in experimental and apparent field cases include cough, tachycardia, tachypnea, respiratory grunting, depression, anorexia, hypogalactia, extension of the head, open-mouth breathing, fever, salivation, lacrimation, and SC emphysema. Auscultation reveals decreased breath sounds and crackles.[518,519] The primary differential diagnoses should include other ARDSs of housed cattle that occur in outbreak form, especially exposure to other toxic gases (manure pit gases, zinc oxide, chlorine, carbon monoxide), and hypersensitivity pneumonitis from moldy hay. Nitrate toxicity should also be considered. Clinical pathologic evaluation is of limited benefit. Leukocyte counts remained normal in experimental cases; methemoglobin levels increased to a peak at 30 minutes after exposure and returned to normal in 12 to 24 hours.[517] The pathophysiologic mechanism probably involves the dissolution of the NO_2 in the water of the respiratory tract to form nitric acid. Nitrates and nitrites are also formed; these are irritating, and the nitrites cause methemoglobinemia.[519] Nitrogen dioxide is also an oxidant itself and may contribute directly to the injury. The disease occurs as an outbreak, usually in housed cattle in proximity to a silo chute in a tight or poorly ventilated barn.[518,519] Nitrogen dioxide is heavier than air and layers on the top of silage or spills out around the bottom of the silo. Corn silage produces more gas than hay, and a high nitrate content increases the danger. The levels are highest in the first 48 hours after filling the silo but may remain dangerous for 2 to 3 weeks.

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Necropsy findings in experimental disease include hyperemia of the upper airways; hemorrhages, fibrinous membranes, and froth in the trachea; distended, noncollapsing lungs with rib imprints; a mottled appearance caused by consolidated lobules alternating with emphysematous lobules; and bullae. Microscopic lesions include alveolar epithelial hyperplasia, large foamy alveolar macrophages, hyaline membranes, hyperemia, hemorrhage, and edema.

Treatment involves the establishment of adequate ventilation; cows should be completely removed from closed buildings if necessary. Corticosteroids have apparently been beneficial in field cases,[518,519] but no controlled studies have been performed. Because of the obvious differences in pathophysiologic characteristics, it would be unwise to extrapolate treatment regimens from those of ABPEE. Suggested empiric therapy might include corticosteroids (dexamethasone at 0.05 to 0.2 mg/kg IM or IV daily), furosemide (0.5 to 1.1 mg/kg IM or IV daily or twice daily), and appropriate antibiotics to prevent secondary bacterial infections.

31.61.6.2

ZINC OXIDE

Zinc oxide (ZnO) fumes have been associated with an ARDS in cattle.[520] Oxyacetylene cutting or arc welding of galvanized pipe results in production of white fumes of zinc oxide containing colloidal particles 0.3 to 0.4 mm in diameter, which can reach the terminal alveoli when inhaled.[520] Construction activities in closed barns containing animals may result in toxicity in animals in close proximity or in the path of ventilation. All ages may be affected.

Clinical signs in severe cases include acute onset of anorexia, frothing at the mouth, anxiety, extension of the head and neck, mouth breathing, expiratory grunting, tachypnea, tachycardia, mild fever, SC emphysema, and crackles on auscultation of the lungs. Death may occur within 12 hours. Less severely affected animals exhibit depression, mild fever, and tachypnea.[520] Differential diagnoses include other ARDS of housed cattle that occur in outbreak form such as exposure to other toxic gases (nitrogen dioxide, manure pit gases) or hypersensitivity pneumonitis. The pathophysiologic process presumably involves direct damage to cells by the ZnO and its products dissolved in the fluid lining the respiratory tract. Necropsy findings include purulent conjunctivitis; SC emphysema; congestion of the airways; tracheal hemorrhages; stiff, noncollapsing lungs; and pulmonary congestion, edema, and emphysema with bullae.[520] Histologic lesions include pulmonary congestion, emphysema, edema, and mixed cellular infiltrates with a prominent eosinophil component. Treatment of severe cases with epinephrine, antihistamine, atropine, and corticosteroids had no effect in one outbreak,[520] whereas mild cases recover spontaneously. Suggested empiric therapy could include ventilation of the area, dexamethasone (0.05 to 0.2 mg/kg IM or IV daily), furosemide (0.5 to 1.1 mg/kg IM or IV daily or twice), and appropriate antibiotics to control secondary bacterial invaders.

31.61.6.3

CHLORINE

Chlorine is a greenish yellow gas widely used in manufacturing. Animal exposure is usually the result of industrial accidents. Exposed animals may be found dead. Signs include depression, profuse nasal discharge, lacrimation, and dyspnea; crackles may be heard on auscultation.[521] The toxic effects are the result of the formation of hydrochloric and hypochlorous acids; the latter breaks down to hydrochloric acid and oxygen, both of which are toxic to tissues. Necropsy findings include congestion of the nasal mucosa, tracheitis, and pulmonary edema, hemorrhage, and emphysema. Histologic lung lesions include edema, emphysema, hemorrhage, atelectasis, hyaline membrane formation, and lymphocytic bronchitis.[521] Treatment is empiric; suggestions include corticosteroids (dexamethasone at 0.05 to 0.2 mg/kg IM or IV daily), furosemide (0.5 to 1.1 mg/kg IM or IV daily to twice daily), and appropriate antibiotics to prevent secondary bacterial infection.

31.61.6.4 MANURE GASES

Manure gases include mixtures of hydrogen sulfide, ammonia, carbon dioxide, methane, and carbon monoxide.[460] Accumulation of these gases can result in asphyxiation of animals in enclosed barns over manure pits.

31.61.6.5 SMOKE INHALATION

Smoke inhalation injury may occur in animals that survive barn fires. Many clinical changes may not become evident for 24 to 48 hours after the fire. It is important to assess the degree of damage as early as possible and to attempt to anticipate sequelae so that early aggressive therapy can be instituted.[522] Common problems for which to check include oral burns, conjunctivitis, and laryngospasm. Hoarseness, expiratory wheezes, and carbonaceous sputum indicate potentially serious sequelae. Crackles and wheezes on auscultation may occur very early or may be delayed for hours. Cough, stridor, and tachypnea may also occur. Bright red mucous membranes may indicate CO poisoning or burns and may mask cyanosis.[522] Carboxyhemoglobin determinations on iced venous blood (often available at human hospitals), serial arterial blood gas determinations, transtracheal wash, and bronchoscopy are useful in delineating the extent of damage and prognosis.[522]

The pathophysiology of smoke inhalation is complex and involves two main mechanisms: CO toxicity and smoke toxicity. CO toxicity results in tissue hypoxia in all organs, especially the brain; O_2 consumption in the fire and the pulmonary effects of smoke may aggravate this hypoxia. Heat damage in animals is usually limited to the upper airways. Smoke toxicity is related to the inhalation of soot, superheated particles, and a variety of noxious gases (e.g., aldehydes, oxides of sulfur and nitrogen, benzene from plastics), which results in the formation of dissolved acids, alkaloids, and other direct irritants in pulmonary fluids. These mechanisms eventually (usually 2 to 24 hours after inhalation) result in alveolar damage, interstitial edema, hypoxia, and secondary bronchopneumonia.[522]

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Treatment involves establishing a patent airway with intubation or tracheostomy if necessary. Oxygen, up to 100% for short periods, is indicated[522]; care must be exercised because 100% oxygen can also cause pulmonary damage. IV fluids should be given, with careful monitoring for pulmonary edema. The use of corticosteroids is controversial.[522] Antibiotics are indicated to prevent secondary bronchopneumonia. Bronchodilators such as aminophylline at 6 to 10 mg/kg IV or PO three times daily may help relieve soot-induced bronchospasm.

31.62 HYPERSENSITIVITY PNEUMONITIS

31.62.1 Definition and Etiology

Hypersensitivity pneumonitis, also known as *extrinsic allergic alveolitis* (EAA) or “bovine farmer's lung,” is an allergic respiratory disease caused by inhalation of organic dusts. Several such conditions are recognized in humans, differing only in the nature of the antigen and the circumstances under which exposure occurs. The classic example, of which the bovine disease is probably the counterpart, is “farmer's lung.” EAA is caused by exposure to the dust from moldy hay, grain, or other plant matter containing spores and products of thermophilic

actinomycetes such as *S. rectivirgula* (formerly *M. faeni*) and *T. vulgaris*.[523,524] Other unidentified forms of hypersensitivity pneumonitis probably occur in cattle.

31.62.2 Clinical Signs

EAA is a disease of confined adult cattle; consequently it is more common in dairy than in beef breeds. Typically a succession of acute cases occurs during the winter housing period, so the clinician is presented with a group problem in which animals are in varying stages of the disease. The acute form is indicative of recent exposure and is characterized by a sudden onset of dullness, decreased appetite, hypogalactia, coughing, expiratory tachypnea, dyspnea, and cranial-ventral crackles on auscultation of the lungs.[523–525] There is a moderate transient fever, which is frequently missed.[524] The chronic form is insidious at onset and may not be detected until there is considerable fibrosis. Animals with the chronic disease may have acute exacerbations as a result of heavy antigen exposure; some may not be detected until turned out in the spring, when increased exercise causes an acute crisis. There is a history of weight loss and coughing for several winters, with remission in the grazing season. Chronic signs include hypogalactia, weight loss, productive coughing, tachypnea, obvious hyperpnea, and widespread crackles and wheezes on auscultation of the lungs, especially in the rostral-ventral areas.[524] Differential diagnoses should include respiratory diseases affecting groups of housed adult cattle in winter. Infectious diseases (viral and bacterial pneumonias) can usually be differentiated from farmer's lung by careful evaluation of factors such as clinical signs of fever and pulmonary consolidation. Therefore the main differential diagnoses are the toxic gases. It should be emphasized that hypersensitivity pneumonitis is not considered an ARDS and that no evidence exists for the involvement of hypersensitivity in the pathogenesis of the ARDS described previously. However, severe cases of EAA with prominent dyspnea and moderate, nonfatal cases of gas intoxication may appear clinically similar. If the group outbreak aspect of EAA is ignored, the clinician who examines one individual may be unable to distinguish this condition from fibrosing alveolitis.

31.62.3 Pathogenesis

The spores of the thermophilic actinomycetes are 0.7 to 1.3 mm in diameter and can easily reach the alveoli, where they induce both humoral (precipitating) and cellular immune responses. It is thought that repeated exposure results in the activation of a number of immunologically specific and nonspecific cellular and humoral effector mechanisms at the alveolar level, which results in tissue damage.[523,524]

31.62.4 Epidemiology

EAA is a problem in areas with wet summers and severe winters, a situation characterized by the combination of moldy hay and housing of cattle in winter. In North America, EAA occurs primarily in the Great Lakes region of the United States and the eastern provinces of Canada.[525] Baling and stacking of hay with a high moisture content (over 30%) results in overheating of the stacks. Thermophilic molds become dominant and produce billions of spores, which are released when the hay is distributed for feeding. A similar situation can occur in stored grains. Affected hay is usually dry, friable, discolored, and dusty; however, it is not necessary for hay to be grossly dusty and poor in quality to release large numbers of spores.[524]

31.62.5 Necropsy Findings

In acute cases the lungs are superficially grossly normal. Closer inspection reveals small gray spots in many lobules, which represent interstitial and peribronchiolar accumulations of lymphocytes. Other lobules exhibit dark red centers of atelectasis surrounded by pale pink raised edges of trapped air that are caused by narrowing of airways with lymphocytic infiltrates. Histologic evaluation confirms the presence of these lymphocytic infiltrates and aggregations, as well as epithelial granulomas, bronchiolitis, and bronchiolitis obliterans. The gross appearance in chronic cases is similar, with the addition of focal areas of interalveolar fibrosis and epithelial hyperplasia; epithelioid granulomas are absent unless a recent acute exposure has occurred.[523,524]

31.62.6 Diagnosis

Precipitating antibodies to *M. faeni* are found in the serum in most cases.[523,524] However, two precautions are necessary. First, the presence of precipitating antibodies only indicates exposure to the antigen; many normal animals also have antibodies. Second, it is possible that other as yet unidentified antigens may cause allergic respiratory disease in cattle. The presence or absence of titers is therefore not necessarily diagnostic of the clinical status of the animal, and the magnitude of the titer does not reflect the extent of disease.[460]

31.62.7 Treatment and Prevention

Treatment and control center around removal of the offending antigen, which is frequently difficult from an economic and management standpoint. Corticosteroids (dexamethasone at 0.05 to 0.2 mg/kg IV or IM daily) may be beneficial in acute cases. Suggestions to decrease the molding of hay or degree of exposure include making silage instead of hay, ensuring proper drying before baling, and feeding hay outside. If the condition can be arrested before significant fibrosis occurs, the prognosis is good.

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31.62.7.1 Anaphylaxis

In ruminants the lung is the major target organ in immediate (type I) hypersensitivity reactions. Precipitating antigens include vaccines, drugs, blood, *Hypoderma bovis* or *Hypoderma lineatum* larvae, insect bites, and bee stings. Signs of anaphylaxis usually develop in 10 to 20 minutes and include severe acute dyspnea, with flaring of the nostrils, extension of the head and neck, open-mouth breathing, frothing of the mouth, hyperpnea, and abduction of the elbows. Pharyngeal and laryngeal edema cause stertor and inspiratory dyspnea. Urticaria may occur in some cases, such as milk allergy in Jersey cows. Shivering, salivation, lacrimation, pruritus, diarrhea, fever, edema (eyes, muzzle, anus, and vulva), collapse, nystagmus, cyanosis, and discharge of froth from the nostrils also may occur. On auscultation there are harsh breath sounds, large airway sounds, and crackles. The primary differential diagnosis is peracute interstitial pneumonia. The pathogenesis involves an initial exposure to the antigen, which results in a genetically determined production of homocytotropic antibodies. In humans and dogs, this is immunoglobulin E (IgE); in ruminants various classes may be involved.[526] This antibody attaches to receptors on mast cells and basophils. On subsequent exposure to the antigen, bridging of the Fab parts of the antibody on these cells results in degranulation, with release of a variety of mediators such as histamine, bradykinin, 5-hydroxytryptamine, serotonin, slow-reacting substance-anaphylaxis (SRS-A), eosinophil chemotactic factor A, platelet activating factor, kinins, and prostaglandins.[526–528] These mediators result in a cascade of vascular events, notably increased vascular permeability, which in turn results in acute severe edema. Pulmonary venous constriction, pulmonary artery

hypertension, splanchnic pooling, increased mucus secretion, and bronchospasm also occur. Ruminants that die of anaphylaxis have severe pulmonary congestion and edema, laryngeal edema, and froth in the airways. Lung lesions of ARDS may be present.

The treatment of choice is epinephrine, 4 to 8 mg (4 to 8 mL of 1:1000 solution) IV or SC or 1 to 5 mg IV for an average 500-kg cow and 1 to 3 mg IV or SC for an average adult sheep or goat. Epinephrine has a short half-life, and animals should be observed closely for relapse. Ancillary therapy includes corticosteroids (dexamethasone, 0.1 mg/kg IM or IV; prednisolone, 2.2 mg/kg IM or IV daily). Other supportive therapies include shock doses of IV fluids (40 mL/kg/hr); aminophylline; diuretics such as furosemide; oxygen therapy; and tracheostomy if necessary.

31.63 MISCELLANEOUS CHRONIC PNEUMONIAS

At least two chronic interstitial pneumonias of uncertain cause have been identified in cattle: fibrosing alveolitis and bronchiolitis obliterans. These are typically chronic diseases of individual animals.

31.63.1 Fibrosing Alveolitis

Fibrosing alveolitis is, by definition, a chronic disease of unknown and possibly multiple causes, characterized by diffuse inflammation of the lung beyond the terminal bronchiole. Approximately 50% of cases produce positive results for precipitating antibody to *M. faeni*, and it is possible that these cases represent chronic farmer's lung whereas others (that have negative *M. faeni* results) may be the chronic stage of hypersensitivity to other unidentified antigens.[460] Field investigations have failed to substantiate any connection between fibrosing alveolitis and repeated episodes of ARDS such as ABPEE. Furthermore, recovery from a single dose of 3-MI does not result in lesions typical of fibrosing alveolitis. However, repeated doses of 3-MI at weekly intervals experimentally cause fibrosing alveolitis—like lesions.[460] Fibrosing alveolitis occurs in individual adult cattle (usually over 6 years of age) in both housing and pasture conditions. The history is usually that of a chronic progressive respiratory disease several weeks to 2 years in duration. Affected cattle remain bright and alert and continue to eat until the terminal stages of cor pulmonale and heart failure intervene. Signs include marked weight loss; consistent coughing; tachypnea (40 to 70 breaths/min); very marked hyperpnea, even at rest; and dyspnea after mild exertion. Auscultation may reveal crackles in the rostral-ventral lung field and widespread wheezes. Fever is not apparent. The primary differential diagnoses to consider are other chronic respiratory conditions of individual adult cattle. Chronic suppurative pneumonia and metastatic pneumonia can usually be differentiated from fibrosing alveolitis by careful physical examination and detection of depression, anorexia, shallow respiration, thoracic pain, and hemoptysis. ARDS caused by feed-associated pneumotoxins and lungworms are typically group problems, with at least some severe cases in the group. Differentiation from EAA may be impossible if the group outbreak nature of farmer's lung is not apparent; in fact, at least some cases of fibrosing alveolitis may represent chronic farmer's lung. At necropsy the lungs are very pale, firm, and heavy throughout. Scattered lobules are gray-red, slightly collapsed, and edematous. Thick mucus may be found in the airways, and there is frequently right ventricular hypertrophy as a result of cor pulmonale. Histologic changes are diffuse and include interalveolar fibrosis and infiltration with plasma cells, lymphocytes, mast cells, and interstitial cells; obliteration of alveolar spaces; mononuclear exudates in alveoli; alveolar epithelial hyperplasia; bronchitis; and bronchiolitis. The epithelioid granulomas characteristic of acute farmer's lung are absent.[460] No treatment exists, and the lesions are irreversible.

31.63.2 Bronchiolitis Obliterans

Bronchiolitis obliterans is a chronic respiratory condition of yearling or young adult cattle characterized by a deep infrequent cough, tachypnea, hyperpnea, and an exaggerated expiratory effort. There is no fever. The cause is unknown; the condition is speculated to be a sequela to viruses (RSV, PI3, IBR), parasites such as *Dictyocaulus viviparus*, or hypersensitivity pneumonitis. The lungs appear grossly normal at necropsy, except that they do not collapse. Histologic examination reveals extensive bronchiolitis and bronchiolitis obliterans, with epithelium-covered polyps with a connective tissue core projecting into and obstructing the lumen.[460]

31.64 PARASITIC BRONCHITIS AND PNEUMONIA

ANNE M. ZAJAC

Two parasites in cattle (*D. viviparus* and aberrant migration of *Ascaris suum* larvae) and three in sheep and goats *(Dictyocaulus filaria, Protostrongylus rufescens*, and *Muellerius capillaris)* may cause respiratory disease characterized by alveolar and interstitial pneumonia. Other species of lungworms also parasitize small ruminants but are less widely distributed throughout the world.

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31.64.1 Lungworms of Cattle

31.64.1.1 Dictyocaulus Viviparus

31.64.1.1.1 Definition and Etiology

D. viviparus is a trichostrongylid nematode parasitizing the bovine trachea and bronchi. Adult worms may reach 8 cm in length. The lifecycle of *D. viviparus* is direct. Adult female worms in the trachea and bronchi lay eggs that hatch almost immediately. First-stage larvae are coughed up, swallowed, and passed in the feces. Larvae develop in a minimum of 5 days (usually longer under normal environmental conditions) to the infective third stage, migrate onto grass, are ingested, penetrate the intestine, and move to the mesenteric lymph nodes, where they molt. Fourth-stage larvae travel through lymph and blood to the lungs and tend to lodge in the pulmonary capillaries of the ventral parts of the caudal lobes. Approximately 7 days after ingestion, they enter the alveoli and molt to the fifth (final) stage in the bronchioles several days later. Egg-laying adults are present in the bronchi 21 to 28 days after ingestion of larvae. Clinically evident infection with *D. viviparus* typically occurs in young, nonimmune stock (less than 12 months old) or in previously unexposed yearling or adult cattle. A reinfection syndrome can also occur when previously infected (and therefore immune) adults are subjected to massive challenge with infective larvae.[529,530]

31.64.1.1.2 Clinical Signs and Differential Diagnosis

Primary infection with *D. viviparus* can be broken down clinically into a prepatent phase, a patent phase, and a postpatent phase.[531] No signs are associated with the initial penetration of larvae until they reach the alveoli, where they provoke an eosinophilic exudate that blocks small airways. During the prepatent phase (approximately 7 to 25 days after ingestion), there is a gradual onset of coughing and tachypnea (35 to 60 breaths/min), which becomes increasingly apparent from day 14 to day 25. The severity of signs in this

stage is proportional to the number of larvae ingested, the rate of ingestion, and the proportion reaching the lungs. Severe illness and death can occur in cases of heavy infection. In the patent phase (approximately 25 to 55 days after ingestion), a parasitic pneumonia with consolidation develops in the ventral areas of the caudal lung lobes as a result of aspiration of eggs and larvae into these areas. Tracheitis and bronchitis associated with the adult worms also develop. Clinical signs vary in severity and range from intermittent to marked coughing, tachypnea (respiratory rate may increase to more than 70 breaths/min), dyspnea, anorexia, and weight loss. Fever may develop with secondary bacterial infection. Auscultation reveals harsh breath sounds and widespread crackles and wheezes. In severe cases animals may exhibit open-mouth breathing, extended head and neck, protrusion of the tongue, and an expiratory grunt. Death is common in untreated, heavily infected animals.[530,531]

Recovery begins in the late patent phase, and the signs gradually resolve, sometimes over several months. During the postpatent phase (about days 55 to 90), adult parasites are expelled by a self-cure phenomenon. In approximately 25% of severe cases the postpatent phase is characterized by a sudden exacerbation of dyspnea at days 45 to 60 that is often fatal, after secondary bacterial infection or alveolar epithelialization.[529,531] The reinfection syndrome occurs 14 to 16 days after adult cattle are placed on heavily contaminated pastures. Signs include acute hypogalactia; severe, frequent coughing; marked tachypnea; and depression. Auscultation reveals only harsh breath sounds with no crackles or wheezes.[529,531]

Differential diagnosis should be straightforward if both the clinical signs and epidemiologic characteristics of the disease are taken into account, especially in endemic areas. This is a disease of groups of cattle at pasture, typically in late summer or fall in northern temperate climates; the situation thus resembles ABPEE, which differs in clinical signs (i.e., less coughing and fewer adventitious lung sounds). The signs associated with lungworm infection are reminiscent of those of farmer's lung, which occurs in quite different circumstances. In typically nonendemic areas, outbreaks associated with climatic changes are frequently mistaken for acute bacterial bronchopneumonia.[529]

31.64.1.1.3

Diagnosis

Larvae of *D. viviparus* are large (390 to 450 µm × 25 µm) and slow moving and contain dark food granules. They are best detected by the Baermann test[532] and may also be seen on a transtracheal wash. It is best to check several animals in the herd. Rectal fecal samples are preferred for parasite examination because samples picked up off the ground may contain free-living nematodes that can be difficult to differentiate from lungworm larvae. Recovery of larvae from fecal samples is substantially diminished if the sample is stored at room temperature for more than a few hours. If the Baermann test cannot be set up soon after fecal collection, the sample can be safely refrigerated for 24 to 48 hours without serious larval loss.[533] No larvae are detected in the reinfection syndrome. In some European countries an ELISA technique that can detect adult infection is also available[534] (Cypress Diagnostics, Langdorp, Belgium). An increase in eosinophils in the peripheral blood may also occur approximately 2 weeks after infection, peaking at 4 to 7 weeks after infection.[535]

31.64.1.1.4

Pathophysiology

Once the fourth-stage larvae enter the alveoli, they incite an eosinophilic exudate that blocks small bronchi and bronchioles, resulting in atelectasis and causing the cough and tachypnea of the prepatent phase. As these larvae mature and migrate up the airways, these lesions may resolve. However, the adult worms

produce an inflammatory response in the larger airways, and aspirated eggs and larvae cause a marked macrophage and giant cell response, with consolidation of the ventral caudal lobes; these lesions are the cause of the signs in the patent phase. At any point in the pathogenesis (prepatent, patent, or postpatent stage), complications may occur that account for acute exacerbation and death. These complications are as follows:

- Development of pulmonary edema caused either by heart failure or by extensive alveolar epithelial damage and hyaline membrane formation
- Severe interstitial emphysema from the severe dyspnea
- Alveolar epithelial hyperplasia
- Secondary bacterial infection, which is actually relatively uncommon

In the reinfection syndrome the immune response cannot completely overcome a massive challenge, and a small number of larvae reach the lungs. The signs are caused by the immune reaction to the migrating larvae. Lymphoid nodules develop around dead larvae in the bronchioles.[529–531]

31.64.1.1.5

Epidemiology

Parasitic bronchitis and pneumonia in cattle occur most often in temperate areas with high rainfall or intense irrigation. In the United States, lungworm infection is widely distributed, but disease outbreaks are uncommon, probably because periods of dry summer weather limit larval survival and accumulation on pasture.[530] In the southern United States, lungworm transmission is probably greatest in the cool winter months,[536] whereas autumn is probably the season of most intense transmission in the northern United States.[537,538]

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Dictyocaulus infections have been studied extensively in Europe, where the parasite is an important pathogen. Disease outbreaks occur most frequently in first season grazing animals. If large numbers of larvae are present on pasture at spring turnout of calves, disease may develop at that time. Often, however, levels of pasture larvae are too low to cause disease, but lead to low-level primary infections in calves that result in the accumulation of additional larvae on pasture. This second wave of infection may lead to clinical lungworm disease when the primary infection did not produce adequate levels of immunity. If infection levels remain low, disease may not be observed until a third generation of parasites occurs. Immunity develops beginning about 10 days after heavy infection, and patent infections usually persist for only a few months. In the absence of continued exposure to parasites, immunity to reinfection will begin to decline after several months.[530,539]

Older animals without immunity also develop lungworm disease when exposed to high levels of pasture contamination with larvae. This can occur when animals from a nonendemic area are moved to an endemic area. In recent years outbreaks of primary parasitic bronchitis have become an important cause of respiratory disease in adult dairy cows in Europe. The increased prevalence of disease in this older age-group is likely the result of decreased levels of immunity after the widespread use of powerful suppressive anthelmintic regimens in first and second season grazing animals. Other management factors, such as isolation of calves from adult carrier animals and increased movement of livestock, may also contribute to a decline in levels of immunity.[534,540] Beef animals are less often affected than dairy cattle because

management practices are more extensive and levels of infective larvae on pastures are generally lower.[530] The reinfection syndrome occurs in immune adult animals when, for example, immune cows are placed on a pasture previously contaminated very heavily by calves with patent disease.[529,530]

In northern temperate climates, the infection is carried from year to year by overwintering of larvae on pasture in some areas, by spreading of manure from infected housed calves in the spring, and by carrier cattle. Lungworm larvae also may be inhibited in the lungs of calves in winter (as with *Ostertagia* species in the abomasum) and mature in the spring.[529,531]

31.64.1.1.6

Necropsy Findings

In the prepatent phase the lungs are largely normal, with a few atelectatic lobules in the ventral caudal lobes; adult worms are not present until late in this phase, but larvae may be detectable by microscopic examination of smears of bronchial exudate. In the patent phase there is usually bilaterally symmetric red consolidation of the ventral caudal lobes. Adult worms can be recognized on necropsy by their relatively large size and location in the trachea and bronchi. The lesions of the postpatent phase are similar, but no adult worms or larvae are present. In those patients that die of an acute exacerbation, there is extensive pulmonary edema and emphysema, with hyaline membranes and alveolar epithelial hyperplasia.

Table 31-12 Anthelmintics Approved for Treatment of *Dictyocaulus viviparus* in the United States

Anthelmintic	Formulation	Residual Efficacy of a Single Treatment	Approved for Dairy Cattle of Breeding Age
Levamisole	Drench, bolus, injection		
Fenbendazole	Paste, suspension, medicated feed, mineral		+
Oxfendazole	Suspension		
Albendazole	Paste, suspension		
Ivermectin	Injection, pour-on	28 days	
Eprinomectin	Pour-on	28 days	+
Doramectin	Injection, pour-on	Injection: 28 days Pour-on: 21 days	
Moxidectin	Pour-on, injection	42 days	+ Pour-on only

In the reinfection syndrome the pulmonary lymphoid nodules may be 3 to 4 mm in diameter and thus grossly visible as raised, gray-red to greenish yellow nodules under the pleura. Initially these are composed of a core of eosinophilic parasitic debris surrounded by macrophages, multinucleated giant cells, hyperplastic bronchiolar epithelium, eosinophils, and plasma cells. The lesions eventually mature to lymphoreticular nodules with a germinal center. There is also greenish mucus in the airways and a greenish discoloration to the tissues, both caused by eosinophil infiltration. There is no edema or emphysema, and the rare lungworms that may be found are small and stunted.[529]

31.64.1.1.7

Treatment, Prognosis, Prevention, and Control

D. viviparus infection can be treated with a number of bovine anthelmintics available in the United States and other countries (Table 31-12). Macrocyclic lactone products also have residual efficacy against *D. viviparus*.[541] Animals with only cough and tachypnea respond well, whereas those with dyspnea, fever, anorexia, and depression have a more guarded prognosis; some of these can be expected to die or remain chronically unthrifty.[529] Control (see also Chapter 49) involves appropriate pasture management and the strategic use of anthelmintics to prevent buildup of infection in the herd and on pastures. Several strategic deworming programs have been developed in Europe, which effectively suppress lungworm infection throughout the grazing season. These programs include use of ivermectin at 3, 8, and 13 weeks after turnout and use of doramectin or eprinomectin at 0 and 8 weeks. Use of an oxfendazole pulse release bolus (not available in the United States) also provides strategic treatments. Alternatively, use of a continuous-release ivermectin or fenbendazole bolus (not available in the United States) will prevent development of lungworm infection during its period of efficacy.[540] A long-acting moxidectin injection product that provides protection from lungworm infection for 120 days is also now available in some countries.[542] Anthelmintic treatment with moxidectin or fenbendazole followed by movement of calves to safe pasture 9 weeks after turnout was also effective in controlling lungworm.[543] None of these control programs have been extensively tested under the variety of grazing conditions found in the United States.

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Despite concern that suppressive programs may limit exposure to larvae and interfere with the development of immunity to lungworm, several studies conducted in Europe have shown that stimulation of the immune response still occurs, although relative levels of immunity may vary with different management systems and annual variation in the intensity of lungworm challenge.[534,544–546] In Europe, methods of control also include an effective irradiated larval vaccine, although use of the vaccine has diminished with the introduction of suppressive anthelmintic programs. Delay of spring turnout is an adjunct to control but should not be relied on as the sole means of control.[545] A targeted selective deworming program was successful in controlling lungworm infection in a dairy herd in Sweden. Only cattle testing positive for lungworm by the commercial ELISA test were treated at each sampling date.[547]

31.64.1.1.7.1

ASCARIS SUUM

Cattle exposed to large numbers of *A. suum* eggs in areas contaminated by swine may have an interstitial pneumonia. Animals are typically affected approximately 10 days after exposure. Signs include depression, anorexia, fever, tachycardia, tachypnea, dyspnea with an expiratory grunt, variable coughing, ruminal stasis, and bloat. Auscultation of the lungs reveals increased breath sounds without adventitious sounds. Some deaths may occur. Differential diagnosis is difficult. Differentiation from the other interstitial pneumonias depends more on history of exposure to the causative agents (e.g., lush pastures, moldy sweet potatoes, *P. frutescens*, toxic gases, moldy hay). Differentiation from viral pneumonia (such as that caused by RSV) and *D. viviparus* reinfection syndrome requires necropsy and demonstration of larvae. Ascarid larvae have characteristic lateral alae in histologic sections. Patent *D. viviparus* infection can be differentiated by Baermann examination of the feces. In fatal cases the lung lobes are firm and mottled blue, red, and gray. The cut surface oozes thin yellow exudate. There is emphysema in the dorsal diaphragmatic lobes and subpleural hemorrhage with neutrophil infiltration and necrosis of bronchiolar and alveolar epithelium. In chronic cases the cellular infiltrate is lymphocytic, and there are proliferation of bronchiolar epithelium and peribronchial fibrosis. Recommended treatments include corticosteroids

(dexamethasone, 0.04 mg/kg IM or IV, or prednisolone 1 mg/kg IM or IV daily) and antibiotics to control secondary bacterial infection.[548] Clinical signs resolved after treatment with oxfendazole in one outbreak of suspected *A. suum* migration.[549] Cattle should not be exposed to areas heavily contaminated by swine.

31.64.1.2

Lungworms of Sheep and Goats

Three species of lungworms are of primary importance in sheep and goats: *D. filaria* and the two metastrongylid nematodes, *M. capillaris* and *P. rufescens*. Other genera of metastrongylid lungworms of minor pathogenic importance in sheep and goats include *Cystocaulus, Spiculocaulus*, and *Neostrongylus*. These parasites are rare or absent in North America.[550]

31.64.1.2.1

DICTYOCAULUS FILARIA

D. filaria has a lifecycle essentially identical to that of *D. viviparus;* the time from ingestion to the appearance of larvae in the feces is about 4 weeks. Mainly young animals are affected, but disease can also occur in adults. Dyspnea, tachypnea and coughing, and loss of condition occur in clinical cases.[550,551] Differential diagnosis includes the progressive viral pneumonias. Diagnosis is made by finding larvae in fresh feces by the Baermann test.[532] Samples should be tested soon after collection because larval recovery is significantly reduced in stored samples.[533] Larvae of *D. filaria* are similar in size and appearance to those of *D. viviparus* but also have a distinctive knob on the anterior end. The pathogenesis is similar to that of *D. viviparus* (see earlier discussion). The adults are found largely in the dorsal-caudal regions of the diaphragmatic lobes. Bronchitis and peribronchitis, along with cone-shaped areas of pneumonia and atelectasis, and emphysema are present. Secondary bacterial infections may also occur.[550,551] Levamisole (8 mg/kg), fenbendazole (5 to 10 mg/kg), ivermectin (0.2 mg/kg PO),[551] and moxidectin (0.2 mg/kg, PO or SC)[552–554] can be used for treatment. When outbreaks occur, all animals should be treated and moved to fresh pasture when possible. Clinical *D. filaria* infections seem to occur most frequently in areas with warm climates. In temperate areas the parasite overwinters either as arrested larvae in ewes or as larvae on pasture.[550]

31.64.1.2.2

MUELLERIUS CAPILLARIS

M. capillaris is probably the most common of the lungworms of sheep and goats. Infection is more pathogenic in goats than in sheep. Surveys in Maryland and Georgia detected the parasite in 64% and 68% of goats, respectively.[555,556] The lifecycle is indirect. First-stage larvae are coughed up, swallowed, and passed in the feces. These larvae are relatively resistant and may survive for several months in the environment. After penetration of an appropriate molluscan intermediate host, the infective third stage develops in a minimum of about 12 days, is ingested with the snail, and passes to the mesenteric lymph nodes. The fourth stage larva proceeds to the lungs, where adults develop in the alveoli. The prepatent period of *M. capillaris* infection is about 6 weeks.[557] Although many infections are subclinical, clinical disease may develop. Goats appear to be more likely than sheep to develop unthriftiness, coughing, and dyspnea. Infection may also predispose to secondary bacterial infection.[551,558] The difference in clinical signs between sheep and goats probably results from a difference in the pathogenesis of infection. The adult worms live in the pulmonary parenchyma, particularly the subpleural tissue. In sheep they produce grayish nodules typically 2 to 3 mm in diameter. On palpation at necropsy, these nodules have been described as

feeling like "lead shot."[557] Each nodule contains a worm and necrotic leukocytes and pulmonary tissue surrounded by a connective tissue wall and giant cells.[550] They may calcify or become secondarily infected with bacteria. Reports of lesions in goats indicate that *M. capillaris* causes an interstitial pneumonia. The lungs are resilient and firm, fail to collapse, and have tan, yellow, or gray patches located especially in the dorsal diaphragmatic lobes. The histologic lesion in goats is a diffuse thickening of alveolar septa, with a mononuclear cell infiltrate and alveolar epithelial hyperplasia that extends far beyond the area immediately around the parasite. The local reaction around the worm is quite variable and does not appear to produce the nodules seen in sheep.[558] Diagnosis is made by Baermann examination of the feces. The larvae are smaller than those of *D. filaria* and have a kink at the end of the tail with a characteristic subterminal accessory spine.[532]

Several anthelmintics have been used in the treatment of *M. capillaris* infections. Moxidectin (0.2 mg/kg in oral or injectable formulation) is effective in treating sheep infected with *M. capillaris* and other small lungworms *(Cystocaulus ocreatus, Neostrongylus linearis*, and *P. rufescens)* and may be equally effective in goats.[559] Although larvae may initially disappear in the feces after treatment, they often reappear in fecal samples again after 1 to 2 months, either because anthelmintics are ineffective against immature worms and/or because of resumption of development by inhibited larvae.[559] Treatments that appear to eliminate adult parasites in goats include fenbendazole (15 to 30 mg/kg),[557,558,560–562] albendazole (10 mg/kg),[562] oxfendazole (7.5 to 10 mg/kg),[563] and ivermectin (0.3 mg/kg).[560,564] *M. capillaris* is largely resistant to levamisole.[551] Better control of immature or inhibited larvae with fenbendazole was achieved by administering the drug (1.25 to 5 mg/kg) for 7 to 14 days, although a regimen of 1 week on/1 week off/1 week on appeared to provide the most effective treatment. Albendazole (1 mg/kg) PO daily for 7 to 14 days was also effective.[562] Possible teratogenic effects of extended benzimidazole treatment in goats have not been thoroughly investigated, and albendazole should be used cautiously in the first 35 days of pregnancy.[560] Administration of ivermectin (0.3 mg/kg) or fenbendazole (15 mg/kg) two or three times at 35-day intervals has also been suggested for treatment.[551] Control methods include avoiding wet pastures and treating animals before the start of the grazing season to reduce infection levels in the intermediate host.[551]

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31.64.1.2.3

PROTOSTRONGYLUS RUFESCENS

P. rufescens also uses molluscan intermediate hosts, and adults develop in the small bronchioles of sheep and goats.[557] Most infections are probably subclinical or produce only mild signs of chronic bronchitis or bronchopneumonia with nasal discharge and cough. Occasionally *P. rufescens* may produce severe or even fatal disease.[565] The diagnosis of *Protostrongylus* species infection is made by finding larvae in the feces with the Baermann technique. The larvae are similar to those of *Muellerius* except *Protostrongylus* larvae lack the subterminal accessory spine on the tail.[532] Fenbendazole, levamisole,[565] and moxidectin[559] can be used for treatment at the dosages used for *Dictyocaulus*. Other macrocyclic lactone products may also be effective but have not been tested. Control strategies are identical to those for *M. capillaris*. Few cases of infection have been reported in the United States, but nonspecific clinical signs, presence of subclinical carriers, and need for a special diagnostic technique may produce an underestimation of the prevalence of *P. rufescens* infection in sheep and goats.[565]

31.65 PROGRESSIVE BACTERIAL AND VIRAL PNEUMONIAS OF SHEEP AND GOATS

JEANNE LOFSTEDT

Chronic progressive pneumonias are diagnosed with some frequency in mature small ruminants. In sheep, OPP and *C. pseudotuberculosis*–induced mediastinal lymph node and lung abscesses are the chief causes of chronic progressive pneumonia. Chronic progressive pneumonia in goats is commonly associated with the pneumonic form of CLA, and less frequently with CAE virus (CAEV)–induced lung lesions. Differential diagnoses that should be entertained in sheep and goats exhibiting signs of chronic pneumonia include OPA, chronic suppurative pneumonia, verminous pneumonia, mycotic pneumonia, tuberculosis, and pulmonary neoplasia.

31.66 OVINE PROGRESSIVE PNEUMONIA (MAEDI-VISNA)

31.66.1 Definition and Etiology

OPP and maedi-visna (MV) are North American and European names for slow viral diseases of sheep characterized by chronic, progressive, debilitating pneumonia, wasting, and indurative mastitis.[566–568] Synonyms are Marsh's progressive pneumonia, zwoegerziekte, la bouhite, and Graaff-Reinet disease.[566,567] The OPP virus (OPPV) and MV virus (MVV) are nononcogenic exogenous retroviruses that belong to the subfamily Lentiviridae.[569] These enveloped, single-stranded RNA viruses contain the enzyme RNA-dependent DNA polymerase (RT). With this enzyme they use cellular machinery to transcribe a segment of DNA from a template of single-stranded viral RNA; the DNA strand or provirus is then incorporated into the host genome. Close similarity of causal viruses, clinical signs, and lesions produced in tissues permits discussion of OPP and MV as a single disease entity.[567] The ovine lentiviruses (OvLVs) are also related to the CAEV of goats, but differences have been demonstrated through nucleic acid hybridization studies.[570]

31.66.2 Clinical Signs and Differential Diagnosis

Conditions in sheep attributed to infection with OvLV include progressive emaciation (“thin ewe syndrome”), progressive respiratory failure, indurative lymphocytic mastitis (“hard bag”), posterior paresis, chronic nonsuppurative arthritis, and vasculitis.[566–571] In North America progressive pneumonia and aseptic mastitis are the most common clinical manifestations.[567] Natural disease is usually observed in 2- to 3-year-old sheep, but adult sheep of any age can be affected.[567,568,570] Emaciation despite a good appetite is one of the earliest symptoms. Clinical signs of progressive pneumonia include exercise intolerance, tachypnea, expiratory dyspnea, open-mouth breathing, and occasionally a nonproductive cough. Thoracic auscultation reveals increased breath sounds, but crackles and wheezes are inapparent. Pyrexia and purulent nasal discharge usually indicate the presence of secondary bacterial pneumonia. Affected ewes give birth to small, weak lambs. Death from anoxia or secondary bacterial infection occurs within 6 to 12 months of first appearance of signs.

Chronic pneumonias of sheep that have to be differentiated from OPP include chronic bronchopneumonia caused by *M. (Pasteurella) haemolytica*, OPA, verminous pneumonia, and pulmonary and lymph node abscesses caused by *C. pseudotuberculosis*.[566,569] Thoracic radiographs, culture of tracheal wash material, and fecal examination by the Baermann technique are useful for antemortem differentiation. Gross and histopathologic evaluations of pulmonary tissues obtained at necropsy are useful for diagnosis of a flock problem.

31.66.3 Diagnosis

Hematologic changes in sheep with OPP are nonspecific and may include lymphocytosis early in the course of disease and mild hypochromic anemia and hypergammaglobulinemia in advanced disease.[570] A presumptive diagnosis of OPP can be made on the basis of clinical signs, lack of response to treatment, and serologic test results. Currently available serologic tests are run by different laboratories using different techniques, making comparisons difficult. The serologic tests commonly used to detect antibodies to OvLV in serum are the AGID test and ELISAs.[566–568] The simplicity and low cost of the AGID test makes it the test of choice for eradication programs.[566,572] Several authors have suggested that ELISA tests are more sensitive than the AGID test.[566,572,573] However, in a study comparing the AGID test with 2 recombinant ELISA tests the AGID test was found to have a specificity of 100% and a sensitivity of 11% 2 weeks postinfection, and 100% 5 weeks postinfection.[566] In comparison, ELISA tests directed against the OvLV core protein or the OvLV transmembrane protein had mean sensitivities of 88% and 86%, respectively, and mean specificities of 95%.[566] ELISA tests may produce false-negative results in recently infected animals as they detect IgG rather than IgM. 656
[566] Virus isolation can be used to definitively identify OvLV-infected animals.[566,569] Virus isolation, which is 657
time-consuming and expensive, is accomplished by coculture of infected fresh or frozen tissue with indicator cell lines. In culture, retroviruses form characteristic multinucleated syncytia.[570] Viral antigens can be detected in these syncytia by use of immunofluorescent staining.[570] PCR testing has been used as a research tool to demonstrate OvLV DNA in clinical specimens from naturally infected sheep.[574]

31.66.4 Pathophysiology

OvLVs are thought to gain access to the body via the oral or respiratory route. Infection is then established in the monocyte or macrophage cell line and spreads via these infected cells to the lungs, lymph nodes, choroid plexus, spleen, bone marrow, mammary glands, and kidneys.[570] The virus is able to persist in the face of humoral and cellular immunity through (1) latent infection of host cells by DNA provirus, (2) long-term nonproductive infection of blood monocytes (virus replicates only on differentiation of monocytes into macrophages), and (3) virus mutation with emergence of new antigenic variants that are not neutralized by preexisting antibody.[570]

31.66.5 Epidemiology

The seroprevalence of OPP in cull ewes in the United States ranges widely and increases with advancing age.[566] With the exception of West Texas, with an infection rate of 0.5%, serologic surveys in cull ewes in other states have revealed infection rates of 30% to 67%. The low seroprevalence in Texas has been attributed to the hot dry climate and extensive grazing practices.[570] Limited studies in large mixed-breed flocks have provided evidence that some sheep breeds may be more resistant to infection than other breeds.[566] Additional research is required before a particular breed or line of sheep can be viewed as resistant to OvLV infection. The lung and mammary gland are believed to be the main sources of excreted virus.[566] Studies conducted in Europe and Iceland have shown that transmission from the ewe to her lambs commonly occurs through the ingestion of infected colostrum and milk.[566] In other studies, close confinement of diseased or seropositive sheep with healthy or seronegative sheep resulted in disease or seroconversion in the previously healthy or seronegative animals; these infections were presumed to have occurred via the respiratory route.[566] OvLV transmission has been shown to occur

through fecal contamination of drinking water.[566] It is likely that other fomites (saliva, nasal discharge, urine) contaminating feed and/or water also contribute to the spread of disease.[507] Transmission through the uterine wall, or via germ cells, can occur but is rare.[566]

31.66.6 Necropsy Findings

Lesions may develop in any or all of the following tissues of OPPV-infected sheep: lungs and regional lymph nodes, brain, joints, mammary glands, and blood vessels.[567] Changes are most obvious in the lungs, which do not collapse on opening of the thorax.[569,570] Vertical rib impressions may be seen on the exterior lung surface. Affected lungs are heavy and have a mottled to uniform pink-brown to gray-blue discoloration. Secondary bacterial pneumonia may cause anterior-ventral pulmonary consolidation. Tracheobronchial and mediastinal lymph nodes are markedly enlarged, bulge on cut surfaces, and are homogeneous, gray-white throughout. Histologic examination reveals a diffuse lymphoproliferative pneumonia characterized by prominent lymphoid follicle formation adjacent to bronchioles and small vessels; discrete nodules of lymphocytes, unrelated to vessels or airways, are also found in the lung parenchyma.[567–570] Lymphocytes, plasma cells, and macrophages infiltrate into interalveolar septa, and hyperplasia of alveolar epithelium and terminal bronchial smooth muscle may be seen.

31.66.7 Treatment and Prognosis

OPP is not treatable. Antibiotics can be used to control secondary bacterial pneumonia, but most sheep die within a year of first exhibiting clinical signs.[567,568]

31.66.8 Prevention and Control

OPPV is difficult to eradicate from a flock once infection is established.[570] Control methods include (1) a “test-and-cull” practice and (2) isolation of infected adults and artificial rearing of their offspring.[567] With the first method, all sheep are tested annually for antibody, and seropositive animals and their progeny younger than 1 year of age are culled or isolated from the negative flock; culling is preferred because of the danger of cross-contamination. New additions should be seronegative and originate from seronegative flocks. Annual testing should be performed until two consecutive negative herd test results are obtained to be reasonably confident that the flock is virus free. With the second method, progeny are removed from their dams before they nurse and are fed cow's colostrum and raised in isolation. The clean herd should be kept isolated from infected sheep and goats and from humans and equipment in contact with infected sheep. Herd additions and annual testing should be handled as described for method one.

31.67 OVINE PULMONARY ADENOCARCINOMA

31.67.1 Definition and Etiology

OPA (sheep pulmonary adenomatosis or jaagsiekte) is a naturally occurring retrovirus-induced bronchioloalveolar carcinoma of sheep and, rarely, goats that has been associated etiologically with a type B/D retrovirus (JSRV).[575,576] OvLVs and herpesviruses have been isolated from OPA tumors; however, they are not consistently present[577] and do not induce OPA when inoculated experimentally.[578,579] One theory is that these

viruses act as cofactors in tumor induction. Defining the role of JSRV in OPA has been complicated by the presence of 15 to 20 endogenous jaagsiekte retroviruses (enJSRVs) that are stably integrated into the genomes of sheep and goats.[580,581] Recent research has indicated that exogenous JSRV is likely not of endogenous origin. There has been speculation that the endogenous viruses may modify the genome of exogenous JSRV, either by inducing the expression of an oncogene or by inactivating a tumor suppressor gene.[576] Sequence analyses of exogenous JSRV and enJSRV suggest that endogenous viruses do not directly contribute to the pathogenesis of OPA through large-scale recombination events, but small-scale recombination or complementation of gene function has not been definitively excluded.[580] There has been speculation that expression of enJSRV in the fetal or neonatal period may influence expression of OPA through induction of immunologic tolerance.[580]

31.67.2 Clinical Signs and Differential Diagnosis

OPA usually affects mature sheep between 2 and 4 years of age, although lambs as young as 3 months of age have been diagnosed with the disease.[576] Clinical manifestations include progressive weight loss, exercise intolerance, tachypnea, dyspnea, occasional cough, and crackles and wheezes on thoracic auscultation. In many cases, presence of abundant watery nasal discharge can be demonstrated by raising the rear limbs and lowering the head of the affected sheep ("wheelbarrow test").[576] Appetite and rectal temperature are usually normal unless secondary infection and intercurrent disease are present. Sheep with OPA typically succumb within a few weeks to months after first exhibiting clinical signs.

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31.67.3 Diagnosis

The only reported laboratory abnormality in sheep with OPA is hypergammaglobulinemia. Some researchers have demonstrated the utility of serologic assays to identify OPA-infected sheep, but other investigators have been unable to demonstrate antibodies to JSRV in the sera of affected sheep.[576] PCR tests, capable of demonstrating viral nucleic acids of endogenous JSRV tissues in OPA-infected animals, have been developed.[575]

31.67.4 Epidemiology

OPA has been reported in many countries in Europe, Africa, and Asia but is a rare occurrence in sheep in Australia and New Zealand.[575,576] The prevalence of OPA varies among countries in which the infection occurs; it is endemic in Scotland, Peru, and South Africa, where annual losses range from 2% to 10%. In contrast, OPA is infrequently diagnosed in the United States and Canada, where totals of 11 and 43 cases, respectively, have been reported.[575,576]

OPA has been reproduced experimentally by intratracheal inoculation of lung homogenates or pulmonary lavage fluids obtained from infected animals.[582] Lambs between birth and 5 weeks of age have been shown to be more susceptible to experimental infection than 10-week-old lambs.[582] This age-related susceptibility to OPA suggests that natural virus transmission occurs in the neonatal period. Aerosol transmission and contamination of feed and water by respiratory secretions are likely methods of disease spread, particularly in confined sheep.

31.67.5 Necropsy Findings

Lungs of OPA sheep are heavy (two to three times normal weight) and exude clear fluid from the cut surface. The trachea and bronchi often contain clear, foamy fluid. Large, firm, gray masses are commonly encountered in the cranioventral regions of one or both lungs. Smaller (1- to 2-cm) nodules are occasionally visualized in the caudodorsal lung regions.[576] Metastasis to regional lymph nodes occurs in approximately 10% of cases, causing pulmonary lymph node enlargement.[583] Metastases to cardiac and skeletal muscles are infrequently reported.[583] Some cases of OPA are complicated by secondary acute or chronic bacterial pneumonia.

OPA is classified by the World Health Organization (WHO) as a bronchioloalveolar carcinoma arising from alveolar type II pneumocytes or nonciliated bronchiolar cells.[583] Neoplastic masses consist of columnar or cuboidal cells arranged in an acinar or papillary pattern. Some tumors are surrounded by areas of fibroplasia.

31.67.6 Treatment and Prognosis

There are no known treatments for this disease. Antibiotics may prolong the life of OPA-affected sheep through control of secondary bacterial pneumonia.[576]

31.67.7 Prevention and Control

Recently a PCR for JSRV, performed on peripheral leukocytes and tissues of naturally infected sheep, demonstrated that this test could detect virus in live sheep before the onset of clinical disease.[575] This may hold promise for instigation of test-and-cull programs in the future. OPA was eradicated from Iceland by slaughtering all sheep in endemic areas.

31.68 CAPRINE ARTHRITIS-ENCEPHALITIS

CAE is a persistent lentiviral infection of goats with two major clinical presentations: leukoencephalomyelitis in kids 2 to 6 months of age and chronic, hyperplastic polysynovitis in mature goats.[584,585] Mild interstitial pneumonia, which is silent clinically, is a common postmortem finding in goat kids with leukoencephalomyelitis.[585] In one study, 60% of goats serologically positive for CAEV had lesions of severe chronic interstitial pneumonia at slaughter.[585] Similarly, chronic interstitial pneumonia, accompanied by exercise intolerance and dyspnea, was described in dairy goats originating from herds that had clinical cases of arthritis and leukoencephalomyelitis.[586] The lung lesions in these goats resembled those of OPP[586,587] and were positive for CAEV. However, CAEV has been recovered from the lungs of goats with advanced arthritis but without pneumonia. In addition, goats inoculated intratracheally with purified CAEV did not develop pulmonary lesions.[586] This may indicate that there is no causal relationship between CAEV and interstitial pneumonia in goats, or that the lesions have a multifactorial cause. CAE is discussed in detail in Chapter 35.

31.69 CASEOUS LYMPHADENITIS

CLA, caused by *C. pseudotuberculosis* (previously known as *C. ovis*), is a worldwide disease of sheep and goats characterized by the development of pyogranulomatous abscesses in lymph nodes and internal organs.[588–591] Once

established in a herd or flock CLA is difficult to eradicate. The disease responds poorly to treatment, infected animals are difficult to detect via clinical signs or diagnostic testing, and the organism tends to persists in the environment.[588,589] CLA most commonly presents as an external form characterized by SC abscesses in superficial lymph nodes.[588] The internal, or visceral, form of CLA manifests as internal abscesses in the mediastinal and mesenteric lymph nodes and internal organs, such as the lungs, liver, spleen, kidneys, uterus, and so on.[588] Goats are more commonly afflicted with external abscesses, whereas the visceral form of CLA appears to be more common in sheep.[588] Visceral CLA may be asymptomatic but is usually associated with ill thrift and significant weight loss.[588,592,593] Clinical signs that may accompany abscesses in the lung parenchyma and mediastinal lymph nodes are exercise intolerance, tachypnea, dyspnea, and chronic cough. Because of the encapsulated nature of pulmonary abscesses and lack of exudate in airways, pulmonary crackles are rarely auscultated.[591] Nonspecific laboratory findings in sheep and goats with CLA include leukocytosis, hyperfibrinogenemia, hyperproteinemia, and hypergammaglobulinemia; however, laboratory findings are frequently normal in animals with chronic abscesses.[591] A definitive diagnosis of visceral CLA with pulmonary involvement can be achieved by demonstrating abscesses in the lungs and mediastinal lymph nodes with thoracic radiography, and by isolating *C. pseudotuberculosis* from a TTA.[588,591] Failure to isolate the organism from tracheal wash fluid, however, does not rule out CLA as the cause of pulmonary disease. Characteristic postmortem findings of the respiratory form of CLA are one to multiple thick-walled, laminated, encapsulated, caseopurulent abscesses in the bronchial lymph nodes, mediastinal lymph nodes, and/or lung parenchyma. The synergistic hemolysis inhibition (SHI) test, which screens for antibodies directed against the phospholipase D exotoxin of *C. pseudotuberculosis*, was developed to diagnose early infections (before the development of SC abscesses) and to assist in the diagnosis of internal abscesses.[594] Any titer higher than 1:4 is suggestive of exposure or early infection.[588] Titers of 1:512 and higher are highly correlated with internal abscesses.[588] In a field study the SHI test had a sensitivity of 96% in sheep and 98% in goats and detected subclinically affected animals.[595] A double-antibody sandwich ELISA directed at *C. pseudotuberculosis* is being employed in Europe to detect subclinically affected sheep and goats and has contributed to successful disease eradication from some flocks.[596] CLA is discussed in more detail in relation to the hemolymphatic system (see Chapter 37).

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31.70 OTHER PNEUMONIAS

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31.71 ASPIRATION PNEUMONIA

Aspiration pneumonia is caused by inhalation of large amounts of foreign material, often liquids. It is also called *gangrenous pneumonia, foreign-body pneumonia, medication pneumonia*, or *lipid pneumonia*. The most common cause is careless drenching or passage of stomach tubes during administration of milk or liquid medication. It also occurs occasionally in pail-fed calves, animals with pharyngeal paresis, animals with necrotic laryngitis, lambs with nutritional myodegeneration, anesthetized animals, sheep that are dipped, cattle that have parturient paresis, and cattle that ingest crude oils or fuel oils.[597,598] Meconium aspiration secondary to fetal distress has been recognized as a possible risk factor of neonatal calf mortality.[599] The condition is characterized by a mild diffuse alveolitis that results in hypoxia and acidosis, which leads to impaired absorption of colostral antibodies and inadequate passive transfer in affected calves.

If large quantities of fluid are aspirated, death may be almost instantaneous, but generally a gangrenous bronchopneumonia develops as a result of infection and the irritating properties of the inhaled material. Affected animals exhibit depression, polypnea, dyspnea, coughing, and fever and may have putrid breath. Crackles, wheezes, and occasionally pleural friction rubs can be heard on auscultation.

Diagnosis is based on the history, sudden onset, and severe signs. Differential diagnoses include acute bronchopneumonia and septicemia. Necropsy reveals consolidation of the anterior ventral areas of the lungs. Affected areas are severely hemorrhagic in acute cases and contain suppuration and liquefactive necrosis in subacute cases.

The prognosis is guarded in all cases of aspiration pneumonia, but some animals can be saved. Antibiotics combined with antiinflammatory agents should be promptly administered, and long-term antimicrobial therapy is required. Prevention of aspiration pneumonia centers on careful administration of medication and avoidance of other risk factors that may promote inhalation of foreign materials.

31.72 MYCOTIC PNEUMONIAS

Ruminants may occasionally have pulmonary infections with *C. immitis, Aspergillus* species, *H. capsulatum, C. albicans*, and fungi of the order Mucorales.[600] Coccidioidomycosis occurs in cattle and much less commonly in sheep and goats in the southwestern United States. It causes very few clinical signs in ruminants, but the occasional animal may exhibit a chronic cough and weight loss. Differential diagnoses include tuberculosis and CLA. Radiologic evaluation is helpful in establishing the presence of pulmonary masses. The diagnosis may be confirmed by culture, histologic identification of the characteristic spherules, and intradermal and complement-fixation tests. The organism is obtained from the soil and is not easily transmitted from animal to animal or to human, but nevertheless it represents a serious zoonotic disease concern. The major lesion is a granuloma with creamy pus in the bronchial and mediastinal lymph nodes. There is no treatment. Control of dust may lessen the incidence.[600]

Aspergillosis is a rare condition that usually occurs in housed calves, particularly in those that have had chronic antibiotic or steroid therapy or that are otherwise immunosuppressed or chronically ill. There are three forms. The acute form is characterized by a fibrinous pneumonia with fever, dyspnea, tachypnea, cough, nasal discharge, groaning, and a short course to death. The subacute and chronic forms are less severe and exhibit mainly anorexia, weight loss, and mild respiratory signs. Differential diagnoses include enzootic pneumonia, tuberculosis, and lungworms. Radiographs, transtracheal washings, histopathologic evaluation (with demonstration of branching septate hyphae), and culture of lesions help establish the diagnosis. The subacute and chronic lesions consist of multiple small, white, discrete granulomas with necrotic centers. The acute lesions are those of a severe fibrinous pleuropneumonia.[600] Treatment is frequently ineffective; antifungal agents such as nystatin, amphotericin B, and ketoconazole may be tried in individual cases. Doses and withdrawal times for these drugs are not established for ruminants, and because treatment of fungal pneumonia in other species requires months of therapy, treatment is not likely to be economically feasible in most cases.

Histoplasmosis is rare in ruminants. It is a polysystemic disease with chronic emaciation, dyspnea, diarrhea, and anasarca. An intradermal delayed hypersensitivity test, culture, or histopathologic identification of the yeastlike organism helps to confirm the diagnosis. Lesions include ascites, liver enlargement, gut edema, pulmonary emphysema, and pulmonary edema with abscesses. As described for aspergillosis, antifungal therapy may be attempted but is not likely to be economically feasible.

Pulmonary candidiasis has been reported as an outbreak in a feedlot. It was characterized by a chronic pneumonia with severe dyspnea but only moderate fever; a mucopurulent, brown-streaked nasal discharge; diarrhea; a crusted muzzle; and lacrimation without conjunctivitis. Differential diagnoses should include the various upper respiratory viruses, particularly IBR and BVDV, and bacterial bronchopneumonia. The diagnosis is made by the presence of the budding yeastlike organism in smears and cultures. Lesions include lung consolidation and abscesses.[600] Treatment has not been investigated.

Zygomycosis, phycomycosis, and mucormycosis are synonyms for a very rare opportunistic disease in ruminants. This is a systemic fungal infection that may affect the lung, stomach, liver, brain, and lymphatic system. Cattle with *Mucorales* species pneumonia exhibit tachypnea, dyspnea, nasal discharge, fever, and anorexia. The pulmonary lesions are a fibrinous pleuritis with firm, heavy, wet, mottled lungs. Histopathologic demonstration of broad aseptate hyphae in affected tissue and culture are the best means of diagnosis.[600] Treatment has not been investigated.

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31.73 VENA CAVAL THROMBOSIS AND METASTATIC PNEUMONIA

31.73.1 Definition and Etiology

Metastatic or embolic pneumonia in cattle, also called *caudal vena caval thrombosis, pulmonary thromboembolism*, and *embolic pulmonary aneurysm*, is a distinct syndrome associated with multifocal abscessation of the lungs caused by septic thromboembolism of the pulmonary arterial system. The septic emboli arise from septic thrombi of the caudal vena cava (Fig. 31-68) or, less commonly, the cranial vena cava. Vena caval thrombi are in turn a sequela to various septic conditions such as jugular phlebitis, mastitis, metritis, foot rot, or, most often, liver abscesses secondary to rumenitis.[601] A variety of bacteria may be involved; those most frequently encountered include *F. necrophorum, Arcanobacterium (Actinomyces) pyogenes*, staphylococci, streptococci, and *E. coli*.

31.73.2 Clinical Signs

Because of its association with rumenitis, this condition is most commonly seen in feedlot cattle, but any age, breed, sex, and class of cattle may be affected. The problem is unusual in cattle less than 1 year of age. Cattle with metastatic pneumonia usually exhibit respiratory disturbance or weight loss or occasionally thoracic pain. The duration of signs is quite variable, ranging from acute respiratory distress to a chronic history of weight loss and coughing for weeks to months.[602,603] The classic presentation includes tachycardia, tachypnea (respiratory rate over 30 breaths/min), expiratory dyspnea and groaning, hyperpnea, coughing, heart murmurs and pale mucous membranes (caused by anemia), widespread wheezes, epistaxis, and hemoptysis.[601,602] Other signs, which are more variable, include fever, thoracic pain on deep palpation of the sternum and intercostal spaces, hepatomegaly (indicated by the ability to palpate the caudal edge of the liver in the right paralumbar fossa), SC emphysema, froth at the muzzle, and melena caused by coughing up and swallowing blood.[601,602] Nonspecific accompanying signs include depression, anorexia, ruminal stasis, scant feces, and decreased milk production. In chronic cases cor pulmonale may lead to signs of right ventricular failure such as jugular distention and brisket edema.[602] The combination of respiratory signs with anemia, widespread wheezes, and especially hemoptysis is generally regarded as pathognomonic for this syndrome.[602] Animals usually deteriorate rapidly once hemoptysis becomes evident, and the condition is essentially 100% fatal. Many patients die suddenly with an acute episode

of severe intrapulmonary hemorrhage or hemoptysis after a variable course of respiratory disease. Some of these cases in which the respiratory signs were overlooked may account for the reports of sudden death attributed to vena caval thrombosis.[602] Caudal vena caval thrombosis can also lead to hepatomegaly and extensive ascites, but most of these animals also have respiratory signs.[603] Sudden erosion of a large hepatic abscess into the caudal vena cava may also result in a massive embolic shower, with acute respiratory distress and death.[603]

Fig. 31-68 Postmortem photograph of thrombus in caudal vena cava, which leads to embolic pneumonia demonstrated in Fig. 31-69. Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.

In patients with the pathognomonic signs (the majority of cases), no differential diagnoses need be considered. However, many patients are examined before the onset of hemoptysis, and a few may die without exhibiting these signs.[603] Differential considerations in such cases, which usually manifest as acute dyspnea, should include anaphylaxis, the various ARDSs, hypersensitivity pneumonitis, lungworms, and acute bronchopneumonia. Patients with right ventricular failure should be differentiated from those with pericarditis, lymphosarcoma, cardiomyopathy, and endocarditis.

31.73.3 Pathogenesis

The classic pathogenesis of this disease begins with the development of rumenitis secondary to lactic acidosis caused by highly fermentable diets such as those used in feedlots, some dairies, and some growing rations. Bacteria such as *F. necrophorum* and *A. pyogenes* are then able to penetrate the damaged ruminal epithelium and are transported to the liver in the portal drainage system, where they are filtered out and result in abscesses. If an abscess is located next to the caudal vena cava (where the vessel is closely applied to the left border of the liver), a septic thrombus may form in the vena cava as a result of infiltration of its wall by the abscess (see Fig. 31-68). Septic emboli detach from the thrombus and reach the lungs through the pulmonary arterial system. Alternatives to this classic pathway are rare; they include the following: thrombosis of the cranial vena cava from primary lesions such as jugular phlebitis, thrombosis of the caudal vena cava from other subdiaphragmatic abscesses, right-sided endocarditis, and emboli arising from other septic foci such as mastitis, metritis, and foot rot. Large emboli may block lobar or larger arteries, causing an acute crisis and death. More typically, smaller emboli lodge in arterioles, where they cause arterial thromboembolism, arteritis, endarteritis, and pulmonary abscesses (Fig. 31-69). The widespread arterial embolism also results in pulmonary arterial hypertension. Arteritis and endarteritis weaken the vessel walls and, in combination with pulmonary hypertension, lead to the formation of aneurysms. In some cases a perivascular abscess not only erodes an arterial wall to produce an aneurysm but simultaneously erodes a bronchial wall; when the aneurysm ruptures, the abscess cavity channels the blood into the bronchus, resulting in massive hemoptysis. In other cases, rupture of aneurysms results in large interstitial hematomas. Both processes result in anemia; when coughed-up blood is swallowed, melena may result. Coughing and wheezes are probably caused by blood clots in airways, peribronchial aneurysms and abscesses, and suppurative pneumonia. Pain results from dissecting aneurysms and hematomas.[602]

31.73.4 Epidemiology

Metastatic pneumonia accounted for 1.3% of necropsy diagnoses in one large feedlot survey, with a rate varying between 1.6 and 7.3 cases per 100,000 head on feed. Cases occurred year round and during all stages of fattening, although 68% of cases occurred during the first 90 days on feed.[604] The case fatality rate is usually 100%.

Fig. 31-69 Postmortem photograph of lung from feedlot steer with embolic pneumonia caused by caudal vena caval thrombosis. Note multiple dark red emboli with raised abscesses scattered throughout lung. Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.

31.73.5 Necropsy Findings

Almost all patients with significant hemoptysis have a thrombus in the posterior vena cava between the liver and the right atrium. There is usually an adjacent hepatic abscess, varying degrees of venous congestion of the liver, and hepatomegaly. The lungs are large, uncollapsed, and firm. Aneurysms may occur in either lung or both. Hematomas associated with ruptured aneurysms are frequently 3 to 10 cm in diameter.[604] Large blood clots may be found in the airways, aspirated blood in the alveoli, and swallowed clots in the rumen. Areas of suppurative pneumonia and multiple abscesses are present (see Fig. 31-69).

31.73.6 Diagnosis

The CBC may reveal anemia and a neutrophilic leukocytosis with a regenerative left shift. Hyperglobulinemia is frequently present. Serum chemical analysis may reflect chronic passive congestion of the liver, with elevation of bilirubin and liver-derived enzymes. Radiographs often reveal only an irregular increase in lung density. Small discrete densities (areas of embolic infarction and collapse); large, discrete, spheric opacities (hematomas);

cavitating nodules, sometimes with gas-fluid interfaces (abscesses); bullae; and areas of consolidation may be observed in some cases.[602,603]

31.73.7 Treatment and Prevention

The prognosis is grave, so treatment is rarely indicated, and salvage is the most feasible recommendation. In valuable individuals, antibiotics and supportive therapy may be attempted. Penicillin is the drug of choice for the most common organisms involved; large doses (22,000 U/kg IM or SC twice daily as a minimum) for extended periods (weeks to months) are recommended. Long-acting oxytetracycline and florfenicol are other drugs that are effective against the bacteria likely to be involved. Supportive therapy for cases with acute severe dyspnea includes furosemide (0.5 to 1 mg/kg IV or IM once or twice daily) and flunixin meglumine (1.1 to 2.2 mg/kg once or divided twice daily). One or two doses of corticosteroids (dexamethasone at 0.05 to 0.2 mg/kg IV or IM q 24 h), or atropine (0.04 mg/kg SC daily), may be helpful in cases with severe respiratory distress.

On the basis of the assumption that rumenitis and liver abscesses are the first steps in the pathogenesis of most cases, measures to reduce the incidence of these problems are appropriate. Recommendations include slow adaptation of animals to high-energy rations and feeding of antibiotics to reduce the incidence of liver abscesses.

31.74 BOVINE TUBERCULOSIS

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31.74.1 Definition and Etiology

Mycobacterium bovis, know as bovine tuberculosis, is the most common cause of tuberculosis in cattle. The bacterium belongs to the *M. tuberculosis* (MTB) complex of organisms, which includes *M. tuberculosis, M. africanum*, and *Mycobacterium microti*. *Mycobacterium bovis* has the widest host range of the species included in this complex.[605] All species of mammals, including humans, are susceptible to *Mycobacterium bovis* infection, although the susceptibility of different species is variable. The importance of this organism as a zoonotic agent has led to the institution of long-standing programs for eradication of the disease, especially in developed countries. The occurrence of *Mycobacterium bovis* as an endemic disease in wildlife populations in mammalian species in numerous countries has created new challenges for control of this disease in domestic livestock.

The organism can affect animals of any age.[606] Commonly infected livestock species include cattle, goats, swine, and cervids. Horses have been regarded as relatively resistant, but reports from New Zealand indicate that large numbers of sheep can be affected.[607,608] Other *Mycobacterium* species occasionally cause clinical disease, especially *M. avium* in swine, but their main importance historically lies in the problems created for control and eradication programs through the reaction of exposed animals to the common tuberculosis tests. Disease caused by *M. avium* subsp. *paratuberculosis* (Johne's disease) has risen as a concern in dairy cattle in recent years.

31.74.2 Clinical Signs and Differential Diagnosis

Signs of *Mycobacterium bovis* infection can be very nonspecific, and in early stages of the disease are inapparent. Infected animals may not show clinical abnormalities, yet may pose health risks to other livestock and to humans. Patients may have chronic weight loss, variable appetite, and fluctuating fevers, which may be

accentuated after calving. Other signs depend on the organs involved. The route of invasion in ruminants is usually respiratory through inhalation; however, recent research and occurrences have demonstrated the capability of ingestion of contaminated feed and other forms of indirect contact to transmit the disease.[609–612] Signs related to the respiratory system are relatively common and usually mild, although severe chronic infections can lead to debilitation. Progressive emaciation can occur that is unassociated with other clinical signs, and such occurrences should lead to investigation of potential *Mycobacterium bovis* infection.[606]

Specific clinical signs of the disease are determined by the initial location of bacterial introduction to the body. Respiratory signs in ruminants include a soft, moist, chronic cough resulting from bronchopneumonia. Obvious dyspnea, tachypnea, hyperpnea, and adventitious lung sounds occur only in the terminal stages. Lung sounds include crackles, wheezes, and silent spots occupied by granulomas; pleural friction rubs may occur rarely. Enlarged mediastinal nodes may cause bloat. Intestinal ulceration and diarrhea may occur, and enlarged 661
mesenteric nodes may cause transport failure or obstructions. Involvement of retropharyngeal nodes may cause 662
dysphagia, stridor, and salivation. Lesions occur rarely in the peripheral nodes, the reproductive tract (causing infertility, abortion, metritis, and vaginitis), and the mammary gland. Other chronic pulmonary infections should be considered for differential diagnosis (e.g., chronic suppurative pneumonia, *Arcanobacterium (Actinomyces) pyogenes* abscesses, *C. pseudotuberculosis* CLA in sheep and goats, and mycotic pneumonias). Pharyngeal lesions should be differentiated from pharyngeal trauma, abscesses, lymphosarcoma or other neoplasia, rabies, botulism, actinobacillosis, necrotic laryngitis, and laryngeal abscesses, trauma, edema, paralysis, and tumors.

31.74.3 Diagnosis

Mycobacterial organisms in general precipitate a cell-mediated immune response but do not cause an immediate or sustained humoral reaction in mammalian species. The lack of specific antibody production in an exposed or infected animal has made development of serum-based laboratory tests for use in a live animal difficult. The intradermal tuberculin test has been the only clinicopathologic test routinely used. Recent advances in diagnostics have led to the introduction of tests that measure specific IFN-γ production in the blood of exposed or infected cattle.[613] In the United States, accredited veterinarians are authorized to administer 0.1 mL of mammalian tuberculin purified protein derivative intradermally in the caudal tail fold (CFT) as a primary diagnostic test. The test result is read in 72 ± 6 hours as negative or suspect. State or federal veterinarians may also use a 0.2-mL cervical test in known infected herds.

Only state or federal veterinarians may use the comparative cervical test (CCT), or state or federal veterinarians and approved accredited veterinarians may use the IFN-γ test (IG), to determine the disposition of cattle determined suspect by the CFT. In the CCT, biologically balanced mammalian and avian tuberculin are injected simultaneously in two sites on the same side of the neck, 12 cm apart and one above the other. The test site is assessed at 72 ± 6 hours and results determined by comparison of the relative increase in skin thickness between time intervals as measured by approved calipers. These relative increases are applied to a normogram to determine the final test result. Alternatively, the IG may be performed on animals suspect to the CFT by collection and submission of a whole blood sample to an approved laboratory for testing.[614] This test compares the relative production of specific IFN-γ of cells exposed to MTB antigen and *M. avium* antigen. The basis for following CFT suspect testing with the CCT or IG tests is that animals infected with mycobacteria other than the MTB complex react to avian antigenic stimulation to a greater degree than to bovine antigens.[613] Tests vary in nonbovid species and include application of the intradermal tuberculin test in the axillary area of new world camelids and in the cervical region of cervid species.[614]

Testing protocols in other countries can vary in relation to the specific composition of tuberculin, interpretation of the tests, and application of tests in different species or situations. The presence of control and eradication programs in most developed countries depend on the ability of these initial test procedures to differentiate herds or animals that may have been exposed to the organism. As there is no economically viable or routinely effective treatment for the disease in livestock, final determination of the presence or absence of *Mycobacterium bovis* is based on specific identification of the organism, such as via genetic identification or bacteriologic culturing.

Other tests no longer in use include the SC and IV thermal tests, in which a temperature spike to over 40° C (104° F) in 4 to 8 hours is the positive response; and the Stormont test, in which the intradermal test is performed twice in the same area 7 days apart. The response is determined 24 hours after the second test, and an increase in skin thickness of 5 mm or greater is the positive result. A tuberculin test may result in locally increased sensitivity for about 12 days; thereafter there is a temporary generalized hyposensitization. Because of this, follow-up intradermal tests must be performed before 10 days or after 60 days, and the IG test performed within 30 days, after initial CFT injection in the United States.[614] A relative hyposensitization also may occur just before and for 4 to 6 weeks after calving.

Animals with chronic disease or advanced pulmonary lesions may be anergic and may not react to immune-based testing.[615] False-positive reactions may occur as a result of human or avian tuberculosis, Johne's disease, saprophytic *Mycobacterium* species, or other agents such as *Nocardia* species.[613] Radiographs may be helpful in establishing the presence of pulmonary masses in individual cases. Postmortem examination of animals delivered to slaughter facilities inspected by the Food Safety Inspection Service and necropsy are used by control officials to determine the presence or absence of lesions. Histopathologic examination, PCR testing, and bacterial culture are all used to determine the final diagnosis in animals with lesions and suspect or reactor animals.

The accuracy of antemortem diagnostics for *Mycobacterium bovis* is limited by the organism's failure to produce a reliable cellular or humoral response, and the prevalence at which animals are exposed to cross-reacting organisms. Sensitivity of the CFT in field trials has been reported to be 63% to 97%, and increased test sensitivity can be seen in cases of individual animals with more extensive lesions and in herds that contain a higher prevalence of *Mycobacterium bovis* infection.[613,615,616] Therefore the test is more valuable in making decisions regarding the presence of *Mycobacterium bovis* in herds rather than individual animals.[617] It has been reported that *Mycobacterium bovis* strain type may influence the effectiveness of the CFT.[605] The specificity of intradermal tuberculin testing has been reported to be 75.5% to 99.0%,[613] although accurate estimates are difficult because of differences in research and field trial testing protocols. In areas with a low prevalence of disease, overall testing specificity is enhanced by using a combination of the CFT and CCT or IG tests in sequence.

Determination of *Mycobacterium bovis* infection through examination of animals presented at slaughter facilities is routinely used in developed countries. Slaughter examination systems have a lowered sensitivity compared with intradermal testing but are seen as a cost-effective surveillance method.[618] Sensitivity of postmortem examination is affected by the procedure used and the tissues examined. The most common areas of lesion development in naturally infected cattle are in the lymph nodes that drain the respiratory tract. From 70% to 90% of *Mycobacterium bovis* lesions are found in the lymph nodes of the head or in the thoracic cavity. In low-prevalence areas, animals may have no, or only one, macroscopically visible lesion.[617–619] Because *Mycobacterium bovis* is difficult to culture, aseptic collection technique and appropriate storage of tissues during transport are critical for appropriate diagnosis.

31.74.4 Pathophysiology

The organism usually enters ruminants through the respiratory route, occasionally by ingestion. The infectious dose has a significant effect on the severity and progression of the disease. Animals exposed to high doses of the organism develop more severe lesions and produce an earlier and more consistent period of bacterial shedding than those exposed to low doses. It has been reported that a dose as small as one CFU can cause disease.[619,620]

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Inhalation of the organism, the most common method of infection, usually results in a small necrotic granulomatous lesion occurring in the lungs. Granuloma formation is less common when the digestive tract is involved. Infection of the upper respiratory tract or pharyngeal area may also be caused by ingestion of infected feeds.[610] From the initial site of entry the organism invades the local lymph nodes (retropharyngeal, tracheobronchial, mediastinal, mesenteric), where it causes necrosis surrounded by a granuloma containing mononuclear cells. Localized lesions stimulate development of a fibrous capsule that varies in severity depending on the rate of development. This combination of lesions at the site of entry and the local lymph nodes forms the primary complex. From there a postprimary dissemination occurs to various organs and can result in diffuse miliary tuberculosis, discrete nodular lesions in various organs, or chronic organ tuberculosis. The disease in cattle is progressive and eventually causes weakness, debility, and death.[605,606,610,619] Hypotheses based on knowledge of human tuberculosis have suggested that the majority of cattle exposed to *Mycobacterium bovis* may have the ability to clear the disease or enter a period of latency.[615] If proven true, this could have significant impact on eradication programs.

31.74.5 Epidemiology

Contact with infected animals is the most common source of exposure, and the organism is present in exhaled droplets, sputum, feces, milk, urine, vaginal discharge, semen, and draining nodes. Tuberculous lesions occur in the head or respiratory lymph nodes in 70% to 90% of reactors with confirmed infections. However, lung lesions are found in 1% to 2%, to less than 10%, of these infected animals on postmortem examination.[617,618] Animals with no visible signs of organ involvement have historically been regarded as nonexcreters and been determined to be unimportant in transmission of the disease. If careful laboratory examinations are made, over 70% of cattle with lesions in respiratory lymph nodes have small lung lesions, and in 19% of confirmed cases *Mycobacterium bovis* is present in the tracheal mucus. All cattle with tuberculous lesions are therefore considered potential shedders.[621] Research has supported that *Mycobacterium bovis* adheres to a commonly held belief about many diseases: cattle with more advanced lesions have a higher shedding rate than animals with less extensive disease.[622] Feces can remain infective for 6 to 8 weeks, and stagnant water for 18 days. Milk historically was a common route of infection in young animals. Recent research has demonstrated that *Mycobacterium bovis* can persist on feedstuffs such as corn, carrots, apples, hay, and sugar beets for up to 16 weeks at 0 ° C (Whipple, unpublished data).

Housing and crowding increases the contact of naive animals with secretions of infected animals and can enhance spread of this disease. The disease can also be transmitted by indirect contact through contaminated feed and water, feeding and watering equipment, cleaning equipment, or movements of personnel—anything that can mechanically transfer the organism between locations. Movement of untested infected animals through purchases, sharing of breeding animals, and fenceline contact with other herds have historically been the most common ways of transferring the disease.

Mycobacterium bovis has been found to occur as an endemic disease of wildlife populations in multiple countries. Such occurrences, and associated transmission from wildlife into domestic livestock herds, poses a new challenge to the control and eradication of the disease. Wildlife involvement in the transmission of disease to cattle has occurred with free-ranging white-tailed deer *(Odocoileus virginianus)* in the United States, badger *(Meles meles)* in Great Britain, and brushtail possum *(Trichosurus vulpecula*) in New Zealand, among others. Studies have demonstrated that these species can be reservoirs for transmission to livestock through indirect contact and contamination of feed, water, and environmental substrates.[610,611,622] The foraging habits of mammalian herbivores may also contribute to an increased risk of exposure to the organism in areas with wildlife reservoirs.[623,624] Movement of infected wildlife species through rehabilitation or reintroduction programs can be an avenue for spreading the disease between areas.

Bovine tuberculosis is an important zoonotic disease because of its potential for spread in nonpasteurized milk from infected animals. The disease may also be spread between animals and humans that are in close association. The incidence of tuberculosis has been greatly reduced by control programs in many developed countries but still persists and presents a potential disease hazard to humans in many areas of the world.[605] Within developed countries the residual cases are the most difficult and expensive to detect and remove, and consequently outbreaks still occur. In the United States, fairly large-scale outbreaks have been reported in dairies that were previously free of the disease, and the proportion of feeder animals that accounts for slaughter cases has increased in recent years. Importation of feeder cattle from Mexico has been shown to be a source of disease introduction for the United States.[625] Movement of infected cattle is also a contributor to the spread of *Mycobacterium bovis* in Great Britain.

31.74.6 Necropsy Lesions

The pathognomonic lesion of *Mycobacterium bovis* infection is the granuloma, which is thought to be a result of chronic antigenic stimulation and an attempt to localize the invading organism.[626] Tuberculous lesions primarily occur in the respiratory tract and associated head and thoracic lymphatic tissue but can exist in other areas depending on the initial location of introduction of the organism. It is common that infected cattle may display no grossly visible lesions or may have a visible lesion in only one lymph node.[616,617,621] Macroscopic lesions appear as firm encapsulated nodules, with thick, yellow to orange, creamy to caseous pus, and may be calcified. They may occur in any lymph node, but especially the bronchial, mediastinal, and mesenteric nodes, and in a variety of organs, particularly the lungs and liver. The organs may be riddled with small miliary tubercles, and in the lungs these may coalesce into a suppurative bronchopneumonia. Swine may have involvement of the joints of the forelimb or hindlimb.[627] Chronic lesions are characterized by a discreet, thickened fibrous capsule containing thick caseous material.[606]

Histopathologically lesions in lymph nodes or organs are granulomatous with a central area of mineralization and necrosis. Macrophages have a distinctly elongated appearance and can coalesce into multi-nucleated giant cells (Langerhans cells). These fused cells form the center of the developing tubercles. The presence of acid-fast bacteria within these lesions strongly suggests the presence of *Mycobacterium bovis*, although there may be only small numbers of widely dispersed organisms. Lesion development can be divided into four different stages: stage 1 (no necrosis), stage 2 (minimal central necrosis), stage 3 (central caseous necrosis with minimal necrosis), and stage 4 (extensive multicentric caseous necrosis with mineralization).[626] Differentiation between the thickness of the fibrous capsule and the histopathologic stage of development may assist in determining the chronicity of the infection.

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31.74.7 Treatment, Prognosis, Prevention, and Control

In developed countries the disease is not treated in livestock, and affected animals are slaughtered. Species infected with *Mycobacterium bovis* that are considered valuable as zoologic exhibits or that are rare or endangered have undergone attempted treatment for the disease. These treatments have included human tuberculosis drugs such as isoniazid, streptomycin, paraaminosalicylic acid, and others.[606] Outside of these rare cases, treatment for bovine tuberculosis in animals is not considered effective on the disease or practical with regard to cost.

The development of an effective vaccine for bovine tuberculosis has been a desired tool to use in preventing and eradicating *Mycobacterium bovis*. Vaccines may increase resistance to infection or reduce the disease severity and potential risk of transmission from an infected animal. Much research is now going into development of an effective vaccine, but field study methods need to be developed that mimic natural infection.[628,629] The use of a vaccine at the end stages of an eradication program may increase the difficulty in locating the last vestiges of infection, because of the tendency of vaccines to mask disease, which is generally not desired. Much of the vaccine research is aimed toward usage in areas with widespread disease or in wildlife species in areas where the disease is endemic in these populations. Recent results in the United States involving challenge studies in white-tailed deer have demonstrated decreased lesion severity in vaccinated animals.[630]

Eradication schemes in numerous countries rely on a program of surveillance in livestock and wildlife, testing of animals before movement, and systems to track animals between farms in order to identify animals exposed to the disease and potential sources of infection. More recently, surveillance and control programs for wildlife species deserve consideration as these may also be a source of infection. In the United States, individual farms infected with *Mycobacterium bovis* are handled through a series of testing protocols intended to eliminate infection through removal of all infected animals, or by whole herd depopulation.[614] Because of limitations in the sensitivity of antemortem diagnostic tests for tuberculosis, depopulation of infected herds and other exposed animals is thought to be the most effective way to ensure eradication of the disease.[616]

When herds are depopulated and the owner intends to repopulate in the future, it is important to remove or thoroughly clean and disinfect facilities and equipment potentially exposed to the organism. The ability of *Mycobacterium bovis* to survive for extended periods in the environment, and the ineffectiveness of disinfection of organic materials, necessitates that pastures and fields to be used in repopulation schemes be left vacant for a period of time before use. This period of “down time” will be affected by climatic conditions, as the organism is less resistant to sunlight and drying, but can survive for longer periods during certain seasons. Instances of infection that are thought to originate from wildlife sources may precipitate changes in facilities, management, feeding practices, or wildlife control to prevent reinfection. Current experience with endemic *Mycobacterium bovis* infections in wildlife in numerous countries have demonstrated that eradication of the disease in these species is difficult, and a long-term proposition. More work is needed in the areas of diagnostic testing, environmental sampling, vaccine development, and management practices that may decrease the risk of disease spillover, in order to achieve successful control and eradication of the disease in the future.

31.75 DISEASES OF THE THORACIC WALL AND CAVITY

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31.76 PLEURITIS AND PLEURAL EFFUSIONS

31.76.1 Definition and Etiology

Acute, primary pleuritis is rare in ruminants. It is almost always a secondary condition. The most common primary cause is most likely bronchopneumonia caused by *M. haemolytica* or *H. somni*. Other possible causes of pleuritis and pleural effusions include traumatic reticulopericarditis, extension from other causes of peritonitis, tuberculosis, liver abscesses, tumors (especially lymphosarcoma), external trauma, fractured ribs, gunshot, perforating injuries, sporadic bovine encephalomyelitis (SBE), contagious bovine and caprine pleuropneumonia, various septicemic conditions, acorn toxicity and other causes of uremia, uroperitoneum, right ventricular failure, hypoproteinemia, ruptured thoracic duct, and hemothorax from trauma or hemangiosarcoma.

31.76.2 Clinical Signs

The signs depend on, and may be overshadowed by, the primary disease process. Pleuritis is a painful, septic process, whereas the signs associated with nonseptic effusions depend largely on the cause. Signs referable to pleuritis itself include anorexia, depression, fever, weight loss, decreased milk production, progressive dyspnea, and a characteristic stance and respiratory pattern, with the head and neck extended, elbows abducted, restricted excursion of the thorax, abdominal breathing, tachypnea, and a grunting or groaning with respiration. The animal may be reluctant to move. If a cough is present, it is often soft and suppressed because of pain. Jugular distention and pulsation may result from interference with venous return.[631] Auscultation may reveal creaking or rubbing noises in dry pleuritis or a cranial-ventral masking of sounds caused by effusion. Percussion may reveal dullness ventral to the fluid line and may elicit pain. Differential diagnoses for dyspnea with abnormally quiet lung fields may include the atypical pneumonias, pneumothorax, and space-occupying lesions such as large abscesses, tumors, and diaphragmatic hernia. Once pleuritis or pleural effusion has been identified, the main differential diagnostic consideration is the determination of the underlying cause, as listed previously.

31.76.3 Diagnosis

A CBC helps to separate infectious from noninfectious causes and distinguish relatively acute conditions (with significant left shifts) from those of a more chronic nature (with mature neutrophilia, hyperglobulinemia, and nonregenerative anemia of chronic disease). Serum chemical determinations and urinalysis identify hypoproteinemia and azotemia. A thoracocentesis should be performed and submitted to cytologic and cultural examination for bacteria, mycoplasma, and chlamydia. Nonseptic transudates indicate conditions such as neoplasia, heart failure, hypoproteinemia, and uremia. Effusions of sporadic bovine encephalomyelitis are relatively acellular with high protein and fibrinogen levels, whereas septic exudates high in both cells and protein occur with pneumonia, hardware, peritonitis, abscesses, penetrating trauma, and septicemias. A transtracheal wash is usually indicated because of the common association with pneumonia. Pericardiocentesis, abdominocentesis, and radiographs may indicate the primary source of an infection. Tuberculosis tests, leukemia virus titers, chlamydial titers for SBE, electrocardiography, echocardiographic examinations, ultrasonographic examination of the liver, and exploratory laparotomy may also help to detect other primary processes.

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31.76.4 Treatment

The primary problem should be treated. Effusions should be drained, either periodically or continuously through a Heimlich valve or a suction device fashioned from a syringe with the plunger transfixed with a pin. Effective drainage can be difficult in ruminants because of their propensity for fibrin formation and loculation of the fluid. Intermittent drainage is as effective as continuous drainage and simpler to maintain. Attempts at lavage have rarely been successful because of adhesions. Appropriate antibiotics are indicated in the presence of sepsis. NSAIDs (aspirin, 100 mg/kg PO twice daily; flunixin meglumine, 1.1 to 2.2 mg/kg IV or divided twice daily) are useful to relieve pain, ease respiration, and improve appetite. Rest and good nursing care are essential. The prognosis obviously depends on the extent and duration of the disease. Although many animals that have severe cases survive, such animals often remain chronically underweight.

31.77 PNEUMOTHORAX

Pneumothorax is not common in ruminants. Most cases result from the rupture of an emphysematous bulla associated with pneumonia, straining, or coughing or from puncture of the lung by a fractured rib. The bullae that occur in BRSV-induced pneumonia are a common source. Trauma to the pharynx or larynx can also lead to pneumothorax,[632] presumably caused by air traveling from the cranial cervical regions through soft tissues and into the thoracic cavity. Penetration from the exterior is possible but less common. A case has been described in a postparturient cow with no other underlying cause found.[633] A retrospective study of 30 cattle with pneumothorax presented to a referral hospital found that 18 of the cases (60%) were associated with bronchopneumonia, seven cases were associated with interstitial pneumonia, three cases were associated with laryngeal or pharyngeal trauma, and two cases were associated with neonatal respiratory distress.[632] Of interest was the finding that 13 of the 18 cases with bronchopneumonia were chronic, based on history and diagnostic findings; an association between pneumothorax and chronic bronchopneumonia had not been previously reported. The rate of survival for cattle with pneumonia and pneumothorax was lower than for cattle presented with pneumonia without pneumothorax, with an overall survival rate of 60% for cattle presented with pneumothorax.

Clinical signs of pneumothorax include inspiratory dyspnea, sometimes severe, with open-mouth breathing sometimes present.[633] One side of the thorax may be relatively collapsed and immobile, with a compensatory increase in the size and excursion of the other side; however, this latter finding is often subtle and difficult to appreciate. Ruminants have a complete mediastinum; thus when pneumothorax occurs it is usually unilateral, and the animal is able to ventilate adequately using the opposite lung. Unless an infectious disease is responsible, affected animals are often alert and anxious. They may attempt to stand with the forefeet elevated. There is a pronounced abdominal component to the respirations. Cyanosis may occur, and airflow may be markedly reduced in severe cases. On auscultation there is an obvious disparity between the two sides; bronchovesicular sounds will be diminished dorsally on the affected side or may be entirely absent. Those lung sounds that are audible have a harsh, high-pitched, large airway character similar to those of a consolidated lung, especially over the carina; these sounds seem to be distant, as if the animal were breathing in a barrel. The point of maximum intensity of the heart may be displaced, and tachycardia is often present. Percussion may reveal an abnormal resonance when compared with that of the normal side, and simultaneous auscultation and percussion may produce a “ping” over the thorax. SC emphysema is a fairly common feature, and pleuritis is often a sequela. Differential diagnoses of the inciting cause should include the various causes of ARDS, bronchopneumonia, viral pneumonias (especially BRSV), pleural effusions, diaphragmatic hernia, other space-occupying lesions (large abscesses, tumors), and clostridial infections.[633]

Pneumothorax can be diagnosed with radiographs, transthoracic ultrasound, or thoracocentesis[632]; radiographs and ultrasound will also be useful to characterize the extent of any underlying lung disease. Other diagnostic tests to characterize underlying lung disease as described for infectious bronchopneumonia or interstitial pneumonia are appropriate.

If the affected animal shows signs of significant distress, the air in the pleural space should be evacuated. Evacuation can be accomplished by aseptically placing a teat cannula into the thoracic cavity at the dorsal aspect of the thorax at the tenth intercostal space and withdrawing air by use of an extension set and three-way stopcock. In some cases this method can be successfully used to intermittently remove air; in other cases, continuous removal with a pleural evacuation device (Pleur-evac A-8000, Deknatel Inc., Fall River Mass.) has been more effective.[634] If continuous evacuation is attempted the animal must be adequately restrained; this is likely to be possible only with hospitalized animals. Other treatment includes therapy appropriate for underlying acute or chronic pneumonia as described previously for infectious bronchopneumonia or interstitial pneumonia. External wounds allowing air to enter the thorax should also be closed if present.

31.78 DIAPHRAGMATIC HERNIA

31.78.1 Definition and Etiology

Diaphragmatic hernias are uncommon in ruminants but have been reported in calves, cattle, sheep,[635] and domestic buffalo.[636,637] The condition appears to be much more prevalent in the buffalo but otherwise is analogous to that in cattle.[638] Hernias may be congenital, but most appear to be acquired, including those occurring in neonates. A congenital weakness in the diaphragm may predispose to some cases. Causes include difficult parturition, external trauma, and, by far the most common cause, traumatic reticuloperitonitis (TRP).

31.78.2 Clinical Signs and Differential Diagnosis

Affected animals can be asymptomatic for a prolonged period.[638] Most affected cattle are in late gestation or have calved recently. The history may include decreased milk production, weight loss, capricious appetite, difficulty in swallowing or regurgitation, previous signs of abdominal pain (possibly associated with acute TRP), vomiting, and abnormal posturing of the head and neck on swallowing or regurgitation. Respiratory signs are actually fairly uncommon, with the exception of large congenital hernias, in which there is obvious severe dyspnea and abdominal respiration from birth. Occasional cough and dyspnea have been reported, and auscultation may reveal asymmetric sounds, with lack of lung or heart sounds in the affected area, or splashing sounds similar to those heard with pericarditis. GI signs are actually more common and include bloat, signs consistent with TRP, difficulty or pain on passage of a stomach tube, diarrhea, constipation, and ruminal hypomotility. Some cows may retch or vomit on regurgitation. Pain is evidenced by odontoprisis or grunting on regurgitation. The primary differential diagnoses are TRP, pericarditis, esophageal stricture, esophageal foreign body (choke), neoplasia, and abscessation.[638]

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31.78.3 Diagnosis

Radiographs are the best means of confirming the diagnosis. The normal outline of the diaphragm and heart may be obscured,[636,637] and the honeycombs or foreign objects in the reticulum may be seen in the thorax[637] because

this organ is most commonly involved. Oral barium may also aid in the radiographic interpretation, particularly in early small hernias that will be missed on plain films. Pleuritis and other masses such as tumors and abscesses can also mimic hernias on plain films.[637] Because TRP is frequently involved, the CBC, pleural effusions, and abdominocentesis may reflect the septic process. In cases not associated with TRP, the pleural effusion may be hemorrhagic in acute cases and normal in chronic cases.[638]

31.78.4 Necropsy Lesions

The hernial ring is usually located at the junction of the musculotendinous portion of the diaphragm, about 12 cm ventral to the vena cava and slightly lateral to the midline. The ring is usually round to oval, with a diameter of 7 to 20 cm. The reticulum is usually herniated, most frequently to the right side of the chest. The liver, spleen, rumen, omasum, abomasum, intestine, and omentum may also be involved. Extensive adhesions usually develop between the herniated organs and the thoracic organs, and evidence of hardware can often be found.[639]

31.78.5 Treatment and Prognosis

Treatment is surgical. A two-stage approach is usually used. First, a standing left flank laparotomy and rumenotomy are performed; the defect is identified, foreign bodies are removed, and the ruminoreticulum is emptied. Because of the complete mediastinum, ventilatory assistance is rarely needed during this stage. Next, the animal is placed under general anesthesia with positive pressure ventilation. Various approaches have been used for this portion, including ventral midline, paramedian, semilunar postxiphoid, paracostal, and transthoracic with rib resection. The hernia is reduced, and the rent repaired with sutures or mesh grafts. Mesh grafts are contraindicated if infection is present.[638]

31.79 PLEURAL MESOTHELIOMA

Mesotheliomas have been reported in cattle and goats,[640] including a congenital form in calves.[641] Most are peritoneal, but pleural mesotheliomas also occur.[642,643] Mesotheliomas result in the accumulation of large amounts of fluid in the involved body cavity; signs of pleural mesothelioma are therefore related to pleural effusion. They include dyspnea, tachypnea, decreased lung and heart sounds (sometimes unilateral, with a concomitant increase in sounds on the normal side), dullness on percussion, exercise intolerance, cyanosis, tachycardia, anorexia, weight loss, decreased production, cough, and weak pulses. If peritoneal lesions are also present, as is common but not universal, ascites is also present. Radiographs confirm the pleural effusion, and thoracocentesis yields a serous, sometimes blood-tinged or gelatinous fluid. Cytologic examination may reveal reactive mesothelial cells. At necropsy the pleura is thickened and contains multiple nodules of gray to yellowish white tissue measuring several millimeters to several centimeters in diameter. Metastasis is uncommon. The tumor can be difficult to diagnose histologically and may resemble inflammation, pleural tuberculosis (“pearl disease”), or metastasis of another tumor.[641] There is no treatment.

31.80 MISCELLANEOUS CONDITIONS

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31.81 LUNG TUMORS

Lung tumors are uncommon in large animals, with slaughterhouse surveys reporting an incidence of 19 per million cattle.[644] Those reported include pulmonary alveolar carcinomas, pulmonary adenomas, pulmonary adenocarcinomas, bronchogenic carcinoma, and pulmonary blastoma.[645–647] Malignant forms metastasize to regional lymph nodes and occasionally to other organs. Lymphosarcoma is the most frequent neoplasm to become metastatic to the lung, and uterine and ovarian adenocarcinoma may undergo metastasis to the lung.[647] Because many lung neoplasms in cattle are incidental findings at slaughter or necropsy, clinical signs are therefore not well documented. The lesions are typically discrete, round, yellow to gray masses distributed throughout the lung tissue. Tumors are most likely to be detected antemortem by radiographic examination. Differential diagnoses in such cases include pulmonary abscesses, mycotic pneumonias, and tuberculosis.

31.82 BRONCHOBILIARY FISTULA

A communication between the bile duct and a cavitating lesion in the lung has been described in a 3-year-old Charolais cow.[648] The cow had weight loss of 8 months' duration, before which she had been normal. Clinical signs were tachypnea, an expiratory press, bilateral crackles and friction rubs in the ventral lung fields, and a greenish yellow nasal discharge. The adventitious sounds were slightly more prominent on the right, and a silent area was detected in the caudodorsal right lung field. Radiographs revealed a cavitation with a fluid line in this area, and thoracocentesis yielded a sterile green fluid. At surgery, pleural-diaphragmatic adhesions and a mass in the right diaphragmatic lobe were found. A drain was installed, and fluid similar to bile, with a bilirubin of 3.1 mg/dL and alkaline phosphatase concentration of 2694 IU/L, was drained. At necropsy the lesion was a smoothlined cyst communicating by way of tracts through the adhesions with the biliary system and the bronchioles. Greenish fluid was found in the airways of both lungs.

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32 Chapter 32 Diseases of the Alimentary Tract

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Samuel L. Jones

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32.1 DISEASES OF THE EQUINE ALIMENTARY TRACT

Samuel L. Jones, Consulting Editor

32.2 DIAGNOSTIC PROCEDURES IN THE EXAMINATION OF THE EQUINE ALIMENTARY SYSTEM

Samuel l. Jones

Anthony P. Pease

A thorough physical examination is compulsory, and tests that provide a minimum database (complete blood count [CBC], serum chemistries, and urinalysis) are often indicated in horses with suspected alimentary tract disease. Once a list of differential diagnoses is compiled, a number of ancillary diagnostic tests are available to narrow the possibilities. Each diagnostic test or procedure is limited in the type and extent of information that can be obtained, and therefore the clinician should select the complement of procedures that is most likely to provide the information required to make a proper diagnosis and determine the appropriate therapy.

32.3 RECTAL EXAMINATION

A systematic approach to examining the abdominal and retroperitoneal viscera should be established and applied during each examination to ensure that all pertinent regions and structures are examined. When feasible and if required, the patient should be sedated to allow a more thorough examination. In some cases, epidural anesthesia is required to obtain adequate access to structures during rectal examination. The principal goal of a rectal examination is to identify changes in size, texture, shape, or location of visceral organs, peritoneum, mesentery, vasculature, or objects that are normally not present.

In the pelvic region of the normal horse, the urethra and accessory sex glands (male) or the vaginal vault and cervix (female) can be palpated. The urethra is usually not discernible in the female, but abnormalities such as uroliths may be felt. In the caudal abdominal cavity the bladder, the uterus in females, and the pelvic flexure and small colon typically should be felt. The pelvic flexure and left ventral and left dorsal colons are normally located ventrally, on midline or toward the left side of the abdomen. The small colon, with formed fecal balls palpable, courses throughout the caudal abdomen, mostly on the left side. In females the left ovary can be felt in the left dorsal, caudal region of the abdomen. Both ovaries should be palpated in conjunction with palpation of the uterus. The peritoneal surface should be felt along the surface of the abdominal wall and the surfaces of the viscera. It should feel smooth, with no crepitus or irregularities. Advancing along the left side of the abdomen, the spleen can be felt as a smooth structure, with the caudal border having a well-delineated, tapered border. The size and location of the spleen are variable, because it can extend from the left body wall to the right ventral region of the abdomen.

Advancing cranially and dorsally, the left kidney can be palpated. The kidney should feel smooth with the renal pelvic fissure discernible, although in the overweight horse extensive perirenal fat may obscure this detail.

From the left kidney, moving toward midline and extending from the abdominal aorta, the cranial mesenteric and ileocecocolic arteries may be felt. Palpation of fremitus in these arteries may be associated with arteritis and thrombus formation secondary to *Strongylus vulgaris* larval migration, although this association has been very inconsistent. Fremitus is frequently absent when severe arteritis exists, or the arteries may be entirely normal and fremitus felt. Fremitus can often be elicited by compressing the wall of the normal artery, thus accelerating flow through the compressed lumen. The mesenteric root of the colon can be felt ventral to the cranial mesenteric artery. This should palpate as a mildly taut band of tissue extending from the dorsal midline ventrally. Excessive tension, displacement, thickening, or masses within the mesentery should be considered abnormalities. It may be possible to palpate an enterolith, fecalith, or gravel impaction in the transverse colon, although this may be beyond the reach of the examiner because the transverse colon is located cranial and medial to the left kidney.

Sweeping to the right side of the abdomen, the base and cupola of the cecum can be felt. The body of the cecum can be followed partially by sweeping along the medial aspect of the cecum, cranially toward midline. The cecum has a prominent ventral band and sacculations. Gas, together with ingesta that is soft and mainly of a fluid consistency, can be felt within the cecum. Firm or excessive ingesta suggests an abnormality.

Findings that are different from normal often must be differentiated as being variations of normal or truly abnormal. Some common abnormal findings include abnormalities of the peritoneal surface. Crepitus, or a “plastic wrap” texture, is indicative of gas secondary to trauma or infection. An irregular or rough surface may be indicative of fibrin on a visceral surface or neoplasia, or with a perforated intestine there may be ingesta adhered to a visceral surface. There are many abnormal presentations of the large colon, most of which are associated with signs of colic. Thickening of the wall of the colon may be appreciated on rectal palpation and is indicative of edema or cellular infiltration of the colon. Palpation of abnormal masses in the wall of the colon or associated with the colonic mesentery is indicative of infection, infarction, granulomatous colitis, or neoplasia.

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Normally the small intestine is not discerned by palpation. Occasionally, though, peristaltic contractions may be felt in the small intestine as it courses across midline toward the base of the cecum. In some cases this will cause the small bowel to palpate as a firm, tubular structure. Relaxation of the peristaltic contraction should be discerned in such cases. Distention of small intestine is abnormal. In some cases the bowel may feel thickened, which can occur with ileal muscular hypertrophy, edema, or inflammatory disorders of the small bowel.

Other abnormal findings that may accompany disorders of the abdominal alimentary system include masses, adhesions, enlarged and thickened mesenteric arteries, and caudal displacement of the spleen (secondary to gastric distention or neoplasia).

32.4 PARACENTESIS

Abdominal paracentesis is performed routinely in patients with suspected disorders of the abdominal viscera. Cytologic examination of peritoneal fluid; white blood cell (WBC) and red blood cell (RBC) counts; protein, fibrinogen, lactate, phosphate, and glucose concentrations; lactate dehydrogenase (LDH), creatine kinase (CK), and alkaline phosphatase (ALP) activity; and pH can be quantitated. The results of peritoneal fluid analysis may help establish a specific diagnosis, but, more important, may reflect inflammatory, vascular, or ischemic injury to the intestine requiring surgical intervention.

32.5 ENDOSCOPY

There are two basic types of endoscopic equipment available: equipment based entirely on a fiberoptic system and equipment based on a video chip system. A typical endoscope found in many private practices is a fiberoptic endoscope that has an insertion tube that is 100 to 110 cm in length and 10 to 14.5 mm in outer diameter. The larger-diameter tube can be inserted only through the nasal passages of older yearlings and adults and is not suitable for alimentary endoscopy, whereas a diameter of 10 mm allows passage through the turbinates of young foals. An insertion tube of 100 cm is sufficient for esophagoscopy in foals up to approximately 3 months of age. For older animals, an insertion tube length of 150 to 180 cm is required for esophagoscopy.

An insertion tube length of 110 cm is sufficient to reach the stomach of foals up to 30 to 40 days of age. A length of 150 to 180 cm is required for weanlings, and 200 cm is usually required for yearlings and adults. An insertion tube length of 200 cm is sufficient to reach the stomach of all adults of warm-blooded breeds, although 280 to 300 cm is required to examine the pylorus in adult horses. A 280- to 300-cm-long insertion tube permits duodenoscopy in adult horses.

Before a gastroscopic examination, suckling foals up to 20 days of age are not routinely kept from nursing for more than 1 hour. Older foals and mature horses should not have solid feed for 6 to 10 hours so that ingesta from the stomach may be adequately emptied. Longer duration of feed deprivation (18 hours) is desirable to view the antrum and pylorus of horses. Many foals less than 30 days old do not require sedation for gastroscopy, although sedation with 0.5 mg of xylazine per kilogram may facilitate the procedure. Sedation is required if the foal is to be placed in a recumbent position so that the entire glandular portion of the stomach can be examined. Sedation of older foals and horses is required. Xylazine (0.5 mg/kg given intravenously [IV]) usually provides adequate sedation. For greater sedation, detomidine (0.005 to 0.05 mg/kg IV) or a combination of xylazine and butorphanol (0.01 mg/kg) are effective.

After insertion of the endoscope, the stomach is distended with air until the nonglandular and glandular regions of the gastric surface can be observed. Distention with air is tolerated by foals and horses and has been associated only rarely with adverse effects. Occasionally, sick neonates with poor intestinal motility developed small intestinal distention and experienced discomfort after gastroscopy.

More complete descriptions of techniques of gastroduodenal endoscopy can be found elsewhere.[1,2]

Endoscopy of the rectum and distal small colon can be performed with most flexible endoscopes in use in equine practice and should be preceded, as much as possible, by evacuation and saline lavage of the rectum and distal small colon. The mucosal surface should appear pink to pale red and should have a smooth, “velvety” appearance. Mucosal edema or thickening, hyperemia, irregularities, defects, tears, and intraluminal masses are abnormal findings. Because of the concern for trauma to the rectum and small colon, the horse should be adequately sedated and restrained before preparation and examination of the distal alimentary tract.

32.6 LAPAROSCOPY

Laparoscopy can offer valuable diagnostic information regarding the abdominal cavity and is only minimally invasive.[3,4] It should always be preceded by a thorough physical examination, including abdominal palpation per rectum, paying particular attention to the sites for trocar insertion to ascertain that there are no adherent masses or viscera in the area. If abdominocentesis is to be part of the diagnostic workup, it should be performed before laparoscopy because of the effect of laparoscopy on abdominal fluid values. In experimental animals undergoing

diagnostic laparoscopy with carbon dioxide insufflation, both the abdominal WBC count and the abdominal total protein increased.[5]

The indications for laparoscopy include palpable abdominal masses, enlarged viscera, adhesions, acute or chronic colic, weight loss, or the desire to obtain visceral biopsy specimens. Contraindications include adherent viscera or masses at the site of laparoscopic trocar insertion, diaphragmatic hernias, or extreme bloating. Horses with acute colic can be safely examined laparoscopically if one is careful when inserting the trocars and telescopes.

The basic instruments for laparoscopic examinations include a laparoscopic telescope, laparoscopic cannula and trocar assembly, fiberoptic light source and cable, insufflator, and biopsy and manipulation instruments. The 30-degree laparoscope allows better visualization of the less accessible areas compared with the 0-degree telescopes. Video cameras make visualization easier with less eyestrain but require more powerful light sources (250 watts). The cost of laparoscopic instrumentation has decreased recently as a result of the explosion of popularity of laparoscopy in humans, increasing the supply and availability of used instruments.

Horses should be fasted for 18 to 24 hours before most laparoscopic procedures; water is allowed on an ad libitum basis. Fasting increases intraabdominal visualization and decreases the possibility of penetrating a gas-distended viscus. The animal is restrained in standing stocks if the procedure is to be done while it is standing. Preoperative antibiotics, antiinflammatory drugs, tetanus prophylaxis, and a sedative analgesic combination are administered. It is important to administer the analgesics before abdominal insufflation. The flank areas are prepared for aseptic surgery. Local anesthetic agents are infiltrated subcutaneously (SC) and intramuscularly (IM) in the middle of the paralumbar fossa slightly above the crus of the internal abdominal oblique muscle for the insertion of the laparoscopic telescope. If additional instruments are to be used, their insertion sites are similarly anesthetized.

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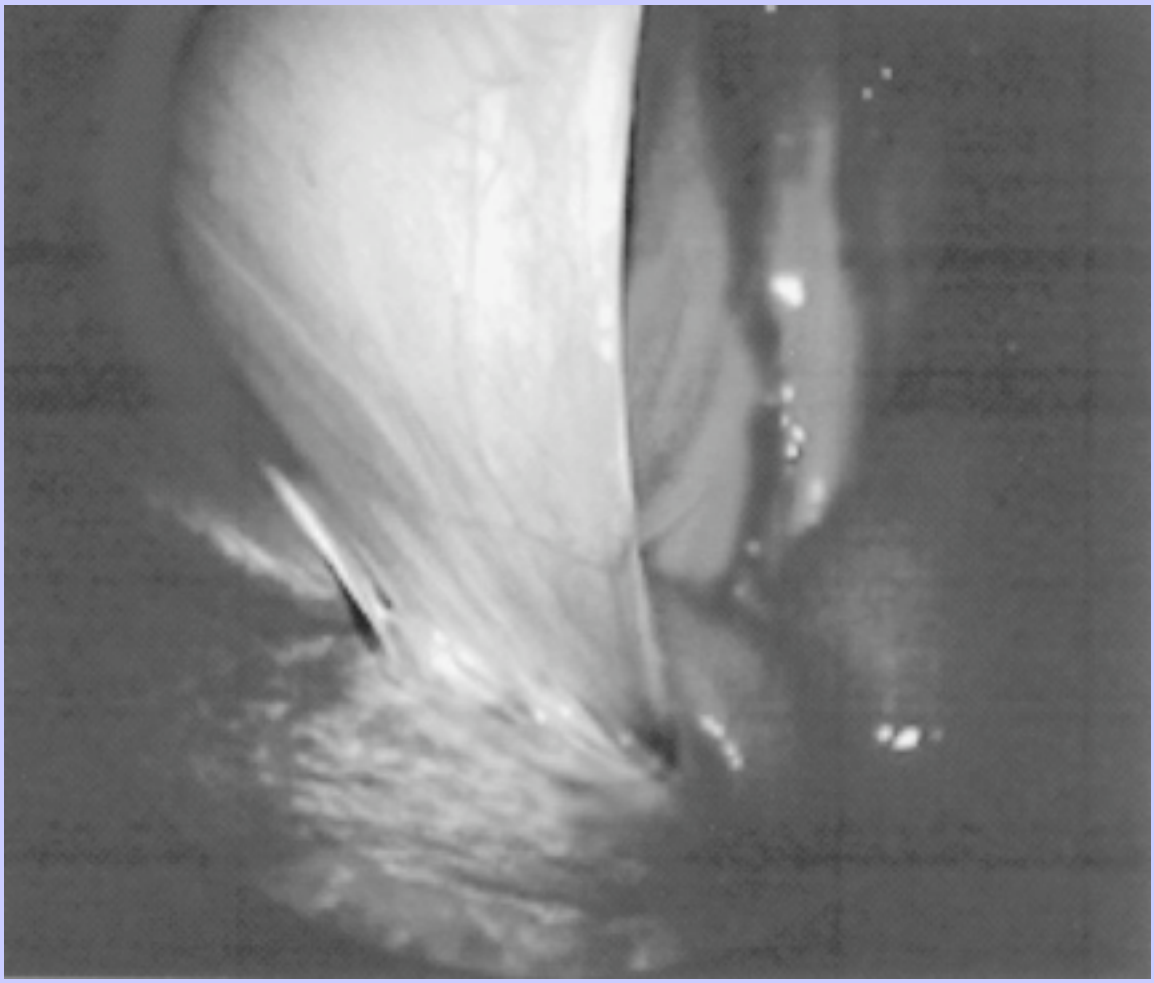
It is preferable to begin the laparoscopic procedure on the left side of the abdomen to minimize the chance of penetrating the cecal base. The horse is then draped and a stab incision is made. The laparoscopic cannula and trocar assembly are inserted through the musculature and into the abdominal cavity. It is useful to orient the trocar toward the opposite coxofemoral joint when inserting it. The trocar is exchanged for the telescope, and confirmation of entry into the abdominal cavity is made before insufflation is commenced. If the abdominal cavity has not been penetrated, a quick thrust with the telescope will usually penetrate the peritoneum. Insufflation of the abdomen with CO_2 to 8 to 10 mm Hg will usually be sufficient for most examinations.

Systematic examination of the abdominal cavity is then carried out. On the left side of the abdomen the spleen, left kidney, nephrosplenic ligament (Fig. 32-1), stomach, left side of liver, diaphragm, and ventral colon may be visualized cranially. Looking caudally, the examiner will see the root of the mesentery, the isolated small intestinal and small and large colon sections, the urogenital tract, the bladder, and the terminal rectum. The procedure is repeated on the right side of the abdomen. Looking cranially, the examiner will see the liver, epiploic foramen, right kidney, descending duodenum, cecal base, and large colon. Caudally, the urogenital tract, root of mesentery, and isolated pieces of intestine are visible. Liver biopsies and right kidney biopsies are taken from the right side. Left kidney and spleen biopsies are taken from the left side of the abdomen. Mesenteric lymph node biopsies are usually obtained via the left flank. Other masses are biopsied from the more accessible side. At the end of the procedure the abdomen is deflated, and the skin is closed with skin sutures only. Closure of the skin incision should wait until examination of both sides is completed in order to minimize subcutaneous emphysema.

In some horses with ventral or cranial abdominal masses as determined with ultrasound, it is useful to anesthetize the animal in dorsal recumbency for better characterization of the mass. Biopsies may be readily obtained. In horses with acute colic but without obvious signs indicating the necessity for surgery, laparoscopy can help in making the decision to continue medical therapy or proceed to surgery. Strangulated sections of small intestine can be seen, proximal enteritis can be diagnosed, and edema and vascular compromise to the large colon can be seen.

No abnormalities may be detected in some animals with very localized lesions, or lesions may be inaccessible, depending on location.

Fig. 32-1 Laparoscopic view of nephrosplenic ligament in a horse.



Laparoscopic complications are similar to those of any other abdominal exploratory procedure. Inadvertent penetration of a viscus may occur. The left kidney may be perforated if the laparoscope is inserted too far dorsally. The spleen may be penetrated if the laparoscope is inserted too far ventrally or is not aimed toward the opposite coxofemoral joint. The cecum may be perforated when entering from the right side. Fasting the horses and carefully inserting the laparoscopic trocars will minimize the occurrence of these problems. Subcutaneous emphysema occurs commonly but has not caused any clinical problems. The peripheral WBC count increased but stayed within normal limits in experimental animals undergoing laparoscopy.[5]

32.7 IMAGING OF THE ALIMENTARY TRACT

Anthony P. Pease

32.7.1 Radiography

In the horse the alimentary tract is a dynamic and complex environment to evaluate with any modality. Because of the size of the animal, as well as the distinct difference between air and soft tissue, radiographs are a useful diagnostic tool to evaluate the teeth, pharynx, esophagus, stomach, and intestinal tract. Portable x-ray units with maximal kVp settings up to 100 and the upper limits of the mAs settings at 30 make it possible for ambulatory practitioners to obtain diagnostic images of the head and cranial esophagus. However, to obtain images of the thoracic esophagus and abdomen, a referral clinic with a more powerful x-ray generator is usually required.

For the average foal, abdominal radiographs have been described using exposures ranging from 80 to 88 kVp and 20 to 26 mAs for the standard abdomen.[6] In adult horses, exposures range from 60 to 140 kVp and 20 to 70 mAs.[7,8] In order to completely evaluate the abdomen, it has been recommended that the abdomen be divided into four quadrants (cranioventral, midabdominal, caudodorsal, and caudoventral).[7] Large cassettes (35 cm × 43 cm) and fast screens are also needed to ensure a diagnostic image is obtained. Because of the large amount of scatter radiation produced from the high exposure and thickness of tissue penetrated, an 8:1 to 10:1 grid should be used.[6–10] Alternatively, an air gap technique can be used to prevent image degradation.

Availability of computed radiography (CR) and digital radiography (DR) has greatly increased the diagnostic capabilities of conventional radiographic examinations. Both of the systems available to the equine practitioner are considered indirect imaging modalities in which the x-ray photon interacts with an intensifying screen to convert the x-ray photons to light. This light then interacts with an imaging plate: film, as with a conventional radiographic system; within a photostimulable phosphor, as with CR; or within a flat-panel detector, as with DR. Regardless of the method, these images are considered “indirect” because the x-ray photon is first changed to light and then detected by the imaging medium.[11] The main benefits of CR and DR are the increased latitude of the film. It is possible to change the contrast and grayscale levels after the exposure if an adequate number of photons are available to the detector. The DR systems also offer a rapid evaluation of the image because the cassette is directly connected to the computer. This makes the portable systems able to show radiographic images within 10 seconds after the exposure is made. In contrast, the CR system requires the cassette to be placed into a reader in order to display the image. Finally, because both CR and DR are generally Digital Imaging and Communications in Medicine (DICOM) compliant, this allows any specialists with standard medical imaging software to view the images via a compact disk (CD) or via the Internet.

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Survey radiography is generally helpful to evaluate the cervical esophagus for evidence of rupture as well as to evaluate the abdomen. Esophageal ruptures secondary to an obstruction or vigorous placement of a nasogastric tube result in a small volume of gas that tracks just dorsal to the trachea (Fig. 32-2). This can be confused with a tracheal laceration; however, with tracheal lacerations generally the gas accumulation will surround the trachea and the volume of gas within the subcutaneous tissues and the cranial mediastinum will be severe. In addition, esophageal obstructions, also called *choke*, can sometimes be identified on survey radiographs depending on the material that is causing the obstruction and the amount of air or contrast medium that is able to surround the structure (Fig. 32-3). Although the nature of the obstruction cannot be determined, the extent of the abnormality can sometimes be identified.

Abdominal radiography is useful to evaluate the small and large intestines for sand accumulation, enterolithiasis, impactions, or small intestinal disorders in foals. When sand is ingested, it generally will accumulate within the large colon along the ventral abdomen[8] (Fig. 32-4). Radiography has been found to be a useful method to monitor the resolution of sand impactions after medical management; however, sequential examinations are

needed to verify that the volume of sand has reduced.[8] If the volume of sand is large enough, it is difficult to determine if an enterolith is present because of summation of the two lesions. Enteroliths are a solid concretion of mineral that usually forms around a nidus, such as a metallic foreign body (Fig. 32-5). The mineral composition is varied, as illustrated by the different opacities present within the enterolith. Radiographs have a 96.4% positive predictive value to detect enteroliths in high-prevalence areas. These enteroliths were generally found to be within the midabdominal radiograph, and 67% of small colon enteroliths caused large colon distention, which was also identified on radiographs.[7] Impactions are more difficult to diagnose because usually there is just increased feed accumulation within the abdomen. Although no enterolith or obstruction is identified, granular material can be seen, usually within the ventral colon near the sternal flexure. This is because pelvic flexure impactions will cause the feed material to accumulate orad, causing distention of the left ventral colon (Fig. 32-6). Intestinal disorders such as functional ileus secondary to enteritis (Fig. 32-7) or obstruction secondary to intussusception or meconium impaction (Fig. 32-8) in foals can also be identified on abdominal radiographs. These images show large dilation of the small intestine, and differentiation between functional and mechanical ileus in foals is generally based on the size of the intestine and the volume of gas that is present.[9] Evaluation of the abdomen using ultrasound may aid in qualifying the small or large intestinal motility as well as identifying the source of an obstruction if the determination on radiographs cannot be made.

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Fig. 32-2 Standing lateral radiograph of a 13-year-old Morgan gelding with an esophageal tear. Note the tubular region of small gas opacities caused by air trapped around the outer border of the esophagus *(arrows)*. An esophageal perforation secondary to an ingested foreign body was confirmed with endoscopy.

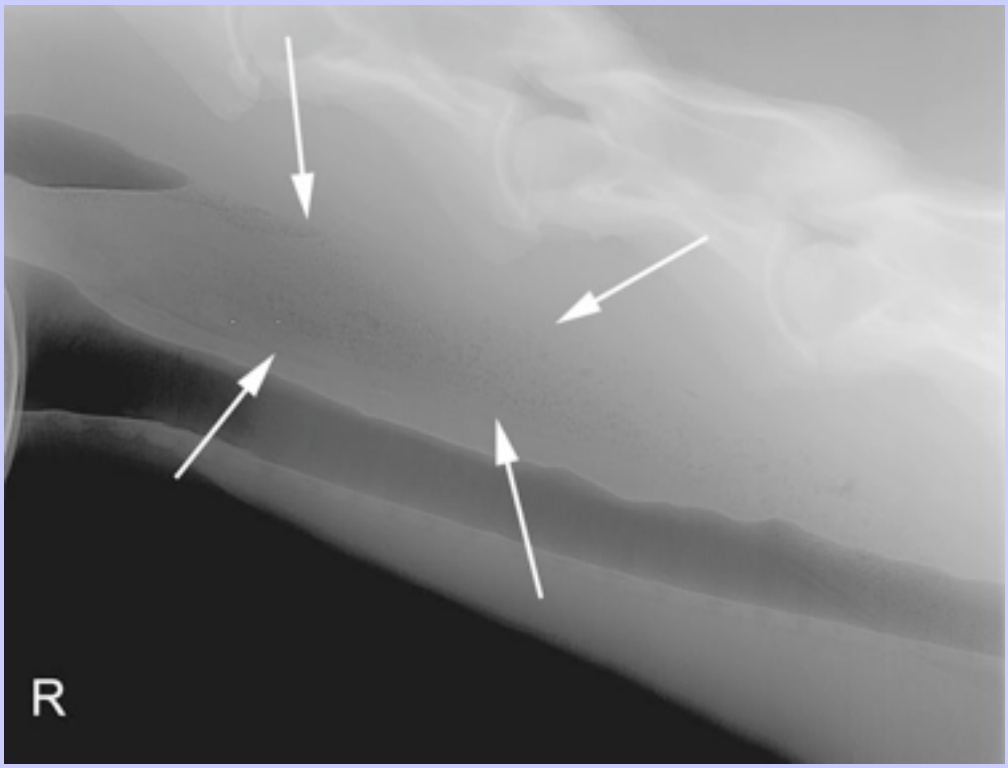


Fig. 32-3 Standing lateral radiograph of a 12-year-old quarter horse mare. Note the ovoid mass surrounded by gas just dorsal to the trachea *(arrows)*. This lesion was a mixture of hay and grass.

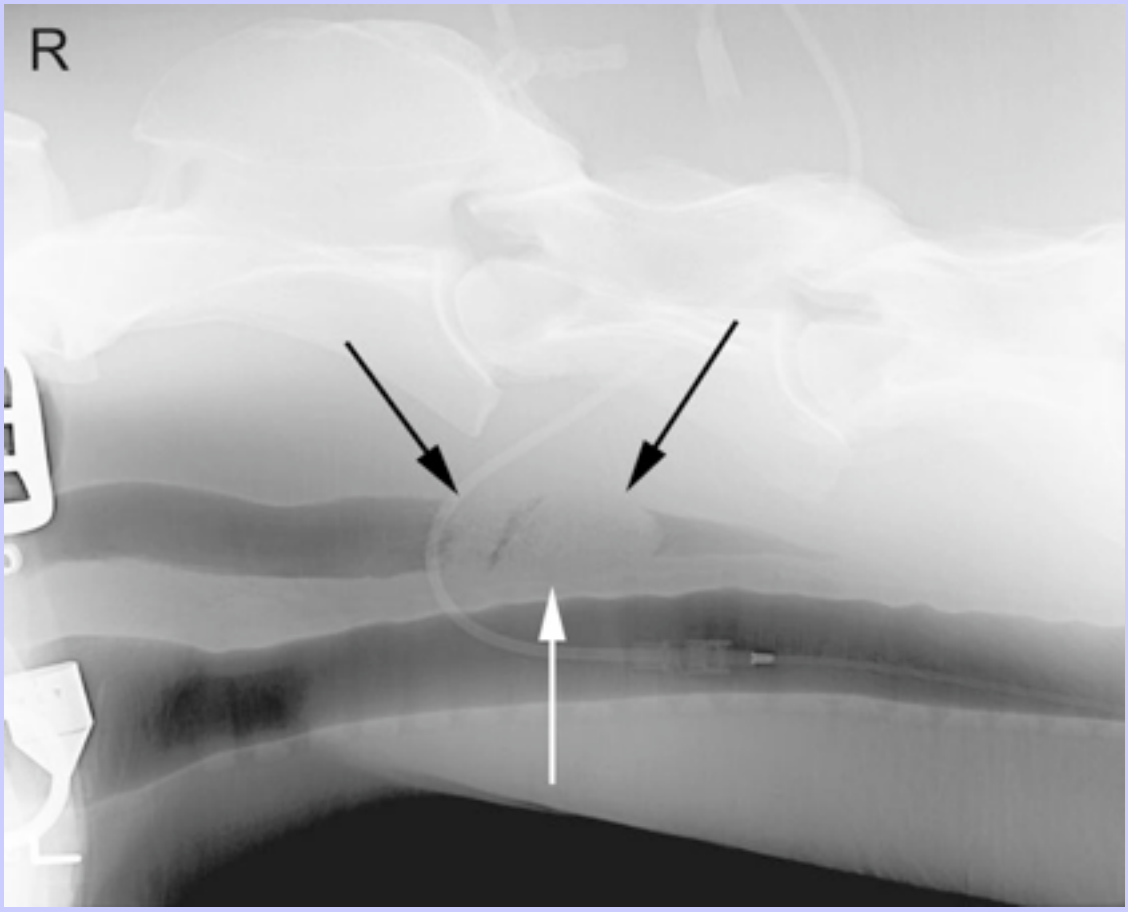


Fig. 32-4 Standing lateral radiograph of a 4-year-old Arab mare with a history of colic. Note the large amount of opaque material within the ventral colon, likely secondary to sand accumulation.

Fig. 32-5 Radiograph of enterolith obtained after surgical removal from the small colon. Note the variation in opacities caused by the various types of mineral that are contained within the enterolith.

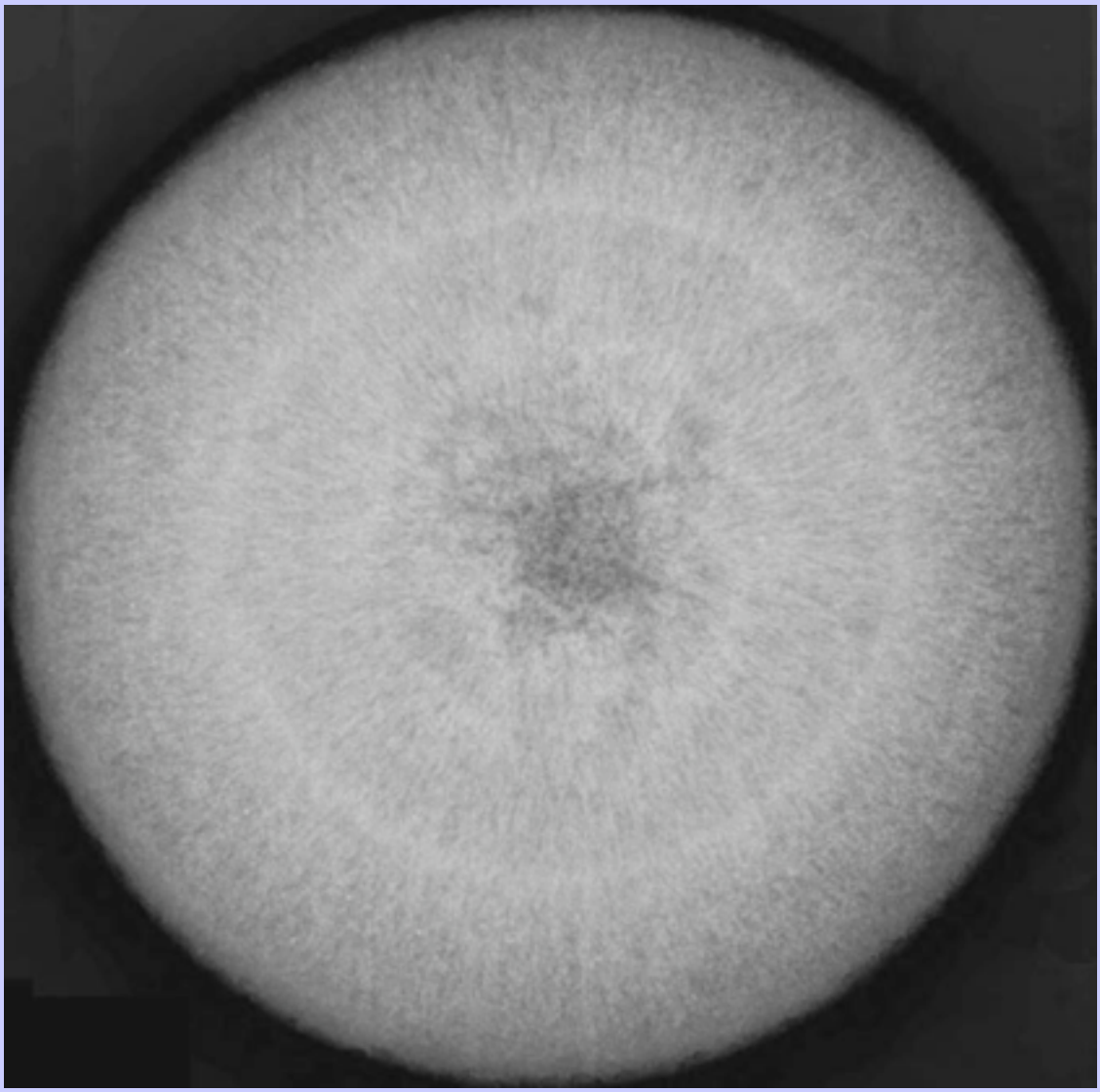
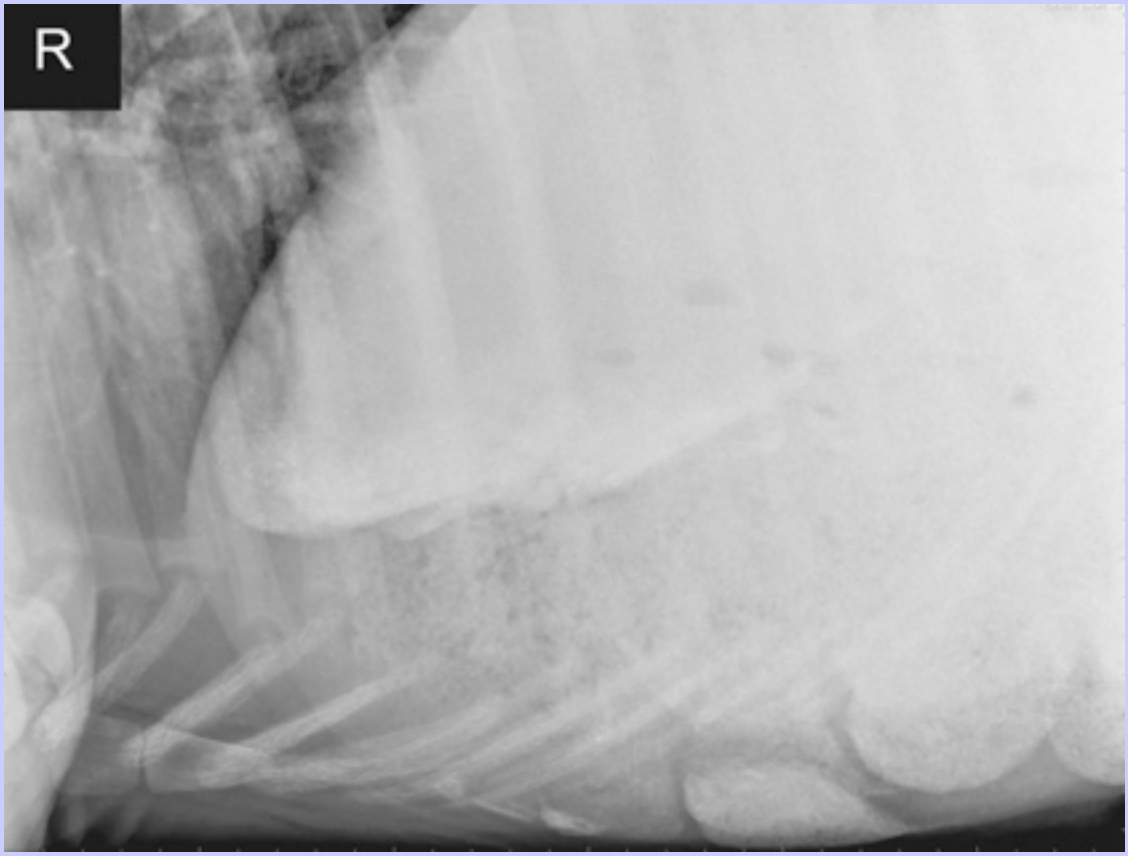


Fig. 32-6 Standing lateral radiograph of a 3-year-old Paint horse gelding with a pelvic flexure impaction. The radiograph shows the sternal flexure with a large amount of granular material and a small amount of sand accumulation in the ventral colon.



Radiography also allows for the use of contrast medium administration to further outline the alimentary tract as well as evaluate pharyngeal function and esophageal motility.[12–14] In my opinion, first administering approximately 60 mL of barium sulfate paste or liquid orally via a 60-mL dosing syringe and obtaining radiographs of the laryngeal region and esophagus provide useful information about swallowing as well as large obstructions. If the barium liquid is identified dorsal to the soft palate, within the larynx or trachea, abnormal pharyngeal function is likely present.[12] The barium paste will coat the pharynx and esophagus and is useful to identify any ulcerations or irregularities in the mucosal surface. After those procedures have been performed or if there is no evidence of an oropharyngeal dysphagia, then an esophagram is performed. This procedure is done using approximately 200 to 500 mL of barium sulfate liquid diluted 1:1 or 2:1 with water to bring the total volume to 500 to 1000 mL. This liquid is administered through a nasogastric tube or cuffed endotracheal tube placed within the cranial esophagus to the level of C2 to C3. If a cuff is available, the cuff can be inflated with approximately 10 mL of room air. A radiograph is then made to verify that the tube is not within the trachea, and when it has been confirmed that the tube is within the esophagus, the dose of barium is administered using a stomach pump. Toward the end of the dose, while still pumping the liquid, radiographs of the cranial, mid, and

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caudal esophagus are obtained (Fig. 32-9). The use of the pump provides distention of the esophagus to help identify strictures or irregularities in the esophageal wall.

Fig. 32-7 Standing lateral radiograph of a 1-day-old, premature quarter horse filly. Note the large amount of gas-distended intestine. Because of the large amount of small intestinal distention, functional ileus is the primary differential diagnosis.

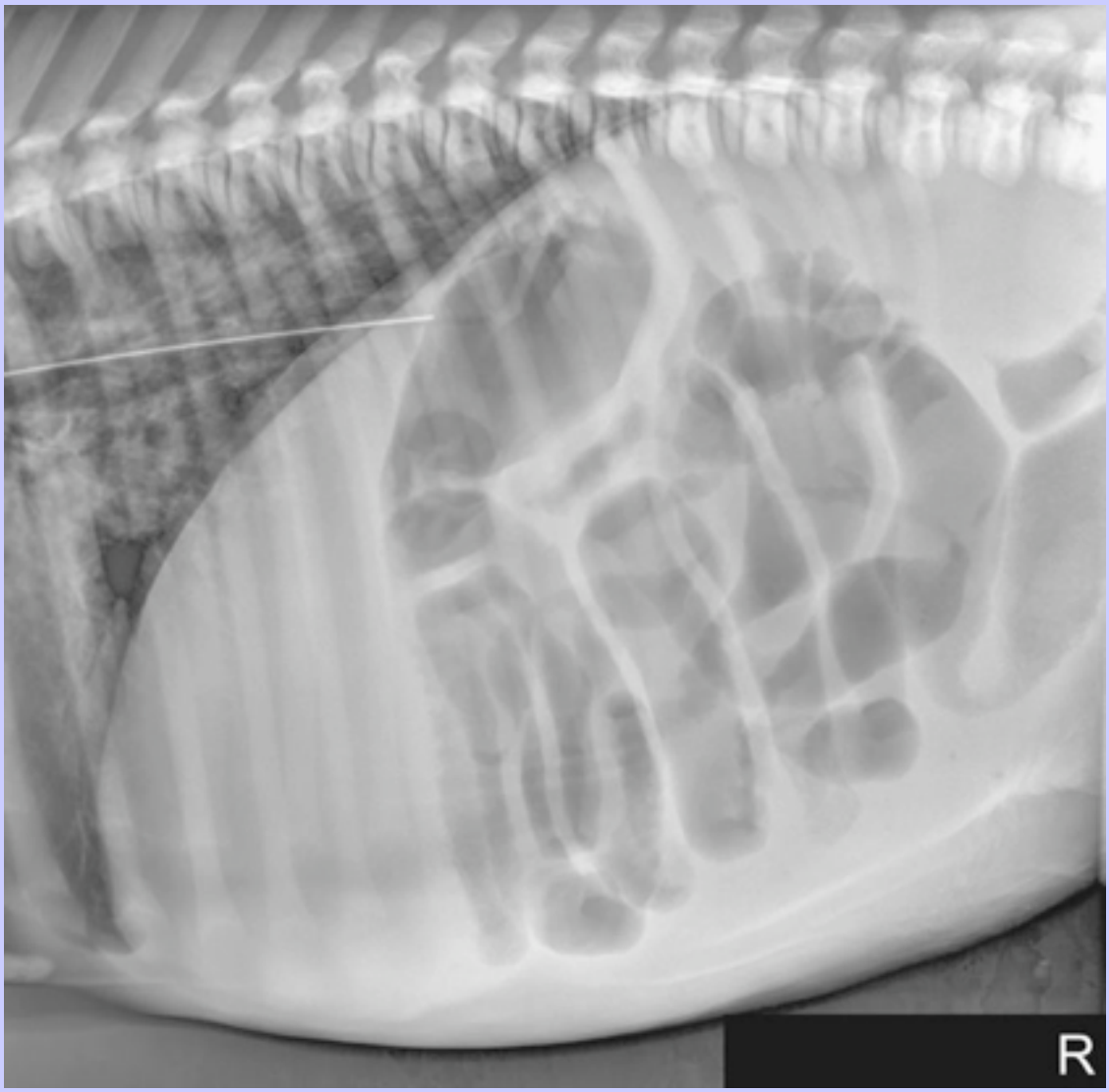


Fig. 32-8 Standing lateral radiograph of a 2-day-old thoroughbred colt with a meconium impaction. Note the large amount of gas distention of the colon.

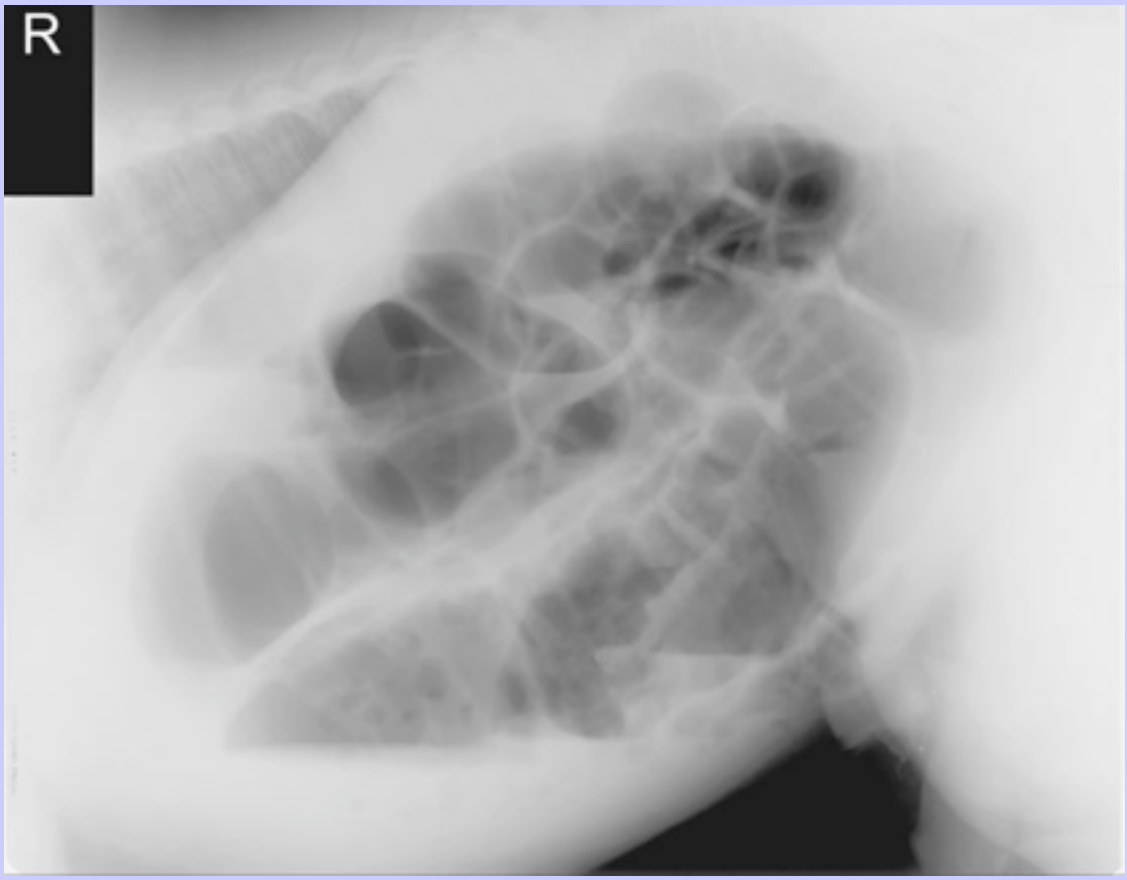


Fig. 32-9 Standing lateral radiograph showing a normal esophagram using barium liquid. The *arrow* marks the region where the nasogastric tube ends. This is approximately at the level of C3.

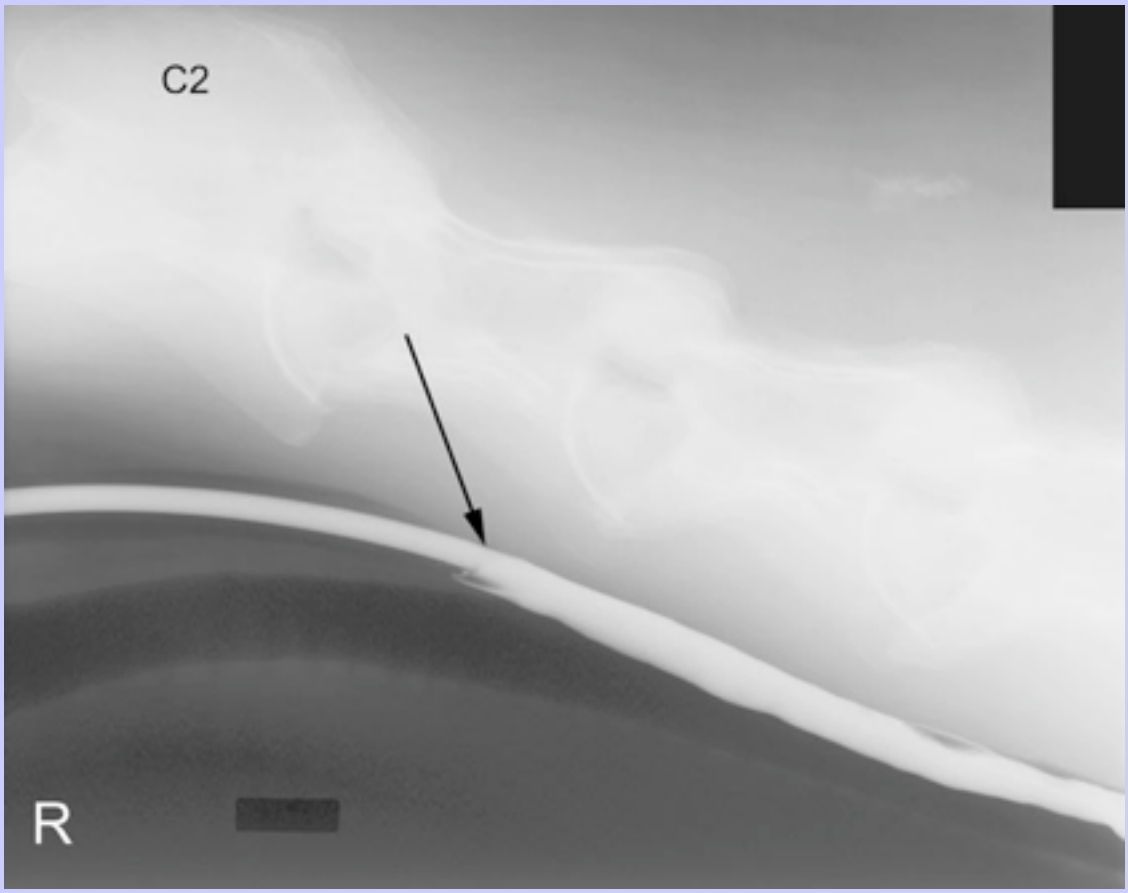
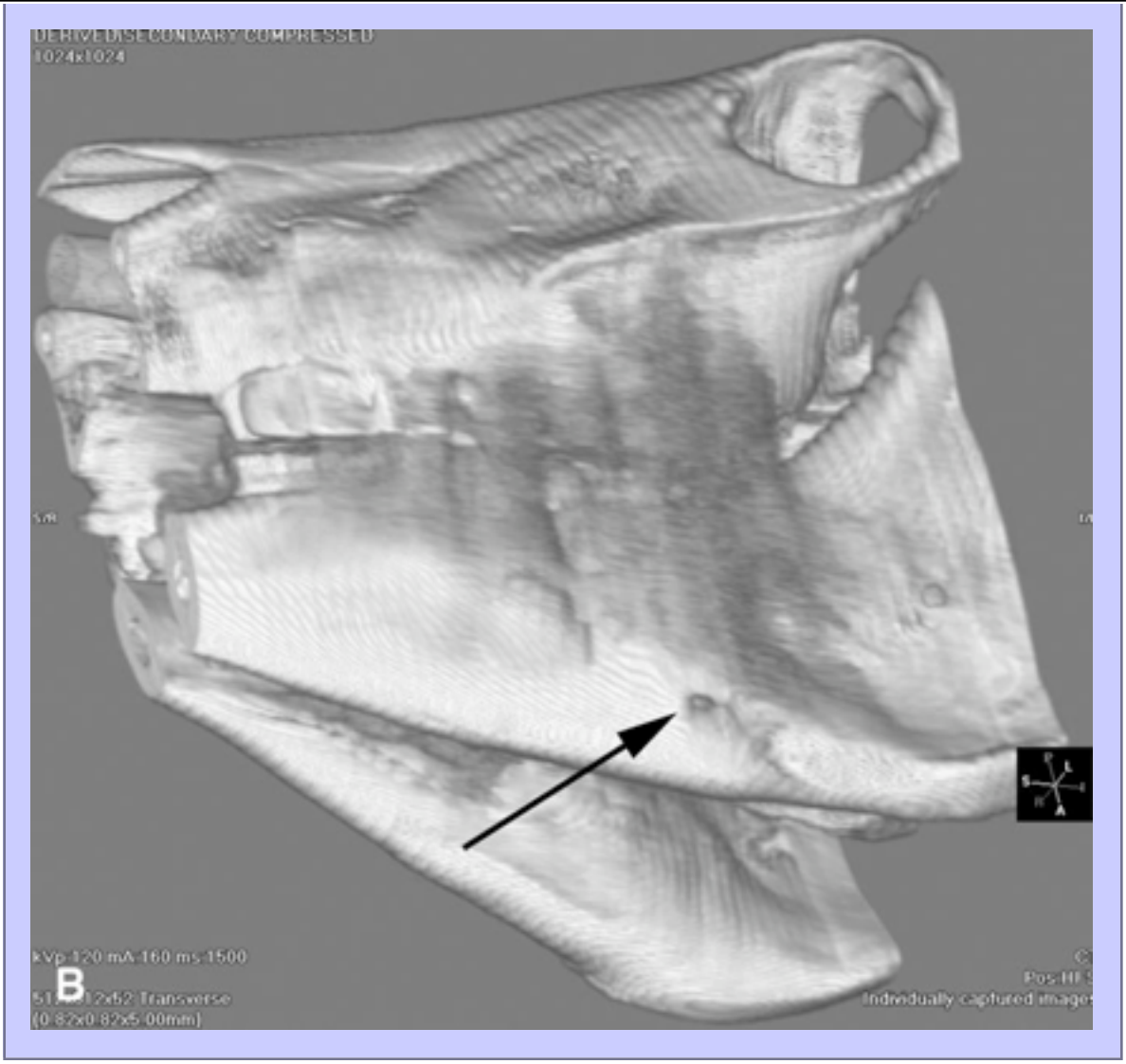


Fig. 32-10 These are transverse **(A)** and three-dimensional reconstructed computed tomography images **(B)** of the head of a 4-year-old pony mare with chronic draining tracts from the mandible. The *arrows* illustrate the tract through the mandible that communicates with the apical portion of the left mandibular first molar (tooth #309).



Positive (barium sulfate) and negative (room air) contrast medium radiography have also been used to evaluate the stomach and intestinal tract through oral administration of contrast medium,[6,15,16] and the rectum and colon have been evaluated via retrograde administration of contrast medium.[16] These methods allow for the evaluation of the stomach, intestinal tract, and rectum for regions of obstruction as well as ulcerations, tumors, motility disorders, and/or malformations. Although these methods have been described, ultrasound has virtually eliminated the need to expose personnel and patients to the repetitive, high doses of radiation needed to obtain sequential radiographs of the abdomen.

Computed tomography (CT) and magnetic resonance imaging (MRI) are of little use for evaluation of the alimentary tract (except for the head). This is mainly because of the size of the patient compared with the size of the gantry and bore in CT and MR units, respectively. Dental disorders such as abscesses and fractures can be clearly seen on CT images, especially after three-dimensional reconstructions (Fig. 32-10), and CT is also useful to detect pharyngeal and esophageal masses that may not be fully identified with conventional radiographs. CT and MRI can be used in foals that are able to be placed within the gantry or bore of the magnet; however,

because of the motion of the gastrointestinal tract and the long acquisition times used with respiratory gating sequences, MRI has not been used widely to evaluate the thorax or abdomen. A single case report has been published that described the use of contrast esophagraphy and CT to aid in the surgical planning of a persistent right fourth and left sixth aortic arch that caused a vascular ring anomaly in a foal.[17] However, the applications for these technologies have yet to be realized.

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32.7.2 Ultrasound

Ultrasound machines have become lightweight, extremely portable, and affordable to the general practitioner. Although the machine is affordable, image quality is highly dependent on the ultrasound probes available for the examination and experience of the sonographer. These ultrasound probes come in various shapes and sizes including linear array probes, curvilinear probes, and sector-phase array probes. The physics behind the probe technology is beyond the scope of this text, but the main generalizations are that phase array probes are mainly used for cardiac examination, curvilinear probes give a large field of view, and linear array probes give exceptional superficial detail. For abdominal evaluation, a curvilinear probe is the most practical choice. The second choice offered with probe technology is the frequency. Frequency of ultrasound probes determines both the resolution and the penetration that can be achieved. The higher the frequency of the probe selected, the better the image quality (resolution). However, the increased resolution comes at the cost of penetration. A 10-MHz probe can generally image only approximately 6 cm into the abdomen, whereas a 1-MHz probe can image approximately 30 to 36 cm. For this reason, one should select the highest frequency probe possible to image to the desired depth. For example, if the ventral colon were examined, because it is relatively close to the skin surface (approximately 5 cm), then an 8- to 10-MHz probe would give the best detail for the desired depth. If the nephrosplenic space were to be imaged, this structure is approximately 12 to 15 cm deep from the skin surface, and a 5-MHz probe would be needed. This will cause a reduction in image quality, but the sacrifice is needed to gain the desired depth. The ultrasound examination requires the use of large volumes of isopropyl alcohol to wet the hair and to serve as a coupling medium to provide airtight contact between the skin and the probe. Acoustic coupling gel and clipping can be performed to enhance image quality, but in my experience, using isopropyl alcohol provides a good image, and clipping can be done in limited areas as needed to enhance the image quality.

In the last 5 years ultrasound has come to the forefront of evaluation of the equine alimentary tract, primarily centering on the abdomen. Ultrasound has been used in foals to determine the growth rate and normal appearance of thoracic and abdominal organs[18] and in adult horses to evaluate the gastrointestinal tract for causes of pain including torsion, small intestinal obstruction, colon impaction, large colon displacement, intussusception, strangulating lesions, and enteritis and colitis.[10,19–23] This modality is even more useful because it provides real-time information to help assess contractility of the intestine. Although this has been explored using both standard two-dimension imaging, also called *B-mode* or *brightness-mode* imaging, and spectral Doppler imaging,[24] the presence of gas within the bowel and the fact that the bowel is usually perpendicular to the image plane makes quantitative evaluation of intestinal contractility difficult at best. When compared with radiography to identify intestinal sand accumulations, ultrasound was found to be 87.5% sensitive and specific using radiography as the gold standard.[10] The main limitations are the artifacts secondary to gas within the colon and the fact that gas and mineral are both echogenic on ultrasound, whereas they have opposite opacities on radiographs.

Ultrasound evaluation of horses with abdominal pain (colic) provides a rapid method to identify abnormalities within the gastrointestinal tract. Distention of the small intestine to a diameter greater than 5 cm has been strongly associated with strangulating or obstructing lesions[19] (Fig. 32-11). In foals with intussusception, the small intestine appears enlarged and there is generally distended small intestine orad to the lesion; however, at

the site of the intussusception there is a normal-appearing small intestinal wall (intussuscipiens) surrounded by a larger structure that appears to surround the inner small intestinal wall (called the *intussusceptum)*[19] (Fig. 32-12). Large colon torsion occurs when the large colon rotates 360 degrees or more around the root of the mesentery to cause occlusion of venous drainage while maintaining arterial flow. This causes the wall to become thick and edematous. If ultrasound is performed in the cranioventral abdomen, just caudal to the xiphoid process, then a colon wall size greater than 9 mm is 100% specific for a large colon torsion[21] (Fig. 32-13). A large colon displacement would have minimal to no vascular compromise, so it would be an ultrasound diagnosis based on exclusion. Chronic displacements did have a mild amount of edema in the colon wall, causing the size to be approximately 7 mm thick but never greater than 9 mm in the one study described.[21] The colon and small intestinal wall will also become thick with inflammation. Small intestinal wall thickness greater than 4 mm is indicative of inflammation.[19] The right dorsal colon can be imaged in the right tenth to twelfth intercostal space around the region of the costochondral junction, and a focal wall thickness of 9 to 12 mm has been identified with right dorsal colitis.[23]

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Fig. 32-11 Transabdominal ultrasonographic image of a 6-year-old thoroughbred gelding with acute onset of colic. The small intestine is 7 cm in diameter and was noted to have minimal to no contractility. This is consistent for mechanical ileus. A strangulating lipoma was identified at surgery. Courtesy of Cornell University.

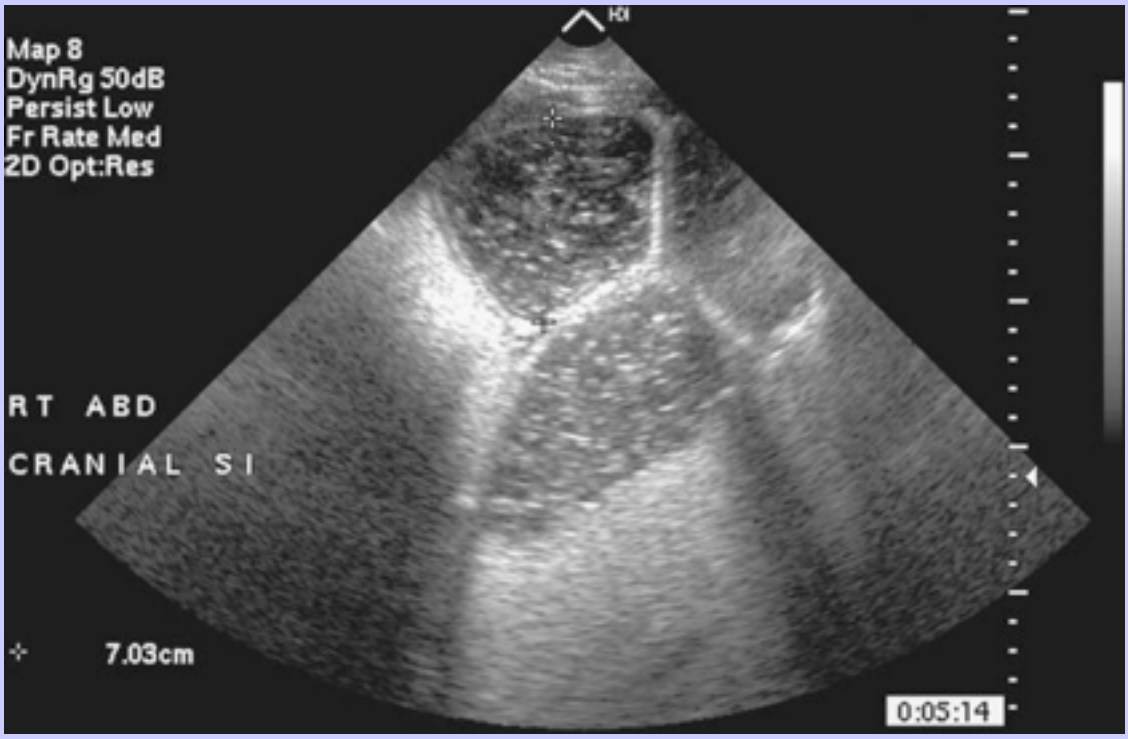


Fig. 32-12 Transabdominal ultrasound image of an adult standardbred mare. The image shows an inner intestinal structure surrounded by a second intestinal structure consistent with an intussusception. At surgery this was confirmed as an ileocecal intussusception. Courtesy of Cornell University.

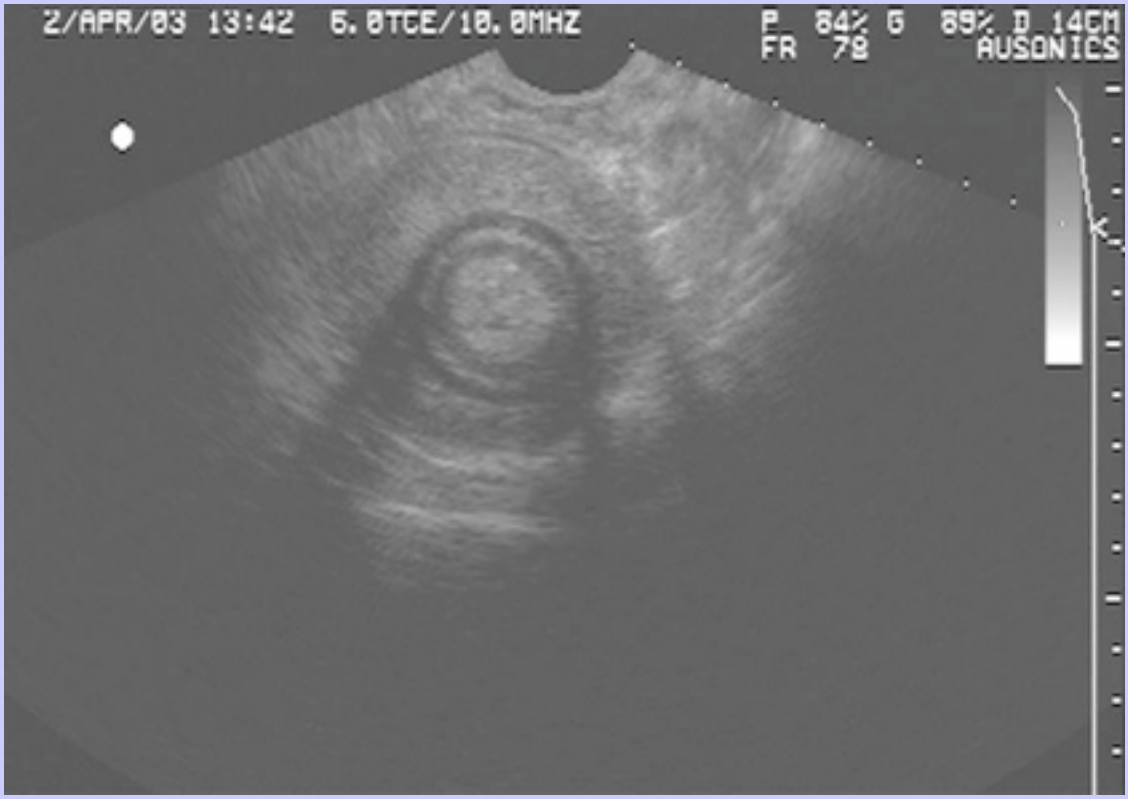
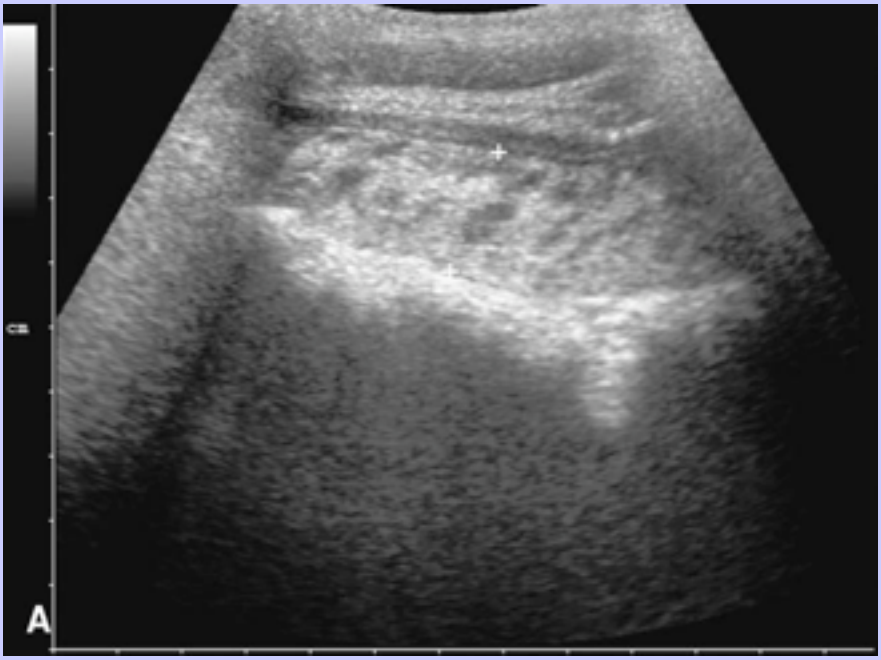
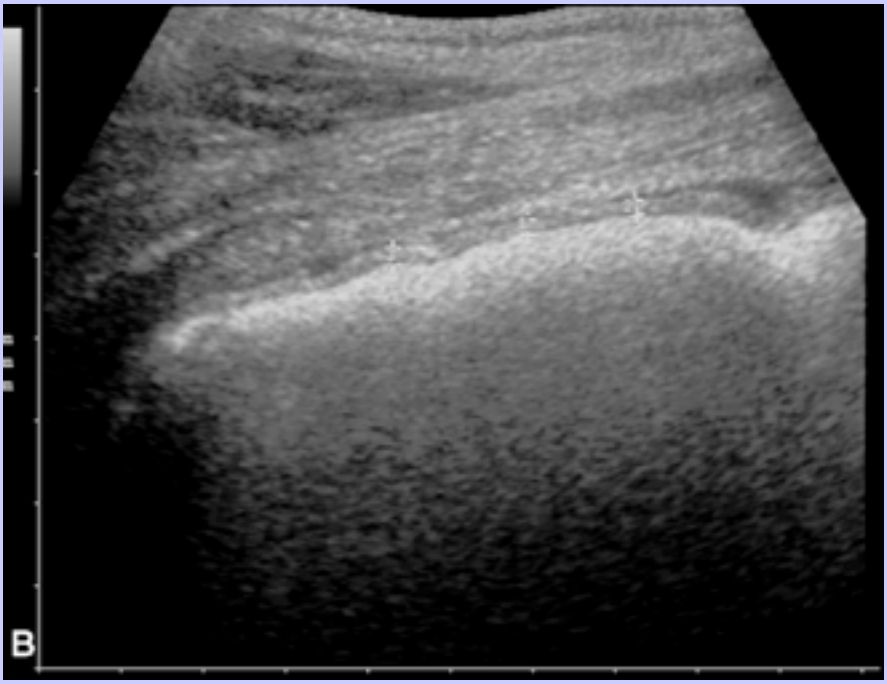


Fig. 32-13 Transabdominal ultrasound images of the large colon. **A**, In colon torsion the large colon wall is severely thick (2 cm) secondary to edema. For comparison, a normal colon wall thickness (**B**) should be 0.2 to 0.4 cm in thickness.





32.7.3 Scintigraphy

Nuclear medicine is a widely used modality to image the gastrointestinal tract in humans and animals. Although physical obstruction can be assessed with endoscopy, ultrasound is unable to identify the pylorus in the normal horse because of the peripheral nature of the colon and colonic gas. Nuclear medicine provides a functional evaluation of the pylorus to determine if delayed gastric emptying compared with normal horses is present. This modality works better than gastric emptying with barium sulfate because of the minimal invasive nature and ease of acquisition of images. However, the need for a gamma camera to generate the images and the licensing requirements to handle radioactive material make this modality less universally available. The primary use for evaluating the gastrointestinal tract with scintigraphy is to evaluate gastric emptying time.[25–28] Two protocols have been outlined in the references provided. The first uses the readily available technetium-99m pertechnetate (^{99m}Tc) bound to disofenin or sulfur colloid.[26,29,30] This combination of radioisotope and radiopharmaceutical is fed in a pelleted ration alone or mixed with radiolabeled eggs. The normal range for the $t_{½}$ gastric emptying has been reported to be 1.49±0.17 hours[30] and 1.56±1.08 hours.[29] The other method is the carbon-13 (^{13}C) bound to octanoic acid breath test (^{13}C-OABT). This method was validated compared with the ^{99m}Tc sulfur colloid and found to have similar results compared with the solid phase gastric emptying $t_{½}$.[24] The main difference is that the ^{13}C-OABT is measured in the exhaled breath of the horse and with spectroscopy rather than using a gamma camera. The rationale for ^{13}C-OABT is that because a gamma camera is not needed, this test may be more portable and useful for field investigations.[29]

Another nuclear medicine procedure in the realm of alimentary tract evaluation involves the use of ^{99m}Tc hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO). This procedure allows for radiolabeling WBCs in order to determine areas of inflammation.[31,32] The use of ^{99m}Tc is a matter of convenience because it is also used in equine bone imaging. Thus, detection equipment, such as a low-energy, all purpose collimator, is readily available in many practices. HMPAO is used because it binds to granulocytes and therefore should travel to areas of increased inflammation.[32] HMPAO also associates with the reticuloendothelial system, enabling localization within the lungs, liver, spleen, kidneys, and urinary bladder. The main drawback is that with the activity bound to WBCs there is a general lack of anatomic information, which can cause lesion localization to be difficult.[32] Although this technique is expensive and labor-intensive, the results from the limited studies available appear encouraging.

32.8 BIOPSY

The decision about whether to obtain a biopsy is often based on the ease of obtaining a sample and the relative value of the evaluation that can be made. Very small samples, such as those obtained with an endoscope biopsy instrument, are relatively easy to obtain, but they provide limited information. Full-thickness bowel specimens, obtained by means of ventral midline or flank laparotomy, are more difficult to obtain, but they provide much more information.

Taking a biopsy sample by endoscopy allows the practitioner to choose the biopsy site on the basis of the appearance of the mucosal surface, which most frequently reflects an inflammatory disorder. Conversely, when a biopsy sample is obtained through laparotomy, the serosal surface of the bowel may not reflect a disorder within the bowel wall. In such instances it may be useful to obtain several biopsy specimens. Rectal mucosal biopsies are easily performed. Many instruments can be used to obtain the biopsy specimen, and a uterine biopsy forceps works

well. A fold of mucosa can readily be pinched between two fingers, and a sample of this tissue is obtained. The size of the sample is adequate for histologic or bacteriologic examination.

32.9 FECAL EXAMINATION

Cytologic, biochemical, bacteriologic, immunologic, and electron microscopic evaluations can be performed on fecal samples. In addition, observation of the consistency and color, the presence of foreign material such as sand or gravel, and the presence of parasites should be included in the examination of the alimentary system. In addition to fecal consistency, fecal particle size can be used to evaluate the efficiency of mastication or the colonic transit time. Increased particle size, with loose or watery stool, is suggestive of decreased colonic transit time.

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Cytologic examinations are primarily used to evaluate the parasite burden of the animal. Ova of large and small strongyles, tapeworms, round worms, and *Strongyloides westeri* are most common. Coccidia are occasionally observed but are clinically unimportant. Examination of fecal WBCs has been advocated in the evaluation of horses and foals with enterocolitis. Because these cells are very labile, their presence in large numbers indicates that an inflammatory process is present and that the inflammation is in the distal colon or is associated with decreased transit time.

Determination of fecal occult blood has been recommended to diagnose gastric ulcers, duodenal ulcers, and other potentially hemorrhagic disorders of the alimentary tract. However, the usefulness of this test has been shown to be quite limited, because negative results can be obtained when blood is present in the proximal portion of the gastrointestinal tract.[33] The sensitivity of most commercially available tests is poor, giving negative results in the face of severe gastric bleeding.

Fecal culture is an essential component in the evaluation of many patients. In bacteriologic culture techniques for fecal samples, selective media that are designed to isolate *Salmonella* are routinely used. These media include selenite broth, tetrathionate broth, brilliant green agar, XLD agar, and *Salmonella-Shigella* agar. Less selective media, McConkey's and eosin methylene blue agars are desirable to culture other potential gram-negative bacterial pathogens such as *Escherichia coli*, but the mere presence of *E. coli* in the feces does not determine its pathogenicity. Enterotoxigenic *E. coli* have been isolated from foals with diarrhea, but special tests, such as polymerase chain reaction (PCR) assays, must be performed to determine whether an isolate produces enterotoxin.

Tests for detection of enterotoxins of *Clostridium difficile*[*] and *Clostridium perfringens*[†] in fecal specimens are available at diagnostic laboratories or can be performed using enzyme-linked immunosorbent assay (ELISA) kits.

The presence of rotavirus in a fecal sample can be determined by use of an ELISA or an agglutination test. Both assays test for the presence of viral antigen in the feces. The ELISA is reported to be more sensitive than the agglutination test but is less specific. Therefore the agglutination test is likely to give more false-negative results, and the ELISA test is likely to give more false-positive results. The ELISA test is more time-consuming and inconvenient to perform than the agglutination test. When rotavirus is a concern, particularly as a farm problem, a reasonable approach is to screen fecal samples with the agglutination test and repeat testing of samples that yield negative findings with the ELISA.

* *C. difficile* Tox A/B Test, TechLab, Blacksburg, VA.

† *C. perfringens* enterotoxin test, TechLab, Blacksburg, VA.

32.10 ABSORPTION AND DIGESTION TESTS

Tests that evaluate the ability of the equine intestinal tract to digest and absorb nutrients have a more limited clinical application than in human or small animal medicine, but they can be useful in the evaluation of horses with chronic weight loss, suspected small intestinal inflammation or neoplasia, gastric and small intestinal partial obstruction, and postoperative small intestinal malabsorptive disorders. For absorption tests to be diagnostic, the intestinal disorder must either be diffuse or affect the delivery to and transit through the small intestine.

Maldigestion tests are performed to evaluate exocrine pancreatic function and small intestinal mucosal brush border disaccharidase activity. Pancreatic exocrine deficiencies have not been described in the horse, probably because equine pancreatic secretions consist primarily of water and bicarbonate and have less enzymatic activity than in monogastric omnivorous species. Mucosal brush border disaccharidase-related maldigestion is relevant in viral and bacterial enteritides of foals, particularly rotavirus and coronavirus enteritides. As a result of these viral infections, there is loss of the superficial villous epithelial cells of the small intestine, in which the disaccharidases lactase, cellobiase, maltase, sucrase, and trehalase are located.[34] Lactase levels are greatest in young suckling foals, and loss of this enzyme activity, secondary to loss of the mucosal villous cells, leads to lactose maldigestion. Lactose tolerance can be tested by administering a 20% solution of D-lactose at a dose of 0.5 to 1 g/kg. This dose should result in an approximate doubling of the serum glucose level within 60 minutes of administration.[35]

Clinically applicable absorption tests include the D-glucose and D-xylose absorption tests. The glucose absorption test has the advantage of being relatively easy and inexpensive to perform. However, cellular uptake and metabolism of glucose, as well as intestinal absorption, influence the results and thus are undesirable variables. The xylose absorption test is therefore advantageous because it more directly measures intestinal absorptive capacity. The results of both tests, though, are affected by gastric emptying rate and small intestinal transit time. In the United States, D-xylose is available only through chemical suppliers and only for research purposes; its availability for clinical diagnostic use is restricted.

The D-glucose and D-xylose tests are performed similarly. After an 18- to 24-hour fast, a 10% solution of D-glucose or D-xylose, 0.5 to 1 g/kg, is administered through a nasogastric tube. For the measurement of glucose, blood is collected in sodium fluoride tubes; and for the measurement of D-xylose, blood is collected in heparinized tubes. Samples are taken at 0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes after administration. Peak levels, which normally range from 20 to 25 mg/dL, occur 60 to 120 minutes after administration, and levels thereafter should decrease. The normal curve resembles an inverted V. Variability in absorption curves occur as a function of age and type of feed the horse is given.[36] Delay or flattening of the absorption curve may reflect delayed gastric emptying, increased intestinal transit time, or impaired intestinal absorption.[37] Accurate interpretation of the results of these tests depends on the results of other diagnostic evaluations. In addition, different types of diet have been shown to affect the height, although not the shape, of the absorption curves significantly. In general, diets that have a higher digestible energy content result in a lower peak in the curve.

32.11 BREATH TESTS

In humans, dogs, and cats, breath tests are used to assess a variety of intestinal disorders. The urea breath test is used as part of an assessment of *Helicobacter* status of the patient,[38] but this is not an issue for horses. The hydrogen breath test is used in assessments of intestinal bacterial overgrowth and in determination of carbohydrate digestion and absorption in the intestine. In patients with an abnormal intestinal bacterial population or carbohydrate malabsorption, there will be excessive bacterial fermentation of carbohydrate, with one byproduct

being hydrogen. Because hydrogen is freely diffusible from the bowel into the blood, and from the blood into the alveoli, measurement of exhaled hydrogen gas can be used to assess the status of intestinal bacterial fermentation of carbohydrates. In horses, the hydrogen breath test is most applicable to conditions in which there is carbohydrate malabsorption and thus increased delivery of soluble carbohydrate to the large intestine for bacterial fermentation to occur. There are two reports of this technique in horses, one in which different carbohydrate substrates were evaluated in ponies[39] and another in which the hydrogen breath test was used in conjunction with D-xylose absorption in nine horses with a variety of clinical disorders.[40] In the study with ponies ($N = 7$), fasting resulted in negligible levels of breath hydrogen excretion. Sustained increases in breath hydrogen concentration greater than 10 ppm were observed for all ponies after the ingestion of oats or the administration of wheat flour, for three ponies after the administration of glucose and xylose, and for two ponies after the administration of lactulose and lactose. The pattern of breath hydrogen excretion was subject to variation among animals after the ingestion of identical test meals. In the clinical study the diseased horses showed higher fasting breath hydrogen (H_2) levels (range 7.5 to 61.5 ppm) than normal horses (range 0 to 5 ppm). After xylose administration, none of the healthy animals showed an increase in breath H_2 production, and five of diseased animals showed increases in breath hydrogen. In this group of patients, abnormalities in hydrogen breath measurement were more apparent than abnormalities in D-xylose absorption.

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32.12 DENTISTRY AND ORAL DISEASE

Jack Easley

The horse has evolved over millions of years to become a continuously grazing animal and in doing so has developed its own dental form and function. The horse's oral and dental structures provide it with the ability to detect, prehend, masticate, and begin the digestion of forage. As we have domesticated and confined the horse, we have altered its diet to consist of less continual grazing and more interval feeding of dry hay, grain, processed forages, and other concentrates. Selective breeding and domestication have increased the incidence of equine dental and oral disease in today's equine population.

32.13 DENTAL AND ORAL ANATOMY

The structures the horse uses in eating include tactile and prehensile lips; hypsodont incisors, premolars, and molars; facial bones; muscles of mastication; tongue and hard and soft palates; buccal mucosa; cheeks; olfactory organs; taste buds; salivary glands and ducts; and blood vessels and nerves that support these structures. The equine mouth is a long cylindric cavity that is the beginning of the alimentary canal and is commonly referred to as the *oral cavity*. The muscular lips make up the entrance to the mouth, which is bounded laterally by the cheeks, dorsally by the hard palate and ventrally by the body of the mandible and the mylohyoid muscles. The caudal aspect of the mouth is composed of the soft palate, root of the tongue, and epiglottis and is continuous with the oropharynx.[41,42]

The blood supply to the mouth is derived from the maxillary, mandibular, labial, and sphenopalatine arteries. The venous drainage is chiefly through the linguofacial veins. Sensation to the mouth and cheeks is derived from the trigeminal nerve (cranial nerve V), and motor function from the facial nerve (cranial nerve VII). The hard palate has a central raphe that divides the surface into right and left halves. The flat portion of the palatal mucosa just caudal to the upper incisors may appear swollen in the young horse when permanent incisors are erupting. This normal mucosal enlargement seen in 2- to 5-year-old horses has been referred to as *lampas*. Farther caudally, the hard palate becomes more concave and contains paired transverse ridges, which are instrumental in moving a food bolus caudally, in a spiral fashion, as the horse masticates forage. The muscular tongue sits in the bottom of the

mouth, supported in a sling formed by the mylohyoideus muscles, between the paired hemimandibular rami. The root of the tongue is attached to the lateral aspect of the soft palate, the pharynx, and hyoid bone. The lingual muscles receive their motor innervation from the hypoglossal nerve (cranial nerve XII) and sensory innervation from the lingual branch of the mandibular nerve and glossopharyngeal nerve (cranial nerve IX).

The mandible is the largest bone of the face and is formed by paired hemimandibles that fuse rostrally at the mandibular symphysis when the horse is approximately 2 to 3 months old. Each hemimandible is composed of a horizontal and a vertical ramus. The dental alveoli are contained within the horizontal ramus. The vertical ramus terminates with the coronoid process rostrally and the mandibular condyle caudally. The temporalis muscle inserts on the coronoid process.

Between the incisors and the rostral aspect of the mandibular cheek teeth, on the horizontal rami of the mandible, are the “bars” of the mouth. This large interdental space or natural diastema is the resting area for the bit. Canine teeth, if present, are located in these spaces. The ventral border of the mandible of the young horse is wide and round, but as the horse ages and the mandibular cheek teeth continue to erupt, the ventral border of the mandible becomes more sharply angled. Eruption swellings or “bumps” often develop along the ventral border of the mandible of young horses as the permanent mandibular cheek teeth erupt.

The paired incisive (premaxillary) bones form the rostral part of the upper jaw and contain the alveoli of the upper incisors. Caudally the incisive bone becomes thinner and forms the rostral part of the hard palate. The suture line between the incisive bones and the maxillary bones is an anatomically weak area and a common site of fracture. The upper canines, if present, are situated just caudal to this suture line.

The paired, large maxillary bones extend from the incisive bone rostrally to the nasal bones dorsally and lacrimal bones caudally. The facial crest is a prominent ridge of bone on the lateral aspect of the maxillae. This crest continues caudally as the zygomatic process and joins the malar and temporal bones to form the zygomatic arch. The ventromedial aspects of the maxillary bones join to form a horizontal shelf that provides rigid support to the majority of the hard palate. The alveoli of the upper canines, premolars, and molars are embedded in the maxillae. The position of the alveoli of the upper cheek teeth is somewhat variable, but usually the alveoli of the first two cheek teeth lay rostral to the sinuses. The apices of the third and fourth cheek teeth lie within the rostral maxillary sinus in the young to middle-aged horse, and the apices of the caudal two cheek teeth lie within the caudal maxillary sinus. Each alveolus is separated by transverse interalveolar bony septa.

The horse has five paired paranasal sinuses: the conchofrontal, sphenopalatine, caudal maxillary, rostral maxillary, and ethmoidal sinuses. The rostral and caudal maxillary sinuses are contained within the maxillae and are usually separated by a thin bony septum, although this septum often breaks down in the presence of sinus disease. The infraorbital canals (one on each side of the head) traverse longitudinally through the maxillary sinuses.

Bacterial sinusitis can occur secondary to disease of the third, fourth, fifth, and sixth upper cheek teeth and classically results in a unilateral, malodorous, nasal discharge. Almost the entire lumen of the maxillary sinuses of a young horse is occupied by dental alveoli, but as the facial bones grow and reserve crowns of the upper cheek teeth erupt, the cheek teeth move rostrally and ventrally, causing the sinus compartments to enlarge. The paranasal sinuses drain into the caudal aspect of the nasal cavity via a slitlike opening, the nasomaxillary aperture. The medial compartment of the rostral maxillary sinus, or ventral conchal sinus, has poor drainage and is a common site for inspissated exudate to accumulate. Its secretions must drain into the lateral compartment of the rostral maxillary sinus before draining into the caudal aspect of the middle meatus through the nasomaxillary aperture.

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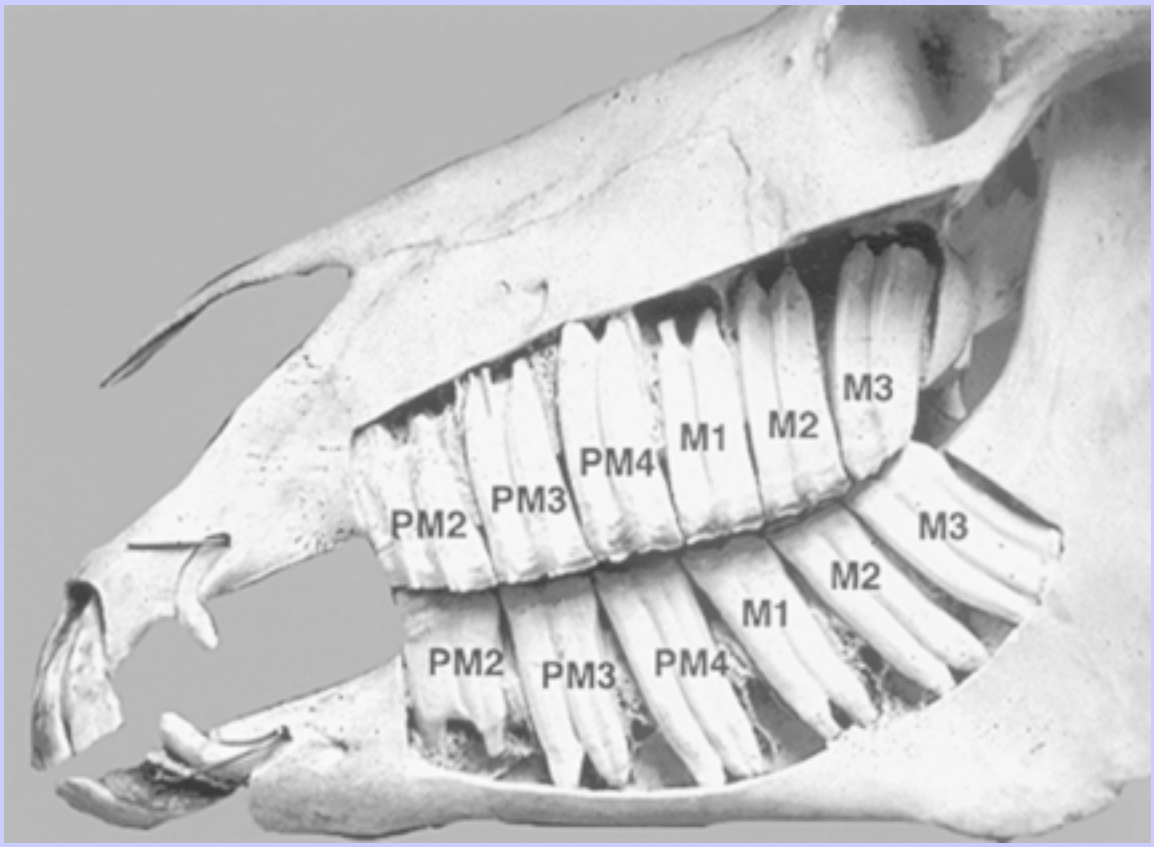
The temporomandibular joint is a synovial joint formed by the articulation of the squamous temporal bone with the condylar process of the mandible. The joint lies approximately 15 cm above the level of the occlusal surface of the

cheek teeth. The cavity of the joint is large and divided by a cartilaginous, intraarticular disk. The joint is bound by a tight capsule and lateral and caudal ligaments. The equine temporomandibular joint has a wide range of lateromedial movements, which allows for the medially directed power stroke of mastication, but limited vertical and rostrocaudal movements.

To affect the wide lateromedial range of motion in the temporomandibular joint during the power stroke of mastication, the masseter and pterygoid muscles have evolved into most highly developed muscles of mastication in the horse. The powerful masseter muscle originates along the full length of the facial crest and zygomatic arch and has wide insertions along the caudolateral aspect of the mandible. The superficial muscle fibers of the masseter run almost vertically, whereas the deep fibers course in a ventrocaudal direction. The masseter pulls the jaw to the ipsilateral side and contributes to closure of the jaw. The origins and insertions of the medial and lateral pterygoid muscles are similar to those of the masseter, but these muscles lie on the medial aspect of the mandible. The digastricus muscle originates on the occipital bone and attaches to the caudal aspect of the mandible. This muscle assists in opening the mouth, but because gravity also assists in opening the mouth, this muscle is small. The temporalis muscle functions to close the jaw, but because the temporomandibular joint of the horse is capable of only slight vertical movement, this muscle is also small and poorly developed. The muscles of mastication are all innervated by the trigeminal nerve (cranial nerve V).

Fig. 32-14 Lateral view of cadaver equine skull. *M*, Molar; *PM*, premolar.



32.14 TEETH

The foal has erupted 24 deciduous teeth by the time it is approximately 6 months old. Expansion of the cranial and facial bones during the first 2 to 3 years of life allows room for the expansion of the dentition from 24 deciduous teeth to the 36 to 44 permanent teeth present in the adult horse. The mouth of the mature horse contains six incisors in both the upper and lower jaws and six permanent upper cheek teeth and six permanent lower cheek teeth on each side of the mouth (Fig. 32-14). The rostral three cheek teeth are premolars, and the caudal three cheek teeth are molars. Incisors and premolars have deciduous and permanent sets. Molars erupt later than the deciduous premolars and do not have deciduous counterparts. The occlusal surface of the cheek teeth of the upper jaw is broad and square, and that of the lower cheek teeth is narrower and rectangular.

The cheek teeth in each quadrant of the horse's mouth are commonly referred to by number (1 to 6), from rostral to caudal. The vestigial and inconsistently present first premolar, often referred to as a *wolf tooth*, is not included in the 1 to 6 nomenclature. To help avoid confusion, the American Veterinary Dental College Nomenclature and Classification Committee has endorsed the use of the Modified Triadan Tooth Numbering System for the horse.[43] This three-digit tooth numbering system is based on a full phenotypic dentition composed of 44 teeth. The first digit designates the location of the quadrant, or arcade, and whether the dentition is deciduous or permanent. The permanent teeth in a quadrant are designated using numbers 1 to 4, and the deciduous teeth in a quadrant are designated using numbers 5 to 8. The numbering sequence for the permanent teeth starts with #1 for the upper right teeth, #2 for the upper left teeth, #3 for the lower left teeth, and #4 for the lower right teeth. In each dental quadrant, the incisors are numbered 01 to 03, and the first or central incisor is always 01. The canines, whether present or not, make up the 04 position in this formula. The premolars are numbered 05 to 08, and the molars are numbered 09 to 11.

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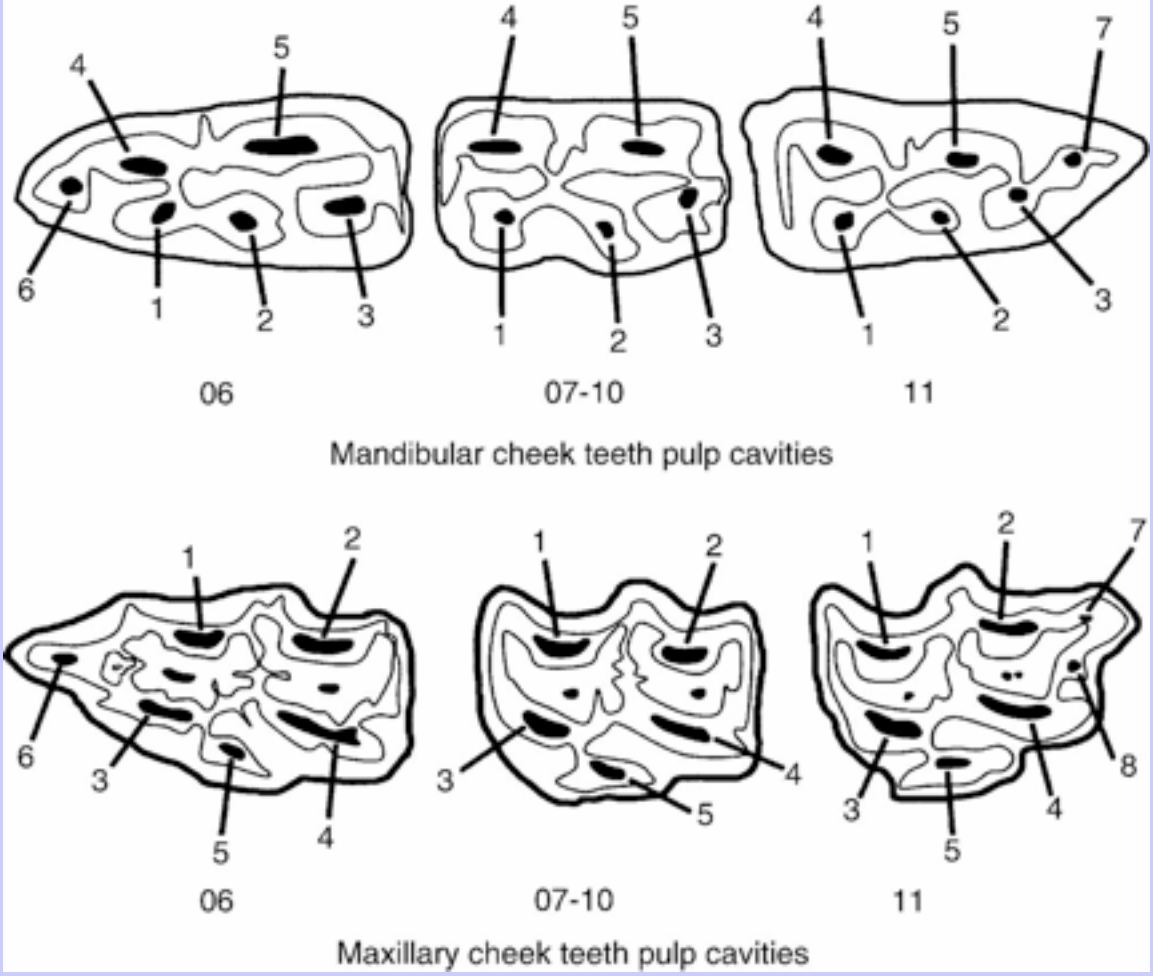
The equine incisors and molarized cheek teeth are hypsodont and have long anatomic crowns. The tooth crown is the enamel-containing portion of the tooth. When these hypsodont teeth erupt, their occlusal surface is covered with thin layers of cementum and enamel, which wear away from masticatory forces and abrasive forage, to expose the true or functional occlusal surface of the tooth. This process is termed *coming into wear*. The functional occlusal surface of hypsodont teeth is composed of thin, brittle sheets of hard enamel sandwiched between softer layers of cementum and dentin. This three-textured occlusal surface is self-sharpening and resistant to wear and fracture. The occlusal surfaces of the molar arcades wear in an undulating fashion with 13 loph basins (food channels) between transverse ridges.

The incisors and upper cheek teeth have enamel invaginations in the crown, termed *infundibula*. These enamel invaginations are partially filled with cementum, which receives its blood supply from the soft tissue covering the tooth before eruption. The shallow infundibulum present on each incisor has a wide opening at the occlusal surface, referred to as a “cup.” As the incisor wears, the small apical portion of the infundibulum eventually becomes exposed at the occlusal surface and is termed “the spot.” Each upper cheek tooth has a rostral and a caudal infundibulum. These enamel invaginations, or cones, give the central area of these teeth a hard wear surface. The center of the cement lake that fills the infundibulum contains a hole, which is the remnant (i.e., a “ghost”) of the central blood vessel that once supplied nutrition to the now dead infundibular cementum.

Fig. 32-15 Diagram of the premolar and molar pulp cavities.



Much of the crown of the hypsodont teeth of the horse is held in reserve subgingivally, in the alveolar bone. The apex of the tooth slowly completes its development by forming roots for several years after the tooth erupts. The interior of the tooth is composed primarily of dentine, with primary dentine lining the common pulp chamber of the newly erupted hypsodont tooth. The pulp chambers of hypsodont teeth are active throughout the horse's life and continuously produce secondary dentine within the pulp cavity. Continuous production of secondary dentine prevents the vital pulp from being exposed at the occlusal surface as the tooth wears. The depth of secondary dentine at the occlusal surface of the pulp horns varies in horses but is at least 5 to 7 mm thick and generally increases in thickness as the tooth ages. Secondary dentine absorbs pigment from feed and is seen as a brown area on the occlusal surface of the tooth.

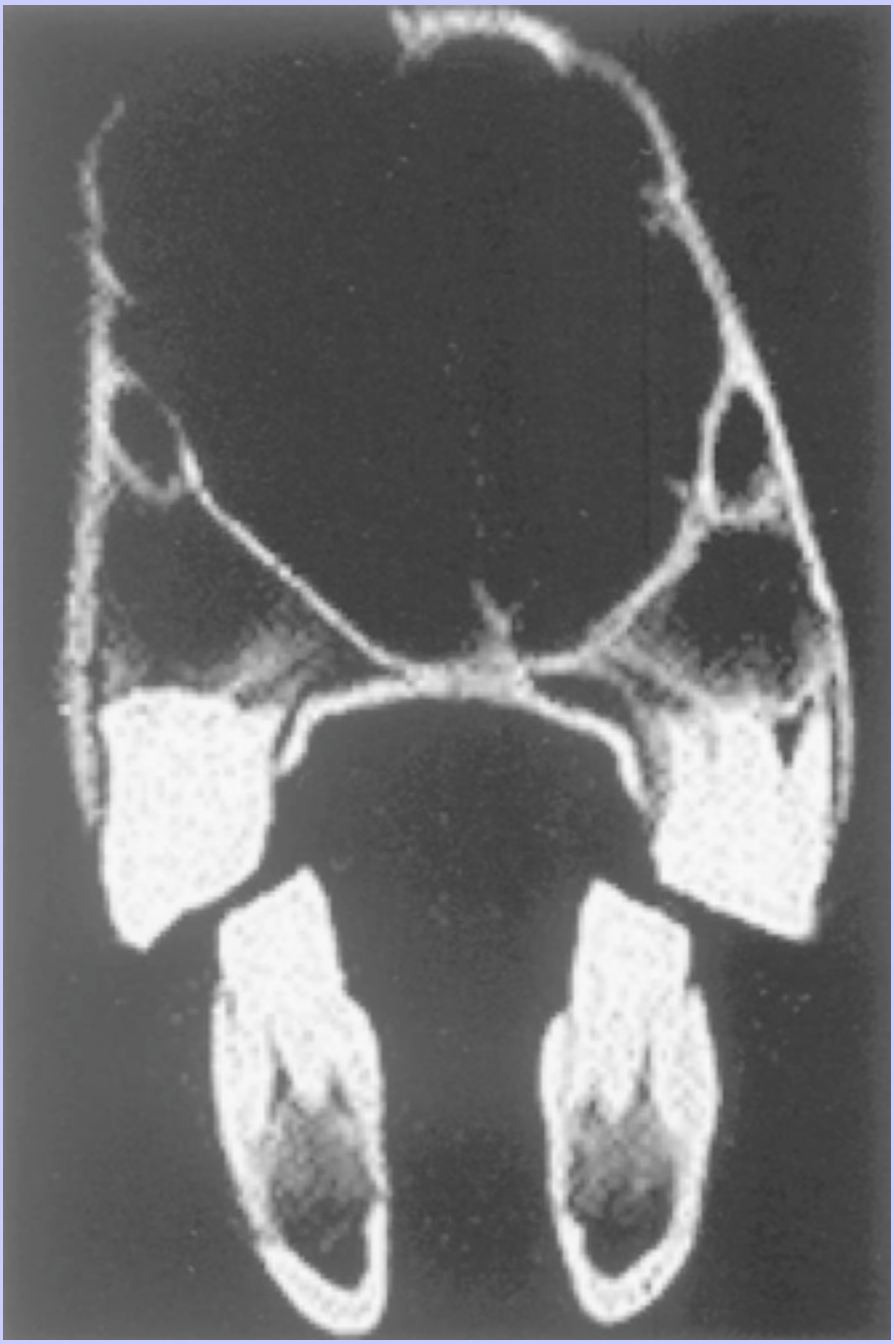
The pulp cavity of the young, permanent cheek tooth is large, but as the tooth ages the pulp divides into smaller pulp chambers, or horns, by deposition of secondary dentine. From 2 to 4 years after eruption, mandibular cheek teeth have a distinct, apically located, common pulp chamber that communicates with the pulp horns. Five pulp horns are present in the 07s to 10s, six pulp horns are present in the 06s, and six or seven pulp horns are typically present in the 11s (Fig. 32-15). By 6 to 8 years after a mandibular cheek tooth erupts, production of secondary

dentine divides the endodontic system of the tooth into two distinct compartments or roots. Each compartment consists of a root canal, a pulp chamber, and two or three pulp horns. Each maxillary cheek tooth has three roots. 678
Because of the continuous production of cementum around the apical or root portion of the tooth and continuous 679
wear of the crown, old equine teeth are primarily composed of cementum. When most of the enamel of the crown has worn away, the softer dentine and cementum are quickly worn flat, leading to the condition known as “smooth mouth.”[44]

Innervation of the dental structures is supplied by the trigeminal nerve, which exits the skull just below the ear. This nerve traverses rostrally and then divides into ophthalmic, maxillary, and mandibular branches. The maxillary nerve enters the caudal aspect of the maxilla ventral to the orbit via the maxillary foramen and runs through the maxilla in the infraorbital canal, giving off branches that supply the maxillary cheek teeth. The nerve then exits the maxilla at the infraorbital foramen, located just rostral and dorsal to the facial crest. As the mandibular nerve runs medially along the horizontal ramus of the mandible, it branches into smaller nerves, including the mandibular alveolar nerve, which enters the mandibular canal at the mandibular foramen on the caudomedial aspect of the mandible and innervates the mandibular cheek teeth. The inferior alveolar nerve exits the mandibular canal at the mental foramen at the rostrolateral aspect of the mandible just rostral to the mandibular cheek teeth to become the mental nerve, which supplies the ipsilateral soft tissues over the incisive portion of the mandible.

The horse is anisognathic, which means that the bottom jaw is narrower (by about 25%) than the upper jaw. The molar tables are sloped at a 10- to 15-degree angle from dorsal lingual to buccal ventral (Fig. 32-16). Lateral excursion of the jaw during mastication favors occlusal wear of the buccal aspect of the lower molar arcades and the lingual aspect of the upper molar arcades. As the horse chews, the jaw moves in a rotary motion from side to side with limited rostral to caudal excursion. The molars are constructed so that the enamel, cementum, and dentine interdigitate to provide a sharp, serrating surface that allows for uneven, continuous wear when the horse is eating.

Fig. 32-16 Computed tomographic scan of the equine skull at the level of the first molars. Dorsal is at the top. Note that because the upper molars are offset laterally from the lower molars, the molar tables are sloped at a 10- to 15-degree angle from dorsal lingual to buccal ventral.



The extent of lateral excursion of the mandible during normal mastication is affected by the length of stem or roughage in the horse's ration. Horses on pasture or hay have a wide area of mandibular excursion, whereas horses eating pellets or concentrates have a more limited range of lateral jaw excursion. Horses fed predominantly pellets or only a small quantity of long-stemmed roughage tend to have incomplete wear of the molar surface, predisposing the arcades to development of sharp enamel edges, a vaulted ceiling of occlusion, or the serious problem of shear mouth. Malocclusion of the incisors or the molar arcades perpetuates abnormal wear patterns that can eventually lead to severe dental disorders.

Rostral or caudal molar malocclusions or problems with eruption (e.g., displaced, deformed, missing, or supernumerary teeth and delayed eruption) lead to uneven dental wear. Horses with asymmetry between the upper and lower molar arcades, such as from mandibular fracture, facial injury, congential deformities such as brachygnathism (parrot mouth) and prognathism (sow mouth), or an abnormally narrow mandible in relation to the maxillae, often develop abnormal dental wear, resulting in sharp enamel points, dental overgrowths, shear mouth, step mouth, or wave mouth.

Equine males normally have two upper and two lower canines (or bridle teeth). The upper canines erupt just caudal to the suture between the incisive and maxillary bones. The lower canines are located further rostrally, producing a long lower diastema or interdental space. Canines of mares are rudimentary or absent.

The rudimentary first premolars, or wolf teeth, are constant in fetal life in both the upper and lower jaws. Many never develop to the point of eruption but instead degenerate and become incorporated in the maxilla or mandible. The upper first premolars erupt in 20% to 80% of horses, whereas the lowers erupt in only 1% to 5% of horses.

The dynamic changes that take place in the horse's head continue at a slower pace throughout life after the horse matures. The hypsodont premolars, molars, and incisors with their large reserve crowns and slowly forming short roots continually erupt and wear. With continuous eruption and wear of the hypsodont teeth, all horses eventually wear their cheek teeth to the roots.

32.15 DENTAL EXAMINATION

A horse's dentition should be examined biannually as a routine part of a health maintenance program. Eating efficiency and oral hygiene are the most important considerations from a medical standpoint when providing dental care, but often owners are more enthusiastic about dental care because of its positive effects on the horse's athletic performance. Written documentation of findings during dental examination is necessary to formulate a problem-oriented treatment plan and to follow progress after the horse receives routine maintenance and/or treatment for dental abnormalities. A consistent routine on the part of the examiner increases the efficacy and quality of the examination (Box 32-1).

Signs of dental disease may be obtained from the history or observed in a horse suffering from dental problems. A history of abnormal head carriage or head tossing while being ridden or during eating, prolonged time of eating, halitosis, dysphagia, drooling, dribbling feed (i.e., quidding) or eating hay before grain should lead one to consider that a dental problem exists.[45] Indicators of a dental problem in performance horses include tail wringing, head shaking, lugging in or out on the track, and fighting the bit (i.e., refusing to collect the head). In addition, intermittent dorsal displacement of the soft palate in performance horses may be a sign of a dental abnormality.

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32.15.1 Box 32-1 Recommended Timetable for Routine Dental Examinations and Common Corrective Procedures

32.15.1.1 BIRTH

1 Examine for congenital defects of lips or palate.

2 Assess tongue motion and strength.

3 Identify dental malocclusions.

4 Evaluate all body systems.

32.15.1.1.1 Recommended Procedures

1 Provide genetic and orthodontic consultation and perform corrective surgery if necessary.

2 Look for other problem signs such as underdeveloped carpal or tarsal bones, ruptured extensor tendons, hernias, etc.

32.15.1.2 6 TO 8 MONTHS OF AGE

1 Check incisor and premolar occlusions.

2 All incisors should be erupted.

3 Check for sharp enamel points or hooks.

4 Check tongue and buccal mucosa for ulcers.

32.15.1.2.1 Recommended Procedures

1 Provide orthodontic consultation, and float teeth if necessary.

32.15.1.3 16 TO 24 MONTHS OF AGE

1 Check for expanded lower wolf teeth eruption.

2 Check points and hooks on premolars.

3 Look for bit lesions.

32.15.1.3.1 Recommended Procedures

1 Float teeth and round off rostral corner of premolar 2.

2 Extract wolf teeth.

32.15.1.4 2 TO 3 YEARS OF AGE

1 Look for upper and lower wolf teeth.

2 Check corners of mouth and interdental space for bite injuries.

3 Evaluate incisors and molars for eruption and premolars for points and loose or retained deciduous teeth.

32.15.1.4.1 Recommended Procedures

1 Float outside of upper and inside of lower cheek teeth.

2 Remove caps if present and ready.

3 Extract wolf teeth.

32.15.1.5 3 TO 4 YEARS OF AGE

1 Check corners of mouth and interdental space for bit injuries.

2 Evaluate incisors for retained deciduous teeth or supernumerary teeth.

3 Evaluate molars for eruption and premolars for points and retained or loose deciduous teeth.

4 Evaluate size and shape of lower jaw and percuss sinuses.

5 Check for blind wolf teeth.

32.15.1.5.1 Recommended Procedures

1 Remove caps if present and loose.

2 Float teeth.

3 Remove wolf teeth.

32.15.1.6 4 TO 5 YEARS OF AGE

1 Check all incisors for eruption and wear occlusion.

2 Check canine teeth for sharp edges or eruption delays.

3 Evaluate entire molar arcade for proper eruption and alignment (third cheek tooth).

4 Visually check upper rostral and lower caudal cheek teeth for hooks from malocclusion.

5 Digital check for points on sharp edges of cheek teeth.

6 Percuss sinuses.

32.15.1.6.1 Recommended Procedures

1 Remove deciduous teeth if loose and ready.

2 Reduce hooks if present.

3 Float teeth.

4 Remove mucosa over canines if gingival cysts are present.

32.15.1.7 5 YEARS AND OLDER

1 Examine mouth visually and digitally, especially noting hooks and uneven wear.

2 Evaluate canines for sharp edges and tartar.

3 Percuss sinuses.

4 Use olfactory senses to detect evidence of oral decay or gingivitis.

5 Observe incisors for even wear.

6 Evaluate lateral jaw excursion.

32.15.1.7.1 Recommended Procedures

1 Float teeth.

2 Remove hooks.

3 Level or shorten incisors if indicated.

Good dental health is extremely important to the equine digestive system. Chronic colic or choke can result from improper mastication of feed, and reluctance to drink cold water may be caused by dental pain. Proper mechanical digestion of feed allows better carbohydrate absorption in the small intestine and improved fiber fermentation in the cecum and large colon. Improper mastication of roughage and concentrate produces large feed particles with decreased surface area per mass. The large particles are poorly digested in the small and large intestine because decreased surface area of the feed does not allow proper enzymatic degradation and bacterial fermentation. Finding whole grain or stem particles more than 5 mm long during examination of the manure indicates that the horse suffers from improper mastication.

The physical examination begins with observation of the horse's body condition, attitude, and temperament. The horse's overall condition should be evaluated in light of its use and dietary intake. Assigning a body score is an accurate way to subjectively record body condition (Table 32-1).[46] Objective assessment of body condition using a scale, a weight tape, or photographs is also beneficial and provides reliable data to evaluate the effects of treatment. The age of the horse should be considered during evaluation, because different conditions need to be addressed as the horse ages. The use of the horse should be considered during evaluation, because horses that wear a bit might require dental care not required by horses that do not wear a bit. Stable surroundings should be carefully observed for evidence of vices, such as cribbing or poor eating habits, such as dribbling hay or grain.

Table 32-1 Henneke Body Condition Scoring System

Condition	Neck	Withers	Shoulder	Ribs	Loin	Tailhead
1 Poor	Bone structure easily noticeable	Bone structure easily noticeable	Bone structure easily noticeable	Ribs protruding prominently	Spinous processes projecting prominently	Tailhead, pinbones, and hook bones projecting prominently
2 Very thin	Bone structure faintly discernible	Bone structure faintly discernible	Bone structure faintly discernible	Ribs prominent	Slight fat covering over base of spinous processes Transverse processes of lumbar vertebrae feel rounded Spinous processes are prominent	Tailhead prominent
3 Thin	Neck accentuated	Withers accentuated	Shoulder accentuated	Slight fat cover over ribs Ribs easily discernible	Fat buildup halfway on spinous processes, but easily discernible Traverse processes cannot be felt	Tailhead prominent but individual vertebrae cannot be visually identified Hook bones appear rounded, but are still easily discernible Pin bones not distinguishable
4 Moderately thin	Neck not obviously thin	Withers not obviously thin	Shoulder not obviously thin	Faint outline of ribs discernible	Negative-crease (peaked appearance) along back	Prominence depends on conformation Fat can be felt; hook bones not discernible
5 Moderate (ideal weight)	Neck blends smoothly into body	Withers rounded over spinous processes	Shoulder blends smoothly into body	Ribs cannot be visually distinguished, but can be easily felt	Back is level	Fat around tailhead beginning to feel soft

6 Moderately fleshy	Fat beginning to be deposited	Fat beginning to be deposited	Fat beginning to be deposited	Fat over ribs feels spongy	May have a slight positive crease (a groove) down back	Fat around tailhead feels soft
7 Fleshy	Fat deposited along neck	Fat deposited along withers	Fat deposited behind shoulder	Individual ribs can be felt with pressure, but noticeable fat filling between ribs	May have a positive crease down the back	Fat around tailhead is soft
8 Fat	Noticeable thickening of neck	Area along withers filled with fat	Area behind shoulder filled in flush with body	Difficult to feel ribs	Positive crease down the back	Fat around tailhead very soft
9 Extremely fat	Bulging fat	Bulging fat	Bulging fat	Patchy fat appearing over ribs	Obvious crease down the back	Bulging fat around tailhead

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Body and head conformation should be considered in evaluating the masticatory system. The head should be observed from both sides and the front to detect asymmetries, protuberances, or swellings. Horses with small heads have more of an angle in the curve of the mandibular ramus (i.e., the curvature of Spee) and are predisposed to dental crowding and ramps on the lower dental arcades.

The horse should be approached at its left shoulder. The tongue should be checked for proper movement, abnormal swelling, and signs of trauma, and the horse's ability to swallow should be evaluated. Excessive lacrimation, abnormal nasal discharge, or halitosis should be noted. The horse should receive a neurologic evaluation if any cranial nerve deficits are detected. Finally, the mandibular rami, masseter muscles, temporomandibular joints, and submandibular lymph nodes should be palpated to detect enlargements or asymmetry.

The frontal and maxillary sinuses should be percussed with the horse's mouth open. The width between the mandibular rami should be noted, because this width correlates with the room in the mouth for the bit. The sides of the head lateral to the upper dental arcades should be compressed, starting at the orbit and moving forward to the first cheek tooth at the level of the nasomaxillary notch, to detect protuberances, depressions, asymmetry, or evidence of pain. The commissures of the lip should be observed and palpated for signs of trauma inflicted by sharp teeth or improperly fitting bits. The incisor arcades should be visually evaluated from the front and both sides. The occlusal surfaces should make good contact and be level. The horse's age should be assessed by the dentition and compared with its actual age.[47] In movement of the lower jaw from side to side, the normal slide and separation of the incisor arcades as the jaw moves through normal lateral excursion should be observed.

For the oral cavity to be examined in detail, the horse should be fitted with a loose-fitting halter. If the horse is fractious or resists examination, it should be sedated before proceeding with the oral examination. Sedation should be given only after the horse's signalment (i.e., breed, age, body condition), temperament, and health (i.e., mucous membrane appearance, capillary refill time (CRT), heart rate, and rectal temperature) have been assessed.

The mouth should be rinsed thoroughly with clean water. Trapped feed in the mouth should be removed manually or with a dental pick and irrigation. Horses with sharp buccal points on the upper dental arcade often resist

application of a full-mouth speculum; therefore floating the upper arcades before applying the speculum may decrease resentment to the speculum. With a full-mouth speculum in place and the head properly restrained, a detailed visual and tactile oral examination should be carried out. A bright light source is necessary to illuminate the entire oral cavity for complete visual inspection. The examiner should manually inspect all hard and soft tissue in the oral cavity. The use of a dental mirror and pick is often necessary to see and probe the occlusal surfaces and pockets between the cheek teeth. Endoscopic examination of the oral cavity using a videoendoscope or an endoscope with a camera aids in identification of obscure lesions. Because rabies is a potential cause of dysphagia in the horse, the examined should have an adequate titer for rabies antibodies.

32.16 DENTAL RADIOLOGY

Diagnostic radiology is a valuable aid in the diagnosis of equine dental disease. The excellent contrast among air, bone, soft tissue and teeth provides good radiographic detail. Good-quality films can be obtained using a portable x-ray machine and rare-earth intensifying screens without a grid. Digital radiology provides high-quality radiographic images and allows for these high-quality images to be shared electronically for consultation with colleagues.

Indications for radiographic examination of the head include a suspicion of dental infection, maleruption, or a diastema and oral pain of unknown origin. The skull should be examined radiographically before and after dental extraction. Any facial swelling, deformity, neoplasm, trauma, or fracture may warrant radiographic evaluation to aid in diagnosis and treatment.

Radiographs can be taken with the horse standing and sedated. The head and radiographic cassette can each be placed on a stand to decrease distortion caused by motion. A lateral projection centered over the rostral edge of the facial crest should be taken to demonstrate fluid lines within the sinuses. The lateral view superimposes the dental arcades and should not be relied on to diagnose diseases involving the dental reserve crown and roots. Lesion-oriented oblique projections demonstrate the apical portion of the upper or lower cheek teeth and are helpful in diagnosing periapical dental disease. Open-mouth, oblique radiographic projections are beneficial in evaluating the exposed crown of the cheek teeth. Special, 4- × 8-inch, flexible dental cassettes can be used to obtain intraoral radiographic projections of the maxillary dental arcades. Dorsoventral radiographic projections centered over the tooth in question or area of concern can demonstrate periodontal disease on the buccal aspect of the upper cheek teeth or a large area of infundibular decay. Intraoral, occlusal radiographic projections are useful in demonstrating fractures of the incisors or other lesions rostral to the bars of the mouth. Other imaging techniques, such as ultrasonography, nuclear scintigraphy, CT, and MRI are helpful in the diagnosis of many oral and dental-related diseases.[48]

32.17 TREATMENT

A plan for treatment based on the results of history, clinical findings, and oral examination should be outlined to the owner and/or trainer before proceeding with a dental procedure. The owner and/or trainer should be informed of any abnormalities and given a plan for treatment, as well as an estimate of the cost, before any corrective procedure is performed.

Therapy must be planned to ensure that all equipment necessary to complete the task is at hand. The horse should be properly restrained, and adequate help should be present to assist in completing the procedure. A dental record aids in documenting findings during examination and the procedures performed (Fig. 32-17).

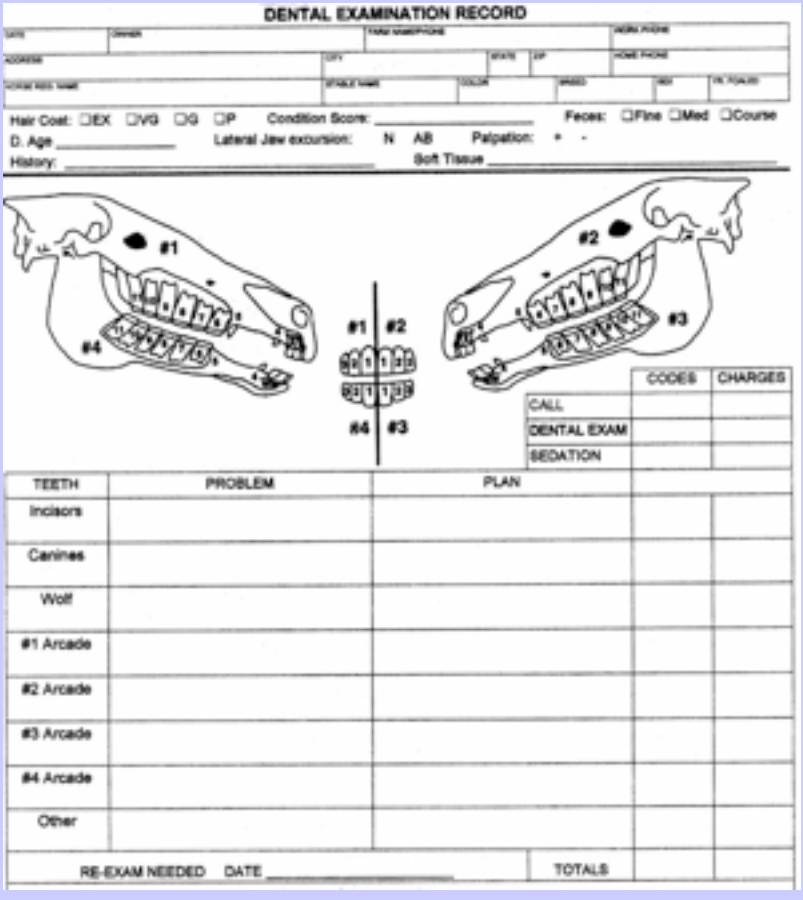
32.17.1 Routine Dental Maintenace

32.17.1.1 FLOATING

Dental floating is an age-old and routine method to correct abnormalities associated with dental eruption and occlusal wear. Floating also allows sculpting of the teeth to accommodate the bit. The main purpose of molar floating, or leveling, is to remove points or sharp edges from the buccal aspect of the upper molar arcades and lingual aspect of the lower molar arcades. Floating may also entail removing minor hooks or ramps from the rostral or caudal aspect of one or more arcades or leveling of minor elevations on the occlusal surface of the arcades. Routine floating and other corrective measures in the mouth may require both the added physical restraint provided by a dental halter and mild, chemical sedation.

Proper equipment is required to float all aspects of the exposed crowns of the cheek teeth, regardless of horse's size. Small instruments are often needed to access the oral cavity of miniature horses or ponies, and extra long and heavy instruments are often required to work effectively in the mouth of the large warmblood or draft horses. Sharp float blades made of carbide chips or sharp tungsten carbide planing blades make the work of floating more efficient and less strenuous than in the past, when steel blades were used. 682 683

Fig. 32-17 Form used to record dental examination findings.



The outward curve of the upper arcade makes the central buccal area (i.e., the area involving premolar 3 [PM3] through molar 2 [M2]) the easiest to reach with the float. To reach all areas of PM2 and M3, the head of the float should be offset or angled. In most cases the lower arcade can be floated to remove the lingual enamel points using a flat, long-handled float. To remove rostral and caudal hooks, special equipment such as carbide planing blades, power burrs, sliding chisels, or single action molar cutters may be required. (Note: Using sliding chisels and molar cutters to remove a hook can result in serious damage to the tooth). The use of dental equipment requires special training and skill to prevent iatrogenic injury to the horse's mouth.

The use of a mouth speculum or a dental wedge aids not only the oral examination, but also floating. (Note: The use of a dental wedge can result in serious damage to the teeth.) A mouth speculum ensures that the horse's mouth remains open, increasing safety for both the horse and the examiner. For horses with slightly ramped back teeth caused by a greater than normal curvature of Spee, a mouth speculum and a slightly curved or swivel-headed float may be needed to float the occlusal surface of the last molar.

To increase a horse's comfort while it wears a bit, the rostral aspect of the first upper and lower cheek teeth are sometimes rounded and the buccal cusps of the upper PM2s and PM3s are reduced. A horse that has received these procedures is said to have received a “bit seat.” In theory, a bit seat is created to prevent the soft tissue of the mouth from pressing against sharp points on the PM2s. To prevent exposing the pulp cavity when forming bit seats or correcting overgrowths, care should be taken not to “overfloat” the occlusal surface of a tooth. An offset float or an S-shaped rasp is usually necessary to create a bit seat.

32.17.1.2

WOLF TEETH

Most horses that are worked with a bit in the mouth benefit from having wolf teeth extracted. Some wolf teeth exfoliate naturally when the horse is approximately 3 years old, at the same time the cap of the first cheek tooth (i.e., 06 or PM2) is shed and the permanent tooth erupts. Although not all wolf teeth cause discomfort, a loose or sharp wolf tooth can be a distraction or even cause pain of such severity that it leads to bad bitting habits. Determining if the wolf teeth are responsible for a bitting problem is often difficult. Sometimes a wolf tooth does not erupt in a normal downward path, but instead migrates rostrally beneath the gum, causing a subgingival enlargement that irritates the horse. Such unerupted first premolars have been referred to as “blind” or “occult” wolf teeth and should be removed. Most wolf teeth are easily elevated with the horse sedated. Infiltrating a few milliliters of local anesthetic solution around the wolf teeth may aid in their removal.

32.17.1.3

CANINE TEETH

Canine teeth are present in most male horses over 4 years old. The unopposed positions of the canine teeth in the diastema make them unlikely to cause or develop problems. Some mares have small or rudimentary canines that can become loose or accumulate tartar, necessitating their removal. Canines of a stallion or gelding, especially canines that are long or sharp, can interfere with bitting and can be a nuisance or danger to the groomer or handler. Canines are more likely to accumulate tartar than are other teeth. Crowns of the canines can be ground 2 to 3 mm and polished to remedy any of these problems. Erupting canines in the 4- to 6-year-old horse may cause subgingival pain, especially when overlying tissue is contacted by the bit, which in turn may cause head shaking or other bad habits. The thin layer of tender mucosa over the canine should be removed. The root of a canine of the male is long and curved, making this tooth extremely difficult to extract. If a canine tooth must be removed because of injury or infection, it is usually removed by creating a bone flap over the root.

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32.17.1.4 DENTAL CAPS

As the developing permanent premolar pushes to the surface, it presses on the roots of the worn down deciduous tooth, gradually cutting off that tooth's nutrition. The deciduous tooth dies as its blood supply diminishes, causing it to become loose and displaced. The osseous alveolar walls adjust to these changes by producing and reabsorbing bone, to provide a new socket for the embedded portion of the newly formed permanent tooth. The remaining portion of the deciduous premolar has up to four “legs” (i.e., root slivers) that straddle the crown of the permanent tooth. If these slivers are fractured, they may remain embedded in the gingival tissue after the cap is shed, causing gingivitis or periodontal disease.

The eruption pattern of the permanent molarized dentition follows a sequence that predisposes to entrapment of the deciduous PM3 and PM4. Delayed shedding of deciduous premolars can predispose to gingivitis, periodontal irritation, or apical infection. Retained, split, or displaced deciduous premolars can be distracting to a young horse in training and have been implicated as a cause of intermittent dorsal displacement of the soft palate.

Retained caps can cause lingual displacement or delayed eruption of the permanent premolars. Horses with retained caps may develop bony enlargements called “eruption cysts,” on the ventral aspect of the horizontal ramus of the mandible or on the dorsal aspect of the maxillae, rostral to the facial crest. Often such swellings are benign, but if eruption is severely inhibited, blood-borne bacteria can colonize in the inflamed dental pulp, leading to anachoretic pulpitis and periapical dental infection, which lead to more severe facial or mandibular swelling. A draining tract often accompanies swellings caused by periapical infection, especially those on the mandible. Caps should be evaluated by palpation as well as visually. A crease or neck can be seen or felt just above the gumline at the juncture separating the deciduous and permanent tooth. Radiographic examination of the premolars may be necessary to identify retained caps.

If a cap has been shed, the caps that remain on the same tooth in the other three arcades should be considered retained and should be removed. By placing a molar forceps on the tooth and rotating the forceps lingually, the cap is easily removed. The cap should be extracted in a manner that ensures that the roots, especially the buccal roots, are removed, because slivers of roots of a retained cap are irritating and can predispose the horse to development of periodontal disease.

32.17.1.5 INCISORS

After the cheek teeth have been evaluated and treated, the horse's mouth should be completely reexamined, both visually and by palpation, to ensure that all sharp or uneven edges have been smoothed and that no teeth have been broken or loosened during floating. The speculum is then removed, the mouth closed, and excursion of the jaw reevaluated to confirm that the mandible is capable of full excursion.

With the jaw in the resting state, normally only the incisors are in occlusion. The incisors should meet evenly and slide to the side unobstructed until the cheek teeth begin to contact. As the mandible moves laterally, the upper and lower arcades contact, and the incisors are lifted apart as the mandibular cheek teeth slide up the sloped occlusal surface of the upper cheek teeth. Uneven or excessively long incisors may need to be aligned or reduced. Minor incisor leveling can be performed with a flat carbide float or a motorized burr. Care should be taken not to reduce the crown to the extent that that the pulp is damaged. When floating has been completed, the horse should have a full, comfortable range of motion of the jaw. As the horse chews, the upper and lower dental arcades should be in proper contact with each other.

32.18 EQUINE DENTAL DEVELOPMENTAL ABNORMALITIES

Equine dental developmental abnormalities can involve tooth number, morphology, or position in the dental arcades. Abnormalities of dental development and eruption occur quite commonly in the horse and result in a wide range of clinical conditions. Some developmental abnormalities of the teeth of a young horse may not cause the horse to exhibit clinical signs of dental disease until the horse reaches middle age. A congenital or developmental problem present at the time of tooth eruption often leads to acquired dental problems as the teeth continue to erupt and wear. Consequently, several different dental abnormalities, the origins of which are interrelated, are often present by the time the horse is presented because of signs of dental disease. A detailed oral examination should include checking for the proper number and position of teeth. Because only the exposed crown of a tooth can be visualized in the oral cavity, many developmental defects may not be recognized simply by oral examination. If a developmental abnormality is suspected, the dentition should be examined radiographically to further delineate abnormalities.

32.18.1 Supernumerary Teeth

Supernumerary teeth are teeth in excess of the normal, expected number in any of the dental arches. This disorder has been referred to as *polydontia* or *hyperdentition*. Supernumerary teeth can be loosely categorized morphologically into two categories: (1) supplemental teeth that resemble teeth of the normal series in crown and root morphology but not always in size, and (2) rudimentary or dysmorphic teeth that are abnormally shaped and smaller than normal teeth.

These extra teeth are usually encountered at the caudal aspects of the arcades, but supernumerary teeth can also occur lingually, buccally, or rostrally to the arcades. Clinical signs caused by supernumerary cheek teeth are most commonly associated with dental overgrowths and diastemata, which often cause periodontal disease. Examination of a radiograph that encompasses the entire affected dental arcade is often necessary to recognize a supernumerary tooth.

Supernumerary incisors are reported more commonly in horses than are supernumerary cheek teeth. The main differential diagnosis for supernumerary incisors or cheek teeth is retained deciduous teeth, and in some cases, determining whether an extra tooth is a retained deciduous tooth or a supernumerary tooth is difficult. Radiographic examination of the affected jaw may be indicated to determine the identity of an extra incisor. A retained deciduous incisor has a more mature root and a shorter reserve crown than those of the adjacent permanent incisors.

Management of horses with supernumerary teeth is generally limited to regular assessment of the dentition, coupled with aggressive floating to minimize the opportunity for soft-tissue damage caused by unopposed dental elongations or sharp enamel points. If complications occur, such as severe periodontal disease or paranasal sinusitis, the supernumerary tooth or displaced adjacent tooth should be extracted, and appropriate therapy undertaken to manage associated disease.

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32.18.2 Oligodontia

Oligodontia is the condition in which the number of teeth is less than normal. Oligodontia can be caused by congenital absence of a tooth germ or by traumatic loss of a tooth. Absence of a tooth in the dental arcade, regardless of the cause, leads to dental drift, or tipping of adjacent teeth. Lack of wear of the antagonist to the missing tooth can lead to dental elongations and abnormal mastication. Radiographic examination of the

dentition is often necessary to confirm a diagnosis of oligodontia. Oligodontia may be associated with other epidermal defects, such as faulty development of hair and hooves.

32.18.3 Dental Dysplasia or Hypoplasia

Dental dysplasia (i.e., abnormal growth and/or development of a tooth or teeth) may result in an irregularly shaped tooth that does not fit properly into a dental arch. The poor fit may lead to entrapment of food and periodontal disease. Enamel hypoplasia can be caused by certain drugs or chemicals administered to the dam during gestation, or it may be idiopathic. Dental dysplasia can involve the abnormal formation of all tissues of the tooth or only a single tissue. When enamel is dysplastic, however, the other calcified tissues of the teeth, cementum and dentine, also become dysplastic because enamel acts as the scaffolding and template for their deposition. Abnormal morphology of enamel has been associated with branched pulp horns and abnormally shaped teeth. Cemental hypoplasia usually involves the infundibular portion of the tooth but can be seen as a defect of the peripheral cement of the coronal or reserve crown or the roots.

32.18.4 Abnormal Dental Eruption

Abnormal dental eruption, or maleruption, is often seen after trauma to developing teeth or surrounding bones but has also been reported to be congenital or idiopathic. Cheek teeth can become vertically impacted when dental buds develop in crowded areas in the dental arcades. Teeth may become rotated or displaced because of developmental malpositioning of tooth buds or overcrowding before, during, or after eruption.

Dixon and colleagues reported that 70% of displacements of cheek teeth were developmental and caused by overcrowding of the cheek tooth arcade at the time of eruption. These researchers frequently found that if a cheek tooth was displaced in one arcade, the same tooth in the contralateral arcade was also displaced. They concluded that the remaining 30% of displacements were caused by abnormal positioning of the dental bud.[44] They found that a tooth might fail to erupt if it is displaced horizontally to the adjacent teeth. Developmental diastemata, or abnormal spaces or gaps between cheek teeth, are often the result of insufficient angulation of rostrally and caudally located teeth toward the center of the arcade to achieve good compression of adjacent teeth. Dental buds with normal angulation that develop too far apart can also result in diastemata.

Malocclusion of incisors can be congenital, developmental, or acquired. Mandibular brachygnathism (i.e., parrot mouth or overjet) is a congenital incisor malocclusion, the origin of which is usually genetic. Many horses have some degree of overjet of the premaxillary incisors, but the overjet rarely causes a problem with prehension unless the premaxillary and mandibular incisors totally lack occlusion. If brachygnathism is discovered when the foal is young, orthodontic treatment may correct or at least improve the condition.

A main consideration with an incisor overjet in the adult horse is the malocclusions of the cheek teeth that accompany this condition. The maxillary cheek teeth arcades of horses with an overjet are usually positioned rostral to the mandibular cheek teeth arcades, causing a rostral overgrowth of the upper PM2s (i.e., 106 and 206) and a caudal overgrowth of the lower M3s (i.e., 311 and 411). These overgrowths must be reduced to allow proper lateral excursion of the jaw and mastication.

Prognathism (i.e., sow mouth or undershot jaw) occurs with less frequency in the horse and is seen most commonly in miniature or dwarf breeds. Early detection and correction of the malocclusion in the foal may prevent the condition from worsening. The cheek teeth of a horse with prognathism should be evaluated for malocclusion caused by overgrowth of the upper M3s (i.e., 111 and 211) and the lower PM2s (i.e., 306 and 406).

Bony malformation or curvature of the skull can result in malocclusion of both the incisors and the cheek teeth. The most common malocclusion caused by bony malformation of the skull is an offset or diagonal incisor bite. Some bony malformations, such as campylorrhinus lateralis (i.e., wry nose), are obvious, but subtle changes to the large bony plates in the head can be difficult to recognize.

Dental overgrowths associated with malocclusions should be corrected gradually to prevent dysphagia and pain caused by inadvertent exposure of pulp horns. Often, incisor malocclusion cannot be completely resolved, but regular maintenance may prevent it from worsening.

32.19 DENTAL DISEASE

Dental disease is grouped into four basic types: abnormal occlusal wear pattern, periodontal disease, dental caries, and disease of the dental pulp. All of these types of basic dental disease are interrelated, and horses with one of these types of disease also have, to varying degrees, the other types of disease.

Proper alignment of the dental arcades is critical to the normal wear of the dentition. Historically, abnormal dental wear patterns have been described as elongations of the crown, descriptive terms for which include *hooks, ramps, waves, step mouth, tall teeth*, and *excessively high transverse ridges*.[49] Elongations are usually found on a normal tooth that opposes an abnormal tooth in the opposite arcade, such as a damaged, misplaced, or missing tooth. This abnormal tooth, as well as the elongation, should be evaluated. Most elongations are reduced with float or a grinding instrument. When reducing an elongation, care should be exercised not to cause iatrogenic damage to the tooth, such as pulpal exposure, thermal injury to the pulp or fracture of the crown.

Periodontal disease is often a painful dental condition and is described as the leading cause of “quidding” in horses. A mild form of periodontal disease primarily affects young horses, 2½ to 5 years old, that are shedding deciduous teeth (caps) and erupting permanent incisors and premolars. A more severe and progressive form of periodontal disease is seen in mature horses and is the result of the chronic effects of diastemata, or spaces that develop between teeth that are not aligned properly in the arcade. Diastemata promote periodontal disease by allowing feed to become trapped between teeth. Diastemata can form secondary to developmental disease, such as when dental buds are spaced too far apart or are abnormally angulated so that the teeth in the dental arcade are not properly compressed. This is usually a progressive condition that when left untreated worsens. Spaces between teeth or teeth out of alignment also predispose to abnormal wear patterns on the affected and opposing dental arcades.

Treatment of horses with periodontal disease involves treating both the cause and the effects of the disease. Periodontal disease caused by feed trapped at the gingival margin of a diastema often improves after the diastema is thoroughly cleansed using dental picks and/or irrigation. Correction of any associated abnormal wear pattern is also indicated. In more refractory cases, opening or widening of the diastema with a special burr or a right angle grinder may be necessary. This procedure may allow the horse's masticatory actions to more easily channel food in and out of the diastema, thus preventing or reducing entrapment, stagnation, and decay of feed.

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The severity of periodontal disease can be decreased using high-pressure irrigation to clean periodontal pockets. After the pockets have been irrigated, the diastema is packed with a perioceutic agent such as doxycycline gel or a powdered antibiotic. This technique places a high concentration of antibiotic in contact with the infected and inflamed tissues, and the packing acts as a temporary barrier to recontamination. This form of therapy may need to be repeated regularly to produce long-term, positive results.

Caries usually involve the cemental layer of the tooth. Peripheral cemental caries is seen secondary to periodontal disease. The most common type of cemental caries involves the infundibular portion of the incisors or maxillary

cheek teeth (Fig. 32-18). The incisors have one infundibulum and the upper cheek teeth have two, and each infundibulum has a cup, or open portion, at the occlusal surface. The occlusal surface of the tooth is covered with cementum for several months after the tooth erupts, and as the tooth wears, the cementum-filled infundibulum is exposed at the occlusal surface. Some degree of decay is always present at the occlusal surface of an infundibulum, because feed and other products of mastication are compressed into the ghost of the vascular canal.

Fig. 32-18 Cadaver specimen of the maxillary dental arcade. Note the black areas of dental decay on the occlusal surfaces of M1 and M2 *(arrows)*.

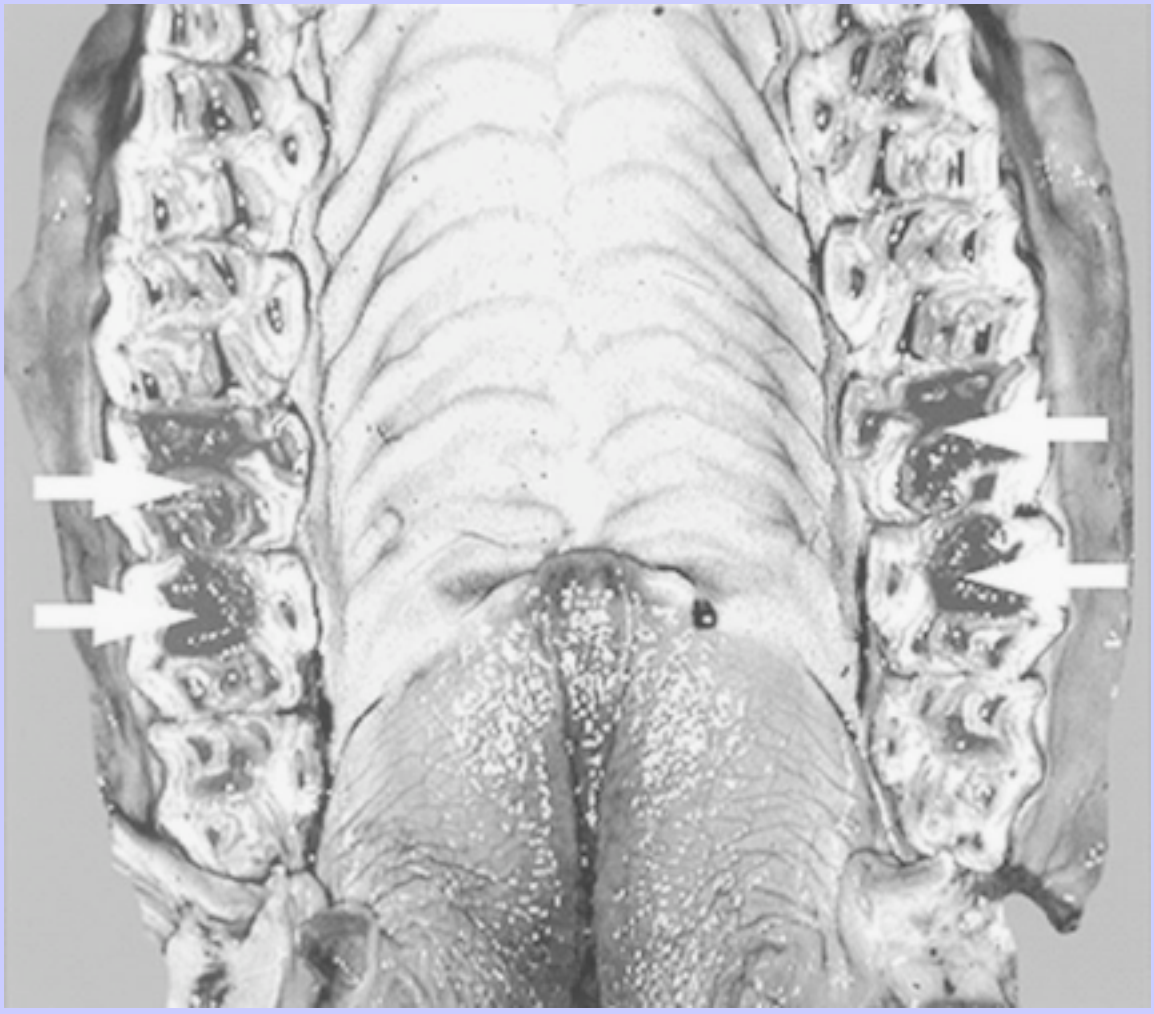
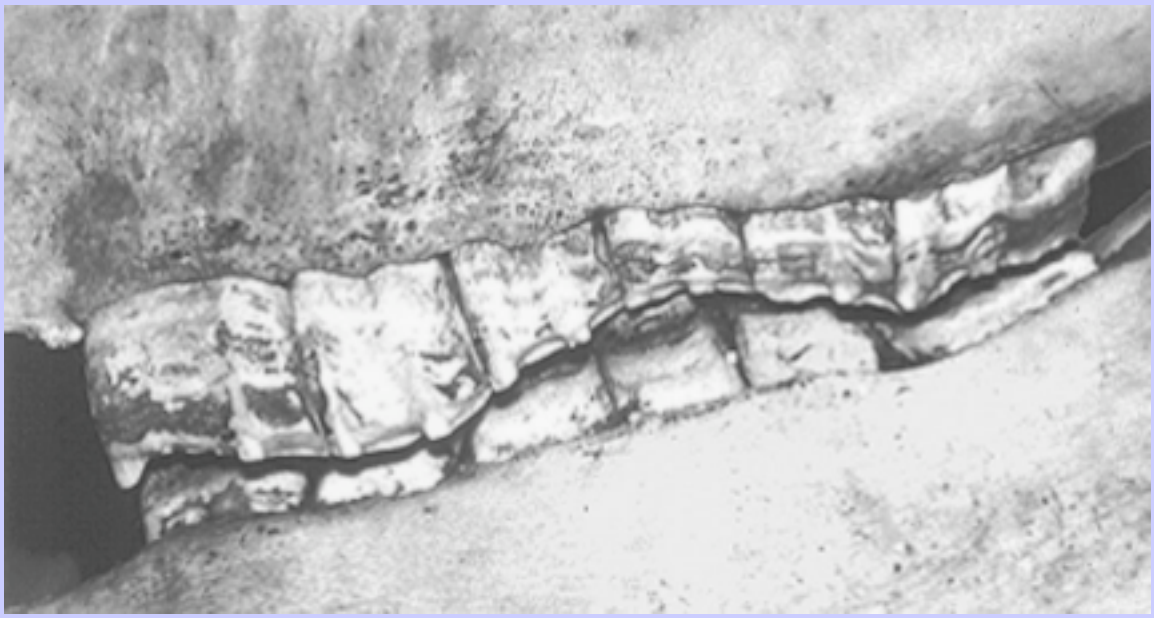


Fig. 32-19 Lateral view of cadaver equine skull illustrating wave mouth.



An infundibulum contains dead cementum that is completely encased in a layer of enamel, which prevents the infundibular caries from causing widespread inflammation or infection. True dental pulp infection secondary to infundibular caries occurs only if caries penetrate this protective enamel layer. Developmental malformations of the infundibulum may weaken this enamel barrier, predisposing the dentine and pulp to exposure from infundibular caries. Infundibular caries may weaken a tooth whose infundibula are congenitally deformed or have an abnormally large vascular channel, predisposing the tooth to excessive attrition or midsagittal fracture of the crown.

Infundibular caries is usually innocuous but can predispose to dental elongations on the opposing arcades (e.g., wave mouth,Fig. 32-19). These abnormal wear patterns should be reduced regularly. To strengthen the tooth and delay the progression of infundibular caries, abnormally large infundibular vascular channels can be cleaned, partially packed, and sealed with a dental composite material. As advanced diagnostic methods, such as CT, become more readily available to the equine practitioner, these abnormal infundibula can be more easily recognized.

Infection of the dental pulp occurs primarily in horses 4 to 10 years old. Horses with infection of the pulp are presented because of clinical signs of associated inflammatory changes at the apical region of the tooth. The clinical signs of pulpal infection vary and depend on the involvement of structures adjacent to the apex of the affected tooth. Horses with infection of one of the lower first four cheek teeth develop swelling on the ventral aspect of the mandible over the apex of the affected tooth, and within this swelling, a draining tract usually develops. The last two lower cheek teeth are embedded in the portion of the mandible surrounded by the large muscles of mastication, so infection of one of these teeth causes the surrounding muscles to swell. Exudate accumulated between the mandible and musculature may be seen during ultrasonographic evaluation of the soft tissues of the mandible.

The apices of the upper two or three cheek teeth are closely associated with the facial bones; therefore when one of these teeth becomes infected, facial swelling usually results. The apices of the caudal three or four upper cheek

teeth reside within the maxillary sinuses; when one of these teeth becomes infected, purulent nasal discharge caused by secondary sinusitis usually results.

Because pulpal infection destroys the tissue responsible for the production of secondary dentin, the pulp horns and root canals of the affected teeth fail to fill with dentine as they normally would. In the later stages of pulpal infection, the affected tooth usually exhibits some degree of decay at the site of the pulp horn on the occlusal surface. This weakened, decayed area may predispose to fracture of the crown.

Administration of antimicrobial drugs has been successful in the treatment of horses with apical dental infection in its early stages, but the most common treatment of horses with an apically infected tooth is removal of the affected tooth and treatment of associated bone or sinus infection. Teeth can be removed by one of three methods: extraction via an oral approach, repulsion via an apical approach, or elevation via a lateral buccotomy approach.

32.20 SALIVARY GLANDS AND DUCTS

Saliva hydrates and lubricates the oral cavity, facilitates swallowing, prevents tooth demineralization, and regulates oral microbial flora.[50] Diseases of the salivary glands of horses are uncommon but include sialoadenitis, salivary calculi, salivary mucocele, trauma and neoplasia. During oral examination the openings of the salivary ducts should be noted. The ducts of the paired parotid salivary glands enter the mouth at the parotid papillae, located next to the upper last premolars (i.e., 109 and 209). The ducts of the paired mandibular salivary glands open into the mouth on the lateral aspect of the sublingual caruncles. The ducts (approximately 30 in number) of the paired sublingual salivary glands are seen as small pores in the sublingual recess.

Slobbering or drooling may indicate excessive production of saliva (i.e., ptyalism) or accumulation of saliva in the mouth from dysphagia. Heavy metal toxicity, poisoning with a parasympathomimetic agent, neurologic disease, or stomatitis may cause ptyalism. Dysphagia can be caused by esophageal obstruction (choke), an oral foreign body, or some neurologic diseases, such as rabies.

Sialoadenitis, or inflammation of a salivary gland, may be the result of obstruction of a salivary duct from accumulated exudate or mucus, feed particles such as grass awns, an orally introduced foreign body, or a sialolith. Sialoliths occur infrequently but are found almost exclusively in the parotid salivary duct. Obstruction of the duct with a sialolith causes salivary retention, which can lead to glandular atrophy or acute sialoadenitis, swelling of the gland, and rupture of the duct. A sialolith causes a hard, usually smooth enlargement at some point along the course of the parotid salivary duct. The horse usually shows no signs of pain when the enlargement is palpated. The sialolith is usually apparent during radiographic evaluation of the skull, but it can be obscured by adjacent bone. Diagnosing the presence of a sialolith is usually straightforward because the condition is easily differentiated from other conditions that produce similar clinical signs, such as trauma, apical dental infection, or facial tumor. Surgical removal of the sialolith and primary closure of the duct and surrounding tissue usually yield good results.

A salivary mucocele is an accumulation of salivary secretions in a single or multiloculated cavity adjacent to a ruptured salivary duct. A ranula is type of mucocele that develops secondary to obstruction of a sublingual salivary duct. Treatment of horses with a mucocele consists of creating a salivary fistula into the oral cavity or excising the mucocele and destroying salivary gland, either with a chemical inserted into the duct or by ligation of the duct.

Laceration or iatrogenic injury to a salivary duct can lead to a salivary cutaneous fistula. The fistula can be resolved by reapposing the severed duct with sutures, by creating a new oral opening for the duct, or by destroying the salivary gland. The parotid salivary gland can be ablated by flushing a solution of 10% formalin into the duct or by

ligating the duct proximal to the fistula. Wounds involving the salivary glands can usually be resolved successfully by cleansing, debriding, and suturing the wound.

Primary neoplasms of the salivary glands of horses include benign mixed tumors, adenocarcinomas, and acinar cell tumors. Neoplasms that invade the salivary gland from an adjacent area or melanomas of old grey horses that metastasize to the salivary gland are more common than primary salivary neoplas

32.21 EQUINE ORAL NEOPLASMS

Equine oral neoplasms are rare, making up a very small percentage of facial or mandibular neoplasms. Oral neoplasms can be divided into three basic types: odontogenic, osteogenic, and secondary (soft tissue).[51]

Odontogenic neoplasms are derived from remnants of dental epithelium. The five types that have been reported in the oral cavity of horses are ameloblastomas, ameloblastic odontomas, complex odontomas, compound odontomas, and cementomas. Histologic examination of odontogenic neoplasms can be confusing because of variation in appearance of tissue obtained at different sampling sites and age-related changes in the neoplasm's appearance. Because of their rarity, ill-defined biologic behavior, poorly defined radiographic features, and histologic variations, odontogenic neoplasms can be difficult to classify.

Primary bone neoplasms of horses are rare, and most (osteoma, ossifying fibromyoma) are benign. More than 80% of equine osteosarcomas occur in the head region. Like odontogenic neoplasms, primary bone neoplasms of horses are difficult to classify. In addition to gross and histologic examination, correlating history and clinical, radiologic, and biochemical findings is often essential to establish a diagnosis.

Secondary neoplasms of the oral cavity include squamous cell carcinoma, lymphosarcomas, papilloma, and melanomas that have extended into the oral cavity from an adjacent site or metastasized into the oral cavity from a remote site. Squamous cell carcinoma is the most frequently reported oral neoplasm in the horse. Generally these neoplasms are seen in old horses; there is no gender or breed predilection. Neoplasms of the tongue are rare and include lymphosarcomas, multiple myeloma, rhabdomyosarcoma, and paraneoplastic bullous stomatitis.

Options available to control progression of oral neoplasms include radiotherapy, hyperthermia, chemotherapy, cryosurgery, immunotherapy, autogenous vaccines, photodynamic therapy, laser therapy, and surgical resection. Results of these treatments vary according to the type of tumor and circumstances, such as whether the neoplasm has invaded bone.

32.22 DISORDERS OF THE ESOPHAGUS

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32.23 ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

The most cranial aspect of the esophagus is located on the median plane immediately dorsal to the trachea. However, at approximately the midcervical region (C4 to C5), the esophagus typically shifts to the left of the trachea and lies just deep to the external jugular vein.[52,53] It is here that intraluminal obstructions or the tip of a stomach tube may be visualized, and this is the region where trauma can readily result in esophageal perforation. When a stomach tube is passed, it is critical that the tube be palpated to ensure the tube is in the esophagus because

jugular pulses can be confused with the appearance of the tip of the tube. In addition to its proximity to the external jugular vein, the esophagus is also located adjacent to the vagosympathetic trunk and the common carotid artery.[52] The esophagus is innervated by branches of the vagosympathetic trunk, and blood is supplied to the cervical esophagus by branches of the carotid arteries. The thoracic esophagus, which lies ventral to the trachea until the tracheal bifurcation, where it resumes a dorsal position, receives its blood supply from the bronchoesophageal artery. Venous drainage is via the external jugular veins in the cervical esophagus and the esophageal vein in the thoracic esophagus.

The muscular wall of the esophagus increases in thickness as the esophagus courses distally, while the lumen gets smaller.[52] The esophagus is not covered by a serosa except for a very short segment that traverses the abdominal cavity between the diaphragm and the stomach.[53] Instead, the outer wall of the esophagus is composed of adventitia that is loosely attached to surrounding tissues. This loose connection allows movement of the esophagus during swallowing and during movement of the neck. The cranial two-thirds of the esophageal wall consists of skeletal muscle, whereas the distal third of the esophagus is composed of smooth muscle. Although the muscular layers are composed of an outer and an inner layer, similar to the remainder of the gastrointestinal tract, the skeletal muscle layers are oriented obliquely to one another.[52] This, and an abundant submucosa, enables extensive dilation of the esophagus as a bolus of food moves toward the stomach. In addition, the velocity of esophageal contraction is faster in the skeletal muscle segment of the esophagus compared with the distal smooth muscle segment.[54] The muscle layers become oriented in more of an outer longitudinal and inner circular configuration in the caudal esophagus.[52] In the resting collapsed state, redundant esophageal mucosa and submucosa become oriented in longitudinal folds. The mucosa is composed of stratified squamous epithelium that is continuous with the stratified epithelium of the cardiac portion of the stomach.[52]

The cranial esophageal sphincter is formed by the cricopharyngeus muscle and maintains a resting intraesophageal pressure of approximately 85 mm Hg and a postdeglutition pressure as high as 200 mm Hg. Although the caudal esophageal sphincter is anatomically indistinct, resting intraesophageal pressure in this region is maintained at approximately 13 mm Hg, and postdeglutition pressure in the caudal esophagus may be as high as 100 mm Hg. The pressure in the caudal esophagus is maintained at approximately 10 mm Hg higher than the intraluminal pressure of the stomach.[54,55] Although the higher pressure in the distal esophagus has been implicated as the cause for the inability of most horses to vomit and for gastric rupture, other factors such as a poorly developed vomiting reflex may be more important.[56]

32.24 DIAGNOSTIC CONSIDERATIONS

Esophageal disease should be a differential diagnosis in any horse that demonstrates excessive salivation. Such signs also indicate the need to assess hydration, electrolyte levels, and acid-base status. In a study in which horses had continual loss of saliva via an experimentally placed esophagotomy, abnormalities included hypochloremia, hyponatremia, and hypokalemia.[57] This results from the relatively high levels of these electrolytes in saliva. Furthermore, because horses depend on dietary intake of potassium, hypokalemia would be exacerbated in a horse that was also unable to eat because of esophageal obstruction. Loss of salivary fluid and bicarbonate also results in dehydration and metabolic acidosis. However, metabolic alkalosis subsequently occurs presumably as a result of renal compensation for electrolyte loss, particularly chloride.[57]

Further examination of horses with esophageal disease may reveal evidence of swelling or emphysema in the region of the cranial or cervical esophagus that should prompt a thorough oral examination and further diagnostics such as radiography and endoscopy to define the nature of any esophageal abnormalities. If the esophagus has been

perforated or ruptured, subcutaneous emphysema is usually evident. The lungs should be carefully auscultated for evidence of aspiration pneumonia. Radiographs of the chest are required for a full pulmonary assessment.

Radiographs of the esophagus should initially include plain films that may reveal evidence of an obstruction or areas of gas opacity within facial planes indicative of esophageal perforation.[58] However, facial and subcutaneous emphysema must be differentiated from other causes, including tracheal perforation.[56] The esophagus is often gas-distended cranial to an obstruction up to the cranial esophageal sphincter. Plain films may be diagnostic, but contrast radiographs are frequently required to fully define the nature of esophageal abnormalities.[58] Administration of barium paste or liquid will reveal linear opacifications as a result of the linear mucosal folds and may help outline intraluminal obstructions or strictures (Fig. 32-20).[58] A double-contrast study is a useful radiographic technique for defining esophageal wall abnormalities, particularly postobstruction mucosal ulceration, and is performed by placing a cuffed nasogastric tube in the cranial esophagus and injecting 300 to 500 mL of liquid barium followed by a similar volume of air. Care should be taken when evaluating such radiographs, because swallowing can create the false impression that there is a stricture.[59] The incidence of swallowing can be decreased by administration of xylazine. Liquid barium is preferable if swallowing function is compromised because it is less harmful to pulmonary tissues than paste, and water-soluble iodinated contrast material is particularly damaging to the lung because of its hypertonicity.[56] However, if an esophageal perforation is suspected, water-soluble contrast material is preferable.[56]

Endoscopic evaluation of the esophagus should be performed as part of a complete evaluation of esophageal injuries and abnormalities. After sedation of the patient, the endoscope should be passed all the way into the stomach before the esophagus is examined; it will be more readily viewed as the endoscope is withdrawn.[58] Inflation of the esophagus must also be performed intermittently as the wall of the esophagus collapses around the end of the endoscope. The longitudinal folds of the esophageal mucosa will be readily appreciated and can be flattened out as the esophagus is distended to more clearly view the entire circumference of the esophagus. Swallowing may create artifacts such as the appearance of strictures, so the esophagus should be carefully reinflated after each swallow to carefully evaluate such findings.[59]

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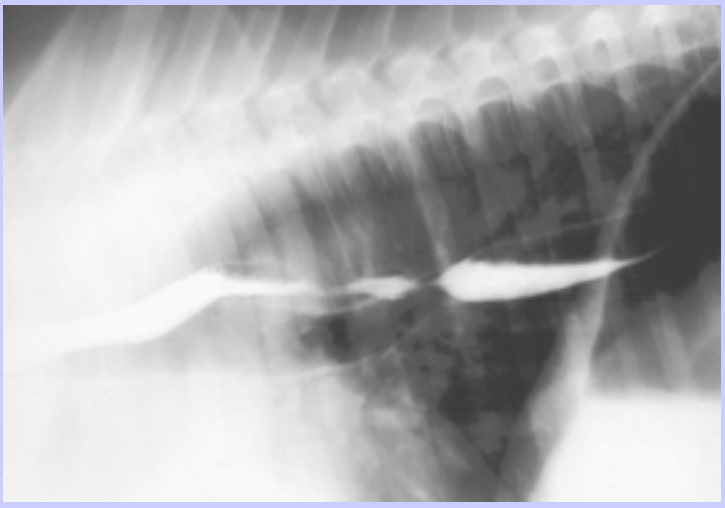
Fig. 32-20 Barium contrast esophagram outlining esophageal luminal structure. Courtesy Dr. K.E. Sullins.



A recent study evaluated structures that could be evaluated via thoracoscopy of the mediastinum, including the thoracic component of the esophagus. Although this procedure caused pneumothorax, a 15-minute period of evaluation allowed observation of a number of structures including the esophagus.[60] Portals placed at the eighth, tenth, and twelfth intercostal spaces were useful for completion of this procedure and could provide additional information aside from radiographic and endoscopic evaluation of the thoracic esophagus.

32.25 ESOPHAGEAL OBSTRUCTION

Esophageal obstruction, either primary (simple choke) or secondary to other disease processes, is the most common esophageal disorder seen in horses. Although primary obstructions may be caused by foreign bodies, including corncobs, potatoes, apples, carrots, medicinal boluses, stones, riding crops, or wood fragments, primary obstructions are most often caused by roughage, particularly leafy alfalfa hay, coarse grass hay, bedding, and even grass.[61–71] Prior esophageal trauma or poor mastication caused by dental abnormalities may predispose horses to esophageal impaction. Obstructions from roughage may be precipitated by wolfing or gulping food, particularly if the horse is exhausted and/or mildly dehydrated such as after a long ride, or weakened from chronic debilitation. Secondary impactions are caused by intramural or extramural abnormalities that mechanically impede food passage. Examples of intramural obstructions include tumors (squamous cell carcinomas), strictures, diverticula, cysts, and vascular ring anomalies.[72–78] Mediastinal or cervical masses (tumors or abscesses) may cause extramural obstructions.

The clinical signs associated with esophageal obstructions are similar whether they are classified as primary or secondary and are rarely specific. Horses with esophageal obstruction are often anxious and stand with the neck extended. Gagging or retching may be noted, particularly with acute proximal obstructions. Bilateral frothy nasal discharge containing saliva and food material, coughing, odynophagia, ptyalism, and dysphagia are usually the primary clinical signs, the severity of which varies with the degree and location of the obstruction. Distention of the cervical esophagus may be evident at the site of obstruction. Other clinical signs may be observed related to complications stemming from the obstruction, such as dehydration, weight loss, aspiration pneumonia, or esophageal rupture.

Thorough physical examination, including a complete oral examination, must be performed to rule out other causes of hypersalivation, dysphagia, and nasal discharge. Palpation of the jugular furrow may reveal a mass associated with the impaction. In most horses the esophagus is located in the left jugular furrow, but it may be found in the right furrow in some animals. Crepitus or cellulitis may be evident, suggesting rupture of the esophagus. Auscultation of the lungs is important to determine whether pneumonia or pleural fluid is present because of aspiration or intrathoracic esophageal rupture. Passage of a nasogastric tube is a good way to determine whether and where an obstruction is present but provides little information about the nature of the obstruction or the condition of the esophagus.

Ultrasonography of the cervical region is extremely useful not only to confirm the presence of a cervical esophageal impaction, but also to provide critical information about the location and extent of the impaction and esophageal wall thickness and integrity. Ultrasonography may also provide information about the cause of the obstruction. Radiography, particularly air or barium contrast studies, may be useful to assess an esophageal impaction but may be more useful for evaluating the esophagus after rather than before relief of the impaction to demonstrate stricture, dilation, diverticula, esophageal rupture, or masses.[79,80] Care should be taken when interpreting radiographic studies in sedated horses, particularly after passage of a nasogastric tube or other esophageal manipulations that may contribute to esophageal dilation.[81] Impacted food material can be detected in

the esophagus by a typical granular pattern, and gas is often observed to accumulate proximal to the obstruction. Foreign bodies may be identified by contrast radiographic studies.

Definitive evaluation of esophageal obstructions often requires endoscopic examination. Most cases of esophageal obstruction occur at sites of natural narrowing of the esophageal lumen, such as the cervical esophagus, the thoracic inlet, the base of the heart, or the terminal esophagus. Therefore an endoscope longer than 1 meter may be required for complete evaluation. Endoscopic evaluation is useful before relief of an impaction to localize the impaction and to investigate the nature of the impaction if a foreign body is suspected. Foreign bodies may be retrievable via transendoscopic tethering.[69] Critical diagnostic and prognostic information is obtained after resolution of the impaction to determine whether mucosal ulceration, esophageal rupture, masses, or strictures are present.

The primary goal of treatment for esophageal impaction is to relieve the obstruction. Parenteral administration of acepromazine (0.05 mg/kg IV), xylazine (0.25 to 0.5 mg/kg IV) or detomidine (0.01 to 0.02 mg/kg IV), oxytocin (0.11 to 0.22 IU/kg IM), and/or esophageal instillation of lidocaine (30 to 60 mL of 1% lidocaine) may help reduce esophageal spasms resulting from pain or increased esophageal tone.[66,81–83] However, recent conclusive studies revealed that detomidine, acepromazine, or a combination of xylazine and butorphanol had the greatest effect on esophageal motility when evaluated by a monomer in conscious horses.[84] However, in vitro studies revealed a relaxant effect of oxytocin on esophageal muscle, suggesting it may be useful for relief of esophageal obstruction.[85]

Resolution of an impaction may require physical dispersal of the material. A nasogastric tube can be used to displace the impacted material in conjunction with external massage if the obstruction is in the cervical region. Often it is necessary to carefully lavage the esophagus with water via an uncuffed or a cuffed nasogastric tube while the head is lowered to aid in breaking up the impaction. Some clinicians advocate a dual tube method whereby a tube is placed through each nasal passage into the esophagus for ingress and egress of the lavage fluid. Because of the risk of aspiration of water and/or food material, esophageal lavagfe is sometimes done under general anesthesia with a cuffed nasotracheal tube.

In refractory cases, intravenous administration of isotonic fluid containing 0.9% NaCl and KCl (10 to 20 mEq/L) for 24 hours at a rate of 50 to 100 mL/kg/day in conjunction with esophageal relaxants such as oxytocin may promote hydration and softening of the impaction and will help prevent or alleviate any electrolyte or acid-base imbalances resulting from salivary losses of chloride, sodium, and potassium. Refractory cases may require esophagotomy to relieve the impaction. Strict restriction of access to food and water, including access to bedding material, must be enforced until the obstruction is resolved and the esophagus has regained function.

Dilation proximal to the site of obstruction, mucosal injury from trauma, and esophagitis are sequelae to esophageal impaction that predispose patients to reobstruction. The rate of reobstruction may be as high as 37%. Depending on the duration of the obstruction and the degree of trauma or dilation, the risk of reobstruction is high for 24 to 48 hours or longer; therefore food should be withheld for at least 24 to 48 hours after resolution of the obstruction. After 48 to 72 hours or when the esophageal mucosa has recovered as assessed by endoscopy, soft food (moistened pellets and bran mashes) can be fed. The patient can be gradually returned to a high-quality roughage diet over a period of 7 to 21 days depending on the degree of esophageal damage induced by the impaction and the nature of any underlying disease. The prognosis for survival is good (78%), but some horses may require permanent dietary modification if persistent chronic obstruction is a problem.[68]

Complications of esophageal impaction include metabolic alkalosis from prolonged loss of salivary chloride and sodium, esophageal ulceration, stricture, perforation, aspiration pneumonia, and megaesophagus. Esophageal endoscopy and/or ultrasonography should be performed immediately after the impaction is relieved to determine whether any complications of the impaction have developed or if an inciting cause of the obstruction is present.

Endoscopic evaluation is critical to determine the postobstruction treatment and followup. Reevaluation should be performed intermittently every 2 to 4 weeks after resolution of the impaction if esophageal dilatation or mucosal injury is noted. Additional evaluation via radiography may be warranted to assess motility and transit times.

If the obstruction was present for 48 hours or longer, dehydration, hyponatremia, hypochloremia, and hypokalemia may occur and should be corrected via oral electrolyte solutions or intravenous administration of 0.9% NaCl and KCl (10 to 20 mEq/L). If aspiration is suspected, administration of broad-spectrum antibiotics that are effective against gram-positive and gram-negative organisms, including metronidazole for anaerobes, is advisable. Sucralfate (20 mg/kg orally [PO] q6h) may hasten healing if esophageal ulceration is evident, but this is controversial. Some clinicians suggest that administration of a nonsteroidal antiinflammatory drug such as flunixin meglumine (1 mg/kg PO or IV q12h) or phenylbutazone (1.1 mg/kg PO or IV q12h) for 2 to 4 weeks after resolution of the impaction may reduce the development of strictures.

32.26 ESOPHAGITIS

Inflammation occurs during many conditions of the esophagus. *Esophagitis* refers to a clinical syndrome of esophageal inflammation, which may or may not be ulcerative. Causes of esophagitis in horses include trauma (foreign bodies, nasogastric tube), infection (mural abscesses), and chemical injury (medicines, cantharidin).[86,87] An important category of esophagitis is reflux esophagitis, caused by reflux or delayed clearing of gastric contents into the distal esophagus and subsequent chemical injury to the mucosa (Fig. 32-21). Similar to ulceration of the squamous portion of the stomach in horses, a major cause of ulcerative esophagitis is epithelial damage resulting from exposure to acid, which is synergistically exacerbated by bile salts.[62,88] The major protective mechanisms of the esophageal mucosa include salivary and food material buffers, normal peristaltic motility, and the barrier formed by the gastroesophageal sphincter. Thus, esophagitis may be seen in conjunction with gastric ulcer disease, motility disorders, increased gastric volume from gastric outflow obstructions, gastric paresis, intestinal ileus, or impaired lower esophageal sphincter function.

The clinical signs of esophagitis are nonspecific and similar to those of esophageal obstruction and gastric ulcer disease. In fact, esophagitis may occur concurrently with esophageal obstruction or gastric ulcer disease, so clinical signs may overlap extensively with these diseases. Gagging, or discomfort when swallowing, may be evident, and hypersalivation and bruxism are signs of esophageal pain. Partial or complete anorexia may be noted such that horses with chronic esophagitis may have significant weight loss. Motility dysfunction secondary to esophagitis may cause recurrent esophageal impaction. Clinical signs of underlying disease that predispose to esophagitis may predominate or mask the signs of esophagitis. Horses with gastrointestinal motility disorders such as anterior enteritis are at high risk for developing reflux esophagitis because of the presence of both gastric acid and bile salts in the fluid reflux. However, signs attributable to esophagitis secondary to ileus may not be noted because of the profound signs caused by the intestinal disorder. Foals with gastric outflow obstructions commonly have reflux esophagitis.

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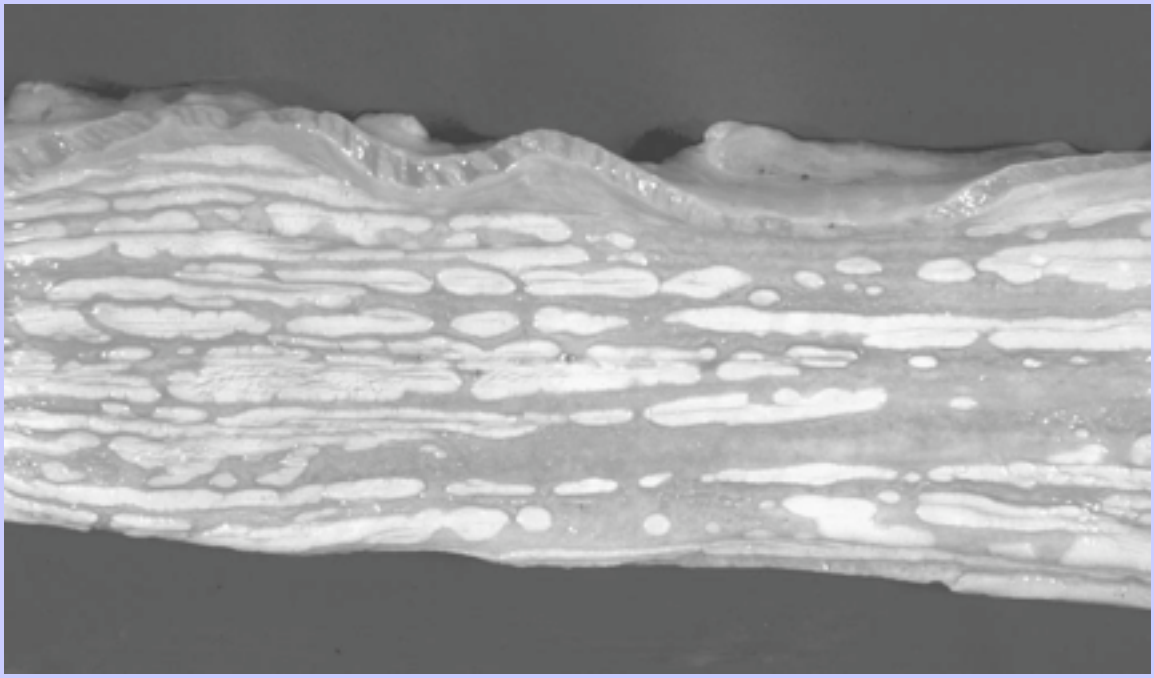
Fig. 32-21 Severe ulceration of the esophagus in a weanling foal that had severe duodenitis and gastric outflow obstruction. Courtesy Dr. M.J. Murray.



Diagnosis requires endoscopic examination of the esophagus. Diffuse, patchy, linear, or coalescing erosion or ulcerations may be noted. Significant edema or hyperemia may also be observed. It is important to determine whether underlying disease, such as infection, neoplasia, diverticula, or esophageal stricture is present. In addition, the stomach must be examined because reflux esophagitis is commonly accompanied by gastritis or gastric ulcer disease. Contrast radiography may be helpful if endoscopy is not available to detect esophageal ulceration and can be used to assess esophageal motility and transit time.

The principles of therapy for reflux esophagitis include control of gastric acidity and correction of any underlying disorder that is contributing to gastroesophageal reflux. Thus, treatment with histamine-2 (H_2)–receptor antagonists such as ranitidine or proton pump antagonists such as omeprazole is important for resolution of the disease. Some clinicians advocate sucralfate administration to aid healing of esophageal ulcers. However, the efficiency of sucralfate binding to ulcerated mucosa in the squamous epithelium of the gastrointestinal tract has recently been brought into question.

Foals with reflux esophagitis secondary to delayed gastric outflow caused by gastroduodenal ulcer disease or gastric paresis may benefit from prokinetic drugs that act on the proximal gastrointestinal tract. Metoclopramide (0.02 to 0.1 mg/kg SC q4-12h) reduces gastroesophageal reflux by increasing lower esophageal sphincter tone, gastric emptying, and gastroduodenal coordination. Caution should be exercised when giving metoclopramide to horses because they are prone to extrapyramidal neurologic side effects. Cholinergic drugs such as bethanechol (0.025 to 0.035 mg/kg SC q4-24h or 0.035 to 0.045 mg/kg PO q6-8h) may improve gastric emptying and are effective for treating reflux esophagitis. For esophagitis from trauma or pressure injury after esophageal impaction,

judicious use of nonsteroidal antiinflammatory drugs may be warranted to reduce esophageal inflammation and pain.

Dietary modification may be necessary in patients with esophagitis, depending on the degree of ulceration or if motility is impaired. Horses with less severe esophagitis should be fed frequent small meals of moistened pellets and fresh grass. Severe esophagitis may necessitate withholding food and complete esophageal rest for several days. Although the prognosis for esophagitis is good in the absence of underlying disease, the risk of stricture formation is high if severe circumferential or coalescing ulcerations are present. Animals with esophagitis from severe trauma or infection may also be prone to stricture formation.

32.27 MOTILITY DISORDERS OF THE ESOPHAGUS

Esophageal hypomotility is the most common motility dysfunction of the equine esophagus and results in esophageal dilation or megaesophagus. Although megaesophagus in horses is most commonly acquired, there are reports of idiopathic megaesophagus in young horses that is likely congenital (Fig. 32-22 and Color Plate 1).[89–92] Acquired megaesophagus in adult horses is usually caused by either primary or secondary esophageal obstruction. Esophageal impactions of relatively short duration cause proximal dilation of the esophagus that is generally reversible. However, if the duration of the obstruction is long, the motility of the esophagus may be permanently impaired. Acquired megaesophagus in foals is often secondary esophagitis resulting from gastric outlet or duodenal obstruction. Other causes of acquired megaesophagus include extraesophageal obstruction by tumors or abscesses, pleuropneumonia, and vascular ring anomalies. In addition, acquired megaesophagus may result from neurologic, neuromuscular, or muscular disorders. Neurologic diseases that cause vagal neuropathy, such as equine protozoal myeloencephalitis, equine herpesvirus myeloencephalitis, and idiopathic vagal neuropathy, have been associated with megaesophagus in horses. Pleuropneumonia may be associated with vagal neuropathy, resulting in megaesophagus. Megaesophagus is also an early sign of equine dysautonomia[93] and may be noted in patients with botulism. Myasthenia gravis is a well-known cause of megaesophagus in other species but has not been reported in horses. Also in other species, electrolyte disorders, cachexia, primary myopathies, myositis, and Addison's disease may affect esophageal motility but have not been associated with megaesophagus in horses.

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Fig. 32-22 Megaesophagus in a 10-month-old Paint horse foal that had two duodenal strictures that appeared to have been present for several months. The trachea *(T)* lies dorsal to the dilated esophagus *(E)*. Courtesy Dr. M.J. Murray.

Esophageal inflammation, particularly reflux esophagitis, may affect motility and cause megaesophagus. However, because esophageal hypomotility may predispose to reflux esophagitis, it may be difficult to determine whether the esophagitis or the megaesophagus is the causative disorder. Iatrogenic megaesophagus can be induced by the α_2-adrenergic agonist detomidine, but this is transient and reversible.[94] However, the use of this drug may complicate clinical evaluation of esophageal motility. Because esophageal hypomotility is a functional obstruction, the clinical signs of esophageal hypomotility or megaesophagus are similar to those of esophageal obstruction. Thus, the clinical signs include ptyalism, dysphagia, and nasal discharge of saliva and food material. The cervical esophagus may be sufficiently dilated to be evident externally. Weight loss is a common sign, and clinical signs attributable to an underlying disease may be evident.

Diagnosis of esophageal hypomotility requires transit studies. Transit time of a bolus from the cervical esophagus to the stomach can be measured by fluoroscopy or contrast radiography.[58,93] Other signs of esophageal hypomotility and megaesophagus include pooling of contrast material and an absence of peristaltic constrictions. Endoscopy may reveal a dilated esophagus and an absence of peristaltic waves. Evidence of underlying disease causing obstruction or esophageal dilation may be observed. The esophagus should be evaluated for evidence of esophagitis that is either causing esophageal motility dysfunction or is a result of impaired esophageal clearance of gastric fluid. Esophageal manometry may be useful to document abnormal postdeglutition contraction pressures, contraction time, and propagation times.[55,89] Other diagnostic tests such as a CBC and chemistry to help identify an underlying cause should be performed. A careful neurologic evaluation should be performed. Signs of neurologic disease and abnormal cerebrospinal fluid analysis suggest an underlying neurologic disorder. Myopathy may be detected by electromyography.

Treatment of esophageal hypomotility or megaesophagus should be aimed at treating the underlying cause. Dietary modification should be aimed at improving esophageal transit of food. Slurries of pellets should be fed. In addition, it may be beneficial to feed from an elevated position to promote transit. In patients with reflux esophagitis associated with megaesophagus, metoclopramide or bethanechol may be beneficial to increase lower esophageal tone, promote gastric emptying, and reduce gastroesophageal reflux. The prognosis depends on the underlying cause and the degree of dilation. Although many cases of megaesophagus associated with reflux esophagitis respond well to treatment, many other forms of megaesophagus including congenital megaesophagus have a poor prognosis.

32.28 CONGENITAL DISORDERS

Congenital disorders of the esophagus are rare. Reported congenital abnormalities include congenital stenosis,[95] persistent right aortic arch, congenital strictures, esophageal duplication cysts,[96,97] and idiopathic megaesophagus.[98] In the one report on congenital stenosis, double-contrast radiography revealed concentric narrowing of the thoracic esophagus in the absence of any vascular abnormalities at the base of the heart. Successful treatment included having the foal stand with the forelimbs elevated off the ground after each feeding.

Persistent right aortic arch is a congenital anomaly in which the right fourth aortic arch becomes the definitive aorta instead of the left aortic arch, which results in constriction of the esophagus by the ligamentum arteriosum as it extends between the anomalous right aorta and the left pulmonary artery.[75] Clinical signs may include dysphagia, drooling of saliva, and distention of the cervical esophagus as a result of partial obstruction of the thoracic esophagus.[99] Endoscopic examination typically reveals dilatation of the esophagus cranial to the obstruction with

evidence of diffuse esophagitis. In addition, evaluation of the thorax usually reveals the presence of aspiration pneumonia. Successful surgical treatment of persistent right aortic arch has been reported in one foal.

Esophageal duplication cysts cause typical signs of esophageal obstruction, including salivation, dysphagia, and swelling of the cervical esophagus as they enlarge. Such signs can make them difficult to differentiate from simple obstruction (choke). However, an aspirate of the mass may aid in the diagnosis by revealing the presence of keratinized squamous cells.[100] Cysts may communicate with the lumen of the esophagus. Surgical treatments have included complete surgical resection and surgical marsupialization. The latter appears to be more successful and to result in fewer complications. Complications of surgical resection have included laryngeal hemiplegia secondary to surgical trauma to the recurrent laryngeal nerve in the region of the esophagus, and esophageal fistula formation.

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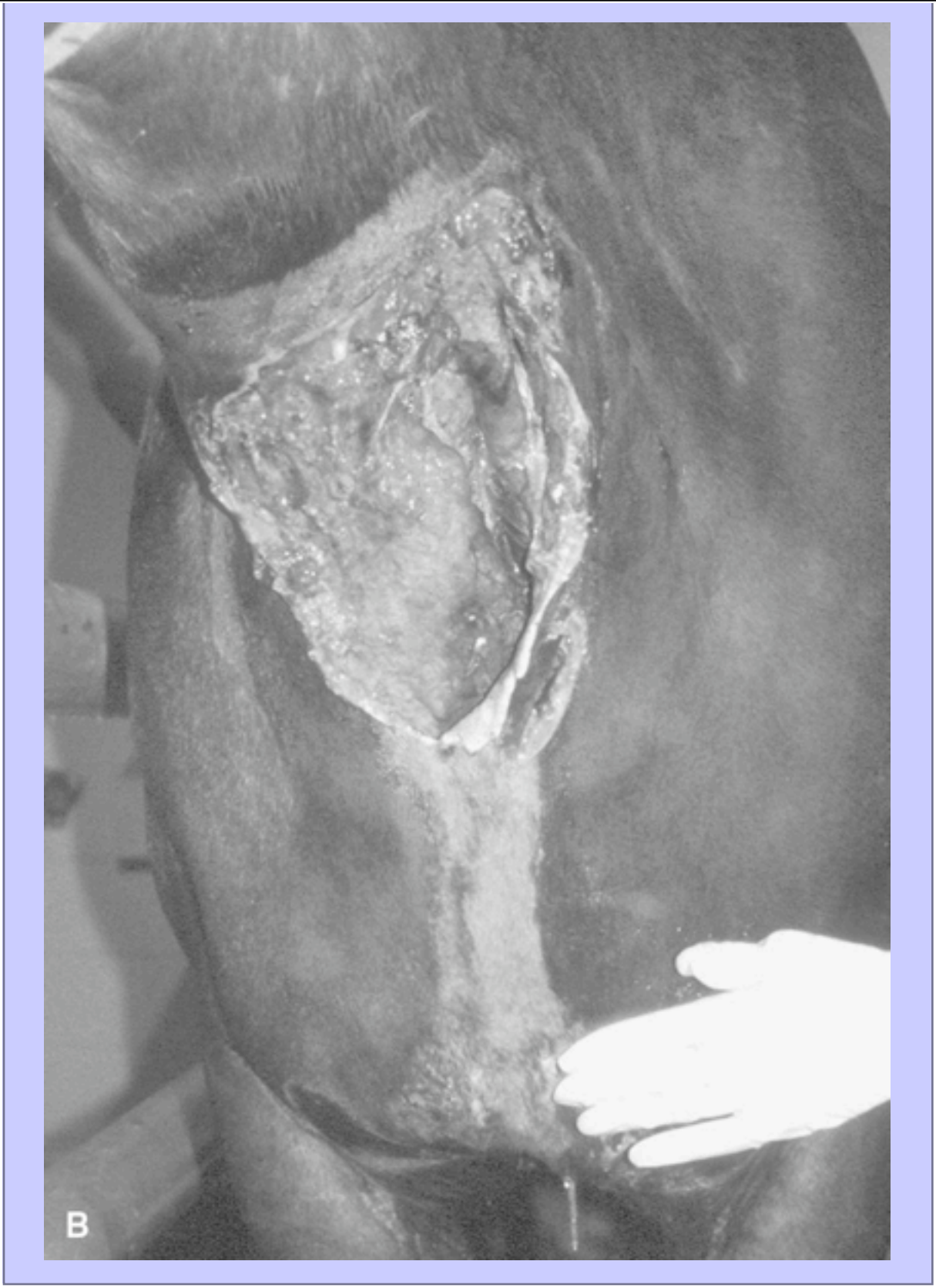
32.29 ESOPHAGEAL PERFORATION

Perforation typically occurs in the cervical region in response to external trauma or rupture of an esophageal lesion such as an impacted diverticulum. The esophagus is particularly vulnerable to external trauma in the distal third of the neck because it is covered by only a thin layer of muscle at this point.[101] Iatrogenic perforation may occur in response to excessive force with a stomach tube against an obstruction or a compromised region of the esophagus. Esophageal perforations may be open or closed and tend to cause extensive necrosis of tissues surrounding the wound because of drainage of saliva and feed material within fascial planes (Fig. 32-23). This may lead to extensive cellulitis and endotoxemia. Closed perforations of the esophagus are particularly troublesome, as wound discharge may migrate all the way to the mediastinum and pleural space via fascial planes and may cause abscessation (Fig. 32-24). In addition, extensive subcutaneous and fascial emphysema frequently develops and is usually evident on cervical radiographs.

Fig. 32-23 Esophageal perforation in a horse. **A**, An open esophageal laceration was detected on presentation in the midcervical region. The wound was treated by lavage and debridement, and the horse was fed via a tube inserted into the esophagus through the wound. **B**, Approximately 14 days later, dissection of esophageal contents within surrounding fascial planes has resulted in extensive sloughing of tissue.


B

Treatment should include conversion of closed perforations to open perforations if possible,[102] extensive debridement and lavage of affected tissues, broad-spectrum antibiotics, tetanus prophylaxis, and esophageal rest. The latter may be achieved by placing a feeding tube into the esophagus via the wound. Alternatively, a nasogastric tube should be placed using a small tube (12-Fr diameter). For open perforations, once the wound has granulated and contracted to a small size, oral feeding may be attempted. Extensive loss of saliva via esophageal wounds may lead to hyponatremia and hypochloremia. In addition, transient metabolic acidosis occurs because of salivary bicarbonate loss, followed by progressive metabolic alkalosis. Although there are reports of esophageal wounds healing well by second intention, it takes a prolonged period of time.[103] In addition, some perforations never completely heal and form permanent esophagocutaneous fistulas that may require surgical correction. The development of esophageal strictures is not common because wounds are usually linear and not circumferential. However, traction diverticula may develop. Other complications of esophageal wounds include Horner's syndrome and left laryngeal hemiplegia.

In a retrospective study on esophageal disorders, only 2 of 11 horses with esophageal perforations survived long term, and in a report on esophageal trauma secondary to nasogastric intubation, 4 of 5 horses were euthanized. The prognosis is therefore poor in horses with esophageal perforations, largely because of the extent of cellulitis, tissue necrosis, shock, and local wound complications.

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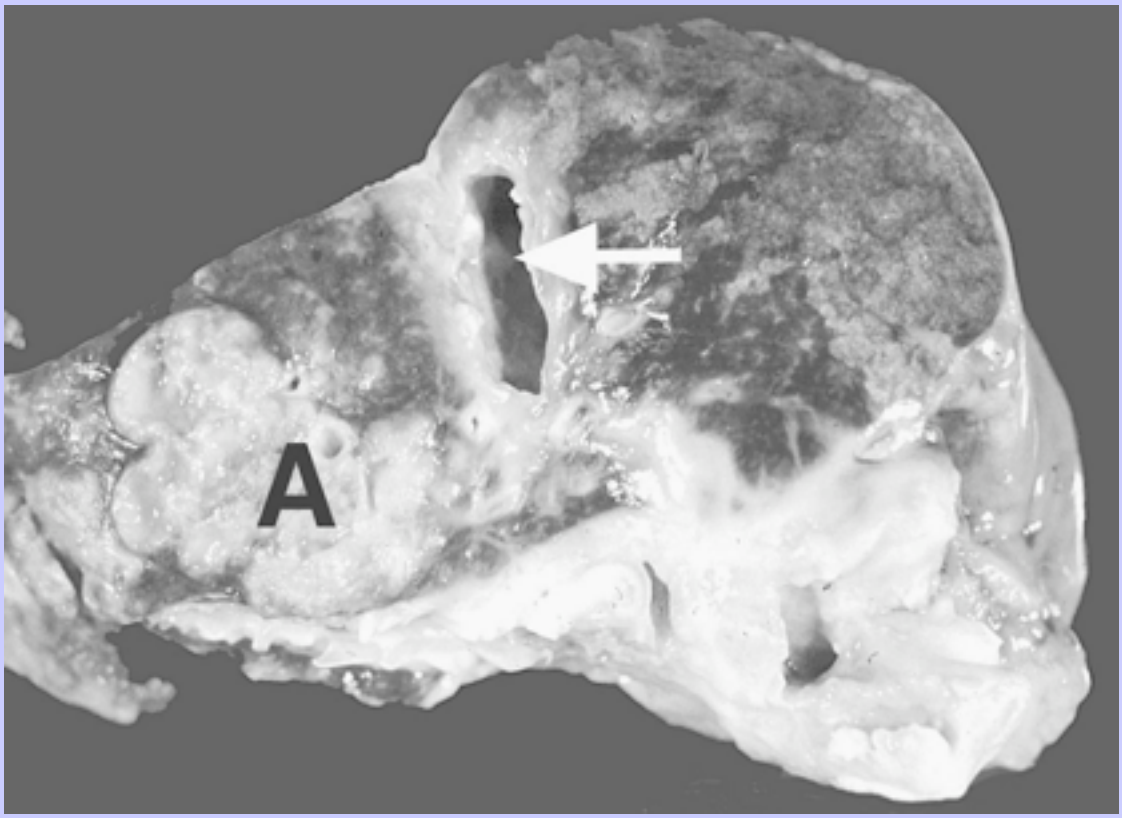
Fig. 32-24 Esophageal abscess *(A)* and cellulitis that developed secondary to an esophageal obstruction. The esophageal lumen is indicated by the *white arrow*. Courtesy Dr. M.J. Murray.

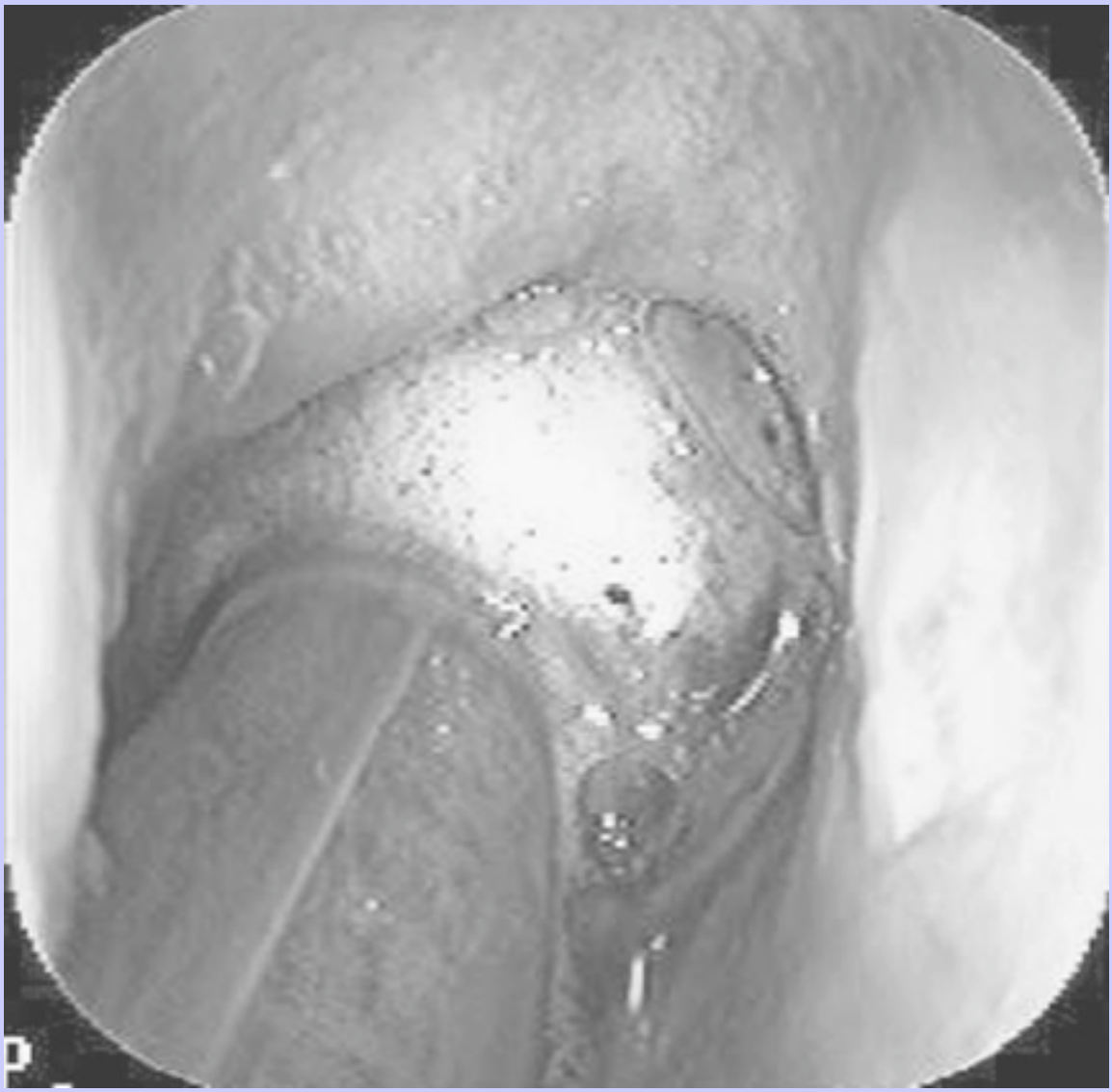


32.30 ESOPHAGEAL STRICTURE

Strictures most commonly occur as sequelae to esophageal obstructions that result in circumferential erosion or ulceration of the esophageal mucosa, although strictures may result from oral administration of corrosive medicinal agents and trauma to the neck.[104] Congenital strictures have also been reported. Strictures that result from mucosal and submucosal trauma are termed *esophageal webs* or *rings*. Strictures may also originate in the muscular layers and adventitia of the esophagus (mural strictures) or in all of the layers of the esophagus (annular stenosis).[105] Horses with these lesions have a presentation similar to that of horses with simple obstructions because strictures result in partial obstruction and accumulation of feed material in the lumen. Esophageal webs or rings can be observed endoscopically, whereas mural strictures or annular stenosis may require double-contrast esophagrams to confirm their presence.

In one study on esophageal stricture after simple obstruction, maximal reduction in esophageal lumen occurred within 30 days of esophageal obstruction. Although surgery has been employed to reduce such strictures, initial medical management is warranted because strictures may resolve with conservative therapy, and the esophagus continues to remodel for up to 60 days after ulceration. In one report, seven horses with esophageal obstruction—induced stricture were treated conservatively by feeding a slurry diet and administering antiinflammatory and antimicrobial medications, and five of seven were clinically normal within 60 days. One of the five successfully treated horses had a 10-cm area of circumferential ulceration, suggesting extensive mucosal injury may resolve without permanent stricture formation. If there is insufficient resolution of strictures within 60 days, other methods to increase esophageal diameter should be investigated. Bougienage has been used successfully in small animal patients and human beings. The technique involves passage of a tubular dilatable instrument down the esophagus and stretching of the stricture. Some authors have suggested that this may be accomplished by passing a nasogastric tube with an inflatable cuff (Fig. 32-25).[106] However, the procedure has to be performed frequently to have any success and is not well tolerated in the horse. Alternatively, several surgical techniques have been used to resolve strictures, including resection and anastomosis,[107,108] temporary esophagostomy with fenestration of the stricture, esophagomyotomy for strictures of the muscularis and adventitia,[109,110] and patch grafting with local musculature.[111] However, such surgeries are fraught with complications, largely because of the propensity of the traumatized esophagus to restricture. The esophagus lacks a serosal layer and does not rapidly form a fibrin seal, as does the remainder of the intestinal tract, so anastomoses tend to leak. In addition, tension on the esophagus during swallowing and movement of the neck impairs healing of anastomoses.

Fig. 32-25 Attempted dilation of esophageal stricture using bougienage. In this case, a cuffed Silastic tube was passed to the site of stricture aided by endoscopy, and the cuff was then inflated to distend the site of structure. Courtesy Dr. M.J. Murray.



32.31 ESOPHAGEAL DIVERTICULA

There are two types of diverticula: traction (true) diverticula and pulsion (false) diverticula. Traction diverticula result from wounding and subsequent contraction of periesophageal tissues, with resultant tenting of the wall of the esophagus. Pulsion diverticula arise from protrusion of esophageal mucosa through defects in the muscular wall of the esophagus and usually result from trauma or acute changes in intraluminal pressure (Fig. 32-26). Traction

diverticula appear as a dilatation with a broad neck on contrast esophagography, whereas pulsion diverticula typically have a flask shape with a small neck on an esophagram.[112] Whereas traction diverticula are usually asymptomatic and of little clinical significance, pulsion diverticula may fill with feed material, ultimately leading to esophageal obstruction.[113] However, a movable mass in the midcervical region may be noticed before onset of complete obstruction.[56] Pulsion diverticula may be surgically corrected by inverting or resecting prolapsed mucosa and closing the defect in the wall of the esophagus.[77,112,113] Inversion of excessive mucosa may predispose horses to esophageal obstruction and should therefore be reserved for small diverticula.

32.32 NEOPLASIA

Neoplasia of the esophagus is rare, but squamous cell carcinoma[114,115] and leiomyosarcoma[116] have reportedly affected the esophagus either as the primary site or in association with a lesion in the squamous portion of the stomach. The predominant clinical signs are weight loss, colic, and recurrent esophageal obstruction. The tumor is typically detected antemortem on esophagoscopy and radiography, but a definitive diagnosis may require a biopsy during laparotomy.[72,116] When neoplasia affects the lower esophageal sphincter, gastroesophageal reflux may contribute to ulceration of esophageal mucosa. The prognosis for malignant neoplasia of the esophagus is grave.

Fig. 32-26 Pulsion diverticulum *(D)* of the esophagus *(E)* in a horse that had intermittent episodes of esophageal obstruction. Courtesy Dr. M.J. Murray.

32.33 DISORDERS OF THE STOMACH

Michael J. Murray

32.34 GASTRIC ULCERATION

Just as the term *colic* describes a clinical presentation and encompasses a large number of disorders, the term *equine gastric ulcer syndrome* (EGUS) describes a clinical finding, the cause of which is likely to be multifactorial and different from case to case. The umbrella of EGUS includes lesions in the squamous or glandular mucosal linings of the stomach, focal or multifocal ulceration, generalized gastritis, gastric emptying disorders, gastroesophageal reflux disorders, and obstructive disorders. In foals, signs attributable to gastric disease can be the result of primary duodenal disease (see Color Plates 1-12).

32.34.1 Prevalence and Incidence

Gastric ulceration is a widespread phenomenon, affecting a large number of foals and horses. The overall prevalence of gastric ulceration in foals up to 60 days old has been reported to range from 25% to 50%, and most lesions were observed in the squamous mucosa.[117,118] In the majority of foals with lesions, clinical signs of ulcers were not apparent, and in one study[119] most lesions observed in foals less than 60 days old healed without treatment.

More than half of apparently normal horses had gastric lesions in one endoscopic study,[120] and lesions were more prevalent and severe in horses exhibiting clinical signs consistent with gastric ulceration (poor appetite, poor body condition, recurrent abdominal discomfort). Horses in training for racing appear to be at particular risk for developing gastric lesions, because 70% to 90% of racehorses have had gastric lesions documented endoscopically[120–125] or at necropsy.[126]

The incidence of gastric ulcers in horses exposed to ulcerogenic stresses has been reported to range from 70% to 86%.[127–129] Ulcers developed within 5 to 7 days in some reports. In one report ulcers developed in the majority of horses in simulated race training within 7 days,[130] and it was reported that 11 of 15 horses exercised using a mechanical exerciser developed gastric ulcers within 7 days.[131] Most studies have been done in horses in race training, but in one study that simulated conditions of traveling to a recreational horse show, 7 of 10 horses developed gastric ulcers within 5 days.[129] The latter two studies demonstrated a high incidence rate and rapid onset of gastric ulcers in horses not in race training regimens.

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In the endoscopic studies referenced in the previous paragraphs, the majority of gastric lesions in adult horses reportedly occurred in the squamous mucosa. To some extent this observation has been influenced by the limitations of the endoscopic examination, in which only the portion of the stomach not obscured by ingesta or gastric secretions was observed. In studies in which the antrum and pylorus were specifically examined, lesions were found in the antral mucosa in 47% and 58% of horses.[132,133] In some horses with moderate to severe antral ulcers, the gastric squamous mucosa was normal.

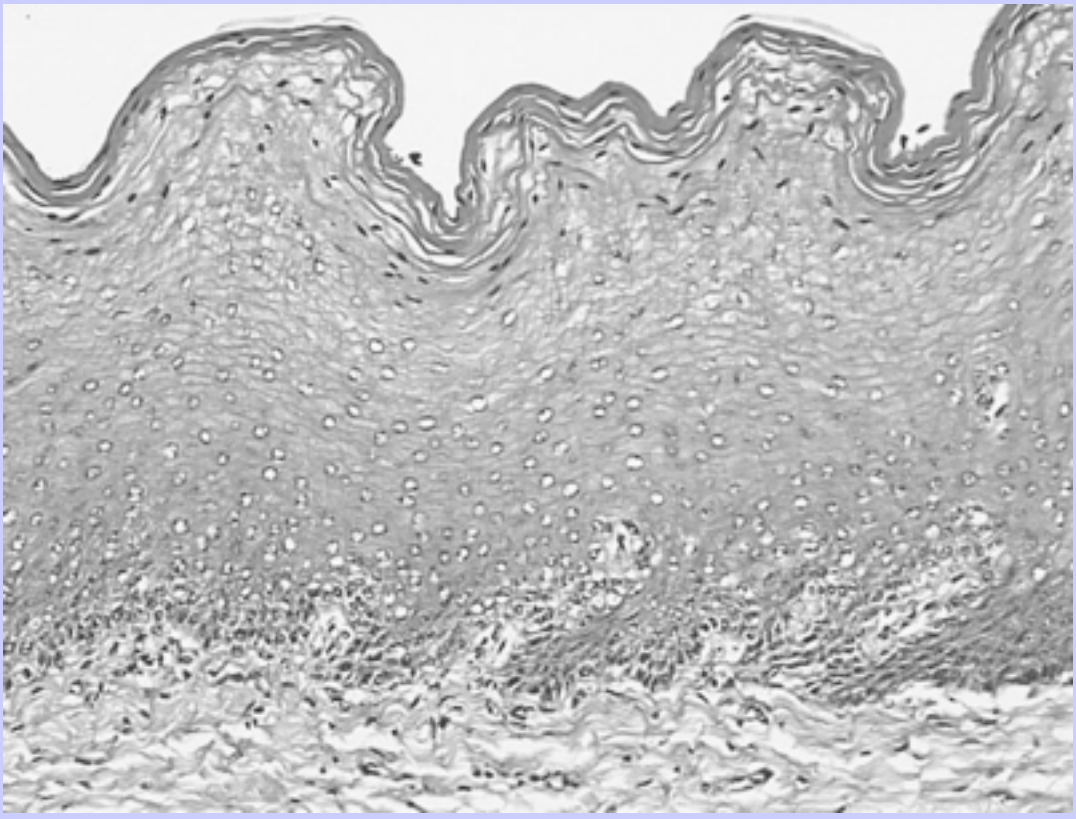
32.34.2 Pathophysiology

Damage to the gastric lining results from a combination of the physical properties of the gastric mucosa, the physiology of gastric acidity in the equine stomach, and the horse's response to potentially ulcerogenic stress factors. The predominant factor in peptic injury to alimentary mucosa is hydrochloric acid, although the proteolytic enzyme pepsin,[134] bile acids,[135] and short-chain fatty acids[136] may facilitate or exacerbate hydrochloric acid—induced mucosal injury.

The dorsal portion of the equine stomach is lined by a stratified squamous epithelial mucosa, which, like esophageal mucosa, has minimal intrinsic resistance to peptic injury (Fig. 32-27).[137] The equine gastric squamous mucosa is highly susceptible to acid-induced injury, with damage to this tissue detected within 30 minutes of in vitro exposure to solutions acidified by HCl.[138] The equine gastric glandular epithelium (Fig. 32-28) is histologically and physiologically similar to the lining of the stomach of other animals and human beings, and this mucosa has evolved elaborate mechanisms to protect itself from peptic injury. These include the mucus-bicarbonate barrier, prostaglandins, nitric oxide, growth factors, mucosal blood flow, and cellular restitution.[139,140]

Perhaps the key factor in whether the gastric squamous mucosa is injured by HCl is the duration of contact of HCl with the mucosa, which is influenced by eating behavior, exercise, and perhaps other factors, which collectively are recognized as “ulcerogenic stresses.” Risk factors, acting singly or interacting together, contribute to the ulcerogenic stress experienced by a horse, and the expression of the ulcerogenic stress as a gastric ulcer depends on individual characteristics of the animal as well as the risk factors themselves.

Fig. 32-27 Photomicrograph of equine gastric squamous epithelial mucosa. There are multiple layers of epithelium arranged in parallel with the luminal surface. The most superficial layers of cells are cornified, and superficial to these cells are layers of keratin. (Hematoxylin and eosin stain.)



Foals and horses and secrete HCl continuously,[141] and gastric acidity is greatest when foals do not nurse[142] or horses do not eat.[143] Gastric pH can fall to highly acidic levels (<2) within minutes of cessation of nursing or eating hay. Any disruption of feeding or nursing, whether it is imposed or caused by a clinical disorder, will prolong gastric acidity and increase the time that the squamous mucosa is exposed to HCl.

Prolonged periods of high gastric acidity (pH < 2) were created in horses using a protocol of alternating 24-hour periods of feed deprivation with free-choice timothy hay,[144] which consistently resulted in erosion and ulceration, often severe, in the gastric squamous epithelial mucosa in horses.[143] Erosions, sometimes bleeding, were seen after 48 hours cumulative feed deprivation, and ulcers were consistently seen after 96 hours. Concurrent administration of the H_2-receptor antagonist ranitidine during feed deprivation significantly minimized the area of lesions in the gastric squamous epithelial mucosa, demonstrating the direct contribution of HCl in the pathogenesis of these lesions.

Feeding practices and management of horses can influence gastric acidity and peptic injury to the gastric squamous mucosa. Changing horses from pasture to stall confinement with free choice timothy hay for 7 days resulted in erosion and ulceration of gastric squamous mucosa.[143] Imposed feed deprivation in the management of cases of colic can result in erosion and ulceration of the gastric squamous mucosa. Similarly, horses that are partly or completely anorectic because of their illness will likely develop erosions or ulcers in their gastric squamous mucosa.

Given the very high prevalence of gastric ulcers in horses in training, exercise is an important risk factor for EGUS. The reasons for the high prevalence and incidence of EGUS in association with exercise have not been fully explained, but in one report it was shown that treadmill exercise was associated with increased exposure of the dorsal part of the stomach to highly acidic gastric contents.[145] This occurred secondary to, and as a possible consequence of, increased intraabdominal pressure during exercise. These changes were observed when horses increased speed from a walk to a trot. It is interesting to note that several horses in that study developed gastric ulcers.

The high prevalence and severity of gastric ulcers in racehorses has contributed to the perception that EGUS is primarily a disorder of racehorses and other horses in intensive training, However, results of a recent study demonstrated that activities considered to be normal by the recreational horse enthusiast are associated with an increased incidence of gastric squamous mucosal ulcers.[131] Ten horses were exposed over 5 days to conditions that simulated activities that are typical for the recreational use of horses, including transportation to an unfamiliar stable environment, twice-daily feeding, and light exercise (lunge line), and return transportation to the premises of origin. Ten age-matched herdmates remained on the premises of origin during the trial. Gastroscopy was performed at the beginning (day −1) and the end of the trial (day 5). The appearance of all horses' stomachs was normal at the beginning of the trial. Two control horses and seven transported horses developed ulcers in the squamous mucosa of the stomach by day 5. The ulcer scores of the transported horses increased significantly from day −1, whereas ulcer scores in the control horses did not change significantly from day −1.

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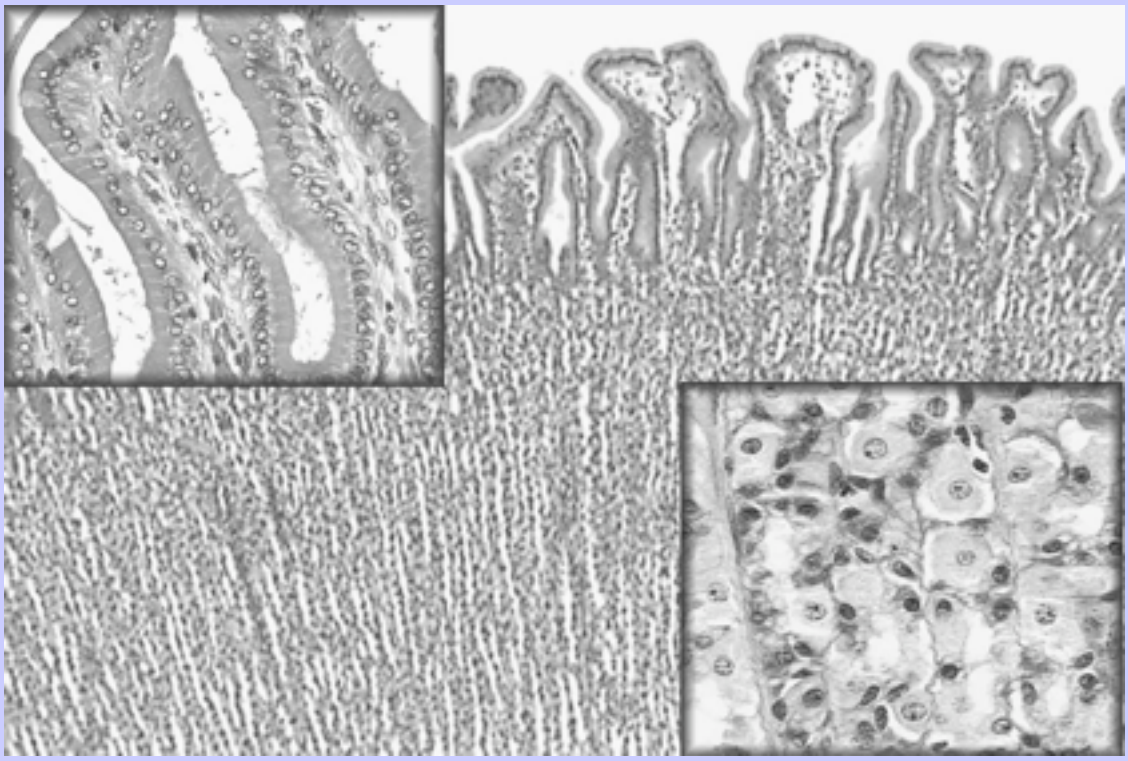
Fig. 32-28 Photomicrograph of equine gastric glandular mucosa. In contrast to the squamous mucosa, the glands are parallel to one another and perpendicular to the luminal surface. There are multiple cell types within the mucosa, with surface epithelial cells and mucus-secreting cells toward the lumen, and parietal cells, chief cells, enterochromaffin-like cells, G-cells, and D-cells deeper in the mucosa. The insert at the top left shows a high-power magnification of cells lining gastric pits on the surface of the epithelium. The insert at the lower right shows a high-power magnification of cells lining the gastric glands deeper in the mucosa. Hematoxylin and eosin stain.



The pathophysiology of lesions in the gastric glandular mucosa of foals and horses is not well understood. Nonsteroidal antiinflammatory drugs can induce gastric ulcers, but this is an infrequent cause of ulcers in most horses. Most lesions in the gastric glandular mucosa are observed in the antrum and adjacent to the pylorus. The role of hydrochloric acid in the development of ulcers in the glandular mucosa, particularly in the antrum, is unclear. In the feed deprivation model, in which prolonged increased gastric acidity induces gastric squamous mucosal ulcers, lesions were not induced in the glandular mucosa.[143] In human beings, *Helicobacter pylori* is considered to be the predominant cause of gastric erosions and ulcers,[146] but *Helicobacter* organisms have not

been reported to have been cultured from equine gastric mucosa. However, antibodies to *Helicobacter* proteins have been demonstrated in sera from foals and horses,[147] and through use of PCR techniques the *Helicobacter*-specific *16s rRNA* gene was identified in equine gastric mucosa.[148] Spiral organisms were identified in equine gastric mucosa by immunofluorescence, using a highly specific antibody to a *Helicobacter* protein (David Scott, personal communication, 2005). The role of an equine *Helicobacter* in the pathophysiology of ulcers in the mucosa of the antrum and pylorus is speculative, but consideration must now be given to this organism as a potential pathogen in the horse.

32.34.3 Clinical Syndromes

The magnitude of adverse health effects in the majority of foals and horses with gastric lesions remains somewhat speculative because the disease often goes unrecognized. In one report, though, the prevalence of gastric ulceration was significantly greater in horses with clinical problems such as colic, poor appetite, and poor bodily condition than in asymptomatic horses.[120]

32.34.3.1 FOALS

The clinical signs that typically are associated with gastric ulcers in foals (e.g., bruxism, dorsal recumbency, salivation, interrupted nursing, diarrhea, and colic) are, in fact, observed in the minority of foals with endoscopically observed ulcers.[118] Therefore when clinical signs are seen, the clinician should consider that severe ulceration exists. Diarrhea was the most frequently associated clinical signs in one report.[149] Colic, bruxism, dorsal recumbency, or ptyalism should alert the veterinarian to the probability of severe ulceration. Ptyalism occurs as a result of esophagitis, which often results from gastroesophageal reflux caused by gastric outlet obstruction or pseudoobstruction. Thus, ptyalism in foals often reflects a serious problem in the stomach and/or duodenum. Weanlings and older foals with chronic gastric ulceration often have intermittent diarrhea and abdominal discomfort, poor growth, rough hair coat, and a pendulous abdomen.

In foals with clinical signs, squamous mucosal lesions often are severe (see Plate 12). Most glandular lesions that result in clinical signs are located in the vicinity of the pylorus, although in young foals (<30 days old) with stress ulcers lesions are often located in the glandular mucosa in the body of the stomach (see Plate 8).

32.34.3.2 ADULTS

Although most adult horses with gastric lesions do not demonstrate overt clinical signs, low-grade discomfort that results in subtle signs may go unnoticed. Indeed, horses that I have treated solely on the basis of endoscopic findings have frequently demonstrated improved attitude and appetite, yet attitude and appetite were not considered problems before treatment began.

In horses, gastric lesions have most frequently been associated with colic, poor appetite, and poor bodily condition.[120,150] Other signs associated with ulcers have included attitude changes, stiffness, a tucked-up abdomen, and poor performance.

It should be noted that all the signs attributable to gastric ulcers have also been reported in horses that were referred for gastroscopy but did not have ulcers. Thus, although many signs appear typical for horses with ulcers, none is pathognomonic. Nonetheless, gastric ulcers should be strongly considered in horses with recurrent colic and other vague disorders for which a diagnosis has not been determined.

Hemorrhage (i.e., either active bleeding or darkened, coagulated blood) can occur with deep gastric ulcers in horses. However, bleeding from ulcers in the gastric squamous mucosa does not cause anemia or hypoproteinemia in adult horses, and if these abnormalities are present, another cause must be determined. 697 698

32.34.4 Diagnosis

Diagnosis of gastric ulceration is based on the presence of age-related characteristic clinical signs, endoscopic findings, and response to treatment. The diagnosis of gastric ulceration in the majority of foals and horses can be definitively determined only by gastroscopic examination. In young foals (<30 days) with an immature colonic flora, the presence of fecal occult blood may be indicative of gastroduodenal ulceration. In older animals, hemoglobin is too extensively degraded by colonic microorganisms for blood originating in the stomach to be detected by fecal occult blood tests.

The use of sucrose as a marker of equine gastric mucosal permeability has been reported in research studies in horses. As a disaccharide, ingested sucrose is digested to its constituent sugars, glucose and fructose, which are absorbed through the small intestine. The presence of ingested sucrose in the blood reflects absorption of the disaccharide through a breach in the gastric mucosa. In one report, horses were administered 454 g of table sugar by nasogastric tube, and urine sucrose was increased after 120 minutes in horses with gastric ulcers, particularly moderate to severe ulcers.[151] Because the need for collection of urine for this test will restrict its utility, a method for detection of sucrose in equine plasma has been developed.[152] To date, a validation of this method as a diagnostic test for gastric ulcers in horses has not been reported.

32.34.5 Treatment

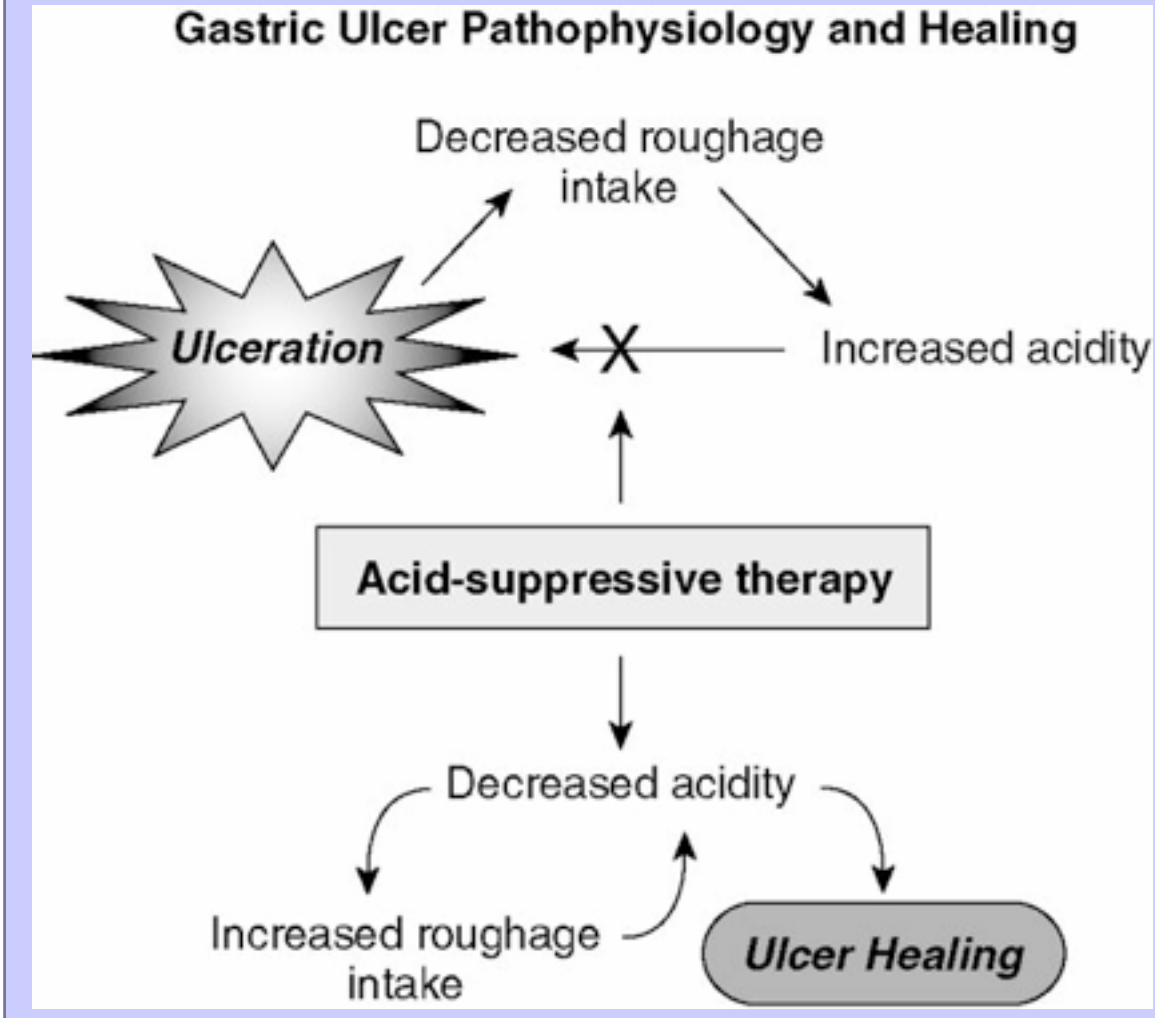
Processes that promote ulcer healing are stimulated by injury to the gastric mucosa. These include increased capillary blood flow, generation of new capillaries (neovascularization), induction of growth factor receptors, and proliferation of epithelium along a capillary scaffold.[153,154] With erosions in the stomach lining, some epithelium remains in the erosion bed and healing can occur within a few days because the epithelium is regenerated relatively rapidly. With severe ulcers that extend through the entire epithelium and lamina propria, a bed of granulation tissue forms in the ulcer bed, and healing results primarily from contraction of the ulcer margins. This type of healing can require weeks to complete.

Gastric ulcers can heal without treatment, even in the face of continued ulcerogenic stress, but in such conditions new ulcers typically form as old ulcers heal.[155] Also, the healing is often incomplete. For example, in racehorses it is typical to observe ulcers with proliferative margins and granulation tissue in the ulcer beds mixed with what appear to be newly formed, bleeding ulcers. In most cases, unless the ulcerogenic stress is removed the stomach will remain ulcerated. This means taking the horse out of training and probably turning it out onto pasture, because even taking the horse out of training but maintaining stall confinement can be ulcerogenic.[155] Successful treatment of gastric ulcers is predicated on addressing the underlying cause and treating with medications that create an environment that is favorable to ulcer healing. Acid-suppressive treatment often is required to break the cycle of inappetence that causes increased gastric acidity, which results in ulceration, which then prolongs and exacerbates the inappetence (Fig. 32-29).

Decisions concerning whether to treat gastric lesions, what medication to use, and for how long are best made on the basis of results of a gastroscopic examination, the type of activity for which the horse is used, and whether the horse will continue in that activity or be rested. If response to treatment is used as a diagnostic aid, clinical

conditions such as poor appetite, colic, or diarrhea (foals) that result from gastric ulcers should improve in 24 to 48 hours of initiating acid-suppressive therapy. If improvement in clinical signs is not observed, gastric ulceration, if present, should be considered to be a secondary, not a primary, problem.

Fig. 32-29 Diagram representing the pathophysiology of ulceration of the equine gastric squamous mucosal epithelium and the permissive effect of acid suppression on ulcer healing.



The primary objective in the treatment of gastric ulcers is to alleviate discomfort, and this is best done by inhibiting or neutralizing acid secretion. Decreasing gastric acidity also creates an environment that is permissive for healing of the gastric mucosal epithelium. Once ulcers form, there are changes in the tissue that promote healing. Suppressing acidity creates an environment within the stomach that permits ulcer healing.

Several acid-suppressing drugs are approved for treating gastric ulcers in horses (Box 32-2).

The H_2 antagonists cimetidine, ranitidine, famotidine, and nizatidine interfere with histamine stimulation of HCl secretion by competitively blocking the H_2 receptor on the parietal cell. Both cimetidine and ranitidine have been shown to suppress gastric acid secretion in horses and neonatal foals.[141,142,144,156,157] Effectiveness of these drugs in blocking acid secretion is dependent on plasma concentrations, and the magnitude and duration of acid inhibition are highly variable in horses. Both the degree and duration of suppression of gastric acidity by H_2 antagonists vary among horses,[157,158] presumably as a result of differences in drug absorption. A dose of 6.6 mg of ranitidine per kilogram given PO every 8 hours provided adequate suppression of acidity in most horses in research studies. This dosage schedule resulted in a median 24-hour gastric pH of 4.6 in horses with free access to hay (compared with a pH of 3.1 in horses fed, but not given ranitidine).[144] However, because of the individual variability in response among horses, the duration of effect may be only 1 to 2 hours. Using lower doses often results in no response.

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32.34.5.1

Box 32-2 Therapeutic Agents Registered for Use in Treating Gastric Ulcers in Foals and Adult Horses

32.34.5.1.1

PROTON PUMP INHIBITOR

Omeprazole (GastroGard [USA, Argentina, Canada, Europe], UlcerGard [USA], GastroShield [Australia]): 4 mg/kg, once daily for treatment, 1 mg/kg/day for prevention

32.34.5.1.2

HISTAMINE TYPE-2 RECEPTOR ANTAGONIST

Ranitidine (Ulcerguard [Australia]): 6.6 mg/kg q8h PO for treatment

Effective doses of cimetidine have not been examined as extensively as those of ranitidine, but an effective oral dose may be as high as 50 mg/kg/day. Lower doses are often given, and sometimes with clinical improvement, but in my experience ulcers have often persisted.

Formulations for parenteral administration of H_2 antagonists are available but are approximately three times the cost of oral products. Ranitidine should be given IV at 1 to 1.5 mg/kg every 8 hours, and cimetidine at 6.6 mg/kg three to four times daily. The parenteral route of administration can be very beneficial in foals and horses that cannot tolerate or use orally administered medications.

Omeprazole is a proton pump inhibitor that blocks gastric acid secretion by inhibiting the parietal cell H^+, K^+-ATPase (proton pump) that secretes HCl.[159] Omeprazole is a potent inhibitor of gastric acidity in horses. The antisecretory effects of omeprazole persist far longer than the drug's plasma level, because binding to the H^+, K^+-ATPase of the parietal cell persists for up to 24 hours after a single dose.[160] This prolonged duration of action enables once-daily dosing.

A paste formulation of omeprazole* has been registered in the United States, Canada, Europe, and elsewhere for use in treating gastric ulcers in foals and horses. In clinical trials, ulcer healing in horses and foals treated once daily with omeprazole paste at a dose of 4 mg of omeprazole per kilogram of body weight was substantially superior to healing in sham-treated horses.[161,162] It is important to note that in one set of these trials,[162] ulcer

healing occurred in more than 77% of omeprazole-treated horses that were in race training, a result that has not been noted in horses treated with H_2 antagonists.[163] Thus, omeprazole brings a new perspective to the treatment of gastric ulcers in horses. Once-daily treatment and a paste formulation should enhance treatment compliance, and the potency of acid suppression permits horses to remain in their activities while being effectively treated for ulcers.

Another important feature of omeprazole paste was the confirmation of its ability to prevent both occurrence and recurrence of ulcers in horses in race training, in which conditions are most ulcerogenic.[164,165] The daily dose used for prevention was one fourth that used for treatment (1 mg of omeprazole per kilogram vs. 4 mg/kg, respectively). In an 8-day study of horses in mild to heavy exercise, once-daily omeprazole paste† at a dose of 1 mg/kg prevented gastric ulcers in 45 of 51 treated horses (12% incidence), compared with an incidence of 73% in 51 untreated horses.[168a]

Antacids can effectively reduce gastric acidity, but only briefly. In a study examining administration of 180 mL of Maalox‡, gastric pH was increased for at most 45 minutes.[157] In another study 240 mL of Maalox TC§ increased gastric pH for 2 hours.[166] Thus, liquid antacid products must be given both in large volumes (240 mL) and very frequently, and these products are not suitable for ulcer treatment. Feed additives that contain antacids are popularly considered to be helpful in controlling gastric ulcers in horses, but there are no supportive data. Also, an acid-neutralizing effect is most desirable when the stomach is empty, not when it is full, because gastric pH naturally is high when horses ingest feed. Antacids containing aluminum may have some effect on healing of gastric glandular lesions, because aluminum hydroxide has been shown to enhance gastric mucosal nitric oxide, which should promote mucosal blood flow.[167]

Sucralfate, the major components of which are sucrose octasulfate (SOS) and aluminum hydroxide, is helpful in the treatment of peptic ulcers in people,[168] although healing rates for sucralfate in treatment of duodenal ulcers were much longer than for H_2 antagonists. The mechanism of action likely involves adherence to ulcerated mucosa, stimulation of mucous secretion, enhanced mucosal blood flow, and enhanced prostaglandin E synthesis. These are all factors relevant to glandular mucosa, and it is doubtful that sucralfate is effective in treating ulcers in the equine gastric squamous mucosa. In fact, I have observed lesions to develop in the squamous mucosa while horses were being treated with sucralfate.

Sucralfate can be administered concurrently with an H_2 antagonist. Concurrent administration may reduce H_2 antagonist absorption by 10%, but this has not appeared to affect efficacy in horses.[169] It is important to note that sucralfate can substantially interfere with the absorption of other drugs, particularly fluoroquinolones, and therefore its use with other medications should be determined on a case-by-case basis.

Few studies have directly compared the effectiveness of different ulcer treatments in horses. In a study of racehorses at a California race track, treatment with cimetidine was compared with treatment with registered omeprazole paste on healing and prevention of gastric ulcers.[124] Horses were treated with cimetidine 20 mg/kg three times daily for treatment or prevention of ulcer recurrence or omeprazole 4 mg/kg once daily for treatment and 2 mg/kg once daily for prevention of recurrence in a randomized controlled trial. There was significant reduction in ulcer severity in horses treated with omeprazole, and ulcer severity did not significantly increase after horses received the prevention dose of omeprazole. Cimetidine did not reduce ulcer severity or prevent recurrence of ulcers after treatment with omeprazole. In a randomized controlled trial conducted in Australia with 60 racehorses in training, ulcer healing was significantly better in horses treated daily with omeprazole paste* (4 mg of omeprazole per kilogram) than in horses treated with a commercial ranitidine product† (6.6 mg

of ranitidine per kilogram three times daily).[170] Furthermore, there was additional ulcer healing in horses treated with omeprazole paste after 28 days of treatment with ranitidine.

A study that included 798 racehorses examined the effect of several medications used to treat EGUS.[171] Two hundred and twenty-seven horses had been treated for at least 2 weeks at the time of gastroscopy with registered omeprazole paste[a] (4 mg/kg/day or 2 mg/kg/day), omeprazole in unregistered compounded products, H_2 antagonists (drugs and dosages not specified), sucralfate, or "buffers." The risk of having moderate to severe EGUS in horses treated with registered omeprazole paste[a] at 4 mg/kg/day or 2 mg/kg/day (0.18) was significantly less ($P < .001$) than in untreated horses, but the risk of having moderate to severe EGUS in horses treated with the other products was no different from that in untreated horses.

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In some cases prokinetic drugs may be required to enhance gastric emptying. Use of a prokinetic drug is indicated when there is suspected gastroesophageal reflux, gastric outlet obstruction or pseudoobstruction, or duodenal ulceration or inflammation. Drugs available for this purpose include bethanechol and metoclopramide.

I have used bethanechol successfully to enhance gastric emptying and minimize gastroesophageal reflux with few mild adverse effects. Bethanechol was reported to enhance gastrointestinal motility while not increasing gastric acid output in horses.[172] In cases of acute gastric atony, 0.025 mg/kg SC every 4 to 6 hours has been effective in promoting gastric motility and emptying, followed by oral maintenance doses of 0.35 to 0.40 mg/kg three or four times daily. Adverse effects can include diarrhea, inappetence, salivation, and colic, but they occur infrequently. Bethanechol can be administered chronically (weeks to months) in horses with pyloric fibrosis and stenosis, although there are no data regarding its long-term effectiveness.

Reported experience with metoclopramide in the equine is limited to its use in postoperative ileus (POI). Doses ranging from 0.10 to 0.25 mg/kg three or four times daily are used by some clinicians to treat suspected delayed gastric emptying, although one report indicated that constant infusion at a rate of 0.04 mg/kg/hr was superior to interval dosing in enhancing postsurgical small intestinal motility.[173] Sudden neurologic excitation is an adverse reaction to metoclopramide but is more common toward 0.25 mg/kg. In one foal I treated, administration of metoclopramide over several days resulted in tachycardia, bilateral facial sweating, miosis, and enophthalmos. These signs resolved when the drug was discontinued.

*	GastroGard, Merial Limited, Duluth, GA. GastroGard is a registered trademark of the AstraZeneca Group of Companies.
†	UlcerGard, Merial Limited, Duluth, GA. GastroGard is a registered trademark of the AstraZeneca Group of Companies.
†	Maalox, Novartis Consumer Health, Summit, NJ.
§	Maalox TC, Novartis Consumer Health, Summit, NJ.
*	GastroShield, Merial Australia Pty. Limited, Paramatta, NSW, Australia. GastroShield is a registered trademark of the AstraZeneca Group of Companies.
†	Ulcerguard, Ranvet Pty. Limited, Botany, NSW, Australia.

32.35 REFLUX GASTRITIS

Reflux gastritis frequently accompanies conditions in which there is small intestinal ileus with large volumes of enterogastric reflux that must be evacuated by nasogastric intubation. This fluid typically has a pH of 5 to 7 and contains substantial biliary and pancreatic secretions. Often gastroscopy reveals that extensive erosion of the

squamous mucosa occurs in association with this reflux. The erosions extend from the margo plicatus dorsally, primarily along the cranial and right sides of the stomach. Presumably squamous mucosal erosion results from the effect of bile acids on the gastric squamous mucosa combined with accumulation of gastric hydrochloric acid.[138] Often in such cases, islands of regenerative squamous epithelium can be observed in the eroded or ulcerated fundus within 2 to 3 days, and in another 2 to 3 days the squamous epithelium can completely regenerate. Horses with reflux gastritis may be slow to regain a normal appetite after feeding resumes, and in some cases administration of an acid-suppressive drug has resulted in a quick improvement in appetite. Intravenous administration of an H_2 antagonist may prevent these lesions from developing or hasten healing, but treatment may not be necessary in all cases.

32.36 GASTRIC IMPACTION

True gastric impaction occurs infrequently and may result from ingestion of certain feed stuffs or eating when there is impaired intestinal motility. Potential predisposing feeds include beet pulp, bran, straw, wheat, and barley. Beet pulp and bran can become desiccated within the stomach and may not become rehydrated by water or gastric secretions. Dental disorders may predispose some horses to gastric impaction if roughage is incompletely masticated. Feeding a horse that has signs of colic may predispose to gastric impaction because there may be poor gastric emptying associated with generalized decreased gastrointestinal motility.

Definitive diagnosis of gastric impaction is difficult. Gastric impaction is occasionally diagnosed during exploratory laparotomy as the primary cause of colic in horses.[174] Other than at surgery, definitive diagnosis of gastric impaction can be difficult. If the horse has not eaten for several hours, yet poorly macerated or digested feed material is recovered from the nasogastric tube, a gastric impaction may be suspected. On rectal examination, the spleen may be displaced caudally and medially, but this finding is not specific for gastric impaction or dilation. Gastric impactions can be confirmed by gastroscopy, although one cannot differentiate a normally full stomach from an impacted stomach. The key to making this diagnosis is the failure of the stomach to empty appreciably in 12 to 24 hours. Radiography may also reveal a distended stomach that distorts the diaphragm cranially.

Gastric impactions can be effectively treated medically by administering dioctyl sodium succinate (DSS), 5% solution, 4 to 8 oz, in 4 to 6 L of water. The DSS acts as a surfactant and allows water to penetrate the impacted, desiccated ingesta, facilitating their removal from the stomach. Alternatively, one can lavage the stomach with water repeatedly by pumping 2 to 4 L of water via nasogastric tube and recovering the infused water and ingesta by gravity flow or aspiration through the nasogastric tube. This is particularly effective in treating bran mash impactions, because of the small particle size of the bran. Mineral oil is less effective in treating gastric impactions because the interior of the impacted ingesta is desiccated and compacted. The mineral oil slides around the impaction and does not penetrate it; thus it does not facilitate passage of the impacted ingesta through the pylorus. When diagnosed at surgery, gastric impactions can be effectively treated by the injection of 2 to 4 L of saline transmurally into the stomach, followed by gentle massage of the stomach and the impacted mass. The impaction usually resolves within 12 to 24 hours. Treatment with bethanechol, 0.02 mg/kg SC every 6 to 8 hours to promote gastric emptying may be helpful in conjunction with these therapies. Bethanechol may have reduced effectiveness in a distended stomach, but it should not contribute to stomach rupture and therefore can be used safely.

Gastric impaction can also accompany grass sickness, in which case the prognosis for survival is poor. Grass sickness occurs in the United Kingdom and in areas of South America. The disease does not occur in the United States, but horses recently imported from the United Kingdom have been diagnosed with grass sickness in the United States.

32.37 GASTRIC RUPTURE

Gastric rupture occurs as a sequela to gastric distention from ingesta, fluid, or gas. The adult equine stomach can hold 20 to 25 L when maximally distended. Gastric rupture can occur from simple excessive distention, but also the integrity of the wall of the stomach may become compromised because of decreased blood flow. Distention of the small intestine has been demonstrated to significantly reduce mural blood flow, and this likely occurs in the stomach with distention. In some cases, it has appeared that rupture occurred as a result of an infarction of a portion of the stomach wall, without apparent substantial distention. Gastric perforation from ulceration happens rarely in adult horses. Because of extensive contamination of the peritoneal cavity with stomach contents, treatment is not possible and humane destruction of the horse is required.

32.38 ABSCESSES

Abscesses in the wall of the stomach are infrequent findings and occur most frequently in foals. Abscesses can form secondary-to-severe gastric ulceration, *Rhodococcus equi* bacteremia, foreign body penetration, or septic peritonitis. Signs of gastric abscessation are variable and similar to those of abscessation in other organs: fever, neutrophilia, hyperfibrinogenemia, anemia, weight loss, and possibly colic. Diagnosis may be made endoscopically, radiographically, or ultrasonographically. In some cases use of labeled WBC scintigraphy may identify an intraabdominal abscess in the region of the stomach. Usually by the time a diagnosis is made, the abscess is very advanced and often it is adhered to multiple abdominal viscera. Treatment should include long-term antimicrobial drugs, but outcomes are usually poor.

32.39 GASTRIC TUMORS AND MASSES

Gastric tumors, neoplastic and nonneoplastic, occur infrequently. Squamous cell carcinoma is the most common neoplastic disorder that affects the equine stomach (Fig. 32-30).[175] The tumor originates from the gastric squamous epithelium and can metastasize to the abdominal cavity and viscera and/or extend into the esophagus. It typically affects horses in their teens or older. Presenting signs include chronic weight loss, anemia, nasal reflux, or colic. Diagnosis can be made by gastroscopy, laparoscopy, barium contrast radiography, or peritoneal fluid analysis when the tumor has metastasized into the abdomen. Metastatic masses may be felt on rectal palpation. When the tumor obstructs the cardia, it is difficult, if not impossible, to pass a nasogastric tube, and saliva and ingesta accumulate within the esophagus. There is no effective therapy.

Primary gastric adenocarcinoma has been described, and metastatic lymphosarcoma, mesothelioma, and bile duct carcinoma have involved the stomach.

Nonneoplastic masses that have been observed in the equine stomach include *Draschia megastoma* masses, proliferative granulation tissue, and adenomatous masses in the antrum and pylorus. Rarely, proliferative squamous mucosa may appear as a mass attached to a stalk (Fig. 32-31). These can occur in a healing ulcer as an ulcer bed contracts while there is rapid proliferation of granulation tissue.

Fig. 32-30 Endoscopic view of a gastric squamous cell carcinoma.

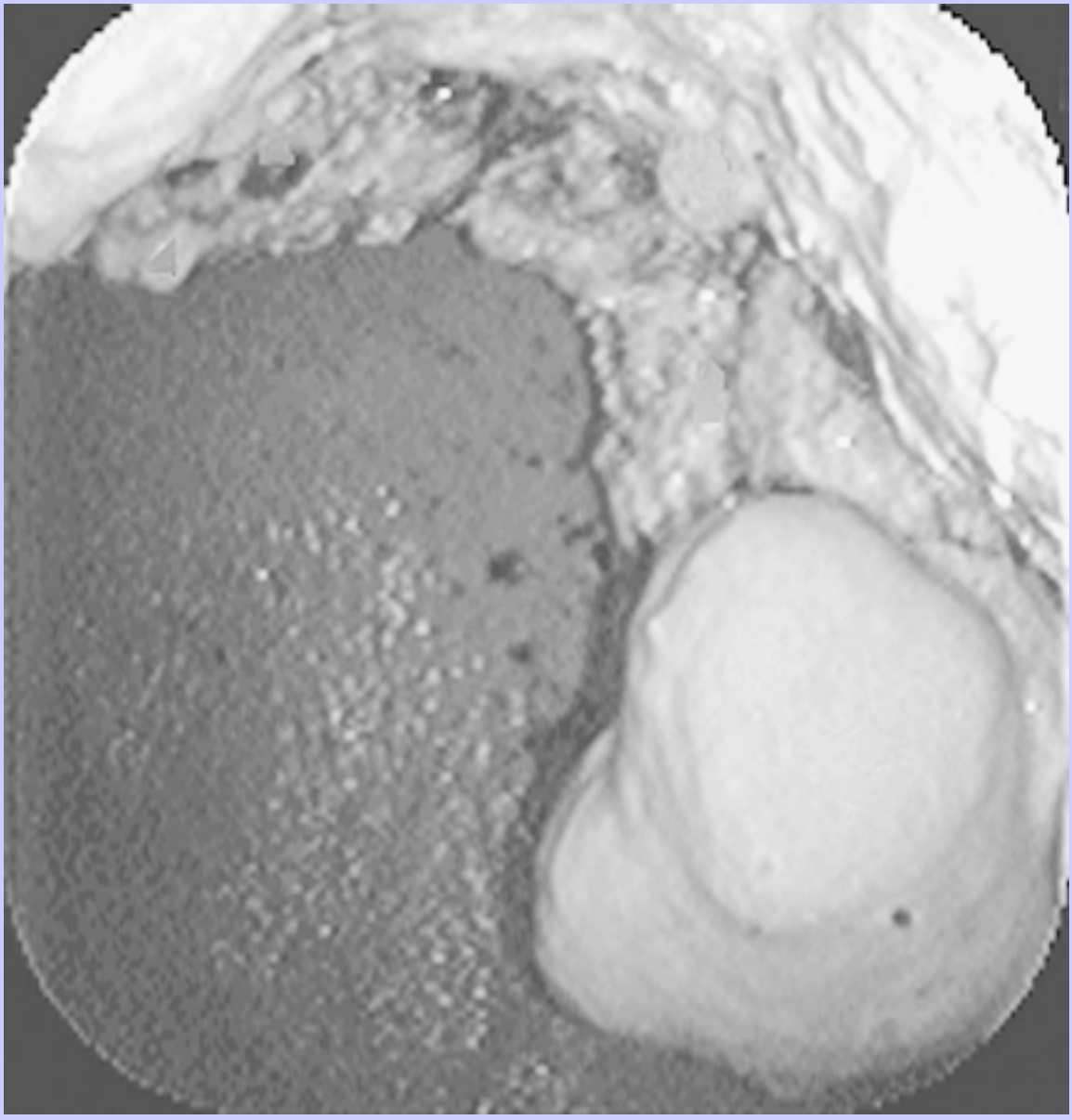
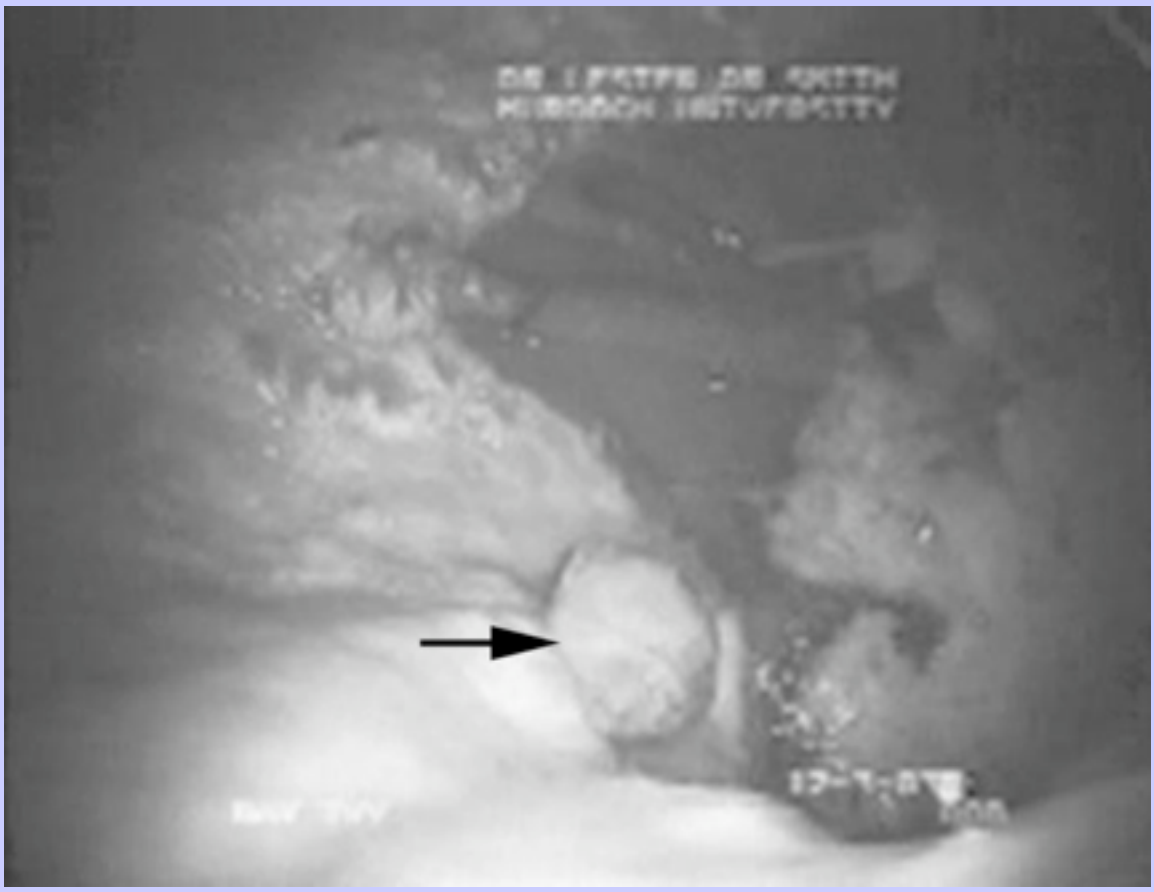


Fig. 32-31 Endoscopic view of the stomach of a horse in which there is a mass *(arrow)* protruding from the squamous mucosa along the lesser curvature. The mass appeared to be a proliferation of granulation tissue, around which margins of a healing ulcer had contracted. Photo courtesy of Dr. Guy Lester, Murdoch University, Murdoch, Western Australia.

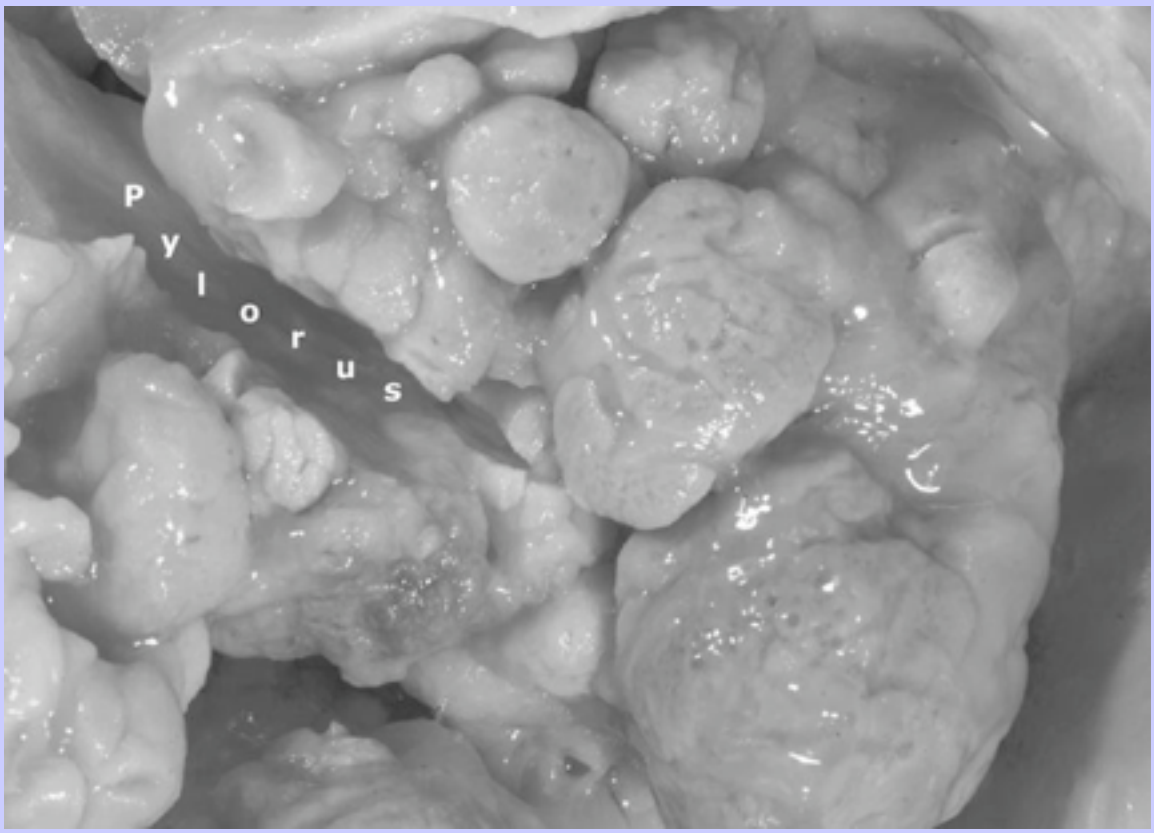


Adenomatous masses in the antrum and pylorus have been reported,[176] and I am aware of several more cases. These appear as large, irregular polypoid lesions (Fig. 32-32) and can obstruct most of the antrum. The cause of these lesions is unknown. Horses with these lesions have been presented with mild, intermittent colic. There is no effective treatment.

32.40 PYLORIC STENOSIS

Pyloric stenosis can occur secondary to chronic ulceration and fibrosis or muscular hypertrophy. The majority of cases occur as a result of chronic ulceration at the pylorus. I have diagnosed pyloric stenosis in foals, yearlings, and adult horses up to 20 years old.[177]

Fig. 32-32 Postmortem photograph of several masses in the pyloric antrum that were identified on histologic examination as gastric polypous adenomas. The masses almost completely obstructed the antrum and pylorus, and there was muscular hypertrophy of the pyloric canal, resulting in stenosis. Photo courtesy of Dr. Udo Hetzel, University of Liverpool, Liverpool, England.



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Diagnosis of pyloric stenosis is best made by endoscopy. Usually there will be active ulceration and inflammation, and the pyloric opening will appear small and fixed. If a biopsy forceps is pushed into the stomach lining at the pylorus, the wall of the stomach will appear to be rigid owing to scar tissue in the stomach wall. With primary muscular hypertrophy, no ulceration of mucosal inflammation should be present.

Treatment of pyloric stenosis caused by fibrosis from chronic ulceration is difficult. The fibrosis, and therefore the stenosis, may be permanent, although I have treated cases in which the pylorus became less rigid and more compliant when the primary ulceration and associated inflammation were resolved. The treatment objectives are to promote ulcer healing and enhance gastric emptying. Long-term acid-suppressive treatment may be required. In some cases vigorous debridement of the chronically ulcerated mucosa may promote generation of healthy granulation tissue, leading to ulcer healing. Gastric emptying can be promoted by bethanechol (0.02 mg/kg SC q8h or 0.35 mg/kg PO q8h).

If medical management is not effective, surgical bypass of the pylorus (gastroenterostomy) is indicated. Whereas pyloromyotomy has been effective in treating cases with primary muscular hypertrophy, the degree of fibrosis that is present in most cases precludes this approach.

32.41 INTESTINAL INJURY AND HEALING IN THE HORSE

Nathaniel A. White, II

There are numerous causes of intestinal injury during equine acute abdomen. Classic pathophysiologic explanations use ischemia, ulceration, and inflammation from infection, parasites, trauma, toxins, or immune complexes to categorize and explain intestinal injury. For the clinician, understanding the underlying pathophysiology of injury is important for recognition and treatment of horses with colic. For many of these intestinal disorders the signs can be similar, making clinical differentiation difficult.

Cellular injury was once characterized by the morphologic change it caused. The new paradigm includes cell injury, which is as much functional as it is structural. The response to a stimulus is mediated by numerous autocrine and paracrine messengers, which include cytokines, chemokines, prostaglandins, neuropeptides, and proinflammatory substances such as interleukins (ILs), tumor necrosis factor alpha (TNF-α) complement, histamine, bradykinin, serotonin, and interferon (IFN).[178–180] In the intestine, inflammatory responses to these messengers can be orchestrated by mucosal cells, fibrocytes, macrophages, mast cells, endothelial cells, neurons, muscle cells, and polymorphonuclear cells.[178] The chain of events is complex, with the relationship of all the different cell responses not yet fully understood. It is clear that the inflammatory response from any insult initiates a multitude of chemical and immune reactions, which, depending on the severity of the insult, can cause both local and systemic effects.

Several mechanisms can stimulate an inflammatory response, including ischemia, reperfusion after ischemia, inflammation from bacterial or viral infection, and inflammation from parasites, trauma (surgical), or toxins. The resulting tissue injuries vary and may be differentiated by their effect on the different layers of the intestine and by the vascular and nervous response. Though the mucosa or serosa is often affected first, the inflammatory response frequently involves the remaining layers of the intestine, the submucosa, and smooth muscle. The inflammatory response may also vary depending on the specific cause. For example, ischemia can be caused by strangulation of the blood supply, distention of the intestinal wall, or poor perfusion resulting from systemic shock. Although the response of individual intestinal cells may be similar for each, each stimulus appears to evoke different sequences of cell response, thereby causing different clinical signs and varying response to treatment. In some instances injury to the intestine may be secondary to another disease process, but the damage to the intestine can still initiate a systemic response resulting in a systemic inflammatory response syndrome (SIRS) with multiple organ failure.

32.42 INTESTINAL INFLAMMATION: GENERAL CONCEPTS

The cascade of events initiated by infection or ischemia has been extensively studied. Inflammatory mediators increased during bowel inflammation are released from numerous cell types, including mucosal cells, endothelial cells, fibrocytes, myocytes, mesothelial cells, and neurons.[178] There is also evidence that the compounds making up the tissue ground substance and cytoskeleton can also initiate an inflammatory response and help transmit signals or cells between immunocytes and afferent neurons. Theoretically all cells in the intestine can act as effector cells, both producing cytokines to send messages to other cells and being activated to respond to the insult by chemokines.[178,180,181] Cytokines, growth factors, and adhesion molecules can all initiate an inflammatory

response.[178,179] This response also alters cell apoptosis, resulting in delayed removal of mucosal cells and neutrophils or early death of immunocytes or specific cells in organs.[182] Cytokines such as IL-1β and TNF-α, platelet-activating factor (PAF) complement (C5a), IFN-γ, and histamine are all reported to be involved in inciting intestinal inflammation.[183] Describing all the effects and interactions of the inflammatory cytokines and eicosanoids is beyond the scope of this chapter, but it is apparent these substances can stimulate and inhibit the inflammatory reaction by directing cell communication and cell response to injury. As a result the disease process should be viewed as a sequence of altered cell functions, which are integrated and designed to protect the intestine from permanent injury.

The cells primarily observed to take part in intestinal injury are mucosal cells, endothelial cells, neurons, fibroblasts, mast cells, eosinophils, neutrophils, and macrophages. Rather than responding independently, these cells likely all respond to the initial insult, each with its inherent cytokine production or cell activation, which stimulates or suppresses other cell responses. Envisioned as a group acting simultaneously, the sequence likely proceeds from an initial stimulus to mucosal or serosal cells or in the case of ischemia the vascular endothelium or enteric neurons.

Mucosal cells react by releasing cytokines to activate macrophages and lymphocytes in the lamina propria.[181] These cells release cytokines and adhesion molecules, which in turn activate other cells while initiating local defenses. Simultaneously, endothelial cells respond to the cytokine message by releasing cytokines to attract neutrophils and eosinophils and subsequently enable them to migrate through the endothelium into the interstitium. Afferent neurons detect cytokine increases and initiate neuropeptide, cytokine, or eicosanoid release from the efferent neurons, resulting in activation of numerous cells including those already activated by the initial cell messengers.[184–188] Fibrocytes, responding to the initial cytokine messages and growth factors, subsequently release 702
cytokines and growth factors such as Il-1α, Il-1β, TNF-α, transforming growth factor, and platelet-derived growth 703
factor. All can be proinflammatory or can help to repair the mucosa.[189,190] Metalloproteinases released in response to inflammatory cytokines alter the basement membranes and collagen in the different layers, allowing migration of cells to the extracellular space and stimulating other cells to release chemoattractants.[178] Muscle cells, once thought to be neutral in the inflammatory cycle, appear to be able to release cytokines, thereby participating in the inflammatory reaction.[178,191] Increased adhesion molecule production in the muscle after surgical manipulation has been linked to neutrophil infiltration and subsequent bowel dysfunction.[192–194]

Although all the cells in the intestine participate in the inflammatory response as effector cells, they can also act as suppressors. Each appears to communicate with other cells locally to cause or suppress the inflammatory response. Production of nitric oxide by endothelial cells can reduce neutrophil adhesion, whereas increased release of growth factor by fibroblasts and the vascular endothelium speeds healing of the mucosa.[189] The response to receptor activation can take only seconds to minutes to upregulate cytokine production. Lack of suppression, perhaps because of chronic or overwhelming stimulation or severe damage to cells, which release the inhibitor messengers, allows amplification of inflammation and permanent cell damage.

The role of each cell type as effectors and messengers is slowly being unraveled. The role of some cells is better understood than that of others. Reperfusion, cytokines, and complement initiate endothelial cell changes. Subsequent production of cytokines and prostanoids by endothelial cells attracts neutrophils and macrophages.[195] Endothelial cells also stimulate the inflammatory response by altering capillary permeability, promoting neutrophil adhesion, and altering blood flow. The interaction between the endothelial cell and neutrophils or eosinophils is a pivotal response in causing intestinal injury. This response is made possible by PAF, leukotrienes (LTB_4), and adhesion molecules produced by endothelial cells and neutrophils.[180,195] Neutrophil migration into affected tissues

subsequently causes severe damage including damage to cells and tissue ground substance, which further promotes the inflammatory response.

Although all intestinal cells can be involved in the inflammatory process, the nervous system is now known to be integral in the inflammatory response. Release of potassium, adenosine triphosphate (ATP), bradykinin, and prostaglandin E_2 all stimulate afferent neurons.[184,196] Neuropeptides released from neurons in response to afferent signals caused by products of cell injury including cytokines, eicosanoids, and histamine.[184,197] Substance P, neurokinin, calcitonin gene-related protein (CGRP), and vasoactive peptide (VIP) have all been found increased levels in inflamed tissues, suggesting that they act as messengers to histiocytes or immunocytes, which subsequently release cytokines.[184,186] The paracrine response differs in different tissues, but inflammatory responses by mast cells, neutrophils, T cells (cytokine release), B cells, macrophages, fibroblasts, and muscle cells are in part caused by neuropeptide stimulation. The coordination of this response is not totally understood, but neuropeptides serve as proinflammatory mediators or suppressors.[188,198] This system allows for immediate response of cells to a stimulus without humoral involvement and likely can cause persistent inflammatory reactions in response to inflamed tissue.[184]

Local inflammation of the intestine is known to cause changes in other organs distant to the intestinal damage, specifically the lung.[199] Circulating cytokines and activated neutrophils rapidly initiate an inflammatory response in the lung after intestinal inflammation. This response is well known in experimental models and humans but has not been reported during intestinal disease in the horse. Other organs are likely affected, creating signs of multiple organ involvement as part of SIRS.[200]

32.42.1 Ischemia and Reperfusion

Ischemia is a deficiency of blood flow in tissue or an organ. The lack of energy production in the cell starts a degenerative process. Within 5 minutes there are alterations in mitochondria, characterized by swelling and disorganization of cristae.[201] Mitochondrial changes precede cytoplasmic and membrane changes, which occur in the first 30 minutes by activation of phospholipases, cytokine production, and accumulation of arachidonic acid. If ischemia persists, the cell degradation continues with failure of the membrane ion pumps, allowing calcium to move into the cytoplasm.[202] This calcium accumulation within the cell activates proteases, which cause cell membrane damage and nuclear clumping. Calcium uptake in the mitochondria is increased, which inhibits oxidative phosphorylation, thereby decreasing the cell's source of energy.[202]

In the intestine, microscopic changes become evident at 30 minutes when the mucosal epithelial cells and serosal mesothelial cells separate from their basement membranes.[203] This appears to be a mechanical separation caused by water movement from the vasculature into the subepithelial space. Metalloproteinases may also be involved in altering the basement membrane. The space, created by the initial separation, named *Grunehagan's space*, occurs at the tip of the villus in the small intestine (Fig. 32-33).[203] If ischemia continues, the cell damage progresses as the mucosal cells progressively slough off the lamina propria toward the intestinal crypts (see Fig. 32-33). The change is similar in the colon, with epithelial cells sloughing off the surface of the mucosa (see Fig. 32-33). However, the slough is somewhat slower in the colon as it proceeds into the crypts. The serosa reacts in a similar fashion, with mesothelial cells lifting off the basement membrane before there is visible cell membrane or cytoplasmic change. Other than vascular congestion, there is minimal change in the architecture of the supporting tissues in the mucosa or the serosa for the first 60 minutes of total ischemia. After 180 minutes of

ischemia the lamina propria and mucosal vascular tuft have lost their architecture. The tissue is necrotic and becoming homogeneous, with lack of nuclear definition and cell structure.

Estimating the time required to create ischemic lesions depends on the experimental methods used. Different types of anesthesia in the horse and other animals have resulted in different rates of mucosal degeneration during ischemia. For example, experiments using animals anesthetized with inhalant anesthetics are different from those that required animals breathing air, most likely from higher tissue oxygen concentrations at the beginning of the experiment.[203–205] Also, some cell types, such as muscle, appear more resistant to ischemia, which probably depends on the intracellular energy reserves of the cells. There are also differences in the response to low-flow ischemia versus total arteriovenous obstruction. Nevertheless, lesions caused by ischemia progress with reperfusion.

If reperfusion—either resumption of blood flow or increased flow after low-flow conditions—occurs while cells are still viable, a cascade of events is set in motion by the delivery of oxygen to the previously ischemic tissue.[195,206] The resultant injury is called *reperfusion injury* and relies on renewed oxygen in the tissue, with participation of endothelial cells and afferent receptors to create the subsequent inflammatory response. Although it makes sense that oxygen is needed to resuscitate the previously ischemic cells, the innate defense system in many cell types is to respond to the ischemic change with an inflammatory response. This response appears to help initiate a defense against bacterial invasion and is aimed at removing the damaged cells from the system. If enough cells have been damaged, the reperfusion effect can cause enough inflammation to prevent cells from surviving, thereby delaying healing.

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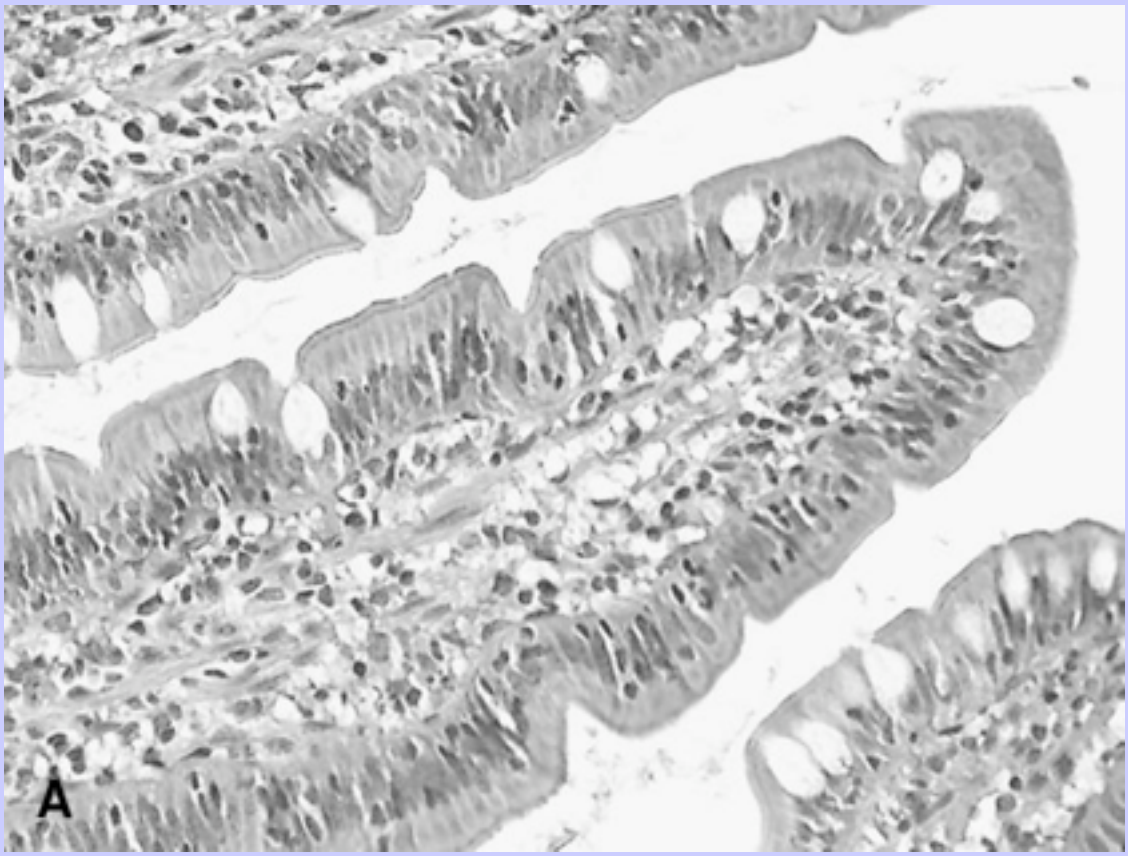
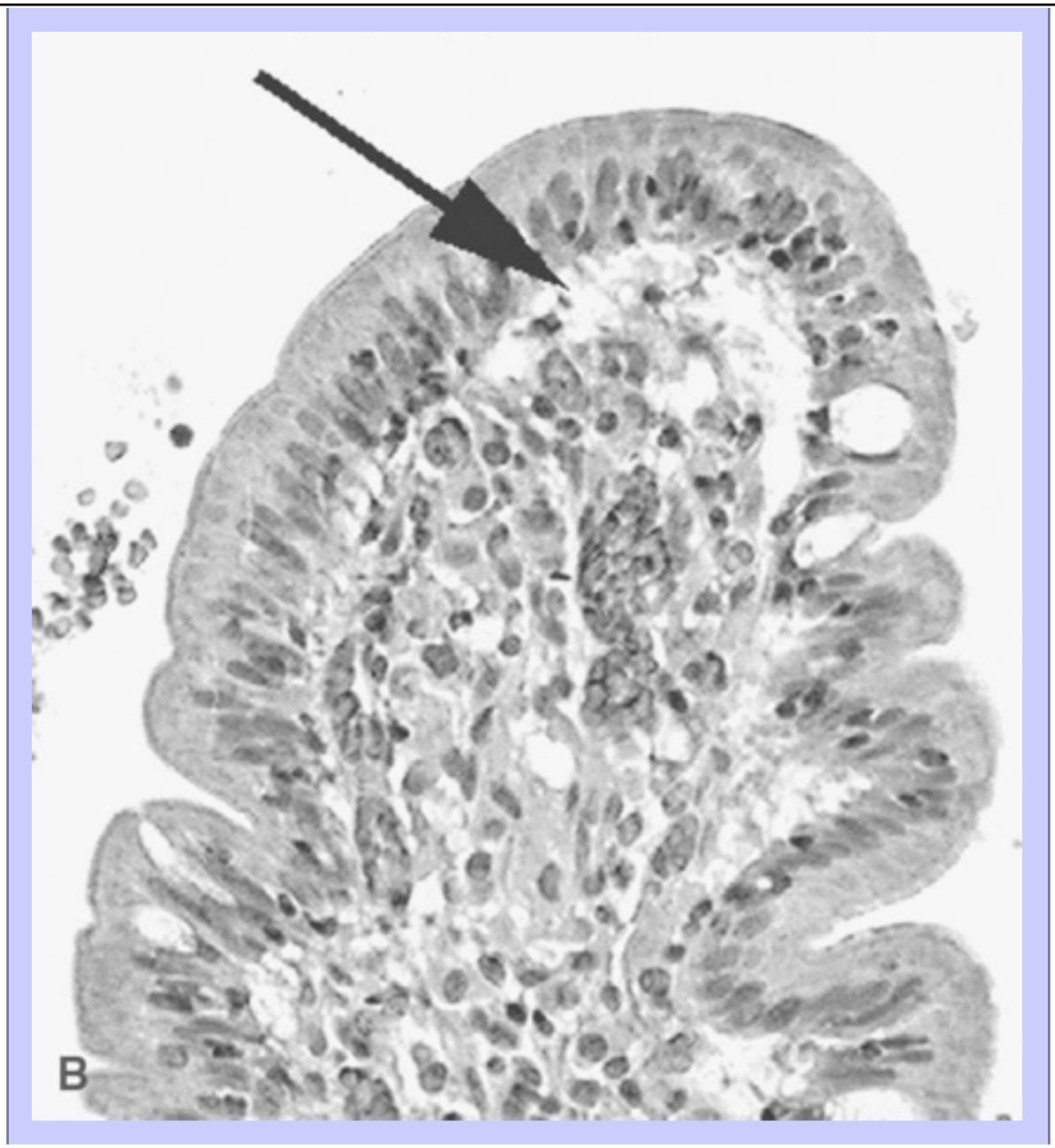
Fig. 32-33 Photomicrographs of **A**, normal small intestinal villus (hematoxylin and eosin stain [H&E]); **B**, grade I epithelial lesion with formation of Grunehagen's space *(arrow)* at the top of the villus (H&E); **C**, grade III lesion with mucosal slough off the sides of the villus (H&E); and **D**, mucosal slough and red blood cell accumulation in the mucosa caused by venous strangulation obstruction of the small intestine (H&E).

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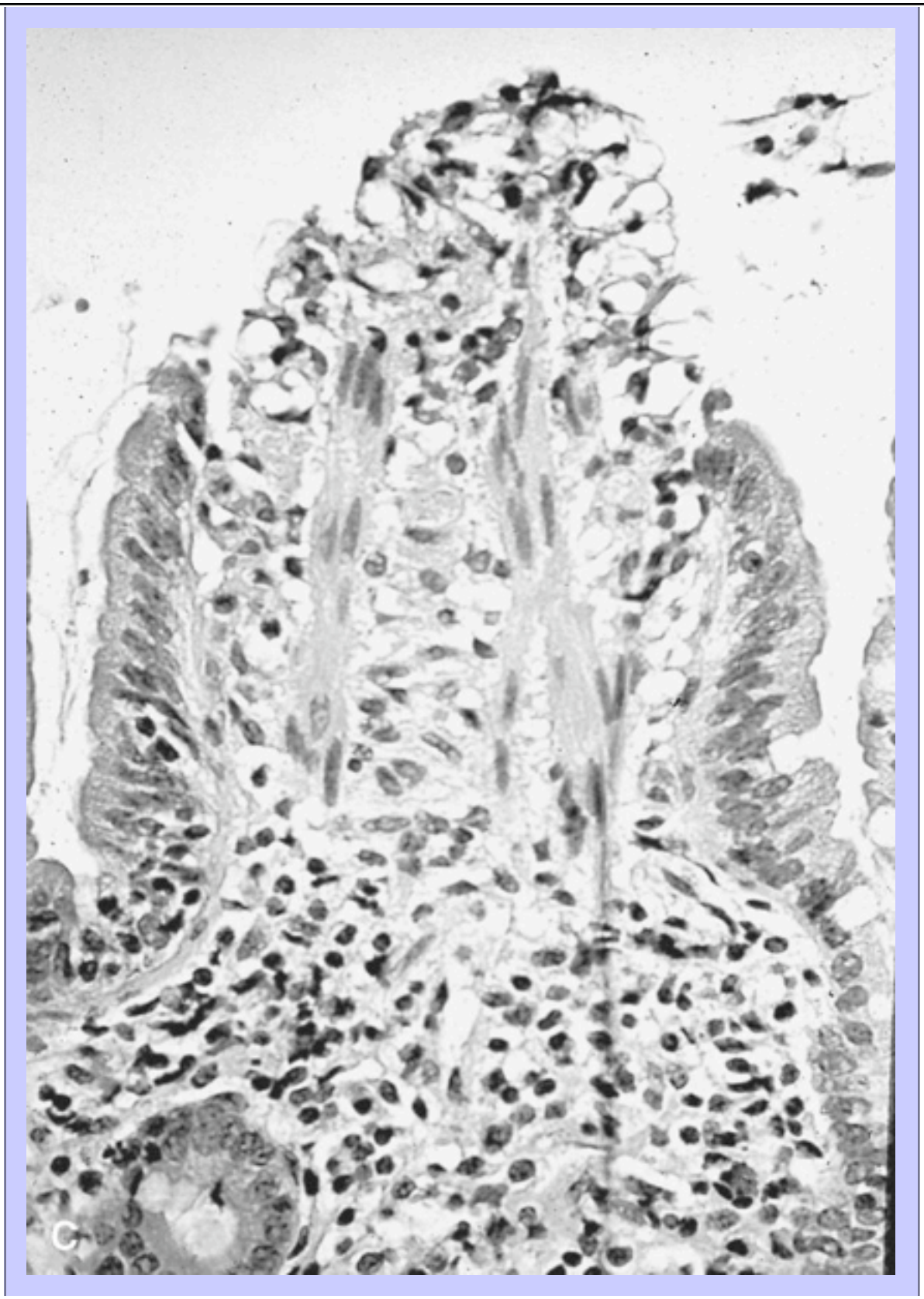

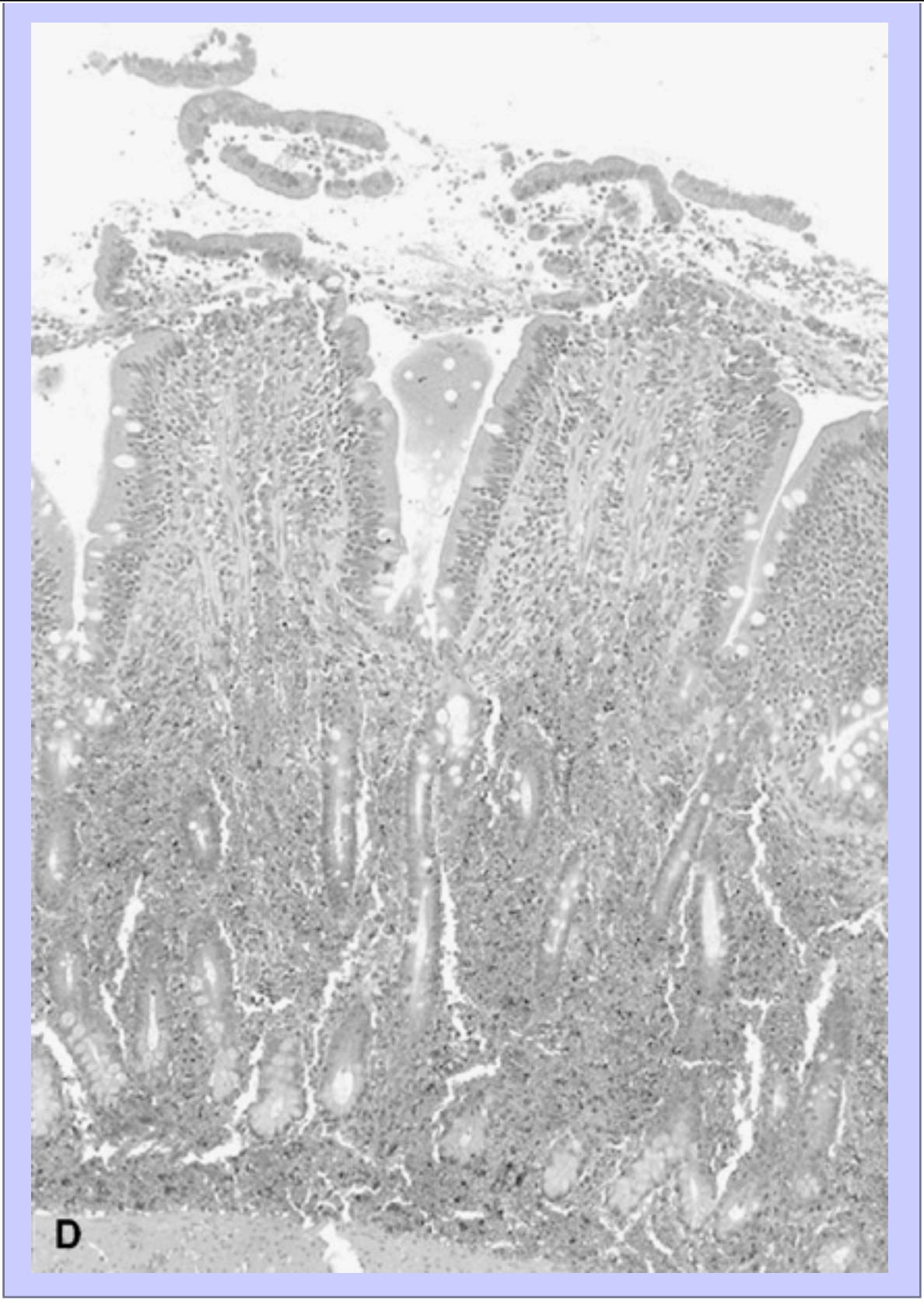
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Reperfusion injury starts as a change in intracellular metabolism in previously ischemic tissue. It does not require exposure to a microbe or toxin, but it does rely on cell production of cytokines and leukotrienes as signals to numerous blood and tissue cells required to complete the process. One primary initiator of reperfusion injury in the intestine is the production of oxygen radicals (O_2•). Oxygen has the ability to take on an extra electron during enzymatic processes in the cell. Most cells including endothelial cells and the small intestinal mucosal cells contain xanthine dehydrogenase, which when converted to xanthine oxidase catalyzes hypoxanthine to xanthine.[206] Hypoxanthine is increased in the cytoplasm of cells during ischemia. Calcium and proteases initiate xanthine dehydrogenase conversion to xanthine oxidase, a process that can be stimulated in endothelial cells by IL-1, TNF-α, and C5a, as well as neutrophil adherence. Oxygen is used in the reaction and ends up with an extra electron, making an O_2• or superoxide.[205]

Once released, O_2• can initiate a number of chemical reactions that cause cell membrane damage directly and by stimulating phospholipase activity. During O_2• production nitric oxide (NO) production is decreased, thereby allowing neutrophil adhesion and migration. Superoxide interaction with iron or catalase causes production of hydroxyl radicals (OH•) or hydrogen peroxide (H_2O_2) respectively. Both are cytotoxic. The OH• alters or destroys cell membranes. Affected cells rapidly express cytokines and leukotrienes, which act as chemoattractants for neutrophils. After the initial free radical production, cell injury progresses as two main events. Calcium, already increased in the cell, increases further, effectively blocking further energy production in the mitochondria and activating proteases, causing further degradation of the cell nucleus and cytoplasm.[202] Second, radicals formed from molecular oxygen can cause cell membrane damage, thereby initiating a similar cellular response. The formation of chemical mediators takes only seconds to minutes after reperfusion and rapidly sets the inflammatory cascade in motion.

Although the mucosal cells and serosal mesothelial cells are damaged early in ischemia and are able to release cytokines to alert other cells locally, endothelial cells appear to be the primary initiators of reperfusion injury.[179] They participate in cytokine production and are involved with neutrophil adhesion and migration from blood into tissues. Endothelial cells are also involved with the changes in blood flow after reperfusion.[188] The platelets and neutrophils accumulate in and obstruct capillaries, altering blood flow. Endothelial cell swelling or contraction causes constriction of blood vessel lumens (Fig. 32-34). Changes in endothelial cells in response to histamine, complement, leukotrienes, and PAF increases capillary permeability, allowing fluid and protein to move into the interstitium.[188] Even though the metabolic state of the tissue during initial reperfusion initially results in overall increased blood flow, the increased vascular permeability increases interstitial pressure, causing capillary collapse. Combined with endothelial cell change, vascular constriction and collapse of the tissue vasculature results in a "no-reflow phenomenon," promoting further tissue ischemia.

Endothelial cell membrane changes allow expression of adhesion molecules and receptors, which are necessary for neutrophil adhesion and migration through the capillary and venule endothelium (Fig. 32-35). This migration of neutrophils causes the most prominent inflammation in the tissue, because activated neutrophils release elastase, oxygen radicals, and other serine proteases, which attack collagen, ground substance, and cell membranes.[207] The respiratory burst, a buildup of oxygen free radicals in neutrophils during activation, is responsible for most of the inflammation and tissue damage seen during reperfusion. It is also apparent that reperfusion injury can expand the initial injury into the surrounding viable tissue and that it can cause irreversible tissue damage.[208–210] Reperfusion injury can also cause injury distant from the local damage and has been observed in the lung because of cytokine and activated neutrophil circulation.[211] Although not reported in

the literature, the resulting lesion can be seen in the lungs of horses that succumbed to severe intestinal strangulation, obstruction, and shock.

Cell necrosis is recognized as a pathologic feature during ischemia and reperfusion. Recently, however, alterations in apoptosis (programmed cell death) have been found to increase during ischemia and reperfusion in experimental studies of the heart, brain, liver, adrenal glands, kidney, and intestine.[212–214] Alternatively, epithelial cells undergoing hypoxia and reoxygenation modulate neutrophils to delay apoptosis, suggesting a role in initiating SIRS.[215] Significantly increased apoptotic cells in muscle, mucosa, neurons, and glia in naturally obstructed or strangulated equine intestine suggests apoptosis is stimulated by and may promote the inflammatory response.[216,217] Apoptosis is also increased in intestine distant to the primary lesion, supporting systemic stimulation by cytokines.[218] The amount of apoptosis observed in experimental animals and in horses with intestinal obstruction suggests this process is excessive during reperfusion and may result in both morphologic and functional changes.

The importance of oxygen radical generation as a mechanism of injury in strangulating lesions has been questioned in the horse.[219] However, both clinical signs and lesions from clinical cases suggest that intestinal damage progresses after reperfusion. Use of a low-flow to no-flow model of ischemia with subsequent reperfusion responded to treatment to counteract injury from superoxide production and neutrophil accumulation.[220] This suggests that free radical production is part of the cascade of events causing an inflammatory response in the small intestine after bowel strangulation. Lack of malondialdehyde and conjugated diene production in the large intestine suggests less of a role for tissue-generated oxygen radicals and that reperfusion injury is primarily caused by the oxygen radical release from migrating neutrophils as seen in xanthine oxidase—deficient rats.[207,221,222]

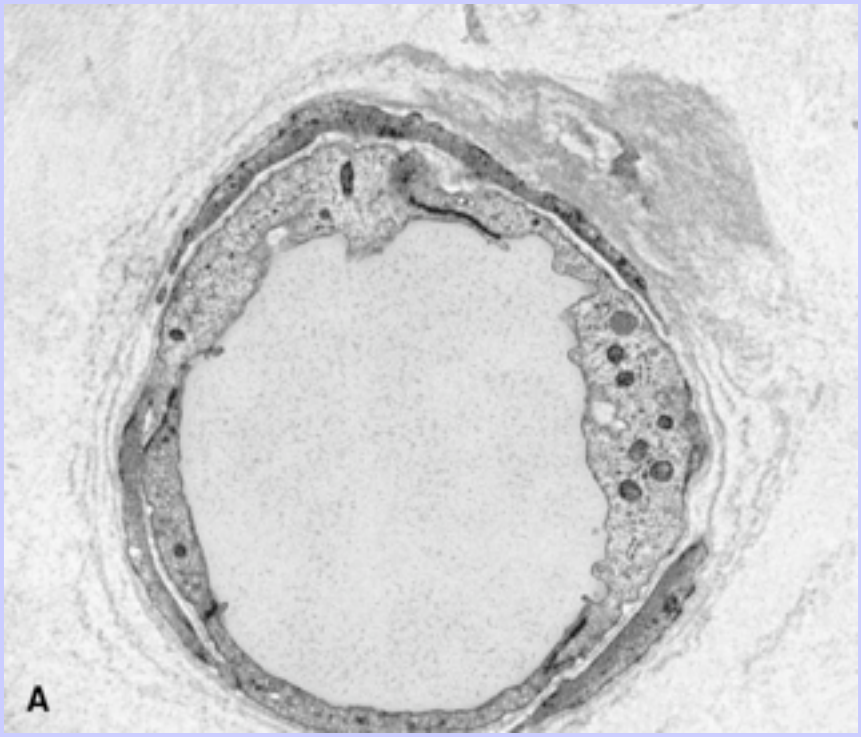
Recent research suggests that endothelial cells are not the only cells that act as “local effectors” of inflammation during reperfusion. Signs of inflammation are present in all parts of the intestine including the muscle and myenteric plexus.[191,223–225] Alterations in muscle mitochondrial morphology have been identified in equine jejunum after low-flow ischemia.[226] Similarly, during large colon volvulus the neurons in the myenteric plexus undergo degeneration and decrease in number compared with normal conditions.[224] Evidence of ischemic injury and inflammation occurs in both muscle and myenteric plexuses. This is relevant in horses with colon volvulus, in which survivors had significantly more neurons than nonsurvivors.[224] Perhaps of greater importance is the long-term effect of the inflammation in the myenteric plexus after ischemia and reperfusion. One can speculate that the high rates of repeat colic episodes in horses after colon torsion or large colon impaction are related to damage to the enteric nervous system.[227]

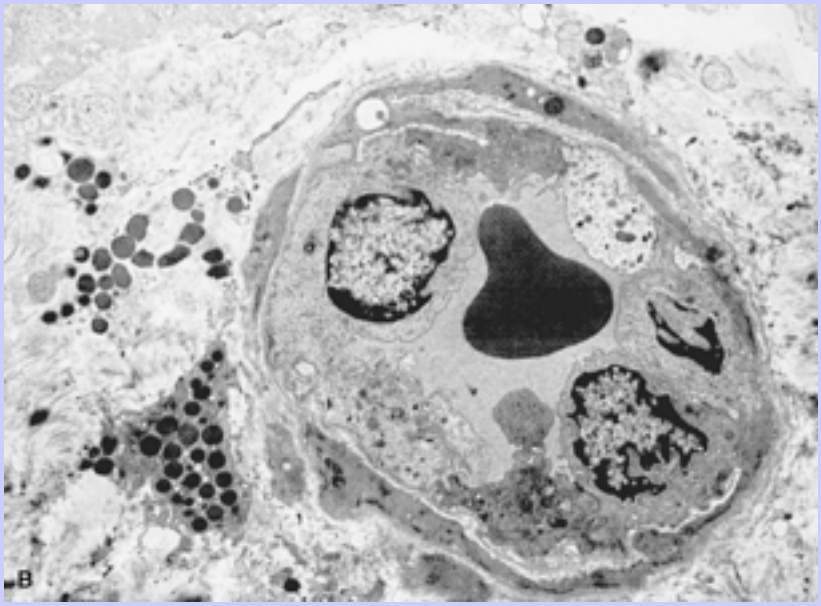
Reperfusion injury occurs after low-flow and no-flow ischemia. These models appear to emulate the clinical event, although the onset of ischemia in strangulation obstruction most likely starts as low-flow progressing to no-flow ischemia. Although the time frame of reperfusion injury is somewhat understood from the experimental models, the functional effects of dynamic events set in motion by reperfusion such as “no reflow” as well as persistent inflammation in the serosa and around the intestinal nerve ganglia are not well understood. The relevance of these myenteric plexus lesions is also questioned, because they do not always correlate with severity of clinical signs.[224]

32.42.2 Low-Flow Ischemia

The effect of ischemia-reperfusion differs with the type of ischemia. Low-flow ischemia is defined as flow less than 25% of normal blood flow. At this flow rate, vascular and cell damage is minimal, with degeneration occurring over a long time period. When normal flow is returned by increasing vascular volume or release of the arterial obstruction, there is a hyperemic response doubling the normal blood flow to the affected intestine.[226] Cell damage accelerates during reperfusion, with marked changes in vascular permeability, mucosal damage, serosal damage, and signs of fluid accumulation in the submucosa, muscle, and serosa.[206,226,228,229] Edema in the submucosa and serosa causes vascular collapse, leading to decreased blood flow and eventually a "no-reflow" phenomenon in the serosa and mucosa, with flow to the affected segment decreased below normal.[230,231] The decreased flow is partially caused by endothelial cell swelling and neutrophil margination in the vasculature. Neutrophils migrate into all tissues but predominately the mucosal and serosal layers. As neutrophils migrate through the capillary or venule, they accumulate around the vessels. As reperfusion progresses, the greatest injury is observed in the serosa, with marked accumulation of neutrophils beneath the serosal basement membrane. Although neutrophil accumulation is most marked in the serosa, neutrophils can be found in all layers of the intestine. This type of low-flow ischemia is rarely documented in equine abdominal disease, but it likely exists in distended intestine in which there is low flow to the affected bowel wall. The flow is directly related to the intraluminal pressure, with pressures causing greater than 50% reduction in blood flow common in severe small intestinal distention.[232]

Fig. 32-34 Transmission electron photomicrographs of small vessels in the serosa (**A**) with normal endothelial cells before ischemia and (**B**) with swollen endothelial cells and accumulation of neutrophils narrowing the vessel lumen during reperfusion.





When examined in experimental models or when observed in clinical cases, most of these changes from acute low-flow ischemia are reversible and the affected intestine survives and heals. The effect varies greatly and is dependent on the length of ischemia. It is suspected that function is compromised temporarily, resulting in ileus, endotoxin absorption, or enteritis with excess secretion.[233] In the small intestine serosal scarring and adhesions are the most common long-term result and may increase the risk of colic episodes in the future. Even if lesions are not grossly evident and appear minor on microscopic examination, horses with colic, particularly those requiring surgery, likely have intestinal injury, which can ultimately result in permanent intestinal dysfunction. Hypothetically this is one possible reason for increased risk of colic after previous colic episodes or previous surgery for colic.[227,234]

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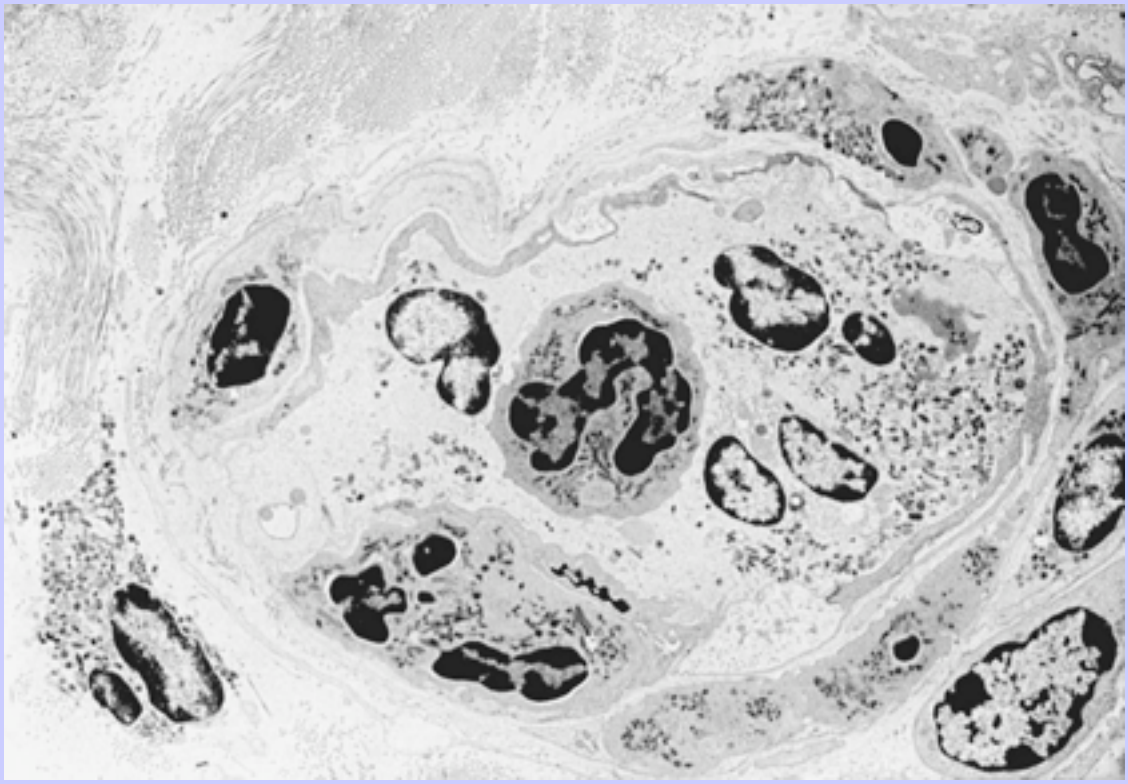
Fig. 32-35 Transmission electron photomicrograph of neutrophils adhering to the endothelium and accumulating in the perivascular space after migrating through the endothelium.



Nonstrangulating infarction is the classic example of low-flow ischemia. In the horse, thromboembolic colic is reported to be caused by thrombosis of the mesenteric artery and its branches in horses infected with fourth stage larvae of *S. vulgaris*.[235] The mechanism of infarction is most likely reduction of blood flow from a thrombus in the artery or thromboembolism obstructing the peripheral vasculature. In nonstrangulating infarction the intestinal injury most likely results from long-term low-flow ischemia or low-flow ischemia with episodes of reperfusion injury. In clinical cases the injury is severe, often resulting in necrosis in all layers of the bowel, with obvious infarction.

Low-flow ischemia may also occur during shock.[194] Intestinal injury in bowel not directly involved in the primary lesion is suggestive that this injury is frequently present in horses with bowel strangulation obstruction.[194] In horses with obstructing or strangulating lesions, biopsies from nonaffected, grossly normal intestine have evidence of some degree of bowel injury including neutrophil infiltration.[209,210,216,236] Endotoxin administration also caused an inflammatory reaction in the intestines, with loss of mucosa and neutrophil infiltration in the mucosa.[237] This may be relevant to assessing horses in shock.

32.42.3 Total Arteriovenous Occlusion

Total ischemia caused by arteriovenous occlusion causes total vascular stasis. The most common cause of this form of ischemia is the mesenteric infarction caused by incarceration of bowel in hernias or constricted spaces. Early in the occlusion, capillary congestion is observed in all layers of the intestine. The intestine undergoes degeneration as previously described for ischemia. When total ischemia exceeds 2 hours in the small intestine and 3 hours in the large colon, the tissue changes during blood flow occlusion are extensive, and cell necrosis may preclude a response to reperfusion.[203–205,238–241] If the capillary damage is not too extensive during total ischemia, reperfusion causes further degeneration including mucosal cell loss, increased edema, and neutrophil migration (see Fig. 32-33). However, oxygen radical production seen with low-flow ischemia and reperfusion may not be responsible for the continued damage during total arteriovenous occlusion.[242] Furthermore, these events cannot be separated from the systemic shock, which can be cause secondary lesions seen in intestine distant to the lesion.[209] Despite the questions about the validity of reperfusion in the total ischemic event, continued intestinal injury during reperfusion is seen in both the small intestine and the large colon after total ischemia.[203,208,243] The epithelial cell loss after reperfusion is progressive and is likely caused by either countercurrent exchange creating a decreased oxygen concentration in the distant mucosa or by inflammation resulting from oxygen radical—induced inflammation from neutrophil activation.[207,223,244] The response in the serosa includes marked edema with initiation of neutrophil migration. Eventually a massive collection of neutrophils fills the outer border of the serosa.[245,246] During this type of ischemia and reperfusion, the damage from the inflammatory reaction can continue for days and if severe enough can prevent healing of the mucosa and serosa and is consistent with persistent ileus and shock.

32.42.4 Venous Occlusion

Venous obstruction without arterial obstruction causes increased pressure at the capillary, resulting in decreased blood flow and RBC and fluid extravasation into the interstitium. The result is separation of the tissues with an increased diffusion distance for oxygen and nutrients. The RBC accumulation causes tissue damage, and if it is severe enough a continuation of cell hypoxia becomes irreversible even with reperfusion. Injury during venous obstruction appears more severe than observed during subsequent reperfusion.[247] Small intestine can survive 2 hours of venous obstruction, although the resultant degeneration is severe and the intestine permanently scarred after healing.[204] The gross lesion is marked with obvious thickening of the bowel, which at first is red and eventually purple. With time the color turns black or green with subsequent necrosis and alterations in hemoglobin.

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Based on both experimental work and observations in clinical cases, irreversible death of a segment of the intestine occurs after 2 hours in the small intestine and 3 hours in the large colon, although this obviously varies depending on the amount of residual blood flow to the affected tissue.[204,205,239] For the surgeon venous

occlusion is the most difficult type of lesion to assess, as intestinal thickness or amount of hemorrhage may not correlate with viability. Recent reports of survival of horses with hemorrhagic lesion at surgery suggest that this injury can be reversed more readily than a lesion caused by total arteriovenous occlusion. The sequence of mucosal degeneration remains the same in this type of ischemia, making the biopsy the most reliable method for determining if the intestine can survive and heal.[205]

32.42.5 Distention

Although distended intestine may appear to have normal color and motility after decompression, alterations in blood flow in the wall of the distended intestine are a form of low-flow ischemia. During intestinal distention intraluminal pressure causes collapse of the veins and capillaries, thereby decreasing the vascular capacity. This occurs even when blood pressure is normal. When small intestinal pressure is increased to 18 cm of water, as previously measured in clinical disease,[248] mesenteric blood flow to the intestine is decreased by at least 50%.[232,249] Increasing capillary back pressure while maintaining arterial pressure alters Starling forces in the intestinal wall. The result is secretion of fluid from the vasculature even with an increase in wall tension. Water and some protein escapes into the interstitium, causing submucosal and serosal edema. At higher intraluminal pressures there is more secretion than absorption of water, creating a cyclic increase in intraluminal pressure after bowel compliance has reached its limit.[250] Fluid and eventually protein leaks through the serosa into the peritoneal cavity.

If the pressure is maintained, intestinal compliance allows blood flow to gradually increase, acting as a form of reperfusion. Serosal and submucosal edema progresses during the period of distention. The mucosal and serosal lymphatics dilate, and RBCs and WBCs migrate into the serosa and submucosa (Fig. 32-36). There is minimal mucosal injury at pressures seen in clinical cases during simple obstruction of the small intestine or colon.

Subsequent decompression of the bowel causes reperfusion with a hyperemic response similar to that seen after low-flow or total ischemia. Blood flow to the affected bowel can initially double, but this effect is temporary, with subsequent blood flow decreasing below normal.[232] The mucosa appears relatively resistant to short-term distention, whereas the edema in the serosa causes capillary closure and increased vascular permeability. Serosal edema increases and more neutrophils migrate into the serosa, causing destruction of collagen and ground substance.[232,245] Intestinal smooth muscle is also affected with edema, and neutrophil migration is evident in the fascial planes around the myenteric plexuses (Fig. 32-37). Although bowel can frequently heal after this type of ischemic insult, the serosa is often thickened by fibrous tissue with the possibility of adhesion formation and mesenteric constriction.[251] The mucosa appears relatively resistant to the low-flow ischemia experienced with bowel distention, but the response is time dependent. Rarely does prolonged distention cause bowel necrosis. Bowel wall necrosis is more common when foreign bodies or impactions cause focal distention. Because the response to distention is both time and pressure dependent, the time frame for permanent damage is difficult to determine. The small intestine is more susceptible to distention injury compared with the large colon. Clinical measurement of intraluminal pressure during obstruction indicates that the large colon can tolerate at least twice the distention pressure with no adverse effects.[252,253]

Fig. 32-36 Photomicrograph of edema, lymphatic dilatation, and RBC and WBC accumulation in the serosa after 18 cm H_2O distention for 2 hours and reperfusion for 1 hour. Hematoxylin and eosin stain.

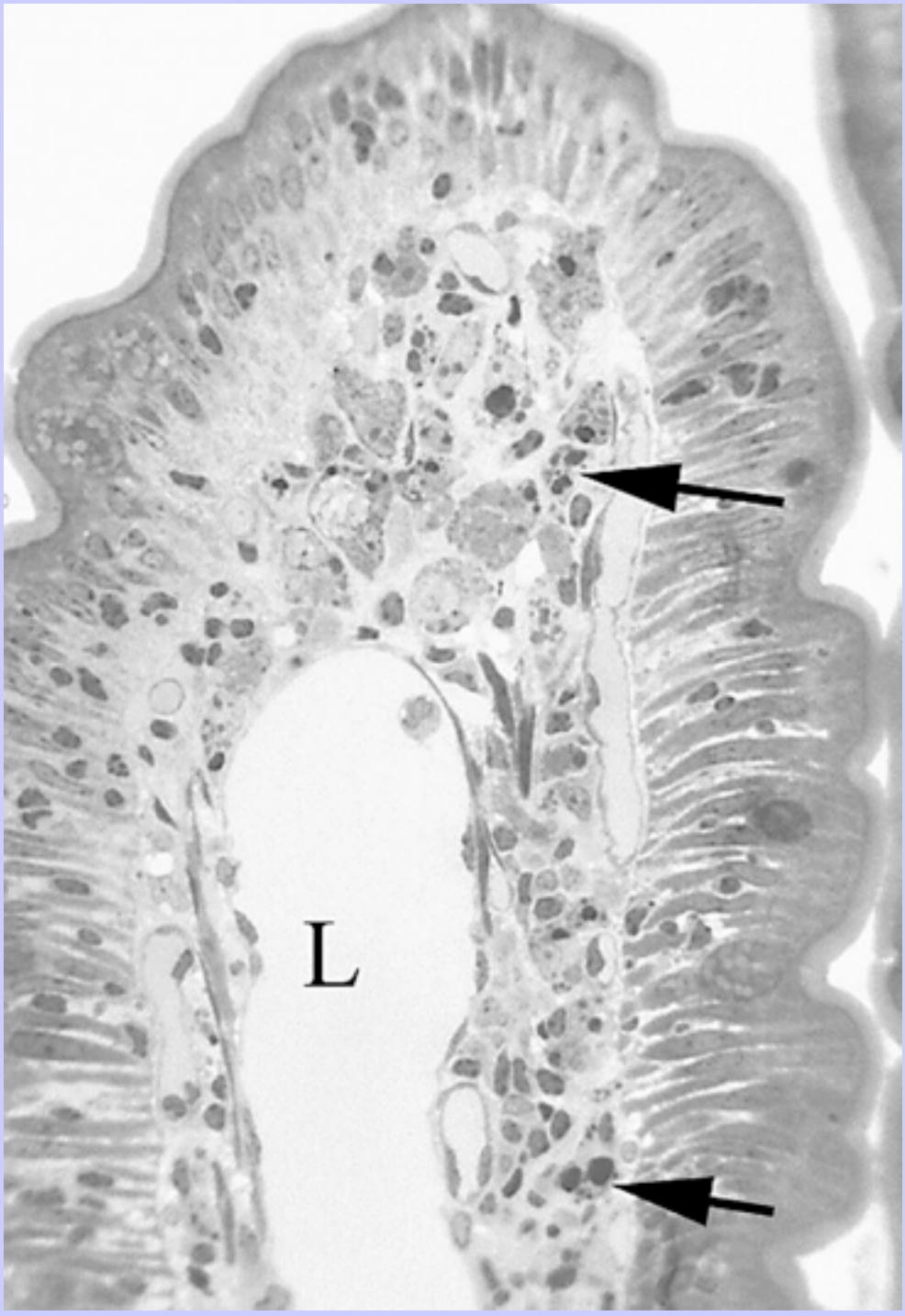
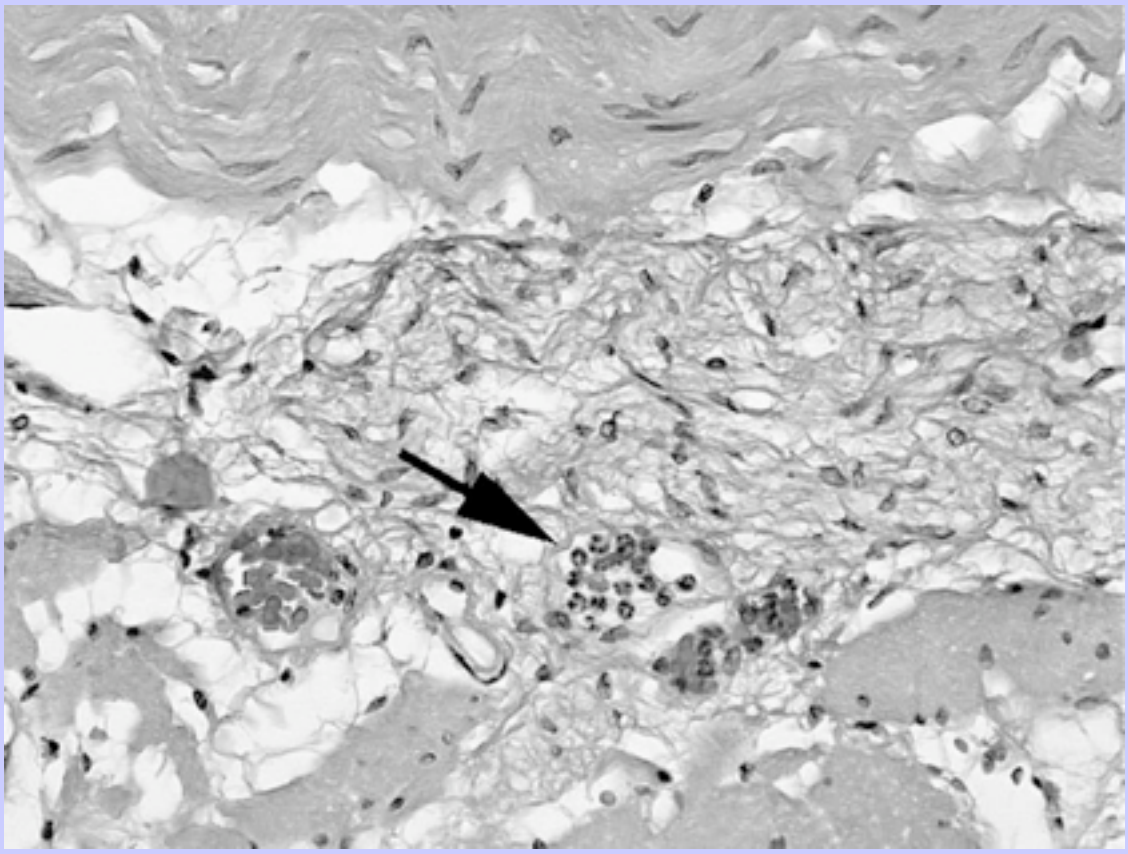


Fig. 32-37 Photomicrograph of neutrophil infiltrate *(arrow)* in the muscle and around a myenteric plexus after low-flow ischemia and reperfusion. Hematoxylin and eosin stain.



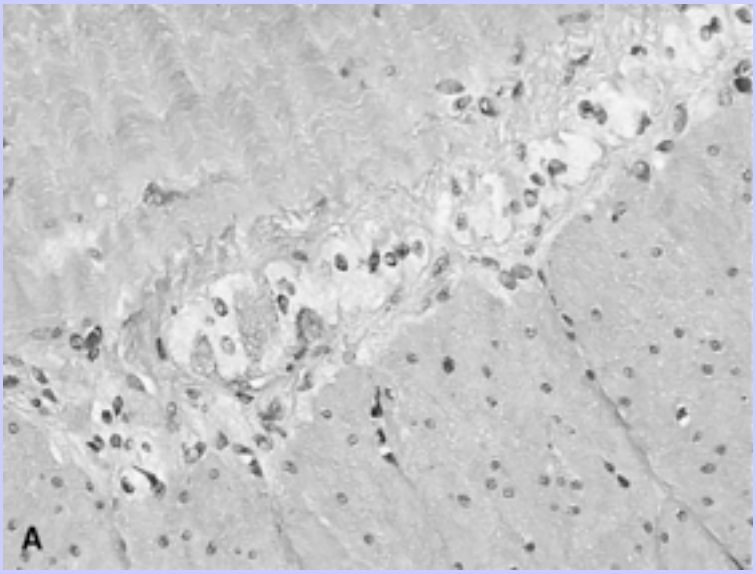
Intestinal dysfunction occurs after decompression of bowel that was previously obstructed. Ileus with gastric reflux is common in horses with previously distended small intestine, and the bowel pressure measured at surgery can predict the severity.[252,253] Abnormal motility with lack of response to prokinetic drugs is also observed after small intestine distention in vitro.[254] Although the injury from distention cannot be separated from conditions in the peritoneal cavity or failure of the cardiovascular system, the correlation of increased intraluminal pressures and survival indicates the importance of intestinal distention in causing injury.[230,232,248,251,252]

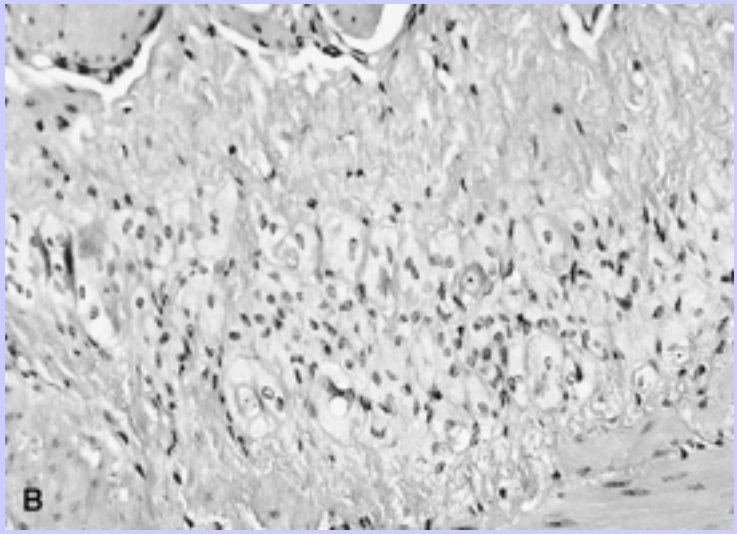
The enteric nervous system also appears to respond to intestinal distention. Chronic obstruction caused by impaction of the colon or cecum or colon displacement has been associated with a significant decrease in the number of neurons in the myenteric plexuses, whereas the number of myenteric plexuses was similar to that in normal horses.[224] This change in neuron number was also associated with increased thickness of the longitudinal muscle in the pelvic flexure or both circular and longitudinal muscle hypertrophy in the cecum.[255] This appears similar to pseudoobstruction in humans and to experimental denervation of intestinal segments in rats. The lack

of nervous inhibition is hypothesized to allow constant and uncoordinated muscular contractions with resulting hypertrophy and eventually poor transit of ingesta.

Myenteric plexuses from distended or obstructed large colons also had an increase in the number of glial cells (Fig. 32-38). This appears to be an inflammatory response by the enteric nervous system to the conditions involved with bowel distention. Alternatively the inflammation and neuron dropout may have been responsible for colon dysfunction in these horses examined because of colon obstruction.

Fig. 32-38 Photomicrographs of **A**, normal myenteric plexus with connective tissue surrounding an accumulation of neurons, and **B**, increase in glial cells in the myenteric plexus in a horse with chronic obstruction of the large colon. Hematoxylin and eosin stain.





32.43 INFECTION

Enteritis caused by infection is frequently a result of *Salmonella* species, *Clostridia* species, *Neorickettsia risticii*, or virulent *E. coli*. Viruses such as rotavirus can also cause infection in foals with subsequent clinical signs. These agents adhere to and attack mucosal cells. When bacteria bind to the mucosal cells, the release of endotoxin or exotoxins causes the mucosal cells to release cytokines, which signal immunocytes and neutrophils of impending invasion. The gut has a large number of lymphocytes and macrophages in the lamina propria, suggesting constant stimulus by agents or substances.[183,256] Although the mucosal cell has an innate ability to resist infection, the communication between the immunocytes and the mucosa is likely the chief defense. The infection can change mucosal function without destroying the mucosal barrier; increased TNF-α concentration has been shown to impair barrier function at the tight junctions.[257] The change can cause lack of absorption and/or massive secretion of fluid into the bowel, causing diarrhea.

Interaction of neutrophils with the apical membrane of epithelial membrane after paracellular migration stimulates adenosine receptors by production of 5′-AMP.[258] Subsequent functional secretion is caused by stimulation of adenyl cyclase and guanyl cyclase, which catalyze formation of cAMP or cGMP respectively. These cyclic nucleotides subsequently activate protein kinases, which block the NaCl absorptive process in the absorptive mucosal cell and stimulate Cl secretion in the crypt cell.[259] Inflammation with release of eicosanoids and bradykinin can also initiate the secretory process. The enteric nervous system can also induce inflammation and secretion in the bowel, which can be inhibited by nerve-blocking agents or indomethacin.[259,260] Neuropeptides from efferent nerves are hypothesized to initiate this response by affecting mucosal cells, fibroblasts, and endothelial cells.[178,261]

When bacteria cause injury by adhering to the mucosal surface and invading the mucosa, the response of the mucosal cells stimulates both the afferent nervous system and an immediate local immune reaction. Cytokines from local macrophages or injured epithelial cells serve as the messengers of recognition, which stimulate macrophages, neutrophils, and eosinophils to migrate to the region of invasion. Lymphocytes are also activated, releasing cytokines including IFN-γ. After an initial delay in mucosal cell apoptosis during bacterial adhesion and invasion, apoptosis is increased, theoretically to increase cell turnover and healing. TNF-α and nitric oxide appear to control mucosal cell apoptosis.[218]

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The inflammatory response to invasion often causes massive mucosal necrosis, with loss of mucosal cells and a massive infiltrate of neutrophils and lymphoid cells. Fibrin exudate creates a cast on the mucosal surface of the bowel. The vasculature is exposed to the bowel lumen, allowing subsequent invasion of the bacteria, both pathogens and others, as well as bacterial toxins. The remaining mucosal cells are stimulated to secrete water via the stimulation of cAMP within the crypt cells. Water is also retained in the bowel because of the lack of absorptive cells; the result is diarrhea.

The infection can involve the other layers of the intestine, although it rarely involves the serosa. Still, some diseases such as hemorrhagic fibrinonecrotic duodenitis—proximal jejunitis (DPJ) affect all layers of the intestine. A causative organism has never been discovered to explain DPJ, but the lesion is similar to that seen with clostridial disease in young swine.[262] Similar to reperfusion injury, the inflammatory process creates dysfunction that can last for days. Although long-term complications from DPJ have not been reported, animals with severe cases have not survived because of the lack of healing and severe residual inflammation in the bowel wall.[262]

32.44 PERITONEAL INFLAMMATION

The serosal layer is made of a single-cell mesothelial layer mounted on a layer of connective tissue. This layer is important for maintenance of a lubricated barrier at the bowel surface, necessary for normal intestinal motility and peritoneal cavity fluid exchange. The mesothelial layer attaches to a basement membrane, which is adjacent to an elastic layer. The mesothelial cells vary in type. Some are short and have channels linking the peritoneal surface to the serosa. Others have long microvilli, which appear to help trap fluid on the surface of the peritoneum, providing the chief mechanism of lubrication on the bowel surface. Mesothelial cells react to circulating or intraperitoneal lipopolysaccharide (LPS), infection, and surgery by releasing TNF-α, IL-1β, IL-6, and macrophage inflammatory protein (MIP).[263] The response in the serosa is attraction and migration of neutrophils into the serosal connective tissue.

The initial response to serosal injury has been studied in laboratory animals using predominantly scarification of organs or fecal contamination of the peritoneal surface. The response to ischemia or distention of the equine small intestine is similar, though often more severe. During ischemia the mesothelium is rapidly lost, with subsequent serosal swelling with edema. During reperfusion the serosal vasculature becomes more permeable, and polymorphonuclear cells and mononuclear cells migrate through capillaries or venules and infiltrate into the serosal connective tissue layer. Neutrophils accumulate at the basement membrane around vessels and within lymphatics. Fibrin accumulates within the serosa and on the surface. WBCs release oxygen radicals and proteolytic enzymes, resulting in disruption of collagen, the primary ground substance of the serosa. The denuded serosal response includes increased vascular permeability, which allows the surface to be covered with a fibrin clot. After 24 to 48 hours there is massive accumulation of cells, which are predominately neutrophils, within the serosa and at the new surface.

Cytokines are involved in the response to serosal injury and the subsequent healing.[264,265] After intestinal anastomosis in rabbits, macrophages increased in number until about day four. Superoxide levels in these cells are high in the first 24 hours. Prostaglandins, cytokine secretion, and plasminogen activator inhibitor activity are known to increase during the first 3 days after peritoneal injury.[264] IL-1 and TNF-α are secreted by peritoneal macrophages after injury and appear to modulate peritoneal healing.[266] Peritoneal macrophages also secrete plasminogen activator. The secretion of both plasminogen activator and plasminogen activator inhibitor is stimulated by IL-1. After intestinal anastomosis there is a decrease in fibrinolytic activity for the first 5 days. Thereafter, plasminogen activator returns to the normal preoperative level. Normally fibrin will be dissolved by plasmin after plasminogen is activated by tissue plasminogen activator (TPA). The severity of the serosal injury is also related to the reduction of TPA and to the suppression of plasminogen activator normally produced by macrophages. If plasminogen is not activated or is absent, adhesions have a greater likelihood of becoming fibrous and permanent.

As healing progresses, fibroblasts migrate into the fibrin and a layer of granulation tissue forms both beneath and on top of the original basement membrane (Fig. 32-39). Mesothelial cells produce connective tissue growth factor in response to IL-1β, which simulates fibroblast proliferation.[190] During this stage IL-1 stimulates and prostaglandin E_2 inhibits fibroblast activity in the injured serosa. Primordial stem cells migrate to the surface and change to form a new mesothelium, a metaplasia likely under the control of growth factor from fibroblasts. The greater the inflammatory reaction within the serosa and on the surface, the more fibroplasia occurs, delaying mesothelium resurfacing and increasing the chance for adhesion formation or bowel scarring. Experimentally the severity of adhesions is correlated with increasing concentrations of TNF-α in peritoneal fluid, and antibodies against TNF-α can decrease adhesion formation.[266,267] Healing of the serosa may not result in bowel-to-bowel

adhesions but can still cause bowel and mesenteric scarring, which can cause luminal narrowing or kinking. The serosa also becomes thickened, which may result in bowel dysfunction or may interrupt the vascular supply, resulting in chronic obstruction.

In the horse the serosal injury is frequently caused by bowel distention. The cellular injury is similar to an inflammatory model except for the vascular sequelae. After small intestinal ischemia there is an initial vascular hyperemia in most of the bowel but a reduction of perfusion to the serosa.[231] This same effect occurs during bowel distention and is even greater after alleviation of distention. The edema formation in distended bowel takes place immediately and increases serosal tissue pressure, which exerts extravascular pressure and closes capillaries and venules.[231] This continues after bowel decompression, resulting in ischemic injury during reperfusion of the serosa. Reperfusion after decreasing bowel distention also causes serosal endothelial cell swelling and capillary plugging. This helps to explain the adhesions seen in bowel that was distended only proximal to an obstruction or strangulating lesion but was otherwise not involved in an ischemic lesion.

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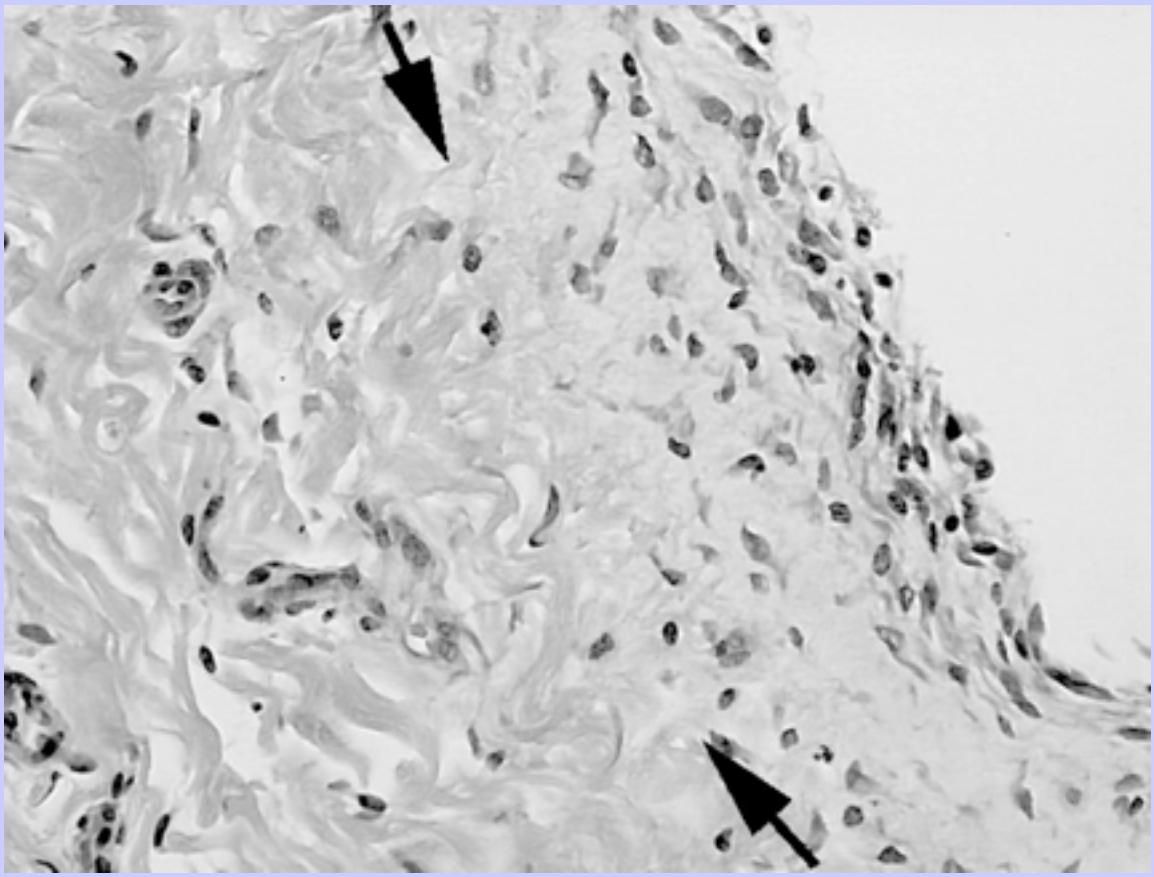
Fig. 32-39 Photomicrographs of the serosa with addition of a fibrous layer extending beyond the original level of the basement membrane *(arrows)* 10 days after bowel ischemia and reperfusion. (Hematoxylin and eosin stain.) The new serosa surface has yet to heal with a new mesothelial layer.



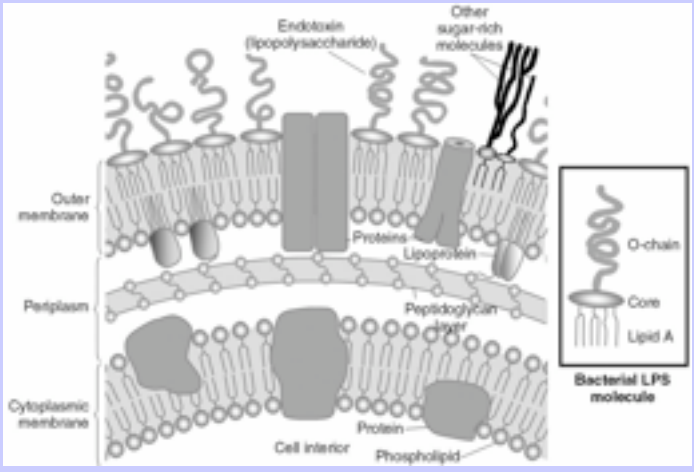
Adhesions resulting from septic peritonitis occur in response to a massive inflammatory response in the serosa. Similar to the response to ischemia, there is neutrophil migration and fibrin deposition in and on the serosa.[265] The inflammatory response may be so great that the proteolytic enzymes may prevent adhesion between bowel loops by breaking down fibrin. However, in most cases there is massive fibrin production, and bowel-to-bowel adhesions occur frequently.

32.45 BOWEL HEALING

After ischemic damage the mucosa heals rapidly.[268–270] Enterocytes migrate along the lamina propria, covering the surface within 24 to 38 hours. In the mucosa the crypt cells are responsible for rapid multiplication and physically forcing the older cells to the mucosal surface. Delayed healing is associated with a massive inflammatory response, which can stimulate delayed epithelial apoptosis and lack of cell replacement.[182,271] Connective tissue growth factor stimulates mucosal growth and may be responsible for excessive fibrosis in chronic inflammatory disease.[272]

Common use of nonsteroidal antiinflammatory drugs (NSAIDs), in particular flunixin meglumine, delays mucosal cell function during reperfusion.[270] Although replacement of the mucosal cell lining after ischemia is rapid, in vitro application of flunixin meglumine delays normal return of mucosal barrier function. Increased permeability to endotoxin in flunixin-treated bowel compared with the control intestine may lead to shock or delayed healing of intestine.[273]

Fig. 32-40 Cross-section of the double lipid bilayer that forms the cell membrane of gram-negative bacteria. As is shown in this figure, lipopolysaccharide (LPS) is the principal component of the outer leaflet of the outer membrane. The *insert* shows a single LPS molecule with an O-polysaccharide chain, a two-part core oligosaccharide, and a hydrophobic lipid A phospholipid. R-mutant bacteria lack the O-chain ± varying amounts of the core oligosaccharide.



Similarly, the serosal mesothelium also heals rapidly after loss from abrasion, though it takes longer than the mucosa to heal with a functional cell boundary. The mesothelial cells come from multipotent stem cells in the serosal connective tissues. These migrate to the serosal surface and form an initial layer of cuboidal cells before transforming to the more characteristic flattened mesothelial cells. The healing time appears to be dependent on the amount of inflammation and subsequent production of fibrous tissue on the serosal surface.

Although healing is thought to be successful when clinical signs of colic, obstruction, or peritonitis are no longer observed, the latent effect of serosal fibrosis, residual mucosal inflammation, and ganglionitis with loss of neurons may increase the risk of future colic episodes. Horses that have had a colic episode or previous abdominal surgery are three to four times more likely to have a second colic episode than horses that have never had colic.[234] Whether chronic inflammation is responsible for recurrent colic has not been determined.

32.46 ENDOTOXEMIA

Robert J. Mackay

The heat-stable endotoxic activity of *Vibrio cholerae* identified by Pfeiffer more than 100 years ago resides in LPS, the principal component of the outer leaflet of the outer membrane of all gram-negative bacteria (Fig. 32-40).[274] Each LPS molecule has three structural domains: a polar polysaccharide O-region, which projects into the aqueous extracellular environment; a hydrophobic lipid A region, which is largely buried in the bacterial outer membrane; and a core acidic oligosaccharide region connecting the two. The O-region is highly variable, consisting of repeating units each of one to eight glycosyl residues, and contains antigens specific for each bacterial strain; the core glycolipid region is relatively constant among bacteria and mediates most of the toxic effects of endotoxin. On bacterial death or during bacterial proliferation, large (>10^6-dalton molecular mass) aggregates of LPS and membrane protein are released. It is these protein-lipid micelles that constitute native endotoxin and are to be found circulating in naturally acquired cases of endotoxemia. In recognition of the fact that most endotoxic activity resides in the LPS component, the terms *endotoxin* (the activity) and *lipopolysaccharide* (the molecule) are used interchangeably except when a specific or purified LPS is being referenced.[275]

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Endotoxemia literally is the presence of endotoxin in the blood. When the term is used clinically, it implies only the presence of clinical signs typically caused by circulating endotoxin. A survey of diplomates of the American College of Veterinary Internal Medicine and the American College of Veterinary Surgeons found that neutropenia, leukopenia, hyperemic mucous membranes, tachycardia, and fever were the clinical and laboratory values most characteristic of horses with presumptive endotoxemia.[276,277] This term should not be confused with either *bacteremia*, which refers only to the presence of viable circulating bacteria, or *septicemia*, which is an older term referring to systemic disease caused by circulating microorganisms and/or their products.

The ability to respond to minute local concentrations of endotoxin by mounting vigorous inflammatory responses is well conserved across species.[278] Endotoxemia as a clinical syndrome in equine patients was first recognized more than 40 years ago.[279] The potential importance of endotoxemia was then shown by reports that intravenous infusion of LPS into horses reproduced many of the adverse clinical signs of diseases such as colitis, metritis, and strangulating intestinal obstruction.[280–288] Further evidence for the importance of endotoxemia was the detection of circulating endotoxin in some horses with experimentally induced laminitis[289] or intestinal strangulation obstruction[290,291] and in horses with naturally occurring gastrointestinal diseases or septicemia,[291–296] hemostatic disorders,[297] and exhaustion associated with endurance[298] or racing[299] events. Since the original case descriptions,

a large body of review literature has documented the efforts that have been made to understand and, more importantly, treat equine endotoxemia.[300–310]

Within the last decade, rapid advances have been made in deciphering the molecular pathologies of sepsis in human beings and experimental animals. Much existing dogma has been swept away by this new information, and the pivotal events of endotoxemia in horses with sepsis can now be discerned. Unfortunately, over the same period it has become distressingly clear that the frequent promise of "silver bullet" treatments thrown up by experimental models and preclinical studies has not been realized in large, controlled, multicentered clinical trials in human patients. Therefore it is conceivable that some of the cherished but largely unscrutinized mainstays of equine endotoxemia treatment are of questionable value (at least in the life-saving sense). This section explores the new information that identifies endotoxin as but one of many pathogen- or host-derived signals that elicit global and destructive host responses and focus on treatment strategies that have evidence-based support (at least in human medicine).

32.47 ENDOTOXEMIA AND SEPSIS

The extraordinary ferocity of the host response to endotoxin was nicely captured by Thomas[311]:

> *"The gram-negative bacteria … display lipopolysaccharide … in their walls and these macromolecules are read by our tissues as the very worst of bad news. When we sense lipopolysaccharides we are likely to turn on every defense at our disposal; we will bomb, defoliate, blockade, seal off, and destroy all tissues in the area …. Cells believe that it signifies the presence of gram-negative bacteria, and they will stop at nothing to avoid this threat."*

Although this picture still accurately describes modern concepts of the early responses to endotoxin, it has become clear that a variety of other pathogen-derived molecules set off similar or identical host responses. For example, toxic shock syndrome resulting from *Staphylococcus aureus* infection[312] and streptococcal toxic shock[313] are examples of hyperinflammatory septic syndromes in horses that resemble diseases characterized by endotoxemia. In severe sepsis (including putative endotoxemia in horses), it is likely that the clinical presentation is an aggregate of responses to multiple microbial signals and certain "danger" signals generated by the host itself.

32.48 DANGER SIGNALS AND INNATE IMMUNITY

Animals have the ability to recognize distinctive patterns on molecules that signal potential danger. As a group, these molecules that express danger motifs are aptly termed *damage-associated molecular patterns* (DAMPs).[314] Included among DAMPs are microbial signals like endotoxin, collectively termed *pathogen-associated molecular patterns* (PAMPs), and *alarmins*, endogenously produced molecules that originate from damaged or inflamed tissues (Table 32-2).[315] A limited number of germ-encoded receptor types, both soluble and cell-associated, are dispersed throughout the body to detect potential threats (both septic and nonseptic). These are pattern-recognition receptors (PRRs) and are exemplified by Toll-like receptors (TLRs) on (and in) cells and complement receptor proteins and Hageman factor in plasma.[316,317] A list of these and other PRRs is given in Table 32-3. The interaction between DAMPs and PRRs is the initial event in the innate immune responses that result in signs of endotoxemia or other forms of sepsis.

Table 32-2 Partial List of Damage-Associated Molecular Patterns[314,315,368]

PAMPs	Alarmins
LPS (endotoxin)	HMGB1
Lipoprotein	S-100 proteins*
Peptidoglycan	HSPs
Flagellin	Defensins
Lipoteichoic acid	Cathelicidins
Zymosan	
Viral double-stranded RNA	
N-acetyl glucosamine	

HMGB1, High-mobility group box 1 protein; *HSPs*, heat shock proteins; *LPS*, lipopolysaccharide; *PAMPs*, pathogen-associated molecular patterns.

* Proinflammatory proteins released by phagocytic cells during innate immune responses.

Table 32-3 Partial Listing of Pattern Recognition Receptors[316,317,368]

Cell-Associated	Soluble
TLR (1-11)	Hageman factor
RAGE	MBL
Nod1/Nod2	C3b, Bb
CD14	Ficolins

MBL, Mannan-binding lectin; *Nod*, nucleotide-binding oligomerization domain; *RAGE*, receptor for advanced glycation end products; *TLR*, toll-like receptor.

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32.49 CLINICAL SEPSIS SYNDROMES

A scheme showing increasingly severe stages of sepsis, with definitions, from local infection to death is shown in Fig. 32-41. The lethality of each grade increases from the base to the apex of the figure. In humans, reported mortality rates for severe sepsis are 25% to 30%[318] and for septic shock are 40% to 70%.[319] Endotoxemia is shown as a subset of sepsis (at all stages) in acknowledgement of the common pathogenesis of all sepsis syndromes. Dysfunction of two or more organs is termed *multiple organ dysfunction syndrome* (MODS) and carries an additional increment of lethality in human beings.[320] Comparable data are not available for the horse. Definitions for SIRS, organ dysfunction, and laminitis are given in Table 32-4. Note that sepsis is defined as *suspected* infection plus SIRS; therefore a horse with a strangulating intestinal obstruction and SIRS but no definable infection is still classified as septic or endotoxemic. Horses with signs of mild endotoxemia—leukopenia and fever—fit the definition for sepsis. With the exception of laminitis, these definitions are not validated for the horse but are reasonable extrapolations from accepted human criteria.

The fundamental difference between serious sepsis in humans and the syndromes seen in equids is the propensity for the latter to be associated with laminitis. In the context of sepsis, laminitis is often life-threatening. Because an organ is defined here as "a dispersed or solid tissue that performs a specialized function," it is probably inappropriate to classify the hoof as an organ as part of an equine MODS definition. It is clear from recent data, however, that the same types of global inflammatory and coagulation disorders that lead to MODS in patients with sepsis also are involved in the pathogenesis of both carbohydrate- and black walnut—induced laminitis.[321–325] In light of their likely common pathogenesis, laminitis and MODS are presented together in Fig. 32-41 (as MODS/L).

Fig. 32-41 Scheme for sepsis classification. Definitions for systemic inflammatory response syndrome, organ dysfunction, and laminitis are given in Fig. 32-42.

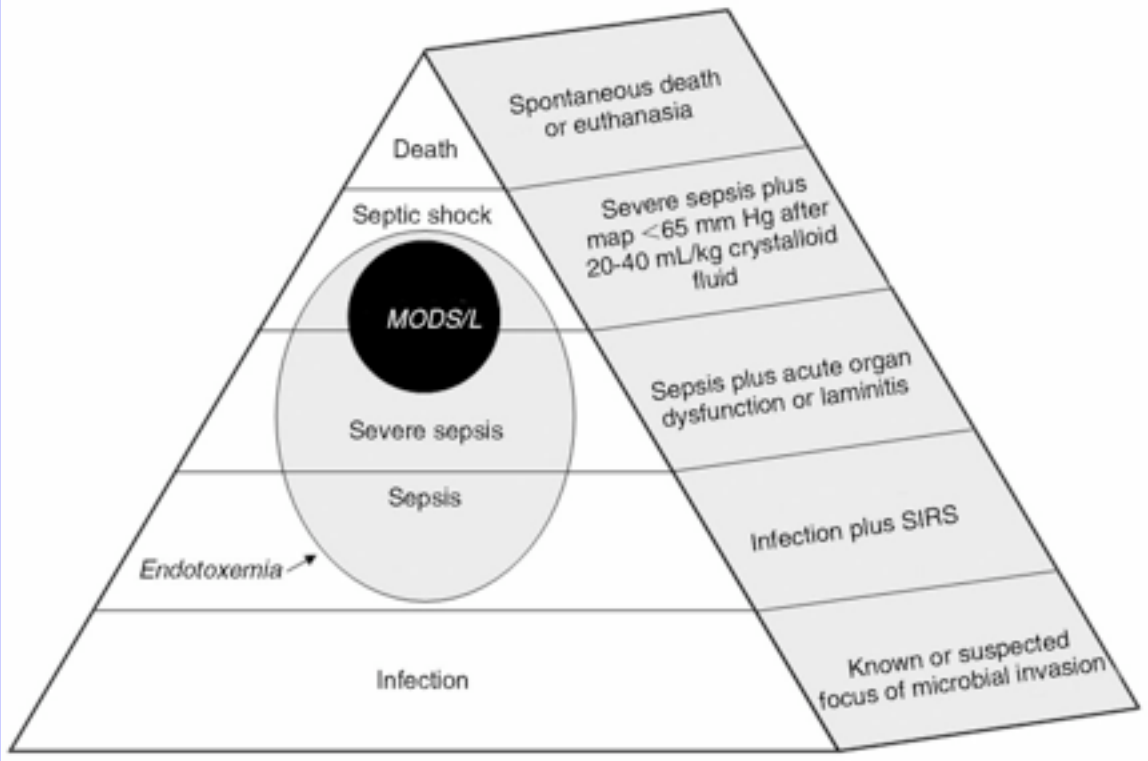

Table 32-4 Criteria for Systemic Inflammatory Response Syndrome, Organ Dysfunction, and Laminitis

SIRS CRITERIA (2 OR MORE OF THE FOLLOWING)	
Hypothermia	<98° F or hyperthermia >101.5° F
Leukopenia	<5000/μL or leukocytosis >14,500/μL
Tachycardia	50 beats/min
Tachypnea	25 breaths/min or $Paco_2$ <32 mm Hg
ORGAN DYSFUNCTION AND LAMINITIS CRITERIA	
Neurologic	Severe obtundation (stupor, semicoma, coma)
Renal	Creatinine >2 mg/dL after ≥20 mL/kg IV crystalloid fluids, or increase of ≥0.5 mm Hg since last measurement
Hemostatic	Platelet count <100,000/μL or aPTT >70 seconds
Respiratory	Pao_2 <65 mm Hg, or <75 mm Hg with oxygen supplementation or mechanical ventilation
Intestinal	Absent gut sounds, or absent motility on ultrasound examination
Hemodynamic	Mean arterial pressure <65 mm Hg after ≥20 mL/kg IV crystalloid fluids
Hepatic	Bilirubin concentration >6 mg/dL; GGT >60 U/L with no other explanation
Laminitis	Bounding digital pulses, sensitivity to digital pressure over the coronary band, sensitivity to hoof tester pressure over the sole, Obel grade >1

aPTT, Activated partial thromboplastin time; *GGT*, γ-glutamyltransferase; *IV*, intravenous; *SIRS*, systemic inflammatory response syndrome.

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32.50 MOLECULAR BASIS FOR ENDOTOXEMIA AND SEPSIS

32.50.1 Endotoxin Enters the Circulation

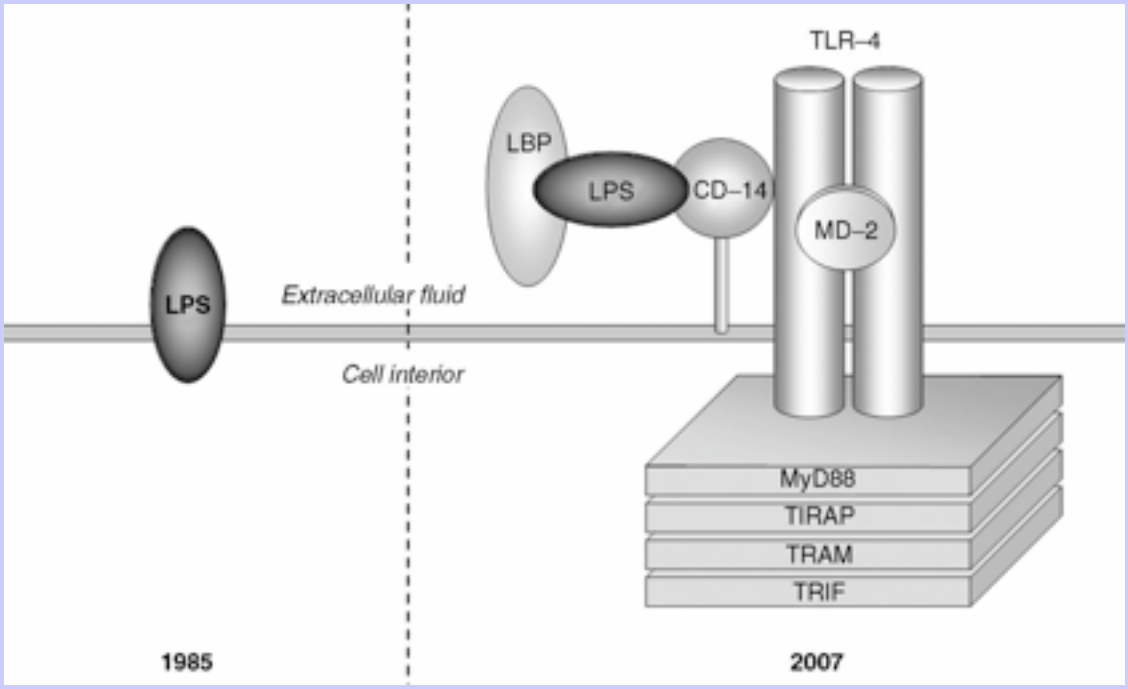
Although endotoxin is ubiquitous in the environment, both free and as a component of gram-negative bacteria, it normally is excluded from the body by the skin and mucous membranes. If the protective integument or mucosae are subjected to gram-negative bacterial infection or otherwise damaged, endotoxin may reach the blood in sufficient amount (<1 μg of purified LPS in experimental situations) to cause clinical signs. Gram-negative bacterial enterocolitis (e.g., salmonellosis), metritis, pleuropneumonia, wound infection, and neonatal septicemia are common examples. Because gram amounts of free endotoxin normally are safely sequestered within the intestine of the adult horse, damage to the gut wall as a result of local (e.g., intestinal volvulus, infarction, incarceration) or systemic (e.g., hypovolemic shock) causes of tissue hypoxia, inflammation (e.g., DPJ or

clostridial enteritis), mechanical trauma (e.g., rectal perforation, prolonged exercise), or intraluminal acidification (e.g., grain overload) is particularly likely to result in endotoxemia. In highly contaminated environments, potentially harmful amounts of endotoxin can be introduced into the lungs via inhalation.[326] Endotoxin may even be delivered directly into the blood via parenteral solutions (e.g., homemade intravenous fluids).

32.50.2 Endotoxin Interacts with Pattern Recognition Receptors

In 1985 almost nothing was known about the way in which LPS molecules interacted with cells of the immune system. In fact, endotoxin was widely believed to enter cells not via engagement of cell-surface receptors but by hydrophobic insertion into the membrane (Fig. 32-42). Since then, sequential discoveries of a plasma LPS-binding protein (LBP; 1989 for humans,[327] 2005 for horses[328]), CD14 (1990 for humans,[329] 2003 for horses[330]), and TLRs (1998 for humans,[331] 2005 for horses[332]) have elucidated the molecular processes of endotoxin binding and signaling (see Fig. 32-42). LPS first interacts with LBP, a normal plasma acute-phase protein; this interaction facilitates binding to the soluble or cell-associated co-receptor CD14. The LPS/LBP/CD14 complex recruits and activates TLR4 dimer and an accessory component MD-2 in preparation for LPS signaling. On ligation of the receptor, the conserved intracellular domain of TLR4 (Toll-IL-1 receptor [TIR]) initiates multiple downstream pathways that culminate in translocation to the nucleus of inducible transcription factors including nuclear factor (NF)–κB and activator protein 1 (AP-1).[333] NF-κB binds to consensus sequences on the promoter or enhancer regions of an array of genes whose products are involved in the inflammatory response.[333] It has recently been argued that the global activation of TLR4 typical of sepsis requires the actions of endogenous agonists (e.g., proteases).[335] Endotoxin also may activate NF-κB via TLR4-independent interactions with β_2-integrins, heat-shock proteins, and the intracellular Nod-1 receptor.[336] Although endotoxin binds predominantly to TLR4, a still-growing family of TLRs (12 in rodents, 11 in humans, unknown in horses) is available to bind to other DAMPs (Table 32-5).[336] During sepsis, this diversity of TLRs allows redundant signaling of inflammatory cells. For example, non-LPS components of gram-negative bacteria may bind other TLRs (e.g., lamellin binds to TLR5, lipoprotein and peptidoglycan to TLR2), whereas PAMPs from gram-positive bacteria or fungi bind different TLRs in the course of polymicrobial sepsis. Tissues subject to attack by mediators produced after the initial round of TLR binding can feed back and amplify the inflammatory response by releasing alarmins (e.g., high-mobility group box 1 [HMGB1][338]), which in turn can bind to TLR or other PRRs.

Fig. 32-42 Binding of lipopolysaccharide (LPS) to mammalian cell membranes. In 1985 it was widely believed that LPS initiated cellular signaling by hydrophobic interactions with the plasma membrane. By 2007 the components of the signaling complex were more fully understood. In addition to the extracellular receptor components (discussed in the text), the intracellular Toll-IL-1 receptor (TIR) domain is shown interacting with four adaptor molecules (MyD88, TIRAP, TRAM, TRIF) to initiate a molecular signaling cascade that ultimately leads to gene activation.



Simultaneous with cellular activation, endotoxin interacts with soluble PRRs normally present in plasma. Of particular importance, endotoxin binds to complement proteins to initiate the lectin-dependent and alternative pathways of complement activation and activates coagulation factor XII (Hageman factor) to set off the "contact" system of coagulation.

Table 32-5 Ligands for Human Toll-like Receptors[316,317]

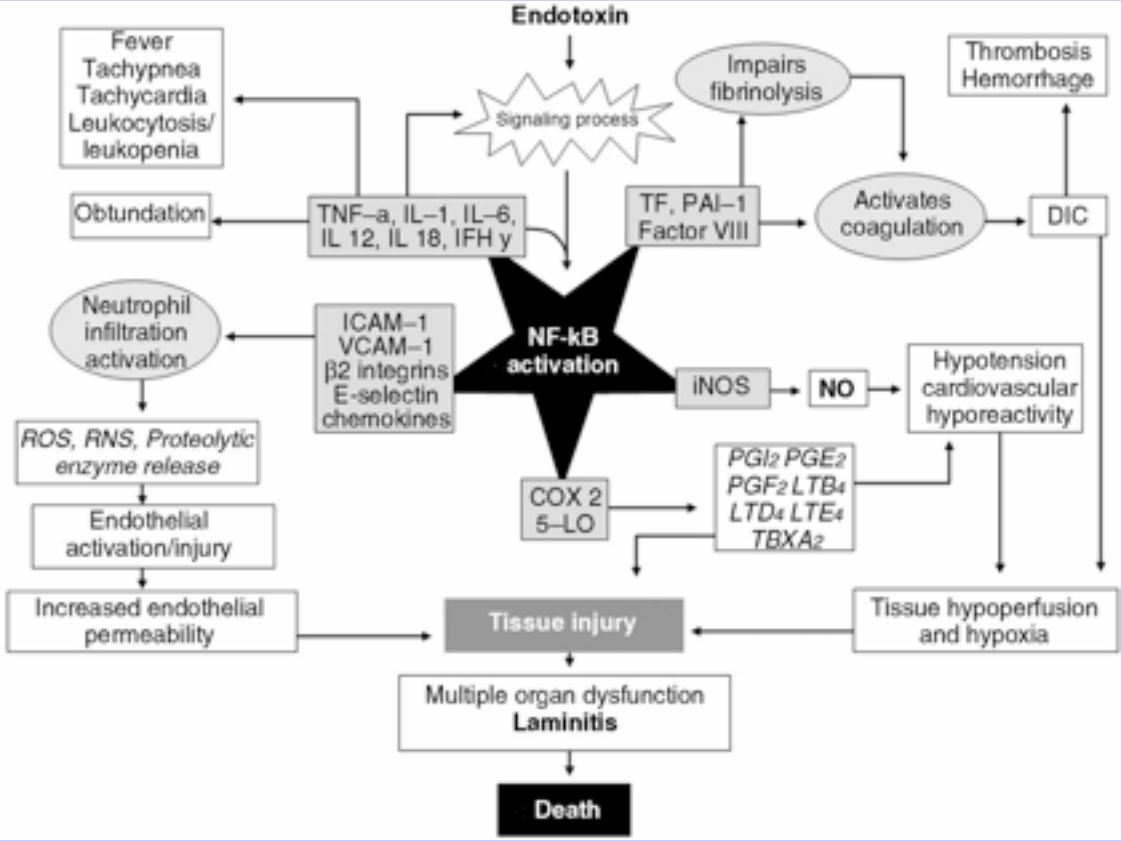
TLR1	Triacyl lipopeptides
TLR2	Lipoprotein
	Peptidoglycan (gram-positive bacteria)
	Lipoteichoic acid (gram-positive bacteria)
	Zymosan (yeast)
Lipoarabinomannan (mycobacteria)	
TLR3	Viral double-stranded RNA
TLR4	LPS
	Respiratory syncytial virus fusion protein
	HSP70
TLR5	Flagellin (*Salmonella* Typhimurium)
TLR6	Diacyl lipopeptides
	Zymosan
TLR7/8	Viral single-stranded RNA
TLR9	Unmyethylated CpG-containing DNA
	Herpes virus DNA
TLR10	Not determined
TR11	Uropathogenic bacteria

LPS, Lipopolysaccharide; *TLR*, Toll-like receptor.

32.50.3 Mediators are Released

As described earlier, endotoxin engages TLR4 on cells of the innate and adaptive immune systems, especially mononuclear phagocytes (monocytes and macrophages), neutrophils, endothelial cells, and dendritic cells. Pulmonary intravascular macrophages[339] and Kupffer cells likely are the most important mononuclear phagocytes in this regard. Endotoxin causes NF-κB activation in these and many other cell types via multiple signaling pathways resulting in the expression of more than 200 genes, many of which are involved in the pathogenesis of sepsis.[333] These include genes for proinflammatory cytokines (e.g., TNF, IL-1β, IL-6, IL-8, IL-12, IL-18), chemokines (e.g., IL-8, MIP), type 1 IFNs, procoagulants, adhesion molecules, immunoreceptors (e.g., TNF receptors), enzymes (e.g., elastase), and acute-phase proteins (e.g., fibrinogen).[341] NF-κB activity is further amplified by the paracrine actions of these proinflammatory cytokines, and by other DAMPs, cellular hypoxia, cellular necrosis, and chemical stress (including oxidant stress). Two of the cytokines secreted by macrophages, IL-12 and IL-18, stimulate IFN-γ synthesis and secretion from NK (natural killer) and other cells.[342] Because IFN-γ is a potent stimulator of both innate and acquired immune responses, it is considered to be a principal link between the two systems.

Fig. 32-43 Nuclear factor—κB signaling plays a central role in the pathophysiology of septic shock. *ICAM-1*, Intercellular adhesion molecule 1; *5-LO*, 5 lipoxygenase; *PAI-1*, plasminogen activator inhibitor 1; *TF*, tissue factor; *VCAM-1*, vascular cell adhesion molecule 1. Other abbreviations are explained in the text. Modified from Fig. 3 of reference333.



Endotoxin activates coagulation factor XII (Hageman factor) leading both to liberation of bradykinin and to initiation of intravascular coagulation. Even more important, complement is activated by alternative, lectin-mediated, and classical pathways to yield numerous active peptide products.

32.51 THE EARLY (HOT) PHASE OF SEPSIS

The early (hot) phase of sepsis is characterized by inflammation, coagulation, and necrosis. The principal NF-κB events during early sepsis are summarized in Fig. 32-43. This phase has been described as a "cytokine storm," during which there is flooding of inflammatory, procoagulant, and vasoactive mediators throughout the body. The net effects of these mediators are to promote microvascular injury and hypotension. The singular contributions of

many mediators to sepsis is demonstrated by experiments using sepsis models in which blocking or deleting a single mediator has had a positive effect on outcome.

32.52 THE LATE (COLD) PHASE OF SEPSIS

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It recently has become apparent that many patients with sepsis are profoundly immunosuppressed as shown by lymphopenia, anergy, and susceptibility to opportunistic infections (e.g., pulmonary aspergillosis in horses with enteric salmonellosis).[343,344] This immunosuppression has been explained by the reactive production of antiinflammatory mediators in response to the cytokine storm and termed the *compensatory antiinflammatory response syndrome* (CARS).[345] Although many such mediators are produced and actually can have favorable antiinflammatory effects when used as therapy in models of sepsis, it is now clear that widespread apoptotic death of lymphocytes (particularly B-cells and CD4-positive T-helper cells) and dendritic cells secondary to activation of intracellular caspases is largely responsible for sepsis-associated immunosuppression.[346,347] During experimental endotoxemia in cats, there also is apoptosis of intestinal epithelial cells,[348] raising the possibility that apoptotic processes may affect intestinal permeability in endotoxemic horses. It is interesting to note that macrophages and neutrophils are spared premature apoptotic death; neutrophils actually are prevented from physiologic apoptosis during sepsis and remain viable in sequestered sites.[349] The relationship between the two "phases" of sepsis is not clear, and it cannot necessarily be inferred that hot and cold phases occur in the same patient.

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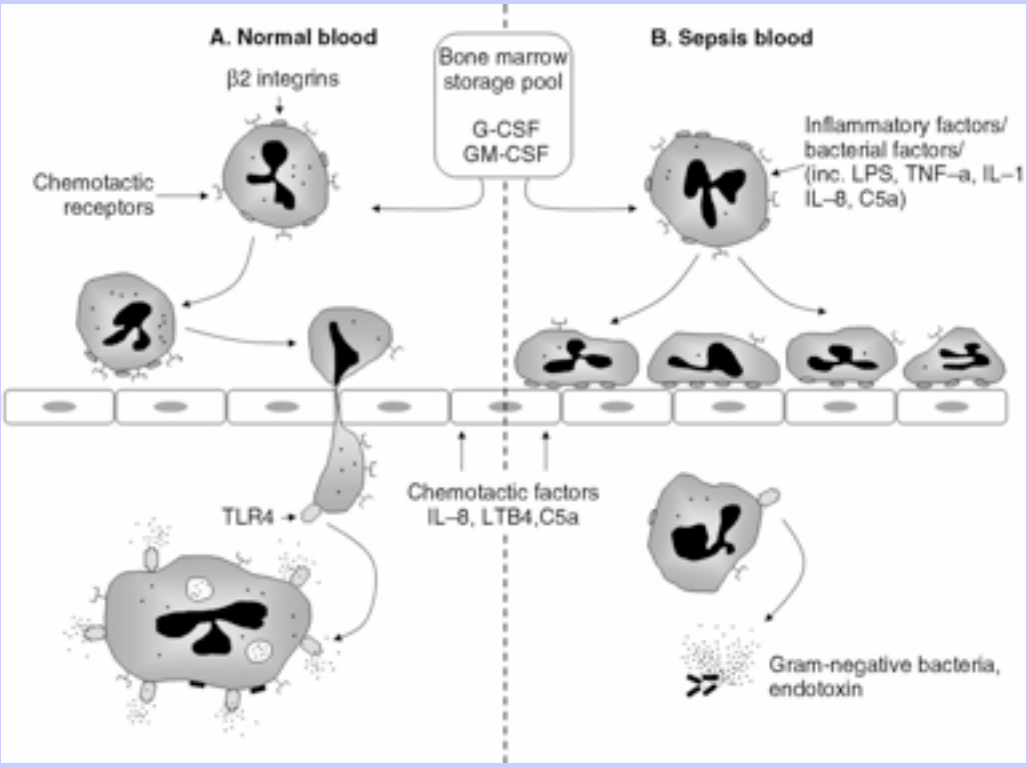
32.53 THE EFFECTS OF ENDOTOXEMIA AND SEPSIS

During sepsis, large numbers of neutrophils accumulate on the endothelial surfaces of organs undergoing failure, and insult to one organ can trigger the widespread recruitment and sequestration of neutrophils in others. Such a scenario likely underlies the association of laminitis with severe intestinal disease.[350,351]

Fig. 32-44 Recruitment and activation of neutrophils to bacterial infection in healthy horses and septic or endotoxemic horses. In response to bacterial infection, cytokines are generated that induce the release of neutrophils from the bone marrow. In the normal state, large numbers of blood neutrophils enter sites of bacterial infection by first adhering to the activated endothelium of local postcapillary venules before migrating up a concentration gradient of chemotactic factors. Endotoxin is bound to TLR4, and bacteria are eliminated by phagocytosis. In patients with endotoxemia or sepsis, high levels of circulating inflammatory factors promote upregulation of surface integrins to promote firm endothelial adhesion to postcapillary venules. However, some of these factors also downregulate the expression of chemotactic receptors. Consequently, neutrophils are strongly bound but less responsive to underlying chemotactic factors. *G-CSF*, Granulocyte colony-stimulating factor; *GM-CSF*, granulocyte-macrophage colony-stimulating factor. Modified from Fig. 2 in reference 349.



In response to PAMPs (including LPS), inflammatory cytokines produced by macrophages and other cells, and complement peptides, endothelial cells, and neutrophils express selectins.[349] Selectins on endothelial cells (E and P) and neutrophils (L) reciprocally engage glycoprotein ligands to "tether" the neutrophil to the endothelial surface. A series of these transient interactions between ligands and receptors allows neutrophils to roll along the endothelial surface (Fig. 32-44). Neutrophil capture is most efficient in areas of low shear force such as the walls of postcapillary venules and in pulmonary capillaries. During rolling, neutrophils are activated or "triggered" by selectins, chemokines, and PAF expressed on endothelial cells. The firm attachment or arrest step of the cascade is mediated by the avid interaction of neutrophil integrins with adhesion molecules of the immunoglobulin superfamily expressed on endothelial cells. During firm attachment the activated neutrophil spreads out and, in the healthy animal, squeezes between the intercellular junctions of adjacent endothelial cells and migrates into tissues up a gradient of chemotactic factors such as microbial chemotaxins, LTB_4, IL-8, or C5a. By contrast, when compared with normal neutrophils, those found in septic animals have defective chemotactic responses but bind with greater avidity to the endothelium and to other neutrophils. When cultured, macrophages and neutrophils from patients with gram-negative sepsis are hyporesponsive to LPS, suggesting a functional switch to LPS tolerance during the early stages of endotoxemia (see Fig. 32-44).[352] Sequestration of neutrophils on activated endothelium and in neutrophil aggregates accounts for the neutropenia found in most horses with endotoxemia. It is interesting to note that the lifespan of these sequestered neutrophils is prolonged during sepsis because normal apoptosis is prevented.[349]

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Tightly adherent neutrophil-endothelial conjugates formed during sepsis seal off microscopic pockets between the juxtaposed cells into which cellular products can be concentrated. Of particular significance are the reactive oxygen species (ROS) produced as a result of the activation of NAD(P)H-oxidase in neutrophils (respiratory burst) and xanthine oxidase in endothelial cells.[354] Digital laminae of horses may be particularly vulnerable to the effects of ROSs because of low content of the endogenous oxidant scavenger superoxide dismutase.[355] In the presence of neutrophil granule myeloperoxidase and H_2O_2, highly toxic hypochlorous acid is formed on the endothelial surface.[356] Superoxide anion generated as part of the neutrophil respiratory burst reacts with nitric oxide (NO) from endothelial cells to yield reactive peroxynitrite radicals. Other potentially corrosive substances are contributed by neutrophil granules and include elastase, serine proteases, matrix metalloproteinases (MMPs), and defensins.[357] In addition to direct damage caused by membrane lipid peroxidation, ROSs indirectly stimulate the expression of multiple inflammatory, procoagulant, and vasoactive mediators via activation of NF-κB in both neutrophils and endothelial cells. Mediators such as bradykinin, PAF, C3a, C5a, and leukotriene B_4 (LTB_4) directly increase vascular permeability by promoting active retraction of endothelial cells via phosphorylation of the light chain of nonmuscle myosin.[358] Vascular leak facilitates the movement of potentially harmful substances into tissues.

In health the antithrombotic phenotype of endothelial cells is maintained by the presence of low amounts of prostacyclin (prostaglandin I_2 [PGI_2]) and NO, and surface expression of thrombomodulin, protein S, and protein C complex and TPA.[359] During endotoxemia, endothelium supports extrinsic pathway activation because of leukocyte-induced physical damage, expression of the procoagulant tissue factor,[360] downregulation of antithrombin-III and protein C, and inhibition of fibrinolysis through expression of plasminogen activator inhibitor 1 (PAI-1).[361,362] Additional procoagulant effect may be provided by deposition on the endothelial surface of all of the components of the intravascular coagulation system. Microvascular perfusion is further compromised by sepsis-associated increase in "stiffness" of both RBCs and WBCs.[363] Such cells are unable to deform and squeeze through narrow capillaries.

The effect of endotoxemia on vascular tone depends on the stage and severity of disease and the particular organ (vascular bed) considered. Neuroendocrine responses to sepsis lead to the upregulation of predominantly pressor mediators including arginine vasopressin, angiotensin II, serotonin, epinephrine, and norepinephrine. Inflammatory mediators are a mix of vasoconstrictors (thromboxane A_2 [TXA_2], endothelin, C3a, C4a, C5a) and vasodilators (PGE_2, PGI_2, adenosine, bradykinin, NO). In animals with serious sepsis, balances of constricting and dilating influences unique to each vascular bed, loss of vasoregulatory tone, and refractoriness of damaged endothelium to vasoactive substances causes maldistribution of blood flow among organs and systemic hypotension.

Because of poor perfusion pressure, direct microvascular injury, thrombosis, and loss of endothelial integrity (capillary leak), ischemia and hypoxia of organs and tissues occur.[364]

32.54 DEVELOPMENT OF GLOBAL TISSUE HYPOXIA

The fundamental event in serious sepsis is the development of global tissue hypoxia. During serious sepsis, widespread microvascular and mitochondrial injury[365] decrease oxygen delivery and consumption at the cell, tissue, and organ levels. Oxygen delivery to tissues is a product of cardiac output and oxygen content (which itself is a product of hemoglobin oxygen saturation and hemoglobin concentration). The product of systemic oxygen delivery and the percentage of oxygen extracted (normally ≤25%) by the tissues is the systemic oxygen consumption. The balance between systemic oxygen delivery and consumption is reflected by the mixed venous hemoglobin oxygen saturation (SVO_2). SVO_2 has been shown in other species to be a useful surrogate for cardiac index as a target for goal-directed therapy.[366] Central venous oxygen saturation ($ScVO_2$), obtained through a central venous line, is a reasonable substitute for SVO_2 (which must be measured via a Swan-Ganz catheter). Global tissue hypoxia results when systemic oxygen delivery fails to meet the oxygen requirements of tissues.

Global tissue hypoxia resulting from cardiovascular insufficiency is the sine qua non of serious sepsis. Various hemodynamic combinations may create a systemic imbalance between tissue oxygen supply and demand[367]:

- *Hypovolemia*. Because of decreased preload caused by hypovolemia, concomitant left ventricular dysfunction, and reflex systemic arterial vasoconstriction, early endotoxemia is often characterized by low cardiac output (i.e., hypodynamic circulatory insufficiency).
- *Compensated but maldistributed perfusion*. After fluid-electrolyte resuscitation, compensatory mechanisms and low afterload drive transition to a hyperdynamic state. Even with normal or increased cardiac output, perfusion abnormalities may persist owing to regional hypoperfusion associated with derangements in blood flow distribution and loss of vasoregulatory control to vascular beds. This state is often described as *distributive shock*.
- *Myocardial depression* secondary to effects of inflammatory mediators and apoptosis of cardiomyocytes is the primary cause of low cardiac output in 15% of human patients with serious sepsis or septic shock.[368]
- *Increased metabolic demands*. SIRS increases metabolic demands, as evidenced by increased splanchnic and total body oxygen consumption.
- *Impaired oxygen utilization*. The bioenergetics of cellular extraction and use or respiration may be abnormal at least partially because of mitochondrial dysfunction.[365,369]

These derangements may occur independently of measured hemodynamic parameters. The theoretic components of each of these hemodynamic states are shown in Table 32-6.

32.55 SIGNS OF ENDOTOXEMIA

32.55.1 Clinical Signs

The clinical signs of horses given intravenous endotoxin experimentally may range from fever without obvious malaise to multiple organ failure and death. Obviously, signs that are not due exclusively to endotoxin (e.g., severe pain caused by intestinal strangulation or diarrhea in horses with *Salmonella* colitis) may greatly influence the overall clinical presentation of horses with naturally acquired endotoxemia.

Typically in an adult horse given a moderate sublethal dose of endotoxin (e.g., 0.1 to 1 μg of LPS per kilogram of body weight), an early period of mild tachypnea peaks within 30 minutes and resolves within 2 hours. During this period, mucous membranes are pale. Beginning within 90 minutes of LPS injection, depression, restlessness, and inappetence are present and rectal temperature begins to rise. Auscultable intestinal sounds usually cease during this period and remain depressed for several hours. Intermittent signs of colic usually are seen, including recumbency (usually without rolling). Small amounts of loose feces usually are passed. Heart rate peaks during the stage of maximal abdominal discomfort (approximately 2 hours after administration of endotoxin), then temporarily declines. During this time, mucous membranes become congested, the capillary refill time is prolonged, and a dark “toxic” line may become apparent around the gingival margins of the teeth. Beginning at 4 to 6 hours after endotoxin administration, there is a secondary phase of tachycardia and tachypnea that likely is related to development of systemic hypotension and fever. This secondary phase persists for several hours. Horses presented clinically with mild to moderate endotoxemia usually resemble experimental animals during the period 2 to 6 hours after intravenous endotoxin administration.

Table 32-6 Effect of Hemodynamic State on Parameters of Cardiovascular Function

Pathologic State	MAP	CVP	$ScVo_2$	Lactate	CO	SVR
Hypovolemia	Variable	↓	↓	↑	↓	↑
Compensated but maldistributed	Normal to ↑	Normal	↑	Normal to ↑	↑	↓
Myocardial depression	Variable	↑	↓	↑	Normal to ↓	Normal to ↑
Increased metabolic demand	Variable	Normal	↓	Normal to ↑	Variable	Variable
Impaired O_2 usage	Variable	Normal	↑	↑	Variable	Variable

Adapted from Fig. 32-41 of reference 367.

CVP, Central venous pressure; *CO*, cardiac output; *MAP*, mean arterial pressure; *$ScVo_2$*, central venous oxygen saturation; *SVR*, systemic vascular resistance.

At higher LPS doses (e.g., 100 µg/kg) in experimental animals or in patients with severe endotoxemia, signs of circulatory failure and disordered hemostasis dominate the clinical picture. Usually these horses are stuporous and totally anorectic. Signs of dehydration such as reduced skin turgor, dry mucous membranes, and sunken eyes are obvious. As systemic blood flow becomes more compromised, rectal temperature may drop into or below the normal range. Urine output is reduced or nonexistent. There are dark, congested mucous membranes, rapid and weak peripheral pulses, cold extremities, and sweating, and the horse may have muscle tremors and become recumbent.

Vascular damage may be seen as petechial and ecchymotic hemorrhages on mucous membranes. A poor prognostic sign is the development of a hypercoagulation syndrome, during which routine venipuncture or catheter placement initiates thrombosis along the entire visible length of the jugular veins (or other superficial veins). If both jugular veins are thus occluded, there usually is massive swelling of the soft tissues of the head, and associated laryngeal edema may cause signs of upper respiratory tract obstruction. In some horses, thrombosed superficial vessels can easily be palpated through the skin of the legs and abdomen. Infarction of bowel segments or lungs may cause severe clinical signs that are unresponsive to treatment. A rare syndrome of thrombosis of major limb arteries found in young foals is likely a result of sepsis syndrome.[370,371] At the time that hypercoagulation syndrome is recognized clinically, there is often evidence of a secondary bleeding tendency (a consequence of platelet and clotting factor depletion and uncontrolled activation of fibrinolysis), seen as prolonged hemorrhage from venipuncture sites and widespread mucosal petechiation. In cases with a severe pulmonary component, there may be hemorrhage into the respiratory tract with progressive tachypnea and dyspnea.

If moderately to severely affected animals survive for more than 24 hours, there usually is visible edema of the ventral abdomen and limbs. Signs of laminitis may first become apparent at this stage and may progress in severity even while the other systemic signs of endotoxemia improve.

32.55.2 Clinicopathologic Signs

Although the measured concentration of endotoxin in blood does not correlate well with severity of clinical signs, demonstration of circulating endotoxin obviously is definitive proof of endotoxemia. In one study, 12% of horses with acute gastrointestinal disease had detectable plasma endotoxin.[372] Reported concentrations in these horses were 0 to 30,400 pg/mL with a mean of 218 pg/mL. Experimentally, plasma endotoxin usually is assayed by some variant of the *Limulus* amebocyte lysate assay. A simple horse-side test for endotoxin that was marketed for use in clinical practice is no longer commercially available.

There is early and profound leukopenia principally caused by neutropenia (usually accompanied by left shift and a toxic appearance of stained cells). Lymphopenia (<1000/μL) is found in the most severe cases and likely reflects sepsis-induced apoptosis and immunosuppression. Adult horses often are hyperglycemic at presentation, whereas neonates with sepsis are usually hypoglycemic. Other abnormalities are nonspecific and reflect altered tissue perfusion and organ dysfunction (see Table 32-4).

In moderate and severe cases of endotoxemia, there also may be evidence of disordered hemostasis; values affected in blood may include any to all of the following: reduction in the circulating platelet count (<100,000/μL), reduction in plasma fibrinogen concentration, prolongation of the activated partial thromboplastin, prothrombin, or thrombin time, increased activity of PAI-1, and increased concentration of fibrin degradation products. In horses with acute gastrointestinal diseases, there also is increased activity in peritoneal fluid of many of the elements of the fibrinolytic system, including TPA. Depletion of key clotting factors can most simply be detected as prolongation of plasma recalcification time.[373]

32.56 NO “SILVER BULLET”

There is no “silver bullet” for treatment of endotoxemia. It has to be admitted that, almost without exception, potentially novel treatments for gram-negative sepsis that have been promising at the experimental level have failed when applied in clinical settings in human beings (and to a limited extent horses). A short list of such trials includes anti-TNF-α,[374] IL-1-receptor antagonist,[375] ibuprofen,[376] PAF antagonist,[377] elastase inhibitor,[378] nitric oxide synthase (NOS) inhibitor,[379] antithrombin III (AT-III),[380] and tissue factor pathway inhibitor.[381] It is clear that most experimental sepsis models do not replicate naturally occurring sepsis, at least as it occurs in humans. Several of many likely explanations for the disparity between the results of experimental models and large clinical studies are (1) heterogeneity of presentations among enrollees in clinical studies; (2) diversity in genetic susceptibility to sepsis among outbred populations; (3) differences between experimental and clinical study species; (4) differences in timing of potential treatments relative to the onset of sepsis between the two study populations; (5) preponderance of cold sepsis and immunosuppression states in naturally occurring sepsis compared with the “cytokine storm” usually recreated in experimental models.

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Even among sepsis models, results for the same candidate treatment are often inconsistent. For example, neutralization and inhibition of inflammatory cytokines usually have salutary effects in LPS-infusion experiments; however, equivalent studies involving the cecal ligation-puncture model in mice (widely considered to be one of the best sepsis models) usually have shown either neutral or negative effects on mortality.[382]

It is sobering to review the most pertinent available data for the three antiendotoxic drugs that are most commonly used to treat horses with suspected endotoxemia—namely, flunixin meglumine, polymyxin B, and pentoxifylline. Although various NSAIDs have been shown to effectively prevent the signs of LPS infusion in horses,[383–392] there is no convincing study that shows NSAIDs actually save lives in patients with naturally occurring sepsis. In contrast, a large multicentered, controlled, masked, prospective study of ibuprofen in humans with sepsis syndrome showed no effect of this drug on the development of shock or the acute respiratory distress syndrome and did not improve survival.[393] Polymyxin B and the nontoxic polymyxin B-dextran 70 conjugate PMX622 also safely prevented signs of endotoxemia when given before LPS to otherwise healthy horses[394–399]; however, the drug has not advanced beyond Phase 1 trials in human patients because experimental studies showed that it did not protect mice if given after intraperitoneal endotoxin.[400] Finally, intravenous pentoxifylline significantly, albeit only partially, reduced adverse signs in horses given LPS.[401] The usefulness of this finding is called into question by the observation that the lethality-sparing effect of pentoxifylline in endotoxemic mice was removed if the drug was given in combination with indomethacin, a potent NSAID.[402,403] It was concluded that upregulation of prostacyclin production by pentoxifylline, which was prevented by concurrent indomethacin, reduced mortality in subject mice by preventing endotoxin-induced leukopenia. It is interesting to note that pentoxifylline alone increased WBC counts in horses. This effect was prevented by flunixin[401,405]; thus, a potential beneficial effect of pentoxifylline in endotoxemic horses may be neutralized by concurrent NSAID administration.

Evidence-based medicine so far acknowledges only one agent, drotrecogin alfa (activated protein C),[406] as able to reduce mortality in patients with sepsis, although there has been some recent controversy regarding the side effects of the drug and the analyses performed in the original study.[407,408] Despite theoretic potential in some patients with endotoxemia, drotrecogin is much too expensive to be considered for equine use.

Fortunately, there is powerful evidence to support the value of early aggressive cardiovascular resuscitation. Use of oxygen, fluids, pressors, inotropes, and packed RBCs during the first 6 hours after admission to achieve a sequence of physiologic goals reduced in-hospital mortality of human patients with serious sepsis from 46.5% in the group that received standard therapy to 30.5% in patients given early goal-directed therapy (EGDT).[409] Similar protocols now are widely used in emergency rooms throughout the United States.[367] Many of the underlying principles of EGDT can be applied to resuscitation of septic horses, especially neonates (see later). It is reasonable to conclude that improvements in cardiovascular support of horses with sepsis will continue to be of much more value than any single “magic bullet” currently available or even on the horizon.

32.57 ASSESSMENT OF THE STAGE OF ENDOTOXEMIA OR SEPSIS

Horses with endotoxemia should be staged according to the criteria found in Fig. 32-41 andTable 32-4. It is especially important to recognize that horses with serious sepsis need aggressive intervention in order to survive.

32.58 TREATMENT OF ENDOTOXEMIA AND SEPSIS

A prioritized strategy for management of horses with endotoxemia is as follows: (1) cardiovascular resuscitation; (2) laminitis prevention; (3) removal of the cause(s) of endotoxemia; (4) neutralization of circulating endotoxin; and (5) inhibition of endotoxin-induced inflammation. These approaches are most applicable to horses with serious endotoxemia or sepsis.

32.58.1

Cardiovascular Resuscitation

Expansion of blood volume remains the cornerstone of treatment for horses with serious sepsis or endotoxemia. Most cases (e.g., adults with blood lactate of 2 to 4 mmoles/L) can be treated successfully with intravenous balanced polyionic solution according to guidelines for estimating water deficits provided in the fluid therapy section of this chapter. Urination should begin during the rapid replacement of estimated losses. Ideally the fine control of fluid replacement should be based on serial measurements of packed cell volume (PCV) or plasma protein concentration and further guided by following blood lactate concentration. Some clinicians prefer the early use of compatible plasma (5 L for a 450-kg horse, 1 to 2 L for a neonate) or other colloid solutions such as 6% hydroxyethyl starch solution (6% hetastarch in 0.9% saline; Abbott Laboratories, North Chicago, IL) to replace the extravasated colloid lost as a result of capillary leak. Plasma has the advantage of providing immunoglobulin, acute-phase proteins, and anticoagulants (see Laminitis Prevention).

In horses with the most life-threatening forms of endotoxemia and sepsis (lactate >4 mmoles/L [>5 mmoles/L in neonates <24 hours old], MODS/L, septic shock), aggressive hemodynamic monitoring and EGDT are indicated. Because such treatment still carries at best a guarded prognosis for survival, financial commitment often in the range or $5000 to $20,000, and transfer to a referral center, a decision to continue treatment requires that a very clear and realistic discussion of these issues take place with the horse's owner. Early intervention is essential in sepsis therapy, in critical care parlance, terms such as the “golden 6 hours” and the “silver 24 hours” exemplify this concept.[410]

Relatively simple equipment and supplies but time-intensive monitoring and treatment are needed for effective EGDT. A central venous catheter (e.g., for 50-kg neonates, two-lumen indwelling catheter, 7 Fr × 30 cm [ES-14702], Arrow International, Reading, PA; 500-kg adults, two-lumen Hickman 9 Fr × 90 cm, Bard Access Systems, Salt Lake City, UT), a blood gas and lactate analyzer, an indirect arterial blood pressure monitor, and a central venous blood pressure monitor (transducer and data display and recorder or water monometer) are required for the full EGDT bundle; however, much can be achieved with a jugular catheter, water manometer, and lactate analyzer. The details of an intensive approach to EGDT for the first 6 hours after admission are shown in Fig. 32-45. $ScVO_2$ has been shown to correlate well in this context with cardiac index. Unfortunately, although measurements obtained via a typical jugular intravenous catheter can be used to approximate arterial lactate concentration and CVP in humans[412,413] (although not in dogs and cats[414]), jugular blood SO_2 did not correlate with central measurements in endotoxemic pigs[415] and probably should not be used for that purpose. Although labor-intensive, none of monitoring techniques is technically difficult. One advantage of being able to measure both lactate and $ScVO_2$ is that inferences can be made as to the particular hemodynamic derangement responsible for signs of global tissue hypoxia (see Table 32-6).

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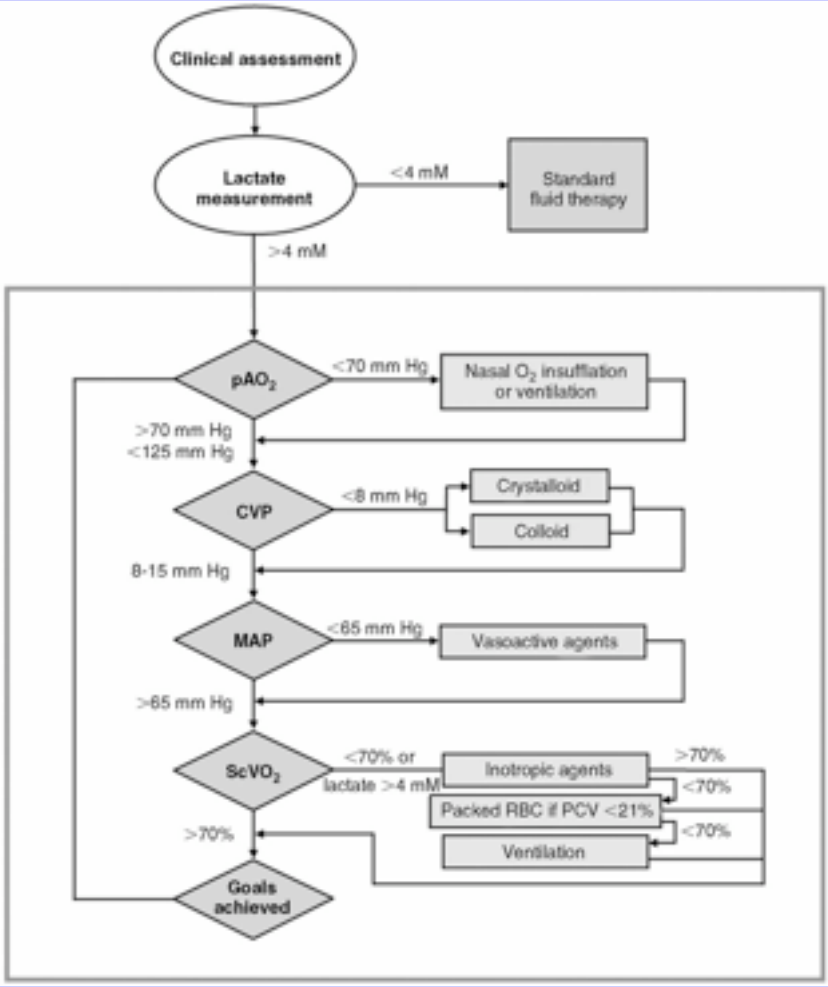
Fig. 32-45 Protocol for early goal-directed therapy. An initial 20 mL/kg bolus of isotonic crystalloid (or equivalent colloid) is given, followed by boluses of 10 mL/kg every 30 minutes until CVP reaches 8 to 15 mm Hg. If the heart-base adjusted MAP is still less than 65 mm Hg, vasopressors are given to effect. Norepinephrine, dopamine, or vasopressin can be used according to the clinician's preference. If the $ScVO_2$ is still less than 70%, dobutamine continuous rate infusion can be increased in increments up to 15 µg/mL. If the PCV is less than 21% after the preceding steps and $ScVO_2$ is less than 70%, packed cells should be given to increase oxygen-carrying capacity. *CVP*, Central venous pressure; *MAP*, mean arterial pressure; *PCV*, packed cell volume.



When the goals of EGDT are met, fluid management should continue according to standard protocols (see Fluid Therapy section) but with adjustments made according to the results of continued monitoring (Pa_{O_2}, Cv_{O_2}, lactate, CVP, mean arterial pressure [MAP]). If the blood bicarbonate concentration is <16 mmol/L after EGDT goals are met (or plasma total CO_2 concentration is <17 mmol/L), sodium bicarbonate should be given IV to replace calculated deficits. During correction of acidemia, intravenous fluids should be supplemented with potassium (10 to 20 mmol/L) to prevent correction-induced hypokalemia. A maintenance-rate infusion of glucose should be given to neonates with sepsis (4 mL of 5% dextrose—containing fluids per kilogram per hour) and hypoglycemic adults (2 mL of 5% or 0.2 mL of 50% dextrose per kilogram per hour). Glucose concentration should be regularly monitored, and the use of concurrent insulin infusion should be considered, especially if blood glucose is normal or high (see Laminitis Prevention section).

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32.58.1.1

Box 32-3 Laminitis Prevention Bundle

Fluid resuscitation

Cryotherapy[479]

Flunixin (0.25 mg/kg every 8 hours)

Pentoxifylline (10 mg/kg PO bid)

Plasma (10 mL/kg)/heparin (4 U/mL plasma)

Insulin (0.01-0.05 U/kg/h)/glucose (0.2 mL 50% dextrose per kilogram per hour) with 2- to 4-hourly measurement of blood glucose concentration

32.58.2

Laminitis Prevention

Adult horses with serious sepsis are at high risk for the development of laminitis. Among the clinical risk factors likely operative in the setting of sepsis are body condition score ≥ 5, being a pony, ≥24 hours since onset of signs of endotoxemia or sepsis, rectal temperature >101.5° F, CRT >2 seconds, or cold extremities. The digital laminae are injured early in the period of hot sepsis, perhaps irreversibly, by processes associated with cytokine storm and global tissue hypoxia. Insulin resistance, hyperglycemia, microvascular injury and thrombosis, and protease activation all may be involved in sepsis-associated laminitis. The laminitis prevention bundle provided in Box 32-3 provides a reasonable preventative strategy, but it must be implemented very early (preferably before increased digital pulses are detected). Global tissue hypoxia is addressed with standard or EGDT fluid resuscitation, small vessel plugging with flunixin (reduced TXA_2), pentoxifylline (vasodilation with PGI_2, suppression of inflammatory cytokines, increased RBC deformability), and plasma and heparin (increased active AT-III), and hyperglycemia and insulin resistance with continuous-rate infusions of regular insulin and glucose (prevention of the damaging effects of hyperglycemia; possible salutary, glucose-independent effects of insulin). If laminitis is already present, or if it develops during the course of treatment, it should be treated as described in Chapter 38.

32.58.3 Removal of the Cause(s) of Endotoxemia and Sepsis

Removal of the cause of endotoxemia usually involves both removal of the source of endotoxin and correction of the abnormality that allows access of endotoxin to blood. In some cases a source of endotoxin can be mechanically removed; for example, gram-negative bacteria and associated inflammatory effusion can be drained from pleural or peritoneal cavities or carefully siphoned from the postpartum uterus. Antimicrobial therapy for gram-negative infection also is essential. In general, broad-spectrum bactericidal drugs should be selected because endotoxemic horses may be immunosuppressed. In horses in which endotoxemia is associated with diarrhea or other signs of colitis or typhlitis, the use of antimicrobial drugs is controversial because of their causal association with severe colitis. They probably should be given only in the following situations: (1) the horse is <3 months old; (2) there is suspicion of clostridial or antimicrobial-associated enteritis (metronidazole or vancomycin); (3) there is degenerative left shift or total neutrophil or lymphocyte count of <1000 μg/mL; or (4) there is clinical evidence of dyshemostasis (e.g., jugular thrombosis or abnormal coagulogram). It should be noted that effective antimicrobial therapy could temporarily worsen clinical signs by causing the release of endotoxin from killed bacteria. This possibility should be anticipated and minimized by the timely use of NSAID or other antiendotoxic therapy (see following paragraphs).

When intestinal strangulation is the cause of endotoxemia, surgical correction obviously is of paramount importance. For the purposes of perioperative management, however, it should be noted that resumption of intestinal blood flow could worsen endotoxemia: sequestered endotoxin may be flushed into the circulation through compromised intestinal walls. At least in the case of small intestinal ischemia, the mucosal barrier to endotoxin may be further compromised by ischemia-reperfusion injury when full blood flow is restored by luminal decompression or other manipulation. Again, prophylactic use of NSAIDs and/or ROS scavengers may be warranted.

32.58.4 Neutralization of Circulating Endotoxin

32.58.4.1 HYPERIMMUNE PLASMA AND SERUM

An antiserum (Endoserum; Immvac Inc., Columbia, MO) and several hyperimmune plasmas (e.g., Polymune J; Veterinary Dynamics, Templeton, CA) produced by immunization of horses against R-mutant endotoxins are used in horses with suspected endotoxemia (in some cases, this is an off-label use). As is the case with studies in human beings and small experimental animals, use of cross-reactive endotoxin antibodies in horses with either experimentally or naturally acquired endotoxemia has yielded conflicting results. In several studies there was impressive reduction of mortality rate or improvement in clinical signs when antiendotoxin serum or plasma was given to horses[416–418]; however, in other studies no improvement was demonstrated.[419,420] Pretreatment of foals with antiserum was associated in one report with significant worsening of clinical response to IV administered endotoxin compared with foals that received no pretreatment.[421] These disparate results probably reflect, at least in part, variation in the quality of antisera and experimental conditions; therefore no blanket recommendation can be made as to the clinical use of such products. As evidence of the potential general value of hyperimmune plasmas, it is worth noting the reduction in mortality achieved when antiendotoxin plasma raised against the *E. coli* mutant J5 was given to bacteremic humans (39% for controls versus 22% for those give antiendotoxin plasma) in a masked, well-controlled study at a single hospital.[422] In contrast, subsequent large multicenter studies of two different antiendotoxin monoclonals failed to show beneficial effects.[423,424] Hyperimmune plasmas (raised against any antigen[s]) also contain colloid,

anticoagulant, and increased amounts of substances such as acute-phase proteins, which might have nonspecific beneficial effect in the setting of endotoxemia and sepsis. Therefore the use of 10 to 40 mL of hyperimmune plasma (of any specificity) per kilogram can be justified in treatment of serious endotoxemia or sepsis.

32.58.4.2 POLYMYXIN B

Polymyxin B is a broad-spectrum cyclic peptide antibiotic with potent endotoxin-binding activity. Potentially lethal side effects of respiratory paralysis and nephrotoxicity have precluded use of this agent as a systemic antimicrobial drug; however, polymyxin B retains endotoxin-neutralizing capacity at nontoxic dosages. Pretreatment of foals with polymyxin B at a dosage rate of 6000 U (1 mg)/kg significantly suppressed clinical and cytokine responses to intravenous endotoxin without causing toxic side effects.[425] Repeated administration to ponies of 15,000 U/kg also produced no sign of toxicity.[426] At dose of 5000 U/kg, polymyxin B protected even when given 30 minutes after the start of LPS infusion.[427] The results of a pharmacokinetic and pharmacodynamic study of polymyxin B in horses suggested that the drug could safely be given at 6000 U/kg every 8 hours to maintain continuous endotoxin neutralization.[428] Horses given polymyxin B at 5 mg/kg as a polymyxin B–dextran 70 conjugate (also known as *PMX622*) were fully protected from the effects of endotoxin but had a transient hypertensive response to treatment infusion.[429] This side effect was prevented by the use of an NSAID. In horses with moderate or severe endotoxemia, consideration should be given to the cautious use of polymyxin B (Polymyxin B sulfate; Bedford Laboratories, Bedford OH) given IV two or three times daily at a dosage rate of 6000 U/kg. Each treatment should be given over at least 15 minutes.

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32.58.5 Inhibition of Endotoxin-Induced Inflammation

32.58.5.1 NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Through inhibition of cyclooxygenase (COX), NSAIDs reduce the formation of prostanoid metabolites (e.g., thromboxanes and prostaglandins) from arachidonic acid and thereby attenuate much of the adverse effect of endotoxin. As stated earlier, it has not yet been established whether or not NSAIDs actually reduce mortality in patients with sepsis. Flunixin meglumine, phenylbutazone, ketoprofen, eltenac, and aspirin are examples of this class of drugs used in horses. When flunixin is administered at 0.25 mg/kg every 6 to 8 hours, endotoxin-induced prostanoid production is prevented, and maximal antiendotoxic effects are produced in experimental situations without obscuring the signs of colic or risking toxic side effects of the drug.[430] It should be noted that flunixin does not reduce endotoxin-induced leukopenia. Because there is evidence that aspirin does not prevent endotoxin-induced aggregation of platelets,[431] there appears to be no rationale for the common practice of adding aspirin to the NSAID regimen. Most NSAIDs inhibit constitutive COX-1 activity (in addition to endotoxin-induced COX-2 activity), so there is some morbidity associated with their use. There may be gastric ulceration, right dorsal colitis, renal papillary necrosis, and possibly impairment of intestinal motility.[432,433] In light of this toxic potential of equine NSAID use, it has been suggested that use of COX-2 selective drugs may minimize side effects while maintaining efficacy. Two NSAIDs with documented analgesic effect in horses, carprofen and meloxicam, have been shown to be COX-2-selective.[434] Etodolac, a COX-2–specific drug in dogs and humans, is not COX-2 selective in horses when used at analgesic doses (23 mg/kg PO once or twice daily).[435] Also, COX-2 activity does have potentially beneficial effects in horses with

sepsis: COX-2 products (e.g., PGE_2, PGI_2) mediate epithelial restitution in damaged equine colon[436] and are thought to be important in maintaining the antithrombotic phenotype of normal endothelium. NSAIDs in the coxib class, which are potently COX-2 specific in humans, have been shown to increase the risk of atherosclerotic cardiovascular disease in humans.[437]

32.58.5.2 METHYL XANTHINE DERIVATIVES

Inflammatory cytokine production by macrophages is suppressed in dose-dependent fashion by methyl xanthine derivatives. This effect appears to be caused by phosphodiesterase inhibition and consequent elevation of intracellular cAMP. Pentoxifylline, a drug that is in widespread use in human beings as a hemorheologic agent, has also been shown to increase RBC deformability in horses.[438] Pentoxifylline also inhibits TNF production in horse blood and in cultured equine macrophages while increasing secretion of prostacyclin.[405,439] Studies in other species suggest that pentoxifylline stimulates production of the antiinflammatory cytokine IL-10, suppresses neutrophil activation, and inhibits activation of NF-κB.[441] A pharmacokinetic study in horses has indicated that administration at 10 mg/kg PO two times daily provides serum concentrations equivalent to those used therapeutically in humans.[442] The potential for flunixin to antagonize the potential beneficial effects of pentoxifylline was discussed earlier in this section. In light of the strong conceptual arguments for its use, pentoxifylline therapy (10 mg/kg PO bid) in endotoxemia is reasonable.

32.58.5.3 CORTICOSTEROIDS

The corticosteroid class of drugs theoretically has many useful actions in combating the effects of endotoxemia. These include reduced production of cytokines, inhibition of TNF production by macrophages, stabilization of cell membranes, and prevention of neutrophil activation. It is surprising, however, that neutral or negative effects of steroid use were found in large, multicenter studies of humans with gram-negative sepsis.[443] Corticosteroids also are widely believed to increase susceptibility to laminitis in endotoxemic horses, perhaps by increasing the sensitivity of digital vessels to the constrictive actions of circulating catecholamines or by inducing insulin resistance and hyperglycemia.[444,445] Use of high-dose corticosteroids is contraindicated in the treatment of endotoxemia in adult horses.

Some human patients with sepsis appear to respond to “physiologic” doses of hydrocortisone.[446] Most of these patients had high baseline cortisol concentrations but were thought to be in a state of adrenal insufficiency. In one study, low-dose hydrocortisone was associated with reduced vasopressor use and lower mortality rates.[446] This concept is not universally accepted, and the use of low-dose hydrocortisone therapy has not yet been reported in equine patients.[448]

32.58.5.4 HEPARIN

The use of heparin in horses with endotoxemia is somewhat controversial. It prevents microvascular thrombosis principally by promoting the anticoagulant activity of AT-III. Unfortunately, heparin cannot reverse existing thrombosis, and because AT-III is consumed during severe coagulopathy, it may not prevent additional intravascular coagulation in such cases. Fresh and fresh-frozen plasma are good sources of AT-III but also provide clotting factors that could potentiate intravascular coagulation. When given at the recommended intravenous or subcutaneous dose of 40 U/kg tid or 150 U/kg bid, respectively, unfractionated

heparin causes intravascular agglutination of equine RBCs.[449] Therefore it could be argued that the use of heparin might actually exacerbate intravascular cellular plugging. This side effect can be avoided by using *low—molecular weight* heparin, which is nonagglutinating but retains anticoagulant activity, principally via inhibition of factor Xa.[450] The use of heparin should be considered in horses that are at high risk for laminitis (e.g., DPJ or grain overload) or hypercoagulation syndrome (early evidence of dyshemostasis such as abnormal coagulogram or spontaneous venous thrombosis). In the latter setting, heparin should be given with plasma (10 to 40 mL/kg) at a dose of either 200 to 300 IU/kg/day for unfractionated heparin (either divided bid SC or as a continuous intravenous infusion) or 50 anti-Xa IU/kg for low—molecular-weight heparin (SC sid).

32.58.5.5 SCAVENGERS OF REACTIVE OXYGEN SPECIES

ROSs are thought to cause corrosive tissue damage during endotoxemia and potentiate the production of inflammatory cytokines via activation of NF-κB. Surgical deflation of distended small intestine is thought to lead to ischemia-reperfusion injury, a process that generates ROSs from epithelial xanthine oxidase. The life-saving process of fluid resuscitation in horses with hypovolemic shock may even lead to whole body ischemia-reperfusion. Despite these presumed associations between oxidant stress and the signs of endotoxemia, little effort has been made to intervene therapeutically at this level. There is some evidence that allopurinol, a hydroxyl radical scavenger and inhibitor of xanthine oxidase activity, has positive clinical effect during sublethal endotoxin infusion.[451] A recommended dose for allopurinol is 5 mg/kg IV. Because dimethyl sulfoxide (DMSO) has been shown to be a potent scavenger of hydroxyl radicals with efficacy in rodent sepsis models,[452] it seems reasonable to use this agent in the treatment of equine endotoxemia. Like allopurinol, DMSO may reduce intestinal mucosal injury after ischemia-reperfusion; to date, evidence for efficacy in this setting has been mixed. DMSO can be given by rapid intravenous infusion (or by nasogastric tube) as a 10% to 20% solution in saline at dose of 0.02 to 1 g/kg every 6 to 12 hours.

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Other antioxidants that are used in equine medicine, including vitamin C, vitamin E, and *N*-acetylcysteine, have shown benefit in rodent sepsis models but have not been evaluated in equine endotoxemia.

Ethyl pyruvate, a stable analog of pyruvate, has been shown to have remarkable protective efficacy in a variety of models of septic and nonseptic shock in rodents and other species.[453] Because this agent is inexpensive and can be given in intravenous crystalloid fluids, it would appear to have potential for the treatment of endotoxemia and sepsis. The beneficial actions of this agent have been ascribed to its antioxidant actions.

32.58.6 Miscellaneous Treatments

Naloxone, a narcotic antagonist, at a dose of 0.2 mg/kg, blunted some of the cardiovascular effects of high-dose endotoxin in one study,[455] but a dose of 1 mg/kg had no effect in another.[456] Of importance, 0.75 mg/kg naloxone caused signs of colic in conscious horses,[457] probably by blocking the actions of endogenous β-endorphins at the high affinity μ-receptor. The detergent tyloxapol was remarkably effective in preventing the effects of endotoxin in anesthetized horses.[458] The mechanism of antiendotoxic action of tyloxapol is unknown, but the detergent has been shown to have wide-ranging effects on cells and proteins, some of which may preclude its use in clinical cases. For example, the detergent has been shown to inhibit cellular phagocytosis, an important event in innate immunity. Also, this agent induces marked hyperlipidemia (up to 100-fold higher than controls) in horses because of interference with lipoprotein metabolism. Similarly, a phospholipid emulsion effectively prevented adverse effects of subsequent endotoxemia; however, the treatment induced hemolysis

sufficient to preclude its use in clinical cases.[459] A published report[460] on the use of the sulfonyl analog of the alpha-phenyl-*N*-tert-butyl-nitrone spin trap molecule suggests that this agent was effective in reducing clinical signs in horses given endotoxin. A cautionary note was the observation that some rodents given the same agent at high doses actually suffered enhanced endotoxin-induced mortality.

PAF inhibitors have been effective antiendotoxic agents in some species but have not yet shown much positive clinical effect in horses or humans.[461] In dogs and other experimental animals, inhibitors of NO production such as N^G-monomethyl arginine reverse endotoxin— or TNF-induced hypotension[462]; however, NOS inhibitors generally have no protective effect in sepsis models. Furthermore, NO production may not be increased in horses with endotoxemia.[463]

A promising method of treatment may be the use of ketamine CRI. Ketamine has been shown in vitro to suppress the production of inflammatory mediators by LPS-stimulated equine peritoneal macrophages.[464] Constant-rate infusion of ketamine at 1.5 mg/kg/h for 320 minutes achieves blood concentrations compatible with this inflammatory effect and has been shown to be safe and nonsedating.[465] The antiinflammatory actions of ketamine appear to be mediated by the actions of adenosine on the adenosine A2A receptor.[466] The equine adenosine A2A receptor was recently cloned and characterized pharmacologically and is itself a potential direct target for antiinflammatory drugs.[467] Because ketamine inhibits inducible macrophage-type nitric oxide synthase and thus potentially causes vasoconstriction,[468] this approach should be used with caution.

32.58.7 Future Treatment Considerations

Current research in horses and other experimental animals suggests that magic bullets will be very hard to find. Most antiinflammatory approaches, even if they are aimed at the "root and trunk" of the inflammatory cascade (e.g., NF-κB activation) do not work consistently in severe sepsis models (e.g., cecal-ligation puncture) or in phase III clinical trials of human patients. It is becoming increasingly clear that much of the morbidity and mortality associated with sepsis results from "cold" sepsis, the state characterized by profound immunosuppression rather than cytokine storm. Affected patients are likely to be injured further by antiinflammatory therapy. There is some indication that IFN-γ, a cytokine that is pivotal in both innate and acquired immunity, can improve survival in immunosuppressed septic mice by preventing apoptosis of lymphocytes.[469] The issue of cold versus hot sepsis raises the issue of the need for accurate recognition of the stages of sepsis. Plasma procalcitonin concentration apparently is able to discriminate levels of sepsis and septic versus nonseptic SIRS.[470,471] Similarly, HMGB1 levels have been used to define sepsis categories in humans and to provide prognostic information.[472] These or equivalent markers need to be introduced into equine sepsis diagnosis.

There remains enthusiasm for strategies aimed at effective means to suppress or scavenge ROSs. In this regard, the remarkable effects of ethyl pyruvate in multiple models of inflammation, which likely mediates via its antioxidant effects, offer considerable promise.[453]

On the horizon are some different approaches that have the potential to be both effective and affordable. One of the most exciting possibilities is that gene therapy might be used to transfect host cells transiently in a targeted way with genes encoding antiinflammatory mediators (e.g., IL-10, TGF-β) or antisense RNA or ribozymes directed against mRNA of proinflammatory or even antiinflammatory or apoptotic mediators.

32.59 MEDICAL DISORDERS OF THE SMALL INTESTINE

Jennifer L. Davis

32.60 ULCERATIVE DUODENITIS

32.60.1 Pathophysiology

Ulcerative duodenitis most often affects foals and, to a lesser degree, yearling horses. Older horses are rarely affected. Lesions occur primarily in the proximal duodenum and may include erosions, focal ulceration, and diffuse inflammation with or without ulceration. The terms *duodenal ulceration* and *ulcerative duodenitis* may refer to differing clinical manifestations of the same problem, and the terms are used interchangeably in this section.

The pathophysiology of duodenal ulcer disease in foals is less well understood than gastric ulcer disease. The disorder is classically considered to be a peptic disease, one in which damage to the duodenal mucosa results from excessive exposure to hydrochloric acid and pepsin. This concept may require revision. Equine duodenal ulcer disease has been presumed to be similar to the disorder in humans, but most cases of duodenal ulcer disease in people are associated with *H. pylori* infection.[480] *H. pylori* bacteria have not been reported in equine gastrointestinal tissues; however, *H. pylori* colonize only gastric (glandular) mucosa, and infection of the duodenum must be preceded by metaplasia of areas of duodenal mucosa to gastric mucosa. This is thought to occur from chronic peptic injury. In humans the incidence of duodenal ulcer disease increases with age,[481] which contrasts with horses, in which duodenal ulcer occurs primarily in animals less than 1 year old.[482]

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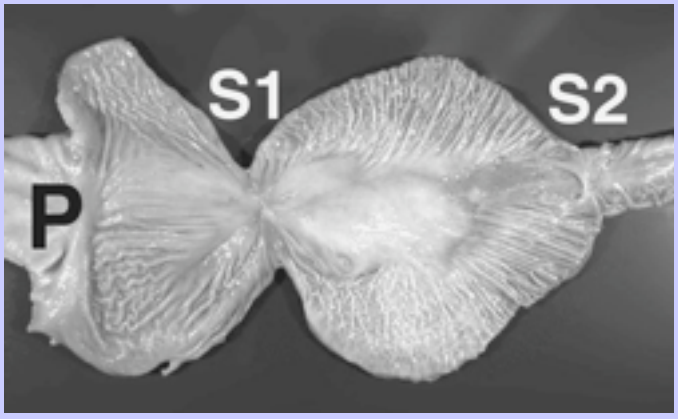
Fig. 32-46 Proximal duodenum of a 10-month-old horse with a history of chronic poor appetite and condition. The pylorus is at the left. There are two strictures in the duodenum: S1 is orad from the major duodenal papilla, and S2 is aborad from the duodenal papilla. The segment of the duodenum between the strictures is dilated. Courtesy Dr. M.J. Murray.



We have recognized occurrences of duodenal ulceration and inflammation in which cases were clustered geographically (same farm) and temporally. These foals all had moderate to severe gastric ulceration, and they had extensive inflammation with varying degrees of erosion or ulceration in the proximal duodenum (see Plates 10, 11). A similar temporal and geographic association was reported in two cases of ulcerative duodenitis in yearlings.[483] These findings seem inconsistent with a purely peptic insult as the cause for the ulcerative duodenitis. In one report of seven foals with ulcerative duodenitis,[484] lesions typically extended into a large area of the proximal duodenum, were characterized by mucosal necrosis, and often had a sharp line of demarcation between affected and more normal-appearing mucosa. In the foals of that report, no common microbial organism other than *E. coli* was identified, and a cause for the ulcerative duodenitis was not determined. In most foals with duodenal disease the lesions were not focal ulcers but rather appeared as more generalized inflammation. An infectious cause seems likely but has not been identified. In the 1980s rotavirus infection was thought to be associated with gastroduodenal ulcer disease in foals, but most foals with duodenal ulcer disease do not have rotavirus infection.

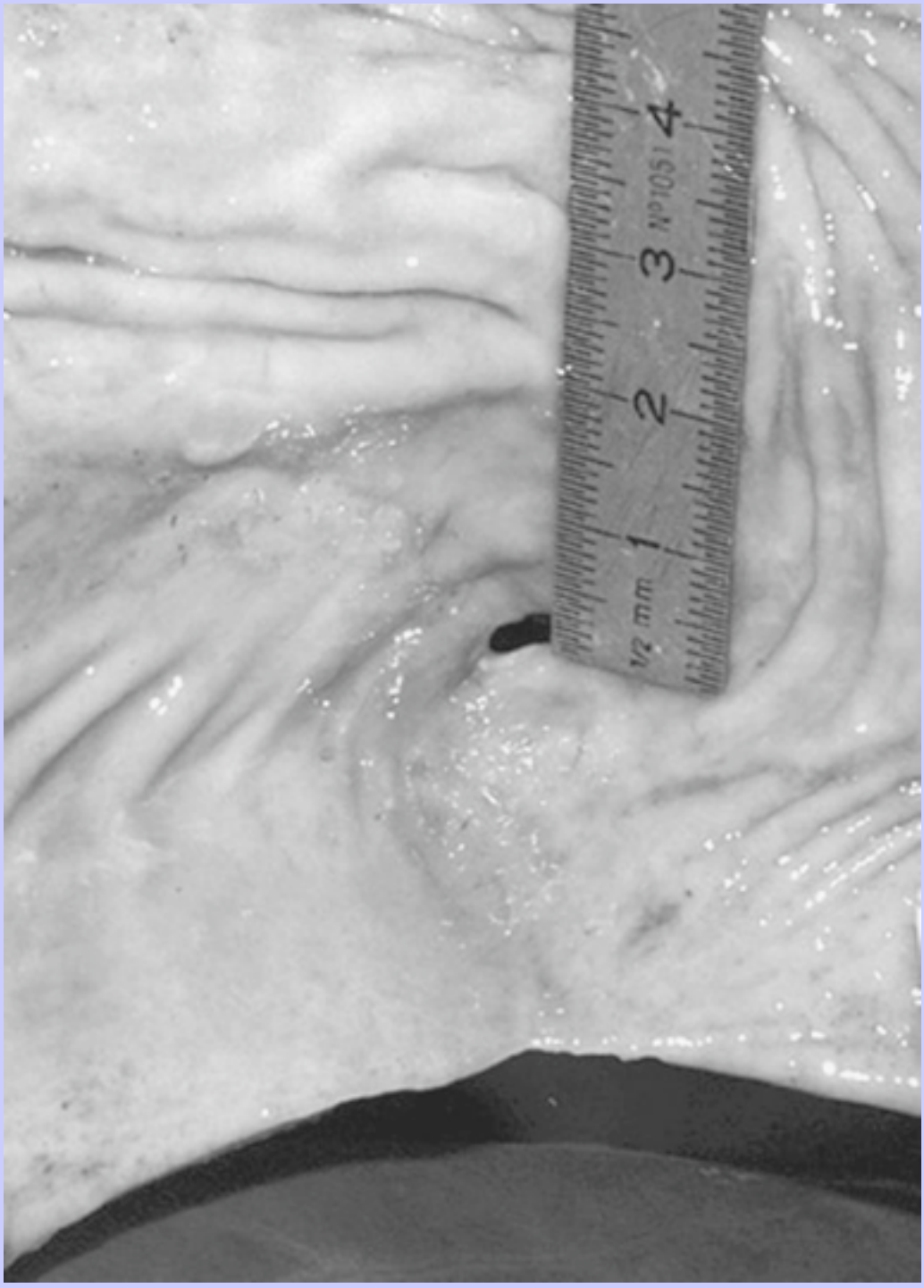
Duodenal ulcer disease in foals may have a component of peptic injury. The duodenal mucosa possesses some intrinsic properties that are protective against peptic injury, although these are not as elaborate as in the gastric glandular mucosa. The most important factor that protects the duodenal mucosa from acidic gastric secretions may be the sodium- and bicarbonate-rich secretions that probably originate from the pancreas and that will neutralize acid entering the duodenum from the stomach.[485]

32.60.2 Clinical Signs

The signs of duodenal ulceration or ulcerative duodenitis have been classically described as being the severe forms of gastric ulcer signs,[486] and in many cases duodenal and gastric ulcers occur simultaneously. However, many foals with ulcerative duodenitis will not have signs similar to those of gastric ulceration until severe gastric ulceration has occurred. Thus the primary signs of duodenitis can be nonspecific; they include fever, mild to moderate abdominal discomfort, mild obtundation, and diarrhea. A CBC will often reveal peripheral blood leukocytosis and hyperfibrinogenemia.

Gastric ulceration frequently occurs along with duodenal ulceration and may be secondary to physiologic or anatomic obstruction to gastric emptying. The gastric ulceration tends to be severe (see Plate 12), often leading to gastroesophageal reflux and esophagitis. Foals with esophagitis often exhibit ptyalism. In general the sequelae of duodenal ulceration are more severe than those of primary gastric ulceration. Complications of duodenal ulceration include duodenal perforation with peritonitis or adhesions, duodenal stricture with complete or partial obstruction (Figs. 32-46 and 32-47), ascending cholangitis and hepatitis, and ascending pancreatitis.

Fig. 32-47 Duodenal stricture *(S1)* of the horse in Fig. 32-46. The diameter of the duodenal lumen at the stricture is only 3 mm. Courtesy Dr. M.J. Murray.



32.60.3 Diagnosis

Duodenoscopy is the most specific means of diagnosis. It requires an endoscope with at least a 200-cm working length in foals up to 6 months of age, and a longer endoscope is required in older foals to examine the duodenal mucosa. Because of the size of the stomach and the anatomic configuration of the duodenum in foals, it is usually not possible to advance the endoscope past the duodenal ampulla. Occasionally the endoscope can be advanced into the descending duodenum.

A diagnosis is most readily made in cases in which lesions are diffuse or located within the ampulla. Excessive enterogastric reflux of bile through the pylorus is consistent with duodenal dysfunction. Ulceration at the pylorus or pyloric antrum may accompany duodenal ulceration and thus provide an indication of potential duodenal involvement. Severe gastric ulceration in foals should alert the endoscopist to the potential for duodenal involvement. In such cases, oral H_2 receptor antagonist therapy may be less effective in resolving gastric lesions than in cases of primary gastric ulceration, because of delayed gastric emptying secondary to duodenal ulceration. Therefore if a foal has received such treatment before endoscopy and if gastric ulceration is severe, suspicion of duodenal ulceration should increase.

Other diagnostic procedures that may be helpful include evaluation of peritoneal fluid; serum liver enzymes, particularly biliary-associated enzymes (γ-glutamyltransferase [GGT], ALP); serum bile acids; and radiography. With severe duodenal ulceration, survey radiographs of the cranial abdomen may reveal accumulation of fluid within the stomach and gas ascending the biliary ducts.[487] If barium contrast medium is placed into the stomach, complete emptying is usually delayed (>2 hours) and an irregular mucosal border may be noted in the descending duodenum. It should be recognized that in most cases radiography would not contribute to a diagnosis of duodenal ulcer per se, although duodenal stricture may be noted. If the descending duodenum is to be imaged, the volume of contrast medium placed in the stomach should not exceed 0.5 to 1 L in a foal and 1 to 2 L in a weanling or yearling, or the proximal descending duodenum will be obscured by contrast medium within the stomach.

32.60.4 Treatment

The effectiveness of treatment of duodenal ulceration or ulcerative duodenitis depends on the extent and severity of ulceration and the absence of complications, particularly perforation and stricture of the duodenum. Treatment objectives are to decrease duodenal inflammation, treat secondary gastric and esophageal ulceration, promote gastric emptying, and treat related problems such as peritonitis. If duodenal ulceration is confirmed or even suspected on the basis of clinical signs, treatment should be aggressive.

In acute cases of ulcerative duodenitis there usually is a pronounced lymphocytic infiltration of the mucosa. In more chronic cases there is a mixture of neutrophils, macrophages, fibroblasts, and fibrinonecrotic exudate. Definitive antiinflammatory therapy has not been described for these cases, and the use of corticosteroids or nonsteroidal antiinflammatory medications is controversial because they may worsen gastric ulcer disease through inhibition of protective prostaglandin synthesis.

Suppression of gastric acid secretion is still an important objective in the treatment of ulcerative duodenitis in foals, because most affected foals have gastric ulcers. Initially, acid suppression should be accomplished via parenteral administration of H_2 antagonist (cimetidine, 7 mg/kg IV q6h, or ranitidine, 1.5 mg/kg IV q8h). Oral medications are unlikely to be adequately delivered to and absorbed from the small intestine in the first days of

treatment. Gastric emptying can be enhanced with bethanechol (0.02 mg/kg SC q6–8h or 0.35 mg/kg PO q8h when the foal can consume orally). In foals that have severe duodenal disease or that have required surgery, bethanechol has been given for up to 3 months. Once the foal can accept oral medication, it should be treated with the proton pump inhibitor omeprazole at a dose of 4 mg/kg once daily for the paste formulation. It should be noted that in the 24 hours after the first dose, acid suppression is incomplete, and maximal suppression of acid secretion is achieved between days 1 and 5.[488] Therefore a common practice is to administer an H_2 antagonist IV for the initial 2 days of treatment with omeprazole in foals with duodenitis.

Misoprostol is a synthetic prostaglandin E_1 analogue that has been successfully used in treating duodenal ulcerations in humans. Doses of 2 to 5 µg/kg q8-12h can be used in horses, although side effects may include abdominal pain and diarrhea. Sucralfate promotes duodenal mucosal healing in humans.[489] The dose of sucralfate that is effective in humans with duodenal ulceration ranges from 1 to 2 g two to four times daily. Foals treated for duodenal ulceration that do not have impaired gastric emptying should be administered 2 to 4 g of sucralfate three times daily. *Sucralfate should not be used as the sole therapeutic agent for duodenal ulceration.*

Foals with duodenitis must usually be prevented from nursing or eating for 1 to 3 days. During this time, parenteral feeding should be considered. Depending on the age of the foal, administration of parenteral nutrition should provide 40 to 60 kcal/kg/day.

If medical therapy is ineffective or if sequelae of duodenal ulceration cause complications, surgical intervention may be required. Gastroenterostomy has been reported to be effective in some cases through bypassing the affected portion of duodenum and allowing for an alternative route for gastric emptying.[487] However, short-term survival and long-term quality of life and use are often unsatisfactory. Patients that have a successful surgical outcome require long-term aftercare and usually require long-term maintenance acid suppression and treatment with a prokinetic drug until gastric emptying is normalized. Therefore an owner should be prepared to make a significant time and financial commitment before surgery is considered.

32.61 DUODENITIS–PROXIMAL JEJUNITIS

DPJ, also known as *anterior enteritis* or *proximal enteritis*, describes a clinical syndrome that is characterized by inflammation and edema of the duodenum and proximal jejunum, excessive fluid and electrolyte secretion into the small intestine, and, consequently, large volumes of enterogastric reflux. The syndrome of DPJ was first described in 1982[490] and was more fully characterized in 1987.[491] A subsequent report[492] described clinical and clinicopathologic parameters in horses with DPJ that differed somewhat from cases in the 1982 report, suggesting that either the cases were of similar etiopathogenesis but of different severity or that the cases were of different etiopathogenesis with the only similarity being the segment of bowel affected. A diagnosis of DPJ is often applied to cases in which there is abdominal discomfort, small intestinal distention, and excessive enterogastric reflux without obstruction, yet it is unclear whether all of these cases lie along a spectrum of severity of DPJ or whether there are several disease entities that affect the proximal small intestine and that share clinical features. The latter seems more likely.

32.61.1 Pathophysiology

In horses with DPJ, lesions are consistently found in the duodenum, but the severity and frequency of lesions in the jejunum are variable. Serositis is a consistent finding, characterized by bright red to dark red petechial and ecchymotic hemorrhages on the serosal surface.[491] Histologic lesions include hyperemia and edema of the

mucosa and submucosa, villous epithelial degeneration, epithelial cell sloughing, neutrophilic pleocytosis, hemorrhages in the muscular layers, and fibrinopurulent exudation on the serosa.

With DPJ there is an increased volume of duodenogastric reflux, typically 50 to 100 mL/min. This reflux has been considered to result from increased intestinal fluid secretion and decreased motility. Mechanisms of intestinal fluid secretion include passive transmucosal exudation, secondary to mucosal and submucosal inflammation and characterized by a protein-rich fluid secretion, and active fluid secretion, caused by increased cyclic nucleotides and characterized by fluid with a high electrolyte and low protein content. The components of fluid in the intestines of horses with DPJ have not been characterized, but it is likely to result from a combination of passive and active secretion. In some horses the hemorrhagic nature of the gastric reflux implies increased capillary permeability of the duodenal mucosa, whereas in other horses the watery nature of the reflux, the presence of serum electrolyte disturbances,[493] and the absence of peripheral hypoproteinemia are most consistent with an active secretory process.

Another potential source of the large volume of fluid secreted into the proximal small intestine and refluxed into the stomach is the pancreas. Normally there is periodic orad movement of duodenal contents into the stomach, which has been observed endoscopically and has been documented by collecting gastric contents with and without pyloric obstruction.[485] The duodenal contents have a large component of water, sodium, and bicarbonate, as well as bile salts from the liver. These secretions are presumed to originate from the pancreas, as well as the liver, and pathology of either of those organs may contribute to the pathophysiology in cases of DPJ.

Suppurative cholangiohepatits has been reported in cases of small intestinal inflammation secondary to DPJ.[494,495] The pathophysiology behind this observation may be related to an increased luminal pressure in horses with DPJ, increasing the likelihood of intestinal content regurgitation into the bile ducts. It is also possible that horses with DPJ absorb inflammatory mediators or bacterial products from the small intestine via the portal blood flow or systemic circulation.

Although the exact cause of DPJ is not known, several bacteria and toxins have been implicated. *C. difficile* has been frequently implicated in causing the disease. One prospective study cultured toxigenic species of *C. difficile* from the reflux of 10 out of 10 horses diagnosed with DPJ, and only 1 of 16 horses diagnosed with other causes of nasogastric reflux. Of the strains cultured from these horses, 8 of 10 produced both A and B toxins, whereas the remaining two produced only toxin B.[496] This is significant in that toxin B as been shown to cause inhibitory electromechanical disturbances to smooth muscle in the small intestine, which may be a possible cause of ileus in these horses.[497] Toxin A has also been shown to promote inflammatory cell infiltration into the smooth muscle layers.[498] Influx of neutrophils and release of inflammatory mediators in the intestinal wall have been shown to activate nitric oxide pathways, which results in inhibition of the enteric nervous system, increases in sympathetic tone, and a subsequent reduction of contractile activity in the gut.[499] *C. perfringens* and *Salmonella* species have also infrequently been associated with DPJ, but the significance of these pathogens remains unknown.

Fusarium moniliforme has been cultured from the feed of horses with naturally occurring DPJ. Under experimental conditions, *F. moniliforme* producing fumonosin B1 mycotoxins caused lesions consistent with DPJ.[500] Neurologic lesions were also present in the horses with DPJ in that study, however, and both of those horses died with lesions consistent with equine leukoencephalomalacia. Cantharidin toxins can also cause reddening of the mucosa in the small intestine, as well as excessive gastric reflux[501] and may be a cause in some cases. It is possible that this one syndrome has multiple initiating causes and that no one causative agent will ever be definitively identified.

32.61.2 Clinical Signs and Differential Diagnosis

The major differential diagnoses for DPJ include simple or strangulating small intestinal obstructions. Differentiation can be extremely difficult in some cases and may delay surgical intervention in cases of small intestinal obstruction, to the detriment of the patient. The criteria used to discriminate between DPJ and obstructive lesions include degree of pain, presence of fever, and changes in hematologic parameters and abdominal fluid.

Horses with DPJ have a history of an acute onset of moderate to severe abdominal pain that often is followed by varying degrees of depression. Nasogastric intubation yields a large volume of enterogastric reflux, which is frequently orange-brown in color, with a fetid odor. Palpation per rectum reveals multiple loops of mild to moderately distended small intestine. The initial volume of reflux may range from as little as 4 to 5 L to up to 32 L. The duration of the reflux may be as short as 24 to 48 hours, but it usually lasts 3 to 7 days. Horses are often febrile (rectal temperature greater than 38° C [101° F]) and dehydrated and have injected mucous membranes, prolonged capillary refill time, diminished intestinal sounds, tachycardia (>60 beats/min), and tachypnea.[490–493,502,503] Although abdominal pain usually abates after gastric decompression, most horses remain depressed, which perhaps is the most consistent and characteristic clinical sign of the disease. If the fluid that accumulates in the proximal intestinal tract is not removed periodically, signs of abdominal pain recur.

Assessment of the degree of small intestinal distention and the thickness of the intestinal wall can be useful indicators. Often, horses with DPJ have generalized distention of small intestine, but when palpated per rectum the intestine does not feel taut. In many cases of small intestinal obstruction the bowel will feel tightly distended, but this is not universally true. Ultrasonography can be used, both transrectal and transabdominal, to determine the diameter of the small intestine, evaluate contractions, and measure the thickness of the wall of the intestine. With acute obstruction one can see several segments of small intestine that are 6 to 10 cm in diameter, have no contraction, and have a wall diameter of 3 to 5 mm. With DPJ small intestinal diameter may be less, and the thickness of the intestinal wall may exceed 6 mm.

Culture of the reflux for *Clostridium* and *Salmonella* species can be attempted. This can be difficult, however, given the special conditions required for anaerobic cultures, as well as the intermittent shedding of *Salmonella* species into the gastrointestinal tract of normal horses. Also, the large volume of reflux in these cases may dilute the bacterial population to the point where isolating low numbers of bacteria is difficult.

32.61.3 Clinicopathologic Findings

Clinical laboratory findings include increased PCV and total plasma proteins (hemoconcentration) and a metabolic acidosis in longstanding or severe cases. Abdominocentesis often reveals an elevated peritoneal fluid total protein concentration and a mild to moderate increase in the peritoneal WBC count (>5000 cells/μL).[502] The peritoneal fluid is usually yellow and turbid, but in severe cases diapedesis occurs, resulting in a serosanguineous color. An abdominal fluid total protein concentration ≥3.5 g/dL is associated with a poorer prognosis.[502] The WBC count in the peripheral blood may be normal or increased.[491,492] In addition, hypocalcemia, hyponatremia, hypochloremia, hypokalemia, and acid-base alterations have been reported in horses with DPJ.[493] An elevated anion gap may be present, secondary to decreased calcium and magnesium or increased lactate or albumin concentrations.[502] Increases in the anion gap to ≥15 mEq/L have also been associated with a poor prognosis.

Elevations in liver enzymes, particularly GGT, may be seen in horses with DPJ and may be a useful way to help differentiate between DPJ and strangulating lesions of the small intestine.[494,495] A study examining a large series of DPJ cases retrospectively to determine the prevalence of hepatic damage in horses with small intestinal inflammation showed that horses with DPJ had significantly higher hepatic enzyme activities than the control group of horses with small intestinal strangulating obstruction (SISO).[495] Over 50% of horses with PE had biochemical evidence of hepatic disease (high GGT, aspartate aminotransferase [AST], or ALP activity). Horses with DPJ had a 12.1-fold higher risk of having a high GGT activity and a 1.8-fold risk of having a high AST activity than horses with SISO. AST activity in horses with PE ranged from 133 to 2994 IU/L (reference range 215.8 to 365 IU/L), GGT ranged from 7 to 117 IU/L (reference range 6.2 to 19.1 IU/L), and ALP ranged from 86 to 1103 IU/L (reference range 69.4 to 293.7 IU/L). Bile acid concentrations were rarely abnormal, indicating that hepatic failure was uncommon. Histopathologic evidence of liver pathology was a common feature in the horses with PE that had either biopsies or necropsies performed. Centrilobular necrosis and inflammation were noted in some cases.

32.61.4 Treatment

Because the causative agent(s) of DPJ are unknown, treatment remains empiric and consists of aggressive supportive therapy. The continuous production of enterogastric reflux requires gastric decompression every 1 to 2 hours to relieve pain and to prevent gastric rupture. Approximately 4 to 8 L of malodorous gastric fluid can be collected during decompression. The stomach should be decompressed frequently, regardless of whether or not the horse is showing signs of abdominal pain, as these signs may be masked by severe depression or the administration of analgesic or antiinflammatory medications. Horses should receive nothing by mouth until small intestinal function has returned, recognized clinically by cessation or reduction of the nasogastric reflux to 1 to 2 L over a 4-hour period and increased frequency of borborygmi. The time necessary for gastric decompression varies with each individual patient. Repeated rectal examinations after the first day of therapy will inconsistently reveal distended loops of small intestine, depending on the frequency of removal of the reflux and the severity of the initial lesion. Ultrasonography may reveal fluid-filled small intestine when such bowel is not discernible by rectal palpation. Loops of small intestine are most frequently visualized in the ventral flank area, near the udder or prepuce; therefore this area should be examined in all cases of suspected small intestinal distention.

Intravenous administration of a balanced electrolyte solution is necessary to maintain intravascular fluid volume and cardiovascular performance. In some horses even rapid administration of fluid fails to adequately restore and maintain intravascular volume because of enteric fluid losses that can be as great as 8 L hour. In addition, the very large volume of isotonic crystalloid fluid that must be given IV to keep pace with enteric fluid losses with DPJ may accelerate the flux of fluid from the vasculature into the intestinal lumen because of reduced intravascular oncotic pressure, increased capillary perfusion pressure, and increased capillary permeability in the inflamed intestine. Consequently the balance between adequate hydration and the volume of enterogastric reflux obtained requires careful and frequent monitoring.

Administration of colloid solutions may be of benefit in preserving intravascular volume without promoting enterogastric reflux. The most frequently used colloids in the horse include hyperimmune plasma, and hydroxyethyl starch solutions. Plasma products require a large volume of administration to exert a colloidal effect, which is cost prohibitive in many cases. Smaller doses, however, may have a beneficial effect in horses with DPJ, particularly in animals showing signs of sepsis or endotoxemia. Hydroxyethyl starch solutions have been shown to significantly increase plasma oncotic pressure in ponies administered 10 mL/kg[504] and represent a reasonably priced alternative to plasma. These solutions have been associated with changes in the hemostatic

profile in normal ponies at higher doses of 20 mL/kg[505] and should be used only with caution in horses already at risk for coagulopathies.

During the initial hours of therapy, even aggressive intravenous fluid administration may result in only moderate clinical improvement. A positive clinical response, as evidenced by improved hydration status, decreased heart rate, decreased enterogastric reflux, improved attitude, and improvement in parameters reflecting kidney function (decreased blood urea nitrogen [BUN] and serum creatinine), correlates with resolving intestinal inflammation.

NSAIDs should be used judiciously to avoid masking the clinical signs of a potential surgical lesion. Flunixin meglumine can be used at a dose of 0.25 to 0.5 mg/kg every 6 hours to reduce the untoward effects of arachidonic acid metabolites.

Antimicrobial agents are typically administered to horses with DPJ, although the necessity for antimicrobial treatment in horses with DPJ is uncertain. Given the association of DPJ with *C. difficile*, administration of intravenous penicillin (22,000 to 44,000 IU/kg q6h) is warranted. Metronidazole also has excellent activity against *C. difficile*; however, administration is difficult because nothing can be administered per os. Rectal administration of metronidazole has been studied[506] and can be used in these cases. The dose and frequency of administration should be increased because bioavailability after rectal administration is much less than after oral administration (30% vs. 74%, respectively). Broad-spectrum antimicrobial treatment may be indicated in horses with low WBC counts, but care must be taken in selecting an antimicrobial to avoid potential adverse effects, particularly nephrotoxicosis with aminoglycosides in a dehydrated patient with compromised renal function.

Horses with DPJ may have to be kept from eating for several days and are often in a hypermetabolic state; therefore they rapidly develop a negative energy and nitrogen balance. In these horses parenteral nutritional support should be considered. Parenterally administered solutions containing glucose, balanced amino acid solutions, lipid emulsions, balanced electrolyte and trace minerals, and vitamins have been administered to adult horses with a variety of intestinal disorders, including DPJ. Providing for part of the horse's nutritional requirements (8000 to 12,000 kcal/day) is possible with glucose—amino acid solutions that are of moderate cost. The rationale for this treatment is that through provision of nutritional support to an anorectic, severely ill horse, the healing process will be facilitated, complications will be reduced, and the duration of hospitalization may be shortened. Thus the overall cost of providing nutritional supplementation, enteral or parenteral, to horses with DPJ may well be offset by quicker recoveries and diminished requirements for other costly treatments.

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Prokinetic agents may also be useful in cases of DPJ. Of the available prokinetics, lidocaine is used most frequently.[507] A loading dose of 1.3 mg/kg slow intravenous bolus followed by a continuous infusion of 0.05 mg/kg/hr has been shown to shorten the time of reflux and decrease the hospital stay in horses with DPJ.[508] It may do this by decreasing sympathetic tone, acting as an analgesic agent, or decreasing granulocyte infiltration in the intestinal wall. Its use should be reserved for horses in which a surgical lesion has been ruled out, as it can very effectively mask intestinal pain. Horses should be refluxed frequently during the infusion and checked for other signs of complications, such as laminitis, routinely. Metoclopramide, erythromycin lactobionate, and cisapride are also used in cases of DPJ.[507] The efficacy of prokinetics in this disease is debated, mainly because they require a healthy intestine in order to exert an effect. A more in-depth discussion of prokinetic agents can be found in the section on gastrointestinal ileus in this chapter.

Medical therapy is sufficient in most cases of DPJ. In patients with prolonged nasogastric reflux (>7 days), excessive fluid losses that cannot be corrected with conventional fluid therapy, or clinical and laboratory findings strongly suggestive of an intestinal obstruction, surgery should be considered. Animals with severe cases of DPJ may develop infarction of a segment of the small intestine that requires surgical removal. Surgery is used to

make the diagnosis and potentially to alleviate enterogastric reflux by providing an alternative route for fluid that accumulates in the small intestine. On entrance into the abdominal cavity, dilated small intestine is immediately apparent. After the extent of the diseased intestine is determined, a segment of normal distal jejunum is laid side to side to the proximal diseased intestine in an isoperistaltic fashion, as far proximal on the affected bowel as possible without extending to bowel that cannot be removed from the abdominal cavity. A small 1- to 1.5-cm hand-sewn anastomosis can then be made between the two segments of intestine.[509] This provides an adequate stoma for direct intestinal decompression while minimally compromising the digestive and absorptive capacity of the small intestine. Potential complications of this procedure include development of an intestinal incarceration through the loop that is formed and the development of small intestinal adhesions.

32.61.5 Complications

Complications of DPJ include septic peritonitis, myocardial and renal infarction, aspiration pneumonia, adhesions of the proximal small intestine, and laminitis. The prognosis for surviving the initial intestinal insult is good in cases of DPJ. The death and function losses from this disease are more commonly related to the secondary complications such as laminitis and intraabdominal adhesions. In one report, laminitis occurred in 28% of horses with DPJ, and associated factors were high body weight and hemorrhagic gastric reflux.[510] Laminitis prophylaxis is routinely incorporated into the medical therapy and can consist of a variety of treatments, none of which is proven to be effective. These include NSAIDs, topical glyceryl trinitrate, and DMSO (200 mg/kg given as a 10% solution in normal saline). Horses that received heparin as a prophylactic treatment for laminitis were less likely to develop clinical laminitis than horses that did not receive heparin in one study.[510]

32.62 PROLIFERATIVE ENTEROPATHY

PE is an infrequently diagnosed disorder of the small intestine of weanling foals or yearlings caused by *Lawsonia intracellularis*, an obligate intracellular pathogen. Alternative names for this condition include *proliferative enteritis, proliferative ileitis*, and *intestinal adenomatosis*. The hallmarks of PE are chronic wasting with severe hypoproteinemia accompanied by grossly thickened small intestine with mucosal ulceration. The disease can occur in individual animals or as a herd outbreak among young animals.[511–515]

32.62.1 Pathophysiology

The mechanism of enteritis after infection with *L. intracellularis* involves invasion of the proliferating crypt cells in the ileum, causing excessive mitotic division and severe hyperplasia.[516] The hyperplastic mucosa becomes grossly thickened and develops a corrugated appearance. As would be expected, this thickening of the mucosa, along with the proliferation of immature crypt cells rather than mature villous cells, leads to a limited brush border development and a decreased absorptive capacity, which results in the weight loss and hypoproteinemia present in these cases. The organism can divide within the infected cells and migrate up to the mucosal layers as the cells proliferate and advance. The main differential diagnosis in these cases is *R. equi* enteritis, which can also cause ulceration in the areas of Peyer's patches throughout the small intestine, cecum, and colon.

A genetic predisposition to *L. intracellularis* infection has been proposed. A recent study showed that polymorphisms in several important immune response genes in foals were related to the fecal shedding of *L. intracellularis* organisms.[517] None of these foals had clinical disease consistent with PE, however, and the significance of these gene polymorphisms is still unknown.

32.62.2 Clinical and Laboratory Findings

PE is a chronic, progressive disorder, and therefore affected animals are typically not presented until the disease is advanced. Horses with PE have a variety of clinical problems, most notably chronic weight loss, intermittent abdominal discomfort, or diarrhea. Some affected animals are erroneously treated for primary gastric ulceration, and indeed there may appear to be temporary improvement in attitude and appetite. This may reflect successful treatment of gastric ulcers that develop as a secondary problem. Many affected animals are diminished in stature, reflecting retarded growth resulting from a chronic intestinal disorder that probably affects absorption of nutrients. Affected animals typically appear lethargic with a rough haircoat and may have concurrent respiratory infection, dermatitis, and intestinal parasitism.

Ventral edema often is present as a result of hypoproteinemia. Some animals have tachycardia and tachypnea. Fever is an inconsistent finding. Abdominal ultrasonography is often useful to identify thickened small intestine. The entire ventral abdomen should be examined, but the affected intestine is most often in the distal jejunum and ileum, which can be most commonly seen along the midline caudally. If transrectal ultrasonography is possible, better detail of the intestinal wall will be appreciated. In affected animals the intestinal wall diameter will be 6 to 12 mm. More normal surrounding small intestine may be seen, and in contrast the affected segment of bowel will appear rigid with a corrugated appearance to the mucosa, and the diameter of the lumen will be decreased in size because of mucosal proliferation (Fig. 32-48).

CBC findings in horses with PE vary. Leukocytosis is a frequent finding, and this may be characterized by a lymphocytosis. Profound hypoproteinemia (serum protein <3 g/dL, albumin <1.5 g/dL) is a consistent finding. A foal in one report had mildly decreased total serum protein with markedly low albumin (0.6 g/dL) and polyclonal gammopathy (4.6 g/dL). Hyperfibrinogenemia occurs in some cases. Other clinicopathologic findings are variable and depend on the chronicity and whether there are excessive fluid and electrolyte losses through diarrhea.

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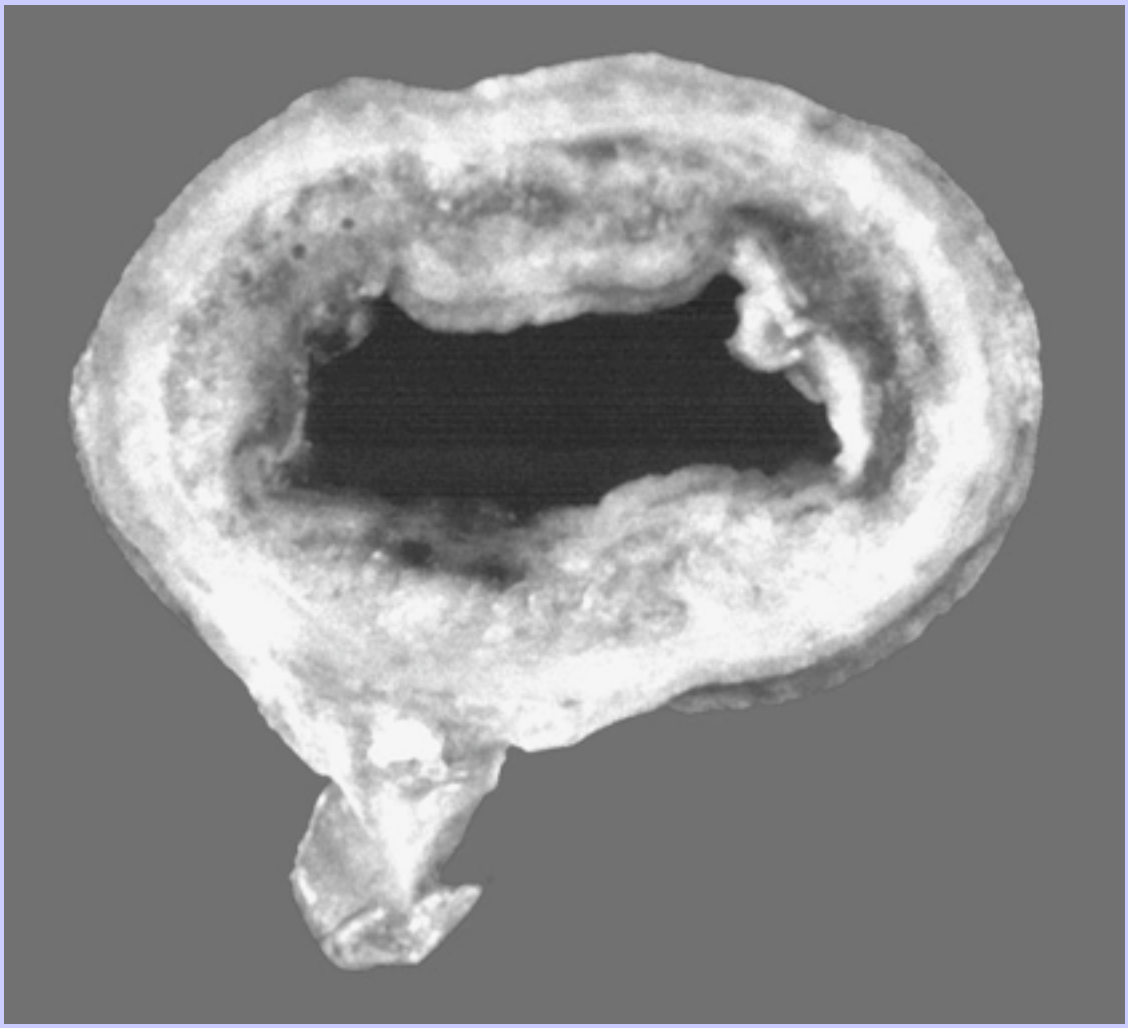
Fig. 32-48 Cross-section of ileum from a 6-month-old horse with proliferative enteropathy. Courtesy of Dr. M.J. Murray.



For definitive diagnosis of PE caused by *L. intracellularis*, isolation of the organism is considered the gold standard. However, culture of this organism is difficult and requires specialized culture media; therefore the sensitivity of this test is questionable. Specific tests for *L. intracellularis* infections in foals have been developed. A PCR can be performed on tissues or feces of PE-suspect foals. Use of this test in tissues is sensitive and specific; however, fecal PCR has a higher incidence of false-negative results.[515] A more useful antemortem test is the indirect fluorescent antibody (IFA) test that detects antibodies against *L. intracellularis* in serum.[515] Titers ≥1:30 were found to be diagnostic of infection in foals.

32.62.3 Pathologic Findings

Lesions are most frequently found in the distal jejunum and ileum, although diffuse thickening of the small intestine may occur. Classically there is pronounced mucosal thickening with varying severity of ulceration and transmural edema. The affected bowel appears to be stiff, and the mucosal surface has a corrugated appearance. Mucosal pleocytosis is a common feature, but in different cases the predominating inflammatory cell type will differ. A lymphocytic or plasmacytic cellular infiltration may be present. There is crypt proliferation, accompanied by crypt elongation and epithelial hyperplasia. The villi are blunted and may become fused. Silver staining with Warthin-Starry stain reveals elongated, curved bacilli in the apical zone of the crypt epithelial cells.[514]

32.62.4 Treatment

Treatment objectives are to eliminate the infection, reduce intestinal inflammation, and maintain hydration and plasma colloid oncotic pressure. Several antibiotics have been reported to be useful for the treatment of *L. intracellularis* infection. Lipophilic drugs with high intracellular penetration are most effective because the bacterium resides within the cells. Ampicillin has good activity against the bacterium in vitro, but because it does not penetrate intracellularly, it is unlikely to be effective in vivo. The most common antibiotic used in PE is erythromycin with or without rifampin for approximately 6 weeks.[515] Other drugs in this class, including azithromycin, may be useful for treatment of this disease owing to their high intracellular concentrations.[518] Chloramphenicol has also been reported to be effective and is a good alternative in foals that develop a worsening of the diarrhea while on erythromycin. The tetracyclines, particularly oral doxycycline, are a cheap and effective alternative to other antibiotics. A recent report looked at 11 cases of PE in foals treated with tetracycline therapy.[519] In this report, 9 of the 11 survived to discharge. The average time to resolution of the diarrhea was 3.5 days after initiation of therapy, and the average treatment time was 3 weeks. The most common administration schedule used was oxytetracycline 6.6 mg/kg IV q12h for 3 to 7 days followed by oral doxycycline 10 mg/kg PO q12h for up to 17 days.[517]

Supportive therapy with crystalloid fluids to correct dehydration, electrolyte imbalances, and azotemia secondary to fluid losses from profuse diarrhea is warranted. Colloidal support with plasma or hydroxyethyl starch solutions can help correct the edema and decreased colloid oncotic pressure. NSAIDs should be used with caution in foals showing signs of dehydration.

Prognosis in these cases is generally good with early and correct diagnosis of the problem. Therapy can be prolonged and should be continued until the diarrhea and hypoproteinemia have resolved and there is no longer evidence of thickened small intestine on ultrasound.

32.63 RHODOCOCCUS EQUI ENTERITIS

R. equi bacteria most frequently cause a severe pyogranulomatous pneumonia in foals 2 to 3 months of age. Extrapulmonary disorders have been associated with *R. equi* infection in foals, however, and include several intestinal manifestations. Enterocolitis and typhlitis were reported in 10 of 61 foals in one study.[520] Diarrhea (13 of 61) and abdominal lymphadenitis (17 of 61) were also reported in the same study.

32.63.1 Pathophysiology

Intestinal infection with *R. equi* can occur through either fecal-oral transmission or swallowing of infected sputum. The organism invades and reproduces within the macrophages, causing a pyogranulomatous disease. In a survey of normal foals on two different farms, *R. equi* was shed in the feces of 16 of 17 and 19 of 26 foals, respectively.[521] Only two foals developed clinical signs of intestinal disease, and the shedding of bacteria in the feces increased threefold to fourfold during those times. Such foals, as well as adults, are likely the source of repeated contamination on endemic farms. Whether or not the organism causes disease is based on the presence of virulence factors, particularly VapA, which has been most commonly associated with disease in pneumonic foals.

32.63.2 Clinical and Laboratory Findings

Foals diagnosed with *R. equi* enteritis typically manifest the signs of pneumonia first, although foals in which the enteric form is the major pathology have been reported.[522] With the enteric form of the disease, diarrhea, weight loss, and colic are present. Foals are often febrile, anorectic, and depressed. Typical clinicopathologic findings include leukocytosis with neutrophilia and severe hyperfibrinogenemia. Ultrasound of the abdomen may reveal pyogranulomatous abscesses in the lymph nodes.

A diagnosis of *R. equi* enteritis can be presumed in pneumonic foals showing signs of gastrointestinal disease 729
that culture positive for *R. equi* in transtracheal wash fluid. *R. equi* can also be cultured from the feces, small 730
intestinal luminal contents, or occasionally the peritoneal fluid of affected animals. A PCR based on the *vapA* gene has been developed and can be used as an adjunct diagnostic in these cases.[523]

32.63.3 Pathologic Findings

The most common small intestinal lesion is multifocal ulcerative enteritis in the area of the Peyer's patches of the ileum. Other parts of the small intestine may be affected, with lesions present throughout the entire small intestine.[523] These lesions frequently extend into the cecum and colon as well. A suppurative exudate is also present, along with pyogranulomatous inflammation of the mesenteric lymph nodes.

32.63.4 Treatment

Treatment of *R. equi* enteritis is similar to treatment of *R. equi* pneumonia. Erythromycin estolate (25 mg/kg PO q6-8h) or erythromycin phosphate (37.5 mg/kg PO q12h) combined with rifampin (5 to 7.5 mg/kg PO q12h) has been the traditional treatment for these foals, and it is still effective but requires a long duration of treatment and is difficult for owners to administer because of the frequency of the treatments. Alternative treatments include azithromycin (10 mg/kg PO q24h for 5 days, followed by q48h) and clarithromycin (7.5 mg/kg PO q12h). It is very important to continue treatment until the hematologic abnormalities and radiographic examinations have returned to normal, in order to prevent relapses.

32.63.5 Complications

Complications associated with *R. equi* enteritis include septic peritonitis and the development of intestinal adhesions. These may lead to death of the animal, or chronic abdominal problems in those that survive. Therapy

is often prolonged in these cases, and owners should be warned that foals with extrapulmonary disorders associated with *R. equi* pneumonia have a more guarded prognosis.

32.64 ENTERIC PYTHIOSIS

Pythium species are protistal organisms that belong to a group of phycomycotic organisms that also includes *Conidiobolus* and *Basidiobolus* species. They are a frequent cause of severely pruritic cutaneous granulomas in horses along the Gulf Coast and southern United States. Much less frequently, the disease can cause granulomatous lesions in the small intestine.

32.64.1 Pathophysiology

Pythium species are presumed to be transmitted via contact with contaminated water. Once ingested the organisms are thought to penetrate the intestinal mucosa through an existing lesion, because necrotic tissue is considered chemotactic.[524] *Pythium* species may be able to penetrate healthy tissue, however, because some cases in dogs have been reported to have mesenteric lymph node involvement without any mucosal lesions.[525]

32.64.2 Clinical and Laboratory Findings

Four reports of enteric pythiosis can be found in the literature.[526–529] In all cases, masses occurred in the mid to distal jejunum. One horse died suddenly, one was euthanized during surgery, and two were successfully treated with a jejunal resection. Organic iodide therapy was instituted in one horse postoperatively for 30 days. In three cases clinical signs of intestinal disease had been present for several months before diagnosis. Chronic colic, weight loss, inappetence, and ill thrift have all been reported and could be related to the intestinal lesion. None of the reported animals had skin lesions. Hematologic evaluation was nondiagnostic in the three cases in which it was performed.

Grossly, lesions are caseous with discrete yellow foci (“kunkers”), and the intestinal wall is thickened because of a pyogranulomatous inflammation. Microscopically, a diffuse, mixed inflammatory infiltrate, along with granulation tissue, is found in the submucosa, tunica muscularis, and mesenteric attachments. Culture of the organism is difficult in these lesions; however, an indirect immunoperoxidase technique to stain for *Pythium*-positive hyphae is available in some laboratories.[528]

32.64.3 Treatment

Treatment of phycomycetes is often difficult. They are not true fungi; therefore they are resistant to many antifungal drugs. Systemic amphotericin B is only rarely effective in treating the cutaneous disorder. Organic iodides are inexpensive and safe when administered orally, but the mechanism of action as an antimicrobial drug is not understood, and the efficacy of this compound has not been proven when treating this disease. A vaccine can be formulated against the organism, and this has been shown to shrink the lesions in horses with cutaneous disease. Whether or not it would work in enteric disease is unknown at this time. In addition, premortem or presurgical diagnosis of the disease is extremely difficult, making surgical resection and biopsy the most effective treatment.

32.65 INFLAMMATORY BOWEL DISEASE

Several intestinal disorders characterized by inflammatory cell infiltration have been placed under the umbrella of inflammatory bowel disease (IBD), including granulomatous enteritis, multisystemic eosinophilic epitheliotropic enterocolitis, eosinophilic enterocolitis, lymphocytic-plasmacytic enteritis, and basophilic enterocolitis.[530–536] IBD in humans is typically characterized by a neutrophilic inflammation, but neutrophils are just the effector cell in a highly complex disease process.[537] The syndromes described for equine inflammatory intestinal disorders therefore appear to differ from human IBD; given the different types of cellular infiltrates found in affected horses, these disorders presumably reflect different pathophysiologic mechanisms. Thus use of the term *inflammatory bowel disease* is not intended to imply either a similarity to the condition described in human beings or similarity among the various syndromes described in horses.

32.65.1 Clinical and Laboratory Findings

Horses with IBD typically have progressive weight loss despite a good appetite and have intermittent abdominal discomfort. If the disease predominates in the small intestine, diarrhea will not be a feature. In some cases there will be associated dermatitis.[538] Horses often present with peripheral edema secondary to hypoproteinemia from enteric protein losses. Ultrasonography may reveal thickened small intestine (>5 mm wall diameter).

Clinicopathologic abnormalities may include anemia, hypoalbuminemia, hypoproteinemia, and malabsorption of glucose and D-xylose. Hypoalbuminemia in the absence of proteinuria or severe liver dysfunction is consistent with protein-losing enteropathy. Some horses may have a relative gammopathy. Serum electrolyte concentrations and total CO_2 are usually normal. Subclinical disseminated intravascular coagulation with thrombocytopenia and increased fibrinogen degradation products have been identified in horses with chronic enteritis.[533,539]

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In many horses inflammatory cells infiltrate throughout the intestinal tract. Therefore rectal mucosal biopsy may be useful to identify cases of IBD in horses.[540] A definitive diagnosis often requires biopsy of the small and/or large intestine. With appropriate instruments this can be done by laparoscopy, although an exploration via a ventral midline approach permits a more thorough evaluation of the abdomen. In most horses cellular infiltration can be found to varying degrees throughout the intestinal tract.

Histopathologic evaluation of biopsy specimens can be used to differentiate among the various IBDs reported in horses, based on the following criteria.[534] A diagnosis of granulomatous enteritis is made when aggregates of macrophages and epithelioid cells are found in the mucosa and/or submucosa, along with villous atrophy. In lymphocytic-plasmacytic enterocolitis, lymphocytes and plasmacytes are present in the lamina propria, and villous atrophy usually occurs. For multisystemic eosinophilic epitheliotropic disease, eosinophils, lymphocytes, and macrophages are found in the mucosa and submucosa. Rarely basophils have also been reported.

A new syndrome has recently been discovered involving focal areas of eosinophilic inflammatory infiltrates within the small intestine, termed *idiopathic focal eosinophilic enteritis* (IFEE).[536,541–544] Affected horses typically are presented not because of chronic weight loss or diarrhea, but rather as acute colic cases. Hypoproteinemia and malabsorption are not present. The lesions are intramural masses or circumferential mural bands. Eosinophils with or without lymphocytes are seen infiltrating all layers of the intestine, with varying degrees of fibrosis.[534] No underlying cause of the disease has been found, although food allergy, parasitism, and

Pythium species have all been suggested.[544] The incidence, or at least the diagnosis, of this disease appears to be increasing.

32.65.2 Treatment and Prognosis

Because the specific diseases included under the general category of IBD are quite different, a generalized treatment recommendation cannot be made. Most reported cases of IBD in horses have been fatal, even with aggressive treatment with corticosteroids. Classically reported cases of eosinophilic, lymphocytic, and basophilic enteritis have failed to respond to treatment. If treatment is attempted, immunosuppressive doses of dexamethasone, up to 0.2 mg/kg, once daily are recommended. Successful remission of granulomatous enteritis was reported in one patient that was treated with dexamethasone[545]; however, in the vast majority of cases treatment is unsuccessful. Cases of IFEE should be differentiated from other causes of IBD with regard to treatment and prognosis. These cases frequently respond to surgical decompression without resection if circumferential mural bands are the only lesion present.[544] In cases of intramural masses, surgical resection of the lesions usually resolves the problem.[543]

32.66 NEOPLASIA

Primary and secondary neoplasia involving the alimentary tract of horses is relatively uncommon, although several cases have been reported.[546] Typical signs associated with, but not diagnostic for, small intestinal neoplasia include colic and weight loss. In most horses with focal intestinal neoplasia the problem becomes apparent when only lumen obstruction develops. Lymphosarcoma can be disseminated throughout a large portion of intestine, eventually resulting in a malabsorption and weight loss syndrome. Lymphosarcoma affects horses of all ages and can be manifested as an enteric disorder, as well as affecting other systems.[547] The diagnosis of enteric lymphosarcoma can occasionally be made on the basis of cytologic examination of fluid obtained by abdominocentesis. In other cases intestinal biopsy is required to diagnose the neoplastic disorder. The prognosis is best if the tumor is discrete and can be removed surgically. A combination chemotherapy protocol of cytarabine (170 mg/m^2 IM), cyclophosphamide (142 mg/m^2 IV), and prednisolone (86 mg/m^2 PO) has been reported to be effective in the treatment of mixed-cell thoracic lymphoma.[548] In other cases, corticosteroid therapy may induce clinical remission for several months, although it is not curative.

Other neoplasms affecting the small intestine are unusual, typically arising from the wall of the bowel, and include adenocarcinoma,[549] leiomyosarcoma,[550] and neurofibroma.[551] These tumors often result in intestinal obstruction and signs of abdominal discomfort. Discrete tumors may be surgically removed.

Paraneoplastic syndromes may the first indication of neoplastic processes in the horse. Pemphigus, hypoglycemia, hypercalcemia, erythrocytosis, and neuropathies have all been associated with tumors in horses.[552] Paraneoplastic processes may also lead to intestinal tract dysfunction in horses with extraintestinal tumors. Amyloid deposition secondary to multiple myeloma in a horse has been described.[553]

32.67 SMALL INTESTINAL FIBROSIS

Small intestinal fibrosis is a rare syndrome that causes weight loss, chronic colic, and progressive debility in horses and ponies. Clusters of affected animals are reported in Colorado[554,555]; however newer reports have been published in horses from Missouri.[556] The pathophysiology behind the fibrosis is not known, although ingestion of

toxins (*Convolvulus arvensis* or common bindweed), inhibitors of 11β-hydroxysteroid dehydrogenase, or compounds with mineralocorticoid activity has been suggested.

Palpation per rectum typically reveals thickening of the small intestinal wall, which may be confirmed by ultrasound.[555] Grossly, the overall length of the intestine may be shortened by as much as 50%.[554,555] The histologic lesions include arteriosclerosis, capillary endothelial hypertrophy, extensive fibrosis of the submucosa, and hypertrophy of the muscularis mucosae and tunica muscularis.[554] The prognosis for the disease is determined by the length of the intestine that is involved. Surgical resection may be attempted.

32.68 LYMPHANGIECTASIA AND CHYLOABDOMEN

There are few reports of lymphangiectasia and chyloabdomen in the literature. Lymphangiectasia is dilation of the lymphatics of the small or large intestine (Fig. 32-49), usually caused by an abscess[557] or neoplasia. There are reports of chyloabdomen resulting from congenital lymphatic defects in a neonatal foal, intraabdominal abscesses in a foal, and abdominal adhesions in a miniature horse.[557–559] Typically, thickening of the intestinal wall and leakage of chyle into the peritoneal cavity results from obstruction or rupture of the lymphatics. Animals can have signs that include abdominal discomfort, diarrhea, and chronic weight loss. Diagnosis is made on the basis of abdominal fluid analysis and ultrasonography. Chylous abdominal fluid appears milky and may contain a high percentage of lymphocytes. Ultrasonography may reveal segments of thickened small intestine. Diagnosis is confirmed at surgery or postmortem examination, and treatment, if possible, is usually surgical, although in my experience medical resolution of the effusion has been achieved.

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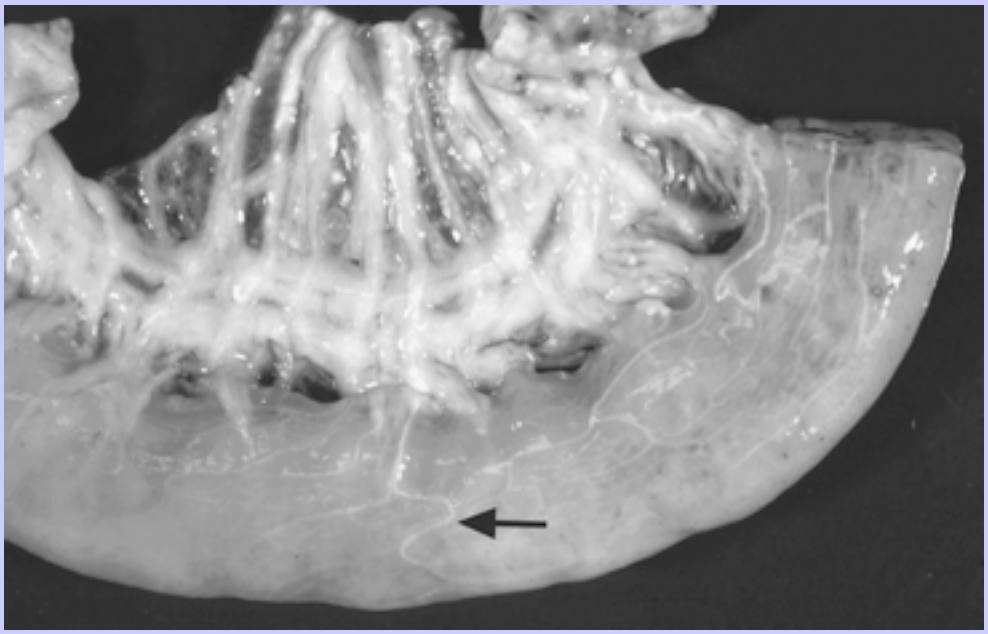
Fig. 32-49 Section of small intestine from a foal with chyloabdomen and a *Rhodococcus equi* abdominal abscess. Mesenteric lymphatics are distended with white chyle, as are serosal lymphatics. Courtesy Dr. M.J. Murray.



32.69 SURGICAL DISORDERS OF THE SMALL INTESTINE

Anthony T. Blikslager

32.70 SIMPLE OBSTRUCTION

Simple intestinal obstruction is a physical obstruction of the lumen without obstruction of vascular flow. The most common causes are intraluminal masses composed of feed material (e.g., ileal impaction) or accumulation of parasites (e.g., ascarid impactions). There are other instances in which the bowel is obstructed without associated compromise of blood supply, most commonly by extraluminal compression by a mass or band of tissue in horses with intraabdominal adhesions. Because a large volume of fluid enters the small intestinal lumen on a daily basis, [560,561] the obstructed intestine becomes distended. The volume of fluid on a daily basis in a hindgut fermenter such as the horse is approximately one extracellular fluid volume, or approximately one third of the horse's body weight. [560] Therefore, although the blood supply is not directly involved in simple obstructions, progressive and marked distention can result in decreased mural blood flow[562] and eventual necrosis of tissues.[563]

32.70.1 Ascarid Impactions

Impactions caused by *Parascaris equorum* typically occur in weanling foals (median age, 5 months; range, 4 to 24 months) that have been on a poor deworming program and that are administered an anthelmintic when they have a heavy parasite burden.[564] Products that cause sudden ascarid paralysis or death, including piperazine, organophosphates, and pyrantel pamoate, have been incriminated.[565] However, it is likely that any effective broad-spectrum anthelmintic, such as the avermectins, will have the same effect. Clinical signs include variable onset of colic after administration of an anthelmintic (usually within 1 to 5 days) and signs compatible with small intestinal obstruction, including nasogastric reflux.[564] The onset of the disease varies according to the degree of obstruction.[565] Diagnosis may be tentatively based on the history in a foal that appears unthrifty, has been recently dewormed, and has signs referable to small intestinal obstruction. The presence of dead ascarids in nasogastric reflux would raise the index of suspicion of this particular form of obstruction.[564] Abdominal radiographs or ultrasound will likely indicate the presence of multiple loops of distended small intestine but are not needed if clinical signs indicate the need for immediate surgery. Surgical treatment typically involves an enterotomy made over the intraluminal impaction and removal of ascarids.

Although simple intestinal obstruction tends to carry a favorable prognosis for survival, ascarid impaction is a notable exception. The mortality rate in these cases is high (up to 92% in one study) as a result of severe intestinal compromise, peritonitis, and development of adhesions. The severe intestinal compromise is almost entirely attributable to the duration of impaction, which for unknown reasons is not as readily recognized in foals as it is in adults. Reasons for this could include failure of the owner or farm manager to recognize colic in foals, or failure on the part of the owner or veterinarian to recognize the implications of colic in foals. Although foals readily display signs of colic, other medical causes of colic such as gastric ulcer disease or enteritis might be higher on the list of differential diagnoses than for adults. Second, the size of a foal may make episodes of colic appear more manageable than in adults, in which colic-induced trauma, especially to the head, may force the issue of referral and surgery at an earlier stage. This is speculative, but early intervention in foals with ascarid impaction would likely result in dramatic reductions in the reported mortality rate.[564]

32.70.2 Ileal Impaction

Ileal impactions occur most commonly in adult horses in the southeastern United States. Although feeding of coastal Bermuda hay has been implicated in the regional distribution of this disease, it has been difficult to separate geographic location from regional hay sources as risk factors.[566] However, a recent study from the Southeastern United States showed that feeding coastal Bermuda hay and failing to deworm with an anthelmintic with efficacy against tapeworms are significant risk factors for ileal impaction.[567] Furthermore, in a study performed in the United Kingdom, horses with evidence of tapeworm infection were at risk for developing ileal impaction.[568] Signs are typical for an adult horse with small intestinal obstruction, including onset of moderate to severe colic and palpable loops of distended small intestine per rectum as the condition progresses. Because the ileum is the distalmost aspect of the small intestinal tract, nasogastric reflux may take a considerable time to develop and is found in only approximately 50% of horses requiring surgical correction of ileal impaction.[569,570] The diagnosis is usually made at surgery, although an impacted ileum may be palpated per rectum.[571] However, multiple loops of distended small intestine frequently make the impaction difficult to palpate. Nonetheless, clinicians working in the southeastern United States who evaluate horses with cases of mild or moderate colic that have a history of eating coastal Bermuda hay, and in which distended loops of small intestine can be detected adjacent to the cecum, should have ileal impaction high on the list of differential diagnoses. Ileal impactions may resolve with medical treatment. In particular, horses that have clinical signs compatible with obstruction of the small intestine but also have normal abdominal fluid should be treated medically unless pain is unmanageable or subsequent abdominal fluid samples indicate intestinal compromise. In those cases in which surgery becomes necessary, fluids (2 to 3 L) can be directly infused into the mass, allowing the surgeon to breakdown the impaction. However, extensive small intestinal distention and intraoperative manipulation of the ileum frequently leads to POI.[572] Therefore some surgeons now elect to perform an enterotomy and to flush the contents from the intestinal lumen with minimal manipulation. Although early studies indicated a guarded prognosis,[570] more recent studies indicate that the prognosis is good.[569,571]

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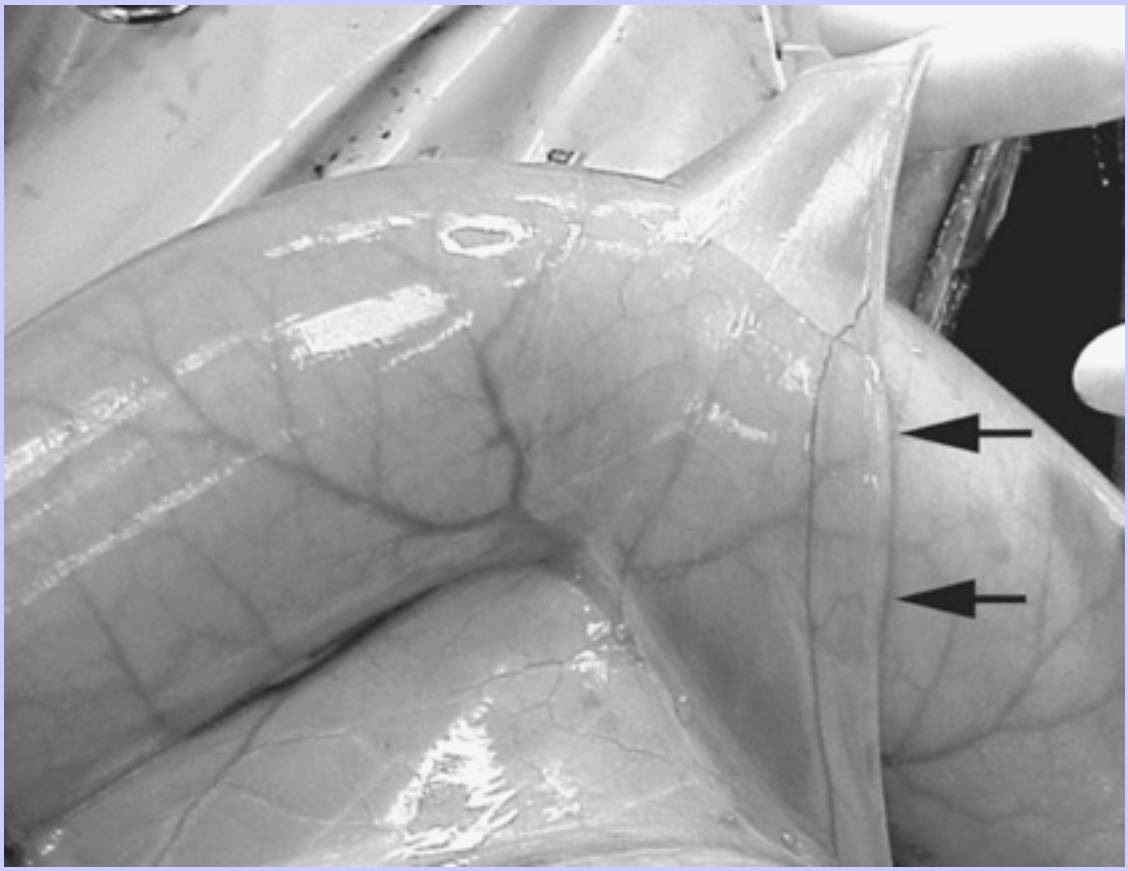
32.70.3 Ileal Hypertrophy

Ileal hypertrophy is a disorder in which the muscular layers (both circular and longitudinal) of the ileum hypertrophy for unknown reasons. Parasitism has been implicated, particularly for those parasites that tend to localize to the ileum (such as tapeworms), but this has never been proven. In some cases the jejunum may also be hypertrophied, either alone or in combination with the ileum.[573] It is clear from these findings that initial functional obstruction initiates this syndrome, causing the musculature of the intestine to hypertrophy in order to push intestinal contents aborally, but there is no evidence as to the mechanisms of this disease. Clinical signs include chronic intermittent colic as the ileum hypertrophies and gradually occludes the lumen. In one study partial anorexia and chronic weight loss (1 to 6 months) were documented in 45% of the horses.[573] The diagnosis is usually made at surgery, although in some cases the hypertrophied ileum may be palpated per rectum or seen on ultrasonographic evaluation of the abdomen. For treatment, an ileocecal or jejunocecal anastomosis to bypass the hypertrophied ileum is performed. Without surgical bypass, intermittent colic persists, and the thickened ileum may ultimately rupture. According to one recent report of 11 horses with hypertrophy of the ileum, only one horse survived, indicating a poor prognosis. The most common reason for euthanasia was spontaneous ileal rupture.[573]

32.70.4 Meckel's Diverticulum

Meckel's diverticulum is an embryonic remnant that may become impacted. The diverticulum arises from the vitelloumbilical duct, which fails to completely atrophy, and becomes a blind pouch projecting from the antimesenteric border of the ileum.[574,575] Occasionally an associated mesodiverticular band may extend from the diverticulum to the umbilical remnant and serve as a point around which small intestine may become strangulated. Mesodiverticular bands may also originate from the embryonic ventral mesentery and attach to the antimesenteric surface of the bowel, thereby forming a potential space within which intestine may become entrapped (Fig. 32-50).[576] Clinical signs range from chronic colic for an impacted Meckel's diverticulum to acute severe colic if a mesodiverticular band strangulates intestine. The diagnosis is made at surgery, and treatment requires resection of the diverticulum and any associated bands.

Fig. 32-50 Jejunal mesodiverticular band. This anomaly was discovered in this horse as an incidental finding during exploration of the abdomen. Intestine may become entrapped within the mesenteric pocket formed by the attachment of the ventral to the dorsal mesentery *(arrows)*.



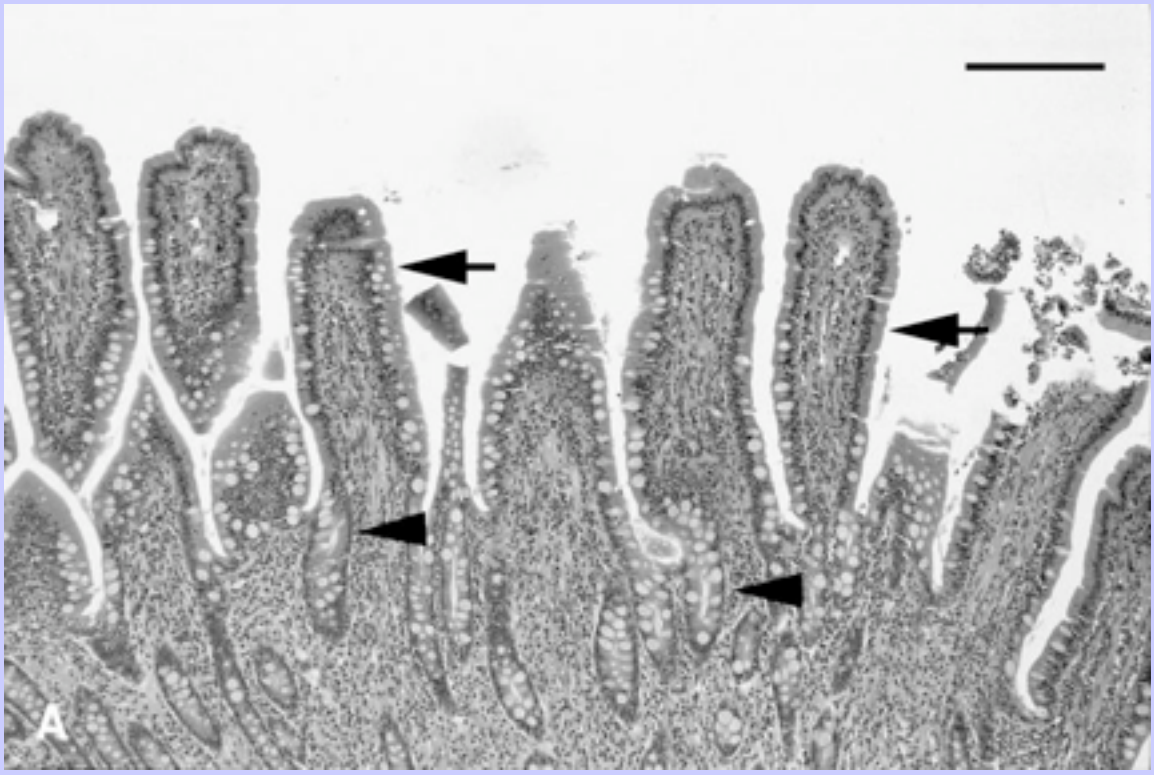
32.71 STRANGULATING OBSTRUCTION

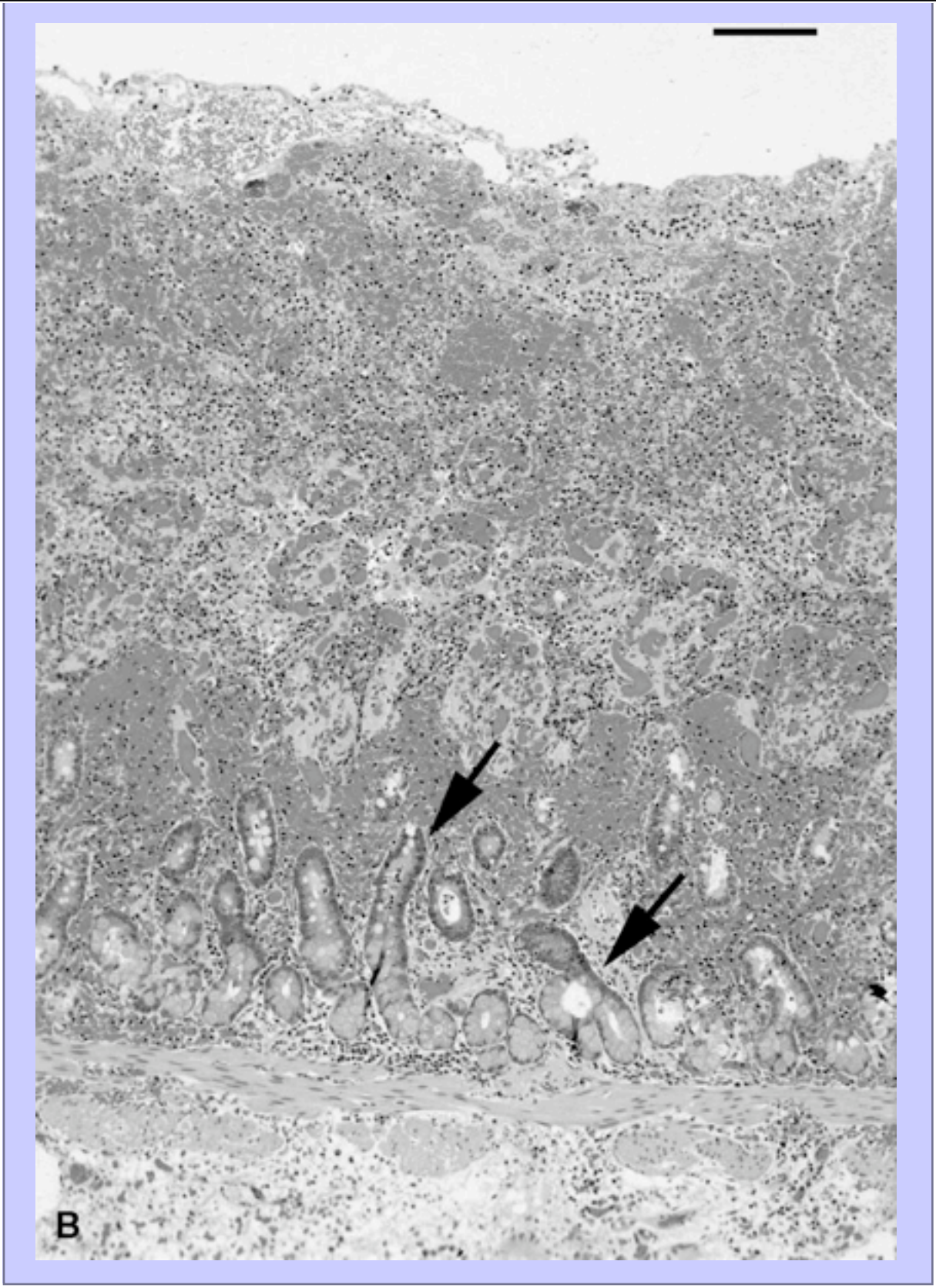
Strangulation obstruction of the intestine is characterized by simultaneous occlusion of the intestinal lumen and its blood supply. Although strangulation of the intestinal lumen results in clinical signs similar to those of simple obstruction, occlusion of the blood supply results in a more rapid deterioration of the intestinal mucosa and subsequent onset of sepsis. Therefore clinical signs (including pain, heart rate, mucous membrane color, and capillary refill time) are typically more severe, and the prognosis is less favorable.

A great deal of work has been done to characterize mucosal injury that occurs during strangulation[577,578] and, more recently, during reperfusion.[579] In general, the lesion that develops during strangulation is severe, leaving little viable bowel for further injury during reperfusion.[580] The severity of the ischemic lesion is partly attributable to the fact that in most cases initial occlusion of veins and partial occlusion of arterial blood supply during strangulation induces a hemorrhagic lesion. This results in extensive congestion and mucosal degeneration (Fig. 32-51).[577] Bowel peripheral to the strangulating lesion may also become injured as a result of distention.[581] In addition, distended small intestine that remains viable after surgical correction of strangulation may be subject to reperfusion injury after surgical correction of the lesion.[582] Unfortunately, attempts at reducing mucosal injury in the horse with antioxidants, which would be expected to inhibit injury attributable to reperfusion injury and associated reactive oxygen metabolites, have been unsuccessful.[583]

The prognosis for survival in horses with small intestinal strangulating lesions is generally lower than with most types of colic. In a large multicenter study, SISO had a fatality rate of 67% compared with that of small intestinal simple obstruction, which had a fatality rate of 48%.[584] Although recent studies indicate higher survival rates in general, the relative fatality of strangulating obstruction compared with simple obstruction is probably similar. One study indicated that in excess of 70% of horses were discharged from the hospital after surgical correction of SISO.[585] These figures should be interpreted cautiously because they are based on the number of horses that are recovered from surgery rather than the number of horses initially presented for evaluation of severe colic. In addition, owners should be warned that the long-term survival rate is reduced by long-term complications.[586] The principal reason for reduced long-term survival in patients that have had small intestinal surgery is intraabdominal adhesions (Fig. 32-52). For example, in one study 22% of horses that had small intestinal surgery required further surgery or were euthanized because of adhesions, and only 25% of horses that had a clinical problem with adhesions survived.[587]

Fig. 32-51 Histologic appearance of normal and strangulated jejunal mucosa. **A**, Normal equine jejunal mucosa, with extensive villi *(arrows)* and mucosal crypts *(arrowheads)*. **B**, Hemorrhagic strangulating lesion of the jejunum, with complete loss of villi and extensive hemorrhage. Note the presence of crypts *(arrows)*, which remain relatively undamaged. 1 cm = 100 µm.

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32.71.1 Epiploic Foramen Entrapment

The epiploic foramen is a potential opening (because the walls of the foramen are usually in contact) to the omental bursa located within the right cranial quadrant of the abdomen. It is bounded dorsally by the caudate process of the liver and caudal vena cava and ventrally by the pancreas, the hepatoduodenal ligament, and the portal vein.[588,589] Clinical signs include acute onset of severe colic with examination findings compatible with small intestinal obstruction. Although the condition was reportedly more prevalent in older horses, recent studies have not detected an age predilection.[590] However, studies have detected a seasonal pattern for this disease. Specifically, more horses appear to suffer from epiploic foramen entrapment during the fall and winter months.[591] An additional factor associated with epiploic foramen entrapment is crib-biting. One potential reason for this association is the development of negative intrathoracic pressure during cribbing, which might then result in cranial movement of intestine into the vicinity of the epiploic foramen. The association between crib-biting and epiploic foramen entrapment has now been shown in separate studies performed in the United Kingdom and the United States.[592]

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Fig. 32-52 Intraabdominal adhesion in a foal. Note the presence of a mature fibrous adhesion between two segments of jejunum *(arrows)* that resulted in kinking and partial obstruction of affected intestine.

The diagnosis is definitively made at surgery, although ultrasonographic findings of distended loops of edematous small intestine adjacent to the right middle body wall are suggestive of epiploic foramen entrapment.[588] Entrapped small intestine may enter the foramen from the visceral surface of the liver toward the right body wall or in the opposite direction. Reports differ as to which is the more common form. Entrapped small intestine may be limited to a portion of the intestinal wall (parietal hernia).[593] In addition, the large colon may become entrapped within the epiploic foramen.[594] In treating epiploic foramen entrapment, the epiploic foramen must not be enlarged either by blunt force or with a sharp instrument, because rupture of the vena cava or portal vein and fatal hemorrhage may occur. In addition, excessive force used to extract entrapped bowel during surgery may also result in rupture of a mesenteric branch of the cranial mesenteric artery. The finding of intraabdominal hemorrhage in some cases of epiploic foramen entrapment before surgery may result from compromise of the mesenteric blood supply rather than the major blood vessels that border the epiploic foramen. Prognosis has substantially improved over the last decade, with current short-term survival rates (discharge from the hospital) ranging from 74% to 79%.[588,595]

32.71.2 Strangulation by Mesenteric Pedunculated Lipoma

Lipomas form between the leaves of the mesentery as horses age, and mesenteric stalks develop as the weight of the lipoma tugs on the mesentery. The stalk of the lipoma and a loop of small intestine or small colon may become intertwined, causing strangulation (Fig. 32-53). Strangulating lipomas should be suspected in mature horses (>10 years old) with acute colic referable to the small intestinal tract.[596] In addition, geldings and ponies appear to be at risk for developing strangulating lipomas,[597] possibly because of differences in fat metabolism. One recent study documented a case of strangulating lipoma in a much younger patient, indicating that although the aging process is associated with development of lipomas, this disease cannot be ruled out preoperatively purely on the basis of age.[598,599] The diagnosis is usually made at surgery, although on rare occasions a lipoma can be palpated per rectum.[600]

Fig. 32-53 Strangulating lipoma of the ileum. A lipoma, together with its mesenteric stalk *(arrows)*, has become intertwined with a loop of the ileum, resulting in a hemorrhagic strangulating obstruction.

Treatment involves surgical resection of the lipoma and strangulated bowel, although strangulated intestine is on occasion viable. Studies indicate that approximately 50% to 78% of horses are discharged from the hospital after surgical treatment.[585]

32.71.3 Small Intestinal Volvulus

A volvulus is a twist along the axis of the mesentery, whereas torsion is a twist along the longitudinal axis of the intestine. Small intestinal volvulus is theoretically initiated by a change in local peristalsis, but the mechanisms of this disease are unclear.[601] It is reportedly one of the most commonly diagnosed causes of small intestinal obstruction in foals.[602,603] It has been theorized that young foals may be at risk for small intestinal volvulus because of changing feed habits as they adapt to a forage-based adult diet. Onset of acute, severe colic, a distended abdomen, and radiographic or ultrasonographic evidence of multiple loops of distended small intestine in a young foal would be suggestive of small intestinal volvulus. However, volvulus is not possible to differentiate from other causes of small intestinal obstruction preoperatively.

In adult horses, volvulus frequently occurs in association with another disease process, during which small intestinal obstruction results in distention and subsequent rotation of the small intestinal around the root of the mesentery (e.g., in horses that have strangulation caused initially by a pedunculated lipoma). Although any segment of the small intestine may be involved, the distal jejunum and ileum are most frequently affected, most likely because the mesentery is longer in the more distal bowel. The diagnosis is made by palpating a twist at the origin of the cranial mesenteric artery during surgical exploration. Treatment includes resection of devitalized bowel, which may not be an option because of the extent of small intestinal involvement. For example, if complete volvulus of the small intestinal tract occurs, the only option would be to untwist the intestine and hope that the bowel was sufficiently viable to survive the disease process. This would in turn depend on the duration of disease and the extent of intestinal ischemia (i.e., how tightly the intestine twisted as the volvulus developed). Prognosis is based on the extent of small intestine involved and its appearance after surgical correction of the lesion.[604] For example, the degree of sepsis may relate to the surface area of devitalized tissue. In addition, the length of the time it takes to complete the surgery can become problematic, particularly in patients with sepsis, in which it is difficult to maintain adequate arterial blood pressure. Nonetheless, survival in patients with extensive small intestinal resection may not relate to the absolute length of intestine resected.[605] A recent study indicated that the prognosis for survival is good (80% of horses recovered from surgery and were discharged).[606]

32.71.4 Inguinal Hernia

Inguinal hernias are more common in standardbred and Tennessee Walking horses, which tend to have congenitally large inguinal canals. Inguinal hernias may also occur in neonatal foals, but they differ from hernias in mature horses in that they are typically nonstrangulating. Typical historical findings in mature horses with inguinal hernias include acute onset of colic in a stallion that has recently been used for breeding. A cardinal sign of inguinal herniation is a cool, enlarged testicle on one side of the scrotum.[607,608] This is attributable to occlusion of the testicular blood supply in most cases rather than strangulated intestine within the scrotum itself. Inguinal hernias can also be detected on rectal palpation, and ultrasound of the testicle is very helpful in determining the diagnosis, particularly considering the differential diagnosis of testicular torsion. The nature of the hernia (direct versus indirect) is determined by the integrity of the parietal vaginal tunic. In horses in which the bowel remains within the parietal vaginal tunic, the hernia is said to be indirect, because strictly speaking the bowel remains within the peritoneal cavity. Direct hernias are those in which bowel ruptures through the parietal

vaginal tunic and occupies a subcutaneous location, followed by strangulation. Direct hernias most commonly occur in foals and should be suspected when a congenital inguinal hernia is associated with colic, swelling that extends from the inguinal region of the prepuce, and intestine that may be palpated subcutaneously.[609,610] Although most congenital indirect inguinal hernias resolve with repeated manual reduction and/or application of a diaper, surgical intervention is recommended in foals with congenital direct hernias in order to reduce the hernia as well as repair the parietal vaginal tunic.

In stallions with indirect inguinal hernias, manipulation of herniated bowel per rectum can be used to reduce a hernia but is not generally recommended because of the risk of a rectal tear. In addition, the inability to visually assess the integrity of the bowel may well be problematic. However, in many cases taken to surgery, the short segment of herniated intestine will markedly improve in appearance once it has been surgically reduced, and in some cases the affected intestine can be left unresected. The affected testicle will be congested because of vascular compromise within the spermatic cord, and although it may remain viable, it is recommended that it be resected. Furthermore, the inguinal canal should be partially closed at surgery to prevent recurrence, and the risk that this procedure will reduce spermatic cord vasculature is a further problem. The prognosis in adult horses is good, with up to 75% of horses surviving to 6 months of age.[608] Horses that have been treated for inguinal hernias may be used for breeding. In these horses, the remaining testicle will have increased sperm production, although an increased number of sperm abnormalities will be noticed after surgery because of edema and increased temperature of the scrotum.

32.71.5 Strangulating Umbilical Hernias

Although umbilical hernias are common in foals, strangulation of herniated bowel is rare. In one study, 6 of 147 horses with umbilical hernias (4%) had incarcerated intestine.[611] Clinical signs include a warm, swollen, firm, and painful hernia sac associated with signs of colic. The affected segment of bowel is usually small intestine, but herniation of cecum or large colon has also been reported.[612] In rare cases a hernia that involves only part of the intestinal wall may be found and is referred to as *Richter's hernia*. In foals that have Richter's hernia, an enterocutaneous fistula may develop. In one study, 13 of 13 foals with strangulating umbilical hernias survived to discharge, although at least three horses died because of long-term complications.[612]

32.71.6 Diaphragmatic Hernias

Herniation of intestine through a rent in the diaphragm is uncommon in the horse, accounting for 0.3% of all cases of colic in a large multicenter study.[584] Any segment of bowel may be involved, although small intestine is most frequently herniated.[613] Diaphragmatic rents may be congenital or acquired, but acquired hernias are more common. Congenital rents may result from incomplete fusion of any of the four embryonic components of the diaphragm: pleuroperitoneal membranes, transverse septum, and esophageal mesentery. In addition, abdominal compression of the foal at parturition may result in a congenital hernia. Acquired hernias are presumed to result from trauma to the chest or a sudden increase in intraabdominal pressure such as might occur during parturition, distention of the abdomen, a sudden fall, or strenuous exercise.[614] In one study, 19 of 40 horses diagnosed with diaphragmatic hernia (48%) had a history of recent trauma.[615] Hernias have been located in a number of different locations, although large congenital hernias are typically present at the most ventral aspect of the diaphragm and most acquired hernias are located at the junction of the muscular and tendinous portions of the diaphragm. In addition, a peritoneal-pericardial hernia has been documented in at least one horse.[616]

The clinical signs are usually associated with intestinal obstruction rather than respiratory embarrassment. However, careful auscultation may reveal an area of decreased lung sounds associated with obstructed intestine and increased fluid within the chest cavity. Such signs may prompt thoracic radiography or ultrasound, both of which can be used to make a diagnosis. In one review, 7 of 40 horses reported in the literature with diaphragmatic hernia (18%) had dyspnea.[615] Auscultation may also reveal thoracic intestinal sounds, but it is typically not possible to differentiate these from sounds referred from the abdomen. In one report, two of three horses diagnosed with small intestinal strangulation by diaphragmatic hernia had respiratory acidemia, attributable to decreased ventilation.[617]

32.71.7 Intussusceptions

An intussusception involves a segment of bowel (intussusceptum) that invaginates into an adjacent aboral segment of bowel (intussuscipiens). The reason for such invagination is not clear, but it may involve a lesion at the leading edge of the intussusception, including small masses, foreign bodies, or parasites. In particular, tapeworms *(Anoplocephala perfoliata)* have been implicated.[618] Ileocecal intussusceptions are the most common intestinal intussusceptions in the horse and typically affect young animals. For example, in one study evaluating 26 cases of ileocecal intussusception, the median age of the horses was 1 year old.[619] Acute ileocecal intussusceptions are those in which the horse has a duration of colic of less than 24 hours and involve variable lengths of intestine that ranged in one study from 6 cm to 457 cm long. In acute cases the involved segment of ileum typically has a compromised blood supply. Chronic ileocecal intussusceptions typically involve short segments of ileum (up to 10 cm long), and the ileal blood supply is frequently intact. Abdominocentesis results are variable because strangulated bowel is contained within the adjacent bowel. There is often evidence of obstruction of the small intestine, including nasogastric reflux and multiple distended loops of small intestine on rectal palpation. Horses with chronic ileocecal intussusceptions have mild, intermittent colic, often without evidence of small intestinal obstruction. A mass may be palpated in the region of the cecal base in approximately 50% of cases. Transabdominal ultrasound may be helpful in discerning the nature of the mass. The intussusception has a characteristic target appearance on cross-section.[620]

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Other segments of the small intestine may also be intussuscepted, including the jejunum. In one study on 11 jejunojejunal intussusceptions, the length of bowel involved ranged from 0.4 to 9.1 m.[621] Attempts at reducing intussusceptions at surgery are usually futile because of intramural swelling of affected bowel. Jejunojejunal intussusceptions should be resected. For acute ileocecal intussusceptions the small intestine should be transected as far distally as possible, and a jejunocecal anastomosis performed. In cases with particularly long intussusceptions (length up to 10 m has been reported), an intracecal resection may be attempted. For horses with chronic ileocecal intussusceptions, a jejunocecal by-pass without small intestinal transection should be performed.

In one study that evaluated the survival of horses with ileocecal intussusceptions, seven of seven horses with chronic intussusceptions survived long term (>4 months), whereas only 5 of 12 horses with acute intussusceptions (42%) survived long term.[619] In a separate study that evaluated survival in horses with jejunojejunal intussusceptions, 6 of 11 horses (54%) were discharged from the hospital after surgery, and 4 of 11 horses (36%) survived long term (>16 months).[621]

32.71.8 Other Small Intestinal Strangulations

Entrapment of the small intestine may occur through rents in the mesentery, internal ligaments such as the gastrosplenic ligament,[622] the broad ligament, and the proximal aspect of the cecocolic ligament.[623] Entrapments may also occur through trauma-induced body wall hernias. For all of these conditions it is often necessary to enlarge the rent or hernia to allow reduction of entrapped small intestine. In the case of body wall hernias, the defect should be closed with suture, or patched using mesh. Entrapment of small intestine within mesenteric rents appears to be particularly problematic because they are difficult to reduce and have an unfavorable prognosis. The latter may be a result of the fact that large lengths of intestine may become strangulated, and because the mesenteric vasculature is frequently compromised to the extent that intraabdominal hemorrhage has been noted in some cases.[624]

32.72 NONSTRANGULATING INFARCTION

Nonstrangulating infarction occurs secondary to cranial mesenteric arteritis caused by migration of *S. vulgaris*[625] and has become a rare surgical disorder since the advent of broad-spectrum anthelmintics. Although thromboemboli have been implicated in the pathogenesis of this disease, careful dissection of naturally occurring lesions has not revealed the presence of thrombi at the site of intestinal infarctions in most cases. These findings suggest that vasospasm plays an important role in this disease.[625] Clinical signs are highly variable, depending on the extent to which arterial flow is reduced and the segment of intestine affected. Any segment of intestine supplied by the cranial mesenteric artery or one of its major branches may be affected, but the distal small intestine and large colon are more commonly involved. There are no clinical variables that can be used to reliably predict or differentiate this disease from strangulating obstruction. In some cases massive infarction results in acute, severe colic. Other cases may have intermittent colic as smaller emboli are released into the colonic blood supply. Occasionally an abnormal mass and fremitus may be detected on palpation of the root of the cranial mesenteric artery per rectum. This disease should be considered a differential diagnosis in horses with a history of inadequate anthelmintic treatment and the presence of intermittent colic that is difficult to localize. Although fecal parasite egg counts should be performed, they are neither indicative of the degree nor specific for the type of parasitic infestation.

In addition to routine treatment of colic, dehydration, and endotoxemia, medical treatment may include aspirin (20 mg/kg q24h) to decrease thrombosis. Definitive diagnosis requires surgical exploration. Surgical treatment depends on the distribution of infarction. Unfortunately, these cases are difficult to treat because of the patchy distribution of the lesions and the possibility of lesions extending beyond the limits of surgical resection. In addition, further infarction may occur after surgery. The prognosis is fair for horses with intermittent mild episodes of colic that may be amenable to medical therapy, but horses that require surgical intervention have a poor prognosis.[625]

32.73 GASTROINTESTINAL ILEUS

Guy D. Lester

A number of factors are responsible for movement of feed through the gastrointestinal tract, and disturbance to any of these could result in ineffective transit and signs of abdominal pain. Gastrointestinal motility involves an extremely complex interaction among the enteric nervous system, the wall of the intestine, and the luminal contents. Other factors that influence the transit of digesta include gravity, the volume and viscosity of the contents,

and pressure gradients created by simultaneous contraction and relaxation of adjacent segments of bowel. Several equine diseases likely involve altered gastrointestinal motility including POI, cecal emptying defect, gastroduodenal ulcer disease, intraluminal obstruction, bowel distention, strangulating obstructions, peritonitis, and primary IBDs, such as DPJ or colitis. Ineffective intestinal motility is also a feature of several neonatal diseases including prematurity, systemic sepsis, and perinatal asphyxia. Certain parasitic infections, electrolyte derangements, and endotoxemia can modify digesta transit in horses of all ages. Intestinal motility is also disturbed during general anesthesia and when specific sedatives, such as xylazine, romifidine, or detomidine, are administered.

32.74 POSTOPERATIVE ILEUS

The inhibition of propulsive bowel activity is usually referred to as *ileus*. Ileus is most frequently ascribed to the condition that occurs after laparotomy and is termed *simple* or *uncomplicated postoperative ileus*. When intestinal motility is disturbed for longer periods after surgery, typically for more than 72 hours, the term *complicated* or *paralytic ileus* is used.[626] POI in horses is most commonly associated with surgery of the small intestine, particularly after resection and anastomosis. The true incidence of POI in horses undergoing laparotomy for gastrointestinal disease is difficult to determine because of variation in definition, surgical skill, and anesthetic technique. POI was reported as a complication in only 10% of horses that underwent laparotomy for a small intestinal lesion at a referral practice.[627] However in a multicenter study 47 of 251 horses undergoing laparotomy for acute colic including small and large intestinal disease developed POI.[628]

POI can have a significant negative impact on short-term postoperative survival.[629,630] Motility dysfunction is likely present in all horses after laparotomy, but most cases are subclinical and require minimal intervention. In symptomatic animals clinical signs are typically observed within 24 hours of recovery and include colic, tachycardia, dehydration, decreased borborygmi and fecal output, and sequestration of fluid within the stomach. Rectal examination and ultrasound may reveal small intestinal distention with rare or absent wall movement. The severity and duration of intestinal stasis is variable, lasting from minutes to days.

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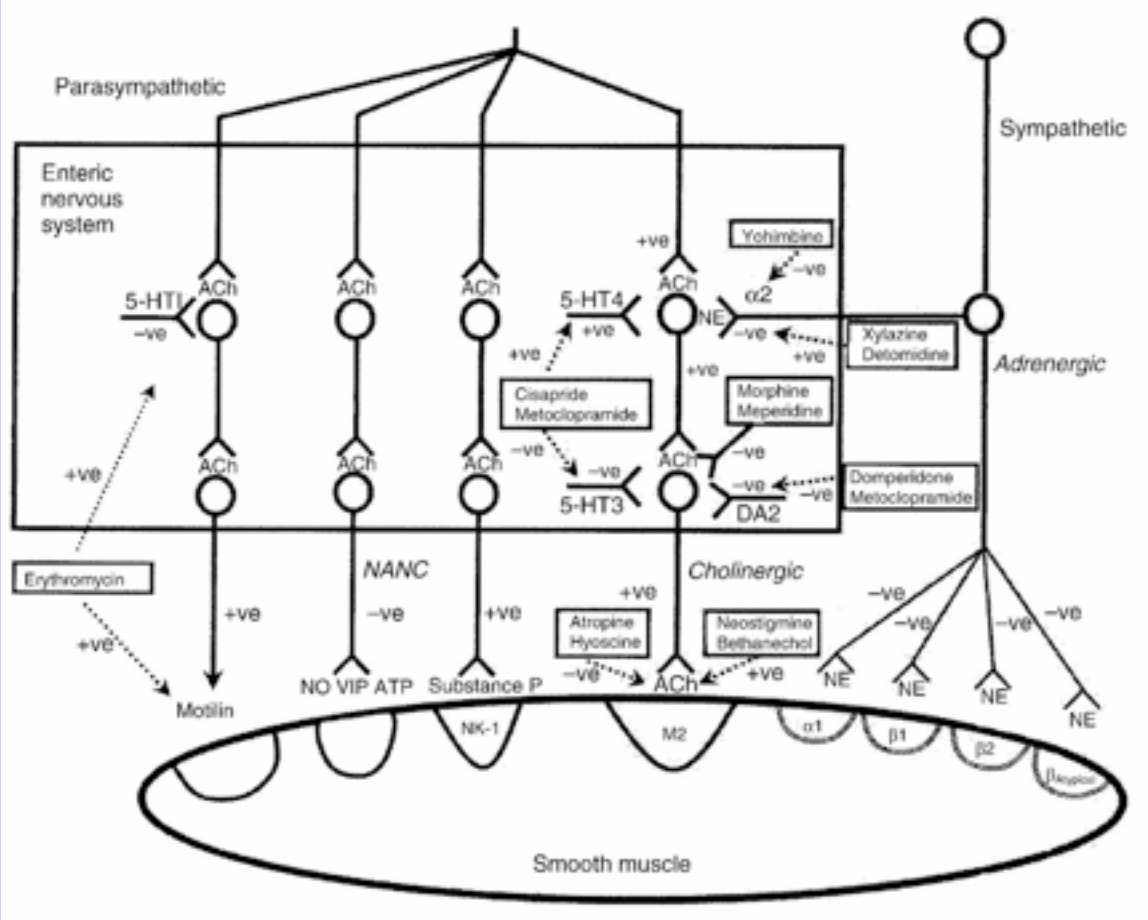
32.75 CECAL EMPTYING DEFECT

An important and specific motility problem involving the cecum occurs sporadically in horses.[631–634] There are limited epidemiologic data about the condition, and key aspects of the pathophysiology are not known. Cecal emptying defect occurs most commonly after general anesthesia and extraabdominal surgery, particularly orthopedic and upper airway procedures, and is therefore often categorized as a form of POI. Young male performance animals appear to be at greatest risk, especially if the procedure is performed with the animal in full work. Other cases occur spontaneously, often in animals with painful primary conditions such as uveitis, orchitis, or septic tenosynovitis. Clinical signs are often subtle unless perforation has occurred. In horses with a cecal emptying defect after anesthesia, clinical signs are usually apparent by 3 to 5 days after the procedure. The earliest detectable signs include depression and a reduction in appetite and fecal output. Ineffective emptying results in overfilling of the cecum with moist contents, which is manifest by signs of mild to moderate colic. If the condition is recognized late or untreated, the cecum may rupture, resulting in fatal peritonitis.

Fig. 32-54 Schematic representation of some neural and hormonal influences on intestinal motility. *ACh*, Acetylcholine; *ATP*, adenosine triphosphate; *DA2*, dopamine type 2 receptors; *+5-HT1*, 5-hydroxytryptamine type 1 receptors; *M2*, muscarinic type 2 receptors; *NANC*, noncholinergic, nonadrenergic pathway; *NE*, norepinephrine; *NK-1*, neurokinin-1 receptors, *NO*, nitric oxide; *+ve*, excitatory; *+ve*, inhibitory; *VIP*, vasoactive intestinal peptide.



32.75.1 Physiology

The control of intestinal motility is complex and involves a combination of central innervation, autonomic innervation, and the enteric nervous system (Fig. 32-54). Intestinal contractions are primarily controlled by the enteric nervous system and do not require extrinsic neural input. The inherent rhythmicity of electrical activity in the intestine is controlled by the interstitial cells of Cajal (ICCs). These are highly specialized cells that are electrically coupled to the smooth muscle syncytium via gap junctions.[635] ICCs are responsible not only for

generation of slow waves (cyclical electrical activity), but also for coordination of pacemaker activity and propagation of slow waves along the intestine. ICCs appear to be critically involved in a range of motility disorders in humans, including gastroparesis, pseudoobstruction, and chronic constipation.[636] In horses a reduction in ICC density was demonstrated with equine dysautonomia (grass sickness) and in horses with large intestinal disease.[637,638]

The inherent "excitability" of smooth muscle cells in response to stimuli varies among regions of the gastrointestinal tract and among species. This variability in cell excitability is dependent on the magnitude of the membrane potential, which in turn is regulated by the number and subtype of potassium channels.[635]

The enteric nervous system plays an important role in control and coordination of intestinal contraction. Contractile events are influenced by central and autonomic innervation, but external neural input is not required for contraction. The parasympathetic supply to the gastrointestinal tract is via the vagus and pelvic nerves, and the sympathetic supply is through postganglionic fibers of the cranial and caudal mesenteric plexuses. A complex network of interneurones within each plexus integrates and amplifies neural input, and the intensity and frequency of resultant smooth muscle contractions are proportional to sympathetic and parasympathetic input. Additional binding sites for a number of other endogenous chemicals, including dopamine, motilin, and serotonin, can be found within the enteric nervous system and on smooth muscle cells.[639] It is important to appreciate that mechanisms to slow progressive intestinal motility are also critical in order to retain feed for adequate digestion and absorption of nutrients. The terms *jejunal* and *ileal brake* have been used to describe the slowing of transit caused by mediators such as peptide YY, noradrenergic nerves, and opioid, serotonergic, and chemosensitive afferent neurons.[640]

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Acetylcholine (ACh) is the dominant excitatory neurotransmitter in the gastrointestinal tract and exerts its action through muscarinic type 2 (M_2) and M_3 receptors. Sympathetic fibers innervating the gastrointestinal trace are adrenergic, postganglionic fibers with cell bodies located in the prevertebral ganglia. Activation of α_2-adrenergic receptors on cholinergic neurons within enteric ganglia inhibits the release of ACh and therefore reduces intestinal contraction. The β_1-, β_2- and β-atypical receptors are directly inhibitory to the intestinal smooth muscle.[641] Inhibitory nonadrenergic, noncholinergic (NANC) neurotransmiters include ATP, vasoactive intestinal peptide (VIP), and nitric oxide (NO).[642,643] These neurotransmitters are critical for mediating descending inhibition during peristalsis and receptive relaxation. Substance P is a NANC neurotransmitter that may be involved in contraction of the small intestine and large colon.[644–646] The rate and force of intestinal contractions along the small intestine and large colon of the horse are key determinants of intestinal motility. Of even greater importance to the net propulsion of digesta are the cyclical patterns of contractile activity. These patterns are known as the *small intestinal* and *colonic migrating motility complexes (MMC)*.[647] The colonic complex usually originates in the right ventral colon and variably traverses the ascending and descending colons. Many of these complexes are temporally related to a specialized motility event of the ileum known as the *migrating action potential complex*.

32.76 MEDIATORS OF GASTROINTESTINAL ILEUS

Inflammation within the intestinal muscularis and inhibitory neural events are important initiators of intestinal ileus.[648,649] Intestinal inflammation is not only important in primary intestinal diseases in horses, such as DPJ and colitis, but is induced after simple intestinal handling during laparotomy. Experimental data from other species suggests that handling of the small or large intestine at the time of surgery induces an intense inflammatory response within the muscularis and a reduction in the intensity of smooth muscle contraction. Furthermore, the

inflamed intestine fails to contract normally in response to putative prokinetic agents. Additional studies have identified that this inflammatory response was not restricted to segments that were manipulated at the time of surgery but also involved other regions throughout the gastrointestinal tract.[649] Intestinal handling in experimental animals causes local overproduction of NO because of the upregulation of iNOS by resident macrophages.[650] NO is a key inhibitory neurotransmitter of the NANC system.[643] Consequently NOS inhibition could be an important target for prevention of ileus.

The inhibition of motility associated with peritoneal inflammation may also be mediated through neural reflexes. The afferent segment is partly composed of capsaicin-sensitive visceral afferent C-fibers that terminate in the dorsal horn of the spinal cord, where they can activate inhibitory sympathetic fibers or, alternatively, synapse directly on the sympathetic ganglia. Consequently the efferent limb of the reflex expresses increased sympathetic outflow, primarily mediated through stimulation of α2-adrenoreceptors, with subsequent inhibition of ACh release. This provides the rationale for alpha-2 blockade in the treatment of ileus. Intraluminal infusion of capsaicin before abdominal surgery ameliorated the severity of POI in experimental rats.[651] This finding highlights the importance of visceral afferent fibers in the development of POI.

Ileus can also occur with intestinal obstruction or displacement. Mild to moderate distention of the bowel, such as that occurring in the early stages of an intraluminal obstruction, evokes an increase in local contractile activity.[652,653] Excessive distention results in inhibition of motility within the distended segment of bowel. Intestinal stasis is not always detrimental and under certain conditions may be protective.

Endotoxemia is a feature of many diseases of the equine gastrointestinal tract, and endotoxins can independently exert a negative effect on intestinal motility and transit.[654] Various mediators are likely involved, but activation of α_2-adrenoreceptors and production of prostanoids appear to be important, as the inhibitory effects of experimental endotoxin infusion are ameliorated by pretreatment with yohimbine or NSAIDs (phenylbutazone or flunixin), respectively.[655,656] Endotoxin infusion induced an inflammatory response in the intestine of rats that mimicked that induced by handling during laparotomy.[657]

The pathophysiology of cecal emptying defect is not known. This syndrome may best mimic POI in humans, which is generally considered a large intestinal disorder. An important difference in horses is that laparotomy is a rare predisposing factor, and most cases occur in horses undergoing routine extraabdominal surgical procedures. General anesthesia itself is a potent inhibitor of gastrointestinal motility in horses, but the effects are short-lived and reversible within hours of anesthetic withdrawal.[658] The return of normal motility in horses after experimental ileus was most delayed in the cecum, suggesting that this may be a common site of ileus in horses.[659] A link between routine postoperative medications, such as phenylbutazone and aminoglycoside antibiotics, has been suspected but not established. An inhibitory effect of NSAIDs on large colon contractility has been demonstrated using in vitro techniques, although the effect of selective COX-2 inhibitors was variable and not as marked as that of mixed isoform inhibitors.[660,661] Primary sympathetic overstimulation could be involved, as many of the affected animals are young, male horses or animals with painful diseases.

The development of small intestinal POI, but not cecal emptying dysfunction, is influenced by the duration of surgery.[628,632] Technique may have a weak influence on small intestinal POI after jejunojejunostomy. The duration of intestinal ileus was shorter in animals that received a side-to-side stapled anastomosis than in those that had a hand-sewn end-to-end procedure.[629] The duration of ileus after stapled end-to-end anastomosis was not different from that after either procedure.

Reported risk factors for the development of POI in horses include age (>10 years), small intestinal resection and anastomosis, breed, and duration of anesthesia and surgery.[628,662] A pelvic flexure enterotomy and emptying the colon and intraoperative lidocaine infusion had a protective effect against POI.

The inhibitory effects of α_2-adrenergic agonists, such as xylazine and detomidine, on intestinal motility in horses are well described.[663–671] The activation of postganglionic cholinergic nerves in the myenteric plexus by this class of drugs results in reduced ACh release from autonomic and enteric nerves. Intravenous xylazine inhibits cecal and large colon motility for 20 to 30 minutes without seriously disrupting small intestinal myoelectric activity, and detomidine can reduce large intestinal myoelectric activity for up to 3 hours. The α_2-antagonist yohimbine has a weak but positive effect on cecal emptying in normal ponies, suggesting that normal motility is under constant α_2-adrenergic tone.[665] Atropine is a postganglionic blocking agent that binds to muscarinic receptors. When administered at 0.04 mg/kg, individual small intestinal, cecal, and colonic contractions are inhibited for about 120 minutes, but small intestinal and colonic migrating complexes are suppressed for up to 8 hours.[672]

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32.76.1 Diagnosis

The diagnosis of ileus is based on history and physical examination findings. Important tests include determination of pulse rate and rhythm, auscultation and percussion of the abdomen, rectal palpation, and passage of a nasogastric tube. A CBC with fibrinogen estimation and cytologic analysis of peritoneal fluid may improve the accuracy of diagnosis. Affected animals may be colicky because of accumulation of fluid in the upper gastrointestinal tract (classical POI) or cecal contents (cecal emptying defect). Decompression of the stomach is important diagnostically and therapeutically in horses with POI after small intestinal surgery. Failure to relieve pain with gastric decompression could point toward mechanical obstruction, severe inflammation of the intestine, or peritonitis. Most animals with ileus are depressed and have reduced fecal output and intestinal borborygmi. Intestinal sounds should, however, be interpreted with caution, because the presence of borborygmi does not always equate to progressive intestinal motility and may merely reflect local, nonpropagated contractions. Rectal palpation findings in cases of persistent POI or DPJ are usually nonspecific but may reveal dilated, fluid-filled loops of small intestine. Roughened peritoneal surfaces can occasionally be palpated if there is peritonitis. Cecal distention with digesta can be palpated in horses with advanced cecal dysfunction.

It is important to distinguish functional ileus from mechanical obstruction. This can be extremely difficult, but horses with mechanical obstruction typically have sustained high volumes of gastric reflux that vary little over time.

32.76.2 Treatment

The management of gastrointestinal ileus is dependent on the segment of gastrointestinal tract involved. Therapy for ileus of the proximal gastrointestinal tract typically involves a combination of gastric decompression, fluid and electrolyte therapy, and antiinflammatory drugs. Nasogastric decompression is the mainstay of management to prevent overdistention of the stomach and small intestine. This often necessitates placement of an indwelling nasogastric tube, a procedure that some have speculated may in itself delay gastric emptying. The placement of an indwelling tube for 18 hours did not adversely affect the emptying of liquids, but in a recent study a delay was noted when the tube was left in place for 72 hours.[673,674] Both studies used apparently healthy animals.

Electrolyte balance is important, particularly with respect to maintaining adequate extracellular concentrations of potassium, calcium, and magnesium. Calculation of the volume of fluid to be administered should include

maintenance requirements (40 to 60 mL/kg/day) plus an estimate of losses, especially those lost through gastric decompression. Overhydration should be avoided in horses with small intestinal ileus. Fluid therapy is the key component in the management of cecal emptying defect, usually in combination with lubricants or laxatives, such as mineral oil or magnesium sulfate, and with careful use of antiinflammatory drugs. Horses with primary cecal impaction or impaction secondary to an emptying defect may require surgery in order to prevent rupture. The surgical management of these cases is controversial and may include typhlotomy alone, typhlotomy with a bypass procedure such as ileocolic or jejunocolic anastomosis, or a bypass without typhlotomy.[675] Most horses that undergo simple typhlotomy have an uneventful recovery, although a small number will reimpact and require a second laparotomy.[633]

A significant clinical or economic benefit of parenteral nutrition in adult horses with gastrointestinal disease has also yet to be demonstrated.[676–678] Parenteral nutrition should be considered when feed has been withheld for more than 96 hours, particularly in the horse with a surgical wound. Limited exercise, in the form of hand-walking, may provide some benefit to these animals, although there is no evidence that exercise has a direct impact on intestinal motility in either horses or humans with POI.[679]

Drugs that may retard normal intestinal motility should be avoided in horses with gastrointestinal ileus. These include the anticholinergics, such as atropine, and opiate receptor agonists, such as morphine and meperidine.[680,681] Butorphanol appears to have little or no adverse effect on either small or large intestinal motility.[682,683] α2-Adrenergic agonists should be used sparingly because of their inhibitory effects on large intestinal motility.

The pivotal role of intestinal inflammation provides a strong rationale for the use of antiinflammatory drugs in affected animals. Flunixin meglumine is widely used in equine practice as an analgesic and antiinflammatory agent, and it also ameliorates many of the adverse systemic effects of endotoxin. A potential negative effect of NSAIDs on large intestinal contractility has been suggested on the basis of in vitro studies[660]; however, a similar response has not been reported in whole animal studies.[663,665,684] There may be a role for novel agents in the future. Carbon monoxide (CO) has prevented POI in experimental animals, a benefit not only when CO was inhaled but also when CO was dissolved in a peritoneal lavage solution, making potential administration considerably easier and safer.[685] CO has potent intestinal antiinflammatory properties and is derived from the degradation of heme by the enzyme heme oxygenase. Expression of a heme oxygenase isoform (HO-1) can be induced by a variety of stimuli.

Broad-spectrum antimicrobial drugs are indicated when sepsis is suspected or if the immune system is compromised, as in cases with moderate to severe endotoxemia. Theoretic concerns have been raised regarding the use of aminoglycoside antibiotics in animals with ileus. Inhibition of intestinal contractions occurred when sections of intestine were exposed to high concentrations of aminoglycoside antimicrobial drugs, but this inhibitory effect is unlikely to occur at clinically relevant doses.[686] The administration of benzyl penicillin and/or ceftiofur was associated with an increased risk of colic in the week after anesthesia for diagnostic imaging or nonabdominal surgical procedures.[687]

Motility-modifying drugs could play an important role in the prevention and treatment of gastrointestinal ileus. An effective prokinetic agent could shorten the length of hospitalization, thereby reducing the cost of treatment and the number of potential complications such as weight loss, thrombophlebitis, and laminitis. There is also evidence that the development of abdominal adhesions could be minimized with the use of an effective prokinetic drug.[688,689] A potential negative impact of prokinetic use in the postoperative period after anastomosis is increased predisposition to dehiscence.[690]

Most motility-modifying drugs require a healthy intestinal wall in order to enhance intestinal contraction. There are several examples in horses in which the expected contractile response to certain drugs is blunted in the face of disease. It is reasonable to assume that many putative prokinetic drugs would be partially or totally ineffective in horses with abdominal disease. This would include intestine that has undergone prolonged or excessive distention or that is in any inflammatory condition, such as after intestinal manipulation or associated with primary inflammatory diseases such as DPJ or *Salmonella* enteritis. Numerous drugs have been investigated in humans with POI, but currently there is no prokinetic agent that has been found to be safe and effective.[691] The financial pressures associated with equine patient management often compel attending veterinarians to "experiment" with a range of putative prokinetic drugs.

Bethanechol is a methyl derivate of carbachol and is an ACh receptor agonist. The drug acts both at the level of the myenteric plexus and directly on intestinal smooth cells through muscarinic receptors. The actions are primarily mediated through activation of M_3 receptors, although M_2 receptors are also involved to a lesser extent.[692] There is evidence in other species that activation of M_2 receptors not only facilitates intestinal contraction but also may lead to antinociception.[693] Bethanechol is not degraded by the enzyme anticholinesterase. As anticipated the drug has a range of cholinergic side effects, including abdominal discomfort, sweating, and salivation, although these are minimal when the drug is administered at 0.025 to 0.05 mg/kg of body weight SC. Bethanechol is one of the most useful prokinetic agents in equine practice, as it exerts effects throughout the gastrointestinal tract; however, it does not appear to be commonly used.[694] It is most commonly used in the management of delayed gastric emptying and slowed small intestinal transit. Experimentally the drug has been shown to significantly increase gastric contractility and hasten the emptying of liquid and solid phase markers from the stomach of normal horses.[695,696] The drug has potent effects in the hindgut as well. Bethanechol increases both the relative strength and duration of wall contractions in the cecum and right ventral colon and consequently speeds up cecal emptying.[665] When given to ponies at a dose of 0.05 mg/kg SC, the drug increased electrical activity in the large colon for approximately 80 minutes.[684] There are wide ranges in reported dose rates of bethanechol, with doses up to 0.25 mg/kg recommended for oral administration in the management of delayed gastric emptying.

Neostigmine increases receptor levels of ACh by inhibiting cholinesterase. The drug (0.022 to 0.025 mg/kg IV) promotes cecal and colonic contractile activity and enhances cecal emptying in normal ponies.[665] Neostigmine has been used in the management of small intestinal ileus but significantly delayed the emptying of 6-mm beads from the stomach of normal adult horses.[697] A survey of prokinetic use indicated that neostigmine was more commonly used in the management of large intestinal disease.[694]

Metoclopramide is a moderate partial 5-hydroxytryptamine 4 (5HT-4)–receptor agonist, a moderate 5HT-3–receptor antagonist, and an antagonist of both dopamine 1 (DA_1) and 2 (DA_2) receptors. It has been suggested that the 5HT-4 agonist properties are primarily responsible for the prokinetic effects of metoclopramide. Antagonism of prejunctional DA_2 receptors facilitates ACh release and smooth muscle contraction. The effect on dopamine receptor antagonism is absent in newer benzamides. Metoclopramide crosses the blood brain barrier, where its antagonist properties on central DA_2 receptors can result in extrapyramidal signs, including seizure. These have been observed when the original reported dose of 0.25 mg/kg, given by intravenous infusion over 30 minutes, was used in practice.[698] These signs were responsible for poor acceptance of the drug in equine practice. An experimental bolus of endotoxin caused a delay in gastric emptying, as assessed using the acetaminophen absorption test; this delay was partially ameliorated through pretreatment with metoclopramide

(0.125 mg/kg in 1 L infused over 15 minutes), but again the investigators reported adverse side effects.[699] Most investigators have failed to demonstrate significant effects of metoclopramide in experimental animals, but constant intravenous infusion (0.04 mg/kg/hr) in a population of postoperative horses significantly decreased the volume and duration of gastric reflux over control and intermittent drug infusion groups.[700] Infusion was well tolerated and was superior to intermittent infusion or no treatment at all.

Cisapride is a second-generation benzamide that is commonly reported to act as a primary 5HT-4 agonist and 5HT-3–receptor antagonist. Furthermore, stimulation of 5HT-4 receptors within the enteric nervous system enhances release of ACh from the myenteric plexus, thereby promoting intestinal contraction. In vitro studies of equine jejunum concluded that the contractile actions of cisapride in the species were primarily mediated through 5HT-2 and not 5HT-4 receptors and that the response was noncholinergic.[701] Several reports suggest efficacy of cisapride in the management of intestinal disease in horses, including the resolution of persistent large colon impaction, treatment of equine grass sickness, and prevention of POI in horses after small intestinal surgery (0.1 mg/kg body weight IM during postoperative period).[702–705] Cisapride has the potential to cause adverse cardiac side effects mediated through blockage of the rapid component of the delayed rectifier potassium current that include lengthening of the QT interval and development of torsades de pointes, a potentially fatal arrhythmia. These adverse effects have resulted in drug withdrawal in the United States and in many other countries. Another benzamide, mosapride, resulted in increased myoelectric activity of the small intestine and cecum of horses after oral administration. The authors reported that mosapride is a selective 5HT-4 agonist; consequently the reported effects are surprising given that the actions of 5-HT on the equine jejunum were reported to be primarily mediated through activation of 5HT-2 and 5HT-3 receptors.[701] Mosapride is marketed in several Asian countries and is not available in the United States.

Domperidone acts as a competitive antagonist at peripheral DA_2 receptors; these receptors are inhibitory. The drug has been used to manage gastroparesis in humans for many years.[706] The primary use in equine practice is in the management of mares grazing endophyte-infected tall fescue (1.1 mg/kg/day PO), principally because of drug-enhanced prolactin release from the anterior pituitary. The potential prokinetic effects of domperidone have not been extensively studied in horses, but a modest efficacy of domperidone (0.2 mg/kg IV) was demonstrated in a model of experimental ileus in two ponies.[702]

Erythromycin is a direct motilin receptor agonist acting directly on smooth muscle cells as well as within the enteric nervous system to facilitate the release of ACh and motilin. Erythromycin enhances gastric emptying in normal horses but in contrast to most other species has a more pronounced effect on the hindgut.[695,707] This is somewhat surprising given that a higher density of motilin receptors was reported in the duodenum than in either the cecum or pelvic flexure of adult horse.[708] Erythromycin lactobionate (1 mg/kg IV) hastens cecal emptying in normal animals and induces propagating colonic MMC-like activity across the colon. Administration is often associated with defecation and abdominal discomfort.

Several problems limit use of erythromycin as a prokinetic agent in equine practice. The principal use in human medicine has been restricted to management of acute exacerbations of diabetic gastroparesis, facilitation of feeding tube placement, and upper gastrointestinal endoscopy.[709] Although it has been shown to enhance emptying in normal horses, it was not as effective as bethanechol.[695] Given its potent prokinetic effects in the cecum, erythromycin may be helpful at preventing cecal impaction in horses after anesthesia. However, its effectiveness on cecal motility appears to be markedly reduced in the immediate postoperative period.[659] High doses, constant infusion, or prolonged use of erythromycin also induces receptor tachyphylaxis and therefore reduced efficacy. There is also evidence that as little as 2 hours of intraluminal distention leads to a reduction in

the total number of motilin receptors and in the amount of motilin receptor mRNA, although erythromycin binding to remaining motilin receptors is not affected.[710] Erythromycin can induce diarrhea in adults; therefore administration over many days should be avoided. The diarrhea induced by erythromycin is most likely mediated by *C. difficile* overgrowth and toxin elaboration.[711]

Given that opiates have an inhibitory effect on normal intestinal motility, it is not unreasonable to assume that antagonists may have the potential for prokinetic activity. Naloxone (0.05 mg/kg IV) have been shown to induce contractile activity in the cecum and left colon.[712] The administration of naloxone was often followed by defecation within 15 to 20 minutes. Naloxone has not been beneficial in preventing POI in human beings.[713] An in vitro study reported a direct contractile effect of the peripherally acting opioid antagonist *N*-methylnaltrexone on the circular muscle layer of the jejunum and large colon.[714] The authors suggested a potential role for the drug in preventing intestinal complications associated with the use of morphine for pain relief.

α_2-Adrenoreceptor antagonists, such as yohimbine and telazoline, counteract increased sympathetic outflow in response to nociceptive stimulation. Yohimbine (75 μg/kg by slow intravenous infusion) hastens cecal motility and emptying in normal ponies and also attenuates the negative effects of endotoxin on motility.[655,665]

Lidocaine (also referred to as *lignocaine* in some countries) appears to be the most commonly used putative prokinetic agent in the management and prevention of POI.[694] Intravenous infusion of lidocaine may suppress primary afferent neurons, thereby limiting reflex efferent inhibition of motility. It is also possible that lidocaine may block the inhibitory effect of NANC neurotransmitters on smooth muscle.[715] Any positive effect of lidocaine could also be related to the drug's significant antiinflammatory properties. These include amelioration of the cytokine response to endotoxemia, reduced neutrophil free-radical production, impaired leukocyte phagocytic function, and inhibition of leukocyte migration through suppression of chemokines.[716] As discussed earlier, inflammation may be the most important initiator of intestinal stasis in the postoperative period.

A combination of intraoperative and postoperative lidocaine infusion is commonly used as a preventative strategy against POI. Postanesthetic treatment typically involves a slow intravenous bolus of 2% lidocaine (1.3 mg/kg) followed by a constant infusion at 0.05 mg/kg/min for 24 hours. The recommended target range for serum concentration of lidocaine is 1 to 2 mg/dL. In a prospective study of horses undergoing laparotomy for colic, the authors failed to demonstrate any difference between lidocaine and saline infusion with respect to return of borborygmi, time to first feces, or gastric reflux.[717] The authors did, however, report some positive differences in several ultrasound parameters, including jejunal diameter and the apparent volume of peritoneal fluid. Unfortunately only several of the horses in the study had a small intestinal lesion that required resection and anastomosis, and only two animals developed significant POI, one in each group. Lidocaine infusion was also contrasted with saline infusion in a group of horses with DPJ or POI.[715] Criteria for inclusion in that study included animals with net gastric reflux of more than 2 L/hr for 24 hours or a cumulative reflux volume of more than 20 L in less than 24 hours. Significant benefits of lidocaine infusion included a reduction in the duration of refluxing, hastened passage of feces, and a shorter total period of hospitalization for survivors. There were horses that did not improve in response to lidocaine infusion, and animals that continued to produce net gastric reflux throughout the 24-hour infusion period had a poorer outcome.

The rate of lidocaine infusion requires close monitoring, because infusion can be associated with reversible side effects that include muscle fasciculations, ataxia, and seizure. The drug is highly protein-bound, so hypoproteinemic horses may be more susceptible to signs of toxicity.

32.77 MEDICAL DISORDERS OF THE LARGE INTESTINE

Samuel L. Jones

32.78 ACUTE DIARRHEA

Diarrhea in the horse can be defined as the passage of fecal material that has increased water content. It can vary from soft, formed stools with a mild to moderate increase in water content to projectile fecal passages that contain little solid matter. The passage of excessive water in the feces reflects disruption of the normal balance of fluid and electrolyte secretion and absorption in the intestinal tract. In adult horses diarrhea results almost exclusively from disorders of the large intestine, although diarrhea may be a feature of some descending small colon disorders. Diarrhea can result in significant losses of water, electrolytes, and plasma protein and is often accompanied by local and systemic inflammatory responses.

Diarrhea disorders in adult horses can be divided into those characterized by inflammation of the cecum and large intestine (typhlitis, colitis) and those in which there typically is not an inflammatory response. Inflammatory disorders can be those characterized by an acute inflammatory response (salmonellosis, Potomac horse fever [PHF], and clostridiosis, described later), disorders associated with endoparasitism (small and large strongyle larval migration or encystation), disorders arising from toxicity (cantharidin toxicity, described later, and nonsteroidal antiinflammatory toxicity, described on p. 754), and disorders included under the umbrella term *inflammatory bowel disease* (see p. 730). Disorders that can manifest with diarrhea but that typically do not have colonic inflammation include those in which there is increased intestinal hydrostatic pressure (congestive heart failure, cirrhotic liver disease), intraluminal osmolarity, and poorly defined disorders in which fluid secretion may be stimulated by the enteric nervous system.

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Colitis is active inflammation within the colon that is usually associated with myriad local and systemic pathophysiologic events. Diarrhea is an important problem in horses with colitis, but impaired cardiopulmonary function, coagulopathies, and other sequelae of activation of inflammatory mediator cascades and septicemia can be most life-threatening. Complications that occur in colitis patients, regardless of cause, include overwhelming sepsis triggered by endotoxemia, septicemia and hematogenous organ colonization by bacteria, immune suppression and susceptibility to superinfection with bacteria or fungi, cecum or colon infarction, jugular vein thrombosis, and laminitis.

A variety of inflammatory cells and mediators affect the equine colon. With acute colitis the neutrophil is the effector cell, and the cascade of activation of inflammatory mediators associated with acute colitis is designed to bring neutrophils to where chemical signals indicative of bacterial infection have been detected. Signs of sepsis associated with endotoxemia (see p. 712) frequently accompany, or even precede, diarrhea in horses. Severe tissue inflammation can result in ulceration of the mucosal epithelium, resulting in chronic malabsorption and protein-losing enteropathy. Malabsorption of volatile fatty acids (VFAs) and metabolic alterations that result from excessive production and release of inflammatory mediators can lead to an energy deficit and catabolism of body tissues.

Specific diseases affecting the equine large colon (e.g., salmonellosis, PHF, clostridial colitis, and cantharidin toxicity) may have different activators of local and systemic inflammatory responses, and they can produce unique toxins that further contribute to tissue injury. Regardless of the cause, the clinical problems of affected horses are often similar, and the clinician must consider treatments that modify inflammatory changes and replace losses of

fluid, electrolytes, and plasma protein. In many cases the cause of the diarrhea is not determined. Descriptions of important causes of diarrhea in horses follow.

32.78.1 Salmonellosis

Salmonella bacteria possess an array of virulence factors that confer attributes of mucosal adhesion and invasion, produce enterotoxins that stimulate intestinal fluid secretion, activate local inflammation, including recruitment of inflammatory cells and the release of their mediators, cause local cytotoxic effects, and initiate systemic responses attributable to LPS.

32.78.2 Epidemiology

Numerous *Salmonella* serotypes have been associated with equine colitis, and overall more than 2500 serotypes of *Salmonella* have been described. *Salmonella* Typhimurium is the most frequently isolated serotype in horses, with dozens of other serotypes isolated sporadically. There are many reports describing clusters of cases of equine salmonellosis in which specific *Salmonella* serovars predominate. Nosocomial infections associated with *Salmonella* Krefeld,[718–720] *Salmonella* Typhimurium,[719] *Salmonella* Anatum,[721] and *Salmonella* Infantis[722] have been reported in recent years. Pertinent features of these bacteria are the ability to withstand a wide range of environmental conditions, the ability to rapidly invade and spread within the host (and thus be shed into the environment through the feces), and the range of severity of illness that results from infection.

Other key elements that influence whether clusters of cases will occur given the presence of a particular *Salmonella* serovar in the environment are availability and population density of susceptible hosts and the size of infective dose of the pathogen. It is for these reasons that veterinary hospitals, breeding farms, and other facilities that may have a high density of horses are most vulnerable to the development of *Salmonella* outbreaks. In one study at a veterinary teaching hospital, horses that were at greatest risk for developing salmonellosis were those treated with antimicrobial drugs or admitted for treatment of colic.[723] Such horses will include the majority of patients in any equine referral hospital. Breeding farms are susceptible to *Salmonella* outbreaks (or other enteric infections) because of the concentration of large numbers of immunologically immature newborn animals. In either case the particular *Salmonella* organism involved in disease outbreaks may not have to be especially virulent, because the inherent susceptibility of the host provides the microbe the opportunity to colonize and invade the host. Also of importance is the ability of the organism (inherent or acquired) to persist in the environment, lying in wait for both susceptible hosts and environmental conditions that favor its propagation and dissemination.

Serovars or strains of *Salmonella* that have newly acquired virulence plasmids can rapidly become established and spread among farms, sales areas, veterinary clinics, and veterinary teaching hospitals. Often the origin of these “new” bacteria is undetermined, but in some cases the organism can be traced to contaminated feed,[724] a specific shedder introduced into the environment, domestic or feral animals (barn cats), birds, and wildlife.

Salmonellae are ubiquitous in the environment, and the prevalence of fecal shedding varies by the group of horses sampled and the method of detection. Prevalence of fecal shedding, based on fecal culture, in asymptomatic horses admitted to teaching hospitals varied from 1% to 5%.[725,726] In a nationwide survey of prevalence of *Salmonella* in fecal samples from horses on farms and ranches. *Salmonella* bacteria were cultured from less than 1% of horses.[727] Use of PCR to detect *Salmonella* DNA in horse feces resulted in a prevalence rate of 17% in horses admitted to a teaching hospital for lameness examination and greater than 60% in

hospitalized horses with gastrointestinal disease.[728] In that report the PCR technique was determined to be specific for *Salmonella* DNA, but the test cannot differentiate between shedding of live bacteria and DNA from dead organisms.

Horses are not considered to be carriers per se of *Salmonella*, because no host-adapted *Salmonella* species have been identified in horses. *Salmonella* Abortus equi has now disappeared in the United States. Horses that shed *Salmonella* species in the feces usually do so transiently for several days to weeks; infrequently horses may shed salmonella bacteria for several months.

In acutely affected horses, large numbers of highly infective salmonellae can be shed in the diarrheic feces. Susceptible animals such as young foals, hospitalized horses receiving antimicrobial drugs, and horses under stress can become ill after becoming infected by numbers of salmonellae 100 to 1000 times less than those required to infect immunocompetent normal horses. Thus particular care should be taken in the management of horses and foals with diarrhea in environments in which there are animals at risk (e.g., hospitals, breeding farms, racetracks). Asymptomatic shedders generally pass relatively small numbers of salmonellae in the feces and do not appear to pose an important threat to healthy horses, although asymptomatic shedders have been responsible for outbreaks of salmonellosis in hospitals and on breeding farms.

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32.78.3 Clinical Findings

Salmonellosis typically is characterized by an acute colitis that results in profuse diarrhea and occasionally abdominal pain. Horses with salmonellosis often have signs of sepsis associated with endotoxemia and suffer from cardiovascular shock, vascular leak syndrome, and coagulopathies. Horses are usually febrile, tachycardic, moderately to severely obtunded, and dehydrated. With other clinical syndromes of salmonella infection, diarrhea is not a feature. These syndromes include fever and leukopenia, colic, and proximal enteritis with gastric reflux.

32.78.4 Diagnosis

Confirmation of salmonellosis requires bacteriologic culture of *Salmonella* bacteria. Multiple fecal cultures for *Salmonella* species should be performed on all horses with diarrhea. It is recommended that at least three to five fecal samples collected 12 to 24 hours apart be submitted to increase the sensitivity of culture.[729] Samples with little solid matter often yield negative culture results, even when the horse is infected with *Salmonella*. Formed fecal samples are more likely to result in a positive culture result from infected horses. A 5- to 10-g amount of feces should be submitted for culture in selective media such as tetrathionate broth or selenite broth and brilliant green agar or XLD agar. Culture of a rectal mucosa biopsy may be a useful adjunctive test for *Salmonellosis*. PCR is a sensitive screening tool for detection of fecal *Salmonella* DNA and is important for environmental monitoring and biocontrol measures in hospitals.

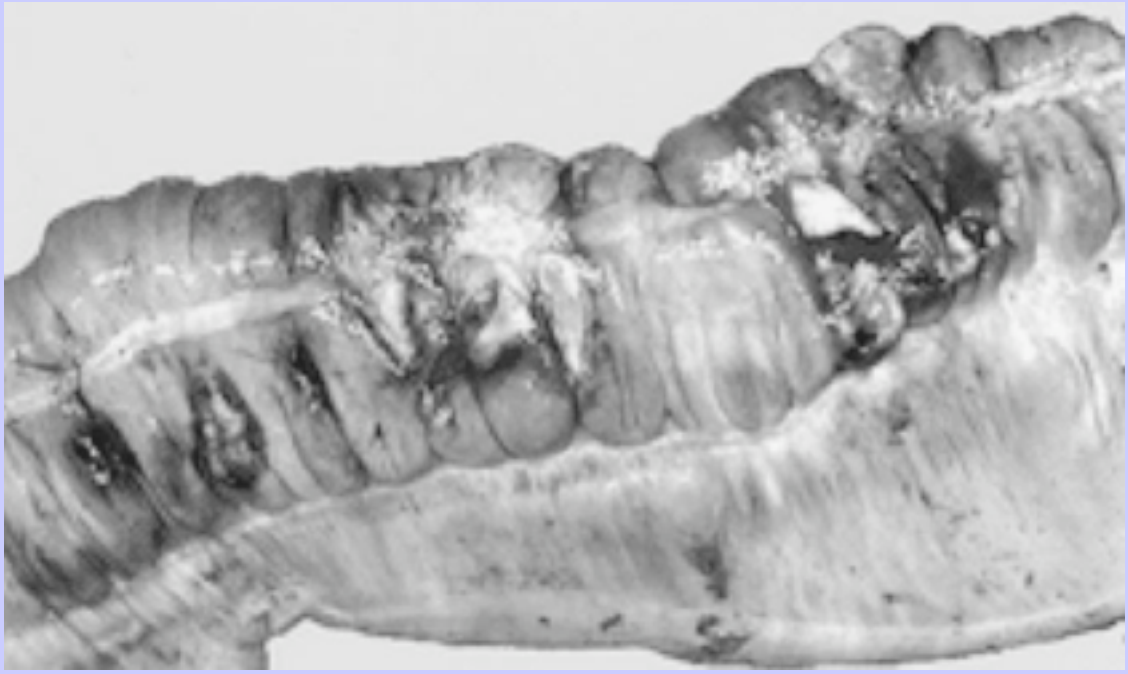
32.78.5 Treatment and Prevention

In most cases of salmonellosis, aggressive treatment facilitates resolution of the severe diarrhea and associated metabolic disorders within 7 to 10 days of the onset of illness. Intravenous administration of polyionic fluids is required to replace fluid and electrolyte losses and to augment preload in horses with poor venous return (see the Fluid Therapy for Horses with Gastrointestinal Diseases section [p. 767] and Chapter 44 for more comprehensive information about fluid therapy in horses with diarrhea). Plasma may be required to replace lost plasma proteins and increase plasma colloidal pressure. Alternative colloidal fluids, such as hetastarch, may be quite useful and

more cost-effective than plasma in horses with vascular leak syndrome and hypoproteinemia. Flunixin meglumine is often used to treat inflammation in horses with signs of sepsis. Flunixin and other NSAIDs should be used with caution and at the lowest dose possible to prevent worsening of colonic mucosal damage or inhibition of mucosal repair. Other antiinflammatory strategies may be used to treat sepsis associated with salmonellosis. Total or partial parenteral nutritional support is often indicated to provide adequate calories and amino acids during the most debilitating period of the illness. Antimicrobial administration to horses with suspected or known salmonellosis is not universally practiced. Antimicrobial administration may decrease the spread of salmonella bacteria to other organs and may have some direct effect on salmonella bacteria in the colon. Traditionally, use of antimicrobial drugs such as chloramphenicol, trimethoprim-sulfa (TMS), gentamicin, and cephalosporins has not appeared to accelerate resolution of signs of colitis. Fluoroquinolones, such as enrofloxacin, although potentially arthropathic in young horses, may be more effective because of high lipid solubility and bactericidal activity against *Salmonella* bacteria.

Horses that have severe diarrhea and sepsis for 10 days or longer are unlikely to survive, even with intensive therapy, because they often have extensive ulceration of colonic mucosa and chronic, severe inflammation within the wall of the colon. Ulceration may be exacerbated by administration of NSAIDs. Complications such as catheter-associated thrombophlebitis, colonic infarction (Fig. 32-55), colonization of other organs by salmonellae or other enteric bacteria, and laminitis can occur.

Fig. 32-55 Colonic infarction in a horse with salmonellosis. Tenesmus and rectal prolapse were early clinical signs of colonic infarction. Courtesy of Dr. M.J. Murray.



Measures designed to prevent the spread of *Salmonella* in an environment with potentially susceptible hosts need not be excessively laborious or expensive. The goal is to minimize the size of the infective dose of an enteric pathogen to which a susceptible host may be exposed. Thorough cleaning of areas where fecal contamination is

likely and prevention of mechanical distribution of contaminated material are the most important measures that should be taken. Extensive use of disinfectants may not be necessary if cleaning measures are adequate. Cleaning must include removal of organic debris, which can be accomplished with several products designed for that task. Areas that require particular attention are stalls, including water buckets or automatic watering systems, drains, and cracks in the floors and wall; stall implements; surgical areas, including drains; and nasogastric tubes and pumps.

If a diarrheic horse is in the environment, it should be isolated to the degree possible. Bedding material should be removed frequently to minimize accumulation of potential enteropathogens. Personnel entering the stall should be restricted to the professional staff, and they should wear disposable plastic boots. Footbaths with disinfectant often are not effective because they quickly accumulate organic material that interferes with the disinfectant activity of the footbath. Once a horse vacates a stall, the stall should be thoroughly cleaned, allowed to dry, disinfected, and determined to be negative for *Salmonella* by culturing selected sites in the stall (floor, drain, waterer). Personnel should use common sense when dealing with diarrheic animals. If bedding is being blown about by wind or if mechanical blowers are used to clean aisles, then potential enteric pathogens may be readily spread to other horses.

32.78.6 Potomac Horse Fever

PHF is an infectious enterocolonic disorder caused by *N. risticii* (formerly *Ehrlichia risticii*).[730,731] The organism is an obligate intracellular parasite, infecting peripheral monocytes and macrophages, colonic and small intestinal epithelial cells, and colon mast cells.[732] The pathophysiology of the disease is incompletely understood, although horses infected with *N. risticii* often have clinical signs and complications similar to those in horses with salmonellosis. After experimental inoculation with *N. risticii* horses had a mild, transient fever 2 to 4 days after infection.[733] By 10 to 14 days after experimental infection horses became febrile, had a poor appetite, and exhibited mild to severe gastrointestinal signs ranging from mild colic and soft stool to profuse diarrhea.

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In clinical cases of PHF, there are signs of sepsis, including fever, leukopenia, congested mucous membranes, and hypercoagulability. The early fever observed in experimental cases is usually not detected by owners, and when clinical signs are seen it is presumed that the horse was infected 10 to 14 days previously. Hypoproteinemia is a frequent finding in horses with clinical cases of PHF, which reflects loss of serum prote in through inflamed intestinal mucosa. It is interesting to note, however, that the magnitude of intestinal inflammation is typically much less than with salmonellosis, yet the magnitude of hypoproteinemia (total protein <3 g/dL) can be as severe.

Laminitis is a frequent sequela and may occur in 30% in horses with PHF. *N. risticii* has also been associated with abortion in mares, although this is an unusual occurrence.[734] In some horses that show significant seroconversion to *N. risticii*, laminitis is the only clinical sign.

32.78.7 Mode of Transmission

Although originally described as a disease of horses living near the Potomac River in Maryland and Virginia, horses with serologic evidence of exposure to *N. risticii* have been reported in most states. Because early research on PHF demonstrated that infection was readily transmitted through blood,[733] it was presumed that the natural mode of transmission involved an insect or arthropod vector. However, several studies have failed to demonstrate any such vectors.[735,736]

The association between an affected horse and proximity to a river (within 5 miles) remains strong. Recently investigators have found a possible link between this association and how the disease may be transmitted. *N. risticii* and *Neorickettsia helmintheca* were found to share a high degree of DNA homology.[737] *N. helmintheca* is transmitted to mammals via a trematode that parasitizes fish and aquatic snails.[737] This prompted investigators to search for evidence that *N. risticii* might reside in trematodes and their hosts found in riverine inhabitants. *N. risticii* DNA was detected in operculate snails (Pleuroceridae: *Juga* species) collected from stream water in a northern California pasture in which PHF is enzootic.[738] Moreover, *N. risticii* was detected in trematode stages found in the secretions of freshwater snails and in aquatic insects.[739,740] The sequences of these genes were virtually identical to those of the genes of an equine *N. risticii* strain isolated from horses located on a property near the snail collection site. Further work demonstrated *N. risticii* DNA in two trematodes. *Acanthatrium* species and *Lecithodendrium* species, found in bats and swallows, suggesting that these animals may serve as a reservoir for the organism.[741] Oral transmission of *N. risticii* with infected cell cultures has been produced experimentally,[742] supporting a role for ingestion of *N. risticii*, rather than blood transmission, as the route of natural infection. Oral transmission and clinical signs of PHF were demonstrated in horses fed infected aquatic insects (caddis flies), suggesting that ingestion of infected aquatic insects may be the natural route of infection.[743,744] Ingestion of water containing infected trematode stages released from aquatic snails may also be a route of infection.

32.78.8 Diagnosis

Accurate confirmation of PHF can be difficult, because clinical signs of disease are nonspecific and available diagnostic tests are not entirely reliable. Conventional recommendation is that paired acute and convalescent blood samples should be submitted for IFA or ELISA testing for antibodies to *N. risticii*. However, serologic evaluation to confirm the disease is not as straightforward as in many other infectious diseases. A fourfold increase in titer between acute and convalescent sera is considered to confirm infection with *N. risticii*, but failure to seroconvert does not rule out infection. Because the onset of clinical signs can be delayed as long as 14 days after infection, horses may seroconvert by the time an acute sample is obtained.[742] The magnitude of titer does not always correlate with active infection, because many horses in endemic areas have high titers but no disease. Vaccination also can affect the titer. There is significant interlaboratory variability in results of IFA tests, and false-positive results occur frequently.[745] Therefore it has been suggested that IFA for antibodies to *E. risticii* not be performed in areas that are not endemic for *E. risticii*.[745]

The current standard for diagnosis of PHF used by most clinicians is PCR testing of whole blood samples to detect *N. risticii* DNA in leukocytes.[746] PCR testing appears to be sensitive and specific in horses with compatible clinical signs, but a thorough evaluation of the test has not yet been completed.

32.78.9 Treatment and Prevention

Treatment with oxytetracycline, 7 to 11 mg/kg IV twice daily for 4 days, effectively eliminates *N. risticii* from the horse. Fever should resolve within 48 hours of beginning treatment with oxytetracycline, and diarrhea typically resolves within 24 to 72 hours of beginning treatment. In one horse we treated, clinical signs persisted until the dose of oxytetracycline was increased to 15 mg/kg twice daily. Orally administered doxycycline (10 mg/kg q12h) may be effective, although in horses with severe gastrointestinal signs, absorption of doxycycline may be adversely affected. Doxycycline must not be given IV because it will cause the horse to collapse. Some

horses have had clinical relapses 2 to 3 weeks after initial resolution of clinical signs that were responsive to tetracycline. Horses do not remain chronic carriers of *N. risticii*.

In most cases of PHF, intravenous administration of polyionic fluids is required to replace fluid and electrolyte losses and to augment preload in horses with poor venous return. Plasma may be required to replace lost plasma proteins. Other colloidal fluids may also be used in patients with hypoproteinemia or sepsis. Because horses improve rather quickly once treatment with oxytetracycline is begun, parenteral nutritional support is usually unnecessary.

Vaccination has appeared to diminish the incidence and severity of disease, but PHF may still develop in vaccinated animals. Experimental results with vaccine were mixed, and the duration of immunoprophylaxis was very limited.[747] Disease severity has appeared to be less in vaccinated animals, although in the summer of 1994 many vaccinated horses developed severe cases of PHF. All of these horses were located in the area where PHF was originally described, and a new strain of *N. risticii* was identified.[748] PCR analysis has revealed multiple strains of *N. risticii*, which may account for the unreliable efficacy of the vaccine.[749] Horses in endemic areas should be vaccinated in the early spring and early to mid summer on an annual basis.

32.78.10 Clostridial Diarrhea

Enteric clostridiosis was reported as a clinical problem in the 1970s, and clostridial bacteria were implicated as the causative agents of colitis X.[750] Difficulty in substantiating clostridial bacteria as the cause of enterocolitis in horses led to a deemphasis of this potential cause for diarrhea in adult horses. In the 1990s, improved laboratory techniques for identification of clostridial toxins resulted in increased confirmation of clostridial bacteria as common causative agents of colitis in foals and adult horses.

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The two most important clostridial species affecting the equine intestinal tract are *C. difficile* and *C. perfringens*. Most reported cases in horses have involved *C. difficile*, although in a recent report the prevalences of *C. difficile* toxin A and *C. perfringens* enterotoxin in fecal samples from horses with diarrhea were similar, and in some horses toxins from both clostridial species were identified.[751]

32.78.11 Pathogenesis

C. difficile is a sporulated obligate anaerobe responsible for most cases of antibiotic-associated colitis, for 15% to 25% of cases of antibiotic-related diarrhea, and for a substantial proportion of nosocomial infections in humans.[752] *C. difficile* produces two important toxins, named toxin A and toxin B. Most isolates of *C. difficile* produce both toxins, but some isolates produce only either toxin A or toxin B. Toxin A can elicit both fluid secretion and a pronounced inflammatory response in the bowel. Toxin A has intestinal secretory and cytotoxic effects,[753,754] increases intestinal permeability,[755] and can activate epithelial cells, neutrophils, mast cells, monocytes, and macrophages to release a multitude of proinflammatory cytokines and vasoactive mediators.[756–758] An interesting feature of toxin A is its induction of the neurotransmitter substance P in both the intestine and dorsal root ganglia, and the apparent dependence on substance P for expression of the full pathologic effects of toxin A in the intestine of rodents.[759] Effects of toxin A appear to be mediated both through direct effects on intestinal cells and via the enteric nervous system.

Toxin B exhibits enterotoxigenic (secretory) activity but recently also has been demonstrated to have potent cytotoxic effects on human colonic epithelium.[760] Toxin B has little relevance to the pathogenicity of *C. difficile*

in animal models, however, and the roles of toxins A and B in the pathogenesis of equine clostridial enterocolitis are not known.

Strains of *C. perfringens* are classified on the basis of the toxins that are produced, with at least a dozen identified to date.[761] *C. perfringens* type A and type C have been recovered from equine specimens,[762] and several *C. perfringens* toxins have been identified in equine specimens.[763,764] *C. perfringens* type A is the most frequently isolated type, and its enterotoxin is released on sporulation of *C. perfringens* within the intestine. Other exotoxins of *C. perfringens* have phospholipase activity (alpha-toxin), necrotizing cytotoxic effects (beta-, epsilon-, and iota-toxins), and hemolytic effects (theta-toxin).

32.78.12 Clinical Features

Clostridial enterocolitis affects foals and adult horses. In some reports, toxigenic *C. perfringens* organisms were isolated from more than 50% of foals with diarrhea.[764,765] The clinical presentation in foals with *C. perfringens* is predominantly a hemorrhagic diarrhea with sepsis. *C. perfringens* can cause septicemia and can often be cultured from the blood of foals with hemorrhagic diarrhea. In some foals, classic necrotizing enterocolitis will be manifested by gas- or fluid-distended intestines and thickened intestinal mucosa. These changes can be appreciated radiographically and ultrasonographically, and intramural gas produced by clostridial bacteria may be detected with ultrasonography as hyperechoic areas within the bowel wall. *C. difficile* infection is also a cause of acute enterocolitis in foals.[766] Adult horses with clostridial enterocolitis frequently have diarrhea but may have abdominal discomfort or fever as the primary presenting problems. There are no clinical features that consistently distinguish clostridiosis from salmonellosis, and a spectrum of clinical signs exists, from moderate illness to severe toxemic colitis. Most horses with clostridial enterocolitis develop diarrhea, but in some cases enteritis manifested by ileus and gas-distention of the small intestine may be the primary problem. Although both *C. perfringens* and *C. difficile* and their toxins have been detected in a significant number of adult horses with colitis. *C. difficile* appears to be more common.[767,768] Indeed, *C. difficile* appears to be the most common cause of antibiotic-associated diarrhea in adult horses.[769] Strain differences among isolates of *C. difficile* cultured from the diarrheic feces of horses in intensive care units are associated with toxigenicity, severity of disease, and metronidazole resistance.[770] *C. perfringens* and *C. difficile* have been implicated in duodenitis proximal jejunitis (see p. 725), but a cause-and-effect association has not been proven.

Similar to salmonellosis, clostridial enterocolitis can develop into a widespread problem affecting several animals in a hospital or an equine facility.[771] Risk factors for developing nosocomial clostridial enterocolitis are similar to those for nosocomial salmonellosis: antimicrobial administration, concurrent gastrointestinal disease, and age susceptibility (foals). In addition, *Clostridium* species are well suited to persist in the environment because of the production of spores that are resistant to environmental extremes and many disinfectants.

32.78.13 Diagnosis

Diagnosis of clostridial enterocolitis requires identification of toxigenic clostridia from intestinal contents or tissue. Several direct and indirect methods are used to detect toxigenic clostridia and include culture, identification of toxins, and identification of toxin genes. Culture of *C. difficile* or *C. perfringens* requires anaerobic conditions, and the ability to culture these organisms from ingesta or fecal specimens rapidly diminishes with increased time from collection to arrival at a laboratory. It is recommended to transport samples, chilled (not frozen) on ice, immediately or by overnight delivery for best recovery of clostridial organisms. Tissue specimens submitted for culture, toxin identification, or toxin gene identification should be handled

similarly. Because nonpathogenic Clostridia are common,[772] isolates should be tested for toxin production either by PCR or bioassay before a definitive diagnosis is made. Commercially available tests for clostridial toxins include an ELISA for *C. difficile* toxin A,[*] a latex-agglutination test for *C. perfringens* enterotoxin,[†] and an ELISA for *C. perfringens* enterotoxin.[‡] Toxin tests have the advantages of being rapid and, at least in the case of *C. difficile*, both sensitive and specific.

* *C. difficile* Tox A/B test, TechLab, Inc., Blacksburg, VA.

† *C. perfringens* enterotoxin kit, Oxoid Division, Unipath, Ogdensburg, NY.

† *C. perfringens* enterotoxin test, TechLab, Inc., Blacksburg, VA.

32.78.14 Treatment

Supportive care may be required, as with other cases of acute diarrhea in horses. Treatment with metronidazole (15 mg/kg q6-8h) appears to be effective in eliminating enteric clostridial infection in most cases. In one veterinary teaching hospital, isolates of *C. difficile* were resistant to metronidazole,[773] and vancomycin was used with reported success. Large-scale resistance to metronidazole has not been reported elsewhere, and it should be the first choice in the treatment of suspected clostridial enterocolitis. *Saccharomyces boulardii* is a nonpathogenic yeast used in the treatment of *C. difficile* diarrhea and colitis in humans. The yeast releases a protease that specifically degrades *C. difficile* toxins A and B, and this has been shown to be protective in experimental *C. difficile* colitis in rats and to prevent damage to human colonic epithelium by *C. difficile* toxins A and B in vitro.[774] Use of *S. boulardii* in horses has not been reported. A typical dose in humans is 1 g PO once daily.[775] DTO smectite powder (Biosponge) has been shown to bind clostridial toxins[776] and may be useful for treating clostridiosis in horses. DTO smectite is available as a powder or paste and should be administered according to the manufacturer's instructions for 3 to 5 days.

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32.78.15 Cantharidin (Blister Beetle) Toxicity

32.78.15.1 Pathogenesis

Cantharidin is the toxic principle found in beetles of the genus Epicauta, commonly known as blister beetles.[777–779] Ingestion of the beetles in contaminated alfalfa hay results in absorption of cantharidin through the gastrointestinal tract. Blister beetles feed on the flowers of alfalfa and are incorporated into baled alfalfa hay if the hay is cut and processed simultaneously.[777–779] Large swarms of beetles may be found in relatively small portions of hay. The lethal dose of cantharidin is less than 1 mg/kg, but the concentration of cantharidin varies from species to species of blister beetles.[777,778] Therefore as many as 100 to as few as six to eight beetles may be lethal. Often more than one horse will be affected. The fatality rate may be 50% or greater.[777,780]

Cantharidin is a potent irritant, causing cell damage and necrosis on contact.[777,779,780] The mucosa of the gastrointestinal tract is most commonly affected in horses because they ingest the toxin. Ulceration throughout the alimentary tract has been observed in natural and experimental cantharidin toxicity. Diarrhea probably results from the severe ulceration and inflammation of the large intestine, causing increased secretion of water, electrolytes, and protein. Large volumes of fluid and protein are lost in the gastrointestinal tract, causing hemoconcentration and profound hypoalbuminemia in some cases.[777,778,780] Cystitis, nephrosis, and myocarditis occur in natural and experimentally produced cases of cantharidin toxicity.[777,779,780] Cystitis and nephrosis occurs from the high concentration of cantharidin in the urine. The cause of the myocarditis and

myocardial necrosis is unknown, but they may also be direct effects of the toxin on the myocardium. Elevated plasma CK activity is often observed and has been postulated to arise from the damaged myocardium.[777,778] Horses have a characteristically stiff gait, but histopathologic evidence of skeletal muscle injury that explains the elevated plasma CK activity has not been observed.[778] Hypocalcemia and hypomagnesemia are characteristic features of cantharidin toxicity in horses that have not been explained.[777,778,780] Hypocalcemia may occur from hypoalbuminemia, but the ionized calcium concentration is often decreased, along with the total calcium concentration, indicating that hypoalbuminemia is not responsible for the hypocalcemia.[778]

32.78.16 Clinical Features

Cantharidin toxicity can cause a range of clinical signs, from mild depression and abdominal discomfort to fulminant signs of toxemia and rapid death, depending on the ingested dose of toxin.[777,778,780] Most commonly, clinical signs include depression, sweating, irritability, abdominal pain, elevated heart and respiratory rates, fever, polyuria, polydipsia, and profuse diarrhea.[777,778,780] Blood is rarely seen in the feces. Affected horses frequently posture to urinate; indeed, stranguria and pollakiuria are characteristic of cantharidin toxicity.[777] Signs of hypocalcemia include synchronous diaphragmatic flutter and tremors. A stiff and stilted gait may be evident. Neurologic signs such as head pressing, swaying, and disorientation may be noted.[780] Signs of systemic inflammation from endotoxemia may be seen in severe cases. Some horses develop severe depression and toxemia and may die within hours after ingestion of cantharidin without developing diarrhea.[777,780] Hematologic abnormalities are similar to those of other causes of acute diarrhea, reflecting dehydration and sepsis. Hypocalcemia (both ionized and total calcium concentrations) and hypomagnesemia are characteristic biochemical features of cantharidin toxicity and may be profound. Azotemia with a urine specific gravity in the hyposthenuric range is common.[777,778,780] Microscopic hematuria and mild proteinuria may be evident.

32.78.17 Diagnosis

Tentative diagnosis can be made based on clinical signs and the finding of blister beetles in the hay. Determining the species of the insects may be necessary to estimate the amount of cantharidin ingested. All species of *Epicauta* contain cantharidin, but some have small amounts. Definitive diagnosis requires the measurement of the cantharidin concentration in gastric or intestinal contents and urine.[777,781]

32.78.18 Treatment

Fluid therapy and maintenance of electrolyte balance are important, as in all cases of acute diarrhea. Particular attention should be paid to the degree of hypocalcemia and renal function as a fluid therapy plan is developed. Specific therapy is limited. Administration of absorbent powders via nasogastric tube is important early to prevent further systemic absorption of cantharidin and local toxicity. Mineral oil administration may also help reduce absorption of the toxin. Pain control may be needed for colic or urinary pain. Nonsteroidal antiinflammatory therapy should be used judiciously to avoid further injury to the intestinal mucosa and renal toxicity. Alternative analgesics, such as butorphanol or a lidocaine controlled rate infusion, may be better choices.

32.78.18.1

ANTIMICROBIAL-ASSOCIATED DIARRHEA

The onset of acute diarrhea in the horse has been associated with the use of several antimicrobial drugs. Lincomycin administered orally and tetracycline administered parenterally have been demonstrated to induce severe diarrhea in horses.[782,783] The oral administration of TMS, erythromycin, metronidazole, and penicillin and parenteral administration of ceftiofur have been implicated with onset of diarrhea, including fatal colitis, in horses. In one report there was no association between TMS and diarrhea.[784] However, in other reports, prior administration of antimicrobial drugs was positively associated with onset of colitis and negatively associated with prognosis for survival in horses with colitis.[785]

Antimicrobial-associated diarrhea is presumed to be secondary to disruption of normal colonic microflora and the proliferation of an enteropathogen, such as *Salmonella* species, *C. perfringens*, and *C. difficile*. Of interest, it was reported that mares whose foals were treated with erythromycin for *Rhodococcus* infection developed severe, acute colitis, from which *C. difficile* and its toxins were isolated.[786] The mares had erythromycin detected in their feces, and exposure to the erythromycin was presumed to have occurred by the mares licking erythromycin from the foals' faces.

32.78.18.2

OTHER CAUSES OF ACUTE DIARRHEA

NSAID toxicity (see p. 754) has been associated with diarrhea secondary to damage to the colonic mucosa. Grain (carbohydrate) overload may cause acute diarrhea resulting from overproduction of lactate in the colon. A combination of hyperosmolarity of the luminal contents and damage to the colonic mucosa account for the pathophysiology of grain overload. The clinical signs are similar to those of other acute diarrheal diseases in horses and depend on the severity of the overload. Hyperlactemia, metabolic acidosis, and sepsis are key features of grain overload, and laminitis is a common sequela. Acute diarrhea in the adult horse has also been associated with conditions such as lymphosarcoma enterocolitis and other IBDs, intestinal lymphosarcoma, peritonitis, heavy metal intoxication, anaphylaxis, and stress.

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32.78.18.3

CLINICAL ASSESSMENTS IN ACUTE DIARRHEA PATIENTS

The diagnostic evaluations performed on horses with acute diarrhea are intended to provide the clinician with information to accurately assess the horse's condition and thus direct therapy toward specific requirements. The first part of the evaluation is a thorough physical examination, with particular attention paid to the horse's hydration status (skin turgor, gum moisture, capillary refill time), evidence of sepsis (fever or hypothermia, hyperemic mucous membranes, prolonged capillary refill time), cardiovascular system (heart rate and rhythm, character of peripheral pulse, capillary refill time), and signs of laminitis (lameness, digital pulse, palpable temperature of hoof walls). Horses with colitis are often moderately to severely dehydrated, with either purplish or brick-red mucous membranes. Purple mucous membrane color reflects venous congestion and poor venous return, whereas brick-red membrane color reflects venous congestion and poor venous return plus arteriole and venule shunting and poor tissue oxygen exchange.

Blood pressure should be monitored, and whereas direct measurements via an arterial catheter are most accurate, indirect pressure measurements obtained using a Doppler transducer placed over the coccygeal artery are satisfactory. Hypotension and hypertension each occur in horses with colitis, and the blood pressure status

of a patient often is unpredictable. Blood pressure can be monitored as frequently as labor permits and should be done hourly if vasoactive pharmaceutical agents are used.

Laboratory tests that should be performed include CBC and plasma protein and total solids. Total hemoglobin and PCV are used to assess hydration status. Total protein is used to assess hydration status and degree of protein loss through inflamed intestinal mucosa, and in more chronic cases through protein catabolism. Comparison of clinical hydration, PCV, and total protein is useful in determining the extent of protein loss, and daily evaluations can be used to determine the rate of protein loss. Colloid oncotic pressure measurements are useful, particularly if colloidal fluids other than plasma are given.

Total WBC count, WBC differential, and WBC morphology are used to assess severity of sepsis; plasma fibrinogen is used to assess the severity of inflammation. Typically the total WBC and neutrophil counts decrease initially. This is primarily attributable to bacterial endotoxins and the host's mediators of systemic inflammation and occurs in most cases of acute colitis, not just in those caused by *Salmonella* species. The morphology of the WBCs reflects the severity of the inflammatory response. “Toxic” changes such as basophilia, granulation, vacuolation of the cytoplasm, and scalloped borders of the cell membrane or adherence of neutrophils to RBCs do not reflect injury to the neutrophils by toxins but reflect the cells' responses to stimulation by proinflammatory agents (TNF, IL-1) and the production of inflammatory mediators by the neutrophils that are toxic to bacteria. The degree of these changes in circulating neutrophils can be used to assess the severity of disease and also to assess the progress the horse is making. Often the initial sign that the horse is improving is a decrease in the “toxic” appearance to the neutrophils and a regenerative neutrophil response. A horse that continues to have severe neutropenia with a degenerating left shift or neutrophils, with cytoplasmic vacuolation, granulation, and basophilia, for more than 10 days has severe colitis that is unlikely to resolve.

Serum chemistry tests that should be performed include electrolytes (sodium, chloride, potassium, and calcium), BUN and creatinine, blood lactate concentration, and assessment of acid-base status (blood pH and bicarbonate, or total CO_2). Horses with diarrhea often are hyponatremic, hypochloremic, and hypokalemic. With decreased feed intake, hypocalcemia occurs. A high gap metabolic acidosis with hyperlactemia may be noted, particularly in horses with sepsis. The severity of these electrolyte disturbances should be monitored, often daily, to allow for appropriate therapy. Parameters that assess renal function, BUN and creatinine, are frequently increased in horses with diarrhea for several reasons. Prerenal azotemia resulting from dehydration and decreased filtration across the glomerulus accounts for some of the increase in these parameters. Hyponatremia and hypochloremia can cause a decrease in glomerular filtration and an increase in BUN and creatinine secondary to tubuloglomerular feedback. Horses that are adequately hydrated yet moderately hyponatremic (serum sodium 120 to 128 mEq/L) often remain azotemic until sodium levels increase above 130 mEq/L. In addition, horses with toxemic colitis often have damage to renal parenchyma, presumably the result of the effects of inflammatory mediators and alterations in renal blood flow.

The acid-base status can be evaluated by estimating serum bicarbonate on the basis of the total CO_2 or directly from a venous or arterial blood gas analysis. Evaluation of a venous blood gas sample is useful in assessing perfusion and oxygen extraction. An increased venous oxygen partial pressure (>60 mm Hg) is indicative of poor capillary perfusion and oxygen delivery to the tissues. Affected horses usually have brick-red mucous membranes.

32.78.18.4 PRINCIPLES OF THERAPY FOR ACUTE DIARRHEA

Because the pathophysiology of equine colitis is complex, treatment is often multifaceted. Many of these treatments provide well-documented benefit, whereas with others the efficacy is based on empiric judgment only. Outcome is determined not only by the severity of the primary disease causing colitis but also by complications that may arise from the disease.

In cases of acute colitis, fluid administration remains the treatment of primary importance. Most patients require intravenous administration in the early stages. The fluids used must replace fluid, sodium, chloride, and potassium losses. Often, large volumes are required for several days. More specific guidelines for fluid therapy in colitis patients are covered in the Fluid Therapy for Horses with Gastrointestinal Diseases section (p. 767) and in Chapter 44.

Most horses with colitis become hypoproteinemic secondary to protein leakage through the inflamed colon and catabolism of albumin secondary to negative energy balance. Hypoproteinemia frequently leads to edema formation in several areas of the body, including the intestinal tract, and can compromise the clinician's ability to keep the patient properly hydrated through fluid administration. Intravenous plasma therapy is often beneficial. Plasma, 3 to 10 L, should be given IV. Other colloidal fluids may be more cost-effective for increasing colloidal oncotic pressures in hypoproteinemic horses but do not have the additional properties of plasma that may be beneficial.

Plasma contains proteins besides albumin and therefore can be of benefit beyond improvement of plasma oncotic pressure. The immunoglobulin present in plasma is of recognized benefit in the treatment of failure of passive transfer in foals. The role of nonspecific immunoglobulin in the treatment of colitis is not known. Fibronectin is essential to the normal function of the monocyte-macrophage system in the processing of a variety of antigens. Other plasma proteins such as elastase and proteinase inhibitors, complement inhibitors, AT-III, and other inhibitors of hypercoagulability may be beneficial to colitis patients. 748 749

The nutritional requirements of the colitis patient need to be considered, particularly in a case that may be protracted. Horses with colitis are typically anorectic, and the disruption of normal physiologic processes in the inflamed cecum and colon limits the effectiveness of these organs in the digestion and absorption of nutrients. In addition, several mediators of inflammation and septicemia alter protein and calorie metabolism, resulting in a catabolic state. Therefore even if the horse eats, it is likely to be in a severe caloric deficit for some time. Normally an average horse requires approximately 15 Mcal/day. An endotoxemic horse may require 25 Mcal/day. In a catabolic patient, muscle and fat tissue are mobilized and used in lieu of ingested nutrients. The plasma protein pool, including albumin and immunoglobulins, also is catabolized. In many cases of colitis the decrease in plasma protein may be as much a result of catabolism as of leakage through the inflamed colon. A variety of products can be used for enteral feeding (see Chapter 50).

Colitis is an inflammatory disease, and limiting inflammation is desirable when treating patients, particularly those with severe disease. Moreover, horses with acute colitis, regardless of the cause, have signs compatible with systemic inflammation associated with sepsis. Flunixin (0.25 to 0.5 mg/kg q6–8h) is the most commonly used antiinflammatory therapy in horses with colitis. However, the use of flunixin should be judicious and must be carefully monitored to avoid unwanted side effects on the gut mucosa and kidneys (see p. 754). Other antiinflammatory therapies, such as lidocaine controlled rate infusions, may also be beneficial.

Sepsis is a common clinical feature in horses with acute colitis. Most of the clinical signs of sepsis are likely attributable to the effects of endotoxin. Therefore specific therapy for endotoxemia may be warranted (see p. 719).

The use of antimicrobial drugs in the treatment of colitis is controversial. In cases of colitis caused by *N. risticii*, the efficacy of tetracycline, 6.6 to 11 mg/kg IV once or twice daily, is documented clinically and experimentally. In other cases of colitis, including *Salmonella* colitis, in which specific antimicrobial sensitivities to the *Salmonella* species have been established, the efficacy of antimicrobial administration is less well documented. Many clinicians believe that the use of an antimicrobial for which the *Salmonella* species have demonstrated sensitivity, such as chloramphenicol, enrofloxacin, gentamicin, amikacin, or a third-generation cephalosporin, does not significantly alter the course of the disease or hasten the elimination of the organism from the body. However, there is no published evidence either supporting or not supporting the efficacy of antimicrobial treatment for salmonellosis, and the use of antibiotic therapy remains a judgment of the clinician. In patients with sepsis the use of broad-spectrum antibiotics is justified to prevent bacteremia or organ colonization by *Salmonella* species or other enteric organisms.

Medications that minimize or abolish colonic fluid secretion would be of tremendous benefit in the treatment of equine colitis. Medications such as kaolin, bismuth subsalicylate, and activated charcoal are frequently used in cases of colitis in adult horses, but their efficacy as antisecretory agents in this context has not been established. These medications are more effective in foals with diarrhea, probably as a result of an effect on the small intestine rather than the colon. Absorbent powders such as activated charcoal or DTO smectite (Biosponge) may be useful to absorb bacterial toxins, particularly in horses with clostridiosis.

32.78.19 Chronic Diarrhea

Chronic diarrhea is one of the most frustrating disorders encountered by equine practitioners, with regard to both determining the cause and therapeutically managing the diarrhea.[789] Chronic diarrhea may be defined as persistent diarrhea of at least a month's duration. Although there are many causes of chronic diarrhea, these cases can generally be divided into two groups: diarrhea resulting from a chronic inflammatory condition and diarrhea resulting from a disruption in normal physiologic processes. With inflammatory conditions there will be histologic changes in the colon mucosa, including pleocytosis (neutrophils, eosinophils, and lymphocytes), mucosal congestion, and mucosal erosion and ulceration. Submucosal edema, capillary congestion, and lymphatic congestion may be present. With physiologic disorders there are no morphologic changes in the colon, and diarrhea is presumed to result from abnormal VFA synthesis or absorption. A small percentage of horses with chronic diarrhea have a primary disorder of a system other than the intestinal tract, such as congestive heart failure or hepatic disease. A thorough physical examination and evaluation of a minimum database (CBC, serum chemistry profile, urinalysis) should differentiate horses with primarily nonenteric disorders.

32.78.20 Causes

Inflammatory disorders that can cause chronic diarrhea include disorders caused by infectious agents such as chronic salmonellosis; chronic parasitism with *S. vulgaris, Strongylus edentatus*, and larval cyathostomiasis; abdominal abscessation; and, in weanling foals. *R. equi* infection of abdominal viscera and rotavirus infection.

Noninfectious inflammatory causes include cellular infiltrative disorders such as granulomatous enteritis and lymphosarcoma, as well as sand enteropathy. Sand causes diarrhea through continued irritation of the mucosal lining of the colon. In weanling foals, gastric ulceration and gastric emptying disorders have been associated

with chronic diarrhea that resolved when H_2 antagonist therapy was started. NSAIDs can cause chronic diarrhea, which is accompanied by varying degrees of pathologic change in the large intestine.

Noninflammatory chronic diarrhea of colonic origin is thought to be a result of abnormal fermentation of cellulose by the resident bacteria in the large intestine. In vitro fermentation of feces from normal horses and horses with chronic diarrhea revealed that feces from the diarrheic horses produced more gas, acetate, and propionate than feces from normal horses.[790] Whether this reflects fermentative activity within the colon is not known, but an abnormal increase in acetate could lead to fluid retention within the colonic lumen, because acetate inhibits colonic absorption of sodium and water.

32.78.2 Diagnosis

The diagnostic approach to cases of chronic diarrhea should be based on an attempt to differentiate inflammatory from physiologic causes. The evaluation can be extensive and expensive, and the owner should be prepared for the cause of the diarrhea to remain undetermined. Horses with chronic diarrhea may be adequately hydrated if water consumption has matched water losses. Often, however, such horses are brought to the veterinarian in a condition of mild to moderate dehydration. Moderate weight loss also has often occurred. On physical examination, signs of toxemia (injected mucous membranes, congested or hyperemic mucous membranes) should be noted.

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A CBC should be evaluated for signs of chronic inflammation. Such changes include a decrease in the RBC count and PCV as a result of decreased erythrogenesis secondary to sequestration of iron by bone marrow macrophages (anemia of chronic inflammation). The WBC count may be normal or moderately increased. The fibrinogen can be normal or increased. Changes in WBC count and fibrinogen levels are influenced by the degree of inflammation and whether the inflammatory response is localized. Therefore a normal CBC does not rule out an inflammatory cause of the chronic diarrhea.

Peritoneal fluid analysis may reveal an increase in protein or WBCs, which is indicative of an inflammatory process within the peritoneal cavity. Often, however, colon inflammation is not reflected by alterations in the peritoneal fluid.

Serum chemistry values vary in horses with chronic diarrhea. Many affected horses have evidence of hyponatremia, hypokalemia, hypochloremia, azotemia, and metabolic acidemia. Other horses with less severe chronic diarrhea may have no serum chemistry abnormalities.

The total serum protein is usually decreased with a chronic inflammatory disorder of the colon, reflecting protein leakage from the capillaries and disruption of the colonic mucosal integrity. This is usually reflected by hypoalbuminemia. In some cases, hyperglobulinemia occurs and total protein concentration may be normal.

Increases in hepatic-associated enzymes, including sorbitol dehydrogenase, GGT, and AST, and serum bile acids indicate that hepatic disease is present. Hepatic changes and dysfunction such as inflammation, fibrosis or fatty infiltration, or biliary inflammation can be associated with diarrhea.

Feces should be examined for parasite ova; cultured for *Salmonella* species. *C. difficile*, and *C. perfringens;* and tested for clostridial toxins. In cases of acute diarrhea, it has been recommended that five consecutive fecal samples be cultured for *Salmonella* species, but in cases of chronic diarrhea, many more are often necessary. As many as 15 fecal cultures may be needed to get a positive *Salmonella* species culture. In addition, a rectal mucosal biopsy should be cultured. In weanlings the feces should be examined for rotavirus by transmission

electron microscopy or ELISA. Although it is an unusual cause of diarrhea in weanlings, rotavirus should be considered when dealing with a problem of chronic diarrhea in several foals on the same farm.

An oral glucose absorption test can be done to determine if there is small intestinal malabsorption, which would indicate a widespread small and large intestinal disorder if both diarrhea and glucose malabsorption are present.

A rectal mucosal biopsy may provide evidence of a widespread inflammatory disorder, such as one of the IBDs (see p. 730).[791] Biopsies should be evaluated by a pathologist experienced in examining equine tissue specimens, and some caution should be taken to avoid overinterpretation of the presence of few lymphocytes, plasma cells, and eosinophils.

Frequently the results of the previously mentioned diagnostic procedures do not determine the cause of the chronic diarrhea. In such cases an exploratory laparotomy may be warranted. This is particularly true if episodes of abdominal discomfort accompany the chronic diarrhea. In addition to exploration of the abdomen for the presence of masses or abscesses, the colon and cecum should be thoroughly examined. Biopsies from several sites of the colon, cecum, and mesenteric lymph nodes should be submitted for histopathology and culture for *Salmonella* species.

32.78.22 Treatment

Treatment of horses with chronic diarrhea is often empiric, because either a cause has not been determined or the cause is not amenable to treatment. With inflammatory causes such as lymphosarcoma and granulomatous enteritis, the disease is usually untreatable. Some cases of eosinophilic colitis have been treated successfully with corticosteroids.

Chronic parasitism may be resolved with appropriate anthelmintic therapy, although damage to the mucosa may have become too extensive to allow normal absorption to occur. Administration of larvicidal doses of fenbendazole (15 mg/kg PO daily for 5 days) is usually effective. Concurrent administration of prednisolone (1 mg/kg PO once daily for 5 to 7 days) may minimize inflammation secondary to killing migrating larvae within the vasculature and mucosa of the colon.

Chronic salmonellosis does not lend itself to specific treatment, because antimicrobial therapy is generally unrewarding in resolving *Salmonella* infection in horses.

Administration of products containing bismuth subsalicylate is effective in some cases of chronic diarrhea. The action of bismuth subsalicylate is mediated through inhibition of prostaglandin synthesis and possibly by other undefined mechanisms. In full-size horses a large volume, 1 to 4 L/day, must be administered to be effective.

Iodochlorhydroxyquin* is effective in managing some cases of chronic diarrhea caused by maldigestion of cellulose by colonic microorganisms.[792] The actual mechanism of action of iodochlorhydroxyquin in resolving the diarrhea is not known. The drug was originally administered to horses with chronic diarrhea because an increase in fecal trichomonads was observed. However, this observation likely reflected that trichomonads were washed out of the cecum and colon rather than that they were the cause of the diarrhea. Iodochlorhydroxyquin has minimal effect on colonic protozoal populations. It is not uniformly effective, and in many cases its effectiveness is only transient. Stools may initially become formed, but the diarrhea often recurs within several days. An initial dose of 20 mg/kg/day is recommended. If diarrhea recurs, decreasing the dose to 10 mg/kg/day is sometimes effective. If the medication is effective, it must be continued, because if it is discontinued, the diarrhea resumes.

Changes in diet occasionally are helpful in horses with noninflammatory chronic diarrhea. Feeding a complete pelleted feed may positively affect the constituent VFAs produced in the colon and thus facilitate water absorption. Alternatively, trying different types of roughage may result in selecting one that creates a more favorable metabolic environment in the large intestine.

The removal of sand from the colon by nonsurgical means is difficult, and in one report the administration of psyllium was not effective.[793] Other treatments used with anecdotal, but undocumented, success include fecal transfaunations, probiotics, cultured yogurt, and brewer's yeast.

* Reaform, Solvay Veterinary, Princeton, NJ.

32.79 SURGICAL DISORDERS OF THE LARGE INTESTINE

Anthony T. Blikslager

32.80 SIMPLE OBSTRUCTION

Simple obstructions of the large intestine tend to have a more gradual onset than those of the small intestine and in the case of large colon impactions are frequently amenable to medical therapy.[794,795] Cecal impactions present much more of a dilemma because of the greater propensity of this organ to rupture[796] and the relative difficulty of surgically manipulating the cecum.[797]

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32.80.1 Cecal Impaction

Cecal impaction may develop as a primary condition or may arise as a complication in hospitalized horses, particularly those that have undergone surgery.[798] Reasons for development of cecal impaction in hospitalized horses are unclear, although motility disturbances arising from postoperative pain may play a role. Cecal impactions may occur as one of two types: impaction of the cecum with firm ingesta or gross distention of the cecum with fluid ingesta. The latter has been termed *cecal dysfunction* and may be initiated by abnormalities in cecal motility. Evidence in favor of this supposition includes the fact that the right ventral colon is typically empty in horses with cecal dysfunction, suggesting a lack of aborad movement of digesta through the cecocolic orifice. However, clinical differentiation of cecal impaction and cecal dysfunction may be very difficult.[799] Horses with dry-ingesta—filled cecal impactions tend to be presented with the condition as the primary complaint, and there is often a gradual onset of abdominal pain over a number of days. Such impactions have a propensity to rupture before the development of severe abdominal pain or systemic deterioration and therefore must be closely monitored. In horses with cecal dysfunction, there is frequently an association with surgery, particularly orthopedic surgery. For horses that develop this condition in the postoperative period, it is often very difficult to detect because there is an expectation for horses to show some degree of depression after surgery and because horses are often already on analgesics such as NSAIDs or opiates. The simplest method to detect these cases is to closely monitor fecal output in the postoperative period.[800] A normal horse should produce six to eight piles of manure per day, whereas an abnormal horse may have no evidence of defection or a marked reduction in fecal production (<three piles of manure per day). These horses should be carefully evaluated for both pain and intraabdominal evidence of an impaction and treated accordingly.

The diagnosis of primary cecal impaction is based on palpation of a firm, impacted cecum or a grossly distended fluid-filled cecum per rectum. According to one study such findings were detected in 89% of horses with cecal

impaction that underwent per rectum palpation of the abdomen.[799] In some cases, cecal impactions may be difficult to differentiate from large colon impactions. However, careful palpation will reveal the inability to move the hand completely dorsal to the impacted viscus because of the cecum's attachment to the dorsal body wall.

Treatment for horses with dry-ingesta—filled cecal impactions may include initial medical therapy, including aggressive administration of intravenous fluids, judicious use of analgesics, and administration of oral laxatives (e.g., 2 to 4 L of mineral oil per 500 kg).[801] Other oral laxatives have also been recommended, including magnesium sulfate (1 mg/kg in 4 L of water PO up to twice daily for up to 3 days) and psyllium (1 kg q6-8h). However, if the cecum is grossly distended or if medical therapy has had no effect within a reasonable period of time, surgical evacuation of the cecum via a typhlotomy is indicated. In addition, it is advisable to perform an ileocolostomy in order to bypass the cecum, as postoperative cecal motility dysfunction with recurrence of the disease is common.[802] However, this aspect of surgical treatment remains controversial, and there are cases of cecal impaction if identified early that can be treated via typhlotomy alone.

In horses with cecal dysfunction, immediate surgery is indicated. In addition, cecal bypass is often warranted because it is suspected that motility disturbances initiate the disease, and therefore recurrence in the absence of cecal bypass may occur. However, this decision can be made based on the appearance of the cecum at surgery.

The prognosis depends on the type of cecal impaction encountered. In a recent report in which dry-ingesta—filled cecal impactions were treated by typhlotomy and ileocolostomy or jejunocolostomy, seven of nine horses lived long-term. The cecum of horses in which cecal dysfunction develops have a great propensity to rupture, which is universally fatal. Because these cases can be difficult to identify before surgery, the prognosis for this condition tends to be unfavorable.

32.80.2 Large Colon Impaction

Impactions of the large colon with ingesta occur at sites of anatomic reductions in luminal diameter, particularly the pelvic flexure and the right dorsal colon.[803] Although there are a number of reported risk factors, most have not been proven. However, a sudden restriction in exercise associated with musculoskeletal injury appears to be frequently associated with onset of impaction. A further consideration is equine feeding regimens, which usually entail twice-daily feeding of concentrate. Such regimens are associated with secretion of large volumes of fluid into the small intestine, resulting in transient hypovolemia (15% loss of plasma volume).[804] This leads to activation of the renin-angiotensin-aldosterone system, and because aldosterone stimulates absorption of fluid from the large colon, this may dehydrate colonic contents.[804,805] Large concentrate meals may decrease small intestinal transit time, resulting in increased presentation of soluble carbohydrate to the cecum and large colon. Large shifts of fluid into the colon occur as concentrates are readily fermented in the large intestine, which would be expected to activate the renin-angiotensin-aldosterone system. This in turn triggers net fluid absorption from the large colon. The effects of these large fluid fluxes on development of large intestinal disorders remains to be fully characterized, but undoubtedly they play some role in the syndrome of colic. From a practical standpoint, intestinal fluid fluxes may be reduced with frequent small feedings in those horses requiring concentrate to maintain condition.[804]

Clinical signs of large colon impaction include slow onset of mild colic that is typically well controlled with administration of analgesics but becomes increasingly more severe and refractory if the impaction does not resolve. The diagnosis is based on palpation of a firm mass in the large colon per rectum. However, the extent of the impaction may be underestimated by rectal palpation alone because much of the colon will be out of reach.

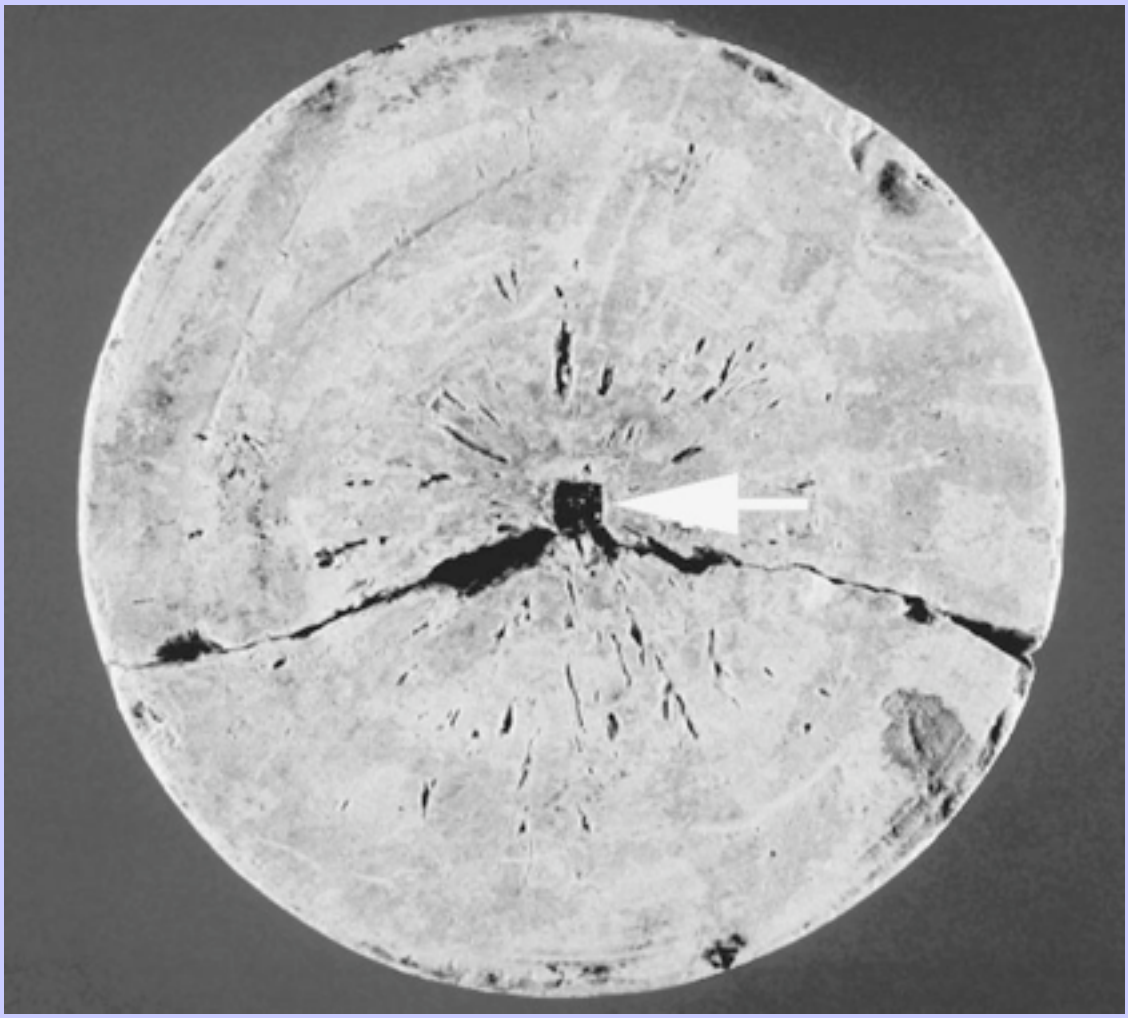
Adjacent colon may be distended if the impaction has resulted in complete obstruction. Initial medical treatment should be attempted. Intermittent abdominal pain is controlled with administration of analgesics (flunixin meglumine 0.25 mg/kg IV q6h to 1.1 mg/kg IV q12h; butorphanol 0.05 mg/kg IV as needed [prn]; xylazine 0.3 to 0.5 mg/kg IV prn). Detomidine (10 to 20 mg IV prn) can be administered with great caution, since this agent readily masks severe pain. In addition to analgesics, mineral oil (2 to 4 L/500 kg PO), water with dioctyl sodium sulfosuccinate (180 to 240 mL in 4 L of water, PO), or magnesium sulfate (1 mg/kg in 4 L of water PO) may be administered by stomach tube for laxative effects. Access to feed should not be permitted. For impactions that persist, aggressive oral and/or intravenous fluid therapy should be instituted. One study demonstrated the increased efficacy of a continuously administered oral rehydration solution in softening feces as compared with 751
intravenous fluids, which are probably best suited to restoring the systemic extracellular fluid compartment.[806] If 752
the impaction remains unresolved, the horse becomes uncontrollably pained, or extensive gas distention of the colon occurs, surgery is indicated. At surgery the contents of the colon are evacuated via a pelvic flexure enterotomy. The prognosis is good for those horses in which impactions resolve medically (95% long-term survival in one study) and fair for horses that require surgical intervention (58% long-term survival in the same study).[795]

32.80.3 Enteroliths

These mineralized masses are typically composed of ammonium magnesium phosphate (struvite).[807] One study has suggested that an increase in magnesium in the diet may predispose to the formation of enteroliths.[808] Enteroliths almost always form around a nucleus such as a silicon dioxide stone, a nail (Fig. 32-56), or piece of rope that has been ingested and are most commonly found in the right dorsal and transverse colons. Although enterolithiasis has a wide geographic distribution, horses in California have a high incidence. In one California-based study, horses with enterolithiasis represented 28% of the surgical colic population. In addition, Arabians, Morgans, American Saddlebreds, and donkeys are at risk of this disease.[809] A more recent study performed in California indicated that horses fed a diet composed predominantly of alfalfa hay are at risk for development of enterolithiasis, and allowing horses to graze on pasture was protective against this disease.[810]

Initially, clinical signs include intermittent abdominal pain in mature horses (almost always greater than 4 years of age),[811] with few abnormalities on rectal examination. As enteroliths become larger, they may occlude the lumen of the colon and cause acute pain and large colon distention that necessitate surgical exploration. In some cases an enterolith is forced into the small colon, where it causes acute small colon obstruction. Enteroliths may be diagnosed by abdominal radiography or at surgery. On rare occasions, an enterolith may be palpated per rectum, particularly if it is present in the distal small colon.

Fig. 32-56 Cut section of an enterolith. Note the presence of a nail head *(arrow)* that served as a nucleus for the formation of a struvite enterolith. Courtesy Dr. David G. Bristol.



In general, surgery is required for these cases, although there are reports of enteroliths being retrieved per rectum. In fact, in one study 14% of horses presented for treatment of enterolithiasis had a history of passing an enterolith in the feces.[809] However, enteroliths are typically located in the right dorsal colon, transverse colon, or small colon. At surgery the enterolith is gently pushed toward a pelvic flexure enterotomy, but removal frequently requires a separate right dorsal colon enterotomy to prevent rupture of the colon. After removal of an enterolith, further exploration must be conducted to determine if other enteroliths are present. Solitary enteroliths are usually round, whereas multiple enteroliths have flat sides. The prognosis is good (92% 1-year survival of horses recovered from surgery in one study of 900 cases) unless the colon is ruptured during removal of an enterolith. In one recent study, rupture occurred in 15% of cases.[809]

32.80.4 Sand Impactions of the Large Colon

Sand impactions of the large colon are common in horses with access to sandy soils, particularly horses whose feed is placed on the ground. Sand accumulates in the large colon, particularly the right dorsal colon and pelvic flexure.[812,813] In addition, sand may trigger diarrhea, presumably as a result of irritation of the colonic mucosa.[814] In horses with sand impactions, clinical signs are similar to those of horses with large colon impactions. In addition, sand may be found in the feces, and auscultation of the ventral abdomen may reveal sounds of sand moving within the large colon.[815] Sand also may be detected on abdominal radiography. The diagnosis is definitively made at surgery but may be tentatively based on clinical signs compatible with a large colon impaction together with evidence of sand in the feces. To determine the presence of sand, several fecal balls are placed in a rectal palpation sleeve or other container, which is subsequently filled with water. If sand is present, it will accumulate at the bottom of the container. In addition, mineral opacity may be detected within the colon on abdominal radiographs.

Initially, medical therapy is warranted. Administration of psyllium hydrophilic mucilloid in water by stomach tube may facilitate passage of sand, although a recent experimental study failed to show a benefit of this treatment.[816] If colic becomes intractable, surgical evacuation of the large colon should be performed. The prognosis is good.

32.81 NONSTRANGULATING OBSTRUCTION OF THE COLON

Several configurations of displacements, including nephrosplenic entrapment of the colon, obstruct the colonic lumen but do not compromise the colonic blood supply. Therefore, technically these are simple obstructions. However, the lumen may not be completely obstructed, and some degree of venous congestion is common.[817] In some cases nonstrangulating obstructions are difficult to differentiate from large colon volvulus, because a volvulus of more than 270 degrees will not result in strangulation of blood supply but can cause considerable abdominal pain and gas distention of the abdomen. In this regard, nonstrangulating obstructions represent early stages of strangulating obstructions. Clinical signs include mild to moderate colic with evidence of large colon distention on palpation of the abdomen per rectum. The diagnosis is confirmed at surgery.[818] If pain is recurrent, particularly if it is of increasing intensity and frequency, or if there is evidence of intestinal compromise (particularly progressive changes in abdominal fluid and cardiovascular parameters indicating systemic deterioration), the horse should be taken immediately to surgery. The prognosis is good, with more than 80% of horses surviving to hospital discharge in a multicenter study.[794]

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32.81.1 Right Dorsal Displacement of the Large Colon

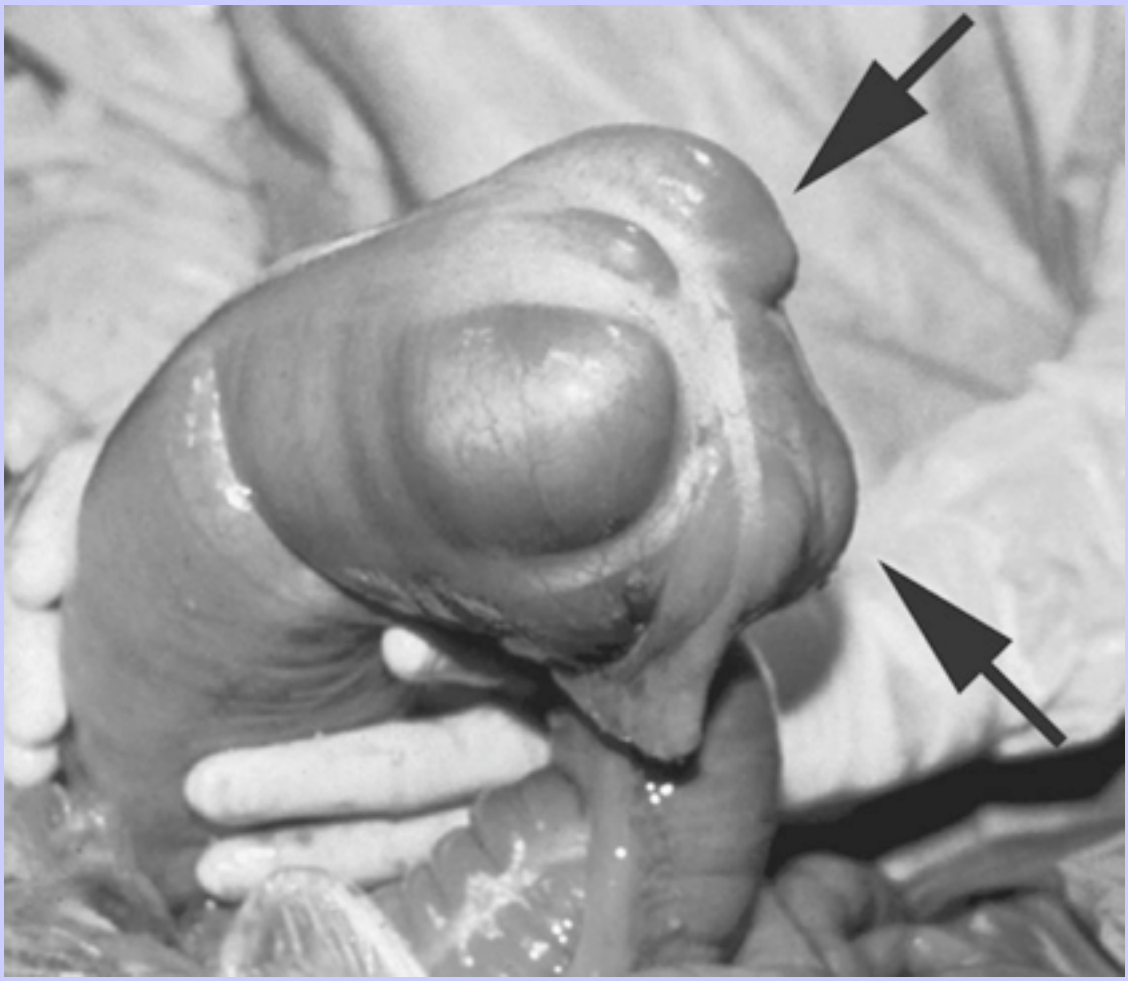
With right dorsal displacement of the colon, the colon displaces to the right of the cecum. Findings on per rectal palpation typically include colonic bands coursing horizontally across the abdomen, with evidence of colon lateral to the cecum. In the most common configuration of right dorsal displacement, the large colon wraps around the cecum (pivoting counterclockwise around the cecum, looking from above the horse) with the pelvic flexure lying in the left dorsal quadrant. Alternatively, the colon may wrap around the cecum in the opposite direction, with the pelvic flexure lying in the right dorsal quadrant.[819]

32.81.2 Nephrosplenic Entrapment (Left Dorsal Displacement) of the Large Colon

On the left side, colon displacements most commonly involve entrapment of the colon over the nephrosplenic ligament, although left dorsal displacements may be detected before the colon is fully entrapped. Clinical signs include gradual onset of mild to moderate colic as the entrapped colon fills with gas. Palpation per rectum will reveal gas-distended ventral colon and displacement of the spleen toward the center of the abdomen. Careful palpation following colonic bands up to the left dorsal quadrant often reveals the presence of colon between the left kidney and the spleen. Diagnosis may be based on palpation per rectum of the colon traversing the nephrosplenic ligament. Alternatively, a tentative diagnosis can be reached using abdominal ultrasonography.[820] The spleen can be visualized on the left side of the abdomen, but the left kidney will be obscured by gas-distended bowel. Evaluation of this technique indicates that there are no instances of false-positive results, although false-negative results may occasionally occur. Therefore, as with other examination techniques, ultrasonography is not uniformly reliable. A definitive diagnosis may require surgery. Treatment has traditionally been surgical intervention, during which the colon is gently rocked free of the nephrosplenic space. More recently, nonsurgical intervention has been successful in select cases.[821,822] If such manipulations are to be attempted, the clinician must be certain of a diagnosis. The horse is anesthetized and placed in right lateral recumbency. The horse is rotated up to dorsal recumbency, rocked back and forth for 5 to 10 minutes, and then rolled down into left lateral recumbency.[823] The nephrosplenic space should be palpated per rectum to determine whether or not the entrapment has been relieved. Phenylephrine (3 to 6 mg/kg/min over 15 minutes) may be administered to decrease the size of the spleen.[824] If the entrapment remains, further attempts may be tried, but in cases where the displacement is not corrected, the horse should be taken to surgery. More recently, phenylephrine has been used in conjunction with 30 to 45 minutes of light exercise (jogging) to successfully reduce nephrosplenic entrapments in four of six horses. This technique can be used on horses with mild to moderate colonic distention, particularly if signs of colic can be readily controlled.

Regardless of technique, the prognosis is good. In one study, survival was in excess of 90%.[822] There are cases in which nonsurgical interventions do not completely correct the problem and others in which nonsurgical manipulations correct the entrapment but result in large colon volvulus or displacement.[825] Such patients should be taken to surgery promptly.

Fig. 32-57 Operative view of a foal with atresia coli. Complete atresia of the pelvic flexure has resulted in a blind-ended ventral colon *(arrows)* resulting in gas distention of the colon. The ventral colon was subsequently anastomosed to the dorsal colon in this foal.



32.81.3 Atresia Coli

Atresia of any segment of the colon is a rare congenital abnormality in horses (Fig. 32-57).[826] The heritability and causes of the condition are unknown. One potential mechanism for development of the lesion is intestinal ischemia during fetal life, which secondarily results in necrosis of a segment of intestine. Clinical signs include a failure to pass meconium and colic within the first 12 to 24 hours of life. Secondary abdominal distention results from complete intestinal obstruction, and abdominal radiographs may reveal gas-distended colon. The diagnosis is made at surgery. Any portion of the colon may be absent, but the distal segment of the large colon and/or the proximal small colon is usually most severely affected. If sufficient tissue is present, anastomosis to the proximal

blind end of the colon may be attempted. The prognosis depends on which segment of the colon is absent but is usually poor because of an absence of distal colon.

32.82 STRANGULATING OBSTRUCTION

Although simple obstruction of the large colon carries a very favorable prognosis, strangulating obstruction of the large colon is associated with high fatality rates. Two forms of strangulating obstruction are recognized: hemorrhagic strangulating obstruction, in which the arterial blood flow remains patent while veins are collapsed, and ischemic strangulating obstruction, in which both the arteries and veins are collapsed. The differentiating factor between the two is likely how tightly twisted the volvulus is. It has been suggested that ingesta-filled intestine is more likely to develop a hemorrhagic lesion during volvulus because the intestinal contents prevent the intestine from twisting tightly.[827]

32.82.1 Large Colon Volvulus

Clinical signs include rapid onset of severe, unrelenting abdominal pain.[828] Although postparturient broodmares appear to be at risk, this association has not been conclusively determined. Once the large colon is strangulated (>270 degrees volvulus), gas distention is marked, leading to gross distention of the abdomen, compromised respiration as the distended bowel presses against the diaphragm, and visceral pooling of blood as the caudal vena cava is compressed. Horses with this condition are frequently refractory to even the most potent of analgesics. These horses may prefer to lie in dorsal recumbency, presumably to take weight off the strangulated colon. An abbreviated physical examination is warranted in these cases, because the time elapsed from the onset of strangulation to surgical correction is critical. Experimentally the colon is irreversibly damaged with 3 to 4 hours of 360-degree volvulus of the entire colon.[829] Despite severe pain and hypovolemia, horses may have a paradoxically low heart rate, possibly related to increased vagal tone. In addition, results of abdominocentesis are often not indicative of the degree of colon compromise,[830] and in many cases abdominocentesis should not be done because of extreme colonic distention. Palpation per rectum will reveal severe gas distention of the large colon, often restricting access to the abdomen beyond the pelvic brim. The diagnosis may be tentatively based on signalment, severity of pain, and degree of distention.

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At surgery the volvulus is typically located at the mesenteric attachment of the colon to the dorsal body wall, and the most common direction of the twist is dorsomedial using the right ventral colon as a reference point. However, the colon may twist in the opposite direction, twist more than 360 degrees (up to 720 degrees has been reported), or twist at the level of the diaphragmatic and sternal flexures. In all cases the colon should be decompressed as much as possible, and in many cases evacuation of colon contents via a pelvic flexure enterotomy will facilitate correction of the volvulus. A determination must be made after correction of the volvulus as to whether the colon has been irreversibly injured. This is frequently based on mucosal color and bleeding (if an enterotomy has been performed), palpation of a pulse in the colonic arteries, serosal color, and appearance of muscular motility. However, determination of viability based on these parameters is unreliable. Currently, one of the most reliable techniques for determining viability is histologic evaluation of frozen sections of colonic mucosa. Biopsies may be obtained at the pelvic flexure because it has been determined that mucosal changes are uniform throughout strangulated colon. A prediction of viability is based on the degree of crypt epithelial loss and the interstitium:crypt ratio (based on measurements of the crypt width and the width of interstitial space between crypts). In one study, 16 of 18 horses that had >50% loss of crypt epithelium and an interstitium:crypt ratio of >3 typically did not survive, whereas 43 of 46 horses that had less severe mucosal changes survived, suggesting high accuracy.[831] In addition, it has been suggested that accuracy of viability

determination can be increased by combining histologic evaluation with surface oximetry or laser Doppler determination of blood flow.[832] Unfortunately, frozen histologic sections are not available at most referral centers on an emergency basis. One recent study assessed intraoperative colonic intraluminal pressure as a more practical potential indicator of outcome in horses with large colon volvulus but found this measurement to be of little benefit in accurately making this determination.[833]

If the colon is judged to be irreversibly damaged, the feasibility of a large colon resection can be considered. Although 95% of the colon can be resected (that part of the colon distal to the level of the cecocolic fold), damage from the volvulus usually exceeds what can be resected. In these cases surgeons may elect to resect as much damaged bowel as possible or may advise euthanasia.

The prognosis for survival is guarded to poor because of the rapid onset of this disease. In one study the survival rate was 35%.[830] In a more recent report, the survival rate was 36% for horses with 360-degree volvulus of the large colon compared with 71% for horses with 270-degree volvulus.[828] However, one study in central Kentucky documented a high success rate, most likely because of early recognition of the disease and the proximity of the hospital to the surgical caseload.[834] Postoperative complications include hypovolemic and endotoxemic shock, extensive loss of circulating protein, disseminated intravascular coagulation, and laminitis. In addition, large colon volvulus has a propensity to recur. Although one study documented a recurrence rate of less than 5%,[830] some authors believe recurrence may be as high as 50%. Therefore methods to prevent recurrence should be considered.[835,836]

32.82.2 Intussusception

The most common intussusception of the large intestine is cecocolic intussusception, although when this is compared with all forms of colic, it is a relatively rare condition of the horse, accounting for 11 of 842 horses (1.3%) taken to surgery because of colic at one hospital.[837] The condition tends to occur in young horses (2 to 3 years of age) and may be associated with intestinal parasites, particularly tapeworms. Clinical signs include acute onset of colic that varies in severity according to the degree of intussusception. Initially, the cecal tip inverts, creating a cecocecal intussusception, which does not obstruct flow of ingesta. As the intussusception progresses, the cecum inverts into the right ventral colon (cecocolic intussusception), which obstructs flow of ingesta and often causes severe colic. In one report on cecocolic intussusception, 10 of 11 horses had severe colic.[837] The cause of abdominal pain is often difficult to differentiate in these cases, although it is sometimes possible to detect a mass on the right side of the abdomen and the concurrent absence of a palpable cecum. Treatment involves manual surgical reduction by retracting the intussusceptum directly or via an enterotomy in the right ventral colon.[838] The prognosis is usually regarded as poor because of severe compromise to the cecum and the risk of cecal rupture or severe contamination during surgery. However, a recent report has indicated that seven of eight horses that underwent right ventral colon enterotomy and cecal resection survived long term.[838]

Colocolic intussusceptions are rare but have reportedly affected the pelvic flexure and the left colon.[839–842] Although the condition is reportedly more common in young horses, older horses may be affected. Clinical findings may include a palpable mass on the left side of the abdomen. Ultrasonography may also be useful. Treatment requires manual reduction of the intussusception at surgery, or resection of affected bowel.

32.83 NONSTEROIDAL ANTIINFLAMMATORY DRUG TOXICITY

Samuel L. Jones

Use of NSAIDs is common in equine practice because of their antipyretic, analgesic, and antiinflammatory properties. These drugs are used to treat horses with colic, endotoxemia, musculoskeletal disorders, and other medical problems. In addition to these therapeutic properties, NSAIDs also exhibit unwanted toxic side effects. The NSAIDs have a relatively narrow therapeutic range, and when they are administered at excessive doses, toxicosis can occur within a few days. Although generally safe when administered at recommended doses,[843] some horses may exhibit signs of toxicosis at these doses within days or weeks.[844,845] The risk of toxicity is exacerbated in animals that are dehydrated or septic (e.g., endotoxemic patients). Recommended doses for NSAIDs commonly administered to horses include the following:

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- Phenylbutazone, 2.2 to 4.4 mg/kg q12h
- Flunixin meglumine, 1.1 mg/kg q12h or 0.25 mg/kg q8h
- Ketoprofen,* 2.2 mg/kg q24h
- Meclofenamic acid,† 2.2 mg/kg q12-24h
- Naproxen,‡ 5 to 10 mg/kg q12-24h
- Aspirin, 12 to 25 mg/kg q12-48h

32.83.1 Pathophysiology and Predisposing Factors

The principal mechanism of the therapeutic and toxic effects of NSAIDs is related to their inhibition of prostaglandin synthesis by inhibition of the COX enzyme. Two isoforms of the COX enzyme have been identified: COX-1 and COX-2.[846] COX-1 is generally constitutively expressed and is thought to play an important role in maintaining physiologic homeostasis; it is found in such tissues as the gastrointestinal mucosa and kidney and in the endothelium and platelets. In contrast, COX-2 is primarily an inducible enzyme that has a critical role in inflammation and is produced by a variety of cells including monocytes, neutrophils, epithelial cells, fibroblasts, synoviocytes, and chondrocytes.

It has been postulated that drugs that nonselectively inhibit both COX-1 and COX-2 have greater toxic potential because they inhibit prostaglandins necessary for physiologic homeostasis as well as prostaglandins that mediate inflammation and pain.[846] Both COX-1– and COX-2–dependent prostaglandins play an important role not only in maintaining the epithelial barrier in the gut, but also in healing the epithelium when the mucosa is damaged (e.g., because of ischemic injury or infection). All of the commonly used NSAIDs in horses are considered to be nonselective. NSAIDs that are COX-2 selective are less ulcerogenic in other species and may be so in horses. For example, COX-2 selectivity decreases the adverse effects of NSAIDs in a model of epithelial repair in horses.[847] COX-2 selective NSAIDs are being developed for use in horses but are not yet approved for use in the United States.

Although the COX-1–versus—COX-2 scheme is currently considered valid, evidence exists that it may be overly simplistic. For example, COX-1 may play an important role in inflammation and is at least partly

inducible.[848] In contrast, COX-2 can be induced physiologically in various organs and tissues and by stimuli other than inflammation.[846,849] In horses, gastric ulcerogenicity of even the nonselective NSAIDs varies (phenylbutazone > flunixin meglumine > ketoprofen).[850] This difference in toxicity among drugs may relate not only to the COX selectivity, but also on other factors such as tissue distribution.

The gastrointestinal tract and the kidneys are the most common targets for NSAID toxicity. NSAID-induced injury can develop anywhere in the gastrointestinal tract (from the mouth to the rectum). Two well-recognized syndromes may be attributed at least in part to NSAID toxicity. The first is gastric ulceration. In the stomach, inhibition of COX can increase acid secretion, decrease output of mucus and bicarbonate, impair vasodilation, and diminish epithelial restitution, cell division, and angiogenesis.[851] Inhibition of COX also impairs the healing of existing ulcers. A second syndrome attributed to NSAID toxicity is right dorsal ulcerative colitis (RDUC). Although the right dorsal segment of the large intestine is most commonly affected, other segments may also be involved. Ulcerative lesions in the large intestine can be particularly troublesome because they can cause chronic debilitation, are difficult to diagnose, and can be refractory to treatment. In the kidney, PGE_2 and PGI_2 (prostacyclin) produce vasodilation in the autoregulatory response of renal blood flow to hypoperfusion; consequently, hypovolemia, hemorrhage, or renal disease will increase the risk of renal NSAID toxicosis. Damage is greatest at the renal crest (papilla), and papillary crest necrosis may be associated with subsequent nephrolithiasis or ureterolithiasis and chronic renal failure.[852] In humans the most common side effect of NSAIDs is bleeding, caused in part by reduced function of platelets and in part by gastrointestinal hemorrhage.

Not all of the adverse effects of NSAIDs are attributable to COX inhibition. The NSAIDs also cause injury from a variety of mechanisms, including microvascular damage, increased intracellular concentration of reactive oxygen and other free radicals, direct local injury (particularly with ion trapping in the stomach), inhibition of cell division, and reduced hydrophobicity of the gastric mucous coat.[849,851] Inhibiting COX may shunt arachidonic acid metabolism toward the lipoxygenase pathway, thereby producing other biologically active eicosanoids. The clinical significance of this shunting is unclear, but the potential for deleterious effects exists.

Although the toxicity of NSAIDs is related to the dose and duration of administration, some horses develop toxicosis at recommended doses. Predisposing factors such as dehydration, renal disease, hepatic disease, or sepsis may contribute to the development of NSAID toxicity. Dehydration, renal disease, and hepatic disease predispose to NSAID toxicosis because of reduced tissue perfusion and reduced drug elimination. Sepsis may predispose to NSAID toxicosis because of secondary hypovolemia, decreased tissue perfusion, and direct and indirect effects of various mediators produced in response to sepsis (e.g., platelet aggregating factor). In humans, risk of NSAID-induced ulceration is increased among those with various gastrointestinal disorders (e.g., IBDs). NSAIDs inhibit the ability of injured equine intestinal mucosa to repair, which may increase the risk of ulceration in horses with ischemic damage or intestinal infections. Body weight may be a predisposing factor in that NSAIDs are often administered to ponies, miniature horses, and small horses at doses higher than those recommended for their body weight. Inadvertent overdosing can occur regardless of body weight or size (e.g., administration of a 12-g tube of phenylbutazone paste when administration of an anthelmintic paste was intended).

Some horses may have an idiosyncratic predisposition, particularly for ulceration of the right dorsal colon. Experimentally, arthritic laboratory animals were more susceptible to NSAID-induced gastropathy than healthy animals.[853] This finding may have relevance to horses because NSAIDs are often administered to chronically lame horses. Two or more NSAIDs are used concurrently in some situations. It is important to recognize that the effects of combining NSAIDs are additive, such that administering two NSAIDs at each of their recommended

doses is similar to giving twice the recommended dose of one NSAID. Combination of two NSAIDs will prolong their pharmacologic effect and increase the risk of toxicity.[854]

* Ketofen, Fort Dodge Animal Health, Fort Dodge, IA.

† Arquel, Fort Dodge Animal Health, Ford Dodge, IA.

† Equiproxen, Fort Dodge Animal Health, Fort Dodge, IA.

32.83.2 Clinical Signs

Clinical signs of NSAID toxicity are usually referable to the alimentary system and vary depending on the segment involved. Oral or lingual ulceration may lead to difficulty in prehension and mastication. Esophageal ulceration may result in excessive salivation and apparent signs of pain (stretching of the neck, groaning) during swallowing. Gastric ulceration may result in slow consumption of feed, inappetence (particularly for grain in some horses), or anorexia. Horses that have gastric outflow obstruction associated with gastroduodenal ulceration may exhibit ptyalism, reflux esophagitis, and, in severe cases, spontaneous nasogastric reflux. Horses with ulceration anywhere in the gastrointestinal tract may exhibit signs of colic, which may be intermittent and varying in severity. Horses with colonic ulceration may have soft stool or diarrhea and ventral edema secondary to enteric protein loss. Diarrhea can be severe, even fatal. Endotoxemia may result from intestinal mucosal damage caused by NSAIDs. Clinical signs of endotoxemia (e.g., tachycardia, altered appearance of mucous membranes, fever, and dehydration) may be seen in some horses with NSAID enteropathy. In some horses, hematuria may be seen.

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Horses may have clinical signs days to weeks after having been administered NSAIDs. Such horses typically are presented because of recurring colic, weight loss, or loose manure. It is particularly important in these horses to determine whether there is any history of NSAID administration, even if it was several weeks previous to the time of presentation.

32.83.3 Diagnosis

Diagnosis is usually made on the basis of history of NSAID use, clinical signs, and clinicopathologic findings. The most consistent clinicopathologic abnormalities in horses with NSAID toxicosis are hypoproteinemia and hypoalbuminemia, presumably from loss of protein through inflamed intestinal mucosa. These findings are more commonly observed with damage to the distal intestinal tract and are not reliable for diagnosis of NSAID gastropathy. Some horses have decreased serum concentration of calcium, presumably attributable to intestinal loss of protein-bound calcium. In horses with NSAID-induced diarrhea, hyponatremia, hypochloremia, hypokalemia, acidemia, and hypovolemia may be observed if the diarrhea is severe. In such cases, hypovolemia may make the serum protein concentration appear to be higher than its actual value would be were the horse adequately hydrated.

In chronic cases, horses may be anemic from inflammation, intestinal loss of blood through ulceration, or reduced function of platelets. Occult blood may be found in the feces of horses with lesions in the more distal portions of the intestinal tract. Tests for occult blood often lack sensitivity, and false-positive results may be expected for up to 24 hours after rectal palpation.

The concentration of leukocytes is usually within the reference range, although leukocytosis and hyperfibrinogenemia, associated with inflammation, and leukopenia and neutropenia, presumably caused by endotoxemia, can be seen in some horses with acute NSAID toxicosis affecting the distal intestine. Generally, results of peritoneal fluid analysis are within reference ranges, but increased concentration of nucleated WBCs,

total protein, and fibrinogen may be seen when there is advanced intestinal damage or intestinal vascular infarction. When findings of cytologic examination of peritoneal fluid are abnormal, results are more consistent with nonseptic than septic inflammation; however, septic inflammation may be observed when severe intestinal ulceration leads to transmural lesions and septic peritonitis.

Several clinicopathologic changes may accompany NSAID-induced renal damage. The most consistent finding is decreased urine specific gravity, from 1.008 to 1.020. Inability to properly dilute urine can be found with acute NSAID toxicosis for years after the original insult. This results from preferential damage to areas of the kidney that contribute most to concentrating urine (medulla, papilla). In chronic cases urine specific gravity typically ranges from 1.013 to 1.020. Some horses with NSAID toxicosis are azotemic. In acute cases azotemia can result from dehydration, NSAID-induced alterations in renal blood flow, and tubuloglomerular feedback mechanisms. Chronic azotemia, with serum creatinine ranging from 2.1 to 3.5 mg/dL, results from tubuloglomerular feedback mechanisms that reduce glomerular filtration to compensate for reduced reclamation of solutes in the medullary collecting ducts. In acute NSAID toxicosis, there may be overt hematuria. In other cases, urinalysis may reveal occult blood, increased renal cells, and increased WBCs. In chronic cases other than decreased urine specific gravity, urinalysis results are typically normal.

Endoscopy can be useful to visualize the location and extent of esophageal and gastric lesions. NSAID-induced gastric lesions are more common in the glandular epithelium, although nonglandular lesions can be observed. Contrast radiography or scintigraphy may be useful to document delayed gastric emptying in some horses. Lesions of the jejunum, ileum, cecum, and colon can be difficult to identify without celiotomy and enterotomy. Isotope-labeled WBC scintigraphic scans may identify colonic ulceration[855]; the sensitivity and availability of the procedure is limited, however. Ultrasonography may reveal thickening of the right dorsal colon or other colonic segments, but the technique appears to lack sensitivity.[856] Horses with renal crest necrosis may have increased ultrasonographic echogenicity of the renal crest and echogenic debris in the renal pelvis.

32.83.4 Management

Administration of NSAIDs should be discontinued if NSAID toxicosis is suspected. Gastric lavage and administration of 1 gallon of mineral oil per 450 kg of body weight via nasogastric tube may be of benefit in horses with acute NSAID overdose to reduce the absorption of the administered NSAID. Treatment for gastric ulceration with a proton-pump inhibitor (e.g., omeprazole[*]), an H_2-receptor blocker (e.g., ranitidine), or sucralfate should be implemented for horses with gastric ulceration.

Regardless of the site of NSAID toxicity, administration of misoprostol[†] may be of benefit because administration of a synthetic analog of PGE_2 has been demonstrated to prevent phenylbutazone-induced gastrointestinal lesions in horses.[857] Misoprostol, a synthetic analog of prostaglandin E_1, can be administered orally starting at doses of 5 µg/kg q12h or 2 µg/kg q6h. Some horses will develop signs of abdominal discomfort or diarrhea at these doses; another protocol is starting at 1.5 µg/kg q8h for 2 to 4 days and increasing at increments of 0.5 µg/kg q8h every 2 to 4 days until a maintenance dose of 2.5 to 3 µg/kg q8h is achieved. Because of the paucity of experimental and clinical data for this drug, dosage schedules should be individually tailored for the horse's illness and tolerance to the drug.

For horses with hypovolemia secondary to colitis, administration of crystalloid fluids is indicated. Infusion of plasma may benefit horses with NSAID-induced enteropathies and signs of endotoxemia. The aim of plasma transfusion in a hypoproteinemic horse with colitis need not be to increase the plasma concentration into the reference range, because this may be cost-prohibitive and infused protein may be rapidly lost via the intestinal

tract. Smaller volumes of plasma (1 to 3 L in an average-size horse) may exert beneficial effects by increasing colloid oncotic pressure and perhaps by modulating the effects of endotoxemia. Alternative colloidal fluids may be beneficial as well. Hetastarch (5 to 10 mL/kg IV q48-72h) may maintain plasma colloid oncotic pressure in the acute stages of the NSAID toxicity. Administration of broad-spectrum antimicrobial drugs may be indicated when signs of endotoxemia are observed. Parenteral administration of antimicrobial drugs is preferable to oral administration in horses with colitis because of the presumed increased risk of antimicrobial-associated diarrhea with the oral route. Oral administration of metronidazole (10 to 15 mg/kg PO q8-12h) might be an exception to this guideline, because evidence exists that metronidazole may exert an antiinflammatory effect and enhance healing in NSAID-induced intestinal ulceration.[858]

For horses with RDUC, dietary management directed toward providing a low-bulk diet in the form of a pelleted concentrate and restricting or eliminating ingestion of roughage is recommended. The aims of this approach are to decrease the mechanical and physiologic load of the colon. A complete pelleted diet (i.e., a diet that contains both concentrate and adequate but relatively low dietary roughage) will decrease intestinal fill in the colon. A diet lower in fiber should decrease the physiologic load of the colon because the cecum and large colon are the primary sites in horses of fiber digestion and exchange of fluid and electrolytes. Concentrate should be fed in smaller amounts and frequently (four to six feedings per day). Addition of corn oil may provide additional calories and may also aid in healing of the damaged intestinal mucosa by promoting PGE_2 production. Some horses will not eat complete pellets, and some horses that have roughage withheld will eat bedding or wood as a consequence. These horses should be allowed to eat fresh grass in small amounts on a frequent basis (four to six times daily). The importance of and optimal duration for restriction of roughage is unknown, but it likely requires months for the colon to heal. Horses should be changed from and returned to their usual diet over a period of several days to decrease the risk of inducing other digestive disorders.

Feeding psyllium mucilloid may promote colonic healing in horses with RDUC. In other animal species, psyllium mucilloid has been demonstrated to increase the concentration of short-chain fatty acids of the large bowel, and increased short-chain fatty acids can promote colonic mucosal repair.[859] The amount and duration of psyllium mucilloid administered orally that is required to alter the colonic concentration of short-chain fatty acids and the role of short-chain fatty acids in repair of RDUC in horses is unknown. Continuous feeding according to manufacturer's recommendations for 3 to 6 months is suggested, or feeding 1 to 2 oz of psyllium mucilloid once or twice daily for the same duration may be considered.

Horses with strictures of the pylorus, duodenum, jejunum, or colon may require surgical management. Bypass or resection of affected intestinal segments may be necessary.

Limiting the extent of predisposing factors, such as dehydration, should decrease the risk of NSAID toxicosis. Avoiding use of NSAIDs or limiting the dose and duration of treatment to the minimum that is required to control the primary problem is recommended to decrease the risk of NSAID toxicosis. Other approaches to analgesia, such as regional (epidural or perineural nerve blocks of distal limbs) anesthesia or administration of butorphanol,* should be considered.

* GastroGuard, Merial Ltd., Iselin, NJ.

† Cytotec, Searle and Co., Chicago, IL.

* Torbugesic, Fort Dodge Animal Health, Fort Dodge, IA.

32.84 DISORDERS OF THE DESCENDING (SMALL) COLON

Vanessa L. Cook

Colic resulting from a problem with the small colon is comparatively rare, being identified in only 4.2% of surgical colics.[860] However, American Miniature Horses (AMHs) seem to be at increased risk for obstruction of the small colon,[861] with a prevalence of 60% of surgical colics in that breed.[862] The Arabian breed may also be overrepresented compared with the hospital population.[860,861] It is interesting to note that horses over 15 years of age also seem to be at an increased risk for small colon conditions,[861] especially strangulating lipoma, foaling injury, and submucosal hematoma.[860] Mares may also be at increased risk for small colon lesions, possibly because of hormonal fluctuations affecting gastrointestinal motility,[861] because of the small colon's predisposition to injury during foaling, or because of the small colon's ability to become entrapped by an ovary.

One of the biggest challenges with small colon lesions is that the associated clinical signs and rate of physiologic deterioration are less severe than with a higher obstruction, often resulting in later referral.[860,861] A complete examination including rectal examination and abdominocentesis provides useful information in determining the diagnosis and indicating surgical intervention.[860] However, because the small colon lies caudally in the abdomen, transabdominal ultrasonography may be less useful than it is for lesions in other sections of the intestinal tract. Transrectal ultrasonography, performed with care, may be a more sensitive method to detect compromised small colon and may aid in earlier diagnosis.[863]

Conditions affecting the small colon can be divided into congenital diseases, simple obstructions, vascular lesions, and strangulating lesions.

32.85 CONGENITAL DISEASES

32.85.1 Atresia Coli and Aganglionosis

Atresia coli is much more rare in foals than it is in calves, with a reported incidence of 0.44%.[864] There are several theories on the pathogenesis of this disease, but an ischemic vascular accident that results in atrophy of the affected segment is the most widely accepted.[865] There are four types of atresia,[866] with type 3, blind end atresia with no connection of the atretic segments, being the most common in foals.[864,867] Atresia coli may be confused with overo lethal white syndrome, in which affected foals have myenteric aganglionosis of the distal intestinal tract resulting from a mutation in the endothelin receptor type B gene.[868,869] However, in this condition the intestinal tract is patent but nonfunctional. Loss of neurons in the myenteric plexus of the small colon can also be found in equine dysautonomia (grass sickness), although it is usually less severely affected than the ileum.[870]

Foals with atresia are usually normal at birth but develop progressive abdominal distention and colic within 24 hours of birth. Atresia can be differentiated from other causes of colic in foals by the lack of feces with no meconium staining even after an enema.[865] It may be possible to confirm a blind ending rectum or distal small colon by digital palpation or passage of a soft catheter or endoscope. However, the defect is usually too proximal to visualize this way, and perforation of the friable colonic mucosa can easily occur; therefore I do not use this method for diagnosis. Plain radiographs do not usually identify the atresia but can help to differentiate it from a meconium impaction. Retrograde contrast radiography, as described later in this section for meconium impaction, may give a more definitive answer.[871] A large volume of barium sulfate, up to 20 mL/kg, may be needed if the atresia is proximal to the transverse colon. If atresia is present, the contrast agent will be seen to end abruptly at the atretic segment.

The only chance for survival in cases of atresia is early exploratory celiotomy to assess the affected segment and determine if surgical correction is possible. In calves with atresia, the prognosis is vastly improved if the diagnosis is made early and the animal is alert and is stabilized medically before surgery.[872,873] However, in foals, despite attempting surgical resection of the atretic segment and anastomosis, the prognosis is grave, with a 100% mortality rate reported in several studies.[864,867]

32.86 SIMPLE OBSTRUCTIONS

32.86.1 Simple Impaction

Small colon impaction is the most common abnormal condition of the small colon in adult horses, affecting 1.9% to 2.5% of all horses seen for colic at referral institutes.[874,875] Several studies report a strong association between small colon impaction and diarrhea. The most recent study documents that horses with diarrhea are 10 times more likely to develop a small colon impaction than horses without diarrhea.[876] In other studies, diarrhea developed during hospitalization in 70% of all horses with small colon impaction, and 43% of those treated surgically cultured positive for *Salmonella* species.[874] These studies suggest that impaction of the small colon may be a sequela to colonic inflammation, such as *Salmonella* infection. Therefore it is advisable to use isolation protocols for all horses with a small colon impaction. Previous reports have documented a dramatic increase in the incidence of small colon impaction in the fall and winter, possibly because of decreased water intake or close housing that increases the incidence of infectious colitis, but a definitive reason is unknown. It is interesting to note that this seasonal incidence was not significant in the most recent study, possibly because of the milder winters in the south.[876]

Diagnosis of a small colon impaction is most easily made by rectal palpation, with an accuracy of 79% to 87%.[874,876] A solid tube of ingesta with loss of the normal sacculations is found. However, great care should be taken when performing a rectal examination because the rectal mucosa may be edematous, and frequently the horse will strain.[877] It now appears that the best parameter for determining when surgical treatment of these cases is required is the presence of abdominal distention. Recently it has been reported that horses with a small colon impaction and abdominal distention are five times more likely to require surgical correction than horses without abdominal distention.[876] Unlike other types of colic, this single factor is more significant than heart rate, temperature, or duration of colic when determining the need for surgical intervention.[876]

Medical therapy should consist of aggressive intravenous and enteral fluid therapy, including correction of electrolyte abnormalities, combined with laxatives and lubricants, and analgesics as necessary.[874,875] The length of time for the impaction to resolve with medical treatment is often longer than for large colon impactions, averaging over 2 days.[876] Surgical correction of the impaction via exploratory celiotomy is usually performed via a high enema combined with extra luminal massage by the surgeon. The impacted small colon is extremely friable, and great care should be taken by the surgeon when manipulating the bowel in order to avoid serosal tears. Application of sterile carboxymethylcellulose to the serosal surface may help lubricate the intestine and reduce the trauma of manipulation. In severe cases, infusion of the impacted contents with isotonic fluids or an enterotomy in the small colon may be necessary to facilitate evacuation of the impaction.[877] An additional concern is the risk of reimpaction of the small colon as ingesta from the large colon move aborally after surgery. Therefore if there are ingesta in the large colon at the time of surgery, a pelvic flexure enterotomy is recommended to empty the large colon and reduce the risk of recurrence.[874] Surgical correction of the impaction

can be time-consuming; therefore to reduce anesthesia time it is advisable to assemble the items needed for a high enema, such as a stomach tube with a rounded atraumatic end, stomach pump, and buckets of warm water, in the operating room before induction.

The prognosis for medical and surgical treatment appears to be similar in most studies.[874,876] It is interesting to note, however, that overall prognosis appears to have improved in recent years, increasing from approximately 75% in cases from 1986 to 1996[874] to approximately 95% in cases from 1999 to 2004.[876] Therefore, overall, the prognosis for small colon impaction is excellent, even if surgical treatment is necessary. However, because of the underlying inflammatory cause of this condition, length of hospitalization and associated costs tend to be higher than those incurred with a simple large colon impaction.[876]

32.86.2 Fecaliths, Enteroliths, and Foreign Bodies

Simple obstruction of the small colon also occurs from inspissated feces (fecaliths), enteroliths, foreign bodies, or, less frequently, concretions of plant material (phytobezoars) or masses of matted hair (trichobezoars).

Fecaliths are improperly formed fecal balls that are larger than normal at 4 to 6 cm diameter in miniature horses.[878] They are a common cause of colic in young miniature horses,[878] with an occurrence rate of 63% in a study of surgical colic in miniature horses.[879] Causes of the formation of fecaliths are probably similar to those of other impactions and include poor-quality roughage, dental disease causing problems with mastication, and reduced water intake.[878,879] Fecaliths that become lodged in the small colon usually cause complete intestinal obstruction and require surgical removal as described later. When managing colic in miniature horses, regardless of the cause, the patient should have serum triglyceride concentration monitored to allow early detection and treatment of hyperlipemia.[880]

Enteroliths are mainly composed of magnesium ammonium phosphate deposited in concentric layers around a nidus such as a small rock.[881] The incidence is very high in certain areas, such as California, where enterolithiasis constitutes 15.1% of all colic seen at the University of California, Davis[882] compared with less than 2% of colic cases at Texas A&M University.[883] Several studies report an increased incidence in Arabians, although the reason for this is unknown. Enteroliths can lodge in the large colon, transverse colon, or small colon, but the last is a relatively common site, with over 45% of cases involving an obstructive enterolith in the small colon.[882] Horses with enteroliths were found to have certain changes in the composition of their colonic contents, compared with other surgical colic cases, which may predispose them to enterolith formation. These differences included a more alkaline pH, more colonic fluid, and higher mineral concentrations.[884] Certain management practices may also predispose to enterolith formation, including feeding a high proportion of alfalfa and giving less access to pasture.[883,884] Clinical signs of enterolithiasis are similar to those seen with other nonstrangulating obstructions of the large or small colon. However, many horses with enterolithiasis have a history of intermittent colic, and some may even have passed enteroliths in the feces.[882] Abdominal radiographs may be a useful aid in diagnosis, although the sensitivity is reduced when the enterolith is in the small colon.[885] Medical management aimed at reducing colonic pH has been suggested to try and prevent recurrence after surgery. However, when an enterolith lodges in the small colon it usually causes complete obstruction and acute colic that requires surgical intervention as described later. Rupture of the gastrointestinal tract is particularly common if the enterolith is lodged in the small colon and surgery is delayed.[882] Such cases should therefore be prioritized as requiring emergency surgery, even when there is a history of chronic colic.

Obstruction of the small colon can also occur from ingestion of foreign material such as rope, twine, rubber fencing, cloth, or tires.[886,887] This is usually a problem of younger horses, possibly because they are more inquisitive and will eat nonfood items found in their environment. It is possible for the foreign body to cause signs of small intestinal obstruction first, followed by a period of quiescence while it passes through the large colon before it finally causes complete obstruction of the small colon and acute onset of severe colic[888] and abdominal distention.[886] The fibers become covered in crystalline material during their transit through the intestinal tract, and the resulting irregular sharp projections cause mucosal ulceration,[860] which can be seen during exploratory celiotomy oral to the site where the foreign body has finally become lodged. These sharp projections make it virtually impossible to manipulate the foreign body orally or aborally within the lumen, making removal more complicated.

The majority of these obstructions require exploratory laparotomy and an enterotomy to allow the obstruction to be removed.[878,882,886] Regardless of the cause of the obstruction, the overlying intestine is friable and can easily rupture either during induction of anesthesia[886] or during surgical manipulation.[882,887] If possible, the mass should be gently manipulated more proximal or distal to the original site at which it lodged, so that the enterotomy can be performed in uninjured intestine.[860] However foreign bodies in particular may be difficult to manipulate, and the enterotomy may have to be performed directly over the top of the obstruction. The site selected for the enterotomy should be isolated from the abdomen with sterile towels before the enterotomy incision is made. The incision should be made longitudinally through the antimesenteric taenia in order to preserve luminal diameter, reduce hemorrhage, and maximize speed and ease of the procedure.[889,890] The enterotomy can be closed in one layer using an inverting suture pattern.[890] Problems arise, however, when intraluminal obstructions occur at the proximal portion of the descending colon, where the lumen narrows between the transverse and descending colon. Here, manipulation of the obstruction aborally into a section of small colon that can be exteriorized may be impossible. In such cases an antimesenteric teniotomy, through the seromuscular layer alone, can be performed. This will allow the obstruction to be advanced aborally into a section that can be exteriorized, while the intact mucosa prevents abdominal contamination.[891] The enterotomy and seromuscular incision are then closed as described earlier.

32.86.3 Meconium Retention

Meconium is composed of substances that are present in the intestinal tract at birth, such as glandular secretions, sloughed cells, and swallowed amniotic fluid, and is therefore sterile. It is thick and tarry and is usually passed within 48 hours of birth. Several studies indicate a higher incidence of meconium retention in colts than fillies, presumably because of the longer narrower pelvis in males.[892,893] Any factors that reduce intestinal motility, such as failure to ingest colostrum, and dysmaturity, can result in difficulty passing meconium, which is described as meconium retention. This results in progressive clinical signs of colic such as tail flagging, straining, and reduced suckling. This can progress to more severe signs of colic over time, such as rolling and abdominal distention. These signs are similar to those seen with ruptured bladder, and the two conditions can occur together; therefore a complete examination of the foal is important.

It may be possible to palpate meconium retained at the pelvic inlet by careful digital rectal examination. If the meconium is retained more proximally, it may be identified on a plain lateral radiograph. Confirmation of the obstruction may be provided by retrograde contrast radiography, which provides excellent sensitivity and specificity for evaluation of the transverse and descending colon.[871] After plain radiographs are obtained, a Foley catheter is placed into the rectum and inflated. Up to 20 mL/kg (approximately 1 L) of 30% barium sulfate

is carefully allowed to flow in by gravity until it squirts around the catheter or discomfort is observed.[871] Lateral and, more important, ventrodorsal radiographs are then obtained. If a meconium impaction is present, the contrast agent is stopped before it reaches the transverse colon.

Supportive medical management of all foals should be performed first, including correction of fluid and electrolyte imbalances, provision of nutritional support, and correction of failure of passive transfer if indicated.[894] Judicious use of analgesics such as flunixin meglumine or butorphanol and oral laxatives such as mineral oil may aid resolution of the impaction. However, the most effective treatment is administration of an enema. The enema can be a commercial phosphate enema or simply soap and water administered through a Foley catheter using gravity flow as described previously. In cases that are refractory to simple enemas, an acetylcysteine enema may be effective. Acetylcysteine is a mucolytic, which acts by breaking disulfide bonds to make meconium less viscous. These enemas are available commercially (E-Z Pass Foal Enema Kit, Animal Reproduction Systems, Chino, Calif.) or can be formulated by adding 20 g of baking soda to 200 mL of water, and then adding 8 g of acetylcysteine powder to make a 4% solution.[892] The solution is infused slowly through a Foley catheter, which is then clamped to allow the solution to be retained for up to 45 minutes to allow maximum activity of the acetylcysteine. Successful resolution of the meconium retention occurred in all acetylcysteine-treated foals in one study, although 5% of foals did require three enemas before resolution.[892]

Previous reports have indicated that approximately one third of foals with meconium retention require exploratory celiotomy for resolution.[893] However, this was before the increased use of acetylcysteine retention enemas, and it is likely that the current rate of surgical intervention is much lower. Considering the high rate of adhesions in neonatal foals undergoing exploratory laparotomy,[893,895] this should result in an improved prognosis for this condition.

32.86.4 Other Causes of Simple Obstruction

Because of the proximity of the descending colon to the urogenital tract, it is possible for the descending colon to be obstructed by structures such as an ovary or retained testicle. Although such conditions occur infrequently, the most common is for the small colon to become entwined around an ovary.[860] The intestine can be freed and is not usually compromised, but the ovary itself is usually nonviable and requires resection.[896] A similar problem has been reported from the spermatic cord of a retained teratoma occluding the small colon.[897]

32.87 VASCULAR LESIONS

32.87.1 Intramural Hematoma

Intramural hematoma of the small colon is relatively rare, although some cases may not be diagnosed if they do not cause complete obstruction and if they resolve without intervention.[898] Hemorrhage occurs between the mucosa and muscularis layers, which expand to occlude the lumen and cause complete obstruction. The length affected has been reported to range from 24 to 65 cm. The cause is unknown, although in people, blunt abdominal trauma has been associated with the condition.[899] In one equine case series, iatrogenic rectal trauma was implicated as the cause.[900] There is an increased incidence in older horses, with those affected having an average age of 11 years in one study.[860] Affected cases frequently have blood in the rectum and may show signs of vascular compromise from blood loss.[860,900]

Exploratory celiotomy with complete resection of the affected segment and end-to-end anastomosis is necessary. Because of the long length of the affected segment, it may be difficult to exteriorize and resect all damaged intestine. However, if the entire affected segment can be removed, the prognosis is good, with 75% of horses surviving in one study.[898]

32.87.2 Mesocolic Tears and Rectal Prolapse

Tears in the mesentery of the small colon can occur as a complication of parturition, especially in multiparous mares,[901,902] and result in segmental ischemic necrosis of the small colon. Trauma and straining during parturition can result in tearing of the mesocolon and devitalization of the associated descending colon, which may progress to an intussusception of the small colon, which manifests as a type III or IV rectal prolapse. In a type III rectal prolapse the rectal ampulla prolapses, as with a type II prolapse, but in addition a portion of the small colon intussuscepts into the rectum. In type IV rectal prolapse part of the small colon and the rectum intussuscepts through the anus.[901,903] Gentle palpation around the prolapse can help determine the type of prolapse. Although a rectal prolapse is readily identifiable, tears of the mesocolon resulting in devitalization of the small colon result in a more insidious onset of clinical signs, including depression and lack of feces.[901,902]

The mesocolic tear is frequently located caudally, resulting in the affected area being inaccessible via a midline celiotomy. Therefore it may be more prudent to first perform standing flank laparoscopy to determine the location and extent of the lesion.[904] This allows assessment of the lesion to determine if resection and anastomosis of the affected segment via celiotomy is feasible, or if a permanent colostomy is required.[905]

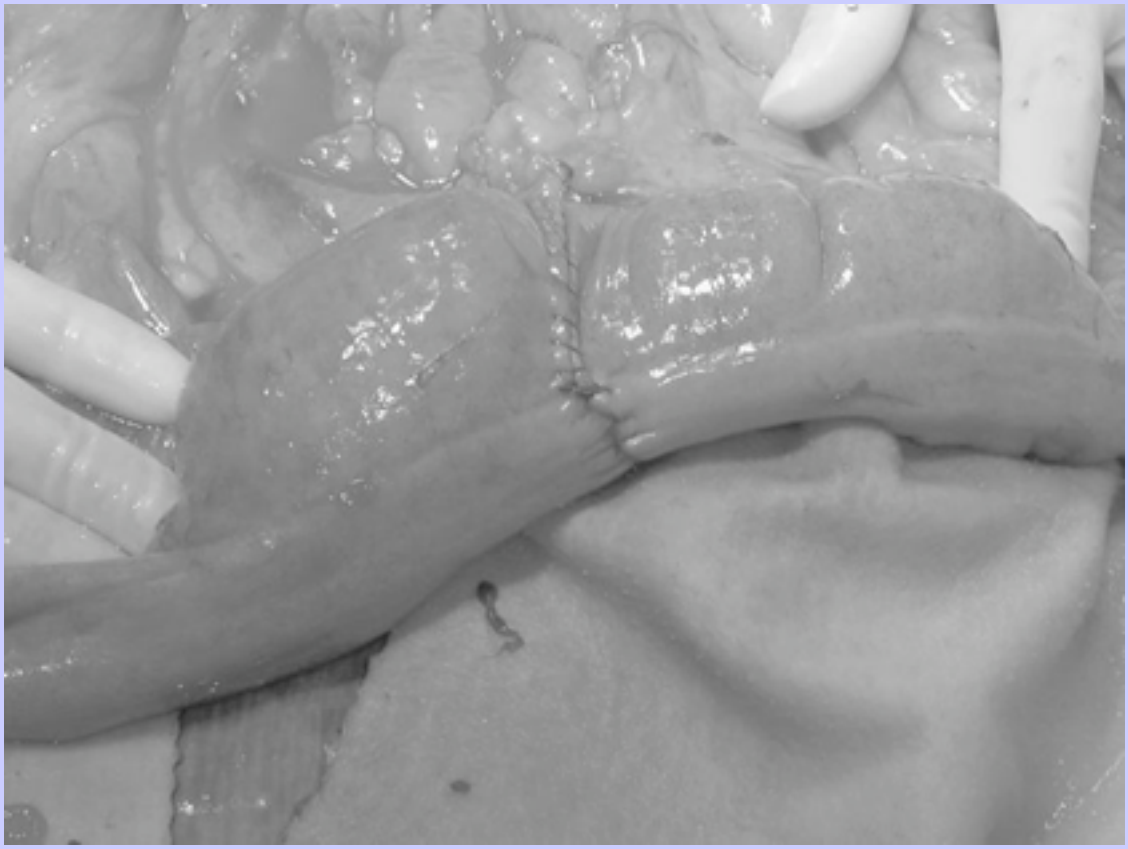
32.88 STRANGULATING OBSTRUCTIONS

32.88.1 Strangulating Lipoma

Pedunculated lipomas can cause a strangulating or nonstrangulating obstruction of the small colon, but this occurs much less frequently than in the small intestine. In a large retrospective study, lipomas were found to involve the descending colon in less than 10% of cases.[906] The overall incidence of lipomas affecting any portion of the gastrointestinal tract is increased in older geldings[906,907] and in Saddlebreds and Arabians.[906] It is therefore likely that lipomas specifically affecting the descending colon have a similar distribution. Fig. 32-58 illustrates a pedunculated lipoma that had strangulated a short section of the small colon. Clinical signs typical of a strangulating obstruction are seen, with a significantly elevated heart rate, abnormal abdominocentesis, and distended large colon on rectal examination.[860] In addition, on rectal examination a constriction of the lumen of the small colon caused by the lipoma may be felt. Surgery is necessary to free the constricting lipoma, followed by resection and anastomosis if the intestine is nonviable (Fig. 32-59). The prognosis is worse if resection is required, with a 50% survival rate in one study, compared with 100% survival for nonstrangulating lipomas.[860]

Fig. 32-58 A short section of small colon that had been strangulated by a pedunculated lipoma.

Fig. 32-59 The same case as in the previous figure after resection of the ischemic segment and end-to-end anastomosis.



32.88.2 Other Causes of Strangulating Obstruction

Several other causes of strangulating obstruction can occur, but each condition is relatively rare. These include volvulus of the small colon[888] and strangulation through internal hernias such as a vaginal tear[861] or tears in the gastrosplenic ligament.[908]

32.88.3 Prognosis

A good survival rate was found in two large studies reviewing small colon disorders, with 71% and 91% of patients being discharged from the hospital.[860,861] The main reason for euthanasia at the time of surgery was an inability to completely exteriorize the affected segment to allow adequate resection and anastomosis.[860] Previous reports have suggested that resection and anastomosis in the small colon may carry a poor prognosis because of a relatively poor blood supply, higher bacterial counts, solid fecal material, and increased collagenase activity compared with the small intestine.[888] However, if the patients euthanized at surgery are excluded, short-term survival after surgery for a small colon lesion is excellent, with a report of 100% survival in one study.[909] In

addition, horses that required resection and anastomosis did not have a worse prognosis for survival[861] and are less likely to develop the complications associated with small intestinal resection, such as POI.[910]

32.89 PERITONITIS IN HORSES

Robin M. Dabareiner

32.89.1 Anatomy and Physiology

The peritoneum is the mesothelial lining of the peritoneal cavity and its contained viscera. It forms a closed sac in males but communicates with the external environment in females via the fallopian tubes. The peritoneum consists of a single layer of mesothelial squamous cells resting on a thin basal lamina, which is attached to a loose connective tissue layer containing collagen, and elastic fibers, allowing a variable degree of motion. The peritoneum is coated with a thin serous film that serves to minimize friction and thus facilitates free movement between abdominal viscera.[911,912] The peritoneum is divided into the visceral peritoneum, which encloses the intraperitoneal organs and forms the omentum and mesenteries, and the parietal peritoneum, which lines the abdominal walls, pelvis, and diaphragm. The visceral peritoneum, mesentery, and omentum are supplied and drained by the splanchnic vasculature.[913] The parietal peritoneum is supplied by arterial branches of the lower intercostal, lumbar, and iliac vessels and is drained by veins entering into the caudal vena cava. Branches of the spinal nerves supplying the abdominal wall innervate the parietal peritoneum, and the phrenic nerve supplies the diaphragmatic peritoneum. As a result, irritation of the parietal peritoneum gives rise to afferent stimuli that are transmitted by the intercostal and phrenic nerves and perceived as somatic pain.[913] In contrast, there are no pain receptors in the visceral peritoneum, and afferent stimuli are conducted centrally by the visceral autonomic nervous system.

Peritoneal fluid is constantly being produced and absorbed. The movement of fluid and solutes occurs by passive diffusion across the semipermeable peritoneal membrane.[914] Solutions or drugs administered into the peritoneal cavity equilibrate rapidly with plasma. Transperitoneal fluid movement can be increased during peritoneal inflammation, causing a rapid and massive transudation of fluid into the peritoneal cavity that can lead to hypotension and shock.[914]

The peritoneal lymphatics, especially the diaphragmatic lymphatics, play a major role in the removal of fluid and solutes from the peritoneal cavity. The diaphragmatic lymphatic valves provide a unidirectional clearance of peritoneal fluid and debris, which empty primarily into the thoracic duct and are probably the first line of defense in peritoneal contamination. These lymphatics are aided by movements of breathing, which encourage cranial flow and clearance of peritoneal fluid.[915–917] Cellular defenses are provided by peritoneal macrophages, mast cells, and mesothelial cells. Activated peritoneal T lymphocytes and local antibody production have also been demonstrated experimentally.[916] Peritoneal macrophages have antimicrobial activity resulting from their complement receptors, phagocytic ability, and T cell—mediated immune responses. In addition, peritoneal macrophages are important in neutrophil chemotaxis and fibroblast stimulation, which aid in bacteria localization. Peritoneal mesothelial cells are an abundant source of plasminogen activator, which is responsible for normal fibrinolytic activity on peritoneal surfaces.[915]

32.89.2 Pathophysiology of Peritoneal Injury

Peritonitis can be induced by a number of infectious (bacterial, viral, fungal, parasitic) and noninfectious (traumatic, chemical, neoplastic) causes. The initial reaction to inflammatory stimulus is the release of histamine and serotonin from peritoneal mast cells and macrophages, resulting in vasodilation and increased vascular permeability with transudation of fibrinogen-rich plasma into the peritoneal cavity. The concurrent loss of mesothelial cells and release of tissue thromboplastin reduce the fibrinolytic capabilities of the peritoneal surface and activate the extrinsic coagulation pathway, thereby shifting the fibrinolysis-coagulation equilibrium toward fibrin formation.[918,919] This response serves to aid in the fibrin seal of the peritoneal defect and provides the framework for fibroblasts to lay down collagen, which produces fibrous adhesions to localize bacteria.

Peritoneal macrophages stimulate neutrophil chemotaxis both directly and indirectly via the release of TNF and IL-1. TNF and IL-1 stimulate neutrophil margination and degranulation and alter the vascular endothelium to promote leukocyte adherence. Metabolism of cell membranes results in phospholipid products such as PAF, prostaglandins, and leukotrienes, which contribute to the vasodilatory response; phospholipase A_2 provides the catalyst for activation of these phospholipid products via the arachidonic acid pathway. Within hours an influx of fluid, protein, and neutrophils enters the peritoneal cavity in response to the inflammatory stimulus.[919]

The combination of enlarged diaphragmatic lymphatics and the cellular defenses described earlier result in rapid clearance of debris from the contaminated peritoneal cavity. If the inflammatory response resolves, the mesothelial cell lining is restored from either free-floating macrophages or differentiated subperitoneal connective tissue cells.[919] The normal fibrinolytic activity of the peritoneal mesothelial cells returns, initiating removal of the accumulated fibrin clots. Severe inflammation, foreign bodies, intestinal ischemia, or infection can result in continued fibrin production from proliferating and migrating fibroblasts, causing fibrous scarring and adhesion formation.[918]

Peritonitis in the horse is usually secondary to intestinal leakage or degeneration, resulting in the transmural passage of bacteria into the peritoneal cavity. Any disease process that causes gastrointestinal, hepatic, or urogenital inflammation or compromise can lead to the development of peritonitis. The adverse effects of intraperitoneal bacteria can be enhanced by the presence of excessive peritoneal fluid accumulation, hemorrhage, [920] fibrin, bile, necrotic tissue, ischemia, anaerobes, and fecal matter. Excessive peritoneal fluid enhances the dissemination of localized bacteria and dilutes opsonic proteins such as complement and immunoglobulins.

761 762

Fibrin formation can be beneficial in confining bacteria; however, excessive amounts can result in abscess formation and prevent phagocytes and antimicrobial drugs from reaching the source of contamination. Fibrinous adhesions may also physically occlude diaphragmatic lymphatics and protect bacteria from opsonins, neutrophils, and antibiotics. Necrotic tissue, fecal matter, and bile all prolong the debridement phase of peritoneal healing and interfere with peritoneal defense mechanisms.

Peritonitis is an inflammation of the peritoneum and can result from many causes, which are classified as primary or secondary, acute or chronic, and localized or diffuse. Primary peritonitis is uncommon in adult horses but may occur by hematogenous spread of bacteria in the septic or immunocompromised neonate or in young horses exposed to *Streptococcus equi* infection.[916] Uroperitoneum and septicemia-induced peritonitis occur predominantly in neonates. Internal abdominal abscesses caused by disseminated *S. equi, Streptococcus zooepidemicus*, or *R. equi* infection are usually found in weanlings or young horses.[921,922]

Peritonitis secondary to another disease process may be caused by perforating abdominal wounds, chemical irritation (bile, urine), neoplasia, breeding and foaling injuries (uterine or vaginal trauma), intestinal parasitism, hepatitis, nephritis, pancreatitis, ruptured bladder or ureter, urinary infection, ruptured or lacerated abdominal viscera (spleen, ovary, liver, diaphragm), castration complications, and factors directly related to gastrointestinal problems, which are divided into preoperative, intraoperative, and postoperative causes (Box 32-4).

32.89.2.1

Box 32-4 Gastrointestinal Factors Associated with Peritonitis

32.89.2.1.1

IATROGENIC FACTORS

32.89.2.1.1.1

Diagnostic Complications

Enterocentesis during abdominocentesis

Inadvertent rectal tears during palpation

Laceration or leakage of distended bowel during percutaneous trocarization

Hemorrhage secondary to splenic abdominal tap

32.89.2.1.1.2

Surgical Complications

Castration

Colpotomy

Surgical trauma to peritoneal surfaces

Enterotomy

Intestinal needle decompression

Intestinal anastomoses

Intraoperative hemorrhage

Break in aseptic surgical procedures

Foreign bodies (sponges, instruments)

32.89.2.1.2 FACTORS ASSOCIATED WITH PRIMARY GASTROINTESTINAL DISORDER

Proximal enteritis

Intestinal ischemia or compromise

Gastric, intestinal perforation

Hemorrhage

Uroperitoneum

Parasitic migration

Abscess

Neoplasia

32.89.3 Diagnosis

32.89.3.1 HISTORY AND CLINICAL SIGNS

Clinical signs of peritonitis vary and depend on the cause and duration of the peritonitis. Localized infections often have limited systemic involvement, whereas diffuse peritonitis can elicit generalized signs of endotoxemia and sepsis. Horses with peracute peritonitis caused by intestinal rupture show signs of acute, severe sepsis and cardiovascular collapse with tachycardia, tachypnea, sweating, and varying degrees of abdominal discomfort with death ensuing within hours.

The most common presenting clinical signs for horses with peritonitis described in retrospective studies of 21 and 30 horses (age range, 2 months to 16 years) included pyrexia (rectal temperature exceeding 38.5° C), anorexia, mild abdominal pain, reduced or absent borborygmi, diarrhea, increased heart rate, and clinical evidence of dehydration.[923,924] In another retrospective study of 67 horses with peritonitis, clinical signs of abdominal pain, signs of circulatory shock, and diarrhea were significantly less severe in survivors compared with nonsurvivors, regardless of the cause of peritonitis.[925]

Rectal examination often elicits pain, and if adhesions are present, distended bowel may be present. In cases of intestinal rupture, either roughened peritoneal surfaces or an abnormally empty abdomen can be palpated. Occasionally, abdominal masses or abscesses can be palpated, and mesenteric lymph nodes may be enlarged; however, in many cases, no abnormalities can be detected. Parietal pain may be characterized by a “guarded” or splinted abdomen with pain on abdominal ballottement and a reluctance to move or defecate.

A urogenital examination should be performed in horses with peritonitis of undiagnosed cause to rule out vaginal, cervical, and uterine tears in mares or infected castration sites in males. Gastrointestinal motility is usually decreased secondary to sympathetic stimulation from parietal pain, hemoconcentration, or serosal surface trauma. Ileus frequently results in intestinal stasis with gastric fluid accumulation and intestinal distention, which subsequently intensifies the abdominal pain. The mobilization of fluid into the peritoneal cavity results in an intravascular fluid deficit, causing reabsorption of fluid from the large colon and cecum. Findings of intestinal ingesta impactions secondary to these fluid shifts or ileus are not uncommon in horses with peritonitis.[924]

32.89.3.2

CLINICOPATHOLOGY

Abnormal laboratory values are dependent on the cause and duration of peritonitis. Hematologic abnormalities seen in acute peritonitis include elevated PCV secondary to transudation of fluid into the peritoneal cavity and endotoxemia. Initially a proportional increase in plasma protein levels occurs, reflecting the degree of dehydration; however, in severe cases protein eventually is sequestered into the abdomen because of increased capillary permeability, resulting in systemic hypoproteinemia. Peripheral blood neutropenia with a degenerative left shift is caused by margination of neutrophils and migration of these cells into the abdomen. Increased plasma fibrinogen levels (up to 1000 mg/dL) can occur after 48 hours. Peritonitis of longer duration and internal abscesses are associated with greater variability in laboratory values, but affected horses often demonstrate a normal or increased systemic neutrophil count, monocytosis, and elevated plasma protein levels as a result of increased immunoglobulin production.[922]

Alterations in blood gas analysis and serum chemistry values often depend on the horse's clinical and hydration status at the time of presentation. Elevations in BUN and creatinine occur secondary to dehydration. 762
Hypokalemia, hypochloremia, and hyponatremia may occur in the anorectic, acidotic patient with 763
gastrointestinal dysfunction. Serum creatinine levels, anion gap, and pH were significantly different between survivors and nonsurvivors at the time of presentation in 67 horses with peritonitis.[925]

Abdominocentesis confirms the diagnosis of peritonitis, although the cause may remain unknown. Normal peritoneal fluid is clear, straw colored, and serous in consistency. The total nucleated cell count and total protein in peritoneal fluid of normal horses were reported to be less than 5000 cells/μL and 2.5 g/dL, respectively, with 24% to 60% of the cells being neutrophils.[926] We have found that normal horses typically have peritoneal fluid protein less than 1 g/dL. The cytologic appearance of the leukocytes and mesothelial cells should be normal, although activated mesothelial cells are not an unusual observation.

Colorless fluid is very dilute, and, if it is present in large quantities, the possibility of ascites or uroperitoneum must be considered. Serosanguineous fluid indicates an increase in erythrocytes or free hemoglobin that may be caused by intestinal degeneration and transmural erythrocyte leakage, splenic puncture during abdominocentesis, abdominal viscera laceration, or skin contamination. Green fluid results from enterocentesis or intestinal rupture, and brown fluid is associated with late-stage tissue necrosis. Turbid fluid indicates an increased cell count, and opalescence suggests chylous effusion. Flocculent fluid with fibrin strands indicates an inflammatory, exudative process in the abdomen. The quantity of fluid varies among horses and can be increased in acute peritonitis (transudate or exudate) or absent in chronic peritonitis with excessive fibrin production.

Peritoneal fluid parameters consistent with peritonitis vary widely, depending on the disease process. High nucleated cell counts ranging from 15,000 to 800,000 cells/μL with greater than 90% neutrophils having toxic

or degenerative changes have been reported for horses with peritonitis[923–926] or internal abscesses.[922] Total protein greater than 2.5 g/dL indicates increased capillary permeability of the abdominal viscera or peritoneum resulting in protein exudation and is associated with peritoneal inflammation, intestinal compromise, or blood contamination of the peritoneal fluid. The presence of fibrin and intracellular bacteria is diagnostic for peritonitis. Cytologic evidence of extracellular bacteria can result from skin contamination and should be interpreted in combination with clinical signs.

It may be difficult to distinguish between early and mild septic peritonitis and nonseptic peritoneal inflammation using clinical and clinicopathologic findings alone. In addition, false-negative bacterial cultures in horses with peritonitis are not uncommon, and positive culture results often require several days of incubation. One study investigated peritoneal fluid pH, glucose concentration, and LDH activity in normal horses and horses with either septic or nonseptic peritonitis.[927] Horses with septic peritonitis had significantly lower peritoneal fluid pH and glucose concentration than horses with nonseptic peritonitis or healthy horses. Serum-to-peritoneal fluid glucose concentration differences >50 mg/dL were diagnostic for septic peritonitis. Peritoneal fluid pH >7.3, glucose concentration <30 mg/dL, and fibrinogen concentration >200 mg/dL were highly indicative of septic peritonitis. LDH activity was not useful in the detection of septic and nonseptic peritonitis. These measurements may provide early indication of sepsis, especially if cytologic evaluation or bacterial culture results are unavailable. The acidic peritoneal fluid pH likely reflects lactate production by peritoneal fluid neutrophils via glycolysis and acid metabolite production by bacteria. The low peritoneal glucose concentration may be secondary to glucose use by bacteria and phagocytic cells, glycolytic enzymatic activity in the peritoneal fluid, or low transport of glucose from the blood to peritoneal fluid.

Peritoneal fluid must be interpreted carefully in horses after abdominal surgery, foaling, castration, or multiple abdominocentesis. Nucleated cell counts between 85,000 and 418,000 cells/μL and protein values from 4.7 to 6.5 g/dL were found on postoperative day 5 in six normal horses that had undergone abdominal exploration.[928] Peritoneal fluid 5 days after open castration (N=24) contained 30,000 nucleated white cells per microliter, with more than 85% being neutrophils. By day 7 after castration the cell counts were normal, with no toxic or degenerative changes.[929] Parturition can cause increased nucleated cell and RBC counts, with elevated total protein values in the peritoneal fluid.[930] In a recent study, postpartum mares having uneventful foaling or uncomplicated dystocia had normal peritoneal fluid except for elevation in percent neutrophils. Mares having complicated dystocia had bloody peritoneal fluid with increased total protein (median total protein = 4 g/dL) and WBCs (median WBCs = 40,5000) 1 day after foaling.[931] Schumacher found no significant alterations in peritoneal fluid in normal horses sampled every 24 hours for 5 days; however, 48 hours after enterocentesis, nucleated cell counts were 113,333 in six of nine horses.[932] Cytologic examination of the peritoneal fluid should include a Wright and a Gram stain. Macrophages should be examined closely for evidence of cellular engulfment and erythrophagocytosis. The peritoneal fluid cell morphology is an important diagnostic aid and can be evaluated from the Wright stain. The Gram stain demonstrates the presence of bacteria and can guide initial antimicrobial treatments until culture and sensitivity results become available. Microbiologic culture is performed to identify aerobic and anaerobic bacteria, and antibiotic susceptibility testing is done to identify specific antibiotic therapy. Serial cultures of the peritoneal fluid may be necessary to identify emerging or resistant bacterial strains. Optimal bacteria isolation techniques when peritoneal fluid is cultured require the use of an enriching broth, blood culture medium, and, if appropriate, an antimicrobial removal device.[*]

Bacteria were cultured or cytologically identified in 48 of 67 horses (71.6%) with peritonitis, and *E. coli* and *Staphylococcus epidermidis* were the most common bacteria isolated from peritoneal fluid samples.[925] Others have reported only a 16% to 25% isolation rate for infective agents.[923,924] Anaerobes have been isolated from

approximately 20% of equine peritonitis cases, with *Bacteroides fragilis* most common.[924] Failure to identify or culture bacteria from peritoneal fluid does not rule out septic peritonitis. Ultrasonography may be helpful in obtaining abdominal fluid, detecting fibrin tags, determining if blood is within the abdomen, or finding an abdominal abscess (Figs. 32-60 and 32-61).

Hemoperitoneum is blood in the abdominal cavity caused by intraabdominal hemorrhage. Although rare in horses, it can be life-threatening. Clinical signs are variable and dependent on cause and severity. Affected horses often show signs of anxiety or depression as well as shock and anemia. Clinical signs of abdominal pain result from high intraabdominal pressure or the irritating effect of blood on serosal surfaces. In one study of 67 cases of hemoperitoneum in the horse, 79% were presented with a primary complaint of abdominal discomfort.[933] Other clinical signs were shock and pale mucous membranes in 60% of horses. Mean heart rate 763
was 76 beats/min, respiratory rate was on average 30 breaths/min, and mean hematocrit was 30% with a total 764
protein concentration of 5.8 g/dL. Causes of the hemoperitoneum were trauma (25%); neoplasia (18%); uterine artery rupture (14%); mesenteric injury (12%); disseminated intravascular coagulation (6%); and idiopathic causes (20%). Fifty-one percent survived to hospital discharge, 37% were euthanized, and 12% died. Poor short-term outcome was significantly associated with a high respiratory rate.

Fig. 32-60 Sonogram of adult horse abdomen showing web of fibrin *(F)* surrounding fluid found in a horse with chronic peritonitis. The wall of the small intestine *(SI)* is thickened. Courtesy Dr. David Schmitz, Texas A&M University.

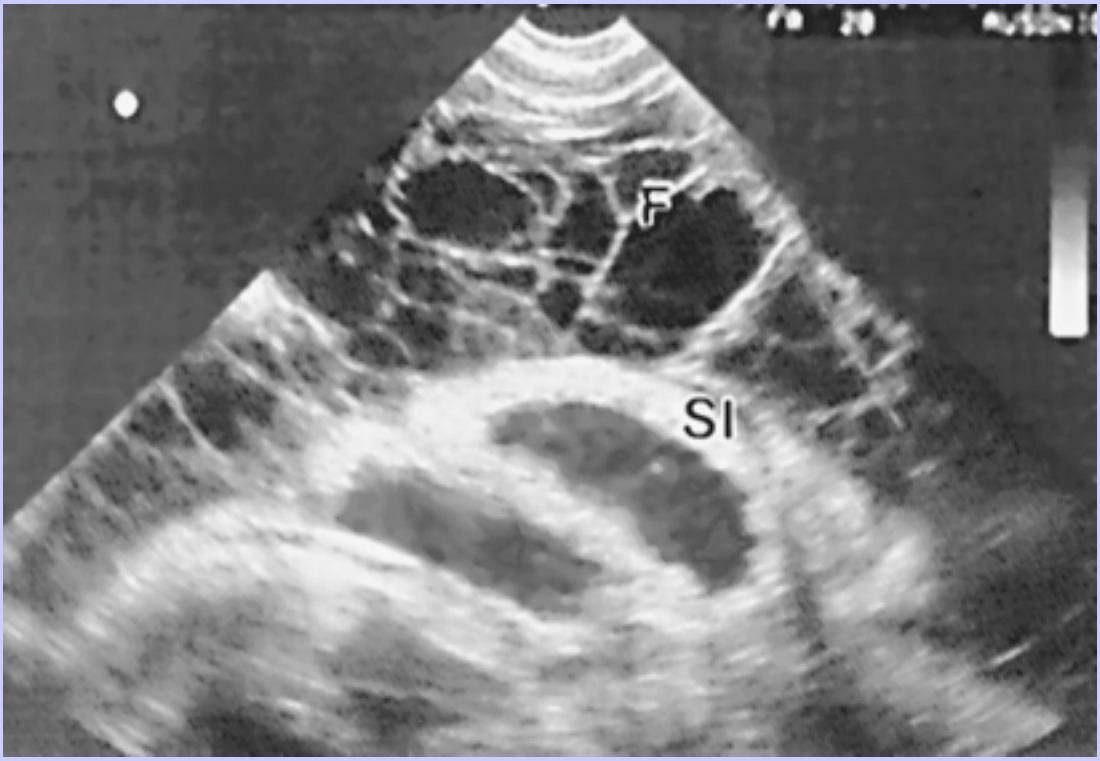
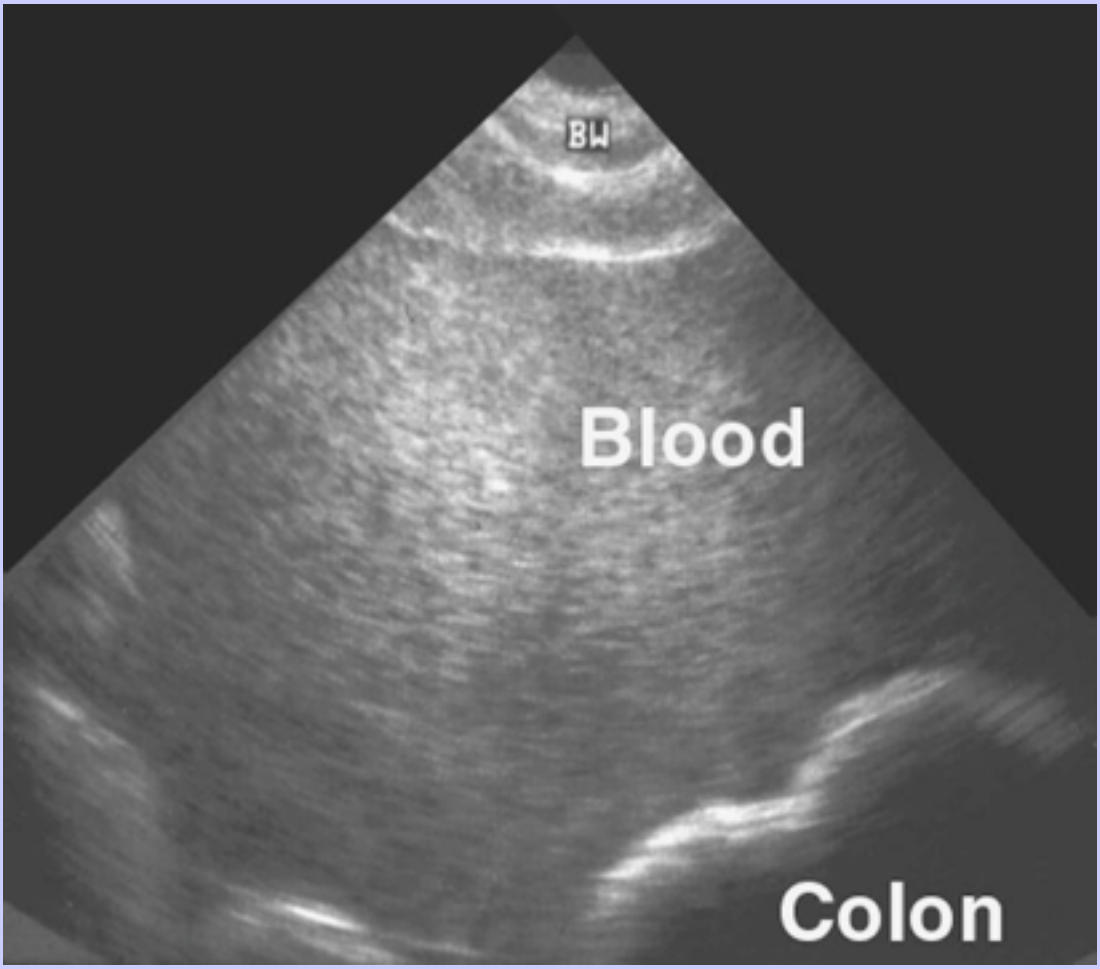


Fig. 32-61 Sonogram of abdomen full of blood. The fluid appears as swirling echogenic fluid. Courtesy Dr. David Schmitz, Texas A&M University.



* BBL Septi-Chek, Becton Dickinson and Company, Cockeysville, MD.

32.89.4 Treatment

Horses with peritonitis require early, aggressive therapy. The treatment of peritonitis involves (1) patient stabilization, (2) correction of the inciting cause, and, in most cases, (3) administration of antimicrobial drugs and/or anthelmintic drugs. Surgical intervention may be required to identify or correct the cause of the peritonitis. See the accompanying algorithm for the treatment of peritonitis in horses.

Stabilization includes treatment of systemic hypovolemia and endotoxic shock. Intensive fluid therapy is usually required to replace fluid losses into the peritoneal cavity and combat cardiovascular collapse. Acid-base disorders should be identified and corrected. Electrolytes, especially calcium and potassium, are important for gastrointestinal function and should be supplemented if deficits exist. If intestinal compromise or gram-negative

bacterial infections are suspected as the cause of peritonitis, J5 hyperimmune plasma* (4.4 mL/kg) may moderate the degree of endotoxemia. J5 is a mutant strain of *E. coli* that lacks the variable oligosaccharide side chains and binds to many gram-negative organisms and endotoxins, providing cross-protection.[934] If serum hypoproteinemia (total protein less than 4 g/dL) is present, administration of additional plasma should be considered to minimize peripheral edema.

32.89.4.1

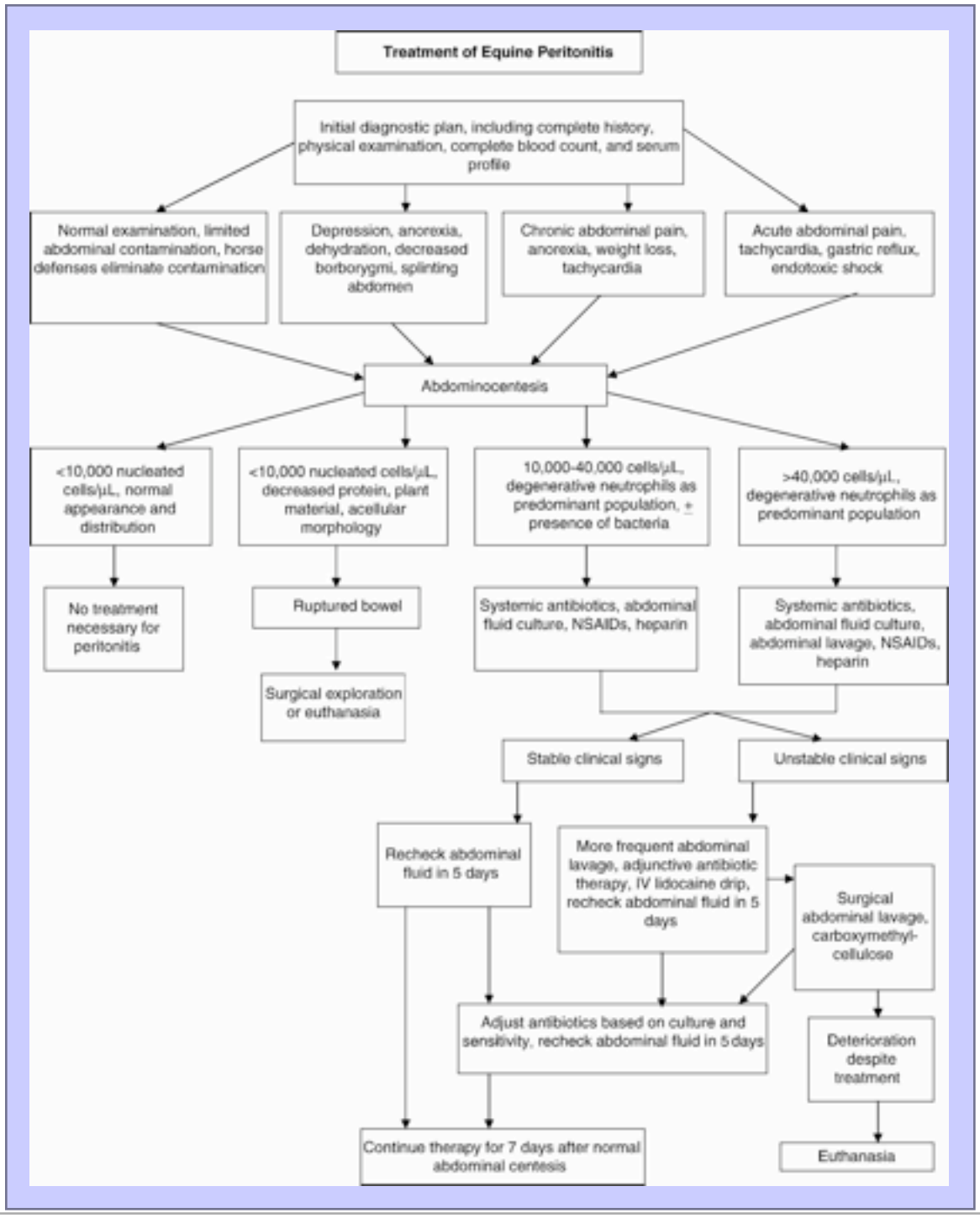
ANTIMICROBIAL THERAPY

Antimicrobial therapy should be initiated as soon as the diagnosis of peritonitis is made and peritoneal fluid is obtained for culture and sensitivity testing. In a study of 30 horses with peritonitis, 70% were treated successfully with antibiotics and supportive therapy.[924] Cytologic examination of the peritoneal fluid can suggest an antimicrobial regimen until the specific causative organism is identified. Intravenous administration is preferred, especially in the hypovolemic or shocked patient with compromised tissue perfusion. The most common organisms isolated from horses with peritonitis include aerobic bacteria *(E. coli, Staphylococcus* species, *Streptococcus* species, *R. equi)* and anaerobic bacteria (*Bacteroides* species, *Clostridium* species, *Fusobacterium* species).[922–925]

Broad-spectrum antimicrobial therapy is recommended, with a combination of an aminoglycoside such as gentamicin (6.6 mg/kg IV q24h) or amikacin sulfate† (9 to 12 mg/kg IV q8h) and potassium penicillin G (22,000 to 44,000 U/kg IV q6h) or ceftiofur (4 mg/kg IV q8h or q12h). After intravenous administration of aminoglycoside antibiotics, antimicrobial activity in the peritoneal fluid reaches 50% to 80% of serum levels, whereas intestinal tissue concentrations are 10% to 25% of serum concentrations.[935]

Aminoglycosides are bactericidal and effective against the majority of gram-negative intestinal aerobes, but pharmacologic monitoring is important especially in the hypovolemic, septic patient. Aminoglycosides can penetrate an abscess capsule but are minimally active in the acidic environment of an abscess. Drugs that penetrate fibrin, such as erythromycin and fluoroquinolones, are effective in the local abscess environment. Important considerations during aminoglycoside use include renal toxicosis and potential neuromuscular blocking effects during general anesthesia.[935,936] Most gram-positive aerobic bacteria are sensitive to penicillins, but the extended spectrum of antimicrobial activity from sodium ampicillin (11 to 25 mg/kg IV q6-8h) or ceftiofur may be beneficial. Trimethoprim-sulfadiazine (30 mg/kg PO q12h), chloramphenicol (25 to 50 mg/kg PO q6h), and enrofloxacin‡ (1.5 mg/kg PO q12h or 5 mg/kg q24h) are broad-spectrum antimicrobial drugs that have good peritoneal penetration and can be useful if warranted from the culture and sensitivity results. Enrofloxacin has been shown to have adverse effects on cartilage surfaces in young animals and should be reserved for adult horses only.[937]

Anaerobic bacteria, especially penicillin-resistant *Bacteroides* species, are reported in 20% to 40% of equine patients with peritonitis.[923,938] Percentages of anaerobic involvement may be artificially low because of difficulty in isolating anaerobic organisms. Metronidazole (15 to 25 mg/kg PO q6–8h) is effective against most anaerobic bacteria but should be



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used in combination with antimicrobial drugs that have antibacterial activity against aerobic bacteria.[938] Of 54 horses with positive anaerobic culture results, 95% also had aerobic bacteria isolated from the same specimen.[938] In the face of ileus, an intravenous route of administration can be used, although cost may be prohibitive. Recently the pharmacokinetics of metronidazole (15 mg/kg, q6–8h) administered to horses per rectum in a suspension of crushed tablets and water (40 mL) was evaluated, and serum minimum inhibited concentration

was reached within 1 hour.[939] Complications attributed to metronidazole administration in horses were reported to be uncommon, with only 4 of 200 horses (2%) that underwent treatment showing appetite suppression.[938] However, peripheral neurologic deficits and central nervous system (CNS) dysfunction have been associated with metronidazole treatment in other species.[938] Protracted antibiotic administration for the treatment of peritonitis is necessary. If an abdominal abscess is identified, 6 to 8 weeks of antimicrobial treatment may be necessary. Horses with diffuse, septic peritonitis are usually treated with antimicrobial drugs for 7 days after clinical signs and peritoneal fluid abnormalities have resolved.

* Plasma-J, Veterinary Dynamics, Templeton, CA.

† Amiglyde-V, Ford Dodge Laboratories, Inc., Fort Dodge, IA.

† Baytril, Miles Inc., Shawnee Mission, KS.

32.89.4.2 ANTIINFLAMMATORY THERAPY

Horses with peritonitis often have clinical signs of endotoxemia and tissue trauma eliciting a cascade of inflammatory mediators. Flunixin meglumine,* an NSAID, inhibits COX production of prostaglandins and blocks many detrimental effects of endotoxemia.[940] Flunixin also may decrease adhesion formation within the peritoneal cavity. Low doses of flunixin (0.25 mg/kg IV q6h) inhibited prostaglandin production during experimentally induced endotoxemia in horses.[940] Analgesia is also important in the treatment of peritonitis in horses to inhibit sympathetic stimulation secondary to parietal pain; therefore flunixin at a dose of 0.5 mg/kg q6h may be clinically more beneficial.

* Banamine, Schering-Plough, Omaha, NE.

32.89.4.3 ANTHELMINTICS

Anthelmintics are required if verminous arteritis secondary to *S. vulgaris* migration is the suspected cause of the peritonitis. A history of mild intermittent colic and a poor or unknown deworming program may be apparent. The abdominal pain arises from ischemia or the initiation of focal infarcts. Often this disease cannot be differentiated from other types that cause mild colic. The heart rate is often normal, and rectal examination usually has no abnormal findings unless there is concurrent impaction or gas distention. Fremitus to the cranial mesenteric artery is an inconsistent finding. Laboratory findings can also vary greatly. Evidence of peritoneal inflammation is indicated by increased peritoneal protein and WBC count. The response to antilarval therapy may be the best way to diagnose peritonitis secondary to parasitic migration. Colic in horses that respond will usually cease, and horses will become more active and alert several days to weeks after therapy. The larvicidal treatment is fenbendazole† (15 mg/kg PO for 5 days or 50 mg/kg for 3 days) or ivermectin (0.2 mg/kg PO), and aspirin (60 grains once daily PO).

† Panacur, Hoechst Roussel Vet, Warren, NJ.

32.89.4.4 OTHER MEDICAL TREATMENT

Gastrointestinal ileus results from peritoneal trauma, intestinal compromise, or sympathetic stimulation. Intestinal ileus can cause respiratory compromise from increased abdominal pressure and reduced intestinal perfusion, leading to further compromise. Intravenous lidocaine infusion is useful in providing analgesic support and prokinetic activity in horses with peritonitis. Lidocaine reduces neutrophil infiltration and endothelial permeability by inhibiting sensory neuronal transmission. Administration of intravenous lidocaine

(a loading dose of 1.3 mg/kg followed by a constant-rate infusion of 0.05 mg/kg/min) provides sufficient analgesia and may stimulate intestinal ileus caused by peritonitis. It also potentiates the analgesic response of other analgesics such as xylazine and butorphanol.

Nasogastric intubation is necessary for relief of gastric fluid accumulation and continued intestinal decompression. Parenteral nutritional support should be considered in the compromised, anorectic patient or in horses with severe, prolonged gastrointestinal dysfunction.

32.89.4.5

SURGICAL TREATMENT

Surgical intervention is often required to identify or correct the inciting cause of peritonitis, which is often secondary to compromised intestine or leakage of the reproductive or urogenital systems. Peritoneal lavage and drainage can be accomplished at the time of surgery to remove any accumulated debris or exudate. Surgical drainage of internal abdominal or perirectal abscesses has been described but is difficult and often results in further contamination of the abdomen.[922] Long-term antimicrobial therapy with marsupialization or aspiration may be the preferred approach in these cases.

A successful technique used in the treatment of peritonitis in small animals and people is open peritoneal drainage, which allows continuous drainage of the entire abdominal cavity and provides an unfavorable environment for anaerobic bacteria.[941] The large size, stall environment, and ambulatory nature of the horse precludes its use in the treatment of peritonitis in horses.

The effectiveness of intermittent peritoneal lavage and drainage in horses with peritonitis is well documented.[942] The benefits of abdominal drainage and lavage include (1) reduction of bacterial numbers, enzymes, and toxins from the large absorptive peritoneal surface area; (2) removal of degenerative neutrophils and cellular debris; (3) elimination of accumulated blood; (4) removal of irritating foreign material such as plant material and urine; and (5) dilution of adhesion-forming substrates such as fibrinogen and fibrin. Some claim that only a small part of the equine abdomen is effectively lavaged and that lavage may disseminate a localized infectious focus.[941] In my opinion, peritoneal lavage and drainage constitute an important and potentially life-saving treatment that should be considered in the treatment of horses with peritonitis. The controversial aspects of its use should be when and whether peritoneal lavage is necessary. In our hospital, use of peritoneal drainage and lavage is reserved for acute cases of purulent effusion in the abdomen and in horses not responding to medical therapy as determined by clinical signs and results of abdominocentesis. We also use standing postoperative peritoneal lavage for prevention of abdominal adhesions after surgery for small intestinal obstructions. In an experimental study, horses having abdominal lavage after colic surgery were significantly less likely to develop abdominal adhesions than horses not lavaged.[943] Foley, mushroom, or thoracic catheters can be used. The catheter should have numerous fenestrations for allowing infusion and drainage through the catheter. The catheter should be covered with a sterile bandage between uses to prevent ascending bacterial infection. A recent retrospective study evaluated 67 horses with an indwelling abdominal drain placed at surgery after celiotomy surgery or in the standing horse with signs of peritonitis. Forty-nine percent had minor complications, which included obstruction of the drain, fluid leakage around the drain, and subcutaneous fluid accumulation. Incisional drainage developed in 32% of horses, and incisional herniation occurred in 11%. Lavage solution is usually lactated Ringer's solution, although heparin or antimicrobial drugs may be added to the abdominal solution. If heparin is used to prevent the development of fibrinous isolation of bacteria, the usual dose is 80 U within the lavage solution or a systemic dose of 40U/kg SC q12h. A sudden but transient decrease in PCV should be expected because of severe rouleau formation. Peritoneal lavage is

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usually performed with 10 to 20 L of fluid twice daily for 2 to 5 days. It is usually continued until the peritoneal fluid becomes clear and cell count and total protein concentration return to normal values.

Stabilization, antimicrobial administration, and hydration of the horse should be performed before abdominal drainage or lavage. Placing an ingress catheter in the paralumbar fossa for fluid infusion and an egress catheter on ventral midline for drainage has been described, but is probably not effective because the infused fluid usually finds a direct path through the abdomen to the egress catheter, providing inadequate lavage. Retrograde irrigation and drainage through an ingress-egress catheter placed on ventral midline have been used effectively for removal of peritoneal exudate in horses.[944]

The site of drain placement is on the ventral midline at the most dependent aspect of the abdomen. Ultrasonography may be useful in locating a site free of abdominal viscera or fetus if the horse is in late gestation. A variety of drains can be used; mushroom drains* and argyle drains are most useful, but a large Foley catheter† is also effective. The horse is properly sedated, and the drain site is prepared aseptically and blocked with local anesthetic. A 1-cm stab incision is made through the skin, subcutaneous tissue, and linea alba. Mushroom and argyle drains should be stretched over a female canine or Chambers mare catheter to aid insertion. If the bowel is inadvertently punctured, the drain should not be removed until the horse is anesthetized to allow removal of the drain and closure of the puncture site.

With the drain acting as an ingress cannula, 10 to 20 L of a warmed balanced polyionic fluid is infused. Abdominal discomfort may be encountered after 10 L of fluid or after rapid infusion. Slowing the infusion rate or further sedation may be required. After fluid infusion the drain is filled with full-strength heparin and clamped closed and the horse is walked for 20 to 30 minutes to promote distribution of the lavaged fluid. The drain is then opened and the fluid is allowed to drain into a clean calibrated bucket to record its volume. The majority of the infused fluid should be collected. This process is repeated two or three times daily for 2 or 3 days until the peritoneal fluid white cell count and total protein show improvement. Between treatments the abdominal drain should be filled with heparin, closed, and protected from the environment by a sterile bandage.

The addition of povidone-iodine or nitrofurazone to peritoneal lavage solutions has been associated with chemical peritonitis, hypovolemia, hyperosmolarity, and acidosis in normal horses and is not recommended.[944] Adding antimicrobial drugs to the peritoneal lavage solution is probably not necessary; however, plasma concentrations of antimicrobial drugs should be measured to ensure proper levels in the face of peritoneal lavage and drainage. Horses treated with peritoneal lavage must also be monitored closely for hydration, protein loss (up to 0.5 to 1 g/dL daily), and electrolyte imbalances. Complications of peritoneal drains include visceral puncture during insertion, ascending infection, subcutaneous leakage and edema, and herniation of intestine or omentum through the drain.[944]

Intraperitoneal or systemic administration of heparin has been recommended in the treatment of peritonitis in many species.[945] Heparin is thought to inhibit fibrin deposition, thereby minimizing the localization and entrapment of bacteria, which can decrease the effectiveness of antimicrobial drugs.[919,945] Heparin has also been advocated in the prevention of abdominal adhesions in humans and decreased the formation of adhesions in ponies after experimentally induced intestinal ischemia.[946] There are no controlled studies in horses that describe the outcome of treatment or recommended dosage of heparin therapy in horses with peritonitis, but I use a dose of 20 to 40 IU/kg SC q8h. The horse's hematocrit and platelet count will usually decrease after 4 days of heparin treatment as a result of RBC agglutination but will rebound within 48 hours after the drug is discontinued.

Adhesion prevention should be a primary concern in treating a horse with peritonitis. Abdominal lavage with or without heparin therapy is beneficial in preventing the development of abdominal adhesions secondary to septic peritonitis. Sodium carboxymethylcellulose provides surface protection through a siliconizing effect and decreases contact between serosal surfaces. In an experimental study, instillation of sodium carboxymethylcellulose (7 mL/kg of a 1% solution) into the abdominal cavity after closure of the incision significantly decreased the incidence of abdominal adhesions in ponies.[947] This treatment may be beneficial in horses with peritonitis that have undergone an exploratory celiotomy as part of the treatment regimen.

* Argyle Trochar Catheter, Sherwood Medical, St. Louis, MO.

† Foley Catheter, CR Bard Inc., Murray Hill, NJ.

32.89.5 Prognosis

The prognosis depends on cause, severity, duration, and complications of the peritonitis. The mortality rate was 59.7% in a recent retrospective study of 67 horses with peritonitis.[925] The prognosis for mortality in that study was dependent on the inciting cause of peritonitis, with postoperative peritonitis having a high mortality rate (56%).

Laminitis, diarrhea, ileus, and coagulopathies can occur after endotoxemia, and abdominal adhesions or abscess formation can have a negative effect on long-term prognosis. There are no specific laboratory parameters that can predict prognosis in affected horses; however, a rapid response to therapy is considered a favorable prognostic indicator. With early diagnosis, correction of the inciting cause, aggressive medical therapy, and peritoneal lavage, a fair-to-good prognosis can be given in acute cases of septic peritonitis in the horse.

32.90 FLUID THERAPY FOR HORSES WITH GASTROINTESTINAL DISEASES

Kevin T.T. Corley

32.91 AIMS OF FLUID THERAPY

The primary goal of fluid therapy is to increase cardiac output by increasing and then maintaining cardiac preload (Starling's Law of the heart). This in turn increases oxygen delivery to the tissues. By varying the electrolyte content of fluids, it is also possible to correct electrolyte and acid-base disturbances.

32.92 FORMULATING A FLUID THERAPY PLAN

Fluid therapy should be based on the clinical status of the horse, an assessment of the severity of ongoing losses, and any laboratory information available. The plan consists of four overlapping phases: resuscitation, rehydration, maintenance and ongoing loss provision, and electrolyte replacement. Each phase should consist of a type of fluid, a rate of administration, and an appropriate delivery system. It should also include a schedule of monitoring the effects of the fluid therapy and adjusting as necessary. It is important to consider the practicality of administering fluids in the environmental conditions (e.g., fluids may freeze in cold weather). In horses that are going to be referred from the field, the impact of any delay associated with fluid therapy should be weighed against the perceived benefit, particularly when only small volumes can be administered.

The most important part of successful fluid therapy is to frequently adjust the plan according to the patient's response.

32.93 IDENTIFYING PATIENTS THAT REQUIRE FLUID THERAPY

Gastrointestinal conditions of horses that result in great fluid loss, such as high-volume diarrhea and gastric reflux, obviously require aggressive fluid therapy. However, many other horses with gastrointestinal disease may require fluid therapy because of prolonged mild to moderate fluid losses or sustained reduced fluid intake. It is the identification of these horses that this section addresses.

32.93.1 Clinical Signs

The clinical signs of hypovolemia and dehydration are listed in Table 32-7. Hypovolemia is an emergency, and the aim of treatment should be to reverse hypovolemia in 1 to 2 hours. Dehydration needs to be addressed in the first 12 to 24 hours of therapy. Unfortunately, attempts to link given clinical signs with a percent fluid dehydration have not proved accurate.[948] It is important to assess all clinical signs and make a judgment on the fluid status based on the whole patient, including laboratory parameters if available. For example, tachycardia in horses with colic may be a result of pain or hypovolemia. Clinical signs and response to analgesics or fluid loading may help differentiate the two.

32.93.2 Laboratory Signs of Dehydration

The most commonly used laboratory tests to assess hypovolemia are PCV and plasma total solids. Unfortunately these tests are neither sensitive nor specific. The PCV may be substantially increased by splenic contraction in the horse, making small increases very hard to interpret. A PCV of over 50% in a resting horse usually represents hypovolemia. Plasma total solids (protein measured by refractometer) or total protein (measured by a chemistry analyzer) concentration also increases with hypovolemia. However, significant protein loss can occur in gastrointestinal disease (particularly with colitis), resulting in a low or normal protein concentration despite marked hypovolemia. Furthermore, hypergammaglobulinemia (e.g., in cyathostomiasis) can increase the plasma total protein concentration in the absence of hypovolemia. The PCV and plasma total solids are most useful when greatly increased or when used serially to monitor the response to fluid therapy.

Table 32-7 Clinical Signs of Hypovolemia and Dehydration Horses

Hypovolemia	Dehydration
Tachycardia	Tacky mucous membranes
Decreased pulse pressure	Prolonged skin tent
Reduced jugular fill	Sunken eyes
Tachypnea	
Cold extremities	
Decreased urine output	

From Corley K, Stephen J, eds: *Equine hospital manual*, Oxford, UK, 2008, Blackwell. Used with permission.

Not all signs are consistently present in all horses.

Plasma or serum creatinine concentrations are useful to assess hydration status in the absence of renal dysfunction. High normal (1.5 to 1.8 mg/dL; 130 to 160 µmol/L) creatinine concentrations can be associated with subclinical hypovolemia and should be evaluated in light of the history and clinical signs. Creatinine concentrations up to 3.5 mg/dL (310 µmol/L) are common with moderate to severe hypovolemia, and concentrations as high as 5 mg/dL (450 µmol/L) are possible with prolonged or marked hypovolemia. Even in severe hypovolemia, the creatinine concentration will not increase by much more than 2.3 mg/dL (200 µmol/L) per day.[949] If the creatinine concentration is higher than would be suggested by the clinical signs and other laboratory parameters and if the creatinine concentration does not decrease appropriately with fluid therapy, renal dysfunction should be suspected.

Increased blood lactate concentrations in the nonexercising horse are sufficient evidence of a metabolic disturbance to initiate fluid therapy. Blood lactate concentrations are an indicator of tissue perfusion. The most common causes of increased lactate in the horse with gastrointestinal disease are endotoxemia, which can increase tissue lactate production by inappropriate anaerobic metabolism, and hypovolemia. Increased blood lactate concentrations were associated with worse outcomes in equine colic.[950] Lactate can be measured in the field with hand-held blood gas analyzers.[*] The expected lactate concentration can also be calculated by means of equations based on electrolyte and acid-base measurements. However, when tested in foals, these equations were only moderately accurate.[951] An increased circulating lactate should be suspected in metabolic acidosis (decreased pH, negative base excess) in the absence of hyperchloremia or hyponatremia.[952] Urine specific gravity can easily be measured in the field. High urine specific gravity (>1.040) indicates probable dehydration and normal renal concentration of urine. Isosthenuria (1.010) indicates possible renal damage or a recent high fluid load. Urine specific gravity is useful to monitor the response to fluid therapy because rising or continually high specific gravities in the face of fluid therapy indicate insufficient fluid is being delivered to the horse.

* i-STAT, Heska, Fort Collins, Colo.

32.93.3 Cardiac Filling Pressures

Assessment of cardiac filling pressures and the changes in these pressures in response to fluids is the most accurate method of determining fluid requirements in the hospitalized animal. It is moderately easy to measure CVP in the horse. A piece of sterile polyethylene tubing (PE190, outside diameter 1.70 mm, at least 1.5 m long)

can be passed through a 12-gauge jugular catheter into the thoracic vena cava or right atrium. Correct positioning of the end of the tubing is estimated by measuring the distance against the horse and confirmed by observing changes in pressure with breathing activity. The catheter is connected to a pressure transducer or manometer at the level of the sternal manubrium.[953] The normal CVP of the horse is 5 to 14 mm Hg.[953] In a horse with normal cardiac function, a high CVP indicates fluid overloading and a low CVP indicates insufficient circulating volume. Perhaps more accurate is the change in CVP in response to a "fluid challenge" (bolus of fluids),[954] but this has not been evaluated in the horse. The fluid challenge method of monitoring fluid therapy may prove to be particularly useful when factors such as acute renal failure or pulmonary edema complicate the gastrointestinal disease.

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32.94 TYPES OF FLUIDS

32.94.1 Crystalloids

For most situations in the field, commercial isotonic polyionic crystalloid solutions are the safest fluids to resuscitate hypovolemic or dehydrated adult horses. They increase plasma volume without causing profound electrolyte disturbances, because they contain approximately the same electrolyte concentrations as plasma. It also follows that polyionic crystalloid solutions are often not sufficient to correct electrolyte imbalances. Isotonic (0.9%) sodium chloride has a higher ratio of chloride to sodium than plasma and therefore causes mild hyperchloremic acidosis in normal ponies.[955] Isotonic sodium chloride should not be used for resuscitation unless indicated by measured electrolyte abnormalities. Sodium chloride solution has been advocated in hyperkalemia in order to avoid the potassium-containing polyionic fluids. In adult horses with gastrointestinal disturbances (with the exception of quarter horses with the hyperkalemic periodic paralysis (HYPP) phenotype), hyperkalemia is likely to reflect acidosis, and polyionic fluids are probably appropriate.

Two classes of polyionic fluids are available, those for resuscitation and those for maintenance. Maintenance fluids (e.g., Normosol-M*, Plasma-lyte M†) contain higher potassium and lower sodium and chloride concentrations than resuscitation fluids (e.g., Normosol-R*, Plasma-lyte 148†, Isolec‡, lactated Ringer's solution†). However, maintenance fluids are not currently commercially available in sizes greater than 1 L. This has led to the practice of adding potassium chloride (at 10 to 20 mEq/L) to resuscitation formulas to use as maintenance fluids in adult equine patients.

The different alkalizing agents (or "bicarbonate substitutes") in resuscitation fluids have some clinical relevance. The alkalizing agent in plasma is bicarbonate. Bicarbonate-containing fluids are unstable when stored and may result in profound metabolic alkalosis. Therefore Hartmann, an American pediatrician, replaced the bicarbonate with lactate to make lactated Ringer's solution (also called Hartmann's solution). Lactate is metabolized in the liver, but this process is slow enough to avoid the rapid changes in plasma pH seen with bicarbonate. Sodium bicarbonate and sodium lactate both increase the strong ion difference, resulting in metabolic alkalosis. The cation (sodium) remains in the extracellular fluid, whereas the anion (bicarbonate or lactate) is metabolized.[956] It is the speed of metabolism of the anion and the renal excretion of sodium that determines the ultimate alkalinizing effect. It may seem counterintuitive to administer lactate-containing fluids to a horse with lactic acidosis resulting from poor tissue perfusion. However, clinical trials in human patients in hemorrhagic shock have shown that lactate-containing fluids do not exacerbate the lactic acidosis of hypoperfusion.[957] It appears that the liver's capacity for metabolizing lactate is not overwhelmed in shock, but the delivery of lactate by the circulation to the liver is impaired. Restoring the circulating volume, even with fluids containing moderate amounts of lactate, is sufficient to allow the liver to clear the circulating lactate. In horses with liver disease,

which may have impaired lactate metabolism, lactated Ringer's solution should be used with caution. Alternative alkalizing agents to lactate are found in some commercial polyionic fluids (e.g., acetate and gluconate in Normosol-R). Acetate is metabolized by the muscles and gluconate by a variety of tissues throughout the body. Lactated Ringers' solution contains calcium, whereas Normosol-R contains magnesium. Calcium is incompatible with whole blood and sodium bicarbonate and is contraindicated in hypercalcemia; therefore fluids containing magnesium can be used in more clinical situations than those containing calcium.

Five-percent dextrose (D5W) and 5% glucose (G5W) solutions are used to replace water without accompanying electrolytes and are effectively hypotonic because the dextrose or glucose is rapidly metabolized. They are indicated in cases in which fluid loss exceeds electrolyte loss, which can occur in strangulating intestinal lesions and colitis.[958] Horses receiving D5W or G5W should be monitored carefully because rapid administration can lead to hyperglycemia. If the plasma glucose concentration exceeds the renal threshold (approximately 180 mg/dL [10 mmol/L]), an osmotic diuresis will result, which can reduce the benefit of the fluid administration. D5W contains 0.17 kcal/mL, and G5W contains 0.19 kcal/mL. They should not be considered a form of parenteral nutrition. In order to provide 11.5 Mcal/day, the maintenance requirement for a 500-kg horse standing in a stall,[959] it would be necessary to administer 60 to 70 L of these fluids per day, which would result in serious electrolyte abnormalities. Although the glucose in D5W and G5W has been recommended for resuscitation of some foals, these fluids are poor choices for hypovolemia. Thirty minutes after administration, only 10% of these solutions remain in the circulation. It is better to separate fluid and glucose replacement, if possible. If this is not practicable, 10 to 20 mL of 50% glucose solution should be added per liter of balanced electrolyte solution for acute resuscitation of hypovolemic and hypoglycemic foals.

Sodium bicarbonate has been advocated for correction of the acid-base disturbances associated with equine gastrointestinal disease. However, its use in lactic acidosis is highly controversial,[960] and it should probably be reserved for use in hyponatremia without hypochloremia and for renal tubular acidosis, manifested by hyperchloremia without accompanying hypernatremia.[952] Both of these electrolyte disturbances occur occasionally in horses with severe colitis. Sodium bicarbonate should be avoided in horses with respiratory dysfunction because the bicarbonate is converted to carbon dioxide that, if it is not excreted by the lungs, leads to an increase in plasma carbon dioxide tension and further acidosis.[952] Caution is also necessary in patients with hypocalcemia, because sodium bicarbonate administration can result in tetany; in patients with severe hypokalemia that can be worsened by increasing the plasma pH; and in patients with congestive heart failure, in whom the large sodium load may exacerbate fluid retention.

Homemade or “carboy” fluids, although considerably cheaper than commercial fluids, have been associated with clinical signs of endotoxemia in normal horses[961] and a sevenfold increase in the risk of thrombophlebitis[962] and therefore cannot be recommended.

* Abbott Laboratories, North Chicago, IL.

† Baxter Healthcare Corporation, Deerfield, IL.

† Ivex Division, Galen Holdings plc, Larne, Northern Ireland.

32.94.2 Hypertonic Saline

The large volumes of isotonic fluids required for resuscitation in the horse and the fact that only approximately 30% of the administered fluid remains in the circulation after 30 minutes[963] have prompted the search for alternative fluids. Hypertonic saline and colloid solutions have received the most attention. 769 770

Hypertonic saline (2 to 4 mL/kg of 7% to 7.5% NaCl) has been advocated as a method of quickly restoring circulating volume in shock patients. Administration of 7% sodium chloride results in an increase in the extracellular fluid of two to three times the infused volume for at least 60 minutes after it is infused. This is the result of fluid shifts from the interstitial fluid, principally from the muscle and liver,[964] without significant fluid replacement. Hypertonic saline should always be followed up by large volumes (at least 10 L for each liter of hypertonic saline) of isotonic polyionic crystalloids within 2.5 hours (the point in experimental studies a which cardiac output begins to fall below baseline).[965] As well as restoring plasma volume, hypertonic saline reduces the capillary endothelial swelling that may occur as part of SIRS and therefore improves tissue microcirculation and oxygen delivery.[966] Administration of 5 mL of hypertonic saline solution per kilogram immediately after experimental endotoxin infusion in horses attenuated the cardiovascular derangements associated with endotoxemia more effectively than an equivalent volume of isotonic saline.[965] However, when compared with pentastarch (a colloid) in horses presented because of surgical colic, hypertonic saline resulted in a lower cardiac output for the first 2.5 hours of anesthesia.[967] Given the beneficial effects of hypertonic saline in experimental endotoxemia and sepsis, it may have a role after initial fluid resuscitation. However, treatment of endotoxic horses with hypertonic saline after fluid resuscitation has not been clinically evaluated.

The combination of hetastarch (10 mL/kg) or pentastarch 10% (10 to 15 mL/kg) with hypertonic saline (4 mL/kg) appears to be an excellent solution for resuscitation of severely hypovolemic horses, especially in severe colitis.

32.94.3 Colloids

Colloids, particularly hetastarch, have recently been advocated for resuscitation and treatment of severe hypoproteinemia in horses.[968] Colloids contain large branched molecules (450 kD average molecular weight for hetastarch compared with 69 kD for albumin). These molecules exert a large colloidal oncotic pressure and do not readily leak out of the vasculature and thus hold fluid in the circulation. Endotoxin[969] and ischemia-reperfusion injury[970] induce capillary damage that allows plasma albumin to leak out into the interstitium. The large colloid molecules may not leak as readily, allowing their oncotic pressure to draw fluid back into the vasculature. They may also plug the gaps in the capillary endothelium. However, if the capillary damage is severe enough, even the larger colloids may leak into the interstitium and exert their oncotic pressure to draw fluid with them.

In normal ponies, hetastarch is safe but prolongs bleeding times at high doses (20 mL/kg).[971] Pentastarch also affects coagulation, but at higher doses than hetastarch.[972] Although these hydroxyethyl starches have been used extensively in horses,[967,968] it is still unclear whether their use alters morbidity or mortality. Pentastarch appears to be superior to hypertonic saline when given before emergency colic surgery, at least in terms of cardiac output during anesthesia.[967] When colloids are used, the plasma total solids or total protein concentration is no longer a useful guide to hydration status or plasma oncotic pressure.[968]

Fresh frozen equine plasma has been used extensively in horses with diarrhea. Although classically prescribed for hypoalbuminemia, its utility for replacing protein is unclear. At least 6 to 8 L need to be given to adult horses to treat clinically significant hypoproteinemia,[973] and the effects may be short-lived. Plasma administration does not have the advantage of the larger colloids of potentially drawing fluid back into the circulation in damaged capillaries, but it prevents low plasma oncotic pressure, which leads to generalized edema. Plasma may have a

role in replacing AT-III and other cofactors that are depleted during the SIRS, and this has led to its continued use in diarrhea cases, with apparently favorable results. Freshly donated, rather than frozen, plasma contains higher concentrations of clotting factors and cofactors and is preferred in diarrhea cases.

32.94.4 Oral Fluid Therapy

It is possible to effectively treat dehydrated (but not hypovolemic) horses with oral replacement solutions.[974] In horses with gastrointestinal disease but no apparent dehydration, administration of an electrolyte paste and provision of fresh drinking water may be sufficient to supplement water and electrolytes.[975] Oral fluids do not need to be sterile and are therefore considerably cheaper than intravenous fluids. It is apparently not necessary to add glucose to oral fluids for the horse,[976] but electrolytes should be added if feasible. It is important to administer hypotonic or isotonic fluids.[976] A possible isotonic solution consists of 4.9 g of table salt per liter and 4.9 g of Lite salt* per liter to give final concentrations of 123 mmol/L sodium, 34 mmol/L potassium, and 157 mmol/L chloride.[976] If sodium chloride is used alone, no more than 9 g should be added per liter. An isotonic solution can be made without the use of weight scales by measuring salt crystals in the barrel of a syringe. Fifteen mL of Lite salt and 15 mL of table salt added to 4 L of water will make an approximately isotonic solution. The fluids should be given via a stomach tube to allow measured quantities to be given. The amount given at one time should not exceed 8 to 10 L in a 500-kg horse, with at least 20 minutes between each administration. Before each dose the stomach should be refluxed and the administration delayed if more than 2 L of fluid are recovered. Some horses will show abdominal pain if large volumes of fluids are given, especially if the fluids are cold.

Oral fluids hydrate the colon contents more effectively than intravenous fluids[977,978] and therefore are an ideal treatment for most horses with large colon impactions.[979] However, oral fluids are not suitable in hypovolemia. The absorption of fluids from the gastrointestinal tract is dependent on its blood supply, and the physiologic response to hypovolemia is to divert blood supply from the gastrointestinal tract to maintain perfusion of other organs.

* Morton Salt, Chicago, IL.

32.94.5 Parenteral Nutrition

Any therapeutic plan in the horse should include a nutritional plan. An enteral diet based on the horse's normal diet is the first choice for nutritional support. However, in adult horses with gastric reflux, ileus, esophageal obstruction, or anorexia, parenteral nutrition should be considered if the interruption to enteral feeding is predicted to last at least 3 days.[980] The use of parenteral nutrition may be especially indicated in acute protein losing enteropathy, where its use may prolong the oncotic effects of exogenously administered plasma, possibly by preventing plasma albumin from being metabolized for energy. Total parenteral nutrition solutions commonly consist of dextrose, amino acids, lipids, and a vitamin-mineral mix. The estimated energy requirement of a normal adult horse standing in a stall is calculated with the following equation[959]:

$$\text{Energy requirement (Mcal / day)} = 0.975 + (0.021 \times \text{body weight [kg]})$$

The protein requirement is calculated with the following equation[959]:

$$\text{Protein requirement (digestible protein [g/day]}) = 18 \times \text{Energy requirement (Mcal/day)}$$

The formulation of parenteral nutrition solutions is described elsewhere.[980] Parenteral nutrition is widely used in some practices for horses with gastrointestinal disease.[981] Although there is much anecdotal evidence that parenteral nutrition (as opposed to no nutrition) may be beneficial in adult horses with gastrointestinal disorders, it has not been formally studied. The administration of parenteral nutrition increases the risk of thrombophlebitis and sepsis in hospitalized human patients.[982]

32.95 FLUID THERAPY DELIVERY SYSTEMS

In the early resuscitation period of moderately to severely hypovolemic horses, it is important to use both a large-gauge catheter and a wide-bore sterile delivery system to be able to provide the fast fluid rates required. A 10- or 12-gauge catheter is recommended for severely hypovolemic adult horses and a 12- or 14-gauge catheter for other horses. Moderately hypovolemic foals, weanlings, and miniature horses can be given 16-gauge catheters. It is necessary to use a large-bore extension set with a large-gauge catheter.

For placement of a catheter, the hair should be clipped over the vein and the area should be given a surgical scrub, ideally with a chlorhexidine scrub solution.[983] The catheter should be handled and placed with sterile gloves. In young and refractory horses, a bleb of local anesthetic placed subcutaneously in the area to be catheterized makes catheterization easier. The sterile scrub should be repeated after the local anesthetic. With 10-gauge and Seldinger ("over the wire") catheters and when local anesthetic is used, a small stab incision through the skin can also be helpful. For fluid therapy the catheter should be directed pointing toward the heart. The catheter should be flushed with heparinized saline (5 units/mL) and fixed either with instant bonding glue (for short-term use) or with suture.

Table 32-8 Flow Rate Chart: Drops per 10 Seconds for Various Flow Rates

Bag Size / Flow Time	Flow Rate (L/hr)	STAT Set* Drops/10 sec	Straight Set, Single Spike† Drops/10 sec	Coil Set, Single Spike‡ Drops/10 sec	Six Spike Set§ Drops/10 sec	10 Solution Set‖ Drops/10 sec	Mini (60) Set‖ Drops/10 sec
5 L/1 hr	5	150	—	—	—	138	—
5 L/1.5 hr	3.33	100	—	—	—	92	—
5 L/2 hr	2.5	75	—	—	—	69	—
5 L/3 hr	1.66	50	32	—	—	46	—
5 L/4 hr	1.25	38	23	25	—	35	—
5 L/5 hr	1	30	21	24	29	28	—
1 L/1 hr	1	30	21	24	29	28	167
1 L/1.5 hr	0.75	—	15	17	21	21	125
1 L/2 hr	0.5	—	11	11	13	14	83
1 L/3 hr	0.33	—	9	8	12	9	55
1 L/4 hr	0.25	—	7	7	11	7	42
1 L/5 hr	0.2	—	6	5	10	—	33
1 L/6 hr	0.16	—	4	4	5	—	28

* Stat Large Animal IV Set, International WIN, Kennett Square, PA.

† V-LACT-24-200-S-C-EC1, Cook Veterinary Products, Spencer, IN.

† V-LACT-24-450-S-C-EC2, Cook Veterinary Products, Spencer, IN.

§ V-LACT-14-60-6S-C-EA3, Cook Veterinary Products, Spencer, IN.

‖ Baxter Healthcare Corp, Deerfield, IL.

The easiest vein to catheterize in the horse is the external jugular vein. The cephalic and the lateral thoracic veins may also be catheterized and carry less serious consequences if they become occluded by thrombophlebitis. However, the maximum fluid rate attainable in these smaller veins (approximately 5 L/hr) is less than with the jugular vein, and infectious thrombophlebitis may be serious in any site. If one jugular vein is thrombosed or occluded, it is certainly prudent not to catheterize the contralateral jugular vein, because life-threatening head swelling can result from bilateral jugular thrombosis. Both the cephalic and the lateral thoracic vein can be technically difficult to catheterize. Good sedation is required to catheterize the cephalic vein because horses have a tendency to move during catheter placement. The lateral thoracic vein can be hard to identify and has a flat profile, which can make it difficult to pass the catheter into the lumen. The vein can be identified by ultrasonography and is probably best catheterized using the Seldinger (“over the wire”) technique. In both of these veins, valves can impede the passing of the catheter stylet or wire.

Various fluid administration sets are commercially available. Sets that include large-bore tubing and a coil are suitable for most situations in adult horses and their use is recommended. The flow rate can be estimated by

counting the number of drips per 10 seconds in the drip chamber (Table 32-8) or can be set by using an electronic fluid pump. In all situations, a record should be kept of the time the infusion was started to ensure that the desired volume is being delivered in the appropriate time.

The frequency of replacement of catheters and administration sets depends on local environmental conditions and the catheter material. Catheters made from polytetrafluoroethylene (Teflon) are associated with an increased incidence of thrombophlebitis and have a tendency to crack and kink.[984] These catheters should not be left in for longer than 72 hours. In contrast, soft catheters made from polyurethane or silicone rubber can often be safely left in place for at least 14 days when properly monitored.[984] These catheters should be replaced only when there is a suspected problem, and in a few horses they can be maintained for as long as 6 weeks. It is unclear how frequently administration sets should be replaced when used in a horse barn. The Centers for Disease Control and Prevention recommendation for human hospitals is not to replace administration sets more frequently than every 72 hours, except when used to administer blood or lipid-containing parenteral nutrition, in which case they should be changed every 24 hours.[985] Indwelling cecal catheters have been proposed for fluid therapy in horses, without the expense of sterile fluids. Unfortunately, although it is possible to deliver fluid by this technique, the high rate of serious complications precludes the use of cecal catheters.[986] For repeated administration of oral fluids, an indwelling nasogastric tube may be placed, which should be plugged with a syringe barrel between administrations to prevent excessive air influx. Some horses will not tolerate a large-bore nasogastric tube, and an adult feeding tube* sometimes can be used successfully in its place.

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* 18Fr Equine Enteral Feeding Tube, Ross Laboratories, Columbus, OH.

32.96 RATES OF ADMINISTRATION AND VOLUME TO INFUSE

There are four overlapping phases to fluid therapy: resuscitation, rehydration, maintenance and ongoing loss provision, and electrolyte replacement. The resuscitation phase aims to rapidly restore circulating fluid deficits; the rehydration phase, to restore intracellular and interstitial fluid deficits; and the maintenance phase, to prevent occurrence of further fluid deficits. Electrolyte replacement usually takes place during the rehydration and early maintenance phases.

32.96.1 Resuscitation

Reversal of hypovolemia is the most important phase of fluid therapy. Although no specific experiments have been performed in the horse, there is plenty of evidence from human medicine that early reversal of hypovolemia dramatically improves outcome.[987,988] The clinical signs of hypovolemia are given in Table 32-7. There is no good evidence for choosing between balanced electrolyte solutions and colloids for treatment of hypovolemia. Therefore factors such as availability, speed of administration, ease of transport, and clinician preference will determine this choice.

The most common concept used to describe treatment of hypovolemia is the “shock dose.” This describes the maximum dose of fluids to be given acutely, as a bolus, to animals in shock. The shock dose for adult horses is 60 to 80 mL of crystalloids per kilogram. In practice, ¼ to ½ of the shock dose is given as a bolus. The animal is then quickly reassessed. If any evidence of continuing hypovolemia is present, a further ¼ of the shock dose is then given. This process is then repeated, with the animal being reassessed and given further boluses of ¼ of the shock dose as necessary, until hypovolemia has been reversed or a full shock dose has been given. It should be possible to deliver a full shock dose to a foal in 30 to 40 minutes and to an adult horse in 60 to 90 minutes. Delivering fluid this fast requires a large-gauge catheter and a wide-bore delivery system. In my practice, wide-

bore tubing designed for delivery of fluid during arthroscopy is used for reversal of hypovolemia in adult horses. Drip sets with inbuilt coils provide a much greater resistance to flow and are reserved for treatment of dehydration and ongoing losses and provision of maintenance needs. In adult horses with severe hypovolemia, both jugular veins may be catheterized with large-bore catheters (10 to 12 gauge) that allow approximately 35 L/hr to be administered by gravity if a wide-bore administration set is used. One of the jugular catheters should be removed immediately after the initial resuscitation phase is over, to reduce the risk of bilateral jugular vein thrombosis. A fluid pump may also be used to achieve high rates of fluid delivery, but the high pressures may cause damage to the intima of the vein and increase the risk of thrombosis. If colloid fluids are being used for initial resuscitation, 1 L should be used to replace each 3 to 4 L of crystalloid. The amount of hetastarch infused should not exceed 10 mL/kg.

In the neonatal foal, there is an alternative method to the shock dose method that is more practical. For this method, give a bolus of 1 L of crystalloids (i.e., approximately 20 mL/kg for a 50-kg foal) and reassess the foal to decide if hypovolemia has been reversed. Up to three further boluses may be given, reassessing the foal after each. Most obviously hypovolemic foals require at least two boluses. In foals in which the body weight is obviously different from 50 kg, the method needs to be adjusted so that the bolus is approximately 20 mL/kg. In pony foals and very premature thoroughbred foals, a bolus of 500 mL is usually appropriate. In large draft foals, the first bolus should be 2 L.

Deciding that hypovolemia has been reversed and that no further fluids are required is not always straightforward. In adult horses the clinical signs of hypovolemia should improve dramatically. Particularly useful to judge are the heart rate, jugular fill, and urination. Heart rate may not return to the normal range (particularly if other factors, such as pain, are also driving heart rate), but it should decrease. Jugular fill may be noticeably quicker. Adult horses often urinate once sufficient acute fluids have been given. In foals the clinical signs of hypovolemia may not have been present. Often there is an improvement in degree of consciousness with administration of fluids. As for adults, foals often urinate once hypovolemia has been reversed. There may also be a change in mean arterial blood pressure with fluid administration in foals, and a MAP that was reduced and now is consistently above 65 mm Hg probably indicates that sufficient acute fluids have been administered.

It is important to remember that reversal of hypovolemia represents the beginning of fluid therapy, and not the end. Almost all horses that have been hypovolemic will also be dehydrated, and this will need to be addressed over the next 12 to 24 hours. Furthermore, these horses may be sufficiently compromised to limit their fluid intake, or increase their losses, resulting in a continued need for fluid therapy.

32.96.2 Uncontrolled Hemorrhage

There is one important exception to aggressive fluid therapy for hypovolemia. This is in the case of uncontrolled hemorrhage (e.g., intraabdominal bleeds).[989,990] Fluids should be given at a rate of 2 to 3 mL/kg/hr until the hemorrhage has been controlled (usually by surgical intervention). When arterial blood pressure can be measured, therapy should be titrated to a moderate MAP (60 mm Hg).

32.96.3 Dehydration

Estimating the degree of dehydration and replacing it with fluid is not as straightforward as it sounds. Although tables relating clinical signs to estimated percent dehydration have been published,[991] it is unlikely that these are sufficiently accurate to be a useful clinical guide. Evidence from dogs and cats demonstrates that similar tables

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are not accurate in those species,[992] and clinical experience suggests that the same is true of the tables designed for horses.

This therefore leaves the clinician without a set recipe to treat dehydration, and with a quandary. The key is monitoring. Once the hypovolemia has been treated, the horse should be examined for clinical and laboratory signs of dehydration. The horse should then be given fluids in excess of the ongoing losses plus the maintenance requirements, until the clinical and laboratory signs of dehydration are no longer present. The aim should be for dehydration to be reversed in 12 to 24 hours. In practical terms, dehydration is usually treated by giving fluids at twice the maintenance rate (see later) with the addition of fluids for ongoing losses. Therefore a dehydrated adult horse will receive 5 mL/kg/hr and ongoing losses, and a foal will receive 9 mL/kg/hr and ongoing losses, until dehydration is reversed. In horses with normal renal function, urine specific gravity is probably the most reliable indicator of when dehydration is reversed. Horses with urine specific gravities below 1.020, and foals with urine specific gravities of 1.010 or less, are unlikely to be dehydrated. Adult horses with normal renal function, frequent urination, and a urine specific gravity of 1.012 or below are probably receiving too much fluid. It is important, however, to check the other clinical signs of dehydration, as isosthenuria (urine specific gravity 1.008 to 1.012) can also occur in horses and foals with renal failure. These horses will usually have increased plasma creatinine concentrations. Horses with polyuric renal failure could become markedly dehydrated or hypovolemic, if fluid monitoring were based on urine specific gravity alone. Skin tent is a reasonably reliable clinical sign to use to judge dehydration in adult horses. It is less reliable in neonatal foals and geriatric horses. Tacky mucous membranes are also reasonably reliable indicators of ongoing dehydration, providing the animal is maintaining its mouth shut most of the time.

32.96.4 Ongoing Losses

Excessive fluid losses from horses with acute abdominal disease frequently do not stop when treatment is initiated, and these must be taken into account in the fluid plan. The most dramatic ongoing fluid losses are with severe diarrhea or nasogastric reflux, which may reach 200 mL/kg/day (100 L/day for a 500-kg horse).[993] Even without such obvious losses, horses may lose significant amounts of fluid through sweating, inadequate intake or, rarely, polyuric renal failure.

Treatment for ongoing losses is aimed to exactly replace the amount lost to maintain hydration. This is relatively simple when the amount of fluid lost can be measured, as in the case of nasogastric reflux. Reflux is collected in a graduated bucket, and the amount collected over a 4- to 12-hour period is compared with the amount of fluid administered. If the fluid lost is in excess of the amounts given, the fluid rates are adjusted both to replace this over the next 12 to 24 hours and to account for the higher level of ongoing losses than originally estimated. If the excessive losses have resulted in hypovolemia (on the basis of clinical and laboratory evidence), this must be treated acutely. It is much harder to estimate losses from diarrhea, sweating, and urination. In the case of diarrhea and urination, it is possible either to attempt to collect the feces or urine or to use absorbent bedding and measure the increase in weight. These are almost never done in clinical practice, except in the case of recumbent neonatal foals, for which feces or urine may be readily collected and weighed on incontinence pads or urine may be collected with an indwelling Foley catheter and closed collection system. When ongoing losses cannot be collected, they must be estimated. These estimates may be inaccurate, and the amount of ongoing loss can dramatically change; therefore it is important to frequently reassess the adequacy of fluid therapy through clinical examination and relevant laboratory investigations. Horses in which ongoing losses are not adequately replaced will become dehydrated initially, then hypovolemic. Urine specific gravity and the clinical signs of dehydration are the best methods of ensuring sufficient fluid delivery.

32.96.5 Maintenance

The mean daily water intake (including the water content of feed) of normal resting adult horses is 57 to 64 mL/kg/day at ambient temperatures of 41° F to 77° F (5° C to 25° C).[994,995] When mares were restricted to 40 mL/kg/day, they demonstrated significant dehydration.[996] A useful guideline for maintenance rate in adult horses is 60 mL/kg/day (2.5 mL/kg/hour). Thus, a 500-kg horse requires approximately 30 L/day for maintenance, in addition to any fluids to replace ongoing losses. The maintenance requirement of neonatal foals is significantly higher and is usually taken to be 4 to 5 mL/kg/hr,[997,998] although some authors use a lower estimate.[999] The fluid intake of nursing foals considerably exceeds this figure.[1000] However, clinical experience suggests that use of 4 to 5 mL/kg/hr is appropriate for maintenance in foals receiving no enteral fluids. It should be emphasized that it is important to take into account the fluid component of all infusions when calculating fluid rates to avoid inadvertent volume overload in neonatal foals receiving a number of intravenous infusions. For both horses and foals with normal enteral function, it is possible to meet maintenance requirements with nasogastric fluids, if this is clinically appropriate.

Monitoring of adequacy of fluid delivery is vital even when dehydration has been addressed and there are no major ongoing losses. The fluid requirements of the animal can change during treatment, and it is important to check that they are matched to requirements. Again, this is best done by monitoring urine specific gravity and assessing for the clinical signs of dehydration.

32.97 ELECTROLYTE REPLACEMENT AND TREATMENT OF ACID-BASE DISTURBANCES

Replacement of water losses is only part of developing a fluid therapy plan, albeit the most important one in acute resuscitation. The effect of the fluids on the electrolyte and acid-base status of the horse should also be considered, and fluids should be chosen to help correct physiologic disturbances. Unfortunately it is not possible to accurately predict electrolyte and acid-base disturbances based on clinical signs because seemingly similar clinical conditions may have quite different physiologic disturbances (Table 32-9).[1001] This limits the ability of the field veterinarian to monitor and treat these disturbances, although the recent availability of relatively inexpensive, portable blood gas and electrolyte measuring equipment has made determining the acid-base status a possibility in ambulatory equine practice. As stated earlier, in the absence of specific laboratory information, fluid therapy should probably be limited to isotonic polyionic crystalloid fluids, possibly with 10 to 20 mEq or potassium chloride per liter added in the maintenance phase.

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When laboratory information is available within 4 to 6 hours, fluid therapy can be tailored to the individual horse, allowing correction of specific physiologic disturbances. Although calculations of whole body electrolyte or base deficits are possible, they are generally based on a simple “chemistry flask” model of the patient, in which addition of a known amount of electrolyte results in a predictable effect. Because this is clearly not the case, the relevance of these calculations to managing the clinical case with ongoing losses and renal responses to changes in plasma electrolyte concentrations is unclear.[1002] A safer and more physiologically relevant approach is to frequently monitor clinical and laboratory responses to therapy and adjust treatment accordingly, rather than relying on a calculated electrolyte dose to restore normality.

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Table 32-9 Fluids of Choice for Specific Metabolic Disturbances

Metabolic Disturbance	Recommended Fluid	Dose
Lactic acidosis	Polyionic crystalloids (Normosol-R, lactated Ringer's solution) or	Up to 60 mL/kg/hr
	Hetastarch	Up to 10 mL/kg/hr
Hyponatremia		Sodium should be corrected no faster than 1 mEq/L/hr
With hypochloremia	Sodium chloride	
Without hypochloremia	Sodium bicarbonate	
Hypernatremia	5% Dextrose or 2.5% Dextrose/0.45% sodium chloride	To lower sodium no faster than 0.5 mEq/L/hr
Hypochloremia	Sodium chloride	0.9% or 7.5%, to effect
Hyperchloremia		
With hypernatremia	5% dextrose	To lower sodium no faster than 0.5 mEq/L/hr
Without hypernatremia	Sodium bicarbonate	5%, slowly, to effect
Hypokalemia	Potassium chloride	0.2 to 0.5 mEq/kg/hr, never to exceed 1 mEq/kg/hr
Hyperkalemia		
With clinical signs	Calcium gluconate	1 mL/kg IV over 10 min
Or >7 mEq/L	Sodium bicarbonate	1-2 mEq/L IV over 15 min
Without clinical signs	50% Dextrose solution polyionic crystalloid fluids	2 mL/kg IV over 5 min
Hypocalcemia	Calcium gluconate	Typically requires 100-300 mL of 23% solution
Hypercalcemia	Non—calcium-containing polyionic fluids Magnesium sulfate	4–16 mg/kg as an initial dose
Hypomagnesemia	Magnesium sulfate IV	4–16 mg/kg as an initial dose
	Magnesium oxide PO	8–32 mg/kg as an initial dose
Hypermagnesemia	Calcium gluconate	250–500 mL of 23% solution
Hypoalbuminemia	Fresh or fresh frozen equine plasma Hetastarch	To effect, not to exceed 10 mL/kg

IV, Intravenous; *PO*, by mouth.

Always take into account all disturbances present before commencing treatment.

32.97.1 Acid-Base Disturbances

The most common acid-base disturbance in horses with gastrointestinal disease is metabolic acidosis, caused by lactic acidosis (hypovolemia, endotoxemia), hyponatremia (colitis, peritonitis, intestinal torsion), or hyperchloremia (occasionally seen in colitis cases). Metabolic alkalosis, resulting from hypochloremia (high-volume gastric reflux) or hypoalbuminemia (severe enterocolitis, excessive fluid therapy), respiratory alkalosis (hyperventilation from pain), and respiratory acidosis (hypoventilation from extreme abdominal distention, central depression) can also occur.[952]

Although the predominant clinical signs in horses with acid-base disturbances are likely to result from the cause of the disturbance, clinical signs can arise from the physiologic consequences of the derangement. Metabolic acidosis can result in reduced cardiac contractility, constriction of the peripheral vasculature, inhibition of glycolysis, decrease in oxygen uptake by hemoglobin in the lungs, and CNS depression. Metabolic alkalosis can lead to overexcitability of nervous tissue, blunting of the hypoxic drive, compensatory hypoventilation, susceptibility to cardiac arrhythmias, and inhibition of oxygen release in the tissues.

Treatment of acid-base disturbances should be directed at the underlying cause and the specific plasma constituent imbalance. It is possible to determine the relative contributions of unidentified anions (principally lactate in horses with gastrointestinal disturbances), sodium, chloride, and protein to the measured acid-base status by the use of equations based on the calculated base excess.[952,1003] However, decisions for treatment can often be based on the absolute values of these blood constituents, and it is only in complex disturbances with changes in multiple blood constituents that the equations are usually necessary.

32.97.2 Lactate

As discussed earlier, increased blood or plasma lactate concentrations are usually a result of poor tissue perfusion in gastrointestinal diseases but may also be caused by inappropriate anaerobic metabolism in endotoxemia. The clinical signs of lactemia are those of the accompanying metabolic acidosis, but the signs of the cause of the lactic acidosis (those of shock) may predominate.

Although lactate can be directly measured, its plasma concentration can be accurately predicted by the anion gap in adult horses with normal plasma protein concentrations.[1004] The anion gap is calculated from the plasma concentrations of (sodium + potassium) minus the concentrations of (chloride + bicarbonate). The normal range is 7 to 15 mEq/L.[1004] At low and high protein concentrations, the equations based on base excess[952,1003] or the simplified strong ion gap ($2.24 \times$ total protein [g/dL]/$[1 + 10^{6.65-pH}]$ – Anion gap)[1004] should be used. Any of these calculations may easily be performed on a pocket calculator, but none was accurate in critically ill foals.[951]

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Lactic acidosis should be treated with large volumes of polyionic crystalloid solutions. The use of sodium bicarbonate in lactic acidosis is highly controversial.[960,1005] It corrects the laboratory value (pH) without addressing the underlying pathophysiology (poor tissue perfusion) by imposing a hypernatremic alkalosis on an already deranged metabolic balance. Although increasing the pH may improve myocardial contractility, this effect may be negated by the myocardial depressant effects of an increased carbon dioxide tension.[1006] In endotoxic ponies, administration of sodium bicarbonate resulted in an increased blood lactate concentration, hypernatremia, hypokalemia, and hyperosmolality.[1007]

32.97.3 Sodium

Low plasma sodium concentrations are most commonly seen in acute colitis, such as salmonellosis, PHF, and clostridiosis. The hyponatremia is usually accompanied by hypochloremia because of an increased loss of electrolytes relative to water.[958] Other gastrointestinal conditions associated with hyponatremia are those that result in third spacing of sodium (peritonitis, torsion or volvulus of gut) and with sodium-wasting disorders (esophageal obstruction leading to loss of saliva). The clinical signs of hyponatremia are neurologic disturbances, including reduced or absent menace response, intention tremor, and hypermetric gait,[1008] but severe clinical signs do not usually occur until the sodium concentration is less than 110 mEq/L.[1009] Hyponatremia will also result in metabolic acidosis.[952]

The fluid choice for hyponatremia depends on whether there is concurrent hypochloremia. If the plasma chloride concentration is also low, sodium chloride should be used. If the chloride concentration is normal or increased (which is rare in gastrointestinal disease), then sodium bicarbonate should be administered. If the hyponatremia is severe, then hypertonic solutions may be administered initially (7% to 7.5% sodium chloride and 5% to 8.4% sodium bicarbonate, respectively). Rapid correction of sodium deficits in other species can cause central pontine myelinosis.[1009] It is unclear whether this is a risk in the horse and therefore whether it is necessary to follow the guidelines for sodium restoration in other species. These guidelines state that sodium should be corrected at a rate of 1 mEq/L/hr in acute hyponatremia and at less than 0.5 mEq/L/hr in chronic hyponatremia, in neither case to exceed 8 mEq/L during the first 24 hours.[1009]

Hypernatremia is rare in horses with gastrointestinal disease[958,1001,1010] and is usually caused by water loss in excess of electrolytes and accompanied by hyperchloremia. To correct hypernatremia, low-sodium fluids such as 5% dextrose or 2.5% dextrose and 0.45% sodium chloride should be administered. Again, in other species it is recommended not to correct hypernatremia too rapidly; sodium should be lowered by 0.5 mEq/L/hr, not to exceed 12 mEq/L over the first 24 hours.[1009]

Clinical signs associated with hyponatremia and hypernatremia are caused by changes in plasma osmolality. Sodium is the major cation in plasma, and sodium and glucose concentrations are the main determinants of plasma osmolality.[958] Changes in plasma osmolality can lead to CNS edema or dehydration, resulting in neurologic signs.[1011] Rapid changes in plasma sodium concentration may also cause CNS edema or dehydration, because the cerebrospinal fluid slowly equilibrates with the plasma, but will rapidly change if osmotic gradients are high.

32.97.4 Chloride

The loss of gastric hydrochloric acid in high-volume reflux (in proximal enteritis and grass sickness) and the secretion and/or lack of absorption of chloride in severe colitis often leads to hypochloremia in gastrointestinal disease.[1001,1010] Hypochloremia in the absence of hyponatremia results in metabolic alkalosis.[952] The alkalosis associated with hypochloremia may also result in increased cellular uptake of potassium, leading to hypokalemia.[1009]

Treatment of hypochloremia can usually be achieved with intravenous 0.9% sodium chloride, which contains more chloride relative to sodium than plasma. In horses with high-volume gastric reflux, administration of intravenous H_2-receptor antagonists (e.g., cimetidine at 6.6 mg/kg IV qid) reduces gastric hydrochloric acid

secretion and therefore should reduce chloride loss. In humans, intravenous hydrochloric acid has been used to treat severe hypochloremia,[1012] but carries substantial risks for the patient.[1013] Hyperchloremia is rare in horses with gastrointestinal disease but may occur in severe colitis because of water secretion in excess of electrolytes. It should be treated with 5% dextrose if accompanied by hypernatremia and with sodium bicarbonate if severe and accompanied by a low or normal plasma sodium concentration.[1009]

32.97.5 Potassium

Hypokalemia is commonly seen in horses after surgery for colic[1010] because of enhanced mineralocorticoid and glucocorticoid release and because of infusion of large amounts of sodium-containing fluids that increase distal tubular flow and renal potassium loss.[1011] Hypokalemia also occurs in colitis and metabolic alkalosis. The most relevant clinical sign of hypokalemia is reduced intestinal motility.[1009,1014] However, the association between hypokalemia and ileus remains undetermined in the horse. Other clinical signs include muscle weakness, lethargy, and inability to concentrate urine.[1009] Cardiac conduction abnormalities are rare except in severe hypokalemia and in preexisting cardiac dysfunction.[1014] The effect of potassium on acid-base status is small and need not be considered clinically.[952]

Potassium is primarily an intracellular ion, and therefore decreases in whole body potassium may not be detected by plasma measurements.[1015] Although erythrocyte potassium content has been used to estimate whole body potassium,[1015] its accuracy is unclear. Moreover, the extracellular potassium concentration (reflected in the plasma) is more relevant to neuromuscular transmission and therefore to the important clinical signs than whole body potassium stores.[1011] The intervention level for treatment of hypokalemia is unclear. In postoperative colic cases and proximal enteritis, the prevention of ileus is a primary goal, and it may be prudent to supplement the plasma potassium concentration below 3.5 mEq/L. In other patients, especially those being fed enterally, it may not be necessary to treat plasma potassium concentration above 3 mEq/L.

Hypokalemia is treated with intravenous potassium chloride solution. The rate of administration is more important than the amount. The rate should not normally exceed 0.5 mEq/kg/hr and should never exceed 1 mEq/ 775
kg/hr.[1009] The addition of 40 mEq of potassium chloride per liter of crystalloid fluids is safe at rates up to 10 776
mL/kg/hr (5 L/hr for a 500-kg horse). This amount is usually required only in severe hypokalemia (<2.7 mEq/L), and smaller disturbances can often be successfully treated with 20 mEq of fluid per liter. If hypokalemia does not respond to potassium chloride administration, magnesium should be supplemented.[1016] Hyperkalemia is not typical in horses with gastrointestinal disease, although it may occur with acidosis, colitis, secondary renal failure, and hyperkalemic periodic paralysis. Artifactual hyperkalemia may be seen in blood samples stored for longer than 2 hours before plasma separation, because of leaching of potassium from the erythrocytes. Clinical signs are due to disruption of neuromuscular transmission and are therefore similar to those of hypokalemia. In the absence of clinical signs, polyionic fluids should be administered. Possible treatments for symptomatic or severe (>7 mEq/L) hyperkalemia include calcium gluconate (1 mL/kg IV over 10 minutes), sodium bicarbonate (1 to 2 mEq/L IV over 15 minutes) and 50% dextrose solution (2 mL/kg IV over 5 minutes).[1009]

32.97.6 Calcium

Low plasma ionized calcium concentrations are common in horses with surgical colic[1017] and in colitis cases. Possible causes of this hypocalcemia include lactic acidosis,[1018] endotoxin-induced changes in calcium

homeostasis,[1019] and functional disturbances to the small intestine (the main site of calcium absorption in the horse[1020]). Clinical signs of hypocalcemia reported in the horse include synchronous diaphragmatic flutter, tetany, muscle spasm, and seizures.[1021] Of these, only diaphragmatic flutter is seen with any regularity in adult horses. Hypocalcemia has also been associated with POI in the horse,[1017,1022,1023] but a causal relationship has not been demonstrated.

Approximately 50% of the total calcium in plasma is bound to albumin or complexed with small ligands. The remaining ionized fraction is the biologically active form. Where possible, the plasma ionized calcium concentration should be measured, rather than the total concentration, because the plasma albumin concentration is often decreased in gastrointestinal diseases. If total plasma calcium measurements are used to guide therapy, the calcium concentration should be corrected for changes in albumin concentration. The intervention level for treatment of hypocalcemia is debatable. There is one report of exacerbation of endotoxemia with calcium administration in a rodent model.[1024] Although the relevance of this to the horse has not been determined, aggressive supplementation of calcium in endotoxemic horses may be inadvisable. Even in endotoxic horses, calcium should probably be supplemented if the ionized calcium concentration is less than 4.8 mg/dL (1.2 mmol/L).

Hypocalcemia is treated with intravenous 23% calcium gluconate or 20% to 40% calcium borogluconate solution. A typical volume required is 100 to 300 mL of the 20% to 23% solution,[1017] but the amount will depend on ongoing losses, and the ionized calcium concentration should be frequently checked during therapy. Calcium solutions are irritating to the veins and should be diluted in crystalloid fluids before administration. They are incompatible with sodium bicarbonate and whole blood. After calcium supplementation, the plasma calcium concentration should be checked after 4 to 8 hours because ongoing losses and redistribution into cells may result in further hypocalcemia. Hypocalcemia can be a sequela to magnesium deficiency, and therefore magnesium should be supplemented in horses with refractory hypocalcemia.

Hypercalcemia occurs in horses with chronic renal failure but is rare in gastrointestinal disease. Clinical signs are usually those of the underlying pathophysiology, but soft-tissue calcification may occur. Treatment for severe hypercalcemia (ionized calcium greater than 9 mg/dL [2.25 mmol/L]) should include non—calcium-containing intravenous fluids (sodium chloride or Normosol-R) and intravenous magnesium sulfate (see treatment of hypomagnesemia, later).

32.97.7 Magnesium

In one report, 44% of horses with gastrointestinal disease had low plasma magnesium concentrations.[1025] Causes of hypomagnesemia include decreased intake, gastrointestinal losses (prolonged nasogastric reflux, malabsorption), alterations in distribution (endotoxemia, parenteral nutrition administration), renal losses (prolonged administration of lactated Ringer's solution or other magnesium-free fluids, hypophosphatemia, acidemia, renal tubular acidosis),[1026,1027] and excessive sweating.[1028] Severe hypomagnesemia can result in ventricular arrhythmias and also muscle tremors, ataxia, seizures, and calcification of elastic tissue[1029] in the horse. Other clinical manifestations of hypomagnesemia reported in human patients include supraventricular tachycardia, atrial fibrillation, thrombosis, anemia, decreased muscle strength, increased nephrotoxicity of aminoglycoside drugs, increased pulmonary vascular resistance, and sudden death.[1026,1030–1032] Hypomagnesemia can also result in hypokalemia refractory to potassium supplementation.[1016]

Extracellular fluid contains approximately 1% of the total body magnesium, and therefore the serum magnesium concentration may not reflect the total body magnesium status,[1027] making diagnosis of hypomagnesemia difficult. Fortunately it is safe to administer moderate amounts of magnesium, irrespective of the magnesium status of the horse, providing the horse has normal renal function. Intravenous magnesium sulfate (at 2 mg/kg/min, not to exceed 50 mg/kg) is recommended for ventricular arrhythmias associated with hypomagnesemia.[1033] Higher doses should be avoided because they cause significant muscle weakness; 140 mg/kg of intravenous magnesium sulfate can induce recumbency in normal horses.[1034] For treatment of hypomagnesemia in the absence of cardiac signs, 2 to 8 mg/kg can be used as an initial dose in horses with normal renal function. Oral supplementation is possible with magnesium oxide, but oral magnesium sulfate should be avoided because of its laxative effects.

In the study by Costa and colleagues, 11% of horses with gastrointestinal disease were hypermagnesemic, but associated clinical signs were not reported.[1025] Severe clinical signs after nasogastric administration of magnesium sulfate were reported in two horses with large colon impactions. The doses given were between 1600 and 2000 mg/kg. Both horses recovered 1 to 6 hours after the onset of clinical signs, which included flaccid paralysis with recumbency, tachycardia, tachypnea, and nondetectable peripheral pulses. The horses were treated with 250 mL of 23% calcium gluconate solution IV, repeated after an hour, and polyionic intravenous fluids to promote diuresis.[1035] The phosphorylation of adenosine diphosphate (ADP) to form ATP is dependent on the intracellular magnesium concentration,[1036] and therefore hypomagnesemia can disrupt ATP-dependent cellular processes. The sodium-potassium ATPase pump, the major mechanism for controlling intracellular and extracellular sodium and potassium concentrations, is ATP dependent and thus magnesium dependent. This may explain the relationship of refractory hypokalemia to hypomagnesemia.[1016] The relationship between the sodium-potassium ATPase pump and magnesium may also explain the effect of magnesium on calcium flux, because sodium is exchanged down its concentration gradient (controlled by the sodium-potassium ATPase pump) for calcium by the sodium-calcium exchanger.[1037] Because of the interaction of the magnesium concentration with these other electrolytes, a main effect of hypomagnesium is to alter depolarization of nerve and muscle cells.[1031] Magnesium also directly competes with calcium for some of its binding sites, allowing greater binding of calcium to enzymes in hypomagnesemia. One such enzyme is phospholipase A_2; increased calcium binding results in greater activity of this enzyme, which leads to the increased formation of eicosanoids, particularly TXA_2,[1030] that may play a role in thrombophlebitis.[1038]

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32.97.8 Phosphorus

Hypophosphatemia has been reported in horses with either strangulating intestinal lesions or intestinal ileus[1001] and is also a sequela to renal dysfunction.[949] Prolonged administration of lactate-containing fluids,[1039] metabolic or respiratory alkaloses, repeated gastric magnesium sulfate administration (because magnesium binds phosphate to form an insoluble complex), and prolonged administration of non—lipid-containing parenteral nutrition solutions[1040] may also result in hypophosphatemia. Reduced intestinal phosphate absorption, apparently without hypophosphatemia, is a sequela to large colon resection.[1041] Clinical signs reported in small animals and humans with hypophosphatemia include hemolysis, skeletal muscle weakness and rhabdomyolysis, leukocyte dysfunction, ventricular arrhythmias, and reduced cardiac output.[1040,1042]

Clinical manifestations and treatment of hypophosphatemia have not been reported in the horse, and in humans there is no good evidence for treatment in the absence of clinical signs.[1040] Treatment options reported in small

animals include intravenous potassium phosphate (0.01 to 0.03 mmol/kg/hr) and oral potassium phosphate (0.5 to 2 mmol/kg/day).[1042] The potential effects of potassium phosphate on the plasma potassium concentration must be considered before this treatment is commenced. Intravenous glucose-1-phosphate[1043] and intravenous sodium phosphate have also been reported in humans. The safety of these treatments has not been evaluated in the horse.

Hyperphosphatemia occurs in horses with strangulating intestinal lesions[1044] and severe colitis[1001] without specifically attributable clinical signs. Clinical findings reported in small animals include diarrhea, hypocalcemia, hypernatremia, and an increased propensity to metastatic soft-tissue calcification. Treatment recommended in small animals includes intravenous fluids, to correct any acidosis and promote renal phosphorus excretion, and dextrose-containing fluids, to promote translocation of phosphorus into cells.[1042]

The clinical signs of hypophosphatemia result from the wide range of physiologic functions of phosphate. These include storage of energy as ATP, which is used for many processes including muscle contraction, neuronal transmission, and electrolyte transport. Because phosphorus and magnesium deficiencies can both result in reduced availability of ATP, the clinical signs can be similar. Phosphate also acts as a buffer in plasma and is a component of many intracellular compounds including phospholipids, nucleic acids, enzymatic cofactors, and signaling molecules such as cyclic adenosine phosphate. It appears that increased plasma phosphate concentrations are not directly toxic.[1045] Hypocalcemia and metastatic soft-tissue calcification caused by hyperphosphatemia result from the calcium-phosphate product exceeding that required for precipitation of calcium phosphate in the tissues.[1042,1045]

32.97.9 Albumin

Hypoalbuminemia is common in horses with moderate to severe compromise of the colon. It may also occur with over-aggressive fluid therapy and parasitism. Clinical signs of hypoalbuminemia are peripheral edema (due to reduced plasma oncotic pressure) and tissue and organ edema, leading to reduced oxygen uptake by cells (increased perfusion distance), and in severe cases organ failure. Albumin is a weak acid, and severe hypoalbuminemia may contribute to metabolic alkalosis or mask concurrent metabolic acidosis.[952] A decrease in albumin concentration of 1 g/dL results in an increase in the base excess of +3.7 mEq/L.[1003]

Hypoalbuminemia should be treated when acute or if there are clinical signs. Although it is advisable to treat all horses with a plasma total solids concentration of less than 4 g/dL, a few horses with chronic hypoproteinemia can have plasma total solids concentrations of 3.5 to 4 g/dL with no apparent clinical signs. The treatment options for hypoalbuminemia include fresh or fresh frozen equine plasma, concentrated albumin solutions, and hetastarch. Plasma has the advantage of containing other factors, such as AT-III, that may be depleted in the disease process. Hetastarch has the advantage of large molecular size and long persistence in the circulation[971] but has questionable efficacy in human patients. Albumin solutions were shown to result in neither benefit nor harm in human critically ill patients when compared with saline.[1046] At the time of writing, equine albumin solutions are not available commercially, and their role in the treatment of horses is unclear.

32.98 COMPLICATIONS OF FLUID THERAPY

32.98.1 Thrombophlebitis

Thrombophlebitis is a common complication of intravenous fluid therapy.[962] It may be a nidus for infection and may cause mechanical blockage of venous drainage, resulting in local edema. Fatal edematous occlusion of the upper respiratory tract can result from bilateral jugular vein thrombosis. It is therefore advisable not to catheterize the contralateral jugular vein if one jugular vein shows any signs of thrombosis. Bacterial endocarditis, particularly of the tricuspid valve, can occur as a sequela to infectious thrombosis.

Thrombophlebitis can be identified by heat, swelling, or the presence of any exudate around the catheter insertion site or by palpation of a thrombus ("corded" feel) in the catheterized vein. Catheterized veins should be checked at least daily. Ultrasonography of the catheterized vein can help identify thrombus formation. It is prudent to continue to check the vein for 2 to 3 days after catheter removal because thrombophlebitis may develop or become apparent in this time period.

The risk factors for thrombophlebitis include administration of carboy fluids,[962] presence of diarrhea[962] or endotoxemia,[1038] polytetrafluoroethylene (Teflon) catheter material, and long duration of catheterization.[984] Several other risk factors for thrombophlebitis have been identified in humans but not studied in horses. These include inexperienced personnel placing the catheter,[1047] administration of total parenteral nutrition,[982] and larger-bore catheters.[1048] Treatment for thrombophlebitis should include topical nitroglycerin ointment[1049] and probably also hot-packing and topical DMSO ointment. Catheters from thrombosed veins should be removed aseptically and cultured (preferably by the roll-plate technique[1050]) to allow in vitro susceptibility directed antimicrobial therapy, if necessary. A fine-needle aspirate of the thrombus can also be used for bacterial culture. Fluid-filled pockets within the thrombus can often be identified by ultrasound[1051] and should undergo aspiration after surgical preparation of the skin over them. Empirical antimicrobial drugs should be broad spectrum with activity against *Streptococci* and *Staphylococci* species[1051] and have good tissue penetration. Such drugs include ceftiofur, gentamicin, and chloramphenicol.

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32.98.2 Overhydration

Clinical signs of overhydration are rare in adult horses with normal cardiac and renal function. The most important clinical sign is pulmonary edema, manifested by dyspnea and a pink-white foamy nasal discharge. Treatment should include furosemide (0.5 to 1 mg/kg IV) and a reduction in the rate of fluid administration. Intranasal oxygen supplementation is indicated when there is significant hypoxemia (detected by arterial blood gas analysis). Further fluid therapy in such horses should be carefully monitored, ideally by means of CVP measurements.

32.99 INOTROPES, PRESSORS, AND VASODILATORS

Some horses with severe cardiovascular compromise will not respond to fluid therapy alone. A proportion of these patients can be successfully managed with inotropes, pressors or vasodilators. These drugs should be considered in cases with continued tachycardia, lactic acidosis, oliguria, and hypotension or hypertension despite appropriate fluid therapy. In general, horses with a jugular venous oxygen tension of less than 35 mm Hg are most likely to

require further cardiovascular support, and those with an oxygen tension over 60 mm Hg are least likely to respond.[1052,1053] The cause of the cardiovascular insufficiency should be considered before therapy is initiated. Horses with necrotic intestine that could not be resected are unlikely to respond to cardiovascular therapy unless the primary problem can be addressed.

The inotropes increase cardiac output by increasing myocardial contractility, resulting in a larger stroke volume. The most commonly used drugs in equine intensive care for this purpose are the β_1-adrenergic agonists. Inotropes that have some β_2-adrenergic activity, such as dobutamine, may also cause mild systemic vasodilation. The pressors cause arterial and venous vasoconstriction, mediated through α-adrenergic receptors, and the vasodilators, such as nitroprusside and fenoldopam, cause arterial or venous vasodilation mediated through the nitric oxide pathway.

The decision to use one of these drugs and the choice of drug should be based on as many cardiovascular parameters as can be measured.[1054] The minimum information required to select an appropriate drug includes heart rate, heart rhythm, indirect (tail cuff) arterial blood pressure, and response to fluid therapy. Direct measurements of CVP and arterial blood pressure, electrocardiogram, and cardiac output, if available, make these treatments safer and easier to titrate. All of these drugs should be carefully titrated to defined endpoints. For inotropes and pressors the goal should be to increase the arterial blood pressure sufficiently to decrease blood lactate concentration and increase urine output[1052] without inducing tachycardia or arrhythmias. For vasodilators the goal should be to reduce the MAP to less than 120 mm Hg without inducing hypotension, tachycardia, or acidosis. It is advisable to use an electronic pump to accurately deliver the diluted drug at the correct rate.

It is extremely important to frequently monitor the response to these drugs, as the underlying cardiovascular disturbances may change rapidly. Improvements in arterial blood pressure may not result in improved tissue perfusion. Heart rate and rhythm, the acid-base balance, venous oxygen tension, and urine output should be monitored in addition to arterial blood pressure. If indirect blood pressure is being used to monitor these drugs, it is important to bear in mind the limitations of the technique. All readings should be done in triplicate, and the cuff size should be matched to the patient. A small adult cuff designed for humans is appropriate for most adult horse tails.

Endotoxemia is the most common cause of severe cardiovascular disturbances in the adult. The initial cardiovascular response to experimental endotoxin administration is decreased MAP, systemic vasodilation, and increased cardiac output.[1055] However, this response varies markedly with the dose of endotoxin[1056,1057] and treatments given,[965,1055] and this pattern of disturbance cannot be assumed.

32.99.1 Dobutamine

In the absence of cardiac output measurements, dobutamine should be the first drug used in hypotensive horses (MAP <65 mm Hg) that have not responded to appropriate fluid therapy. Dobutamine is a β_1-adrenergic agonist and increases cardiac output.[1058] Dobutamine also has significant β_2 activity, which could cause vasodilation. Dobutamine should be diluted in isotonic saline, 5% dextrose, or lactated Ringer's solution. The dose should be carefully titrated from a starting dose of 1 to 3 μg/kg/min. The horse should be carefully monitored for tachycardia, which in some cases may indicate inadequate fluid resuscitation, and for dysrhythmias.

In horses with endotoxemia and increased cardiac output, dobutamine is unlikely to improve tissue oxygenation. Despite increasing cardiac output, dobutamine did not ameliorate experimental colon ischemia in the pig.[1059]

32.99.2 Norepinephrine

In hypotensive horses that either do not respond to dobutamine or have a measured increased cardiac output, norepinephrine (noradrenaline) administration should be considered. Norepinephrine is an α-adrenergic and moderate β_1-adrenergic agonist. It is a powerful vasoconstrictor in the horse.[1060] Norepinephrine should be diluted in 5% dextrose. A starting dose is 0.1 μg/kg/min, and effects may be seen in some patients at doses as low as 0.01 μg/kg/min. The highest reported doses are 1.5 μg/kg/min in the horse[1060] and 3.3 μg/kg/min in human patients.[1061] Concurrent infusion of dobutamine (5 μg/kg/min) with norepinephrine has been demonstrated in humans to result in improved tissue perfusion[1062] and might be prudent when cardiac output is not being directly monitored. It is important to carefully monitor urine output when using norepinephrine, as inappropriate doses may reduce renal blood flow.

32.99.3 Dopamine

Dopamine has β-adrenergic (inotropic), α-adrenergic (pressor), and dopaminergic effects. In other species the dopaminergic effects predominate at low doses (1-5 μg/kg/min), the β-adrenergic effects at moderate doses (5 to 10 μg/kg/min), and the α-adrenergic effects at high doses (above 10 μg/kg/min),[1063] but these distinctions may be blurred in the horse.[1064] In anesthetized horses a dopamine infusion started 5 minutes after endotoxin administration improved cardiovascular variables but did not prevent hypoxemia or metabolic acidosis.[1065] Dopamine causes significant vasoconstriction of equine colonic arteries at higher doses in vitro[1066] and is associated with reduced gastric mucosal perfusion in human septic patients in vivo.[1067] Furthermore, dopamine may disrupt normal equine gastrointestinal activity, even after the infusion is stopped.[1068] In normal horses low doses of dopamine (5 μg/kg/min) can cause cardiac arrhythmias.[1064]

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Dopamine is not recommended for horses with gastrointestinal diseases because of the reported deleterious effects on the gastrointestinal system and because the predominant effects vary with the plasma concentration,[1064] which cannot be predicted from the infusion rate.[1069,1070] Low-dose dopamine has been demonstrated not to have any efficacy in preventing or treating acute renal failure in human patients,[1071] and dopamine infusion does not increase creatinine clearance in the normal horse.[1064]

32.99.4 Nitroprusside

In severely hypertensive horses, sodium nitroprusside administration should be considered.[1058] A diastolic blood pressure greater than 110 to 120 mm Hg is considered to be a hypertensive crisis in human medicine.[1072] Nitroprusside liberates nitric oxide by a nonenzymatic one-electron reduction that occurs on exposure to tissues such as vascular smooth muscle membranes.[1073] Hypertension, particularly pulmonary hypertension, has been reported in experimental horses and foals treated with a low dose of endotoxin.[965,1057,1074] Laminitis is also associated with hypertension (MAP up to 158 mm Hg).[1075] However, this increase in arterial pressure may be associated with increased cardiac output rather than a generalized increase in vascular tone (systemic vascular resistance).[1075] Nitroprusside induces relaxation of palmar digital arteries and veins isolated from carbohydrate-overloaded horses.[1076] Treatment of acute laminitis with glyceryl trinitrate applied topically to the pasterns results in some amelioration of clinical signs.[1077] Assuming that this response is due to nitric oxide, parenteral

nitroprusside administration would represent a method of delivering a more controlled source of nitric oxide. The potential beneficial role of nitroprusside administration in ameliorating laminitis remains to be investigated.

Sodium nitroprusside should be diluted in 5% dextrose solution and wrapped in foil to protect the solution from light. The dose should be carefully titrated from a starting dose of 0.1 to 0.3 µg/kg/min. It is imperative to monitor the blood pressure continuously during the initial titration phase and frequently thereafter. As with all nitric oxide donors, there is a reduced responsiveness with time that may necessitate increasing doses.[1073] Hepatic metabolism of nitroprusside produces thiocyanate and cyanide, which may result in altered neurologic status, acidosis, and death at high concentrations.[1078] In human patients, cyanide toxicity has not been reported at doses of less than 2 µg/kg/min.[1078] Fenoldopam, a selective dopamine-1 receptor agonist, is a possible alternative antihypertensive agent that has been used experimentally in the horse and foal.[1079,1080] However, the current cost of fenoldopam is likely to prohibit its use in adult horses.

32.100 RUMINANT ALIMENTARY DISEASE

Bradford P. Smith, Consulting Editor

32.101 DENTAL AND PERIODONTAL DISEASES

Guy St. Jean

32.102 ERUPTION OF TEETH

Determining an animal's age by examining the teeth is not an exact science, because the appearance of the teeth can be affected by inherited factors, nutrition, and geographic location.[1,2] At birth or within 2 weeks, four deciduous incisors usually are present. All eight deciduous incisors erupt within the first month.[3] The fourth incisor (corner) is a modified canine tooth. The incisors meet with the dental pad of the upper jaw for the purpose of gripping and cutting herbage. Usually all three pairs of deciduous premolars have erupted at birth or shortly afterward.[1,2] In cattle the formula for the deciduous teeth is as follows:

$$2(\text{incisors } 0/4,\ \text{premolars } 3/3) = 20$$

The age at which permanent teeth erupt often is the best criterion for determining the animal's age if a registration certificate is not available. However, systemic illnesses and malnutrition can retard dental development and cause retention of the deciduous teeth.[4] The first molars erupt at 8 months of age and are fully developed at 12 months. At 18 months the second molar is fully developed. The third molar erupts at 24 months and is fully developed at 30 months. The permanent premolar teeth start to replace the deciduous teeth at 24 months, and all three permanent premolars usually are present at 3 years of age.[1,2] The first pair of permanent incisors (centrals) erupts at 18 to 24 months of age, the second pair (medials) appears at 24 to 30 months, the third pair (laterals) erupts at 3 years of age, and the fourth pair (corners) erupts between 3½ and 4 years of age.[3,4] Cattle therefore have a complete set of permanent teeth at age 4 to 4½ years. The formula for the permanent teeth in cattle is as follows:

$$2(\text{incisors } 0/4,\ \text{premolars } 3/3,\ \text{molars } 3/3) = 32$$

The deciduous and permanent dental formulas of the sheep and goat are identical to those of cattle.[3] In sheep and goats the periods of eruption are as follows: The incisors are present at birth or within the first 4 weeks. The

premolars erupt 2 to 6 weeks after birth. The first pair of permanent incisors (centrals) replaces the deciduous teeth at 12 to 18 months of age. The second pair appears at 18 to 24 months. The third pair (laterals) erupts between 30 and 36 months, and the fourth pair (corners) appears at 3½ to 4 years. The three permanent premolars have erupted by 18 to 24 months of age; the first molar erupts at 3 months, the second molar between 9 and 12 months, and the last molar between 18 and 24 months.[3]

32.103 EXAMINATION OF TEETH

Dental disease in ruminants should be considered first on a flock or herd basis.[5,6] Determining dental health is particularly useful when unconventional feeds are incorporated into the herd nutritional program.[7,8] The clinical manifestations of dental diseases include inadequate food intake, inadequate calf development, weight loss, unthriftiness, low body condition score, quidding, low pregnancy rate in replacement heifers, and mandibular or maxillary swellings or draining tracts.[3,6–9] Examination of the herd should be followed by dental examination of individual animals. For examination of the premolars and molars, the tongue should be withdrawn from the mouth and held at the commissure of the mouth opposite the teeth being examined. A small dose of xylazine (0.03 to 0.04 mg/kg IV) and use of a mouth speculum allow for a much more thorough dental examination, including manual palpation in cattle.

The incisors have a sharp edge in front and are used for gripping and cutting herbage.[3,6] They should be aligned closely, with little space between them.[3,6] In sheep the periodontium of the incisor allows movement of up to 2 mm anteroposteriorly to accommodate rotating or turning forces during grazing.[9] This makes the sheep incisor very prone to loss with periodontal damage. The length of the premolar and molar teeth and their firm placement in the alveolar bone means that they are lost less often than the incisors.[1,2,6]

32.103.1 Dental Attrition and Erosion

Rapid wearing of teeth is seen most commonly in grazing sheep 5 years of age or older. Sheep and cattle grazing forage-deficient or sandy pastures and arid ranges in Africa, Australia, New Zealand, and the southwestern United States often show an accelerated rate of tooth wear.[6,10] In Rhodesia the incisors of Hereford cattle showed an increased rate of wear because of the softer enamel of this breed compared with that of indigenous cattle.[11]

Examination of an animal with dental attrition reveals worn incisor or molar teeth (or both); often only short stumps are seen. The teeth also may be loose, fractured, or missing. Dental attrition from excessive wear must be differentiated from periodontal disease that causes tooth loss.[6,12,13] The pathogenesis of excessive tooth wear relates to tooth hardness and diet quality. Ingestion and mastication of soil and sand with forage abrades and wears the incisor and molar teeth. In New Zealand dental attrition in sheep was attributed to the action of the acids and enzymes in the herbage on tooth dentin.[10] A calcium deficiency or calcium-phosphorus imbalance, which results in softness of the tooth enamel and dentin, may accelerate the rate of wear.

In the United States the feeding of fermented sweet potato cannery waste to cattle resulted in substantial increases in incisor erosion.[7,8] Cattle producers who fed the waste noticed a poor growth rate, inadequate calf development, low pregnancy rates in heifers, and worn, mottled, discolored incisors.[7,8] Sweet potato cannery waste is highly acidic (pH 3.2) and causes calcium loss and tooth erosion. Deciduous teeth are etched more rapidly, placing young cattle at higher risk for severe tooth wear and dental infection. In addition, the original

enamel surface and the pulp chamber are closer together in deciduous teeth than in permanent teeth, which also is more significant in younger cattle.[7,8] Mixing 10% broiler litter with sweet potato cannery waste raised the pH to 4, providing a palatable, high-quality feed and preventing the severe dental problems associated with feeding sweet potato cannery waste alone.[7]

A syndrome involving excessive wear of deciduous incisor teeth, maleruption of permanent incisors, and an increased prevalence of dentigerous cysts in sheep has been reported from New Zealand.[14] Excessive wear of the incisor teeth of cattle was recorded on the same farms. Ingestion of soil during winter because of the inclement weather, overgrazing of pastures, and low blood levels of copper were the main causes of the syndrome.[14] Dental attrition can be prevented by providing supplemental feed to avoid overgrazing of pastures. Adding 1% ground limestone to the feed in calcium-deficient areas is recommended.[15]

32.103.2 Periodontal Disease

Periodontal disease is a disease condition of the supporting tissue that surrounds the teeth.[16,17] Periodontal disease of sheep is endemic in parts of New Zealand. A periodontal disease known as *cara inchada*, or swollen face, has caused losses of cattle in Brazil.[9,18]

Periodontal disease is characterized by protruding, loose incisors.[2,6] With time, incisors, premolars, and molars may be missing. Why periodontal disease is prevalent in sheep but less common in cattle is unknown. Periodontal disease causes pain on mastication, leading to poor maceration of food and reduction in food digestibility.

Periodontal disease has been associated with bacterial plaque-induced gingivitis.[16,19–21] The acute gingivitis is replaced progressively by a chronic inflammation in the gingival sulcus. The periodontal ligament is destroyed by plaque-forming oral microorganisms and host enzymes. At this stage, periodontal pockets are formed and lead to loosening of teeth. This process may take months or years. With time the infection extends to the apical area. The gum margin begins to recede over the lesion, food accumulates in the pocket, and the entire alveolus becomes infected. At this point the tooth becomes a sequestrum. The alveolar pyorrhea causes a periostitis of the external surface of the alveolar process, and swelling is observed. Once a tooth has been lost from an affected alveolus, granulation tissue fills the alveolus. Deep to the granulation tissue, alveolar bone is redeposited.

Bacteria such as *Bacteroides* species, *Actinomyces* species, and spirochetes, metabolic or immune disorders in the host, and mechanical or chemical agents have been implicated in the pathogenesis of periodontal diseases in sheep.[6,20,22,23] Bacterial invasion in the gingival pockets has been associated with a defect of host immune competence.[24] Hypomagnesemia has been a common finding in sheep with periodontal disease, but this may be a secondary development.[23] Gingival trauma may be important in the etiology.[25] Dissolution of the enamel at the attachment of the gingival epithelium by organic acids from microorganisms of the soil may be a predisposing factor.[26] The serum values for calcium, albumin, and alkaline phosphatase (AP) were lower for sheep with periodontal disease than for sheep unaffected by dental disease.[27]

A postmortem examination of Scottish hill sheep revealed that 60% of 478 aged sheep had either loose or missing teeth. Gingival pockets were present in 87% of the population and were correlated with tooth looseness.[28] In the United States a 25% mortality rate caused by dental disease in a herd of 300 ewes was reported.[29] The clinical signs were depression, anorexia, ataxia, and emaciation.[29] Necropsy revealed dental disease of the

mandibular teeth with plaque, plant fibers in periodontal pockets, and osteomyelitis of the mandibular bone. Initial trauma to the gingivae from cheatgrass awns in the hayfield was implicated.[29]

A particular type of periodontal disease in cattle has been reported from Brazil.[18,19] This condition involves an inflammatory process of the periodontium of calves and older Zebu cattle that results in alveolar periostitis of the maxilla or, less often, the mandible.[18,19] Examination reveals deep periodontal pockets and loss of or loosened teeth. Affected animals suffer from malnutrition, diarrhea, and loss of condition and often die. *Bacteroides* and *Actinomyces* organisms often are found in the lesion and are suspected of causing the disease.[18] This disorder is seen only in certain areas of Brazil, and the cattle improve if moved to unaffected areas. In one trial the development of periodontal disease in calves was avoided by administration of the antimicrobial drug spiramycin.[19]

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The assumption that incisor condition is a good indicator of future productivity is not well founded. Little scientific evidence exists on which to base the practice of culling sheep with periodontal disease. Three farms with a high prevalence of periodontal disease were selected, and the body condition and weight of affected sheep were compared with those of sheep with no signs of periodontal disease. On only one farm was a significant association noted between periodontal disease and body condition or weight. It was concluded that periodontal disease in sheep may impair productivity on some farms but not others.[30,31]

Treating periodontal disease on a flock basis often may prove impractical. Dental treatment, drug therapy, and management change have been tried in sheep. One form of dental treatment, tooth grinding, consists of trimming the incisors to the levels of the lower dental pad.[12] Two trials of the productivity effects of tooth grinding have been conducted, and neither showed any benefit from the procedure.[30] An attempt to influence the development of periodontal disease in sheep through long-term treatment with tetracycline and metronidazole has proved ineffective.[21] In commercial sheep surgical treatment could improve conditions such as periapical and gingival abscesses, but such treatment is not economically feasible.

Sheep can live without incisors provided they do not have to graze too closely. Supplementary feeding or improved pasture usage for sheep that have lost incisors should provide a net gain to the owner. However, this approach is unlikely to be effective when premolar and molar teeth are involved, because of the inability to chew and ruminate efficiently.

32.103.3 Dentigerous Cysts

Dentigerous cysts have been described in ruminants, particularly sheep.[14,31] These are odontogenic cysts of unknown cause that manifest as localized, bony swellings. Radiographs demonstrate the cystic nature of the swelling and reveal one or more teeth in the cyst.[14,31] For valuable individuals, treatment is surgical.

32.103.4 Developmental Anomalies and Retention of Deciduous Teeth

Developmental anomalies have been reported in cattle.[5] Occasionally tooth buds fail to develop, and the fourth pair of permanent incisors is the set most often absent. The first mandibular premolar on one or both sides also occasionally fails to form. The permanent incisor teeth have been observed to be rotated up to 180 degrees in the alveolus. Rotation of the first permanent mandibular premolar also has been seen; the rotation was 90 degrees, and no cause could be detected. Retention of a deciduous premolar is common in 12- to 18-month-old cattle.

This results in difficulty in masticating and excessive salivation. Treatment consists of removing the deciduous premolar with forceps.

32.103.5 Overgrown or Loose Molar Teeth

Overgrown molar teeth are found most commonly in old ruminants. The opposite tooth often is missing. Food accumulates between the affected tooth and the cheek, causing obvious swelling of the face. Interference with mastication often is noted. The offending tooth should be rasped regularly or removed. A power tool to grind cheek teeth works well. Premolar or molar teeth can become loose in advanced cases of actinomycosis, affecting the jaw. It may be difficult to determine whether the loose tooth is a cause or a result of the bony abnormalities. One cow with maxillary lymphosarcoma and loose teeth has been reported.[32]

32.103.6 Broken Teeth

Broken incisors are not common because of the loose alveolar attachment of these teeth. Broken premolars and molars are more common because these teeth are more solidly attached in their alveoli; breakage usually results from attempts to masticate hard objects. Most fractures usually involve only a portion of the tooth, do not involve the root, and are asymptomatic. A sagittal tooth fracture that includes the root causes pain and may result in reduced feed intake and loss of condition. Treatment is described later, in the section Tooth Root Abscess.

32.103.7 Dental Caries

Dental caries, or decay, creates areas of decalcification of the tooth.[3] Dental caries is rare in ruminants,[3] but it sometimes can be found in both temporary and permanent teeth and in both dentin and enamel.[5] Interference with prehension usually is not seen. On oral examination an orange or black pigment is seen in the defective enamel or exposed dentin; these areas should be probed with a fine dental pick or needle. Caries may be filled or the tooth extracted. In rare cases the caries can reach down the pulp cavity to the root apex, causing periodontal abscesses. (See Tooth Root Abscess, later.)

32.103.8 Osteodystrophia Fibrosa

Osteodystrophia fibrosa is caused by resorption of calcium from bone and its replacement with connective tissue.[33] It is seen most commonly in the goat. Osteodystrophia fibrosa can result from calcium, phosphorus, or vitamin D deficiency or from hyperparathyroidism. The affected individual usually is a growing animal with a bilateral, soft, painless swelling of the maxilla or mandible or both.[33] The diagnosis is based on radiographic evidence of poorly mineralized bone and inward rotation of the premolar and molar teeth. Treatment consists of supplementing the ration with adequate mineral levels while maintaining a ratio of calcium to phosphorus of 2:1.

32.103.9 Tooth Root Abscess

Dental repulsion is done preferably using general anesthesia with the affected tooth uppermost. A straight incision is made directly over the longitudinal axis of the tooth, or a trephine hole over the base of the root can be made. Only the bone lateral to the tooth is removed. If necessary, a chisel is used to free the tooth of bone at its rostral and caudal surface, taking care not to disturb the neighboring teeth. A dental punch is placed on the tooth root, and dental repulsion is performed. The ventral aspect of the incision can be left open for drainage, or

the alveolus can be packed with dental wax, gauze, or dental material, such as Optisil. Abscessed maxillary cheek teeth often cause maxillary sinusitis. The sinus must be curetted at the time of surgery and flushed daily for 1 to 2 weeks after surgery. The alveolus must be packed until granulation tissue fills the hole. Antibiotics are administered for 1 week according to culture and antimicrobial sensitivity results. After removal of the affected tooth, the abscess and clinical signs usually resolve, but chronic sinusitis may require a bone flap and extensive curettage.

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32.104 SALIVARY GLAND DISEASES

Guy St. Jean

The parotid, mandibular, and sublingual glands are the three largest salivary glands in ruminants.[34] In cattle the mandibular gland is larger than the parotid gland. The adult bovine produces 50 L or more of saliva in 24 hours. Saliva is secreted continuously, but the rate of secretion is increased by feeding, rumination, and the presence of coarse feed in the rumen.[34] The saliva provides a fluid medium for transport of ingesta during deglutition and regurgitation. It also maintains adequate phosphate for bacterial digestion of cellulose in the rumen and contains bicarbonate, which acts as a buffer to maintain ruminal pH above 5.5. Ruminant saliva contains approximately 80 mEq of bicarbonate per liter.

32.104.1 Excessive Salivation

Excessive salivation (ptyalism) is a sign of many pathologic conditions. The volume of saliva may be normal, but if it is not being swallowed, salivation can appear excessive. Gloves should be worn to examine the mouth of any animal that is salivating excessively as a precaution against exposure to rabies. Excessive salivation may be seen with dental disease, stomatitis, foreign objects in the mouth or pharynx, or esophageal obstruction. It also has been seen with ruminal disorders, in cows that have eaten spoiled silage, and with impaction of the abomasum. Ptyalism may be a clinical sign in rabies, pseudorabies, meningoencephalitis, and slaframine toxicity.[34,35] Mercury, iodine, lead, copper, and arsenic also can stimulate secretion by the salivary glands. Treatment depends on the underlying causes.

32.104.2 Sialocele

A sialocele develops when saliva escapes from a duct or salivary gland and enters the surrounding tissue. The saliva contains enzymes that irritate the tissue. The accumulation of saliva is surrounded by inflamed tissue, which gives the lesion a cystic appearance. A soft, fluctuant swelling usually is seen. Signs of pain may be observed during mastication. Trauma or foreign body usually is the cause of a sialocele. The diagnosis is based on the history, palpation, paracentesis, and sialography. Needle aspiration may yield mucoid saliva. Two treatments have been described.[36,37] The first involves removal of both the mandibular and sublingual glands and ducts.[36] Surgical extirpation of the mandibular salivary gland in the caudal area of the mandibular spaces has been performed successfully in cows, sheep, goats, and buffaloes.[34] Exposure of the tissue by opening the capsule of the gland facilitates the process of extirpation and prevents trauma of the surrounding nerves and blood vessels.[36] In the second treatment option the sialocele is opened, drained, and chemically debrided using copper sulfate.[37]

32.104.3 Parotid Gland Carcinomas

Three cows at slaughter had parotid gland carcinomas.[38] The neoplastic cells appeared to originate from ductal and acinar epithelium.[38] Ocular squamous cell carcinoma may spread locally to the parotid or mandibular lymph nodes.[39]

32.104.4 Sialoadenitis

Inflammation of the salivary glands usually is caused by nonspecific infections, penetrating wounds, or plant awns. Diffuse swelling of the salivary glands may be observed, and the swelling may be hot and painful on palpation. Abscess formation is a common complication. Treatment consists of systemic antibiotics and antiinflammatory and analgesic drugs. Abscesses should be drained when they localize. Salivary fistulas can be sequelae to salivary abscesses.

32.105 ACTINOBACILLOSIS (WOODY TONGUE, WOODEN TONGUE)

Bradford P. Smith

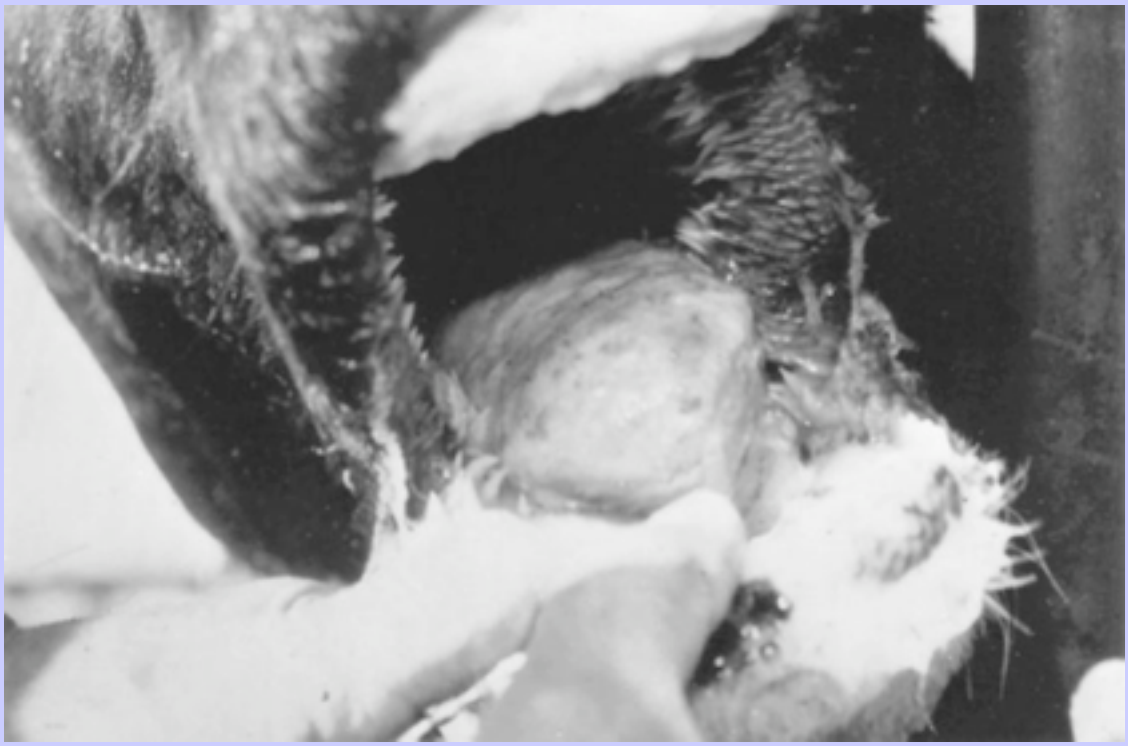
32.105.1 Definition and Etiology

Actinobacillus lignieresii, a gram-negative rod, is a normal inhabitant of the rumen and mouth of many cattle and sheep and probably goats. When the organism enters the soft tissues through a lesion, actinobacillosis results in a granulomatous abscessation. Ruminants of all ages can be affected, and the disease appears to have a worldwide distribution. The classic site of infection is the bovine tongue; because the condition causes a very hard, diffuse nodular swelling, it has been given the name “woody tongue” or “wooden tongue.” The prevalence of woody tongue in bovines at slaughter is 0.7% to 3.6%.[40] Atypical actinobacillosis lesions of cattle can occur in the lips, nose, or lymph nodes of the head or neck or at other sites.[41–43] Although the lesions normally occur sporadically, herd outbreaks with up to 73% morbidity have been reported.[44,45] Sheep are most commonly affected by hard swellings of the lips, often with fistulous tracts.[46] Actinobacillosis has also been reported to cause tongue lesions in sheep[46,47] and horses.[48] These lesions appear to be rare in goats.

32.105.2 Clinical Signs and Differential Diagnosis

Actinobacillosis lesions usually involve soft tissues. When the tongue is affected, the major clinical signs are inability to prehend food normally, excessive salivation, and sometimes a visibly enlarged tongue that protrudes from the mouth. The submandibular area often is enlarged and firm. On palpation the tongue is firm to very hard, painful, and nodular (Fig. 32-62). Nodular lesions often are slightly ulcerated. The base of the tongue is most frequently affected, but the shaft may also be involved. An ulceration filled with plant awns or stems often is seen in the sulcus lingualis at the junction of the base and shaft of the tongue. Because cattle use the tongue to prehend food, anorexia results when the tongue is painful and inflexible. Actinobacillosis must be differentiated from dental disease, oral foreign bodies, pharyngeal trauma, and other diseases that cause oral pain.

Fig. 32-62 Firm, enlarged bovine tongue typical of woody tongue caused by *Actinobacillus lignieresii*. Partly ulcerated areas of mucosa overlie hard nodules.



Atypical lesions in cattle involve sites other than the tongue. Lymph nodes of the head and cranial cervical area are most frequently affected, but where any abrasion is present, granulomas or abscesses may develop, followed by licking or contact with pus draining from a lesion on another animal. Because plant awns and stems create entry sites for the organism in the mouth, most lesions are in the head. Granulomas in the nose and eyelids and needle puncture wounds over the left jugular vein have been reported.[41] These granulomas may be confused with tumors, polyps, or cysts. Granulomas have been reported in the esophagus, pharynx, palate, flank,[42] internal iliac lymph nodes,[43] and testes[43]; multiple subcutaneous lesions with regional lymph node involvement also have been reported.[45] Three cases involving cutaneous lesions of the facial tissues were described as extensive swollen plaques under alopecic areas.[49] Most granulomatous abscesses in a herd outbreak of actinobacillosis involved the tongue, muzzle, and lips and the submandibular, parotid, and cranial cervical areas.[44] Generalized involvement or granuloma formation in internal organs may also occur.

Lesions in sheep typically involve the lips and face or parotid and submaxillary regions.[47] The nasal cavity and internal organs occasionally may be involved. Soft tissues of the head may be infected through fight wounds.[47] Lesions of the lips must be differentiated from those of contagious ecthyma (CE), and granulomatous abscesses in other sites must be differentiated from caseous lymphadenitis lesions. Lesions of the tongue of sheep,

essentially identical to those found in cattle, have been reported as a cause of green staining of the lips and "cud-dropping" in sheep.[46]

32.105.3 Clinical Pathology

Diagnosis of actinobacillosis requires biopsy and culture of the lesion. The pus usually is not malodorous. Pus crushed between two glass slides shows "sulfur granules," "clublike rosettes," or "club colonies." Similar colonies may be found in actinomycosis and some staphylococcal infections.[47] *A. lignieresii* are small, gram-negative rods. Definitive diagnosis relies on culture. No reliable serologic test is available for actinobacillosis, and the hematologic and clinical chemical findings may be normal or typical of a response to chronic infection.

32.105.4 Pathophysiology

A. lignieresii is a normal inhabitant of the mouth of ruminants and can be found in many plant awns. When mucosal lesions occur as a result of plant awns (e.g., foxtails), thistles, or particularly stemmy coarse feed, actinobacillosis may occur. Cattle often have a small ulcer in the sulcus lingualis at the junction of the base and shaft of the tongue. Plant fibers are sometimes found in the granulomatous lesions of actinobacillosis.[44] Once inoculated into tissues the organism may cause a local lesion, lesions in draining lymph nodes, or both. Lesions elsewhere on the body may be contaminated by saliva or by pus from other draining lesions or directly by plant awns on which *A. lignieresii* resides.

32.105.5 Epidemiology

Most cases of actinobacillosis are sporadic. Herd outbreaks may be associated with abrasive feedstuffs and crowded conditions in which the organism is spread rapidly to wounds on other animals by way of saliva. In one herd outbreak, 73% of a group of heifers (4 to 24 months of age) were affected 1 month after feeding of a coarse, stemmy haylage had begun.[44] Atypical lesions often are associated with a previous wound at the site, such as a nose lead wound,[41] multiple needle punctures,[41] or a head butting wound.[47] Outbreaks of actinobacillosis in wounds of the head, neck, body, and limbs have been reported.[49,50]

32.105.6 Necropsy and Biopsy Findings

Actinobacillosis lesions typically are firm, pale, gritty, granulomatous abscesses. Grossly they are similar to exuberant granulation tissue and connective tissue, often appearing to have a yellowish granular (1 to 3 mm) surface. Masses contain multifocal necrotic foci, often filled with nonodorous, thick, yellow-white pus. Histologically the lesion is a granulomatous abscess.[41] An outer capsular region of connective and granulation tissue surrounds an area of leukocytes and rosettes ("club colonies"). Mononuclear cells, plasma cells, and eosinophils predominate. Many neutrophils are seen at the center of the lesion. Multinucleated giant cells or plant fibers, or both, may be seen.

32.105.7 Treatment and Prognosis

Treatment usually is successful, and the condition has an excellent prognosis when only the tongue is involved. The prognosis may be only slightly less optimistic when internal organs and atypical sites are involved. Sodium iodide (70 mg/kg given IV as a 10% to 20% solution) is the treatment of choice. Intravenous treatment is given

once and repeated at least one more time at a 7- to 10-day interval. In refractory cases intravenous therapy may be repeated more often (2- to 3-day intervals). In severe cases daily organic iodides can be administered orally at a rate of 60 mg/kg/day[41] in addition to the intravenous iodide. If signs of iodinism develop (excessive tearing, coughing, inappetence, diarrhea, and/or dandruff), iodine administration should be halted; the adverse signs normally disappear shortly thereafter.

The onset of therapeutic benefit of sodium iodide is remarkably rapid. Within 48 hours after treatment, the tongue is flexible enough to allow the animal to eat. Although the mode by which iodides exert their beneficial therapeutic effect in actinobacillosis is not well understood, it seems most likely that they exert some antiinflammatory effect on the granulomatous inflammation. Iodides have little in vitro bacteriostatic or bactericidal effect at the concentrations given,[51] yet the onset of action is very rapid. They probably act in some way other than by direct antimicrobial effect. The old belief that iodides cause abortion at the recommended dose has been cast into doubt by my clinical experience and by reports of others,[52] who gave one and one-half to two times the recommended intravenous dose without inducing abortion. Nevertheless, there are anecdotal reports of the association, and when products are labeled with a contraindication for use in pregnant cattle, due caution should be exercised. Iodides should be given slowly and with caution to horses because of the possibility of severe generalized adverse reactions to intravenous sodium iodide.

Most strains of *A. lignieresii* are sensitive in vitro to a number of antimicrobial drugs, including ceftiofur, ampicillin, penicillin, florfenicol, sulfas, aminoglycosides, and tetracyclines. Each isolate should be tested for antimicrobial sensitivity. Therapy with an antimicrobial drug to which the isolate is sensitive is recommended in severe, generalized, or refractory cases of actinobacillosis. Therapy should also include iodides.

Surgical debulking of lesions, particularly if they interfere with airflow, is also possible for atypical cases in which a large granulomatous mass is present and the mass has proved refractory to medical therapy. Hemostasis may be a problem after surgical debulking. 783 784

32.105.8 Prevention and Control

Prevention relies mainly on avoidance of coarse, stemmy, scabrous feeds and pastures full of hard, penetrating plant awns (e.g., foxtails) or thistles. If an outbreak occurs, immediate change to a softer feed is advised, and affected animals should be treated individually. Rapid resolution of the outbreak can be expected once these steps have been taken. If atypical lesions occur, a cause of skin wounds in the area should be sought and resolved.

32.106 ACTINOMYCOSIS (LUMPY JAW)

Bradford P. Smith

32.106.1 Definition and Etiology

Actinomycosis is caused by *Actinomyces bovis*, a gram-positive, nonencapsulated, branching, filamentous bacterium that is a normal inhabitant of the ruminant mouth. The disease occurs mainly in cattle but on rare occasions may affect sheep or goats. It enters the tissues and bone through oral abrasions, openings, and punctures associated with dental or gingival disease, hard plant awns (e.g., foxtails), thorns, stickers, or dry, coarse, stemmy feeds. Lesions may begin as cavities (caries) in the dentin or dental pulp.[53] Lesions are sporadic and occur mainly in the mandible[54–56] and less commonly in the maxilla. The preponderance of mandibular

lesions, with the development of periosteal new bone and fibrosis, gives the disease its common name of "lumpy jaw." Lesions occasionally occur in soft tissues of the head, esophagus, forestomachs, and trachea.[57–60] Occasionally *A. bovis* may cause granulomatous abscesses in other soft tissues. Most of the early reports of esophageal groove and forestomach involvement incriminate actinobacillosis rather than actinomycosis.[61]

Osteomyelitis of the mandible in a horse associated with nocardiosis has been reported,[61] but no cases of mandibular actinomycosis in horses have been reported.

32.106.2 Clinical Signs and Differential Diagnosis

Bovine actinomycosis typically causes a hard, immovable, painless, bony mass on the mandible (Fig. 32-63). The lesion is most common on the horizontal ramus. Initially it is nondraining (has no fistulous tracts), but it may develop fistulous tracts and involve tooth roots as the condition progresses. When teeth become involved, evidence of pain when chewing may be seen, and weight loss may result. A careful examination of the mouth is required to detect loose teeth, plant awns, or severe gingivitis and to rule out a pathologic fracture. If a fistula is present, it is useful to flush the tract with organic iodine and perform contrast radiographs to determine if it communicates with the mouth. The differential diagnosis includes tooth root abscess, fracture, tumors, and osteomyelitis caused by other organisms. A mandibular swelling that continues to enlarge despite therapy should be radiographed for evidence of a fracture or sequestrum. Atypical actinomycosis with lesions in soft tissue causes a variety of clinical signs, depending on the location.

32.106.3 Clinical Pathology and Diagnosis

Hematologic and clinical chemistry findings may be normal or may reflect a chronic infection. Radiographs of the lesion are helpful in determining if there is dental involvement or a pathologic fracture. The radiographic lesion consists of multiple central radiolucent areas of osteomyelitis surrounded by periosteal new bone and fibrous tissue. If a fistulous tract is present, a contrast study done while flushing into the tract may help determine the extent of the fistula. Before flushing, material from the core of the lesion should be aspirated or biopsied. A Gram stain and culture of pus should be performed. The organism is gram-positive, filamentous, and branching. "Sulfur granules" similar to those described for actinobacillosis may be seen. Many authors report that they were unsuccessful at culturing the organism.

Fig. 32-63 Hard swelling on the distal mandible of a cow, typical of lumpy jaw caused by *Actinomyces bovis*. Loss of teeth and bone destruction, along with fibrosis and callus formation, are seen in this advanced case. The oral mucosa is secondarily ulcerated by trauma.

32.106.4 Pathophysiology and Epidemiology

A. bovis appears to enter the bone through mucous membrane punctures caused by foreign bodies, plant awns, or coarse, stemmy feeds or through a diseased tooth or areas of gingivitis that allow oral bacteria access to the bone. Cases usually are sporadic.

32.106.5 Necropsy and Biopsy Findings

Actinomycosis causes a granulomatous abscess.[59] Scattered through the mass of tissue are basophilic clumps of bacteria surrounded by eosinophilic clublike projections. The bacteria are long, filamentous, branching rods. Surrounding them is cellular reaction composed of neutrophils, epithelioid cells, macrophages, and occasional multinucleated giant cells. In the outer fibrous tissue are plasma cells.

32.106.6 Treatment and Prognosis

Treatment of actinomycotic bone lesions usually results in arrest of the lesion, but seldom does the size of the hard mass regress significantly. The prognosis for arrest of the lesion with vigorous treatment is good. If the mass does not have any fistulous tracts and no affected teeth are loose, medical therapy alone may be sufficient. If the mass has fistulous tracts, it should also be vigorously curetted and flushed with povidone-iodine or other organic iodine. The lesion has a rich blood supply, and curettage can result in severe hemorrhage. If the cavity is large, it may be necessary to flush and pack with iodine-soaked gauze daily for several days, then less frequently as healing progresses. One paper reports on the successful treatment of three cases of actinomycosis by using repeat treatments consisting of curettage followed by cryotherapy with liquid nitrogen poured into the lesion. The authors repeated the treatment on day 2, day 9, and day 16.[62] If there is an open fistula into the mouth (as judged by vigorous flushing) or if teeth are involved, the affected tooth or teeth should be carefully removed or repaired endodontically.[53] Care must be taken to prevent mandibular fracture, and the animal must be sedated or anesthetized to allow for proper intraoral manipulation. The empty alveolus should be carefully packed with gauze or a dental acrylic to which a wire or umbilical tape is attached and pulled through the fistula. The wire is tied externally to a small gauze roll to keep the alveolar packing firmly in place. The wire should be untied daily and the tract flushed thoroughly with povidone-iodine until the wound is completely granulated. Once granulation begins, it may not be necessary to check and flush the lesion more than once a week. The alveolus will take several weeks to close, pushing the gauze or acrylic out as it does so.

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Medical treatment of actinomycosis involves the use of sodium iodide, isoniazid, and penicillin or another antimicrobial drug to which the organism is sensitive. Sodium iodide is given IV at a dose of 70 mg/kg as a 10% to 20% solution. It can be given every 7 to 10 days or more often until signs of iodinism occur (i.e., lacrimation, cough, inappetence, diarrhea, and dandruff). If repeated intravenous treatments are difficult, oral organic iodides can be given at the rate of 60 mg/kg/day for 3 weeks. As with actinobacillosis, the beneficial therapeutic effects of iodides appear to lie in their ability to reduce granulomatous inflammation rather than in direct antimicrobial effects.[63] Iodides do not appear to cause abortion and can be safely given to pregnant cows,[64] although care should be used because there are anecdotal reports to the contrary, and products are labeled with a contraindication for pregnant cattle.

Isoniazid (10 mg/kg/day given PO for 1 month) is effective at arresting actinomycosis of the mandible in cattle.[54] It is inexpensive and readily consumed in a small amount of grain. A prolonged withdrawal period before

slaughter for human consumption is required. The drug appears to be nontoxic at this dosage, but it may cause abortion and should not be used in pregnant cattle.

Penicillin (10,000 U/kg IM twice daily) or another antimicrobial drug such as florfenicol or ampicillin can be added to the treatment regimen in cases involving valuable animals or when twice-daily treatment for 7 to 14 days is possible. Streptomycin was found effective in one study,[56] but because of the prolonged persistence of tissue residues, aminoglycosides generally are considered unacceptable in food animals.

32.106.7 Prevention and Control

A. bovis is a normal mouth inhabitant of ruminants; therefore the only possible means of prevention is to avoid feeding coarse, stemmy feeds, feeds with hard, penetrating plant awns, or feeds with other sharp materials. The recommendations in this regard are similar to those for actinobacillosis.

32.107 PHARYNGEAL TRAUMA AND ABSCESS

Bradford P. Smith

32.107.1 Definition and Etiology

Pharyngeal trauma occurs relatively frequently in cattle, resulting in cellulitis,[65] abscessation,[65] or hematoma formation.[66] One case resulted in megaesophagus.[67] Pharyngeal trauma is almost always associated with use of a balling gun,[65,68] long dose syringe, speculum, paste wormer gun, rigid probe of calf esophageal feeder, or rigid stomach tube.[65] Occasionally a foreign body such as a sharp stick or wire can perforate the pharynx. Hematomas may result from unidentified blunt trauma.[66] The puncture or laceration may be very small and usually is located in the area near the origin of the esophagus. The result is that feed and saliva enter the retropharyngeal area, and eventually inflammation develops (also see Chapter 31, Retropharyngeal Abscess).

32.107.2 Clinical Signs and Differential Diagnosis

The clinical signs include anorexia, drooling of saliva, malodorous breath, extended head and neck, localized or diffuse pharyngeal pain, feed coming from the external nares, and forestomach stasis or bloat.[65] Severe cases may involve obvious pharyngeal swelling, fever, easily elicited cough on laryngeal palpation, dyspnea, and aspiration pneumonia. Intraluminal submucosal pharyngeal abscesses with similar clinical signs have been reported.[69] Differential diagnosis in cattle must include retropharyngeal abscesses (also see Chapter 31, Retropharyngeal Abscess), pharyngeal foreign body, actinobacillosis, and lymphosarcoma or other tumor that involves the pharyngeal lymph nodes.

If megaesophagus occurs, it must be differentiated from diaphragmatic hernia with herniation of the reticulum into the thorax; other outflow obstructions involving the reticulum can result in frequent regurgitation and vomiting, as can a number of other diseases, including esophageal foreign body and esophageal diverticulum. Several toxins also cause vomiting (see Chapter 7). Rabies is easily differentiated, because the only clinical signs common to both are anorexia and salivation. Careful digital palpation of the pharynx often is diagnostic, although restraint is difficult because the area is painful and swollen, causing dyspnea and struggling. A well-lubricated stomach tube should be gently passed to relieve bloat and ascertain that no esophageal obstruction is

present. Pharyngeal trauma is rare in sheep and goats, and retropharyngeal abscesses caused by *Corynebacterium pseudotuberculosis* (caseous lymphadenitis) are the most common cause of pharyngeal swelling.

32.107.3 Clinical Pathology and Laboratory Aids

Endoscopy and radiography may be of great help in diagnosing the site of the lesion, the extent of cellulitis, and the presence of a foreign body. Endoscopy reveals a swollen, collapsed pharyngeal air space. The wound may be visible, and it may have exudate at its origin. Endoscopy can help rule out intraluminal masses and foreign bodies. Retropharyngeal cellulitis, abscess, or hematoma often can be visualized radiographically, and radiopaque foreign bodies can be seen (Fig. 32-64). Gas in the soft tissues or a discrete mass can be seen with cellulitis and abscess, respectively. Gas often can be seen in the lumen of the esophagus as well. Radiographs of the lung may be helpful if aspiration pneumonia is suspected. The results of hematologic analysis may reflect an infectious inflammatory process.

32.107.4 Pathophysiology

Inflammation, swelling, and necrosis in the retropharyngeal tissues interfere with normal swallowing by causing pain when swallowing is attempted, physical interference with passage of a bolus, and neurologic involvement. The resultant dysphagia may predispose the animal to inhalation of feed and saliva.

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If the retropharyngeal inflammation affects the pharyngeal branch of the vagus nerve on the dorsolateral surface of the pharynx, the esophageal and pharyngeal phases of swallowing and eructation are disturbed.[65,70] The resultant pharyngeal paresis may lead to reflux of feed through the nares. Involvement of the adjacent cranial laryngeal nerve makes the laryngeal mucosa less sensitive to foreign material and thus diminishes the cough reflex.[65] Severe inflammation may involve the vagus nerve itself and cause forestomach stasis with bloat and laryngeal motor dysfunction.[65,71] Eructation also involves pharyngeal muscular activity, and the maneuver is likely to be quite painful when cellulitis is present in the area.

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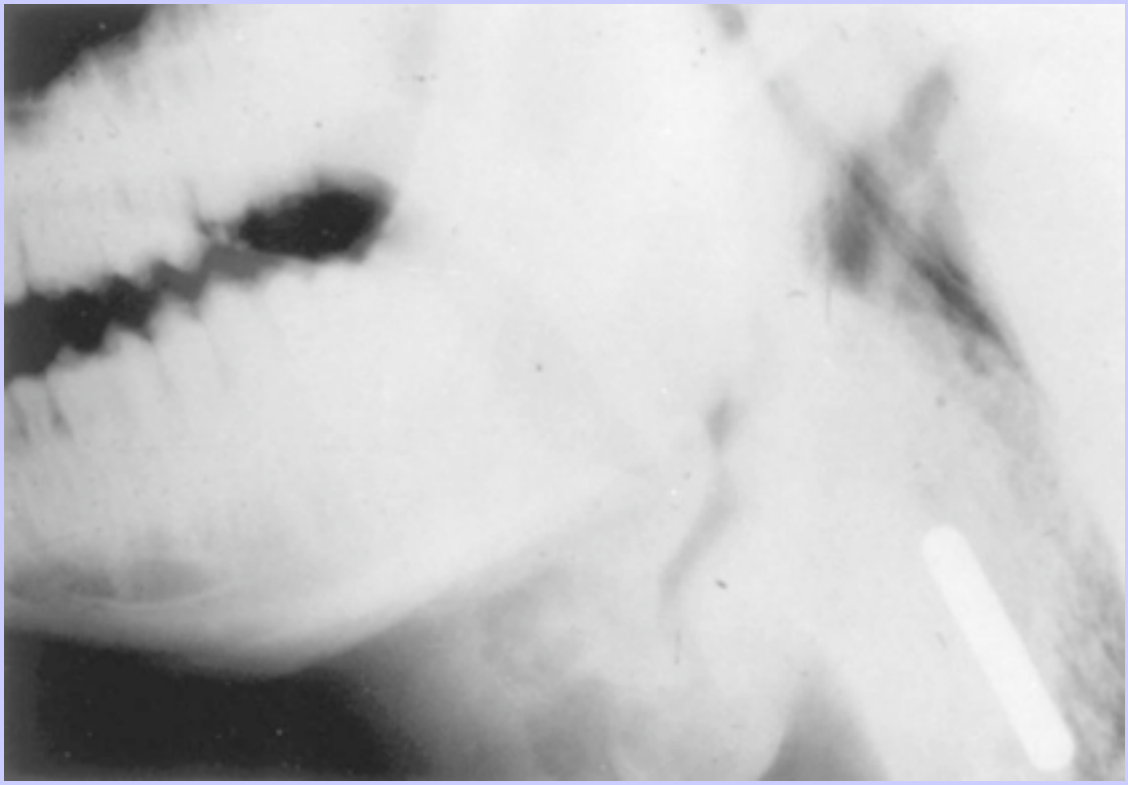
Fig. 32-64 Pharyngeal trauma in a 2-year-old bull caused by a magnet that was given forcefully with a balling gun 24 hours previously. The magnet is visible in the retropharyngeal tissues surrounded by cellulitis, with swelling and gas in the tissues. The area is swollen and painful.



32.107.5 Treatment and Prognosis

In spite of the fact that affected animals often are completely anorectic and febrile and look very ill, most cases of pharyngeal puncture or laceration resolve successfully if the animal can be vigorously treated with broad-spectrum antimicrobial drugs for 7 to 14 days, if aspiration pneumonia can be controlled by limiting access to feed, and if adequate supportive care can be given. Tetracyclines, sulfas, ampicillin, ceftiofur, TMS, and florfenicol or penicillin plus an aminoglycoside have been used successfully. NSAIDs should be given for analgesia and for their ability to reduce inflammation. Oral administration of boluses should be avoided.

The animal should have access to water; if it cannot drink, a soft stomach tube should be used several times daily to gently administer a total of 30 to 50 L (8 to 13 gallons) of water plus electrolytes daily. The most important electrolyte to administer is potassium: 60 to 100 g of potassium chloride should be given daily with the water. Once the animal can drink without coughing or nasal reflux, soft green grass or a soft mash should be offered. If this is well tolerated, it should be continued for 2 weeks, after which green pasture or soft, green, leafy alfalfa hay or other equally palatable feed should be gradually and carefully introduced into the diet.

If a discrete retropharyngeal abscess forms, it is best first to attempt drainage into the pharynx through the original laceration by pushing a finger into the healing wound until pus escapes. If this fails, a surgical approach to the area may be necessary. Surgery is rarely required in cases of pharyngeal trauma or laceration with cellulitis.

32.107.6 Prevention and Control

Careful use of balling guns, paste wormer guns, and other equipment that can damage the pharynx is the best prevention. Adequate restraint of the head of any animal that is to be orally treated also helps prevent pharyngeal trauma.

32.108 BLUETONGUE

Paul G.E. Michelsen

Bradford P. Smith

32.108.1 Definition and Etiology

Bluetongue is an arthropod-borne noncontagious viral disease of domestic and wild ruminants with complex interactions with the host, the host's immune system, the vector or vectors, other similar viruses, and the biopolitical environment. Clinical disease is largely restricted to sheep, but other ruminants may show disease in some circumstances. Cattle and other ruminants are considered amplifying reservoir hosts.[72] Epizootics of bluetongue disease such as one on the Iberian peninsula in 1956 that killed 179,000 sheep in 4 months led to the idea of bluetongue as an emerging exotic disease that threatened livestock industries. Since 1999 there have been reports of bluetongue from Greece, Italy, France, Spain, Portugal, Turkey, and the Balkans.[73] It occurs in the United States, South Africa, and parts of Asia. Bluetongue virus (BTV) has now been isolated from ruminants and insect vectors from all continents except Antarctica, yet the international movement of ruminants is often severely restricted for fear of importing BTV.[72] Epidemic disease outbreaks, the wide host range, the potential for establishment of endemic disease, and the similarity of some signs of bluetongue to those of vesicular diseases have made bluetongue infection the subject of intense regulatory interest worldwide. Import regulations promulgated in reaction to the disease have been more of a threat than the disease itself to the livestock industries of some countries.[74]

BTV is the prototypic orbivirus, a genus (or subfamily) within the family Reoviridae. It is inactivated by iodophores and phenols but stable in the presence of protein. Other viruses in the genus, some of which cross-react serologically with BTV, include Palyam virus, the epizootic hemorrhagic disease of deer virus and the agent of African horse sickness. The virus has a segmented genome of 10 double-stranded RNA pieces, each of which codes for one or two polypeptides. The genome of BTV was recently determined down to atomic resolution using crystallography, the largest molecule known in such detail to date.[75] The serologic classification is based on the protein product of one or two genomic segments, but virulence and other characteristics may not be related to this protein, and genetic reassortment of the pieces occurs in infections of cells with more than one serotype.[76] BTV reproduces in both arthropod and mammalian hosts and must evolve quickly to maintain itself in these imperfectly overlapping realms. Reassortment of the segmented genome contributes to the prodigious genetic diversity and rapid evolution of BTV.[77]

Strains of the virus with the same serotype may have markedly different virulence.[78,79] The discovery of BTV in Australia in 1975 originally was a cause of great concern, because the continent had been thought to be free of the virus. Subsequent investigation showed the presence of antibody in stored sera, and the Australian strains of serotypes that are pathogenic elsewhere proved to have almost no pathogenic capability. Twenty-five serotypes are recognized worldwide, five (2, 10, 11, 13, and 17) in the United States. Recently BTV-1 was isolated from an ill white-tailed deer fawn in Louisiana.[80]

32.108.2 Clinical Signs and Differential Diagnosis

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Clinical bluetongue disease is manifested in two ways: reproductive syndromes and bluetongue per se, a vasculitic disease of several organ systems. Cattle and goats rarely manifest clinical disease; infected sheep commonly do.

In sheep the first clinical signs appear after an incubation period of 3 to 20 days. These signs include a transient fever (up to 41.1° C [106° F] or higher); edema of the face, lips, muzzle, and ears; excessive salivation; and hyperemia of the oral mucosa. Affected sheep usually produce a profuse serous nasal discharge that becomes mucopurulent after a few days, leaving crusts around the nostrils and muzzle. The tongue may be cyanotic (hence the name), but this is an infrequent sign. The oral lesions progress to petechial hemorrhages, erosions, and ulcers, which are especially prominent on the dental pad and the commissures of the mouth. Pulmonary edema is often marked, and some cases appear to owners to be pneumonia. Secondary bacterial bronchopneumonia frequently complicates bluetongue. Lameness and stiffness caused by coronitis and myopathy are later signs, occurring 7 to 12 days after exposure, and the coronary band shows petechial hemorrhages and hyperemia. Cardiac myopathy may result in sudden death at any time, even in an animal that appears to be recovering. Lameness may progress to “knee walking” or recumbency. The hooves may slough, and breaks in the wool are common. Diarrhea, with or without blood, is frequently seen. Many sheep become depressed, are unable to rise, and die, but some severely affected sheep make a full recovery. The differential diagnosis for sheep showing some of these signs includes sore mouth (CE), foot-and-mouth disease (FMD), peste des petits ruminants (PPR), and sheeppox.

The reproductive and teratogenic effects of BTV in sheep and cattle appear to vary greatly depending on the strain, the host, and the ecologic factors. Reproductive effects, including abortions, stillbirths, and weak, live “dummy lamb” births, were prominent when live attenuated vaccine was given to pregnant ewes in California. In South Africa, which has been recognized as bluetongue-endemic since the first descriptions of the disease before 1900, teratogenic effects have not been firmly linked to the virus despite the use of polyvalent attenuated live vaccines and near-continuous exposure to the virus.[78]

The virus has been shown to be both abortigenic and teratogenic in cattle under experimental conditions,[81] but despite evidence of high seroprevalence in cattle, abortion and teratogenesis are very uncommon under field conditions.[82] Early embryonic wastage and decreased reproductive efficiency may be more important in cattle than teratogenesis and abortion; bluetongue-seropositive cows had more services per conception, longer calving-to-conception intervals, and a greater number of total services compared with age-matched bluetongue-negative cows on the same large California dairy.[83] Experimental early gestation infections in cattle produce severe deformities that preclude live birth; later infections can cause premature delivery of low-birthweight, weak, viremic calves.[79]

Clinical disease in cattle is rare, but it can show many of the same signs as in sheep. Excessive salivation may be the first clinical sign. Hyperemia and necrosis of the muzzle ("burnt muzzle") and a patchy dermatitis may also be seen. In cattle, depending on which signs are exhibited, the differential diagnosis should include mucosal disease (BVD), malignant catarrhal fever (MCF), vesicular diseases, rinderpest (RP), photosensitization, bovine papular stomatitis (BPS), and infectious bovine rhinotracheitis. Clinical disease in cattle can be difficult to distinguish from FMD and vesicular stomatitis (VS), and appropriate regulatory officials should be notified in such outbreaks.

"White eye calf" syndrome has been described in Harney County, Oregon. The problem has a low incidence on affected ranches (0.5% to 8%). The calves are full-term stillbirths or weak, recumbent animals that rarely survive, even with good nursing care. Most affected calves have congenital cataracts, often bilaterally, which clear at 3 weeks to 3 months in the few that survive. Hydranencephaly and arthrogryposis are seen in a few calves, together with the lens opacity. The calves test negative for BTV antibody on agar gel immunodiffusion (AGID) tests, but BTV or epizootic hemorrhagic disease virus, or both, can be isolated from the spleen or bone marrow.[84] Lenticular, other ocular, and brain abnormalities may also be caused by bovine virus diarrhea (BVD) virus, and that cause should be considered in the differential diagnosis of suspected bluetongue teratogenesis in cattle.

32.108.3 Laboratory Diagnosis and Immunology

Two types of viral antigen are involved in bluetongue diagnosis by serologic testing. All BTVs have one of the types, the group antigen, which is a protein called *P7*. The other type of antigen, the P2 protein, determines the serotype (1 through 25) of the virus in question. The serum commonly is tested with complement fixation (CF), AGID, or one of several ELISAs for P7, which indicates bluetongue infection. Antibodies detected by AGID persist for years in normal animals exposed to BTV. CF tests detect shorter-lived antibodies and can be difficult to perform but are still used to determine BTV exposure status for export. The AGID test cross-reacts with related orbiviruses and can also produce a rather high number of false-negative results. The competitive ELISA (C-ELISA) has proved to be the best serologic test for detecting group antibodies to BTV.[85,86] Because of the wide pathogenic variability among BTVs (aided, no doubt, by reassortment of the segmented genome) and the fact that some other nonpathogenic orbiviruses have antigenic similarities to BTV, a positive result on the bluetongue group test does not prove that an animal's clinical disease was caused by BTV.

Virus isolation from blood obtained during the viremic, febrile stage is the most definitive means of bluetongue diagnosis. Splenic tissues or, in the case of aborted fetuses, brain tissues also can be a source of virus for isolation. Virus isolation is done by inoculation of samples into a variety of test animals and culture systems, but it is being at least partly replaced by detection of viral RNA using PCR technology. PCR-based tests for bluetongue are extremely sensitive and specific for BTV RNA and currently are being performed on clinical samples at several diagnostic laboratories. A positive PCR result is not synonymous with infection, however, because viral RNA can be detected for some time after viremia (as detected by standard virus isolation methods) has waned.[87]

Other laboratory aids to diagnosis include the presence of leukopenia during the early febrile stage of the disease and an often marked increase in serum creatinine kinase that corresponds to the latter phase of reluctance to move and stiffness.

The development of immune tolerance to BTV (in utero infection producing antibody-negative, virus-positive individuals), as happens in BVD infections, now is regarded by many as rarely if ever occurring under natural conditions,[86,88] but some controversy remains.[89]

32.108.4 Pathophysiology

BTV is capable of reproducing in a variety of mammalian cells. In clinical cases the disease appears to be a vasculitis caused by infection of vascular endothelial cells. Vasculitis results in edema and necrosis of epithelial and mucosal surfaces. In bulls the virus can cause inflammation and degeneration of the seminiferous tubules. 787
Teratogenic effects appear to be caused by general disruptions of organogenesis by viral infection of the 788
developing fetus. The development of clinical disease in cattle may require previous sensitization to the virus, operating through an IgE-mediated hypersensitivity reaction.[84] The disease in sheep also appears to be most severe when previous exposure has occurred.[90] Late-term in utero infections produce elevated fetal cortisol in calves, which could be the mechanism for the induction of premature delivery.[81]

32.108.5 Epidemiology

The development of clinical disease is the product of a complex interaction among host, strain, vector, and environmental characteristics. Bluetongue disease provides a model of host-vector-pathogen coevolution; the pathogenicity of endemic virus to endemic livestock breeds usually is low.[91] Epizootics occur when new virus, new animals, or new vectors are introduced into the stable prevailing system.

BTV infects both wild and domestic ruminants and camelids, primarily through the bite of the vector midge of the genus *Culicoides*. There are over 1400 *Culicoides* species; however, only a few have been identified as BTV-competent vectors. This midge is most prevalent in midsummer to early fall, and natural bluetongue in animals usually is limited to this time as well. The virus also can be transmitted sexually in infected semen and transplacentally from dam to offspring but apparently not through embryo transfer if the embryo is washed 10 times.[86,89] Vector transmission is by far the most important method of transmission in endemic areas. In the United States, bluetongue prevalence closely mirrors *Culicoides* prevalence, with lower rates in northern climates inhospitable to the midge and higher prevalence in California and southern regions. *Culicoides sonorensis* (formerly called *Culicoides variipennis)* is the principal vector of BTV in North America, but not all *C. sonorensis* populations are competent vectors of the virus.[92,93] In the absence of competent vector populations, animal-to-animal transmission is incapable of maintaining the endemic state. The overall seroprevalence in cattle in the United States exceeds 18%.[94]

The location of “overwintering” virus or the reservoir for infection in endemic areas is unclear. After infection the BTV virus can be isolated for over 9 weeks from ovine skin biopsies.[95] Cattle have been suspected because of the high seroprevalence in cattle and the longer course of viremia possible in some cattle compared with sheep, but a recent paper demonstrated that BTV survived for only 1 to 5 weeks after infection in cattle skin biopsy samples.[96] In the Iberian epidemic of bluetongue in 1956 that killed 179,000 sheep in 4 months and caused clinical disease in cattle, the disease failed to become established despite the presence of vectors, suggesting that cattle were not an effective reservoir in this instance. White-tailed deer showed a high BTV seroprevalence (81%) in a survey in northeastern Mexico.[97] The virus reproduces in *C. sonorensis*, and the vector may be the overwintering site in some situations. Another intriguing possibility that needs more

investigation involves the prolonged presence of viral RNA in blood as detected by PCR; the vector may be able to recover BTV infectivity from PCR-positive but virus isolation—negative blood.[98]

The severity of clinical signs varies by breed. Early in the history of the bluetongue investigation, it was noted that African Landrace breeds showed few if any signs of infection, whereas imported European breeds showed fulminant disease.[99] More recently, breed differences in immunologic response to a bluetongue vaccine have been reported.[100]

32.108.6 Necropsy Findings

No one gross or histologic lesion points with certainty toward bluetongue. Some animals that die appear surprisingly normal at necropsy. Most show unusual hemorrhage in some organ, particularly the heart. Some experts consider subendocardial hemorrhage at the base of the pulmonary artery to be pathognomonic. Petechial and ecchymotic hemorrhages are also seen under the tongue, on the hard palate, and in the esophagus, forestomachs (especially on the ruminal folds), lymph nodes, bladder, and spleen. Gross hemorrhage may be seen in skeletal muscles (often alternating with linear areas of pallor, indicating Zenker's necrosis) and in the pulmonary artery. Erosions and ulcers are seen on any surface of the oral mucosa, prominently on the dental pad and tongue, and less often in other digestive organs. Gelatinous subcutaneous edema of the head, neck, forelimbs, and trunk is commonly encountered. Pulmonary congestion and edema probably are caused by vasculitis and occur secondary to heart failure.[101] Microscopically, lesions show evidence of inflammatory cell infiltration, cellular vacuolation, blood stasis, hypertrophy of small vessel endothelial cells, and fragmentation of small vessels. Cattle, but not sheep, show eosinophilic infiltrates histologically, suggesting the role of hypersensitivity in the rare clinical cases in cattle.

32.108.7 Treatment, Prevention, and Control

Treatment is nonspecific and aimed at supportive and nursing care. Animals with severe oral lesions are reluctant to eat. Valuable animals can be fed gruels of alfalfa pellets by stomach tube and can be encouraged to eat soft feeds or green grass. Muscle and coronary band pain may limit mobility; therefore water and shade must be close at hand. Sulfas or other relatively broad-spectrum antimicrobial drugs should be administered in an attempt to prevent or treat secondary bacterial pneumonia. NSAIDs, including aspirin and flunixin, are commonly used.

Elimination of *C. sonorensis* from the environment usually is not practical, but housing sheep indoors during the peak of activity (dusk, early evening) to avoid the house-shy midge may be beneficial. Grazing wet areas such as irrigated pasture only during the heat of the day also may help. Midges that feed on ivermectin-treated cattle are killed, but the exchange of virus may be made before the insect's demise. *C. sonorensis* larvae develop in fine-grained mud with high organic matter content, such as around farm reservoirs, overflowing watering troughs, and shallow septic systems. Elimination of these breeding grounds combined with larvicidal treatments may help in some situations.

Modified live vaccines are available in some parts of the world and should be based on the local strains and serotypes. Some cross-protection between some serotypes does occur. A modified live virus containing serotypes 10, 11, and 17 is available in California from the California Woolgrowers' Association. The vaccine should be given at least 2 weeks before breeding season to avoid teratogenic effects. In the face of an outbreak, lambs and breeding rams should be vaccinated; pregnant ewes in late gestation may be vaccinated, but there is some risk of inducing abortion. Vaccinated breeding rams may have a slight risk of decreased fertility. Pregnant animals cannot be vaccinated with modified live vaccines with impunity, because the teratogenic effects may manifest.

Genetic engineering techniques may produce effective killed vaccines, perhaps as subunits, but both cellular and humoral immunity appear necessary for complete protection. The capability of the virus to reassort the genome in mixed infections makes some aspects of modified live vaccines problematic. For example, a host-adapted, low-virulence vaccine strain could gain virulence from wild-type virus and be serologically indistinguishable in its pathogenic form from the mild vaccine virus.

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32.109 CONTAGIOUS ECTHYMA (SORE MOUTH, ORF, CONTAGIOUS PUSTULAR DERMATITIS, SCABBY MOUTH)

Paul G.E. Michelsen

Bradford P. Smith

32.109.1 Definition and Etiology

CE (sore mouth, orf, contagious pustular dermatitis, scabby mouth) is a common disease of sheep and goats that is transmissible to humans and has a worldwide distribution. A good review of human lesions was published in 2005.[103] The colloquial name *sore mouth* describes the most common presentation of the disease in sheep and goats; the name orf (possibly from the old Norse term *hrufa*, meaning a crust or scab) is more commonly used for the disease in all species in England and for human disease in the United States. The agent is a DNA poxvirus of the parapoxvirus subgroup, which includes the closely related viruses pseudocowpox (the cause of orflike “milker's nodules” in humans), the agent of BPS, parapoxvirus of red deer in New Zealand, squirrel parapoxvirus, and parapoxvirus of grey seals. Biologic and genetic differences exist among strains of CE virus, but these differences are not expressed antigenically; only one serotype of orf (CE) is recognized. A study demonstrated that the sheep orf virus does not cause lesions in camels, and vice versa,[104] so it is likely that no infection is transmitted between camels and sheep or goats. Wild ruminants (reindeer, musk ox, and others) and camels are also affected.[105] The virus is epitheliotropic, usually creating proliferative lesions in the skin of the lips, nostrils, oral mucosa, teats, and occasionally the vulva.

32.109.2 Clinical Signs and Differential Diagnosis

The most common presentation is of a young animal with crusting, proliferative lesions of the mucocutaneous junctions of the mouth and nose (Fig. 32-65). Proliferative lesions may be seen on the gums (Fig. 32-66). Older immunologically naive animals may be affected, and lesions may occur at the coronary band, on the tongue, interdigitally, on the conjunctiva of the eye, on the external genitalia, or on the udder or teats, with the last site affected especially in does or ewes nursing affected kids. The disease progresses through papular, vesicular, and pustular stages, which are rarely seen, before the characteristic presentation of proliferative, coalescing, scabbed lesions appears. One recent report described the characteristic proliferative scabs on the margins of healing burn wounds.[106] Affected animals may be reluctant to nurse, eat, walk, or be nursed, depending on the location of lesions. Secondary bacterial infection or myiasis of affected parts may occur. The disease usually runs its course in 3 to 6 weeks, but chronic cases have been reported.[107] Complete healing without scarring is the norm as scabs fall off. Severe infections may result in stunting of growth. Overwhelming infection has been noted on rare occasions, with extension of lesions into the deeper respiratory or gastrointestinal tracts. Does and ewes with severe udder infection may develop mastitis from secondary bacterial infection. Sheeppox and goatpox may occasionally produce lesions similar to those of CE, but they are virulent diseases with systemic signs, including conjunctivitis, pyrexia, anorexia, and rhinitis. Animals with bluetongue may have a crusted mouth and nose and

eye lesions in the convalescent phase, but bluetongue is a disease with more evidence of oral erosive rather than proliferative lesions and systemic signs, including pyrexia, reluctance to move, lesions on the tongue, and conjunctivitis. Bluetongue has a seasonal incidence (late summer, early fall) that coincides with the activity of its insect vector. CE may be seen at any time but typically occurs in spring in the lamb or kid crop. Ulcerative dermatosis (lip and leg ulcer) is an uncommon disease caused by a virus similar to that of CE, but the lesions are crusted ulcers, to be distinguished from the crusted proliferations of CE. I have seen a series of cases of what appeared to be mild CE of long duration (several years in one individual) in a family of Nubian goats; this was confirmed by an immunofluorescence assay. Smith and co-workers reported on five sheep, 4 months to 3 years of age, that developed severe refractory distal limb lesions resembling warts. Two also had lesions on the head. The sheep were from three different flocks; one was a Hampshire and four were Suffolk. Lesions were confirmed as orf by electron microscopy and immunohistochemistry.[108] A report from Texas describes severe multifocal persistent orf lesions in 16 Boer or Boer cross-bred goat kids 2 to 5 months of age, from two different farms. Some of the kids had been vaccinated with live-virus vaccine at 1 day of age, others at 2 weeks of age. Lesions were found on lips, nose, ears, body, legs, and feet.[109]

Fig. 32-65 Typical scabby lesions of contagious ecthyma (sore mouth, orf) on the lips of a young goat. Lesions tend to be proliferative rather than ulcerative.

Fig. 32-66 Typical proliferative lesions of contagious ecthyma (sore mouth, orf) on the gums of a young sheep.

32.109.3 Laboratory Diagnosis

The diagnosis usually is made in the field by recognition of the typical lesions in a naive flock or in a naive group (young lambs or kids) in a disease-endemic flock. Definitive diagnosis usually involves identifying the distinctive cross-hatched virus particles in early lesions with electron microscopy, PCR,[110] immunohistochemistry, or inoculation into known protected or susceptible animals. Vesicular fluid or minced biopsy tissues have been used as a source of virus that is identified by fluorescent antibodies after it has been growing in embryonic ovine kidney cell cultures.[111] CF tests to detect antibodies (using patient serum) or antigen (using vesicular fluid or a suspension of scabs) have also been used.

32.109.4 Pathophysiology

The disease follows a similar time course in animals and human beings-approximately 6 weeks. Six stages have been described,[112] which begin after an incubation period of 3 to 14 days. Each stage lasts approximately 1 week.

1 *Maculopapular stage:* An erythematous spot becomes elevated. Histologically this stage shows vacuolization of cells in the upper one third of the epidermis with intracytoplasmic eosinophilic inclusions in the affected cells.

2 *Target stage:* A red halo of dilated blood vessels and inflammatory cell infiltrates surrounds a white ring of vacuolated epidermal cells with intracytoplasmic and intranuclear inclusions, which surrounds a red center of pyknotic epidermal cells.

3 *Acute stage:* The lesion is a red, weeping nodule. Microscopically there is reticular degeneration of the epidermis with vesicles. The dermis is infiltrated with macrophages and lymphocytes and is denuded of epidermis in places. The hair follicles are distended with pyknotic epidermal cells.

4 *Regenerative stage:* The nodule is now dry with small black dots (the pyknotic follicle cells, now extruded to the surface) in a thin yellow surface.

5 *Papillomatous stage:* The surface of the nodule is roughened with papillomas, which microscopically prove to be fingerlike, downward projections of epidermis through a full thickness of dermis.

6 *Regressive stage:* The lesion decreases in size and elevation above the surface, the papillomas regress, and several crusts may come off. Microscopically the papillomas and infiltrates regress, leaving normal architecture.

Orf virus encodes for a protein that is apparently homologous to mammalian vascular endothelial growth factors. This family of molecules mediates vascular permeability, angiogenesis, and endothelial cell proliferation, which may account for the swollen, proliferative nature of orf lesions.[113] Transient fever and lymphadenopathy are occasionally seen in humans. Lesions in humans that are not biopsied or excised heal without a scar.

Orf virus encodes a range of immunomodulatory genes that interfere with host antivirus immune and inflammatory effector mechanisms, allowing time for virus replication in epidermal cells.[114]

32.109.5 Epidemiology

The naturally occurring disease is primarily one of sheep, goats, and human beings, but it has also been reported in a variety of wild ruminants.[115] Experimental transmission has been achieved in cattle, rabbits, horses, and monkeys. No clinical cases in these species have been reported. All ages and classes of sheep and goats are affected, and clinically normal sheep can infect naive individuals.[116] In herds and flocks in which the disease is endemic, it usually is seen in the lamb crop and on the udders and teats of some of the nursing mothers. Animals that have had a bout of disease are solidly immune for 1 to several years, but morbidity is high (often 80%) among naive individuals. Humans are infected through contact with affected animals or fomites that have contacted affected animals (including one report of transmission by a pickup truck that had been used to haul sheep).[112] Human-to-human transmission can occur.[115] Mortality is low among animals except when young individuals are severely affected and quit nursing or have mothers with severe udder lesions. Overwhelming infections are rare, but some outbreaks are more severe than others.

The virus is quite resistant to many environmental conditions and persists from year to year on infected premises. Dried scabs allow the virus to persist for years, but wet conditions are less hospitable to it.[117] Reports of persistently infected sheep[118] point to another possible source of infection in wet climates.[117]

32.109.6 Treatment, Prevention, and Control

The infection usually is self-limiting and of minor consequence. Young individuals may need to be tube-fed if the lesions are severe enough to preclude suckling. Secondary infections, myiasis, or mastitis may be treated with topical disinfectants, antibiotics, or insecticides as appropriate.[118] The hard crusts should not be removed, because doing so may delay healing and promote scarring. Also, humans should limit contact with affected animals and should wear gloves when handling them is necessary. Anecdotal reports, each consisting of one case, have claimed good results for treatment of human orf with intralesional corticosteroids,[119] IFN,[120] idoxuridine in DMSO,[121] or diethyl ether[122] or cryotherapy.[123] An immunosuppressed human with a huge orf lesion on the finger was successfully treated with topical cidofovir antiviral cream.[124] Similar good results were obtained in a group of 12 severely affected, bottle-fed lambs with painful intraoral lesions. The proliferative tissues were debrided and cauterized with a portable diathermy unit. The exposed submucosa was then frozen twice with liquid nitrogen spray. Healing occurred by second intention, with rapid recovery of affected lambs.[125]

The infection is prevented by maintaining a virus-free herd or flock by not introducing or contacting infected individuals. Lesions often are not apparent on carriers.[116] Once established, the disease is persistent on the premises because of virus in scabs. Vaccination should be undertaken only if the infection is persistent, because the vaccine consists of virulent live virus. Vaccination can also be achieved with dried scabs from the previous year's outbreak; the scab material is rubbed into scarified skin in an inconspicuous location (inner thigh, under the tail, in the axilla). A localized inflammatory reaction at the site 1 week after vaccination indicates a successful inoculation. Infected or vaccinated animals should not contact unexposed animals (as at shows) until the lesions have healed. Lambs born to immunized ewes may not be protected by colostral antibodies even though their levels of antibody postsuckling are high,[126] pointing to the importance of cell-mediated immunity in protection from the disease. Lambs should be vaccinated at 6 to 8 weeks of age and are immune 3 weeks later.[118] Yearly vaccination of the new lamb crop and new additions to the herd should prevent devastating outbreaks on infected farms. Vaccine failures may be related to virulence of the disease-causing strain rather than to serologic differences between vaccine and field strains.[127]

32.110 BOVINE PAPULAR STOMATITIS (PROLIFERATIVE STOMATITIS)

Bradford P. Smith

BPS is a disease principally of young cattle caused by a parapoxvirus closely related to CE and pseudocowpox. There are many similarities among BPS, CE, and pseudocowpox, and they may indicate a single virus adapted to different species.[128] There are as many antigenic differences among strains of BPS as among BPS, CE, and pseudocowpox.[128] Local strains therefore are recommended for vaccination. Infection usually is asymptomatic,[129] but lesions consisting of raised papules may be noted on the muzzle, nose, oral mucosa (particularly the hard palate), or esophagus, where they are important differential diagnoses for lesions caused by VS, FMD, and BVD.[129] In young feedlot cattle, 2- to 10-mm lesions of BPS are common for the first 4 weeks after arrival.[130] Morbidity may approach 100%.[129] BPS may also occur as a chronic disease in young cattle.[131] It may be the same disease as proliferative stomatitis, muzzle disease, mycotic stomatitis, erosive stomatitis, ulcerative stomatitis, and necrotic stomatitis.

Ulcerative esophagitis caused by BPS virus in a 5-month-old, unthrifty calf was associated with a 20% morbidity rate in a group of 25 calves.[132] Outbreaks of severe disease associated with BPS with a mortality rate over 50% have been reported.[132–134] Weight loss and diarrhea accompanied by papular lesions are commonly associated with the severe syndrome. Many lesions are erosions or shallow ulcers with elevated borders,[134] whereas others are obvious raised papules. Lesions are found in the mouth, esophagus, and rumen.[134] There are no lesions on the feet. BPS is commonly seen in calves 1 to 12 months of age and is rare in adult cattle. The disease is spread by animal contact and appears to be worldwide in distribution.[134]

The first evidence of the disease is the appearance of 2- to 4-mm hyperemic foci, most commonly in the ventral margins of the nares. Similar lesions next appear in the mouth. Within 18 hours they become raised papules. Some lesions enlarge to form raised plaques over 1 cm in diameter. Lesions regress in 1 day to 3 weeks, leaving a yellow, red, or brown spot that persists for several weeks more.[129] Secondary lesions come and go, with some calves being visibly infected for 4 months.[129] Most animals have no fever or obvious clinical signs, and they continue to eat normally. Leukopenia was not seen in experimentally infected calves.[129] Secondary lesions appear to be spread through the blood; intravenous inoculation results in similar upper alimentary tract lesions.[135]

Histologic lesions consist of hydropic degeneration of the epithelial cells of the oral mucosa, hyperplasia of the papillae of the lamina propria, and eosinophilic inclusions in the cytoplasm of the degenerating epithelial cells.[134] Lesions reaching the ulcerative stage show secondary necrosis, bacterial invasion, and sloughing of epithelium.

BPS has been associated with the “rat tail” syndrome of feedlot cattle.[136] Thirty-six of 84 Texas feedlots reported the problem, with a morbidity rate of 1% to 10%. The syndrome consists of diarrhea, salivation, poor weight gain, and loss of hair from the end of the tail.[136] Sarcocystosis has also been mentioned in association with “rat tail” syndrome. BPS is capable of causing painful proliferative lesions in human beings.[137] The lesions resemble those caused by CE or pseudocowpox. Most often the affected individual has a recent history of examining the mouths of cattle, often with cuts or abrasions on the hands. Lesions in humans apparently are limited to the primary site of inoculation on the hands.

Although ovine ecthyma vaccines are commercially available, no vaccine is marketed for protection against BPS. Local strains of parapoxviruses would be most likely to be more protective than commercial vaccine strains.

32.111 DISEASES CAUSED BY BOVINE VIRUS DIARRHEA VIRUS

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32.111.1 Definition and Etiology

Disease in cattle resulting from infection with BVD virus (BVDV) is responsible for economic losses throughout the world. These economic losses are realized through decreased performance, loss of milk production, reproductive wastage, and increased rates of morbidity and mortality. More than 50 years ago an enteric disease of cattle was described in North America that was characterized by outbreaks of diarrhea and erosive lesions of

the digestive tract.[138,139] The virus was named *bovine virus diarrhea virus*. Subsequently the virus was associated with a sporadically occurring, highly fatal disease referred to as *mucosal disease*. Mucosal disease occurs only in cattle that are born persistently infected (PI) with BVDV. Persistent infection occurs as a result of in utero exposure of the fetus to BVDV at less than 125 days of gestation.[140]

BVDV is a member of the family Flaviviridae,[141] which consists of three genera: Pestivirus, Flavivirus, and Hepacivirus. BVDV is the prototypic member of the genus Pestivirus, which includes two other viruses of veterinary importance: classical swine fever virus (hog cholera virus) and border disease virus of sheep. Isolates of BVDV can be classified in vitro as cytopathic (CP) or noncytopathic (NCP); this classification is referred to as the *biotype*.[142] The NCP biotype predominates in the cattle population and is associated with persistent infection. It has been established that mucosal disease occurs when cattle born immunotolerant to and persistently infected with an NCP-BVDV become superinfected with a CP-BVDV. There also is genetic and antigenic variation among isolates of BVDV.[143] BVDV has been divided into two groups based on genotype: BVDV type 1 and BVDV type 2.[144] BVDV type 2 infections have been associated with a severe acute disease and a hemorrhagic syndrome characterized by thrombocytopenia and death.[145] BVDV genotypes can be further divided into subgenotypes (e.g., BVDV type 1a). The significant genetic and antigenic variations among BVDV isolates may be factors in achieving complete control of BVDV infections through vaccination.

The virus is unstable at low or high pH and at high temperatures. On the basis of research with the related classical swine fever virus, BVDV probably does not persist in the environment longer than 2 weeks.[146] This same work with the classical swine fever virus also suggests that BVDV is susceptible to common disinfectants such as chlorhexidine, phenols, iodophors, aldehydes, and hypochlorites.[146]

32.111.2 Epidemiology

32.111.2.1 PREVALENCE

Evidence of BVDV has been documented in many countries throughout the world. Serologic surveys have demonstrated considerable differences in the prevalence of antibody-positive cattle, ranging from 20% to 90%.[147–152] Cattle density, management practices, and vaccine use are likely to account for these differences. Several studies have shown the prevalence of persistently infected cattle to be less than 2% of the general cattle population.[153–155] In individual herds the prevalence of persistently infected cattle may be substantially higher. No significant differences have been noted between dairy and beef breeds. The prevalence of U.S. herds containing at least one persistently infected animal has been estimated to be 4% to 15%.[154,155] Economic losses attributable to BVDV are difficult to assess. Losses in individual herds have been documented and range from a few thousand to $100,000 per herd.[156,157] National-level losses are estimated to range from $10 to $40 (U.S. dollars) per calving.[157–159]

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32.111.2.2 TRANSMISSION

Cattle persistently infected with BVDV shed large amounts of virus their entire life and are the major source of BVDV transmission both within and among herds. Acutely infected cattle are also an important source of BVDV transmission, but the level of virus shed is considerably lower and the length of shedding is limited. Inhalation or ingestion of virus is the most common mode of infection. The most efficient mode of

transmission is direct contact with body fluids from persistently infected cattle.[148] Virus has been isolated from nasal swabs, aerosols, saliva, urine, feces, and uterine fluids.[160] Indirect transmission can occur through blood-feeding insects[161] or contaminated mechanical vectors such as common needles, nose tongs, and animal caretakers.[162] Horizontal transmission has also occurred with frozen semen collected from BVDV-infected bulls and inseminated into susceptible cows.[163] Vertical transmission results with transplacental infection of the fetus in cows acutely or persistently infected with BVDV. The role of other species of animals in the transmission of BVDV is unclear. Transmission of BVDV between cattle and sheep has been demonstrated.[164] In addition, BVDV has been isolated from many captive and free-living ruminants as well as pigs.[165] Recently, camelid species have been identified as being susceptible to BVDV and have emerged as a potential source of transmission to cattle.[166]

The rate of transmission of BVDV within a herd varies depending on the source of the virus. Introduction of a persistently infected animal into a herd can result in rapid dissemination of the virus among the majority of susceptible cattle in less than 6 months.[148] Conversely, if acutely infected cattle are the source of the virus, the spread of BVDV may require an extended period.[148]

Spread of BVDV between farms most commonly occurs by the acquisition of new cattle that are persistently infected or pregnant and carrying a persistently infected fetus. Cattle operations that have purchased cattle within the past 5 years are at highest risk for having persistently infected animals.[167] The purchase of new cattle incubating an acute infection is also an important source of virus introduction into a herd. Exposure to other cattle through fence line contact, communal pastures, and animal exhibitions may all be important modes of herd-to-herd transmission.

32.111.3 Clinical Disease, Differential Diagnosis, and Patho-genesis

Infection with BVDV can result in a wide assortment of clinical manifestations ranging from subclinical conditions to death. The clinical outcome after infection is complex and depends on a number of factors. Host factors that influence the clinical outcome include whether the host is immunotolerant or immunocompetent to BVDV, pregnancy status, gestational age of the fetus at the time of infection, immune status (passive or active from exposure or vaccination), and concurrent level of environmental stress at the time of infection. In addition, genetic diversity, antigenic variation, and differences in virulence among BVDV isolates may account for variations in the clinical response to infection.

32.111.4 Subclinical Bovine Virus Diarrhea Virus Infection

Most animals infected with BVDV have subclinical infections that result in mild fever, leukopenia, and the development of serum neutralizing (SN) antibodies. These infections often go undetected. Subclinical infections explain the positive serum neutralization titers to BVDV found in most unvaccinated cattle. It has been estimated that 70% to 90% of BVDV infections occur without manifestation of clinical signs.[168]

32.111.5 Acute Bovine Virus Diarrhea Virus Infection

Acute BVDV infection often is defined as clinical disease that occurs in immunocompetent cattle that are not persistently infected. Acute BVDV infection has also been referred to as “primary BVDV” or “transient BVDV” infection. This disease syndrome usually occurs in cattle 6 to 24 months of age and traditionally has been

thought of as primarily causing disease in cattle that are seronegative (i.e., passive immunity has waned but active immunity has not yet been acquired). The acute BVDV incubation period is 5 to 7 days, with clinical signs of fever, leukopenia, depression, anorexia, oculonasal discharge, oral erosions and ulcerations, diarrhea, and decreased milk production in lactating cows after infection. A rapid respiratory rate may be observed, which may be interpreted incorrectly as pneumonia. Viremia typically lasts 2 to 5 days and starts around day 3 postinfection but may last for up to 15 days. Viral shedding is in low amounts when compared with the amount of virus shed by cattle persistently infected with BVDV. This form of the disease, as it was initially described, has been traditionally referred to as *bovine virus diarrhea*.

Neonatal infection with BVDV may result in enteritis or pneumonia, occurring most often when failure of passive transfer has occurred. Passively derived humoral immunity in calves is thought to be protective unless sufficient antigenic diversity exists between the challenge strain and the strain against which the colostral immunity was developed. Viral infection in young calves without suitable or sufficient passive immunity may result in secondary disease because of the disease's immunosuppressive effects.

The differential diagnosis for acute BVDV infection for the neonatal period includes other causes of diarrhea in young calves such as rotavirus or coronavirus infection, cryptosporidiosis, *E. coli* infection, salmonellosis, and coccidiosis. Other causes of calf pneumonia such as bovine respiratory syncytial virus, pasteurellosis, hemophilosis, or mycoplasma infection should also be considered. Diarrheal diseases considered as differential diagnoses for acute BVDV infection in adults include salmonellosis, winter dysentery, Johne's disease, intestinal parasites, MCF, arsenic poisoning, and copper deficiency. Differential diagnoses for diseases that cause oral lesions in cattle include MCF, VS, papular stomatitis, foot-and-mouth disease, and bluetongue.

Acute BVDV causes disease in infected cattle by damaging the epithelial tissue of the gastrointestinal, integumentary, and respiratory systems.[169] Viral antigen has been demonstrated in the epithelium of the tongue, esophagus, intestinal crypts and villi, bronchi, and basal layer of the skin of cattle clinically affected with acute BVD or mucosal disease.[169] In infected animals the viral antigens may also be detected in the phagocytic cells of the thymus, lymph nodes, Peyer's patches, tonsils, and spleen. In vitro studies support the theory that phagocytic cells become infected.[170] These phagocytic cells probably represent the antigen-trapping cells of lymphoid structures such as the thymus, lymph nodes, Peyer's patches, tonsils, and spleen. As demonstrated by the presence of viral antigen, the first tissues to be infected are in the respiratory tract and tonsils.[169] From there, BVDV is disseminated to the epithelial surfaces and lymphoid tissue. Mononuclear phagocytic cells in the lymphoid tissue retain the virus.

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32.111.6 Severe Acute Bovine Virus Diarrhea Virus Infection

Before 1993 it was believed that most BVDV infections in immunocompetent adult cattle resulted in subclinical or mild disease as described earlier. Beginning in 1993, however, an atypical form of BVDV infection was recognized in Canada and the United States.[145,171] The disease had a peracute course, caused high morbidity, and resulted in a substantial number of deaths in all age groups. This new form of BVDV infection killed approximately 25% of veal calves in Quebec.[145] Clinical disease in the Ontario outbreaks was characterized by fever, pneumonia, and sudden death in all age groups of cattle.[171] Abortions in cattle also were a common occurrence. The severity of the disease varied among herds, with some herds experiencing 10% to 20% mortality rates. The gross lesions were similar in appearance to those of mucosal disease, which is the primary differential diagnosis (see the section on Acute Mucosal Disease later in this chapter).

Viral isolates obtained from these severe acute outbreaks were obviously of enhanced virulence. Nucleotide sequencing of the 5′ untranslated end of the RNA of these isolates followed by comparison with classic BVDV isolates revealed a distinct group, designated BVDV type 2.[144,145] Classical BVDV isolates are now referred to as BVDV type 1.

A further observation from the Ontario outbreaks was that cattle properly vaccinated with BVDV type 1 vaccines appeared to be protected from clinical disease.[171] It should be emphasized that outbreaks of severe acute BVDV infection should not always be assumed to be caused by BVDV type 2. Not all BVDV type 2 isolates cause severe disease, and it is likely that some type 1 isolates are capable of causing severe disease.

32.111.7 Hemorrhagic Syndrome

Acute BVDV infections in cattle can cause a hemorrhagic syndrome.[172] These infections are characterized by marked thrombocytopenia, bloody diarrhea, epistaxis, hemorrhages on mucosal surfaces, hyphema, bleeding from injection sites, pyrexia, leukopenia, and death.[172] Hemorrhagic syndrome appears to be associated with noncytopathic isolates of BVDV,[172] and thus far only BVDV type 2 has been associated with the syndrome.[144,145] Thrombocytopenic BVDV infections have been experimentally reproduced in calves.[173] Diseases that can mimic hemorrhagic syndrome include septicemia with subsequent development of disseminated intravascular coagulation, sweet clover poisoning, and bracken fern poisoning.

Virus-induced thrombocytopenia is the major pathogenic mechanism responsible for the BVDV-induced hemorrhagic syndrome. The mechanism by which BVDV infection induces thrombocytopenia has not been clarified. BVDV does appear to be associated with platelets; a recent study demonstrated that in addition to thrombocytopenia, platelet function is altered.[173] Also, BVDV antigen has been demonstrated in megakaryocytes that are undergoing necrosis.[173]

32.111.8 Acute Bovine Virus Diarrhea Virus Infections and Bovine Respiratory Disease

Bovine respiratory disease (BRD) is the most common cause of morbidity and mortality in North American feedlots.[174,175] (For a more complete description of BRD, see Chapter 31, Ruminant Respiratory Disease.) BVDV has been implicated in BRD complex since its first descriptions. Although this theory has been the subject of controversy, both circumstantial and experimental evidence suggests a role for BVDV in ruminant respiratory disease.[176,177] In the United States BVDV has been reported as the virus most often isolated in outbreaks of BRD. Experimentally it has been difficult to reproduce respiratory disease with BVDV alone, but synergistic effects have been documented between BVDV and *Mannheimia haemolytica*,[178] bovine herpesvirus type 1,[179] and bovine respiratory syncytial virus.[180] Recent evidence also supports a role of BVDV in the development of *Mycoplasma* species pneumonia and arthritis in feedlot cattle.[181,182] Differences in pneumopathogenicity have been reported for isolates of BVDV.[183] The results of epidemiologic studies attempting to define the role of BVDV in BRD have been equivocal. Studies have both implicated and shown no evidence of BVDV involvement in outbreaks of respiratory disease.[177] Taken together, the majority of evidence supports the theory that BVDV plays a role in BRD, and the contribution of BVDV to respiratory disease is likely from the immunosuppressive effects of BVDV infection (see next section).

32.111.9 Acute Bovine Virus Diarrhea Virus Infections and Immunosuppression

It has been well established that acute BVDV infection can result in immunosuppression.[184] The importance of BVDV-induced immunosuppression is that it increases the host's susceptibility to other pathogens and may enhance the pathogenicity of co-infecting organisms. Stress on the host at the time of BVDV infection undoubtedly adds to the viral-induced immunosuppression. As previously described, synergistic effects of BVDV infection have been demonstrated with *M. haemolytica*, bovine herpesvirus type 1, and bovine respiratory syncytial virus. BVDV infections have also been associated with concurrent salmonellosis, *E. coli* infection, BPS, and rotavirus and coronavirus infections.[176] The ability of BVDV to cause immunosuppression contributes to the broad range of clinical disease associated with this virus.

The pathogenesis of BVDV-induced immunosuppression involves several aspects of the immune system, and more mechanisms continue to be uncovered. BVDV is known to target lymphocytes and macrophages.[185] Acute BVDV infection may result in transient leukopenia with lymphoid depletion.[186] Also, a decrease in CD 4^+ and CD 8^+ T lymphocytes, as well as B lymphocytes and neutrophils, can occur.[187] In vitro studies have demonstrated different causes of immunosuppression, including decreased responsiveness of infected lymphocytes to mitogen stimulation[188]; decreased production of IFN,[189] IL-1,[190] IL-2,[191] and TNF-α[192]; and diminished chemotactic response by monocytes.[170] In addition, neutrophil-mediated, antibody-dependent, cell-mediated cytotoxicity can be impaired by BVDV.[193] Neutrophils from BVDV-infected cattle have reduced bactericidal activity.[194] It should be noted that the degree of immunosuppression and the mechanisms by which immunosuppression is induced are strain dependent.[195]

32.111.10 Reproductive Consequences of Acute Bovine Virus Diarrhea Virus Infection

Reproductive losses may be the most economically important consequence of BVDV infection. Reproductive losses associated with BVDV infection were documented in the first clinical description of BVDV.[139] Since that time it has become evident that BVDV can cause a wide array of reproductive losses that are largely dependent on the stage of gestation at which infection occurs and the virus strain (Fig. 32-67).

32.111.10.1 VENEREAL INFECTIONS

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Semen from bulls with acute infection or that are persistently infected with BVDV contains virus and may serve as a source of infection.[163] In acutely infected bulls, shedding of virus in the semen may extend beyond the period of viremia because of local replication in the genital tract. Although it occurs rarely, bulls that are immunocompetent to BVDV and that lack evidence of systemic virus persistence have been found to be persistently shedding virus in semen.[196] It is hypothesized that acute BVDV infection around the time of puberty may become localized in the testes and protected from the systemic immune response by the blood-testes barrier.

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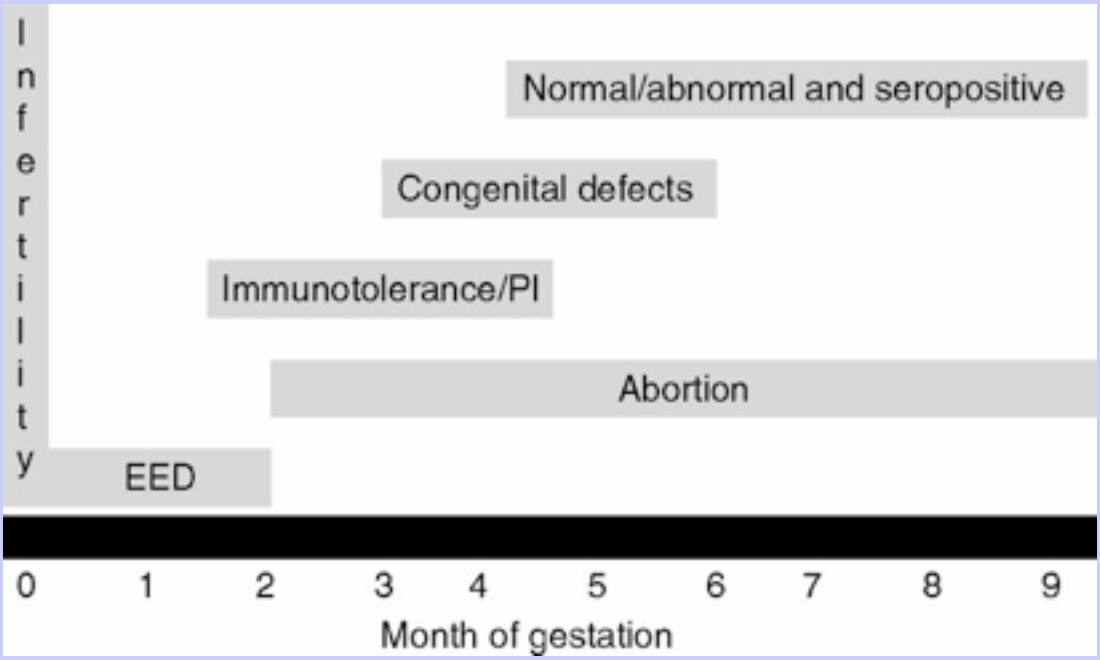
Fig. 32-67 Potential reproductive outcome after infection with BVDV during different stages of gestation.



32.111.10.2

INFERTILITY AND EARLY EMBRYONIC DEATHS

Field and epidemiologic studies provide evidence that BVDV can have a significant impact on early reproductive performance.[197,198] The mechanism for decreased conception rates is not clear but may depend on the time of infection with respect to the stage of early reproductive events. Virus and pathologic changes have been localized in ovarian tissue for prolonged periods of time after acute infection with cytopathic BVDV and noncytopathic virus.[199,200] Acute infection with BVDV has also been shown to affect ovarian function.[201–204] During the early embryonic stages, BVDV has been shown to have detrimental effects, especially after the embryo has hatched from the zona pellucida.[205]

32.111.10.3

ABORTIONS

Transplacental infection by BVDV virus is a common event and occurs with high efficiency. BVDV has been shown to be detrimental to early embryonic development and a cause of embryonic death.[206] Transplacental infection of the fetus at 50 to 100 days of gestation may result in fetal death.[207] Expulsion of the fetus may occur days to months after infection. In general, late-term fetal infections do not result in abortion, but late-term abortions in association with BVDV have been reported. It should be remembered that BVDV infection can cause abortion during any stage of gestation. Although the incidence of abortion is generally low in immune herds, it can increase dramatically in nonimmune herds.

32.111.10.4

CONGENITAL DEFECTS

Infection of the fetus at 100 to 150 days' gestation may result in a number of congenital anomalies. This period of fetal development corresponds to the final stages of organogenesis of the nervous system and the development of the fetal immune system, which can result in the generation of an inflammatory response to BVDV infection. At this stage of gestation, BVDV infection may inhibit cell growth or cell differentiation or cause direct cellular lyses. The more common congenital defects induced by BVDV infection include hydrocephalus, cerebella hypoplasia, hypomyelinogenesis, microphthalmia, cataracts, retinal atrophy or dysplasia, hypotrichosis, brachygnathia and other skeletal abnormalities, growth restriction, and pulmonary hypoplasia.

32.111.10.5

BOVINE VIRUS DIARRHEA VIRUS INFECTION DURING THE LATER STAGES OF GESTATION

In the later stages of gestation, immunocompetence and organogenesis are usually complete. Although abortions and the birth of weak calves have been attributed to infection with BVDV late in gestation, fetuses infected during this time period are normally able to mount an effective immune response to BVDV and effectively clear the virus. These calves are usually normal at birth and have precolostral neutralizing antibodies to BVDV.[208] Congenital infection may contribute to neonatal calf loss during a herd outbreak of BVDV, with weak undersized calves being born. In addition, calves congenitally infected with BVDV may be at greater risk for experiencing a serious postnatal health event.[209,210]

32.111.10.6

PERSISTENT INFECTION

Infection of the fetus with NCP-BVDV isolates before the development of fetal immunocompetence may result in the birth of calves that are immunotolerant to and persistently infected with BVDV. The development of immunotolerance to BVDV is rare after 100 days' gestation but has been reported to occur as late as 125 days' gestation.[140] Cattle persistently infected with BVDV are viremic, continuously shed virus, and may appear healthy. Persistently infected cattle are immunocompetent with respect to other antigens. The immunotolerance is specific to the infecting NCP-BVDV; therefore persistently infected cattle can respond immunologically to heterologous isolates of BVDV.[211] For this reason, persistently infected cattle can be seropositive for BVDV. Persistently infected females produce persistently infected offspring,[212] which may result in the production of persistently infected family lines. It appears likely that persistently infected cattle are the main mechanism by which BVDV is maintained in the cattle population.

Persistently infected cattle are at risk for developing mucosal disease and appear to be at risk for other diseases and have decreased survivorship.[213] Persistently infected calves have death rates of 50% in the first 12 months of life,[146] and it is believed that fewer than 10% of persistently infected dairy replacement heifers reach the lactating herd. Persistently infected calves may be born undersized and have slower growth rates. Some persistently infected calves appear to be predisposed to infections; this often results in pneumonia and enteritis,[214] which tend to become chronic and unresponsive to treatment. An alteration in immune response, such as suppression of neutrophil and lymphocyte function, also has been reported in persistently infected cattle.[215] Subclinical disease that eventually becomes clinical or immunosuppression that allows secondary

bacterial infections may explain unthriftiness and mortality in persistently infected cattle. Postmortem findings such as glomerulitis and encephalitis have been reported in persistently infected animals.[216]

32.111.11 Disease Occurring in Persistently Infected Cattle

32.111.11.1 MUCOSAL DISEASE

Mucosal disease occurs when cattle that are immunotolerant to and persistently infected with an NCP biotype of BVDV become infected with a CP biotype of BVDV that shares close antigenic homology with the persistently infecting noncytopathic virus.[217] Thus not every combination of NCP and CP virus results in mucosal disease. The origin of the CP virus can be external, as demonstrated by the documented occurrence of mucosal disease after the use of modified live BVDV vaccines and in experimental studies in which mucosal disease was produced by superinfection with CP-BVDV. It is more commonly believed that the CP-BVDV arises de novo from the NCP, persistently infecting BVDV by molecular rearrangement.

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Mucosal disease takes different clinical forms. The differences in the relatedness of NCP-BVDV and CP-BVDV may be responsible for the variations in clinical response. One extreme is acute mucosal disease, in which the CP virus shares close homology with the persistently infecting NCP virus. The other extreme is no clinical disease but seroconversion, in which the CP virus is heterologous to the NCP virus. Between these extremes lie other clinical forms of mucosal disease (chronic mucosal disease and possibly mucosal disease with recovery), which are determined by the antigenic relationship of the NCP and CP viruses. A delayed onset form of mucosal disease recently was described.[218] As the name implies, delayed onset mucosal disease occurs after the expected time frame for acute mucosal disease after exposure of a persistently infected animal to an exogenous CP virus. Although the CP virus is heterologous to the persistently infecting NCP virus, a genetic recombination of the two viruses results in a CP virus that is antigenically identical to the resident NCP, and mucosal disease results.

32.111.11.2 ACUTE MUCOSAL DISEASE

The occurrence of acute mucosal disease is sporadic, with less than 5% of the herd being affected. Often the animals affected in a herd are grouped by age and represent calves that were all persistently infected with the same NCP-BVDV. In rare cases, up to 25% of the herd may be involved, but a high number of persistently infected animals would be necessary for this to occur. The case fatality rate for acute mucosal disease approaches 100%.

Acute mucosal disease is characterized by an incubation period of 10 to 14 days after exposure. Clinical signs of mucosal disease include a biphasic fever, anorexia, tachycardia, polypnea, decreased milk production, and profuse, watery diarrhea (occasionally with frank blood, fibrinous casts, and a foul odor). The oral papillae may be blunted, and the epithelium of the tongue, palate, buccal surfaces, and pharynx may have erosions. Erosive lesions also may be present in the interdigital regions and on the teats and vulva. All erosive lesions may be ulcerative to diphtheric, depending on their duration. Other clinical signs may include nasal and corneal discharge, corneal opacity, excessive salivation, decreased rumination, and bloat. Cattle may have inflammation of the coronary band and, in some cases, laminitis. Acutely infected animals often are neutropenic (without a left shift) and thrombocytopenic. Animals with mucosal disease commonly have secondary bacterial infections, resulting in pneumonia, mastitis, and metritis. Cattle with mucosal disease

become progressively dehydrated and debilitated and usually die within 3 to 10 days. Some animals survive the acute phase but experience the chronic form of the disease.

The differential diagnosis for bovine diseases with oral lesions and diarrhea includes severe acute BVDV infection, RP, bovine MCF, and mucosal disease. Diseases characterized by oral lesions but no diarrhea include FMD, VS, and BPS. Diseases involving diarrhea but no oral lesions include winter dysentery, salmonellosis, Johne's disease, parasitism, and copper deficiency.

32.111.11.3 CHRONIC MUCOSAL DISEASE

Some cattle that develop mucosal disease do not die in the expected time frame but rather become chronically affected. Cattle with chronic mucosal disease are unthrifty and may have persistently loose feces or intermittent diarrhea, chronic bloat, decreased appetite, weight loss, interdigital erosions, or nonhealing erosive skin lesions. Nasal discharge and persistent ocular discharge are common findings. Areas of alopecia and hyperkeratinization of the skin may develop, typically in the neck area. Chronic lameness may develop because of laminitis, interdigital necrosis, or hoof deformities. These animals may be persistently anemic, neutropenic, and thrombocytopenic. Cattle with chronic mucosal disease rarely survive beyond 18 months and ultimately die of severe debilitation. Chronic mucosal disease should be distinguished from calves born persistently infected with BVDV that are poor doers from birth.

32.111.11.4 MUCOSAL DISEASE WITH RECOVERY

A single report exists of several persistently infected calves that showed transient signs of mucosal disease and subsequently recovered.[219] These calves remained healthy until slaughtered. The observation is interesting, and mucosal disease with recovery is a possibility based on the current understanding of the pathogenesis of mucosal disease.

32.111.12 Necropsy Findings

The postmortem examination findings for animals that died from BVDV vary depending on the form of the disease.

32.111.12.1 MUCOSAL DISEASE

Animals that die of mucosal disease usually have severe, necrotizing erosive or ulcerative lesions involving the mouth, tongue, esophagus, ruminal pillars, omasum, abomasum, intestines, and cecum. Erosive lesions may extend onto the external nares and into the nasal cavity. Ulcers involving the esophagus typically are elongated. The Peyer's patches in the small intestine often are necrotic and hemorrhagic. Bowel contents are watery, hemorrhagic, and foul smelling. Pathologic gastrointestinal conditions may be absent or very mild in cattle with chronic mucosal disease, although histopathologic lesions usually are present. Skin lesions are often found and include patchy hyperkeratosis around the neck, shoulder, and perineal areas. Erosive lesions involving the perineal area, the prepuce, and the interdigital cleft and coronary band of the hoof may be present. Skin lesions are most apparent in cattle suffering from chronic mucosal disease.

32.111.12.2 ACUTE DISEASE

Animals that die of acute BVDV infection have less severe lesions, but some or all of those mentioned for mucosal disease may be present. Often, secondary bacterial infections such as pneumonia or mastitis are present and have contributed to the animal's death. Animals that die of hemorrhagic syndrome may have evidence of hemorrhage in many organ systems, including the gastrointestinal, cardiovascular, respiratory, and urinary systems. Petechial or ecchymotic hemorrhages are often apparent on mucosal surfaces, and significant hemorrhage in the gastrointestinal submucosa and Peyer's patches may also be present.

32.111.12.3 ABORTIONS AND CONGENITAL DEFECTS

Fetuses aborted as a result of in utero BVDV infection often are autolytic when expelled. Lesions found in aborted fetuses and the accompanying placentas are nonspecific for BVDV. Under experimental conditions or when aborted fetuses are expelled soon after death, lesions observed include conjunctivitis, peribronchiolar and interalveolar pneumonia, and nonspecific myocarditis. A significant decrease in cerebellar mass may be evident in calves affected by cerebella hypoplasia as a result of in utero infection with BVDV during the second trimester of gestation. Other common congenital defects associated with BVDV infection that may be noted at necropsy include cataracts and thymic hypoplasia.

32.111.13 Diagnosis

A diagnosis of BVDV infection can be made by serologic evaluation, virus isolation, viral antigen detection, and viral RNA detection using amplification methods such as the PCR technique.

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32.111.13.1 VIRUS ISOLATION

Virus isolation is commonly used for identifying cattle infected with BVDV. Serum is most often used to isolate virus from cattle persistently infected with BVDV, whereas buffy coats or nasal swabs are most appropriate for attempting to detect acute infections. Antemortem differentiation of persistently infected cattle from those acutely infected with BVDV requires serial isolation of virus at least 2 weeks apart. At postmortem examination, BVDV is best isolated from lymphoid tissues such as Peyer's patches, lymph nodes, thymus, and spleen.

BVDV is isolated by inoculating appropriate samples onto bovine cells in culture. Isolates can be characterized as cytopathic or noncytopathic biotypes by the presence or absence of characteristic cytopathic effects in cell culture. Noncytopathic isolates are identified in cell culture using immunoenzymes or immunofluorescence. The immunoperoxidase monolayer assay (IPMA) is a common adaptation of virus isolation and immunoenzymatic antigen detection used for rapid BVDV screening.[220]

32.111.13.2 ANTIGEN DETECTION

Virus can be identified in tissue samples by using fluorescent antibodies or immunohistochemistry. Immunohistochemistry has been reported to be more accurate than virus isolation and immunofluorescent methods in diagnosing BVDV in cases of abortion and perinatal death.[221] BVDV can also be identified in blood and tissue samples by using an antigen-capture ELISA. Antigen-capture ELISAs are equal in sensitivity

to virus isolation for detection of persistently infected cattle but less sensitive for identification of acute infections with BVDV.[222] Skin and "ear notches" are common samples to use for both immunohistochemistry and antigen capture ELISAs for detecting cattle persistently infected with BVDV.

32.111.13.3 VIRAL RNA DETECTION

Nucleic acid detection assays involve the direct identification of BVDV viral genomic RNA or a synthesized copy of the RNA called *cDNA*. The PCR test is the most commonly used nucleic acid detection assay. The advantage of PCR assays are that they can be very sensitive and specific. It is estimated that PCR is 10 to 1000 times more sensitive than virus isolation. Detection of BVDV by PCR requires that genomic RNA be extracted from the sample of interest. This can be problematic because RNA is rapidly degraded if exposed to RNases, which are ubiquitous in nature. Careful sample handling is necessary to reduce this pitfall. Samples in which BVDV RNA has been detected include serum, WBC preparations, nasal swabs, homogenized tissues, semen, and milk. Specific PCR primers have been designed to differentiate among the reported genotypes of BVDV. This may be useful in epidemiologic investigations and when designing vaccine programs aimed at controlling different genotypes of BVDV.

Because of its ability to detect low levels of virus in samples, a PCR-positive sample does not allow the differentiation of viremia due to an acute or transient infection from viremia due to being persistently infected. Similarly, interpretation of PCR results must consider timing of vaccination with modified live virus products, as PCR is able to detect a transient viremia present 3 to 10 days after vaccination with a modified live virus BVDV vaccine.[223]

PCR can be used to screen pooled samples of blood, milk, or tissues (skin) in herd surveillance programs. This strategy takes advantage of the high sensitivity of the assay while reducing the cost per animal tested.

32.111.13.4 SEROLOGIC EVALUATION

Serologic detection of BVDV exposure is most commonly done by serum neutralization assays. It is important to realize that serum neutralization titers can vary significantly from laboratory to laboratory.[224] In most situations, evaluation of paired acute and convalescent titers must be used. Single point titers are very difficult to interpret, especially if vaccination programs are used in the herd. Demonstration of a fourfold increase in SN antibodies in association with appropriate clinical signs is considered significant. Use of paired serologic evaluation for diagnosis of abortion may be difficult because seroconversion may already have occurred by the time the event is noticed. Persistently infected cattle generally have no or very low serum neutralization titers. However, persistently infected cattle may seroconvert to field virus or vaccination, especially if the vaccine or field virus is antigenically distinct from the virus with which the animal is persistently infected.[225] As a result, the identification of seronegative cattle cannot be used as a sole criterion for determining persistently infected status. Serologic evaluation may be useful in determining the infection status of a herd. The presence of high serum neutralization titers in unvaccinated heifers older than 6 months of age indicates that BVDV is currently or has recently been circulating and is correlated with the presence of persistently infected cattle in dairy herds.[155,226] This strategy has been less successful when used in beef herds.[227]

Table 32-10 summarizes diagnostic testing that can be used for specific forms of the disease.

32.111.14

Treatment and Prognosis

No specific treatment is available for animals showing clinical signs of BVDV infection. Owners should be informed that severely ill animals may have mucosal disease, which normally is fatal. The goals of therapy for cattle suspected of having acute BVDV infection are supportive care and prevention of secondary bacterial infection. Broad-spectrum antimicrobial agents, fluids, electrolytes, and vitamins may be indicated.

32.111.15

Prevention and Control

Practices aimed at preventing the introduction of BVDV to a farm are primarily applicable only for closed breeding operations (dairy farms or beef cow and calf operations) and cannot be used for feedlot or veal operations. Strict biosecurity systems with isolation and testing of all cattle entering the farm are necessary to ensure that no virus enters the farm; this may be difficult for most dairy and cow and calf operations to achieve. A reasonable compromise is to limit movement of cattle on and off the farm to the essential traffic, to avoid moving pregnant animals, and to purchase replacement animals (including bred heifers) from herds for which accurate records of disease history and vaccination programs are kept. Isolation of new additions for 3 weeks should prevent transmission of virus from acutely infected (non-persistently infected) cattle. Purchased cattle should be tested for BVDV before entering the resident herd. If pregnant cattle are purchased, their offspring should be tested to ensure that they are free of BVDV. Semen used for artificial insemination should be from bulls that have been tested for BVDV infection. It is important to test embryo transplantation recipients before their use to ensure that they are not persistently infected. Exposure of cattle to small and wild ruminants should be limited through separate housing for sheep and goats and well-maintained fences to reduce contact with deer.

In stocker or backgrounder and feedlot operations, immunity to BVDV has been shown to be protective against BRD complex.[228] Vaccination against BVDV before the expected occurrence of respiratory disease (as is done in preconditioning programs for beef calves) may minimize the consequences that accompany infection with field strains of BVDV. This, in turn, reduces the severity of infection by other pathogens involved in the respiratory disease complex. Although strict biosecurity measures designed to keep BVDV off the farm may not be possible in the feedlot, large feedlots have found economic advantage in screening incoming calves to ensure no persistently infected animals are present in feedlot pens. Presence of persistently infected calves can result in increased disease, treatment costs, and death in the persistently infected calves as well as increased disease and treatment costs for the pen as a whole.[153]

Table 32-10 Diagnostic Testing for Bovine Virus Diarrhea Virus (BVDV)

Clinical Form	Specimen	Diagnostic Test	Comments
Subclinical or acute BVD disease	Serum	Serum virus neutralization	Pair sera 3–4 weeks apart Serology for both types 1 and 2 BVDV should be performed
	Serum or whole blood	Virus isolation PCR	Whole blood preferred Viremia may be too transient for successful virus isolation
	Nasal swabs	Virus isolation PCR	Useful for establishing role of BVDV in bovine respiratory disease complex
	Postmortem tissues	Fluorescent antibody Immunohistochemistry Virus isolation PCR	Tissues of choice include ileum, Peyer's patches, mesenteric lymph nodes, spleen, thymus (calves), lung (BRD)
Infertility	Serum	Serum virus neutralization	May need to establish serum bank on at risk animals as seroconversion complete when reproductive problem noticed or compare titers of affected to unaffected cattle Serology for both types 1 and 2 BVDV should be performed
Abortion	Serum	Serum virus neutralization	Pair sera 3–4 weeks apart Serology for both types 1 and 2 BVDV should be performed
	Fetal fluid	Serum virus neutralization	Presence of antibodies or BVDV suggestive but not definitive for BVDV-induced abortion Serology for both types 1 and 2 BVDV should be performed
	Fetal tissues	Fluorescent antibody Immunohistochemistry Virus isolation PCR	Tissues of choice include ileum, mesenteric lymph nodes, spleen, thymus, liver, lung

Persistent infection	Serum or whole blood	Virus isolation (IPMA) Antigen capture ELISA PCR	Should be repeated in 2–4 wk to confirm persistent infection For virus isolation, buffy coats should be used on calves less than 6 months of age
	Skin biopsy	Antigen capture ELISA Immunohistochemistry Fluorescent antibody PCR	Should be retested in 3–4 wk with blood sample to confirm persistent infection Pools of skin or blood may be tested initially by PCR
Mucosal disease	Serum or whole blood	Virus isolation PCR	Isolation of both CP and NCP-BVDV
	Postmortem tissues	Fluorescent antibody Immunohistochemistry Virus isolation PCR	
Herd Screening	Bulk milk tank	PCR	Screens only lactating cows; 300 cows per milk pool
	Serum from sentinel cattle	Serum virus neutralization	Unvaccinated cattle 6–12 months of age Serology for both types 1 and 2 BVDV should be performed

BRD, Bovine respiratory disease; *BVD*, bovine virus diarrhea; *BVDV*, bovine virus diarrhea virus; *CP*, cytopathic biotype; *ELISA*, enzyme-linked immunosorbent assay; *IPMA*, immunoperoxidase monolayer assay; *NCP*, noncytopathic biotype; *PCR*, polymerase chain reaction.

Vaccination programs are routinely used to limit disease from BVDV infection. The goal of a BVDV vaccination program is to induce immunity that will limit viral replication after infection and thereby prevent the subsequent effects of viral infection. On dairy farms or in beef cow-calf operations, ensuring adequate immunity in breeding females is aimed at preventing in utero infections and harmful sequelae (infertility, abortion, congenital malformation, birth of weak calves, and persistent infection). An additional benefit of vaccination of breeding stock is enhancement of the level of colostral immunity passed to the offspring. 797 798

Many practitioners have concerns about commercial BVDV vaccines. Concerns over vaccine safety with modified live BVDV vaccines have traditionally centered on “vaccine breaks,” transmission of vaccine strains, and vaccine-induced immunosuppression, abortion, and congenital anomalies. New technologies and better quality control of vaccine reagents has greatly reduced the occurrence of vaccine contamination. Immunosuppression has been demonstrated experimentally after the use of modified live BVDV vaccines.[229] Vaccinal strains of modified live BVDV are reported to cross the placenta and induce the same detrimental outcomes as seen in fetal infection with field strains of BVDV except persistent infections. This is of greatest concern during the first and second trimesters. Modified live vaccines may or may not induce mucosal disease in persistently infected cattle. The possible induction of mucosal disease in persistently infected cattle should not be a deterrent to using modified live vaccines.

Killed BVDV vaccines are safe for use in pregnant cows and do not result in vaccine breaks or cause immunosuppression unless improperly attenuated. When using a killed virus vaccine in cattle that have never been vaccinated against BVDV, a booster dose must be administered 2 to 4 weeks after the initial vaccination to ensure proper vaccination.

Concerns about the efficacy of BVDV vaccines have centered on the ability of vaccines to stimulate an immune response capable of protecting against the broad antigenic spectrum represented by BVDV types 1 and 2. Current BVDV vaccines appear to be capable of preventing severe disease in cattle infected with heterologous field viruses.[230,231] However, the ability of vaccines to protect against fetal infection is not clear. The majority of fetal challenge studies have demonstrated that vaccines reduce the risk of fetal infection with BVDV but do not eliminate it.[232–236] BVDV vaccines should be used strategically to optimize immunity during gestation, especially during the first two trimesters when the fetus is most susceptible to the detrimental effects of the virus. This would include vaccination of all breeding stock before the animals are bred. Replacement heifers should be vaccinated at 5 to 6 months of age when colostral immunity declines and again before breeding. When possible, modified live vaccines should be used to ensure broader and longer protection. In calves, vaccination before the decline in colostral antibodies occurs is of questionable value, although some studies indicate that it is beneficial in protecting against calf hood disease associated with BVDV.[230] Vaccination against BVDV should be part of any preconditioning program for beef calves before entry into a commingled environment.

In herds experiencing problems with BVDV infections, screening for persistently infected cattle may be warranted. In breeding herds, persistently infected animals serve as a continuous source of infection to susceptible cattle. In addition, because persistently infected females may produce persistently infected offspring, it is desirable to cull these females before they spread virus to their offspring or before they have disease themselves, resulting in economic loss. Before instituting a herd-screening program, several points should be emphasized. First, there should be a definitive diagnosis of BVDV infection in the herd before the expense of testing is undertaken; second, the herd should be experiencing a disease syndrome that is associated with BVDV infection; third, the owner must be willing to implement biosecurity measures aimed at reducing the risk of reintroducing BVDV into the herd. Herd screening involves testing strategic subsets or all cattle on the farm for BVDV. This includes in utero calves that are tested after birth.

Cattle that are determined to be persistently infected with BVDV will remain so for their entire life and will continually serve as a virus reservoir for susceptible animals. Once detected, persistently infected animals should be removed from the herd immediately and appropriate actions taken so that they do not come in contact with other susceptible animals.

32.112 MALIGNANT CATARRHAL FEVER (BOVINE MALIGNANT CATARRH, MALIGNANT HEAD CATARRH)

Bradford P. Smith

32.112.1 Definition and Etiology

Acute MCF is a highly fatal disease of cattle, deer, bison, buffalo, some other ruminants (33 species to date), and pigs caused by a herpesvirus. It has worldwide distribution and has also been a major problem in zoos and game parks. The African strain, identified as alcelaphine herpesvirus type 1 (AlHV-1), is a wildebeest-associated gammaherpesvirus[237] carried by the blue or white-bearded wildebeest *(Connochaetes taurinus)* AlHV type 2 is a

closely related but nonpathogenic gammaherpesvirus from other species of African antelope. The name *ovine herpesvirus type 2* (OvHV-2) has been proposed for the sheep isolate. OvHV-2 is carried by numerous species of domestic and wild sheep and goats worldwide. OvHV-2, AlHV-1, and AlHV-2 are closely related antigenically to bovine cytomegalovirus (bovine herpesvirus type 3), which offers some cross-protection.[238] Goats may carry caprine herpesvirus type 2 (CpHV-2), which can be transmitted to Sitka deer[239] and perhaps other species.

The sheep-associated form of MCF can be acute or chronic, and animals may recover. European, Australian, Asian, and American sheep-associated viruses have been isolated. These herpesviruses appear to represent species-adapted variants of the same virus.[240] The disease usually occurs sporadically, with only one animal affected, but many large outbreaks have been reported. Cattle are considered dead-end hosts and usually do not spread the infection by contact transmission because there is no cell-free virus in secretions.[241] The virus is fragile and unlikely to survive outside a host for more than a day or even hours.

The African and North American forms of the disease are similar except for the reservoir host and the fact that the African herpesvirus appears to be more contagious and is more easily transmitted experimentally. The incubation period for American MCF is more than twice as long as that for African MCF, but the course of clinical disease is one third as long. A higher percentage of cattle develop acute disease with severe diarrhea with the American form.[242]

Some African hoofed ungulates may have clinical signs, and infected animals in wild animal parks may pose a danger to domestic livestock. Bison, Dall sheep, muskox, elk, moose, deer, and other species can also be infected. Acute outbreaks in bison have been reported.[243] In one report exposure of bison to sheep for less than a day at an auction resulted in heavy mortality.[244] Pigs were infected and developed clinical disease in Norway.[245] Both the African and North American viruses can be transmitted to rabbits, in which infection causes an acute, fatal lymphoproliferative disorder.

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Sheep are usually asymptomatic, but a heavy experimental intranasal inoculation of OvHV-2 resulted in illness and lesions in three sheep.[246]

32.112.2 Clinical Signs and Differential Diagnosis

Cattle from 4 weeks of age to adulthood can be infected and develop clinical illness. After an incubation period of 3 to 10 weeks, the disease attacks vascular endothelium (vasculitis), and all epithelial surfaces are affected. The incubation period can be prolonged, and in at least one case the incubation period was 200 days. Oral erosions, diarrhea, dysentery, severe keratoconjunctivitis, mucopurulent nasal discharge, thickened cracking skin, encephalitis, lymphadenopathy with very enlarged nodes, and high fever may be seen (Fig. 32-68). Generalized weakness and dyspnea occur. Ropy saliva may be dropped from the painful mouth, and scabs may develop on the muzzle. The hoof or horns may be shed, and lameness may be pronounced. Hematuria often is present. When particular signs predominate, the condition may be labeled the alimentary form, the encephalitic form, the head and eye form, or the skin form. One strain of virus can cause all forms, and animals with most of these signs can be seen in a given outbreak. Clinical signs in any single animal may progress rapidly or over a course of weeks. In California a pygmy goat had vasculitis, sloughing skin, keratitis, neurologic signs, fever, and a positive titer to MCF before dying (Smith BP, unpublished data). Disease in Sitka deer (and perhaps other species) may consist primarily of dermatitis and alopecia.[247]

The course of the acute disease usually is 3 to 7 days; some animals survive longer. The mortality rate is very high. In some outbreaks an acute form has predominated, with affected cattle dying 1 to 3 days after developing

a high fever, severe diarrhea, and conjunctivitis.[248,249] Peracute deaths without any visible symptoms also were recorded. A mild form, with transient fever and mild oral and nasal mucosal erosions followed by recovery, has been seen in experimentally infected cattle. In a natural outbreak in the United States, three of the animals survived longer than 3 months with clinical signs, and evidence indicated that some animals seroconverted and remained infected for years. The main lesion in chronic or recovered cases is obliterative arteriopathy.[250] Cattle with chronic MCF and cattle that have recovered from sheep-associated MCF have been described.[251,252] The authors concluded that sheep-associated MCF can manifest with a full range of clinical signs. Some animals recovered after treatment with corticosteroids, but there is also a report of recrudescence of MCF in a deer given corticosteroids.

Fig. 32-68 Yearling steer with malignant catarrhal fever. Note the corneal opacity, lacrimation, and mucopurulent nasal discharge.

MCF must be differentiated from BVD-mucosal disease (BVD-MD), RP, bluetongue, VS, and FMD. The last two diseases are not usually associated with diarrhea, and VS and FMD tend to have high morbidity and low mortality rates. Clinical bluetongue is rare in cattle and not usually associated with dysentery. Arsenic toxicity and chlorinated naphthalene toxicity have some clinical similarities to the intestinal forms of MCF. Ocular signs, including corneal opacity, conjunctivitis, and discharges, must be differentiated from bovine pinkeye, in which the lesion starts at the center of the cornea. The corneal opacity of MCF starts at the limbus and is caused by edema secondary to the loss of the internal endothelial layer of the cornea.[253]

32.112.3 Clinical Pathology and Serology

Some affected animals show leukopenia caused by neutropenia if sampled early in the course of disease, but this is a very inconsistent finding in natural outbreaks.[248] Joint fluid is cloudy and may contain increased protein and mononuclear cell numbers. Cerebrospinal fluid has elevated protein concentrations (up to 584 mg/dL) and elevated WBC counts (up to 945/mm^3), mainly because of an increase in mononuclear cells.[254] Serologic tests include ELISA, indirect immunofluorescence,[250,255] CF, and virus neutralization. Virus isolation can be attempted. PCR[256–258] tests have been developed for AlHV-1 and recently for OvHV-2. The wildebeest-associated and sheep-associated viruses appear to be closely related antigenically, cross-react serologically, and offer some cross-protection.[259]

Diagnosis is based on a history of exposure, clinical signs, and gross and histologic lesions. PCR and competitive inhibition ELISA are definitive.[260] Rabbit inoculations can also be used. Nasal swabs and 500 mL of blood, as well as spleen and lymph node samples, should be collected for viral isolation (these should not be frozen). A cytopathic effect on thyroid cell cultures may be observed 4 to 20 days after inoculation.[261]

32.112.4 Pathophysiology

Although the incubation period has been described as 3 to 10 weeks, a period of 150 days has been documented between the first and last cases in an outbreak.[248] Persistent asymptomatic infection for 5 months after inoculation with MCF virus followed by 4 weeks of viremia and death was documented in a steer.[262] The MCF virus appears to cause proliferation of cytotoxic T lymphocytes. The evidence suggests that the vasculitis observed with MCF is mediated by lymphoid cell infiltration rather than by virus or immune complexes.[263] Lymphocytes and lymphoblasts are found in all affected tissues, whereas neutrophils and plasma cells are rare. No visible viral particles are involved in the arteritis. Large granular lymphocytes are a subpopulation of T cells that act as NK cells and also as T lymphocyte suppressor cells. If these cells are malfunctioning, suppressor dysfunction can result in exuberant T cell proliferation, whereas NK cell dysfunction can result in indiscriminant killing of normal cells.[264] Major histocompatibility complex restriction and macrophages also appear to play a role in the pathogenesis. AlHV-1 has similarities to other oncogenic lymphotrophic herpesviruses such as the Marek's disease virus and the Epstein-Barr virus.[237] The molecular structure of the MCF virus genome supports this view.

32.112.5 Epidemiology

The African form of MCF is spread to cattle and other susceptible species by wildebeests, especially during the wildebeests' calving season.[265] AHV-1 has been isolated from asymptomatic wildebeests, from the nasal and lacrimal secretions of wildebeest calves,[241] and from a wildebeest fetus.[242] The virus does not survive more than a few hours in the environment. In South Africa, however, MCF occurs in cattle without wildebeest contact (except at a distance) and when wildebeest calves are usually 8 to 10 months old.[266] The exact mode of transmission is thus incompletely understood at present. Hartebeests and topis are also reservoir hosts for the virus.

The sheep-associated form of MCF is spread to cattle by contact or housing in nearby fields, even without direct contact between sheep and cattle.[248] There is evidence of aerosol transmission for over 70 meters.[253] Lambing is associated with many outbreaks as ewes shed more virus in the periparturient period. A high proportion of sheep sera yields positive findings for antibody to AlHV-1 by indirect immunofluorescence, including some from cesarean-derived lambs, which may indicate transplacental virus transmission,[267] and 99% of North American domestic sheep are infected.[268]

Although the disease usually occurs sporadically in a single individual, many severe outbreaks involving large numbers of cattle[248,259,269] and bison[244] have been reported. The dairy cow outbreaks[248,259] that occurred in the late 1970s in California and Minnesota were sheep associated, whereas recurrent North American feedlot outbreaks may not be.

Asymptomatic carrier cattle,[262] bison,[253] or deer[237] may be sources of the virus, which would explain how outbreaks can occur without apparent contact with wildebeests, hartebeests, topis, or sheep. OvHV-2 infection of cattle can occur without concurrent development of clinical MCF.[260] A steer inoculated with MCF virus was asymptomatic for 5 months before becoming viremic for 4 weeks[262] and having clinical MCF. A deer that had previously had MCF as a fawn but had been asymptomatic for 4 months recrudesced (shed virus and had clinical MCF) when given dexamethasone.[237] Cattle (and bison) traditionally have been considered dead-end hosts for MCF virus because isolated individuals usually are affected, but this may not always be the case if an asymptomatic or symptomatic bovine were to shed cell-free virus in secretions. Vertical transmission in cattle and bison through in utero infection has been documented.

32.112.6 Necropsy Findings

The nasal mucosa is hyperemic to hemorrhagic. The oral mucosa has necrotic papillae and large areas of necrosis and ulceration. Multiple focal ulcerations are seen in the esophagus. Parts of the forestomachs and intestines are thickened, edematous, and occasionally ulcerated and hemorrhagic. The lymph nodes, tonsils, and Peyer's patches are enlarged, moist, and friable. Splenic lymphoid follicles are prominent, and the liver is swollen. The adrenal glands are hemorrhagic. The mucosal surface of the bladder has focal areas of hemorrhage. The eyes are hyperemic and ulcerated and show severe corneal edema. The brain has intersulcal cloudiness and meningeal petechiation. Joints have swollen and reddened synovium with an increased quantity of cloudy fluid.[254]

Microscopic lesions involve blood vessels and epithelial surfaces. There is a marked lymphoid accumulation around vessels, as well as necrosis of the tunica media and intima. There is generalized lymphoid hyperplasia and lymphoid infiltrates in subepithelial and intraepithelial locations, associated with epithelial necrosis and sloughing. Similar changes occur in all epithelial tissues.[254] Chronic cases develop chronic obliterative arteriopathy.[250]

32.112.7 Treatment and Prognosis

Treatment of full-blown cases does not appear to be successful, but fluid therapy and good nursing care may allow some animals to survive. The morbidity rate may be quite high, running to 37% in one outbreak. Although some animals that exhibit mild disease may survive, close to 100% of those with severe clinical signs die.

32.112.8 Prevention and Control

There is evidence that cattle-to-cattle and bison-to-bison transmission may occur in endemically infected herds; thus carriers should be identified by PCR and competitive inhibition ELISA (CI-ELISA) and isolated or culled. Incoming animals in bison herds should be tested.[253] During an epidemic animals that are exposed or that show clinical signs should be separated from unexposed animals, and no across-the-fence contact should be allowed. Exposed or recovered cattle may serve as a reservoir for the virus for months. Sheep should be kept well away from cattle, and cattle should not be exposed to African wildlife, especially wildebeests, hartebeests, and topis, which may be infected carriers of the MCF virus. Vaccination with live or killed MCF virus has not proved consistently protective against challenge[270] and generally is not used.

32.113 VESICULAR STOMATITIS

Bradford P. Smith

32.113.1 Definition and Etiology

Vesicular stomatitis (VS) is a rhabdoviral disease of the genus *Vesiculovirus* that causes sporadic (cyclic) outbreaks in cattle, horses, donkeys, mules, and pigs and typically has a high morbidity but a low mortality rate. Cattle under 1 year of age rarely show clinical signs. VS is seen in the United States, Mexico, and Central and South America. Human beings have sometimes been infected with an influenza-like disease. Two distinct antigenic strains have been designated, the New Jersey (NJ) and Indiana (I) serotypes. Vesicles occur in the mouth, on the teats, and in interdigital areas. Lesions may occur only on the teats or only in the mouth.[271,272] The vesicles rapidly turn to painful ulcerations that cause dysphagia and reluctance to eat, frothing at the mouth, drooling, agalactia, weight loss, mastitis, and lameness. Death is rare. Epizootic waves of VS have tended to occur at about 10-year intervals, usually in the summer or fall, but since the major epizootic in 1982 and 1983 in the western United States, the NJ serotype has been identified in the United States each year.[271] An outbreak occurred in 1995 in the western United States, in New Mexico, and Colorado.[273] More cases occurred in 1997 and 1998. Although the NJ serotype has at least 14 distinct genotypes, only a few of these have been found in recent outbreaks in the United States. The NJ serotype should be considered a collection of serologically related but genetically variant viruses.[271] The I serotype has three subtypes; I-1 occurs in the United States. State and federal regulatory veterinarians should be contacted immediately when VS is suspected so that quarantine and disease identification measures can be used quickly to contain an outbreak.

Numerous outbreaks occur yearly from southern Mexico to northern South America.

32.113.2 Clinical Signs and Differential Diagnosis

After a mean incubation period of 9 days (the range is 3 to 21 days), there is onset of fever and oral lesions that cause excess salivation and reluctance to eat.[274,275] From 5% to 60% of cattle on a farm may show clinical signs. 800
Vesicles are only occasionally visible, because the epithelium rapidly necroses and many lesions quickly turn to ulcers. Lesions on the gums and tongue may coalesce to form large eroded areas (Fig. 32-69). Milk yield falls quickly. Teat lesions are common in dairy cattle, and small ulcers in the interdigital area and on the coronary band are occasionally seen. Recovery varies from 2 to 21 days, depending on the severity of the lesions and 801

management factors such as the type of feed and milking sanitation.[274] Actual healing of the lesions may take 34 to 59 days.[275]

Fig. 32-69 Severe ulceration of the tongue of a dairy cow caused by vesicular stomatitis. A plaque of dying mucosa covered by fibrin is visible at the tip of the tongue, and excessive salivation is obvious. Photo courtesy of Dr. Mark Thurmond.

The major differential diagnostic consideration is FMD, which causes almost identical clinical signs. Other diseases of cattle that result in oral lesions (BVD, BPS, bluetongue) do not usually appear as epidemics but rather in one or a few animals (although BPS may have a high morbidity). Other causes of oral lesions such as bristle grass irritation and toxins should be ruled out.

32.113.3 Clinical Pathology and Laboratory Diagnosis

The VS virus is difficult to isolate from blood, urine, feces, and oral swabs but has been isolated from tongue epithelium.[275] A CF test and a fluorescent antibody test are available for virus identification. Serum neutralizing (SN) titer rises rapidly after exposure and then gradually falls over the first year. SN titers that follow natural exposure may persist for years. Vaccination with inactivated virus results in a rapid rise in titer followed by a gradual decline for a year.[276] The presence of an SN antibody titer does not prevent reinfection or development of clinical signs.[277] ELISAs are also available.[278] Hematologic and clinical chemistry findings generally reflect an acute to chronic inflammatory disease and are nonspecific in helping to make a diagnosis.

32.113.4 Pathophysiology

After a short incubation period of 24 hours, fever and viral invasion of the germinative layer of oral epithelial cells occur. Oral abrasions or trauma may increase susceptibility.[274] Contact of virus with teats or feet can result in lesions in these areas, especially if the teats are chapped or cracked[274] or the feet are traumatized. The lesions progress rapidly from blanched macules to vesicles and soon rupture, leaving sloughed epithelium and ulcerated areas. Healing occurs quite rapidly if feed is soft and nontraumatic.

32.113.5 Epidemiology

Older, higher-producing dairy cows that have been in milk longer are more susceptible than herdmates to clinical disease caused by VS.[274] Because the virus cannot penetrate intact mucosa, cattle fed coarse feeds or hard pellets that traumatize the oral mucosa are at higher risk.[274] Cows with chapped or cracked teats and those on farms with poor milking hygiene are more likely to get teat lesions.[274] Cow-to-cow contact is a major mode of transmission in outbreaks, and increased interpen movement of cattle, as well as shared feed and water troughs, unless cleaned frequently, increases the risk of development of VS.[274] The virus is transmitted by milking machines and human hands during outbreaks. Insect vectors also contribute to the mechanical spread.

Outbreaks are often associated with the movement of animals from another area, but disease epidemics not associated with new animals do occur. The infection tends to be seasonal (occurring in the summer and fall in temperate areas and at the end of the rainy season in the tropics) and behaves like an arthropod-borne virus.[279] The midge *C. sonorensis* was found in 2005 to be an efficient vector of VS virus.[280] Other vectors include black flies (*Simulium* species).[281] Antibodies have been found in a number of wild species of animals (deer, raccoon, bobcat, monkey), which may provide a virus reservoir.[279] Active cases of VS occur in Mexico between U.S. epidemics, giving rise to the possibility that cattle from Mexico arriving in the United Sates may also act as sources of VS virus.[271] Sheep and goats in contact often seroconvert, although clinical signs in these species are rare. The virus survives several weeks in cool soils and is very resistant to pH changes. Cattle generally show a high morbidity rate and a low mortality rate (1% to 5%). Although many in-contact cattle do not show obvious clinical signs of disease, many more have oral lesions if closely examined, and most animals in the herd seroconvert.[275]

The economic losses associated with an outbreak of VS can be severe, especially in dairy cattle. In the 1982 epizootic in California, losses on two dairies (principally decreased milk production and culling for mastitis) totaled $225,000 during 2 months.[282]

32.113.6 Necropsy Findings

Deaths are rare and usually are attributed to secondary bacterial diseases, including environmental mastitis and pneumonia. Cattle become gaunt and weak as a result of dysphagia and resultant reduced food intake. Erosive and ulcerative lesions are usually confined to the mouth. The teats frequently are involved in lactating cows, and lesions on the coronary band and interdigital area occasionally may be seen.

Histologically, intracellular and extracellular edema, ballooning and degeneration of epithelial cells, and vesicle formation accompanied by neutrophilic infiltration are present. There are no inclusion bodies. The characteristic

bullet-shaped structure of the VS virus sometimes can be seen with electron microscope examination of fresh lesions or vesicular fluid.[279]

32.113.7 Treatment and Prognosis

Mortality can be almost completely prevented if ill cattle are offered shade, fresh water, clean bedding, and soft feed. Offering soft feed hastens recovery and reduces the anorectic period. Debilitated cattle should be given broad-spectrum antibiotics in an effort to control secondary bacterial pneumonia. Cattle with teat lesions are at high risk for developing mastitis and should be carefully milked last and monitored closely for mastitis. The prognosis for survival is very good, but agalactia and mastitis may result in culling of a large number of animals.

32.113.8 Prevention and Control

The reader should use websites such as the World Organisation for Animal Health (OIE) and the U.S. Department of Agriculture (USDA) for the latest information on contagious illnesses. During an outbreak of VS, quarantine of the premises and isolation of sick animals are required. Regulatory officials will help organize and maintain a quarantine. Feed should be soft and fine, because coarse or hard-pelleted feeds increase the spread of the virus and prolong the recovery time.[274] Leftover feed should be removed from feed bunks twice daily, and the bunks disinfected. Water troughs should be cleaned and disinfected daily. Disinfection can be accomplished by using 1% formalin, organic iodines, hexachlorophene, or phenyl-phenolic preparations. Two hours of exposure to lye (2% NaOH) will *not* deactivate the virus.

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Vaccination using killed[283] or live virus vaccines[284] is rarely practiced preventively because the disease occurs as rare epidemics in small areas and because vaccination interferes with serologic testing and monitoring. Vaccination with a killed virus vaccine may be used by regulatory veterinarians in at-risk animals during an epidemic, as it has been shown to be an effective vaccine.[283] Owners and managers should consult state and federal veterinarians before considering VS vaccination.

32.114 FOOT-AND-MOUTH DISEASE (AFTOSA, APHTHOUS FEVER)

Bradford P. Smith

32.114.1 Definition and Etiology

FMD is an acute, highly contagious viral disease of cloven-hoofed livestock characterized by vesicular lesions, erosions, and ulcers in the mouth and interdigital areas and on the muzzle, teats, and coronary band.[285] Natural hosts include cattle, sheep, goats, swine, water buffalo, bison, deer, elk, antelope (all wild ruminants), bears, llamas, camels, giraffes, elephants, rats, yaks, capybaras, and hedgehogs.[286] Of these, cattle and swine are the most susceptible, and camelids have low susceptibility. Mature sheep and goats usually have mild signs. Livestock of all ages are susceptible, but the mortality rate is higher in young animals because cardiac lesions occur. The horse is resistant to infection. In rare cases, humans have contracted the disease. It is endemic in Asia, Africa, parts of Europe, and most of South America, where losses involve not only those caused by the disease itself but also the monetary losses that result because fewer animal products are available for export as a result of loss of foreign markets. Great Britain experienced a major epidemic in 2001.

The FMD virus is a picornavirus of the genus Aphthovirus. At least seven immunologically distinct types of FMDV have been identified: A; O; C; SAT 1, 2, and 3; and Asia 1. Within the seven types at least 60 subtypes have been recognized. Vaccination against one subtype may not protect against another.[287] This fact, together with the fact that immunity is generally short term, means that effective vaccination programs are difficult. The virus is rapidly inactivated by high or low pH, sunlight, and very high temperatures but is very resistant to normal environmental conditions and drying.[285] Sodium hydroxide, sodium carbonate, iodophors, chlorine dioxide, and acetic acid are effective disinfectants, but many common disinfectants are ineffective, and the virus is resistant to iodophors, quaternary ammonium, hypochlorite, and phenol.

32.114.2 Clinical Signs and Differential Diagnosis

FMD is clinically indistinguishable from VS except that VS also affects horses. Clinical signs of FMD include fever, depression, anorexia, listlessness, occasional shivering, excess salivation, lip smacking, nasal discharge, and lameness.[287] Agalactia may occur. In addition to VS the differential diagnosis includes BPS, bluetongue, RP, MCF, and severe cases of infectious bovine rhinotracheitis. Teat lesions can be confused with those caused by bovine herpes mammillitis or parapoxviruses.

Vesicular lesions (blisters) 0.5 to 10 cm in diameter rupture within 48 hours, followed by a mucosal slough and large erosion.[287] These lesions appear to be very painful, and affected animals are reluctant to eat or move. The morbidity rate is high, but the mortality rate is low. The disease is economically devastating because it spreads rapidly and causes weight loss, mastitis, loss of milk production,[288] and frequent abortion. An outbreak of FMD in a country previously free of the disease can cost billions of dollars in trade losses over ensuing years. Deaths may occur in young calves, mainly from myocardial necrosis, and secondary bacterial pneumonia and foot infections are common.

32.114.3 Laboratory Diagnosis

Because FMD is clinically indistinguishable from VS and other viral mucosal diseases, laboratory confirmation of the diagnosis is obtained through CF, virus neutralization, agar gel precipitation, ELISA, or fluorescent antibody tests.[287] ELISA appears to be more sensitive and type specific than CF[289] and virus neutralization.[290] When VS or FMD is suspected, state and federal authorities should be contacted immediately. In FMD-free countries, quarantine is practical to control spread. Slaughtered animals are burned. All animals within 3 km may be destroyed during efforts to halt the disease.

32.114.4 Pathophysiology

The usual incubation period is 2 to 14 days. The usual primary sites of infection and replication by the FMD virus are the pharyngeal and digestive mucosa[287] and alveolar epithelium of the udder.[291] The virus replicates in the cells of the stratum spinosum.[292] It spreads locally and also enters the circulation and is carried to other susceptible tissues. Within 2 to 21 days a fever begins, and some vesicles appear.[293] Vesicles develop in the mouth and on the ruminal pillars, and myocardial and skeletal muscle degeneration characterized by Zenker's necrosis may occur in young cattle. The mucosal cell disruption results in separation of superficial epithelium from basal epithelium, which fills with tissue fluids. When these epithelial layers slough, erosions are left behind that take days to weeks to heal, depending on their size.[287]

32.114.5 Epidemiology

Transmission occurs primarily by means of aerosols,[287,294,295] animal contact, and fomites such as shoes, tires, and equipment. The virus may be spread to farms 50 miles distant. Human beings can carry (and subsequently transmit) the virus on their shoes or clothing or in respiratory tract tissues for longer than 24 hours. Recovered cattle usually stop shedding the virus by 2 weeks, but some harbor it for 6 to 24 months and may act as sources of the virus at the start of an epidemic.[293] The virus has been isolated from semen,[296] and the possibility exists of sexual transmission from the African buffalo to cattle.[297] African Cape buffaloes can be lifelong carriers.

The virus exists in milk, and it may survive pasteurization. Uncooked or partly cooked meat products or garbage scraps, hides, or other tissues contaminated with the FMD virus from an endemic area of the world may transmit the disease long distances. The virus can persist in frozen meat for years. Besides actively infected animals, sources of infection include bedding, feed, milk, shoes and hands of humans, and equipment.[287]

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32.114.6 Necropsy Findings

In addition to oral erosions and ulcerations, ulcers may be seen on the ruminal pillars. In young cattle myocardial and skeletal muscle degeneration and necrosis may be noted. Histologically the vesicles are characterized by ballooning, cellular degeneration, intracellular and extracellular edema, and separation of the basal epithelium.[292] There are no inclusion bodies. Muscle lesions (skeletal and cardiac) are characterized by necrosis (Zenker's degeneration).

32.114.7 Treatment and Prognosis

Where FMD is endemic, quarantine, local eradication, virus typing, and revaccination of contact and at-risk cattle with the appropriate virus subtype should be considered. Good nursing care and administration of systemic antimicrobial drugs to limit secondary bacterial pneumonia and mastitis are recommended. Soft feeds such as chopped green grass are much more palatable than hay to sore-mouthed animals. The prognosis is good for survival, although many animals abort, lose weight, stop lactating, or have severe bacterial mastitis secondary to viral teat lesions and must be culled. The virus destroys mammary alveolar epithelium permanently.[291]

32.114.8 Prevention and Control

The reader should also consult the OIE and USDA websites for current status of this disease. In endemic areas, vaccination and quarantine are the basis for prevention and control. In FMD-free areas (Great Britain, the United States, Canada, Japan, New Zealand, and Australia), the method of choice is rapid identification of an outbreak, quarantine, and slaughter of all affected and exposed herds.

Vaccines must be type specific. Most European and South American countries use trivalent inactivated vaccines against types A, O, and C from cell culture virus. Vaccine-induced and naturally occurring immunity is short-lived, and vaccination usually must be repeated two or three times a year.[287] Newer oil-adjuvanted vaccines can protect for up to 1 year. Because the protection is partial, infection usually results in subclinical or mild disease. Calves nursing immune dams are likewise partly protected by passive antibody for up to 5 months.[287] In an outbreak the most effective vaccine is autogenous.

32.115 RINDERPEST (CATTLE PLAGUE) AND PESTE DES PETITS RUMINANTS

Bradford P. Smith

32.115.1 Definition and Etiology

RP is an acute, highly contagious, and usually fatal disease of ruminants. Cattle and water buffaloes are most frequently affected, but the disease also occurs in yaks, gaur, sheep, goats, pigs, and other cloven-hoofed animals, in which it is usually less severe. It is rarer in camelids. Many wild animals in Africa are susceptible, including buffalo, lesser kudu, eland, giraffe, warthog, and wildebeest.[298] RP virus (RPV) is in the Paramyxoviridae family, genus Morbillivirus. There is only one known strain of RPV. It is closely related serologically to the virus that causes PPR. The virus can remain viable for at least 1 year in frozen tissue, but it is killed by direct sunlight in 2 hours. The disease is intermittently active in Africa, the Middle East, and Asia.[299] Other morbilliviruses pathogenic for animals include canine distemper and the 1995 Australian morbillivirus, which occurred in horses and humans.

RRP is a closely related highly fatal virus of goats and sheep. Cattle and pigs develop inapparent infections. Clinical signs of PPR in goats and sheep are similar to those of RP in cattle. Bronchopneumonia is also common. The reader is referred to the World Animal Health and OIE websites for current information.

32.115.2 Clinical Signs and Differential Diagnosis

The incubation period in cattle is 3 to 15 days, which is followed by sudden onset of fever, depression, and anorexia. The nose is dry, and mucous membranes are congested. Within days oral erosions appear where necrotic foci have sloughed. Purulent lacrimation occurs. Diarrhea is severe and may be bloody. Dehydration and emaciation often lead to death. The disease in sheep and goats usually is mild or subclinical,[300] but the PPR virus can cause outbreaks with high morbidity and mortality in small ruminants.

In endemic areas RP is suspected when the signs described earlier occur in groups of animals. In nonendemic areas diseases that appear similar clinically are BVD, MCF, arsenic poisoning, severe coccidiosis, and severe fulminating infectious bovine rhinotracheitis, as well as FMD and VS. Other causes of severe gastroenteritis and diarrhea (e.g., salmonellosis) must also be considered. Oral lesions of RP are similar to these seen with VS. In small ruminants, bluetongue, PPR, and Nairobi sheep disease must be ruled out.

32.115.3 Laboratory Diagnosis

Laboratory confirmation of RP can be accomplished by (1) virus isolation; (2) PCR; (3) detection of viral antigen by fluorescent antibody testing, virus neutralization, CF, or AGID; (4) detection of rising antibody titer by ELISA or virus neutralization; and (5) histopathologic evaluation including immunohistopathology.[301] Virus isolation is most successful in the first days of infection (often before the onset of diarrhea). Blood should be taken in heparin. The lymph nodes and spleen are reliable sources of virus, and in cattle, tears and ocular discharges are also reliable sources.[302] Lymph node biopsy after day 3 of infection is the most reliable means of diagnosis in a living goat.[300] Tissues should be shipped frozen on ice to the laboratory for virus isolation or detection of antigen. Detection of a rising antibody titer can help diagnose the disease retrospectively. Leukopenia may be noted in the acute early states of RP.

32.115.4 Pathophysiology

The virus usually enters through the respiratory mucosa. Lymphoid tissue is the primary target of the RPV. Lymphocytes are destroyed in the germinal centers of the lymph nodes, Peyer's patches, tonsils, splenic corpuscles, and cecal lymphoid tissue. Immunosuppression occurs as lymphoid tissue is destroyed.[303] The virus also attacks the alimentary tract mucosa; Peyer's patches are the most severely affected. As alimentary mucosa is lost, diarrhea and emaciation become severe.

32.115.5 Epidemiology

RP is highly contagious; it is spread mainly through airborne droplets, direct contact, feces, and contaminated fomites such as human beings. All secretions and feces of infected animals are contagious throughout the course of the disease. The virus is susceptible to most disinfectants. Wild ruminants frequently are a source of infection for livestock. The morbidity rate often approaches 100%, with a 25% to 90% mortality rate, making treatment unrewarding and the prognosis poor. Innate or specific resistance may protect individuals or herds from clinical signs after infection. Recovered animals do not appear to act as carriers. Valuable individuals may be helped by supportive therapy and hydration.

32.115.6 Necropsy Findings

Lesions are found mainly in the alimentary tract and lymphoid tissues. Subendocardial hemorrhages may also be seen in animals that die of acute illness. Oral erosions, edema, and congestion of the abomasum are typically seen, and ulcers and hemorrhagic to necrotic Peyer's patches occasionally are seen. The cecal and colonic mucosae are hemorrhagic, ulcerated, or necrotic. The lymph nodes are enlarged and have necrotic germinal centers.

32.115.7 Prevention and Control

Because there is only one known strain of RPV and protection after infection usually is lifelong, vaccination of cattle at 6 months of age and older in endemic areas with a live cell culture attenuated virus is an effective means of controlling RP.[304] Although there is some debate as to whether this vaccine causes immunosuppression,[305] it has been used safely and effectively in millions of cattle in Africa and Asia.[304] The vaccine does not produce adverse reactions, has a long shelf life, and produces solid immunity.[304] Its major disadvantages are that the lyophilized virus has to be kept cold, and once a vial has been reconstituted, it must be used quickly before the virus dies. A vaccinia-vectored gene vaccine currently under field testing is effective and has the advantages of long-term stability in harsh environments and ease of application (scratch on).[306] There is also a specific PPR vaccine available for goats and sheep.

Control of epidemics in areas where the disease is not endemic involves quarantine and slaughter of infected and contact animals, as well as other contact ruminants and swine. Disinfection of premises while under government quarantine is essential in controlling the disease. The virus is susceptible to most disinfectants and survives in the environment only for 2 to 3 days.

Global eradication of RP remains a viable goal.[298,306]

32.116 CHOKE AND ESOPHAGEAL DISORDERS

Charles L. Guard

32.116.1 Definition and Etiology

Choke is the term used for esophageal obstruction. In ruminants it is most common in cattle because of their eating habits. If the obstruction is complete, the condition is rapidly fatal (except in neonates) because of the inability to eliminate the gases of fermentation produced in the rumenoreticulum. Partial obstruction produces dysphagia or anorexia. Obstruction may be caused by the ingestion of foreign objects or large chunks of solid feedstuffs such as apples, potatoes, beet tops, or corn cobs. It also may be the result of space-occupying lesions in or near the esophagus. Choke must be differentiated from diseases that cause dysphagia by means of pharyngeal lesions and resultant neuromuscular dysfunction. Congenital or acquired lesions of the esophagus such as aortic arch anomalies and diverticula may cause signs similar to those of esophageal obstruction.

32.116.2 Clinical Signs and Differential Diagnosis

The earliest signs of complete esophageal obstruction from intraluminal objects are anxiety and ptyalorrhea (i.e., saliva dripping from the mouth because of an inability to swallow). The animal may violently swing the head from side to side and make repeated attempts to swallow. Staggering (which must be differentiated from ataxia caused by neurologic diseases) may be observed. In a 2-week-old calf with a cloth foreign body obstructing the distal esophagus at the cardia, regurgitation after drinking milk was observed.[307] Bloat develops soon after at a rate that depends on the nature of the ruminoreticular contents. Objects such as potatoes, apples, or mangels may be swallowed whole or in chunks too large to pass the entire esophagus, especially in cattle. Dry grain, particularly in pellet form, may be consumed so rapidly that sufficient saliva is not produced to lubricate the passage of the feed boluses. This is more common in sheep than in other ruminants; spontaneous resolution usually occurs within minutes to hours.

Obstruction from intraluminal objects commonly occurs in the cranial part of the cervical esophagus, at the thoracic inlet, or at the base of the heart. External palpation may localize the site of obstruction in the cervical esophagus. With more slowly developing and incomplete obstruction, anorexia and dysphagia may be observed. Bloat may occur repeatedly and resolve spontaneously or after passage of a stomach tube. The underlying cause may result in signs severe enough to mask the esophageal problem. Cellulitis along the cervical esophagus may result in a reluctance to lower the head or bend the neck laterally. Possible causes of cervical cellulitis include perivascular injection of irritating substances, abscesses, and reaction to *Hypoderma lineatum* larvae.

Esophageal stricture may follow a previous episode of esophageal obstruction or inflammation in adjacent tissues.[308] If no site of obstruction is externally evident, careful attempts to pass a stomach tube usually reveal the site of the problem. Radiography with barium contrast material may help identify the site of strictures, perforations, and diverticula.[309] Endoscopy of the esophagus may also aid in identifying the specific nature of functional or structural abnormalities. Megaesophagus has been observed after pharyngeal trauma,[310] as a congenital disorder,[311] and with hiatal hernia.[312] An animal with an esophageal stricture or a diverticulum may reflux boluses of feed mixed with saliva or regurgitate liquid ruminal contents. Failure to gain weight or progressive weight loss accompanies the failure to swallow feed successfully. Signs may be seen only when forage is consumed, whereas water and grain are swallowed normally.

Systemic diseases may lead to esophageal dysfunction. Rabies must always be considered when dysphagia is present, and appropriate precautions must be taken. Botulism also leads to esophageal transport failure, although dysphagia and a weak tongue are more prominent in the failure of affected animals to eat. Tetanus may be similar in appearance to esophageal obstruction because of the presence of bloat, dysphagia, and drooling. Several poisonous plants, including sneezeweed, larkspur, and milkweed, may cause excessive salivation, drooling, and bloat. Consumption of red clover infected with the fungus *Rhizoctonia leguminicola*, which produces the toxin slaframine, results in copious salivation. Pharyngeal trauma and subsequent cellulitis lead to dysphagia and drooling; severe bloat does not occur unless swelling is sufficient to occlude the esophagus. However, mild bloat frequently accompanies pharyngeal trauma caused by associated vagal nerve inflammation and dysfunction.[313]

32.116.3 Clinical Pathology

Common features of longstanding choke are dehydration and metabolic acidosis resulting from continued loss of sodium bicarbonate and sodium phosphate in saliva. As sodium depletion develops, the composition of saliva shifts to include more potassium under the influence of aldosterone. Inflammatory diseases lead to predictable changes in the hemogram.

32.116.4 Necropsy Findings

Animals that die of acute esophageal obstruction are bloated and may have saliva and feedstuffs in the upper airway. Postmortem examination of animals with protracted esophageal dysfunction may reveal focal dilations or stenoses of the esophagus. Esophageal perforation may have occurred because of pressure around an intraluminal foreign body or necrosis caused by extension of an adjacent septic process. 804 805

32.116.5 Treatment and Prognosis

In cases of complete esophageal obstruction, relieving bloat is the first concern. Passage of a stomach tube may be attempted if the animal is not in respiratory distress. Trocharization of the rumen or installation of a temporary fistula may be required. Until the esophagus has been cleared, it is important to keep the muzzle level or pointed down to reduce the risk of aspiration of saliva. Sedative drugs such as acepromazine or xylazine may be useful to calm the animal and permit careful examination. Suitable precautions should be taken if rabies is remotely possible. The history and an examination of the environment should enable the clinician to anticipate the nature of the obstructing object. Palpation of the neck along the left jugular furrow may reveal the site of obstruction in lean or thin-necked individuals. A manual oral examination should precede probing attempts with a stomach tube. Gentle pressure on the stomach tube as it passes down the esophagus should allow localization of the obstruction. A small hand can reach into the cranial part of the esophagus and may retrieve some solid objects. If the object is solid (e.g., a potato), it may be possible to massage it into the pharynx by pressing in the jugular furrow on both sides of the neck. Specialized equipment, such as a probang, is available with a corkscrew-like or pincer-like end that can be used to grasp or engage a foreign body and expedite its retrieval. If a mass of grain is obstructing the esophagus, external massage, probing with the stomach tube, or pumping fluid against the mass through the tube may break it up.

If the choke is intrathoracic and probing with a stomach tube does not relieve the problem, several courses of action are possible. A small ruminal fistula can be inserted to prevent bloat, and the animal can simply be placed in a pen without bedding, feed, or water. Many masses consisting of grain or hay spontaneously pass within 24

hours, whereas solid objects rarely pass spontaneously. If the obstruction does not resolve in 24 hours, the animal can be heavily sedated, a cuffed endotracheal tube can be passed to prevent aspiration, and vigorous lavage with water through a stomach tube can be attempted. The head should be held lower than the body to minimize the risk of aspiration. If the obstruction still cannot be relieved or it is believed that the obstruction is a solid object, a rumenotomy can be performed. Access to the esophagus through the cardia should allow snaring of the object with a loop of stiff wire or breakup of a mass of grain.

The long-term prognosis after choke is good unless esophageal mucosal damage has occurred. Stricture formation may follow cellulitis or pressure necrosis at the site of the obstruction. Aftercare for the choked animal consists of a soft diet and antiinflammatory drugs to minimize tissue swelling. Well-soaked alfalfa cubes made into a mush may pass partly obstructed areas. Hay and grain should be moistened before feeding, and grain should be offered only in small amounts at each feeding. Broad-spectrum antibiotics should be given if mucosal damage is suspected. Maintenance of an indwelling nasogastric tube for feeding for up to 10 days after severe esophageal trauma may be helpful in preventing strictures during healing.[309] Thick gruels made from soaked alfalfa cubes or pellets can be pumped into the rumen by a bilge pump designed for boats, or the animal can be fed and watered through a ruminal fistula. Surgical exploration may be required to determine the cause of esophageal obstruction from space-occupying lesions or strictures.[309] Abscesses may be drained, and granulomatous lesions resected. Esophageal diverticula, aortic arch anomalies, and intrathoracic surgical problems may not be easily treated.

32.117 ESOPHAGEAL DILATION (MEGAESOPHAGUS) AND HIATAL HERNIA

Bradford P. Smith

Megaesophagus rarely occurs in ruminants. It has been reported in association with pharyngeal trauma and resultant inflammatory involvement of the vagus[314] and with hiatal hernia (diaphragmatic hernia with herniation of the reticulum into the thorax) in which there was a large megaesophagus (10 cm in diameter by 20 cm in length).[315] Vagotomy and hiatal hernia are recognized as causes of diminished esophageal pressure.[316] A 4-month-old calf with megaesophagus lacked esophageal muscle cells and ganglion cells, and many fat cells were present.[317] The esophagus of a 12-month-old ram with megaesophagus was found to be heavily infected with *Sarcocystis arieticanis*, and eosinophilic inflammation and degeneration of muscle fibers were noted.[318] However, *Sarcocystis* species have been found in the esophagus of many sheep without megaesophagus,[319,320] making the diagnosis difficult. An 18-month-old heifer with megaesophagus also had eosinophilic submucosal infiltration, but no sarcocysts were seen.[321]

The principal clinical signs of megaesophagus are regurgitation or vomiting, usually shortly after eating. Mild, recurrent bloat and discomfort when a stomach tube is passed are also observed. In other cattle with a hiatal (diaphragmatic) hernia[322] or an esophageal diverticulum,[323] regurgitation or vomiting and bloat have also been reported. Contortion of the neck while eating, apparently caused by pain, was seen in one cow[315] and is reported in human beings with hiatal hernia.[324] In some cases of herniation of the reticulum into the thorax, bloat and regurgitation are not seen[325,326]; in others diaphragmatic hernia resulted in chronic bloat.[327] Diaphragmatic hernias may be either congenital or acquired. It appears that acquired diaphragmatic hernias are most common.

A stomach tube should be passed to the rumen to rule out choke or an intraluminal mass obstructing the esophagus as a cause. If a tube can be passed freely to the rumen, plain and contrast radiographs of the esophagus should be

taken. If this is not possible, surgical exploration of the abdomen for a diaphragmatic hernia and digital palpation of the cardia and terminal esophagus by means of rumenotomy should be considered.

Megaesophagus associated with pharyngeal trauma has a good prognosis,[314] whereas megaesophagus associated with hiatal hernia has a more guarded prognosis.[315,322] Supportive treatments and stomach tubing with fluids may be required for 1 to 2 weeks until the animal is able to drink unaided. Longer-term support can be given to a valuable animal by surgically creating a ruminal fistula fitted with a rubber cannula through which feed and water can be given until normal deglutition is resumed.

32.11 RUMINANT ABDOMINAL ULTRASONOGRAPHY

Betsy Vaughan

The key to diagnosing ruminant abdominal disorders is the thorough physical examination (see Chapter 1). A relatively new, noninvasive, and useful adjunct is the use of ultrasound.

Abdominal ultrasound provides a readily available, real time, noninvasive method of imaging the abdomen in ruminants suspected of abdominal disease. Radiographic examination of the adult bovine abdomen offers limited information because of the large size of the patient and the need for expensive equipment with high milliampere-seconds (mAs) and kilovolt peak (kVp). Although radiographic examination of the small ruminant abdomen offers clinically useful information, it should be used in conjunction with abdominal ultrasonography to evaluate the abdominal organs and to further characterize radiographic abnormalities. Exploratory laparotomy is still commonly performed in cattle with unexplained illness referable to the abdominal cavity. Ultrasonographic evaluation of the ruminant abdomen has become an important part of the diagnostic workup in ruminants suspected of abdominal disease in combination with CBC, serum chemistry, peritoneal fluid analysis, urinalysis, and ruminal fluid analysis and can often provide valuable information that may preclude the need for exploratory laparotomy.[328–331] Abdominal ultrasound is indicated in patients with signs of abdominal pain, stasis, decreased motility, increased motility, lethargy, anorexia, bloat, regurgitation, fever of unknown origin, and suspected renal or liver disease. Ultrasound is also useful for diagnosing thoracic disorders.

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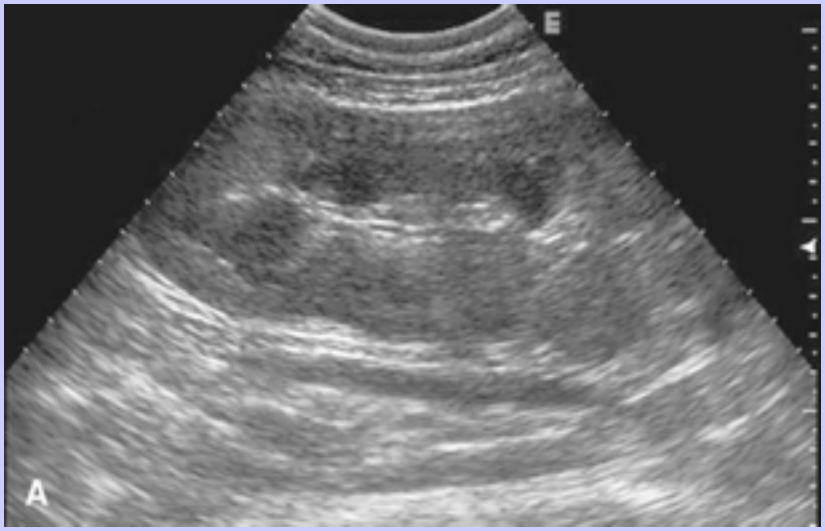
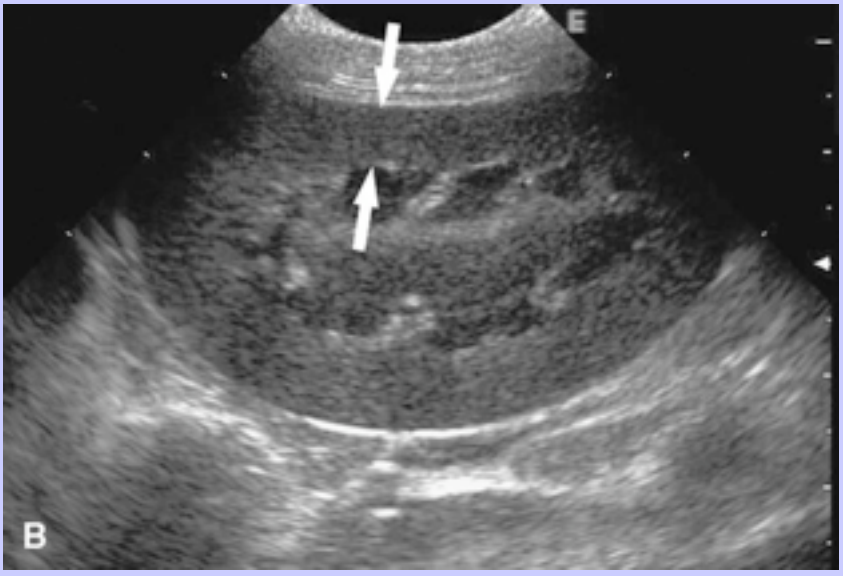
Bovine patients should be restrained in a head gate and standing stocks. Squeeze chutes are not ideal because access to the complete abdomen is seldom possible. Small ruminants can usually be restrained with halters or collars. Bovine and small ruminant patients seldom need sedation for restraint during the examination. Patients should be prepared for complete abdominal ultrasound examination by surgical clipping of the left and right sides of the abdomen ventral to a diagonal line extending from the transverse processes of the lumbar vertebrae to the level of the elbow joint approximately at the level of the ventral lung margin. The entire ventral abdomen should be clipped from the xyphoid to the inguinal region (Fig. 32-70). If only one organ is to be examined, then the specific anatomic region should be clipped with wide margins. The clipped area should be washed thoroughly with water, and ultrasound coupling gel should be applied to the region. If clipping is not possible, alcohol saturation of the skin and hair may be adequate in patients with a short hair coat. The examination is performed with a low-frequency, curvilinear transducer (2.5 to 5 MHz) in large patients such as adult cattle, which provides penetration to a depth of 24 to 30 cm. A medium frequency (4 to 8 MHz) “microconvex” curvilinear transducer is ideal for evaluating calves and small ruminants. In large patients, superficial structures near the skin surface should also be evaluated using the medium-frequency transducer when image quality permits. This transducer is also useful for performing transrectal ultrasonography of the left kidney, urinary bladder, ureters, and urethra in cattle.

Fig. 32-70 Patient preparation for abdominal ultrasound examination. The region to be clipped for complete abdominal evaluation is shown, including the paralumbar fossa region, the intercostal spaces from the ventral lung margin to the costochondral junctions and the entire ventrum from the xiphoid to the inguinal region.

Fig. 32-71 **A**, Sonogram of a normal right kidney viewed from the right paralumbar fossa region in a 5-year-old Holstein dairy cow. Note the lobulated shape and indistinct corticomedullary junction. This image was obtained with a 2.5-MHz curvilinear transducer at a depth of 20 cm. **B**, Sonogram of a normal right kidney viewed from the right paralumbar fossa region in a 4-year-old castrated male Nigerian Dwarf goat. Note the smooth renal capsule, ovoid shape, and distinct corticomedullary junction *(arrows)*. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 7 cm.





The examination should begin with detailed evaluation of the right paralumbar fossa region followed by evaluation of each intercostal space beginning at the ventral lung margin and scanning ventrally beyond the costochondral junctions. The ventral abdomen is then evaluated from xyphoid to inguinal region. The examination is repeated on the left side. The abdomen is evaluated for abnormalities of the kidneys, liver, gall bladder, pancreas, spleen, rumen, reticulum, omasum, abomasum, duodenum, small intestine, cecum, and colon and for the presence and character of peritoneal fluid.

32.118.1 Kidneys

32.118.1.1 NORMAL APPEARANCE (Fig. 32-71)

The right kidney is imaged from the right paralumbar fossa region and right eleventh to twelfth intercostal space at a scanning depth of 10 to 20 cm in cattle and 6 to 14 cm in small ruminants. The anatomic detail of the right kidney is greater than that of the left because of its more superficial location within the abdomen. In small ruminants the left kidney is routinely imaged in the right paralumbar fossa caudal to the right kidney at scanning depths of 8 to 14 cm. The left kidney in cattle can often be seen in this region as well. The left kidney cannot usually be visualized from the left side of the abdomen because it is obscured by the gas-filled rumen. Transrectal imaging of the left kidney should be performed in adult cattle suspected of having renal disease even when it is visualized transcutaneously, because it offers superior anatomic detail.

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In cattle the normal right kidney has been reported to range from 8.1 to 11 cm in length and 4 to 7 cm in width.[332] Transrectally the left kidney has been reported to range in width from 4.5 to 7.5 cm in normal cattle. Transrectal length measurements of the left kidney were not reported, as it cannot be imaged in its entirety.[333] However, in the author's experience, normal bovine kidneys routinely measure up to 16 to 18 cm in length. Normal bovine kidneys demonstrate a lobulated appearance with an indistinct corticomedullary junction. Renal parenchyma should be less echogenic than hepatic parenchyma. The renal sinus demonstrates a hyperechoic appearance because of the presence of the renal calyces, adipose tissue, and connective tissue.[332,333]

In small ruminants, renal size can vary greatly depending on the size of the animal. In sheep the right kidney ranges from 7.1 to 8.9 cm in length and 3.4 to 5.5 cm in width, and the left kidney from 7.2 to 9.2 cm in length and 3.5 to 5.4 cm in width.[334,335] Small ruminants demonstrate smoothly marginated, oval kidneys. The renal capsule may be visible as a thin hyperechoic line. As in cattle, the renal parenchyma should be less echogenic than hepatic parenchyma. In contrast to cattle, the corticomedullary junction is clearly distinguishable. The renal pelvis demonstrates a hyperechoic appearance because of the presence of renal calyces, adipose tissue, and connective tissue.[334,335]

32.118.1.2 ABNORMAL FINDINGS

Changes in size, shape, architecture, and echogenicity are nonspecific ultrasonographic abnormalities that can be seen in ruminants with acute or chronic renal failure, amyloidosis, nephritis, and pyelonephritis. Abnormalities seen in patients with acute renal failure include renal enlargement, thickening of the renal cortex, and perirenal edema (Fig. 32-72). In cases of chronic renal failure, the kidneys are often smaller than normal and may be misshapen. Echogenic material can sometimes be seen within the ureters and renal calyces

of cows with pyelonephritis.[336] Ultrasound-guided percutaneous biopsy is commonly required to distinguish the specific cause of disease in patients with acute or chronic renal disease.

Fig. 32-72 Sonogram of the right kidney viewed from the right paralumbar fossa region in a 12-year-old pygmy goat buck with acute renal failure. Note the increased cortical echogenicity and thickness *(arrows)*. Perirenal edema *(arrowheads)* is seen surrounding the kidney. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 8 cm.

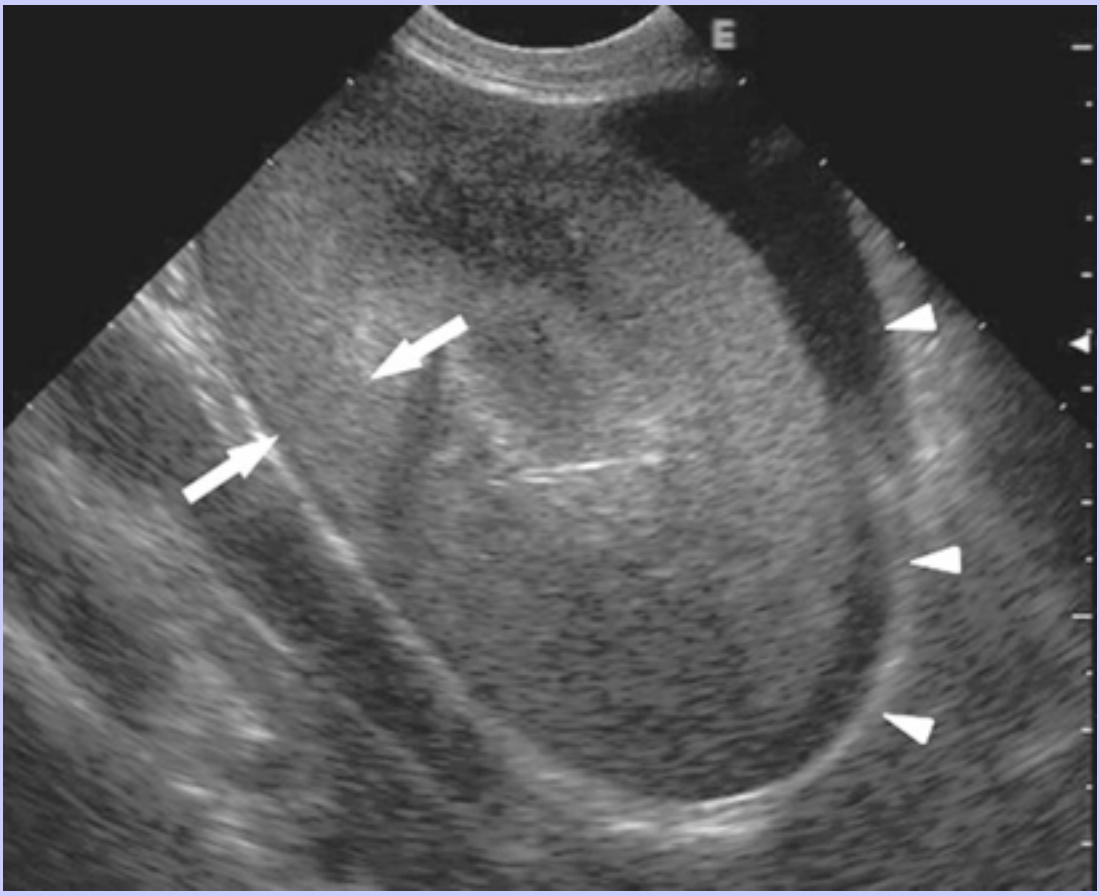
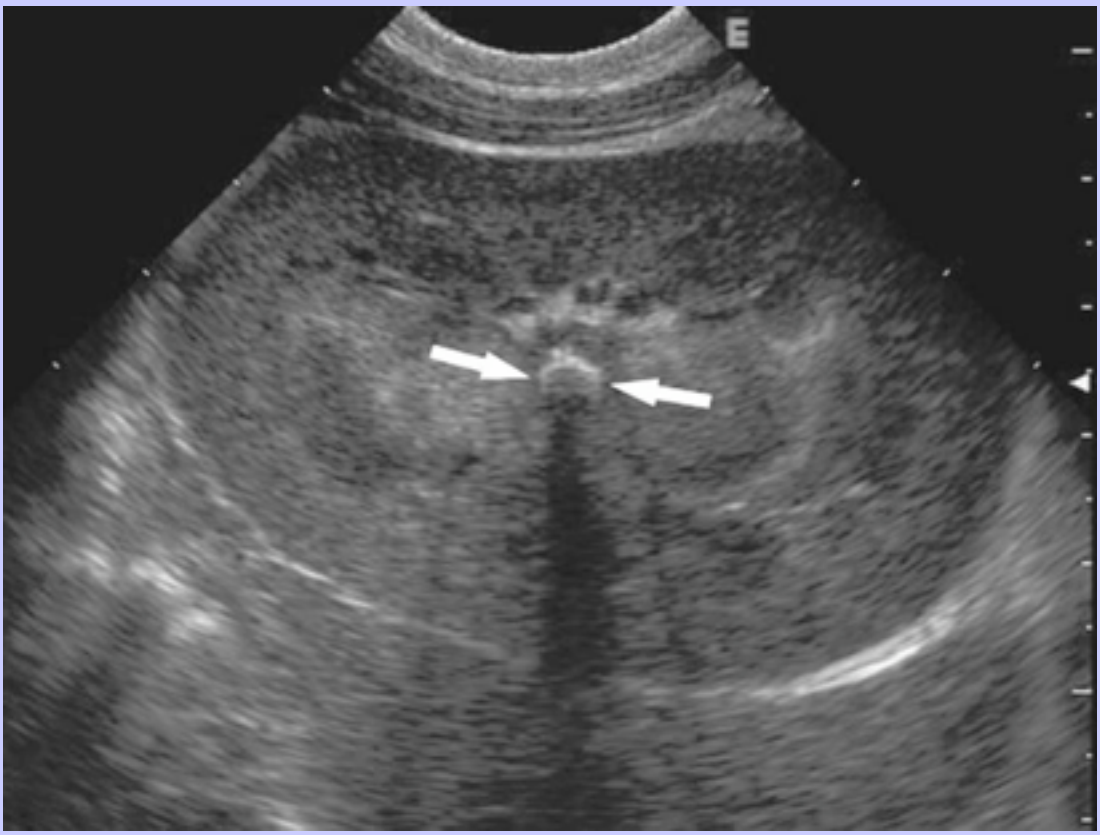
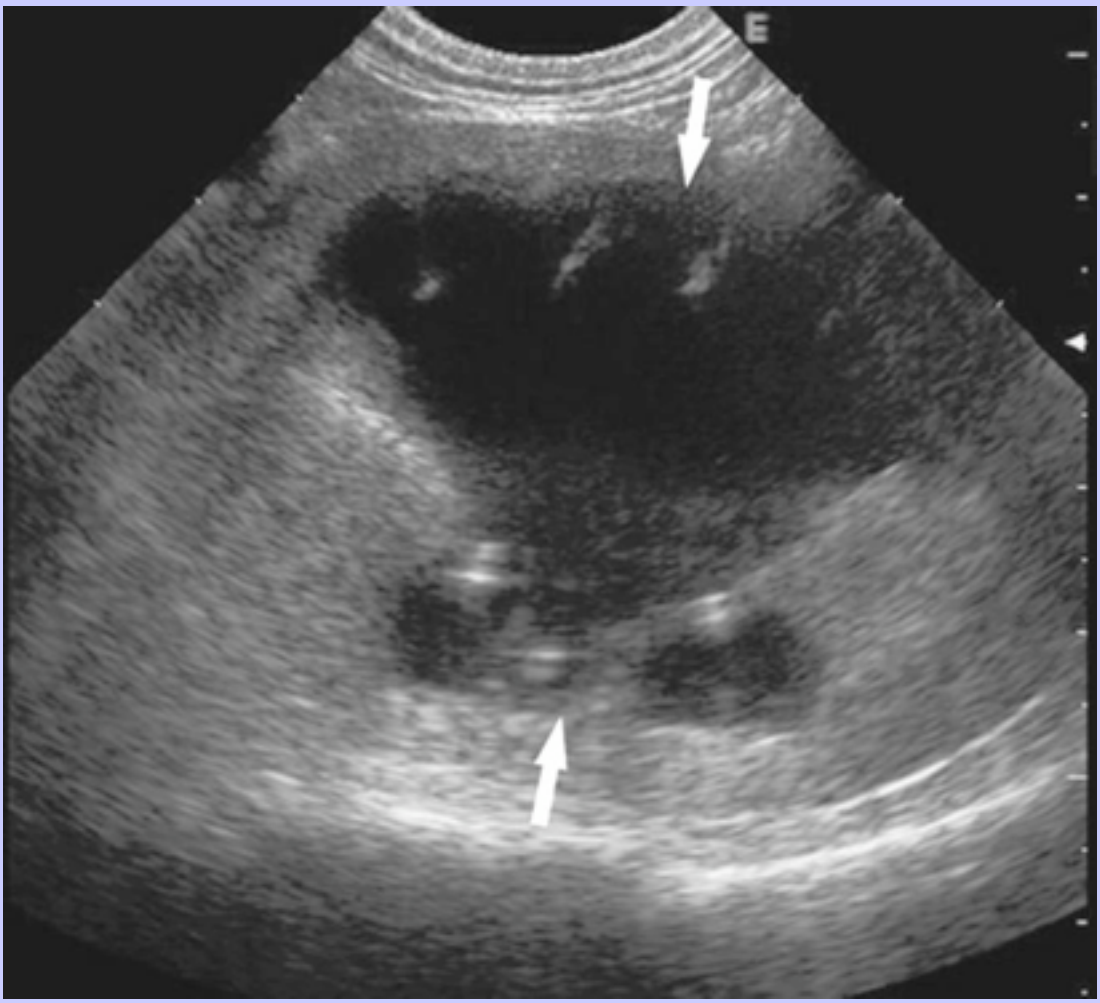


Fig. 32-73 Sonogram of a small right nephrolith *(arrows)* viewed from the right paralumbar fossa region in a 3-year-old Nigerian Dwarf doe presented because of abdominal pain. Note the strong shadow cast by the nephrolith. No dilation of the renal pelvis is seen. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 8 cm.



Specific renal abnormalities include nephrolithiasis, hydronephrosis, cortical cysts, renal neoplasia, and renal abscessation. Nephroliths are round or irregularly shaped, hyperechoic structures within the renal sinus that cast strong acoustic shadows (Fig. 32-73). Associated dilation of the renal sinus or calyces may be seen with obstructive nephrolithiasis. Hydronephrosis is characterized by dilation of renal calyces with anechoic urine and may be seen with a postrenal obstruction (Fig. 32-74). Hydronephrosis is commonly seen in small ruminants with obstructive urolithiasis. Transrectal evaluation of the ureters and urinary bladder is indicated in 807
bovine patients with hydronephrosis or obstructive nephrolithiasis to evaluate for the presence of ureteroliths 808
or uroliths within the bladder.

Fig. 32-74 Sonogram of severe hydronephrosis of the left kidney viewed from the right paralumbar fossa region in a 10-year-old pygmy doe. This doe had a uterine mass that was compressing the left ureter. Note the severe dilation of the renal pelvis *(arrows)*. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 7 cm.



The ultrasonographic appearance of cystic renal disease in ruminants has not been reported; however, congenital renal cysts are relatively common in cattle, sheep, and goats and should be readily recognizable via abdominal ultrasound.[337–339] Cortical cysts have been described in horses as thin-walled anechoic spheric structures seen within the renal cortex.[340] Single small cysts may be considered incidental findings.

Mass lesions within or obliterating the normal renal parenchyma can be seen with neoplasia or abscessation. Both renal abscessation and renal neoplasia are rare in ruminants.[337,338,341] Renal abscesses may be

distinguished from neoplasia based on their ultrasonographic appearance. Renal abscesses are usually encapsulated and contain anechoic to echogenic fluid. Ultrasound-guided percutaneous aspiration can be used to obtain a sample for cytology and culture and to facilitate drainage in affected animals. Ultrasound-guided biopsy is necessary to identify specific neoplastic processes.

32.118.2 Urinary Bladder and Ureters

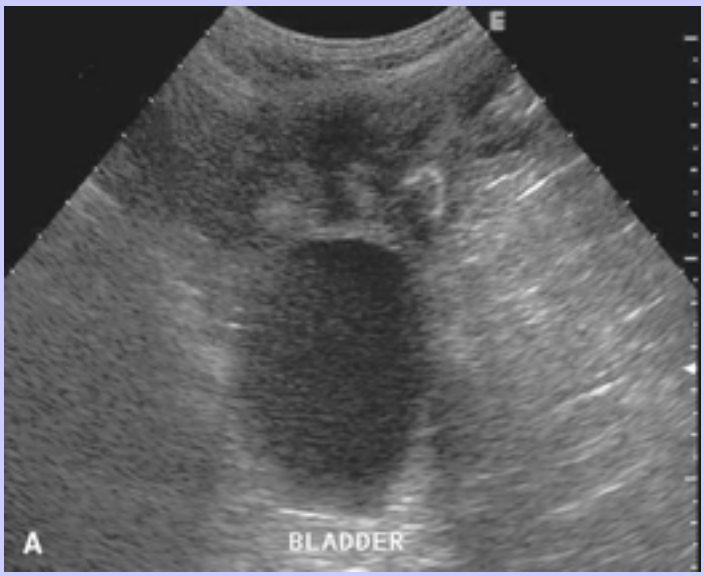
32.118.2.1 NORMAL APPEARANCE

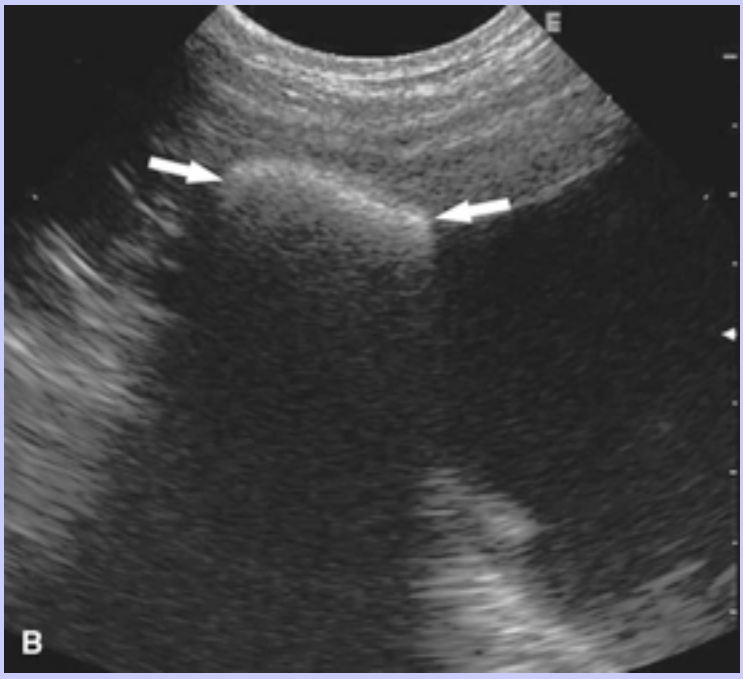
The urinary bladder is normally imaged from the right or left caudoventral abdomen in small ruminants at a scanning depth of 5 to 14 cm and appears as an oval or spheric structure with a thin wall containing anechoic urine (Fig. 32-75, *A*). The size and shape of the urinary bladder are dependent on its distention at the time of examination. The urinary bladder is often not visible transcutaneously in cows but can be evaluated transrectally along with the urethra and the distal portion of the right and left ureters.[333,342,343] The normal urethra is not visualized except at the onset of urination and appears as a thin anechoic line when distended with urine.[333] An attempt should be made to locate the ureters to the right and left of the urinary bladder at the trigone region. The ureters should then be followed cranially as far as they can be visualized.

32.118.2.2 ABNORMAL FINDINGS

Abnormalities of the urinary bladder include distention secondary to obstruction, thickening of the bladder (cystitis), cystic calculi, mass lesions, and rupture. Severe distention of the urinary bladder can be indicative of mechanical or functional obstruction. For this reason, transabdominal ultrasound examination is commonly used as a screening procedure for obstructive uropathy in small ruminants.[334,337,338] In affected animals the bladder will be markedly distended and may demonstrate multiple pinpoint echogenic or hyperechoic particles within the urine as well as cystic calculi.[334] Cystic calculi are seen within the bladder and can be hyperechoic or hypoechoic with a round or irregular shape. They may or may not cast strong shadows (Fig. 32-75, *B*). Mass lesions associated with the urinary bladder wall include neoplasia and hematoma that may be difficult to differentiate ultrasonographically.

Fig. 32-75 **A**, Sonogram of a normal urinary bladder viewed from the left inguinal region in a 2-year-old pygmy goat cross doe. This image was obtained with a 4-MHz curvilinear transducer at a depth of 15 cm. **B**, Cystic calculi *(arrows)* in an 11-year-old pygmy doe with urolithiasis. This image was obtained in the left inguinal region with a 7.5-MHz curvilinear transducer at a depth of 5 cm.





Urinary bladder rupture may occur secondary to obstructive urolithiasis or trauma. Ultrasound examination reveals an increased amount of free anechoic fluid within the abdomen. Definitive diagnosis can be made by comparing the concentration of creatinine in abdominal fluid to the serum concentration.

Ureteroliths may be seen on transrectal ultrasound examination in bovine patients and demonstrate the appearance of hyperechoic structures within the ureter that cast strong shadows. Marked ureteral dilation that appears as a tubular structure dilated with anechoic fluid is seen cranial to the ureterolith.[343] Thickening of the ureteral wall may occur secondary to inflammation. Ureteral rupture can occur secondary to obstruction and results in accumulation of anechoic fluid within the retroperitoneal space.[329]

32.118.3 Liver

32.118.3.1 NORMAL APPEARANCE (Fig. 32-76)

The right liver lobe is imaged from the right sixth to twelfth intercostal spaces at a scanning depth of 6 to 14 cm in small ruminants and 20 to 30 cm in cattle and demonstrates a homogenous, echogenic appearance. The branching vasculature of the portal and hepatic veins can be seen in addition to fine vascular markings scattered throughout the hepatic parenchyma. The liver parenchyma is normally more echogenic than renal parenchyma and less echogenic than splenic parenchyma. In contrast to horses, an anatomic window for direct comparison of the liver and spleen does not exist in ruminants. Subjective comparison between the spleen on the left side and the liver on the right side should be undertaken with caution because changes in image quality and machine settings may lead to a false assessment of echogenicity. Bile ducts are not normally visible ultrasonographically. The ventral borders of the liver are usually sharp or mildly rounded and extend near or beyond the costochondral junctions. The most accurate method of assessing hepatic size in cattle is to measure the thickness of the liver overlying the portal vein (normally 5.1 to 14.1 cm) and the caudal vena cava (normally 8.2 to 15.4 cm).[344] Cows with high body condition scores and milk production will have larger livers than thin cows with decreased milk production.[334,345] The portal vein and caudal vena cava should also be assessed during the hepatic ultrasound examination. The portal vein is round and is commonly seen deep to the liver in the right eighth to twelfth intercostal spaces, ventral and lateral to the caudal vena cava. The caudal vena cava is usually seen only in the right eleventh and twelfth intercostal spaces, dorsal and deep to the portal vein.[345–348]

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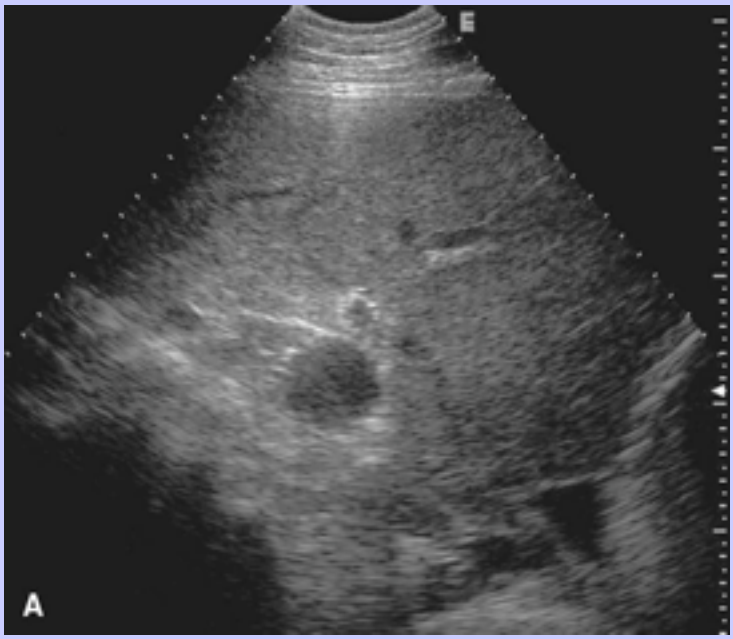
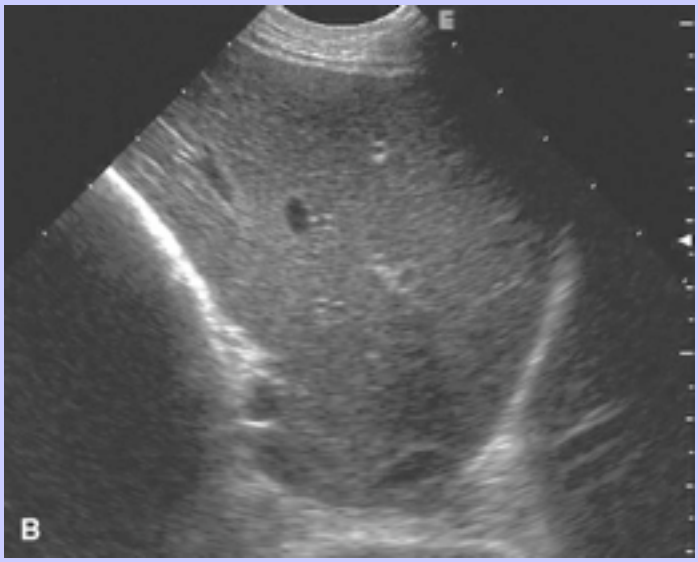
Fig. 32-76 **A**, Sonogram of normal liver viewed from the right tenth intercostal space in a 5-year-old Holstein dairy cow. This image was obtained with a 2.5-MHz curvilinear transducer at a depth of 27 cm. **B**, Sonogram of normal liver viewed from the right tenth intercostal space in a 12-year-old pygmy buck. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 10 cm. Dorsal is to the right and ventral is to the left.



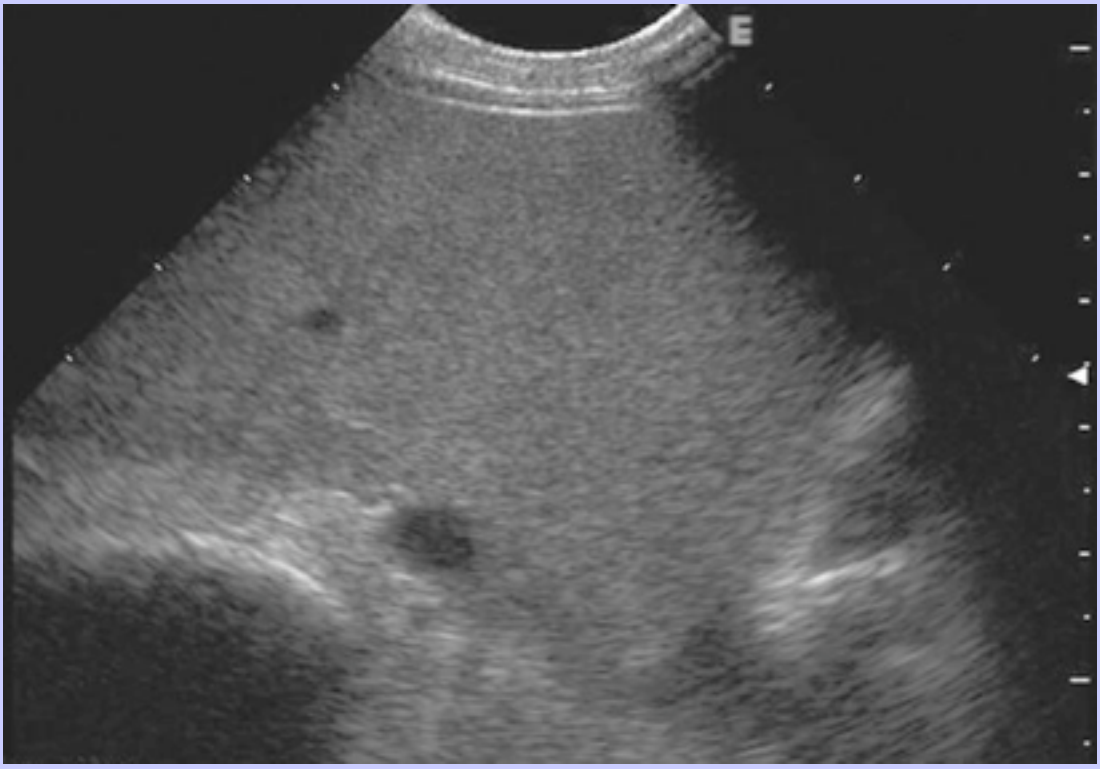


32.118.3.2 ABNORMAL FINDINGS

Nonspecific ultrasonographic abnormalities of the liver, including hepatomegaly, changes in echogenicity, and a decreased number of fine vascular markings, can be seen with hepatopathies from numerous causes including pyrrolizidine alkaloid toxicosis,[349] fatty liver disease, and diffuse infiltrative disease[350] (Fig. 32-77). Fatty liver disease, in particular, has been reported to result in an overall increase in hepatic echogenicity with decreased fine vascular markings.[350] Variable changes in echogenicity can also be seen during the parenchymal stage of fascioliasis.[351] Ultrasound-guided liver biopsies can be used to obtain a definitive diagnosis.

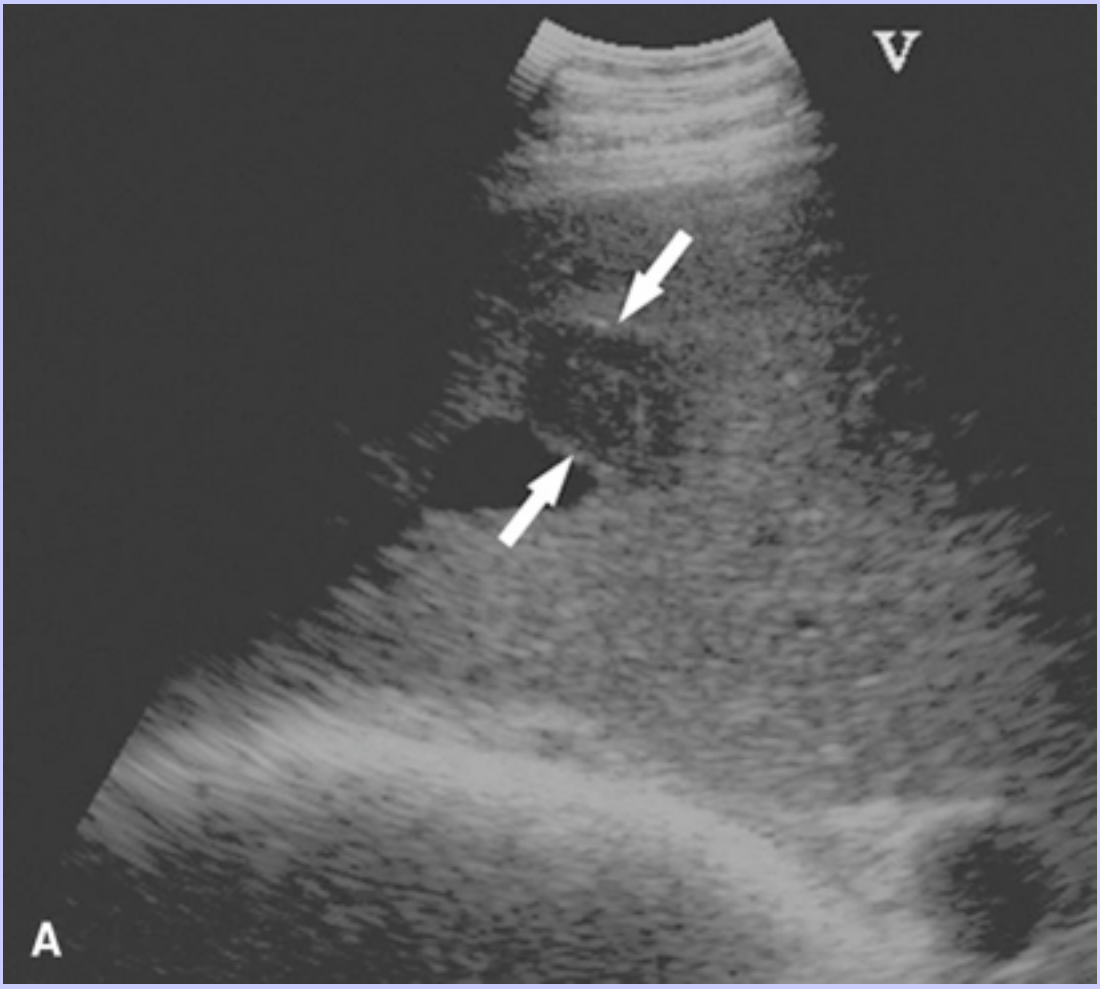
Hypoechoic or hyperechoic mass lesions within the hepatic parenchyma may represent abscessation or neoplasia. Hepatic abscessation is common in cattle and can occur with numerous disease processes, including cholangitis, traumatic reticuloperitonitis (TRP), or bacteremia secondary to rumenitis or omphalophlebitis. Hepatic abscesses demonstrate a variable appearance with a homogenous or mixed echogenicity, hyperechoic or hypoechoic contents, and a variable degree of encapsulation (Fig. 32-78).[345,352,353] The appearance of the abscess can change throughout the course of disease. Early abscesses may demonstrate a hypoechoic appearance without visible encapsulation. More chronic abscesses are usually well encapsulated with more echogenic contents. Gas echoes within the abscess are indicative of anaerobic infection. Ultrasound-guided percutaneous aspiration commonly yields fluid for culture and sensitivity.[345,352,353] Thrombosis of the caudal vena cava can occur secondary to hepatic abscessation. Affected cows show dilation of the caudal vena cava characterized by a change in shape from triangular to oval or round. Dilation of the hepatic veins may also be seen. Thrombi are typically not visualized ultrasonographically because of their location deep within the abdomen or in the thorax.[354]

Fig. 32-77 Sonogram of an abnormal liver demonstrating increased echogenicity and decreased fine vascular markings viewed from the right ninth intercostal space in a 4-year-old castrated male Nigerian Dwarf goat with hepatic lipidosis. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 8 cm. Dorsal is to the right and ventral is to the left.



Hepatic neoplasia is uncommonly reported in ruminants.[355] The ultrasonographic appearance of the liver is variable in these cases. The hepatic parenchyma may be diffusely affected, or discrete single or multiple masses may be seen. Metastatic lesions can be seen within the hepatic parenchyma or may distort the hepatic capsule along the serosal surface.[345,355] Ultrasound-guidance is recommended when obtaining percutaneous biopsies to avoid sampling unaffected parenchyma.

Fig. 32-78 **A**, Hepatic abscess measuring 3.6 cm × 2.2 cm *(arrows)* viewed from the right tenth intercostal space in a 4-year-old Holstein dairy cow with anorexia. This image was obtained with a 2.5-MHz curvilinear transducer at a depth of 20 cm. **B**, Small hepatic abscess *(arrows)* viewed from the right eleventh intercostal space in an 8-month-old Angora kid with disseminated *Rhodococcus equi* infection. This image was taken with a 13-MHz linear transducer at a depth of 3 cm. Dorsal is to the right and ventral is to the left.



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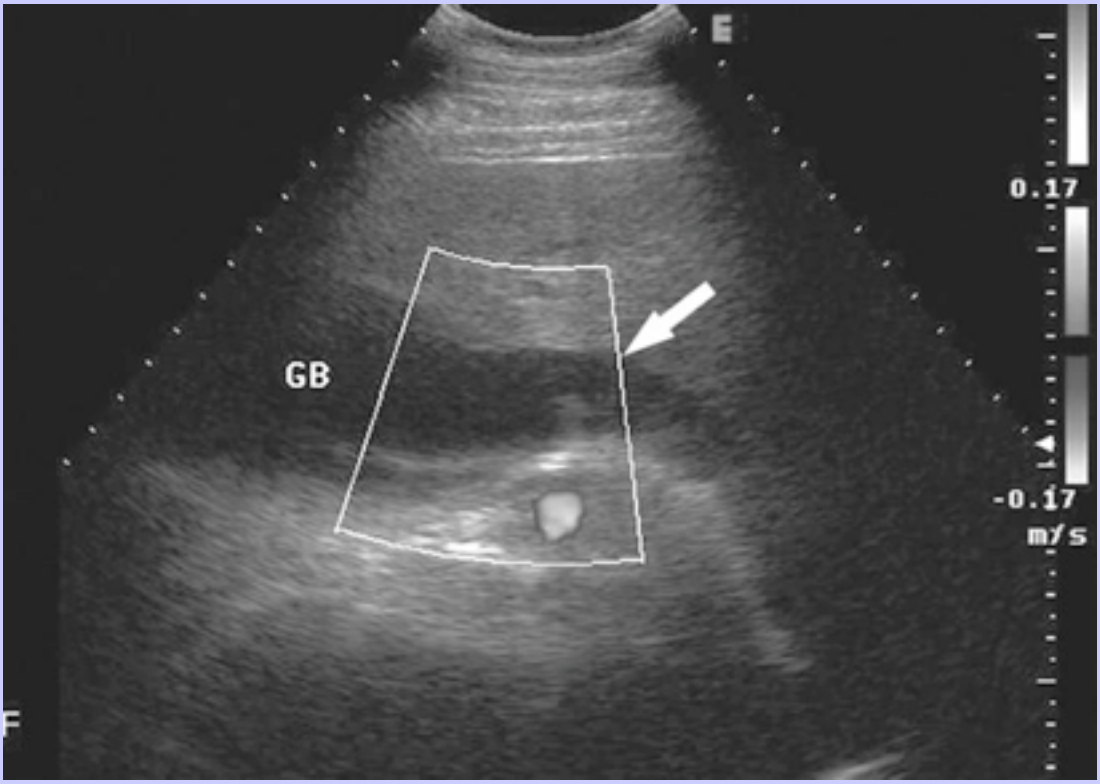
Ultrasound can be helpful to differentiate hepatocellular from obstructive cholestasis.[345,356,357] Ruminants with obstructive cholestasis will show changes consistent with extrahepatic or intrahepatic obstruction. Extrahepatic obstruction usually occurs at the level of the duodenal papilla. Ultrasonographic findings include dilation of the gall bladder with bile and echogenic sludge, dilation of the common bile duct, and dilation of the intrahepatic ducts (Fig. 32-79). Dilation of the intrahepatic ducts results in a “parallel channel sign” because intrahepatic ducts lie parallel to portal veins. The presence of gas echoes within the bile ducts is consistent with anaerobic suppurative cholangitis. The ductal phase of fascioliasis results in distention and tortuosity of the bile ducts.[351] Occasionally, moving echogenic forms can be seen within these bile ducts in infected sheep.[351] Mineralization of individual bile ducts can be seen in cases of chronic fascioliasis.[345,357] Ruminants with hepatocellular cholestasis may show ultrasonographic changes consistent with infiltrative disease or hepatic congestion or may have a normal hepatic ultrasound examination.

Fig. 32-79 Dilated cystic duct *(arrow)* viewed from the right ventral abdomen in a 3-year-old Holstein dairy cow with extrahepatic cholestasis. Color Doppler confirms the absence of blood flow in the cystic duct. This image was obtained from the right ventral abdomen using a 4-MHz curvilinear transducer at 21.5 cm. Dorsal is to the right and ventral is to the left.



32.118.4 Gall Bladder

32.118.4.1 NORMAL APPEARANCE (FIG. 32-80, *A*)

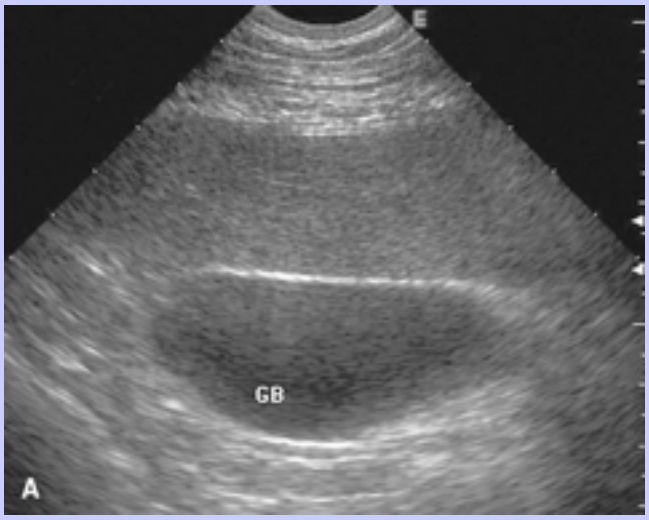
The gall bladder is visualized deep to the liver in the right ninth to eleventh intercostal spaces and is a thin-walled, round or oval structure filled with anechoic fluid that is usually visualized in only one or two intercostal spaces. However, ruminants with anorexia have no reflex stimulus for emptying the gall bladder. This creates a distended appearance without obstruction (Fig. 32-80, *B*).[347] The gall bladder is usually seen at a scanning depth of 6 to 10 cm in small ruminants and 12 to 18 cm in cattle.

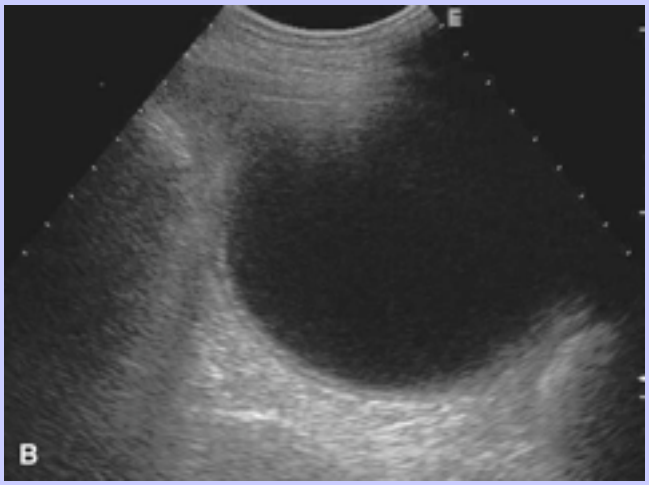
32.118.5

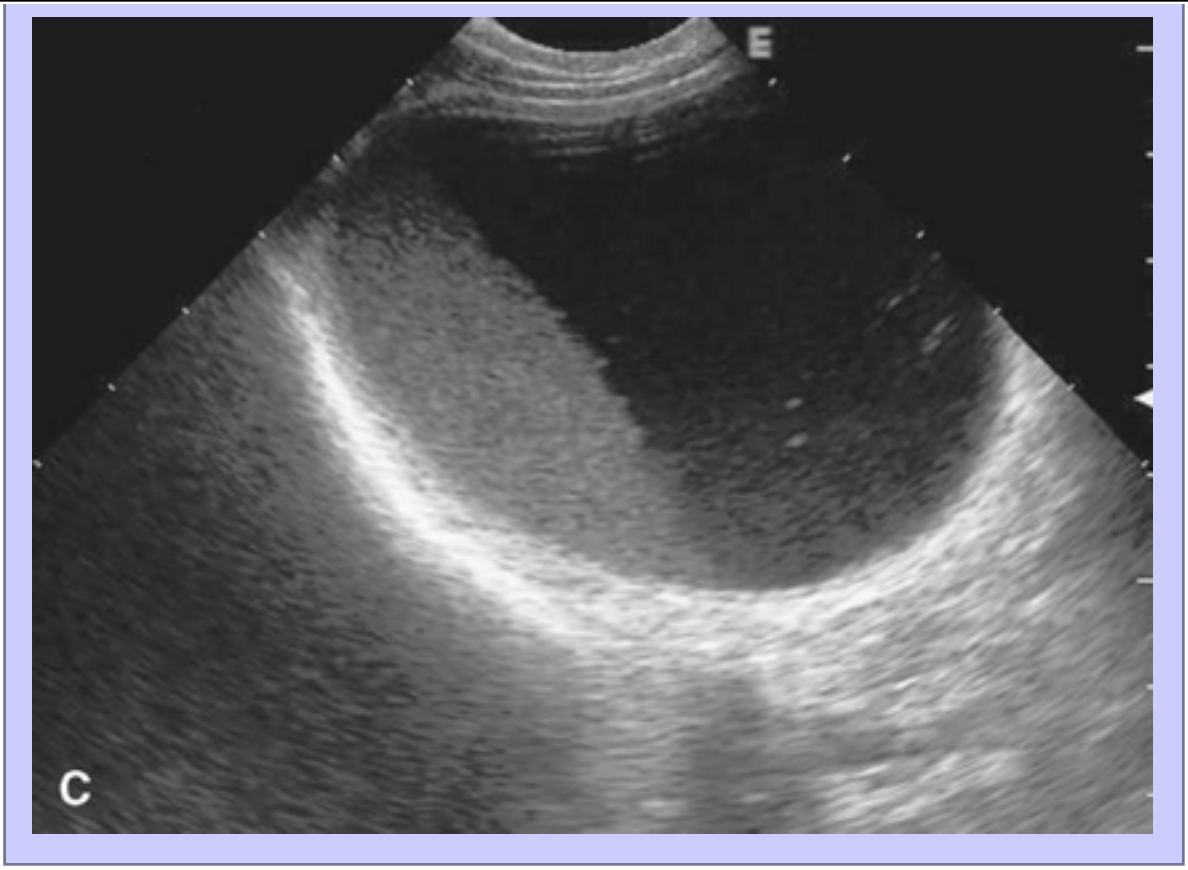
Abnormal Findings

Abnormalities of the gall bladder include, biliary distention, wall thickening, sediment accumulation, or cholelithiasis. As mentioned earlier, it is important to differentiate gall bladder distention secondary to anorexia or fasting from distention secondary to cholestasis. Cholestatic obstruction is a serious condition that can lead to rupture if the obstruction is not resolved.[358] Wall thickening may be secondary to edema or inflammation. Choleliths appear as discrete hyperechoic structures that cast strong shadows. Sediment, on the other hand, demonstrates an amorphous echogenic to hyperechoic appearance and will have a dependent location (ventral in standing animals) within the gall bladder (Fig. 32-80, *C*). Ultrasound-guided cholecystocentesis has been reported to be a valuable diagnostic technique in cases suspect for liver fluke infection *(Fasciola hepatica, Dicrocoelium dendriticum)*.[359] Transhepatic cholecystocentesis is considered safer than transcutaneous aspiration as it decreases the likelihood of peritonitis secondary to bile leakage into the abdomen.[360] Bile examination for detection of fluke eggs is superior to fecal examination because liver fluke eggs are stored in the gall bladder for weeks.[359]

Fig. 32-80 **A**, Sonogram of a normal gall bladder viewed from the right tenth intercostal space in a 2-year-old Hampshire ram. This image was obtained with a 5.5-MHz curvilinear transducer at a depth of 10 cm. **B**, Sonogram of a distended gall bladder viewed from the right tenth intercostal space in a 3-year-old Holstein dairy cow with anorexia. This image was obtained with a 3.5-MHz curvilinear transducer at a depth of 16 cm. **C**, Sonogram of gall bladder distention with bile sediment viewed from the right twelfth intercostal space in a 12-year-old Pygmy buck. This image was obtained with a 7.5-MHz transducer at a depth of 10 cm. Dorsal is to the right and ventral is to the left.







32.118.6 Pancreas

32.118.6.1 NORMAL APPEARANCE

Ultrasonographic imaging of the right lobe and body of the bovine pancreas has been reported in the literature.[361] The pancreas is visualized in the right paralumbar fossa region and the right eleventh and twelfth intercostal spaces ventral to the liver and right kidney. The left lobe cannot be visualized because of its deep location within the abdomen. The pancreas demonstrates a triangular shape and is isoechoic or slightly hyperechoic to the adjacent liver.[361]

32.118.6.2 ABNORMAL FINDINGS

Ultrasonographic abnormalities of the ruminant pancreas have not been described; however, changes in echogenicity secondary to pancreatitis and dilation of the accessory pancreatic duct secondary to masses or calculi have been reported in other species.[361]

32.118.7 Spleen

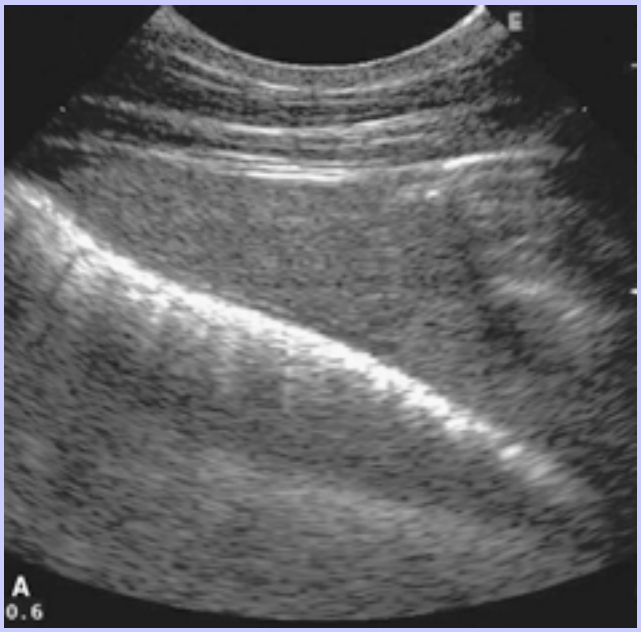
32.118.7.1 NORMAL APPEARANCE (Fig. 32-81)

The spleen is visualized in the left seventh to twelfth intercostal spaces between the rumen and body wall at the cranial extent of the rumen at a scanning depth of 6 to 14 cm in small ruminants and 16 to 28 cm in cattle. Splenic size is variable, and the spleen may extend to the ventral midline in normal cows.[362] The spleen demonstrates a homogenous appearance and appears more echogenic and less vascular than the liver. The splenic capsule appears as a thin hyperechoic line.[362]

32.118.7.2 ABNORMAL FINDINGS

Splenic abnormalities may include changes in echogenicity indicative of diffuse parynchemal disease or discrete masslike lesions consistent with neoplasia or abscessation. Suppurative splenitis or abscessation can occur secondary to septicemia or TRP (Fig. 32-82).[331] Splenic neoplasia has also been reported in ruminants.[362] Ultrasound-guided percutaneous aspiration or biopsy may provide definitive cytology, culture, or histopathologic diagnosis but should be undertaken with caution in compromised patients because of the risk of hemorrhage.

Fig. 32-81 **A**, Sonogram of normal spleen viewed from the left ninth intercostal space in a 12-year-old pygmy buck. Note that the spleen appears less vascular relative to normal liver. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 4 cm. **B**, Sonogram of normal spleen viewed from the left tenth intercostal space in a 4-year-old Holstein dairy cow. This image was obtained with a 2.5-MHz curvilinear transducer at a depth of 16 cm. Dorsal is to the *right* and ventral is to the *left*.



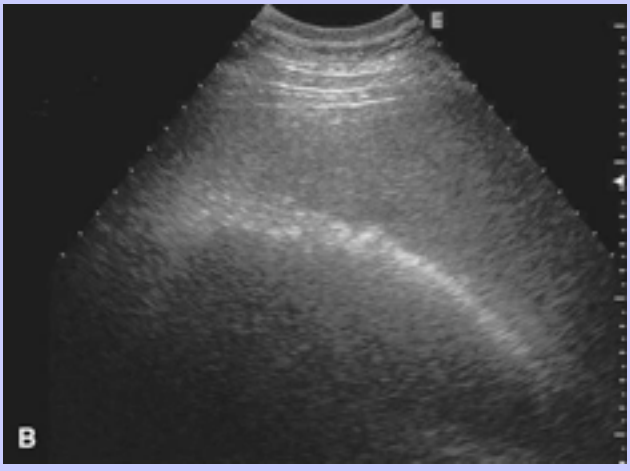
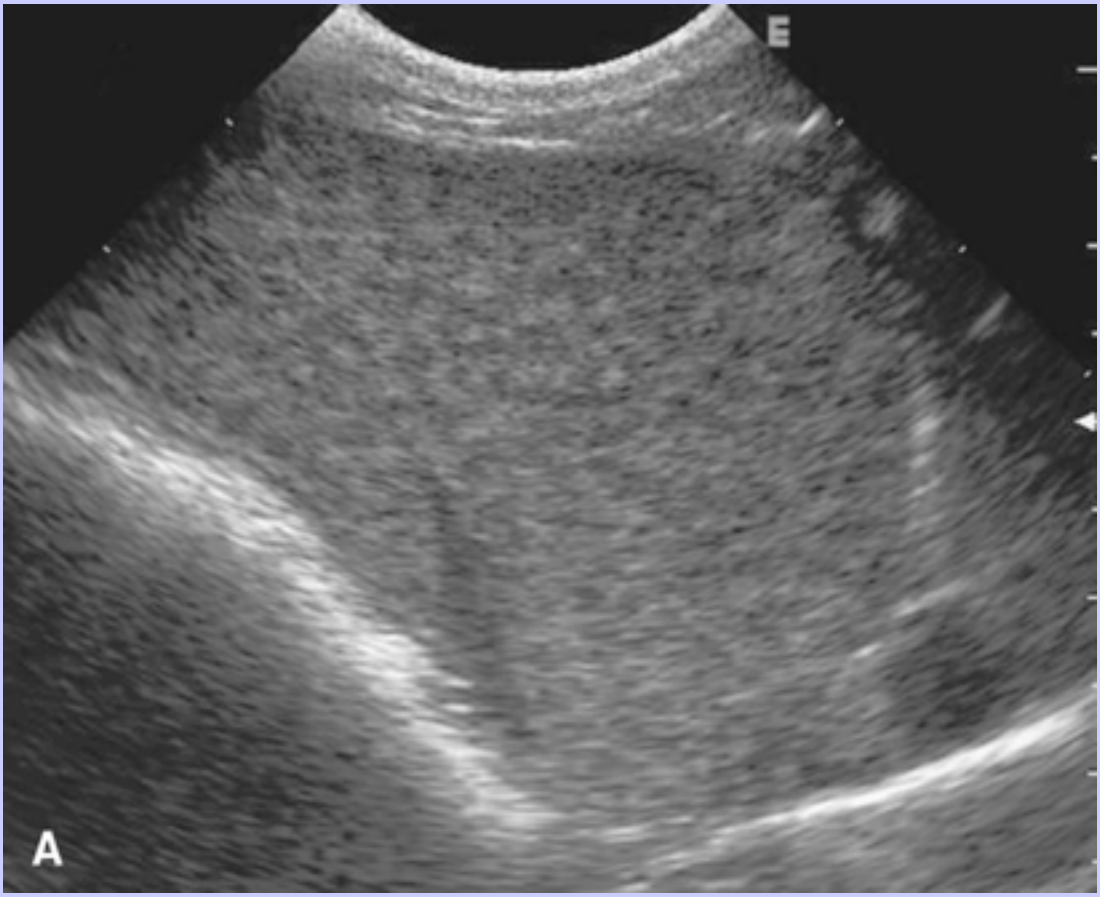


Fig. 32-82 Sonograms of severe diffuse splenitis viewed from the left twelfth

intercostal space in an 8-month-old Angora kid with disseminated *Rhodococcus equi* infection. **A**, Note the diffusely mottled appearance of the spleen. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 6 cm. **B**, This image illustrates the importance of evaluating superficial structures with the highest-frequency transducer available. Note the superior anatomic detail in this image obtained with a 13-MHz linear transducer at a depth of 4 cm. Dorsal is to the *right* and ventral is to the *left*.

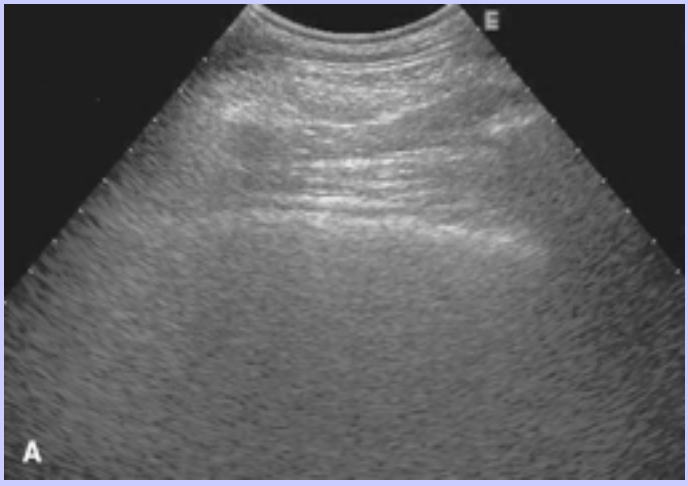


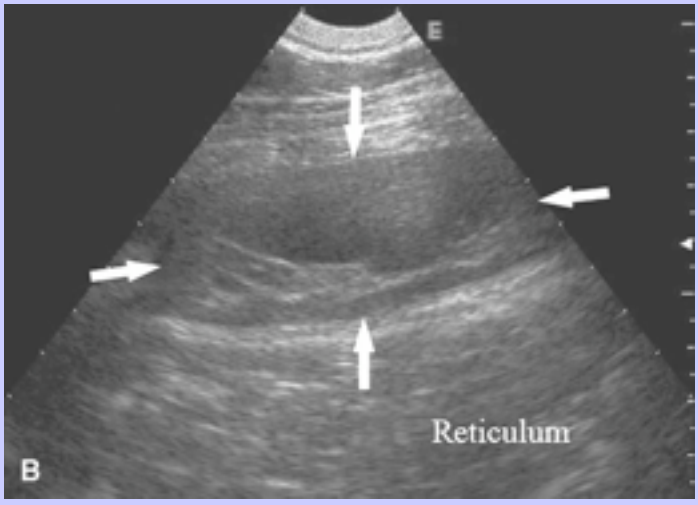
32.118.8 Reticulum

32.118.8.1 NORMAL APPEARANCE (Fig. 32-83, *A*)

The reticulum is seen in the cranioventral abdomen and both the left and right sixth and seventh intercostal spaces ventral to the spleen and cranial to the rumen at a scanning depth of 4 to 8 cm in small ruminants and 10 to 14 cm in cattle. The reticulum should be evaluated during the examination for normal biphasic contractions, which should occur approximately once per minute. The reticulum contracts approximately 5 to 10 cm away from the abdominal wall during the first phase of contraction and more than 17 cm away during the second phase of contraction.[363] When in a relaxed state the reticulum appears as a semicircular structure immediately adjacent to the ventral abdominal wall. Reticular contents cannot normally be visualized because of their gaseous composition. The honeycomb appearance of the reticular mucosa is not commonly distinguishable ultrasonographically.

Fig. 32-83 **A**, Sonogram of normal reticulum viewed from the left cranioventral abdomen in a 5-year-old Holstein dairy cow. This image was obtained with a 3.5-MHz curvilinear transducer at a depth of 14 cm. **B**, Sonogram of a small reticular abscess *(arrows)* viewed from the left seventh intercostal space in an 8-year-old Charolais beef cow suspected of having traumatic reticuloperitonitis. A small wire was seen within the reticulum on abdominal radiographs. This image was obtained with a 5.5-MHz curvilinear transducer at a depth of 12 cm. Dorsal is to the *right* and ventral is to the *left*.



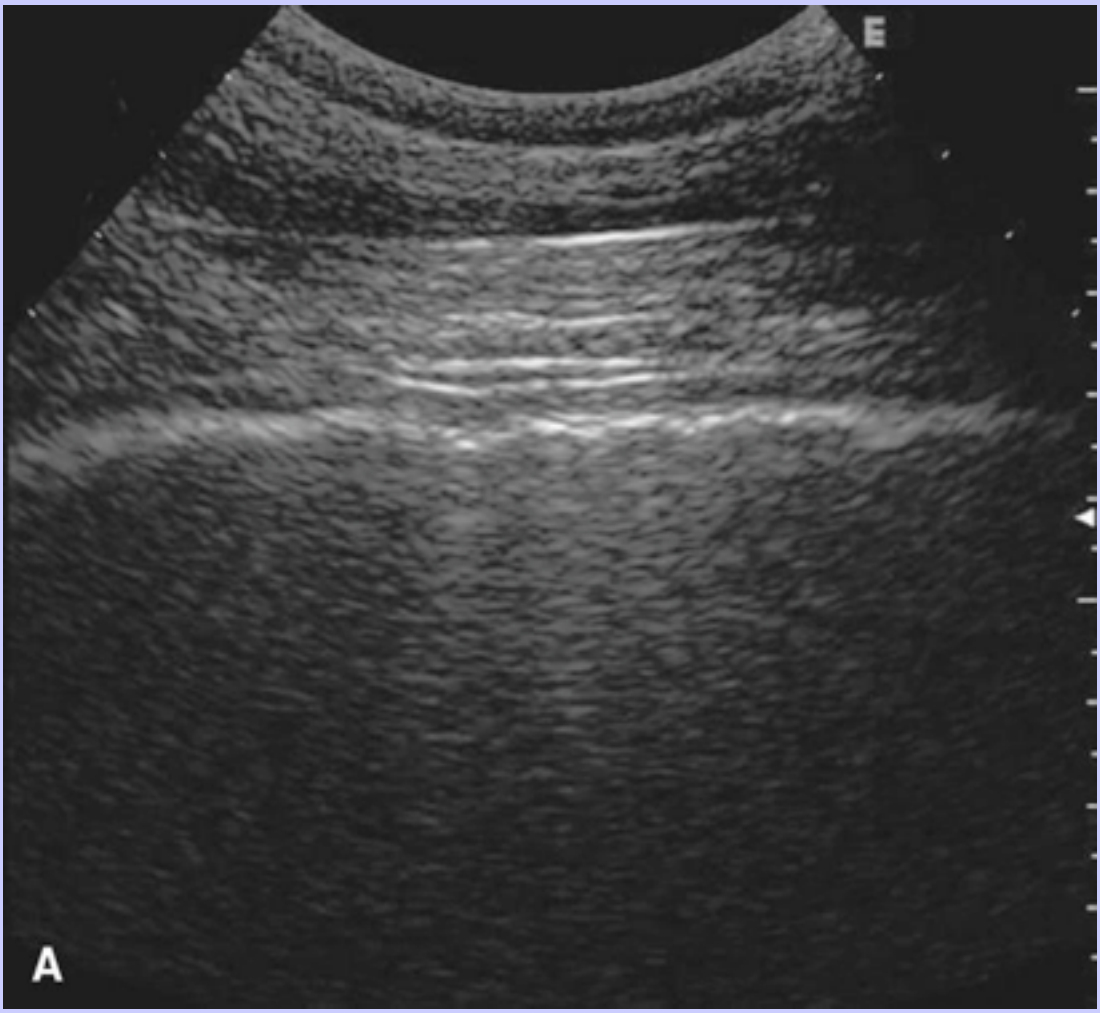


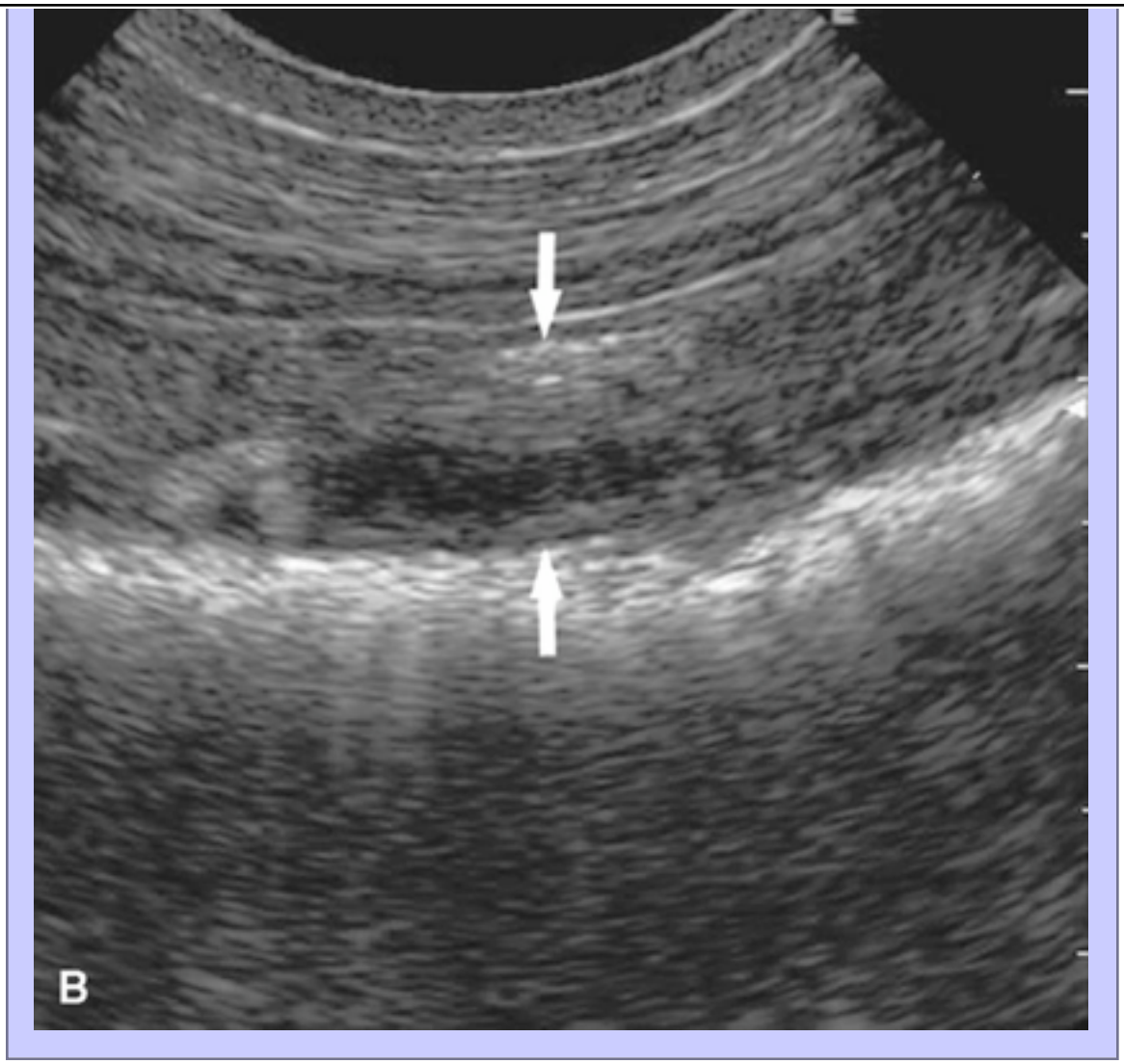
32.118.8.2 ABNORMAL FINDINGS

Reticular abnormalities are primarily associated with TRP. Reticular abscesses caused by TRP can be seen between the reticulum and body wall, spleen, diaphragm, or liver.[364] These abscesses are usually well encapsulated with an echogenic capsule and may contain anechoic to echogenic contents (Fig. 32-83, *B*). Abscesses adjacent to the body wall can be incised and drained transcutaneously with ultrasound guidance.[364] Other abnormalities associated with TRP include changes in the contour of the reticulum, echogenic fibrinous deposits on the reticular serosa, nonencapsulated fibrinous exudate between the reticulum and body wall, and adhesions between the reticulum and the peritoneum or adjacent organs.[331,364,365] Reticular contractions are often absent, reduced, or indistinct in affected animals and can be an indication of adhesions between the reticulum and body wall. The causative foreign bodies are rarely identified ultrasonographically because of the gaseous composition of reticular contents and are better assessed via radiography.[331,365] Reticular hypermotility has been described in cows with reticuloomasal obstruction.[366]

Fig. 32-84 **A**, Sonogram of normal rumen viewed from the left paralumbar

fossa region in a 5-year-old Holstein dairy cow. This image was obtained with a 2.5-MHz curvilinear transducer at a depth of 9 cm. **B**, Sonogram of severely thickened ruminal wall measuring 14.9 mm *(arrows)* viewed from the left paralumbar fossa region in a 12-year-old pygmy buck that recently underwent rumenotomy. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 4 cm. Dorsal is to the *right* and ventral is to the *left*.





32.118.9 Rumen

32.118.9.1 NORMAL APPEARANCE (Fig. 32-84, *A*)

The rumen normally occupies the entire left paralumbar fossa region, the left eighth to twelfth intercostal spaces, and the left caudoventral abdomen and is seen directly adjacent to the body wall. The ruminal wall is seen as a smooth, thin hypoechoic line. Hyperechoic gas within the rumen creates a hyperechoic line immediately adjacent to the wall. Ruminal contents are not commonly visualized because of their gaseous composition. The wall of the craniodorsal blind sac, the ventral sac of the rumen, and the ruminoreticular groove are seen immediately caudal to the reticulum in the cranioventral left intercostal spaces.[331] Contraction of the craniodorsal blind sac of the rumen is commonly seen after the second reticular contraction.[331]

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32.118.9.2 ABNORMAL FINDINGS

Thickening of the ruminal wall may be seen in cases of ruminitis or secondary to ruminotomy or ruminal trocarization (Fig. 32-84, *B*). Abcesses between the rumen and the left body wall may also develop secondary to surgical procedures performed in the left flank region.[367] Such abscesses are usually well encapsulated and contain anechoic to echogenic contents. Echogenic strands of fibrin or fibrinous deposits may be found in association with the abscess. Localized or generalized peritonitis may also occur secondary to abscessation. Abscesses adjacent to the body wall can be aspirated via ultrasound guidance for cytology and culture.

32.118.10 Omasum

32.118.10.1 NORMAL APPEARANCE

The omasum is seen adjacent to the body wall in the right cranioventral intercostal spaces. Although fairly similar to the reticulum in appearance, the omasum can be differentiated by an increased wall thickness.[331] Omasal contents are seldom visualized because of their gaseous nature.

32.118.10.2 ABNORMAL FINDINGS

Ultrasonographic abnormalities of the omasum are uncommon and have not been reported in the literature.

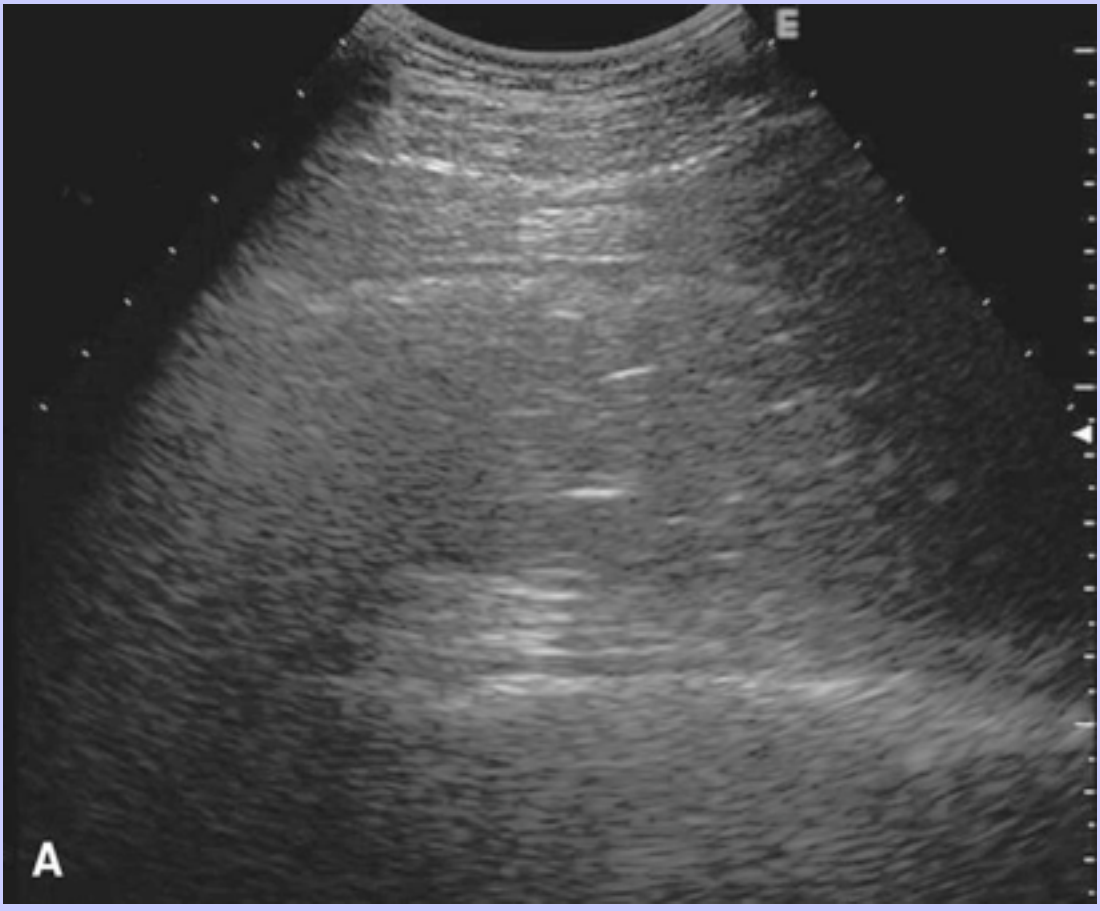
32.118.11 Abomasum

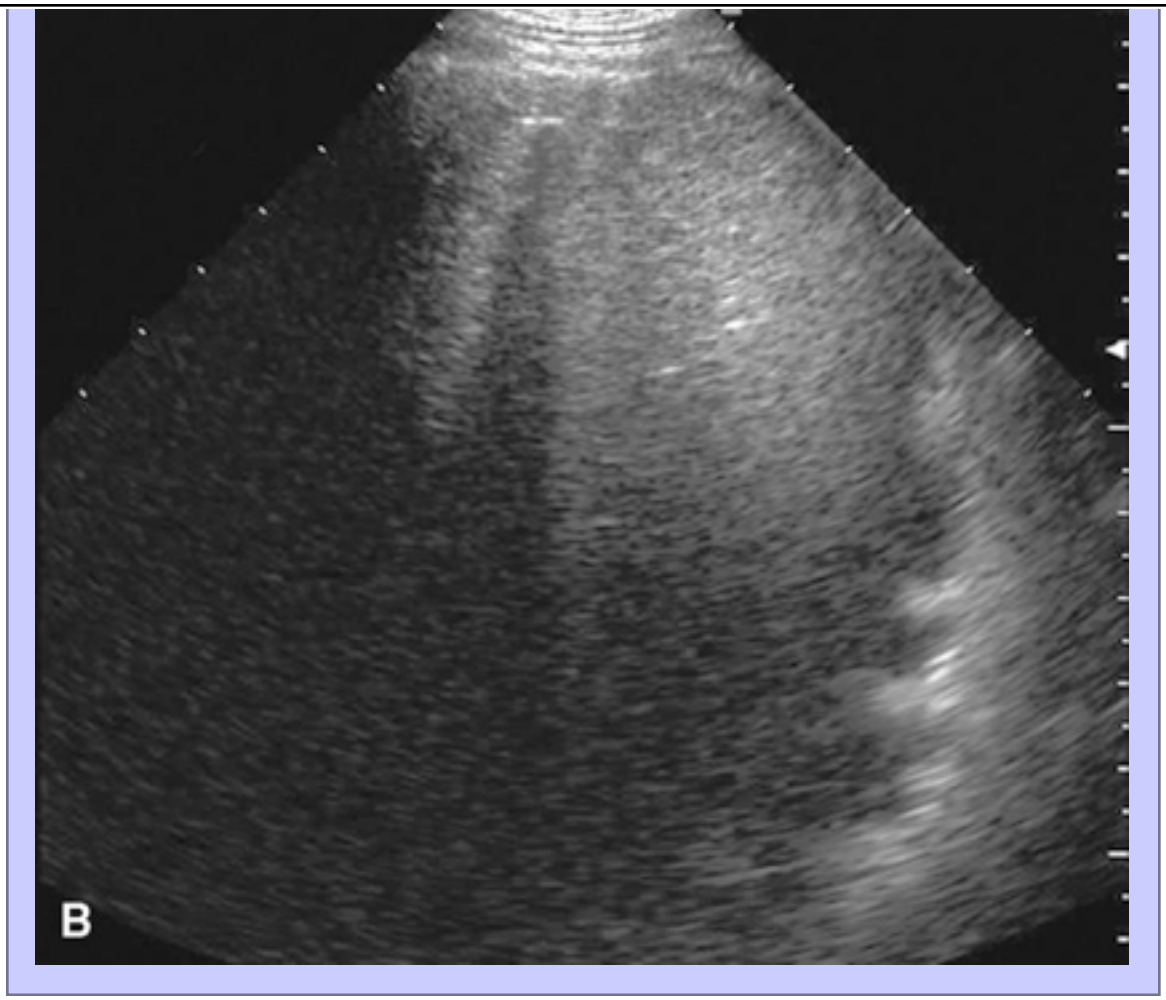
32.118.11.1 NORMAL APPEARANCE (Fig. 32-85, *A*)

The abomasum is normally visualized in the cranioventral abdomen along ventral midline and in both the right and left paramedian regions caudal to the xiphoid process. In general, the abomasum is situated more to the right of the ventral midline. The abomasum can be distinctly identified because of its visible fluid contents, which demonstrate a heterogeneous anechoic to echogenic appearance. The abomasal wall appears as a thin hyperechoic line. Abomasal folds are sometimes visible. Passive movement of the abomasum is seen during reticular contractions; however, abomasal contractions are usually not seen. The pylorus is rarely identified.[368]

Fig. 32-85 **A**, Sonogram of normal abomasum viewed from the right

cranioventral abdomen in a 5-year-old Holstein dairy cow. This image was obtained with a 2.5-MHz curvilinear transducer at a depth of 9 cm. Note that abomasal contents are visible. **B**, Sonogram of severe abomasal distention viewed from the right ventral paralumbar fossa region in an 8-year-old pygmy doe with severe bloat. Postmortem examination revealed marked pyloric stenosis. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 9 cm. Dorsal is to the *right* and ventral is to the *left*.





32.118.11.2 ABNORMAL FINDINGS

Reported ultrasonographic abnormalities of the abomasum in cattle include left and right abomasal displacement and functional or mechanical pyloric stenosis.[329,331] In cattle with left abomasal displacement, the rumen is seen adjacent to the body wall ventrally; however, the abomasum is imaged between the rumen and the left body wall dorsally. The rumen is displaced medially at this level, deep to the abomasum. Fluid and ingesta are visible ventrally within the abomasum, and a gas cap is visible dorsally.[369] With right abomasal displacement, the abomasum is imaged adjacent to the right body wall in the right intercostal spaces. In this case the liver is displaced medially, deep to the abomasum, and cannot be seen. Similar to left dorsal displacement, fluid and ingesta contents are visible in the ventral aspect of the abomasum, and a gas cap is visible dorsally.[329,331] In cases of pyloric stenosis, the abomasum is dilated but not displaced (Fig. 32-85, *B*).[331] No gas accumulation is seen, and the abomasal contents demonstrate an anechoic or hypoechoic, fluid appearance. If the abomasal distention is a result of delayed abomasal emptying secondary to ileus, distended, amotile loops of small intestine will be visible in the right ventral abdomen.[331]

32.118.12 Small Intestine

32.118.12.1

NORMAL APPEARANCE (Fig. 32-86, *A*)

The descending duodenum is visualized from the right tenth intercostal space caudally to the right paralumbar fossa region. The ascending duodenum cannot be visualized because of its location deep within the abdomen. The cranial duodenum may be seen deep or ventral to the gall bladder in the right tenth or eleventh intercostal space. The descending duodenum is then visible deep to the liver in the right eleventh and twelfth intercostal spaces and becomes progressively superficial as it courses caudodorsally such that it is seen adjacent to the body wall in the right paralumbar fossa region. Duodenal contents are often visible and consist of a fluid, feed, and/or mucous mixture with mixed echogenicity. Occasionally, gaseous contents are seen within the duodenum. The descending duodenum can be differentiated from jejunum and ileum by its anatomic location within the abdomen.

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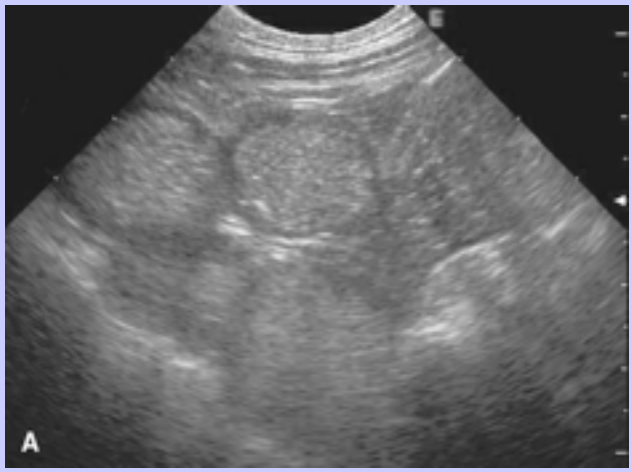
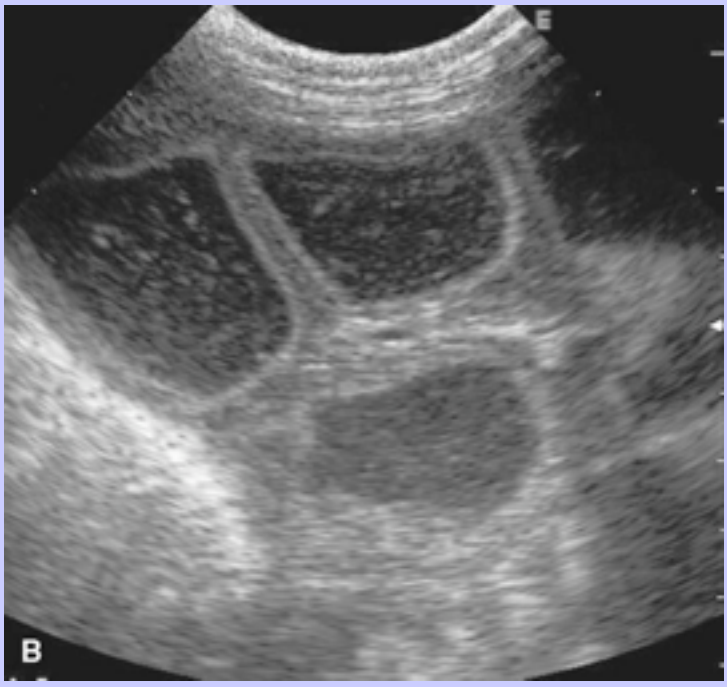
Fig. 32-86 **A**, Sonogram of normal small intestine viewed from the right

paralumbar fossa region in a 5-year-old Nubian buck. This small intestine demonstrated normal consistent motility. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 7 cm. **B**, Moderate small intestinal distention viewed from the right ventral abdomen in a 2-month-old Holstein heifer calf with clostridial enteritis. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 5 cm.





The jejunum and ileum cannot be differentiated from one another in adult cattle and are usually seen in the

right caudal intercostal spaces, right paralumbar fossa region, and right caudoventral abdomen. Loops of jejunum and ileum demonstrate a similar appearance to the duodenum, with anechoic to echogenic fluid and feed contents. Gaseous contents may also occasionally be seen in the jejunum and ileum. Loops may be seen both longitudinally and transversely and demonstrate consistent, active motility. The wall thickness of normal small intestine is 2 to 3 mm, and the normal diameter ranges from 2 to 4 cm in adult cattle.[370]

32.118.12.2 ABNORMAL FINDINGS

Motility, distention, and wall thickness are the most important variables for evaluating small intestinal abnormalities via ultrasound. Ultrasonographic evidence of ileus, characterized by distended, hypomotile to amotile loops of small intestine, can be seen in patients with functional ileus, obstruction, strangulation or incarceration, volvulus, intussusception, and impaction of the small intestine. Small intestinal obstruction may be intraluminal, caused by foreign body, bezoar, impaction, or intraluminal mass or clot formation (hemorrhagic bowel syndrome [HBS]).[329,331,370,371] The ventral abdomen should be carefully evaluated in patients suspected of having small intestinal obstruction because affected small intestine is heavier than normal and falls to the most dependent portion of the abdomen. Distended small intestine demonstrates the appearance of a static tubular structure filled with anechoic to echogenic fluid (Fig. 32-86, *B*). Small intestinal intussusceptions demonstrate a characteristic appearance often described as a “target sign” or “bull's eye” created by a loop of bowel imaged within a second loop.[371] Extraluminal causes of small intestinal obstruction include compression from adjacent structures such as intraabdominal abscesses or masses or entrapment, which can occur secondary to adhesion formation, rents in the mesentery, extramural masses, or malposition of other abdominal organs.[372] Regardless of cause, small intestinal distention will be seen oral to the obstruction. Small intestinal thickening may also be seen oral to the obstruction owing to secondary hypertrophy. Fluid and feed contents may be seen flowing back and forth with little to no progressive motility. This movement should not be confused with normal peristalsis. Small intestine aboral to the obstruction may appear collapsed and hypomotile. Despite thorough evaluation of the ventral abdomen, the specific cause of ileus may be obscured by the presence of gas-filled bowel or may be too deep within the abdomen to be imaged.[371]

32.118.13 Cecum and Colon

32.118.13.1 NORMAL APPEARANCE

The cecum is normally imaged in the mid to dorsal portion of the right paralumbar fossa region adjacent to the body wall and demonstrates a smooth, curved appearance. Estimates of the diameter of the cecum vary depending on the amount of gas distention present at the time of examination and have been reported to range from 5.2 to 18 cm in normal cattle.[373] The proximal loop of the colon and spiral colon can be visualized dorsal to the cecum in the right paralumbar fossa region and the right twelfth intercostal space. The spiral colon has been described as demonstrating a “garland” appearance with segmental arched lines adjacent to one another.[373] Estimation of the diameter of the proximal loop of the colon also varies dependent on gas distention and has been reported to range from 3.1 to 15 cm. The diameter of the spiral colon is smaller, ranging from 2 to 4 cm. The proximal loop of the colon and spiral colon may be difficult to distinguish from gas-filled small intestine; however, the proximal loop and spiral colon seldom demonstrate visible motility or contractions.[373]

32.118.13.2 ABNORMAL FINDINGS

The diagnosis of cecal dilation is commonly made via rectal palpation but may be more challenging in cases in which dilation of the cecum is not palpable because of retroflexion.[374] In cows with cecal dilation, the cecum demonstrates a large radius of curvature and is seen to extend to the ventral portion of the right paralumbar fossa region and sometimes cranially into the right tenth to twelfth intercostal spaces. The proximal loop of the colon will also be dilated in and can be difficult to differentiate from the cecum. The liver may be displaced cranially in cows with severe cecal dilation. Torsion and retroflexion cannot be differentiated by ultrasonographic examination alone but may be diagnosed with a combination of rectal examination and ultrasonographic findings.[374]

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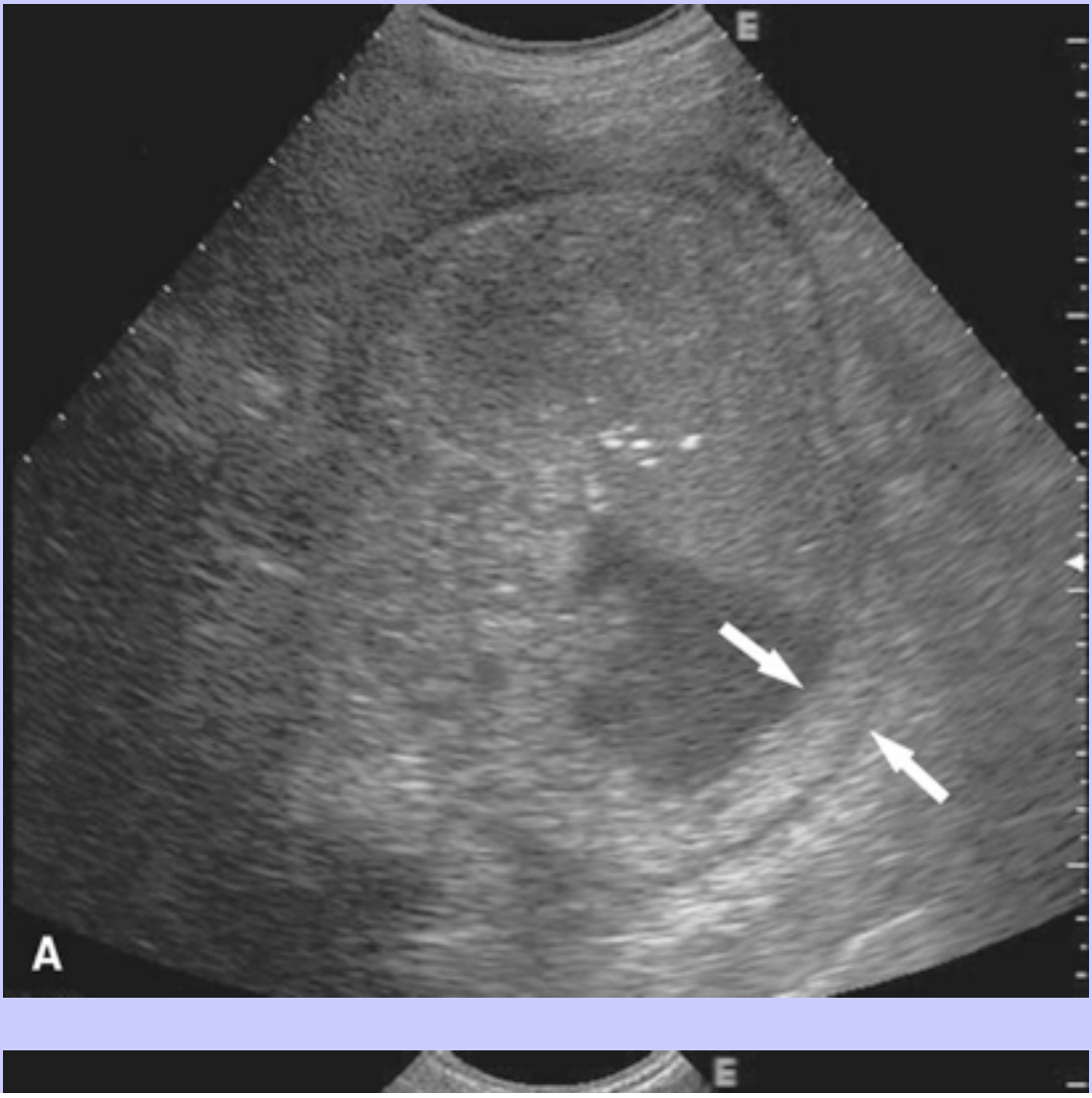
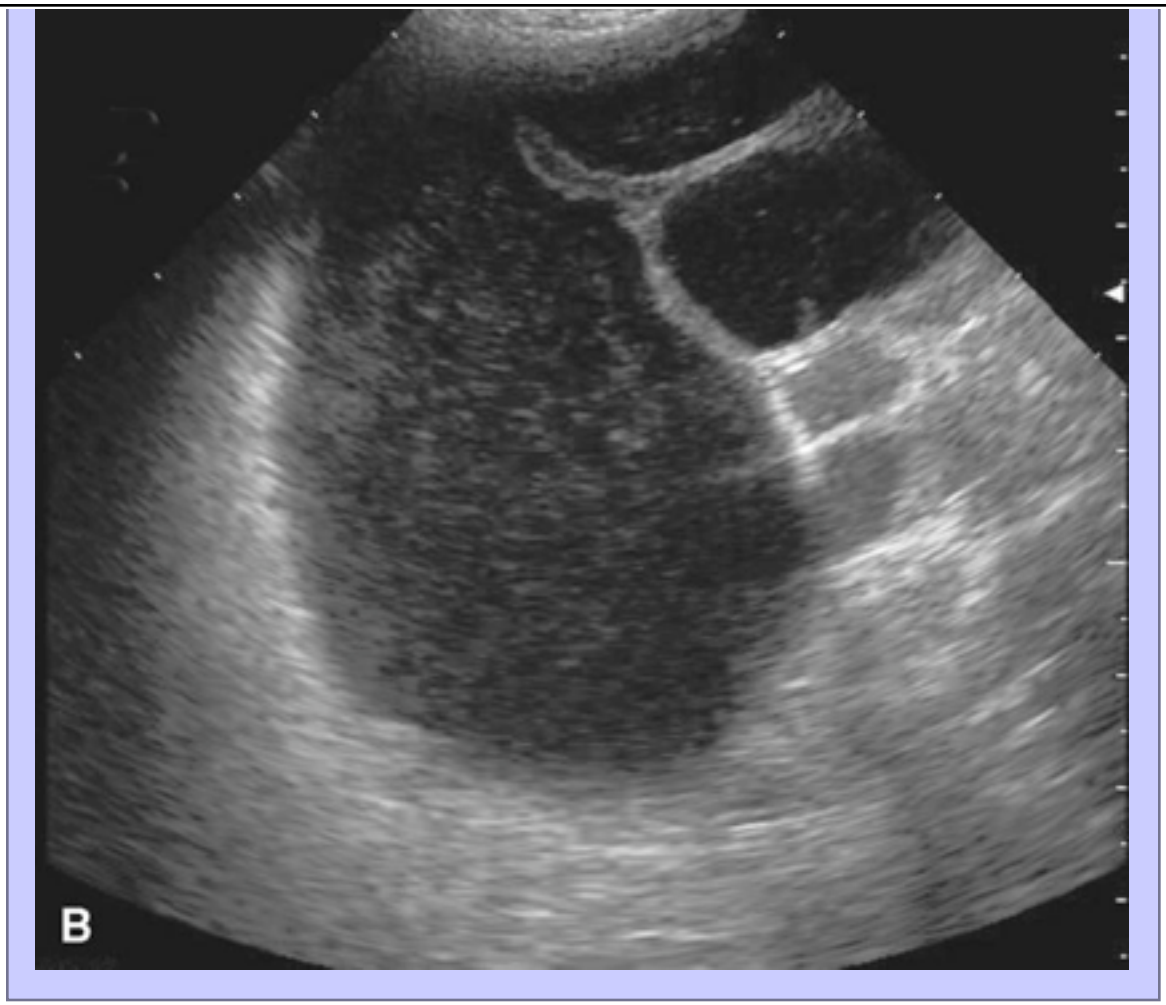
Fig. 32-87 **A**, Sonogram of an enlarged uterine horn distended with

echogenic fluid in a 5-year-old Holstein dairy cow with metritis. This cow had a history of aborting twins 4 days before presentation. Note the associated thickening of the uterine wall *(arrows)*. This image was obtained transabdominally in the right inguinal region with a 3.5-MHz curvilinear transducer at a depth of 18 cm. **B**, Sonogram of an enlarged uterine horn distended with relatively anechoic fluid in a 6-year-old Shetland ewe with hydrometra (pseudopregnancy). This ewe was reported to be 3 months pregnant. This image was obtained in the left flank region with a 7.5-MHz transducer at a depth of 9 cm.





32.118.14 Nongravid or Postpartum Uterus

Abnormalities of the uterus may be encountered during transabdominal ultrasound examination in ruminants and will be briefly addressed in the following sections. Evaluation of the gravid uterus and pregnancy diagnosis and monitoring are beyond the scope of this section.

32.118.14.1 NORMAL APPEARANCE

The normal nongravid uterus is seldom visualized during transabdominal ultrasound examination in ruminants. However, the involuting uterus may be encountered in females that have recently given birth.[375] Transrectal ultrasound is the method of choice to evaluate the bovine uterus.[376] However, abnormalities of the bovine and small ruminant uterus can be identified during transabdominal examination.

32.118.14.2 ABNORMAL FINDINGS

Abnormalities of the nongravid or postpartum uterus include metritis, pyometra, hydrometra, and uterine neoplasia. In ruminants with metritis or pyometra, the uterus is variably distended with fluid. This fluid may be relatively anechoic, echogenic, or hyperechoic depending on the nature of the debris and inflammatory material within the uterus[375–378] (Fig. 32-87, *A*). Hyperechoic gas echoes can be seen within the uterine fluid in cases of anaerobic or mixed infection. The uterine wall may also be thickened. Hydrometra, or pseudopregnancy, is most commonly reported in goats and is readily diagnosed via ultrasound.[375,379–380] The uterus appears distended with anechoic fluid in the absence of fetuses or placentomes. The dilated uterine horns may be curved or tortuous such that several cross-sections of the horn may be seen in any given scanning plane (Fig. 32-87, *B*).[375] It should be mentioned that small pockets of fluid may be seen in the normal involuting bovine uterus for up to 4 weeks postpartum.[376,381]

Uterine neoplasia is uncommonly reported in ruminants, but leiomyosarcomas, leiomyomas, carcinomas, chorionepitheliomas, fibrosarcomas, rhabdomyosarcomas, adenosarcomas, and multicentric lymphoma have been found.[382,383] Mass lesions visualized within the uterine wall or lumen are consistent with neoplasia. Masses may be single or multiple with variable echogenicity (Fig. 32-88). Diffuse infiltration of the uterine wall has been reported in cases of lymphoma.[382,383]

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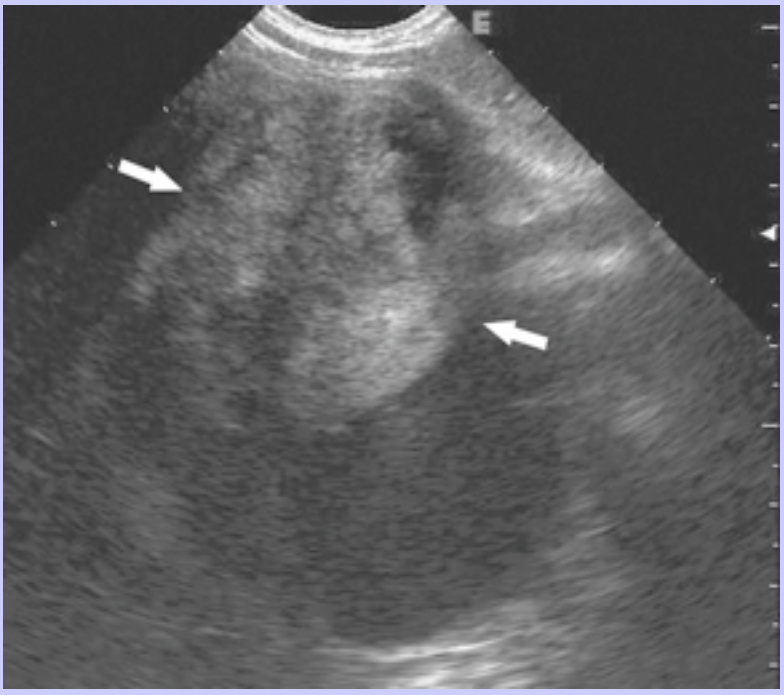
Fig. 32-88 Sonogram of a large uterine mass viewed from the right ventral abdomen in an 11-year-old pygmy doe diagnosed with uterine adenocarcinoma postmortem. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 10 cm.



32.118.15 Peritoneal Cavity

32.118.15.1

NORMAL APPEARANCE

The peritoneal lining can be seen as a very thin, smooth hyperechoic line adjacent to the body wall. Minimal free abdominal fluid is seen within the peritoneal cavity. Retroperitoneal adipose tissue appears as a hypoechoic layer of varying thickness between the body wall and abdominal viscera and should not be misinterpreted as cellular peritoneal effusion. Adipose tissue may also be seen within the omentum and mesentery, demonstrating a similar appearance between or among the gastrointestinal viscera. This omental and mesenteric adipose tissue can often demonstrate an organized appearance with visible fine vasculature that can be mistaken for liver, especially in small ruminants.

32.118.15.2

ABNORMAL FINDINGS

Peritoneal fluid is readily identified on ultrasound as anechoic to echogenic fluid between the body wall and abdominal organs (Fig. 32-89). In cases of severe effusion, the abdominal organs and viscera appear to float within the free fluid. Fibrin deposits are commonly seen in ruminants with inflammatory peritoneal effusion and appear as linear strands extending between organs or between peritoneal surfaces and serosal surfaces of abdominal organs (Fig. 32-90).[329,367] Fibrin can also demonstrate a “shag carpet” appearance along the peritoneal and/or serosal surface. Localized peritonitis may also be seen and has been reported in cows secondary to left flank laparotomy.[367] Hemoabdomen appears as hypoechoic cellular-appearing fluid that swirls with ballottement, peristalsis, or respiration. (Fig. 32-91)

Other abnormalities of the peritoneal cavity include mesenteric abscessation, mesenteric lymphadenopathy, and neoplasia. Intraabdominal abscessation may be identified within the mesentery or associated with abdominal incisions. Abscesses are generally well encapsulated with anechoic to echogenic contents. Enlarged mesenteric lymph nodes can be seen within the small intestinal mesentery and are a nonspecific finding that has been seen by the author in cases of abdominal disease from numerous causes (Fig. 32-92). Ruminants with neoplasia may demonstrate severe peritoneal effusion, most notably in cases of mesothelioma.[384,385] In cases of mesothelioma, multiple echogenic nodules are seen overlying the serosal surfaces of the peritoneum and abdominal organs (Fig. 32-93). Nodules can also be seen in the omentum.[384,385]

Fig. 32-89 Sonogram of mild peritoneal effusion *(arrows)* seen between

several loops of normal small intestine and the ventral body wall viewed from the right ventral abdomen in a 2-year-old Hampton cross ram. This image was obtained with an 8.5-MHz curvilinear transducer at a depth of 7 cm.

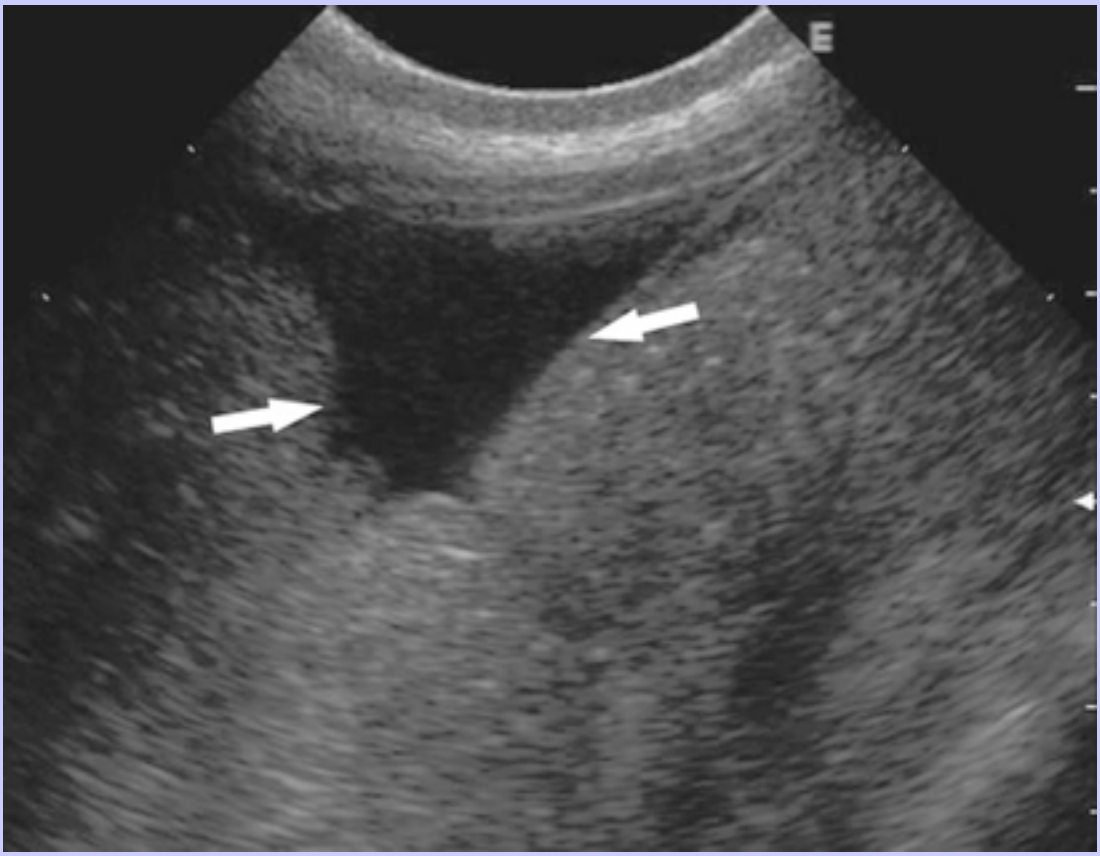


Fig. 32-90 Sonogram of severe fibrinous peritonitis thought to be secondary

to an intestinal rent viewed from the right paralumbar fossa region in a 3-year-old Holstein dairy cow. Note the hyperechoic fibrin strands creating a weblike appearance within the peritoneal cavity. This image was obtained with a 5-MHz curvilinear transducer at a depth of 27 cm.

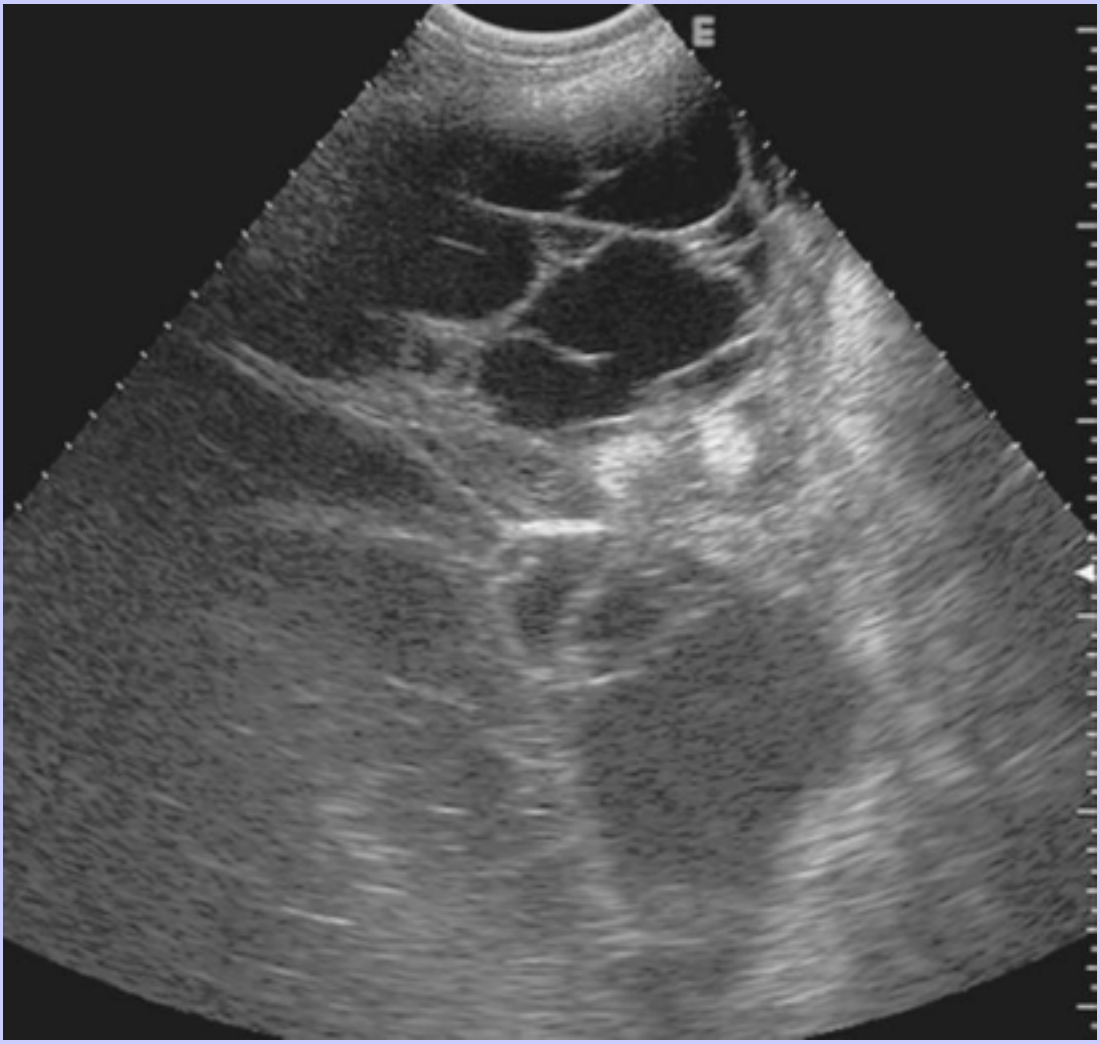


Fig. 32-91 Sonogram of severe hemoabdomen viewed from the right

cranioventral abdomen in a 2-year-old Shorthorn heifer with metastatic granulosa cell tumor. Note the very cellular appearance to the fluid within the peritoneal cavity. The liver is displaced from the body wall and appears to float in the effusion. This image was obtained with a 2.5-MHz curvilinear transducer at a depth of 27 cm.

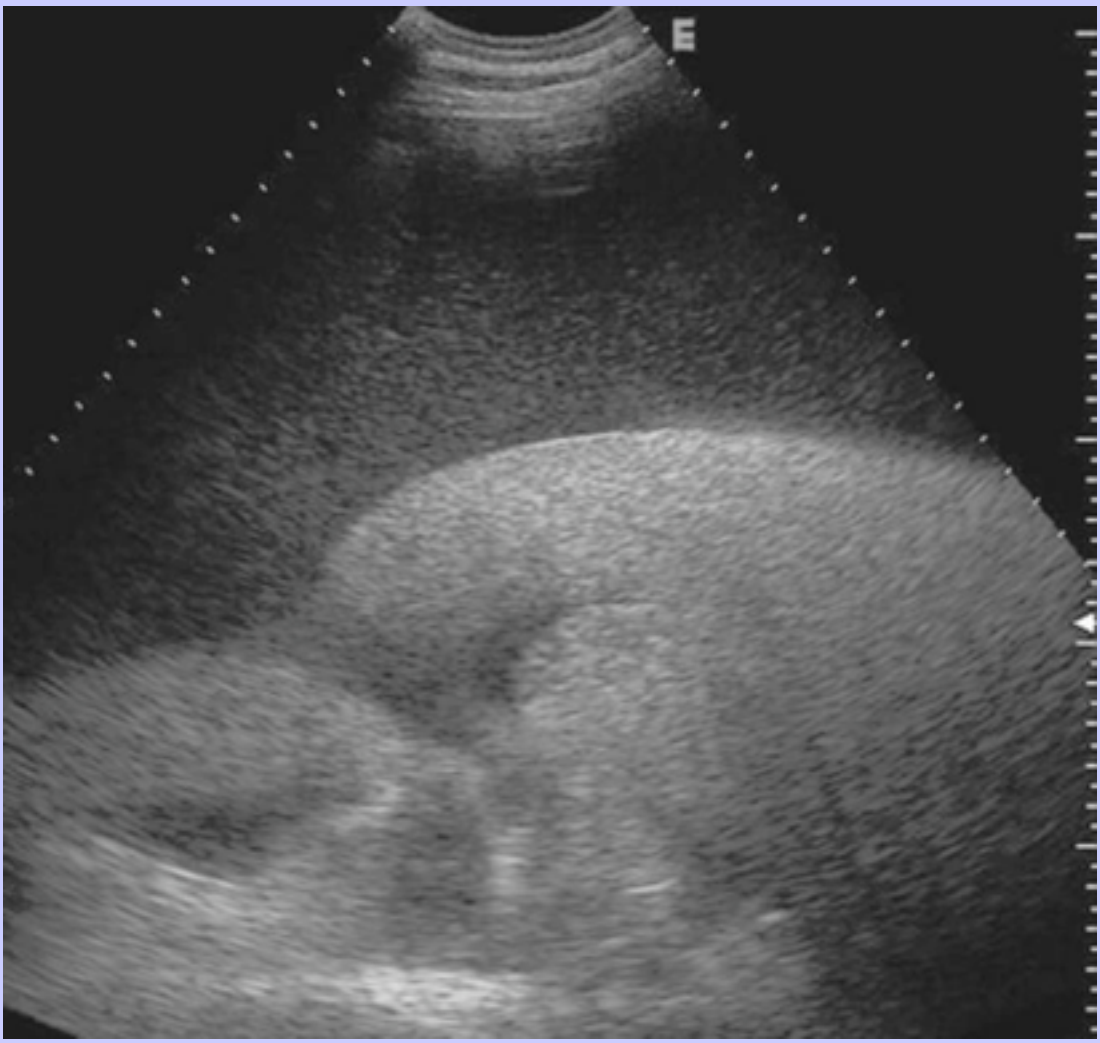


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Fig. 32-92 Sonogram of an enlarged mesenteric lymph node viewed from

the left ventral abdomen in an 8-month-old Angora kid with disseminated *Rhodococcus equi* infection. This image was obtained with a 7.5-MHz curvilinear transducer at a depth of 5 cm.

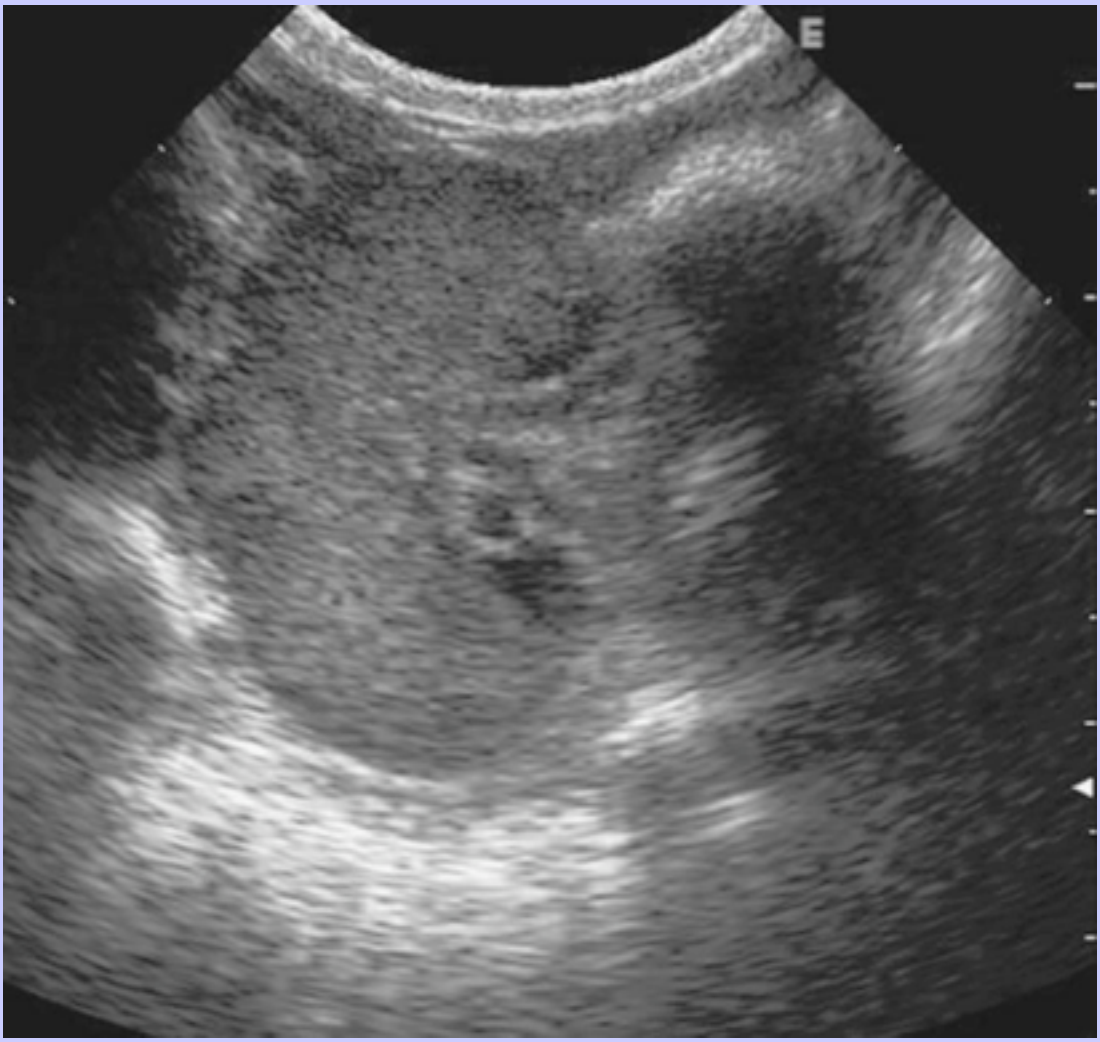
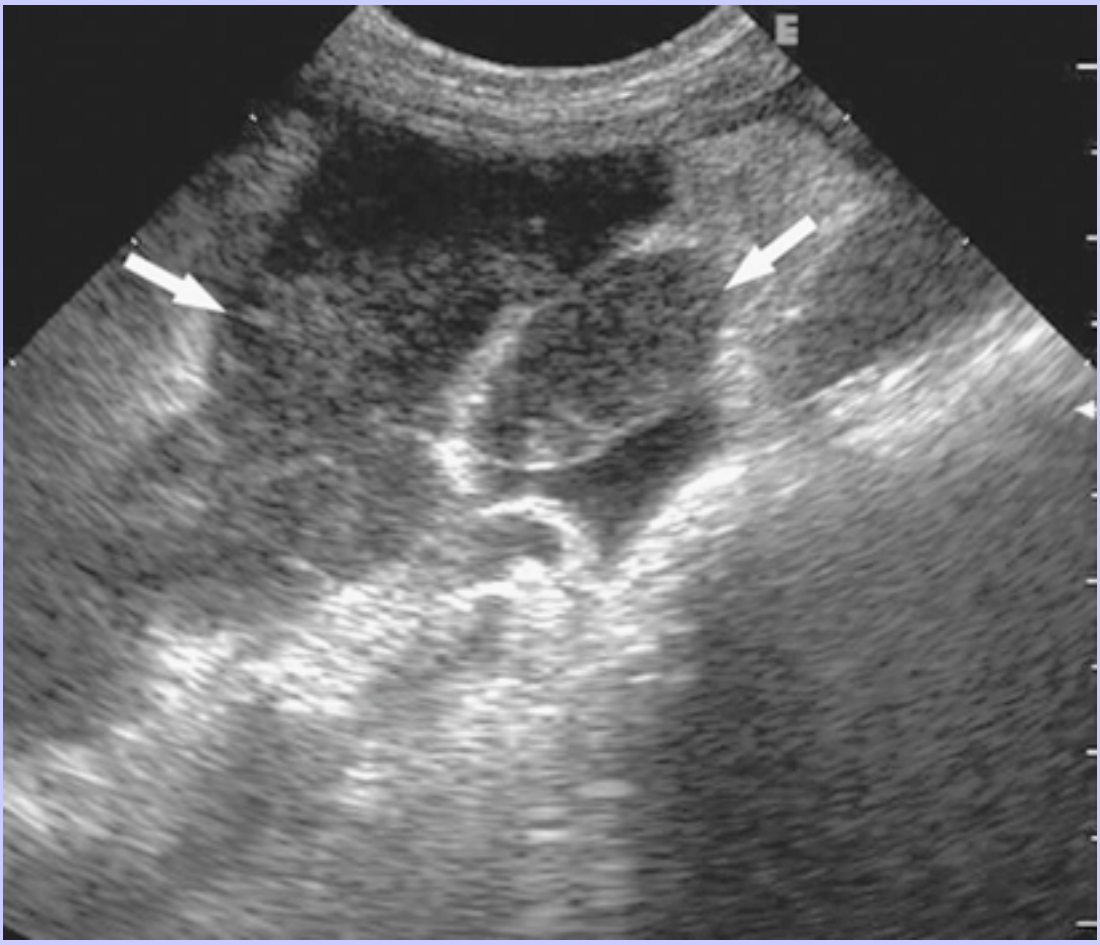


Fig. 32-93 Sonogram of multiple peritoneal masses *(arrows)* between the

rumen and body wall viewed from the left paralumbar fossa region in a 10-year-old pygmy doe with mesothelioma. This image was obtained with an 8.5-MHz curvilinear transducer at a depth of 6 cm. Dorsal is to the right and ventral is to the left.



32.119 INDIGESTION IN RUMINANTS

FRANKLYN GARRY

CRAIG McCONNEL

32.119.1 Definition and Etiology

Indigestion is a general term for a group of diseases characterized by dysfunction of the reticulorumen. Some texts have limited the use of the term to a single, poorly defined entity that includes inappetence, decreased reticuloruminal motility, and abnormal feces, with a nonspecific cause that involves intake of abnormal feed.

The more generalized term applied here incorporates a pathophysiologic classification scheme of forestomach disturbances that has been devised by workers in Germany.[386] An absolute division of the pathologic processes is impossible because the various forestomach functions are interdependent; that is, abnormal motor function affects microbial fermentation by altered mixing or passage of ruminal fluid out of the forestomach chambers, whereas abnormal fermentation products secondarily alter motor function. Nevertheless, this classification provides a clinically useful diagnostic framework by emphasizing the underlying pathophysiologic mechanisms of different forestomach disturbances.

32.119.1.1 Box 32-5 Classification of Ruminant Indigestion

32.119.1.1.1 PRIMARY INDIGESTIONS

32.119.1.1.1.1 Reticuloruminal Motor Disorders or Diseases of the Ruminal Wall

Traumatic reticuloperitonitis (p. 849)

Frothy bloat (p. 855)

Free gas bloat (p. 821)

Reticulitis or rumenitis (p. 822)

Ruminal parakeratosis (p. 822)

Vagal indigestion (failure of omasal transport, failure of pyloric outflow, and free gas bloat) (p. 822)

Obstruction of the cardia (p. 825)

Obstruction of the reticuloomasal orifice (p. 825)

Diaphragmatic hernia (p. 825)

32.119.1.1.1.2 Reticuloruminal Fermentative (Microbial and Biochemical) Disorders

Inactivity of ruminal microbial flora (caused by poor quality roughage—ruminal impaction) (p. 827)

Simple indigestion (p. 827)

Acute ruminal lactic acidosis (p. 828)

Subacute ruminal acidosis (p. 829)

Ruminal alkalosis (p. 830)

Putrefaction of ruminal ingesta (p. 830)

32.119.1.1.2 SECONDARY INDIGESTIONS (SECONDARY TO SYSTEMIC ILLNESS)

Secondary reticuloruminal motor inactivity

Secondary reticuloruminal microflora inactivity

Abomasal reflux

The primary indigestions include those diseases in which the reticulorumen is directly affected and responsible for the major disease signs (Box 32-5). These problems can be divided into two categories:

1 Abnormal motor function of the reticulorumen, including disease of the reticuloruminal wall, its innervation, or impedance to the passage of ingesta

2 Abnormal contents of the reticulorumen, with dysfunction of microbial and biochemical fermentation

Secondary indigestions are the sequelae of systemic problems or disease in other organ systems. For example, problems such as endotoxemia, fever, or depression can produce anorexia, secondary ruminal hypomotility, and decreased microbial fermentative function. Primary abomasal disease can depress ruminal function, inhibit ruminal outflow, and reflux abomasal contents back into the rumen.

With the exception of penetrating foreign bodies and sporadic infections of the forestomach wall (e.g., actinomycosis, mucormycosis), indigestions are physiologic abnormalities. In the adult ruminant one or more of the homeostatic processes of the fermentative environment are disturbed (e.g., an excessive carbohydrate intake generates an excessive amount of acid product; abnormal neural regulation of the ruminal motility pattern disturbs the mixing or aboral passage of ingesta). In the young ruminant the forestomachs are actively developing, and indigestions can result from disturbances of the developmental mechanisms. The forestomach diseases of young ruminants generally have received little attention, but they can be recognized and appropriately treated within a classification scheme similar to that for adult ruminants.[387]

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32.119.2 Pathophysiology

Digestion of feedstuffs in the reticulorumen is accomplished by microbial fermentation. The mucosal epithelium absorbs and exchanges products of fermentation but performs essentially no secretory function. Appropriate forestomach fermentation depends on the coordination of processes that provide a fairly constant reticuloruminal environment. The requirements include addition of appropriate amounts and types of feed substrate and water by ingestion; buffering of substances from the saliva to counteract the acid nature of fermentation products; eructation of the gaseous products of fermentation; coordination of reticuloruminal motility to provide mixing; rumination and remastication; aborad passage of ingesta; temperature maintenance; and exchanges of electrolytes and VFAs across the ruminal wall. Because these functions are intimately interrelated, abnormalities of any one of them can lead to digestive disturbances.

32.120 DISORDERS OF RETICULORUMINAL MOTOR FUNCTION

32.120.1 Normal Motor Activity

The two reticuloruminal contraction sequences function independently. The primary cycle of contraction occurs approximately once a minute but more often during feeding and rumination. It consists of a biphasic contraction of the reticulum followed by a contraction that runs caudally across first the dorsal and then the ventral ruminal sacs. At the height of the second reticular contraction the omasal orifice relaxes, and fluid, mostly composed of reticular ingesta, passes into the omasum. This reticuloruminal motility pattern directly influences ruminal fermentation by mechanically mixing the ingesta to provide contact with the microbes and to macerate the particulate matter. The mixing function prevents local accumulations of substrate or end products of fermentation, distributes the buffering saliva for neutralization of acids, and provides increased contact of the fluid with the ruminal wall to promote VFA absorption. The coordinated sequence of contraction of various parts of the ruminal wall maintains a stratification of fluid and particulate matter that selectively sorts the ingesta by particle size. The sorting function serves to retain large particles for further digestive breakdown while promoting passage of small particles (smaller than 6 mm) into the omasum and lower gastrointestinal tract.[388–391]

The secondary contraction cycle does not involve the reticulum. It begins in the caudal blind sacs, and a wave of contraction runs cranially across the dorsal rumen, pushing the gas cap into the cardia region. Eructation ensues, eliminating the gases generated by fermentation. Typically one secondary cycle contraction follows two primary cycles, so that three contractions occur every 2 minutes.[389–391] Two additional special contractions have been identified in sheep: primary-secondary contractions and prosecondary contractions.[392,393] These contractions appear when intraruminal pressure becomes elevated and function as secondary contractions by expelling ruminal gas. The primary-secondary and prosecondary contractions appear to help minimize free gas bloat when gas production is high.

Maintenance of the motility patterns requires well-coordinated neural control. The pathophysiologic mechanism of the first group of primary indigestions (i.e., diseases of the reticuloruminal motor function) involves disturbance of the mechanisms of normal ruminal motility, which secondarily affects ruminal fermentation.

The ruminal contraction sequences described rely almost completely on motor nerve activation arising from the

medulla oblongata, in contrast to the intrinsic segmental and peristaltic movements of the intestine. Gastric centers in the medulla integrate sensory input and generate motor impulses, both of which are carried in the vagus nerves. The gastric centers have neither spontaneous activity nor an inherent rhythm. Generation of motor impulses relies on a greater excitatory than inhibitory input from the sensory nerves to determine the rate, magnitude, and duration of primary cycle contractions. During the quiescent period between the primary contractions, while the medulla collects the sensory information, there are no tonic vagal motor impulses.[394–400]

The splanchnic nerves also affect reticuloruminal motility by direct innervation and by neurohumoral effects of adrenal secretion. These nerves are not required for generation of normal contractions. The effect of splanchnic stimulation is inhibition of reticuloruminal motility. Splanchnic sensory nerves innervate sensory receptors in other areas of the gastrointestinal system, and some abnormalities such as intestinal distention or surgical manipulation produce reticuloruminal inhibition by means of reflex from splanchnic afferent activity.[390,398,401]

32.120.2 Primary Cycle Activity

A decrease or absence of normal primary cycle activity (i.e., ruminal hypomotility or stasis) implies either a decrease of vagal motor discharges originating from the gastric centers or an ineffective motor response after motor impulse, as in cases of hypocalcemia. Causes of decreased motor discharges can include the following:

1 Decreased excitatory input to the gastric centers

2 Increased inhibitory input to the gastric centers

3 Depression of the gastric centers

4 Defective vagal transmission of motor impulses

5 Other factors

32.120.2.1 DECREASED EXCITATORY INPUT

The three most important excitatory inputs to the gastric centers are from (1) low-threshold tension receptors in the reticulum, (2) buccal receptors in the mouth, and (3) acid receptors in the abomasum (Table 32-11). The tension receptors are located in the musculature of the medial wall of the reticulum. They are stimulated by mild distention during the resting phase and thereby influence contraction frequency. They are further stimulated by the tension generated during contraction and thus increase amplitude and duration of the primary cycle contraction. This mechanism is probably responsible for the increased motility seen after feeding or during incipient bloat. Any cause of anorexia leading to decreased ruminal fill decreases this excitatory input, leading to ruminal hypomotility. Feeding mechanically stimulates buccal sensory receptors, providing a potent stimulus to both primary and secondary contraction cycles. This reflex can double the rate of primary contractions but is short-lived and declines as soon as chewing activity ceases. Therefore anorexia effectively eliminates this potent excitatory input. Abomasal acidity increases as the abomasum empties, and this, too, provides excitatory input to the gastric centers. The resultant increased reticuloruminal motility leads to increased flow of ingesta to the abomasum, diluting the abomasal acid and maintaining normal filling of the abomasum. Certain types of abomasal disease diminish this stimulus to forestomach motility.[396,398,402]

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Table 32-11 Factors Influencing Vagal Motor Discharge from the Gastric

Centers of the Medulla*

Input	Location	Stimulus
EXCITATION OF THE GASTRIC CENTERS (CAUSES INCREASED RUMINAL MOTILITY)		
Low-threshold tension receptors	Reticulum, medial wall	Mild distention, and tension generated during contractions
Buccal receptors	Mouth	Feeding (only during chewing)
Acid receptors	Abomasum	Increased acidity as abomasum empties
Tension receptors†	Medial wall of cranial ruminal sac	Increased ruminal gas pressure
INHIBITION OF THE GASTRIC CENTERS (CAUSES DECREASED RUMINAL MOTILITY)		
High-threshold tension receptors	Reticulum and cranial ruminal sac	Bloat or other severe ruminal distention
Tension receptors	Abomasum	Abomasal distention
Chemical receptors	Reticulum, rumen	Increased concentration of undissociated volatile fatty acid with ruminal acidosis; also locally activated by some toxins
Pain receptors in body increase sympathetic tone and adrenal secretory activity	Anywhere in body; can act directly and through medullary gastric centers	Pain, especially abdominal
Gastric centers	Medulla	Anesthesia, depressant drugs, toxins, endotoxins, fever, acidosis
Hypocalcemia	Reticuloruminal smooth muscle	Hypocalcemia

* There is no inherent reticuloruminal motility such as that found in the intestines.

† Secondary cycle activity; independent of primary cycle activity.

Less well-defined stimuli of reticuloruminal motility include the physical and chemical characteristics of the ruminal ingesta. Fiber and water content, as well as the normal chemical products of fermentation, are important for normal ruminal contraction. The exact mechanisms by which these factors enhance ruminal motility have not yet been clearly defined, but low levels of any of these ingesta characteristics impair normal function, causing decreases of both rumination and primary cycle activity. That these excitatory stimuli are decreased or absent under some feeding regimens and with some of the diseases attributable to abnormal fermentation may account for the impression of hypomotility observed clinically.[396,403,404]

32.120.2.2

INCREASED INHIBITORY INPUT

Inhibitory inputs to the gastric center arise from (1) high-threshold tension receptors in the reticulum and cranial ruminal sac, (2) tension receptors in the abomasum, (3) epithelial receptors that detect high concentrations of nondissociated VFAs in the rumen, and (4) pain elicited at any site in the body (see Table 32-11). The high-threshold tension receptors are sensory nerve endings below the epithelial basement membrane of the reticulum and cranial ruminal sac. They respond to extreme distention of the wall and serve

to modify the end stage of reticuloruminal contraction. With severe bloat or gross ruminal distention from other causes, such as overfilling with indigestible fibrous roughage, they can be continuously activated, producing ruminal stasis. Abomasal distention can inhibit primary ruminal contraction cycles, presumably because of tension receptors in the abomasal wall. In normal circumstances this activity would serve to decrease the flow of ingesta to the abomasum when it is full. With abomasal displacement or impaction, this reflex may partly account for the observed ruminal hypomotility. Epithelial receptors in the reticulum and cranial ruminal sac are sensitive to increased concentrations of nondissociated VFAs. Inhibition of forestomach contractions occurs when conditions of excessive fermentation or acidosis increase the concentrations of these substances. Pain can reduce forestomach motility by increasing sympathetic nervous and adrenal secretory activity and by inhibiting the gastric centers. Although painful stimuli in the abdominal viscera are particularly potent, pain from anywhere in the body can inhibit or abolish reticuloruminal motility.[396,398,402]

32.120.2.3 DEPRESSION OF THE GASTRIC CENTERS

Depression of the gastric centers reduces vagal motor activation of forestomach motility and can be induced by CNS depressant drugs and anesthetics. Endotoxemia, fever, and possibly blood pH and electrolyte abnormalities can induce ruminal hypomotility or stasis through central effects on the gastric centers. These factors may also inhibit ruminal motility by increasing sympathetic nervous activity. In addition, some toxins or other abnormal fermentation products reduce ruminal motility. These substances may act locally at the ruminal epithelial receptors to generate inhibitory impulses, as do increased VFA concentrations, or they may act centrally after absorption into the blood. For the most part the nature of the substances capable of chemically suppressing ruminal function is unknown, but abnormal fermentation end products are the likely cause of ruminal stasis in indigestion associated with abnormal ruminal contents.[386,388,396,400,403–409]

32.120.2.4 DEFECTIVE VAGAL INNERVATION

Failure of vagal nerve transmission of motor impulses has been implicated as the cause of a reticuloruminal contraction abnormality that leads to failure of aborad flow of ingesta (hence the name *vagal indigestion*). The left and right vagi in the thorax divide into dorsal and ventral branches that unite to form dorsal and ventral vagi as the nerves enter the abdomen. The ventral vagus innervates the cranial and medial parts of the reticulum, the omasum, and the abomasum. The dorsal vagus innervates the rumen and parts of the other segments of the ruminant stomach. Sectioning of more than 50% of the vagal nerve trunks leads to impaired motility function, but most cases of vagal indigestion show much less nerve involvement. The importance of vagal nerve lesions in the pathogenesis of forestomach disease has been a subject of considerable debate and is discussed more fully later in this chapter.[396,397,401]

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32.120.2.5 OTHER FACTORS THAT AFFECT THE PRIMARY CYCLES

Other influences on forestomach motility have been identified. Hypocalcemia inhibits motility by preventing contraction of the musculature after motor nerve discharge. This may explain the reduced ruminal motility seen in early cases of milk fever.[409–411] Low environmental temperatures[412,413] and milking[414] have been shown to increase ruminal motility mildly, whereas some drugs,[400,401,415–417] hyperglycemia,[418] and gastric hormones[400,419] are effective in decreasing reticuloruminal primary cycle contractions. These factors are not discussed further in this text.

32.120.3 Secondary Cycle Activity

The secondary cycle activity responsible for eructation is elicited independently of the primary cycles. An increase in ruminal gas pressure excites tension receptors in the medial wall of the cranial ruminal sac. This triggers relaxation of the cardia and eructation of the gas accumulated in the cardia region by the secondary contraction cycle. Receptors that apparently distinguish gas from fluid or solid matter inhibit opening of the cardia if it is covered by material other than gas.[420] This reflex inhibition of cardia opening is responsible for bloat in cases in which abnormal ingesta cover the area, such as in recumbent animals, in frothy bloat, and when abnormal motility or overfilling of the rumen precludes clearing of the cardia. Under such circumstances and when ruminal distention is not yet extreme, both primary and secondary cycle contractions may increase in frequency. In other forms of bloat, hypomotility is a prominent feature, and the gas accumulates as a result of the poor motility function.[391] This is the most probable cause of bloat in some of the disturbances of fermentative function.

Gross overdistention of the ruminal wall may inhibit motility by stretching the musculature beyond its ability to contract forcefully. If the process leading to the distention develops slowly, the high-tension receptor inhibition of motility appears to adapt, and complete inhibition of motor impulses does not seem to occur. Rather, in these cases motility is present but weak and relatively ineffective. This motility disturbance is likely when poorly digestible roughage accumulates in the forestomach. Patients with this condition often have mild to moderate chronic free gas bloat, which may result from poor ability of the weakened rumen to clear the cardia and dispel the gas.[386]

Table 32-12 Causes of Ruminal Tympany (Bloat)

Mechanism	Cause	Disease Examples
Obstruction of eructations	Esophageal obstruction	Choke, tetanus, thoracic inflammation or neoplasia with swollen mediastinal lymph nodes
	Cardia obstruction	Papilloma, fibroma, actinobacillosis
	Failure to clear cardia of fluid or ingesta	Lateral recumbency, reticulorumen overfilled with ingesta (as in vagal indigestion, ruminal microbial inactivity with poorly digestible roughage, obstruction of the reticuloomasal orifice)
	Gas trapped in stable foam	Frothy bloat
Ruminal motor dysfunction	Failure of smooth muscle contraction	Hypocalcemia
	Weakened muscle contraction	Chronic ruminal distention with indigestible roughage, outflow obstruction, or vagal indigestion, hypokalemia
	Abomasal distention	Displaced abomasum (especially in calves)
	Vagus nerve damage	Thoracic inflammation (especially in calves, neoplasia)
Chemical inhibition	Ruminal stasis	Ruminal acidosis, ruminal alkalosis, abnormal fermentation products with simple indigestion

32.120.4 Free Gas Bloat

Accumulation of free gas in the dorsal rumen should not be considered a primary disease entity but rather a sign of disease (Table 32-12). However, because free gas bloat often is the most prominent sign and because it accompanies several different forms of indigestion, its pathogenesis is reviewed briefly here.

Ruminal microbial fermentation and neutralization of salivary bicarbonate continually produce gas as an end product (primarily methane and carbon dioxide) in proportion to the rate of fermentation. Normally the ruminant can eructate volumes of gas that exceed the amount produced even at maximum rates of fermentation.[392,393] Therefore an excessive production of gas is not the cause of bloat. Bloat develops either because the evacuation of gas is hindered by a physical obstruction or because the mechanisms that expel the gas are inhibited.[421–424]

As in choke, physical obstruction of the esophagus by a foreign body can produce dramatic and peracute bloat. Other forms of esophageal occlusion (which may additionally involve inflammation of nerves or ruminal muscle malfunction) include muscular spasm (e.g., tetanus), swollen mediastinal lymph nodes (e.g., chronic pneumonia, thymic lymphosarcoma), and tumorous or inflammatory swellings of the cardia region (e.g., papilloma, actinomycosis). These problems tend to show bloat of a slowly progressive or chronic nature, although the degree of bloat may be marked.

Bloat is a common feature of indigestions caused by microbial fermentative disorders. When ruminal hypomotility occurs, the fermentative rate may decline, but weak ruminal contractions may be inadequate to move the gas layer and to clear the cardia preparatory to eructation. Thus dietary, microbial, or metabolic factors that affect the excitability of the gastric centers or the reticulorumen can result in bloat. Ruminal stasis can result in bloat because eructation occurs only with ruminal contraction. Bloat also accompanies indigestions that produce gross distention of the reticulorumen with fluid or solid ingesta (e.g., vagal indigestion, ruminal

acidosis, and microfloral inactivity caused by indigestible roughage). The cause of bloat in these cases may be a combination of ruminal stasis, weakening of the ruminal wall caused by the gross distention, and failure to clear the cardia.

Some authors have attributed chronic bloat in calves to a form of vagal nerve damage resulting from mediastinal inflammation.[425,426] However, it has not been demonstrated that vagal nerve involvement is the source of the failure to eructate in these cases. It appears that free gas bloat in calves has numerous causes, as is true in adult cattle, including fermentative indigestions, ruminal wall disturbances, and esophageal involvement in an intrathoracic inflammatory process.[427] Distinguishing between vagal nerve impairment and esophageal compression or inflammation as the cause of free gas bloat requires a thorough assessment of ruminal motor function, as described under the section on clinical signs (p. 832).

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32.120.5 Reticulitis and Rumenitis

The most important inflammatory problem is reticuloperitonitis caused by sharp foreign body punctures (TRP, hardware disease). This disease is discussed elsewhere in the text (p. 848). The localized infection established by reticuloruminal perforation causes inflammation of the forestomach wall and adjacent peritoneal cavity and pain in the anterior abdomen, inhibiting forestomach motility, appetite, and aborad flow of ingesta. Other causes of ruminal wall inflammation can cause acute or chronic forestomach dysfunction.

Most infections of the ruminal wall follow primary mechanical or chemical damage to the mucosa. The secondary invaders colonize the damaged areas and may gain access to the circulation and invade other tissues as well. The ruminal wall may be the niche for some of these microorganisms, and isolates from the ruminal wall have been matched with those isolated from liver abscesses.[428] Probably the most common cause of the initial mucosal injury is acute ruminal acidosis produced by grain engorgement. Chemical damage resulting in ruminal ulcers also occurs in oak or acorn toxicosis and with ingestion of caustic chemicals. Common secondary ulcer invaders include *Arcanobacterium (Actinomyces) pyogenes, Fusobacterium necrophorum*, and several mycotic species.[428,429] Mycotic rumenitis can follow ruminal acidosis and septic diseases, especially after the use of oral antibiotics; it also can occur after feeding spoiled and moldy feeds and without apparent predisposing causes.[430–434] Diseases that cause anorexia plus abomasal reflux of gastric acids may predispose an animal to mycotic rumenitis and omasitis. Mycotic rumenitis can be severe, with vascular thrombosis and infarction and mural necrosis and gangrene sufficient to cause death. Less frequently occurring specific infections of the ruminal wall include actinobacillosis, actinomycosis, and tuberculosis. These infectious inflammatory diseases of the ruminal wall may be distributed widely throughout the forestomach, depending on the initial site of mucosal injury, but they tend to localize in the ventral regions of the reticulorumen. The granulomatous inflammatory lesions of actinobacillosis and actinomycosis are most commonly found in the cranial forestomach in the area of the esophageal groove.

Neoplastic growths in the rumen have also been identified. These uncommon lesions include papillomas, myxomas, fibromas, carcinomas, and lymphosarcoma.[386,435,436] These lesions are most commonly localized in the reticulum and cranial rumen near the cardia and esophageal groove.

The importance of these inflammatory reticuloruminal lesions depends on their extent and location. Acute and extensive lesions have been associated with signs similar to those of reticuloperitonitis caused by foreign body puncture, including pain, inappetence, impaired forestomach function, and in some cases death. The more chronic cases may cause forestomach motility disturbances and signs of vagal indigestion. Pedunculated masses especially, but not exclusively, may obstruct the cardia or reticuloomasal orifice, leading to bloat or

reticuloruminal outflow disturbance.

Reticuloruminal inflammation can also result from certain generalized infections. These include BVD, FMD, MCF, and RP. In these cases the forestomach problems are unlikely to be the most important clinical manifestation.

32.120.6 Ruminal Parakeratosis

In parakeratosis the papillae are darkly colored, enlarged, thickened, and clumped together. Histologic changes of the epithelial cells include a thickened, cornified layer with abnormal retention of nuclei in the cornified cells. These morphologic changes appear to represent a reaction to persistently high concentrations of VFAs. The changes occur predominantly in animals on pelleted or very finely ground rations, especially when the ration contains a high amount of energy. These rations tend to increase the proportions of propionate and butyrate, reduce the proportion of acetate generated by microbial fermentation, and produce a lowered ruminal fluid pH. The growth of the ruminal papillae is promoted by contact with the VFAs, especially butyrate, and secondarily propionate.[388,423] It appears that a disproportion of the concentrations of these VFAs may be the cause of an excessive change in the epithelium of the papillae.[437,438] Initial changes in the epithelium under these conditions appear to increase the absorption of the VFAs, but in severe cases the absorption decreases. This disease of the ruminal wall is not usually diagnosed as a primary problem. Although it may lead to impaired performance of the animal, the disease signs that lead to its discovery are usually those of chronic acidosis, a disease with which it often coexists. Parakeratosis can predispose to other injuries of the ruminal wall, however, because the abnormal papillae are more easily traumatized, leading to chronic inflammatory disease of the wall as discussed previously. In calves the problem is also associated with the development of hairballs (trichobezoars) because of the propensity of calves on the rations associated with parakeratosis to lick their hair coat.[386,422,439,440]

32.120.7 Vagal Indigestion

Vagal indigestion syndrome (vagus indigestion, Hoflund's syndrome) is composed of a group of motor disturbances that hinder passage of ingesta from the reticulorumen or abomasum or both. The pathogenesis of the disease has been debated for years and has yet to be completely clarified because many investigations have yielded conflicting information.[*]

The name *vagus indigestion* was introduced by Hoflund, who experimentally produced motor defects and disease signs similar to those seen in clinical cases by transecting various branches of the abdominal vagal nerve.[442] On the basis of his experimental results, he defined four types of functional disturbance, with obstruction of ingesta flow at two sites:

1 *Omasal transport failure* (anterior functional stenosis), which impairs flow of ingesta through the reticuloomasal orifice and occurs with

   a atony of the reticulorumen, often associated with chronic recurrent bloat, or

   b normal to increased ruminal motility

2 *Pyloric outflow failure* (posterior functional stenosis), which impairs flow through the pylorus and occurs

   a continuously or

b in an intermittent, recurrent pattern (incompletely)

Hoflund's description of the syndrome is convenient for explaining the observed functional defects, but its presumed pathogenesis is not supported by the findings of several later investigators.[400,441,444,449] The use of the term *stenosis* has also led to some confusion, although it was appropriate in its original context. *Functional stenosis* suggested that the defect was a functional one that mimicked a stenosis at the site of outflow. However, vagal denervation does not produce a true stenosis, but rather a paralysis and relaxation of either the reticuloomasal orifice or the pylorus. The paralysis can be appreciated in both experimental and clinical cases.

32.120.7.1

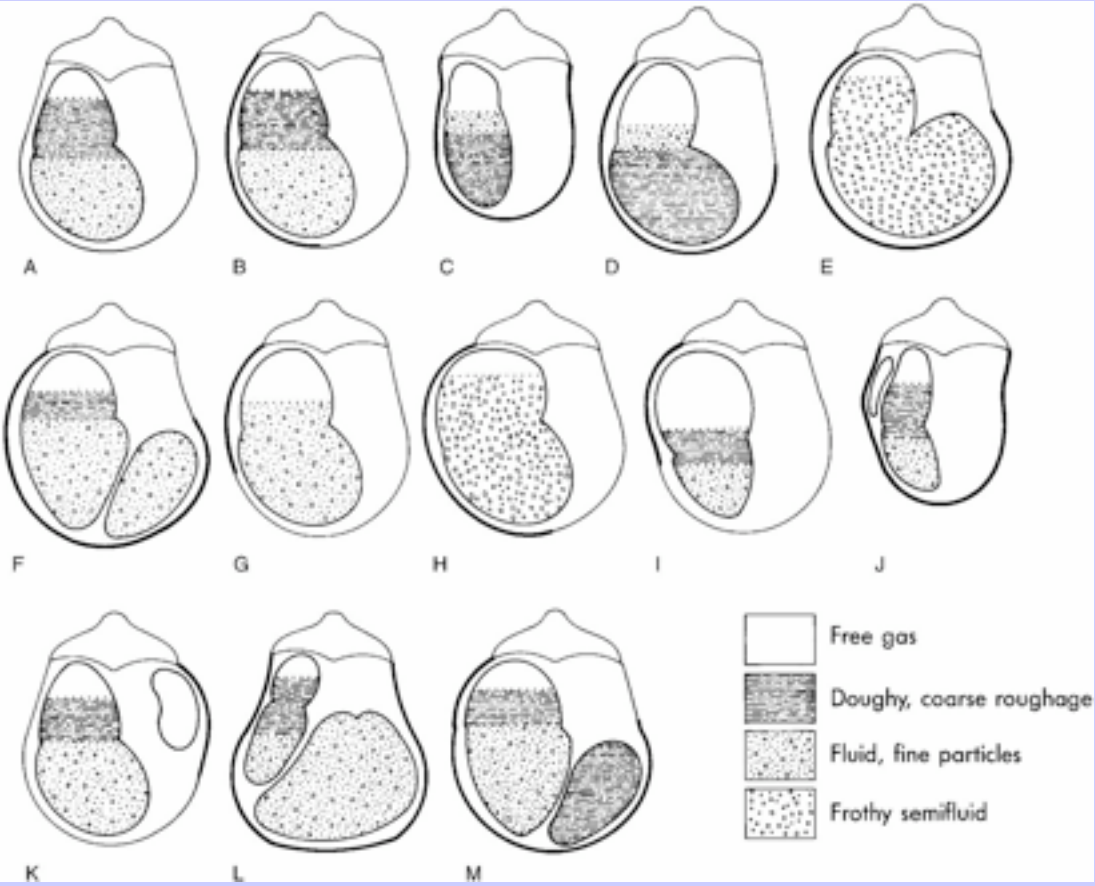
FAILURE OF OMASAL TRANSPORT

Failure of omasal transport with hypermotility of the rumen is the most common naturally occurring form of the disease. Accumulation of ingesta in the reticulorumen leads to gradually progressive distention of the forestomachs, whereas the omasum and abomasum remain relatively empty. The animal's appetite diminishes as the rumen becomes overfilled, producing one of the most characteristic signs of the disease: inappetence with gross distention of the rumen in the left flank. Continued dilation of the rumen eventually leads to a marked and almost pathognomonic overfilling of the ventral ruminal sac. The rumen assumes an L shape because the ventral sac occupies both the right and left ventral quadrants of the abdomen. The resultant characteristic abdominal contour often is called a “papple” shape (Fig. 32-94, *E*) because the left side of the abdomen is distended and assumes the appearance of an apple, whereas the right side assumes the contour of a pear. The diminished passage of ingesta results in reduced fecal volume. The normal ruminal process of selective retention of fibrous material is disturbed, leading to large particle passage and feces with increased fiber length and a greasy or pasty consistency. Some cases show firm feces with large particle size.[447,450] Affected animals often continue to drink water, but absorption from the rumen is poor, and the water accumulates in the forestomach while the animal becomes mildly dehydrated. Vigorous contractions of the rumen can be palpated in the left paralumbar fossa in most affected animals, although some display almost complete atony. The contraction pattern does not produce the typical stratification of material in the forestomach, but rather it churns the ruminal contents into a uniform frothy fluid.[450,453]

Fig. 32-94 Abdominal contours (viewed from the rear) and abdominal

palpation findings characteristic of cattle with various types of indigestion and other abdominal diseases. A thin line for the abdominal contour indicates the normal configuration. Bold lines indicate areas of the abdominal contour that typically deviate from normal in affected animals. **A**, Normal. **B**, Acute onset of ruminal stasis with simple indigestion, traumatic reticuloperitonitis (findings: mild ruminal distention with normal layering of ruminal content). **C**, Prolonged ruminal stasis, anorexia. The most common result of subacute or chronic disorders such as microbial or fermentative indigestions, traumatic reticuloperitonitis, and secondary indigestions (findings: reduced ruminal fill, "tucked-up abdomen," firm, doughy contents that gravitate ventrally). **D**, Ruminal inactivity with indigestible roughage (findings: rumen distended with firm, doughy contents that accumulate ventrally; recurrent free gas bloat often present). **E**, Omasal transport failure (findings: L-shaped rumen with gross accumulation of frothy ingesta; ruminal hypermotility often present; free gas accumulation varies). **F**, Pyloric outflow failure (findings: fluid accumulation in abomasum; abomasal reflux to rumen common; doughy ruminal content that usually accumulates dorsally until ruminal stasis or anorexia is prolonged; abdominal contour similar to that for omasal transport failure). **G**, Acute ruminal acidosis (findings: rumen distended with fluid; some free gas bloat common). **H**, Frothy bloat. **I**, Free gas bloat or chronic free gas bloat (findings: accumulation of gas in dorsal sac; layering or ruminal contents usually normal; with chronicity, ruminal fill often decreased; associated with some microbial or fermentative disorders and with esophageal and cardiac disorders). **J**, Left displaced abomasum (findings: gas-filled abomasum that often causes slight bulge of paralumbar fossa; ruminal fill usually reduced). **K**, Right displaced abomasum, abomasal volvulus, cecal torsion (findings: distention of right flank with gas-filled viscus; ruminal fill and consistency usually normal). **L**, Hydrops (findings: ventral abdomen distended with fluid-filled uterus; ruminal fill usually

abdomen distended with fluid-filled uterus. Ruminal fill usually decreased). **M**, Abomasal impaction (findings: abdominal contour similar to **E** and **F**; abomasum filled with firm ingesta).



The signs just described, with abnormal flow of ingesta and normal or increased forestomach contractions, can be experimentally reproduced by sectioning the ventral vagal trunk at the cardia and the dorsal trunk just distal to the branching of the ruminal nerves.[397,442] The forestomach distention, empty omasum and abomasum, and stasis of the forestomach with resultant free gas bloat can be reproduced by sectioning both abdominal vagal trunks along the esophagus. The paralysis produced by vagal denervation can explain the failure of ingesta flow into the omasum by two mechanisms. First, the lower end of the esophageal groove is formed by two muscular lips. These overlap in a manner that allows a passive valve effect that blocks flow into the omasum when they are relaxed or paralyzed. Second, it appears that the flow into the omasum is accomplished by an active pumping motion of the omasum that reduces pressure and draws fluid through the reticuloomasal orifice. Paralysis of the omasal musculature after denervation would eliminate this effect. Decreased reticular motility caused by adhesion or paralysis may contribute to the changes in ruminal content and the alteration in particle passage.[450,453]

The most common predisposing cause of naturally occurring omasal transport failure (anterior functional

stenosis) is TRP. Other causes of anterior functional stenosis include abscesses, adhesions, and peritonitis at the reticulum (especially the right side of the reticulum) or reticuloomasal area without identification of an offending foreign body; hepatic abscesses; diffuse peritonitis; neoplasia of the ruminoreticular fold and esophageal groove; inflammatory disease of the reticular and ruminal walls; papilloma or other mass at the reticuloomasal orifice; and herniation of the reticulum through a diaphragmatic defect. Foreign bodies that obstruct the reticuloomasal orifice cause a syndrome indistinguishable from vagal indigestion except by exploratory rumenotomy.[436] To reconcile the experimental findings with those from clinical cases, the development of omasal transport failure has been explained as involvement of the vagal trunks in the inflammatory process at the reticulum. Several findings make this an unlikely explanation in most clinical cases[396,397,443,449,451]:

1 Although sectioning the vagus nerves as described reproduces the syndrome, disturbing only one of the two trunks still allows normal cyclic contractions in most cases. For a clinical lesion to produce disease development, massive involvement of the vagal nerves would be required. By contrast, less than a third of examined cases reported show actual lesions in the nerve branches.

2 The ratio of sensory to motor nerve fibers in the abdominal vagi is approximately 9:1, suggesting the important sensory role of the nerve.

3 Inflammatory lesions of the reticuloruminal wall reported in cases of vagal indigestion are predominantly in the same areas as the important tension receptors that send afferent excitatory impulses to the gastric centers. Induration of the right (medial) wall of the reticulum and in the esophageal groove region may affect intramural nerves and ganglia and reduce the tension receptor activity and therefore the drive for primary cycle activity.

These considerations allow an explanation of some of the inconsistencies found in various cases. Anterior functional stenosis may occur with insufficient vagal sensory excitation, which in turn reduces excitatory input to the gastric centers, diminishes primary cycle motor drive, and results in paralysis of the omasum and reticuloomasal orifice. Alternatively, substantial reticular adhesions that develop after TRP could prevent normal delivery of small particle ingest, with fluid consistency, to the reticuloomasal orifice.[453] Because this reduces or abolishes flow into the omasum, both the omasum and abomasum would remain relatively empty, a common finding in these cases. The hypermotility observed in these cases may be the result of secondary rather than primary cycle contractions. Distention of the cranial ruminal sac would still be able to induce the secondary contractions if this region is not involved in the induration. Without normal primary cycle activity, the typical stratification of the ingesta would be disturbed, as is usually observed. The existence of hypermotile secondary contractions with absence or severe reduction of primary contractions can be detected clinically. Damage to the thoracic or abdominal vagi by inflammatory or neoplastic lesions may lead to the occasional cases that show both anterior functional stenosis and atony of the forestomachs, with resultant free gas bloat. This would be similar to the experimental sectioning of both vagal trunks.

32.120.7.1.1

Pyloric Outflow Failure

Failure of pyloric outflow (posterior functional stenosis) causes accumulation of ingesta in the abomasum and omasum. Advanced stages of this form of the syndrome also display gross distention of the reticulorumen. Generally the motility of the forestomach is not markedly affected in the early stages, and normal stratification of ingesta is maintained. Overfilling of the forestomach as a result of reflux of ingesta from the abomasum (internal vomiting) may occur, causing the chloride content of the ruminal fluid to increase (normal is less than 30 mEq/L). In contrast, the ruminal fluid of animals with anterior functional

stenosis has a normal chloride content.[444,446,447,453] With severe distention forestomach motility is reduced, and the ruminal contents become more fluid. Failure of ingesta to flow into the intestinal tract, combined with sequestration of chloride-rich fluid in the stomach chambers, can cause both marked dehydration and hypochloremic metabolic alkalosis. In cases with a gradual, prolonged development, however, as in anterior stenosis, any dehydration tends to be mild, and body fluid electrolyte concentrations do not show remarkable abnormalities. Fecal production in these cases tends to be even less than with the anterior stenosis form of the syndrome.[441,453]

Failure of pyloric outflow can be experimentally reproduced by sectioning the ventral vagus trunk at the cardia and the continuation of the dorsal trunk as it crosses the omasum.[397,442] This mimics the usual clinical form of the disease, which is characterized by complete inhibition of flow from the abomasum. Combinations of more distal resections of the nerves produce the syndrome of recurrent atony of the abomasum as it occurs in natural clinical cases. Again, the term *stenosis* is a misnomer, because a true stenosis or spasm of the pylorus is not identified. Rather, the experimental vagal nerve resection and the naturally occurring cases show a flaccid paralysis, and ingesta accumulate as a result of failure of propulsive activity. The dilation of the abomasum is in the fundus and body and not in the pyloric part.[399,441,442]

A common predisposing cause of pyloric outflow failure syndrome is volvulus of the abomasum. Other abomasal disturbances, including right and left displacements of the abomasum and abomasal ulceration, can cause the disease as well. After surgical correction of a volvulus, the abomasum remains atonic, and the disease may develop within several days. Clinical signs compatible with vagal indigestion may arise from gross distention and twisting of the abomasum and lesser omentum, resulting in potentially coexisting but distinct injury to the vagal nerves or structural damage to the gastric wall, with or without peritonitis. Although focally extensive vagal nerve lesions have been associated with concomitant vascular damage, indicating that even with nerve regeneration there may not be a return to normal function, the damage appears reparable in some cases, because a return to normal function has been observed.[452]

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Inflammation and adhesions involving the abomasal fundus and reticulum have been associated with posterior functional stenosis in some studies.[441,453] Inflammation of the reticular wall may account for the reticular atony reported in some cases. This form of vagal indigestion may be more frequently associated with true vagal nerve impairment than appears to be the case in anterior functional stenosis. Alternatively, reticular adhesions may prevent normal motility, alter the flow of ingesta to the omasum and abomasum, and lead to abnormal filling of the abomasum because of decreased fluidity of abomasal contents.[453]

Another predisposing cause of pyloric outflow failure is advanced pregnancy with a large fetus. An exact pathogenesis has not been clearly defined. Presumably the large, gravid uterus distorts the positioning of the abomasum or physically compresses and obstructs the anterior small bowel, preventing outflow of ingesta from the abomasum. In these patients the gravid horn typically occupies most of the space in the omental sling. In support of these conclusions, the problem can be resolved by inducing delivery of the calf or performing a cesarean section. Supportive care may be required for severely affected cows, but the gastrointestinal system returns to normal function, suggesting that it was secondarily affected by the pregnancy. This problem is referred to as a form of vagal indigestion because it appears as a pyloric outflow failure. Some patients have such severe obstruction of ingesta passage that they may be diagnosed as having an anterior bowel obstruction. This disease has been called *indigestion of late pregnancy*.

Animals affected with any form of vagal indigestion for a prolonged time lose body condition because the

failure to pass ingesta into the intestinal tract produces a state of starvation. The weight loss may be overlooked because of the impression of full body size produced by the abdominal distention.

* References 386,396,397,401,425,441–453.

32.120.7.2 CHRONIC RECURRENT BLOAT

Chronic recurrent bloat is commonly identified with vagal indigestion in any of its forms. It is mild to moderate in severity, commonly waxes and wanes, and adds to the visual impression of gross abdominal distention. The pathogenesis of this ruminal tympany varies from case to case. Experimental resection of both abdominal vagal trunks stops eructation by causing complete forestomach stasis. In naturally occurring cases in which lesions of the vagal nerve truly inhibit motor impulse transmission, bloat may arise from this mechanism. When vagal nerve damage does not appear to be involved, other mechanisms may explain the bloat (see Table 32-12). Overfilling of the reticulorumen with frothy ingesta, a common finding, can inhibit the cardia dilation reflex that is a prerequisite of eructation. Gross distention of the forestomach can also weaken the contractile ability of the rumen, so that the contractions are not strong enough to clear the cardia before eructation.

Bradycardia is often identified in association with vagal indigestion but can also occur with other forestomach diseases. The finding that atropine administration can abolish the bradycardia of vagal indigestion suggests increased cardiac vagal tone as the direct cause.[425,454] However, the origin of the vagotonia is unclear. When vagal nerve lesions exist distal to the cardiac innervation, reflex excitatory discharges may effect bradycardia. Experimental resection of the vagal nerves causes bradycardia as a striking feature in most cases, although advanced cases show increased heart rates. By contrast, naturally occurring vagal indigestion shows bradycardia as a feature in only a third or fewer of the cases.[441,445,447] These variations may exist because the experimental and natural cases have different causes or because the disease varies in duration. Once the forestomach has become severely distended, the heart rate tends to be elevated, probably as a result of deterioration of hydration and cardiovascular parameters.

32.120.8 Obstruction of the Cardia or Reticuloomasal Orifice

True mechanical obstruction of the forestomach is an uncommon occurrence. The obstruction can be either full or partial and can occur at either the cardia or the reticuloomasal orifice. The inflammatory and neoplastic conditions described previously can appear to be obstructive disease when the tissues are sufficiently distorted and lesions involve one of these orifices. Papillomas are most prone to causing an obstruction when they become pedunculated. A variety of foreign bodies create obstruction. In calves, trichobezoars are most commonly the cause, occurring predominantly in animals on a low roughage diet that consequently lick their hair coats vigorously. In adult cows, ingestion of the placenta occasionally results in an obstruction. Curious ruminants, especially goats, sometimes consume plastic bags or discarded rectal palpation sleeves. These and other nondegradable materials can lead to obstruction even after considerable time has passed.

Cardia obstruction leads to the signs typical of esophageal obstruction, with free gas bloat as a prominent, perhaps life-threatening development. Obstruction of the reticuloomasal orifice produces the same consequences as some forms of vagal indigestion. Failure of ingesta flow beyond the rumen results in accumulation of fluid material in the forestomach and diminished or no passage of ingesta through the intestines. The degree and duration of obstruction determine the severity of associated problems such as dehydration, depression, elevated heart rate, forestomach stasis, colic, and muscular weakness. Only rumenotomy can effectively differentiate these obstructive diseases from other problems with similar signs.

32.120.9 Diaphragmatic Hernia

Defects in the diaphragms of cattle are uncommon. Most cases involve a tear through which the reticulum can herniate. Other abdominal organs may also be involved if the rent is large. The diaphragmatic defect may be congenital or an acquired lesion caused by a local inflammatory process (TRP), sudden external trauma (fighting, hanging up on a fence), or internal pressure (parturition, acute tympany). Entrapment of the reticulum may lead to acute changes in intrathoracic pressure and cause sudden dyspnea, tachycardia, and poor venous return to the heart. Generally, however, this reticular problem causes signs identical to those of vagal indigestion with anterior functional stenosis.[386,445] Failure of flow through the reticuloomasal orifice may result from vagal nerve damage, or the anatomic distortion alone may explain the motility defect. Entrapment of the reticulum hinders normal reticular movements and distorts the esophageal groove and reticuloomasal orifice. Reticular ingesta can be heard moving inside the thorax; therefore complete reticular paralysis is unlikely. Motility disturbance is reflected by hypermotility of the rumen, generation of frothy ingesta, persistent or recurrent moderate tympany, and overfilling of the rumen. Signs of pain may also be present, as in cases of TRP. Rumination usually is impaired, and large volumes of ingesta may be vomited, especially after eating.

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32.121 DISORDERS OF RETICULORUMINAL FERMENTATIVE FUNCTION (SeeBox 32-5)

32.121.1 Forestomach Microbial Population

The continuous culture system of the rumen involves an ongoing selection of microorganisms best adapted to grow in a variety of ecologic niches that are in a dynamic state. Numerous control mechanisms govern the environment and the resultant microbial population. Some of these mechanisms are related to the animal itself, such as salivation, mixing and rumination, removal of substances by absorption or diffusion, outflow through the reticuloomasal orifice, and eructation. Others are related to the diet, including nutrient quality of the substrate (feed), balance of required elements, solubility, particle size, presence of inhibitory substances, nutrient quantity, and rate of delivery to the rumen. Control of fermentation also results from microbial interactions such as competition and symbiosis: cross-feeding between species, removal of inhibitory end products, and maintenance of the oxidation-reduction potential. The complexity of the system tends to promote an overall stability. Changes in the controlling factors create selective pressures that lead to population changes in the rumen.[424,455–456]

The ruminal bacteria are predominantly anaerobes, with some coexisting facultative anaerobes. Although the facultative organisms are not important in normal ruminal function, they may be in some forms of ruminal dysfunction. Some microbes ferment the primary nutrients in the feed such as cellulose, hemicellulose, pectin, starch, and simple sugars. Other species ferment the products of the primary group, such as pentoses, glucose, lactate, succinate, and formate. Many species are very specialized and have numerous growth requirements that may be supplied by the general fermentation. The last group is important for its role in removing end products and cycling essential factors back to the other organisms.[424,455–457]

Table 32-13 Effects of Feed Characteristics on Ruminal Digestion and Health

Feed	Ruminal Content	Effect on Health
Primary forage of high quality, long fiber length, crude fiber >18% of dry matter; with concentrate supplement at 20%–50% of total intake, moderate protein level	pH 5.5–7, VFA 60–120 mmol/L, acetic > propionic > butyric acid	Normal, healthy, productive
Excessive forage of low nutrient value (late cut) with little concentrate or protein supplementation	pH 6.5–7, VFA decreased, microbial activity decreased	Poor production or growth, microfloral inactivity and ruminal impaction, malnutrition caused by protein, energy, mineral, and vitamin deficiency
High level of concentrate feeding (>60%) with decreased forage and/or fiber length	pH 5–6.5, VFA increased, microbial activity increased	High production, rapid growth; possible chronic ruminal acidosis, milk fat depression, chronic laminitis, ketosis, ruminal parakeratosis, excessively fat condition
Extremely high level of concentrates (especially with sudden exposure to ration), low intake of forage	pH 4.5–5, VFA increased, lactic acid increased	Acute ruminal acidosis
Normal levels of forage intake, concentrate with very high protein or NPN supplementation	pH 6.5–7.5, VFA decreased, ammonia increased	Ruminal alkalosis, possible urea toxicity

NPN, Nonprotein nitrogen; *VFA*, volatile fatty acid.

32.121.2 Effects of Feed Characteristics

The concentrations and proportions of the microbial species vary with the composition of the diet (Table 32-13). An abundant supply of a certain substrate tends to favor a microbial population with a predilection or high capacity for using that material. The most important factors in the rate of digestion are the properties of the carbohydrates and protein in the feed. High-protein diets favor proteolytic organisms, whereas high-starch, low-fiber diets favor starch users. Cellulolytic bacteria are prominent in a high-fiber diet, but their numbers also depend on the fiber size, as this factor determines the rate of passage or retention in the forestomach; therefore cellulolytic species can be abundant with a high-concentrate diet if some long-stemmed roughage is included because the retention time of the fiber is prolonged. Diets with readily fermentable carbohydrates and low fiber favor species capable of rapid metabolism and tolerant of low pH. Acid production is rapid and high, and populations of microbes less tolerant of such changes decline.[455,457,458]

The microbial population is also influenced by the limits of supply of certain feed substrates.[455] High rates of fermentation and microbial growth on the abundant substrates depend on sufficient amounts of the more limited nutrients. Optimum carbohydrate use requires adequate sources of nitrogen, sulfur, and essential mineral nutrients.[459] When any essential nutrient is deficient, the rate of digestion and therefore the digestibility of the feedstuff decrease. Whether the affected animal shows signs of nutrient deficiency or forestomach dysfunction with microbial and forestomach inactivity depends on the limiting nutrient and relative requirement of the host and bacteria for the nutrient. Substances and conditions that inhibit fermentation further reduce digestibility.

The feed material also affects ruminal fermentation by influencing the rate of passage from the reticulorumen.

Fine grinding and pelleting of feed increase the rate of passage of the particulate matter from the rumen. Very finely ground rations also reduce the stratification of fibrous material in the rumen. This affects the ability to sort material in the rumen selectively by particle size and density, so that larger particles less thoroughly fermented pass more readily into the lower bowel. Microbes associated with the feed particles are passed out of the rumen with the feed. Thus a faster rate of passage influences the bacterial population because it competes with the generation time of the organisms. Populations of slower-growing microbes tend to be most influenced by changes in the retention or passage times. Slow-growing cellulolytic bacteria decline in numbers as the passage rate increases (transit time decreases). High passage rates usually produce faster digestion rates. Although these factors are primarily important to the feed efficiency of the animal, they also affect ruminal function and the adaptation of microbes to feeding changes.[388]

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Adaptation of the microbial flora to dietary changes requires a week or longer. The abruptness of a dietary change determines the degree of alteration of the ruminal microbial population and fermentation pattern and the potential for digestive disturbances. With abrupt and dramatic shifts to higher-carbohydrate diets, the facultative species may overwhelm the more normal flora by producing excessive acid and lowering the pH. The importance of microbial adaptation to a particular diet is evidenced by the reduction in forestomach disturbances seen when the rumen is inoculated, before a feeding change, with fluid from animals already adapted to the new ration.[424,456]

The end products of microbial fermentation influence not only the microbial population but also ruminal function. High concentrations of nondissociated VFAs excite sensory epithelial receptors that reflexively inhibit ruminal motility.[424,460,461] If a sudden increase in concentrate feeding induces lactic acid fermentation, the ruminal pH suddenly declines and a greater proportion of the VFAs shift to the nondissociated state, inducing ruminal stasis. A consistently high level of concentrate feeding produces rapid fermentation, a high concentration of VFAs, and low pH, and the nondissociated VFA level may reach the threshold for stimulation of the inhibitory epithelial receptors. The ruminal stasis reduces the fermentation rate. Mild cases of ruminal acidosis may show spontaneous recovery of ruminal functions as the absorption of VFAs reduces the concentrations to a noninhibitory level. With more severe ruminal acidosis the generation of acid continues despite the ruminal stasis, giving rise to more severe complications of the disease.

In some instances the effects of ruminal microbial metabolism and microbial end products extend beyond impacts on nutritional status and digestive system function. Several ruminant diseases represent rumen-generated toxicities. These have extremely variable manifestations and include toxicoses from ammonia, nitrate and nitrite, 3-methylindole, dimethylsulfide (*Brassica* species, onion toxicity), and sulfur-associated polioencephalomalacia.[462–465]

In summary, excesses, deficiencies, or rapid changes of feed substrate can cause imbalance in the microbial population and the fluid milieu. The result can be bacterial overgrowth and overproduction of microbial end products or insufficient microbial growth and fermentation. The effects of these abnormalities on the animal range from ruminal motility dysfunction to poor growth and performance to outright toxicity and organic damage.

32.121.3 Inactivity of Ruminal Microbial Flora (Caused by Poor-Quality Roughage,

Haybelly, or Ruminal Impaction)

In ruminal microbial flora inactivity, the microbial populations and their metabolic and fermentative processes are diminished as a result of deficiencies of one or more nutrients. This occurs most commonly with poor-quality roughage deficient in protein and readily digestible carbohydrates (late-cut, highly lignified hay or straw). Microfloral inactivity can also occur when specific mineral nutrients are deficient, or it can be caused by inhibitory substances such as antibiotics or some plant products.[388,424,459] Microfloral inactivity also occurs with prolonged anorexia, which abolishes the intake of all nutrients and is the primary pathogenesis of many cases of secondary indigestion.

When microbial digestive processes decline, the breakdown of ingested feedstuffs is prolonged. Failure to reduce the particle size of the ingesta leads to a prolonged retention in the forestomach and gradual accumulation of the undigested feedstuff. Gradual distention of the reticulorumen is commonly observed (haybelly). In extreme cases this can mimic the signs of vagal indigestion. Forestomach distention can result in weak contractions and moderate recurrent tympany. Ruminal hypomotility alters the normal stratification of the ruminal contents, and the fibrous components are found mixed in the fluid or compacted ventrally on the ruminal floor. Abnormal passage of ingesta from the forestomach results in decreased fecal passage, and the feces usually are dried and contain undigested plant fibers. Other effects on the animal are those of generalized or specific nutrient deficiencies (e.g., decreased growth or production, ketosis, emaciation, and a poor hair coat). When anorexia is the cause of the microbial inactivity, the ruminal fill decreases and the lack of normal distention also induces ruminal stasis.[386,466]

32.121.4 Simple Indigestion

Simple indigestion is the most common sequela of an abrupt change in the ration. Such feed changes present the ruminal microflora with nutrient substrates (1) to which they are not metabolically adapted, (2) to which they are adapted but in lesser quantities, or (3) that contain inhibitory substances or produce inhibitory substances on fermentation. The result is an imbalance in the microflora and its fermentation products. The difference between this problem and some of the other fermentation disorders is mostly a matter of degree. Generally the disease is relatively mild and self-limiting. Most affected animals show anorexia for 1 to 2 days, break with diarrhea in about 24 hours, and return to feed without treatment when the ruminal fermentation has stabilized and inhibitory substances have been eliminated. Ruminal motility is reduced but usually not absent, the filling of the rumen is not remarkably altered, and if bloat occurs, it is mild. In some cases the ruminal fluid pH may change, but usually not dramatically. Mild acidosis or alkalosis of the ruminal fluid may develop, depending on the nature of the causative feedstuff and its resultant fermentative degradation. Signs of ruminal microfloral inactivity are common. Simple indigestion is an acute problem, in contrast to the microfloral inactivity discussed in the previous paragraphs, in which deficiencies produce microfloral inactivity over time.

Feeds commonly implicated as causes of simple indigestion include moldy or overheated feeds, frosted forages, and partly fermented, spoiled, or sour silages. This form of indigestion also occurs in animals fed high-quality feed, usually after an increase in the rate of feeding or after a change of one of the feed constituents. Thus these mild forms of indigestion can range from a mild acidosis to an excess of VFAs to the generation of some bacterial inhibitory products. Because the rumen and its fermentative bacteria are very adaptable, the ways, if any, in which animals given a certain feed experience the problem vary considerably. Often only one or a few animals from a group on the ration may have signs.

32.121.5 Acute Ruminal Lactic Acidosis (Grain Overload, Toxic Indigestion)

Acute ruminal acidosis is the most dramatic of the forms of ruminal microbial fermentative disorders and in some cases is lethal in less than 24 hours. It has also received the most research attention; therefore the events in its pathogenesis are more clearly defined than those of the other forestomach disorders. The condition has been named *lactic acidosis, acute ruminal impaction, ruminal overload, acid indigestion, toxic indigestion, grain engorgement, grain overload*, and *D–lactic acidosis*.

This problem is the result of excessive consumption of readily fermentable carbohydrates, which causes a rapid fermentation with production of lactic acid and a decrease in ruminal pH to physiologically inappropriate levels. This occurs when animals consume an excess of concentrate feeds (e.g., if animals are suddenly exposed to the feeds without prior adaptation; if animals already on such feeds suddenly consume an excessive quantity because of accidental access; or if animals that have been off feed return to feed and are offered unrestricted access to concentrates). The problem is more common when animals are grouped than when they are separate, probably because the psychology of competition induces them to overconsume. In general the feeds involved include the cereal grains commonly used in high-production rations and fruit and root crops (e.g., feed beets, sugar beets, potatoes) where they are available. Starch and soluble sugars promote an overgrowth of bacteria that produce glucose and organic acids. The acid end products increase ruminal acidity and osmolality, inhibit or destroy other ruminal microbes, and cause forestomach dysfunction and metabolic disturbances.[467–469]

Specific characteristics of the feedstuffs contribute to acidification of the ruminal fluid. Cereal grains inherently possess less buffering capacity than the fibrous forages. Low structured fiber content and decreased forage particle size induce less salivation at the time of ingestion and less rumination subsequently; therefore salivary buffering declines when concentrate feeds are consumed. Some silages contain both high carbohydrate and lactic acid and thus introduce more acid at both ingestion and fermentation.[437,468,470,471]

Feeding regimens that include significant fibrous roughage limit carbohydrate availability and rates of microbial fermentation and growth. Carbohydrate fermentation efficiency relative to the amount of ATP derived from each sugar provides competitive survival value. Slower-growing cellulolytic bacteria use substrate most efficiently. When starch or sugar is available in excess, the faster growing species such as *Streptococcus bovis* metabolize carbohydrate faster and produce more ATP per unit time, even though they are less efficient in ATP production per carbohydrate molecule. Under these conditions they can overgrow, producing lactic acid as their end product.[458,472]

The severity of ruminal acidosis and disease signs varies considerably, depending on the amount and type of carbohydrate-rich feed consumed and the degree of prior ruminal microbial adaptation to the carbohydrate substrate. The disease can range from a mild form of indigestion to an overwhelming toxemia that may be difficult to distinguish from other acute toxicities or various diseases with endotoxemia.

If consumption of fermentable carbohydrate is only mildly excessive, *S. bovis* proliferation decreases when the carbohydrate has been fermented, pH rises toward normal, and the efficient fermenters reestablish dominance. If the carbohydrate source is abundant and its supply is not exhausted, the acidosis becomes more severe. Continued production of lactate by *S. bovis* reduces the fluid pH to the range of 5 to 5.5, and the ruminal fluid osmolality rises concurrently. Both of these factors inhibit or kill the ruminal protozoa, which normally use starch and small sugars and help to limit increasing lactic acid levels. There are also numerous species of lactate-using bacteria, of which *Megasphaera elsdenii* and *Selenomonas ruminantium* are the primary examples. These bacteria, which increase in numbers when animals slowly adapt to a high-concentrate diet, are eliminated by abrupt changes and generation of excessive acid; therefore lactate use decreases when the acid is generated too quickly.[458]

The lactobacilli are the major group of lactic acid producers in the rumen. The increasing acidity of the fluid enhances the growth of these organisms. Because the lactate-using bacteria are killed off before the lactobacilli overgrow, their diverse end products are unavailable as substrate for other bacteria. The lactobacilli are left as the predominant organisms to use the available carbohydrates. Even the *S. bovis* organisms that began the lactic acid production are inhibited below pH 4.5, leaving the lactobacilli, the most acid-resistant species, to generate more lactic acid.[470]

The acidification of the fluid milieu enhances lactic acid production by altering microbial metabolism. The loss of the fluid bicarbonate buffer and the increase in available hydrogen ions block the conversion of lactate to propionate even before the lactate users die off. Also, when the pH is above 5, as pH declines, ruminal fluid amylase activity increases, liberating more free glucose from starch. However, glucose use is reduced, and ruminal glucose accumulates. Apparently the lactate-using bacteria such as *S. ruminantium* degrade less lactate to acetate in the presence of increased glucose concentrations. Therefore not only does the microbial population change, but the characteristics of the fluid accelerate the lactic acid production when the available carbohydrate is excessive.

The effects on the animal from the ruminal fluid changes are numerous and detrimental. In the early stages of the acidic fermentation, the VFAs are produced in abundance. Although VFA production decreases as the microbes are increasingly inhibited, VFA concentrations remain elevated in advanced acidosis. The VFAs are much weaker acids than lactic acid; thus, as pH drops they accept hydrogen from lactic acid and serve as buffers in the fluid, so that a greater proportion of the VFAs exist in the nondissociated state. This form is more readily absorbable than free ions through the ruminal wall. During absorption some VFAs undergo metabolism by the ruminal wall epithelium, resulting in the release of lactate and ketone bodies into the circulation. Excessive absorption of the VFAs leads to systemic acidosis, and circulating lactate and VFAs may also directly damage the liver.[473] In addition, the high concentration of nondissociated VFAs at the ruminal epithelium provides a strong inhibitory effect on reticuloruminal motility and leads to ruminal stasis. This effect tends to protect the animal because it reduces the absorption of detrimental fermentation products from the rumen.[460–466,468–470]

The osmotic pressure of the ruminal fluid increases as lactic acidosis develops.[437,468–470,474] In a normal animal, ruminal osmolality remains relatively constant at approximately 280 mOsm/L, but osmolality may double in some cases of acute acidosis. Lactic acid accounts for a major fraction of the increase, but some of the components of this change remain unidentified. The increased osmolality inhibits and kills some of the microflora and draws fluid into the rumen, mostly from the extracellular compartment. This accounts for the increased ruminal fluid volume, ruminal distention, and severe dehydration observed clinically. The loss of circulating fluid volume leads to circulatory impairment, decreased renal blood flow and glomerular filtration, and in some cases eventual anuria. Poor peripheral circulation results in hypoxic metabolism and contributes to systemic acidosis.

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Although it has been assumed that the systemic acidosis that develops with this disease is attributable to ruminal lactic acid absorption, such absorption does not appear to occur readily.[470,475,476] Lactate is absorbed from the rumen at a much slower rate than are the VFAs because it is highly ionized at a pH near physiologic normal, which tends to inhibit absorption. At lower pH the rumen becomes static, thereby also inhibiting absorption. The hypertonicity of the ruminal fluid further limits absorption of lactate and other substances. It appears that the peak entry of lactate into the circulation occurs in the early phases of the disease. Some lactate may be absorbed from the intestinal tract from fluid passed before the onset of complete stasis. Many experimental trials do not show the development of severe systemic acidosis in the early phase of the disease. It may be that a large

component of the later severe systemic acidosis is attributable to circulatory insufficiency rather than to absorption of lactic acid.

Some absorption of the lactic acid does occur, however, as evidenced by the appearance of D–lactic acid in the circulation.[422,470,475] Microbes produce both the L and D forms of lactic acid, whereas animal tissues produce only L–lactic acid. The animals' pathways for metabolism of D–lactic acid are not as efficient as those for L–lactic acid; therefore absorption of both forms leads to an accumulation of predominantly D-lactate in the animal's system. The lactate is eliminated by oxidation, gluconeogenesis, and renal excretion. The animal's hydration status, liver and muscle metabolism, and renal function determine how readily it can eliminate excess lactate. Animals that survive ruminal acidosis often have metabolic alkalosis after the acidotic phase, as a result of lactate metabolism and production of bicarbonate.

Lactic acid is a strong corrosive agent that can destroy the ruminal epithelium, giving rise to the name *toxic rumenitis*. The increased ruminal fluid osmolality also damages the epithelium as extracellular water influx across the epithelium occurs in response to osmotic pressure imbalance and disturbed Na transport.[467] The effects of epithelial destruction can be far-reaching because the damage persists after resolution of the acute acidosis.[437,477] Some yeast and fungi that are resistant to the high acidity readily colonize the damaged sites, invade the vasculature, and cause thrombosis or spread to the liver and other organs.[430,431] Ruminal acidosis is considered one of the primary causes of mycotic rumenitis (discussed earlier under Reticulitis and Rumenitis) and mycotic omasitis, although other predisposing causes have been identified.[430–434] Bacterial rumenitis can also result from the chemical damage and may lead to abscess formation, diffuse cellulitis, or perforation and peritonitis. If the animal survives the acute acidosis, it may succumb to secondary ruminal damage.[431,433] Alternatively, the rumen may heal uneventfully, leaving scars in the ruminal wall, but access of bacteria to the circulation through these chemical lesions can result in hepatic abscessation, a common problem of animals fed high-concentrate rations.[429,478,479]

In addition to lactic acid, several toxic factors have been implicated in acute ruminal acidosis.[422,458,470] The altered metabolism of the ruminal microflora has been shown to generate increased quantities of histamine, ethanol, methanol, tyramine, and tryptamine. These may play a role in the pathogenesis of the disease, but conclusive evidence is lacking. Histamine has been implicated as an agent in the development of laminitis that sometimes accompanies ruminal acidosis. However, histamine is poorly absorbed from the rumen, especially at diminished pH levels. The destruction of ruminal gram-negative bacteria has been suggested to release large quantities of endotoxin for absorption through damaged mucosal surfaces. Endotoxin would contribute to most of the signs of the disease such as ruminal stasis, poor tissue perfusion with cardiovascular deterioration, weakness, and depression. Increased ruminal and blood concentrations of endotoxin and increased blood arachidonic acid metabolites have been found in cattle with experimentally induced ruminal acidosis, but their importance in naturally occurring disease is not clear.[480–483] With liver impairment or ruminal wall damage, toxin absorption and clearance are likely to be altered. Premature delivery and retained placenta may occur in pregnant animals after acute ruminal acidosis, possibly resulting from the effects of these circulatory toxins and metabolites.[484]

32.121.6 Subacute Ruminal Acidosis

Like acute ruminal acidosis, subacute ruminal acidosis (SARA) is caused by feeding of excessive quantities of concentrate with low levels of well-structured fibrous roughage; however, SARA results from continued ingestion of these feeds over a prolonged period rather than sudden exposure without adequate adaptation. Beef feedlot cattle may be chronically exposed to a ruminal pH of 5 to 5.5 from the start of the feeding period until slaughter. Dairy cattle are more likely limited to short periods of low ruminal pH typically between calving and approximately 5 months postpartum, with the risk for SARA very low outside these time periods.[485,486] The ruminal microbial population adapts to the high grain ration, and large numbers of lactate-using and lactate-producing organisms are found. The proportion of cellulolytic bacteria decreases, whereas the starch- and glucose-fermenting species proliferate. The overall effect of the adaptation is development of a microbial population that rapidly ferments the ingested feedstuffs. Lactic acid does not accumulate because it is further metabolized by the bacteria. The high rate of fermentation instead produces high concentrations of VFAs, resulting in moderately acidic ruminal fluid with pH values usually ranging from 5 to 5.5.[487] Ruminal buffering of the increased acid load is impaired because the fine particle size of the high-energy rations induces less chewing and less saliva production. As the name implies, the effects on the animal are chronic and insidious.

Along with the high concentration of VFAs and the low pH, a shift occurs in the proportions of the VFAs in the ruminal fluid. The proportions of butyric and propionic acids increase, and acetate decreases. Butyric and propionic acids stimulate proliferation of the ruminal papillae epithelium. When this process is exaggerated, it can progress to parakeratosis. The ruminal papillae develop an excessively keratinized epithelium and clump together. The parakeratotic changes are associated with decreased absorption of the VFAs and increased susceptibility to trauma and inflammation. Epithelial damage and the acidic nature of the ingesta appear to be responsible for inflammation of the deeper tissues of the ruminal wall in some cases. The ruminal wall lesions allow penetration by bacteria with dissemination to the liver. This commonly results in liver abscessation in a high proportion of affected animals. Liver abscesses usually have no pathognomonic signs. Affected animals tend to show reduced productivity and may have signs of a chronic inflammatory response.*

The diagnosis of SARA is made on a herd level rather than on an individual cow basis. Cattle afflicted with SARA may demonstrate numerous clinical signs including reduced appetite and ruminal hypomotility.[486] High ruminal VFA concentrations can inhibit ruminal motility by stimulating the inhibitory receptors in the epithelium. The finely ground ingesta also induce less active ruminal motility because it lacks the physical bulk of high-roughage diets that stimulate strong and sustained contractions. Although the bacterial population is metabolically very active, the number of species of bacteria is reduced. Likewise the protozoal population is inhibited when the pH remains in the lower end of this range. The microfloral environment is less stable when fewer species are present and is therefore more susceptible to sudden changes in the diet.

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A continual high acid load may also reduce metabolic efficiency and overall animal performance. High-concentrate diets have been associated with poor use of dietary protein.[457,489] Other pathologic conditions have been attributed to SARA, including chronic laminitis[490] and cerebrocortical necrosis. These conditions may be induced by some of the toxic by-products of acidic ruminal fermentation, such as endotoxins and hydrogen sulfide.[464,465,470,480–483,488]

* References 417,423,437,451,461,464,470,472,478,485,488.

32.121.7 Ruminal Alkalosis

An alkaline ruminal fluid pH occurs most commonly when microbial fermentation is reduced while the animal continues to ingest saliva. A ruminal fluid pH between 7 and 7.5 is found with prolonged anorexia, microfloral inactivity caused by poorly digestible roughage, and some cases of simple indigestion. The low rate of fermentation does not generate enough acid to neutralize the alkaline pH of the saliva. In addition, the absorption of VFAs through the ruminal epithelium proceeds with the generation of bicarbonate in the ruminal fluid.[491] Acetate absorption is associated with greater generation of bicarbonate than is absorption of the other VFAs, and acetate is the predominant VFA produced during fermentation of roughage. Although the fermentation rate is low, the VFA absorption contributes to the ruminal alkalinity. Ruminal alkalosis occurring with these diseases is not the primary problem; therefore these entities are discussed separately.

Ruminal alkalosis can occur with the generation of excessive ammonia. Ammonia concentrations rise when high-protein diets are fermented. The pH usually does not increase above neutral because these diets also contain sufficient readily fermentable carbohydrate to maintain a slightly acidic pH.

More dramatic elevations in the ammonia concentration, with a ruminal fluid pH above 7.5, occur with overfeeding of nonprotein nitrogen sources such as urea, biuret, and ammonium phosphate (see Chapter 54). Accidental ingestion of some common fertilizers that contain ammonium salts can produce the same results. For the purpose of this discussion, it is important to realize that some of the signs of urea poisoning involve ruminal dysfunction. Severe cases of urea poisoning result in generalized signs such as muscle tremors, incoordination, weakness, tachypnea, and CNS excitation, and affected animals die quickly. Signs of forestomach dysfunction such as ruminal hypomotility, bloat, vomiting, and abdominal pain are also present. In milder cases, diminished appetite, ruminal hypomotility, recurrent tympany, and diarrhea may be the most prominent signs, along with muscular weakness and incoordination. Thus the disease may appear as a form of forestomach disease. The ruminal fluid shows an alkaline pH between 7.5 and 8.5 and has a strong odor of ammonia.[462,492,493]

32.121.8 Putrefaction of Ruminal Ingesta

Putrefaction of ruminal ingesta infrequently results from overgrowth of a microflora that decomposes feed material in a putrefactive manner. The existence of a high ruminal fluid pH, such as occurs with high-protein feeds, and repeated inoculation with abnormal bacteria allow the development of the putrefactive decomposition. Fermented feeds undergoing spoilage, feed and water contaminated with feces, and spoiling, contaminated concentrates supply the offending microflora, which includes the coliform group and *Proteus* species.[386] This type of abnormal decomposition is normally inhibited by the existence of an active physiologic microflora. Therefore most cattle are remarkably resistant to aberrant digestive patterns even when spoiled feeds are ingested. Cattle affected with this form of indigestion typically follow a chronic course of disease. Ruminal motility declines, appetite is poor, and recurrent tympany develops, sometimes with the generation of frothy ruminal contents. The ruminal fluid characteristically has a blackish-green color, a foul, putrefactive odor, poor protozoal and bacterial activity, and a pH in the neutral to alkaline range of 7 to 8.5. The cause of the forestomach hypomotility may be inhibitory products generated by the abnormal fermentation. In cases of prolonged duration, animals lose weight and display a poor hair coat, probably as a result of dietary deficiencies in the abnormal fermentation products.

32.122 FORESTOMACH DISEASES OF CALVES

Normal forestomach development and diseases of the forestomachs of calves have been reviewed.[387,388,494] The newborn ruminant has the same anatomic division of the stomach into four compartments as the adult ruminant. The abomasum is functional as a secretory digestive organ, like the stomach of monogastrics, and has a capacity approximately twice that of the other compartments. The remaining stomach compartments are small and do not perform digestive functions in the first days of neonatal life. The reticulorumen may not develop an adult-type function until 4 months of age or older and does not completely develop proportional dimensions similar to those of the adult until 9 to 12 months of age.[386–388,494–496]

The preruminant calf has been viewed as a functionally monogastric animal, and little importance has been assessed to diseases of the forestomachs. Under most management conditions, however, the forestomachs have begun to develop their digestive function within the first week or two after birth. During the development process the calf's forestomach is susceptible to problems different from those of the adult. After the rumen has developed a functional status similar to that of the adult, it is susceptible to the diseases discussed previously. Typically the feeding management of maturing young stock includes pasture or a mainly forage diet and does not predispose to digestive disturbance.

32.122.1 Esophageal (Reticular) Groove Function

Liquid feed bypasses the reticulorumen in the young ruminant, flowing directly into the abomasum through the esophageal groove. The groove consists of two lips that extend from the cardia to the reticuloomasal orifice. These lips close together, forming a tube to shunt liquid material to the abomasum when the soluble proteins and salts of milk stimulate a reflex through the glossopharyngeal nerve. Other salt solutions and even water can stimulate the reflex in very young animals, but the reflex weakens with age, especially after weaning. The response to stimuli varies among individuals, but generally milk produces the strongest response and plain water the weakest. Both nipple and bucket feeding stimulate closure in very young calves, but beyond 12 weeks of age closure is weak unless stimulated by nipple feeding. In older, weaned animals the reflex can be stimulated weakly for short durations by orally administered strong solutions such as copper sulfate or sodium salts. Intravenous vasopressin can induce more profound closure of the groove and has been advocated to aid ruminal bypass of orally administered treatment.[497,498]

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Milk replacers that contain nonmilk protein appear to stimulate a weaker closure of the esophageal groove than do whole milk or milk replacers containing real milk protein. Likewise unpalatable fluids and spoiled milk do not seem to induce normal closure of the groove. Even in healthy calves that consume unspoiled whole milk, some overflow into the forestomach may occur.[499] Failure of esophageal groove closure allows these fluids to pass into the rumen rather than bypassing it. Milk or other fluid administered through a stomach tube or esophageal feeder does not contact the pharynx; therefore the reflex closure is not stimulated and the fluid deposits in the forestomachs. Under normal conditions fluid in the forestomach of neonatal calves less than 2 weeks old overflows into the abomasum when an amount more than 400 mL has accumulated.[500]

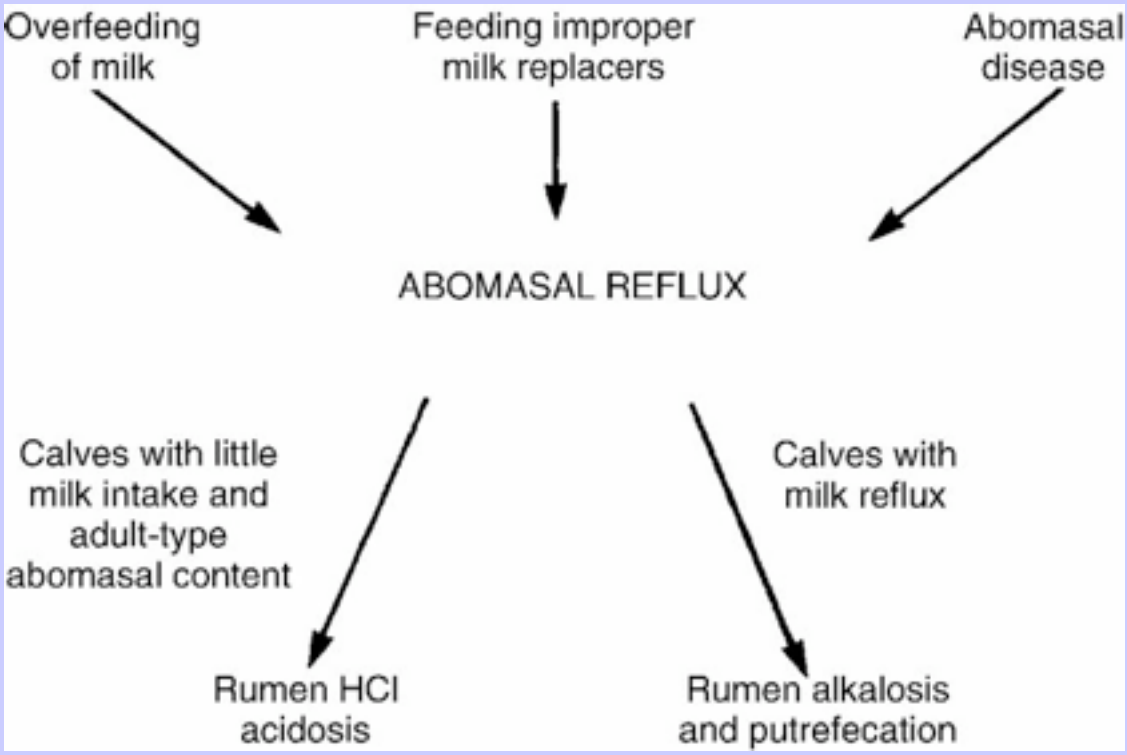
32.122.2 Reticuloruminal Milk Accumulation (Ruminal Drinking)

Milk can gain access to the reticulorumen by several means. Failure of esophageal groove closure, just discussed, is one possibility. In addition, if calves are maintained as preruminants for longer than 3 to 4 months, groove closure weakens and may allow greater escape of fluid to the reticulorumen. Fluid can also accumulate in the forestomach from abomasal reflux (Fig. 32-95). Overfeeding fluids beyond the capacity of the abomasum

(approximately 2 L in the newborn, 35-kg calf) promotes backflow into the reticulorumen. Certain fluids affect abomasal motility and emptying times, prolonging their retention in the organ. These include acidic and hypertonic fluids and severely heat-treated skim milk powder. Nonmilk protein does not curd in the abomasum, as does casein, when it contacts the abomasal enzyme renin. Prolonged fluid retention and failure of curd formation in the abomasum may promote backflow into the rumen, especially when more fluid feed is consumed. Abomasal inflammation or ulceration may also inhibit normal emptying and promote abomasal reflux.

Some amount of milk reflux from the abomasum appears to be a physiologically normal occurrence. In fact, this route supplies some of the inoculum for ruminal microfloral development and strongly influences the species distribution of the microbial population. But prolonged, repeated, or excessive retention of milk in the forestomach can lead to the development of abnormal fermentation patterns. Although amounts of fluid greater than 400 mL do not normally accumulate in the forestomach of the neonate, more fluid can accumulate when the abomasum is already filled and when ruminal size has increased during the development process. In some cases milk flow into the rumen accumulates significantly over prolonged periods.[499]

Fig. 32-95 Abomasal reflux in calves.



The predominant organisms comprising the forestomach microflora of the 1- to 4-week-old ruminant are the coliforms and lactobacilli. These lactose-fermenting, facultative anaerobes tend to maintain the ruminal pH in the acidic range before the adult-type, anaerobic, cellulolytic flora becomes established. The high fat and protein content of milk in the rumen can predispose to a flora that decomposes these constituents and produces spoiled and rancid ruminal ingesta. Problems associated with ruminal milk accumulation are compounded when the milk or other fluid ingested is already contaminated or spoiled. The abnormal microflora established under these

circumstances does not supply the young animal with the necessary digestive end products, and signs of dietary insufficiency develop. Affected animals fail to grow normally, show a poor hair coat potentially with widespread alopecia, and may have a depraved appetite. The stimuli for normal forestomach development are also deficient; affected animals have a potbellied appearance, and the rumen is distended with fluid and clots of milk. Ruminal motility is poor, and recurrent bloat is a common sequela. The ruminal fluid pH may be alkaline as a result of the proteolytic formation of ammonia, but in most cases the ruminal pH is acidic (below 6) because of an accumulation of VFAs and lactic acid from bacterial fermentation, and the fluid has a putrid, foul odor.[501] An enteric imbalance also seems to occur, and the feces are commonly pasty or fluid in consistency. Ruminal "drinking" appears to compound problems in calves with infectious enteritis and diarrhea, and affected calves frequently develop systemic acid-base and fluid balance disturbances.[502–504]

32.122.3 Problems in Ruminal Development

The age at which the calf has reticuloruminal digestion depends largely on its diet. A plentiful supply of milk delays the time until the calf consumes significant quantities of dry feed. Veal calves maintained without access to solid feed do not have forestomach development. The nervous reflexes that drive ruminal motility, eructation, and regurgitation are already functional before birth, awaiting only the drive of normal stimuli to begin operating. Dry feeds pass into the rumen, and bacterial inoculation from the environment or from abomasal reflux stimulates fermentation to begin. This process can be initiated as early as 1 week of age when calves are encouraged to consume dry feeds.[495,505]

The increase in the size of the forestomach results from the bulk effect of ingestion of bulky, fibrous feeds.[506] Mild distention stimulates ruminal motility and the development of the muscular wall. Mucosal development is stimulated by the presence of VFAs in the ruminal fluid, resulting from microbial fermentation. Butyrate and propionate are most effective in this regard, whereas acetate is less stimulatory. The thickness of the mucosa increases with proliferation of the ruminal epithelium and elongation of the papillae.[438] These changes serve to increase the ability of the mucosa to absorb the VFAs. Dietary excesses or deficiencies affect the developing rumen by altering the balance of these stimuli.

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Calves fed concentrate diets to the exclusion of forages or mixed diets with the hay pelleted or finely ground may experience ruminal parakeratosis as a result of a lack of feed abrasion[507] and the excessive production of the stimulatory VFAs: butyrate and propionate.[438] These calves can have a form of chronic ruminal acidosis that results in a reduced growth rate and poor body condition. Ruminal contents are typically fluid with an acidic pH, ruminal hypomotility occurs, and recurrent free gas bloat is common. Affected calves often display a craving for fibrous materials. Hair coat licking is common in these individuals, and hairball formation in the reticulorumen is a common sequela. The hairballs may not be deleterious, but occasionally they cause obstructive disease or abrade the parakeratotic papillae or the abomasal mucosa, predisposing to ulcers and inflammatory lesions. Acute ruminal acidosis is not typically recognized in the young, developing ruminant, probably because feed consumption is limited and because the predisposing adult-type ruminal microflora has not yet developed.

An opposite extreme can occur when the young calf is fed dry forage to the exclusion of more readily digestible carbohydrates. Concentrates and grass contain soluble carbohydrates and are well digested by the developing ruminant. Hays contain much less soluble carbohydrate and an abundance of the structured, slowly digestible forms. These substances are not as well digested by calves because the appropriate cellulolytic microflora is not fully developed. With moderate hay intake and the supply of other sources of nutrition, problems are rarely encountered. When dry roughage is the only available feed, especially when the hay is of poor quality, adequate breakdown of the fiber is prolonged. The low availability of nutrient substrate that results from delayed digestion

of the structured carbohydrates decreases microbial proliferation and fermentation. Inadequate fermentation of the feedstuff deprives the animal of required nutrients as well and results in poor performance and growth. When the only available feed source is the hay ration, the calf continues to consume while the long undigested fiber accumulates in the rumen. The rumen continues to expand as a result of the increased filling, eventually becoming grossly distended. Recurrent bloat is common in these animals because of the overfilling and poor ruminal contractility. This phenomenon is a frequent occurrence under some management conditions and has commonly been called "haybelly." Affected animals display a typical abdominal contour, with gross distention of the abdominal wall that is more prominent on the left side. The ruminal contents are very firm, the fluid has a pH around neutral and shows little microbial activity or odor, ruminal motility is poor, and despite the full abdomen the animal is thin. This form of microfloral inactivity is more common in calves than in adults because the young ruminant is less able to ferment fibrous roughage.[386,387]

32.122.4

Recurrent Bloat (Ruminal Tympany)

Moderate gas distention of the rumen is a common sign of disease in calves, usually as a result of free gas accumulation, whereas frothy fermentation is very uncommon in the young ruminant. The pathogenesis of free gas bloat has been discussed, and the same principles hold for the young ruminant. The differences between free gas bloat in the adult and in the young calf are more a matter of chronicity and frequency of occurrence than cause. Digestive disturbances of the adult rumen tend to develop more rapidly and are more readily identified than those of the calf. Because of the involvement of ruminal developmental processes in the pathogenesis of calf indigestion, in young ruminants the diseases are more chronic than acute in nature. In most cases the calf continues to consume feed, and the abnormal ruminal function and development may be easily overlooked.

Ruminal tympany seems to accompany indigestion in calves more often than in adult cattle and also assumes a more prominent appearance in calves than adults. These factors may be reflections of the juvenile anatomy and the incomplete development of adult function. It is worth noting, for instance, that although left-sided abomasal displacement is an uncommon occurrence in young calves, it almost invariably is accompanied by marked ruminal tympany.[508] In contrast, the disease is common in adult cattle, but ruminal tympany is an infrequent sign of the disease.

Purulent lung infections appear to be a common cause of bloat in calves, probably as a result of intrathoracic compression or irritation of the esophagus or possibly the vagal nerves. However, other causes of bloat that are associated with abnormal ruminal function are also common in calves with indigestion. They include overdistention of the rumen, insufficient clearing of the cardia, and inhibition of motility by abnormal fermentation products. A thorough examination is required to determine the underlying cause of the individual case.

One presumed cause of bloat in calves that is not a cause of adult bloat is sudden filling of the abomasum by milk feeding during weaning. Calves not yet completely converted to a diet of solid feed still consume milk eagerly. In some cases acute free gas bloat occurs immediately after the milk feeding. Because the esophageal groove directs the milk into the abomasum but the abomasum is already partly filled by ingesta from the developing rumen, acute overdistention of the organ can occur and reflexively inhibit forestomach motility. Feeding smaller milk meals or discontinuing the milk feeding resolves the problem in these cases, lending support to the presumed cause.

32.122.5

Clinical Signs and Differential Diagnosis of Indigestion (Table 32-14)

32.122.5.1

GENERAL SIGNS

A general physical examination allows the practitioner to recognize signs of reticuloruminal problems and to assess whether a disease that could induce reticuloruminal dysfunction as a secondary phenomenon is present. General signs common to all forms of indigestion include a reduction or absence of appetite, dullness or depression, and decreased animal productivity. The most common signs of ruminal dysfunction are a decrease, absence, or abnormality of ruminal contraction sounds in the left paralumbar fossa or an abnormal left-sided abdominal contour. The left abdominal wall may show gauntness and decreased filling or may display gross distention. It is often the failure to detect signs of another primary disease as the cause of ruminal dysfunction that directs attention to the forestomach as the possible primary site of disease. Indigestion in calves effectively produces a state of malnutrition, and additional signs in these growing animals include poor growth rate and long, rough hair coat. The acuteness of onset and the severity of these signs depend on the inciting cause of the indigestion. Specific abnormalities in the ruminal motility pattern are discussed in more detail, but most indigestions are marked by decreased or absent ruminations (regurgitation and cud chewing) and depressed ruminal contractions. Only early cases of frothy bloat and some cases of vagal indigestion display increased ruminal motility.

Body temperature usually is within normal limits because the causes of indigestion are mainly physiologic abnormalities. Exceptions include TRP and occasional cases of rumenitis with significant inflammation. 832
Disturbances of heart rate, respiratory rate, and body fluid vary tremendously among different forms of 833
indigestion and different cases of any one form of indigestion. For example, an acute onset of severe ruminal bloat can produce severe embarrassment of the cardiovascular and respiratory systems, whereas mild or chronic bloat may produce no remarkable change in these systems. Rapid accumulation of fluid in the forestomach chamber in severe ruminal acidosis with grain overload can induce severe dehydration, systemic acidosis, and increased heart and respiratory rates, whereas slow fluid sequestration in some cases of vagal indigestion may not induce marked changes in these parameters.

Table 32-14 Clinical Signs Typically Associated with Primary Indigestions

Signs	Associated Problems
Fever	Traumatic reticuloperitonitis, reticuloruminitis
Decreased ruminal filling	Fermentative indigestions and secondary indigestions (especially with chronic anorexia) in which passage of material from the rumen is not impeded
Abdominal distention	See Fig. 32-94
Excessive fluid (or froth) in the rumen with loss of normal ingesta stratification	Acute ruminal acidosis, vagal indigestion, frothy bloat, anterior intestinal obstruction
Excessive firm, fibrous material in rumen	Ruminal inactivity caused by poor-quality roughage
Firm, doughy ingesta in ventral rumen with decreased ruminal filling	Prolonged ruminal stasis caused by chronic disease with anorexia
Ruminal hypermotility	Early cases of frothy bloat, some cases of vagal indigestion
Abdominal pain present or can be elicited	Traumatic reticuloperitonitis, abomasal ulceration, reticuloruminitis
Abnormal feces	
Decreased quantity, firm, dry, with increased fiber length	Traumatic reticuloperitonitis, omasal transport failure, ruminal inactivity with poor-quality roughage, also dental disease and some abomasal disease
Feces with abnormal amounts of whole cereal grains	Acute or chronic ruminal acidosis
Greasy consistency with very fine particle size	Pyloric outflow failure, abomasal displacement
Foamy, fluid, yellowish color, acidic odor	Acute ruminal acidosis
Pasty to fluid consistency with foul odor	Fermentative indigestions, enteritis
Decreased quantity, dry, otherwise unremarkable	Anorexia (various causes), acute indigestions before later developing abnormalities
Vomiting (rare)	Ruminal overdistention with vagal indigestion, inflammation of reticulorumen, reticuloomasal orifice obstruction, diaphragmatic hernia, some intoxications (differentiate from esophageal disease)

The anamnesis is important, especially with regard to the animal's feeding. Characteristics of the feed determine the type of fermentation pattern to be expected. Knowledge of the nutrient content thus allows an assessment of the biochemistry of microbial digestion. Consumption of a high-concentrate, low-fiber ration or legume pasture may lead to frothy bloat. A ration of poor-quality hay or straw may result in low microbial fermentative activity and accumulation of impacted indigestible roughage. Overeating of carbohydrates or sudden access to concentrate feeds without adequate adaptation time can induce chronic or acute ruminal acidosis. The feeding history should agree with the findings from inspection of the ruminal contents, or the history should be suspected to be inaccurate. The amount and consistency of the feces should also provide supportive evidence of the type and amount of feed intake.

32.122.5.2 ABDOMINAL CONTOURS AND ANIMAL STANCE (See Fig. 32-94)

Visual inspection of the abdominal contours allows assessment of the degree of abdomen filling. Indigestions can be characterized by decreased, normal, or excessive filling of the reticulorumen. Most primary and secondary indigestions are associated with ruminal hypomotility and anorexia. Therefore the rumen usually shows no obvious distention and may have less filling than normal, especially when the duration of the disease is prolonged. Forms of indigestion in which abnormal ingesta or abnormal ruminal motility prevents effective forward flow of ingesta (overfeeding of poor-quality roughage, vagal indigestion) or in which fluid is actively sequestered in the reticulorumen (acute ruminal acidosis) typically cause some degree of forestomach distention (see Fig. 32-94).

A left-sided or bilateral ventral abdominal wall distention indicates ventral ruminal dilation, although advanced pregnancy and hydrops conditions must be considered. Distention of the dorsal left flank results from ruminal tympany with or without distention of the ventral rumen. Abomasal displacement to the left can produce mild distention of the dorsal left flank under the caudal ribs and extending into the paralumbar fossa, but the abdomen usually is gaunt and empty when viewed from the side or the rear. Occasional cases of left-displaced abomasum appear to inhibit eructation and produce gross ruminal tympany as the primary sign. Release of free ruminal gas through a stomach tube and reexamination for abdominal pings reveals this cause of secondary ruminal dysfunction. Frothy bloat in ruminants is discussed further elsewhere in this text (see p. 855). Free gas accumulation often occurs secondary to the causes of ruminal motility inhibition and is important as a sign of indigestion (Table 32-15). Right-sided abdominal distention suggests the various conditions of dilation, displacement, and obstruction or ileus of the intestines and abomasum. The diseases that cause obstruction and reflux of abomasal ingesta into the rumen may result in reticuloruminal distention. Both prolonged cases of gastrointestinal obstruction at any site and generalized peritonitis can produce gross bilateral dorsal and ventral distention of the abdomen.

The animal should be studied for signs of pain. A pain-filled expression, a reluctance to move, an abnormal, stilted gait, an arched back with a tucked-up abdomen, and an extended neck are typical signs of anterior abdominal pain. These signs may indicate TRP, abomasal ulceration, or another source of pain. A similar stilted gait and reluctance to move are typical of laminitis, a common sequela of acute ruminal acidosis.

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Table 32-15 Differentiation of Types of Bloat Through NasogastricIntubation

Results of Intubation	Probably Causes of Bloat
Tube does not pass	Esophageal obstruction
Tube passes with resistance and releases ruminal gas	Esophageal compression caused by thoracic inflammatory or neoplastic disease Distortion of the cardia caused by inflammation, neoplasia, or abnormal anatomy such as abomasal displacement
Tube passes easily and releases ruminal gas	Ruminal stasis caused by reticuloruminal fermentative disorder, hypocalcemia Obstruction of cardia with ingesta (overfilling of rumen) or pedunculated mass Rumenitis (reticulitis) Weakened ruminal contraction caused by chronic overdistention with ingesta (vagal indigestion, indigestion with poorly digestible forage)
Tube passes easily but does not release gas or releases small amount of foamy ingesta	Frothy bloat Frothy ruminal contents caused by abnormal motility in some forms of vagal indigestion

32.122.5.3 PALPABLE FINDINGS (SeeFig. 32-94)

Deep palpation of the left side of the abdomen is used to determine the consistency of the ruminal contents and thus the nature and volume of the ingesta. In normal animals the organized contraction sequence produces a layering effect.[388,454] Ventrally a fluid consistency can be palpated, whereas dorsally the consistency is firm and doughy. The doughy layer consists of the fibrous portion of the feed. Generally an animal fed a high-roughage diet has a more prominent layer of doughy ingesta. The ruminal contents of an animal fed concentrate feed are softer. In sheep and goats the normal dorsal rumen is softer than that of cattle no matter what the feed. In the normal condition a small layer of free gas is present in the most dorsal region. Distention with gas or foamy feed produces a taut, elastic tension. With free gas bloat the doughy layer can still be appreciated ventral to the gas accumulation, but in cases of frothy bloat the doughy layer is much less prominent. Most cases of vagal indigestion and some cases of high intestinal obstruction cause a grossly dilated rumen filled with fluid or foamy contents that may fluctuate on ballottement.

Overfeeding of indigestible poor hay or straw with resultant inactivity of ruminal microbial fermentation leads to accumulation of more fibrous material than normal that barely yields to deep palpation. With prolonged or severe ruminal stasis, as may occur in TRP, the lack of ruminal motility leads to failure to maintain the normal layering of the contents. In these instances the ventral portion of the forestomach is firmer than the area above. During severe ruminal acidosis, fluid accumulates in the forestomach. This can lead to some degree of abdominal distention, and on palpation the ruminal contents are fluid and may even splash with ballottement.

The rumen should also be palpated per rectum; a comparison of these findings with those obtained externally may be revealing. Moderate degrees of free gas accumulation are often more easily detectable per rectum. Palpation per rectum is also useful in distinguishing the presence of an L-shaped rumen, in which the ventral sac of the rumen is grossly distended in cases of vagal indigestion. It is important to differentiate an L-shaped rumen from either abomasal distention or impaction, which can display a similar external abdominal contour. It is also important to palpate for the size of the lymph nodes in the longitudinal groove of the rumen. These can enlarge to prominent size when rumenitis is present. The organs in the right half of the abdomen should be assessed as sources of abdominal problems.

Rectal examination is impossible in small ruminants and calves. External palpation using both hands can be valuable in these animals. In calves and goats it is the best method for detecting bezoars or clotted clumps of milk in the rumen and for palpating intussusception, umbilical abscesses, or grossly abnormal kidneys.

Palpation of the left paralumbar fossa reveals the presence of ruminal contractions. In a normal animal, three contractions should occur over a 2-minute period. One of these contractions should be associated with an eructation of gas, which can be appreciated both visually and audibly. The rate of eructation increases or decreases in proportion to the fermentative production of gas. Most indigestions produce decreased ruminal motility or ruminal stasis. Early cases of frothy bloat and some forms of vagal indigestion can result in prominent hypermotility. The motility pattern is characterized by changes in both frequency and strength, and weak contractions can also be detected by palpation. Some cases of secondary indigestion, in which the decreased ruminal function is a result of inappetence rather than an inhibition of ruminal motility, show a normal contraction frequency but decreased contraction strength. The duration and strength of ruminal contraction are primarily determined by the nature of the forestomach contents, whereas the frequency relies on medullary gastric center control. Decreased ruminal fill, decreased fiber content of the ingesta, or overdistention of the ruminal wall musculature results in reduced strength and duration of the contraction sequence. These distinctions can be important in determining the cause of decreased ruminal motility.

32.122.5.4 AUSCULTABLE FINDINGS

Auscultation of abdominal sounds is performed over several sites in the left flank and rib areas. Initial auscultation assesses the nature, frequency, and strength of ruminal sounds. This information can be compared with the assessment of ruminal motility gathered on palpation. The sounds represent the friction of fibrous ingesta rubbing against the ruminal wall as the ruminal sacs contract and mix their contents. In healthy cattle on a roughage diet, the normal rustling sound is prominent and prolonged with each contraction cycle. The ruminal contents of animals fed a high-concentrate diet produce less sound because very—low-fiber rations induce weaker contractions and because less fibrous material is in contact with the ruminal wall.

As with palpation, both the frequency and the nature of the sounds yield information about reticuloruminal motility. The ruminal motility pattern is disrupted in vagal indigestion. Although contractions are present and may be more frequent than normal, their lack of normal coordination can lead to a churning of the ingesta without the usual progression of transport. This disrupts the normal stratification of the contents and produces abnormal sounds that are heard as a rumbling, bubbling, or splashing. When stratification is disrupted because of a hypoactive rumen and more fluid is present in the dorsal area of the rumen, contractions produce splashing sounds. The accumulation of gas under these circumstances may produce ringing tones as the fluid moves, similar to the pings found with a displaced abomasum.

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Some circumstances require a distinction between primary and secondary contraction cycles, and they can be differentiated by ausculting for reticular contractions. Holding the stethoscope at the seventh intercostal space at the level of the costochondral junction, the examiner can detect a tinkling fluid sound as the reticulum contracts. A hand held in the paralumbar fossa can detect the tensed bulging of the dorsal sac as it contracts, allowing the examiner to determine if the ruminal contraction is associated with a reticular contraction. Reticular contraction and motility can also be assessed by transabdominal ultrasound.[509] Hyperactivity of primary cycles associated with feeding or the immediate postprandial period is normal. Mechanical stimulation of buccal sensory receptors can lead to an approximate doubling of the primary cycle rate. Hypermotility that results from excessive secondary contractions, without the normal mixing and propulsion of primary contractions, is abnormal and represents ruminal dysfunction.

Combining the auscultation with percussion or ballottement allows assessment of gas or fluid accumulations. The sounds heard in the left flank should be compared with those in the left rib area and right side of the abdomen. High-pitched pings and fluid tinkling sounds suggest a viscus filled with gas and fluid. In the left flank this may represent a displaced abomasum, gas-forming abscess, pneumoperitoneum, or static rumen. Careful comparison of the sounds heard at different sites, combined with the results of rectal palpation, should allow localization of the source. Generally the rumen can be ruled out as the source of pings if palpation reveals normal doughy ruminal contents, no ruminal tympany is felt per rectum, and sounds of normal ruminal contractions are heard in the paralumbar fossa. Prolonged anorexia associated with infectious or inflammatory diseases such as pneumonia or mastitis can result in a static, underfilled rumen, and occasionally a prominent ping can be ausculted in the left flank, where a filled rumen normally would be found. This condition has been called “ruminal collapse,” and careful evaluation is required to distinguish it from left-displaced abomasum.[510] Ballottement of the rumen may reveal splashing fluid sounds without a high pitch in cases in which the rumen has accumulated significant fluid. This occurs frequently in cases of severe ruminal acidosis. It may also occur in cases of marked inactivity of the ruminal flora with loss of the normal stratification of ruminal contents.

32.122.5.5 PAIN ELICITATION

Tests of pain sensitivity in the anterior abdomen (percussion, deep palpation, withers pinch, xiphoid pressure) are performed to examine for localized peritonitis caused by TRP or abomasal ulceration. The same procedures, especially percussion or application of pressure to a localized area in the ventral abdomen, can be used to localize pain associated with rumenitis or ruminal abscessation or perforating abosomal ulceration.[511]

32.122.5.6 FECAL ABNORMALITIES

The rectal examination presents an opportunity to assess the volume and nature of the feces.[512] The feces are abnormal in most cases of forestomach dysfunction. In adult cattle, passage of ingesta through the digestive tract requires 1½ to 4 days. Changes in the feces caused by acute diseases therefore are often delayed by a day or longer beyond the first appearance of other clinical signs. Mature cattle typically pass a total of 30 to 50 kg of feces per day divided into 10 to 24 defecations. The color and consistency of feces are influenced by the feed and should be assessed in light of the feeding history.

Diseases that reduce the flow of ingesta from the rumen to the lower gastrointestinal tract typically result in feces of reduced volume that are firm and dry. These findings are also present with reduced feed or water intake. Assuming that normal intestinal function is present, a decreased flow of ingesta from the forestomach allows longer retention in the bowel with greater resorption of water. In severe instances the feces form into firm disks or balls with a dark, shiny mucous covering. These findings are typical of vagal indigestion and forestomach diseases that produce ruminal stasis without a grossly abnormal fermentative pattern. Indigestions with abnormal fermentation may produce decreased quantities of dry feces initially but usually result in other fecal abnormalities as the abnormal ingesta pass into the lower tract. Intestinal obstructions also decrease fecal passage to the point of absence, but usually the material passed also presents other gross abnormalities such as blood, melena, or discolored mucus.

The particle size of fecal material depends on the frequency and duration of rumination, the activity of the

ruminal flora, and the function of the rumen in appropriately sorting out material for passage through the reticuloomasal orifice. Abnormalities of these digestive functions lead to passage of ingesta of inappropriate particle size. Plant fibers in normal bovine feces measure up to 0.5 cm. Particles with inadequate breakdown may measure 1 to 2 cm or longer. This long particle size may be seen in the feces of cattle with TRP, some cases of vagal indigestion, and poor-quality roughage with insufficient microfloral activity.[447,450,512] Similar findings occur with tooth disease and some cases of abomasitis or cellulitis at the cardia or esophageal groove, in which rumination or activity of the reticuloomasal orifice is inhibited. Whole cereal grains (especially whole corn) may pass in the feces of normal cattle, but excessive amounts of grain should raise suspicion of excessive intake and acute ruminal acidosis. Feces with an abnormally fine particle size and greasy-pasty texture are associated with delayed passage from the forestomach. These are common findings in most cases of vagal indigestion and abomasal displacement.

The odor of bovine feces is relatively inoffensive in healthy individuals. Foul odors are the result of abnormal fermentation or decomposition. Thus abnormal odor typically occurs when the ruminal fermentation pattern is altered, as in simple indigestion caused by abnormal feed, ruminal acidosis, ruminal alkalosis, or ruminal content putrefaction. A repugnant odor is also typical of enteritis when blood products, inflammatory products, or tissues decompose in the intestinal tract (e.g., *Salmonella* enteritis). Foamy, fluid feces with a yellow-brown color and acidic smell are typical of ruminal lactic acidosis in adult cattle. Abnormal ruminal fermentation not only produces feces with abnormal odor but also typically leads to a pasty or fluid consistency as well. Exceptions occur in acute cases, when ruminal stasis or the delay in the passage of ingesta from the forestomach can result in normal or firm feces during initial stages of the disease.

32.122.5.7

ACUTENESS OF SIGNS

The various forms of indigestion may be manifested as acute, subacute, or chronic illness. In general they do not appear as critical emergencies with fulminating systemic signs and life-threatening conditions. The exceptions to this are frothy bloat (see p. 855) and acute ruminal lactic acidosis or grain engorgement.

Cattle examined a few hours after engorgement of grain may yet be alert but anorectic with a mildly distended rumen, weak ruminal contractions, and mild signs of colic. If the acidosis is mild, affected cattle show the signs of indigestion discussed in previous paragraphs and with or without treatment may show return of appetite within a few days. The severe form of indigestion leads to severe systemic involvement, with depression, severe dehydration, weakness, recumbency, profuse diarrhea, and eventually death. The temperature usually is normal to subnormal. The heart rate elevates with the progression of dehydration and systemic acidosis, with rates above 100 beats/min usually associated with a poor prognosis. Respiration generally is increased (60 to 90 breaths/min) and shallow. The rumen accumulates fluid. Animals capable of rising may show a staggering gait and appear blind. The pupillary light reflex may be slower than normal. Recumbent animals usually lie quietly and may be stuporous. As the cardiovascular system becomes more severely affected with increasing dehydration and acidosis, the extremities become cool, and mucous membranes dry. Anuria may follow poor renal perfusion. Rapid progression of signs leading to recumbency bespeaks a poor prognosis, and animals may die within 24 to 72 hours. Therefore if the progression of signs is rapid, emergency therapeutic measures are mandatory.

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In cattle with intermediate degrees of ruminal acidosis, other signs may develop secondarily. Acute or chronic laminitis is a common complication. The damage to the ruminal mucosa can lead to mycotic rumenitis or ruminal wall abscessation or can disseminate infection through the bloodstream to other organs, most notably the liver, resulting in the formation of hepatic abscesses.[478]

32.122.5.8 HEART RATE

Bradycardia of 40 to 60 beats/min is frequently associated with certain types of indigestion. This sign suggests reflex vagotonia to the heart and has been considered indicative of vagal indigestion. The bradycardia can be alleviated by subcutaneous administration of 30 mg of atropine, differentiating increased vagal nerve tone from a primary cardiac conduction disturbance. The atropine test is not especially useful because only a minority of vagal indigestion cases show bradycardia.[444,445,447] Animals with advanced cases with severe abdominal distention or fluid imbalances (or both) frequently show elevated heart rates (over 80 beats/min). In most cases the other physical signs are more reliable for establishing the diagnosis. Furthermore, bradycardia may accompany other forms of indigestion when ruminal hypomotility is prominent and no significant abnormalities of fluid or electrolyte balance are present. Even in normal cattle, postfasting heart rates may drop below 50 beats/min.[513] Therefore recognition of bradycardia in association with other signs of ruminal dysfunction is probably most useful as evidence that stimuli for an increased heart rate, such as inflammatory, infectious, or fluid balance disturbances, are not prominent factors in individual disease occurrence.

32.122.5.9 VOMITING

Vomiting is uncommon in ruminants, but when it does occur, it generally reflects forestomach disease. Regurgitation from the abomasum frequently occurs with abomasal or intestinal disease. Abomasal reflux is not manifested externally and is discussed elsewhere (see pp. 837 and 838) because it relates to forestomach disease. Small volume regurgitation and remastication are routine and normal ruminant functions that do not result in expulsion of material from the mouth. Explosive vomiting of fluid ingesta in large quantity occurs when the reticulorumen is irritated and occasionally when it is overdistended. Vomiting may accompany diaphragmatic herniation of the reticulum, inflammation of the reticulorumen caused by actinobacillosis, vagal indigestion, or obstruction of the reticuloomasal orifice. Animals are more prone than normal to vomiting around an orally passed stomach tube when they have almost any indigestive disturbance. Vomiting also occurs with certain intoxications, most notably azalea, rhododendron, and sneezeweed toxicity and some organophosphate toxicities.

32.122.6 Clinical Pathology

32.122.6.1 RUMINAL FLUID ANALYSIS

Evaluation of ruminal fluid characteristics is an essential procedure in establishing the cause of the indigestions of abnormal fermentation.[454,468,514] Several important determinations can be made at cowside in an ambulatory practice. Acquiring an appropriate sample is simplified by using proper equipment. The advantages of various collection techniques and devices have been discussed.[515–518] Needle puncture of the ventral ruminal sac (rumenocentesis) may yield a satisfactory fluid sample, and studies demonstrate that rumenocentesis samples provide the most reliable evaluation of ruminal fluid pH for field evaluation of SARA.[517,518] Oral or nasal passage of a collection tube produces more fluid volume with no risk of peritoneal contamination but with an increased risk of saliva contamination. An adequate tube for aspiration of a ruminal fluid sample should be at least 2.3 m long to reach the ventral ruminal sac and should have an internal diameter of 1 cm or larger to reduce the incidence of plugging with ingesta. A plastic stomach tube passed orally or nasally can be adapted for use by cutting multiple holes into the ruminal end of the tube. A digital

examination glove can be placed over the end during passage to limit saliva contamination of the sample and then is forcefully blown off before sampling. The sample can then be withdrawn by a dose syringe. This technique is successful when ruminal fluid is accessible in the dorsal rumen, but the flexibility of the tube is disadvantageous when a prominent layer of fibrous feed is present. Several instruments with a flexible steel outer tube are commercially available and have the advantage of enough stiffness and weight to penetrate the overlying firm layer of ingesta.

Ruminal fluid samples collected in an expeditious manner yield the most useful results. When the animal strongly resists sampling and a prolonged time is required from introduction of the tube until the fluid is obtained, saliva contamination of the sample increases. This contamination alters the pH and consistency of the sample. The specially designed ruminal fluid collection tubes reduce this problem. If the sample must be collected with a standard nasogastric tube, passing the tube nasally avoids the presence of a device in the mouth. This reduces the amount of struggling (once the tube has passed the pharynx) and thus reduces excessive salivation.

The sample should be evaluated as soon as possible after collection to minimize the effects of cooling and air exposure on protozoal activity and pH. The more elaborate chemical tests such as chloride, acid, and ammonia concentrations can be delayed up to 9 hours for a room-temperature sample and up to 24 hours for a refrigerated sample and still yield reliable results.[519] Ruminal fluid collected for therapeutic transfaunation also retains its beneficial activity for a similar duration.[520] The ruminal fluid parameters important in a clinical examination are listed in Table 32-16.

32.122.6.1.1

Color, Consistency, and Odor

The color, consistency, and odor of aspirated fluid are assessed immediately after collection. Normal color varies depending on the nature of the feed. Animals fed a hay ration have olive to brownish-green ruminal fluid, those on grass show a deeper green color, and cattle fed grain or silage, a yellowish-brown color. Fluid from cattle with acidosis tends toward a milky gray. Ruminal fluid from animals with prolonged stasis or decomposition of the ruminal ingesta (or both) is a darker greenish-black, and fluid from calves with milk sequestered in the rumen as a result of abomasal reflux or esophageal groove failure is gray and may contain clots of milk.

Normal ruminal fluid has a slightly viscous consistency. The fluid becomes more watery when the microflora is inactive. Saliva contamination causes greater viscosity; therefore the results from a highly viscous sample should be evaluated with care, and it may be best to discard such samples. Ruminal fluid has a typical odor that has been called “aromatic.” The odor is less prominent when the microflora is inactive. Abnormal odors include the acidic smell of lactic acidosis, the putrid, foul odor of protein decomposition or spoiled milk with putrefaction of ruminal ingesta, or the ammonia smell of urea poisoning.

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Table 32-16 Diagnostic Ruminal Fluid Analysis

Parameter	Normal
Color	Olive, brownish-green
Consistency	Slightly viscous
Odor	Aromatic, strong odor
pH	6–7 on roughage
	5.5–6.5 on grain diet
Sedimentation or flotation	4–8 min
Redox potential (methylene blue reduction time)	3–6 min
Protozoal activity	Multiple forms, active motion
Gram stain	Predominant gram-negative bacterial population
Chloride concentration	<30 mEq/L

32.122.6.1.2

Ruminal Fluid Ph

The pH of ruminal fluid fluctuates within a broad range of normal values, varying considerably during the course of a day with shifts of 0.5 to 1 pH unit common during a 24-hour period.[485,521] The pH measured in a given fluid sample depends on the type of feed and fermentation pattern and the interval since the last feeding. Physiologic ruminal fluid pH typically ranges between 6 and 7 in animals on a mostly forage diet but is lower, at 5.5 to 6.5, in animals fed mostly grain.[469,470,485,518,522] The lower pH develops with the faster rate of amylolytic versus cellulolytic fermentation. Immediately after feeding the pH tends toward the high end of normal with the addition of feedstuff and saliva, the production of which is determined by the duration spent eating, ruminating, and resting.[523] Over a 2- to 4-hour period the pH decreases to the lower range as the feed undergoes fermentation. With no further feed consumption, fermentation declines and the pH rises with salivary buffering and acid end-product absorption.[491] In animals held off feed the ruminal pH rises above 7 within 12 hours after a hay meal and within 24 hours after a high-grain meal. Therefore consideration of the most recent feed consumption is important to the interpretation of the ruminal fluid pH measurement.

Saliva contamination of the sample falsely elevates the measured pH value. Because it is impossible to exclude saliva completely from samples collected by tube, a minor false elevation of the pH likely occurs in all such examinations.[515,516,518] This can be minimized by expedient collection of a large fluid volume (more than 100 to 200 mL). If the collected volume is small and the sample viscosity is high, the pH measurement will be inaccurate. Modest contamination (5% to 10%) raises the measured pH by approximately 0.1 to 0.2 pH units, whereas excessive contamination with approximately 50% saliva may increase pH by 1 pH unit.[454,515] Ruminocentesis of the ventral ruminal sac below the left paralumbar fossa is preferred by some clinicians for preventing saliva contamination. This is particularly advantageous for samples collected to monitor ruminal pH for balancing rations and minimizing chronic ruminal acidosis. A sampling strategy that incorporates ruminocentesis and ruminal fluid pH measurement in groups of cows in a herd has been developed to optimally identify cow groups with feeding problems that lead to subacute ruminal acidosis.[517,518]

Ruminal pH values of 7 to 7.5 are common in animals with anorexia and in those that have ingested feed that is not suitable for fermentation (e.g., simple indigestion and inactivity of microflora caused by indigestible roughage). Even higher pH values may be measured with ruminal alkalosis caused by urea ingestion or putrefaction of ruminal ingesta. Low pH values result from engorgement with readily digestible carbohydrates and generation of ruminal lactic acidosis. In extreme cases values occasionally decline to 4 to 4.5. It is important to remember that prolonged anorexia and continued saliva ingestion result in rising pH values in these cases as well and that the ruminal pH of a cow with ruminal acidosis can be normal if a sufficient period of anorexia precedes the ruminal fluid analysis. Conversely, a ruminal pH of 5.5 to 6 is abnormal for a cow fed a roughage diet and may be indicative of unobserved access to grain and resultant lactic acidosis. Subacute or chronic ruminal acidosis usually is accompanied by a ruminal pH in the range of 5 to 5.5.[468,469,485,518] Abomasal reflux into the reticulorumen caused by abomasal disease, vagal indigestion, or intestinal obstruction can cause mild decreases in ruminal pH because of the acidic nature of abomasal contents. However, ruminal pH measurement is a poor means of detecting abomasal reflux because the pH will remain within the wide range of normal values. Abomasal reflux is better assessed by measurement of the ruminal chloride concentration.

32.122.6.1.3

Sedimentation

The sedimentation activity time, or sedimentation-flotation test, provides a quick evaluation of microfloral activity.[524] It must be conducted promptly after collection of the sample. The aspirated fluid is allowed to sit in a tube, and the time for completion of sedimentation and flotation of the solid particles is measured. Normally the finer particles settle to the bottom and the coarser particles float, buoyed by the gas bubbles of fermentation. Some of the finer particles sink and then rise again when the fermentation is very active. The normal time for completion of this activity is 4 to 8 minutes. Grossly inactive fluid shows very rapid sedimentation, and none of the material may float. This occurs with ruminal acidosis, prolonged anorexia, and inactive microflora caused by indigestible roughage. When the ingesta are particularly frothy, as in cases of frothy bloat or some cases of vagal indigestion, there may be no appreciable sedimentation or flotation. This test provides a crude evaluation of microfloral activity but does not differentiate well among the different forms of indigestion.

32.122.6.1.4

Redox Potential

The redox (reduction-oxidation) potential of ruminal fluid is a biochemical characteristic that reflects the anaerobic fermentative metabolism of the bacterial population.[455] An indirect determination of the redox potential can be achieved by measuring the time required by ruminal fluid to decolorize methylene blue dye.[525] A mixture of 1 mL of 0.03% methylene blue with 20 mL of ruminal fluid at normal body temperature is observed in a tube and compared for color with another unaltered tube of the fluid. With a highly active microflora from an animal fed a hay and grain diet, the initial dark blue color of the mixture decolorizes within 3 minutes, leaving a narrow ring of blue color at the top of the decolorized sample. Fluid from a diet of hay alone requires 3 to 6 minutes and from a mostly grain ration requires as little as 1 minute for methylene blue reduction. Reduction times up to 15 minutes and longer occur with diets of indigestible roughage, in anorexia of several days' duration, and after ruminal acidosis.[466,514] Thus the methylene blue reduction time provides an assessment of the degree of bacterial fermentative activity.

32.122.6.1.5

Microscopic Examination

Evaluation of the number and activity of protozoa in the ruminal fluid provides a sensitive indicator of the normalcy of the sample.[454,455] This is easily accomplished by examining a drop of fresh, warm fluid under a microscope. The examination requires only low magnification (×40 to ×100) and no special stains. In very active fluid samples the largest protozoa can be seen with the naked eye. They are detectable in a tube as small gray specks of material in active motion in the fluid, and they tend to localize above the sedimented particulate matter. Microscopically both ciliate and flagellate forms of varying sizes and shapes can be observed, with ciliates usually outnumbering the flagellates. The protozoa are normal inhabitants of a healthy ruminant's ruminal fluid, although their specific function is not completely clear and their presence does not appear to be a prerequisite of normal digestive activity. The importance of the protozoa from a clinical viewpoint is their sensitivity to abnormalities in the fluid milieu. The normal animal should show a wide variety of sizes of protozoa, in large numbers that are easy to see, and with active motility. Reduced numbers occur in inactive fluid samples. The larger species are more susceptible to abnormalities; therefore a predominance of only small protozoa would suggest a mild indigestive disturbance. All protozoa are killed off when the ruminal pH drops below 5. A recent bout of acidosis would result in lack of protozoal activity, even if the pH has subsequently risen back into the normal range. Fluid from such an animal should also show other abnormalities of color and consistency. Very recent disturbances of the fluid may result in the observation of a large number of dead protozoa.

Although elaborate isolation methods for evaluating ruminal bacterial growth are not clinically applicable, examination of an air-dried, Gram-stained smear of ruminal fluid can be useful in diagnosing ruminal acidosis. Normal ruminal fluid should contain a variety of morphologically distinguishable bacterial forms, with a predominance of gram-negative organisms. After the overconsumption of readily digestible carbohydrate (grain engorgement), a population of streptococci and lactobacilli proliferates as ruminal lactic acidosis develops. This shift in the bacterial population can be distinguished microscopically, and a predominance of gram-positive cocci and rods is seen. The findings are best confirmed by comparing a smear from a herdmate.

32.122.6.1.6

Ruminal Fluid Chloride

The chloride concentration in ruminal fluid can be determined from the supernate from a centrifuged sample using standard chloride titration devices. A delay in measurement does not appreciably affect the value. Saliva contains concentrations of chloride similar to those of normal ruminal fluid, so that saliva contamination has minimal effect on the results. The normal ruminal fluid chloride concentration is less than 30 mEq/L, with elevated values demonstrating reflux of abomasal ingesta into the rumen or administration of chloride in the feed or as therapy. Accurate assessment of measured values requires information about possible previous administration of electrolytes via the rumen. In the clinical evaluation of forestomach dysfunction, elevated ruminal chloride suggests secondary indigestion caused by abomasal disease or obstruction of intestinal flow. This test can be very helpful in differentiating abomasal reflux from ruminal lactic acidosis as the cause of low ruminal pH and abnormal fluid accumulation in the reticulorumen. With vagal indigestion a high ruminal chloride level suggests that the failure of aborad flow is posterior at the pylorus rather than anterior at the reticuloomasal orifice.[446,453,454] Generally cattle with elevated ruminal chloride also have hypochloremia and metabolic alkalosis as a result of the chloride sequestration in the forestomach, although very slow development of the sequestration may allow the animal to maintain normal plasma levels by altering other excretion rates.

Numerous other tests of the ruminal fluid have been described for the evaluation of digestive activity of the

ruminal microflora. These include cellulose digestion, glucose fermentation, nitrite reduction, and measurements of titratable acidity, VFAs, lactic acid, and ammonia concentration. These procedures can more clearly define the nature of the ruminal fluid but are not generally used in a clinical setting.

32.122.6.2 HEMATOLOGY

Hematologic abnormalities are not generally a significant feature of the indigestive disorders. The primary exceptions are TRP or rumenitis, in which neutrophilia and hyperfibrinogenemia are routine findings. This feature of the disease can aid in its differentiation from other forestomach diseases. An inflammatory leukogram can also be observed in some cases of vagal indigestion when inflammatory disease is responsible for dysfunction of vagal innervation and forestomach motility. Chronic bronchopneumonia in calves and TRP in adult cattle are commonly implicated as causes of vagal dysfunction. A hematologic reflection of an inflammatory response may also be seen after ruminal acidosis if the ruminal wall and other organs suffer secondary pathogen invasion, and likewise in the occasional cases of primary rumenitis or reticulitis.

The more common hematologic abnormalities associated with indigestion are reflections of fluid disturbance or stress response. Hemoconcentration is routine and may be severe in ruminal acidosis. Mild dehydration may also accompany the other forms of indigestion, especially when the disease shows a protracted course. A stress leukogram would be anticipated in cases of indigestion that are acute or distressing, such as acute bloat. The hematologic response in secondary indigestions depends on the primary disease.

When indigestion is chronic, especially in calves, in which the indigestive disturbance may go unrecognized or undiagnosed for a long time, a state of malnutrition may develop. In these instances a mild to moderate anemia may develop that may be attributable to micronutrient or macronutrient deficiencies.

32.122.6.3 BIOCHEMICAL ABNORMALITIES

Most of the primary forestomach diseases do not induce remarkable changes in the biochemical profile. In lactating or heavily pregnant animals, anorexia may induce a secondary form of acetonemia, which is detected by the presence of urine ketones. The animal must be carefully examined to differentiate ketosis with secondary anorexia and decreased ruminal activity from primary indigestion with secondary ketosis. Mild to moderate hypocalcemia and hypokalemia are commonly identified abnormalities in many cases of indigestion, especially when anorexia has been prolonged.

Dramatic alterations of the blood biochemical characteristics may accompany severe ruminal acidosis. Usually the laboratory findings correlate with the degree of severity assessed on physical examination. Affected animals have metabolic acidosis with decreased blood pH and plasma bicarbonate. Blood lactate levels rise with the acidosis. The urine pH falls into the acidic range as the kidneys excrete some of the excess acid, but eventually severe dehydration results in renal failure and anuria, eliminating this route of acid excretion. Decreased renal function is reflected by elevated serum creatinine and urea nitrogen concentrations. Other findings commonly include increased serum phosphate concentration, possibly caused by massive cellular destruction, and mildly decreased serum calcium concentration, presumably the result of decreased gut absorption. Other serum electrolyte abnormalities, such as changes in the sodium and chloride concentrations, may reflect fluid balance changes in response to ruminal fluid hyperosmolality.[467] Concentrations of serum enzymes of muscle and liver origin rise when acidosis and dehydration produce cardiovascular impairment with poor tissue perfusion, increased recumbency, and cellular destruction. Portal bacteria and toxins from the damaged ruminal mucosa contribute significantly to the increased serum liver enzymes: AST, sorbitol dehydrogenase, and ornithine carbomyltransferase.

Vagal indigestion may cause no significant blood biochemical abnormalities or can result in severe disturbances of fluid and electrolyte homeostasis.[446] Measurement of the serum electrolyte concentrations provides important clues about the site of obstruction of ingesta flow and is useful in adjusting fluid therapy. When the primary problem is failure of flow through the reticuloomasal orifice, the rumen fills and grossly distends with fluid, but significant abomasal reflux does not occur. Affected patients generally show mild or no serum electrolyte abnormalities. When ingesta fail to pass from the abomasum, reflux of the high-chloride abomasal contents into the rumen results in elevated ruminal chloride concentrations and associated hypochloremic, hypokalemic metabolic alkalosis. In some instances these abnormalities can be dramatic. Prolonged or severe hypochloremia and hypokalemia may also result in the paradoxic aciduria associated with avid renal sodium resorption in the face of low concentrations of chloride and potassium. Some slowly developing cases may accumulate significant fluid in the reticulorumen but have minimal blood electrolyte changes.

32.122.7 Treatment and Prognosis

32.122.7.1 Ruminal Wall and Motor Function Disorders

Signs such as ruminal tympany, ruminal hypomotility or stasis, and forestomach distention can all result from a number of causes. Eliminating the underlying causative problem more effectively resolves the disease than does treatment directed at the disease signs. Ruminal hypomotility, for example, is commonly a physiologic response to problems such as abnormal ruminal contents, a ruminal wall lesion, pain, or overdistention. In many cases the ruminal motility disturbance serves as a protective role for the animal. Former treatments that were directed at stimulating ruminal motility without addressing the causative disturbance included rumenatorics (e.g., nux vomica, ginger, tartar emetic) or parasympathomimetics (e.g., neostigmine, carbamylcholine). Such agents are not indicated under these circumstances.[400] Likewise the treatment of indigestions with alkalinizing agents such as magnesium hydroxide is indicated only when the pH of ruminal contents is low.[526]

32.122.7.2 FREE GAS BLOAT

When ruminal tympany is a prominent sign, it requires very critical assessment. Frothy bloat and free gas bloat can be differentiated by a thorough physical examination and knowledge of the feeding history. Passage of a stomach tube to help in this differentiation is very important and may alleviate the acute problem if free gas is present (see Table 32-15). Evidence of respiratory or cardiovascular distress indicates that the bloat is an acute, life-threatening problem that requires emergency treatment. With the exception of cardia or esophageal obstruction, the free gas bloat associated with indigestive disturbances is mild to moderate in severity and chronic or recurrent in nature. It does not represent a major threat to the animal and can be handled by treating the primary forestomach disturbance. Chronic free gas bloat does not respond to the antifermentatives or surfactants commonly used for frothy bloat. Only the restoration of physiologically normal reticuloruminal function corrects this type of bloat. Inhibition of eructation caused by lesions of the cardia region can usually be confirmed only by exploratory rumenotomy. This approach also determines whether the lesion is surgically correctable. Inflammatory lesions may respond to long-term administration of broad-spectrum antibiotics. This is also the treatment of choice when purulent lung infections appear to be the cause of the bloat. Failure to respond within about 3 weeks suggests that the treatment is not effective, and slaughter should be recommended after an appropriate withdrawal time. Detection of abnormal forestomach ingesta should direct

treatment to the primary fermentative or feeding disorder.

The various causes of chronic or recurrent bloat usually require chronic treatment for correction. It follows that the bloat will also not completely resolve until the underlying disturbance is corrected. Repeated relief of the bloat may be accomplished by passage of a stomach tube during the treatment regimen. In many cases this proves too tedious or too traumatic for the animal, and the most viable alternative often is the establishment of a temporary ruminal fistula. Several devices are manufactured for this purpose, or the fistula can be created by suturing the rumen to the skin. Release of the fermentative gas in this manner is important for the reestablishment of normal forestomach motility, which is inhibited if distention is extreme. When free gas bloat is the result of an obstruction of eructation or another gastrointestinal tract disease such as abomasal displacement, surgical treatment of the primary problem may be necessary. The tympany responds rapidly in these cases, and ruminal fistulation is not required.

32.122.7.3

LESIONS OF THE RUMINAL WALL

Diseases of the ruminal wall may be suspected on the basis of the physical examination findings and results of a CBC, abdominocentesis, and ruminal fluid analysis. In most cases exploratory laparotomy is required to confirm the diagnosis. Rumenitis or reticulitis may respond to antibiotic therapy, but the prognosis in these cases is guarded. Not only is the forestomach inflammation difficult to resolve, but the hematogenous spread of infection to other organs often causes intractable multiple organ system disease. Parakeratosis is best treated by correcting the causal feeding error (reducing the amount of concentrate and increasing the feeding of long-stemmed forage). The ruminal papillae can grow or regress in a period as short as 3 weeks when the feed is changed from low- to high-concentrate content or vice versa. Exactly how long it takes for parakeratotic papillae to return to normal is not certain, but it probably depends on the degree of change of the diet. The prognosis associated with this problem is good if inflammation of the ruminal wall is not also involved.

32.122.7.4

RUMINAL DISTENTION

Vagal indigestion is a chronic and insidious problem that generally warrants a guarded to poor prognosis. The syndrome of abdominal distention with an L-shaped rumen and possibly ruminal tympany has several different causes. Exploratory laparotomy and rumenotomy are essential for establishing an accurate assessment (see Fig. 32-94). Diaphragmatic herniation and masses that obstruct the reticuloomasal orifice cause signs indistinguishable from those of vagal indigestion that results from inflammatory lesions of the reticulum. Surgical correction of a diaphragmatic hernia involving the reticulum can be attempted but has usually proved unrewarding, especially if the lesion is chronic, involves a large defect, or is accompanied by inflammatory reaction. Removal of pedunculated masses or foreign bodies at the reticuloomasal orifice can promptly correct such problems.

The two most common causes of vagal indigestion syndrome are inflammatory lesions of the reticuloomasal region and abomasal diseases that involve gross distention, twisting, or vascular impairment of the organ. Vagal indigestion caused by abomasal disease carries a poor prognosis, whereas the prognosis for animals with reticular involvement is more variable. Animals in either category may respond favorably with appropriate therapy[448,451,527] (Box 32-6). Surgical exploration not only allows an assessment of the cause of the problem but may also allow repair. When abscesses are identified at the reticulum or liver, surgical drainage may help resolve the forestomach motor disturbance.[448,453] Identification of adhesions and active inflammation indicates that broad-spectrum antibiotic therapy may be beneficial; it is essential that aggressive antimicrobial therapy be administered before and after the surgical correction of a right-sided abomasal

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displacement or volvulus.[452] Gross abomasal distention, indicating pyloric outflow failure, usually warrants a poorer prognosis, as does the presence of granulomatous or neoplastic processes or generalized peritonitis and adhesion formation.[453] When the presence of a large gravid uterus appears to be the inciting cause of outflow failure, induction of parturition or cesarean section usually resolves the problem completely.

32.122.7.4.1

Box 32-6 Principles of Treatment of Vagal Indigestion

1 Determine likely cause, often by means of exploratory laparotomy

2 Administer specific therapy (e.g., antibiotics, antiinflammatory agents, removal of foreign body or relief of obstruction, drainage of abscesses) for causative lesion

3 Relieve forestomach distention; often must be repetitively performed

4 Limit feed and water intake; feed palatable, high-fiber ration

5 Transfaunate

6 Fistulate rumen if chronic bloat is a problem

The evaluation of animals with vagal indigestion with a large fluid-filled rumen should include assessment of the fluid and electrolyte status. Abnormalities such as dehydration, hypocalcemia, hypochloremia, and hypokalemia should be addressed with supportive fluid therapy. Treatment should be administered parenterally, because oral treatments are ineffective or deleterious. The forestomach should be emptied of the excessive ingesta accumulation either at surgery or with a large-bore stomach tube. This procedure may have to be repeated if the recovery period is prolonged. Relief of persistent forestomach distention is *critical* to the reestablishment of normal motility. Limited feed and water should be offered to prevent repeated accumulations in the reticulorumen, and intravenous fluid therapy should be continued until reticuloruminal motility is reestablished and oral fluid intake can be allowed at normal levels. Once the ruminal distention has been alleviated, several liters of ruminal fluid transfaunate from a healthy donor should be administered.[528] The limited diet must be palatable and should consist primarily of long-stemmed hay or green feed for maximum stimulation of the normal forestomach motility pattern. A temporary ruminal fistula may be indicated if tympany is a prominent sign.

Response to treatment of vagal indigestion usually is a slow process and may require several weeks. Favorable signs include a return of the normal primary and secondary contraction patterns, improvement in appetite, maintenance of normal forestomach dimensions, weight gain, and increased fecal production. Repeated development of forestomach distention, continued scant fecal output, poor ruminal motility, and recurrent bloat are indications that the animal is not responding to treatment and the prognosis is grave.

32.122.8

Fermentative Disorders

With the exception of severe acute ruminal acidosis, the disturbances of reticuloruminal fermentation generally are not fatal unless the disease is undiagnosed for a prolonged period, leading to extreme debility. Treatment of fermentation disorders centers around restoring a normal ruminal fluid environment that allows normal microbial metabolism. Identification of ruminal fluid parameters (see Table 32-16) and the nature of the forestomach ingesta directs the appropriate treatment (Box 32-7).

32.122.8.1

Box 32-7 Principles of Treatment of Fermentative Indigestions

1 Determine and resolve initiating cause; adjust feed regimen

2 Correct ruminal pH

3 Correct systemic acid-base and electrolyte abnormalities through parenteral fluid therapy (especially Ca^{++} and K^{+})

4 Remove grossly abnormal ruminal ingesta

5 Correct ruminal fill (overdistention or emptiness)

6 Transfaunate repeatedly

7 Resolve inspissation or impaction of ruminal contents when present

8 Provide oral and parenteral mineral and vitamin supplementation when indigestion or anorexia is chronic

32.122.8.2

FEEDING

The first and most important step in treatment of nutritionally related indigestions is correction of the specific causal feeding error. Because the imbalance may have gone on for weeks, especially in cases of calf indigestion, correction of the problem may also take some time. The evolutionary development of the ruminant has adapted it to be a grassland grazer. Economic pressures in the animal industry have caused managers to institute feeding practices that diverge widely from a pasture setting. Fresh green grass, however, remains one of the best means of stimulating normal forestomach digestion and motility. The second best type of diet includes a balance of palatable and digestible sources of energy, protein, fiber, and mineral nutrients. Fiber requirements should be determined by considering both the physical effectiveness of fiber and the production of fermentation acids.[529] The content of structured roughage should not fall below 10% of the ration dry matter, and a crude fiber component above 17% is desirable for any ration.

32.122.8.3

ALTERATION OF RUMINAL CONTENTS

When the viability or activity of the ruminal microflora is in question, as in the primary fermentative disorders and most cases of secondary indigestion, ruminal transfaunation is indicated.[528] This should be obtained from a healthy individual that preferably is adapted to a ration similar to the one the patient is expected to consume. The fluid can be obtained from an animal with the rumen fistulated, by removal with a stomach tube, or from a local abattoir. After the large particulate matter has been strained from the fluid (cheesecloth or large stockinette can be used), it can be administered through a stomach tube. The transfer from donor to recipient is best accomplished immediately, but fluid that contains active and healthy microflora remains viable for up to 9 hours at room temperature or 24 hours under refrigeration.[519,520] In calves inoculation with 1 L is appropriate, whereas 3 L is minimal in an adult cow, and 8 to 16 L is more desirable.

Many animals with indigestion exhibit decreased ruminal fill. As discussed, one of the primary stimuli for

active ruminal contraction is mild forestomach distention. In addition to the administration of ruminal transfaunate, it usually is beneficial in these cases to administer enough oral fluid to produce mild ruminal distention. This can be accomplished with water warmed to body temperature, and 20 to 30 L of fluid administered through a tube may be required to achieve the desired effect. The addition of salt (sodium and potassium chloride) in amounts sufficient to produce an isotonic solution (approximately 2 tsp/L) supplements deficiencies and promotes rapid turnover of the fluid from the rumen to the lower tract. Cathartic agents such as magnesium sulfate have been used and may be beneficial but do not serve to supplement the common electrolyte deficiencies.

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Correction of pH abnormalities to the normal range of 6 to 7 is important when ruminal acidosis or alkalosis is detected. Alkalinizing agents such as magnesium hydroxide and sodium bicarbonate are indicated for treatment of acidosis at an initial dose of 1 g/kg. Magnesium hydroxide is commonly used by some as a routine treatment for any animals in which ruminal hypomotility has been identified. This practice is not justifiable in most cases of ruminal hypomotility because the fluid pH is commonly at or near neutral. The use of magnesium hydroxide in such settings may induce a mild systemic alkalosis, and the agent is better reserved for true cases of acidosis.[526] Ruminal alkalosis can be corrected with the infusion of acetic acid (vinegar, initial dose of 2 mL/kg, up to 12 L). All of these agents are best administered in several liters of warm water to ensure good distribution through the ruminal fluid.

Overdistention of the ruminal wall may be a primary inhibitor of forestomach motility in some cases of indigestion caused by abnormal fermentation. Treatment of free gas bloat has been discussed. When the distention is caused by accumulation of abnormal ingesta, normal contractions do not return and the ruminal tympany is not resolved until the distention is relieved. This situation is best exemplified by cases of microfloral inactivity caused by poor-quality roughage and is the underlying problem in calves with haybelly. One approach to this problem is to restrict the animal to small quantities of readily digestible feed given several times a day. Between meals the animal can be kept in an unbedded stall or muzzled. This process is continued until the accumulated ingesta have passed out of the forestomach. Repeated transfaunations during this time help reestablish a more normal microflora. This approach relies on motility and microbial activity sufficient to break down the ingesta and pass them to the lower tract. An alternative approach is to remove the accumulated ingesta by means of rumenotomy, after which the animal is transfaunated and allowed access to moderate amounts of feed until normal motility is restored. Emptying the rumen surgically is the treatment of choice when spoiled milk, putrefactive ruminal ingesta, or severe ruminal acidosis is detected. Prolonged cases of microbial inactivity or anorexia (or both) with ruminal hypomotility can result in loss of the normal stratification of forestomach ingesta. The fibrous, floating layer sinks to the ventral ruminal sac in these cases, forming a dense, firm mass. Return of normal forestomach motility will be delayed unless this accumulation of material can be eliminated. This can be accomplished during the process of microfloral reestablishment by massaging the mass through the lateral and ventral body wall. Dissolution and passage of the material can be enhanced by the administration of mineral oil (4 L) or DSS (4 to 6 oz in 2 to 3 L of water). Because DSS kills ruminal protozoa when given in amounts greater than required to saturate the fibrous matter, at least one ruminal transfaunate should be given 1 to 2 days after the last application of this agent.[530]

Animals with prolonged anorexia caused by a depressant or febrile disease that produced secondary indigestion may not return to feed or have normal ruminal motility even after normalcy of the ruminal contents has been restored. Chewing activity is one of the strongest stimulants for ruminal motility, and these individuals sometimes benefit if palatable hay or grass is placed forcefully into the mouth by hand. An alternative is to give such individuals access to pasture. Both the ruminant and its ruminal microflora have trace mineral requirements that are often not met by the type of diets that may induce microfloral inactivity.[459] The ruminal microflora is also responsible for supplying the animal with its vitamin B requirements.[423] The

The ruminal microflora is also responsible for supplying the animal with its vitamin B requirements. The stunted, poor body condition of calves affected by chronic indigestions may reflect these deficiencies, as well as protein energy malnutrition (see Chapter 9). Oral supplementation of minerals and parenteral supplementation of the B vitamins may be helpful until normal ruminal digestive function is established. Adult cattle, especially lactating animals with high metabolic demands, may also benefit from B vitamin supplementation when ruminal function is impaired.

Intraruminal administration of antibiotics has been used to kill undesirable populations of ruminal microflora. A 2- to 3-day course of treatment with a broad-spectrum antibiotic that is not readily absorbed is useful only when an overgrowth of undesirable bacterial species is present and should be followed by transfaunation. Drugs used for this effect include neomycin or tetracycline for ruminal alkalosis or urea toxicosis and chlortetracycline or erythromycin for ruminal acidosis. Feeding changes and ruminal transfaunation are also effective in inhibiting the undesirable population and inoculating the desirable population. When spoiled milk, putrefactive ingesta, or extremely acidic ruminal contents are found on ruminal fluid analysis, rumenotomy, removal of the contents, and flushing of the rumen seem the more desirable treatment.

32.122.8.4

ACUTE RUMINAL ACIDOSIS

Therapy for cases of mild to moderate or chronic ruminal acidosis can follow the guidelines outlined previously. The prognosis in these cases is usually good, although ruminal inflammation and hematogenous dissemination of infection to other organs can produce chronic problems with a poorer prognosis.

Severe grain overload requires prompt and aggressive treatment. Animals showing severe depression, an unresponsive condition, apparent blindness, and gross ruminal distention warrant a grave prognosis. Immediate slaughter should be considered for animals with similar signs that are still able to stand.

Emergency rumenotomy and removal of the acidic ruminal contents may be lifesaving if the procedure can be performed before significant amounts of ingesta have passed into the lower gastrointestinal tract. An alternative treatment in less severe cases is repeating flushing of the rumen with warm water through a large-bore stomach tube. Administration of magnesium hydroxide into the rumen and sodium bicarbonate solution (5%) IV is necessary to counter the acidosis. Intravenous fluid therapy should be continued until the animal has recovered, to provide support against hypovolemic shock. Other treatments that may be considered include NSAIDs and intraruminal antibiotics. The other therapeutic measures discussed, such as transfaunation and dietary adjustment, should be continued during the recovery phase.

32.122.8.5

SUPPORTIVE TREATMENTS

Indigestion often is accompanied by varying degrees of dehydration and electrolyte imbalance. When these abnormalities are only mild or moderate, the animal's fluid homeostasis may correct as the normal digestive processes are restored. More rapid recovery is achieved if these problems are addressed during the initial treatment, and animals must be treated if the imbalance is severe. Restoration of normal fluid balance improves attitude and appetite and normal gastrointestinal motility.

When laboratory facilities are available and the specific electrolyte imbalances can be assessed, fluid therapy can be tailored to the individual case. Empiric treatment with a balanced electrolyte solution administered IV is sufficient in most cases, because gross disturbances of the body fluid electrolytes are uncommon in most indigestions. The greatest exceptions to this are cases of severe ruminal acidosis or vagal indigestion with pyloric outflow failure and sequestration of abomasal chloride. These problems should be identified during the examination.

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Hypocalcemia and hypokalemia are routinely present in many cases of indigestion. Low serum concentrations of these elements can produce muscular weakness and impair gastrointestinal motility. Both calcium and potassium should be included in the administered fluids. As an alternative, calcium salts should be administered SC if intravenous fluid administration is not elected. When anorexia has been prolonged, an additional oral dose of potassium chloride (120 g/day) may be required even after adequate hydration has been achieved and fluid therapy has been discontinued.

32.122.9 Prevention

Some of the sporadically occurring diseases of the forestomach wall such as granulomatous infections, neoplastic invasions, and diaphragmatic herniation cannot be foreseen or prevented. The most common cause of vagal indigestion syndrome is inflammation of the reticular area caused by TRP. Prevention of this disease by keeping metallic foreign bodies out of the feed or by prophylactic administration of a ruminal magnet is the best prevention of vagal indigestion as well.

The microbial-fermentative forestomach disorders are best prevented by proper feeding management. A well-balanced diet of palatable feeds with an adequate amount of well-structured roughage (not finely ground or pelleted) prevents most problems. Dietary changes should be introduced slowly (over 2 to 3 weeks) to allow adaptation of the microbial flora to the new substrate. Calves undergoing ruminal development and cattle fed high-production diets or changing between production groups are at risk of oversights in proper feeding management. Some feed additives have proved effective in preventing the overgrowth of the high-acid—producing ruminal microflora. Feed-grade buffers are widely used in both dairy and beef cattle production, in which high-concentrate diets are fed to maximize production. These buffers stabilize the ruminal pH and alter the mechanics of ruminal fluid outflow, thus decreasing the chances of overgrowth of the lactate-producing organisms. Commonly used buffers include sodium bicarbonate, sodium sesquicarbonate, sodium bentonite, magnesium oxide, and calcium-magnesium carbonate, of which only the sodium carbonates are truly buffering agents in the chemical sense. The other agents do tend to stabilize ruminal pH, however, and all of these have shown some benefit in reducing the disease problems associated with heavy grain feeding and diets that are low or marginal in effective fiber.[531] The ionophore antibiotics (e.g., lasalocid, monensin) and some other antibiotics (e.g., the sulfur-containing peptide antibiotic thiopeptin) have also proved effective in reducing lactate production in animals fed high-grain diets. The effect of these agents is to suppress the lactate-producing organisms while not appreciably affecting the lactate users. The ionophores are in common use in feedlot cattle and dairy heifer rations because the selective effects of these antibiotics on the ruminal microbes alter the ruminal metabolism in a manner that promotes increased animal weight gain.[532,533] In 2004 the FDA approved the use of the ionophore monensin for lactating cattle in the United States. Although approval was based on increases in milk production efficiency, ionophore use may also reduce the risk of ruminal acidosis and ketosis.[534]

32.123 ACUTE ABDOMEN IN RUMINANTS

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Abdominal emergencies in ruminants are both a therapeutic and a diagnostic challenge for the veterinary

practitioner. Some of them will require immediate surgical treatment, and others can be treated medically (see Fig. 32-96). They are associated with numerous conditions that affect the abdominal cavity and can also be mimicked by diseases of extraabdominal origin (see Fig. 32-97).

Four important questions should be addressed while dealing with an acute abdomen in ruminants: (1) Where does the pain originate? (2) Is it a medical or surgical problem? (3) Is medical treatment indicated before surgery? (4) What is the likelihood for survival and productivity? To answer these questions, the clinician should use a systematic approach based on adequate signalment and history, complete physical examination, and judicious choice of ancillary tests. Prognosis should be based on past experiences of others as well as one's own experience.

Even though a precise diagnosis facilitates the institution of appropriate treatment and helps to better predict outcome, emphasis should not be placed solely on the diagnosis. Precise information is not yet available for accurately making a prognosis on the outcome of an acute abdomen in ruminants.

32.124 A CONCISE BUT PRECISE EVALUATION OF THE ANIMAL

An animal with acute abdomen may need immediate medical assistance. Therefore the clinician should identify life-threatening problems and take appropriate action rapidly. Acute abdominal emergencies are often associated with either hypovolemic or septic shock.[535] Hypovolemic shock is characterized by increased heart rate, pale mucous membranes, slow capillary refill time, and dehydration.[535] Increased heart rate and dehydration are also observed in case of septic shock, but mucous membranes are hyperemic or bluish in color, and scleral vessels are engorged and dark.[535] Intensive fluid therapy is the treatment of choice for both hypovolemic and septic shock.[535] Consequently, an intravenous catheter should be placed and fluid therapy instituted immediately. However, a complete history and meticulous physical examination should be performed before emergency medical therapy if the condition of the patient is stable.

32.124.1 History

32.124.1.1 SIGNALMENT

Signalment may identify an animal at higher risk of particular diseases. Age, sex, breed, and production stage are important parameters to take into consideration when elaborating the differential diagnosis. For example, abomasal volvulus develops far more frequently in dairy cows than in beef cattle.[536,537] Similarly, uterine torsions are essentially observed at the time of parturition or in the last trimester.[538] Colic in a wether or a buck goat should be considered a result of urolithiasis until proven otherwise.

32.124.1.2 MANAGEMENT—FEEDING PROGRAM

Feeding management system (feeding cows with silage or a total mixed ration [TMR]), herd size (dairy farms with more than 100 cows), and high-intensity milk production are risk factors associated with the development of hemorrhagic bowel syndrome (HBS).[539] Struvite urolithiasis in cattle occurs more frequently in bulls or steers fed with high-grain diets.

32.124.1.3 HISTORY AND CLINICAL SIGNS

Previous history of surgery can be associated with the development of adhesions and colic. Recent calving and obstetric manipulations may cause a full-thickness uterine tear and subsequent peritonitis. Paralytic ileus associated with hypocalcemia may occur during estrus.[540] Pleuritis, pleuropneumonia, or rib fractures may mimic abdominal pain.[541] Previous treatments, especially those that can modify clinical signs or the interpretation of laboratory results, should also be noted. Administration of analgesics such as NSAIDs may partially control abdominal pain, attenuate signs of colic, and decrease the heart rate.

Description of the clinical signs observed by the owner and the chronologic sequence of events are of particular interest. Intussusception in cattle is characterized by an acute onset of anorexia, decreased fecal output (often with dark feces containing blood) and milk production, as well as colic. However, even though the abdominal pain eventually becomes less severe, the depression progresses.[541–544] Torsion of the mesenteric root has an acute onset with severe colic and rapid deterioration.[541,545,546] Fecal output, consistency, and appearance are relevant information. Stranguria manifested by unsuccessful micturition efforts is associated with urolithiasis.

32.124.2 Complete Physical Examination

A thorough and complete physical examination is the most important step when approaching an acute abdomen.

32.124.2.1 VISUAL EXAMINATION

The animal's abdominal profile or silhouette should be observed from the rear and both sides to detect and characterize abdominal distention.[541,547] Bilateral ventral distention is associated with small intestine disorders, whereas distention in the right paralumbar fossa is associated with cecal and/or colon disorders. In cases of abomasal volvulus, the distended abomasum can be observed caudal to the last rib in the right paralumbar fossa. Gas in the rumen causes a distended upper left abdomen, whereas some forms of vagal indigestion have a “papple” shape (pear on the right and apple on left). Lateral views of the abdomen help to determine whether the distention arises primarily from the paralumbar fossa or extends cranially under the ribs. An arched back may be observed in cases of cranial abdominal pain or laminitis (sore feet).

Evaluation of pain severity and differentiation between visceral and parietal pain can be performed using history and observation of the animal. Abdominal pain is an important criterion in deciding if surgery is necessary. Severe colics are classically associated with some surgical intestinal conditions,[548,541] although animals with severe jejunal distention secondary to acute enteritis may have a similar clinical presentation. Abdominal pain may be a consequence of excess distention of a hollow viscus (excessive intestinal distention), spasms of intestinal smooth muscles, stretching of the mesenteric supporting structure, intestinal ischemia, or chemical irritation of the visceral or parietal peritoneum.[549–551] Abdominal pain can be classified into two main categories: visceral pain (hollow viscera and solid organs) and parietal pain (parietal peritoneum, abdominal muscles, rib cage).[551] Although the task is often difficult in animals such as cattle that have unpredictable behavior in response to pain, differentiation between visceral and parietal pain should be attempted.

Pain sensation from the parietal peritoneum travels through the peripheral spinal nerves and usually localizes

over the affected area.[551] Because parietal pain is exacerbated by pressure and tension modification, the patient is reluctant to move and has a tonic reflex contraction of the abdominal muscles.[550] No active clinical signs of colic are present. This is typically observed in cases of peritonitis. The animal is reluctant to move, has a splinted abdomen, and is responsive to external palpation,[541] such as having a positive xiphoid grunt test or not dipping the back when pinched over the withers.

Some pain fiber endings are located in the submucosa and muscle layers of hollow viscera (intestines, bladder) and in the capsule of solid organs (kidney, liver). Consequently, distention, forceful contraction, or traction will produce pain in a hollow viscus. Capsule stretching will create pain in solid organs. Visceral pain is typically recognized by active manifestations of colic: kicking at the abdomen; treading with the rear feet; lying down, standing, and stretching out[541]; and grinding the teeth. Goats may also vocalize. The animal is anxious and has an apprehensive attitude. Contrary to parietal pain, visceral pain is transmitted via sensory fibers in the autonomic nerves.[549] Visceral pain is often diffuse and difficult to localize.[549]

32.124.2.2 EVALUATION OF VITAL PARAMETERS

Assessment of cardiovascular status is essential in the evaluation of an animal with an abdominal emergency. Hypovolemic and septic shock are associated with increased heart rate, pale or hyperemic mucous membranes, slow capillary refill time, and dehydration. Low heart rate and adequate hydration status are considered good prognostic indicators regarding the outcome of abomasal volvulus.[552,553] Circulatory insufficiency, secondary to hypovolemia and caudal vena cava compression, is a complication of abomasal volvulus.[553] Dehydration and acid-base abnormalities are principally caused by fluid accumulation in the abomasum and are associated with a high mortality rate.[552,554] Heart rate is increased secondary to hypovolemia, compression of the caudal vena cava, and sympathetic nervous system stimulation in response to distention and twisting of the abomasum.[552] Determination of rectal temperature, pulse or heart rate, and respiratory rate (TPR) should always be performed first, as manipulations performed during the physical examination of an abdominal emergency can elicit pain, modifying the heart rate.

The TPR and amount of pain exhibited may also be used to monitor the evolution of the condition and the response to the initiated treatment.

32.124.2.3 EXTRAABDOMINAL EXAMINATION

Once vital parameters have been evaluated and the animal appears hemodynamically stable, a thorough physical examination of the body systems should be performed. Examination of the thorax (pleuropneumia, rib fractures) and the musculoskeletal system (laminitis, myopathy) are important in eliminating diseases that mimic abdominal pain.

32.124.2.4 ABDOMINAL EXAMINATION

Abdominal examination is performed by auscultation, percussion, ballottement, and succussion of the abdomen. Pings are tympanic resonance caused by a gas-fluid interface in a distended organ and can be detected by simultaneous auscultation and percussion.[541] Because rectal palpation may create an area of increased resonance on the right dorsal part of the abdomen, detection of pings should be performed before rectal palpation.[541]

On the right side of the abdomen, many organs may be responsible for pings. Location, pitch characteristics and variability of the ping are essential to establish a differential and precise diagnosis. Pings localized from the thirteenth rib cranially to the ninth rib are typical of abomasal volvulus or a right-displaced abomasum.[541] Cecal dilatation or volvulus creates a ping in the right paralumbar fossa and caudal quadrant,[541] often extending to the hip. Abomasal volvulus will be more likely to have a high-pitched ping, whereas animals affected with peritonitis may have a bilateral low-pitched ping in the upper paralumbar fossa. Many cattle 843
have a round area of monotone pinging some 15 to 20 cm in diameter centered high on the right under the last 844
rib, which is gas in the spiral colon (see Figure 1-3). Moving or constantly contracting viscera will have changing pitch of their pings, like gas in the left-displaced abomasum, descending duodenum, or proximal colon. For this particular reason, it is important to auscultate and percuss for a certain period of time to notice ping variation.

On the left side, pings are principally associated with left abomasal displacement, ruminal collapse, and pneumoperitoneum. Left abomasal displacement typically creates variable pitch pings dorsally from the eighth to the thirteenth ribs. Pings associated with gas in the rumen, ruminal collapse, and pneumoperitoneum are localized dorsally in the left paralumbar fossa and extend cranially to the eleventh rib. Illustrations and details are presented in Chapter 1 of this textbook. Simultaneous auscultation and ballottement (succussion) of the abdomen may permit detection of fluid trapped within the intestine or in a hollow viscus like the rumen or abomasum.[541] The location of the fluid splashing sounds on auscultation-succussion may help to confirm and differentiate among auscultation-percussion findings.[541] Tense abdominal muscles, secondary to parietal peritoneum inflammation, may also be detected during succussion.

Cattle with cranial abdominal pain are reluctant to move; they stand with elbows abducted and back arched.[541] During examination, bruxism (grinding of the teeth) may be present.[541] Pain can be elicited by pinching over the withers or applying forceful movement with the knee or upward pressure with a bar or pole over the xyphoid area or anterior abdomen. In response, the animal in pain may grunt or kick and be reluctant to dip the back.[541] Sensitivity of this test may be increased by simultaneous auscultation of the trachea. Cranial peritonitis, secondary to TRP or abomasal ulcers, is an important cause of cranial abdominal pain. A complete cardiorespiratory examination may help to differentiate this from thoracic pain.

32.124.2.5 RECTAL PALPATION

Per rectum abdominal palpation of cattle is helpful in the differential diagnosis of an acute abdomen because the urogenital and digestive systems can be evaluated.

Cecal disorders are clearly diagnosed per rectal palpation. Moreover, cecal dilatation or volvulus can be differentiated by location of the apex. Based on these findings, medical treatment can be started if the caecum is only dilated and the apex is mobile.[548,555] Multiple, dilated, turgid small intestine loops and a firm mass may be palpated in cases of intussusception[543,542] or HBS.[539] Typical signs of peritonitis (adhesions between the kidneys and the rumen, and the intestinal convolutions, and decreased rectal mobility) may be palpated when the posterior aspect of the abdomen is affected.[556] Uterine wall integrity may be evaluated during rectal palpation, although examination per vagina may be necessary to confirm a full-thickness laceration in the postpartum cow. In cases of urolithiasis in bulls or steers, rectal palpation reveals a pulsatile pelvic urethra and a distended bladder. In cases of pyelonephritis, enlargement of one or both ureters may be palpated. The left kidney may be painful as well as bigger, without lobulation. Enlargement of the right kidney is sometimes

palpable. In small ruminants, urolithiasis is manifested by pulsations in the pelvic urethra that may be felt by digital rectal examination, and distended bladder or enlarged kidney can be detected by deep abdominal palpation.

Presence and macroscopic appearance of feces can be evaluated during rectal examination. A decreased volume of feces is principally associated with intestinal stasis or obstruction, which may occur secondary to a direct mechanical obstruction (requiring surgical treatment) or to gastrointestinal ileus (requiring only medical treatment).[557] However, feces may be present in the first few days after an intestinal obstruction.[557]

32.124.3 Ancillary Tests

32.124.3.1 PACKED CELL VOLUME AND TOTAL SOLIDS

Shock, sepsis, and toxemia cause hemoconcentration and dehydration and are associated with an increase of PCV and total solids. On the other hand, increased PCV and decreased total solids are observed during the formation of a third compartment filled with a protein-rich fluid such as in generalized peritonitis.[558]

32.124.3.2 BLOOD GAS ANALYSIS AND ELECTROLYTES

Blood gas analysis as well as determination of electrolyte imbalance may be useful before initiation of treatment. Most adult ruminants with acute abdominal diseases suffer from metabolic alkalosis.[559] Metabolic alkalosis is often associated with abomasal volvulus, intussusception, cecal disorders, abomasal ulcers, peritonitis, renal diseases, and reticuloperitonitis.[559] Hypochloremia and hypokalemia are frequently combined with metabolic alkalosis.[560] Metabolic acidosis may be observed if urinary tract disease, small intestinal strangulation or obstruction, or enteritis with severe diarrhea is present.[559]

Serum chloride concentration,[554,561] anion gap,[561] and base excess[562,563] have been proposed as preoperative prognostic indicators in dairy cattle suffering from abomasal volvulus. Poor short-term prognosis was associated with serum chloride concentrations less than 79 mEq/L,[554] base excess values of −0.1 or less,[562] and anion gap values of more than 30 mEq/L.[561] However, a prospective study on the outcome of abomasal volvulus reported that serum base excess and anion gap values did not differ between productive and nonproductive animals.[552] In this study, serum chloride concentration was significantly lower in nonproductive animals, but this prognostic test had numerous false-negative results.[552]

Blood gas analysis and electrolyte measurement results are helpful in the institution and monitoring of fluid therapy.

32.124.3.3 BLOOD LACTATE CONCENTRATION

Blood lactate concentration, although rarely used in ruminants, can be used to assess cardiovascular or respiratory system compromise, to monitor the response to treatment, and to establish a prognosis for survival. In cattle, high blood lactate concentrations have been associated with a poor outcome for abomasal volvulus in one study,[553] whereas Constable and co-workers did not find any association in their study.[564] In humans[565–568] and horses,[569] blood lactate concentrations are an important indicator of adequate response to treatment and reperfusion of ischemic tissues.

32.124.3.4 COMPLETE BIOCHEMICAL PROFILE

Evaluation of specific enzyme activity (e.g., hepatic enzymes, BUN, and creatinine) combined with physical examination and other ancillary tests may be useful in establishing a diagnosis and assessing progress.

32.124.3.5 WHITE BLOOD CELL COUNT AND DIFFERENTIAL

A WBC count rarely provides further information for establishing the exact cause of an acute abdomen. Hematologic findings are rarely specific to a condition and reflect the underlying inflammatory process. In most cases a minimal to moderate inflammatory process characterized by a neutrophilic leukocytosis is observed. Hematologic findings may also provide information about the acuteness of the disease and the severity of the sepsis and toxemia associated. Severe sepsis is associated with neutropenia, degenerative left shift, toxic changes of neutrophil morphology, and lymphopenia. Hematology is also an important ancillary test to monitor the response to treatment.

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32.124.3.6 FIBRINOGEN

In ruminants, increased fibrinogen concentration is an early indicator of inflammation. Studies in cattle report that fibrinogen concentration may increase within 1 to 2 days after induction of inflammatory conditions.[570,571] Consequently, increased fibrinogen concentration may be observed in some cases of acute abdomen. Normal fibrinogen concentration despite severe visceral involvement should be observed only in peracute cases (within a few hours) (e.g., torsion of the root of the mesentery). Moderate to marked increased fibrinogen concentration is also the signature of an active localized inflammatory condition such as reticuloperitonitis, liver abscesses, or pyelonephritis.

32.124.3.7 URINALYSIS

Urinalysis is helpful in differentiating between colic of urogenital origin versus gastrointestinal disorders. Urinalysis can be rapidly performed using a urinary dipstick* and gross morphologic examination. Renal diseases are associated with proteinuria (>1+), glucosuria, and positive blood reaction. In case of acute urethral obstruction, hematuria and proteinuria are consistently observed. Determination of urinary specific gravity may help to characterize azotemia.[572]

* Chemstrip 9, Roche Diagnostics Corporation, Indianapolis, IN.

32.124.3.8 ABDOMINOCENTESIS

Collection and evaluation of peritoneal fluid is helpful in the diagnosis and the establishment of treatment, as well as prognosis, in many gastrointestinal disorders in cattle.[541] Abdominocentesis is considered an essential ancillary test in the approach to acute abdomen in many species.[535,573] Because of the ability of cattle to wall off and localize infections in the abdomen, a four-quadrant method of abdominocentesis is suggested by some authors.[541] Fluid can be evaluated macroscopically for color, volume, odor, and turbidity. Normal values are reported in the section of this chapter on peritonitis. Peritoneal fluid changes to cloudy yellow, then blood-tinged with fibrin, and finally to black in color as bowel necrosis and hemolysis of extravasated RBCs occur. In case of generalized peritonitis, fluid is abundant, cloudy, and sometimes foul-smelling. Occasionally,

digestive fibers can be observed macroscopically if rupture has occurred.

Biochemical variables may be evaluated in peritoneal fluid. Lactate, glucose, alkaline phosphatase, and pH of the peritoneal fluid concentrations have been reported to be indicators of intestinal ischemia and peritonitis in horses.[574] Such information is not published for ruminants.

32.124.4 Diagnostic Imaging

32.124.4.1 ULTRASONOGRAPHY

With the advance of multifrequency abdominal transducers, ultrasonography is used more frequently in ruminant medicine. Information on ultrasound of the ruminant abdomen is available in this chapter.

32.124.4.2 RADIOGRAPHS

Although the use of abdominal radiographs in adult cattle is limited to referral hospitals, and their effectiveness is limited to the cranial abdomen, they are one of the most helpful ancillary examinations for the diagnosis of reticuloperitonitis.[575,576] Abdominal radiographs may help in the diagnosis of intestinal atresia and intussusception in calves.[541]

A lateral view of the abdomen of small ruminants may assist in the diagnosis of urolithiasis because stones in the urethra or in the bladder may be detected.

32.124.5 Medical or Surgical Decision

A differential diagnosis list and a decision for surgical or medical treatment should be established based on clinical signs and ancillary tests results (Fig. 32-96). If a precise diagnosis is made, adequate treatment can be instituted. When a precise diagnosis cannot be established, attempts should be made to differentiate surgical and medical cases (Fig. 32-97). Among surgical cases, intestinal obstructions are those requiring immediate surgery. A mechanical obstruction may be suspected when there is a suspicion of intestinal or cecal torsion on rectal examination, pings indicating a right abomasal displacement or volvulus, peritoneal fluid indicating bowel devitalization, or severe signs of active colic or rapid deterioration.[557,577] If an intestinal mechanical obstruction is not suspected during the first examination, exploratory surgery may be delayed for up to 36 hours.[557] However, frequent monitoring should be performed and appropriate medical treatment provided to the animal.

32.124.5.1 SURGERY

Most abdominal surgeries in adult cattle are performed with the animal standing under sedation and local or regional anesthesia. Cattle can tolerate intestinal resection and anastomosis standing if adequate local anesthesia and systemic analgesia are provided. However, some animals with acute abdomen are reluctant to stand and may be expected to lie down. If that occurs, surgery should be performed with the animal in lateral recumbency.[578] Because a right paralumbar fossa celiotomy provides the best exposure to the intestinal tract, left lateral recumbency should be favored. Other than the general status of the animal, the suspected affected organ, presence of aggressive behavior, surgeon preferences, and facilities should be considered in the choice of doing the surgery with the animal standing or in lateral recumbency. If the animal is dehydrated and/or

manifests signs of shock, preoperative fluid therapy and analgesics are recommended.[546,557,577,579] For the prevention of surgical infection, appropriate preoperative antibiotic administration is also recommended.[577,580]

32.124.5.2 MEDICAL AND SUPPORTIVE TREATMENT

The goal of therapy in an animal with acute abdomen is to initially correct the hemodynamic and metabolic imbalances associated with hypovolemic or septic shock, to control pain, and to correct or treat the primary cause of the disease, when identified. Consequently, medical treatment is based on fluid therapy, NSAIDs, and antimicrobial drugs.

32.124.5.2.1 Fluid Therapy

Crystalloid solutions (0.9% NaCl, Ringer's solution) are indicated initially to replenish fluid loss and improve the circulating blood volume.[560,581] To resuscitate critically ill neonatal patients, recommended intravenous fluid administration rates of isoosmotic crystalloid solution are 80 to 90 mL/kg of body weight per hour.[581] However, such rates are difficult to achieve through a catheter in adult ruminants. Studies demonstrated that perfusion rates of 40 and 80 mL of an isoosmotic crystalloid solution per kilogram of body weight per hour can be used safely in adult ruminants and dehydrated calves, respectively.[582–584] If the animal is not critically ill, fluid and electrolyte deficits should be corrected over 2 to 8 hours. The maximal flow rate usually achieved through a catheter in an adult is 15 to 20 mL/kg/hr.

Hypertonic solutions (7.2% or 7.5% NaCl) are also an alternative. Intravenous administration of hypertonic saline provides rapid resuscitation in dehydrated or endotoxemic ruminants.[585] A rate of 4 to 5 mL of hypertonic solution per kilogram should be administered IV through the jugular vein over 4 to 5 minutes. Animals should be provided with a supply of fresh water immediately after the treatment, or an intravenous infusion of an isotonic crystalloid solution should be instituted. Cattle not observed to drink within 5 minutes should have 20 L of water pumped into the rumen.[585] An administration rate for a hypertonic solution of over 1 mL/kg/min should be avoided because it induces a potentially fatal hypotension coupled with a decrease in cardiac contractility.[585]

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Fig. 32-96 Suggested decision tree for cattle with acute abdomen.

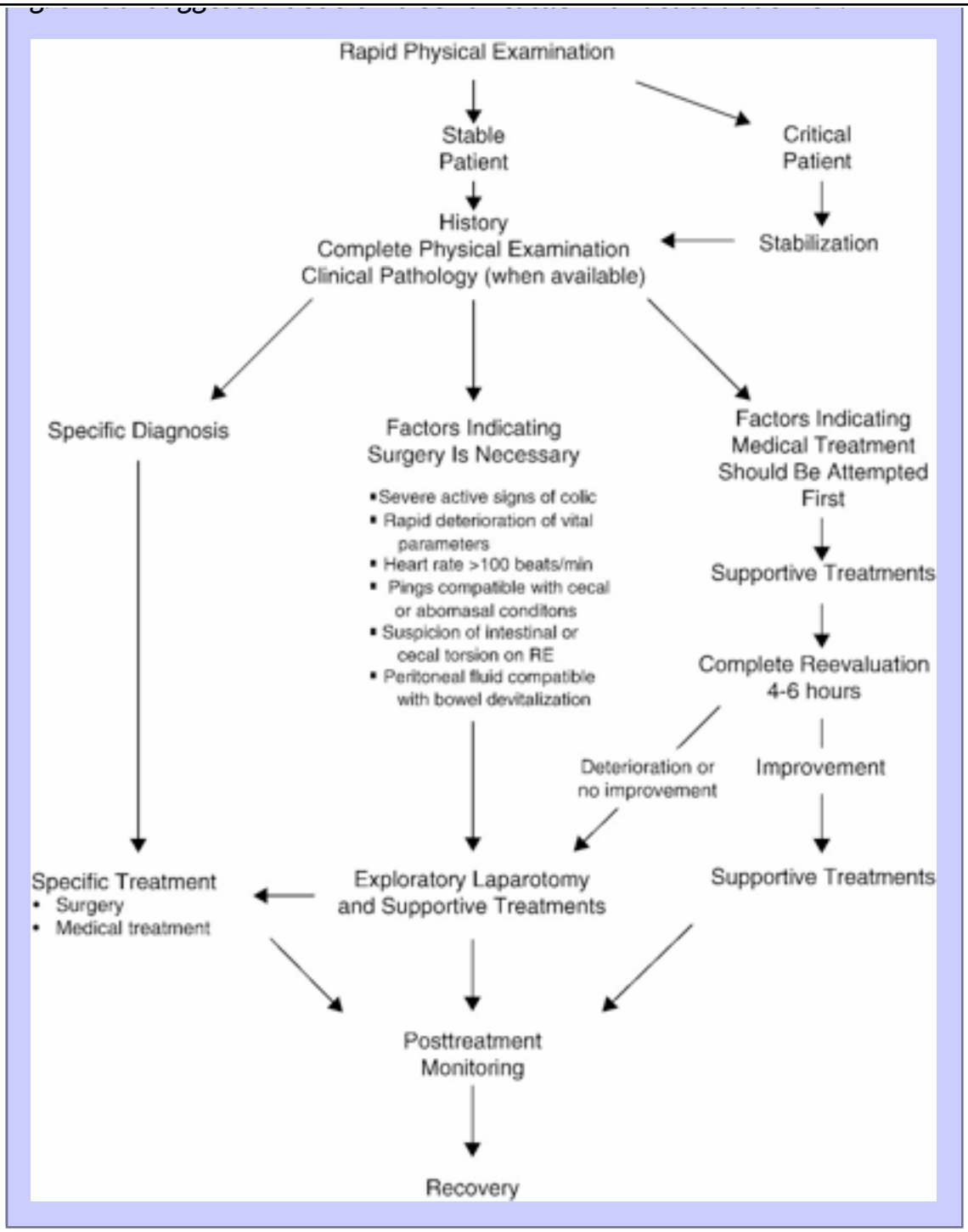
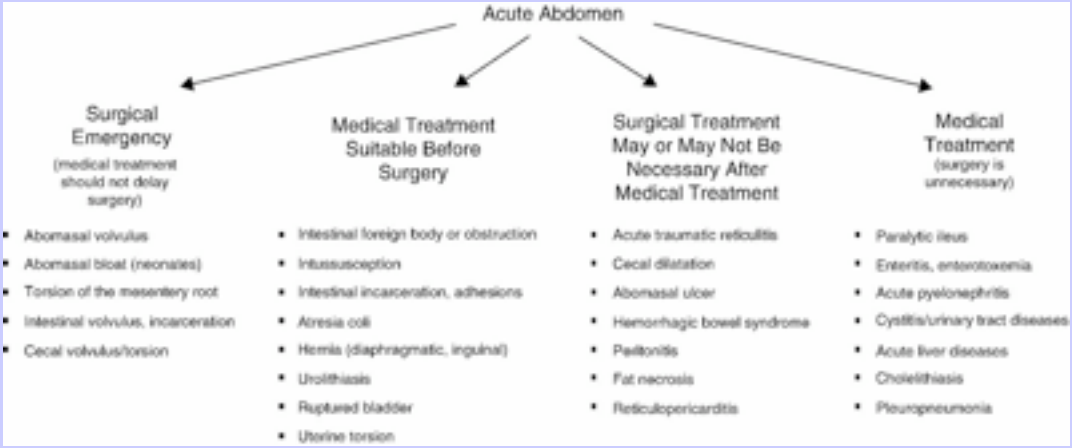


Fig. 32-97 Classification of abdominal causes based on the need for

surgical exploration or medical treatment.



32.124.5.2.2

Correction of Acid-Base and Electrolyte Imbalances

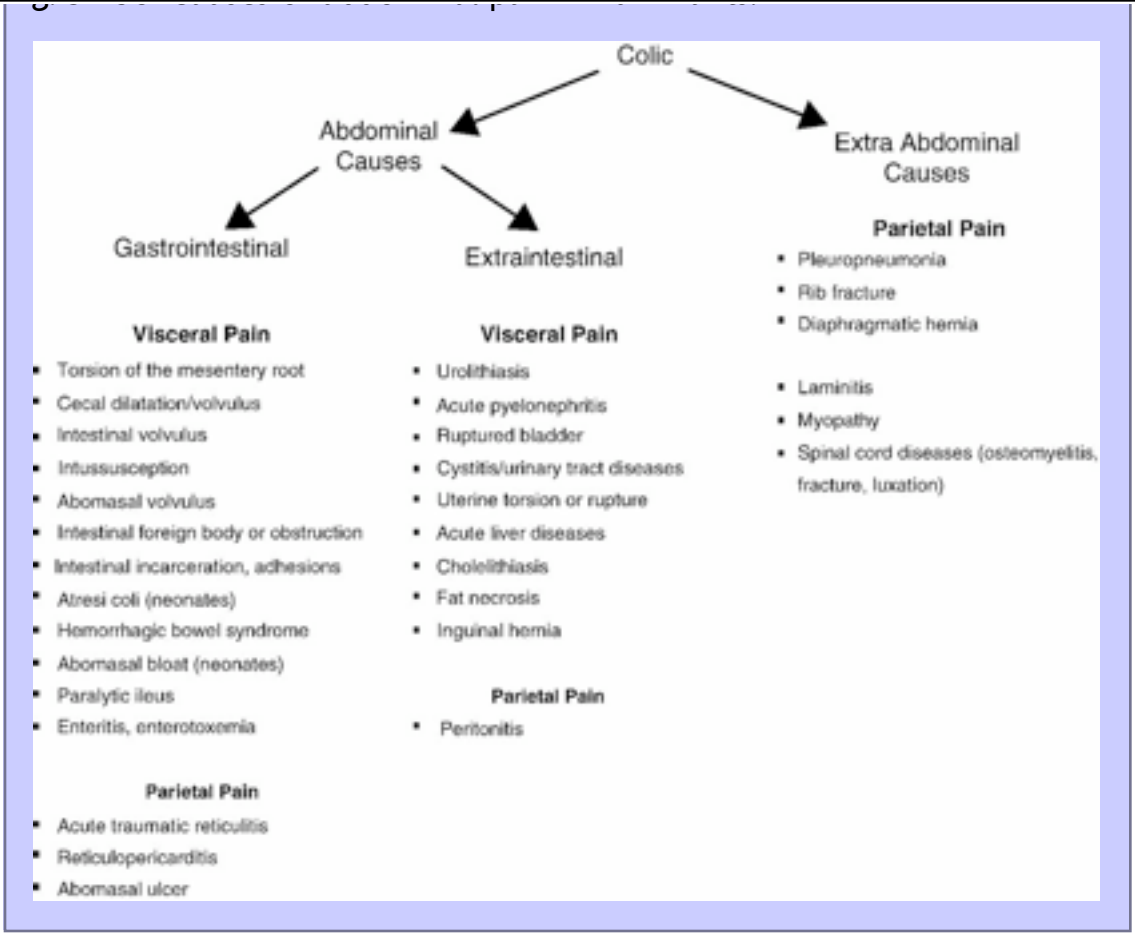
Correction of electrolyte imbalances should be based on laboratory results when available. Previous treatments should be considered (e.g., intravenous calcium, orally administered magnesium hydroxide) to initiate the most appropriate fluid therapy if no laboratory results are available.[560] Most animals with acute abdominal diseases suffer from metabolic alkalosis, hypochloremia, and hypokalemia.

Calcium homeostasis is in a precarious balance in postpartum dairy cattle. Hypocalcemia is common in anorectic ruminants or in ruminants with gastrointestinal diseases.[560,581] Moreover, metabolic alkalosis, frequently observed in cases of acute abdomen, is strongly associated with subclinical hypocalcemia.[540,586] Calcium ions are of particular importance in gastrointestinal motility. First, in the gastrointestinal smooth muscles, the channels responsible for generating action potentials are calcium-sodium channels.[551] Second, gastrointestinal smooth muscle contraction occurs in response to the entry of calcium into the muscle fiber.[551]

Based on these considerations, the intravenous solutions used for the medical treatment of acute abdomen, secondary to a suspected digestive disorder, should contain Na, Cl, K, and Ca.

The Ringer's solution containing 8.6 g of NaCl per liter, 0.3 g of KCl per liter, and 0.3 g of $CaCl_2$ per liter, yielding 147 mEq/L Na, 155 mEq/L Cl, 4 mEq/L K, and 4 mEq/L Ca, is the commercially available solution of choice. In our clinics in Quebec, we use a beneficial homemade solution composed of 7.5 g of NaCl per liter, 1.5 g of KCl per liter, and 5.75 g of Ca^{2+} per liter (25 mL of 23 % calcium borogluconate per liter), yielding 128 mEq/L Na, 148 mEq/L Cl, 20 mEq/L K, and 26 mEq/L Ca, for adult cattle. We usually begin our fluid therapy with rapid administration of a 0.9% NaCl solution (15 to 20 mL/kg/h, which is the highest rate possible through a catheter) for rapid correction of dehydration and then administer this homemade solution with an infusion rate of approximately 4 to 5 mL/kg/hr.

Fig. 32-98 Causes of abdominal pain in ruminants.



32.124.5.2.3

Control of Pain and Inflammation

Pain and inflammation are important causes of gastrointestinal hypomotility (Fig. 32-98). Gastrointestinal pain increases sympathetic tone, causing general inhibition of the gastrointestinal tract.[551,587,588] Numerous inflammatory mediators are released during disease of the gastrointestinal tract, leading to alteration of intestinal motility.[587,589] Peritoneal inflammation or irritation and associated pain are well-recognized initiating factors of ileus in multiple species.[587,589] Release of proteinases, vasoactive substances, free oxygen radicals, and endorphins secondary to ischemia and reperfusion injury, or to endotoxemia, impairs cardiovascular function and decreases gastrointestinal motility.[589] Inflammatory mediators lead to a pain response and modulate the intensity of noxious stimuli.[588,587] Consequently, analgesic and antiinflammatory drugs appear essential in the management of acute abdomen. These drugs must be used with caution. NSAIDs may induce abomasal ulcers, particularly in an anorectic patient. Analgesics may mask clinical signs (pain, fever) and compromise adequate case management by delaying surgery.

NSAIDs are the most commonly used drugs for gastrointestinal pain management in cattle. There is no information comparing the efficacy of the different NSAIDs available in food animal medicine related to their use in the management of acute abdomen. Some authors report that, based on clinical observations, flunixin provides an excellent visceral analgesia.[590] Ketoprofen and flunixin appear to have similar activities in endotoxic calves.[591] Consequently, no single NSAID can be recommended based on scientific

activities in endotoxic calves.[588] Consequently, no single NSAID can be recommended based on scientific evidence for the management of abdominal emergencies in cattle. The choice of NSAID becomes a matter of previous experience, comparative medicine, legislation, and cost. In our experience, flunixin and ketoprofen are both adequate for the management of acute abdomen in cattle. In equine gastrointestinal pain, a poor or short duration response to NSAIDs indicates a need for surgery.[588] This principle can be applied to cattle with caution because of their unpredictable behavior in response to pain.

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α_2-Agonists that function as sedatives and analgesics, such as xylazine, detomidine, and medetomidine, could also be used to relieve pain in cases of acute abdomen. All are considered to be strong analgesics that can alleviate most visceral pain, at least temporarily, in equine medicine.[588] There are few data on the use of α_2-agonists for the management of acute abdomen in cattle. In a cow with a large intestinal obstruction, signs of abdominal discomfort disappear immediately after the administration of a single dose of xylazine (0.05 mg/kg IV) for at least 1 hour.[592] Different side effects must be considered before the administration of alpha-2 agonists. Xylazine is reported to have significant effects on the gastrointestinal tract in cattle, decreasing reticuloruminal and intestinal motility.[593] Because of the hemodynamic changes associated with the administration of α_2-agonists, these drugs must be used with caution in patients with arterial hypotension and/or shock.[594] α_2-agonists can mask surgical pain and delay the decision for surgery. This is particularly critical with the use of detomidine.[588] Finally, dose and administration of α_2-agonists should be used with care if standing surgery is planned.

32.124.5.2.4

Antimicrobial Drugs

Bacterial translocation from the intestines can occur in cases of mechanical or functional ileus secondary to bacterial overgrowth, inflammation, and impairment of barrier function of the intestinal wall.[555,595] A systemic broad-spectrum antibiotic treatment should be instituted when a septic process is suspected, until bacterial culture results become available. This initial antibiotic therapy should be effective against gram-negative, gram-positive, aerobic, and anaerobic pathogens. The choice of antibiotic should also take into consideration legal aspects and the cost of the treatment. β-Lactams, tetracyclines, and trimethoprim-sulfadoxine appear to be good choices. In cattle there is no accepted recommendation for the duration of treatment. In human medicine, prolonged broad-spectrum antibiotic therapy in case of surgical acute abdomen does not appear beneficial.[596] Prevention of infective complications was not affected by prolonging the course of antibiotic treatment.[596] In human medicine the current recommended dose is a single prophylactic antibiotic administration when there is no or minimal evidence of contamination, and 5 to 7 days when pus or contamination, either localized or diffuse, is present.[596]

32.124.5.2.5

Other Treatments

The use of purgatives (magnesium hydroxide, mineral oil, liquid paraffin) in cases of suspected gastrointestinal obstruction or ileus in cattle has no therapeutic basis.[557] Moreover, these treatments may exacerbate the condition. Because the intestines are already filled with gas and fluid, purgatives only impose additional distention. In human medicine, laxatives are frequently used for the treatment of postoperative ileus (POI); however, no study could demonstrate their actual benefit.[597] Braun and colleagues reported that the use of purgatives for the treatment of cecal disorders delayed the time to first defecation.[555] Moreover, magnesium hydroxide may be responsible for detrimental effects such as metabolic alkalosis,[598] sedation caused by hypermagnesemia,[598] increased ruminal pH,[599] and decreased

metabolic alkalosis,[—] sedation caused by hypermagnesemia,[—] increased ruminal pH,[—] and decreased ruminal microbial activity.[599]

Motility-modifying agents may be used in the management of gastrointestinal disorders. In most cases intestinal motility is restored when pain is relieved and electrolytic imbalances are corrected. Steiner reviewed the different prokinetics that can be used in ruminant medicine and their clinical implication.[593] For cattle, he recommends the use of bethanechol (0.07 mg/kg SC tid for 2 days; not approved for food animal use in the United States) alone or in combination with metoclopramide (0.1 mg/kg SC or IM tid for 2 days; not approved for food animal use in the United States), or erythromycin in polyethylene glycol (10 mg/kg IM bid for 2 days, Erythro-200) for the postoperative treatment of right abomasal displacement or torsion.[593] Bethanechol (0.07 mg/kg SC tid for 2 days; not approved in the United States) can be used for conservative or postoperative treatment of cecal disorders and treatment of paralytic ileus.[593] Contrary to cattle and sheep, in goats metoclopramide (0.5 mg/kg IM or IV; not approved in the United States) has been reported to significantly increase myoelectric activity of the duodenum.[593] Continuous infusion of neostigmine (87.5 mg in 10 L of sodium chloride-glucose infusion at 2 drops/sec per cow) was successfully used for the conservative and postoperative treatment of cecal disorders.[555] In this clinical report, this protocol was preferred to those previously reported (neostigmine SC every hour over 2 to 3 days in doses that gradually decreased from 12.5 mg to 2.5 mg).[555] Drug administration was easier and involved fewer disturbances for the animal.[555] However, no control group was included in this study. Also, neostigmine has been reported to have a pronounced effect on intestinal contractility, causing uncoordinated spikes to become more frequent, thereby compromising the potential beneficial effect.[600]

No prokinetic drug is reported to directly increase ruminal motility. In cases of prolonged anorexia or acute indigestion, ruminal flora can be disturbed and reduced. Transfaunation may help to rapidly reconstitute the ruminal flora and hasten return to normal function of the rumen and the digestive tract. The technique for and beneficial effects of transfaunation (reduction of ketonuria, increased feed intake, and higher milk yield) have been reported in the postsurgical treatment of left abomasal displacement.[601]

32.124.6 Follow-Up

When a definitive diagnosis cannot be made, a close monitoring of the animal may be indicated. Follow-up must also be performed secondary to surgery to ensure adequate response to surgical treatment and to allow possible adjustment of treatment. In a referral hospital the animal should be reevaluated every 4 to 6 hours. In field practice, vital parameters, rectal examination, presence and consistency of feces, and pain may be reevaluated every 6 to 12 hours. A significant reduction of heart rate was observed 4 and 6 hours after the initiation of treatment in cases of cecal dilatation.[555] Feces are passed within 4 to 6 hours after surgery in cases of intestinal volvulus[546] or cecal disorders.[555] Failure to defecate for 24 hours or more is abnormal in cattle and therefore indicates persistence of intestinal obstruction and may adversely affect the prognosis.[557] Deterioration or persistence of clinical signs despite the initiation of supportive treatment is also an indication for surgery. Surgical exploration is indicated if the following clinical signs are observed: persistence of colic, development of abdominal distention, heart rate over 100 beats/min, scant feces, typical abomasal or cecal pings, or paracentesis indicating bowel devitalization.

The decision for surgery or medical treatment remains challenging in cases of acute abdomen in ruminants.

Optimal management of acute abdomen prevents any unnecessary delay in cases requiring surgery and avoids unnecessary surgery. Knowledge of diseases associated with signs of acute abdominal pain is important, but no clinical signs are specific for a particular problem, and a specific diagnosis cannot be established postoperatively in many cases. Based on a systematic approach to clinical examination and a judicious use of ancillary tests, the clinician may be able to identify cases that require immediate or delayed surgery, avoid unnecessary surgery, and establish a cost-effective management plan.

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32.125 TRAUMATIC RETICULOPERITONITIS (HARDWARE DISEASE, TRAUMATIC RETICULITIS)

David Francoz

Charles L. Guard

32.125.1 Definition and Etiology

TRP or hardware disease is a common disease of cattle but is rarely seen in small ruminants. It is the most common cause of anterior abdominal pain in cattle. The ingestive behavior of cattle predisposes them to the accidental swallowing of metal foreign objects that settle in the reticulum. Ingestion of a foreign body may also be associated with diseases that cause pica, such as phosphorus deficiency. Subsequently, the foreign object may enter the reticulum and (1) attach to a magnet without clinical diseases; (2) penetrate the reticulum wall only with intramural inflammation; (3) perforate the reticulum wall, penetrate into the peritoneal cavity, and create localized peritonitis; or (4) migrate into the peritoneal and thoracic cavities.[602] The diaphragm, pericardium, and heart muscle are located just cranial to the reticulum, with the liver positioned medially and dorsally and the spleen laterally and dorsally. These organs may sometimes be penetrated by foreign bodies and become involved in the inflammatory process.

32.125.2 Clinical Signs and Differential Diagnosis

TRP in the most severe, acute form is characterized by fever, anorexia, decreased or absent ruminal contractions, and evidence of cranial abdominal pain. Pinching of the withers or upward pressure on the xiphoid region may elicit a grunt on expiration. Affected cattle may stand with an arched back and resist ventral flexion of the back when pinched over the withers (normal cattle flex ventrally). Some cattle grunt spontaneously when forced to move or when defecating or urinating. Lactating cows show a sudden decrease in milk production.[603,604] Some cows regurgitate ruminal fluid, especially if the oropharynx is mechanically stimulated. Tachycardia, reluctance to move or lie down, mild bloat, constipation, or abducted elbows may also be seen. These typical signs often abate within the first day or two, making diagnosis more difficult. Auscultation may reveal a pounding heart or muffled heart sounds bilaterally if pericarditis with effusion has developed by the time of examination. Sudden death has occurred as a result of the laceration of a coronary blood vessel or puncture of the heart by the foreign body.

Less severe or more long-standing cases may have signs that are more subtle and confusing. Cows in early lactation may have ketosis; however, a distinguishing feature of hardware disease is the abrupt onset of anorexia and hypogalactia. Fever may be absent. Weight loss, rough hair coat, diarrhea, or generalized lameness, along with cranial abdominal pain that is difficult to localize, may be the only signs.

If the pericardial sac has been seeded with bacteria, pericarditis usually develops. There is no initial change in

heart sounds, but over a period of several weeks as septic fluid accumulates, the heart may become muffled. When there are both fluid and gas in the pericardium, sloshing sounds like a washing machine may be auscultated. Distended jugular and superficial abdominal veins and other signs of congestive right-sided heart failure are most common after pericardial effusion. Dyspnea may occur if left-sided failure is also present.

The foreign body may penetrate the liver or spleen, leading to abscess formation. These abscesses as well as reticular adhesions may be responsible for ruminoreticular outflow problems and may lead to vagal indigestion.[605] These are further discussed with vagal indigestion.

TRP must be differentiated from other causes of cranial abdominal pain. They mainly include abomasal ulcers, hepatic abscesses from other causes, and pleuritis. More informations about the differential diagnosis of abdominal pain is presented in the section on acute abdomen in cattle. When thoracic structures are involved, TRP must be differentiated from primary pneumonia or pleuritis, diaphragmatic hernia, and heart diseases such as endocarditis, lymphosarcoma of the heart, and cor pulmonale. Finally, TRP must be differentiated from others causes of ruminal distention and vagal indigestion.

32.125.3 Clinical Pathology

The WBC count and differential, as well as the determination of plasma proteins and fibrinogen, may indicate an acute or chronic inflammatory process depending on the stage of the TRP. Neutrophilia and a left shift are expected in acute cases. However, in more chronic cases changes are less pronounced, and WBC count as well as differential may be normal.[602,606] High fibrinogen concentration may be observed in acute cases (2 to 3 days after the beginning of the disease) and chronic active cases. Studies in referral centers[607,608] have demonstrated highest plasma fibrinogen concentration with TRP compared with other abdominal disorders. High total plasma proteins, primarily reflecting high globulin levels, were expected in chronic cases of TRP. Higher concentrations of total plasma proteins have been observed in cases of TRP compared with other abdominal disorders.[607–609] Plasma protein concentration cutoff points of 87 to 100 g/L have been proposed in these studies. All the results of the studies demonstrated that high values of plasma fibrinogen and plasma protein concentrations are highly suggestive of TPR. However, other disorders can induce the same modifications, and absence of these abnormalities does not rule out TRP. Consequently, other diagnostic tests (diagnostic imaging) must be performed to confirm the diagnosis. Biochemical profile and blood gas analysis are usually within normal range but may reflect hypochloremic metabolic alkalosis associated with ileus and dysfunction of the abomasum.

Radiography and ultrasonography of the reticulum are very useful for the diagnosis of TRP. Radiographs of the reticulum are limited to referral centers. They are performed on standing animals and allow the detection of a metallic foreign body and the determination of its location in or outside the reticulum. Different parameters may be observed on radiographs for the diagnosis of TPR. They include presence or absence of a foreign body, position of the foreign body, presence of focal gas shadows or gas-fluid interface near the reticulum, and the shape, size, and location of the reticulum.[610–612] Of these parameters, location of the foreign body is the most reliable indicator for the diagnosis of TPR.[610,612] Ultrasonography of the reticulum is presented elsewhere in this chapter. Ultrasonography and radiography are two complementary methods that provide different useful information for the diagnosis and the management of TPR.[613] Ultrasonography is also the most useful complementary examination for the diagnosis of pericardial effusion.

Abdominocentesis and pericardiocentesis may be performed blind or with ultrasound guidance. Abdominal fluid

analysis and its limitations in cattle are discussed in the section on peritonitis. Pericardiocentesis may be performed at the level of the point of the elbow in the fifth left intercostal space. Aseptic preparation of the skin and local anesthesia of the region to be punctured are required; pulling the left forelimb forward may be helpful. A 5- to 10-cm spinal needle or intravenous catheter can be used; the length required depends on the size of the 849
animal and the amount of subcutaneous fat. Previous ultrasonographic examination is helpful for the choice of 850
the needle. Caution is advised when advancing the needle to prevent laceration of the myocardium. Ultrasound-guided centesis prevents trauma to the myocardium. Visual inspection of the fluid obtained is usually adequate to confirm the diagnosis of pericarditis; it is cloudy and foul smelling. The fluid may be examined bacteriologically and cytologically.

If ileus occurs or vagal indigestion develops, analysis of the ruminal fluid may reveal elevated chloride ion concentration as a result of reflux from the abomasum and omasum.

32.125.4 Pathophysiology

The indiscriminant eating habits of cattle lead to accidental consumption of foreign bodies. Those that are of high specific gravity initially settle to the bottom of the ventral sac of the rumen. Subsequent contraction cycles of the forestomach move those objects from the rumen into the reticulum. If the object is large enough and sharp enough, it can be pushed, most often through the cranial wall of the reticulum, by the forceful, normal reticular contractions. Normal forestomach bacteria leak through the hole thus created and may establish infection locally along the foreign body. Infection also may spread as in the pericardium or locally during abscess formation. The pain and inflammation associated with the trauma and infection lead to decreased appetite and ruminal hypomotility or stasis. Agalactia is abrupt because of the acute anorexia and subsequent failure to absorb precursors for milk synthesis.

Rehage and colleagues[605] demonstrated that the disturbances of digesta through the forestomachs and the abomasum in cows affected with TRP develop in three phases. The first one, characterized by poorly comminuted feces, occurs secondary to virtual immobilization of the reticulum caused by pain and inflammatory adhesions. With extension of the adhesions, additional impairment of reticulum motility develops. At this time, stratification of the food particles in the reticulorumen is lost, volume of these two forestomachs is increased, and ruminal outflow is inhibited. Finally, the consistency of ruminal contents is changed to a pasty mass with high viscosity. Increase in viscosity of ruminal outflow leads to inhibition of the transpyloric outflow. At this time, abomasumal volume increases and internal vomiting occurs.

32.125.5 Epidemiology

The ingestive techniques of cattle allow sharp nonfood items to be prehended and swallowed. Ingestion of such items by sheep or goats is extremely rare. The disease affects confined cattle where mechanical processing of forages or construction activities increase the chances that wire or nails will be included in the feed. Most cases are sporadic, but outbreaks have occurred when such things as multistranded cable have been chopped up by a forage harvester and ensiled.

32.125.6 Necropsy Findings

Cattle that die peracutely may have a lacerated myocardium with resulting hemorrhage or cardiac tamponade. Diffuse peritonitis characterized by copious, foul-smelling peritoneal fluid with an obvious reticular defect may be seen in acute cases. More chronically affected animals may have extensive pericardial effusion with a thick epicardial layer of fibrin. The penetrating foreign body generally is still present in the wall of the reticulum or pericardium.

32.125.7 Treatment and Prognosis

Conservative treatment generally is attempted first and includes the administration of a forestomach magnet, parenteral antibiotic therapy, and confinement. Often the animal is confined to a stanchion or box stall. Many cattle recover after such a course of therapy with resumption of forestomach motility and appetite within 1 to 3 days. Different drugs have been used to enhance the chance of the magnet to enter the reticulum cavity. The effects of premedication with atropine, scopolamine, or xylazine and of standing the cow with its forelimbs 30 cm lower than the hindlimbs on successful administration of a magnet (i.e., adequately located in the reticulum cavity) have been evaluated in healthy cows.[614] Adequate location of the magnet was evaluated radiographically 1½ hours after the administration of the magnet. None of the procedures increased the chance of the magnet being successfully placed in the reticulum. Moreover, in all groups (treatment groups and control groups) only 57% of the magnets were adequately located in the reticulum.[614] Braun and co-workers demonstrated that foreign bodies that have penetrated the reticulum wall or that have clearly perforated the reticulum had about 54% and 32% chance, respectively, to become attached to the magnet.[615] Animals that have not significantly improved by the third day may require a rumenotomy to remove the foreign object. Ideally, radiography combined with ultrasonography is recommended at this time to verify the diagnosis and objectively assess the response to treatment, but ultrasonography alone is most feasible in most practices.[615]

During rumenotomy, abscesses that are tightly adhered to the reticulum may be drained into the lumen of the reticulum.[616] In some instances reticular abscesses may also be drained through an ultrasound-guided transcutaneous incision,[617] ultrasound-guided insertion of a chest trocar, or insertion of a trocar during ventral laparotomy.[602] Treatment of peritonitis requires systemic antibiotic therapy and possibly drainage of the affected area; surgical correction of the inciting cause is discussed in the section on peritonitis.

32.125.8 Prognosis

The prognosis of TRP depends mainly on the location of the foreign body and the other organs affected. The prognosis is fair to good when TRP is associated with localized peritonitis and when only the spleen or the liver is also affected. In most cases as inflammation diminishes, the reticular function can return to normal.[618] The prognosis is poor to guarded in TRP associated with pericarditis, pleuritis, or diffuse inflammatory adhesions in the abdomen.[602,618]

32.125.9 Prevention and Control

Eliminating sources of sharp foreign objects in the feed supply prevents TRP. Installation of large magnets on feed handling equipment and prophylactic administration of forestomach magnets to all animals at 6 to 8 months of age prevent almost all cases caused by magnetizable objects.

32.126 PERITONITIS IN THE RUMINANT

Gilles Fecteau

Despite the frequency with which peritonitis is included in a list of differential diagnoses, it remains a very frustrating disease for all food animal clinicians. A diagnosis is often based on clinical signs and history and rarely confirmed by ancillary tests. If the patient improves with treatment, the clinician may never identify the cause of the peritonitis.

32.126.1 REVIEW OF PERITONEAL CAVITY

32.126.1.1 Histology

The peritoneal cavity is lined by a serous membrane composed of two layers called the *peritoneum*. The deeper layer (subserosa) is composed of loose connective tissue containing collagen, fat cells, reticular cells, and macrophages.[619] Covering that layer is a single-surface layer of mesothelial squamous cells (serosa). On the surface of the diaphragm, special lymphatic collecting vessels are located under the mesothelial basement membrane. Small stomata are found between mesothelial cells. They act as channels for lymphatic drainage from the peritoneal cavity to the thoracic duct.[620–622]

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32.126.2 Normal Peritoneal Fluid

The peritoneum is a highly permeable membrane. Most of it acts as a bidirectional semipermeable barrier to the diffusion of water and low—molecular-weight solutes between the blood and the peritoneal fluid.[620–624] Peritoneal dialysis uses this principle to treat renal failure. Normal peritoneal fluid provides lubrication for the movement of abdominal organs and apposed peritoneal surfaces.[625] It is formed and resorbed constantly. Normal fluid movement is achieved by normal movement of the viscera and contraction of the diaphragm during respiration. A normal animal has no more than 1 mL of peritoneal fluid per kilogram of body weight.[624] In acute severe peritonitis, the inflammatory process may induce a net flow of liters of proteinaceous fluid (80 mL/kg/day in humans), leading to hypoproteinemia and/or hypovolemic shock.[620]

Normal peritoneal fluid has a wide range of values.[622,626–629] It should be clear, with a specific density less than 1.016 (Table 32-17). Protein content should be less than 3 g/dL, although some authors have reported normal values up to 6.3 g/dL for cattle.[629] Normal bovine peritoneal fluid may contain some fibrinogen and may clot when exposed to air.[630] Normal fluid contains fewer than 10,000 cells with a majority of macrophages. Lymphocytes, eosinophils, and desquamated mesothelial cells may also be present, but there are normally very few neutrophils. Normal periparturient cattle have significantly more abdominal fluid with a lower protein concentration.[630] With peritonitis there may be a complete absence of collectable peritoneal fluid because of dehydration or fibrous adhesions.

Table 32-17 Normal Range for Classification of Bovine Peritoneal Fluid According to Different Authors

Parameters	Normal Values	References
Turbidity	Clear	
Total protein (g/dL)	0.1–3.1	626,629
	2.2–4	626
	1.2–6.3	633
Specific gravity	1.005–1.015	629
Total cell count (per µL)	425–2950	633
	2000–5000	629
	<10,000	626
Differential	Ratio 1:1, neutrophils to mononuclear cells	626
Neutrophils	45–2183	633
Lymphocytes	8–168	633
Mononuclear cells	36–960	633
Eosinophils	5–545	633
Comments	Eosinophils may predominate	626
	Serosa cells may predominate	629

32.127 PATHOPHYSIOLOGIC MECHANISM OF DISEASES IN THE PERITONEAL CAVITY IN RESPONSE TO INJURY

32.127.1 Healing

Peritoneal regeneration is completed within 5 to 7 days, regardless of the defect size. Healing can occur by reperitonealization or creation of an adhesion with an adjacent nearby mesothelial surface. This adherent type of healing occurs more frequently if the inflammation is severe, with presence of bacteria and/or foreign material.[620,621,624]

32.127.2 Host Defenses Against Peritoneal Infection

The first mechanism of defense is physical removal of the bacteria. In normal dogs, for example, it is possible to retrieve bacteria in the bloodstream 12 minutes after an experimental injection into the peritoneum.[624] The second mechanism of defense relates to the response to noxious stimuli. This intense acute inflammatory response includes degranulation of peritoneal mast cells with release of vasoactive substances. This creates a net influx of fluid rich in complement and serum opsonins that can bind to the bacteria.[620,621,624] Third, the

omentum contributes to the defense mechanism by adhering to an infected and/or damaged area to wall off the problem site. Finally the rapid movement of neutrophils, and later, macrophages, is also an important mechanism of control of infection.[624]

32.127.3 Adhesions

Adhesions are defined as fibrinous or fibrous bands that create an abnormal attachment of two or more surfaces that should be moving freely against each other. Formation of adhesions is part of the healing process and should be interpreted as an effort to control an injury. The omentum is often involved in adhesions and acts as a natural sealing device to control the acute phase of inflammation. Whole blood potentiates adhesion formation by providing more fibrinogen.[620] The various suture materials are approximately equal in their capacity to induce adhesions, with chromic gut perhaps inducing the most reaction.[620] Adhesion may or may not be reversible, depending on the amount of organization that takes place in the process. Adhesions that are cut or broken usually rapidly reform. As the fibrin deposition process is replaced by capillaries and fibroblasts, the adhesion becomes solid fibrous tissue. The three major elements responsible for dissolution of the fibrinous adhesions are (1) adequate oxygen and nutrient supply for the mesothelium, (2) liberation of plasminogen-activating substance by mesothelial and submesothelial cells, and (3) control of the inflammatory process.[620,621] Mechanical obstruction to the normal flow of ingesta and subsequent development of bowel obstruction are major undesirable side effects of formation of adhesions.

32.128 PERITONITIS

32.128.1 Definition and Etiology

Peritonitis is an inflammatory process involving the peritoneal cavity and its serosal surface, the peritoneum. Peritonitis is not a true synonym of intraabdominal infection because the latter is defined as an inflammatory response of the peritoneum to microorganisms and their toxins that results in purulent exudates in the abdominal cavity. Peritonitis should be considered as the localized equivalent of SIRS, whereas intraabdominal infection is the localized equivalent of sepsis. Intraabdominal abscess is an intraabdominal infection confined within the abdominal cavity. Because most often in farm animals peritonitis is caused by bacteria, the two terms are often used as synonyms. The inflammation may result from trauma, surgery, or vascular damage associated with an intestinal obstruction and/or accident or from gastrointestinal ulceration (Box 32-8). Peritonitis is a serious and complex process that is often accompanied by various degrees of abdominal pain, progressive signs of hypovolemia and septicemia, and/or endotoxemia.

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32.128.2 Classification

Peritonitis may be classified according to the clinical presentation and/or the cause. Clinically relevant classifications include acute versus chronic, septic versus chemical, localized versus generalized, and primary versus secondary. Although it is useful to classify types of peritonitis, it is imperative to recognize that it is a dynamic process. An apparently localized nonseptic peritonitis can evolve toward a more diffuse septic process if the primary cause is not resolved.

32.128.3 Pathophysiology

After peritoneal injury or contamination, mesothelial cells initiate an inflammatory response, modifying the permeability of the peritoneum and its vascular supply. Several blood constituents are then able to move into the peritoneal cavity. Macrophages and polymorphonuclear cells, humoral opsonins, natural antibodies, serum complement, and a protein-rich fluid are the most important. The inflamed peritoneum also becomes more permeable to toxins, allowing them to be absorbed into the bloodstream. Although this initial response is beneficial to the organism, it induces several systemic abnormalities that the clinician must recognize and treat adequately.

32.128.3.1 **Box 32-8 Causes and Examples of Peritonitis in Approximate Order of Frequency**

32.128.3.1.1 **TRAUMATIC PERFORATION**

Traumatic reticuloperitonitis

Septic abdominal surgery

Vaginal perforation in heifer during coitus

Penetrating wound

32.128.3.1.2 **VISCERAL RUPTURE**

Perforated abomasal ulcer

Perforated ulcer in other part of gastrointestinal tract (oak toxicity of other cause)

Abomasal rupture after torsion

Small intestinal rupture after volvulus, strangulated hernia, intussusception

Ruptured bladder secondary to urolithiasis

Spontaneous uterine rupture during gestation or dystocia

32.128.3.1.3 **ABSCESS FORMATION AND POSSIBLE INTRAABDOMINAL RUPTURE**

Reticuloperitonitis, localized

Liver

Umbilicus

Perimetritis

Pyelonephritis

32.128.3.1.4 IATROGENIC

Intraperitoneal injection of irritant solution or contaminated solution

Uterine rupture during dystocia

Perforation of the uterine wall with a pipette

Rectal tear secondary to palpation

32.128.3.1.5 MISCELLANEOUS

Hematogenous with systemic infection: tuberculosis, septicemia

Fat necrosis

Hypovolemia, hypoproteinemia, bacteremia or septicemia, and toxemia are commonly observed in acute diffuse septic peritonitis. The major adverse effects of peritoneal contamination are (1) rapid clearance of bacteria, producing endotoxemia and/or bacteremia, (2) rapid influx of fluid rich in protein, leading to hypovolemia and hypoproteinemia, (3) deposition of fibrin, occluding lymphatic drainage, contributing to abdominal distention, and enhancing the chance of abscess formation, (4) ileus, and (5) adhesion formation, which may lead to obstruction (Fig. 32-99).

32.128.4 Clinical Signs and Diagnosis

Clinical signs are often nonspecific but suggestive of gastrointestinal dysfunction. Severity of clinical signs ranges from mild recurrent discomfort caused by a localized abscess to an acute severe onset of toxemia and hypovolemia leading rapidly to death after the sudden rupture of a viscus. Cattle suffering from acute peritonitis tend to show more characteristic signs. As the condition becomes less acute, the ability of the bovine to seal the infection will attenuate the clinical signs. Chronic but active peritonitis remains to this day a very difficult

diagnosis to make without ancillary tests. Abdominal rigidity and tenderness, abdominal distention, scleral injection, fever, anorexia, and sudden reduction in milk production are classic but not pathognomonic findings of acute peritonitis. In the acute stage, abdominal pain and the release of catecholamines often lead to a complete gastrointestinal stasis and ileus. The rumen is then completely atonic. Feces are abnormal in quantity and quality. In the acute stage, feces are present in small amounts and often dry. In more chronic cases feces are present with a tendency to be diarrheic. Pain, decreased plasma volume, and endotoxemia often result in persistent tachycardia. Anterior abdominal pain, evaluated by the withers pinch test, may be difficult to interpret. This procedure is based on the normal reflex of the bovine to drop its back when the withers and back are pinched (ventroflexion). Cattle with anterior abdominal pain may be reluctant to ventroflex on withers pinch. You can increase the sensitivity of this test by simultaneous auscultation of the trachea during the manipulation. Production of an expiratory grunt is considered as a sign of pain during ventroflexion. Cranial ventral pressure with the fist, knee, or some other external force (transverse pole under the abdomen) just behind the xiphoid can help identify the presence of pain (expiratory grunt) and even localize it in some cases. It is my impression that one of the most reliable clinical sign of abdominal discomfort in cattle is reluctance to move. Scleral injection, fever, tachycardia, gastrointestinal stasis, and distention are the clinical signs that should be monitored to evaluate peritonitis.

32.128.5

Ancillary Tests

Hematologic findings associated with peritonitis range from a completely normal hemogram to severe leukopenia with degenerative left shift and presence of toxic neutrophils, depending on the severity of the peritoneal contamination. In severe cases variations observed reflect the degree of sepsis and toxemia. PCV tends to increase as proteins decrease. In less severe cases, a neutrophilic leukocytosis and hyperfibrinogenemia are often present. Hematologic analysis has been a useful tool to monitor response to therapy after a diagnosis has been made by other ancillary tests. Immature cells in the peripheral blood and/or leukocytosis were better indicators of recurrence than body temperature in one human study.[631] Plasma fibrinogen concentration is also used to monitor the progress of a particular case.

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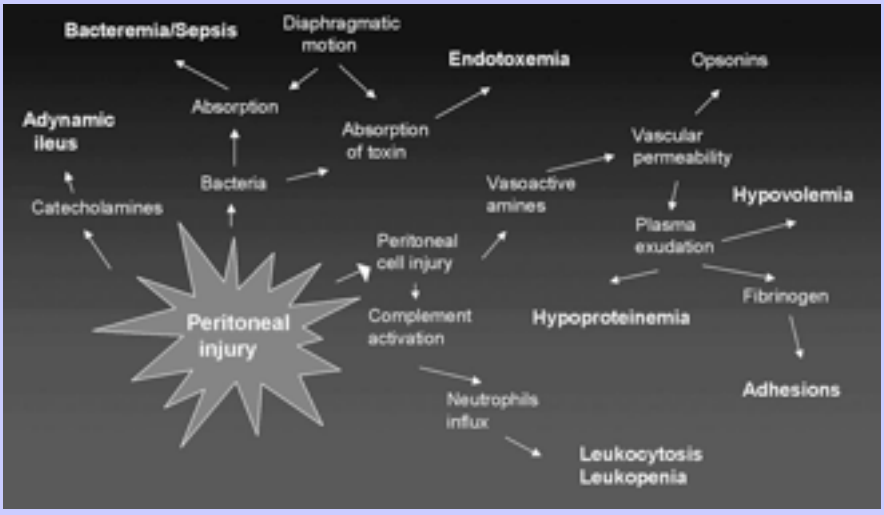
Fig. 32-99 Pathophysiology of peritonitis.



The blood chemistry profile is rarely altered by peritonitis in a way that is diagnostically useful. Chronic

inflammation causes a marked increase in serum proteins, particularly the globulin portion. In acute severe cases, secondary findings may include increased serum urea nitrogen and creatinine, mildly increased liver enzymes, reduction in total CO_2, and strong ion difference and reduction in serum albumin. Ileus and upper gastrointestinal stasis may result in marked hypochloremia and alkalosis.

Cytologic examination of the peritoneal fluid is a useful aid in making a definitive diagnosis of peritonitis (see Table 32-17).[632] Abdominocentesis techniques have been described elsewhere.[630] The right side just cranial to the udder is the preferred site (to avoid stomach and omentum) (Fig. 32-100). A needle, a blunt teat canula, or a bitch catheter and scalpel blade may be used with success (Fig. 32-101). The heavy fascia of bulls makes a needle preferable. It is imperative to remember that failure to secure fluid is common and should be interpreted with caution (because fibrinous peritonitis with fluid loculation is common). More than one site should be attempted if no fluid is secured on the first attempt. Interpretation and classification of peritoneal fluid analyses have been reviewed by several authors.[622,626,627,630] After exploratory celiotomy and omentopexy on normal cattle, peritoneal fluid has increased specific gravity, total protein, and WBCs for at least 6 days, even without any peritonitis.[633] One should remember that because of the bovine's ability to deposit fibrin and seal areas of the peritoneal cavity, the interpretation of peritoneal fluid analysis applies only to the immediate area that was sampled. The clinician can be misled to conclude that a nonseptic process is occurring on the basis of a caudal tap, when in fact a septic process has already been sealed by the fibrin deposition in the cranial abdomen.

Abdominal radiographs using a high-power unit are extremely useful in cases in which TRP is suspected.[634] They have limited value in other causes of peritonitis. A review of radiography of the bovine cranioventral abdomen is available.[635]

Ultrasound examination is useful for assessing the size and anatomic relationships of lesions, particularly when considering drainage, aspiration, or surgical exploration of a mass surrounding vital structures. The reader should see the section on ultrasound in this chapter. Knowledge of the underlying anatomy is important to prevent misinterpretation. Clarity of the image is affected by the size of the probe and the depth of tissue being evaluated. Higher-frequency probes produce finer images but have limited tissue penetration. Images reflect the echogenicity of the tissues viewed; relative echogenicity helps to differentiate structures. Abscesses can have mixed echogenicity, varying from anechoic (absence of internal echoes) to echogenic, depending on the relative amount of fluid, fibrin, and gas. The fibrous capsule of abscesses may be identified as echogenic bands around the area in question. Ultrasound is particularly useful for evaluating the integrity of the body wall for presence of hernias resulting from traumatic injuries, secondary to abscessation or incision dehiscence. Normal and abnormal appearances of umbilical structures have been described.[636,637] Recognition of free abdominal fluid is easily accomplished by ultrasound examination, and it is also useful to guide a peritoneal tap. Areas that should be scanned include the caudal lower flank area (right and left), right perirenal area, liver, abomasum and pylorus, and right paramedian area. Normal liver and liver abscess formation have been described.[638,639] References are available to describe normal appearance of the reticulum and the small intestine in cows.[640,641] During exploratory surgery, ultrasound can be used to image an internal mass or a viscera appearing abnormal. Intraoperative ultrasound is performed by placing the probe in a sterile sleeve filled with ultrasound gel.

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Fig. 32-101 Material used to perform abdominocentesis of the bovine.

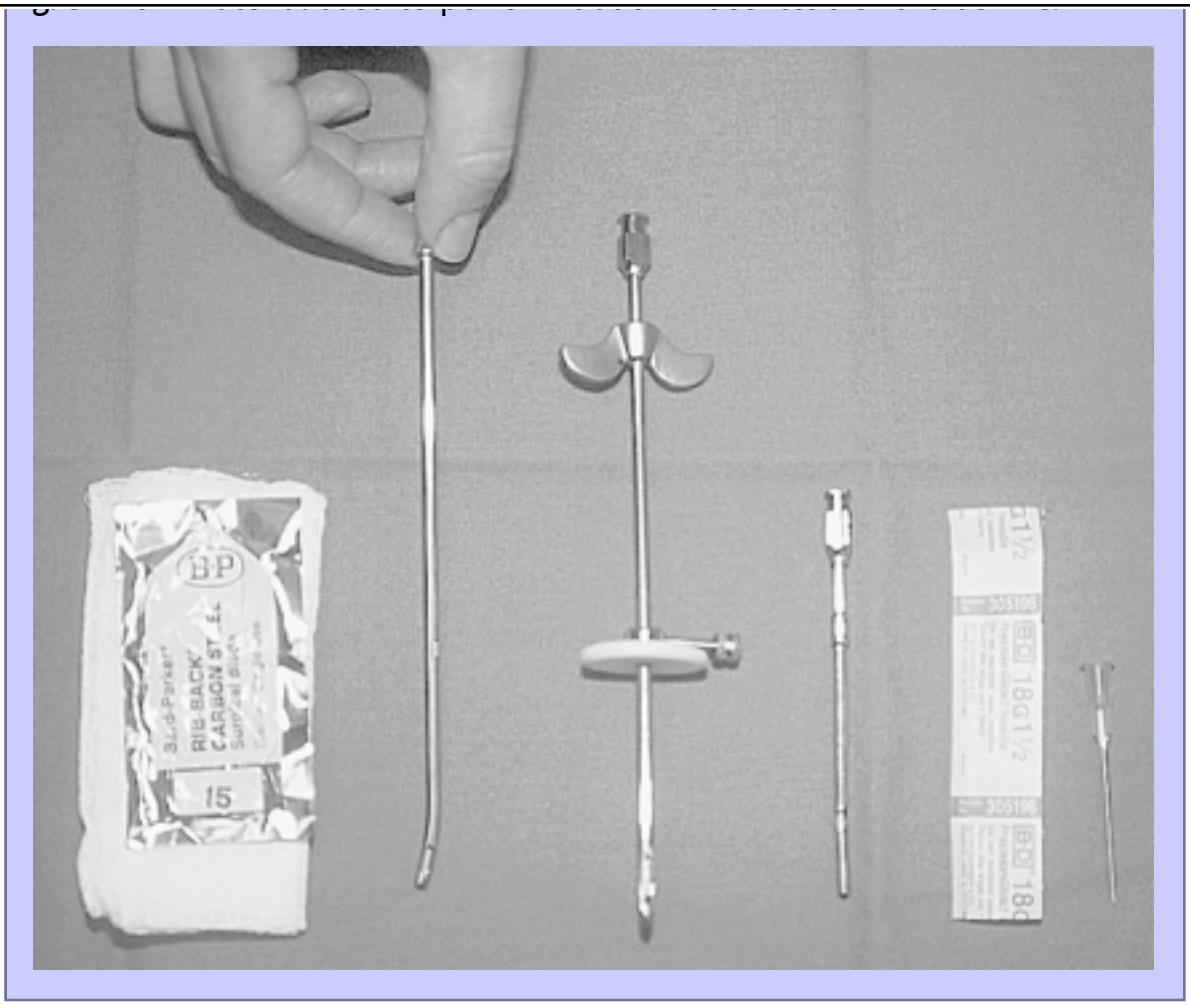

Fig. 32-100 Site of caudal abdominocentesis.

Surgical exploration is often used to confirm or rule out an intraabdominal problem.[642] Information obtained from physical examination and laboratory data is often indicative of a diagnosis but does not provide a specific cause. Cattle are particularly amenable to exploratory surgery, as the procedure is performed when they are standing and is not often associated with complications. Recent advances in minimally invasive surgical technique in cattle are promising. Laparoscopy can be used to diagnose acute and chronic peritonitis, which is otherwise difficult to identify with ultrasound or abdominocentesis. It is easier to evaluate the extent of the lesions with the organs in situ.[643]

32.128.6 Treatment

The basic elements of therapy are support, antibiotics, and surgery.

32.128.6.1 Supportive Therapy

Depending on the severity of the process, the patient may be presented in shock. Large volumes of isotonic intravenous fluids are then indicated. Correction of any acid-base deficit is indicated. Electrolyte abnormalities (hypokalemia and hypocalcemia) should be identified and corrected. If the animal is hypoproteinemic, plasma or whole blood transfusions may be beneficial. Nonsteroidal and/or steroidal antiinflammatory drugs may be of importance to prevent the synthesis of more inflammatory mediators. Pain control is also important. Transfaunation may be beneficial in cases of prolonged anorexia. In one study, ruminal transfaunation was shown to reduce ketonuria and increase feed intake and milk yield after surgical correction of left-displaced abomasum (LDA).[644]

32.128.6.1.1 Antibiotic Therapy

Systemic antibiotic therapy should be instituted as soon as a decision to treat is made. Until results of culture and antimicrobial susceptibility become available, a broad-spectrum antibiotic should be used. The choice should take into consideration the following: cost of treatment, withdrawal period in food animals, spectrum of activity, and treatment regimen (frequency and route). Tetracycline or a β-lactam antibiotic (third-generation cephalosporin or a synthetic penicillin) appears to be a good choice. Diffusion into the peritoneal cavity is not a major limiting factor, because the permeability of the peritoneum is always increased in peritonitis. However, when fibrin becomes organized and forms multiple small pockets of infected peritoneal fluid, then diffusion becomes more problematic. In human medicine, single antimicrobial therapy with a broad-spectrum agent is effective in patients suffering from secondary peritonitis.[645,646]

32.128.6.1.2 Surgical Therapy

Surgical control of peritonitis includes peritoneal debridement and irrigation and drainage. Using ultrasound guidance, it is possible to safely establish drainage from the abdominal cavity. A thoracic chest trocar can be used temporarily until all fluid has been removed.

The concept of abdominal lavage during surgery was adopted by human surgeons around the turn of the century and has been accepted as a part of the treatment of peritonitis since then with fluctuating support.[647] Although the principle of removal of any gross contamination is not in question, the level of aggression with which we should institute abdominal lavage during surgery is still open to debate in human and veterinary literature. There is evidence of negative effect of lavage on the mesothelial cells, the peritoneal defense mechanism, and the risk of spreading the infection.[647,648] The solution used to irrigate is also under debate. There is no significant advantage to adding antibiotics to the lavage solution[647,648] and controversy regarding the possible advantages of adding an antiseptic.[647] In our experience, drainage of the abdomen with Foley catheters or negative pressure drains has been consistently unsuccessful in the bovine. Large amounts of fibrin may be deposited in a short period of time; in combination with the omentum, this makes those drains plug and become rapidly ineffective.

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32.128.6.1.3 Prognosis

The ultimate outcome of a bacterial peritonitis episode is determined by many factors, some of which are controlled by the clinician. The early decision on treatment (medical and surgical), correct choice of antimicrobials, and adequate supportive therapy contribute to the success or failure of a therapy. The owner's delay in seeking therapy, the primary cause of peritonitis, and the patient's age are examples of important factors beyond the clinician's control. When aggressive therapy is economically possible, survival rates will be good, but long-term sequelae may compromise a complete recovery.

32.129 MISCELLANEOUS CONDITIONS

32.129.1 Ascites

Ascites is a collection of serous fluid in the peritoneal cavity. It must be considered as a secondary sign rather than a primary diagnosis.[649] In that regard the primary cause must be identified in order to treat the patient adequately. Common causes of ascites in ruminants include severe liver disease and congestive right-sided heart failure. Young cattle with mesothelioma have remarkable ascites. Ascites remains an uncommon condition that needs to be differentiated from septic causes of peritonitis and from urine accumulation with ruptured bladder.

32.129.2 Pneumoperitoneum

Pneumoperitoneum is commonly observed postsurgically in the bovine. Presence of air in the abdomen can be recognized by simultaneous percussion and auscultation. A low-pitch resonance can be auscultated in the upper flank on both sides of the abdomen. Presence of pneumoperitoneum normally resolves in the week after surgery. No clinical signs seem associated with the presence of pneumoperitoneum, although some clinicians describe abdominal pain associated with no other cause than the presence of air in the peritoneal cavity. Pneumoperitoneum not associated with surgery is indicative of bacterial peritonitis and the presence of gas-producing bacteria (Box 32-9).

32.129.3 Retroperitoneal Abscess

Retroperitoneal abscess is a particular condition occurring in cattle after a flank laparotomy. Animals are often presented several days after surgery. They are mildly febrile, not performing adequately, and showing clinical signs compatible with peritonitis. The skin wound is often unremarkable, but some pain may be elicited while the flank area is palpated. A substantial mass may be palpated per rectum, localized in the upper quadrant of the side of the previous surgical approach. The mass will be firm, smooth, unmovable, and close to the previous flank incision. Transabdominal or rectal ultrasound examination reveals a large amount of fluid located between the peritoneum and the rectus abdominis or the internal oblique of the abdomen. More superficial abscesses can also occur. A needle aspiration allows visual inspection of a thick, opaque, foul-smelling fluid. Treatment is aimed at establishing drainage and systemic antimicrobial therapy. A large volume of purulent and fibrinous material (up to 40 L) can be removed from the abscess. Rapid decompression may provoke hypovolemic shock, and intravenous fluids should be administered before a large abscess is drained. Prognosis is good, but the recovery phase is extremely long because of the large cavity left after drainage. Early closure of the drain is often observed, necessitating reopening.

32.129.3.1 Box 32-9 Causes and Examples of Pneumoperitoneum in Approximate Order

of Frequency

32.129.3.1.1 TRAUMATIC PERFORATION

Traumatic reticuloperitonitis

Septic abdominal surgery

Vaginal perforation in heifer during coitus

Penetrating wound

32.129.3.1.2 VISCERAL RUPTURE

Perforated abomasal ulcer

Perforated ulcer in other part of gastrointestinal tract

Abomasal rupture after torsion

Small intestinal rupture after volvulus, strangulated hernia, intussusception

Ruptured bladder secondary to urolithiasis

Spontaneous uterine rupture during gestation

Uterine rupture during dystocia

32.129.3.1.3 ABSCESS FORMATION AND POSSIBLE INTRAABDOMINAL RUPTURE

Reticuloperitonitis, localized

Liver

Umbilicus

Perimetritis

Perimetritis

Pyelonephritis

Iatrogenic

Intraperitoneal injection of irritant solution or contaminated solution

Perforation of the uterine wall with a pipette

Rectal tear secondary to palpation

32.129.3.1.4 MISCELLANEOUS

Hematogenous with systemic infection: tuberculosis, septicemia

Fat necrosis

32.130 FROTHY BLOAT

Charles L. Guard

Gilles Fecteau

32.130.1 Definition and Etiology

Frothy bloat is caused by diets that lead to the formation of stable froth in the rumen. Ruminal tympany is synonymous with bloat. The condition may be fatal if the distention is extreme enough to compromise ventilation by compressing the thoracic viscera. Cattle are more susceptible than sheep, but the disease does occur in the same circumstances in small ruminants.

32.130.2 Clinical Signs and Differential Diagnosis

The degree of forestomach enlargement varies from that producing an even filling of the left paralumbar fossa to that causing a uniform, extreme abdominal enlargement when the animal is viewed from the rear. With intermediate degrees of distention, the left paralumbar fossa bulges beyond the contours of the last rib and the tuber coxae. Clinical signs of colic may be seen, including kicking at the abdomen, treading, frequent lying down and rising, and vocalizations. Some animals adopt a stretched stance with the rear feet placed far back. Sheep with heavy fleece may be significantly bloated without the changes in abdominal contour being obvious. As the forestomach enlarges and compresses the diaphragm, breathing becomes more labored. Open-mouth breathing, cyanosis of mucous membranes, and collapse leading to death may occur within a few minutes if the animal becomes frantic from the abdominal pain and dyspnea. Other conditions to consider in the diagnosis of frothy bloat in ruminants include other causes of ruminal enlargement: free gas bloat and vagal indigestion. Advanced

pregnancy, hydropic conditions of the uterus, left or right abomasal displacements, cecal dilation or volvulus, intestinal volvulus, omasal bursitis, ascites, diffuse peritonitis, and pneumoperitoneum are conditions creating abdominal enlargement that may be included in the differential diagnosis.

Many systemic conditions influence the motility of the forestomach and thus may produce mild bloat coincidentally.

32.130.3 Clinical Pathology

Clinical pathologic measurements are not required for the diagnosis and management of most cases of frothy bloat in ruminants. When no cause for forestomach enlargement is obvious, evaluation of a sample of ruminal contents may provide information useful for prescribing treatment and prevention. The presence or absence of froth and the pH are critical features relating to the cause that influence the choice of therapy. The normal pH of the rumen varies with time after feeding but should be between 5.4 and 6.8.

32.130.4 Pathophysiology

Regardless of the cause of forestomach distention, the process may become self-perpetuating because of reflex inhibition of motility. Low-threshold stretch receptors in the ruminal wall augment cyclic forestomach contractions when stimulated. However, stimulation of high-threshold stretch receptors leads to inhibition of motility. Thus, beyond a certain degree of stretching of the ruminal wall, further contractions that may relieve the distention through eructation are prevented.[650]

Frothy bloat is caused by the retention of gases of fermentation within the mass of ingesta that fail to rise and coalesce into a dorsal gaseous layer. This condition can arise from diets of lush legumes or winter wheat pasture or may be seen with high-concentrate finishing rations in the feedlot. In the case of legume-induced disease, bloat has occurred after grazing or feeding of fresh-cut forages or the feeding of alfalfa hay. The structure of stable froth in the affected ruminal contents is not a true foam. The ingesta in the septa between adjacent bubbles form a complex structure that prevents coalescence. The viscosity of the fluid may prevent gravitational flow through the septa that would lead to the bubbles' rising and coalescing. Frothy ruminal fluid is higher in chloroplast membrane fragments, soluble protein, and very fine particles than nonfrothy ruminal fluid.[651] The presence of the resulting frothy ingesta at neural receptors believed to be near the cardia prevents the reflex relaxation of the cardia during the secondary contractions of the forestomach that ordinarily lead to eructation.[652] In addition, the viscosity of the frothy ingesta is such that the cardia may become plugged during attempts to eructate.

Current research[651] supports both animal and plant characteristics as predisposing to legume bloat. Individual cattle have been classified as having either high or low susceptibility to legume bloat. Thus far, highly susceptible cattle have been shown to have larger ruminal volumes and specific salivary proteins in consistently different proportions than bloat-resistant cattle. The actual mechanisms that lead to larger forestomach volume in susceptible cattle have not been determined. There is a relationship between plant factors associated with bloat and the rapidity with which leaf structure is disrupted after ingestion.[651] Bloat-inducing plants are more readily macerated, thus providing quicker bacterial access to the inner leaf cells. Less bloat-predisposing cultivars of the main bloat-causing species, such as alfalfa *(Medicago sativa)*, red clover *(Trifolium pratense)*, and white clover *(Trifolium repens)*, have a thicker leaf cuticle, smaller stomata, and a more fibrous leaf structure. Ionophore antibiotics such as monensin inhibit ruminal protozoa that normally ingest chloroplasts, leading to a reduction in the bloat potential of some forages.[653,654]

Grain bloat occurs in a manner similar to that caused by legumes; a stable froth is produced from high-concentrate rations. Particle size and the rate of fermentation are thought to be the determining factors in the froth production. A mucoprotein slime composed of bacterial byproducts stabilizes the froth.[653,655] This material tends to be stable at a lower pH than is found in non—grain-fed ruminants, so grain feeding promotes slime accumulation by lowering ruminal pH. Genetically susceptible cattle lack adequate mucin in their saliva to disrupt the tiny gas bubbles. Animals (such as dairy cattle) that are fed grain and then legumes may be particularly susceptible to frothy bloat because all the factors leading to froth production and accumulation are present. Both legume bloat and grain bloat may resolve spontaneously if the animal stops consuming the bloat-producing feed and microbial digestion eliminates the froth-stabilizing factors.

Acute distress, often appearing as colic, is caused by overdistention of the forestomach that stimulates pain receptors in the ruminal wall. As the abdominal distention increases, the ability to achieve normal respiratory movements of the diaphragm and rib cage is impaired. Death from asphyxia ultimately results as the lungs are compressed by the cranially expanding diaphragm.

32.130.5 Epidemiology

Frothy bloat often occurs as an epidemic. Pasture bloat occurs wherever alfalfa, red clover, or white clover is grazed. Environmental conditions that produce rapid, early growth lead to a higher incidence of bloat. Frothy bloat also occurs when stocker cattle are grazed on winter wheat pastures in the southern Great Plains of the United States. Death losses at pasture range from 0.5% to 2.5% of cattle at risk on an annual basis. The incidence of feedlot bloat has been estimated at about 1%, with death losses of about 0.1%.[651]

32.130.6 Necropsy Findings

The finding of tenacious froth in the rumen along with other evidence of bloat is grounds for a presumptive diagnosis of frothy bloat. The challenge for the diagnostician is to determine if the bloat occurred before death; this may not be possible if the animal was not observed before death. The increase in intraabdominal pressure prevents venous return from the hindquarters and may lead to obvious edema in the intermuscular areas. Unfortunately this is not a consistent finding; other evidence of impaired circulation or a differential degree of edema between fore and hind parts must be used to make a diagnosis.

32.130.7 Treatment and Prognosis

Passage of a stomach tube is indicated to determine the cause of the ruminal distention and possibly initiate treatment. A sample of the ruminal contents for pH measurement should be obtained at this time. Care must be taken to exclude saliva from the tube by blowing into the rumen, flushing water through the tube, or using a ruminal sampling device that carries the tip of the stomach tube down into the liquid ingesta. If no gas can be released with a stomach tube, the tube should be withdrawn after suction has been applied and examined for the presence of froth. If the animal is not in respiratory distress or extremely colicky, surface-active agents should be administered by means of a stomach tube. Poloxalene is recommended for forage bloat,[654] and mineral oil or animal tallow for feedlot bloat.[657]

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Some cattle are in violent pain with bloat but not in respiratory distress. Sedation with xylazine may be necessary

for further examination and treatment. Animals with extreme distention of the forestomach and in respiratory distress require immediate surgical intervention. A trocar introduced through the left paralumbar fossa after local anesthesia relieves bloat caused by free gas accumulation but may not be adequate for frothy bloat. An emergency rumenotomy may be necessary to evacuate frothy contents.

32.130.8 Prevention and Control

Prevention of frothy pasture bloat has historically relied on attempts to anticipate when forages were most likely to induce bloat. Cattle were fed other feeds and allowed limited access to the problem forages. Accurately predicting when forages are safe has not been reliable. As an alternative the cattle at risk have been treated with supplemental surface-active agents such as poloxalene.

In Australia and New Zealand, oils and tallows have been drenched daily, sprayed on fields, and smeared on the flanks to be later licked off, to prevent pasture bloat. Although poloxalene has proved effective, it is more expensive than oils. It can be fed in molasses blocks or individually administered. More recently ionophore antibiotics have shown promise for controlling bloat. Rumensin (1 mg/kg daily) greatly reduced the incidence of legume bloat, and lasalocid (1.32 mg/kg/daily) effectively reduced the incidence of grain bloat.[653,654] In both circumstances, beginning treatment before exposure to the bloat-inducing feed was more effective than waiting until bloat occurred. Agronomists are selecting cultivars of the bloat-producing forages for slower rates of initial fermentation. These are likely to become more widely used in the regions in which bloat is a regular occurrence.

Providing adequate fiber in feedlot rations and slowly introducing higher proportions of concentrates, particularly corn, barley, and soybean meal, permit ruminal adaptation that helps prevent bloat.

32.131 ABOMASAL DISPLACEMENT AND VOLVULUS

GILLES FECTEAU

CHARLES L. GUARD

32.131.1 Etiology

Although the precise cause of displacement of the abomasum remains unknown, general agreement exists in veterinary literature that it is a multifactorial syndrome and that abomasal hypomotility is an absolute prerequisite. Abomasal motility can be decreased in many ways. Overdistention of the rumen, reticulum, or omasum can inhibit motility of the abomasum,[658] as can ulcers and ostertagiasis.[659]

Many of these conditions occur commonly in the immediate postpartum period or are related to common disorders of postpartum dairy cattle (Table 32-18).

32.131.2 Prevalence and Incidence

Abomasal displacement occurs either to the right or to the left side of the abdomen when gas accumulates within this viscus. Left-displaced abomasum (LDA) is the more common, accounting for 85% to 95.8% of cases.[680] By far the highest incidence is in adult dairy cattle in the early postpartum period, but cases have been seen in all other classes of cattle. LDA is probably a worldwide problem, and one survey of the prevalence of disease in dairy herds indicates that 24% of herds reported at least one case of LDA during a 3-year period.[662] In one

Canadian study the lactational incidence risk of LDA was estimated to be 2%.[681] The prevalence among dairy herds is variable depending on geographic location, management practices (confinement vs. pasture), feeding practices, climate, and probably several other factors.

Table 32-18 Factors Associated with Influencing Abomasal Motility and Contributing or Possibly Contributing to Abomasal Displacements

Factor	Reference
Low pH	660,661
Particle size and fiber content	662,663
Amino acid, peptide, and fat content of duodenal fluid	658
High volatile fatty acid content	665
High ruminal histamine synthesis	666
Endotoxemia	667
Hyperinsulinemia	668
Hypokalemia	669
Epinephrine release	670,671
Histamine release	672
Metabolic alkalosis	673
Hypocalcemia	674
Prostaglandins	672,675,676
Lack of exercise	665,677
High blood gastrin concentrations	667,678
Acetonemia	679

32.131.3 Pathophysiology

After abomasal atony, distention with gas produced by microbial fermentation occurs and most likely precipitates the displacement. Diets with more grain result in an increase in the amount of gas produced in the abomasum. It has been hypothesized that the displacement will be oriented (left or right) according to the size of the rumen. A large and filled rumen will make the left displacement less likely, and the abomasum will dilate and in some cases twist to the right (Figs. 32-102, 32-103, and 32-104). If the rumen is small and empty (as in the postpartum period), the abomasum can move to the left and LDA can occur.[664]

Fig. 32-102 Schematic view of a left-displaced abomasum. Courtesy André

Desrochers, from *Surgery of the abomasum in cattle*, Version 2.0, Université de Montréal.

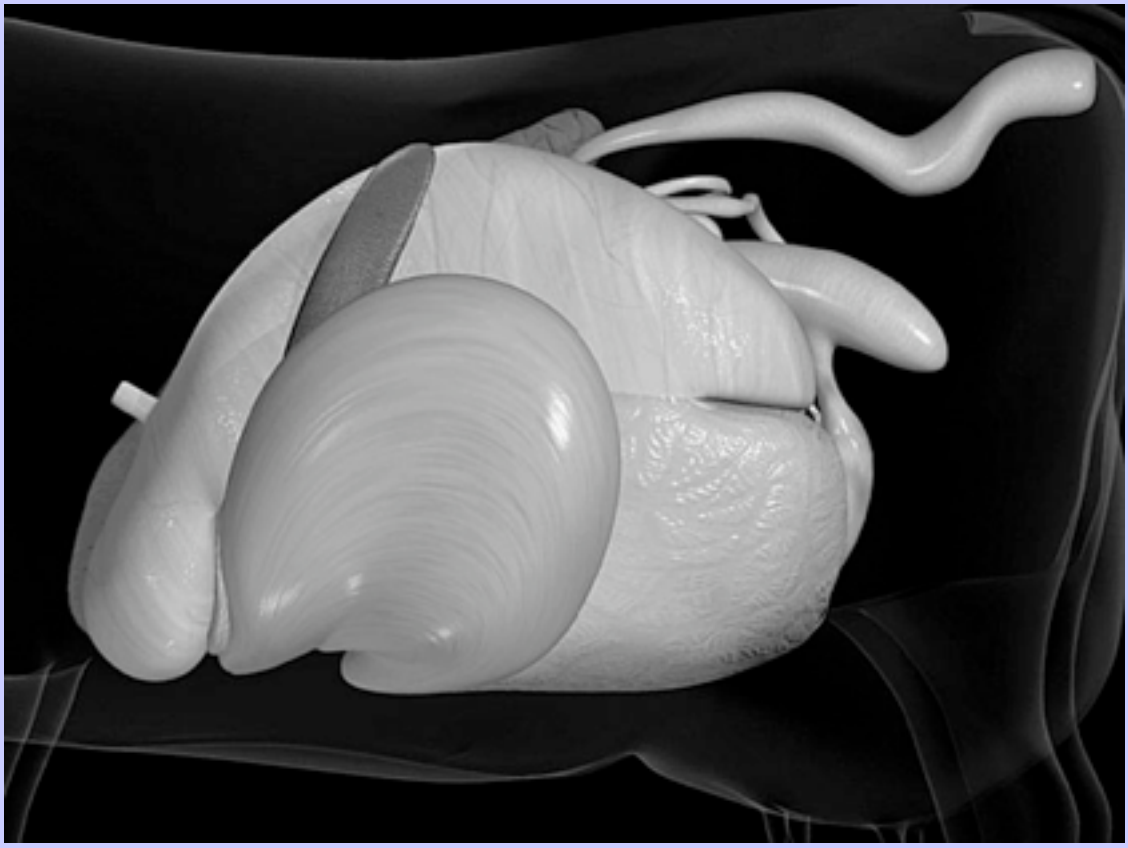

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Fig. 32-103 Schematic view of a right-dilated abomasum. Courtesy André

Desrochers, from *Surgery of the abomasum in cattle*, Version 2.0, Université de Montréal.

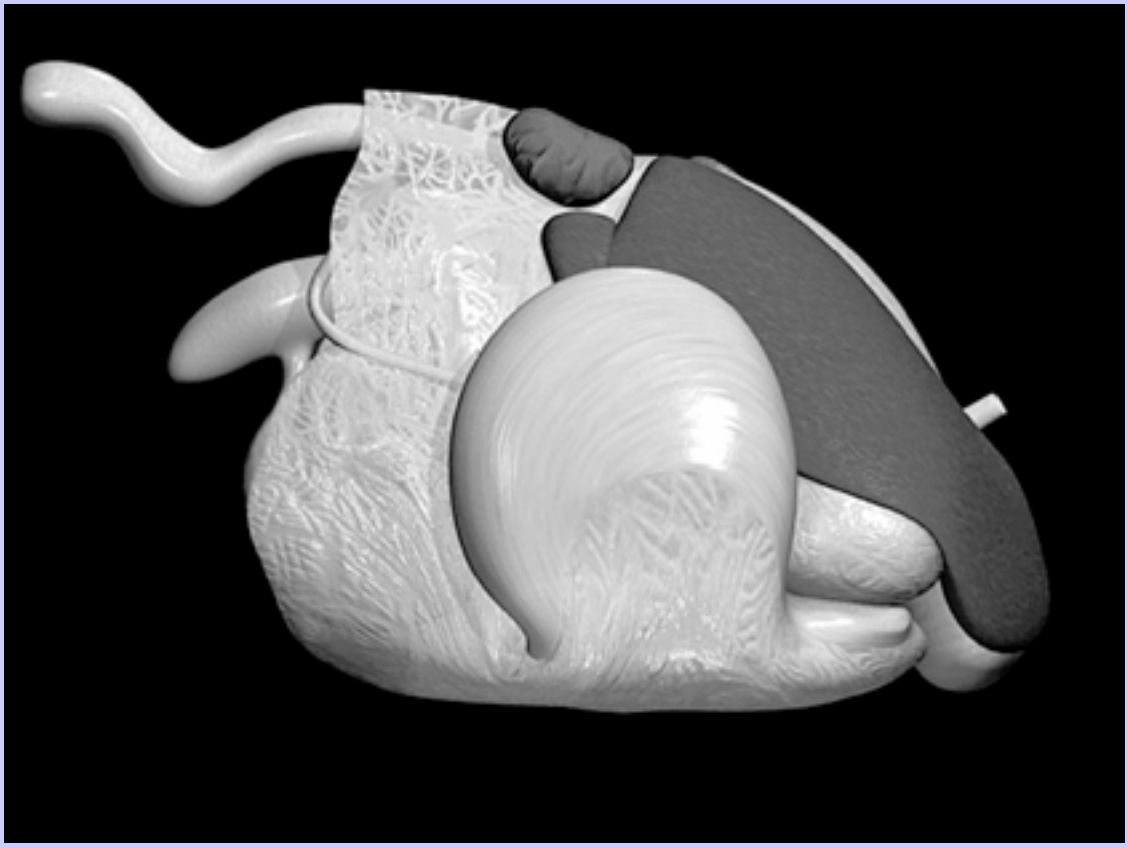
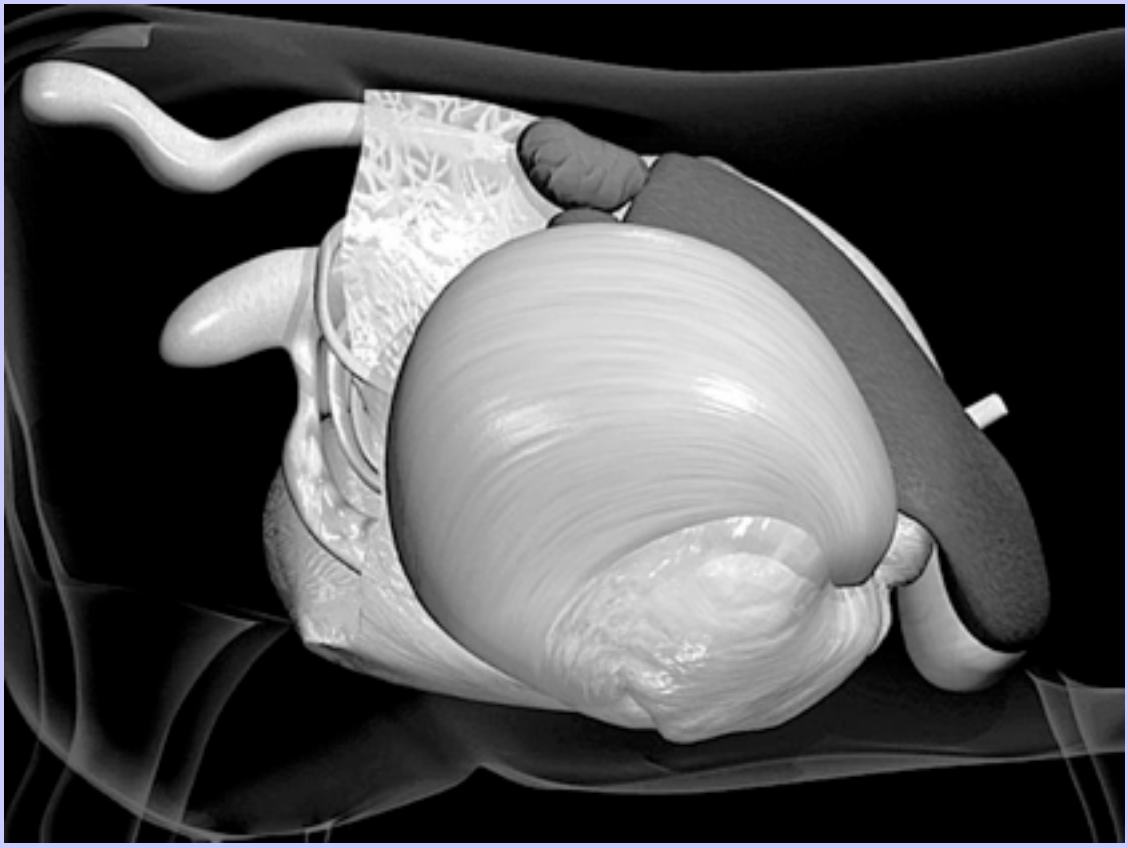


Fig. 32-104 Schematic view of an abomasal volvulus (AV). Courtesy André

Desrochers, from *Surgery of the abomasum in cattle*, Version 2.0, Université de Montréal.



32.131.4 Surgical Therapy

Numerous surgical techniques are used and have been described elsewhere.[680] The comparison of their advantages and disadvantages has also been studied.[682] The permanent attachment is usually created by suturing either the abomasum or the greater omentum to the abdominal wall. The techniques may be classified into three different broad categories: blind technique, surgical (open) technique, and laparoscopic technique. Multiple factors influence the decision; cost and preference of the surgeon are very important. Recently, laparoscopic technique has been described and studied.[683–686]

All techniques have been successful when performed adequately. Understanding the limitations of each of them will allow the food animal clinician to best serve the patient and client in all situations.

32.132 LEFT DISPLACEMENT OF THE ABOMASUM

32.132.1 Clinical Signs and Differential Diagnosis

Cattle with simple LDA have a reduced appetite (complete anorexia, reduced consumption of concentrates, or alternating periods of normal appetite and anorexia). Milk production is reduced. Ketosis may develop as a secondary problem. Feces are often normal to softer than normal but reduced in volume. Rectal temperature is normal, unless a concurrent infectious problem is present (metritis, mastitis). Pulse and respiration are normal or slightly above normal, unless a concurrent or secondary problem is present. Ruminal contractions are decreased to absent and difficult to hear because the abomasum interferes with transmission of the sound. The last one or two ribs on the left are sprung, but the abdomen is sunken in the paralumbar fossa. Gurgling or tinkling rather than normal scratching sounds may be heard on auscultation in the left paralumbar fossa. Simultaneous auscultation and percussion reveal a ping over the gas-filled portion of the abomasum (see Fig. 1-5). With LDA the area of ping may be anywhere from the lower third of the abdomen in the eighth intercostal space to the paralumbar fossa. Attention should also be given to the cranial and lower aspect of the flank because in some cases the ping will be audible only in this area.

On rare occasions, during rectal examination the clinician may be able to palpate the abomasum to the left of the caudodorsal blind sac of the rumen or at least perceive that the rumen is displaced medially.

Ruminal tympany, pneumoperitoneum, and collapsed rumen[687] may all produce pings on the left side of the cow. Physometra (air in the uterus) and dilation and displacement of the cecum to the left of the rumen (which is rare) may also produce left-sided pings. Having an assistant blow on the stomach tube passed into the rumen while auscultating over the left side differentiates the rumen from other structures. Percutaneous needle aspiration of fluid or gas from the suspected abomasum aids in correct identification. A pH of less than 4.5 as determined with wide-range pH paper or the odor of abomasal gas (slightly acrid or burnt almonds) confirms the presence of LDA.

32.132.2 Clinical Pathology

The most important abnormalities detected by clinical chemical evaluation usually are the serum electrolyte and acid-base levels.[688] Sequestration of the hydrochloric acid secreted into the abomasum within the abomasum or by means of reflux in the ruminoreticulum may occur and lead to metabolic alkalosis. The blood pH and bicarbonate concentration are slightly elevated, with a concomitant small decrease in the blood chloride concentration. Cattle examined on the farm usually are hypoglycemic and ketonuric. However, any important stress (e.g., transportation) may create a transient hyperglycemia. The serum calcium level may be below normal as a result of decreased intake and absorption. Hypokalemia may develop as a consequence of both the metabolic alkalosis and reduced intake and absorption.

The CBC may reveal a mild dehydration and a stress leukogram. If LDA is combined with bleeding abomasal ulcers it may produce severe anemia. The presence of a concurrent disease may lead to specific changes (e.g., left shift with acute coliform mastitis).

32.132.3 Epidemiology

Cows in early lactation are at greatest risk of developing LDA. In one prospective study of 3172 lactations in New York, 81% of 48 LDAs occurred in the first 30 days after calving.[689] The overall incidence was 1.5% of lactations. An older study reported a lower incidence rate (0.35% from 1970 to 1972), but even within that period the rate increased each year.[690] A higher incidence has been reported in late winter and early spring after the winter housing season.[691] Cows in this study had LDA in association with parturition as expected, but a preponderance of cases occurred in cows calving in February to April. Increasing parity was associated with an increased incidence of LDA in studies from Ontario, Canada, New York, and Israel.[690–692] Milk production potential is not thought to be related to the risk of LDA.[693] Most cows produce 300 to 500 kg less milk in lactations with LDA than would be expected if the disease did not occur.[694] For unknown reasons, about 80% of recovered cases produce about 400 kg less milk, and 20% produce 2000 kg less milk. Length of time a cow remains in the herd after correction of LDA is not affected. The financial consequences of LDA for an individual cow with the smaller reduction in milk production favor maintaining the cow in the herd.

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Energy and protein nutrition of the prepartum dry cow were suggested to be causally related to LDA in one study.[695] On a herd basis, in cows fed levels of energy and protein above National Research Council recommendations, LDA was less likely to develop. Genetic factors may also play a role in the predisposition to LDA. In a retrospective case-control study, cows with LDA were 1½ times more likely to be sired by bulls in one group than controls.[691] Fox[696] suggested that body depth had increased in dairy cattle since 1945 and that this may provide more room for the relatively empty abdominal viscera to move about at parturition. An experimental herd composed of two groups of Holstein cows, continuously mated and selected to produce large and small body sizes, had a 4.5% incidence of LDA in the large size group and a 1% incidence in the small cows during a 14-year period.[697] Body weight was 514 kg versus 464 kg, wither height was 134 cm versus 129 cm, and fat-corrected milk production was 6163 kg versus 6135 kg for the two groups. Thus some evidence exists to support a genetic basis for predisposition to LDA, and perhaps this is mediated through body size or conformation.

32.132.4 Treatment and Prognosis

Treatment for LDA involves returning the abomasum to its normal anatomic location and preventing reoccurrence (“pexy”), treating the electrolyte and acid-base abnormalities, and providing therapy for concurrent disease conditions. Prognosis for LDA is good but is influenced by the severity of the concurrent disease. Cattle with severe hepatic lipidosis and LDA should be given a guarded prognosis, as their recovery is often slow and incomplete.

32.132.5 Prevention and Control

The incidence of LDA has been reduced in problem herds by dietary manipulation that reduces the likelihood of forestomach and abomasal atony caused by high-concentrate rations. This includes slow introduction of concentrates after calving, prepartum introduction of ensiled and concentrate feeds and increase in the particle size of the forage. Maintaining serum calcium concentration around parturition may be achieved by dietary management during the prepartum period. Dietary cation-anion difference (DCAD) is a reliable method of controlling hypocalcemia in dairy cows (see Chapter 41). Reduction in other periparturient inflammatory diseases such as mastitis and metritis also reduces the incidence of LDA.

32.133 RIGHT DISPLACEMENT OF THE ABOMASUM

Simple right displacement of the abomasum (RDA) occurs at approximately 10% to 15% the frequency of LDA. The exception to this is the reported higher incidence of RDA than LDA in Denmark.[698]

32.133.1 Clinical Signs and Differential Diagnosis

The general systemic state of the cow with a simple RDA is the same as that of the cow with LDA. On the other hand, as the simple RDA evolves toward the volvulus, the systemic changes observed in cattle with abomasal volvulus progressively appear. An area of tympanitic resonance is heard on the right side with simultaneous auscultation and percussion. The ping usually is confined to an area under the last five ribs in the upper half of the abdomen. The condition must be differentiated from other causes of right-sided pings, such as cecal distention (with or without volvulus), gas in the spiral colon, pneumorectum after rectal examination, pneumoperitoneum, physometra (gas in the uterus), and abomasal volvulus (see Fig. 1-4).[699,700] Cecal and rectal pings usually are detectable in a linear pattern just below the transverse processes of the lumbar vertebrae extending to the tuber coxae. Rectal examination identifies the gas-filled structure. Pings heard with gas in the spiral colon typically have a variable pitch, depending on the location over the cranial paralumbar fossa and last three or four ribs. Generally the spiral colon may be palpated per rectum as a laterally flattened, mildly distended viscus adjacent to the right body wall. Gas in the uterus can be detected per rectum. Pneumoperitoneum creates a ping that is distributed all along the dorsal portion of the abdominal cavity and is usually heard on both sides.

Abomasal volvulus is the most difficult to differentiate from RDA. Determination of the difference by physical diagnosis in an early case of abomasal volvulus is probably impossible. With time the cow becomes progressively more dehydrated and more severely ill with volvulus than is usual with RDA. Heart rate (above 100 beats/min), ruminal motility (totally absent), and fecal output (almost none) are clinical signs in favor of a diagnosis of abomasal volvulus. Advanced cases of volvulus also have a ping that has an arched dorsal border and a horizontal ventral border caused by the fluid level in the abomasum. This fluid is auscultable on succussion of the abomasum.

32.133.2 Treatment and Prognosis

Surgical treatment is required to correct RDA. Because of the difficulty of differentiating RDA from early volvulus, intervention should be as prompt as possible. The prognosis for a successful recovery after surgery is comparable to that for LDA if no other concurrent disease is present.

32.134 ABOMASAL VOLVULUS

Abomasal volvulus, or right torsion of the abomasum, leads to complete obstruction of the flow of ingesta into the duodenum and therefore is a surgical emergency. The condition occurs in all classes of cattle. Although RDA is thought to precede its development, unknown factors lead to abomasal volvulus.

32.134.1 Clinical Signs and Differential Diagnosis

The systemic effects of the gastrointestinal obstruction that results from abomasal volvulus progress to a much more severe degree than in LDA or RDA. Sunken eyes and loss of skin turgor accompany the dehydration that develops. The heart rate increases above 100 beats/min, and the pulse is weak and thready. Abdominal distention is marked bilaterally. Complete ruminal stasis develops, leading to bloat, and the abomasum greatly enlarges on the right. Despite the severe degree of gastric distention, colic rarely develops in abomasal volvulus; it is much more likely with cecal distention. The skin is cool to the touch. Feces are absent or watery but scant. A large area of tympanitic resonance with uniform pitch throughout is detectable on the right, extending from the eighth rib to the middle of the paralumbar fossa (see Fig. 1-5).[700] The ventral border of the ping is a horizontal line reflecting the fluid level in the greatly distended abomasum. Borborygmi are absent. Splashing fluid sounds can be heard when the abomasum is ballotted (succussed) behind the last rib.

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Other causes of proximal intestinal obstruction and torsion of the intestinal mass around the root of the mesentery must be differentiated from abomasal volvulus. On rectal examination the abomasum can usually be felt with abomasal volvulus. With intestinal obstruction or intestinal volvulus, distended loops of small intestine can be palpated. Pings caused by gas in the intestines have a variable pitch over the area involved.

Cecal distention with rotation can produce a similar degree of abdominal distention high on the right, but the abdomen usually is less filled cranioventrally on the right. A ping extends to the tuber coxae, and the cecum can be palpated per rectum. Diffuse peritonitis leads to complete atony of the gastrointestinal tract, and the abdomen may become distended with gas in all parts of the tract; there is no discrete ping extending over a large area of the right side.

As abomasal volvulus progresses, cattle become recumbent and depressed. Death occurs within hours of this stage, which occurs 1 to 3 days after the development of the volvulus.

32.134.2 Clinical Pathology

The serum biochemistry profile will show much more dramatic changes with abomasal volvulus than with RDA or LDA. Clinicopathologic consequences include hypovolemia, dehydration, hemoconcentration, metabolic alkalosis, hypochloremia, hypokalemia, and paradoxic aciduria. Hyperglycemia, hypocalcemia, and hyponatremia may also be observed. Later in the condition a superimposed metabolic acidosis is also present. Anion gap gradually increases with the severity of the disease. Systemic shock eventually causes fatality. Reduced fluid intake and sequestration of large quantities of chloride-rich fluid in the stomachs (third space problem) leads to dehydration and hypovolemia.

Under the influence of carbonic anhydrase, hydrogen ions are normally pumped into the abomasal lumen. A chloride ion follows into the lumen, whereas bicarbonate and sodium remain in the blood. Under normal circumstances the HCl leaves the pylorus, where the hydrogen ions are neutralized by pancreatic and intestinal secretions and the chloride is resorbed. When abomasal volvulus occurs, the HCl is sequestered in the abomasum and regurgitated into the omasum and rumen (internal vomiting). Ruminal chlorides increase. The animal becomes alkalotic and hypochloremic. Because of shifts between intracellular and extracellular compartments, potassium moves intracellularly as hydrogen ions move extracellularly in response to the metabolic alkalosis. This, plus the total anorexia, lead to severe hypokalemia. The hallmarks of abomasal volvulus are metabolic alkalosis, hypochloremia, and hypokalemia.

Paradoxic aciduria occurs in the face of metabolic alkalosis, when the cow should be retaining hydrogen ions.

[701,702] The overwhelming renal physiologic drive appears to be sodium retention. Dehydration and reduced cardiac output result in falling blood pressure. The animal must respond by volume expansion; thus sodium is resorbed in the renal tubules. Chloride is also resorbed. Because there is hypochloremia, the electrical gradient that must be corrected is high; if 140 mEq/L of sodium is resorbed and only 60 mEq/L of chloride is available, there is a net of 80 mEq/L (140 − 60) of cations that must be secreted back into the tubules. This is normally accomplished by secretion of potassium. Because hypokalemia is severe, hydrogen ions are paradoxically secreted to retain electrical neutrality so that blood pressure can be maintained by means of maximum sodium resorption.

32.134.3 Pathophysiology

At least some of the factors predisposing to LDA or RDA probably contribute to the paths of abomasal volvulus. Whether true RDA precedes abomasal volvulus is not known. Dissection of naturally occurring cases of abomasal volvulus demonstrated that the structures involved in rotation can vary from the reticulum to the omasum at the orad end.[698,703,704] The rotation probably occurs most frequently at the reticuloomasal junction. The duodenum is looped around the omasum, regardless of the degree of volvulus. Creating the condition manually in an anesthetized calf was easier if the gas-filled fundus ascended around the cranial surface of the omasum, pulling the reticulum with it.[703] The ensuing displacement leads to a counterclockwise rotation of the abomasum and omasum as viewed from the right side and the rear. The duodenum is pulled medial to the body of the omasum and wraps around the neck of the omasum in the final configuration. The continued hydrochloric acid secretion of the abomasum and the gas produced in the omasum and abomasum further stretch and occlude the duodenum. The abomasal blood vessels and the ventral vagal trunk are compromised near the site at which the duodenum wraps around the omasum in long-standing cases. Thrombosis of vessels may occur.

The acid-base and electrolyte abnormalities of **early** abomasal volvulus are the same as those of LDA. In cases of severe distention of the abomasum and omasum with vascular compromise, systemic cardiovascular insufficiency develops. Reduced perfusion of peripheral tissues may lead to metabolic acidosis terminally. Hemoconcentration develops, although bleeding into the abomasum may occur from devitalized mucosa, leading to a low hematocrit. These changes are compounded by the developing necrosis of the abomasum. The abomasum may physically leak contents through a weakened, overstretched wall. Endogenous inflammatory mediators and bacterial toxins may diffuse from the abomasum to viable surrounding tissues, where absorption occurs. In either case, the viability of the abomasum is lost, and death follows shortly.

32.134.4 Treatment

Immediate surgical intervention usually is necessary to save the animal's life. Simultaneously fluid, electrolyte, and acid-base abnormalities need correction. For early cases of hypokalemic, hypochloremic alkalosis and dehydration, intravenous fluids consisting of 20 to 80 L of 0.9% sodium chloride with 25 to 100 mEq/L potassium chloride added are administered. Intravenous potassium should not be given at a rate greater than 1 mEq/kg/hr to prevent cardiotoxicity. For advanced cases with metabolic acidosis, balanced electrolyte solutions such as Ringer's solution are indicated. Broad-spectrum antibiotics are appropriate if the integrity of the abomasal mucosa is questionable. NSAIDs are indicated to control pain, inflammation, and shock. Both standing right-sided and recumbent right paramedian approaches have been successful for correcting abomasal volvulus.[682,705]

32.134.5 Prognosis

Establishing an accurate prognosis before surgery is optimal because at that time salvage remains a possibility and little expense has occurred. A second critical time is after surgery in cows not recovering appropriately. The decision will be whether to continue to treat (cost) or salvage, if that still is an option.

Preoperative assessment is difficult. In our experience, assessment cannot be based on a single clinical observation or serum biochemistry value. The best published studies looked at two different classifications of outcome: death versus survival and productivity versus nonproductivity. A logistic regression model,[706] looking at heart rate, base excess, and serum chloride level, was developed as a preoperative predictor of death or survival. The study by Constable and colleagues found that four presurgical variables (hydration, heart rate, duration of inappetence, and AlP level) could be used to best predict cattle as productive or nonproductive after surgery.[707]

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Surgical assessment of outcome has been investigated. The overall success rate of surgery varies between 61.5% and 86.3%.[708–711] The number of forestomachs involved in the twist has been found to adversely affect survival and productivity. Wallace found only 20% success in cattle with reticulo-omasal-abomasal volvulus.[711] Another study reported success in 55% of cattle with omasal-abomasal volvulus and 87% success in cattle with only an abomasal volvulus.[707] Edema of the abomasum carries a guarded to poor prognosis.[711–713] Edema around the proximal duodenum was associated with a poor outcome in Pearson's study,[712] but Fubini and co-workers found no association with outcome.[714] Purple discoloration of the abomasal serosa tends to bode poorly for long-term outcome, as does total distention of this organ, abomasal necrosis, and thrombosis of the gastric veins.[706,711] When it has been necessary to drain the abomasum of fluid to correct the twist, the animals have usually not done well.[709] The measurement of intraluminal pressures of greater than 16 cm Hg also carries a poor prognosis because of mucosal damage.[707] A logistic regression model using some of the surgical findings did not predict outcome any better than with the preoperative model.[706]

After correction, cattle with abomasal volvulus often have diarrhea for 24 hours. Feces then firm up to normal consistency. Postoperative clinical signs associated with a poor prognosis include melena, anorexia, persistent tachycardia, and dehydration.[709,713,715] In our experience, even if appetite and general attitude are initially good (24 to 48 hours after surgery), persistence of a loose low-volume stool 72 hours after surgery may indicate complications and possible vagal indigestion.[717] Once vagal signs develop, the survival rate is only 11.5% to 20%.[711,716] Prolonged treatment seems irrelevant, because neither surgical treatment (pyloroplasty, abomasal or ruminal fistula) nor medical treatment (prokinetic drugs or laxatives) has been shown to be effective.[672,709]

32.134.6

Necropsy Findings

Cattle that die of abomasal volvulus are grossly dehydrated, and the abomasum is greatly distended or ruptured. The omasum often is also greatly distended when torsion occurs at the reticuloomasal junction. Cattle that die or are euthanized after developing postoperative complications have one or more of the following postmortem lesions: gastric compartment dilation, peritonitis, abomasal wall necrosis or ulcer, vascular thrombosis, or vagal nerve lesions.[717]

Table 32-19 Abomasal Ulcers

Type	Lesions	Clinical Signs
Nonperforating	Mucosal and some submucosal tissue loss; focal mural thickening; local serositis	Partial anorexia; decreased ruminal motility; positive fecal occult blood
Nonperforating with severe blood loss (bleeding)	Penetration of mucosa and submucosal blood vessel; hemorrhage into abomasum	Partial anorexia; decreased ruminal motility; anemia; pale mucous membranes; melena; tachycardia; cool extremities
Perforating with local peritonitis	Penetration from mucosa to serosa; leakage of abomasal contents; localized peritoneal reaction with adhesion formation	Total anorexia; low-grade fever; decreased to absent ruminal motility; localized abdominal pain; very similar to traumatic reticuloperitonitis
Perforating with diffuse peritonitis	Penetration from mucosa to serosa; widespread contamination of the peritoneal cavity with abomasal contents; significant exudate in peritoneal cavity; fibrin deposition of all serosal surfaces	Total anorexia; fever early, then hypothermia; ileus of entire gastrointestinal tract; tachycardia; shock; terminally recumbent with grunt on respiration

32.134.7 Prevention and Control

Because factors predisposing to atony of the forestomach and abomasum probably are important in the genesis of abomasal volvulus, prevention should be similar to that outlined for LDA.

32.135 ABOMASAL ULCERS

David Francoz

Charles L. Guard

32.135.1 Definition and Etiology

Abomasal ulcers occur in cattle of all ages and rarely in sheep and goats. Signs of loss of gastric epithelium may range from no clinical signs, to hemorrhage and anemia and subsequent melena, to peritonitis if the erosive processes penetrate all layers of the abomasum. The exact cause of abomasal ulcers is still obscure and may be multifactorial. In calves, development of abomasal ulcers has been proposed to be associated with mineral deficiencies (mainly copper),[718,719] stress,[720] proliferation of microorganisms (*C. perfringens* type A, fungi, or others),[720–724] and/or abrasion of the abomasal mucosa by roughage, geosediments, or trichobezoars.[725,726] However, all of these hypotheses have failed to demonstrate alone their involvement in the development of abomasal ulcers.[720,723,727] In adults the disease is associated with stress such as recent parturition, peak milk production, or presence of concurrent diseases (mainly those of the peripartum period), and with diets high in starch.[728–730] Lymphosarcoma of the abomasum also may lead to clinical signs of ulcer disease. Abomasal ulcers are also an adverse effect of NSAIDS.

32.135.2 Clinical Signs and Differential Diagnosis

Smith, Munson, and Erb[729] have classified abomasal ulcers into four types: (1) nonperforating with minimal signs, (2) nonperforating with severe blood loss, (3) perforating with local peritonitis, and (4) perforating with diffuse peritonitis (Table 32-19). These classifications are useful for describing the various clinical pictures that may be observed when examining an animal with abomasal ulceration.

The mildest form (type I) is caused by nonperforating ulcers that do not result in extensive hemorrhage. Affected animals may have mild or no clinical signs. The signs are mild abdominal pain, shown by partial anorexia, decreased ruminal motility, and mild ruminal tympany. There is usually no febrile response. Manure may be normal or reduced in amount and stale because of prolonged transit. In some cases abdominal pain may be evident on manual pressure on the right ventral abdomen. TRP or indigestion may be suspected. In one study about two thirds of such cows had a positive test finding for fecal occult blood.[731]

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In cattle with ulcers that erode into major gastric blood vessels (type II), blood loss can be sufficient to cause signs of anemia and hemorrhagic shock. These animals have dark blood clots in their manure or tarry, black feces with the characteristic smell of partly digested blood. The mucous membranes may be pale, tachycardia may be pronounced, and the respiratory rate may be elevated. Total anorexia and ruminal stasis usually are present. The rumen may have a fluid consistency, and if the animal is able to stand, abdominal pain sometimes is evident. There are other possible sources of proximal gastrointestinal hemorrhage in cattle, but abomasal ulcers are by far the most common cause. Among them, bleeding abomasal ulcers must be differentiated from melena sometimes seen with intussusception or HBS (jejunal hemorrhage syndrome [JHS]). The PCV usually is increased with intussusception,[732,733] normal or increased in HBS,[734,735] and decreased with a bleeding ulcer.[736,737]

Abomasal ulcers that perforate the serosal surface lead to localized peritonitis (type III) from contamination with abomasal contents. If the lesion is small or the local inflammatory reaction sufficiently swift, localized peritonitis results. This condition is most like TRP in presenting signs. The animal may be moderately febrile and partly or totally anorectic, and milk production may decrease acutely. There is evidence of abdominal pain, usually localized to the right ventral quadrant (positive withers pinch test). Ruminal motility may be absent, and mild bloat may be present. As with hardware disease, the signs usually abate over the course of a few days if the infection is successfully contained. In some cases the infection is confined to the omental bursa, where extensive fluid and pus may accumulate. The course of omental bursitis is much more prolonged than that of simple localized peritonitis and usually results in a guarded prognosis.

Major leakage from a perforating ulcer leads to acute diffuse peritonitis (type IV). The course of the disease usually is rapid, with signs of septic shock developing within 24 hours of the onset. Total anorexia and ruminal stasis are accompanied by tachycardia with a weak, thready pulse and a heart rate over 100 beats/min. Pain may be evidenced by grinding of the teeth or groaning. The extremities are cool, and the animal generally becomes recumbent. Abdominal enlargement may be evident as a result of both ruminal tympany and the accumulation of peritoneal fluid. Dehydration is detectable by skin pinch or by observation of the position of the eye in the orbit. Septic shock from other causes may be difficult to distinguish from that caused by perforated abomasal ulcers in the terminal stages of the disease. Diffuse peritonitis from uterine, cecal, or intestinal ruptures have the same final course. Abomasal volvulus of more than a day's duration has similar characteristics but can be differentiated by the right-sided ping and fluid in the abomasum.

32.135.3 Clinical Pathology

The most useful diagnostic test for abomasal ulcer disease without visible melena is the fecal occult blood test. In an evaluation of 296 hospitalized cattle with gastrointestinal disease, this test had a sensitivity of 0.77 and a specificity of 0.97 for ulcers confirmed at surgery or necropsy.[731] The test is inexpensive and can be performed during the physical examination.

Abdominocentesis confirms diffuse peritonitis (a large quantity of abdominal fluid is obtainable); centesis fluid may contain leukocytes with phagocytosed or free bacteria, and even feed particles. In localized peritonitis the results of abdominocentesis may be normal.

Abdominal ultrasonography is also useful for the diagnosis and the evaluation of peritonitis (see section on abdominal ultrasound). Braun and colleagues reported that percutaneous ultrasound-guided abomasocentesis can be safely performed for the evaluation of abomasal fluid.[738] The presence of blood or hemoglobin is principally associated with abomasal ulcers.[738,739]

If peritonitis is present, leukocytosis usually is present, with neutrophilia predominating in many cases. The plasma fibrinogen is increased (over 700 mg/dL) in most cattle with peritonitis. This may be evaluated in the field with a glutaraldehyde coagulation test on whole blood. The hematocrit is normal or elevated with peritonitis, but plasma protein levels may be decreased as a result of protein accumulation in the peritoneal cavity or increased if dehydration is severe. If blood loss is severe, the PCV is decreased. Cattle over 5 years of age with a bleeding abomasal ulcer should be tested for bovine leukosis virus. Results of a complete biochemistry profile or blood gas analysis are nonspecific. In most cases, they reflect a digestive stasis (hypochloremic metabolic alkalosis), but in animals in shock a metabolic acidosis may be observed. BUN may be increased. This can be a result of blood degradation in the intestine or hypovolemia and prerenal azotemia. The utility of BUN in the diagnosis of abomasal ulcers by identifying digestive hemorrhage remains to be determined.

32.135.4 Pathophysiology

The specific events leading to erosion and ulceration of the abomasal mucosal epithelium are unknown but probably are similar to those in other species. Cytoprotective mechanisms include a mucous barrier, cloudy mucus containing bicarbonate ions to neutralize back-diffusing hydrogen ions, and high submucosal rates of blood flow to remove back-diffusing hydrogen ions. When these mechanisms are disturbed, gastric (abomasal) ulcers can occur. Stress, concurrent diseases, corticosteroids, and NSAIDs are among factors known to contribute.

32.135.5 Epidemiology

Abomasal ulceration occurs in cattle of all ages. At slaughter many calves are found to have clinically inapparent abomasal erosions and ulcers, with prevalence reported ranging from 32% to 76%.[740–743] In clinically affected calves, perforation with peritonitis (rather than hemorrhage) usually develops. In clinically normal slaughter cows, 20.5% had type I ulcers.[744] However, a much lower prevalence (1% to 2.6%) of abomasal ulcers in healthy adult cows has also been reported.[745,746] In adult cattle with abomasal ulcers causing illness, approximately one third of clinical cases in a referral population had significant hemorrhage.[736] Of these, half had lymphosarcoma and for the most part were older than 6 years of age. The age of the cattle with non—tumor-associated bleeding ulcers was generally younger (7 of 12 were less than 5 years old). In the remaining two

thirds of the cattle, ulcers had perforated, with about half having diffused and half having localized peritonitis.[747] Most adult cattle with abomasal ulcer disease are in the first month after calving and have a concurrent disease. Many cows have been discovered to have an abomasal ulcer at surgery for displaced abomasum. Metritis, mastitis, and ketosis are the other diseases commonly seen with abomasal ulcers. The incidence of abomasal ulcers apparently increased with the advent of heavy corn silage and high-moisture corn feeding. In the recent past, as feeding and management practices have addressed the most common abomasal displacements, the incidence of ulcer disease has also decreased.

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32.135.6 Necropsy

Cattle with bleeding abomasal ulcers resulting in death are very pale and may have blood or bloody fluid throughout the distal gastrointestinal tract. The lesion in the abomasum is typically small and involves an abomasal blood vessel in the submucosa. Most bleeding and perforating ulcers were found in the fundic portion of the abomasum in the region of the proper gastric glands. The most ventral portion of the abomasum in its normal position is frequently affected.[737,745,746,748] Most animals have a single ulcer significantly bleeding, but approximately 60% have one or more additional ulcers or erosions.[737,745] Cattle with diffuse peritonitis have many liters of foul-smelling fluid in the peritoneal cavity. Fibrin usually covers the serosal surface of all abdominal organs. The defect in the serosal surface of the abomasum is usually nearly round and 3 to 6 cm in diameter. Abomasal fluid freely enters the peritoneal cavity. Omasal bursitis may be present, with the omental recess filled with purulent to fibrinous fluid. In these cases the remainder of the abdomen may not be grossly affected. Asymptomatic abomasal ulcers (often 50 to 200) may be found coincidentally in cattle that die of septic metritis or mastitis. These ulcers generally show no signs of hemorrhage and go undetected until necropsy.

32.135.7 Treatment and Prognosis

Treatment is aimed at correcting dietary problems, reducing stress, ameliorating concurrent disease problems, and initiating specific therapy for the clinical problems caused by the ulcer. Removal of high-energy feedstuffs and replacement with good-quality hay plus confinement to a stall are beneficial.[728] The buffer effect of food is very important for the control of abomasal pH. Consequently, the return to a normal appetite is the main goal of the treatment of abomasal ulcers.[749]

Blood transfusions may be necessary for cattle that have lost enough blood to lower the hematocrit to 14% or below. Usually 4 to 6 L given once is adequate, but repeated transfusions occasionally may be necessary. Cross-matching usually is not necessary for cattle unless repeat transfusions are performed over a period of more than 3 days. Broad-spectrum antibiotics are administered to cattle with signs of peritonitis. Principles and details on the treatment of peritonitis are described in the section on peritonitis in ruminants. Intravenous or oral fluids may be necessary to treat dehydration and metabolic or acid-base disturbances that occur concurrently. Animals with diffuse peritonitis must be given intravenous fluids with caution because of the risk of pulmonary edema associated with the low colloid oncotic pressure of their plasma.

Numerous recent studies have been performed to evaluate the effect of different therapeutic agents on abomasal pH of healthy calves. Results of these studies have been summarized by Constable and colleagues.[749] The therapeutic agents studied in normal calves included oral administration of an antacid agent containing aluminum hydroxide and magnesium hydroxide (25 mL and 50 mL, tid), oral administration of specific H_2-antagonists (cimetidine, 100 mg/kg and 50 mg/kg, tid; and ranitidine, 10 mg/kg and 50 mg/kg, tid), and oral administration of the proton pump inhibitor omeprazole (4 mg/kg sid). All these treatment regimens induce an increase in mean

24-hour abomasal luminal pH. Oral administrations of the antacid agent induced a dose-dependant increase in luminal pH and were more efficacious when administered postprandially. Because some deleterious effects were observed when this antacid was administered at the dose of 50 mL tid, this should be considered the maximal dosage rate in calves.[749] Cimetidine (100 mg/kg tid) was the most effective. However, ranitidine (50 mg/kg tid) was the most cost-effective in theses studies. Results of theses studies need now to be confirmed in ill calves. In adults, oral administration of these therapeutic agents is of doubtful benefit because of dilution in the rumen and slow release into the abomasum. Oral medications administered after stimuli that induce reflex esophageal groove closure would be more likely to have the desired effect. Traditional stimuli to close the esophageal groove have included copper sulfate solutions and 10% sodium bicarbonate solution. Vasopressin (0.25 IU/kg IV) was shown to induce reliable abomasal deposition of materials given by drench to adult goats.[750] Intravenous administration of H_2-antagonists at lower doses may be efficacious, but their use by this route is cost-prohibitive ($100 to $200 USD per day) or reserved for very high-value animals. In our clinic in Quebec, we use ranitidine 1 to 1.5 mg/kg IV tid for high-value animals; our clinical impression is that this is effective.

The prognosis is good for ulcers that are not bleeding and not perforated. For those animals that stop bleeding and those with localized peritonitis, survival and eventual return to normal function can be expected. Many dairy cattle stop lactating during the acute course of the illness and do not return to milk until the next lactation. Because abomasal ulcers generally occur within the first month after calving, most of these animals are salvaged for slaughter. Most cattle with diffuse peritonitis die despite aggressive specific therapy. Early recognition and immediate surgery followed by antibiotic and fluid therapy may save some valuable individuals. Cattle with ulcers that occur secondary to lymphosarcoma should be euthanized or slaughtered.

32.135.8 Prevention and Control

Because the exact cause of development of abomasal ulcers is unknown, prevention is difficult. Dietary management that reduces other abomasal diseases likewise reduces the incidence of abomasal ulcers. Avoiding abrupt changes in rations and including adequate fiber sources of sufficient particle size to facilitate normal ruminal function also promote normal abomasal function. Minimizing stress caused by overcrowding, excessive competition, and adverse environmental conditions, and minimizing mastitis and metritis should also reduce problems with abomasal ulcers. Elimination of animals infected with the bovine leukosis virus from the herd eliminates lymphosarcoma as a cause of abomasal ulcers. Judicious use of corticosteroids and NSAIDs is also important.

32.136 ABOMASAL DILATION AND EMPTYING DEFECT OF SUFFOLK SHEEP

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32.136.1 Definition and Etiology

A syndrome of abomasal dilation and mechanical transport failure has been described in adult Suffolk sheep.[751–754] The condition resembles but is uniquely different from abomasal impaction of cattle wintering on very-poor-quality roughage. It has been mainly reported in Suffolk sheep but a similar syndrome has been described in two Hampshire,[755] one Dorset[756] and one Texel sheep.[757] No hereditary pattern of disease has yet been found.[753,754]

32.136.2 Clinical Signs and Differential Diagnosis

The disease is primarily manifested by anorexia and weight loss. Most patients eventually die. Animals described in reports from several teaching hospitals were adults of both sexes.[751–754] Not all animals had all of these signs, but the following have been reported: watery green diarrhea or normal feces; ruminal tympany; pear-shaped abdominal distention; increased, normal, decreased, or absent ruminal contractions; a palpable firm mass in the right lower abdomen; mild abdominal pain; tachycardia; duration of observed signs from days to months; partial to total anorexia; dullness and depression; marked to undetectable weight loss; ketonuria.

Wasting diseases of sheep include malnutrition, parasitism, dental problems, Johne's disease, caseous lymphadenitis, other chronic infections, and neoplasia. Abomasal emptying defect is distinguishable by the palpable abomasum in advanced cases and the exclusion of other possible problems. Other causes of abomasal enlargement or impaction resembling those reported in cattle must also be considered. However, when a mature Suffolk from a well-nourished flock shows weight loss and a palpable abomasum, this syndrome must be considered highly likely. Confirmation should involve response to therapy but may require necropsy or exploratory surgery.

32.136.3 Clinical Pathology

Reports on cases seen in North America have found hematologic and blood chemical determinations of little benefit in the diagnosis. The hypochloremic metabolic alkalosis common in cattle with abomasal problems has not been consistently observed in affected sheep. Elevated ruminal chloride ion values have been the most consistent laboratory findings in published reports.[752,753,758] The normal ruminal chloride level in sheep is 8 to 15 mEq/L; affected sheep have had values ranging from 34 to 130 mEq/L. Mild hypocalcemia was observed in all cases in one report.[753]

32.136.4 Pathophysiology

The mechanisms underlying the dilation of the abomasum and the failure to transport ingesta to the intestines are unknown. None of the problems commonly associated with abomasal impaction and dilation in cattle have been identified in affected Suffolk sheep. Recently Pruden and colleagues advanced that abomasal emptying defect of Suffolk sheep may be an acquired form of dysautonomia.[754]

32.136.5 Epidemiology

The disease has been mainly reported in sheep of the Suffolk breed. The disease has mostly been seen in winter months in association with lambing and feeding of concentrates. Both rams and ewes have been affected. Most cases are sporadic but at least two outbreaks have been reported.[753,754] The incidence in one report was 13 of 92 mature ewes affected in the flock during one winter.[753] In the other, five ewes of the same flock (200 ewes) were submitted for necropsy the same day.[754] In both studies, pedigree analysis of affected sheep in the flock showed no hereditary pattern. One report from a diagnostic laboratory in England described abomasal impaction in a Texel ewe and in a Suffolk ram that were simultaneously diagnosed as having scrapie.[757] It remains to be seen if any causative connection exists between the two diseases. Because no antemortem tests exist for the diagnosis of scrapie, this relationship will be difficult to establish. In one study, six sheep were immunohistochemically tested

for scrapie; five were negative, and one was positive and presented equivocal microscopic lesions.[754]

32.136.6 Necropsy Findings

The abomasum is greatly distended in sheep that die of this condition. The contents are either dry or liquid but most often have resembled normal ventral ruminal sac contents. The pylorus has always been patent. Normal ingesta have been observed throughout the remainder of the intestinal tract. Incidental findings have included aspiration of ruminal contents and subsequent pneumonia, abomasal ulcer with local peritonitis, passive congestion of the liver, megaesophagus, and esophageal ulcers. Reports of histopathologic findings include no lesions other than thinning of the abomasal muscle layers[753] (presumably as a result of stretching), mononuclear cell infiltration of the main muscle layers of the abomasums,[751] and one case of myxomatous changes in the abomasal branches of the vagus nerve.[752] Chromatolytic and necrotic neurons without signs of inflammation within the celiacomesenteric ganglia were found in six of six sheep examined.[754]

32.136.7 Treatment and Prognosis

Medical therapy alone with cathartics and laxatives has been of limited benefit. Mineral oil, dioctyl sodium sulfosuccinate, and magnesium sulfate have all been used. Neostigmine and calcium gluconate were not useful.[751] Abomasotomy has led to death from complications in many affected sheep, but those that have survived more than 2 days and have been treated with metoclopramide (dosage not reported) have shown varying degrees of recovery. Metoclopramide is a dopamine antagonist that has been used in ruminants to facilitate abomasal emptying. However, experimental studies in cattle and sheep have failed to demonstrate any beneficial effect of metoclopramide on abomasal emptying.[759,760] On the other hand, erythromycin, a motilin agonist, has been shown to increase abomasal emptying rate in cattle.[759,760] Its utility in sheep remains to be determined. Despite these successes, most affected sheep die of cachexia. Because of the expense, poor response, and risks associated with abomasotomy, this treatment is reserved for valuable breeding stock.

32.136.8 Prevention and Control

Until more is known about the pathogenesis of this specific defect in abomasal function in Suffolk sheep, no useful recommendations for prevention can be made.

32.137 ABOMASAL IMPACTION

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David Francoz

32.137.1 Definition and Etiology

Abomasal impaction is the accumulation of firm ingesta in the abomasum with failure of aboral transport. Depending on the cause, abomasal impaction can be classified as primary or secondary. In primary abomasal impaction, no underlying cause can be identified and the impaction is considered idiopathic. On the other hand, secondary abomasal impaction can be the result of feeding poor-quality, coarse roughage as the sole feed. Several animals in a herd may be affected over a short period. Calves may also have impaction of the abomasum

caused by eating bedding or indigestible objects when fed low-quality milk replacers. The distended abomasum is filled with a firm mass of fibrous ingesta. Animals on low-fiber diets may consume wood or baling twine. Hairballs occasionally accumulate in the abomasum of calves. Indigestible material creates a mechanical outflow obstruction. Abomasal distention may occur with normal diets after correction of abomasal volvulus, secondary to reticuloperitonitis, or secondary to the development of adhesions between the abomasum and the rumen and or the abdomen. These conditions are referred to as vagal indigestion. Lymphoma involving the abomasum or other space-occupying lesions adjacent to the pylorus may lead to abomasal distention. Abomasal emptying defects of Suffolk sheep were addressed in the previous section.

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32.137.2 Clinical Signs and Differential Diagnosis

Beef cows with abomasal impaction develop abomasal and ruminal enlargement over a period of days to weeks. Closely monitored animals have reduced feed intake and a reduced volume of firmer than normal feces. The animal may have bilateral ventral abdominal enlargement and bulging of the left paralumbar region. Ruminal contractions are of normal or increased frequency but often reduced in amplitude. In the later stages of the disease, ruminal motility often is absent. Cattle with advanced abomasal impaction may be recumbent and groan with each respiration. The consistency of the ruminal ingesta, as judged by ballottement, may be more fluid than expected on the basis of the coarse diet in some animals, whereas other animals have a uniformly firm and distended rumen. The pulse and respiration are usually normal until the animal is near death, at which time tachycardia develops. The abomasum may be palpable as a firm mass following the right coastal arch. Rectal examination reveals a distended rumen; often the ventral sac extends to the right body wall (L-shape rumen). The pyloric part of the distended abomasum may be palpable in the right ventral quadrant. Wintering beef cows usually are pregnant, and therefore the uterus prevents palpation of the abomasum. Mucus may be all that clings to the clinician's sleeve after rectal examination. Clinical signs in adult dairy cows are reported to be inconsistent, with the exception of decreased appetite.[761] In calves the abomasum may fill most of the abdomen and be doughy or firm on external palpation. The body condition of affected animals is invariably poor because negative energy balance precedes and is amplified by the impaction. If the abomasum ruptures, signs of generalized peritonitis occur. Death usually follows within hours of rupture.

In dairy cows, abomasal impaction should be considered in the differential diagnosis of nonspecific clinical signs of decreased milk production and appetite.[761] Conditions that cause dehydration and bilateral abdominal distention with absence of feces must be considered in the diagnosis. In many of these cases exploratory celiotomy is necessary to arrive at a definitive diagnosis.

32.137.3 Clinical Pathology

The hypochloremic, metabolic alkalosis typical of upper gastrointestinal obstruction in ruminants does not always develop in abomasal impaction.[761] Initially some fluid ingesta may pass through the abomasum, preventing chloride sequestration. However, some cattle have metabolic alkalosis with chloride accumulating in the rumen (internal vomiting). Terminally a metabolic acidosis from starvation may mask the metabolic alkalosis. Anemia and leukopenia can accompany the cachexia of chronic abomasal impaction in poorly fed animals. If abomasal rupture has occurred, profound hemoconcentration and leukopenia are present. Abdominocentesis generally is not useful in diagnosing abomasal impaction, because peritoneal fluid is abnormal only after abomasal rupture.

32.137.4 Pathophysiology

Animals fed roughage that is poorly digestible and incapable of meeting their energy requirements consume as much as the rumen will physically permit. The flow of ingesta from the forestomachs to the abomasum normally contains only small, finely digested particles of forage material. With chronic engorgement of highly lignified, poorly digestible forage, larger particles escape the forestomach and accumulate in the abomasum. Once a mass of fiber forms in the abomasum, further accumulation of particulate material is enhanced. With time, the mass fills the abomasum. Additional ingesta distend the abomasum to several times normal size. Also, abomasal secretion may be inhibited by the cachexia and chronic distention of the organ.

Abomasal transport failure after correction of abomasal volvulus is typical of vagal indigestion syndrome. Abomasal wall and vagal nerve damage, as well as peritonitis occurring secondary to the volvulus, prevent the return of normal abomasal muscular activity.[762] Vagal tone sometimes increases, and bradycardia is observed. Hypochloremic, metabolic alkalosis does develop frequently, with chloride accumulating in the ruminoreticular contents. The abomasum distends moderately, presumably as a result of atony.

Pyloric obstruction caused by foreign bodies or occlusion caused by lymphoma leads to mechanical outflow obstruction and must be considered. Chloride escapes back into the rumen, and metabolic alkalosis develops. The abomasum retains motility, but it is ineffective in moving ingesta into the duodenum.

32.137.5 Necropsy Findings

Emaciation and a firm, grossly enlarged abomasum are consistent with primary abomasal impaction. In Holstein cows a syndrome has also been described in which the impaction affected only the pyloric part of the abomasum.[761] The abomasal contents resemble normal, dry ruminal contents. The rumen is also enlarged but either filled with homogenous, watery ingesta that lack normal stratification or impacted with dry ingesta, similar to the abomasum. The abomasum is dilated, flaccid, and filled with fluidy ingesta if secondary to an abomasal volvulus. Intraluminal foreign body or tumor involvement of the abomasal wall is self-evident.

32.137.6 Prognosis

Because most cases of abomasal impaction are quite advanced when brought to the attention of the veterinarian, treatment usually is unrewarding. In dairy cows the short-term prognosis was reported to be good (93%) for impaction that affects only the pyloric antrum and guarded (50%) for impaction involving the entire abomasum.[761] The clinician must weigh the severity of the metabolic disturbances and the likelihood of recovery. Salvage by slaughter is often the most economic recommendation. If therapeutic measures do not resolve the impaction, death usually occurs within a few days of the onset of severe signs.

32.137.7 Treatments

Medical management includes correction of fluid and electrolyte abnormalities. Early cases may be resolved with easily digestible feeds, aggressive fluid therapy, and oral administration of laxatives such as mineral oil (4 L daily). Metoclopramide at a dose of 0.3 mg/kg given SC four to six times daily has been used to increase passage of ingesta through the pylorus. However, recent studies have failed to demonstrate any efficacy of metoclopramide on increasing abomasal motility.[763,764] Erythromycin (8.8 to 10 mg/kg IM bid) and bethanechol (0.07 mg/kg SC tid) alone or in combination with metoclopramide (0.1 mg/kg SC or IM tid) have been reported to increase abomasal emptying rate.[763,764] Pregnancy may be terminated by induction of parturition with

corticosteroids and/or prostaglandin, leading to improved comfort.

Different approaches have been proposed for a surgical treatment of abomasal impaction. Baker[765] recommended rumenotomy followed by installation of a nasogastric tube inserted into the abomasum through the omasum. Through the indwelling tube laxatives and emulsifiers may be given during the postoperative days to aid in softening and removing the abomasal contents. Mineral oil (8 mL/kg/day), dioctyl sodium sulfosuccinate (50 mg/kg/day), magnesium hydroxide (1 g/kg/day), or magnesium sulfate (2.5 g/kg/day) have all been recommended. Right flank or right paracostal approaches could also be used in order to gain direct access to the abomasum. Abomasotomy could be performed to remove the abomasal content, but it has not been reported successful in restoring abomasal function.[766] External massage may help break up the contents of the abomasum. Intraluminal administration of 5% dioctyl sulfosuccinate solution or saline could also be performed.[761]

32.137.8 Prevention and Control

Prevention of primary abomasal impaction requires proper dietary management of cattle in cold weather. Because animals outside without shelter have substantially increased maintenance energy requirements in cold, windy weather, straw or corn stover (stalks) is not adequate as the sole feed. Concentrates and better-quality forage prevent abomasal impaction. Monitoring body condition during winter weather alerts the good manager that supplemental feed is needed before abomasal impaction occurs.

32.138 OBSTRUCTIVE INTESTINAL DISEASES

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32.138.1 Definition and Etiology

Several conditions may lead to obstruction of the flow of ingesta through the intestinal tract. They can be divided into functional and mechanical obstructions. Functional obstructions (pseudoobstruction or ileus) are the consequence of neuromuscular perturbations of the gastrointestinal tract. Mechanical obstructions are the consequence of physical obstruction of the gastrointestinal tract secondary to digestive tract lesions (intussusception, volvulus, or congenital lesions) or extradigestive lesions (mesenteric fat necrosis, fibrous adhesions, or hernia). Each of the specific diseases is discussed in the following paragraphs and summarized in Table 32-20.

Table 32-20 Causes of Intestinal Obstruction in Ruminants

Disease	Animals Most Commonly Affected	Signs
Intestinal atresia or stenosis	Neonates	No feces; abdominal distention
Intestinal volvulus around mesenteric root	All ruminants; neonates more common	Colic; rapid abdominal distention; collapse; shock
Intussusception	All ruminants; LI or SI of neonates; SI of adults	Colic early, then chronic low-grade pain; dehydration; mucus plus blood in dark red feces; slow abdominal distention; decreased fecal output; mass palpated per rectum; distended loops of intestine per rectum
Cecal dilatation and volvulus	Adult dairy cattle in early lactation	Mild to severe colic; distended abdomen, especially upper right; ping in right paralumbar fossa; distended cecum palpated per rectum
Intestinal tumors	Sheep, rare in cattle	Progressive weight loss; cattle—may palpate mass per rectum; sheep—identify by celiotomy or necropsy
Mesenteric fat necrosis	Cattle, especially Channel Island breeds	May discover masses on routine examination; progressive weight loss; scant or no feces; dilated loops of bowel per rectum
Intestinal incarceration	All ruminants	See Intussusception
Pseudoobstruction or ileus	All ruminants	Scant or no feces; right-sided ping; succussable fluid on right; often associated with peritonitis

LI, Large intestine; *SI*, small intestine.

32.138.2 Clinical Signs and Differential Diagnosis

Acute manifestations of obstructive diseases include a reduced amount of feces or failure to pass feces, progressive abdominal enlargement with areas of tympanic resonance on the right side of the abdomen, and sometimes colic. If pain is severe, forestomach atony may occur. Mechanical obstructions may lead to circulatory shock and collapse. Electrolyte abnormalities depend on the site of the obstruction; those near the duodenum or pylorus lead to sequestration of abomasal secretions and result in hypochloremic, hypokalemic metabolic alkalosis. Obstructions of the cecum, colon, or rectum may lead to dehydration without alkalosis. If bowel necrosis or rupture occurs, acidosis may result from the circulatory collapse that accompanies peritonitis and the absorption of toxins.

32.139 INTESTINAL ATRESIA OR STENOSIS

Intestinal atresia or stenosis is a congenital anomaly reported in calves and lambs.[767–769] Clinical signs usually become evident within a few days after birth. Animals with anal or distal rectal atresia usually have the slowest onset of signs, whereas proximal obstructions lead to more rapid onset of signs. Malformations of the anus and rectum are believed to be hereditary,[770] and breeding of surgically corrected survivors should be discouraged. Jejunal atresia in the Jersey cow has been reported to be inherited as an autosomal recessive trait. The etiopathogenesis of atresia coli in calves is not well understood, but autosomal recessive inheritance has been reported[771] and Holstein calves seem to be predisposed.[772] Rectal palpation of the amniotic vesicle for early pregnancy diagnosis (<42 day of gestation) is also suggested to be a cofactor for the development of atresia coli.[772–774] If the anus or distal rectum is atretic, animals strain or pump their tails in an attempt to defecate. A fistulous connection may exist between the rectum and the urogenital tract (e.g., either the vagina or the pelvic urethra). Visual and digital exploration of the perineum reveals the absence of feces and may permit definition of the specific defect. Stenosis or atresia of the intestinal tract may occur to any degree and can be differentiated in four types according to classification in humans: narrowing, a membranous diaphragm with a perforation, or an imperforate membrane (type I); a cordlike remnant of the intestine (type II); a unique blind-ended dilation with complete separation of the intestine (type III, the most frequent); and multiple sites of atresia (type IV).[775] All have been described in cattle.[768] Affected neonates show depression and mild colic and progress to cardiovascular collapse after the intestine proximal to the obstruction becomes distended with fluid and gas. Tympany may be easily detected by percussion. If the anus and rectum are normal, a digital examination usually reveals only mucus or blood (or both). Because the rectal and descending colon walls are thin in cases of atresia coli, retrograde tubes or catheters should be used with extreme caution to avoid rupturing the bowel.[775] Complete intestinal volvulus must be considered in the differential diagnosis, but histories are often different.

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Surgical repair is indicated if the animal is of high value. However, the prognosis for normal and productive life is guarded. Many affected neonates develop severe complications in the immediate postoperative period. Pneumonia, sepsis and peritonitis are among the most frequent, and the development of bowel stasis or ileus is common. When registered animals are involved, a letter should be sent to the appropriate breed registry stating that the defect has been corrected.

32.140 VOLVULUS OF THE LARGE AND SMALL INTESTINE AROUND THE MESENTERIC ROOT

Volvulus of the large and small intestine around the mesenteric root leads to severe colic and relatively rapid abdominal enlargement. Circulatory shock develops rapidly. Ruminants of any age are susceptible, but most cases are seen in preruminant neonates. Casting and rolling to correct a left-displaced abomasum may predispose to volvulus. Robertson[776] reported that 1% to 2% of surgical abomasopexies were followed by torsion of the intestinal mass around the mesenteric root. Severe colic is seen, including kicking and vocalization. Affected animals rapidly become recumbent, and hypovolemic shock develops.[777] The heart and respiratory rates increase greatly as shock develops. Variable-pitched resonant sounds may be heard bilaterally over the abdomen using simultaneous percussion and auscultation. In adult cattle the tympany is restricted to the right side. Succussion reveals splashing sounds, particularly on the right side. Rectal examination reveals distended loops of gut. Surgical correction is the only successful treatment option. The prognosis depends on the degree of devitalization of bowel. Animals surgically corrected during the early stages respond better.[777]

Volvulus of smaller portions of the intestinal tract leads to signs similar to those of complete intestinal volvulus

around the root of the mesentery but often is slower in onset. Colic with accompanying tachycardia, ruminal stasis, and anorexia is present to varying degrees. The abdomen is moderately distended on the right when the animal is viewed from the rear. Simultaneous auscultation and percussion on the right side reveal multiple-pitched resonant pings from the gas accumulated proximal to the obstruction. Rectal examination may reveal scant feces, mucus, or blood. The affected bowel usually is palpable as grossly distended with gas and some fluid. Because of their relatively long mesentery, the spiral colon (or part of it), the distal jejunum, and the proximal ileum may develop an obstructive volvulus. Therapy requires correction of acid-base and electrolyte abnormalities and rapid surgical manipulation by means of celiotomy.

32.141 INTUSSUSCEPTION

In the development of an intussusception, the oral portion of gut (intussusceptum) usually is engulfed and propelled distally by peristaltic action of the enveloping portion (intussuscipiens). Constable and colleagues reported an increased prevalence in calves less than 2 months of age compared with adults, and in Brown Swiss compared with Holstein cows.[778] The condition has also been reported in goats[779] and in sheep.[780–782] Intussusception may occur in either the large or the small intestine of calves but is almost invariably in the jejunum of adults.[778,783] Clinical signs include colic caused by the tension on the mesentery on the invaginating portion of the intestine. With time, ischemia of this portion leads to pain and eventually loss of sensation. Distention of the intestine with fluid and gas proximal to the obstruction leads to abdominal pain. Therefore a cow may show violent behavior or kicking at the abdomen in the first few hours that is eventually succeeded by treading and repeated lying and standing.[778,784,785] Over the course of several days the intussusceptum may become totally devitalized and slough. This is accompanied by severe peritonitis, and in the event of bowel rupture, toxic shock will develop. The exact cause of intussusception remains unknown. Most cases in adults were thought by one author to be associated with an intramural mass or polyp,[786] but others reports did not find such association.[778,784] The mass is propelled into the intussuscipiens by normal peristaltic contractions. In contrast, in the young animal no such mass lesion is usually associated with intussusception, but enteritis often is. *Oesophagostomum columbianum* causes nodules in the intestinal wall of sheep but has not been proved to be linked to multiple deaths from intussusception.[780]

Dehydration develops as gastrointestinal secretions accumulate in the gut lumen. In adults, hypochloremic, hypokalemic metabolic alkalosis develops gradually. The rumen becomes distended with fluid as its contents become more finely digested and abomasal reflux accumulates. The right side of the abdomen (or both sides) also enlarges as a result of the distention of the small intestine. Simultaneous auscultation and percussion of the right side of the abdomen reveals areas of variable-pitched resonance.[787] Rectal examination reveals distended loops of small intestine. The intussusception may be palpable as a firm mass. The cow may demonstrate pain when the mass is palpated. Feces are absent within hours of the onset of signs. The examiner may find mucus and blood in the descending colon. In long-standing cases the scant feces are very dark red and must be distinguished from the black feces (melena) associated with abomasal bleeding. Fluid obtained by abdominocentesis shows an increase in erythrocytes and leukocytes and an elevated protein level. Fever is often present because of peritonitis. If the condition is long-standing and bowel rupture has occurred, bacteria may be present. The CBC may reveal neutrophilia and an elevated plasma fibrinogen level.

In neonates with enteritis, fecal output decreases as appetite is lost after intussusception. A fever may develop as peritonitis occurs. Calves and other neonates may not exhibit obvious signs of colic. Abdominal palpation using both hands in an attempt to detect a mass is often successful in delineating an intussusception in a neonate. When neutrophilia, hyperfibrinogenemia, and loss of appetite develop after enteritis, intussusception should be suspected.

Treatment requires both surgical correction of the obstruction and parenteral restoration of fluid and electrolyte

balance. Because of the losses of chloride and potassium and the development of alkalosis, 0.9% sodium chloride solution with 30 mEq/L or more of added potassium chloride is recommended. Once intestinal patency has been restored, oral fluid and electrolyte supplementation usually allows the patient to achieve normal status. The prognosis is usually good if surgery is performed early in the course of disease. Complications such as peritonitis can occur and need to be controlled to maintain the chance of success. The surgical incision should be made high in the caudal right flank. A retrospective study of 336 cases of intussusception reports a postoperative survival rate of 43% and an overall survival rate of 35%.[778] The exceptions are animals with intestinal neoplasia that has metastasized.[788]

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32.142 CECAL DILATATION AND VOLVULUS

Reports of hospitalized animals indicate that the postpartum interval to the development of cecal disease may be longer than that for left displacement of the abomasum; 57% of cases occurred within 2 months of parturition[789] and 46% within 4 weeks.[790] Dirksen and Doll[791] described 19 cases in calves less than 6 months old. Of these, 84% were being raised for early slaughter, and the remainder for herd replacements. This suggests that feeding or management differences may predispose to cecal disease in calves. In adult cattle, cecal dilation generally is believed to precede cecal volvulus or torsion. The cause and pathophysiology of cecal dilation and volvulus remain unknown. Increased luminal concentration of VFAs was classically believed to play a major role in the etiopathogenesis of cecal disorders.[792] However, results of studies on the impact of VFA on cecal motility have been contradictory. A recent study demonstrated that increased concentration of VFA had only minimal effect on large intestine motility and was unlikely to play an important role in the development of cecal disorders.[793] Factors that affect motility, as described for displaced abomasum, are likely similar.

Cattle with cecal dilation have a more gradual onset of illness than that noted with cecal volvulus. The time required for dilation to develop into volvulus is unknown. With simple dilation, feed intake and milk production decrease. Mild abdominal pain may be observed. The right paralumbar fossa usually is distended without the ribs being sprung. A large area of resonance is auscultable from the tuber coxae to a variable distance cranially[787] (see Fig. 1-3). Feces are usually still present, but the consistency may be loose and the amount reduced. The apex of the gas-filled cecum may be felt in the pelvic canal or nearby by rectal examination.

Cattle with cecal volvulus show an abrupt onset of anorexia, agalactia, and severe abdominal pain. Tachycardia and forestomach stasis are also present. Feces are scant or absent. The abdominal distention usually exceeds that caused by simple cecal dilation. The area of resonance in the right paralumbar fossa is larger, and fluid usually can be detected in the cecum and proximal colon by succussion. Although some cows with simple dilation have no acid-base abnormalities,[790,794] most with cecal volvulus have some degree of metabolic alkalosis with hypochloremia and hypokalemia.[790] The apex of the cecum is usually not palpable per rectum; rather, the distended body of the cecum or proximal colon impinges on the pelvic canal because the apex is directed cranially. Distended small intestine may be palpated with either cecal dilation or volvulus. Medical management of cecal dilation is usually successful with use of fluid therapy to restore normal hydration status and administration of nonsteroidal antiinflammatory drugs to control abdominal pain. In lactating cows, fluid therapy may contain calcium. Laxatives have also been recommended for the medical treatment of cecal dilation. However, Braun and co-workers[795] reported that the use of laxatives (liquid paraffin) for the treatment of cecal disorders delayed the time to first defecation. Moreover, magnesium hydroxide may be responsible for detrimental effects such as metabolic alkalosis,[796] increased ruminal pH,[797] and decreased ruminal microbial activity.[797] Prokinetic drugs that can be used in the management of cecal disorders are presented in the section on the acute abdomen in cattle. Finally, animals should be fed a high-fiber diet. Some cattle have recurrent episodes of cecal dilation, and preventive

surgery such as typhlectomy may be indicated. In two reports the recurrence rate after surgery was about 10% within a year of the first incident.[789,790] Cattle with cecal volvulus require immediate surgical intervention, fluid management to correct the hypochloremic, hypokalemic metabolic alkalosis, and administration of NSAIDs to control pain. The prognosis for surgical patients depends on the degree of ischemic injury to the cecum and other structures involved in the obstruction.

32.143 INTESTINAL TUMORS

Intestinal tumors are rare in cattle. The most commonly reported intestinal tumors in cattle are adenocarcinomas. However, lymphosarcoma, adenoma, adenomatous polyps, carcinoid, leiomyoma, leiomyosarcoma, and fibrosarcoma have also been described.[798] The incidence in sheep is relatively high in some areas of the world. An unusually high incidence of intestinal tumors was seen in cull ewes in New Zealand in the mid 1950s.[799,800] The rate of gross lesions in asymptomatic ewes going to slaughter ranged from 0.4% to 4.4%.[801,802] Breeds of British origin were observed to have a higher incidence than “fine wool” breeds. In subsequent studies in New Zealand, Australia, South Africa, and Iceland, the type of husbandry practiced was linked to a higher incidence of tumors. Details of which specific common factor or factors might be responsible await further research. No specific environmental or toxicologic exposures could be incriminated.

Affected cattle or sheep may have a protracted course of weight loss with no other observable signs until near death. Alternatively there are reports of acute gastrointestinal disturbances manifested by colic, abdominal distention, and auscultable right-sided pings.[803] Although these cases are rare, they must be differentiated from other causes of acute obstruction in cattle such as cecal volvulus, intussusception, or abomasal volvulus. In cattle in which rectal examination is possible, the lesion may be detected on routine examination as an intramural mass or annular constriction of the jejunum or ileum. In sheep, the diagnosis is usually made at necropsy. Clinical signs in affected animals might include diarrhea, abdominal distention caused by the accumulation of gas and ingesta proximal to the obstruction, or ascites. The well-characterized lesions in sheep involve local spread of the tumor through the lymphatics and intraperitoneally. Ultimately, cellular deposits occur on all visceral and parietal peritoneal surfaces, severely impairing lymphatic drainage from the abdomen.

32.144 MESENTERIC FAT NECROSIS

Mesenteric fat necrosis affect cattle of all breeds, but more commonly Aberdeen Angus and Jersey cattle.[804] It has also been reported in a pigmy goat.[805] The cause remains unknown but dietary factors have been implicated, such as consumption of feed containing long-chain, saturated fatty acids; trace element deficiency; trauma; hormonal disturbance; and ingestion of endophyte-infected fescue.[804,805] The lesions develop as an inflammatory response around degenerating adipose cells. The triglycerides in these cells are thought to undergo hydrolysis to glycerol and fatty acids. The longer the carbon skeleton and the greater the degree of saturation, the more resistant are the fatty acids to removal by normal cellular mechanisms. Remaining clumps or crystals of fatty acids serve as inflammatory foci for the subsequent necrotic masses.[804] Affected cattle have subnormal serum free cholesterol and elevated serum free fatty acids.[806] Cattle with fat necrosis may eventually develop an intestinal obstruction. The clinical signs resemble those of progressive intestinal obstruction from other causes. Weight loss, anorexia, diarrhea, bloody stool, abdominal enlargement, and right-sided ping are all possible signs. Fever, tachycardia, and signs of discomfort such as tenesmus, treading, and teeth grinding may be seen as the obstruction becomes more severe. Many affected cattle have no clinical signs, and the condition is discovered during rectal examination for other reasons. Rectal examination may be impossible because of stricture of the rectum, or dystocia may occur as a

result of the necrotic fat masses in the pelvic canal. Fat necrosis usually affects mature cattle,[804] but there is a report of a 6-month course of illness attributed to fat necrosis in a 13-month-old Black Angus heifer.[807]

Animals with fat necrosis that become clinical usually are not treated. Different treatments have been attempted over the years, but none was considered effective. Experimental therapy of subclinical fat necrosis using a compound that alters lipid metabolism in fungi was successful in one study.[806] The fungicide isoprothiolane was given at a dosage of 20 g/day PO for 8 weeks. Approximately half of the treated cows had a 50% reduction in necrotic masses by 12 weeks; at follow-up evaluation in 1 year the masses were not detectable in half the surviving cows. Cows given such unapproved drugs should not be used for food.

32.145 INTESTINAL INCARCERATION

Intestinal obstruction may occur in ruminants as a result of accidental entrapment of loops, usually of jejunum, around remnants of embryonic structures or through acquired defects in mesentery or the abdominal wall. Duodenal obstruction caused by malposition of the gallbladder was also reported in a heifer.[808] Intestinal adhesions caused by intraperitoneal injections of irritating substances may also lead to intestinal obstruction. Initial signs of colic followed by depression, anorexia, progressive abdominal distention, and absence of feces usually develop. Distended loops of small intestine usually are palpable per rectum. Remnants of the urachus,[809] the omphalomesenteric duct,[810] and the left umbilical vein[811] in cows and of the ductus deferens[812] in steers have been described as responsible for incarceration of the jejunum. The authors of one report indicated that 26% of cows examined had a persistent round ligament of the liver and falciform ligament.[811] Therefore tears in the falciform ligament leading to intestinal entrapment may be among the most common causes of the relatively rare problem of intestinal incarceration in cattle. Treatment of intestinal incarceration requires surgical intervention.

32.146 HEMORRHAGIC BOWEL SYNDROME (JEJUNAL HEMORRHAGE SYNDROME)

HBS or JHS is an acute enteric disease of cattle characterized by segmental intraluminal hemorrhage with subsequent obstruction of the small intestine. The disease seems to have been described for the first time in 1991[813] and is now considered an emerging disease in different countries.[814–817] HBS mainly affects dairy cows, but it is also reported in beef cows and a bull.[816,817] It is principally a sporadic disease, but outbreaks in dairy herds have been reported.[818,819]

The pathogeny of HBS is still unknown and may be multifactorial. *Aspergillus fumigatus* has been implicated in the disease,[820] but *C. perfringens* type A and *C. perfringens* type A with alpha 2–toxin are considered the most likely causes by many authors.[815,818,819,821] However, it is very difficult to clearly define the precise role of *C. perfringens* in the pathogenesis of HBS because *C. perfringens* type A is present in the intestine of healthy cows and is known to proliferate rapidly after death. Ewoldt and Anderson were unable to reproduce the disease by direct inoculation in the abomasum or jejunum of *C. perfringens* type A with alpha2–toxin.[822] According to the authors, this may be explained by the multifactorial pathogenesis of HBS. Different risk factors have been described in the development of HBS. They include lactation stage (being in the first 100 days of milk and in the second or higher lactation), feeding regimen (being fed with a TMR, or a high-energy diet with low fiber), and herd size (herds with more than 100 cows).[815,818,819,823] Berghaus and colleagues, in their study on risk factors associated with HBS, conclude that all management practices associated with high-producing cows may promote the occurrence of HBS.[823]

Affected animals may be found dead, but they typically demonstrated an acute decrease in milk production, anorexia, mild increase in heart rate, normal temperature and respiratory rate, and slight to moderate dehydration. These clinical signs worsen rapidly as the condition evolves. Mucous membranes are frequently pale or congested, which reflects the cardiovascular and hypovolemic shock. Animals usually have slight to moderate right abdominal distention. Clinical signs of abdominal pain may be present. Ruminal contractions are decreased or absent depending on the stage of the disease. The rumen may also be distended. In most cases, transrectal examination demonstrates intestinal distention, and scant to absent feces. An intestinal mass is rarely palpable per rectum. When present, feces contain digested and/or clotted blood. HBS must be differentiated from other cause of intestinal obstruction (intussusception, intestinal incarceration, volvulus of the intestine around the mesenteric root), dysentery (salmonellosis, coccidiosis, winter dysentery, coagulopathies), and melena from abomasal ulcers.

Signs of intestinal obstruction are observed during the transabdominal ultrasonography (distended intestinal loops, decreased or absent peristalsis). In some cases hyperechoic structures (blood clots) are observed in the lumen of the intestine.[815,817] Hematologic findings are consistent with a slight to moderate inflammatory process. Hematocrit is usually normal as a result of combined hemorrhage and hypovolemic shock. A hypochloremic, hypokalemic metabolic alkalosis is frequently observed on blood gas analysis, consistent with a proximal intestinal obstruction. Postmortem lesions consist of segmental necrohemorrhagic enteritis of the small intestine. The jejunum is the portion of the intestine most frequently involved.[815–817] An intraluminal blood clot associated with intramural hematoma and ulceration is observed. Histologic examination of the intestinal wall frequently reveals submucosal hemorrhage, edema, and neutrophilic infiltration, as well as necrosis and ulceration of the mucosa.[815–817]

The medical treatment of HBS consists mainly of fluid therapy to restore electrolyte imbalance and to correct dehydration and antimicrobial drugs and NSAIDs to control pain and inflammation. In our clinics we also found a beneficial effect of transfusion of 5 to 6 L of blood.[817] Surgical treatment consists of right flank laparotomy associated with enterectomy of the affected intestines. If the intestines do not look devitalized, the clot can be dislodged by manual massage or enterotomy.

The prognosis for animals with HBS is guarded. Mortality rates of 100%[816] and 77%[815] have been described. However, 55% of cases survived at Saint-Hyacinthe.[815] Two animals out of five that were treated medically and 18 animals out of 30 treated surgically survived.

Because the etiopathogenesis of HBS is not well understood, it is difficult to provide recommendations for the prevention of HBS. Prevention may be focus on management practices, and particularly feeding practices in order to provide adequate fiber length and quantity in the diet. There is currently no available vaccine against *C. perfringens* type A. Vaccination with the commercially available seven-way clostridial vaccines does not appear to protect against development of HBS.[823]

32.147 ILEUS (PSEUDOOBSTRUCTION)

Failure to pass feces usually is a sign of intestinal obstruction. However, in adult, lactating dairy cattle, a condition of ileus of the intestinal tract that mimics complete intestinal obstruction is commonly observed. The condition often resolves spontaneously or with medical treatment (fluids, calcium, and pain management); in rare instances surgical decompression of the affected bowel is required. In a series of 100 referred cases of intestinal obstruction, 39 were judged to be simple ileus.[824] Cows are most often in early lactation, and treatment is sought for partial anorexia. Colic sometimes is the presenting sign. Clinical examination reveals a normal temperature, a normal to elevated heart rate, and normal respiratory rate. Ruminal motility is decreased. Slight right-sided abdominal

enlargement may be seen early and may progress to extreme distention of the abdomen on the right. No borborygmi are heard on the right side, but fluid tinkling sounds may occur. Simultaneous auscultation and percussion reveal areas of variable-pitched resonance. Succussion produces sloshing sounds. On rectal examination a distended spiral colon, cecum, or small intestine may be palpated. Early in the course of the disease the distention is not extreme, and compression easily flattens the affected bowel. If abdominal distention is severe, introducing the arm into the abdominal cavity may be difficult because of the pressure of distended bowel at the pelvic inlet. No feces are passed, but the examiner's arm may be coated with sticky mucus and feces with a stale odor. Evaluation of serum electrolytes usually reveals no abnormalities or hypochloremic hypokalemic metabolic alkalosis. Serum calcium may be decreased. Differential diagnoses to consider include intussusception, intestinal incarceration, intestinal volvulus, and cecal dilation. There is no blood in the feces, and no masses are palpable per rectum with pseudoobstruction.

Because most obstructive lesions of the intestine in cattle are not immediately life-threatening, symptomatic therapy or simply close observation may be elected for 24 hours. If surgery is elected in the absence of an obstructive lesion, the bowel may be decompressed and drained. This is a laborious procedure that requires multiple punctures unless the distention is restricted to the cecum and spiral colon. Despite the lack of correction of a specific underlying defect, many cows begin passing feces soon after an exploratory celiotomy. Manipulation of the intestinal tract alone seems to have beneficial effects.[824] This response is difficult to differentiate from the spontaneous recovery that may occur without surgery in cows. Relief of distention of portions of the intestinal tract may remove reflex inhibition of motility that can occur in response to extreme stretching of mural tension and pain receptors. The cause of pseudoobstruction of the intestine is unknown, and little pathophysiologic information has been elucidated. Medical management is described in detail in the acute abdomen section. It mainly includes administration of fluids, calcium, and NSAIDs. Numerous practitioners also administer oral laxatives, but as mentioned earlier the practice of using magnesium salts may be questionable and could have deleterious effects.

32.148 DISEASES CAUSED BY *CLOSTRIDIUM PERFRINGENS* TOXINS (ENTEROTOXEMIA, YELLOW LAMB DISEASE, LAMB DYSENTERY, NECROTIC ENTERITIS)

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32.148.1 Definition and Etiology

C. perfringens is a toxin-producing, anaerobic, spore-forming rod. It is a variable species that causes a variety of diseases in human beings and animals. Some biotypes are normal inhabitants of soil, and some are commensal intestinal organisms of animals. A sometimes confusing nomenclature has evolved to organize the complexity of *C. perfringens* biology. Clinical isolates are assigned to one of the types (A through E) on the basis of possession of the major toxins (alpha, beta, epsilon, iota) (Table 32-21). In addition to these four major toxins, strains of *C. perfringens* may produce any of at least eight other recognized soluble antigens, some of which have pathogenic importance and could be called toxins. Beta 2–toxin may be an important toxin as well.[825] Most of these antigens are named with Greek letters.[826] The soluble *C. perfringens* toxin responsible for one type of food poisoning in humans has not received a Greek-letter name but is commonly known as enterotoxin (or CPE for *C. perfringens* enterotoxin). Enterotoxin is also the general name for toxins that affect the intestines, and many of the *C. perfringens* antigens with Greek-letter names are also enterotoxins. In this discussion the toxin that causes food poisoning in human beings is denoted CPE to distinguish it from enterotoxin as a class of toxins. CPE is not

recognized as the major component of classic *C. perfringens* disease in animals, but it may be important in some cases.[827,828]

The different biotypes of *C. perfringens* cause different diseases because they have different toxins, but a clear-cut assignment to one of the groups is not always possible, and overlap is considerable in the clinical signs caused by the various toxins. Many different diseases in many different animals have been ascribed to *C. perfringens*, but the ubiquitous nature of the organism and the fact that it rapidly overgrows into tissues after death makes the significance of its isolation questionable at times.

One additional potentially confusing bit of nomenclature concerns the term "enterotoxemia." Although this term is widely applied to various diseases caused by *C. perfringens*, it is strictly appropriate only for diseases in which the major signs are caused by systemic spread of the toxin in the blood.

One group of diseases caused by *C. perfringens* type C is commonly called "hemorrhagic enterotoxemia," even though the disease is not always hemorrhagic and, although the toxin may incidentally reach the circulation, it is produced in the intestine and exerts its major effects locally. A better descriptive name for this disease has been proposed to be necrotic enteritis.[829] It is important to realize that many of the effects of other biotypes of *C. perfringens* are systemic and that enteric clinical signs may be entirely lacking with disease caused by *C. perfringens* types A and D. Each type is discussed in the following paragraphs. Type E is only occasionally isolated from livestock and is not discussed.

32.148.2 Diagnosis of Disease Caused by Clostridium Perfringens

Meaningful diagnosis of *C. perfringens* as the cause of death or disease in an animal requires an integrative, open-minded approach. Type A is routinely isolated from soil and clinically normal animals. Types C and D are only rarely isolated from soil but can be isolated from asymptomatic individuals, especially those with neutralizing antibody to toxin. The bacterium proliferates after death, often crowding out other enteric organisms and invading tissues beyond the gut. The isolation of *C. perfringens* from a necropsied animal is not by itself sufficient basis for the diagnosis; however, if toxin is also demonstrated in gut contents and the history and lesions are compatible, a diagnosis of death from *C. perfringens* intoxication can be made.

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Table 32-21 Types of *Clostridium perfringens* by Toxin Type and Diseases That

Have Been Attributed to the Type*

Group Typing Toxins					
Type	**Alpha**	**Beta**	**Epsilon**	**Iota**	**Diseases Attributed**
A	XX	—	—	—	Gas gangrene (along with other organisms) Avian necrotic enteritis Hemorrhagic enteritis in cattle Yellow lamb disease Enterotoxemia of mink Type A enterotoxemia of horses Abomasal tympany and ulcers of calves[837] Sudden infant death syndrome (crib death) Food poisoning in humans
B	X	XX	X	—	**Lamb dysentery**[829,840] Enterotoxemia of sheep and goats (Iran) Enterotoxemia of foals (Britain)
C	X	XX	—	—	**Necrotic enteritis** (neonatal hemorrhagic enterotoxemia of calves, lambs, kids, foals, piglets)[829,839] Necrotic enteritis of fowl, struck (enterotoxemia) of sheep (Britain) Necrotic enteritis of humans (pigbel, Darmbrand)[829]
D	X	—	XX	—	**Enterotoxemia** ("overeating disease," "pulpy kidney disease") of sheep, goats, and cattle
E	X	—	—	X	Enteritis in rabbits Occasionally isolated from sheep and cattle Abomasal tympany and ulceration of calves[837]

X, Toxin of minor importance; *XX*, toxin of major importance; —, not present.

* Diseases of major veterinary importance are in boldface.

Until recently, an isolate of *C. perfringens* was assigned to one of the five biotypes by demonstrating toxin production with mouse-protection assays or ELISA techniques. This has been replaced by a multiplex PCR technique that detects the genes for toxin production in a clinical isolate.[830] CPE, which causes food poisoning in human beings, can be detected with commercially available assays and is also detected by the multiplex PCR technique.[831] Meaningful samples for bacterial isolation come from freshly dead animals. Samples of gut contents should be collected into sterile containers and cooled or frozen. In addition to typing bacterial isolates, demonstration of toxin itself in gut contents may aid in diagnosis. False-negative results may occur in type C disease if proteases inactivate the beta-toxin.

In the absence of definitive microbiologic evidence, a presumptive diagnosis of type C or D disease must be based on the history, clinical signs, pathologic findings, and differential diagnoses. Administration of toxoid vaccines is cheap and effective and may be recommended without conclusive evidence for causation. This "whole herd" protection test may be as close as one gets to definitive diagnosis in field situations. Examination of gut-content smears from various levels of the gastrointestinal tract to demonstrate large numbers of bacteria resembling *C. perfringens* may be a helpful piece of information, but the significance of such a finding by itself is questionable. Glucosuria in urine obtained from the bladder at necropsy is often seen in sheep (but not other species) with type D disease.

Type D disease should be distinguished from other causes of acute death (see Chapter 14). A history of sudden

death in a rapidly growing, apparently healthy individual is characteristic. A single lamb is much more likely to have overeating disease than is a twin. Other causes of acute disease in well-fed individuals include systemic pasteurellosis (lambs), acute bloat, grain overload, polioencephalomalacia, and thromboembolic meningoencephalitis (cattle). These generally have a longer disease course than type D enterotoxemia.

32.149 *CLOSTRIDIUM PERFRINGENS* TYPE A (JEJUNAL HEMORRHAGE SYNDROME, YELLOW LAMB DISEASE, AND OTHERS)

C. perfringens type A can be found in many soils and is a normal inhabitant of the gut in many species. Although all five types of *C. perfringens* produce alpha-toxin, type A strains usually produce more than other types. The toxin is a phospholipase and causes lysis of red cells, platelets, and leukocytes (equine and caprine red cells are resistant to the hemolyzing effects of toxin). The toxin also causes vascular permeability through endothelial damage and can cause necrosis at the villous tips in the intestines.[826] There is also a report of type A having the gene to produce a beta 2–toxin.[832] The beta 2–toxin may act synergistically with alpha-toxin to cause necrotic and hemorrhagic intestinal lesions.[825]

32.150 HEMORRHAGIC BOWEL SYNDROME

HBS (JHS, hemorrhagic enteritis) is an acute often fatal condition of cattle characterized by segmental intraluminal hemorrhage in the small intestine.[833] The jejunum is the most commonly affected portion of the small intestine. The disease is considered to be an emerging disease of lactating dairy cattle in the United States, with 9.1% of herds in a 2002 National Animal Health Monitoring System (NAHMS) study reporting at least one case of HBS during the previous 5 years. It appears that high milk production is related to the condition, probably through feeding practices and management factors.[834]

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Affected animals usually are anorectic, have a moderately elevated heart rate, and have a normal to subnormal temperature. Other signs consistent with small intestinal obstruction also develop, but abdominal pain is not usually observed. Feces may contain partially digested or clotted blood, and distended loops of intestine may be palpable per rectum. Transabdominal ultrasound may show an increased intestinal diameter proximal to the lesion, hyperglycemia, hyponatremia, hypochloremia, hypokalemia, and hypermagnesemia.[835]

Both medical and surgical approaches to treatment have had limited success. On postmortem examination *Clostridium* species may be seen in affected tissues. The odds of isolating *C. perfringens* type A from intestines of cows affected with HBS was 8.5 times greater than for cows with LDA.[833] Another theory is that *A. fumigatus* is the causative agent of HBS.[833]

Increasing the percentage of long stem fiber in the diet is associated with a decrease in number of cases of HBS.[834] The value of vaccination in preventing HBS has yet to be documented.[833] An attempt to reproduce the condition by inoculating either abomasa or jejuna of cows with *C. perfringens* type A failed to produce illness or lesions.[836]

Yellow lamb disease (so named because of the icteric nature of necropsied lambs) is an uncommon disease attributed to *C. perfringens* type A. Widespread hemolysis leads to anemia, weakness, hemoglobinuria, and icterus. The animals have a high temperature and usually die within 6 to 12 hours of onset. Differential diagnoses for yellow lamb disease include other causes of hemolytic disease, including leptospirosis and copper toxicosis. As with other type A infections, the diagnosis is always questionable owing to the commensal nature of the organism and its rapid invasion after death. The finding of predominantly large gram-positive rods in impression smears from

intestinal mucosa lends support to the diagnosis. No vaccine against type A disease is marketed in the United States, and types C and D toxoids are not expected to protect against type A unless they also contain alpha-toxoid.

One report implicates type A in neonatal calves with ruminal and abomasal tympany, abomasitis, and abomasal ulceration. The calves were 2 to 21 days old and died acutely or had signs of colic and depression of short duration.[837] Type A is a relatively common cause of food poisoning in human beings. Speculation links this type to human sudden infant death syndrome ("crib death") as well.[838]

32.151 *CLOSTRIDIUM PERFRINGENS* TYPE B (LAMB DYSENTERY)

Lamb dysentery is a disease of young lambs in Britain and South Africa. Type B has not been isolated in North America. Its clinical course and presentation are similar to those of necrotic enteritis caused by *C. perfringens* type C. Lambs less than 1 week of age become depressed and die. A yellowish diarrhea becomes brown from blood as the disease progresses. Morbidity may be high, and mortality approaches 100%. Necropsy findings include ulcers (rarely perforating) in the small intestines and dehydration of the carcass and tissues. Sanitation and the use of type B vaccine aid in prevention and control. Types C and D toxoid cross-protect because of the overlap in toxin types.

32.152 *CLOSTRIDIUM PERFRINGENS* TYPE C (NECROTIC ENTERITIS; NEONATAL HEMORRHAGIC ENTEROTOXEMIA; PIGBEL; STRUCK)

32.152.1 Definition and Etiology

C. perfringens type C elaborates the alpha (hemolytic)-toxin common to all types, in minor amounts, and the beta-toxin in major amounts. The amount of beta-toxin produced may determine the pathogenicity of a type C strain. In addition, type C strains produce the cytotoxic and hemolytic alpha-toxin, which is used to assign strains to group C if they have lost the ability to produce beta-toxin in culture.[839] Beta-toxin appears capable of producing all the signs of necrotic enteritis; the role of alpha-toxin or CPE in disease is unclear.[829]

Necrotic enteritis is primarily a disease of neonates and occurs in calves, lambs, foals, and piglets. A similar disease in adult sheep, known as *struck*, has a very limited geographic range in Great Britain.

32.152.2 Clinical Signs and Differential Diagnosis

Affected animals may die acutely without diarrhea, but this is rare. The diarrhea may be yellow or, in more hemorrhagic cases, brownish. Gray-red streaks of necrotic mucosa may be present in the stools. Foals with type C disease at first show acute abdominal pain, then explosive yellow diarrhea that becomes brown and hemorrhagic.[839] Animals become dehydrated, anemic, weak, and moribund, despite intensive therapy. Morbidity and mortality are high, but the disease is quite sporadic in occurrence. Salmonellosis and coccidiosis should be considered in the differential diagnosis, but necrotic enteritis is the more common disease in very young animals.

32.152.3 Pathophysiology

The causative beta-toxin is readily destroyed by proteolytic enzymes such as trypsin. The neonate is especially predisposed to beta-toxin attack by the presence of trypsin inhibitors in colostrum, the function of which is to prevent proteolytic degradation of immunoglobulins. Necrotic enteritis in humans is believed to be caused by decreased proteolytic activity arising from low-protein diets or the consumption of sweet potatoes, which contain heat-stable inhibitors of trypsin.[829] The scattered cases of necrotic enteritis in adult animals may be the result of similar dietary factors. Type C disease has been reproduced experimentally in maturing lambs by administering type C cultures and soybean flour, which contains potent protease inhibitors.[840]

Fig. 32-105 Perirectal and vulvar edema in a 3-month-old calf with acute oak bud toxicity. Acute acorn or oak poisoning causes similar lesions.

Ingestion of a protein-rich diet into a protease-deficient intestinal tract allows rapid growth of *C. perfringens* organisms. The bacteria attach to the villi, and elaboration of the cytotoxic beta-toxin results in necrosis and invasion of deeper intestinal layers. Death may result from the direct effects of the severe diarrhea or may be caused by secondary bacteremia or toxemia from the compromised gut barrier.

32.152.4 Epidemiology

Neonates that ingest type C organisms during the first few days of colostrum feeding are at risk. They pick up the organism from an environment contaminated by an asymptomatic shedder or from contaminated feed. Type C may be isolated from asymptomatic individuals on occasion, but it is not considered a normal commensal as is type A. Once established on a premises, the disease may become endemic. In foals the disease is significantly associated with housing in a stall or drylot during the first 3 days of life, previous presence of livestock on the farm, low amounts of grass hay fed postpartum, being born on dirt, and having stock horse parentage (e.g., quarter horse, Paint). Feeding smaller amounts of grain prepartum is associated with decreased incidence of the disease.[841]

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32.152.5 Necropsy Findings

Necrosis of the mucosa of the small intestine, especially the jejunum, is the consistent finding in all species. The large intestine may be normal except for intraluminal blood. The peritoneal cavity often contains excessive fluid, which clots when exposed to air. The mesenteric lymph nodes may be hemorrhagic. Microscopically, affected gut shows hemorrhage throughout the mucosa and submucosa. The tips of the necrotic villi are covered with numerous, large, gram-positive rods.

32.152.6 Treatment, Prevention, and Control

Once a case becomes clinically apparent, treatment generally is unsuccessful because of the fulminant nature of the disease. Foals can be treated with supportive intravenous broad-spectrum antibiotics (to cover gram-negative bacteremia caused by loss of gut integrity), fluids, plasma (intravenous and oral), withdrawal of milk for 24 hours, oral metronidazole, and intravenous *C. perfringens* types C and D antitoxin. Metronidazole (10 mg/kg PO or IV given twice daily) can be given to at-risk foals in the face of an outbreak, beginning at 8 to 12 hours of age and continuing for 5 days.[842] Toxoid has been administered to horses[843] to control the disease on an apparently endemic property, with good results. Antitoxin* may be given to animals at risk in an outbreak, and *C. perfringens* types C and D are common components of multivalent vaccines. The primary vaccination series consists of two injections 1 month apart, with the final dose given 2 weeks before parturition, and a yearly booster thereafter. Neonates should be vaccinated at 8, 12, and 16 weeks of age on problem farms.

* Dybelon *C. perfringens* types C and D antitoxin, Bio-Ceutic, St. Joseph, MO.

32.153 *CLOSTRIDIUM PERFRINGENS* TYPE D (ENTEROTOXEMIA, OVEREATING DISEASE, PULPY KIDNEY DISEASE)

32.153.1 Definition and Etiology

Enterotoxemia caused by *C. perfringens* type D is a disease of major importance in sheep and of lesser importance in cattle and goats. It is caused by strains of the bacterium that produces the epsilon-toxin. This type is not a common soil organism, as is type A, but it may be isolated from the feces of apparently normal sheep and, less often, cattle.[844] Most clinical disease occurs in animals fed a highly nutritious diet, especially grain-fed livestock.

32.153.2 Clinical Signs and Epidemiology

The sudden death of a well-fed, rapidly growing animal is the most common presentation of enterotoxemia. The disease may run its course in 30 to 90 minutes, with affected lambs showing ataxia, trembling, stiff limbs, opisthotonus, convulsions, coma, and death. At the onset of clinical signs, the animal is hyperglycemic. At death it is glucosuric. The differential diagnoses should include other causes of neurologic signs and acute death: anthrax, botulism, black disease, leptospirosis, listeriosis, enterotoxigenic *E. coli* infection, septicemia, polioencephalomalacia, toxic indigestion (grain overload), systemic pasteurellosis, and tetanus.

Sublethal doses may result in brain damage and focal symmetric encephalomalacia (see diseases of nervous system, Chapter 35). Affected lambs are dull and unresponsive to normal environmental stimulation. The major differential diagnosis is polioencephalomalacia. Experimental intravenous injection of type D epsilon toxin into calves produced neurologic signs and severe acute pulmonary interlobular edema. The histologic lesions in the brain consisted of perivascular proteinaceous edema in the interna capsule, thalamus, and cellebellar white matter, whereas in the lung intraalveolar and interstitial edema were found. These are similar to some of the lesions found in sheep and goats with type D enterotoxemia.[845]

The disease in goats is usually confined to the intestinal tract and seldom involves system signs seen in sheep.[846]

32.153.3 Pathophysiology

In some feedlot situations the animal ingests *C. perfringens* type D on a regular basis, but the acid environment of the abomasum and continuous peristalsis, as well as low amounts of fermentable substrate, conspire to keep bacterial numbers low and moving out of the animal. The intestinal environment also influences the amount of toxin produced.

Some factor of overnutrition, often heavy grain feeding or very rich pasture, provides substrate for rapid proliferation of the type D organism, leading to elaboration of the prototoxin. Cleavage of the prototoxin by proteases yields the active toxin. Epsilon toxin increases intestinal permeability, causing edema in a variety of organs, notably the lungs, kidney (hence the name “pulpy kidney disease”), and brain (focal symmetric encephalomalacia). Excess pericardial, peritoneal, and pleural fluid (with or without fibrin) and subcapsular petechiation in the kidneys may be seen.[847] These lesions cause rapid deterioration and death. Hyperglycemia and glucosuria are the result of massive hepatic glycogen release caused by the epsilon-toxin.

32.153.4 Necropsy Findings

Postmortem lesions are inconsistent. The pulpy kidney lesion may not be seen in freshly examined specimens. The epicardium, serosa, thymus, and diaphragm may have small areas of hemorrhage. The pericardial sac often contains excess fluid. The lungs may be edematous. Glucosuria is considered a hallmark of type D enterotoxemia but is sometimes not present. Histologic lesions include pleural and interlobular and perivascular edema in the lung, as well as perivascular edema in the brain of some affected animals.[847]

32.153.5 Treatment, Prevention, and Control

If initiated at the first suspicion of overeating disease, type D antitoxin and oral antibiotics (sulfa) may have dramatic results.[848] The diet should be adjusted downward in outbreaks to try to minimize the substrate, especially starch, that reaches the bacteria. Lambs on rich pasture should be moved to poorer pasture or corralled and fed hay until they have been vaccinated twice. Lambs and calves brought into a feedlot should have the concentrate ration increased slowly to minimize microfloral disruptions.

Antitoxin can be given in an outbreak, but previous vaccination is more effective. Vaccination with type D bacterin-toxoid is effective in preventing disease. Two doses are given 14 to 56 days apart, before heavy grain feeding or exposure to rich pasture begins. The aluminum hydroxide adjuvanted vaccines may cause raised subcutaneous lumps (most noticeable on goats) that may go on to abscess. Dairy goats fed continuous high-grain rations may need to be vaccinated more often for continuous protection. One study of three commercial vaccines found that one of the vaccines provoked no antibody response in goats 14 days after vaccination and that at 28 days after vaccination, even the goats that had responded to the other two vaccines had titers no higher than unvaccinated controls.[849] The vaccine is not licensed in the United States for use in goats but is routinely used. Bummer lambs may be protected by feeding bovine colostrum from cows vaccinated several times with the sheep vaccine to provide high titers in colostrum.[850] Colostral titers from the dam are protective to 12 weeks of age, after which vaccination should be used to provide active immunity against the disease.[851]

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32.154 BETA 2–TOXIGENIC *CLOSTRIDIUM PERFRINGENS* TYPHLOCOLITIS IN HORSES AND RUMINANTS

Beta 2–toxin is a newly described *C. perfringens* toxin that may play a role in intestinal diseases of ruminants and adult horses, particularly typhlocolitis. Affected animals may have a history of recent stress or antibiotic administration and show hemorrhagic, profuse, watery diarrhea, low body temperature, severe leukopenia, and hypoproteinemia.[852] The diagnosis depends on demonstration of the beta-2 gene by PCR.[853]

32.155 OAK (ACORN) TOXICOSIS

Bradford P. Smith

32.155.1 Definition and Etiology

Toxic signs can appear in ruminants[854,855] and occasionally in horses[856] that ingest large quantities of oak buds, oak leaves (green or dried), or acorns. Most species of oak (*Quercus* species) cause similar signs when ingested, although there are marked differences in the amount of toxins among the 75 oak species.[857] The metabolites of oak tannins and volatile phenols present in the buds, leaves, twigs, and acorns are responsible for causing toxicosis. The mouth, esophagus, gastrointestinal tract, and kidneys (renal tubular nephrosis) are the organs most affected. Because they are less selective in what they ingest, cattle seem to be the most frequently affected species. Signs begin shortly after ingestion of 50% or more of the diet as oak, and young cattle (under 300 kg) often appear to be more severely affected than adult cattle.

Factors leading to toxicosis include the presence of large acorn crops when forage is scarce, wind or hail that

causes large numbers of acorns to drop suddenly, or the sudden presentation of oak buds and young leaves to hungry cattle, as in spring windstorms or snowstorms that cover the grass and break branches. In the southwestern United States, range cattle regularly consume some oak species, which are apparently highly palatable and nutritious.[858] The condition has been described wherever oak grows, including most of the United States, France, Great Britain, Germany, Sweden, Australia, China, and South Africa.

Acorn calf syndrome is completely different from the oak toxicosis described in this section. Acorn calves are congenitally malformed calves born to dams that ingest large numbers of acorns under poor forage conditions during the second trimester of pregnancy. The cause appears to be a combination of poor nutrition and exposure to acorns. The calves have very short leg bones and may have abnormal hoof development and a short or long narrow head. In badly affected herds as many as 15% of calves are affected. The disease has been reproduced experimentally. Supplementation of the herd with adequate protein and energy eliminates the disease.

32.155.2 Clinical Signs and Differential Diagnosis

The course of oak toxicosis usually is 1 to 12 days, but some cattle have a protracted, debilitating disease.[854,855] In the peracute stages cattle are recumbent, weak, anorectic, and listless.[854] The rectal temperature is normal or below normal, and the heart and respiratory rates are elevated. Marked edema is present in the perineum and vulva (Fig. 32-105), and edema is obvious in the submandibular area, brisket, and ventral abdomen. Hydration appears adequate, but anuria is present. Firm, dark, mucus-covered feces usually are present. Evidence of hydrothorax, hydropericardium, and ascites may be noted on physical examination. Some cattle may simply be found dead.

A day or two after ingestion the animals appear anorectic and listless and have decreased ruminal motility. Many calves have hemorrhagic diarrhea or dark diarrhea that tests positive for fecal occult blood. The feces may have a smell of phenol. Dehydration occurs rapidly, but vital signs may be remarkably normal until hypovolemia develops. As uremia progresses, scleral vessels become dark and engorged, and the breath may take on the smell of ammonia. The major differential diagnoses are other causes of renal failure and other toxins and clostridial diseases; viral diseases that cause ulceration of the alimentary tract should also be considered. Protracted cases most often result from renal failure and uremia, although some animals have chronic oral, esophageal, or gastrointestinal ulceration or perforation with abscessation.

In horses signs usually are peracute or acute; they include sudden death or colic, tenesmus, and hemorrhagic diarrhea.[856] Acorn husks and shells may be noted in the feces. As with most colics, tachycardia, hyperpnea, and injected oral mucous membranes are seen. Increased abdominal borborygmi often are present, and hemoglobinuria may occur. Determination of serum or urinary phenolic (hydrolyzed tannin) content, based on a gallic acid standard, may be used in acute cases.[856]

32.155.3 Clinical Pathology

In cattle with peracute and acute signs, the serum urea nitrogen and creatinine are elevated, whereas other laboratory values may show considerable variation.[855,856] Initially hyponatremia, hyperkalemia, hypochloremia, hyperphosphatemia, and a marked hypocalcemia (5.1 to 6.8 mg/dL) accompany a mild metabolic acidosis with a very high anion gap (29 to 32).[854] Neutrophilia with mild hyperfibrinogenemia may be present. Although sorbitol dehydrogenase and GGT may be elevated, biopsy does not indicate that significant hepatic disease occurs with oak toxicosis. Animals may be anuric. If urine is being produced, often isosthenuria, proteinuria, and glucosuria occur. The urinary fractional excretion of sodium was elevated in one steer.[858]

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In protracted cases the major findings are elevated serum urea nitrogen, creatinine, and anion gap, with variable hyponatremia, hypokalemia (versus hyperkalemia in acute stages), hypochloremia, and hyperphosphatemia. A mild metabolic alkalosis may be present. Hyperfibrinogenemia and an increase in total plasma proteins also are variable. An elevated WBC count most often reflects chronic ulceration or abscessation (neutrophilia or monocytosis or both). Liver enzymes usually are normal in protracted cases. Urinalysis results are similar to those in acute cases; in addition, hematuria often is present. By 6 weeks after exposure, a normocytic, normochromic anemia may develop as a result of chronic inflammation and uremia, and hypoalbuminemia may result from chronic renal and gastrointestinal losses. By 8 weeks after exposure, surviving cattle have largely returned to normal renal function as determined by normal serum urea nitrogen and creatinine concentrations and by the ability to concentrate urine after a 24-hour water deprivation test.[854]

Laboratory findings in horses are similar to those in ruminants, except that during the acute stages rapid hemoconcentration and marked increases in PCV occur.[856] Although protein, occult blood, and hemoglobin casts have been reported to be present in the urine, the urine specific gravity was 1.052.

32.155.4 Pathophysiology

The toxicity of oak is attributed to its high concentration of tannins, which are hydrolyzed in the rumen to gallic acid, pyrogallol, and other compounds. The tannins themselves may contribute to oral, esophageal, and gastrointestinal damage by binding to proteins, including those in epithelial cells. This results in oral, esophageal, and ruminal ulcers or perforations. Protein-bound tannins are liberated in the acidic abomasum, making them available once again to damage intestinal epithelium. Some hydrolyzed tannins are absorbed and bound to plasma proteins and endothelial proteins, resulting in hemorrhage and fluid loss from the vascular compartment into body cavities and tissues; this results in edema. The gallic acid and pyrogallols are extremely toxic to renal tubules, causing acute tubular necrosis, anuria, electrolyte abnormalities, and uremia. Ruminants are more susceptible than horses because of the hydrolysis of the gallotannins in the rumen.

32.155.5 Epidemiology

Young cattle in the 100- to 300-kg range seem to be particularly susceptible. In the southwestern United States oak toxicosis accounts for considerable economic loss in cattle.[858] The disease is seen sporadically in other ruminants and in horses. The morbidity rate in cattle varies considerably, with several to many calves in a pasture usually affected, and case fatality rates frequently exceed 80%.[855]

The disease is most often associated with ingestion of acorns in the fall and buds or young leaves in the spring. Cattle turned onto a pasture with oak trees under which acorns have accumulated may have toxicosis even when adequate forage is available.[855] In other cases windstorms have dropped numerous acorns or branches in a pasture to which cattle were already accustomed. In the early spring a heavy, unseasonable snowstorm may occur, covering the grass and bending young trees and breaking branches so that oak buds and young leaves are accessible.[854] Young leaves and acorns are more palatable than older leaves and also contain more tannins (up to 10% dry matter in acorns). The seedlings, buds, and acorns of small scrub oak may be important forages for cattle in parts of the United States.[858]

32.155.6 Necropsy Findings

In peracute and acute cases prominent edema is often the most striking lesion. Ascites, hydrothorax, hydropericardium, perirenal edema, and subcutaneous edema are found. The kidneys are normal in size with multiple diffuse hemorrhages on the surface and extending into the cortex. The liver is slightly swollen and pale or mottled. Digestive tract lesions vary from congestion to hemorrhage and deep ulceration or perforation with necrotizing inflammation. Mucosal ulceration is found in the pharynx, esophagus, rumen, abomasum, small intestine, cecum, and colon. Free blood or melena may frequently be observed.

Diffuse renal tubular damage is present. The changes include coagulation necrosis of cortical tubular epithelium and dilated tubules devoid of epithelium but with intact basement membranes. Many medullary tubules contain hyaline, granular, or cellular casts. The principal renal lesion is necrosis of the proximal convoluted tubules, but glomerular degeneration and fluid in Bowman's capsules are also seen.

By 3 to 6 weeks after exposure, the lesions include gastrointestinal ulceration, often with secondary infection; some healed ulcers; secondary bacterial bronchopneumonia; and slightly swollen, pale brown kidneys. Histologically, atrophy of the cortical tubular epithelium with a marked interstitial fibrosis and mononuclear infiltrate is seen. Evidence of tubular epithelial regeneration may be present. The liver appears normal.

32.155.7 Treatment and Prognosis

In acute stages intravenous fluid therapy aimed at promoting diuresis and correcting acid-base and electrolyte abnormalities may be lifesaving. Calcium, sodium, and chloride deficits should be replaced, and sodium bicarbonate should be given if needed to correct metabolic acidosis. In anuric animals furosemide (1 mg/kg given IV) can be administered every 12 hours, along with adequate fluid therapy. Corticosteroids and NSAIDs are not likely to have a measurable effect on the course of the disease because they are unlikely to alter the direct toxic effects of the toxic metabolites. The prognosis is guarded and must be considered poor in animals that remain anuric despite therapy. The case fatality rate undoubtedly depends more on the amount of toxic material ingested than on therapy. Antibiotics, given to prevent secondary pneumonia and abscessation, ruminal transfaunation, and readily accessible grass hay and water are recommended components of nursing care.

If the animal survives the acute stage and begins to eat voluntarily, the prognosis for recovery is good unless secondary pneumonia or gastrointestinal abscessation after perforation occurs. Renal function can return to normal by 5 to 10 weeks, and weight gains as high as 1.76 kg/day may be recorded in recovered cattle.[854]

Colicky horses can be treated as one would usually treat colic (intravenous fluids, analgesics, oral laxatives). Particular attention should be paid to diuresis, acid-base balance, and maintenance of serum calcium levels.

32.155.8 Prevention and Control

No specific antidote exists for oak toxicosis, but supplementation with calcium hydroxide (hydrated lime) immediately before anticipated exposure to oak has been effective under experimental conditions.[859] Feed containing 10% or less calcium hydroxide is palatable. Consumption of 0.9 kg/head/day of cubed or pelleted supplement containing 10% hydrated lime is effective in preventing toxic manifestations.

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Supplementation of cattle suddenly exposed to oak with any feed reduces death losses, apparently by allowing

hungry cattle to consume the supplemental forage preferentially.[854,859] In an outbreak in California caused by spring snows in which 2700 cattle died of oak toxicosis, ranches where hay was immediately supplemented had minimum losses compared with ranches where feed supplementation was not offered.

32.156 WINTER DYSENTERY IN CATTLE

Charles L. Guard

Gilles Fecteau

32.156.1 Definition and Etiology

Winter dysentery is an acute, contagious diarrheal disease of cattle that occurs in epizootic fashion in a herd, usually during the colder months of the year. It is usually recognized by the clinical syndrome that occurs in herds and by exclusion of other causes of contagious diarrhea.[860] In the United States the disease is more common in the northern states; however, it has been reported in Australia, Sweden, the United Kingdom, Israel, France, Belgium, Japan, and Canada. The period of illness in an individual is brief, and within a herd the outbreak usually lasts less than 2 weeks. Recovery is spontaneous in most individuals, but in some cases supportive therapy may be indicated. The morbidity rate may be high in a herd that has not experienced winter dysentery for several years; regardless, mortality usually is rare. Although most reports indicate this to be a disease of adult cattle, in a herd outbreak mild diarrhea may be observed in animals as young as 4 months old.

There is still uncertainty regarding the precise cause of winter dysentery, but most recent attention has focused on a coronavirus that may be the same as or related to the coronavirus that causes diarrhea in neonatal calves. In Japan, France, Belgium, and the United States, investigators have identified a coronavirus or similar virus particle in the feces of cattle with winter dysentery.[861–866] The disease was reproduced by contaminating feed with untreated feces in one of two attempts.[861] By immune electron microscopy, antigenic cross-reaction has been demonstrated between the original Nebraska calf coronavirus diarrhea agent and coronavirus isolated from field outbreaks of winter dysentery.[863,865] A rise in serum antibody titer to the calf coronavirus after an outbreak of winter dysentery in adult cattle was found.[863]

32.156.2 Clinical Signs and Differential Diagnosis

Winter dysentery is an explosive diarrheal disease accompanied by some degree of anorexia and depression. In lactating cows, milk production is reduced. In rare cases mild colic may be observed; other animals may appear weak and prefer to lie down. If the diarrhea is severe or persists longer than a day, dehydration may develop. Weight loss is apparent and is caused by loss of ruminal fill and depletion of extracellular fluid. Ruminal motility usually is reduced, but intestinal borborygmi may be increased. Thirst often is increased, and polydipsia follows the diarrhea. Rectal examination may reveal dilated intestinal loops. The feces vary from light tan to dark brown; bubbles commonly form in the puddles that are deposited several feet behind the cow. Blood may be present in the feces of several animals in a group, typically in the first lactation heifers. The amount of blood may range from just visible to large clots, or it may be uniformly mixed into the feces. Some animals may have thick mucus in the feces. The odor in a barn during an outbreak of winter dysentery has been described as musty, fetid, and sweet and nasty.[867]

Fever usually is not present during the diarrheal phase of the disease but has been reported to precede it[860] or

have no consistent relationship.[868] Mild respiratory signs consisting of serous nasolacrimal discharge and a soft cough have been inconsistently observed before diarrhea. Diarrhea caused by BVDV, coccidiosis, and salmonellosis must be considered in the differential diagnosis of winter dysentery. With winter dysentery no mucosal lesions are visible on physical examination. The absence of coccidial oocysts or parasite ova in the feces helps exclude these agents as responsible for the diarrhea. However, diarrhea caused by parasites may precede the shedding of detectable organisms in feces. The rapid occurrence of multiple cases within a herd, and often within herds in a locality, suggests winter dysentery. Fecal culture for *Salmonella* yields negative results in uncomplicated cases of winter dysentery.

32.156.3 Clinical Pathology

No consistent hematologic changes that would be of diagnostic benefit have been observed. If significant dysentery persists for longer than a day, signs of anemia may develop.

32.156.4 Pathophysiology

If the current contention that a coronavirus or coronavirus-like agent is causal in winter dysentery is correct, the pathophysiologic characteristics of the disease can be attributed to lesions of the colonic mucosa.[864] Epithelial cells of colonic crypts are destroyed by viral action, leading to necrosis and hemorrhage. Even though histologic changes have been observed only in the colonic mucosa, blood was observed from the distal duodenum aborally in cattle that died of winter dysentery.[866] Loss of intestinal mucosal epithelium from colonic crypts leads to transudation of extracellular fluid and blood. The exact mechanism leading to the voluminous, watery diarrhea has not been clarified but may be related to the inflammatory nature of the disease. Mediators of inflammation may lead to hypersecretion in the small intestine and colon.

32.156.5 Epidemiology

The incubation period is thought to be 2 to 8 days. The most susceptible animals are first and most severely affected. In a small, housed herd, the typical incidence of diarrhea during an outbreak begins with the explosive appearance of signs in 10% to 15% of animals on the first day. The second day another 20% to 40% are affected. On subsequent days similar proportions become ill. By the end of a week the first affected animals are completely recovered, and only a few new cases occur. Typically within 2 weeks of the onset of diarrhea, all animals have recovered. This period is marked by significant reduction in milk production. In large herds the outbreak may be prolonged for 6 to 8 weeks. Animals in their first lactation usually are most severely affected, but other cattle recently fresh or otherwise stressed may also have a longer clinical course. This scenario is typical of a herd that had not experienced an epizootic of winter dysentery during the preceding few years. In some herds milder outbreaks occur annually, with fewer animals showing diarrhea and with less severe clinical signs.

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32.156.6 Treatment and Prognosis

Most animals with winter dysentery recover spontaneously in a few days without specific treatment. Many palliative treatments have been recommended and used over the years, including intestinal astringents, protectants, and adsorbents. On the basis of 30 years of observations, Roberts[869] considered none of these treatments to alter the course of the disease. Provision of adequate fresh water, palatable feed, and free-choice salt is the most useful nonspecific therapy. The occasional animal with prolonged or severe dysentery may need

a transfusion of 4 to 8 L of whole blood.

32.157 SALMONELLOSIS IN RUMINANTS

Bradford P. Smith

32.157.1 Definition and Etiology

Salmonellosis is one of the few diseases that are increasing in prevalence. According to one study, 75% of dairies sampled in California had evidence of *Salmonella* infection.[870] A recent multistate study found that 56% of dairies sampled contained cows shedding *Salmonella* in feces.[871]*Salmonella* of concern for livestock fall mainly into one species, *Salmonella enterica*, with numerous serovars or serotypes, such as *S. enterica* serovar Typhimurium, with the words *serotypes* and *serovars* used interchangeably. We shorten it to *Salmonella* Typhimurium by convention. More than 2200 *Salmonella* serotypes (serovars) have been identified, and many are potential animal and human pathogens. Multidrug-resistant *Salmonella* Typhimurium DT104 and *Salmonella* Newport are particularly virulent to animals and human beings. The presence of identical strains of *Salmonella* Newport among bovine and human isolates indicates that zoonotic transmission is likely.[872] Fortunately 10 serotypes of *Salmonella* in serogroups B, C, D, and E are responsible for most disease in cattle; therefore control programs can be aimed at these. Table 32-22 lists the serotypes most commonly isolated from ill cattle in 2006 in the United States.[873] *Salmonella* organisms are gram-negative enteric bacteria that are facultative intracellular parasites. Most serotypes are non—host-specific, but a few are host-adapted. *Salmonella* Dublin is host-adapted to cattle, *Salmonella* Abortus ovis, and *Salmonella* Arizonae to sheep, and *Salmonella* Abortus equi to horses. Host-adapted serotypes are found most often in their host species, where true long-term carriers exist.[874] In contrast, non—host-adapted serotypes rarely achieve carrier status and usually infect an animal for a period of 3 to 16 weeks before infection is cleared,[874] although one cow with multidrug-resistant *Salmonella* Newport excreted the organisms for 190 days.[872] Infection with either host-adapted or non—host-adapted serotypes can be symptomatic or asymptomatic, depending on the dose, the virulence of the serotype, and the host's immune status. There appears to be an association between an increased incidence of *Salmonella* infections and intensive management practices such as large farms, crowded conditions, and high-protein diets. In the absence of carriers, chain infections and persistence of *Salmonella* in the environment are responsible for long-term persistence of a given strain on a given dairy.[872]

Table 32-22 Most Frequently Identified Salmonella Serotypes from U.S. Cattle

from July 2005 Through June 2006

Serotype	Serogroup
Typhimurium	B
Newport	C2
Orion var 15+34+	E1
Montevideo	C1
Agona	B
Courtesy Dr. Brenda R. Flugrad, APHIS, USDA, NVSL, Ames, IA.	

Salmonella are grouped into serogroups (A to Z and 51 to 65), depending on their cell wall antigens (somatic antigens that comprise specific oligosaccharides, often called *O antigens, LPSs*, or *endotoxin*). Thus, for example, local and regional laboratories often report that an isolate is a group D *Salmonella*. The most common group D isolate of cattle is *Salmonella* Dublin. Final confirmation that the *Salmonella* isolated is indeed *Salmonella* Dublin comes from the National Veterinary Services Laboratory in Ames, Iowa, or from some other laboratory in which antisera and facilities exist for identification of all 2200 serotypes on the basis of flagellar (H) antigens and somatic (O) antigens. Some serotypes also express capsular (Vi) antigens composed of mucopolysaccharide. Identification of the serotype is important in planning control strategies. In addition to the serotypes listed, lambs may be infected with *Salmonella* Arizonae, which comes from several different serogroups. *Salmonella* organisms are relatively easy to culture from the feces or tissues of infected animals, using common enteric agar such as XLT4 or brilliant green (BG) agar, with tetrathionate and selenite as selective enrichment media.

32.157.2 Clinical Signs and Differential Diagnosis

Salmonella infection can cause a variety of clinical signs. The most common signs are fever and diarrhea[875] after an incubation period of 1 to 4 days after exposure or a recrudescence from the carrier state. Animals of all ages may be affected, but serious illness is observed most frequently in very young animals and parturient dairy cattle.

The character of the diarrheic feces varies from watery to mucoid with fibrin and blood. Sheets of fibrin may appear to be sloughing mucosa. The feces often have a putrid, foul odor because of the presence of plasma proteins associated with severe IBD. Salmonellosis causes an acute protein-losing enteropathy. The systemic effects of endotoxins (and other toxic material) absorbed through the damaged bowel mucosa may be severe (fever, anorexia, depressed attitude, shock).

Bacteremia may occur rapidly, especially in neonates infected with *Salmonella* Dublin, *Salmonella* Typhimurium, or *Salmonella* Newport. Peracute to acute septicemia in calves may produce lesions in many organ systems. Affected calves usually are under 2 months of age (the range is 1 day to 6 months). Dyspnea, respiratory symptoms, sudden death, and occasionally diarrhea are the principal signs of *Salmonella* Dublin infection, the incidence of which usually peaks in 6-week-old calves. Blood culture results frequently are positive. Pure cultures of *Salmonella* Dublin often can be grown from specimens from the lungs of 4- to 8-week old calves with pneumonic (septicemic) salmonellosis. Calves infected with *Salmonella* Typhimurium are only 14 days of age on average (the range is 1 to 35 days) and have mainly enteric lesions, including enlarged mesenteric lymph nodes, abomasitis, fibrinonecrotic plaques in the ileum, and hemorrhage of Peyer's patches.[876]

Dry gangrene of the extremities may occur in calves after *Salmonella* infection, particularly with *Salmonella* Dublin. Legs, ears, and tails are most commonly affected, and cold agglutinins are suspected to be involved.[877]

In adult cattle, diarrhea or abortion may occur.[874] Abortion may occur by two mechanisms, because both culture-positive and culture-negative fetuses and placentae may be found in an outbreak. In the former, bacteremia in the dam results in infection of the placenta or fetus, with resulting fetal death and expulsion. Bacteremia and endotoxemia associated with diarrhea and damaged gut mucosa in cattle may result in release of $PGF_{2\alpha}$ and subsequent lysis of the corpus luteum. Abortion follows in 2 to 3 days, and the fetus and placenta will have culture-negative findings. When the fetus has a culture-negative finding, many other causes of abortion must be considered. Many infectious agents that infect only the dam can act similarly to cause luteolysis and abortion.

Differential diagnoses for the enteric form of salmonellosis in neonates include all the common enteropathogens of neonates: *E. coli*, rotaviruses and coronaviruses, clostridia, cryptosporidia, and other forms of coccidia. Concurrent infection with these agents is common. In older animals outbreaks should be differentiated from those caused by BVD, winter dysentery, and feed-induced indigestion. Pneumonic and bacteremic salmonellosis in 4- to 8-week-old calves must be differentiated by culture from pneumonic pasteurellosis; in goats, from mycoplasmal infection; and in lambs from septicemic pasteurellosis.

32.157.3 Clinical Pathology

Salmonella enteritis often results in changes in the hemogram,[878] as effects of endotoxin manifest.[879] Plasma fibrinogen frequently is elevated because of the inflammatory nature of the disease, and either neutrophilia or neutropenia may be seen. In severe cases a left shift may be present. Initial dehydration may result in an elevated PCV and plasma protein level. The plasma protein level often drops over a period of days as protein is lost into the bowel lumen. Many other nonspecific abnormalities in clinical chemistry values are often seen, including elevated liver enzymes, decreased plasma calcium, and indications of prerenal azotemia if dehydration occurs.

Definitive diagnosis of salmonellosis requires culture of the organism from feces, blood, or tissues. PCR is also available. Serologic evaluation to confirm the development of anti-*Salmonella* antibodies is useful[881] but is not commonly performed and is not currently available in most laboratories.

32.157.4 Pathophysiology

Salmonellae are invasive organisms that may penetrate ocular, nasal, oral, or intestinal mucous membranes. *Salmonella* infection is most often transmitted by fecal-oral contamination from livestock or rodents, or by feeding of contaminated protein source animal byproducts (e.g., fish meal, meat meal, bone meal, or feather meal, 40% of which are contaminated in the United States) or contaminated forages or plant proteins such as soybean or cottonseed.

Once eaten, salmonellae attach to mucosal cells, probably by means of a nonfimbrial adhesion.[881] Attachment is increased if gastrointestinal stasis is present or the normal competitive flora has been disturbed. Salmonellae cause degeneration of nearby cells and penetrate both through microvilli and through tight junctions between cells.[882] The bacteria pass through the enterocytes to the lamina propria, where they stimulate an inflammatory response and are engulfed by macrophages and neutrophils.[883] Intracellular bacteria reach regional mesenteric lymph nodes or beyond. The organism has a predilection for lymphoid tissues and is found in highest numbers in

Peyer's patches and mesenteric lymph nodes.[884] Thrombi form in vessels, and tissue damage can be severe. Virulent salmonellae are capable of surviving in host tissues and multiplying, often as facultative intracellular parasites in macrophages and reticuloendothelial cells.[885] In the case of carrier animals, salmonellae survive in cells in the presence of high titers of specific extracellular (i.e., serum) immunoglobulins. Intracellular salmonellae can also avoid many antimicrobial drugs and complement. Stress may cause a latent infection to recrudesce, resulting in fecal or mammary gland shedding or clinical disease.

The cell wall of all gram-negative bacteria contains LPS as a component. LPSs are also called *endotoxins*, and they are extremely biologically active, setting off an immunologic cascade of events that can lead to leukopenia, fever, anorexia, and eventually shock and death.[879]

32.157.5

Epidemiology and Control

A study of calves in California found that 18% of 1-day-old calves shed *Salmonella*, but this percentage declined rapidly over the first 11 weeks of life. Farms that received calves from other sources were 35 times more likely to have calves that were shedding *Salmonella* in feces than were closed herds.[886] Infection with host-adapted *Salmonella* serotypes may occur as a cyclic endemic disease, especially in calves when *Salmonella* Dublin is involved. *Salmonella* infections on a farm are maintained by (1) carrier animals shedding *Salmonella* Dublin in the feces[874] or milk,[880] (2) chain infections in infected calves and cows, (3) rodents, and (4) environmental contamination. *Salmonella* carriers infected with a host-adapted serotype such as *Salmonella* Dublin may shed constantly or intermittently. Cattle with the highest risk of becoming *Salmonella* Dublin carriers are heifers infected between 1 year of age and first calving and cows infected in the parturient period,[887] but calves surviving *Salmonella* Dublin infection and illness may also become carriers. Infected carriers that are not shedding are called *latent carriers;* stress may cause shedding in feces or milk to recrudesce. A single infected, asymptomatic fecal shedder may produce one billion *Salmonella* Dublin organisms per day to contaminate the environment (one million organisms per gram of feces). Unlike other serotypes, *Salmonella* Dublin may be carried as a chronic gut and mesenteric lymph node infection and passed in feces or carried as an intramammary infection and passed in contaminated milk.

Calving areas must be constantly cleaned and disinfected between calvings. Raw milk feeding to calves may be a source of *Salmonella* (100 to 100,000 organisms per milliliter of milk).[880] Infected calves constantly amplify the number of organisms in the environment, causing exposure of other calves. Calves with clinical signs may shed billions of *Salmonella* into the environment daily.

Environmental contamination can be difficult to eliminate, because salmonellae survive for months in moist areas out of direct sunlight and in lagoons and drainage areas. *Salmonella* Dublin was recovered from feces dried for 41 months.[888] Freezing feces at −20° C (−4° F) kills 85% of salmonellae in 2 days and over 95% by 1 month.[889] Direct sunlight and drying in hot weather are effective at eliminating salmonellae.

Research has documented contaminated irrigation water as an important source of *Salmonella* organisms. In some cases municipal sewage treatment plant effluents had contaminated water.[890] On one dairy farm, river water used to sprinkler irrigate green chop contaminated the green chop, which was fed to cows. On another farm, *Salmonella*-contaminated river water was used to irrigate cotton. When the cottonseed from that gin was used as feed, cattle became infected. On a third dairy, contaminated irrigation water resulted in haylage containing *Salmonella* organisms.[891]

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Feedlot cattle colonized by *Salmonella* organisms could pose a public health risk when meat is contaminated at slaughter. In a study by NAHMS, 7.5% of cattle on feed the longest shed salmonellae, whereas 3.5% of cattle that had recently entered the feedlot were shedding salmonellae in the feces.[892] Contamination of the animals before entry can cause the entering cattle to have a higher rate of shedding than was found in cattle that had been in the feedlot for several months[893] Standing water contaminated with feces is frequently highly contaminated with *Salmonella*; culture of temporary shallow lakes (called *playas* in the southwestern United States) yielded numerous *Salmonella* serotypes.[894] In one study 1.4% of cattle, mostly from dairies, shed salmonellae when in a veterinary clinic,[895] whereas I have found an average of 7% of cattle (mainly dairy cows) in our large animal clinic are shedding *Salmonella*.

Control of *Salmonella* infection requires an integrated herd approach. Sick pens were found to be 7.4 times more likely to yield *Salmonella* as were pens of preweaned calves.[896] Management interventions that were found effective in helping control *Salmonella* on dairy farms include separation of sick and parturient cattle into hospital and maternity pens respectively (considered the most important and effective intervention), switching from a phenolic disinfectant to a peroxygen biocide such as Virkon S for equipment disinfection, use of separate footwear or footbaths for personnel in the hospital and maternity pen sections, strict protocols for disinfection of hands and equipment between handling each sick or periparturient cow, strict separation of feeds used in the hospital and maternity pens, and use of clean bedding in the hospital and maternity pens.[872] To detect herds infected with *Salmonella* Typhimurium or other serotype except *Salmonella* Dublin, a herd serologic profile based on ELISA can be used.[897] Rectal swab sampling and culture of cull dairy cows was found not to be a satisfactory method of detecting *Salmonella*-infected herds.[898] To control *Salmonella* Dublin, carrier cows and calves over 6 months of age are identified by serologic testing (ELISA) for anti-*Salmonella* antibody.[880,899–901] Suspect animals are culled or tested further by serologic means or by multiple fecal cultures and milk cultures (five samples at weekly intervals). Animals with positive test results are culled. In infected herds, *Salmonella* Dublin carriers (fecal or mammary) usually make up 0.4% to 3% of a dairy herd. Animals that remain seropositive over a 2-month period should be considered carriers, even if a culture result is negative on five samples.[880] A Danish study[902] found that only 14 of 31 persistently seropositive animals were culture positive for *Salmonella* Dublin at postmortem examination, and one seronegative animal was culture positive. One study found that ELISA serology had a good negative predictive value for cattle 100 to 300 days of age, whereas fecal culture had a poor predictive value.[903]

To control all non—host-adapted and host-adapted serotypes of *Salmonella*, calves and cows are promptly treated when signs of illness occur, and strict procedures to prevent the spread of infection are instituted. A study of 14 farms infected with *Salmonella* Typhimurium DT104 showed that clinical disease ceased by 4 months, but widespread infection and contamination continued. Over time the number of infected farms gradually declined, and vaccination correlated positively with a herd remaining free of clinical illness from DT104.[904] Control measures include the use of separate feeding utensils for each calf, washing of boots and hands by calf raisers between calves, isolation of ill calves to noncontact pens, and thorough disinfection of pens between calves. Decontamination of pens is most effectively accomplished if an all-in, all-out system is used. Pens are divided into four groups, with each group of pens used for calves born during a given week. When 3- to 4-week-old calves leave their pens as a group, these pens are cleaned and disinfected with a chlorine product such as bleach, a peroxygen product such as Virkon S, or a phenylphenolic disinfectant. This helps prevent continuous recycling of bacteria to each group of new calves. Environmental monitoring by frequent swab cultures of pens is the best way to check the effectiveness of the sanitation and disinfection program. Infection with *Salmonella* Typhimurium and other non—host-adapted serotypes most often occurs as an epidemic after the organisms enter

the farm by means of purchased cattle, rodents,[905] rendering trucks, or feedstuffs. Even *Salmonella* Dublin may be maintained on a farm by mice.[905] A case control study of farms infected with *Salmonella* Typhimurium DT104 found that the most effective interventions included purchasing cattle directly rather than through a sales yard, quarantining purchased cattle for 4 weeks, housing sick cattle in dedicated isolation areas, and preventing wild bird access to feed storage areas.[906] Feeds may be contaminated by irrigation water,[891] in manufacturing when byproduct ingredients contain *Salmonella* organisms, on the farm, or in shipment by birds or rodents or contaminated trucks. When an epidemic involving an exotic serotype occurs, feedstuffs should be examined as a likely source. Exotic serotypes are *Salmonella* from serogroups other than B, C, D1, and E1; that is, all those groups not listed inTable 32-22. Feedstuff contamination with the serotypes not considered exotic may also occur. High-protein supplements, rumen bypass protein, or calcium-phosphorus supplements of animal origin are sources of epidemics of various *Salmonella* serotypes in livestock. Forty percent of all animal byproduct feedstuffs in the United States are contaminated with *Salmonella* organisms. Once a *Salmonella* serotype enters a herd, the bacteria are rapidly spread among livestock and into the environment, where they may cause a prolonged course of herd illness and can be difficult to eliminate. Such appeared to be the case with *Salmonella* Newport and *Salmonella* Montevideo in dairy cattle in California in the past (Table 32-23). These and other group C *Salmonella* species tend to become endemic and persist for years on a dairy farm once it has become infected. Culture of feeds before use on a farm currently is the only means of preventing the introduction of exotic *Salmonella* serotypes, because national and international controls currently appear to be inadequate.

32.157.6

Vaccination

Control by vaccination of dams using killed bacterins may be somewhat beneficial in protecting neonates under 3 weeks of age through colostral and milk immunoglobulin. Because most dairy calves are taken from their dam and fed milk replacer after day one to day 3 of age, the potential benefit of intraluminal milk antibody from the dam is lost. This may account in part for the fact that vaccination of cows by itself often is insufficient to protect calves from salmonellosis. In neonates over 3 weeks of age, colostral immunity appears to play only a small role in protecting against salmonellosis. Because both humoral and cell-mediated immunity are important in protecting against salmonellosis,[907–909] active immunity is superior to passive. Modified live, genetically altered vaccines that stimulate humoral and cell-mediated immunity offer better protection for calves.[909,910] Modified live vaccines have been available in Europe for years. Such a vaccine recently became available in the United States.* The role of increased nonspecific immunity to gram-negative core antigens (through immunization with rough mutants of *E. coli* and salmonellae lacking complete cell walls) is being investigated. Some studies have been able to demonstrate an increased survival rate for salmonellosis after vaccination with a mutant stain of *E. coli* (J5),[912] designed to produce antibodies to the common core antigens of gram-negative bacteria. Endovac-Bovi (Re mutant *Salmonella*) is marketed with the same goal.

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Table 32-23 Changing Incidence of *Salmonella* Serotypes on California Dairy

Farms as Illustrated by the Percentage of Farms from Which each Serotype was Isolated in 1985 to 1986 Compared with 1987 to 1988

Serotype	1985–1986 Percentage of Farms (No.)	1987–1988 Percentage of Farms (No.)
Dublin	78 (29)	53 (49)
Newport	19 (7)	36 (33)
Typhimurium	3 (1)	7.6 (7)
Montevideo	0	6.5 (6)
Infantis	0	2.2 (2)
Anatum	0	1.1 (1)
Arkansas	0	1.1 (1)

Blanchard P, Anderson M: Unpublished data based on calves brought for necropsy from Tulare area farms, 1988.

Available commercial *Salmonella* vaccines are killed whole cell bacterins for use in cattle, and a new genetically altered modified live *Salmonella* Dublin vaccine for calves.* Some practitioners report that they have used the live vaccine orally and found it to be effective but with fewer adverse reactions than when used parenterally. The only products that are solely *Salmonella* vaccines contain *Salmonella* Typhimurium or *Salmonella* Typhimurium and *Salmonella* Dublin or live *Salmonella* Dublin organisms (see Chapter 48). Autogenous bacterins can be made for serotypes not commercially available when they are isolated from animals on a farm and believed to be the causative agent of disease. A new subunit vaccine with siderophore receptor protein (SRP vaccine) is being marketed by AgriLabs under conditional USDA license. Siderophores are iron chelating proteins produced by all *Salmonella*, so producing antibodies against SRPs from *Salmonella* Newport should theoretically be effective for all serotypes of *Salmonella*, and because they are a subunit, they should be less toxic.

A major problem associated with *Salmonella* bacterins and modified live *Salmonella* vaccines is adverse reactions. Adverse reactions vary from fever, depression, and anorexia to collapse and death after vaccination. Animals may have severe reactions after the first, second, or third dose. The apparent cause of these severe reactions is a high degree of sensitivity to the presence of gram-negative endotoxin, which results in a rapid immune cascade leading to shock.[879] This sensitivity is genetically controlled, possibly accounting for the high frequency of adverse reactions in one herd and their absence in a neighboring herd. High ambient temperatures also increase sensitivity to the adverse effects of endotoxin. Adverse reactions usually can be reversed by using epinephrine (1 mL of 1:1000 [1 mg/mL] for every 50 kg of body weight given IM or IV) as soon as evidence of polypnea, dyspnea, or weakness appears.

Lack of efficacy of killed *Salmonella* bacterins in calves is evident in experimental studies. Commercial bacterin vaccines in aluminum hydroxide administered directly to calves at 2 and 4 weeks of age failed to protect the calves when they were orally challenged at 6 weeks of age.[912] Other research has demonstrated protection in older vaccinated calves that were challenged intravenously.[913] Calves under 12 weeks of age do not serologically respond with anti-LPS antibodies after vaccination with two or three doses of killed bacterins in aluminum hydroxide.[914] On the other hand, calves over 12 weeks of age and cows do respond serologically to two doses of the same vaccine.[915] The ELISA titer in cows is short-lived (2 to 4 weeks); therefore the timing of

two doses of the same vaccine.[915] The ELISA titer in cows is short-lived (2 to 4 weeks), therefore the timing of vaccination before parturition is critical if the aim is to increase the anti-*Salmonella* colostral immunoglobulin G titer.[915] Under experimental conditions, calves fed colostrum from vaccinated dams were not protected against oral challenge at 3 weeks of age.[878] One report suggests that vaccination with killed *Salmonella* Typhimurium vaccine prevented reinfection and recrudescence of clinical signs after an outbreak of DT104 and helped in eliminating the organism from the farm.[906] As mentioned previously, these differences may in part be explained by whether or not a calf continues to receive milk from its dam and thus has or does not have intraluminal antibodies. Other live vaccines have been found effective in calves and capable of cross-protection against other serotypes, including a DNA adenine methylase—deficient *Salmonella* Typhimurium[916] and an avirulent live *Salmonella* Choleraesuis strain 54,[917] but neither was licensed for cattle in the United States as of 2007.

* EnterVene-D, Fort Dodge Animal Health, Fort Dodge, IA.

* EnterVene-D, Fort Dodge Animal Health, Fort Dodge, IA.

32.157.7 Necropsy Findings

32.157.7.1 ENTERIC FORM

Calves often are emaciated and have serous atrophy of fat. Especially with *Salmonella* Typhimurium, the ileal, cecal, or colonic mucosae may be thickened and hemorrhagic with adherent fibrinonecrotic plaques. Fibrin may be found in sheets, especially pronounced in the areas of Peyer's patches. The abomasum, duodenum, and jejunum are often involved but less severely. The abomasum usually contains brown, fetid liquid. Bowel contents often are watery and may contain fibrin or blood or both.[876] The mesenteric lymph nodes frequently are enlarged and dark. Chronically affected cows or calves may have discrete areas of necrosis in the cecum or colon that may involve the entire thickness of the wall.[876]

32.157.7.2 SEPTICEMIC FORM

Gross lesions of bacteremic *Salmonella* infection are acute and usually subtle. Serosal and subcutaneous petechiae are widespread. The spleen usually is enlarged. The lungs are edematous and fail to collapse and have random foci of hemorrhage or congestion.[876] The wall of the gallbladder is thickened and may contain hemorrhages.[876] The bile frequently is inspissated into a firm coagulum.[876] Less common lesions include jaundice, cystitis, meningitis, osteomyelitis, arthritis, and dry gangrene of ears, tail, or feet. Gastrointestinal lesions may or may not be present.

32.157.8 Treatment

The keys to successful treatment of bacteremia caused by gram-negative bacteria are (1) antimicrobial drugs, (2) fluids and electrolytes, and (3) NSAIDs. *Salmonella* Typhimurium antiserum is available commercially. Adverse reactions by cattle to horse serum are common; care should be taken. 880 881

Early in the course of disease in calves, appropriate antimicrobial therapy often increases the survival rate markedly, because bacteremia frequently occurs. Appropriate antimicrobial therapy depends on culture and antimicrobial sensitivity patterns. Many of the most virulent *Salmonella* types are now multidrug-resistant, but isolates of relatively nonpathogenic *Salmonella* on dairies and feedlots found on surveys are usually sensitive to most antimicrobials.[886,918] In general, most *Salmonella* organisms are sensitive to florphenicol, ceftiofur (and

other third-generation cephalosporins), TMS, gentamicin, amikacin, and fluoroquinolones such as enrofloxacin.[885,886] Higher than label doses of ceftiofur used in calves with experimentally induced *Salmonella* Typhimurium infections did not alter mortality but did reduce fecal shedding and promote more rapid clearance.[919] Sulfas and fluoroquinolones may not be used extralabel in food animals in the United States. Aminoglycosides such as neomycin, gentamicin, and amikacin produce long-term tissue residues and should be avoided in animals intended for use as food. Susceptibility to ampicillin, amoxicillin, sulfas, and tetracycline varies considerably, whereas resistance to penicillin, streptomycin, erythromycin, and tylosin is anticipated. TMS combinations are relatively inexpensive, especially when given orally, but oral TMS should be used only in calves younger than 3 weeks of age. In calves over 3 weeks of age, trimethoprim should be given IV because it is destroyed in the rumen and not absorbed. Antimicrobial drugs such as fluoroquinolones, florphenicol, or TMS that achieve good intracellular levels and have a large volume of distribution appear to be more effective than those that do not achieve good intracellular levels (e.g., gentamicin and amikacin). Florphenicol or cephalosporins such as ceftiofur are good choices for therapy against many *Salmonella* isolates depending on susceptibility testing results. Antimicrobial drugs may not be effective at altering the clinical course of strictly enteric infections without bacteremia, but because bacteremia frequently accompanies salmonellosis, systemic antimicrobial therapy often is chosen.

The effects of endotoxins can be partially dampened or controlled by the judicious use of NSAIDs. The cascade of events caused by bacterial endotoxin (LPS from the cell wall) must be brought under control early and rapidly, by the use of drugs such as flunixin (Banamine) at a dose of 1.1 to 2.2 mg/kg every 12 hours. Once the animal is stabilized, NSAIDs should be discontinued, as continued administration can lead to adverse side effects such as abomasal ulceration.

Intravenous fluid therapy to maintain blood volume and pressure and correct acid-base or electrolyte abnormalities is important in any animal that is dehydrated or in shock (see Chapter 20, Neonatal Diarrhea, Chapter 32, Equine Fluid Therapy, for adult equine, and Chapter 44 on critical care). Measurement of blood gases and electrolyte values is useful to assist in fluid therapy formulations. Fluids containing sodium, with supplementation of glucose, should be administered intravenously as needed. Metabolic acidosis with mixed water by electrolyte losses is most often seen. Oral fluids and electrolytes may also be effective supplements. The prognosis is good if animals are treated aggressively and early in the course of illness.

32.157.9 Control of Infectious Disease in a Veterinary Hospital

Veterinarians must also be aware of preventing the spread of *Salmonella* and other nosocomial diseases within an animal hospital and should have an effective written infectious disease control program in place.[920] See Chapter 46.

32.158 JOHNE's DISEASE

Robert H. Whitlock

32.158.1 Definition and Etiology

Johne's disease is an insidious chronic infection of primarily ruminants but also includes rabbits,[921–923] foxes, stoats, weasels, Eurasian badgers, bears, wild boar, brown hare, brown rat, crow, rook, jackdaw, and long-tailed field mouse, among other species. It is caused by *Mycobacterium avium* subsp. *paratuberculosis*.[924–932] Despite having 99% DNA homology,[933,934] *M. avium* subsp. *paratuberculosis* can be differentiated phenotypically from *M. avium* subsp. *avium* by its dependence on mycobactin[935] and genotypically by the presence of multiple copies of an insertion element, IS900,[936] or a single copy of heat shock protein (HSx), among other DNA markers.[937] The two major strains of *M. avium* subsp. *paratuberculosis* identified by DNA strain typing are the cattle strain (c) and the sheep strain.[938] Other strains of *M. avium* subsp. *paratuberculosis*, with the exception of the Bison strain, have less species specificity.[939–942]

After ingestion of *M. avium* subsp. *paratuberculosis* during the perinatal period, the bacteria are absorbed by the M cells of the small intestine and gradually spread to regional lymph nodes.[943] Given adequate time, *M. avium* subsp. *paratuberculosis* infection becomes systemic, spreading to other body organs including the liver, mammary gland, uterus, pulmonary lymph nodes, and peripheral lymph nodes such as the popliteal and superficial cervical nodes. The term *Johne's disease* typically refers to the clinical disease condition with weight loss and diarrhea, whereas the term *paratuberculosis* refers to the condition of being infected with the causative organism, *M. avium* subsp. *paratuberculosis*, but not necessarily having clinical signs.

32.158.2 Clinical Signs

The great majority of infected animals appear clinically normal when compared with herdmates. Only after a prolonged incubation period, typically longer than 2 years and up to 10 years, do infected animals begin to develop subtle clinical signs including gradual weight loss despite a normal appetite and usually decreased milk production. Over a period of several weeks, concurrent with the weight loss, the manure consistency changes to become softer then loose and usually progresses to a pipestream diarrhea without tenesmus. The diarrhea is initially intermittent, with periods of normal manure consistency. Other than the loose consistency, the manure appears normal; blood, excess mucus, and tenesmus are not present during this time, and the animal continues to lose weight despite a normal appetite. In rare cases diarrhea begins suddenly as a persistent loose manure or watery scours. Other than the loose consistency, the manure appears normal. As the disease progresses, affected animals become increasingly lethargic and emaciated. Intermandibular edema and possibly ventral sternal edema caused by hypoproteinemia typify advanced stages of the disease. Cachexia and “waterhose” diarrhea characterize the terminal stages of the disease. Most animals are culled from the herd before this time because of decreased milk production and/or severe weight loss.

32.158.3 Stages of Infection and Disease

32.158.3.1 STAGE I: “SILENT” INFECTION (CALVES, HEIFERS, YOUNG STOCK, AND ADULT CATTLE)

Most cattle with Johne's disease are infected as young calves in the perinatal period. Recent evidence suggests horizontal transmission may occur among older heifers and even adult cattle. Once infected the organism proliferates slowly in the jejunal and ileal mucosa then gradually spreads to the regional lymph nodes. Animals in stage 1 of infection are rarely detected with even the most sensitive laboratory tests, including a fecal culture. At postmortem examination the organisms in the tissues may not be visible on microscopic

examination of tissues but may be detectable by culture of the tissues, because culture is a much more sensitive test than histopathology. This silent or eclipse phase of infection usually lasts for a minimum of 2 years and possibly for 10 years or more. However, in herds with a high prevalence of Johne's disease, cattle in stage I may proceed to stage II or even stage IV (clinical Johne's disease) by 1 year of age. Clearly the rate of progression of Johne's disease is *M. avium* subsp. *paratuberculosis*–dose-dependent and to a lesser degree dependent on age when infected. Cattle infected in the perinatal period typically progress to stages III and IV over a period of 1 to 3 years before being culled from the herd.

32.158.3.2 STAGE II: INAPPARENT CARRIER ADULTS

Inapparent carrier adults do not have weight loss or diarrhea but may have an altered immune response with increased IFN-γ response by sensitized T cells to specific mitogens and or increased antibody response to *M. avium* subsp. *paratuberculosis*. Some animals in stage II may have a positive fecal culture, shedding *M. avium* subsp. *paratuberculosis* in the manure, contaminating the environment, and serving as sources of infection to other animals on the farm. Animals may remain in stage II for several years depending on the age at the time of infection, the dose of organisms, and the immune response of the host.

Adult exposure to *M. avium* subsp. *paratuberculosis* occurs commonly in larger herds fed TMR that has been contaminated by *M. avium* subsp. *paratuberculosis*–infected manure from a super-shedder. These super-shedder cattle shed up to 10,000,000 colony-forming units (CFU) of *M. avium* subsp. *paratuberculosis* per gram of manure. Ingestion of less than 1 gram of manure from these super-shedder cattle may result in infection of the naive adult cow and/or a positive fecal culture. These periodic passive shedders should be suspected if the environmental *M. avium* subsp. *paratuberculosis* concentrations are high (equivalent to heavy shedders), suggesting the presence of a super-shedder in the herd. Subsequent fecal cultures over many months or years from these passively infected cattle should be negative, and the serum ELISA results should also be negative.

32.158.3.3 STAGE III: CLINICAL DISEASE

Animals at this stage have gradual weight loss and chronic diarrhea. The appetite remains normal. Intermittent diarrhea is often present for weeks. The vital signs, heart rate, respiratory rate, and temperature are normal. Emaciation and cachexia develop gradually with a decrease in milk production. Most animals at stage III are fecal culture positive and have increased antibody, usually detectable by a commercial Johne's ELISA and AGID test. Cattle at this stage of infection rarely remain in the herd longer than a few weeks and are culled for weight loss and unresponsive diarrhea.

32.158.3.4 STAGE IV: ADVANCED CLINICAL DISEASE

Animals in the advanced stages of the disease are weak and emaciated and usually have a profuse pipestream diarrhea. Intermandibular edema or bottle jaw is characteristic of this phase of the disease. Animals can progress quickly from stage II to stage IV, sometimes within a few weeks. Once the diarrhea is profuse and hypoproteinemia (bottle jaw) occurs, the animal's condition deteriorates rapidly, often in a matter of days. Most animals are sent to slaughter for salvage at this point. Otherwise, death occurs as a result of dehydration and cachexia.

For every cow with advanced Johne's disease born on the farm, it is likely that 15 to 25 others are infected.[944]

Only 25% to 30% of these infected animals will be detected with even the most sensitive testing techniques, fecal culture. The animal with advanced clinical signs is the "tip of the iceberg." As an example, consider a herd with 100 adult cattle and 100 young stock replacements. One cow born on the farm several years earlier develops clinical signs with weight loss and diarrhea. It is likely that 15 to 25 other cattle are infected, but less than 30% of these will be detectable by fecal culture (Box 32-10). It is also reasonable to conclude that if 25 to 30 of the adult cattle in a herd of 100 adult cattle are positive on a single herd fecal culture, most of the herd is probably infected.

32.158.3.4.1

Box 32-10 "The Iceberg Effect" in a Cow Herd

Stage IV	Advanced clinical disease	1 animal
Stage III	Clinical disease	1–2 animals
Stage II	Inapparent carrier adults	6–8 animals
Stage I	Silent infection of calves—young stock	10–15 animals
Total		15–25 animals

32.158.4

Clinical Pathology

Early stages of infection are not associated with any characteristic biochemical or hematologic changes. Animals with clinical signs are typically hypoproteinemic (TPP <5.5 g/dL) with reductions in albumin (<2 g/dL) and all classes of immunoglobulin. The marked muscle loss may be associated with elevated plasma phosphorous levels (up to 10 mg/dL), which is attributed to the catabolic state with phosphorus release resulting from muscle wasting. The animals are often mildly anemic (PCV <25%) with concurrent hypocalcemia (caused in part by the hypoalbuminemia), hyponatremia, and hypokalemia.

32.158.4.1

ANTIBODY-BASED DIAGNOSTIC TESTS

32.158.4.1.1

Agar Gel Immunodiffusion

The AGID test or rapid Johne's test (RJT) has diagnostic value only if the tested animal is showing weight loss and/or diarrhea. A positive test result in an animal with clinical signs has high specificity (>95%) for Johne's disease.[945] Lack of sensitivity and failure to detect animals that are fecal culture positive but not showing clinical signs are the major drawbacks of the AGID test.[946] The test should be reserved for the individual cow with clinical signs that are compatible with Johne's disease. One major advantage of the AGID test compared with serum ELISA is the near 100% specificity of the AGID; ELISA specificity ranges from 95% to 99%.[947] A small proportion (10% to 15%) of cattle with clinical signs will have a positive AGID test result but a negative result on the Johne's ELISA, seemingly a paradox, because the ELISA test will detect fewer antibodies than the AGID test.

32.158.4.2

ENZYME-LINKED IMMUNOSORBENT ASSAY

The ELISA detects and quantitates the host's serum antibody response to an antigen derived from *M. avium* subsp. *paratuberculosis*. The sensitivity and specificity of the ELISA are 25% to 45% and 95% to 99%, respectively.[948,949]

Animals with higher ELISA antibody titers or sample/positive (S/P) ratios are more likely to be infected with *M. avium* subsp. *paratuberculosis*.[950,951] The ELISA may be used to screen cattle to identify those at highest risk for Johne's disease. Those high-risk animals should have a fecal culture, considered the current gold standard test on live animals, to determine true infection status. If the culture test is negative, then the cow should remain in the herd. Advantages of serum ELISA are rapid turnaround time (2 to 4 days), low unit cost, and the large number of samples that can be processed each day. This screening process would permit a much higher number of cattle to participate in a Johne's disease control and/or certification program. An ELISA result should *not* be accepted as a definitive diagnostic test for the individual animal, nor should cattle be culled on the basis of an ELISA result. With less than 100% (range 94% to 99%) specificity,[952–960] any ELISA will identify some noninfected cattle as ELISA positive, especially in low-prevalence herds, a major disadvantage of the serum ELISA.

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32.158.4.2.1

Milk ELISA

Early reports found that milk ELISA testing was not considered adequate for routine diagnostic use in the United States.[961,962] Then in 2001 a company in Michigan introduced a more sensitive and specific milk ELISA based on existing serum ELISA for Johne's disease. Two reports on this commercial milk ELISA found the sensitivity and specificity to be similar to those of serum ELISA.[947,963] The 2002 NAHMS dairy study indicated both the sensitivity and specificity of the milk ELISA to be similar to those of serum ELISA.[964] Studies in Denmark indicated that cows in early and late lactation had higher levels of antibody than midlactation cows.[965–968] There are two major advantages of the milk ELISA over blood ELISA. The first is that milk samples are taken at monthly intervals for routine Dairy Herd Improvement Association (DHIA) testing, which saves labor costs of having the cows restrained to take a blood sample as well as the cost of taking the sample. The second advantage is that because the samples are routinely available at monthly intervals, dairy operators may choose which cows to test at what times, thus providing the opportunity of “target testing” such as at time of dry-off or when cows are checked for pregnancy. As with any ELISA test, blood or milk, some infected cows (as determined by fecal culture) will test ELISA negative. Elisa tests do not detect as positive about 15% to 20% of culture positive heavy shedders, 50% of culture positive moderate shedders, and 75% of culture positive low shedders. The use and validation of milk ELISAs is increasing, with more sensitive milk ELISAs on the horizon. Some countries are pursuing bulk tank milk tests as a herd detection test for Johne's disease.[969]

32.158.4.2.2

Complement Fixation Test

The CF test may be required for export purposes but is not recommended for diagnostic purposes. The test is plagued with major faults, including false-positive results and lack of sensitivity to detect infected cattle.[970,971]

32.158.4.3

ANTIGEN OR ORGANISM DETECTION TESTS

PCR tests to identify specific DNA segments (IS900 or HSx protein) in *M. avium* subsp. *paratuberculosis* represent state-of-the-art technology to detect this fastidious pathogen.[972–976] Until recently most PCR methods were less sensitive than fecal culture.[977–979] The PCR approach potentially has the greatest sensitivity and exquisite specificity to detect *M. avium* subsp. *paratuberculosis*. A recently approved USDA-licensed real-time PCR (qRT-PCR) test detects *M. avium* subsp. *paratuberculosis* in fecal samples at low concentrations and may be more sensitive than the standard culture method. Not only is the qRT-PCR test sensitive and 100% specific, but it quantifies the mycobacterial concentration in the manure and has a high correlation with fecal culture colony counts when serially diluted.[980]

32.158.4.4

HISTOPATHOLOGY

Microscopic examination of the intestinal tissues and adjacent lymph nodes after acid-fast staining with Ziehl-Neelsen stain, Kinyoun's method, or Auramine-O stain provides an accurate assessment of infection status if clinical signs of weight loss and diarrhea are present.[981,982] Finding acid-fast organisms in clumps within macrophages helps declare the biopsy positive for Johne's disease. Infected cattle with clinical signs should have a positive biopsy result. A negative biopsy report suggests that other causes for the weight loss and diarrhea should be explored. However, failure to demonstrate acid-fast organisms or to identify Langhans giant cells especially in the stages I and II of the disease does not necessarily imply the absence of infection. Other tissue sites may be infected but not selected for examination. Currently qRT-PCR on a fecal sample offers a more rapid and more sensitive test than histopathology of tissues. Histopathologic examination of tissues for Johne's disease should be reserved for cattle with clinical signs and is not appropriate for subclinical Johne's disease.

32.158.4.5

FECAL CULTURE

Isolation of *M. paratuberculosis* from feces remains the gold standard for routine detection of individual infected animals in a herd suspected of having cattle infected with *M. avium* subsp. *paratuberculosis*.[983,984] Fecal culture techniques employing both centrifugation and double incubation are able to detect 10 to 50 organisms per gram of manure[985] and identify two to three times as many infected animals as the current ELISA tests.[986] *M. avium* subsp. *paratuberculosis* can be detected in fecal samples of most infected cattle 1 year or more before the development of clinical signs. The major disadvantage of fecal culture is the prolonged incubation period of 12 to 16 weeks and higher cost than the ELISA.

Implementation of liquid culture systems for *M. avium* subsp. *paratuberculosis* has reduced the incubation time to 35 days or less.[987,988] Another advantage of liquid culture is the correlation of time to detection (TTD) to *M. avium* subsp. *paratuberculosis* concentration in the sample. However, the liquid culture detects *M. avium* subsp. *paratuberculosis* indirectly based on pressure changes in the culture vial or fluorescence of the sensor within the tube. This indirect detection necessitates more rigorous confirmation testing to verify that *M. avium* subsp. *paratuberculosis* rather than another organism or chemical reaction is causing the tube to flag positive. Liquid culture methods have been successfully developed to culture the sheep strain, which does not grow readily on culture media designed for cattle strains.[989]

Occasionally a positive fecal culture will be followed by several negative fecal cultures from the same cow.

This may be a result of passive excretion after consumption of contaminated feed materials.[990] With the recent description of super-shedders or cows shedding up to 5 million CFU per gram of manure, a small amount of manure in the TMR could easily result in a positive fecal culture owing to passive shedding or "pass-through" *M. avium* subsp. *paratuberculosis*. In some herds the rate of positive fecal cultures attributable to passive shedding could exceed 50% of positive cultures. Passive shedding usually results in low *M. avium* subsp. *paratuberculosis* CFU or low shedders, but on occasion moderate shedders may be the result of pass-through from super-shedders in the herd. Typically, low shedders constitute approximately 50% of positive cultures, whereas mid-level shedders represent about 20% and heavy shedders about 30% of all positive cultures over a period of time.[991] Herd owners need to focus on culling heavy shedders and super-shedders to reduce the herd bioburden of *M. avium* subsp. *paratuberculosis* and be less concerned about the detection of low shedders.

32.158.4.6

CELLULAR IMMUNITY TESTS

An ELISA to measure IFN-γ, a mediator released by sensitized T lymphocytes in response to stimulation by specific mitogens, may be a useful diagnostic tool in the future. Current studies suggest that the IFN-γ test may be more sensitive than other currently available serologic tests.[992–994] At this time a commercially available IFN-γ test is available, but the kit does not include an antigen for *M. avium* subsp. *paratuberculosis* and the laboratory has to provide an antigen. Research suggests that IFN-γ has promise, if a well-characterized and reproducible antigen can be consistently manufactured.

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32.158.4.7

DIAGNOSTIC TESTS FOR THE INDIVIDUAL ANIMAL WITHOUT CLINICAL SIGNS

The usual reason for a request to test an animal without clinical signs is to determine if the animal is free of *M. avium* subsp. *paratuberculosis* infection before it is introduced into a herd. Confirming the absence of infection in an animal without clinical signs remains a challenge for even the seasoned clinician. A negative AGID test or ELISA result does not prove the absence of *M. avium* subsp. *paratuberculosis* infection. Many animals in the early stages (I or II) of Johne's disease are nearly impossible to detect with any currently available diagnostic test. The clinician should obtain a complete history to determine if Johne's disease was present in the herd at any time during the previous 5 to 10 years. If both the herd owner and the herd veterinarian of record are willing to sign a statement to the effect that it was not, then the risk of purchasing an infected animal from this herd will be lower. Further evidence for the absence of Johne's disease may be obtained by finding negative ELISA test results on a group of 30 second-lactation or older cattle in the herd. qRT-PCR testing of composite environmental manure samples (four to six samples) that represents all cow groups within the herd offers rapid turnaround and high sensitivity to detect herd infection. Pooled (composite) environmental manure samples should include manure samples from five or six sites within the area where the cattle are grouped. Negative environmental samples from the herd of origin as well as a negative herd history increase the confidence that an animal is at low risk for *M. avium* subsp. *paratuberculosis* infection.

32.158.4.8

DIAGNOSTIC TESTS FOR THE HERD

The recommended herd test is an ELISA; performed on cattle in the herd, it is an excellent screening tool to determine the presence of *M. avium* subsp. *paratuberculosis* infection within the herd. Although the ELISA test is relatively specific, the sensitivity to detect lightly infected cattle is less than 20%.[948] If the commercial ELISA test detects one ELISA-positive animal, which is then confirmed positive by fecal culture, it is likely there are many more infected animals in the herd, perhaps as many as three times the number of ELISA- and

culture-positive cattle. If paratuberculosis is to be eliminated from the herd, annual whole herd fecal cultures are required to identify and cull those animals that may be spreading the disease to other animals, along with implementation of a strict biosecurity program.

32.158.4.9 ENVIRONMENTAL AND POOLED FECAL SAMPLES

Johne's disease continues to be considered a herd disease, with some diagnostic efforts designed to detect infection at the herd level as efficiently as possible. Initially, serum ELISA tests on 30 second-lactation cows or older were designed to address this need because this sample subset was relatively inexpensive with a rapid turnaround time. Over time, less expensive and more sensitive alternatives were sought, especially for sheep. An Australian report showed that one positive fecal sample from a sheep with multibacillary paratuberculosis could be readily detected when combined with fecal pellets of 49 uninfected sheep.[995] Later this approach to testing sheep flocks became the standard approach as a sensitive, efficient means to detect *M. avium* subsp. *paratuberculosis* infection.[995] Subsequently reports from the United States with cattle manure samples showed that culture of pools of five samples was sensitive to detect infected cows and could be done at a fraction of the cost of whole herd cultures on all adult cattle.[996] In this experimental study, 1:5 and 1:10 pools were tested. The sensitivity of pooled cultures ranged from 30% to 100% and was strongly dependent on pool size and the shedding level of the positive sample (low shedder compared with a heavy shedder). Occasionally culture of the pooled sample will be positive while each individual sample is found to be culture negative.[997,998] Evaluation of pooled fecal samples (1:5) in a range of Johne's disease—infected dairy herds detected at least 88% of samples that contained at least one animal shedding moderate (>10 CFU/tube) to high colonies per tube.[999] Later studies with pools of 10 fecal samples in low-prevalence herds proved cost-effective for herd screening and may provide an estimate of *M. avium* subsp. *paratuberculosis*–infected dairy cows within large herds.[1000] Optimal pool size depends on both prevalence and herd size, which has varied from three samples per pool for a 500-cow herd with low prevalence to five samples per pool for a 1000-cow herd with high prevalence.[1001]

Composite environmental manure samples (a combination of three or four manure samples from a specific area) from high—cow traffic areas in 64 herds known to be infected with *M. avium* subsp. *paratuberculosis* detected 50 of the 64 herds (78%) with positive fecal pools, thus providing evidence that environmental manure samples serve as an excellent proxy to detect herd infection.[998] With refinement of the environmental manure samples—composite or pooled manure samples within high—cow traffic areas, manure storage areas, and pens or lots representing all cow groups within the herd—the diagnostic sensitivity to detect herd infection is further increased.[1002] Additional investigations have shown that composite environmental manure samples from high—dairy cow traffic sites and manure storage areas have a greater sensitivity and would be less expensive for detection of herd *M. avium* subsp. *paratuberculosis* infection than 30 serum ELISAs of second-lactation and older cattle.[998,1003] Samples of lagoon water from larger herds (350 to 2500 cows) were significantly more likely to give positive results than composite manure samples from high—cow traffic areas.[1002] Because composite environmental samples are collected from high—cow traffic areas where cows defecate daily, the weather or season of collection should not affect the ability to isolate *M. avium* subsp. *paratuberculosis*. In addition, *M. avium* subsp. *paratuberculosis* has been shown to remain viable for long periods in the environment.[1004–1007]

32.158.5 Pathophysiology

M. avium subsp. *paratuberculosis* enters the intestinal tract typically by fecal-oral contamination and is taken up preferentially by the M cells, specialized absorptive cells in Peyer's patches,[943] where the organisms are resistant to intracellular degradation and eventually phagocytosed by subepithelial macrophages.[1008] However, recent work would suggest that these organisms may be taken up by absorptive cells throughout the entire length of the small intestine. Typically the organisms proliferate slowly within macrophages in the intestinal mucosa then spread to regional lymph nodes. In the regional lymph nodes the bacteria stimulate inflammatory and immunologic responses.[1009,1010] The elicited response is similar to that to other mycobacterial infections, most importantly T lymphocytes with cytokines from T helper cells. IFN-γ, one of these cytokines, is an important component of the protective host response and may be an early indication of *M. avium* subsp. *paratuberculosis* infection.[1011] In some infected cows the cellular response is able to control infection, with the animal never developing clinical signs but remaining subclinically infected for life.[992,1010] Poor nutrition, stress related to transport, lactation, and parturition have been proposed as accelerating or precipitating the onset of the clinical phase of infection.[992]

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The minimum time from infection to the onset of clinical signs requires at least 12 months of heavy and repeated doses of *M. avium* subsp. *paratuberculosis*, and small doses of organism may require more than 10 years before clinical signs appear. In heavily infected herds with many clinical cases, yearling heifers may show evidence of ill thrift and loose manure because of Johne's disease, but this is rare. Typically the first evidence of weight loss and diarrhea occurs within several months of calving or another period of stress. On some occasions noninfected adult cattle become infected as adults when introduced to a heavily infected herd and then develop clinical signs several years later. The infected animal responds to the mycobacterial organism with the recruitment of macrophages and development of giant cells.[1012] As the organism multiplies over weeks and months, the thickened intestine is less able to absorb nutrients and the animal loses weight despite a normal appetite. The thickened intestinal wall begins to gradually leak protein, mainly albumin, from the blood into the intestine, resulting in a direct nutrient loss from the bloodstream and hypoproteinemia.

32.158.6 Transmission

Fecal-oral transmission is the primary mode of transmission from an infected adult to the neonate. Most infections with *M. avium* subsp. *paratuberculosis* occur in the early neonatal period, often associated with the calf sucking the manure-contaminated teat and udder when ingesting colostrum.[1013] Multiple-use maternity pens serve as focal points to spread the infection. An uninfected cow may lie on manure from a moderate or high shedder and contaminate her udder with the organisms. Approximately 25% of calves born to cattle with clinical signs will be infected in utero, but only 18% of calves born to asymptomatic cows are infected in utero.[1014,1015] *M. avium* subsp. *paratuberculosis* has been isolated from uterine flush fluids of infected cattle.[1016]

M. avium subsp. *paratuberculosis* may be passed through the colostrum and milk from cattle in the later stages of infection.[1017,1018] Feeding pooled colostrum or pooled waste milk from several cows will serve to spread the infection from adults to calves during their most susceptible stage of life. Physical separation to calf hutches or better yet to another property such as a commercial heifer-raising facility decreases the risk of transmission to young calves. Although calves are most susceptible, older heifers and adult cattle can become infected from the ingestion of contaminated feed material. Feeding manger sweepings from the adult cows to older heifers has been shown to be a risk factor for spread of Johne's disease. Semen from bulls kept in commercial bull studs represents a very low risk because these animals are tested twice yearly for Johne's disease and must test negative. Although several species of wild animals may become infected with *M. avium* subsp. *paratuberculosis*,

they represent a very low risk to spread the disease to calves.[1019]

32.158.6.1 GRASSLAND PASTURE

Some dairy herds use intensive grassland grazing of their adult milk cows. This system relies on moving milk cows to a new fresh growth of lush pasture each 12 or 24 hours on a rotational basis for 15 to 30 days. Typically heifers or steers follow the milking cows to graze the pasture closer to the ground, so the pasture will not need to be clipped or mowed mechanically. This leader-follower system has been used in New Zealand for many years and is an excellent way to provide less expensive lush pasture to the milking herd, negating mechanical harvest and greatly reducing the need to feed expensive concentrate rations. However, in herds that have Johne's disease, the follower heifers or steers also are consuming *M. avium* subsp. *paratuberculosis* along with the lush grass left by the milk cows. Thus the follower cattle have a rather continuous uniform exposure to *M. avium* subsp. *paratuberculosis* over the months they follow the milking herd. Veterinarians need to be aware of this high-risk feeding practice, which perpetuates the transmission of *M. avium* subsp. *paratuberculosis* to younger cattle in the herd.

32.158.7 Prevalence

Johne's disease is widely distributed throughout the world in many ruminant species. Reports suggest 7% to 18% of cattle from slaughterhouse surveys are infected.[1020–1022] In Holland the true prevalence at cow and herd levels, based on an ELISA test sensitivity of 0.3 to 0.4 and a specificity that ranged from 0.985 and 0.995, was estimated to be 2.7% to 6.9% for cows and 31% to 71% for herds.[1023] Herd prevalence based on bulk tank milk antibody showed that 70% of dairy herds in Denmark were positive.[1024] A recent prevalence estimate, based on culture of ileocecal lymph nodes and ileum from dairy cows at slaughter in New Brunswick, Canada found 16.1% of cows positive, whereas 21.7% of cows from Maine were positive.[1025] In 1998 the NAHMS survey indicated the dairy herd prevalence to be 30% to 50%.[1026] More recent estimates of prevalence suggest 65% to 75% of dairy herds are infected in the major dairy states. Beef cattle have lower infection rates than dairy cattle.[1027] Paratuberculosis is extensively distributed among other ruminants including sheep, goats, deer, bison, and many exotic ruminant species kept in zoologic gardens. The apparent prevalence seems to be increasing, but this phenomenon may be a result of an increased awareness by producers and veterinarians.

32.158.8 Treatment

No practical therapy for Johne's disease is available. However, for cattle with significant genetic or sentimental value, several therapeutic agents have been used to effect remission of clinical signs. Isoniazid* given orally at 10 mg/lb daily, rifampin† at 10 mg/lb daily, and clofazimine‡ orally at 5 mg/lb daily have resulted in the amelioration of clinical signs facilitating collection of embryos and semen over an extended period of time.[1028–1029] The drugs must be given daily, and if therapy is stopped clinical signs may reappear within a few weeks. No drug or combination of therapeutic agents has been shown to eliminate the infection. Treated animals continue to shed *M. avium* subsp. *paratuberculosis* in the manure, contaminating the environment, and have viable organisms in their tissues, indicating the possibility that semen and embryos from treated animals may be infected. If animals with Johne's disease are treated with chemotherapeutic agents, the owners should agree with the prescribing veterinarian that milk or meat from that animal will never be used for human consumption. Drugs used to treat Johne's disease are being used in an “extralabel” manner with an appropriate client-patient relationship but without any data regarding appropriate withdrawal times. For further information, refer to

articles by Hoffsis and colleagues[1028] and St-Jean and Jernigan.[1029]

Brumbaugh and colleagues[1030] demonstrated a reduction in the number of CFU of *M. avium* subsp. *paratuberculosis* from the livers of experimentally infected mice treated with monensin compared with nontreated controls. Later, monensin was shown to either halt the progression of lesions or reverse the lesions in cattle with clinical signs of Johne's disease.[1031] Sections of tissues including liver, ileum, and adjacent mesenteric lymph node and a rectal mucosal biopsy were compared histologically with similar tissues obtained at necropsy after feeding 450 mg of monensin for 120 days. Taken together, the results of these two studies suggest that monensin may play a useful role both in the prevention of *M. avium* subsp. *paratuberculosis* infection in young cattle and in the treatment of established infection in adults.

Neonatal calves fed 70 mg of monensin twice daily in their milk replacer suggested in a proof-of-concept study that monensin is efficacious in controlling *M. avium* subsp. *paratuberculosis* infection in the neonatal calf. The amount of monensin (70 mg) administered per day to calves in this study is higher than the amount that would normally be consumed by a neonatal calf in a calf starter formula. In experimental dairy calves, monensin greatly reduced (>60%) both the passive fecal shedding and systemic tissue uptake.[1032] Monensin added to cattle rations at all phases of life, coupled with stringent implementation of biosecurity management practices at the farm level, offers new hope to help reduce the unyielding spread of this disease among the nation's cattle herds. Monensin seems to offer cattle producers another potent weapon in their management armamentarium to reduce the spread of Johne's disease within their herds. The costs are modest compared with many other management tools designed to reduce *M. avium* subsp. *paratuberculosis* bioburden within cattle herds. No other management technique evaluated to date has been shown to reduce *M. avium* subsp. *paratuberculosis* shed in manure of cattle and to reduce the tissue uptake of the organism to this extent.

* Available from multiple companies including Henry Schein, Inc., Port Washington, NY; Barr Labs, Inc., Northvale, NY; and Eli Lilly & Co, Indianapolis, IN.

† Rifadin, Merrell Dow, Cincinnati, Ohio.

† Lamprene, Geigy Pharmaceuticals, Summit, NJ.

32.158.9 Economic Losses Attributed to Paratuberculosis

Economic losses associated with Johne's disease have been attributed to many factors, including decreased milk production, decreased fat and protein yield, increased susceptibility to other diseases, loss of genetic potential, loss of export market, increased medical costs, reduced weight at slaughter, premature culling, poor feed conversion, increased calving interval, and financial loss at auction sales if animals are designated “exposed to Johne's disease.”[1033–1042] In dairy herds where 10% or more of cull cows have clinical Johne's disease, the estimated loss per cow exceeds $220 for each adult cow in the herd.[1043]

32.158.10 Biosecurity Practices and Herd Management Plans

The key to preventing, controlling, and eliminating Johne's disease in a herd is by implementation of a rigorous herd management plan designed to reduce *M. avium* subsp. *paratuberculosis* exposure to young calves.[1044] Factors such as finances, movement of cattle on the farm, maternity and sick cow pen locations, feed delivery to adult cattle, location and structure of feed bunks, and personnel issues are but a few of the specific issues that need to be reviewed with the final focus on how to best limit transmission of *M. avium* subsp. *paratuberculosis* to young calves. Farm managers should adopt two fundamental control principles: (1) prevent highly susceptible

newborn calves and young animals from ingesting manure from infected adults, and (2) reduce total farm environmental contamination of *M. avium* subsp. *paratuberculosis* by culling infected animals shedding the highest concentrations of *M. avium* subsp. *paratuberculosis*. Calves should be separated from their dams at birth and fed single source colostrum from culture-negative and/or ELISA-negative cows. The same management factors that reduce the risk for Johne's disease also reduce the risk of other fecal-oral diseases such as *Salmonella, Cryptosporidium, E. coli*, and *Campylobacter* infection.[1045]

Fecal culture testing of the whole herd followed by aggressive culling of infected animals is very effective in reducing the prevalence of paratuberculosis in the herd.[1044] The risks of transmission of *M. avium* subsp. *paratuberculosis* within both dairy and beef herds have been compiled into three major documents, entitled "How to Do Risk Assessments for Johne's Disease," "Handbook for Veterinarians and Dairy Producers," and "Handbook for Veterinarians and Beef Producers." These documents are available at the national office of United States Animal Health Association (USAHA) and the National Institute for Animal Agriculture (NIAA) website.[1046] A companion document entitled "U.S. Voluntary Johne's Disease Herd Status Program for Cattle" is also available from the USDA website.[1047–1049]

In herds with low to moderate infection levels (1% or fewer clinical cases per year), wise use of a combination of testing, culling, and biosecurity measures may eliminate clinical disease within 1 to 3 years and most infected adults in 5 to 7 years, as the adult cattle are culled over time. Complete elimination of infected cattle is likely to take many years after clinical Johne's disease is no longer apparent. Biosecurity measures should remain in place, or Johne's disease is likely to recur. Herds at low risk for Johne's disease need to be reminded that a major risk factor for Johne's disease is the purchase of replacement cattle from herds of unknown Johne's status. As herd owners continue to expand herd size with the acquisition of purchased animals, Johne's disease is often included in the purchased cattle.[1050]

Herds with more severe, widespread infection require aggressive control programs and many years to eliminate clinical Johne's disease. These herds should consider Johne's vaccination as one serious alternative to control Johne's disease. However, a practical control program and sound herd management can eliminate clinical disease in these herds and reduce the economic impact of Johne's disease to a minimum. Feeding monensin to heifers and all adult cows should reduce the *M. avium* subsp. *paratuberculosis* bioburden on the farm and therefore reduce transmission to young susceptible calves.[1032] Rather than focused attention to detect all *M. avium* subsp. *paratuberculosis* shedders, the diagnostic efforts should focus on elimination of those cattle shedding the highest concentration of *M. avium* subsp. *paratuberculosis*, that is super-shedders.[980]

In addition to the United States, with its well defined voluntary Johne's disease herd status program,[1049] Australia was one of the first countries to implement a national Johne's disease control program. The National Johne's Disease Market Assurance Program for Cattle was launched in 1996.[1050,1051] Subsequently both Denmark and Holland[1052] and more recently Canada have implemented voluntary Johne's disease programs.[1053]

32.158.11

Vaccination

A killed Johne's vaccine is available in several states through an accredited veterinarian with the approval of the state veterinarian required. The vaccine is effective at reducing the prevalence and delays the onset of clinical signs,[1054,1055] but does not eliminate infection. Investigations with Johne's vaccines in sheep and cattle provide the following insights: (1) most Johne's disease vaccines reduce fecal *M. avium* subsp. *paratuberculosis* shedding by approximately 90% compared with nonvaccinated controls; (2) onset of fecal shedding is delayed

approximately 1 year postvaccination in sheep; (3) Johne's disease—vaccinated sheep have reduced mortality compared with nonvaccinates; (4) Johne's disease vaccines stimulate both a humoral and a cellular immune response in the host, but the site of vaccination may progress to develop granulomas or draining abscesses; and (5) massive *M. avium* subsp. *paratuberculosis* challenge may overcome the protective immunity of the vaccine, resulting in clinical Johne's disease in animals.[1056–1062] On occasion in some flocks a vaccinated sheep will develop multibacillary lesions and excrete millions of *M. avium* subsp. *paratuberculosis* CFU per gram of manure and thus expose all other sheep in the flock. Thus some vaccinated sheep may serve as vectors if moved to flocks at low risk for Johne's disease.[1063]

Animals must be younger than 35 days old when vaccinated. Reasons some oppose the use of vaccination for Johne's disease include the following: (1) vaccinated animals will often have a positive skin test for tuberculosis; (2) injection site lesions may develop into granulomas, even abscesses that break and drain; (3) accidental injection of humans is a risk that has resulted in severe painful granulomas[1064]; (4) vaccination interferes with immunologic tests for Johne's disease; and (5) some producers rely on the vaccine as the sole management tool for Johne's disease and neglect herd management changes to reduce the risk of transmission.

32.158.12 Paratuberculosis and Crohn's Disease

An increasing body of literature implicates mycobacteria as one of the causes of Crohn's disease, a chronic smoldering inflammatory disease of the gastrointestinal tract of people.[1065,1066] Abundant evidence suggests human exposure to *M. avium* subsp. *paratuberculosis* may occur from the milk or meat of infected cows and/or the water supply.[1067] Many research publications suggest *M. avium* subsp. *paratuberculosis* is killed by pasteurization, whereas others provide evidence that *M. avium* subsp. *paratuberculosis* does survive pasteurization but in decreased numbers.[1067–1072] More recently, retail pasteurized milk from three states was shown to harbor viable *M. avium* subsp. *paratuberculosis* in 2.9% of samples tested, with *M. avium* subsp. *paratuberculosis* genetic material detected in 64% of the 702 samples of milk tested.[1073] Later the same group found *M. avium* subsp. *paratuberculosis* in samples of soft cheeses.[1074] Because most metropolitan water is not filtered and is collected from rural areas, drinking water may also represent a major potential source of the pathogen. Intestinal cohabitation may change parasitism to clinical disease after a long latency period. Numerous cofactors such as genetic susceptibility, coexistence of other enteric diseases, hormonal factors, and other, poorly understood stress factors may enhance the likelihood of clinical disease after a long incubation period.[1075–1078] An association between Crohn's disease and paratuberculosis has been shown, but a causal relationship remains to be demonstrated. *M. avium* subsp. *paratuberculosis* isolates from humans with Crohn's disease have been shown to be genetically similar to isolates from cattle with Johne's disease.[1079] Recent reports indicate an increasing number of patients with Crohn's disease in whom *M. avium* subsp. *paratuberculosis* has been isolated from breast milk and from the peripheral blood.[1080] One critical report defines the characteristics of Crohn's disease that differentiate it from Johne's disease, suggesting the two syndromes are in fact different disease processes.[1081] For an unbiased review of a possible connection between Johne's disease and Crohn's disease, see the report entitled “The Diagnosis and Control of Johne's disease” by the National Academies of Science.[1082]

32.159 COPPER DEFICIENCY IN RUMINANTS

John Maas

Bradford P. Smith

32.159.1 Definition and Etiology

Copper deficiency occurs when the diet contains an abnormally low amount of copper (primary copper deficiency) or when copper absorption or metabolism is adversely affected (secondary copper deficiency). If inadequate amounts of copper are available to tissues in the form of essential metalloenzymes, the signs of copper deficiency (hypocuprosis) may occur. Clinical signs in ruminants include diarrhea, decreased weight gain, unthrifty appearance, anemia, changes in coat color (achromotrichia) or wool quality, anemia, spontaneous fractures, lameness (epiphysitis), and demyelinization (enzootic ataxia of sheep and goats, or swayback). One of these syndromes usually predominates in a given herd.

The minimum recommended dietary copper concentration (dry matter basis [DMB]) is 4 to 10 ppm (mg/kg) for cattle,[1083,1084] 5 ppm for sheep,[1085] and 7 ppm for merino sheep.[1085] Young animals and fetuses are more susceptible to copper deficiency than mature animals, and cattle are more susceptible than sheep. Secondary copper deficiency is associated with high dietary levels of molybdenum, sulfates, zinc, iron, or other compounds. Secondary copper deficiency often manifests with clinical signs of diarrhea and weight loss or unthriftiness. It has been called *teart, peat scours, renguerra, pine*, and *salt lick disease*.[1086] Salt sickness in Florida appears to be the result of combined copper and cobalt deficiencies. The cause of copper deficiency in clinical cases is often multifactorial and can be difficult to quantify. In addition, unknown factors cause clinical expression of copper deficiency in ruminants to be manifested as a variety of syndromes.

32.159.2 Clinical Syndromes and Differential Diagnosis

Profuse watery diarrhea with poor weight gain and/or weight loss is a common syndrome seen in ruminants with copper deficiency.[1086] When it occurs in animals on boggy pastures that contain high concentrations of molybdenum, it has been referred to as *teart*.[1086] Decreased weight gain or weight loss as a herd problem can have many other causes, including parasitism, trace mineral deficiencies (selenium, cobalt), protein calorie malnutrition, and Johne's disease. A syndrome characterized by epiphyseal enlargement, stiffness, and unthriftiness is seen in young ruminants as a result of copper deficiency[1087] and is sometimes called *pine*.[1086] Copper deficiency can cause spontaneous fractures in ruminants. Enzootic neonatal ataxia (swayback) of lambs and kids is characterized by progressive incoordination and recumbency that begins with the hindlimbs and progresses to the forelimbs. It has also been reported in deer and pigs. Inadequate keratinization of wool and achromotrichia are the result of imperfect oxidation of free thiol groups during hair growth and keratinization. Subsequently the wool fibers do not crimp normally, and they appear to be “stringy” or “kinky.” A copper-containing enzyme, tyrosinase (polyphenyloxidase), is needed to convert L-tyrosine to melanin. With copper deficiency, this conversion is slow and hair is lighter in color than normal (achromotrichia). Loss of wool crimp and pigmentation changes in sheep or cattle, respectively, occur late in the course of copper deficiency. In addition to the described clinical syndromes, which may occur alone or jointly, copper deficiency may be associated with anemia[1088] (altered iron metabolism) or infertility.[1089] Infertility is probably multifactorial and may not respond to an increase in copper intake alone. Copper deficiency also seems to result in decreased immune function in ruminants.[1090,1091]

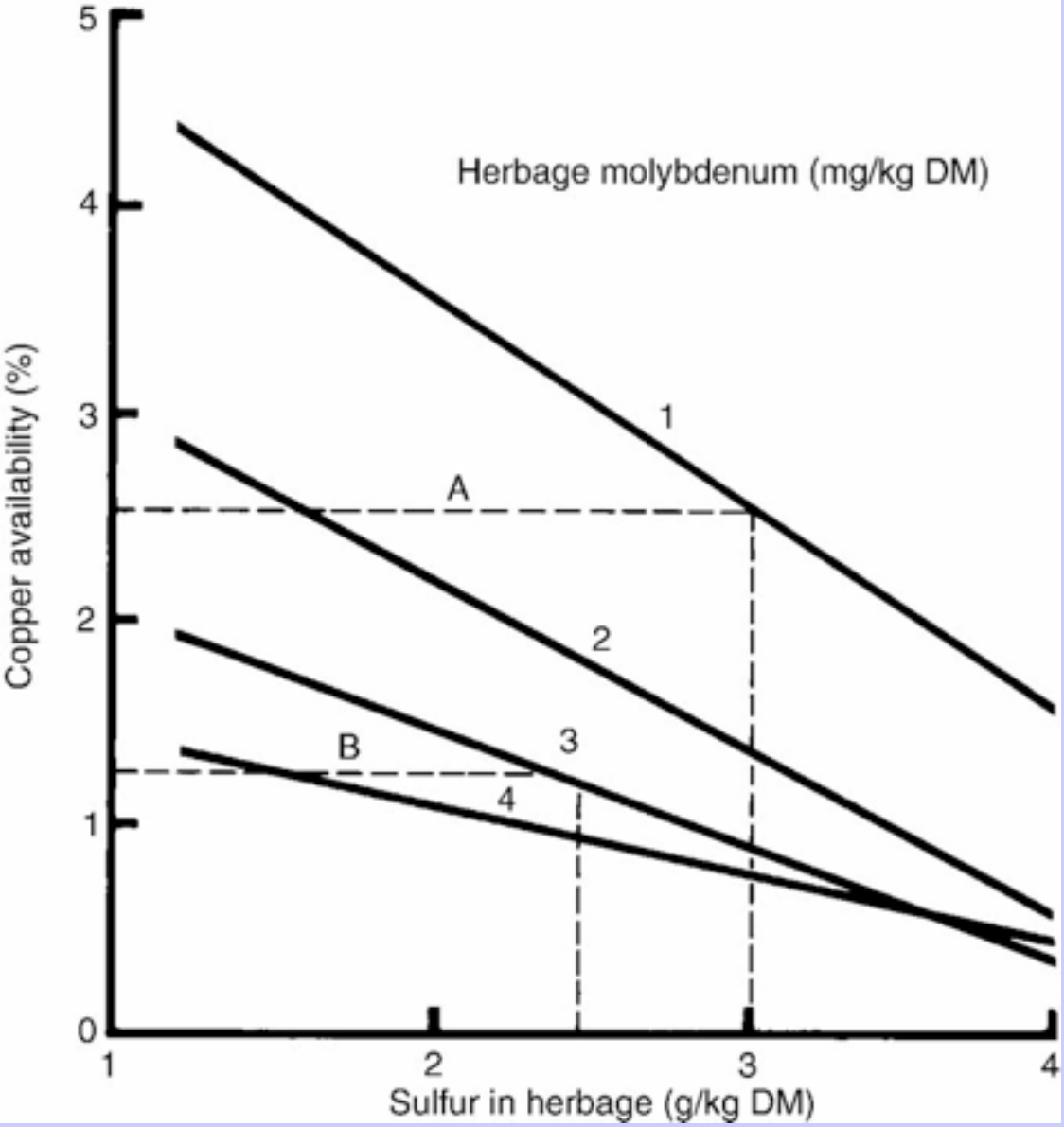
887 888

32.159.3 Pathogenesis

A frank dietary deficiency of copper results in hypocuprosis and eventual clinical signs. Also, a variety of conditions can decrease copper absorption from the gastrointestinal tract (large intestine in sheep and small intestine in cattle). The interactions among dietary copper, molybdenum, and sulfates (or sulfur) are important (Fig. 32-106). Excess dietary molybdenum can lead to the formation of sparingly soluble cupric molybdates in the rumen that are not absorbed from the intestine. The addition of excess sulfur or sulfates in the diet and/or water can result in the formation of insoluble copper thiomolybdates in the rumen. The interactions among these three elements are complex.[1092] The infertility seen with secondary copper deficiency may be a result of excess circulating oxythiomolybdates, which interfere with the release of luteinizing hormone.[1093] It is important to note that at low sulfur concentrations in the diet excess molybdenum has a minimum effect on decreasing copper absorption. Even when no dietary molybdenum or sulfates are present, only about 5% of ingested copper is normally absorbed. Excessive calcium in the diet, particularly in the form of limestone, decreases copper absorption. Excessive iron, 30 mg/kg of body weight or 1200 ppm in the diet of calves, reduces copper absorption.[1094] Overgrazing, with the subsequent ingestion of excess soil, also decreases copper absorption. In addition, excess cadmium (3 to 7 ppm) or excess zinc (100 to 400 ppm) reduces hepatic copper concentration, probably through the combined effects of decreased absorption and competition with copper for hepatic metallothionein.[1095,1096] It had been suggested that excess dietary selenium might interfere with copper absorption and/or usage; recently this was shown not to be the case.[1097] Copper is an essential component of a number of mammalian enzymes. Some of the medically important copper-containing enzymes are (1) the cytosol form of superoxide dismutase (copper and zinc), (2) cytochrome oxidase (c and aa_3), (3) lysyl oxidase, (4) ascorbic acid oxidase, and (5) ceruloplasmin.[1098] In addition, normal copper nutrition appears essential for iron absorption and transportation of iron to the liver and reticuloendothelial system and is therefore necessary for normal hemoglobin formation. The precise pathophysiology of most of the copper deficiency syndromes is not known. However, the central role of copper in preventing cellular oxidative damage and its role in iron and sulfur metabolism are probably important.

Fig. 32-106 Estimating the availability of copper in herbage from its

molybdenum and sulfur concentration. The difference of 3 mg of molybdenum and 0.5 g of sulfur per kilogram of dry matter between pastures A and B is sufficient to reduce availability from 2.6% to 1.3%, doubling the grazing animal's requirement of copper from the pasture. From Suttle NF: Copper deficiency in ruminants; recent developments, *Vet Rec* 119:519, 1986.



32.159.4 Epidemiology

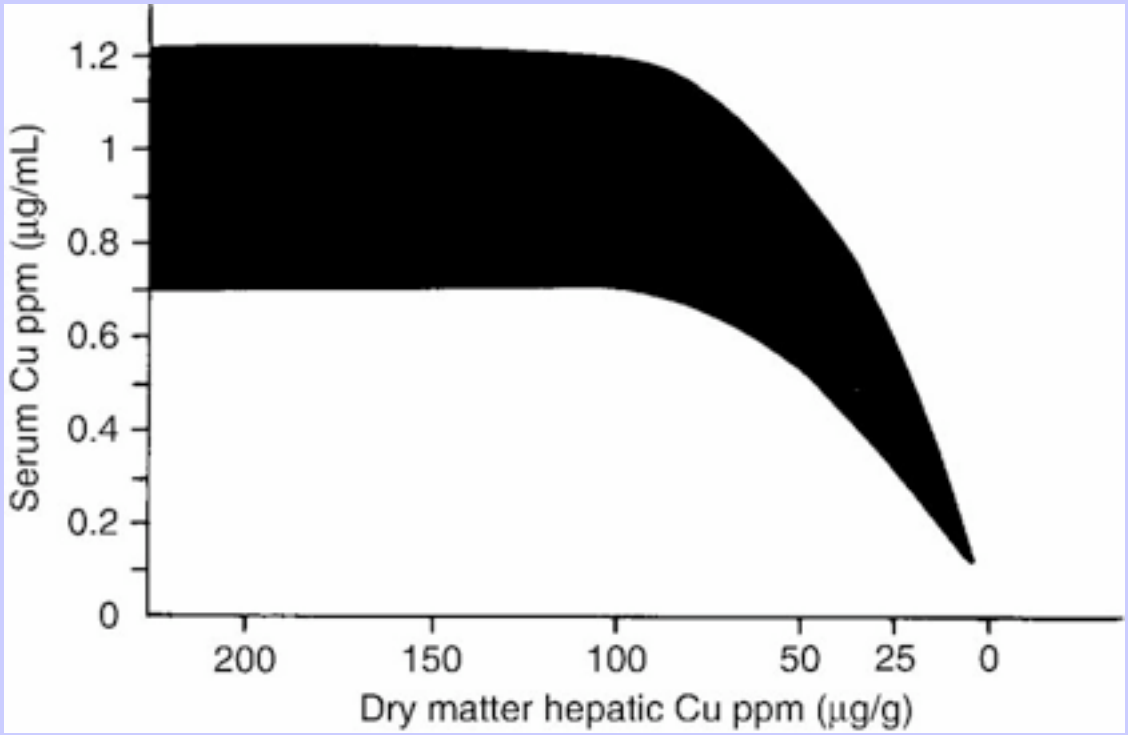
Copper deficiency can occur when diets are inadequate in copper or contain excess amounts of interfering substances, particularly sulfates and molybdenum. This occurs in many parts of North America. Forages and water can be sources of molybdenum, sulfur, and sulfate. To avoid primary copper deficiency, pasture (dry matter) should contain over 5 ppm of copper, with 3 to 5 ppm considered marginal, and less than 3 ppm deficient. Soil copper concentrations are generally slightly lower than those of the harvested forage. Molybdenum adversely affects plant uptake of copper. Forage molybdenum concentrations greater than the copper concentrations often lead to secondary copper deficiency, even when forage copper is adequate. Because copper content in grasses and legumes can be different, forage samples must be randomly selected to reflect dietary intake. Forage copper concentrations as high as 12 to 27 ppm have been associated with copper deficiency when molybdenum levels are high.[1086] The critical ratio of copper to molybdenum in feeds is 2:1, with 5:1 recommended for sheep and 5:1 to 10:1 for grazing cattle.

32.159.5 Clinical Pathology and Diagnosis

The primary site of copper reserves is the liver, and the copper concentration in the hepatic tissue is the best indicator of copper status (Fig. 32-107). The reference range for hepatic copper concentrations in cattle is approximately 90 to 200µg/g (ppm) and in sheep 90 to 250µg/g on a dry weight basis (DMB).[1086,1099,1100] Hepatic copper concentrations as high as 250µg/g DMB are not unusual in supplemented ruminants (even over 350µg/g DMB in sheep). Blood copper concentrations can be maintained near normal until hepatic copper concentration falls to 35ppm DMB or less, at which time the serum copper concentration invariably begins to decrease.[1101] When using blood samples for copper determination, serum or plasma is normally preferred. Plasma copper concentration is usually about 5% greater than an identical serum copper concentration.[1102] Normal serum copper is 0.7 to 1.2ppm (µg/mL).[1086,1098] Serum or plasma copper concentrations of 0.4ppm or less are considered evidence of frank deficiency. Values of 0.4 to 0.7ppm are marginal, and it is difficult to estimate the actual liver copper concentration. Approximately 50% to 90% of the copper in serum or plasma is present in ceruloplasmin. The remainder is bound to albumin or amino acids. The correlation between serum copper and serum ceruloplasmin was found to be weak (0.50)[1102]; therefore ceruloplasmin is not commonly used to aid in diagnosing copper deficiency. Hepatic copper concentration is the preferred diagnostic sample and is easily secured at necropsy. Hepatic copper values less than 35ppm DMB are considered deficient.[1086,1099–1101] However, surgical biopsy is necessary for live patients, and because laboratories generally require 100mg or more of tissue, a biopsy instrument with an internal diameter of 3 to 5mm is necessary.[1103] The biopsy procedure in cattle is performed by locating the tenth intercostal space on the right side of the animal along a line from the tuber coxae (point of the hip) to the point of the shoulder.[1103] This site is surgically prepared and blocked with lidocaine (12mL of 2% lidocaine), and a stab incision is made. The biopsy instrument is directed slightly ventrad and craniad and advanced through the intercostal space and the diaphragm to enter the liver, where the biopsy sample is obtained.[1103] The liver biopsy can place the patient at increased risk for black disease or bacillary hemoglobinuria in some areas of the United States. This risk should be decreased by prior vaccination and a single dose of procaine penicillin G (4 million I.U. SC) administered at the time of the biopsy.[1103] This technique has been shown to be safe and effective.[1103] The tissues of young animals (neonates) contain variable amounts of copper compared with adults of the same species. In sheep, serum and liver copper concentrations are the same for lambs (1 week of age) and adults.[1104] The plasma copper levels in lambs are low at birth but rise to adult values by 1 to 7 days of age. Plasma copper levels in the bovine neonate are lower than in mature cattle.[1105] In the bovine neonate hepatic copper concentration changes little from birth to maturity; however, copper distribution in the liver is quite variable in the neonate.[1100,1105] Because of these differences, interpretation of

distribution in the liver is quite variable in the neonate.[1105] Because of these differences, interpretation of neonatal serum copper concentrations is difficult. Milk is a poor source of copper, containing only 0.2 to 0.6ppm in normal ewes and 0.01 to 0.02ppm in severely copper-deficient ewes or cows. Milk copper in cattle is 0.05 to 0.2ppm. To make matters worse, molybdenum is concentrated in milk.[1106]

Fig. 32-107 Relationship between the serum and hepatic copper concentrations in ruminants.



32.159.6

Treatment and Control

Treatment of copper-deficient animals is usually possible, and the prognosis is guarded to good, depending on the severity of the deficiency and the associated syndrome(s). When excess molybdenum, sulfate, and other factors leading to secondary deficiency are present, they can be overcome to some extent by increasing dietary copper or by injecting copper glycinate. Copper glycinate must be prescribed by the attending veterinarian and dispensed by a compounding pharmacy because no commercial over-the-counter products are currently available. Injectable copper glycinate (30% copper by weight) is given to adult cattle at the rate of 400mg (120mg of copper) SC. Calves are given 100 to 200mg of copper glycinate (30 to 60mg of copper), depending on their age. One injection may be effective as a treatment or supplement for up to 4 to 6 months in cases of primary copper deficiency. However, in cases of excess molybdenum, sulfates, and/or sulfur, repeat injections may be necessary. Injections of copper glycinate frequently result in large swellings, granulomas, or abscesses and may be cosmetic considerations for some cattle. The reactions can be minimized by using sterile technique and using the subcutaneous tissue of the brisket as the injection site. Acute deaths can occur in calves after the use of copper glycinate injections. In some countries copper disodium edetate (copper EDTA) solutions are used as injectable copper supplements. The dose of copper is usually the same as that recommended for copper glycinate

solutions. However, acute deaths can also occur after use in cattle.[1107] Copper can be supplemented to cattle in salt-mineral mixes in situations in which adequate consumption (1 to 2oz [28 to 56g]/cow/day) of the salt-mineral mix occurs. These mixes are usually 0.2% to 0.6% copper. Feed-grade copper sulfate ($CuSO_4$-5 H_2O) is 25% copper on an as-fed basis (40% copper DMB). Feed-grade copper oxide is usually 50% copper as fed (80% copper on 100% DMB). To make a 0.4% copper salt mixture, add 7.2g of $CuSO_4$ or 3.6g of CuO to each 454g (1lb) of salt. For large batches add 32 ob of $CuSO_4$ or 16lb of CuO per ton of salt. Salt mixtures for copper-deficient sheep should usually contain only 0.0625% to 0.13% copper (0.25% to 0.5% copper sulfate). Copper supplements can be added to a TMR easily in the form of trace mineral—vitamin premixes or premix-containing pellets. Copper sulfate can be added to molasses or other sweet feed at 0.363g/head/day for mature cattle and correspondingly less for calves. This would supply approximately 91mg of copper to a 450-kg (1000-lb) cow per day or 10ppm of the total diet (20lb [9.1kg] of dry matter). The copper in $CuSO_4$ is more available than that in CuO. Another method of copper supplementation involves the oral administration of copper oxide needles (fine rods, 1 to 10mm long) placed in gelatin capsules, which dissolve in the reticulorumen and liberate the CuO wires. These wires reside in the reticulum and abomasum and slowly release copper for absorption. These boluses are currently available in the United States (Copasure) and contain either 25g or 12.5g per bolus. The usual recommended dose is 25g per animal 500lb or heavier. One 12.5-g bolus is recommended for calves, and the usual dose is 2 to 4g for ewes and does,[1086,1108,1109] which is an extralabel recommendation for sheep and goats. The copper oxide needles are thought to provide copper supplementation for 4 to 12 months. Sheep are particularly susceptible to copper toxicity, and appropriate care is necessary when supplementing them. Sheep can easily be intoxicated when consuming cattle supplements or feeds. Continued monitoring of hepatic copper concentration from slaughtered animals or via liver biopsy is an important tool in evaluating copper supplementation methods in cattle and sheep. Lambs can be given 35mg of copper sulfate per head twice weekly to prevent swayback in endemic areas. The usual recommendation by the National Research Council is 10ppm (10mg/kg) of the total diet DMB for cattle. However, diets of 20ppm are commonly fed to lactating dairy cattle. The most important goal of copper supplementation is to provide adequate dietary amounts without oversupplementing or risking toxicity.

32.160 COBALT DEFICIENCY IN RUMINANTS

John Maas

32.160.1 Definition and Etiology

A number of syndromes occur in ruminants as a result of a primary cobalt (Co) deficiency in their diet. These include ill thrift or enzootic marasmus and anemia. These conditions are characterized by decreased growth, weight loss, diarrhea, decreased feed efficiency, unthrifty appearance, anorexia, and anemia. Recently, a Co deficiency syndrome referred to as *ovine white liver disease* has been described in sheep.[1110–1112] This syndrome is also characterized by ill thrift, weight loss, serous ocular discharge, and occasionally photosensitization.[1110–1112] Histopathologic lesions of this syndrome included accumulation of lipid droplets and lipofuchsin particles, dissociation and necrosis of hepatocytes, and sparse infiltration by neutrophils, macrophages, and lymphocytes.[1112]

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32.160.2 Clinical Signs and Differential Diagnosis

Co deficiency in ruminants is associated with the nonspecific signs of decreased growth, weight loss, diarrhea, ill thrift, pica, emaciation, pale mucous membranes (anemia), and lacrimation. Clinical disease is more common in young, growing animals. Sheep are apparently more susceptible to Co deficiency than cattle. Primary differential diagnoses include helminthic parasitism; protein-calorie malnutrition; coccidiosis; Johne's disease; nutritional deficiencies of selenium, copper, or vitamin D; and other causes of chronic disease that may be associated with weight loss.

Co-deficient ruminants are commonly anorectic and fail to thrive on lush pasture or high-quality feeds. Anemia with cobalt deficiency is characterized as normocytic normochromic and must be differentiated from other causes of anemia. Co-deficient cattle are more susceptible to infestation with *Ostertagia ostertagi* and to the effects of parasitism.[1113] The primary differential diagnosis when considering Co deficiency is invariably internal parasitism.

32.160.3 Clinical Pathology and Diagnosis

Because the role of Co in ruminant nutrition is tied to the formation, absorption, and use of vitamin B_{12}, the most significant clinical chemistry analysis is tissue vitamin B_{12} concentration. However, the effects of starvation tend to increase vitamin B_{12} concentrations in liver and kidney.[1114] If Co deficiency occurs with other conditions that cause anorexia, the tissue vitamin B_{12} concentrations may appear falsely normal. Criteria used for sheep[1115] (and by extrapolation for cattle) are found in Table 32-24.

Serum vitamin B_{12} analysis is advantageous in many clinical settings. Serum or plasma vitamin B_{12} levels exhibit a marked diurnal variation.[1116] Serum vitamin B_{12} concentration more closely reflects short-term Co intake and can be decreased when adequate liver reserves of vitamin B_{12} remain. In normal, Co-sufficient ruminants, serum vitamin B_{12} values are usually 1 to 3ng/mL. When serum vitamin B_{12} values decrease to 0.3ng/mL, the threshold for clinical signs has been reached; when serum vitamin B_{12} values of 0.2ng/mL or less are reached, marked signs of Co deficiency are evident.[1117]

Severe Co deficiency in ruminants results in the excretion of methylmalonic acid (MMA) and formiminoglutamic acid (FIGLU) in the urine.[1118] Urinary FIGLU levels of 0.08 to 0.2µmol/mL would be presumptive evidence of Co deficiency, and the urinary FIGLU level should return to zero after vitamin B_{12} administration. Use of urinary MMA for diagnosis is best accomplished by loading the rumen with propionate and then comparing the urinary excretion of MMA with and without vitamin B_{12} supplementation. The fact that urinary MMA and FIGLU excretion occur very late in the course of Co deficiency limits the routine use of these methods for diagnosis.

Table 32-24 Criteria Used to Determine Cobalt Deficiency in Sheep

Condition of Animal (Co or B_{12} status)	Concentration of Vitamin B_{12} (mcg/g of Fresh Liver)[1115]
Severe cobalt deficiency	<0.07
Moderate cobalt deficiency	0.07–0.10
Mild cobalt deficiency	0.11–0.19
Cobalt sufficiency	0.19

32.160.4 Pathophysiology

Co deficiency in ruminants induces a deficiency of vitamin B_{12} (cyanocobalamin). It is the lack of vitamin B_{12} that is thought to cause the majority of clinical signs and clinicopathologic abnormalities observed. Monogastric species need to ingest vitamin B_{12} preformed, whereas ruminants can manufacture adequate vitamin B_{12} if the ruminal microorganisms are supplied with adequate Co in the diet. The ruminal microorganisms incorporate Co into vitamin B_{12} and a number of physiologically inactive vitamin B_{12}-like compounds. The production of vitamin B_{12} from dietary Co was estimated in one study to be about 15% in Co-deficient sheep and only about 3% in Co-sufficient sheep.[1119] About 50% of the vitamin B_{12} produced is absorbed in normal animals, but only 3% to 5% of vitamin B_{12} is estimated to be absorbed by Co-deficient sheep.[1120] Although the absorption of vitamin B_{12} formed in the rumen is not particularly efficient, with normal dietary Co there are usually no clinical problems, and interference by other dietary components does not appear to be important.

Ruminants use the VFAs acetate, propionate, and butyrate as their primary energy source. Propionate produced in the rumen is the precursor of glucose for ruminant metabolism. The general metabolic steps for conversion of propionate to glucose are shown[1121] (Fig. 32-108).

A primary defect in Co-deficient ruminants is the inefficient metabolism of propionate at the point in the pathway at which methylmalonyl-CoA mutase, a vitamin B_{12}-requiring enzyme, catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA.[1122] As Co deficiency becomes severe, the rate of propionate clearance from the blood decreases, and the intermediate metabolite methylmalonyl-CoA accumulates.[1123] With severe Co deficiency, the amount of MMA excreted in the urine increases.[1118] As the half-time for propionate clearance increases, the voluntary feed intake of Co-deficient sheep decreases.[1123] These changes correlate with the degree of anorexia and weight loss observed in severely Co-deficient sheep.

The decreased growth, weight loss, unthrifty appearance, and anorexia are closely correlated to the observed abnormalities of carbohydrate metabolism. The diarrhea commonly observed with Co deficiency is not well explained; however, an increase in susceptibility to parasitism[1110] might explain a portion of this clinical observation.

The anemia that is associated with Co deficiency occurs late in the development of the syndrome and is characterized as normocytic normochromic.[1124] Cobalt deficiency results in the depression of the vitamin B_{12}-containing enzyme 5-methyltetrahydrofolate homocysteine methyltransferase.[1125] This interference with the recycling of methionine has a marked influence on folate metabolism. In addition to potentially resulting in anemia through inefficient folate metabolism, the decreased activity of this methyltransferase could lead to a

deficiency of methionine; this is a possible reason for nitrogen retention and decreased body growth and wool growth observed.

32.160.5 Epidemiology

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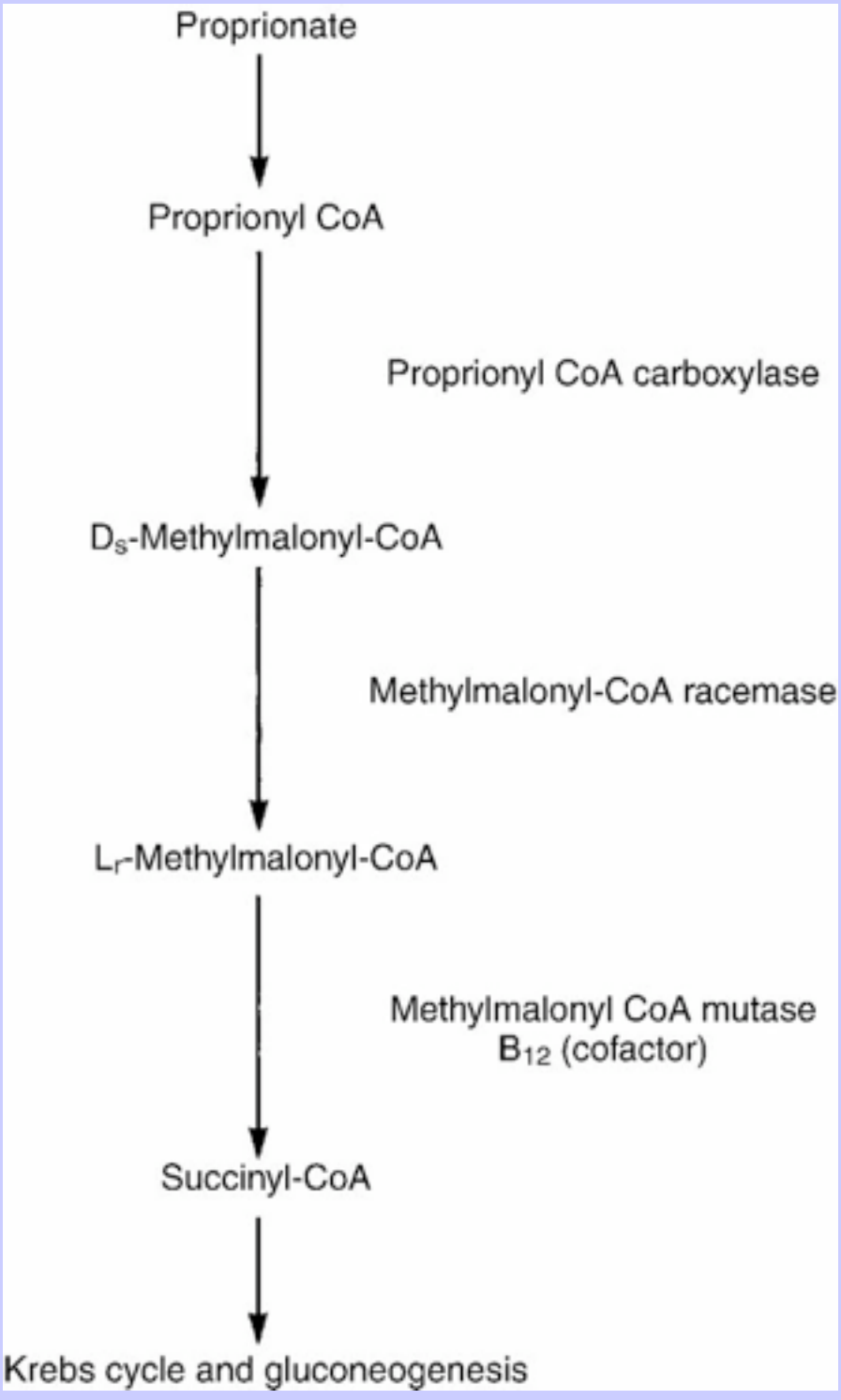
Co deficiency in ruminants occurs in selected regions throughout the world and in association with a variety of soil types. Clinically recognizable Co deficiency is reported in New Zealand, Australia, Brazil, the United Kingdom, Ireland, Scandinavia, and North America. In the United States, Co deficiency is most commonly seen in Florida, in the Northeast, along the eastern seaboard, in the upper Midwest, and around the Great Lakes.[1126] Although various soil types are associated with Co deficiency, heavy fertilization with limestone reduces the Co available to plants and animals.[1127]

Fig. 32-108 Pathway for conversion of propionyl CoA (from propionate) to

succinyl CoA.



The dietary intake of Co by ruminants is generally recommended to be 0.1mg/kg of dry matter (DM) of the

complete ration.[1128–1130] The Co requirement of young, rapidly growing lambs is thought to be 0.2mg/kg of DM of the diet.[1131] When pasture Co concentrations are less than 0.07mg/kg of DM or 0.04mg/kg of DM for sheep and cattle, respectively, signs of deficiency can be expected to develop. On a practical basis, diets with 0.1mg/kg of DM are considered to be adequate. Legumes have relatively high Co concentrations. Rapidly growing grasses have much lower Co concentrations, and cereal grains are poor sources of Co.[1128] Oilseed meals are generally good sources of Co.

32.160.6 Treatment and Control

Treatment is best accomplished in the short term with vitamin B_{12} injections. Ruminants poorly absorb oral vitamin B_{12}; therefore injections are more efficient. Lambs receiving 100µg of vitamin B_{12} per week or 150µg of B_{12} every other week show remission of clinical signs.[1132] Sheep receiving injections of 300µg of vitamin B_{12} weekly or cattle receiving 2000 to 3000µg of vitamin B_{12} weekly would also be expected to regain normal status.

Rations with 0.1 to 0.2mg of DM Co per kilogram (ppm) would be expected to prevent Co deficiency in ruminants. Salt-mineral mixes containing 0.1% Co also provide adequate supplementation. 0.1% Co in salt can be made by mixing cobalt carbonate (which is 46% cobalt) at the rate of 4.35lb/ton of salt, or 1g of cobalt carbonate per pound of salt.

Cobalt sulfate as a top dressing for pastures (1.5kg/hectare every 3 to 4 years or 0.3kg/hectare every 1 to 2 years) has been used to increase Co concentration of pasture forage. Heavily limed pastures[1127] and soils high in manganese oxide[1133] decrease Co availability, and Co top dressing of the pastures or Co (B_{12}) supplementation to the animals should be considered.

A variety of ruminal pellets containing Co are used to supplement grazing ruminants. These pellets have been successful in maintaining normal Co status in animals.[1131–1134] The pellets are not commercially available in the United States at this time.

The perennial grass, *Phalaris tuberosa*, can cause a syndrome in ruminants that is referred to as “phalaris staggers.” Co supplementation can aid in prevention of this syndrome because it inactivates or decreases absorption of the neurotoxin contained in *P. tuberosa, Phalaris minor* (canary grass), or *Phalaris* hybrids (ronpha).[1135] The increased level of Co in the rumen is the important factor in preventing this condition; administration of oral or parenteral vitamin B_{12} is not effective.[1135] Treatment of clinical phalaris staggers with Co is not effective, however.

Because Co is poorly absorbed, toxicity is an uncommon problem, and diets in excess of 30mg/kg of DM are necessary for toxicosis to occur in most cases.[1128–1130]

32.161 RECTAL PROLAPSE IN RUMINANTS AND HORSES

Spring K. Halland

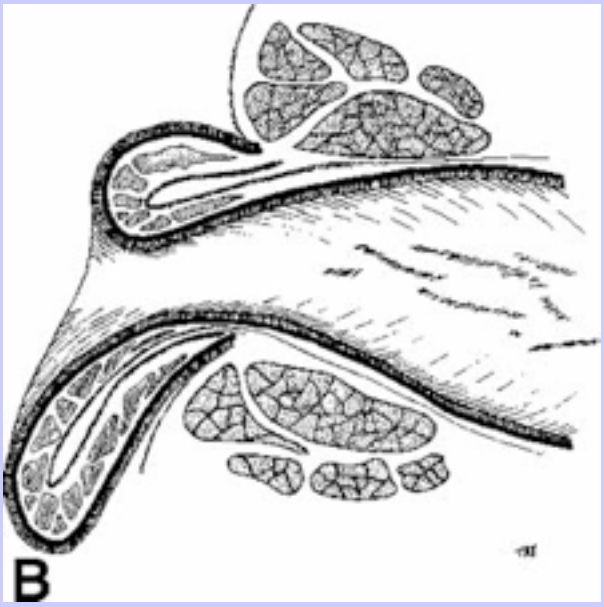
32.161.1 Definition and Etiology

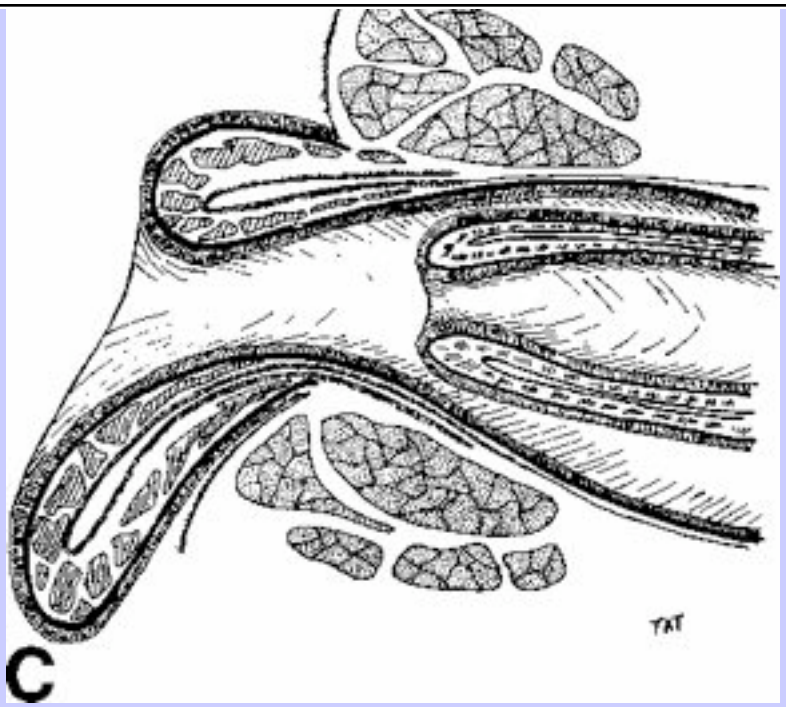
Rectal prolapse is the protrusion of the rectal mucous membranes through the anus. This evagination may be extensive and may include part of the small colon. Rectal prolapse occurs in all domestic animals, with the highest incidence in cattle, sheep, and swine. The age at which prolapse most commonly occurs is 6 to 12 months in sheep, 6 months to 2 years in cattle, and 6 to 12 weeks in swine.[1136] Rectal prolapse is much less common in horses and occurs more often in mares than in males.[1137]

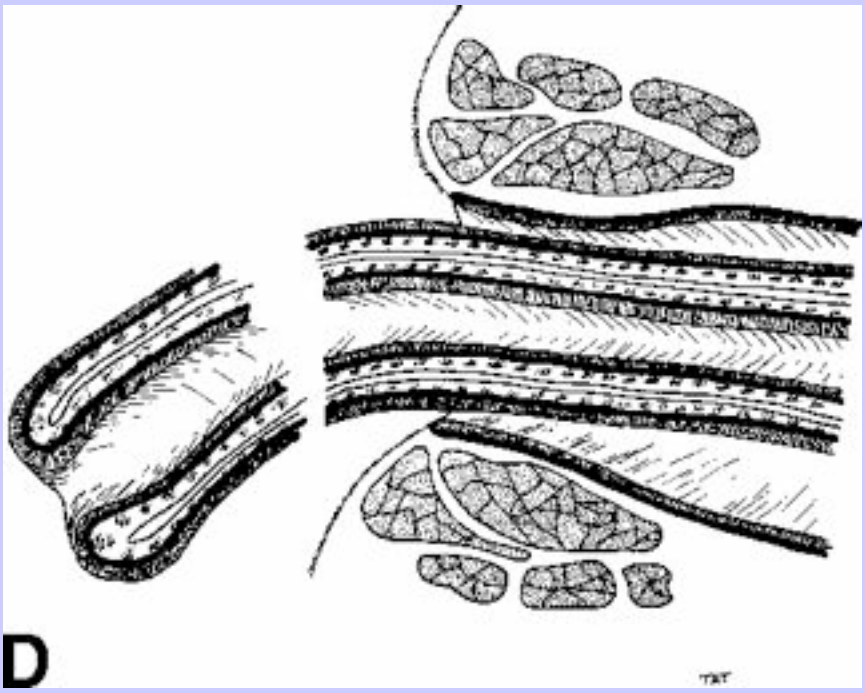
Rectal prolapse generally is the result of an increase in the pressure gradient between the abdominal or pelvic cavity and the anus. Factors that cause the increased pressure gradient can be divided into four categories: (1) factors that result in increased abdominal fill (e.g., excess fat, bloat, and large or multiple fetuses); (2) factors that cause tenesmus (e.g., enteritis, colitis, intestinal parasitism [coccidiosis], liver disease, constipation, proctitis, urinary obstruction, dystocia, aftermath of rectal examination, and false copulation); (3) conditions that result in chronic or excessive coughing (e.g., pneumonia, parasitism, and adverse environmental conditions); and (4) miscellaneous conditions (e.g., use of growth implants, space-occupying lesions, congenital or acquired sphincter tone problems, and short tail docking [especially noted in sheep]). One study strongly revealed that sheep with short docked tails (as close to the body as possible) had a 7.8% higher incidence of rectal prolapse when finished on a high concentrate diet.[1138] Certain toxicities such as from lead, fluoride, estrogen, and zinc have been implicated as playing a role in rectal prolapse.[1139] Any combination of factors may precipitate a rectal prolapse. Identification of predisposing factors becomes important in management of the case.

Fig. 32-109 **A**, Type I rectal prolapse. Mucosal prolapse, involving only mucosa

and submucosa of the rectum. **B**, Type II rectal prolapse. Complete prolapse, involving full wall thickness of the rectum. **C**, Type III rectal prolapse. Complete prolapse plus intussusception of peritoneal rectum or small colon. **D**, Type IV rectal prolapse. Intussusception of the peritoneal rectum or small colon or both. From Robinson NE, ed: *Current therapy in equine medicine*, ed 2, Philadelphia, 1987, Saunders.







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32.161.2 Clinical Signs

Four categories have been used to described rectal prolapse: type I, mucosal prolapse; type II, complete prolapse; type III, complete prolapse with invagination of the colon; and type IV, intussusception of the peritoneal rectum or colon through the anus (Fig. 32-109).[1140] Types I and II are much more common and more amenable to correction. On physical examination, types I, II, and III are continuous with the mucocutaneous junction of the anus, whereas with type IV a protrusion with a palpable trench inside the rectum is seen.[1140] Chronic cases can be seen and usually are type I or II. Types III and IV often cause loss of vascular integrity to the rectum or small colon and require more immediate intervention. Types III and IV may accompany dystocias in mares.[1141]

32.161.3 Treatment and Prognosis

The first aim of therapy is identification and alleviation of the cause if possible. Early identification and correction of the prolapse is essential to saving tissues and the animal. The animal's value and intended use and the affected tissue's viability need to be considered when deciding on conservative or surgical options. The color of the membranes is a good parameter for determining if the tissue is salvageable. In general, the rectum is a forgiving structure, and attempts should be made to salvage the prolapsed tissue unless it is obviously cyanotic, necrosed, and devitalized.[1136] To prevent further damage, animals should remain standing and restrained in a small area until the prolapse can be corrected.

Types I and II usually are treated conservatively. A caudal epidural is necessary to reduce straining and facilitate correction of the prolapse. Sedation may also be necessary, depending on the individual animal. Effective conservative therapy includes thorough cleansing of the prolapse with warm water and mild soap to remove all debris. This allows evaluation for trauma, tears, necrosis, or sloughing. Edema can be removed by gentle kneading combined with topical application of glycerin or sugar. Generous lubrication and massage allow for reduction of the mass into the rectum. To ensure that the rectum is maintained in place, purse-string sutures using umbilical tape or other nonabsorbable suture are placed circumferentially around the anal sphincter, with care taken not to enter the rectum. The purse-string should not be so tight as to prohibit the passage of feces. If necessary, it should be loosened daily to expedite removal of accumulated fecal material. The purse-string should be removed in 3 to 4 days. In addition to purse-string sutures, counterirritants such as Lugol's iodine are often used.[1136] Two to 3mL of these irritants are injected with a 7.5-cm needle at the 4, 8, and 12 o'clock positions around the rectum. The counterirritants create an inflammatory response that results in scar formation, which retains the prolapsed tissue after the purse-string has been removed. Broad-spectrum antimicrobial drugs should be administered if tissue compromise is a factor. When indicated, stool softeners and enemas may be used to ease the passage of feces through the rectum.

Surgical intervention often is necessary if type I or type II prolapse cannot be reduced, if tissue necrosis is extensive, or if prolapse recurs after conservative therapy.[1140] Submucosal resection, amputation, or the use of a prolapse ring are all accepted surgical options. Prolapses of types III and IV that cannot be manually reduced often require a celiotomy for surgical reduction of the intussusception or resection or both. An important fact to remember is that even with manual reduction of a type IV prolapse, significant vascular compromise may have occurred, resulting in bowel leakage and peritonitis. Vascular damage encountered by the colon may necessitate a colostomy.[1486] Broad-spectrum antimicrobial drugs should be administered in these cases.

Unique problems are encountered when conservatively managing equine rectal prolapse versus ruminant

prolapse. Equine patients may experience more hindlimb ataxia with caudal epidurals, which can be prevented by using different combinations of xylazine, lidocaine, detomidine, morphine, and/or mepivacaine in the epidural. Placement of an epidural catheter can facilitate long-term therapy if needed.[1142] Another problem encountered is that horse feces often are too large and dry to readily pass through the purse-string in the anus. The use of enemas and stool softeners offers some assistance. The sutures tend to cause greater anal irritation than is seen in ruminants, causing the horse to strain against them.

The common complications after rectal prolapse include prolapse recurrence, rectal strictures, obstipation, formation of a pararectal abscess, and peritonitis. The prognosis for all types of rectal prolapse depends on early identification and reduction of the prolapse. Prolapses of types I and II that can be managed conservatively have a favorable outcome. Surgical correction of types I and II also carries a good prognosis but with a higher incidence of postsurgical complications. Because of the cost of surgical repair, market animals often are slaughtered if conservative management fails. Rectal prolapses of types III and IV carry a fair to guarded prognosis, which depends on the extent of tissue involvement and viability, the surgeon's skill, and postsurgical complications.

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33 Chapter 33 Diseases of the Hepatobiliary System

Consulting Editors

Erwin G. Pearson

33.1 DIAGNOSIS OF LIVER DISEASE

ERWIN G. PEARSON

In making a diagnosis, the clinician should first determine that the animal has liver disease and then try to identify the specific cause. Therefore, this chapter first discusses the diagnosis of liver disease, then the individual conditions causing disease. The liver cannot be examined directly in large animals. The signs of liver disease are caused by failure of some of the liver's many functions, but these signs may not appear in the early stages of disease. Special tests may be needed to detect early damage or minor impairment of function that has not yet produced clinical signs.

33.2 LIVER DISEASE VS. LIVER FAILURE

As with many other organs, such as the heart and kidney, the liver can be diseased long before it fails to function. Thus, early cases of liver disease are not apparent to the owner or veterinarian through physical findings alone; such cases usually are detected by finding elevated levels of liver enzymes or bile acids in the serum. Pathologic changes in the liver may include biliary hyperplasia, death of hepatocytes, and fibrosis, and these may occur long before any signs of failure develop. Some functions may fail before others, and the onset of liver failure varies with the species and the disease process involved.

33.3 LIVER RESERVE AND REGENERATION

The liver has a large reserve capacity, and close to 80% of it can be removed before regeneration and recovery are no longer possible. It also has a remarkable capacity to regenerate. Regeneration can occur in areas receiving portal blood, but most cell division takes place in Rappaport zone 1 (the portal area), and the cells are pushed to the central lobular area. The liver undergoes constant repair, and in people it is estimated that the hepatocytes are renewed every 50 to 75 days.[1]

Normal regeneration does not occur in some cases. Antimitotic agents such as metabolites of pyrrolizidine alkaloids or antineoplastic drugs can prevent cell division. Regeneration may be restricted by connective tissue. Once fibrosis has bridged the various lobules, additional regeneration is impaired because the fibrosis itself perpetuates the condition. Loss of a stroma to build on or lack of portal blood supply also reduces regeneration.

33.4 SIGNS OF LIVER DISEASE AND PATHOPHYSIOLOGY

Many signs can be present with liver disease, but no sign is pathognomonic or present consistently. Table 33-1 provides some of the signs that may be present and other possible causes of the same signs.[2]

The clinical history is useful in some cases, but consumption of pyrrolizidine alkaloid—containing plants may not be apparent because of the delay between consumption and the onset of clinical signs. Exposure to other

hepatotoxins could be detected. Ruminants grazing on land infested with snails are more likely to have liver fluke disease. Administration of horse serum to Equidae 4 to 8 weeks previously will make acute serum hepatitis more likely.

With the exception of pain over the liver elicited with pressure and change in liver size, most signs are related to failure of some function. Liver flukes may cause anemia and hypoproteinemia because of the effect of the parasite and its metabolites. Liver abscesses and other infections may produce signs such as fever and anorexia because of the release of pyrogens and other mediators (caused by the organism and not necessarily related to the liver itself).

Icterus is typically seen in acute liver disease in horses but is not seen in many cases of chronic liver disease, and it is seen less often in ruminants unless biliary blockage occurs. Icterus is caused by failure of uptake, conjugation, or excretion of bilirubin. Excess production caused by hemolysis must also be considered when icterus is present, and is the most common cause of icterus in cattle. Horses are frequently icteric (up to 6 mg/dL unconjugated bilirubin) from anorexia or fasting even when the liver is normal.

Weight loss is a common but nonspecific finding in some cases of chronic liver disease. It may be caused by anorexia or failure of metabolic functions of the liver and is probably not related to impaired fat absorption in the large herbivores. *Diarrhea* is also seen, especially in cattle with chronic liver disease. It is thought to be related to portal hypertension and increased hydrostatic pressure, although the exact mechanisms are not yet understood. Diarrhea probably is not caused by fat malabsorption or steatorrhea, because the normal herbivore diet contains less than 3% fat.

Ascites is a common finding in calves with liver cirrhosis. The ascites results from portal hypertension caused by venous blockage producing increased hydrostatic pressure and by protein leakage into the peritoneal cavity. Production of hepatic lymph high in protein (>3 g/dL) is increased. Because the liver sinusoids are permeable to plasma proteins, the protein-containing lymph leaks into the interstitial space and then into the peritoneal cavity.[3,4] Fluid moves into the abdominal cavity because of both osmotic and hydrostatic forces, according to Starling's law. The abdominal fluid present with liver disease is a modified transudate, but the protein content may be relatively high (3 to 3.5 g/dL) because of leakage of protein from the liver. Hypoalbuminemia can aggravate the ascites, but if it occurs alone, it more likely will cause intramandibular and brisket edema.

Table 33-1 Signs of Liver Disease or Failure

Sign	Pathogenesis	Other Causes
Icterus (E)	Failure of uptake, conjugation, or excretion of bilirubin	Massive hemolysis Bile blockage Fasting in the horse
Weight loss (E, B)	Energy demand greater than absorbed or metabolized	Poor nutrition, chronic inflammation, parasites, neoplasia, maldigestion, malabsorption
Ascites (B)	Portal hypertension and lymph leakage caused by cirrhosis or venoocclusion	Cardiac failure Hypoproteinemia Cushing's syndrome
Change in liver size	Nodular hyperplasia, tumor, cirrhosis Fatty degeneration	Right-sided heart failure Work hypertrophy Anemia
Diarrhea (B)	Bile deficit malabsorption Intestinal edema, portal hypertension	Gastrointestinal (GI) or systemic disease
Pruritus	Retention of bile salts	Dermatologic or central nervous system (CNS) disorders
Dermatitis Unpigmented areas	Hepatogenic photosensitization	Primary phototoxic photosensitization
Central nervous system signs Behavioral change, ataxia, dysmetria, circling, stupor, coma, tremors, bellowing	Hepatic encephalopathy (see text)	Brain diseases Metabolic diseases Toxic diseases
Tenesmus (B)	Hepatic encephalopathy	Rectal or colonic disease CNS disease Urogenital disease
Rectal prolapse (B)	Tenesmus	Rectal or colonic disease
Change in feces color	Bile pigment deficit	Diet
	Undigested fat	GI disease
Hemorrhage	Failure to synthesize clotting factors II, V, VII, IX, X	Other clotting factor or platelet deficit, trauma, disseminated intravascular coagulation
Pain over liver	Inflammation, swelling	Abscesses Traumatic reticulitis
Inspiratory stertor (E)	Hepatic encephalopathy	Upper airway obstruction
Dyspnea		

E, Frequent sign in horses; *B,* frequent sign in cattle.

Dermatitis of the white areas may occur because of hepatic photosensitization. The skin of the white areas first becomes erythematous, then thickened with keratin crusts, and finally necrotic. This is caused by the photodynamic agent *phylloerythrin,* which is formed in the gastrointestinal (GI) tract of herbivores by the bacterial degradation of chlorophyll. After absorption into the portal circulation, phylloerythrin should be conjugated by the liver and excreted into the bile. With cholestasis, the phylloerythrin may be carried to the skin, where it acts as a

photodynamic agent.[5] After bile duct ligation, the level of phylloerythrin steadily increases.[6] Although a small amount is removed by the kidneys, the rate is not fast enough to prevent accumulation in the plasma and the skin. Phylloerythrin in the skin reacts to sunlight and emits energy that causes lesions of the white areas.[5]

Pruritus is seen in a few cases of liver disease in horses. In people, pruritus is assumed to be caused by bile acid accumulating in the skin when it is not excreted by the liver. This same process may occur in horses, but pruritus is not usually seen in large animals with liver disease.

A change in fecal color is not usually noted in adult herbivores with liver disease because other pigments such as chlorophyll contribute to the color. In young animals with simple digestive tracts, much of the fecal color is from *stercobilin,* a metabolite of bilirubin. Therefore, with cholestasis, the feces may be a lighter color.

A few signs may be seen terminally in liver disease. Hemorrhage may occur when the clotting factors are not synthesized in adequate amounts. Factors I, II, V, VII, IX, and X are all produced by the liver,[1,4] but the disease is usually advanced before a deficit develops.

Tenesmus, often followed by rectal prolapse, is seen in some cattle with liver disease. This may be associated with diarrhea, may be part of hepatic encephalopathy, or may be aggravated by edema of the bowel caused by portal hypertension.

Pharyngeal or laryngeal collapse with loud stertorous inspiratory noises and dyspnea has developed in some cases of hepatic failure, especially in ponies. The exact mechanism for this is not known, but it may also be part of hepatic encephalopathy.[7]

Horses sometimes develop a terminal hemolytic crisis caused by increased red blood cell (RBC) fragility. This has not been observed in ruminants.

33.5 HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a neuropsychiatric syndrome caused by hepatic dysfunction or portosystemic shunting of the intestinal blood.[8] It is considered a potentially reversible metabolic or neurotransmitter disorder, but it is associated with characteristic (although not specific) lesions in the central nervous system (CNS) such as altered astrocytes.

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Signs of hepatic encephalopathy are often subtle and nonspecific. Behavioral changes may be detected by the owner, who is more familiar with the patient's normal activity. Some docile animals become excitable and difficult to control, whereas other, normally unruly animals may become passive. Depression and incoordination are frequent manifestations, and some animals may walk aimlessly or even head press.[9,10] Apparent blindness is seen in some horses, and foot stomping was reported in 7 of 25 cases.[11] The animals eventually develop a stupor and may end up in hepatic coma. Yawning may be seen in horses, and ponies may have a stertorous respiratory noise. Ruminants show signs of tenesmus and sometimes vocalize excessively. In humans, hepatic encephalopathy is diagnosed by neuropsychological tests, which are not possible in animals.[12]

The pathophysiology of hepatic encephalopathy remains undefined and is controversial.[10] It occurs when portal blood bypasses the liver, as with congenital shunts in dogs, or with shunts secondary to portal hypertension induced by alcoholic cirrhosis in humans, or when the blood goes through an inadequately functioning liver. How neurologic function is altered has not been determined, but speculation abounds.

It seems plausible to incriminate synergistic neurotoxins that bypass the liver. Most will agree that ammonia level plays a central role in the pathogenesis. Blood ammonia is elevated in most cases of hepatic encephalopathy because the liver is not metabolizing ammonia to urea. Encephalopathy can be precipitated in cirrhotic patients by adding ammonia-generating substances, and there is an increase in cerebrospinal glutamine, the product to which ammonia is detoxified. The astrocytes contain the enzyme *glutamine synthetase,* which adds a molecule of glutamate to ammonia to form glutamine. The amount of glutamine formed in the brain correlates with the severity of hepatifc encephalopathy.[13] However, much higher concentrations of ammonia are needed to induce coma in normal animals, and there is poor correlation between ammonia levels and degree of encephalopathy.[11] Four horses with hyperammonemia and encephalopathy without liver disease have been reported.[14]

Magnetic resonance imaging (MRI) of human cirrhotic patients revealed increased image intensities from the globus pallidus region, probably caused by manganese deposits.[12] Serum manganese is increased in these patients, which correlates with the increased MRI intensities and negatively with the neuropsycological tests. This would indicate that manganese is another potential toxin that can enter the brain if not effectively removed from the blood by the liver.

There may be an imbalance of true inhibitory and excitatory neurotransmission. γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter. The increase in GABAergic tone was originally thought to result from an increase in GABA or its receptor sites. More recently, it has been proposed that neurosteroids with GABA-agonist properties could be involved.[15] Ammonia is believed to play a role in the metabolism of GABA in the brain and thus could act synergistically.[16] Also, receptor sites for benzodiazepine are increased in the brain of animals with hepatic encephalopathy.[17] Benzodiazepine augments the activity of GABA in stimulating the inhibitory neuron and causing sedation.

False neurotransmitters have been proposed to cause the abnormal nerve function. Increased amounts of tryptophan, phenylalanine, and tyrosine in the brain could cause more *serotonin,* a false neurotransmitter, to accumulate in the brain. Plasma amino acid ratios are altered in horses with pyrrolizidine alkaloid—induced liver disease.[18] Concentrations of branched-chain amino acids (valine, isoleucine, leucine) are decreased, and the concentration of aromatic amino acids (tyrosine, phenylalanine, free tryptophan) are increased, partially because the liver is not adequately metabolizing the aromatic amino acids. The amino acids are transported across the blood-brain barrier by a common transport system, so they compete for entry into the CNS. It has been suggested that higher levels of aromatic amino acids in the CNS would lead to the formation of increased amounts of inhibitory neurotransmitters or to the alteration of catecholamine or monoamine neurotransmitters, such as GABA or L-glutamate.

33.6 LABORATORY TESTS AND LIVER-DERIVED SERUM ENZYMES

No single test can consistently confirm or rule out the presence of liver disease. Only serum concentrations of γ-glutamyltransferase, globulins, and alkaline phosphatase were found significantly different in horses with or without histologic evidence of liver disease in one study.[19] A combination of tests, including serum enzymes, total bile acids, and liver biopsy, may be needed.

Some blood constituents may be altered because of failure of certain metabolic functions of the liver, but none of these changes is specific for liver disease. Blood glucose is sometimes slightly lower in severe liver disease, especially in young animals, possibly because of decreased gluconeogenesis, but none of 28 adult cases in one

study had low blood glucose concentrations, and in fact, 14 cases had hyperglycemia.[11] Blood ammonia levels can increase fourfold or more in some toxic liver diseases because the urease needed to convert ammonia to urea is found only in the liver. For the same reason, blood urea nitrogen (BUN) may decrease, especially in the terminal phases. In the later stages, the blood-clotting factors may be diminished, with delayed partial thromboplastin time (PTT) and other clotting times.

Terminally, serum albumin concentration may decrease. A large amount of protein synthesis takes place in the liver; all the plasma proteins except γ-globulins are produced by the liver. The amount of these proteins in the blood, however, depends not only on the rate of synthesis but also on the rate of removal. The albumin half-life in cattle is about 16.5 days; in the horse, 19.4 days; and in sheep, 14 days.[20] Therefore, serum albumin is reduced mainly in chronic liver disease. With liver damage, the synthesis of α-globulins and β-globulins is increased so that the total plasma protein concentration is invariably normal or elevated, but the albumin/globulin (A/G) ratio may be decreased. The healthy liver has a large reserve for protein synthesis, and lost protein can be replenished. Less than 5% of horses with hypoalbuminemia had liver disease in a group from our teaching hospital. In one study, 18% of the horses with chronic liver disease and 6% of those with acute liver disease had albumin concentrations below the reference value.[21] In a British study, only 6 of 37 liver disease cases were hypoalbuninemic, and none of these was hypoproteinemic.[11] Therefore, it is assumed that hypoalbuminemia is not a common feature in horses with liver disease, and that hypoproteinemia is rare.

Amino acid ratios are altered in liver disease; the short, branched-chain amino acids are decreased, whereas the aromatic amino acids are increased.[18]

33.7 LIVER ENZYMES

A number of enzymes are compartmentalized in the hepatocyte or in bile duct epithelium. This compartmentalization is useful in holding insoluble molecules close to the enzymes for chemical reactions. Hepatocyte damage may result in release of the enzymes into the circulation, and cholestasis may cause increased release from bile epithelium. Serum levels of these enzymes therefore may be an indication of hepatocyte integrity or bile excretion. Table 33-2 lists frequently tested enzymes and their characteristics. Serum concentrations for some of these enzymes vary with the age of the animal and sometimes even with type or use. Table 33-3 lists some approximate upper limits of normal for animals of various ages. Normal values, especially for the enzymes, should be established by each laboratory. Chapter 22 provides normal adult values from one laboratory.

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Table 33-2 Liver-Derived Enzymes

Enzyme	Specificity	Problems
GGT	Liver	High in young animals from colostrum
	Kidney*	
	Pancreas	
ALP	Liver	Not specific
	Bone	
	Intestine	
	Macrophages	
	Placenta	
SDH	Liver	Not elevated in chronic disease; short life; not stable
GLDH	Liver	Not elevated in chronic disease
AST (SGOT)	Liver	Not specific
	Muscle	
	Heart	
ALT (SGPT)	Liver	Low concentration in cattle and horses; not a good indicator in large herbivore
LDH	None unless isoenzymes	Not elevated in chronic disease; short life; not specific
OCT	Liver	Analysis not routinely available
Ar	Liver	Analysis not routinely available

GGT, γ-Glutamyltransferase; *ALP,* alkaline phosphatase; *SDH,* sorbitol dehydrogenase; *GLDH,* glutamate dehydrogenase; *AST,* aspartate aminotransferase; *ALT,* alanine aminotransferase; *LDH,* lactate dehydrogenase; *OCT,* ornithine carbamoyltransferase; *Ar,* arginase.

* Elevated in urine, not blood.

Table 33-3 Upper Limits for Normal of Some Liver Function Tests (from Various Sources)

Test	Sheep				Cattle				Sheep	Goat
Age	<1 wk	1-4	1-12 mo	Adult	<1 wk	1-4 wk	1-6 mo	Adult	Adult	Adult
Total bilirubin (mg/dL)	4.5	3.0	2.0	2.0	2.4	0.9	0.4	0.3	0.4	0.5
Direct bilirubin (mg/dL)	0.8	0.7	0.7	0.4	0.6	0.3	0.2	0.1	0.1	0.1
Total bile acids (μmol/L)	N/A	N/A	N/A	14	45	35	60	120	25?	N/A
BSP (half-life, T½min)	N/A	N/A	3.7	3.7	15	8	5	5	4.0	2.1
AST (IU/L)	600	540	700	270	60	60	60	60	110	80
GGT (IU/L)	170	170	40	30	4200	1300	N/A	24	55	50
ALT (IU/L)	2800	1200	840	194	1150	1000	N/A	81	188	386
SDH (IU/L)	8	8	N/A	5.8	N/A	N/A	N/A	15.3	28	23
GLDH (IU/L)	N/A	N/A	N/A	11	24	22	19	19	N/A	N/A
LDH (IU/L)	N/A	N/A	N/A	412	1380	1280	N/A	1445	440	392

N/A, Not available; *BSP,* Bromsulphalein (sodium sulfobromophthalein); *AST,* aspartate aminotransferase; *GGT,* γ-glutamyltransferase; *ALT,* alanine aminotransferase; *SDH,* sorbitol dehydrogenase; *GLDH,* glutamate dehydrogenase; *LDH,* lactate dehydrogenase.

γ-Glutamyltransferase (GGT) is a frequently tested and fairly specific enzyme that is almost invariably elevated in chronic liver disease. It is found mainly in the biliary tract and indicates biliary damage (flukes) or hyperplasia (pyrrolizidine alkaloid toxicity or aflatoxicosis). GGT also is present in pancreas, mammary gland, lung, kidney tubules, and other duct epithelium; but serum levels usually are not elevated with renal disease because the enzyme is lost in the urine. Serum concentrations are normally higher in neonatal calves (sometimes >4000 IU/L after suckling)[22] because the enzyme is concentrated in colostrum.[23] GGT levels are also higher in foals than in adult horses, but the higher concentrations may partly be the result of increased production.[24] GGT is elevated in many horses with right dorsal displacement of the large colon, possibly caused by transient extrahepatic bile duct obstruction.[25] Elevated GGT is the most sensitive indicator of liver disease in the horse.[11,26] GGT levels will remain elevated for several weeks.

Alkaline phosphatase (ALP) is usually elevated in chronic liver disease of the horse and is variable in ruminants. ALP can come from other sources, such as bone, intestines, placenta, and macrophages, so it is not specific. Both ALP and GGT are elevated with cholestasis.[27] The dehydrogenases, such as sorbitol dehydrogenase (SDH), lactate dehydrogenase (LDH), and glutamate dehydrogenase (GLDH), are found in hepatocytes and are elevated with acute hepatocyte damage, but serum concentrations may return to normal or below normal in chronic liver disease. SDH is liver specific and extremely useful in detecting active hepatocellular necrosis, but it is not as stable as some of the enzymes. LDH is found in many tissues other than liver; thus it is not specific unless isoenzymes are determined.

33.8 EXCRETION TESTS FOR FUNCTION

Because the liver excretes a number of endogenous compounds and foreign substances injected into the animal, the rate of excretion or clearance of these substances can be used to test the excretory function of the liver. Bilirubin itself can be used and, if elevated above normal, would indicate liver failure, bile blockage, or excess production from hemolysis. In the horse, bilirubin is also increased during fasting in animals without liver disease.[28] With liver damage in the horse or ruminant, most of the retained bilirubin is *unconjugated* (indirect reacting), and the direct-to-total ratio is usually less than 0.3. With bile blockage or intrahepatic cholestasis, the direct-to-total ratio may be greater than 0.3 in the horse or 0.5 in cattle.

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Bilirubin is the main bile pigment and is produced from heme, 75% of which comes from RBCs.[29] When the erythrocytes are broken down, heme is converted first to biliverdin and then to bilirubin in the macrophage system. This unconjugated bilirubin is insoluble and must be bound to albumin for transfer, and this bound bilirubin is not removed by the kidneys. Unconjugated bilirubin is taken up by the hepatocytes with cytosolic binding proteins within the hepatocyte. In the hepatocyte, some bilirubin is conjugated to the diglucuronide, but in the horse, more than half the bilirubin in bile is conjugated with glucose. *Conjugated* (direct reacting) bilirubin is water soluble, and some will enter the general circulation; if concentration is sufficiently high, it will be filtered by the kidneys into the urine. Conjugated bilirubin is secreted into the bile canaliculi by an energy-dependent transport process. In most species, this is the rate-limiting step, but this may not be true in the large herbivores. Conjugated bilirubin passes into the intestine through the bile ducts, and if they are blocked, both conjugated and unconjugated bilirubin will increase in the plasma. In the intestinal tract, bilirubin is converted to urobilinogen by anaerobic bacteria. Some urobilinogen is absorbed and reexcreted by the liver, but a small fraction will pass the normal liver and be excreted in the urine. Therefore, with complete biliary blockage, there will be no urobilinogen in the urine, and with hemolysis, there may be increased urobilinogen in the urine. Urobilinogen is not very stable in the urine; thus analysis must be done within 1 or 2 hours, or the amount detected will be erroneously low.

Fasting decreases the efficiency of plasma bilirubin removal in all species, but the horse shows a greater rise in plasma bilirubin, often reaching a plateau two to three times the normal state. This increase is caused by a decrease in removal of bilirubin by the hepatic transport and not by an increase in its production.[30,31]

Serum total bile acid concentration is a good test of liver function. The concentration of bile acids in the serum will be increased if there is hepatocyte damage, blockage of bile flow, or shunting of portal blood to the systemic circulation, bypassing the liver. Bile acids are synthesized by the liver from cholesterol. Cholic and chenodeoxycholic acids are the primary bile acids that are conjugated with amino acids before excretion into the bile. Only conjugated bile acids are present in the intestine, are soluble, and form micelles with fat because of their detergent properties. Most of the bile acids excreted in the bile are resorbed by an active transport system in the ileum and carried by the portal circulation back to the liver for reexcretion. In most species, more than 95% of the

bile acids are resorbed and recirculated through the enterohepatic circulation.[32] The daily synthesis of bile acids is much less than the daily requirement, and one study in ponies showed that the bile acids secreted each day are about 38 times the total pool.[33]

Many simple-stomached animals have a postprandial increase in serum bile acid because of the release of bile from the gallbladder during eating and subsequent resorption by the ileum. This does not seem to be important in the horse, which has no gallbladder, or in cattle, in which no relationship to feeding could be found.[34]Table 33-3 lists upper limits of normal for liver function tests in large animals of various ages. In cattle there is an hour-to-hour fluctuation that could be as much as 60 μM/L.[34] In the horse, serum concentration above 14 μM/L would indicate liver damage, bile blockage, or shunting.[35,36] Serum total bile acid concentration is likely a more sensitive indicator of liver disease in the horse than serum bilirubin; only 8 of 34 horses with liver disease had elevated bilirubin, but 31 of 37 had elevated bile acids.[11] In adult cattle, because of the hour-to-hour variations, bile acid concentration on a single sample would have to be above 126 μM/L in beef cattle and 88 μM/L in dairy cattle to be an indication of liver disease.[37] Levels are lower (<64 μM/L) in calves less than 6 months old. Serum bile acid concentration is a very specific test that has a high positive predictive value.[38]

A number of dyes are excreted primarily by the liver; sulfobromophthalein (Bromsulphalein, BSP) is used most often. In large animals, BSP clearance (half-time) is used much more than the retention test. In the test, 500 to 1000 mg (~2 mg/kg) of BSP is injected intravenously. Blood samples are taken before the injection and two to four times 5 to 12 minutes after the injection (i.e., at 5, 7, 9, and 11 minutes). These samples are analyzed for color produced by BSP, and a half-life is determined by plotting the points on semilog paper. Normal horses have a BSP half-life of less than 3.5 minutes, and for ruminants it is less than 5 minutes. This may be increased in very young animals (see Table 33-3) and in pregnant females. Other dyes, such as indocyanine green, have some advantage (less renal excretion than BSP) but at present are too costly for use in large animals.

33.9 LIVER BIOPSY

Liver biopsy can be very useful not only in confirming the presence of liver disease, but also in determining or ruling out some etiologies. It is a relatively safe and simple procedure but should be avoided when liver abscesses are suspected. A number of biopsy instruments are available, including aspiration punches, but the Histo-Cut* or TrueCut† and similar notch-cutting needles seem to work quite well. In all species the skin over the biopsy site should be clipped and prepared for aseptic insertion of the needle. A local infiltration of 2% lidocaine helps to reduce the animal's reaction, but it may still flinch when the pleura and peritoneum are penetrated. A small stab wound is made through the skin at the site of insertion with a No. 11 or a No. 15 Bard-Parker blade. The horse should have a twitch applied or be given chemical sedation if necessary.

The site of skin puncture for liver biopsy in the horse is the right fourteenth intercostal space at the intersection of a line drawn from the tuber coxae to the point of the shoulder. Some operators recommend more cranial insertion (twelfth or thirteenth space), but more lung is penetrated at points farther craniad. If a more cranial position is selected, it should also be more ventral. If the needle is directed slightly craniad and ventrad, it is more likely to remain in the liver parenchyma and not penetrate larger vessels on the visceral surface or pass on through into the right kidney, pancreas, or colon. Ultrasound guidance will increase the chances of obtaining liver specimens without penetrating other organs.

Cattle need to be suitably confined for liver biopsy. A biopsy can often be performed on quiet dairy cows in a stanchion while the tail is elevated (“tailed”). The puncture site in cattle can be located by extending a horizontal

line craniad from the middle of the paralumbar fossa. The needle is inserted where this line crosses the eleventh intercostal space on the right side. The lungs do not extend as far caudad as in the horse, so the liver is more exposed. The needle is directed slightly craniad and ventrad, as in the horse.[2]

Liver biopsy in sheep and goats is slightly more difficult; additional sedation is usually required. A site at the ninth or tenth intercostal space at the level of the ventral end of the last rib has been recommended. The biopsy needle is advanced in a craniomedial direction until the liver is penetrated.

Diffuse or zonal lesions, as seen in most toxic, infectious, and metabolic liver diseases, can usually be diagnosed by liver biopsy. Focal lesions, such as abscesses, granulomas, and neoplasias, as well as liver flukes, are easily missed by liver biopsy. If a liver abscess is suspected, biopsy is contraindicated because of the potential danger of rupturing an abscess. A scoring system has been developed for the prognostic evaluation of equine liver biopsies.[39] Examining liver biopsy tissue can confirm the presence of liver disease and help establish the type of disease in addition to aiding in the prognosis.

* Jorgenson Laboratories, Loveland, CO.

† MWI, Meridian, ID.

33.10 ULTRASOUND EXAMINATION

Ultrasonographic examination of the liver is useful in determining its size, its situation, and the diameter of its vessels. Cholelithiasis, neoplasia, and fibrosis can be diagnosed by ultrasound in the horse.[40] Liver abscesses can often be detected, and the circumference of the gallbladder can be determined in cattle.[41,42] Parenchymal pattern of the liver is changed with diffuse fibrosis. An ultrasound examination is performed on cattle on the right side in the tenth to twelfth intercostal space. On sheep the examination is done on the right side in the seventh through twelfth intercostal spaces.[43] In horses the ultrasonic examination is performed below and caudal to the lung in the eighth to fourteenth intercostal spaces. The liver can also be visualized on the left side of the horse in the lower intercostal spaces. Horses with evidence of liver disease should have a percutaneous liver biopsy regardless of the ultrasonic appearance.[40]

33.11 PROGNOSIS

The severity of clinical signs may be the most useful noninvasive prognostic test in horses with liver disease.[44] Indicators of a poor prognosis in liver disease include an albumin concentration less than 2.5 g/dL in horses or an increased globulin level, a prothrombin time (PT) greater than 30% of normal, and greatly elevated GGT and ALP, especially if there is a normal or decreased SDH or GLDH. Marked fibrosis that bridges the liver lobules on histopathology suggests a poor prognosis. Severe pyrrolizidine alkaloid toxicosis carries a particularly grave prognosis because remaining hepatocytes are inhibited from regeneration by mitotic arrest. Terminal clinical signs include development of hemolytic crisis in the horse and marked hepatoencepalopathy in the patient with a fibrotic liver.

33.12 INFECTIOUS, TOXIC, AND PARASITIC LIVER DISEASE

33.12.1 ACUTE HEPATITIS IN HORSES

Nat T. Messer IV

Idiopathic acute hepatic disease (IAHD) is the most common cause of acute hepatitis and hepatic failure in horses.[45] IAHD is also known as Theiler's disease,[46] serum hepatitis,[47] postvaccinal hepatitis,[48] and acute liver atrophy.[49] The disease was first recognized by Theiler in large numbers of horses in South Africa following immunization against African horse sickness with simultaneous administration of live virus and hyperimmune equine serum.[50] Since then, IAHD has been documented as a potential complication of any equine serum or plasma product used in horses. It is primarily a disease of adult horses[51] and recently has been most often associated with the use of either tetanus antitoxin (TAT) or commercial equine plasma.[47,49,52–55]

Mares appear to be affected with IAHD more frequently than males, with recently parturient, lactating mares at greatest risk.[51,54] The seasonal nature of some epidemics of IAHD[51,56] (most reported cases occur in summer months) and the observation that some affected horses in outbreaks of IAHD have not been treated with TAT or plasma[45,51,56] have led to the concern that a virus is involved, similar to hepatitis B virus in humans, but this remains unproved.[46] Alternatively, IAHD has been proposed to be a type III (immune complex—mediated) hypersensitivity reaction.[57]

The clinical effects of IAHD are associated with signs of acute hepatic failure and include depression, jaundice, inappetence, pica, yawning, photoactive dermatitis, and hepatic encephalopathy.* Fever has been described as absent or rare in horses affected with IAHD.[48] Atypical signs that have been reported include progressive weight loss, ventral subcutaneous edema, jugular pulses, ileus, and acute respiratory distress.[54,55,59] Intravascular hemolysis has been reported to lead to hemoglobinuria in some terminal cases of IAHD.[46] Evidence exists for a subclinical or chronic component in some cases of IAHD.[54,60] However, some horses that received TAT have clinicopathologic evidence of liver dysfunction without developing clinical signs, indicating that disease severity may vary.[49,54,60]

Diagnosis of IAHD is based on the anamnesis, clinical signs, and findings from serum biochemical analysis, hepatic biopsy, and necropsy. High serum levels of unconjugated and total bilirubin and serum bile acids, coupled with high serum activity of GGT, SDH, aspartate aminotransaminase (AST), LDH, and ALP, are indicative of hepatic necrosis in horses. IAHD may be confirmed by hepatic biopsy or postmortem examination of hepatic tissue. Typical histopathologic changes seen in biopsy specimens or obtained at postmortem examination include widespread necrosis of hepatocytes that is most severe in the centrilobular and midzonal areas, with the few living cells confined to the periportal areas.[53] The normal architecture of the centrilobular and midzonal areas is replaced by a pale, eosinophilic granular mass in which ghost outlines of necrotic hepatocytes are present.[53] A mild inflammatory cell infiltrate is seen in the portal areas, as well as a number of spindle-shaped fibroblastic cells.[53] The histopathologic lesion is frequently more advanced than the clinical course of the disease would suggest.[53]

There is no specific treatment for IAHD.[61] Treatment should be aimed at supporting liver function and controlling abnormal behavior. Dietary adjustments are important and should consist of reducing the quantity of protein in the diet while increasing carbohydrate intake.[46] Sorghum, milo, or beet pulp, which contains high levels of branched-chain amino acids, can be mixed with molasses to improve palatability and caloric content.[46] Diets high in branched-chain amino acids tend to lessen the degree of abnormal behavior associated with hepatic encephalopathy.[61] Oral neomycin, lactulose, and mineral oil may be administered to decrease ammonia production and absorption from the GI tract. It may become necessary to sedate horses that display severe signs

of hepatic encephalopathy with xylazine or detomidine.[61] Continuous intravenous (IV) administration of dextrose and balanced electrolyte solutions to reduce hepatic workload and maintain plasma volume is recommended.[60] If spontaneous bleeding occurs at injection sites or at sites of self-inflicted injury, plasma transfusions may be necessary to replace the deficient clotting factors.[46] The use of glucocorticoids for treating IAHD is controversial but may be indicated based on some histopathologic evidence of an immune-mediated etiology.[57]

Although the cause of IAHD is unknown, the administration of TAT to recently parturient, lactating mares is associated with substantial risk for development of fatal IAHD.[51,54,60] The susceptibility of postparturient mares to IAHD after TAT administration at foaling is unexplained. Postparturient mares may be the most likely adult horses to receive TAT. Therefore the use of TAT is not without risk, and its use should be restricted to clinical situations necessitating tetanus prophylaxis and in which a history of active tetanus (toxoid) immunoprophylaxis is absent or unknown. The risk of postvaccinal IAHD should be addressed with the owner before administration of TAT.

Routine administration of TAT to parturient mares should be strongly discouraged, and the routine use of active tetanus immunoprophylaxis should be reemphasized. Although the prevalence of serum hepatitis associated with administration of commercial plasma appears to be low in the horse, it should be considered an uncommon risk that can have a fatal outcome.[55] IAHD may be observed sporadically or may affect a group of horses. Recognition of IAHD in one horse should necessitate careful observation of horses on the same premises for either clinical or serum biochemical signs of IAHD.[60] Based on recent case reports, it appears that not all cases of IAHD are clinically apparent and that screening for its presence utilizing routine serum biochemical analysis is useful in detecting subclinical cases of IAHD.[54,55,60]

* References 46,47,51,53,57,58.

33.12.2 BLACK DISEASE

Joseph H. Snyder

Stanley P. Snyder

33.12.2.1 Definition and Etiology

Black disease *(infectious necrotic hepatitis)* is a disease of grazing animals, primarily sheep, resulting most often in sudden death.[62–65] It is caused by toxins produced by the bacterium *Clostridium novyi* type B. *C. novyi* occurs in soils and is normally present in the digestive tracts and livers of animals grazing affected pastures. Disease occurs only when there is sufficient liver damage to provide the anaerobic environment required for growth of the organism and subsequent toxin production. In practice, the liver insult is almost always caused by larval migration of the common liver fluke, *Fasciola hepatica*. Therefore, this is a seasonal disease related to the liver fluke cycle and occurring in animals typically infested by *F. hepatica*. Other liver parasites, such as *Fascioloides magna, Dicrocoelium dendriticum,* and *Cysticercus tenuicollis,* are occasionally implicated, as is damage to the liver by biopsy or trauma that is severe enough to result in localized anaerobiosis in the liver, but these cases are rare. Such a scenario should be considered when sudden deaths occur at times flukes are not usually migrating or in families such as Equidae that are not normal hosts for *F. hepatica*. The disease occurs worldwide where liver flukes are present. The *C. novyi* strains that cause black disease produce at least three potent exotoxins: the *alpha-toxin,* which is the classical lethal toxin; the

beta-toxin, which has both lethal necrotizing and hemolytic lecithinase activities; and the *zeta-toxin,* which is hemolytic.[66]

33.12.2.2

Pathophysiology

C. novyi type B is widely distributed in soils, and its spores are continuously ingested and shed in feces of grazing animals. Some of these organisms cross the intestinal mucosa and become disseminated throughout the animal's mononuclear macrophage system, including the Kupffer's cells of the liver. When localized anaerobic conditions occur in the liver, as with migration of liver fluke larvae, these resident spores may germinate and enter a vegetative state. As they proliferate, they release their toxins and create enlarging zones of coagulation necrosis in the liver. The exotoxins produced will enter the general circulation, where they cause damage to neurons, vascular endothelium, and other vital cells and tissues, eventually causing sudden death of the animal.

33.12.2.3

Clinical Signs

Clinical black disease consists almost entirely of animals found dead. In the unlikely event that an affected animal is recognized before its demise, the signs are nonspecific. The animal will often be off to itself and will appear depressed, anorexic, and possibly in respiratory distress. Temperature is elevated initially, 40° to 41° C (104° to 106° F), but declines before death. Unlike closely related bacillary hemoglobinuria, or “redwater,” affected animals do not show red urine or bleeding from nose or rectum. Diagnosis of clinical black disease can often be accomplished at necropsy or with the help of simple laboratory tests. History will include sudden death, usually in an endemic area during warmer weather, when fluke transmission is active. Flock or herd vaccination will be either overdue or absent. It is also helpful to know the history of fluke infestation on the farm and the timing of fluke control measures, if any have been taken. Time of death should be ascertained as closely as possible. The animal is usually presented in lateral recumbency without signs of struggle. It will be severely bloated, even if death has occurred quite recently, and gives the impression of a carcass in a more advanced state of decomposition than timing would suggest.

33.12.2.4

Necropsy Findings

Postmortem lesions are often obscured by rapid putrefaction of the tissues. Skinning the animal reveals engorgement and hemorrhage of subcutaneous blood vessels, resulting in “black” discoloration, thus the name of the disease. Once the body cavity is entered, blood-tinged abdominal, thoracic, and pericardial fluids are present. Urine is grossly normal. Subendocardial and subepicardial hemorrhages are present. There may be hemorrhages on serosal and pleural surfaces, but these are not always present. Tissues, especially solid organs such as liver and kidney, appear to be in a state of autolysis much more advanced than time of death would suggest. In addition to the presence of migrating fluke channels, the liver is swollen and congested and has one to several small, pale areas of coagulative necrosis. These lesions are typically along the diaphragmatic surface of the liver, have hyperemic borders, and extend for a variable distance into the hepatic tissue. Careful slicing of the organ may be required to find these lesions.[64]

33.12.2.5

Diagnosis

If necropsy does not confirm a diagnosis of black disease, or if there is need for additional documentation, a simple Gram stain of an impression smear taken from the margin of the liver lesion or from any area of a liver

without lesions will reveal numerous large, gram-positive rods typical of the clostridia. Because clostridial organisms proliferate rapidly after death, such findings must always be interpreted carefully, with consideration of time elapsed between death and necropsy. Further diagnostic measures include anaerobic culture and isolation of *C. novyi* type B, identification of the specific toxins, and fluorescent antibody identification of the organism. Characteristic histopathologic changes may also be seen in fixed sections of liver associated with necrotic lesions. Impression smears obtained from the liver lesions are ideal for the fluorescent antibody identification of *C. novyi* type B. Specific toxin identification is impractical for most laboratory settings but is the confirming procedure of choice. 900

33.12.2.6 Treatment and Prevention

Treatment of black disease is rarely undertaken because of its acute to peracute presentation, with animals usually found dead. *C. novyi* is highly sensitive to penicillin and the tetracyclines, but toxin production is usually too far advanced for antibiotics to be of value. If used, they should be administered at high doses, intravenously if possible for most rapid onset (20,000 IU/kg crystalline penicillin or 5 mg/kg oxytetracycline), followed by intramuscular (IM) or IV doses at appropriate intervals. Supportive IV and/or intraluminal fluid therapy should be initiated to correct dehydration. Antiserum is not available. Care should be exercised in handling affected animals because stress may result in sudden death. Chances of success are small. In the event of an "outbreak," vaccination should be initiated immediately, along with mass administration of penicillin or tetracycline, preferably in a long-acting form.

A good prevention program requires consideration of both the pathophysiology and immunology of the disease and the natural history of the liver fluke *(F. hepatica)* that is so intimately involved in expression of black disease. Efforts to clear soils of the offending organism are unrewarding. However, it is recommended that carcasses of animals dying from black disease be burned, buried deeply, or removed from the premises.

Commercial bacterin/toxoids against *C. novyi* are available in combination with other clostridial vaccines. These products are generally safe and highly efficacious. Duration of protection is short, however, and should not be relied on more than 5 to 6 months. Field experience suggests that monovalent *Clostridium haemolyticum* vaccine is more effective than combination products in high-risk herds, and efficacy may vary among commercially available combination vaccines. Animals vaccinated when less than 3 to 4 months old require revaccination at weaning. Local reactions at the site of subcutaneous vaccination are common but primarily of cosmetic concern. Intramuscular vaccination should be avoided because it frequently results in permanent damage to muscle tissue, with a negative impact on meat marketing. Timing of vaccination must be determined by the local climate and liver fluke season. In more severe climates where the fluke season is relatively short, a single annual injection before fluke transmission season may suffice. In more moderate climates with longer periods of fluke exposure, a second injection about 5 months later may be required.

Control of liver fluke infestation is closely linked to prevention of black disease. Control measures include pasture or range management; control of water sources; limiting access to streams, canals, ponds, and marshes; and strategic treatment of animals with products effective against flukes. Appropriate disposal of infected carcasses is important. This is a complex subject, and the reader should refer to the section on liver flukes for more detail.

33.13 Bacillary Hemoglobinuria ("redwater")

Joseph H. Snyder

Stanley P. Snyder

33.13.1 Definition and Etiology

Bacillary hemoglobinuria (redwater, icterohemoglobinuria) is a disease causing sudden death in cattle and other ruminants and, rarely, horses. It is caused by the toxins of *Clostridium haemolyticum* (*Clostridium novyi* type D). This organism is closely related to the etiology of black disease, in which toxin production is closely linked to bacteriophage infection of the clostridial organisms.[67] The major biologically active toxins in *C. novyi* type D (*C. haemolyticum*) are the *beta-toxin,* which is a phospholipase C and has both lethal necrotizing and hemolytic lecithinase properties; the *zeta-toxin,* which is a tropomyosinase; and the *theta-toxin,* which is a lipase. Prominent actions of the toxins induce localized hepatic necrosis and intravascular hemolysis. *C. haemolyticum* occurs in soils, and its spores are routinely found in the livers and passed in the feces and urine of healthy animals grazing affected pastures. Disease occurs only when there is sufficient insult to the liver to provide the anaerobic conditions required for bacterial growth and toxin production. In almost all cases the liver insult is caused by migration of *Fasciola hepatica* (common liver fluke) larvae.[68–70] As in black disease, *Fascioloides magna, Dicrocoelium dendriticum* (the lancet liver fluke), and *Cysticercus cellulosae* have also been occasionally implicated in the disease, as has liver biopsy or trauma severe enough to result in bruising of the liver.[71] Redwater is then, for all practical purposes, a seasonal disease occurring at the time of larval fluke migration.

Bacillary hemoglobinuria is a regionalized disease. It has been reported that *C. haemolyticum* is limited to alkaline soils, but the disease is also endemic in regions with acid soils. The factors affecting distribution of the disease are not well understood. Even in areas where it is common, distribution is erratic, with some farms severely affected, whereas others nearby are disease free. The disease is expanding from areas where it has traditionally been seen, probably in large part because of the shipment of cattle carrying *C. haemolyticum* and *F. hepatica*.

33.13.2 Pathophysiology

Spores of *C. haemolyticum* are ingested by susceptible animals, cross the intestinal mucosa, and are transported to the liver and other organs, probably within the phagosomes of cells of the mononuclear macrophage series. The spores can persist for long periods in the liver within Kupffer's cells. Any localized area of anaerobiosis, as caused by migrating fluke larvae, allows these spores to germinate and proliferate. Release of toxins from the vegetative cells further increases the anaerobic environment, favoring accelerated bacterial proliferation, toxin production, and hepatic necrosis. Absorption of toxins into the circulatory system rapidly leads to intravascular hemolysis, icterus, hemoglobinuria, and death.

33.13.3 Clinical Signs

In most cases of bacillary hemoglobinuria, animals are found dead. In the rare cases in which disease is recognized antemortem, signs include malaise (animal by itself, “humped up,” reluctant to move), anorexia, and fever of 40° to 41° C (104° to 106° F), declining as death approaches. Breathing may be rapid and shallow, and blood or blood-tinged froth may be present in the nostrils. Rectal bleeding or bloody feces may also be observed. The eponymous sign is passage of dark-red, “port wine”–colored urine (hemoglobinuria), but this sign is seen relatively infrequently. Blood is thin and watery and coagulates slowly. Mucous membranes are pale and icteric. Severity of signs increases as the disease progresses.

Bacillary hemoglobinuria is usually diagnosed at necropsy as a cause of sudden death. Historical concerns include occurrence in or origination of the animal from an endemic area, season of the year, last known sighting of the live animal, approximate time of death (and time from estimated death to necropsy), and farm history of vaccination and liver fluke control. Frequently the animal has been seen apparently healthy 12 to 24 hours before death. Herd vaccination is either nonexistent or overdue. The animal is usually in lateral recumbency, severely bloated, and without signs of struggle. Blood is often present in the nostrils, mouth, rectum, or vagina. The carcass appears to be in an advanced state of decomposition, even when it is actually quite fresh. A tentative diagnosis can be made on the basis of history and observation of the carcass.

33.13.4 Necropsy Findings

On closer examination, membranes and tissues are icteric. Skinning the animal reveals numerous subcutaneous petechial and ecchymotic hemorrhages, edema, and sometimes emphysema. There will be copious amounts of red-tinged abdominal and thoracic fluid. Hemorrhages are present on all serosal surfaces. Dark-red urine (or traces) is present in the bladder. Lymph nodes are congested and usually hemorrhagic. There may be hemorrhage into the bowel lumen. The spleen is enlarged. The tracheobronchial tree is usually filled with blood-tinged froth or foam. Lungs show hemorrhages, edema, and frequently emphysema. Pericardial fluid is blood tinged, and hemorrhages are present on both the epicardium and the endocardium. Solid organs such as liver and kidney appear to be in advanced stages of autolysis, even in fresh carcasses. The confirming (pathognomonic) lesion is the so-called ischemic hepatic “infarct,” which has a zone of hyperemia at its interface with viable liver tissue. This area of coagulative necrosis, sometimes partially liquefied at its center, can reach up to a 30-cm diameter and have a very irregular outline.[69] Unlike a classic infarct, the lesion in bacillary hemoglobinuria results from the progressive enlargement of the focus of coagulative necrosis caused by the bacterial toxins. Any thrombosis seen in the lesion is secondary, with the vasculature being included in the necrotic process, along with other hepatic tissue.[71] A thin coat of fibrin may cover the capsule of the liver where it overlies the necrotic lesion.

33.13.5 Diagnosis

In most cases, diagnosis of redwater can be confirmed at necropsy. Some peracute cases may be less typical, or laboratory confirmation may be needed in certain, unusual cases. A simple Gram-stained impression smear from the liver will reveal numerous typical clostridial organisms. Smears may also be made from spleen, blood, or abdominal fluid, with the same outcome. Postmortem presence of clostridial organisms must be interpreted with caution because they are always present and proliferate rapidly after death. It is important to have an accurate estimate of time of death to determine the significance of these findings. Laboratory confirmation depends on identification of the causative bacterium. Both fresh (refrigerated) and formalin-fixed liver lesions should be submitted. Fluorescent antibody tests on impression smears taken from a liver “infarct” will be positive for *C. novyi* type D antigens. Extensive biochemical and toxin identification tests are confirmatory but are seldom used if lesions and fluorescent antibody tests are compatible. Histopathology reveals numerous clostridial rods within the hepatic lesion, particularly immediately subjacent to the zone of neutrophils at the advancing margin of the lesion.

33.13.6 Treatment and Prevention

Treatment of bacillary hemoglobinuria is seldom undertaken because of the acute nature of the disease. If there is opportunity for treatment, penicillin at high dosages (at least 20,000 IU/kg IM twice daily) is the antibiotic of choice, although tetracyclines (5 mg/kg IV twice daily or 10 mg/kg IM daily) are acceptable. Because time is

critical, initiating treatment with crystalline penicillin IV (20,000 U/kg) is indicated if available. Fluids are given intravenously (IV) or intraruminally to correct dehydration. Because of severe hemolytic anemia, blood transfusion is advisable and should be repeated as necessary. Affected animals must be handled with great care because stress or excitement may result in sudden death. In the rare instance of recovery, hematinics should be given to support RBC regeneration.

An effective prevention program requires consideration of both the pathophysiology and immunology of the disease and the natural history of the liver fluke *(F. hepatica)* that is so intimately involved in expression of bacillary hemoglobinuria. Efforts to clear soils of the offending organism are unrewarding. However, it is recommended that carcasses of animals dying from bacillary hemoglobinuria be burned, buried deeply, or removed from the premises.

Commercial bacterin/toxoids against *C. haemolyticum* are available in both monovalent form and in combination with other clostridial vaccines. These products are generally safe and highly efficacious. Duration of protection is short, however, and should not be relied on more than 5 to 6 months. Animals vaccinated when less than 3 to 4 months old require revaccination at weaning. Local reactions at the site of subcutaneous vaccination are common but primarily of cosmetic concern. Intramuscular vaccination should be avoided because it frequently results in permanent damage to muscle tissue, with a negative impact on beef marketing. Timing of vaccination must be determined by the local climate and liver fluke season. In more severe climates where the fluke season is relatively short, a single annual injection before fluke transmission season may suffice. In more moderate climates with longer periods of fluke exposure, a second injection about 5 months later may be required.

Control measures include pasture or range management; control of water sources; limiting access to streams, canals, ponds, and marshes; and strategic treatment of animals with products effective against flukes. This is a complex subject, and the reader should refer to the section on liver flukes for more detail.

33.14 HEPATIC FAILURE IN FOALS

Thomas J. Divers

Hepatic failure in foals might result from infectious, parasitic, congenital, metabolic, or toxic causes. Iron fumarate is the best documented of the toxic causes.[72] Iron toxicity most often occurs when newborn foals are given iron before nursing. Colostral-acquired glutathione or other protective substances may explain the great decrease in iron hepatotoxicity when the iron is administered after colostrum.[73] When the iron is given at birth and before colostrum, clinical signs develop 2 to 5 days later. In rare cases, clinical signs may not develop until the foal is older. The initial clinical signs are associated with hepatoencephalopathy and include seizures, marked depression, ataxia, aimless wandering, head pressing, or any sign of abnormal behavior. Icterus is noted in most foals at the time neurologic signs are exhibited, although some foals may die so peracutely that icterus is not noticed. Although not documented in foals, nonsteroidal antiinflammatory drugs (NSAIDs), such as carprofen and mycotoxins, are other potential toxic causes of hepatic failure. Rarely, foals treated with macrolides, trimethoprim-sulfas, or histamine-2 (H_2) blockers for pneumonia or diarrhea develop an increase in serum hepatic enzymes, despite the foal improving clinically. With changes in drug treatment, the serum enzymes return to normal, suggesting these cases may have drug-induced hepatopathy.[74] Steroid-induced hepatic lipidosis has been observed in foals receiving both prolonged and high doses of corticosteroids.

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Other causes of hepatic failure in foals include perinatal herpesvirus infection, leptospirosis, *Actinobacillus equuli* infection, streptococcal bacteremia, Tyzzer's disease, other bacterial infections, systemic inflammatory response syndrome (SIRS) and multiple organ system dysfunction, septic portal vein thrombosis (e.g., *Rhodococcus equi*),

chronic neonatal isoerythrolysis, hepatic lipidosis/hyperlipemia in miniature equine foals, cholangitis associated with duodenal ulcer disease, *Parascaris equorum* migration, congenital anomalies (e.g., atresia of bile duct, portosystemic shunts), and hyperammonemia in Morgan weanlings.

Equine herpesvirus 1 (EHV-1) infection of a near-term fetus may result in the birth of a nonviable foal with hepatic, respiratory, and/or gastrointestinal disease.[75] Generally, the clinical condition rapidly declines within 5 days after birth. Affected foals may have severe neutropenia and lymphopenia. Treatment with oral acyclovir (8 to 16 mg/kg every 8 hours) may improve survival rates.[76]

Leptospirosis was reported to cause jaundice and death in a 10-day-old foal.[77] Although *Leptospira pomona* is known to cause abortion and liver disease (giant cell hepatopathy) in the equine fetus, it is also apparently a rare cause of neonatal liver disease. *A. equuli* typically causes bacteremic embolic nephritis and acute death in very young (~3-day-old) foals. It may also cause widespread multifocal hepatitis in foals. *Streptococcus zooepidemicus* bacteremia may also cause multifocal hepatic abscesses. *Tyzzer's disease* is the best-documented cause of bacterial hepatitis in foals, as briefly discussed in the following section. Other bacteria and bacterial toxins may initiate an exaggerated response to sepsis (SIRS), which may result in multiple organ dysfunction, including hepatic failure. Many vasoactive mediators are involved in this process; the hemodynamic system becomes ineffective, and certain organs (e.g., liver) may fail because of hypoxia. Diffuse hepatic necrosis and hepatocellular apoptosis are the characteristic lesions. The clinical signs may be identical to Tyzzer's disease, except the syndrome may affect a much wider age range. Prompt and aggressive treatment is often successful. Appropriate treatments include broad-spectrum antibiotics, fluids, oxygen, and antioxidants such as dimethyl sulfoxide (DMSO) and acetylcysteine. Bacterial sepsis rarely may cause acute portal vein thrombosis. Variable degrees of hepatic hypoxemia and inflammation accompany the thrombosis. Hepatoencephalopathy does not generally occur in foals, unlike in adult horses, with portal vein thrombosis. Diarrhea may occur in foals from portal hypertension. The thrombus can be seen on ultrasound examination. A complete recovery may occur with long-term antimicrobial therapy.

Foals with severe and prolonged *neonatal isoerythrolysis* may develop liver failure,[78] which may result from a combination of chronic hypoxia and iron overload from multiple transfusions. Levels of conjugated bilirubin are generally high enough to suggest that bile stasis is also present. With severe and persistent hemolysis, bile excretion may become the rate-limiting step in bilirubin clearance. Physical obstruction of bile flow may result from duodenal scarring after a duodenal ulcer,[79] congenital biliary atresia, or parasitic obstruction.

Congenital *portosystemic shunts* occur infrequently in the equine and bovine.[80] Clinical signs may not be noted until foals are 2 to 3 months old and begin ingesting large amounts of grain or grass. Waxing and waning signs of encephalopathy are the most common signs in foals. Encephalopathic signs and tenesmus are characteristic of the disease in calves. Elevated plasma bile acids and ammonia levels in foals with encephalopathic signs and normal concentration of hepatic-derived serum enzymes should arouse suspicion of a portosystemic shunt. Shunts may be single or multiple and may be intrahepatic or extrahepatic. Positive-contrast portography is the diagnostic technique of choice. The shunt may also be detected by transrectal portoscintigraphy (in foals) or transabdominal ultrasound examination. Successful medical management followed by shunt ligation has been described in a foal and calf.[80,81]

Hepatic failure has been seen in Morgan foals.[82,83] The onset of clinical signs (depression and weight loss) occurred soon after weaning. Liver enzymes are elevated; and variable degrees of portal and bridging fibrosis with bile duct hyperplasia, karyomegaly, and cytomegaly are often seen on microscopic examination. The disease is fatal and may end with a terminal hemolytic crisis. The cause of the disease is unknown, but it may be inherited.

The best laboratory aids in confirming hepatic failure are abnormally high concentrations of serum bilirubin (both conjugated and unconjugated), ammonia, and prolonged PT. Elevation in serum enzymes that are hepatic specific may indicate hepatic disease. Some foals with toxic hepatic failure have had normal or only modestly elevated SDH levels. GGT levels may be high in normal neonatal foals.[84] Plasma glucose concentrations are frequently abnormally low in neonatal hepatic failure. The measurement of bile acids may be useful in determining hepatic dysfunction in foals older than 1 week.[85]

Treatment of these conditions is discussed later under Therapy of Liver Failure or under the specific condition.

33.15 TYZZER's DISEASE IN FOALS

Erwin G. Pearson

Tyzzer's disease is a sporadic, acute focal bacterial hepatitis that occurs in foals 7 to 40 days of age.[86] It has been reported in calves and other species.[87] The causative organism is *Clostridium piliforme,* formerly called *Bacillus piliformis*.[88] Multiple strains can infect Equidae.[89]

In many cases of Tyzzer's disease, the foal will be found dead with no previous signs of illness. The diagnosis in most cases is made postmortem. Recently, a polymerase chain reaction (PCR) test has been used to diagnose the condition in live foals.[90] If detected, clinical signs may include fever, icterus, depression, anorexia, diarrhea, and seizures, none of which is specific for the disease.[90,91] Serum chemistry values will show elevated liver enzymes, hyperbilirubinemia, hyperfibrinogenemia, and a severe hypoglycemia. Histopathologic examination of the liver reveals multifocal areas of necrosis in which the organism can be identified with the Warthin-Starry method.

There is one report of successful treatment of a proven case of Tyzzer's disease in a foal.[90] Early antimicrobial therapy and IV fluids to correct the severe hypoglycemia and acidosis, along with antiinflammatory drugs and parenteral nutrition, could be helpful.

33.16 CHRONIC ACTIVE HEPATITIS

Erwin G. Pearson

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33.16.1 Definition, Etiology, and Epidemiology

Chronic active hepatitis represents a sustained inflammatory process within the liver. The diagnosis is made histologically when the principal features are infiltration of inflammatory cells into the portal areas, necrosis, and fibrosis.[92] Some pathologists do not recognize this as a large animal disease, and although there are few recent reports in the literature, a number of cases fulfill these criteria.

The etiology of chronic active hepatitis in large domestic animals is not known, but several factors likely are involved. In humans, persistence of the hepatitis B or hepatitis C virus accounts for most cases of chronic hepatitis. In dogs, most cases are reported to be “idiopathic,” even though more cases are reported.[93] In horses the histologic diagnosis is often cholangiohepatitis.[94] Cholelithiasis and cholangiohepatitis are encountered as forms of liver disease in adult horses and involve ascending infections from the small intestine.[95] These are discussed further under Choledocholithiasis, Cholelithiasis, Hepatolithiasis.

Cholangiohepatitis that is not associated with liver flukes also has been confirmed in cattle. Bacterial infection through the portal drainage of the bowel or by ascending infection from the bile duct is a potential cause of cholangiohepatitis. Toxins may play a role.[96] Immune-mediated processes are thought to be potential causal factors in humans and may be involved in horses because some respond to corticosteroids, but no definitive work has been done in large animals.

33.16.2 Clinical Signs and Differential Diagnosis

The signs of chronic active hepatitis are similar to those of other types of chronic progressive liver failure, as described previously under diagnosis. Progressive weight loss and depression associated with intermittent fever and icterus may be noted initially. Fever is most consistent with bacterial cholangiohepatitis. Other signs may develop progressively as liver functions begin to fail. Signs of concurrent intraabdominal diseases may be present, and some horses develop peculiar cutaneous lesions at the coronary band or areas of necrotic leathery skin.[97] These lesions usually appear as a moist, exfoliative dermatitis caused by an aseptic vasculitis. Differential diagnosis includes pyrrolizidine alkaloid toxicity, bile stones, abdominal abscesses, and other chronic wasting diseases.

33.16.3 Liver-Derived Serum Enzymes and Diagnostic Tests

Serum liver enzyme activities are usually elevated, reflecting active hepatocyte damage. ALP and GGT tend to be greatly elevated in the active stages of the disease process. Serum bile acid concentrations are increased, and the bromosulfophthalein clearance half-life is prolonged. In most cases, serum bilirubin, especially the direct reacting (conjugated) bilirubin, is elevated. A definitive diagnosis is made from histopathologic examination of tissue obtained by liver biopsy (see following discussion). A part of the liver biopsy, tissue should be submitted for bacterial culture and sensitivity. The lesion is described under Necropsy Findings.

33.16.4 Pathophysiology

The exact pathophysiology of chronic active hepatitis is not known. The early stages are associated with inflammation of the bile ducts and the portal areas of the liver. Extension of bacterial infection through the bile duct or through the portal venous drainage may be responsible for the lesion distribution in animals with suppurative cholangiohepatitis. When lymphocytes and plasma cells are predominant in the cellular infiltrate, immune-mediated processes are more likely.

The liver responds by proliferation of bile ducts and bile duct epithelium, which may impair bile excretion. Because hepatocytes are destroyed more rapidly than they are replaced, connective tissue takes their place. Eventually, areas are joined so that the fibrosis itself limits regeneration. At this stage, some cholestasis may occur, along with failure of other metabolic functions. Portal hydrostatic pressures could increase gradually, potentially leading to other clinical signs (e.g., ascites), but this has not been reported in large animals.

33.16.5 Necropsy Findings

Grossly, the liver appears firm and is often pale brown to green in color, and the cut surface may have prominent, irregular markings. Histologically, most of the lesions are present in the periportal areas. Inflammatory cell infiltration consists primarily of mononuclear cells in some cases, whereas a neutrophilic infiltrate that may contain bacteria (often coliforms) is found in others. These infiltrates are believed to indicate

the nature of the primary disease process. Biliary hyperplasia may be marked if there is cholangiohepatitis. Loss of hepatocytes and increased fibrous connective tissue may be pronounced in the periportal area.

33.16.6 Treatment and Control

Supportive care is most important in these cases, especially for the maintenance of proper appetite and nutrition (see Chapter 50).[98] General measures for treating liver disease apply in these cases (see p. 921). Corticosteroids have been especially useful in horses with a lymphocytic plasmacytic hepatic infiltrate. They act to increase appetite, stabilize cell membranes, and reduce inflammation and connective tissue formation. Initial treatment with dexamethasone at 20 to 40 mg/day for the first 4 to 7 days is followed by a gradual reduction in dosage rate over 2 to 3 weeks, depending on response to therapy.[99] Low-level treatment with prednisolone at 400 mg once daily may be required for an additional 2 to 4 weeks. Antibiotics are indicated when a bacterial cholangiohepatitis is suspected on the basis of the histologic features of the liver, the culture of the liver biopsy, and the presence of a persistent, intermittent fever. Although data are limited, enteric organisms are likely to be encountered, and antibiotic therapy should be directed at the likely organism. Bacterial culture and sensitivity from the biopsy specimen can guide appropriate antimicrobial therapy.

33.16.7 Prognosis

The prognosis for cases of chronic active hepatitis in the horse may be more favorable than with other liver diseases, such as toxicities and serum hepatitis. A recent retrospective study reported that five of nine horses with chronic active hepatitis survived.[100] Case records at Oregon State University Veterinary Teaching Hospital indicate that about half the cases of chronic active hepatitis with no evidence of *Senecio* poisoning improved. Liver biopsy and response to therapy are the best guides in formulating a prognosis. The prognosis for improvement and long-term survival is extremely poor in horses that have functional hepatic failure with widespread fibrosis and disruption of normal hepatic parenchyma. The prognosis is fair to good in patients with early (less severe) lesions, particularly those with a lymphocytic plasmacytic cellular infiltrate that responds well to corticosteroids.

33.17 PYRROLIZIDINE ALKALOID TOXICITY

Erwin G. Pearson

33.17.1 Definition and Etiology

Pyrrolizidine alkaloid (PA) toxicity is a chronic, progressive, often-delayed intoxication that results when animals consume plants containing PAs. The condition is manifested by signs of liver failure.[101] More than 350 PAs have been identified in over 6000 plant species.[102] Table 33-4 lists common plants containing PAs.

33.17.2 Clinical Signs and Differential Diagnosis

The clinical signs of PA poisoning are basically those of liver failure, as previously described under Diagnosis of Liver Disease. The most common signs of PA toxicity in the horse are weight loss, slight to moderate icterus, and abnormal behavior (e.g., wandering, ataxia).[103] Signs seen less frequently in horses include photosensitization of the white areas and, in rare cases, diarrhea. A few cases in ponies have shown loud,

stertorous inspiratory noises, possibly caused by pharyngeal-laryngeal paralysis.[7,104] We have seen pruritus in two cases involving horses, but never in cattle. Abortion may occur from ingestion of sublethal doses,[105] and PA has been shown to be teratogenic in rats.[106] Subtle signs such as poor performance (inability to race up to previous standards) may be seen in horses with pyrrolizidine-induced liver damage before the onset of liver failure. Secondary gastric impaction has been reported in ponies.[107]

Cattle more frequently show diarrhea, weight loss, tenesmus, prolapsed rectum, and ascites. Calves are much more susceptible than mature cattle. Behavioral changes or subtle neurologic signs may also be seen in cattle, but icterus is uncommon. Differential diagnosis includes other diseases causing liver failure (e.g., aflatoxicosis), as discussed in Chapter 54, and some chronic, debilitating diseases such as gastrointestinal parasites, liver flukes, and Johne's disease.[101]

Sheep and goats are more resistant to PA toxicosis but can be affected by certain alkaloids at doses 30 times or more the dose that affects cattle and horses. A consortium of ruminal microbes from sheep degrades PAs found in *Seneio jacobaea* to less toxic metabolites.[108] PA injected directly into the portal vein is toxic in sheep, as is *Senecio* when put in the abomasum.[109] Liver microsomal enzymes in sheep may also play a role in detoxifying PAs[110]; however, this alone does not seem to account for the differences in susceptibility.[111]

Table 33-4 Common Plants Containing Pyrrolizidine Alkaloids (PAs)

Botanical Name (Genus/Species)	Common Name
Senecio jacobaea	Tansy ragwort
Senecio vulgaris	Common groundsel
Senecio douglasii var. *longilobus*	Threadleaf groundsel
Senecio riddellii	Riddell groundsel
Senecio trianularis	Tarweed
Senecio alpinus	Alpenkreuzkraut (Europe)
Amsinckia intermedia	Fiddleneck
Crotalaria species	Rattlebox
Echium plantagineum, E. lycopsis	Viper's bugloss, Salvation Jane
Heliotropium europaeum	Common heliotrope
Symphytum officinale	Comfrey
Cynoglossum officinale	Hound's tongue (houndstongue)
Eupatorium maculatum	Bruner's trumpet
Baccharis pteronoides	Yerba de pasmo
Borago officinalis	Borage
Erechtites species	
Trichodesma species	

33.17.3 Clinical Pathology And Diagnostic Tests

The liver-derived serum enzyme activities are elevated during periods of active hepatocyte destruction caused by PA poisoning. Although the dehydrogenases (e.g., SDH, GLDH, LDH) are elevated initially, they may have returned to normal by the time the animal first shows clinical signs of functional failure. Because lesions are largely in the portal region, GGT and ALP tend to be consistently elevated.[112,113] In a study of sublethally poisoned horses, AST and the ratio of branched-chain/aromatic amino acids were persistently elevated.[105] Bile acids are increased and are increased early in some horses. Serum bile acid concentrations have a good predictive value, and levels above 50 μm/L would be a poor prognostic indicator in the horse.[114] Serum protein concentration is usually normal, and only terminally does albumin decrease or blood clotting become altered. Bilirubin, both direct and indirect, tends to be increased in the horse at the later stages of the disease process.

Liver biopsy is useful in arriving at a definitive diagnosis, but other causes of chronic hepatitis (e.g., aflatoxins) may produce a similar histologic appearance. The triad of fibrosis, bile duct proliferation, and megalocytosis is characteristic of PA toxicity. The histologic lesions are described more fully under Necropsy Findings. Some of the changes can be used for prognosis. Modest changes in the hepatocytes and biliary hyperplasia are reversible. Fibrosis bridging portal areas indicates an eventually fatal condition, as does the extensive fibrosis of an end-stage liver.

Feed samples can be examined for PA-containing plants. Cubed or pelleted feeds can be analyzed for PAs, but this is often time-consuming and relatively expensive.* A sulfur-bound pyrrolic metabolite was identified by thin-layer chromatography (TLC) on the hemoglobin of horses exposed to PAs.[115]

* AM Craig Laboratory, c/o VDL, Oregon State University, Corvallis, OR.

33.17.4 Pathophysiology

There are a number of PAs, and many of the poisonous plants contain four to six different alkaloids. About 50% of the alkaloids are toxic, and some are more toxic than others. The alkaloid concentrations vary slightly among plants from different areas, but there is greater variation in concentrations from different parts of the same plant.[116] After absorption the portal circulation carries the alkaloids to the liver, where they are metabolized by microsomal enzymes of the hepatocyte to more toxic pyrroles.[117] The pyrroles may cross-link double-strand DNA in a dose-dependent manner.[118] The degree of DNA cross-links depends on the concentration of the pyrrol, but not on the base sequence of the oligonucleotide target.[119] The cross-linking of DNA produces an antimitotic effect.[120] The hepatocytes cannot divide and often become megalocytes as cytoplasm expands without nuclear division. As cells die, they are replaced by connective tissue rather than new hepatocytes. This antimitotic effect may explain why megalocytosis (large hepatocytes and large nuclei) is seen with the disease. Besides cross-linking DNA, pyrroles, which are alkylating agents, may disrupt the hepatocyte in other ways.[121] They bind to protein and nucleic acid, thereby inhibiting enzymes and blocking protein synthesis. All these actions may lead to faster death of hepatocytes. With chronic doses, hepatocyte death is more severe in the portal areas (Rappaport zone 1), although some islands of necrosis do occur.[112,113] Centrilobular necrosis may be seen with massive doses.

With progressive death of hepatocytes and subsequent fibrosis, liver function begins to fail. The blood supply through the hepatic lobule is disrupted by fibrosis, making regeneration impossible. This becomes a

venoocclusive disease, resulting in marked portal hypertension. The increased portal hydrostatic pressure leads to diarrhea and ascites in ruminants. It is unclear why diarrhea and ascites are seen infrequently in horses with PA toxicity.

33.17.5 Epidemiology

PA toxicity is seen wherever plants containing the alkaloids are found. The plants are not very palatable and in most cases are not readily eaten, but animals may eat them when the growth of the toxic plant is so thick that the animal cannot separate it from normal forage, or when other forage is sparse. The plants are toxic in hay, including pelleted and cubed hay. Some herbicides may make the plants more palatable as they begin to die. PAs also survive ensilage; oat silage contaminated with *Amsinckia* or other PA-containing plants has been responsible for illness in dairy cattle. Seeds of *Heliotropium* plants have poisoned feedlot cattle.[122]

The approximate toxic dose of dried *Senecio* as a percentage of body weight for each species is horses, 5%; cattle, 2% to 5%; goats, 125% to 400%; and sheep, over 150%. Most tansy ragwort contains less than 0.2% PA by weight, but there are reports of much higher levels in some of the other plants.[123] Horses were consistently poisoned by greater than 250 mg of total PA per kg body weight.[114] The PA in hound's tongue is extremely toxic to horses.[124] This dose does not have to be eaten all at once, since the effects are cumulative. Because signs often are delayed, some animals may not become ill until a year or more after removal from feed sources containing the toxins.[113,125] Signs do not occur until hepatocyte loss and replacement by fibrous tissue have caused failure of liver function.

33.17.6 Necropsy Findings

Cattle dying of PA poisoning have ascites and prolapsed rectums and are thin and emaciated. Horses are usually thin and may be icteric. In all species the liver tends to be small, pale brown to yellow, and firm and may appear to be scarred. Hepatic megalocytosis is considered the hallmark of PA poisoning, but it has also been seen in aflatoxicosis and is not always apparent in the earliest stages of PA toxicity. Biliary hyperplasia may occur early in the disease. Nonspecific nuclear changes, such as invaginations of cytoplasm into the nucleus, have been seen.[112,113] Isolated hepatocyte necrosis is seen later, and finally, portal or massive generalized fibrosis develops. Once bridging of connective tissue between the portal areas occurs, the disease is fatal. The condition is called a "venoocclusive disease" because perivascular fibrosis sometimes occurs, but this is not a constant or characteristic feature.[126] Most of the vascular complications are caused by the generalized fibrosis and remodeling of the liver.

33.17.7 Prognosis

Liver failure may occur with either acute or chronic liver disease; the two must be differentiated for prognosis because end-stage fibrosis caused by PAs has virtually no chance for regeneration and recovery.

No satisfactory treatment for PA poisoning exists. Once obvious clinical signs of liver failure develop, the animal usually dies within 5 to 10 days. Horses with mild clinical signs and reversible histologic lesions survived if they retained an appetite and were not exposed to any more PA-contaminated feed.[105] An accurate prognosis concerning mildly affected cases may best be obtained from a combination of consecutive liver biopsies and liver-derived serum enzyme activity,[105] as well as from serum bile acid concentration.[114] Preventing further

exposure to the toxic plants is indicated and may delay or stop the progression of the liver lesions, particularly if an uncontaminated feed source is provided before clinical signs develop.

33.17.8 Treatment

Therapy of liver failure is inappropriate if severe fibrosis has occurred because regeneration is impossible. If the animal still has a reasonable appetite and only modest degrees of fibrosis histologically, treatment may be attempted by providing a low-protein, high-energy diet. The principles of treatment of hepatic disease should be followed (see p. 921).

33.17.9 Prevention and Control

PA poisoning is prevented by keeping susceptible animals from pasture, hay, cubed hay, or seeds that contains PA plants. *Senecio vulgaris* tends to contaminate mainly first-cutting alfalfa, whereas *Amsinckia intermedia* is often found in planted fields of oat hay. *Senecio* can be controlled by cultivation because it is a biennial, or by herbicide spraying in the early, rosette stage. Biologic controls for *Senecio jacobaea* include the cinnabar moth, *Tyria jacobae,* and the tansy flea beetle, *Longitarsus jacobae*. Sheep are sometimes used to graze *Senecio*-infested pastures to control the weed because they are less susceptible to the poisoning.

33.18 OTHER HEPATOTOXINS

Erwin G. Pearson

The liver is particularly vulnerable to toxic insults because it is the first organ to receive toxins absorbed from the GI tract. Enzymes in the hepatocyte may either activate a toxin or, in some cases, metabolize it before it can cause damage. Most hepatotoxic agents are described in more detail in Chapter 54. Some of the more common liver toxins are listed in Tables 33-5, 33-6, and 33-7, but these are not complete lists because many other plants and chemicals can damage the liver under the right conditions. Once a toxic liver disease has been diagnosed, possible sources of the toxin might be identified from these tables. A more detailed description of the toxin could then be found in Chapter 54.

33.19 LIVER FLUKES IN RUMINANTS

John B. Malone

The common liver fluke *Fasciola hepatica* causes a disease of production in ruminants that mimics the production effects and clinical appearance of the GI nematode-parasite complex. The disease often has its maximum economic effect in late fall and winter, when animals are most likely to be under seasonal nutritional stress. *F. hepatica* is unique among the common helminths of ruminants in that it has an asexual multiplication phase of the life cycle in snail intermediate hosts that is highly sensitive to environmental conditions. *F. hepatica* is well known for its exponential propagation of infective stages under favorable conditions, sometimes leading to explosive seasonal outbreaks of severe parasitism, especially in sheep. In addition, liver parenchyma migration forms leave necrotic tracts in their wake that are a primary predisposing factor in some areas for acute fatalities caused by *Clostridium novyi* (black disease) and *C. haemolyticum* (bacillary hemoglobinuria).[127]

33.19.1 Epidemiology

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The geographic distribution of *F. hepatica* in the United States is limited mainly to areas in the south-central states and Florida and to the Pacific Northwest, where neutral, well-buffered soils are found and local hydrologic conditions provide suitable habitats for *Lymnaea* species, the snail intermediate hosts. The important vector species in temperate climates are semiaquatic "mud" snails found in disturbed mud banks and hoofprints in shallow depressions in fields, drainage channels, and temporary water bodies in alluvial river basins, bottomlands, and coastal regions of the southeastern United States. Springs, small streams, seeps, and sloughs serve as habitats in areas of greater terrain relief in the western states. Most infections occur by grazing in and around water in fluctuating habitats that stay wet for more than half the year.

Table 33-5 Hepatotoxic Plants

Common Name (Botanical Name)	Approximate LD_{50} (%BW)*	Geographic Distribution	Liver Lesion
For pyrrolizidine alkaloid—containing plants, see Table 33-4.			
Lantana *(Lantana camara)*	1	Northern North America	Necrosis, canalicular collapse
Rabbitbrush *(Tetradymia glabrata)*	0.5	Dry desert	Necrosis
Horsebrush (*Tetradymia* species)		Western U.S.	Necrosis
Sacahuista *(Nolina texana)*	1.1	Southwestern U.S.	Fatty and centrilobular necrosis
Lechuguilla *(Agave lecheguilla)*	4-15	Southern U.S., Mexico	Necrosis, photosensitivity
Puncture vine *(Tribulus terrestris)*	?	Warmer regions	Biliary fibrosis, necrosis (big head)
Whitebrush (*Lippa/Alosia* species)	?	Southern U.S., Mexico	Fatty degeneration
Panic grasses (*Panicum* species)	?	Texas-California, South America	Biliary fibrosis, necrosis
Kleunegrass *(Panicum coloratum)*	?	Southern U.S.	Necrosis, obstructed bile ducts
Bermudagrass *(Cynodon dactylon)*	?	North America	?
Cocklebur *(Xanthium orientale)*	0.75-3	North America	Hemorrhagic centrilobular necrosis
Lupine (*Lupinus* species) Mycotoxin from *Phornopsis inferior*	Varies	Western North America	Necrosis
Cottonseed (*Gossypium* species) Gossypol pigment	Varies; gossypol content	Southern U.S.	Necrosis Cardiac lesions
Poisonous mushrooms *(Amanita phalloides, Galerina veneta)*	Few mushrooms	North America	Necrosis Central nervous system signs
Blue-green algae *(Microcystis aeruginosa, Nodularia spumgena)*	? 0.001	Ponds, worldwide	Necrosis, dissociation
Alsike clover *(Trifolium hybridum)*	Varies	Cultivated	Portal fibrosis, biliary hyperplasia

Mexican fireweed *(Kochia scoparia)*	?	Southwest U.S. Central and South America	?
Cycad palm (*Cycas/Zamia* species)	?	South America, Australia	?
Yellow-wood *(Terminalia oblongata)*	?	Australia, Africa	Centrilobular necrosis
Sneezeweed (*Helenium* species)	0.25	Northern U.S., Canada	?
Moldy alfalfa *(Medicago sativa)*	?	Wet areas	Biliary hyperplasia, necrosis
Bitterweed (*Hymenoxys* species)	1	Southwestern U.S.	?

?, Unknown.

* Lethal dose (as percentage of body weight).

Table 33-6 Hepatotoxic Chemicals

Chemical	Source	Approximate Lethal Dose*	Liver Lesion
Carbon tetrachloride ($CC1_4$)	Tremacide	10-40 mg/kg	Fatty degeneration, centrilobular necrosis, cirrhosis
	Fumigant		
	Solvent		
C1-Hydrocarbons	Insecticides	Varies with species, chemical, and route	Necrosis
	PCBP		
	Solvents		
Pentachlorophenols	Wood preservative, herbicide, fungicide, molluscacide	100-200 mg/kg	Centrilobular fatty degeneration
Polybrominated biphenyl (PBB)	Fire retardant	100 mg/kg	Hemorrhagic necrosis, fatty degeneration
Carbon disulfide (CS_2)	Boticide	100 mg/kg	Necrosis
	Solvent		
	Fumigant		
Coal tar pitch	Clay pigeons	Swine 15 g/pig	Hemorrhagic necrosis
	Pipe sealer		
	Tar paper		
Phenol	Wood preservative	30 mg/kg	Hemorrhagic centrilobular necrosis
Iron	Iron supplements	>150 mg/kg young animals Older animals	Portal necrosis
	Injectable iron		
Copper	Species inappropriate supplements	Depends on species and molybdenum intake	Portal vacuolation and necrosis (hemolytic crisis)
	Fungicides, algicides		
	Molluscacide		
	Foot baths		
Phosphorus	Fertilizer	1-4 mg/kg	Portal necrosis and fatty degeneration
	Matches		

	Rodenticide		
Tannic acid	Oak	20 mg/kg	Centrilobular necrosis (also renal damage)
	Skin astringent		
Paraquat/diquat	Herbicide	4-10 mg/kg	Centrilobular necrosis (also lung damage)
Mycotoxins, aflatoxin B	Moldy feed	3 mg/kg	Centrilobular necrosis, biliary hyperplasia, megalocytosis
Rubratoxin B	Moldy feed	?	Necrosis
Sporidesmin	Moldy feed	?	Bile duct occlusion (big head)
Ochratoxin A	Moldy feed	?	Necrosis (also renal damage)
Phomopsin A	Lupine	?	Necrosis

?, Unknown.

* Lethal dose varies with individual, species, route of entry, rate or chronicity, enzyme induction, and many other factors.

Table 33-7 Drugs Used in Large Animals That Could Damage the Liver

Drug	Lesion*
Carbon tetrachloride	Centrilobular necrosis or fatty degeneration
Hexachloroethane	Centrilobular or massive necrosis
Carbon disulfide	Necrosis
Alcohol	Necrosis/cirrhosis
Tetracycline	Fatty degeneration (also renal damage)
Clindamycin	Cholestasis, icterus
Erythromycin	Cholestasis, icterus
Isoniazid	Active hepatitis → cirrhosis/massive necrosis
Rifampin	Cholestasis, icterus
Nitrofurantoin	Active hepatitis → cirrhosis
Anabolic steroids	Cholestasis, icterus
Phenothiazine	Cholestasis, icterus tranquilizers
Halothane	Active hepatitis → cirrhosis/massive necrosis
Fluothane	Active hepatitis/massive necrosis
Isoflurane	Active hepatitis/massive necrosis
Some diuretics	Cholestasis, icterus
Diazepam	Cholestasis, icterus
Phenobarbital	Necrosis/cholestasis icterus
Aspirin	Active hepatitis → cirrhosis
Oil of pennyroyal	Centrilobular necrosis
Tannic acid	Centrilobular necrosis, fatty degeneration (renal damage)
Dantrolene	Active hepatitis → cirrhosis
Copper disodiumedetate	Massive centrilobular necrosis
Iron (injectable)	Necrosis, portal, cirrhosis, hemosiderosis
Glucocorticoids	Hepatocellular vacuolization

* May vary with dose and time.

The life cycle development of both the snail host and the parasite in the snail occurs only when temperatures are above 10° C (50° F) and while snail habitats are wet. This leads to a distinct seasonal transmission in the mild, wet winter and spring of the south-central states and Florida and a late spring to fall transmission in the cooler climates of the western states (Figs. 33-1 and 33-2). It takes a minimum of 42 days at 25° C (77° F) or the accumulation of approximately 600 growing-degree days to complete intramolluscan development, with release of cercariae that encyst as infective metacercariae on pasture vegetation (600 growing-degree days = 25° C

minus the base temperature of 10° C = 15 growing-degree days × 42 days; an equivalent value for the life cycle is 15° C or 5 growing-degree days × 120 days). Using soil water budget analysis to indicate the length of time habitats are wet and the accumulated sum of growing-degree days over 600, a climate forecast index can be calculated for use in describing the pattern of seasonal transmission at a given site and to provide an indicator of the risk of economic losses in a given climate year. Two weeks of sustained summer heat and drought ends the transmission season by killing pasture metacercariae and forcing snail populations to estivate in soil or perish. In the cooler climates of the western United States, the season ends with drying of springs, seeps, sloughs, and other habitats or with the onset of sustained, cold winter weather. Variation in the annual climate alone may lead to a 100-fold variation in fluke burdens in different climate years (Table 33-8).[128]

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Fig. 33-1 Pattern of *Fasciola hepatica* transmission typical of the southern United States (based on 10 years of experimental data from Alexandria, Louisiana) and strategic treatment recommendations with adulticidal drugs. From Malone JP et al: *Prev Vet Med* 3:131, 1985.

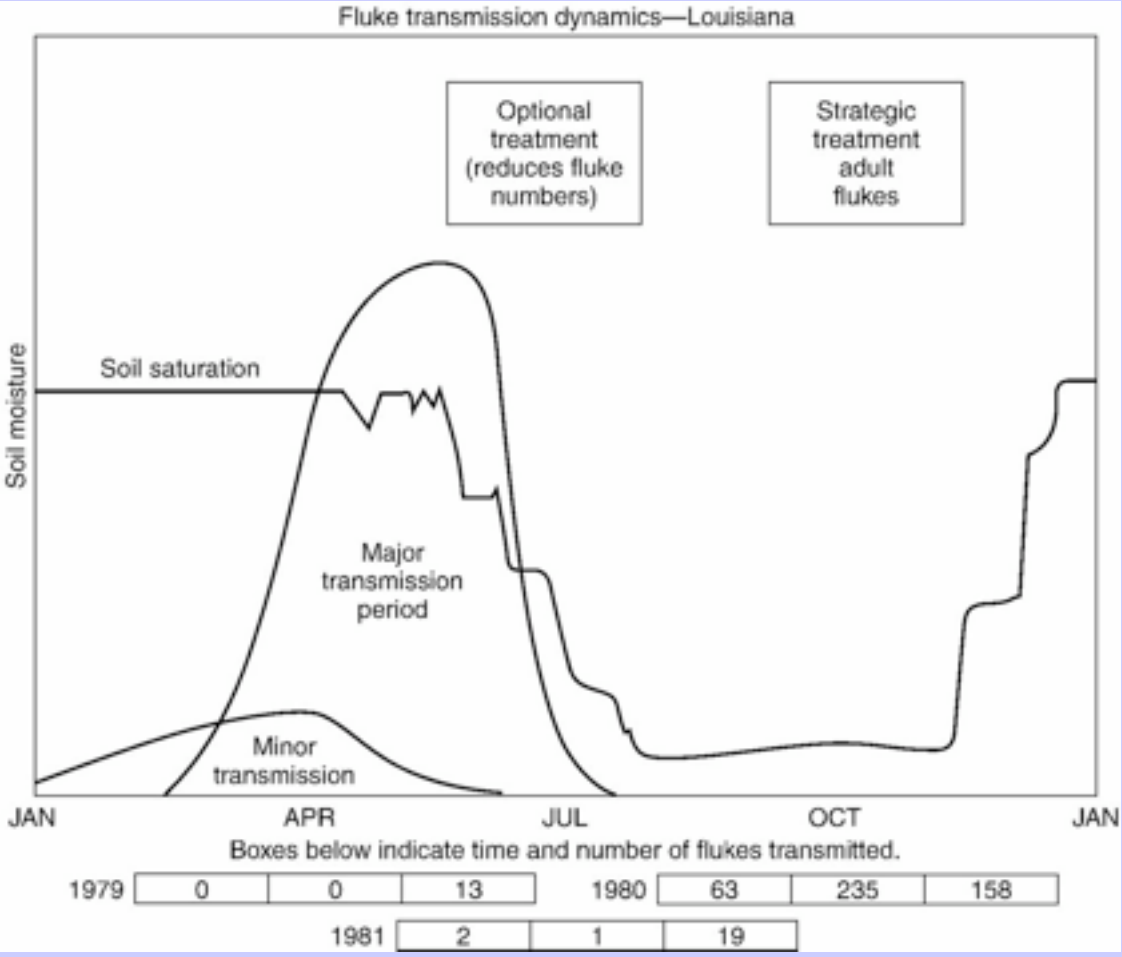
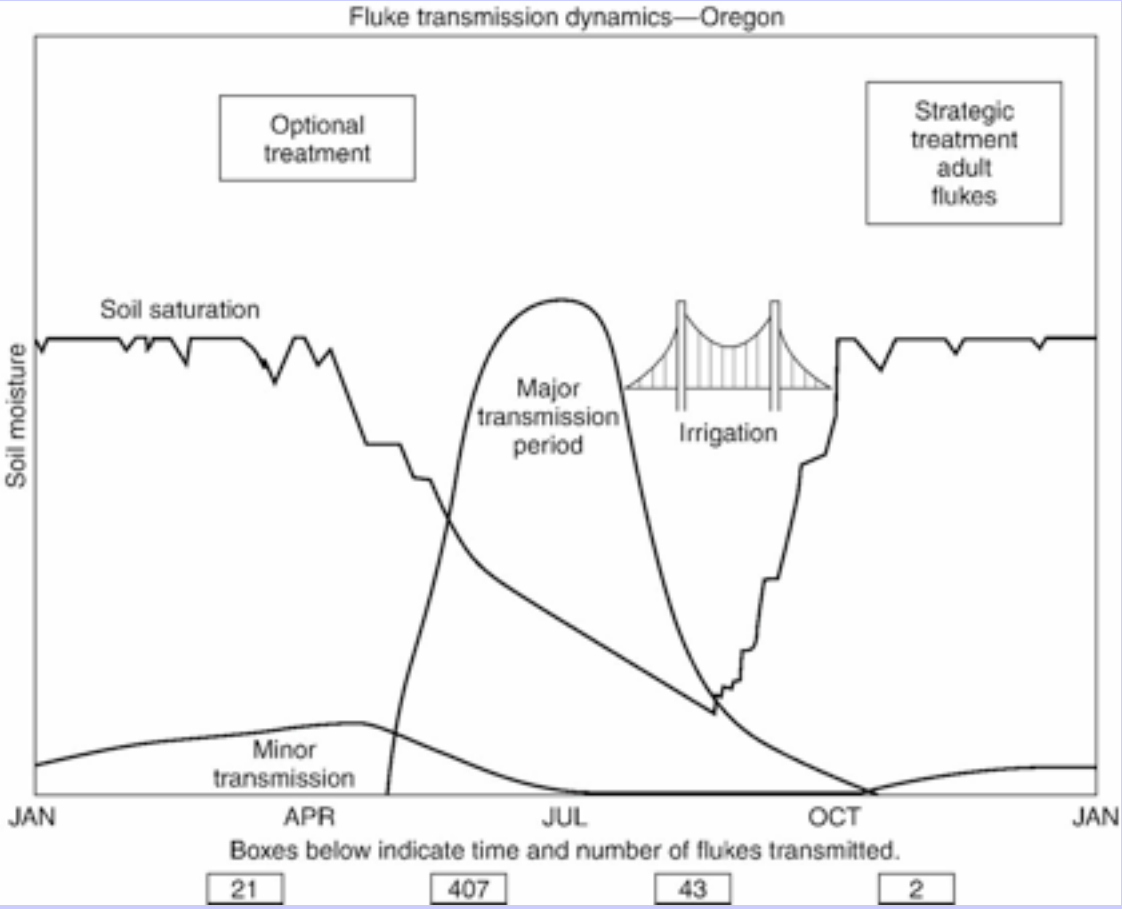


Fig. 33-2 Pattern of *Fasciola hepatica* transmission typical of the U.S. Pacific Northwest in natural rainfall and irrigated zones (based on experimental data from Langolis, Oregon) and strategic treatment recommendations with adulticidal drugs. From Rickard LG et al: *Vet Parasitol* 41:45, 1992.



The amount of snail habitat present on individual farms related to pasture wetness conditions, such as premises with low-lying, heavy clay soils with a high water table, is also an important consideration in evaluating the need for fluke control. This factor has also been shown to lead to a 100-fold variation in the risk of fluke losses in the same year on different premises in otherwise ecologically similar areas.[129] The snail habitat area on most enzootic livestock operations typically is only 1% to 5% of the total land area; operations with over 5% habitat may be associated with a high risk of liver fluke losses.

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Table 33-8 Spring and Autumn Forecast Index Values and Observed *Fasciola* risk at Dean Lee Research Station, Alexandria, Louisiana

Year	Spring Index	Autumn Index	Flukes per Calf	Risk
1979	416	1423	2	Low
1980	757	2949	75	High
1981	326	956	5	Low
1982	370	1134	28	Moderate
1983	1304	3671	251	Very high
1984	549	1168	ND	Moderate
1985	2899	3187	325	Very high
1986	2151	2470	146	High
1987	1619	2081	146	High
1988	669	1459	ND	Low-moderate
1989	830	5741	124*	Very high
Average†	1081	2385	110	

From Malone JB, Zukowski SH: *Parasitol Today* 8:266, 1992.

ND, Not determined.

* Average fluke number despite subterranean drainage of half of the farm and improved preventive herd treatment in 1983. The neighboring farm averaged 189 flukes per calf.

† The 30-year-average reference value computed by the model was 579 for spring and 1978 for autumn.

33.19.2

Clinical Signs and Pathophysiology

Subclinical production effects of *F. hepatica* include reduced rate of gain and feed efficiency in growing stock. Economic effects have been experimentally demonstrated in calves on a marginal nutritional plane in the first 5 to 6 months after infection, resulting in an 8% loss in the rate of gain with a mean of 40 flukes and a 28% loss with 140 flukes. In cattle it is estimated that herd economic losses are “negligible” with a burden of less than 10 flukes per animal, “possible” at 10 to 40 flukes, and “probable” with over 40 flukes; clinical disease is seen with a burden of more than 200 flukes. In cow-calf operations flukes often act in concert with periods of nutritional stress and concurrent heavy GI nematode infections, causing further reduction of body condition, poor milking ability, and slower return to estrus. This translates to reduced reproductive efficiency, prolonged calving interval, and lightweight calves at weaning.[130]

In cattle, flukes may lead to chronic disease or, in rare cases, subacute disease. When clinical signs occur, the typical population “overdispersion” (individual variation in parasite burdens) is manifested first in the 10% to 20% minority of the herd that harbor most of the parasite numbers. Signs may consist of weight loss, emaciation, depression, anorexia, rough hair coat, anemia, hypoproteinemia, submandibular edema, and, in rare cases, mild icterus. The anemia associated with *F. hepatica* infections is more than can be accounted for by blood feeding by

flukes. Evidence indicates that depression anemia and biliary hyperplasia result from high levels of proline, a product of fluke metabolism.[131] Cattle are able to mount a protective immune response, with partial acquired resistance to *F. hepatica,* beginning at 5 to 6 months after initial exposure.[132] This and the short lifespan of flukes in cattle typically lead to a linear reduction of fluke numbers, with few surviving by the end of 1 year. Sheep and goats are more susceptible, and fatal acute disease with ascites, abdominal hemorrhage, pallor, and icterus can occur in association with massive entry to the bile ducts at 6 to 10 weeks after infection by 1000 to 5000 or more migrating immature forms from the liver parenchyma. Subacute disease has been associated with a burden of more than 800 flukes acquired over time. Chronic clinical disease in sheep with submandibular edema, ascites, and emaciation has been associated with fluke burdens above 200.[133]

33.19.3 Necropsy Findings

Necropsy findings attributable to migrating young flukes are caused by tortuous tunnels of coagulative necrosis that organize and fibrose, ultimately leading to a diffusely fibrotic liver parenchyma, especially in the ventral lobe, which in severe cases undergoes marked atrophy. Fibrous tags may result from fibrinohemorrhagic deposits left by large numbers of flukes at liver penetration 3 to 4 days after infection. Inflammatory events associated with penetration of the bile ducts at 6 to 8 weeks after infection are especially pathogenic. Once in the bile ducts, flukes grow rapidly from 1 mm to 2.5 cm or more and induce a proliferative cholangiohepatitis. The spines and suckers of flukes erode and denude the bile duct epithelium, leading to a fibrosed, thickened duct wall that is irregularly dilated and stenotic and begins to calcify in cattle (but not sheep) at about 20 weeks after infection. The bile becomes darkly discolored and laden with regurgitated fluke ingesta, plasma proteins, and inflammatory cells. The extent of pathologic change is generally proportional to the fluke burdens of current or recurring previous infections.[133]

33.19.4 Diagnosis

Fecal sedimentation methods are the standard means of diagnosing liver flukes. A reusable commercial kit based on sieve-sedimentation of 2-g samples (Flukefinder, Visual Differences, Moscow, Idaho) reduces sample processing time by half and is suitable for use by practitioners for quantitative examination of an individual animal or of 10- to 15-animal herd composite samples. For herd or lot evaluations in cattle, egg counts of less than one egg per 2 g (EP2g) and 25% prevalence 2 to 4 months after the transmission season ends have a “low probability” of economic losses; 1 to 3 EP2g indicates “possible” economic loss; and 10 EP2g or more indicates “high probability” of heavy infections and economic loss. It is important to differentiate *F. hepatica* eggs from the eggs of *Paramphistomum* species, a nonpathogenic “rumen fluke” often found in the same herds in both the southern and the western enzootic areas. Flukecides used against *F. hepatica* are ineffective against rumen flukes, and egg counts thus persist after treatment. *Paramphistomum* eggs are gray (rather than amber), slightly smaller, and more pointed at the operculum end than *F. hepatica. Paramphistomum* egg counts can be used as a general indicator of the probable risk of *F. hepatica* in the absence of control in the southern states, because *Paramphistomum* flukes are known to be transmitted by the same snail vector in that region.[130]

Diagnostic enzyme-linked immunosorbent assays (ELISAs) have been developed to detect serum antibodies and coproantigen in the feces of infected animals[134] but have not yet found wide use outside of research or diagnostic laboratories. Blood and serum clinicopathologic results reflect the anemia, hypoproteinemia, and mild eosinophilia caused by *F. hepatica*. Pathologic changes in the liver bile ducts and parenchyma are reflected by an elevation in serum liver enzymes (e.g., GGT, GLDH).

33.19.5 Treatment and Control

Prevention is the key to control in foundation herds and flocks because even low numbers of eggs shed can multiply asexually in snails and lead to significant infection rates during the following transmission season. A single routine fall or late fall-winter treatment after the end of the transmission season with a highly effective drug is recommended to remove adult flukes before winter stress and to prevent egg shedding and snail infection in the next season (see Figs. 33-1 and 33-2). Most of the pathogenic and economic effects of flukes in cattle are reported to occur within the first 5 to 6 months after the major exposure period and may be related to metabolic products associated with the rapid growth and heavy egg production phases of the life cycle. This, coupled with linear loss of heavy fluke burdens in cattle and the onset of effective immunity at 20 weeks after exposure, suggests the value of early flukecide treatment, within 2 to 3 months after the transmission season ends. In some herds an optional curative treatment in spring may be needed in very high-risk years or on high-risk premises, or as a second treatment to remove flukes acquired during late, extended transmission on irrigation pastures or wet coastal areas in the west.

Flukecidal drugs available in the United States are effective against mature flukes in bile ducts (albendazole, 10 mg/kg; closulon, 2 mg/kg). Closulon at 7 mg/kg has added efficacy against juvenile flukes over 6 weeks old in the bile ducts. The optimum time to treat should be based on the estimated susceptibility of mature fluke populations (>12 weeks old after end of transmission season) but early enough to remove flukes while they are most pathogenic (<6 months old). Triclabendazole, which is widely used in other countries, is more than 90% effective against migrating flukes over 2 weeks old and 99% effective against mature flukes and can be effectively given just after transmission ends. Worldwide, a number of other drugs are available, including oxyclozanide, niclofolan, bithionol, and hexochlorophene (80% to 99% of adult flukes), nitroxanil, closantel (>90% adult and 50% to 90% juvenile bile duct flukes), rafoxinide (>50% late migratory flukes, >90% juvenile and adult bile duct flukes), and diamphenathide (>90% migratory flukes, 50% to 80% bile duct flukes).[135]

The economic benefit of routine flukecide treatment of feedlot calves from enzootic areas in the United States has not been consistently demonstrated industry-wide because of the high variability of fluke burdens in animals from enzootic areas, or because lots are often of mixed origin. Fluke-related losses would be expected to be mainly absorbed by stocker operations, where lightweight calves are typically placed on small grain pastures for extended periods before feedlot, a common practice in the south-central states. The economic return of treatment at feedlot should be evaluated on a case-by-case basis because significant losses may occur if the lot originates from the same premises and the history suggests a high risk of recent, heavy infection rates, such as in favorable climate years or use of irrigated pastures in fluke areas. Fecal egg counts on 10 to 15 randomly selected animals may aid in herd evaluation. An example case of the explosiveness of the life cycle is the greatly reduced feedlot performance and 100% liver condemnations of a lot from a stocker operation in the Pacific Northwest. The animals originated from irrigated pastures where some habitats stayed wet year-round, and untreated calves from fluke areas were allowed to contaminate pastures with eggs, which translated to infection later in the grazing season and to the next stocker group rotated onto the premises.

33.19.5.1 OTHER FLUKES

Fascioloides magna, the large American liver fluke, may infect cattle and sheep that graze common areas with deer, the natural host. The life cycle is similar to that of *Fasciola hepatica,* but with a wider variety of lymnaeid snail hosts and a broader geographic distribution in the Gulf States, the Great Lakes area, and the Northwest. Cattle are abnormal, dead-end hosts that react with an intense encapsulation response, forming a

closed cyst that does not allow escape of eggs and obviates diagnosis by fecal examination. The liver parenchyma and regional lymph nodes have a characteristic diffuse, black pigmentation. The major economic effect of *F. magna* in cattle is condemnation of livers and other organs, such as lungs, in which aberrant migration sometimes occurs. In sheep and goats, however, *F. magna* does not encyst and migrates uninterrupted. One or two *F. magna* flukes kill sheep before the flukes have time to mature, and this parasite limits sheep production in some areas. Albendazole given at high dosage is moderately effective against *F. magna*.

In tropical regions, *F. hepatica* is replaced by *Fasciola gigantica,* a similar species that is somewhat larger, has a longer prepatent period (10 to 12 weeks), and is of somewhat greater pathogenicity. *Dicrocoelium dendriticum* occurs worldwide but in North America is an unimportant species, mainly limited to areas of central New York, with smaller foci in Pennsylvania, New England, Quebec, and British Columbia. Albendazole (20 mg/kg) and high doses of thiabendazole (150 to 300 mg/kg) are effective treatments.[127]

33.20 HEPATIC ABSCESSES

T.G. Nagaraja

33.20.1 Definition and Etiology

Hepatic abscesses occur sporadically in most animals but are most common in ruminants, particularly cattle fed high-grain diets. Hepatic abscesses occur at all ages and in all types of cattle, including dairy cows, but have the greatest economic impact in feedlot cattle, in which the incidence ranges from 1% to 2% to as high as 90% to 95%, but averages 20% to 30% in most feedlots.[136] Because hepatic abscesses are generally a direct result of feeding practices, diet is an important factor influencing the prevalence. The prevalence of liver abscesses in dairy cows has not been documented, other than the anecdotal observations of liver abscesses “being not uncommon” in slaughtered heifers and cows. Most of the cows slaughtered are culled animals with low productivity, often related to disease, removed as a routine strategy to improve herd productivity.

Hepatic abscesses are generally polymicrobial infections, and in most cases the organisms are anaerobes. In the bovine, *Fusobacterium necrophorum* (formerly *Sphaerophorus necrophorus*), a gram-negative, pleomorphically rod-shaped anaerobe, is the primary etiologic agent. The organism also is implicated as the primary pathogen in necrotic laryngitis (calf diphtheria), foot rot, and foot abscesses in cattle.[137,138] *F. necrophorum* is a normal inhabitant of the rumen, and its role in ruminal fermentation is mainly to utilize lactic acid and degrade protein. The organism is in higher concentration in grain-fed than forage-fed cattle, possibly because of the increased availability of lactic acid from starch fermentation. Several virulence factors have been implicated in the pathogenesis of *F. necrophorum* infections.[138] These include leukotoxin, endotoxic lipopolysaccharide (LPS), hemolysin, hemagglutinin, capsule, adhesins or pili, platelet aggregation factor, dermonecrotic toxin, and extracellular enzymes (e.g., proteases, deoxyribonucleases).[139] Leukotoxin is believed to be the major virulence factor. The leukotoxin is cytotoxic to polymorphonuclear neutrophil leukocytes (PMNs), macrophages, hepatocytes, and ruminal epithelial cells. Because of leukotoxin, the organism is able to survive, proliferate, and establish itself, to set up infection of the ruminal wall and liver. There are two subspecies of *F. necrophorum,* subsp. *necrophorum* (formerly biotype A) and subsp. *funduliforme* (formerly biotype B). These two subspecies differ in cell morphology, colony characteristics, growth patterns in broth, and most importantly, in virulence factors. Subspecies *necrophorum* is more virulent (produces more leukotoxin) and thus more frequently encountered in liver abscesses than subsp. *funduliforme,* which tends to occur more often in mixed infections.[140,141]

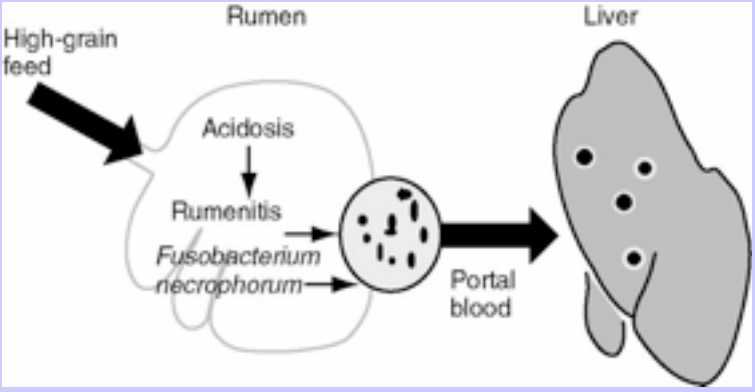
In most situations, *Arcanobacterium pyogenes* (formerly *Actinomyces, Corynebacterium*), a gram-positive rod shaped organism, is the second most frequent pathogen isolated from liver abscesses. The ruminal wall appears to be the niche for *A. pyogenes,* an aerobe, because the wall provides an aerobic microenvironment in an otherwise anaerobic environment of the rumen.[142] The organism may also act in synergy with *F. necrophorum* to cause liver abscesses.[143]

33.20.2 Pathogenesis

Abscesses in the liver result from entry and establishment of *F. necrophorum* either alone or with other bacteria. The routes by which the bacteria can gain access to the liver include: the portal vein, hepatic artery, umbilical vein (in newborn with omphalophlebitis), bile duct system, and direct extension. Entry through the hepatic artery (after an episode of septicemia) or the bile ducts (usually from obstruction, infection ascending from duodenum, or migration of flukes) is a rare occurrence. The direct extension of infection from adjacent tissues and organs, usually of traumatic origin, such as direct puncture of the liver by a foreign body lodged in the reticulum, is more likely to occur in dairy cows. Traumatic reticuloperitonitis caused by metallic objects lodged in the reticulum and perforating through the reticular wall, rarely involving the ruminal wall, is often a predisposing factor for liver abscesses in dairy cows. However, in both dairy cows and feedlot cattle, the most common route of entry of bacteria into the liver is the portal vein.

Liver abscesses are secondary to the primary foci of infection in the ruminal wall. Evidence to support this is the high correlation between ruminal wall lesions (rumenitis) and liver abscesses, thus the term *rumenitis—liver abscess complex* (Fig. 33-3). It is well accepted that ruminal lesions resulting from acidosis are the predisposing factors for hepatic abscesses. Acid-induced rumenitis and damage of the protective surface usually are associated with a sudden change to high-energy diets and other dietary indiscretions, such as a change in feeding patterns, letting cattle become overly hungry, feeding unpalatable diets, and feeding very little roughage.[144] The ruminal damage often is aggravated by foreign objects in the feed, sharp feed particles, or hair.[143] The ruminal wall that is damaged from acidity or penetration of foreign objects becomes susceptible to invasion and colonization by *F. necrophorum*. Once colonization has occurred, *F. necrophorum* can gain entry into the blood or cause ruminal wall abscesses and subsequently shed bacterial emboli to the portal circulation. Bacteria from the portal circulation are filtered by the liver, leading to infection and abscess formation.

Fig. 33-3 Pathogenesis of liver abscesses in cattle fed high-grain diets. Modified from Nagaraja TJ, Chengappa MM: *J Anim Sci* 76:287, 1998.



Undoubtedly, the virulence factors of *F. necrophorum* play a critical role in the penetration and colonization of the ruminal epithelium and entry and establishment of infection in the liver. The protease activity, dermonecrotic activity, and cytotoxic effect of leukotoxin on ruminal cells may aid in penetration and colonization of the ruminal wall. *F. necrophorum*, being an anaerobe, must overcome both high oxygen concentrations and phagocytic mechanisms to survive, proliferate, and initiate abscess formation. The leukotoxin may protect it from phagocytosis. Also, the release of cytolytic products such as lysosomal enzymes and oxygen metabolites, resulting from destruction of phagocytes, has a detrimental effect on the liver parenchyma. Synergism with facultative bacteria, intravascular coagulation induced by endotoxic LPS and platelet aggregation factor; formation of fibrin-encapsulated abscesses, and impairment of oxygen transport by damaged erythrocytes (action of hemolysin) all may contribute to the establishment of an anaerobic microenvironment conducive to the growth of anaerobic bacteria within the ruminal wall and liver.

33.20.3 Pathology

Abscesses found in the liver at slaughter or necropsy often are well encapsulated, possessing thick, fibrotic walls. Histologically, a typical abscess is pyogranulomatous, with a necrotic center, encapsulated, and often surrounded by an inflammatory zone.[141] Hepatic abscesses are pus filled, have capsules that vary in thickness, and range in size from a minute pinpoint to over 15 cm (6 inches) in diameter. The number of abscesses in the liver can vary from one to hundreds, and sizes range from less than 1 cm (0.4 inch) to greater than 15 cm in diameter, often encircled by a hyperemic zone. The larger abscesses may be the result of small abscesses coalescing early in development. The distribution of abscesses in the liver shows no consistent pattern, with superficial and deep abscesses distributed almost evenly. Often, small abscesses are scattered throughout the organ, whereas large abscesses are located close to the portal entry.

33.20.4 Clinical Signs and Diagnosis

Liver abscesses are detected only at the time of slaughter. Cattle, even those that carry hundreds of small abscesses or several large abscesses, seldom show any clinical signs. Occasionally, the rupture of a superficial abscess or erosion and perforation of the caudal vena cava could lead to extensive spread and massive infection of other organs and eventual death. Generally, hematology and liver function tests have not proved to be good indicators of liver abscesses.[145] In animals in which abscesses were induced by experimental inoculation of *F. necrophorum,* hepatic dysfunction was documented by elevated serum protein, bilirubin, and enzymes, such as GGT and SDH concentrations.[146]

Ultrasonography is a useful technique in the diagnosis of various hepatic diseases in cattle because of the location and tissue consistency of the liver.[147] The technique has been shown to be useful for monitoring the onset and progression of experimentally induced abscesses where the site of injection is known.[146] The development of abscesses in feedlot calves has been recorded by ultrsonographic examination at regular intervals from weaning to slaughter.[145] However, its application to the diagnosis in feedlot cattle is limited because the ultrasonographic scanning cannot visualize the whole liver, particularly the left side facing the internal organs, and parts of lobes are covered by other organs (e.g., lungs, kidneys).

33.20.5 Treatment

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Both *F. necrophorum* and *A. pyogenes* are susceptible to penicillins and macrolides. However, antibiotic treatment is seldom practical in cattle because complete recovery is difficult to attain. Cattle with sequelae (e.g., CVCT syndrome), for economic reasons, are generally culled for slaughter.

33.20.6 Prevention

According to the U.S. *Feed Additive Compendium,* five antibiotics (bacitracin methylene disalicylate, chlortetracycline, oxytetracycline, tylosin, and virginiamycin) are approved for prevention of liver abscesses in feedlot cattle.[148] These antibiotics vary in their inhibitory effect on *F. necrophorum* and *A. pyogenes* and their effectiveness in preventing liver abscesses. Tylosin, a macrolide, is the most effective antibiotic and the most commonly used feed additive (6 to 8 g/ton, or 60 to 90 mg/head/day) in the feedlot. Studies show that tylosin feeding reduces abscess incidence about 40% to 70%. A vaccine combination of *F. necrophorum* leukotoxoid and *A. pyogenes* bacterin given to feedlot cattle has been shown to reduce the prevalence and severity of liver abscesses.[149] In addition to inclusion of antimicrobial compounds in the feed or vaccination, prudent bunk management to minimize ruminal acidosis is well accepted as a key factor for effective control of liver abscesses.

33.20.6.1 SEQUELAE

Septic cardiac and pulmonary emboli are also associated with liver abscesses in feedlot and dairy cattle. Occasionally, sudden death has been reported in cattle secondary to rupture of liver abscesses, with septic embolization in the right side of the heart. Generally, the condition starts as phlebitis caused by the extension of liver abscesses involving caudal vena cava. The phlebitis leads to thrombus formation anywhere between the liver and right atrium, but most often at the point of entry of caudal vena cava into the diaphragm. The clinical syndrome and the extent of lesions observed depend on the degree of thrombosis and type of organisms involved. The syndrome can range from death caused by rupture of caudal vena cava to various degrees of pulmonary embolism, pneumonia, infarction, endocarditis, hemoptysis, and epistaxis. Collectively, these lesions are categorized under *caudal vena cava thrombosis* (CVCT) *syndrome*.[150,151]

33.20.6.2 ECONOMIC IMPORTANCE

Liver abscesses are a major economic liability to the producer, the packer, and ultimately the consumer of beef. Abscesses are the leading cause of liver condemnation in the United States. The National Beef Quality Audit indicated that liver condemnations ranked as one of the top-10 concerns of packers.[152] The greatest economic impact of hepatic abscesses is not from the condemnation of liver but from the reduced animal performance. Cattle with abscessed livers have reduced feed intake, reduced weight gain, decreased feed efficiency, and decreased carcass dressing percentage. These effects are evident only in cattle with the most severe abscesses (one or more large abscesses or multiple small abscesses).[153]

33.20.6.3 HEPATIC ABSCESSES IN HORSES

Hepatic abscesses occur sporadically in horses and are generally part of the intraabdominal abscess complex. In studies that have evaluated horses with intraabdominal abscesses, 12% (3/25)[154] and 53% (8/15)[155] of horses had abscesses in the liver. Hepatic abscesses in horses are usually associated with septic portal vein thrombosis but may also develop as an extension of the inflammatory process involving the intestinal tract, or as sequelae to abdominal surgery.[156] A variety of bacterial species, particularly anaerobes, have been cultured from the pus. The most frequently isolated bacteria include *Streptococcus equi, Escherichia coli, Bacteroides fragilis, Corynebacterium pseudotuberculosis, Fusobacterium necrophorum,* and *Peptostreptococcus* species.[155–157]

Clinically, horses with hepatic abscesses cannot be differentiated from other intraabdominal abscesses. Generally, horses have a history of fever, loss of appetite, signs of colic, depression, and weight loss. Clinicopathologic changes are typical of chronic bacterial infection and include leukocytosis, thrombocytosis, hypoalbulinemia and decreased A/G ratio.[154–156] The prognosis is generally poor because of failure to respond to antimicrobial treatment. Percutaneous or surgical drainage has been shown to be effective, with high survival rate in humans with hepatic abscesses.

33.21 HEPATIC LIPIDOSIS

John Maas

Erwin G. Pearson

The conditions described next can cause hepatic lipidosis. Pathophysiology and prevention are similar for each and are described at the end of this section.

33.22 FAT COW SYNDROME, LIPID MOBILIZATION SYNDROME

33.22.1 Definition and Etiology

Fat cow syndrome is a multifactorial condition occurring in dairy cows after parturition. The syndrome is characterized by progressive depression and failure to respond to treatment of other predisposing diseases. It is associated with excessive mobilization of fat to the liver in well-conditioned or overconditioned cows. This mobilization of fat is induced by the negative energy balance and hormonal changes that occur during the periparturient period. This negative energy balance in most cases is aggravated by concurrent periparturient diseases that reduce feed intake and increase energy needs.[158–161]

33.22.2 Clinical Signs

The clinical condition occurs in the postparturient period. Most affected cows are either obese or very well conditioned, with a large amount of omental and subcutaneous fat. Presenting signs usually include depression, anorexia, weight loss, and weakness that can lead to recumbency. Most will have nonspecific signs, such as decreased rumen motility and decreased milk production. Other signs vary and are related to concurrent diseases. The concurrent diseases most frequently seen are metritis, retained fetal membranes, mastitis, parturient paresis,

and displaced abomasum.[158,159] It is important to look for these other diseases; even if mild, they could be significant in these cases and must be treated.

33.22.3 Clinical Pathology and Diagnostic Tests

Most laboratory tests are poor indicators of hepatic lipidosis and are of little value in determining the severity of the disease.[162] Liver-derived enzymes are usually elevated above the level in the dry cow but are often within normal ranges. Some serum enzyme levels increase in the periparturient period in normal cows. Many cows with hepatic lipidosis have a leukopenia and a degenerative left shift, but this is not specific. As expected, serum free fatty acids (FFAs) will be increased, and triglycerides and cholesterol will be decreased. Most of the total cholesterol is in lipoproteins. Serum total bile acids are not significantly increased in most cows with fatty livers.[163] The sulfobromophthalein dye excretion test may be useful prognostically, because those with a half-life longer than 9 minutes have a more guarded prognosis.[164] Table 33-9 provides common abnormal laboratory findings.

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Table 33-9 Common Clinicopathologic Abnormalities in Fat Cow Syndrome

Test Parameter	Change from Normal	Amount	Normal (X ± 2 SD)	
			Prepartum Dry	Postpartum (1-2 wk)
Ketonuria	↑	>(1+)	0	Trace +
FFA (μEq/L)	↑	>800	343-575	597-821
Triglycerides (mg/dL)	↓	<5	—	—
BUN (mg/dL)	↑ or Normal	>20	16-24	16-24
BSP clearance T½ min	↑	<5	4.4-4.8	4.7-5.5
GGT (IU/L)	↑	>16	44-56	65-78
AST (IU/L)	↑	>70	44-56	65-78
Insulin (U/mL)	↓ Variable	—	12-17	6.8-9.2
Glucose (mg/dL)	↓	—	52-57	48-52
White blood cells	↓	<4000 Neutrophils > lymphocytes	4000-12000 Neutrophils < lymphocytes	—

FFA, Free fatty acids; *BUN,* blood urea nitrogen; *BSP,* Bromsulphalein (sulfobromophthalein); *GGT,* γ-glutamyltransferase.

Liver biopsy may confirm the fatty infiltration of the hepatocytes, but a moderate to high amount of fat (15% to 30% total fat on a wet-weight basis)* is present in the liver of all postparturient, high-producing dairy cows, even those that remain healthy.[165,166] Fat is usually quantified by histologic methods, by measuring total hepatic fat on a wet weight basis, or by floating in copper sulfate solutions of various specific gravity (to estimate total fat

on a wet-weight basis).[167] A recent review advocated the use of tricacylglycerol analysis on a wet-weight basis to differentiate degrees of hepatic lipidosis.[161] These workers categorized hepatic lipidosis as normal, mild, moderate, and severe by the triacylglycerol concentrations of less than 1%, 1% to 5%, 5% to 10%, and greater than 10%, respectively.[161] At present, triacylglycerol analysis of hepatic tissue is not a routine procedure in veterinary diagnostic laboratories. Thus, total hepatic fat concentrations remain the "gold standard" for laboratory diagnosis. Clinically, little correlation exists between the amount of hepatic fat and signs of disease until the fat is more than 34% wet weight, at which point the liver tissue will float in distilled water with a specific gravity of 1.000.

* Extraction by solvent and stereologic postcounting for estimation of fat volume.

33.22.4 Pathophysiology

See pp. 915 and 916.

33.22.5 Epidemiology

Fat cow syndrome occurs sporadically in dairy cows but more frequently in those with loose housing where the dry cows are managed with the lactating cows in one group. Cows often become overconditioned during late lactation and during the dry period. The overconditioning may be caused by a poor breeding program associated with cows spending prolonged time in the low lactation strings and having excessive weight gain. Morbidity as high as 90% occurred in the original reports.[160] Mortality can exceed 25%, with even higher rates without intensive treatment and correction of concurrent diseases. Clinical disease in obese cows that enter the dry period can be minimized by carefully controlling their diets to meet National Research Council (NRC) requirements and preventing milk fever.

33.22.6 Necropsy Findings

Generalized obesity is noted unless the animal has been ill for more than 1 to 2 weeks. Changes in the liver are most striking; it is enlarged, with swollen and rounded edges, is pale yellow in color, and may float in water. Histologically, there is fatty infiltration of the hepatocytes, especially in the centrilobular and intermediate areas. However, these liver tissues are not much different from those of healthy, high-producing dairy cows in early lactation. The pathologist must make an extra effort to find lesions of other periparturient diseases, even if mild.

33.22.7 Treatment and Prognosis

Prognosis must be guarded unless the concurrent diseases can be treated successfully and the liver fat mobilized. It is most important to treat the primary disease. Reducing the negative energy balance and treating the hepatic lipidosis as described on p. 916 must be tackled vigorously. Prevention is based on preventing overconditioning during the late lactation period and the dry period and treating periparturient diseases in a timely manner. General prevention of hepatic lipidosis is covered in more detail on p. 917.

33.23 PROTEIN-ENERGY MALNUTRITION/PREGNANCY TOXEMIA OF BEEF COWS

33.23.1 Etiology

Protein-energy malnutrition (PEM) and pregnancy toxemia of beef cows are conditions of pregnant beef cattle on marginal diets, usually occurring in the winter and manifested by weight loss, weakness, depression, and sometimes inability to rise. The condition is the result of the negative energy balance caused by decreased quality and quantity of feed when caloric requirements are increased by fetal development and cold weather. Growing, pregnant heifers are especially susceptible because energy requirements for growth are superimposed on the other caloric requirements. A number of other factors, such as unpalatable feed, snow cover, and diseases, may reduce caloric intake (see Chapter 9). Fatty infiltration of hepatocytes occurs transiently in early PEM, and at necropsy the liver is smaller than normal.

33.23.2 Clinical Signs and Differential Diagnosis

Animals are usually thin and have a long hair coat. In some cases they are down and unable to rise but are still alert. The body temperature may be normal or subnormal. Occasionally, the cows also develop diarrhea. Most animals die 7 to 14 days after becoming recumbent.[168] Differential diagnosis includes Johne's disease, lymphosarcoma, parasitism, chronic pulmonary disease, other deficiencies, and debilitating diseases.

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33.23.3 Clinical Pathology and Diagnostic Tests

Diagnosis is usually based on demonstrating decreased caloric intake and ruling out other chronic diseases that could cause debility. Laboratory tests support but do not rule out the disease. Total serum calcium may be decreased. Packed cell volume also may be decreased, and serum insulin levels may be reduced. A ketonuria is not typical in PEM.

33.23.4 Necropsy Findings

Muscle mass usually is decreased. Serous (brown) atrophy of fat is often present, especially in the coronary groove, bone marrow, and perirenal areas. Lesions of concurrent disease also may be found if PEM is acute, and a fatty yellow liver may be noted.

33.23.5 Treatment and Prognosis

Treatment is often unrewarding. Efforts to reverse an advanced catabolic state may fail. A 454-kg cow requires 13 Mcal of metabolizable energy daily, or approximately 6.5 L of 50% glucose solution by continuous drip. Alfalfa pellet gruels are helpful if force-fed, and approximately 11 kg/day of alfalfa is recommended. Propylene glycol (150 to 200 mL) orally twice daily can be helpful as a glucose precursor. Treatments include IV fluids, improving the energy balance as described later, and treating any concurrent disease. Prevention and control by nutrition are discussed on p. 917.

33.24 PREGNANCY TOXEMIA IN EWES AND DOES

33.24.1 Definition and Etiology

Pregnancy toxemia, also known as ketosis or twin-lamb disease, is a condition occurring in ewes and does during the last 2 to 4 weeks of gestation. It is characterized by anorexia, weakness, and depression. The condition is caused by a negative energy balance resulting from increased energy demands of rapid fetal growth in late gestation and insufficient intake.

33.24.2 Clinical Signs

Animals with pregnancy toxemia are usually separated from the rest of the flock or herd. They have a poor appetite, and many appear blind. They eventually become more depressed and recumbent. Neurologic signs such as tremors, star-gazing, incoordination, circling, and grinding the teeth may precede terminal depression. Differential diagnosis includes other periparturient diseases, such as mastitis and hypocalcemia, as well as polioencephalomalacia, enterotoxemia type D, and toxicoses.

33.24.3 Clinical Pathology and Diagnostic Tests

Ketonuria is usually present and detected before ketonemia. Hypoglycemia is not a consistent finding but is sometimes present. The ewes and does often are acidotic and may have lowered serum calcium and potassium levels. The BUN and creatine levels are elevated terminally in some cases. FFA concentration in the plasma is usually elevated above 500 μEq/L. Serum β-hydroxybutyrate concentrations are elevated (>1 mmol/L).[169] A nonspecific but marked neutrophilia may be found in some affected animals and is particularly dramatic in does, sometimes reaching 35,000 neutrophils/μL.

33.24.4 Pathophysiology

See p. 915.

33.24.5 Epidemiology

The incidence of pregnancy toxemia is greater in ewes with more than one fetus, during the last 2 to 4 weeks of gestation,[170] and in does with three or more fetuses. Poor-quality feed, cold weather, lack of exercise, and stress of movement also may increase the incidence. Many ewes are overly fat initially. Does seem to be more resistant to pregnancy toxemia than ewes, in that three or more fetuses are usually required to produce the condition.

33.24.6 Necropsy Findings

These animals have a pale, swollen, friable, fatty liver. The animals may be somewhat dehydrated, and the uterus usually has more than one fetus.

33.24.7 Prognosis and Treatment

Mortality is high unless treatment is started early and the fetuses are removed. The most important step is removing the fetuses, either by inducing parturition or by cesarean section. Parturition can be induced in ewes with 15 to 20 mg of dexamethasone; in does the dose is either 10 mg of dexamethasone or 10 μg of prostaglandin $F_{2\alpha}$.[170] A cesarean section may be performed if the animal's value warrants it and there does not seem to be enough time to induce parturition. Besides removing the fetuses, the ketotic condition should be treated; 250 to 500 mL of 10% to 20% glucose is given intravenously, followed by a slow IV drip of 5% to 10% glucose. Acidosis and hypocalcemia must be corrected if present. Many practitioners use B vitamins in an attempt to stimulate appetite. Transfaunation of rumen liquor from a normal ruminant (a cow is acceptable) is useful in promoting voluntary feed intake and rumen motility. Cyanocobalamin (vitamin B_{12}) and biotin are particularly indicated as adjuncts to glucogenesis. The energy intake must be increased. Glucose precursors such as propylene glycol (15 to 30 mL every 12 hours) or sodium propionate are often used, but excess propylene glycol may lead to acidosis and cause diarrhea.

33.25 HYPERLIPEMIA/HYPERLIPIDEMIA IN PONIES

33.25.1 Definition and Etiology

Hyperlipemia occurs mainly in ponies and occasionally in horses and is characterized by a fatty liver and serum that is cloudy with accumulation of lipids. Triglycerides (TGs) are usually much higher than 500 mg/dL.[171] The condition is caused by decreased caloric intake, which causes fat mobilization and fat accumulation in the liver and accumulation in the plasma.[172] The decreased food intake may be secondary to other diseases. In horses, azotemia is usually also present and may block further TG uptake by the liver.[171] Equine hyperlipemia is characterized by production of an abnormal very-low-density lipoprotein (VLDL) fraction ($VLDL_1$), which has a reduced content of apolipoprotein B-100 and an increased content of apolipoprotein B-48.[173] The substitution of B-48 for B-100 is thought to allow greater TG content because B-48 is the apolipoprotein of importance in chylomicrons. The activities of lipoprotein lipase and hepatic lipase, the enzymes responsible for VLDL catabolism, were increased in hyperlipemic ponies.[173] It was concluded that overproduction of VLDL is the cause of hyperlipemia, and agents that reduce VLDL synthesis should be candidates for clinical investigation.[173]

Hyperlipidemia is a mild condition of ponies and horses characterized by mildly elevated TG concentrations (>500 mg/dL), clear plasma, and no evidence of hepatic dysfunction.[171] An increase in caloric intake is usually sufficient to reverse the condition. The more severe condition, hyperlipemia, is discussed further.

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33.25.2 Clinical Signs

The clinical signs of hyperlipemia are not specific. Ponies usually are anorexic, depressed, weak, and incoordinated. Diarrhea is a common clinical sign.[174]

33.25.3 Clinical Pathology and Diagnostic Tests

Diagnosis is based on examination of the blood and plasma to detect the white to yellow opacity caused by the presence of lipids. Bilirubin usually is elevated, as in most horses that are fasted. TGs are increased to above 500 mg/dL in hyperlipemia. FFAs are also increased. Bromosulfophthalein clearances are delayed (see p. 897), and terminally a large base deficit may be caused by metabolic acidosis.[171]

33.25.4 Epidemiology

The incidence of hyperlipemia is greater in ponies than in horses. It is seen more often in the winter, especially from February to May in animals receiving poor feed. Pregnant animals and those that are lactating are affected more frequently.

33.25.5 Necropsy Findings

Postmortem examination reveals fatty infiltration of the liver and kidneys, which are pale and swollen and have a greasy texture. In ponies the liver is sometimes ruptured, resulting in intraabdominal hemorrhage and death. Renal lesions may be seen histologically. There may be a primary disease that produces anorexia and secondarily has resulted in hyperlipemia.

33.25.6 Treatment

It is most important to treat any primary disease to alleviate the cause of anorexia and to correct the negative energy balance, as described in the following paragraphs. Insulin, along with 100 g of glucose intravenously, has been used in some affected ponies.[174] The recommended dose of protamine zinc insulin (PZI)* is 30 IU intramuscularly twice daily with 100 g of glucose orally for a 200-kg pony. This is continued on odd days; on even days, 15 IU of PZI intramuscularly and 100 g of galactose orally is given twice daily.[171] A slow IV drip of glucose for several days or until lipemia clears may be indicated. Heparin (100 to 250 IU/kg twice daily) has been used to alter the lipoprotein lipase activity and inhibit hormone-sensitive lipase of adipose tissue, but it may alter coagulation enough to cause hemorrhage. Glucose administration also stimulates insulin levels, but overdoses may result in a more severe acidosis.[123]

* Protamine zinc and iletin insulin, Lilly, Indianapolis, IN.

33.25.7 Pathophysiology of Hepatic Lipidoses(Fig. 33-4)

Storage of excess energy as fat and the periodic mobilization of fat for use as energy by the body is crucial.[175] The liver plays a major role in lipid metabolism and must process the absorbed chylomicrons, the volatile fatty acids, and many of the FFAs and much of the glycerol obtained by mobilization of fat from adipose tissue. The liver of large herbivores has unique functions because much of the dietary energy is absorbed as volatile fatty acids and not glucose. Glucose is still needed (in high amounts in lactating animals) and must be produced by gluconeogenesis, 85% of which takes place in the liver.[176]

Negative energy balance is induced by lactation, fetal growth, exercise, decreased feed consumption, environmental chilling, and diseases (Fig. 33-5). During these periods of negative energy balance and before

lactation, blood glucose may drop slightly, the insulin/glucagon ratio drops, and these and other hormones (e.g., catecholamines, growth hormone) activate hormone-sensitive lipases that convert tissue fat to FFAs or nonesterified fatty acids (NEFAs) and glycerol (Fig. 33-6). In the liver the glycerol may be used to produce glucose or may be recombined with FFAs to make TGs. In addition to being recombined with glycerol to make TGs, the FFAs may be degraded through β-oxidation, and the two carbon fatty acids converted to acetyl coenzyme A (CoA). The acetyl CoA combines with oxaloacetate to enter the tricarboxylic acid cycle for the production of energy. This pathway is in competition with the use of oxaloacetate for gluconeogenesis.[159] If there is not enough oxaloacetate available, the acetyl CoA is converted to ketone bodies, which in high concentrations can reduce feed consumption and perpetuate the negative energy balance.

When the liver is overwhelmed with mobilized FFAs, greater amounts of TGs are deposited within the hepatocytes. These TGs eventually leave the liver as VLDLs, which are plasma-soluble complexes of phospholipid, cholesterol, TG, and apolipoprotein A. Hepatic lipidosis results when the rate of hepatic TG formation exceeds oxidation of fatty acids and the formation and release of VLDLs into the peripheral circulation. A number of factors have been incriminated for the inability of the liver to secrete adequate VLDLs to keep up with the deposition of TGs brought about by FFA mobilization from fat. Ruminants have a poor ability to export excess lipid from the liver as VLDLs. This is particularly true in bovine hepatic lipidosis[177,178] and is theorized to result from a shortage of apolipoprotein A. Hepatic lipidosis can be induced in cows by inhibiting the production of apolipoprotein,[179] and the lowest concentrations of lipoproteins occur in the serum of cows with the most severe hepatic lipidosis.[178] Cows on low-protein diets in the dry period are more likely to develop hepatic lipidosis than those on higher protein diets, regardless of the energy content.[177,180] Depression in dry matter intake in the final week before calving will increase the liver TG content after calving in dairy cows.[181] In the past, a lack of phospholipid or its precursor choline has been incriminated but never substantiated. However, in the face of an energy shortage, it seems redundant and a waste of energy to repackage fat and send it back to the tissues, even if the liver is being overwhelmed with FFAs. Some of the same endocrine hormones that activate hormone-sensitive lipase and inhibit lipogenesis and glycogen synthesis may also inhibit the production of VLDLs.

It has also been suggested that subclinical liver damage may inhibit the production of VLDLs, but experimental studies have indicated no significant elevation in liver-specific enzymes before lipid accumulation.[165,166] Function may eventually be impaired by the accumulation of fat, because fasted cows have a decrease in the surface area of rough endoplasmic reticulum and the number of mitochondria per unit volume.[182] Changes in the liver seem to be functional and not degenerative.[183] Hepatic lipidosis appears to be a reversible condition if the cause is removed and energy balance becomes positive (less negative). In cows fasted and refed, all major liver functions returned to normal within 18 days of refeeding,[182] and all lactating dairy cows with postparturient hepatic lipidosis had normal liver fat (<15%) content at 6 months after calving.[166]

All high-producing dairy cows have increased amounts of fat (15% to 32% by weight) in the liver before calving 915
and during the first few weeks after parturition[165,166,183] (Fig. 33-7). These fat accumulations in the liver begin 916
before calving as the animal prepares for lactation, and the blood glucose concentration is actually lower before calving.[184] The amount of fat in the liver depends on the amount available and the extent of negative energy balance. Fatter cows tend to lose weight more rapidly and have more fat accumulation in the liver.[165,166] Serum cholesterol values (lipoprotein) are inversely related to loss in condition.[185]

Fig. 33-4 Metabolism of fat in animals with hepatic lipidosis.

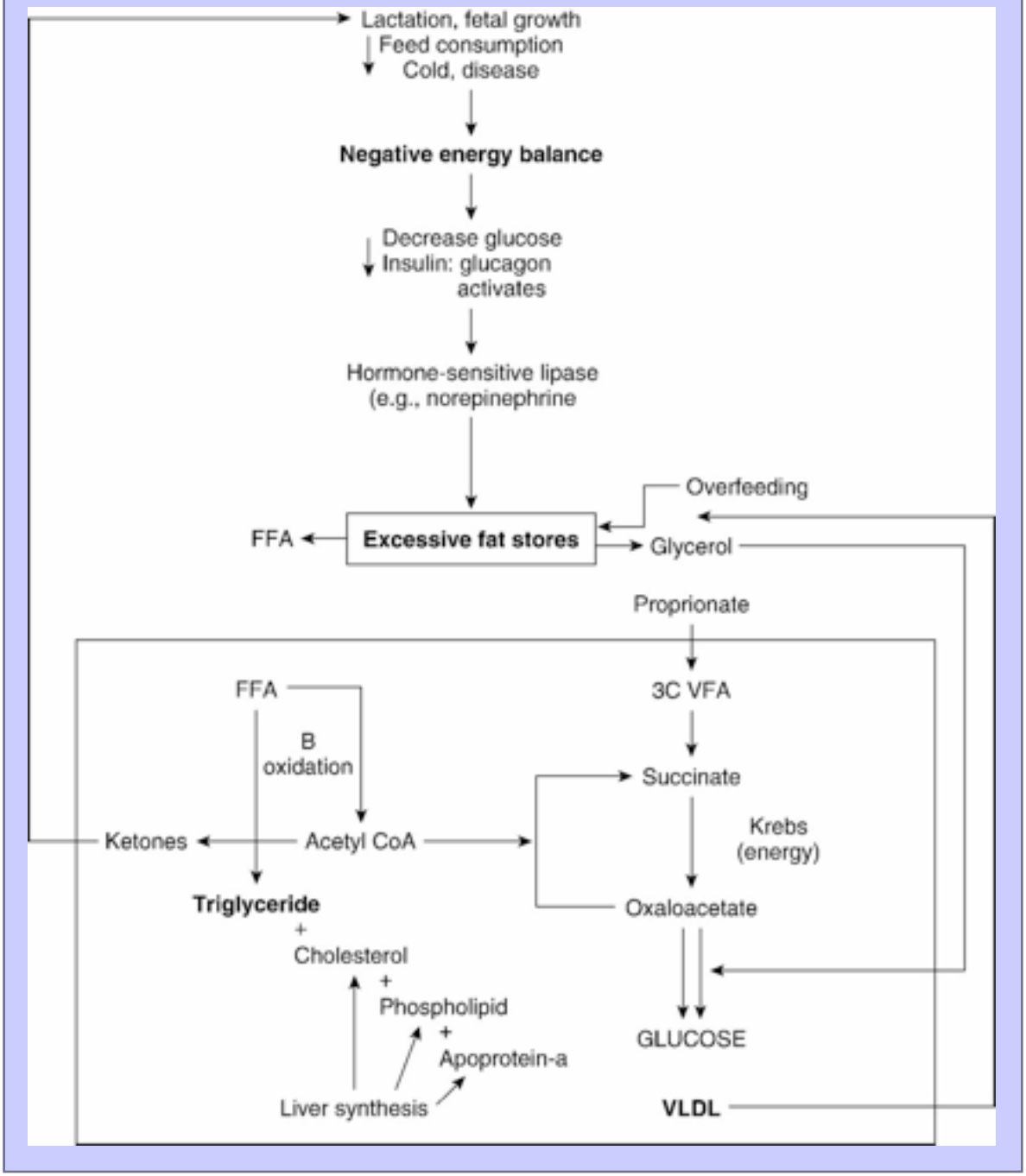
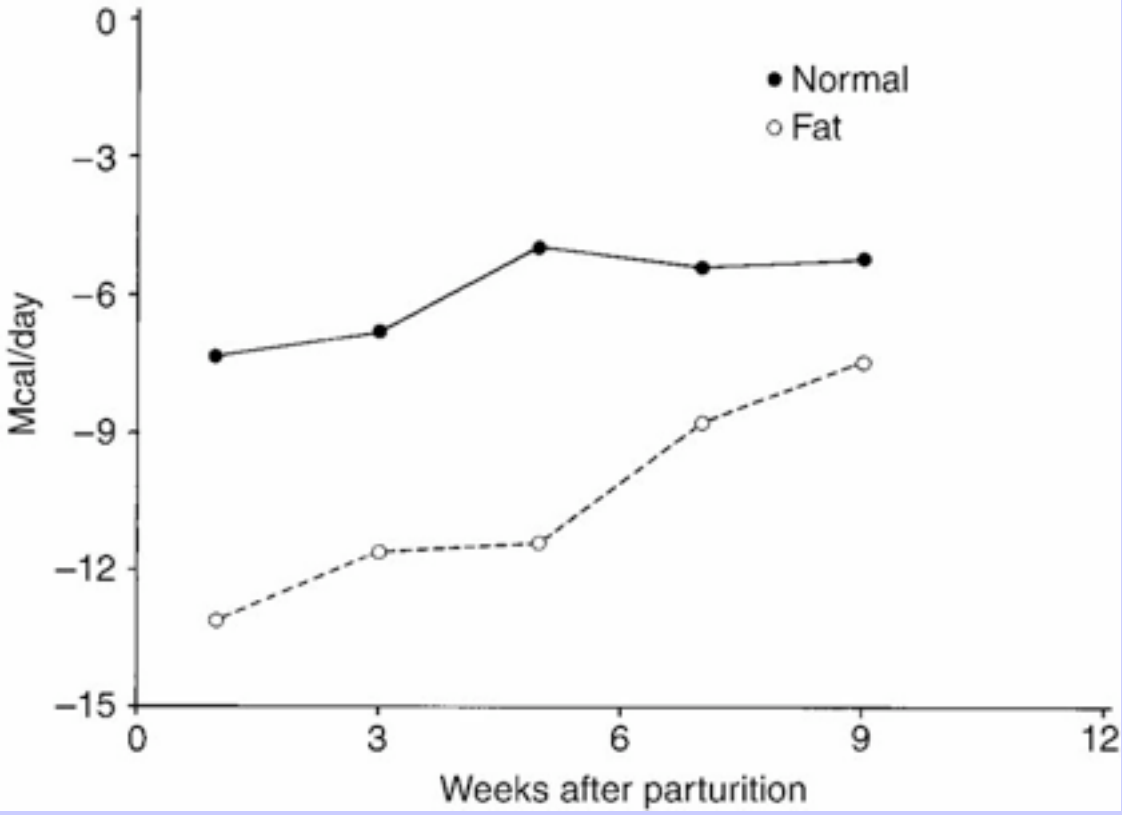


Fig. 33-5 Energy balance (megacalories per day) in normal-condition and obese dairy cows after parturition. From Perkins B: PhD thesis, Ithaca, NY, 1983, Cornell University.



33.25.8 Treatment of Hepatic Lipidosis

The most important principle in treating hepatic lipidosis is the elimination of negative energy balance and the factors or diseases causing it. Continual IV glucose at a rate of approximately 100 to 200 mg/kg/hour may provide continuing energy and induce an insulin/glucagon ratio that will decrease hormone-sensitive lipase mobilization of FFAs and stimulate production of VLDLs. Insulin itself may be given to alter this ratio directly. In cattle, 200 U of protamine zinc (NPH or Lente) insulin is given every 12 hours per 1000 pounds of cow, along with glucose.

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Fig. 33-6 Plasma levels of glucose, insulin, and free fatty acids in dairy cows before and after parturition. From Perkins B: PhD thesis, Ithaca, NY, 1983, Cornell University.

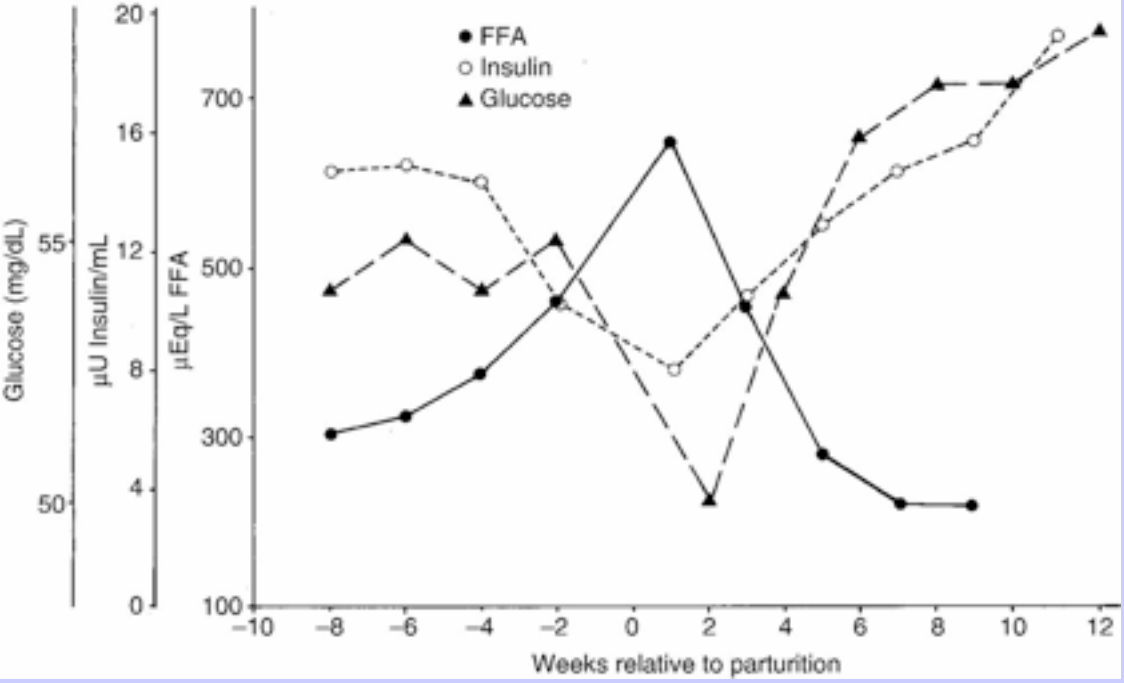
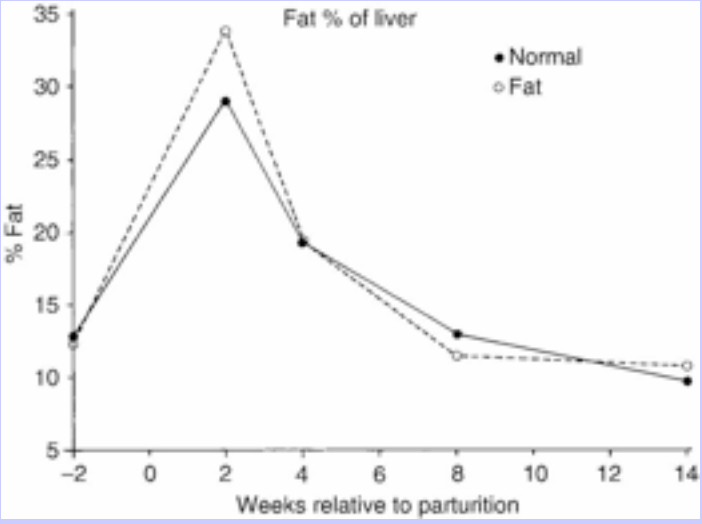


Fig. 33-7 Liver fat as a percentage of total dry weight in normal-condition and obese dairy cows before and after parturition. From Perkins B: PhD thesis, Ithaca, NY, 1983, Cornell University.



Precursors of lipoproteins such as choline, which is a component of phospholipid, have been advocated to increase the rate at which TGs leave the liver as phospholipids (VLDLs), but no controlled studies have proved their efficacy. Choline is degraded in the rumen,[186] but theoretically, choline chloride (25 g in 250 mL of sterile saline) given subcutaneously could have limited efficacy. Choline should *not* be given intravenously because it acts as a neuromuscular blocking agent. Addition of inositol both before and after birth did not reduce the incidence or severity of hepatic lipidosis.[187] Methionine at 40 to 50 g/day has also been used for the same purpose. Nicotinic acid (niacin) fed at 6 to 12 g/head/day may help reduce lipolysis at the tissue level and thus reduce the amount of fat presented to the liver.[188] Treatment of hepatic lipidosis with nicotinic acid is often associated with a rebound of clinical signs, and its use as a preventive measure is recommended.

Corticosteroids to treat ketosis may be useful but should not be used repeatedly over a long-term period because they may make the animal less resistant to infections.[188] Corticosteroids usually increase appetite, reduce milk production, and induce gluconeogenesis. Both vitamin E and selenium, which function as cellular antioxidants, have been found to be low in many of the cows with fatty liver syndrome;[189] thus, supplementation may be helpful in selected cases.

Digestion in the forestomachs can be enhanced by transfaunating with rumen fluid from a normal cow. This may increase the absorption of volatile fatty acids used for energy and for glucose precursors.

33.26 PREVENTING HEPATIC LIPIDOSIS AND HANDLING NEGATIVE-ENERGY BALANCE AND OVERCONDITIONING

Hepatic lipidosis and associated conditions are most common in dairy cattle. Preventing obesity in cows during late lactation is an important factor in controlling this condition. This process involves a successful breeding program (maintaining a 12- to 13-month calving interval) and closely matching energy in the ration to the level of milk production during late lactation. Once the cow reaches 7 months of pregnancy and the dry period, any dietary restriction below requirements for maintenance and pregnancy are certain to be counterproductive. Table 33-10 lists the recommended nutrient requirements for a 600-kg cow.[190]

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Table 33-10 Daily Nutrient Requirements for 600-kg Cow During Dry Period for Maintenance Plus Last 2 months of Gestation

Body Weight (kg)	NE_1 (Mcal)	TDN (kg)	Total CP (g)	Calcium (g)	Phosphorus (g)
600	12.61	5.5	<31	37	26

NE_1, Net energy of lactation (same as net energy of maintenance) in dairy cows; *TDN*, total digestible nutrients; *CP*, crude protein.

Adequate protein in the dry period is essential.[176,179,180] It has been shown that cows fed higher protein diets during the dry period will perform better in the lactation that follows. Feeding good-quality to excellent-quality roughages (hay, silages) to meet most of these requirements is preferred. Additional grain (starch) 2 to 4 weeks before parturition is important to acclimate the ruminant to anticipated changes in the rations fed after calving. It must be stressed that high-quality dry cow rations be fed *but not overfed*. Dry matter consumption should be limited to approximately 2% of body weight per day while meeting requirements. Other factors in the dry cow

ration also must be considered to prevent periparturient diseases such as milk fever, displaced abomasum, mastitis, metritis, ketosis, ruminal lactic acidosis, and retained placenta.[191] Rations should be adequately supplemented with cobalt, the precursor of vitamin B_{12} that is a cofactor in the rate-limiting step in conversion of propionate (the primary glucose precursor) to succinyl CoA. Nicotinic acid has been included in the dry cow ration at 6 g/head/day and in the early-lactating cow ration at 12 g/head/day to aid in the prevention of ketosis, which is a major risk factor for the development of hepatic lipidosis. The use of monensin in the dry cow ration and the early-lactation ration shows promise to aid in the prevention of ketosis and thus may be of some benefit in preventing hepatic lipidosis.[192,193]

Nutrient requirements increase greatly for beef cattle during the third trimester of pregnancy; these requirements are listed in Chapter 9. As forage quality (digestibility) decreases, the time that feed material stays in the rumen increases (increased rumen turnover time). Therefore, as quality decreases, the maximum dry matter intake (DMI) decreases, which greatly decreases the maximum nutrient (energy) intake. This compounding effect of poor-quality forage on maximum intake is particularly important for preventing hepatic lipidosis and the accompanying protein-calorie malnutrition (PCM) of pregnant beef cattle in the winter. The approximate maximum DMI of forage of poor quality (oat straw, corn stover), medium quality (meadow grass hay), and excellent quality (alfalfa hay [25% crude fiber], corn silage) is 1% to 1.5%, 2%, and 2.5%, respectively. Environmental temperature can increase energy needs for beef cattle on pasture or range; as the temperature falls from 20° C (68° F) to 10° C (50° F), approximately 10% more energy is necessary for maintenance, and at freezing temperatures, 0° C (32° F), 20% additional energy is required. The key to preventing PCM and hepatic lipidosis in pregnant beef cattle is adequate body condition (scores 5 to 7) entering the third trimester and availability of good-quality to excellent-quality forage in adequate amounts.

Preventing pregnancy toxemia and the associated severe hepatic lipidosis in ewes and does requires measures similar to those outlined for PCM in beef cattle. Both overconditioned and thin ewes and does in the third trimester of pregnancy are at increased risk. Because of the common occurrence of twins and triplets, nutrient requirements for pregnant ewes greatly accelerate during this period. Good-quality to excellent-quality forage for feeding sheep is very important. An additional tool for diagnosing underfeeding in ewes is measurement of plasma β-hydroxybutyrate (BHB). This test greatly facilitates assessment of nutritional inadequacy in pregnant ewes.[194] Plasma BHB concentrations of 0.8 mmol/L or higher are diagnostic of the need for increased energy consumption by pregnant ewes.[194] This clinicopathologic tool is of great benefit in diagnosing malnutrition before irreversible pregnancy toxemia develops.

The nutrient requirements of horses and ponies have been covered elsewhere (see Chapter 9). The presence of hyperlipidemia is readily detected and easily solved by increasing caloric intake. Although therapy of hyperlipemic ponies and horses is often unrewarding, the diagnosis is relatively straightforward, and prevention depends on providing adequate feed of good quality.

33.27 CONGENITAL HYPERBILIRUBINEMIA

Erwin G. Pearson

33.28 GILBERT's SYNDROME

Gilbert's syndrome is an unconjugated hyperbilirubinemia in the presence of normal erythrocyte lifespan. It occurs in 7% of humans[195] and has been described in Southdown sheep.[196] Gilbert's syndrome involves a failure of unconjugated bilirubin to cross the liver cell membrane and be conjugated. This is most likely caused by a defect in

carrier proteins or the conjugating enzyme.[197] Hepatic bilirubin clearance is about 30% of normal when tested with a loading dose of radiolabeled bilirubin.[198]

Affected Southdown sheep may have icterus or at least elevated plasma bilirubin levels, both conjugated and unconjugated. Affected sheep also cannot excrete sulfobromophthalein (Bromsulphalein, BSP) into the bile. No histopathologic lesions are present, other than some pigment in the hepatocytes. The condition is inherited as an autosomal dominant trait in humans.[197] The bile acid levels are normal in humans, but one sheep exhibited defects in hepatic bile acid clearance.[199]

33.29 DUBIN-JOHNSON SYNDROME

Dubin-Johnson syndrome is a failure of conjugated bilirubin to enter the bile canaliculi. This has been diagnosed sporadically in humans and in Corriedale sheep.[200] There may be an impairment not only in bilirubin but also in the excretion of other conjugated organic anions. Sheep affected by this syndrome may be jaundiced or have hyperbilirubinemia. Both conjugated and unconjugated bilirubin are increased, and BSP clearance is delayed. Bile acids are reported to be normal in humans, but delayed clearance was reported in three Corriedale sheep.[199] Histologically, the hepatocytes contain a black, melanin-like pigment.[200]

33.30 PERSISTENT HYPERBILIRUBINEMIA IN THOROUGHBREDS

A persistent hyperbilirubinemia has been reported in a Thoroughbred racehorse that had no evidence of liver damage, cholistasis, or hemolysis and was not fasting.[201] The horse was persistently icteric and had serum total bilirubin concentrations of 8.7 to 9.4 mg/dL; 90% or more of the plasma bilirubin was the unconjugated form. Serum bile acid concentration, along with the liver enzymes GGT, AST, and SDH, were within normal limits. The horse acted clinically normal, and the plasma FFA concentration was also within normal limits. The condition was similar to Crigler-Najjar type II syndrome in humans, which involves a deficiency in bilirubin—uridine diphosphate glucuronyltransferase needed to conjugate bilirubin, but this was not verified.

33.31 MISCELLANEOUS LIVER DISEASES

Erwin G. Pearson

33.32 RIFT VALLEY FEVER

Rift Valley fever, also known as *enzootic hepatitis,* is an acute febrile arthropod-borne disease of sheep, goats, cattle, and humans present in most countries of sub-Saharan Africa.[202] With the current threat of bioterrorism, it could appear in other parts of the world. Rift Valley fever is caused by a virus of the genus *Phlebovirus*. More than 20 species of mosquitoes have been implicated as possible vectors for the virus, including some North American mosquitoes that are competent laboratory vectors.[203] The disease causes abortion in pregnant females and a febrile condition with rapid death in lambs, kids, and calves. The mortality rate in young animals approaches 100%, but it is much less (20% to 30%) in older animals.[203] Clinical signs may include fever, anorexia, weakness, salivation, diarrhea, and sometimes abdominal pain, and almost all pregnant animals will abort.[202] The primary gross lesion is hepatomegaly and hemorrhage. Histologically, a focal hepatic necrosis is identified, and eosinophilic intranuclear

inclusion bodies are present.[203] Confirmation of the diagnosis is made in the laboratory by virus isolation or immune tests. If the disease is suspected, state and federal regulatory veterinarians should be contacted.

33.33 TELANGIECTASIA

Hepatic telangiectasia, commonly known as “sawdust livers” in packing houses, is a focal degeneration in liver lobular circulation characterized by red-brown foci 1 to 5 mm in diameter.[204] These lesions account for more than 10% of the bovine liver condemnations but do not result in any clinical signs.[205] Microscopically, hepatocytes are distorted and sinusoids congested.[206] Hypotheses proposed to explain the pathogenesis of the lesions include necrotizing hepatitis, ischemia induced by emboli or other vascular pathologies,[207] dilation of Disse's spaces, reduced density of reticulin framework, vitamin E–selenium deficiency, alteration of the sinusoidal barrier, and immune-mediated disease.[204,205] Some human pathogens have been isolated from these livers as well as normal livers, but livers are condemned on the basis of aesthetics according to current U.S. Department of Agriculture (USDA) regulations.[205]

33.34 ISCHEMIA, HYPOXIA, AND CONGESTION

Ischemia and hypoxia can lead to death of hepatocytes, but less severe insults cause fatty infiltration, because lipoprotein synthesis depends on oxidative metabolism.[204] This damage is more apparent in the centrilobular areas, which are the last to receive blood and oxygen.

Chronic passive congestion causes the grossly visible nutmeg liver. This is caused by the distention of the sinusoids and central veins with blood. The liver may be enlarged in these cases, but other signs related to the liver are not usually present. More significant findings will be detected in the cardiovascular system.

Portocaval shunts are rare in large domestic species but have been described in several foals.[208]

33.35 FETAL LIVER DAMAGE

The liver of the fetus may be damaged by infectious and toxic agents, but the result is usually abortion or birth of a weak neonate with signs related to other systems. The lesions in the liver may be diagnostic of the disease. Equine herpesvirus infection of the fetus causes hepatocyte necrosis, with acidophilic intranuclear inclusion bodies in more than 50% of the hepatocytes. Aborted fetuses of cattle caused by infectious bovine rhinotracheitis may have some focal necrosis of the liver, but not enough to be diagnostic.

33.36 FAILURE OF DRUG METABOLISM AND EXCRETION

A number of drugs are excreted by the liver and may have delayed clearance with hepatic insufficiency. These include antimicrobials such as chloramphenicol, erythromycin, and tetracycline. Chlorthiazide, most steroids, digitalis, morphine, many tranquilizers and anesthetic agents, and lecithin also are removed by the liver, and excretion may be reduced with hepatic insufficiency.[209]

33.37 NEOPLASIA OF THE LIVER

Erwin G. Pearson

Primary neoplasia of the liver is uncommon in large domestic species. Only 0.011% of abattoir animals seen in one study had liver tumors.[210] Metastatic tumors are more common, but the clinical signs of these are more likely to reflect changes at the primary site. Metastasis of lymphosarcoma in cattle is most common, but signs produced by growth in other organs, such as the lymph nodes, abomasum, heart, uterus, and spinal cord, are more predominant. In the horse, lymphosarcomas and carcinomas have metastasized from the digestive tract.[211]

33.37.1 Horses

Although uncommon, a number of different primary hepatic neoplasias have been reported in horses.[212] The nomenclature seems inconsistent throughout the years of reporting, and the signs are usually more consistent with neoplasia in general than with hepatic failure. Weight loss, weakness, anorexia, lethargy, and occasionally colic may be seen in these animals. Serum concentrations of liver-derived enzymes are elevated in many cases. The tumor can often be located by ultrasonography, but the definitive diagnosis of the type of tumor is based on histopathologic examination of biopsy tissue.

Hepatoblastoma has been reported in foals, young horses, and an equine fetus.[213] Young horses present with weight loss or failure to grow, lethargy, anorexia, and possibly icterus. Serum concentrations of several hepatic enzymes are increased. Ultrasonography reveals hepatomegaly and a heterogenous appearance of the hepatic parenchyma. Erythrocytosis is seen in some cases because of a paraneoplastic syndrome and increased production of erythropoietin.

Hepatocellular carcinoma is seen in both old and young horses. These horses lose weight and are listless. Serum concentrations of LDH, GGT, and AST are often elevated. Erythrocytosis with a normal concentration of serum protein is seen in most cases as a result of paraneoplastic syndrome with elevated erythropoietin.[212,214]

Cholangiocarcinoma or cholangiocellular carcinoma arises from the intrahepatic bile duct epithelium and appears to be a disease of older horses.[215] Lethargy, fever, abdominal pain, anorexia, and ventral edema have been reported with this tumor. Some of these animals have anemia rather than the erythrocytosis reported with hepatocellular tumors. GGT and ALP concentrations may be elevated, but SDH (which comes from hepatocytes) is usually within normal range.

33.37.2 Cattle

In addition to the lymphosarcomas, primary hepatocellular carcinomas have been described in cattle.[216] Liver-derived enzymes may be elevated, and polycythemia (erythrocytosis) is a common laboratory finding in these cases.[217]

33.38 HEMOCHROMATOSIS

John Maas

Erwin G. Pearson

Hemochromatosis is a disorder caused by deposition of hemosiderin in the parenchymal cells, resulting in tissue damage and dysfunction of the liver and other tissue. It is most frequently seen in humans and mynah birds, but

hemochromatosis has been described as a new disease of Salers cattle[218] and has been reported in three horses.[219] In people the types include idiopathic hemochromatosis, an autosomal recessive familial condition associated with increased iron stores, cirrhosis, and saturation of the iron transport capacity.[220] Both horses and cattle show increased iron deposits in the liver; histopathology of liver biopsy specimens reveals brown pigment that stains for iron in the hepatocytes as well as Kupffer's cells. An increased concentration of iron can be measured in the liver, and there is fibrosis and elevated liver-derived enzymes.

In Salers cattle the condition appears to be a homozygous recessive condition more like the human familial type. There is an inappropriate absorption of iron (Fe) by the GI tract, with subsequent hepatic storage (Fe overload) and eventual loss of hepatic function. It has been reproduced by experimental breeding in Salers cattle.[221] The primary clinical signs in cattle are decreased weight gains, poor body condition, dull hair coat, loss of incisor teeth, and sometimes diarrhea. Serum concentrations of liver enzymes are elevated, and there is marked hepatic fibrosis, in addition to the hemosiderin deposits in the liver. Total serum Fe, total iron-binding capacity (TIBC), and saturation of transferrin (>60%) are increased, similar to the familial disease in humans. Liver iron concentration will be greater than 5000 µg/g (ppm) on a wet basis (normal herdmates of affected cattle, 84 to 100 ppm).[222]

Horses with hemochromatosis present with evidence of liver disease. Serum concentrations of the liver enzymes ALP, GGT, and AST are elevated; and serum total bile acids are greater than 40 µM/L. In the cases reported, total serum iron was not elevated, and unlike the idiopathic human condition or the cattle cases, there was no saturation of the iron-binding capacity. Total liver iron has been as high as 6700 ppm (normal, 100 to 300 ppm).[219]

Hemochromatosis should be suspected in animals with emaciation or elevated liver enzymes and in Salers cattle with greater than 60% saturation of transferrin. It is confirmed by histopathologic examination of the liver, with excessive iron accumulation in hepatocytes. Clinicians should differentiate hemochromatosis from *hemosiderosis,* in which iron accumulates in the reticuloendothelial system and not hepatocytes, and which can be caused by hemolysis and other conditions.

In humans, hemochromatosis is treated by reducing the iron stores through phlebotomies and blood removal. The one horse on which this was tried had advanced disease with severe cirrhosis, and it succumbed a few days after the blood removal. Removal of 160 L of blood over 12 months failed to reduce liver iron concentration in one heifer[218] but produced some improvement in other calves.[221] Deferoxamine is given to some human patients to induce a negative iron balance and reduce the rate at which iron accumulates.

33.39 GALLBLADDER AND BILIARY TRACT DISEASE

Terry C. Gerros

Biliary tract disease in large animal medicine is rare and results from both intrahepatic and extrahepatic causes. Intrahepatic causes of cholestasis include cholangitis, cholecystitis, choledocholithiasis, and presence of a foreign body. Extrahepatic causes include abscess formation, inflammatory disease near the common bile duct, and neoplasia.

33.40 CHOLEDOCHOLITHIASIS, CHOLELITHIASIS, HEPATOLITHIASIS

By definition, *cholelithiasis* describes the presence of biliary calculi in either the bile ducts or the gallbladder, whereas *choledocholithiasis* describes stones found in the common bile duct. *Hepatolithiasis* indicates the presence of calculi in the intrahepatic bile ducts above the right and left hepatic ducts and is a variation of cholelithiasis.

These conditions have been described in horses, cattle, sheep, and pigs; however, they do not seem to be recognized as a clinical problem in sheep, and rarely in cattle.[223–244] Choledocholithiasis is the most common cause of biliary obstruction in large animals and occurs more frequently in horses.[223–236]

Biliary stone formation begins with the precipitation or aggregation of normally soluble components of bile. Other mechanisms involved in the pathogenesis include ascariasis, ascending biliary infection or inflammation, biliary stasis, changes in bile composition, and presence of a foreign body.[228,243] Several pathogenic bacteria (*Salmonella* species, *Escherichia coli, Aeromonas* species, *Citrobacter* species, group D *Streptococcus* species, *Clostridium perfringens*) have been cultured from the bile ducts of horses and cows with cholelithiasis.[224,234,238,245] Whether these bacteria were the cause or the result of the stone formation remains unclear. In most reports the chemical analysis has shown that choleliths have a mixed composition, containing bilirubin, bile pigments, cholesterol esters, esters of cholic and carboxylic acid, calcium phosphate, and sodium taurodeoxycholate.[225,228,234,236,238] In one study, 80% of the choleliths contained less than 10% cholesterol.[238]

33.40.1 Clinical Signs, Diagnostic Test, and Differential Diagnosis

Cholelithiasis should be suspected in horses when a triad of clinical signs exists: recurrent abdominal pain, pyrexia, and icterus. Hyperammonemic hepatic encephalopathy, photosensitization, and weight loss are other, less common features of cholelithiasis.[226–229,233,234,243,245] A subclinical presentation, caused by partial obstruction of the biliary tree, may be recognized only on postmortem examination.[239] A large cholelith was the cause of duodenal obstruction in a horse presented for colic.[240]

Elevations in the serum activity of ALP, AST, GGT, SDH, and total bilirubin are associated with cholelithiasis.[226–229,234,238,243,245] The rise in total bilirubin is caused by an elevation in both direct and indirect bilirubin. In the horse, cholestasis should be suspected if more than 25% to 30% of the total bilirubin is the direct type.[223] Serum bile acid concentrations also increase when bile flow is obstructed.[246] Other laboratory abnormalities that may be seen include hyperammonemia, increased urine bilirubin, and prolonged partial thromboplastin and thrombin times.[225,229,233,234,238] The most common alterations in the leukogram include a neutrophilic leukocytosis. Elevations in globulin and fibrinogen may also occur.[225,226,228,233]

Ultrasound examination of the liver is a safe, noninvasive tool for diagnosing cholelithiasis. Hepatomegaly and bile duct dilation are seen in horses with biliary calculi. The echogenicity of the hepatic parenchyma is increased compared with that of normal horses and may approach that of the spleen; the bile ducts are thick and distended. The parallel channel sign (dilation of interhepatic biliary radicals adjacent to portal vein) may also be seen. Several choleliths generally are seen, but a single stone may be present. Choleliths may be hyperechoic, casting acoustic shadows, or they may be sonolucent. Choleliths are most likely to be visualized in the cranioventral part of the right hepatic lobe, especially in the sixth to eighth intercostal spaces. Cholelithiasis can accurately be diagnosed by ultrasound in at least 75% of horses if an adequate scanning image of the liver is obtained and bile duct dilation and choleliths are visualized.[236]

The differential diagnosis for a horse with the clinical signs associated with cholelithiasis include other causes of liver disease and mild, recurrent abdominal discomfort, including verminous arteritis, mesenteric abscesses, enterolithiasis, abdominal neoplasia, and urolithiasis.[226,227]

33.40.2 Necropsy Findings

Hepatomegaly is usually noted at necropsy, although a shrunken liver may be observed. The liver is firmer than normal, has a consistent texture, and varies in color from red to green-brown. The hepatic ducts and common bile duct are generally dilated and may contain the calculi. Histologically, periportal fibrosis is a common finding. Bile duct stasis and hyperplasia are usually noted; suppurative cholangitis is less common.[225,238,243,245]

33.40.3 Treatment

Treatment of cholelithiasis includes relief of biliary flow obstruction and management of hepatitis and associated complications. Choledocholithotomy and choledocholithotripsy, described in horses, have had limited success.[233–235] Because the potential for bacteremia with surgical manipulation for cholelithiasis is high, treatment with potentiated sulfa drugs, ampicillin, tetracycline, or chloramphenicol before surgical intervention is warranted. In humans, chenodeoxycholate or ursodeoxycholate is used to dissolve cholesterol gallstones;[247] their use has not been reported in animals. Dietary management for cholelithiasis has yet to be determined.

The prognosis remains guarded for horses with cholelithiasis or choledocholithiasis.

33.41 DISEASES OF THE GALLBLADDER

33.41.1 CHOLANGITIS

Clinical disease of the bovine gallbladder is rare. Obstructive gallbladder disease has been associated with abdominal fat necrosis, choleliths, fascioliasis, foreign bodies, hepatic abscesses, neoplasia, and suppurative cholecystitis.[248,249] Adenomas and adenocarcinomas (most common tumors found in gallbladder), papillomas, and lymphosarcoma (rare) can cause obstruction.[248,250] Rupture of the gallbladder was found on necropsy of a cow in which icterus, anorexia, decreased milk production, and diarrhea had been present.[251]

Cholangitis is considered the most common cause of bile duct obstruction in large animals and has also been observed in horses with chronic active liver disease. Clinical signs associated with cholangitis in the horse may include anorexia, subtle behavioral changes, chronic weight loss, colic, and icterus. Alterations in hepatic enzyme activity may indicate either hepatocellular damage or cholestasis, or both. Histopathologic examination and bacterial culture are indicated to further identify the causative agent. In cases of suspected bacterial etiology, long-term antibiotic therapy is indicated.[252] The antibiotic choice should be based on bacterial sensitivity; however, in cases in which no bacterial organism is identified, an antibiotic that is secreted or cleared in the bile is warranted.

Several foreign bodies have been recovered from the biliary tract, including grain, nails, sticks, stones, and sand. Retrograde motion of the intestine may have allowed these foreign bodies to enter the duodenal papilla and become lodged.

33.41.2 CHOLANGIOHEPATITIS

Cholangiohepatitis has been reported both as a primary disease and as occurring secondary to cholelithiasis, duodenal inflammation, intestinal obstruction, neoplasia, parasitism, and certain toxins.[253] Sporidesmin, a fungal toxin from *Pithomyces chartarum,* causes cholangiohepatitis in cattle and sheep.[254] Horses with cholangiohepatitis, either primary or secondary, may show anorexia, icterus, pyrexia, and intermittent signs of colic.[243,253] Biochemical analysis revealing elevated cholestatic and hepatocellular enzyme activity and conjugated hyperbilirubinemia, combined with inflammatory leukogram, supports a diagnosis of cholangiohepatitis. Hyperammonemic hepatic encephalopathy may also be a feature. Cholangiohepatitis can be successfully treated in the horse, which primarily depends on long-term antimicrobial therapy and supportive treatment with IV fluids.[255] Treatment failure is associated with hepatic biopsy results and inadequate treatment duration. Severe periportal and bridging fibrosis with or without hyperammonemic hepatic encephalopathy carries a poor prognosis. Clinical recovery may be seen before normalization of biochemical indices of hepatobiliary function. GGT levels may increase during the early stages of treatment, before they decrease. It is recommended that treatment be continued until GGT levels return to normal.[255]

33.42 THERAPY OF LIVER FAILURE

Thomas J. Divers

Hepatic failure usually is treated medically and supportively, although surgery may be indicated in a few cases. Therapy is best indicated in cases of acute liver failure without chronic fibrosis, such as with serum hepatitis, suppurative cholangitis, and toxic hepatopathies other than with pyrrolizidine alkaloids, because these animals have the best long-term prognosis for regeneration. Prognosis is generally poor if severe hepatoencephalopathy or hemolysis or severe acidosis or diarrhea is present. The initial therapy for hepatic failure should be directed toward any abnormal behavior (hepatoencephalopathy) the patient may be exhibiting.[256]

Hepatoencephalopathy (HE) is a metabolically induced, potentially reversible, functional disorder of the brain. The pathophysiologic mechanisms of HE are undoubtedly complex but mostly result from abnormal protein metabolism.[257,258] Cerebral edema is characteristic of HE in humans, but it is rarely observed on microscopic examination of the brain in dying horses with HE. Complex interactions of both excitatory and inhibitory neurotransmitters determine if the patient is depressed or manic.[259]

If the animal is extremely agitated or convulsing, sedation should be accomplished before attempting further therapy. Detomidine will provide adequate sedation in most cases and is the drug of choice for horses with manic behavior caused by the HE. Most sedatives and tranquilizers are metabolized by the liver, so their use should be kept to a minimum, and doses of detomidine that cause marked lowering of the head or abnormally low respiration should be avoided. Diazepam should be avoided in animals with HE because it may enhance the effect of GABA on inhibitory neurons and worsen HE signs.[260] The use of the benzodiazepine receptor antagonist flumazenil has been reported to lessen HE signs temporarily in humans.[261] The overall success of flumazenil in treating HE in humans and dogs has been low, and it has rarely been used in the horse. Sarmazenil, which has a different mechanism of action, appears to be more promising for reversing signs of HE in some humans and has been used for treating moxidectin intoxication in a foal.[262,263]

After chemical restraint of the affected animal, therapy can be directed at the physiologic events that may be causing HE. If the blood glucose concentration is low, 0.2 to 0.4 mL/kg of a 10% glucose solution should be initially administered intravenously. This may result in a dramatic alleviation of the clinical signs of HE in a few cases (e.g., Theiler's disease, hepatic neoplasia, Tyzzer's diseases). Therapeutic measures directed toward decreasing the blood ammonia concentration are also indicated. These include oral administration of neomycin at 10 to 30 mg/kg two or four times daily for 1 or 2 days, either alone or in combination with oral lactulose (90 to 120 mL per adult horse three or four times daily), or oral acetic acid at 0.5 mL/kg twice daily.[264,265] A carbohydrate and prebiotic, lactulose is poorly absorbed from the small intestine and in the large intestine may decrease colonic pH and enteric ammonia concentration. Vinegar (acetic acid) should do the same. Metronidazole (10 to 15 mg/kg twice daily) may also be used to decrease ammonia-producing bacteria but is not preferred because it is metabolized by the liver, and signs of toxicity may mimic HE.

Nasogastric intubation should be performed with care because excessive trauma to the nasal cavity, esophagus, or stomach may result in severe and prolonged hemorrhage, swallowing of blood, and worsening of HE. Therefore, I prefer to administer oral drugs by dose syringe mixed with molasses and Karo syrup. Neomycin administration should not be prolonged because this may have a toxic effect on the intestinal mucosa[266] and cause severe diarrhea in some horses. Following neomycin therapy, probiotics can be given, some of which may result in decreased intestinal ammonia production.[267] Some clinicians prefer not to treat with oral drugs that affect intestinal flora, but rather to rely mainly on a low-protein diet and a laxative.

Acidosis may be severe in many horses with hepatic failure, but attempts at correction must be made slowly.[264] Too rapid an increase in pH may exacerbate the HE. I recommend bicarbonate therapy only when the venous pH is less than 7.1 and IV therapy with an alkalizing, balanced electrolyte fluid has failed to improve the acidosis. The prognosis is poor in horses that maintain persistent acidosis. It is of utmost importance that dehydration be corrected with a balanced electrolyte solution (preferably without lactate), dextrose (20 to 50 g/L), and supplemental potassium (20 to 40 mEq/L). Additional potassium should also be given orally (5 to 20 g twice daily). Maintaining potassium intake is important because low potassium increases production and absorption of ammonia from the kidney.[268]

Urine dipstick and plasma glucometer measurements should be used to monitor glucose concentration. Although most adult horses with hepatic failure have normal blood glucose concentration, it is important to supplement the fluids with glucose unless the horse is hyperglycemic. Glucose decreases ammonia concentration, reduces the reliance on catabolic gluconeogenesis, decreases protein catabolism, and spares hepatic energy consumed in hepatic gluconeogenesis. Glucose must not be given as the sole source of fluid. It is also important that glucose be continually maintained within the normal range (90 to 120 mg/dL). Polycythemia may be relatively unresponsive in some cases of hepatic failure and should not be used as the primary guide for judging adequate fluid therapy. Fresh or fresh-frozen plasma can be used, to increase colloidal oncotic pressure, clotting-factor transport proteins, and antiproteases. Stored whole blood should not be used because ammonia levels may be high. Hetastarch should also not be used in hepatic failure.

Antioxidant, antiinflammatory, and antiedema therapy may be useful in some cases of acute hepatic disease and failure. Dimethyl sulfoxide (DMSO), acetylcysteine, vitamin E, and mannitol are antioxidant and antiedema drugs that may be useful.[269] *S*-adenosylmethionine (SAMe) appears to have protective effects against oxidative hepatic injury and is the preferred antioxidant for therapy in equine hepatic disease.[270] Antiinflammatory therapy should include flunixin meglumine and pentoxifylline (7.5 mg/kg PO every 12 hours). Horses with acute hepatic failure

that cannot be controlled by this therapy would require extracorporeal liver support systems. Although these have not been used in the horse, dialysis, charcoal adsorption, or plasma exchange methods are available.[271]

Treatment of ponies with hyperlipemia is covered in the section on hepatic lipidosis. If the hyperlipemia is thought to be associated with a pituitary adenoma, the treatment with pergolide (1 to 5 mg/day) is warranted and may be successful. Hyperlipidemia may also occur in horses in late pregnancy associated with diarrhea and azotemia.[272] If the pony or horse is in late pregnancy, it may be advisable to abort the mare.[273] Fatty liver in ruminants is discussed on p. 912. Hepatic failure in cattle associated with septic metritis or mastitis and in those with biliary obstruction from hepatic abscesses can often be successfully treated by forced feeding (e.g., alfalfa gruel, electrolytes) and systemic antibiotics.[274] Treatment of hepatic fascioliasis is discussed on pp. 909 and 910.

Animals with hepatic disease that maintain a fair appetite often are best treated by dietary management. Dietary management is important in the recovery of animals with acute hepatitis or hepatopathy and in prolonging the life of those with chronic hepatic disease. Energy and protein requirements (especially branched-chain amino acids) should be met.[275] An example of a reasonable diet is one part beet pulp with one-quarter to one-half part cracked corn mixed with molasses four to six times daily. Milo or sorghum may also be used as a grain mix. Small meals given frequently are ideal because of difficulties with gluconeogenesis and insulin regulation. Sorghum, oat hay, or grass hay may be substituted for beet pulp. If the affected horse will not eat, forced feeding should be considered, but nosebleeds should be avoided. An oral paste with a high branched-chain/aromatic amino acid ratio can be formulated or purchased for forced feeding.[276] Vitamin B_1, folic acid, vitamin K_1, or fresh plasma transfusion might be indicated with chronic biliary obstruction. Grazing of mixed grasses is permitted and should be encouraged, as long as affected horses can be protected from sunlight. Spring-cut hay or grass should be limited because these can be very high in protein. Alfalfa is also generally high in protein and is best avoided with hepatic dysfunction, except in cows that seem to be more tolerant of high-protein feeds. It is important that a horse with hepatic failure eat something, even if it is not one of the more desirable feeds previously mentioned.

Bactericidal antibiotic therapy is indicated for horses with bacterial cholangitis and in cattle with liver abscesses. A diagnosis of suppurative bacterial cholangitis usually is made before the organism or its antibiogram is known. Therefore, broad-spectrum aerobic drug therapy, such as a combination of ampicillin and gentamicin, trimethoprim-sulfa, ceftiofur, or enrofloxacin, is preferred for the initial therapy. Anaerobic organisms may also be involved, and metronidazole can be added to any of these drug therapies. Antimicrobial therapy can be adjusted if the offending organism can be identified from a liver biopsy. Gram-negative enteric organisms are the most common causative organisms, and in my experience, only 50% or less are sensitive to trimethoprim-sulfa. This is unfortunate, since prolonged (2 weeks to 3 months) antibacterial therapy is usually required for suppurative cholangitis.[277] Ultrasound examination is important in treating equine suppurative cholangitis because some cases are associated with biliary stones, which makes the treatment more difficult and worsens the prognosis. If there are small obstructing stones or sludge, DMSO (0.5 to 1.0 g/kg IV for 3 to 5 days) may help dissolve the calcium bilirubinate stones or debris.[278] IV crystalloids may also thin secretions and promote bile flow. Ursodeoxycholic acid, a commercially prepared bile acid, is used for a variety of chronic biliary disorders in humans and small animals and will induce choleresis. This drug's benefit in horses has not been proved, and safety is a concern because rabbits, which have a GI system similar to the horse, metabolize this bile acid into noxious bile acids.[279] If a large, obstructing stone is present, surgery is indicated. Although the most distal bile duct opening into the duodenum cannot be visualized by ultrasound examination, it can be seen during gastroduodenal endoscopy.

Cattle with singular or multiple liver abscesses often respond to penicillin therapy, but long-term therapy is required, and there is a significant rate of recurrence of clinical signs after therapy is withdrawn. Abscesses of small

to medium size and echolucent have the best prognosis. Abscesses with echodense appearance are difficult to treat. Single, large abscesses are best treated by surgical drainage, especially those interfering with vagal nerve function. High levels of IV penicillin and an aminoglycoside should be administered to foals with suspected Tyzzer's disease. Penicillin in high dosages and/or metronidazole should also be used for treating suspected anaerobic abscesses of the liver. Foals with salmonellosis should be given antimicrobial therapy based on culture and sensitivity results from previously affected foals on the same farm and from results of blood and fecal cultures of the affected foal.

Surgery may be indicated as part of the therapy for liver failure in foals with duodenal stricture or in horses with colonic displacements (usually 180 degrees volvulus) that result in biliary obstruction.[280] Foals and calves with portosystemic shunts require surgical repair if desirable growth and performance are expected.[281] Surgery for cholelithiasis is indicated if there is an obstructing stone and unless diffuse fibrosis is already present. Cattle with a single, large hepatic abscess or calves with an umbilical vein hepatic abscess are best treated by surgical drainage.

Horses thought to have chronic active hepatitis with bridging necrosis that is not believed to be associated with a bacterial infection may be given corticosteroids, pentoxifylline, and/or colchicine (0.03 mg/kg orally every 24 hours), but the therapeutic benefits of these drugs appears to be variable. If steroids are to be used, 200 mg of prednisolone orally per day for the adult horse is recommended.

33.43 PANCREATIC DISEASE

Terry C. Gerros

Pancreatic disease is rare in both cattle and horses. In the horse, acute and chronic disease has been reported, whereas only chronic disease has been reported in cattle.

Recognized causes of pancreatitis include migrating parasites; bacterial and viral infections; immune-mediated damage; biliary or pancreatic duct inflammatory disease; deficiencies of vitamin A or E, selenium, and methionine; and vitamin D toxicity.[282–285] Drugs known to induce pancreatitis in humans that are used frequently in horses include furosemide, tetracycline, estrogen, and certain corticosteroids and sulfonamides.[282,284] One case report in a pony suggests an association with Cushing's syndrome.[286] The cause of acute pancreatitis in the horse is unknown; however, it has been associated with grain overload and severe abdominal pain.[287] The final common pathway may result from autodigestion by activated enzymes, but the exact mechanism remains speculative. Pancreatitis was also diagnosed postmortem secondary to severe gastroduodenal ulceration in a foal.[288]

The clinical signs associated with acute pancreatitis are not specific and mimic those associated with an acute GI crisis. The characteristic clinical features are moderate to severe abdominal pain, gastric reflux, hypovolemic shock, and cardiovascular compromise.[282,285,289,290] Gastric distention accounts for the pain and gastric reflux associated with acute pancreatitis. Hypovolemic shock, occurring secondary to fluid losses into the peritoneal cavity and bowel lumen, results from the release of vasoactive substances from the pancreas. Tachycardia, tachypnea, prolonged capillary refill, and congested mucous membranes result from hypovolemia and cardiovascular compromise.

Laboratory confirmation of pancreatic disease is difficult and not routinely attempted. The diagnosis is usually confirmed on histologic evaluation of the pancreas after necropsy. Laboratory tests that may be of value in the diagnosis of pancreatitis in the horse include measuring serum amylase and lipase activity, peritoneal fluid (PF) amylase concentrations, fractional excretion of amylase, and plasma trypsin levels.[285] Serum amylase values from normal horses range from 14 to 35 IU/L (mean, 21 ± 6), whereas PF values range from 0 to 14 IU/L (mean, 5 ± 4).

[291] Elevations of pancreatic enzyme activity are difficult to interpret, because the enzymes may be elevated in horses with proximal enteritis, colic, primary renal failure, and damage to intestinal mucosal cells, as well as in pancreatitis.[285,291,292] Amylase also originates from the salivary glands, and lipase can be released from the liver. Clinical cases documented at necropsy had serum amylase activity greater than 700 IU/L; this magnitude of elevation may be helpful in differentiating acute pancreatitis from other causes. In acute pancreatitis, PF amylase levels are higher than serum levels.[292] Plasma trypsin levels increase in horses with suspected pancreatic damage and may be a better indicator of pancreatic disease.[293] Trypsin is specific to the pancreas and activates its own zymogen and those of all the other pancreatic enzymes. In one study, in horses with acute abdominal disease in which pancreatic damage was suspected, trypsin activity was significantly higher than in healthy horses (196 ± 128.2 ng/mL vs. 28.5 ± 19.2 ng/mL).[293] Pancreatitis has not been imaged successfully in the horse with ultrasonography.[294] A technique for ultrasound examination of the right lobe of the pancreas in healthy cattle has been described.[295]

Medical management of acute pancreatitis is symptomatic. Prevention of gastric rupture by continuous gastric decompression and control of abdominal pain are crucial in the treatment of pancreatitis.[284] Large volumes of balanced polyionic electrolyte solutions are necessary to maintain the circulating volume and prevent shock. Because hypocalcemia may be a problem, serum calcium concentration should be monitored. Broad-spectrum antibiotics are warranted because of the potential for secondary bacterial infection. NSAIDs and analgesics are used to control inflammation and pain.

Chronic interstitial pancreatitis (CIP) in horses and cattle seldom has clinical significance. In horses, *Strongylus equinus* and *Stronglyus edentatus* are most often identified as the etiologic agent of CIP; however, *Parascaris equorum* has been identified in one case report.[284,296,297] In cattle, CIP has been primarily associated with the trematodes *Eurytrema pancreaticum* and *E. coelomacticum*; these parasites have not been isolated in the United States.[292]

Reports of pancreatic disease in adult cattle have been limited to endocrine dysfunction.[298–300] The most frequently reported disorder is type I diabetes mellitus; however, the etiology in most cases is not determined.[298–300] Histopathologic examination generally reveals an absence of β-cells in the islet tissue. Foot-and-mouth disease virus has been associated with diabetes mellitus in cattle following convalescence.[292] Hypoplasia of the acinar pancreatic tissue has been described in calves.[292] Clinical signs include steatorrhea and diarrhea. Adenocarcinoma of the exocrine pancreas is reported in rare equine cases and should be considered in horses exhibiting the clinical signs of pyrexia, depression, weight loss, and icterus.[283,301,302]

Pancreatic calculi found in older cattle (>5 years) during necropsy are considered incidental findings.[292,303] The calculi are composed primarily of calcium carbonate and calcium phosphate. Their presence may be associated with grazing on silica-rich soil, vitamin A deficiency, or chronic inflammation of the pancreatic ducts.[292]

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34 Chapter 34 Diseases of the Renal System

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34.1 EQUINE RENAL SYSTEM

34.1.1 ACUTE RENAL FAILURE

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Acute renal failure (ARF) in the horse is usually a consequence of exposure to nephrotoxins or vasomotor nephropathy (e.g., hypoperfusion or ischemia). The most common pathologic lesion with ARF is acute tubular necrosis (ATN).

34.2 TOXIC NEPHROPATHIES

34.2.1 Aminoglycosides

Administration of aminoglycoside antibiotics is one of the most common causes, if not the most common cause, of ATN in the horse. Neomycin is the most nephrotoxic of the aminoglycosides, followed by gentamicin, kanamycin, and amikacin (all three of similar toxicity), with streptomycin being the least nephrotoxic. The aminoglycoside antibiotics exert their toxic effect by accumulating within proximal tubular epithelial cells. Their entrance into the tubular epithelial cell is thought to be via urine, after filtration through the glomerulus.[1] Once toxic amounts are sequestered within the cell, cellular metabolism is disrupted, and tubular cell swelling, death, and sloughing into the tubular lumen occur. Release of lysosomal enzymes and intracellular accumulation of calcium are likely involved in cell death.

Most cases of aminoglycoside nephrotoxicity are not the result of overdosing of the drug or administration of the drug to an azotemic patient.[2] The healthy kidney can usually tolerate a single major overdose (i.e., 10 times the normal amount) without detrimental effects. Toxicity is almost always the cumulative effect of repeated administration of aminoglycosides. Nephrotoxicity typically develops after several days of aminoglycoside administration to horses with diarrhea or septicemia that are not adequately hydrated,[3] or because of other factors that may exacerbate a decrease in renal perfusion (e.g., concurrent treatment with nonsteroidal antiinflammatory drugs [NSAIDs]). Prolonged administration (>10 days) of aminoglycoside antibiotics without monitoring of aminoglycoside trough concentrations or serum creatinine concentration is a common history with aminoglycoside nephrotoxicity in the horse. Gentamicin or amikacin may be safely administered for longer than 10 days if the patient is adequately hydrated and appropriate trough concentrations and creatinine concentration are maintained. With regard to the latter, experimental induction of gentamicin nephrotoxicity in ponies was reflected by a rather small increase (0.3 mg/dL) in creatinine.[4]

Although it has not been proved that the neonatal equine kidney is more susceptible to aminoglycoside toxicity than the adult kidney, sick foals appear to be at greater risk for aminoglycoside nephrotoxicity.[5] This apparently greater risk may simply reflect an increased incidence of septicemia in sick neonates and longer courses of treatment with aminoglycosides. Nevertheless, special attention (close monitoring of trough concentrations and creatinine) should be given to premature or young foals that are being treated with aminoglycoside antibiotics.[6]

When aminoglycosides are administered to high-risk patients (those with concurrent dehydration or neonates), volume deficits must be replaced, and serum trough concentrations or creatinine should be monitored frequently.[7] Aminoglycoside nephrotoxicity rarely develops in horses receiving appropriate fluid therapy. Increased urinary sodium excretion and fluid diuresis appear to have a protective effect on the kidney. In contrast, hypokalemia (or total body potassium depletion) and low calcium intake may predispose horses to aminoglycoside nephrotoxicity by decreasing urine output.[8] Supplementation with oral electrolytes (e.g., 1 to 2 oz of NaCl and KCl daily) may be of benefit to horses being treated with aminoglycoside antibiotics by increasing water intake and urine output and by replacing potassium deficits in anorectic horses. In contrast, furosemide should not be administered prophylactically in an attempt to prevent aminoglycoside nephrotoxicity.[9] The recent shift to once-daily aminoglycoside dosing, compared with previous dosing of aminoglycosides two or three times daily, has become a standard practice that likely reduces the potential for nephrotoxicity (by ensuring a longer period of the day with appropriate serum trough concentrations) but still provides a similar therapeutic response.[10–13]

In patients with prerenal azotemia that receive aminoglycoside antibiotics, it is important to monitor creatinine closely and to consider prolonging the interval between drug administration until volume deficits are corrected. However, because nephrotoxicity is a cumulative effect of repeated dosing, delay of administration of the initial dose of an aminoglycoside pending rehydration of a critical patient (e.g., septic neonate, extremely dehydrated horse) is unwarranted.

Aminoglycoside nephrotoxicity should be considered in horses that become inexplicably depressed and inappetent while being treated with aminoglycosides or within a few days after aminoglycoside therapy is discontinued. Renal failure can develop even after the drug is withdrawn; thus, monitoring renal function 2 to 4 days after discontinuing aminoglycoside therapy may be advised in high-risk patients. Polyuria may be observed before the onset of depression and anorexia or, if the patient becomes oliguric, mild stranguria and repeated posturing to urinate may be observed. A tentative diagnosis of nephrotoxicity is based on history of aminoglycoside use and supportive laboratory data. Abnormal laboratory findings associated with tubular damage that may be detected before onset of azotemia include enzymuria and cylindruria.[4,14] Although these parameters can be monitored for early detection of tubular injury, their finding does not necessarily indicate if or when aminoglycosides should be discontinued or to what degree the interval of administration should be prolonged.[15]

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When ARF from aminoglycoside use develops, it is usually manifested as nonoliguric to polyuric renal failure, and outcome is generally favorable as long as the duration of ARF is not prolonged and other underlying disease processes can be corrected. Peritoneal or pleural dialysis, plasmapheresis, or hemodialysis might be considered as methods to lower serum concentrations of nephrotoxic agents and uremic toxins; however, the amounts removed by a single use of some of these therapies are small and generally not worthy of pursuit in horses with nephrotoxic renal failure.[16]

34.2.2 Pigment Nephropathy

Acute tubular necrosis and development of ARF consequent to rhabdomyolysis is uncommon unless the tying-up episode is severe or the associated dehydration is prolonged.[17] Observation of grossly discolored urine is not a prerequisite for the development of renal failure. Hemolysis appears to be a less common cause of pigment nephropathy than myopathy, although ARF can occur sporadically. Horses with severe hemolysis or those with hemolysis accompanied by disseminated intravascular coagulation (DIC) are at greater risk of developing pigment nephropathy.[18] Although 40% of the 32 horses with red maple toxicosis and hemolysis had evidence of renal insufficiency, it was not an important risk factor for mortality.[19] Renal failure consequent to pigment nephropathy should be suspected in horses that become anorectic and more depressed during the week after an episode of tying-up or during a hemolytic crisis. Measuring serum activities of creatine kinase and aspartate aminotransferase may help confirm that ARF has developed in association with rhabdomyolysis. Because there is little preformed creatinine in muscle, rhabdomyolysis alone does not produce an increase in creatinine.[20]

34.2.2.1 VITAMIN K_3

Vitamin K_3 (menadione sodium bisulfite) was a common cause of ATN and ARF in certain parts of the United States before its withdrawal from the market. The development of ARF was thought to be idiosyncratic.[21]

34.2.3 Nonsteroidal Antiinflammatory Drugs

Most horses do not experience appreciable adverse effects from NSAIDs as long as they are administered at the proper dose and animals are not dehydrated. However, NSAID use may produce ARF in an occasional horse when excessive doses are administered or when dehydration is not corrected promptly.[22,23] The lesion produced by NSAID toxicity is medullary crest necrosis, which can be manifested by gross hematuria.[22–26] Unless severe, this lesion rarely causes overt clinical signs, and creatinine may actually decrease with fluid therapy in the face of medullary crest necrosis. An occasional horse may also develop chronic interstitial nephritis and nephrolithiasis after prolonged use (months to years) of NSAIDs at recommended doses.[27] Presence of concurrent gastrointestinal (GI) disease (ulceration) and protein-losing enteropathy would further support NSAID toxicity in both acutely and chronically affected horses.

When renal blood flow decreases because of dehydration or redistribution of cardiac output, counteracting vasodilatory mediators are produced and released within the kidney to attenuate the decrease in renal blood flow. The best studied of these vasodilatory mediators include renal prostaglandins (PGI_2 and PGE_2) and dopamine. Although the role of renal prostaglandins in control of basal renal blood flow is likely insignificant, renal prostaglandins are important mediators of vasodilation during periods of renal hypoperfusion.[28] Further, production of renal prostaglandins is several-fold greater in medullary tissue, such that action of these mediators leads to a greater increase in inner cortical and medullary blood flow. Thus, it should not be surprising that the lesion associated with NSAID toxicity is renal medullary crest necrosis (consequent to ischemia).[29] Similarly, it is important to remember that use of NSAIDs in dehydrated or hypovolemic patients increases the risk of acute nephrosis.[30]

34.2.4 Vitamin D

Vitamin D intoxication may result from ingestion of feed additives or plants (e.g., *Cestrum diurnum*) containing high amounts of vitamin D metabolites or parenteral administration of vitamin D.[31–33] Cholecalciferol (D_3) is thought to be more toxic in the horse than is ergocalciferol (D_2).[32] In general, horses do not need dietary supplementation with vitamin D as long as they are exposed to sunlight and have access to green forages. Further, because the effect of vitamin D supplementation is cumulative, signs of toxicity may not develop until several weeks after supplementation was started.

Clinical signs of vitamin D intoxication may be referable to the musculoskeletal, cardiovascular, or urinary systems.[33] Calcification of tendons and ligaments results in lameness, and calcification of cardiac muscle and great vessels can lead to cardiovascular problems. Mineralization of tendons and ligaments may be detected directly by palpation or indirectly through ultrasonographic imaging. Heart murmurs may accompany calcification of the great vessels, and ultrasonographic imaging of the heart and kidney may also reveal evidence of mineralization. Further clinical signs of renal toxicity include polyuria and weight loss.

Abnormal laboratory findings with vitamin D intoxication include azotemia, isosthenuria, hypochloremia, and elevations in both serum calcium and phosphorus concentrations. The latter combination of hypercalcemia and hyperphosphatemia is unusual for any other disease in the horse, although it may be seen with neoplasia on rare occasions. A definitive diagnosis of vitamin D toxicosis can be made by measuring serum concentrations of 25-OHD_3, 25-OHD_2, and 1,25-$(OH)_2$D. Treatment of vitamin D intoxication includes removal of the inciting cause (feed or medication), fluid diuresis, and corticosteroid administration. Provision of feeds low in both calcium and phosphorus may be of benefit in less severely affected horses, but treatment is usually unrewarding once clinical signs attributable to tissue mineralization have developed.

34.2.5 Heavy Metals

Accidental ingestion of heavy metals may result in ATN and ARF in horses. Mercury, cadmium, zinc, arsenic, and lead are all nephrotoxic but are rare causes of renal failure in the horse. Mercury has been used experimentally to study renal failure in horses,[34,35] and there are reports of ARF in horses that have had legs “blistered” or “sweated” with products containing inorganic mercury.[36,37] Because inorganic mercury also causes severe damage to intestinal mucosa, signs of GI irritation (e.g., increased salivation, oral erosions, colic, hemorrhagic diarrhea) predominate with mercury intoxication. Further evaluation may reveal oliguria. Exposure to excessive amounts of zinc and cadmium can result in nephrocalcinosis and renal failure, but gait deficits (resulting from osseous effects, particularly in foals) and ill-thrift are more likely presenting complaints than oliguria.[38]

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Laboratory findings with heavy metal intoxication are characteristic for ATN (i.e., azotemia, isosthenuria to hyposthenuria, hyponatremia, hypochloremia). In horses with ARF concurrent with GI disease, as with mercury toxicity, severe hypocalcemia may be present. A tentative diagnosis of mercury intoxication may be made from history of exposure, clinical signs of erosive GI disease, and oliguric renal failure. The diagnosis can be confirmed by measuring increased blood and tissue (kidney and liver) concentrations of the metal. In addition to judicious fluid therapy, treatment of ARF induced by exposure to heavy metals should include dimercaprol, 3 mg/kg every 4 hours parenterally and 1 lb of charcoal orally. Visceral analgesics (flunixin meglumine) and sedatives (xylazine or detomidine) are often necessary to control abdominal pain.

34.2.6 Acorn Poisoning

Acorn poisoning is less common in equids than cattle (see Chapter 32), but it has been reported in horses.[39] Death in horses is usually the result of erosive GI disease, changes in vascular permeability, and resulting shock rather than a consequence of uremia. Immature leaves and green acorns are considered more toxic than mature acorns because the former have a higher tannin content. Clinical signs may include diarrhea, edema, and body cavity effusion, and laboratory evaluation usually reveals azotemia, isosthenuria to hyposthenuria, hyponatremia, and hypochloremia. Detection of increased urinary excretion of phenols may be useful to confirm the diagnosis.

34.2.7 Miscellaneous Drugs and Agents

Several other drugs and agents, particularly tetracycline, have been suspected of causing nephrotoxic ARF in horses.[40] When high doses of oxytetracycline (up to 70 mg/kg) are administered to neonatal foals for correction of limb contracture, ARF is a potential complication, especially if the foals are dehydrated or have concurrent sepsis or hypoxic-ischemic encephalopathy.[41] With renewed interest in polymyxin B as an adjunct treatment for endotoxemia, it is prudent to remember that this drug also has nephrotoxic potential. However, experimental studies have demonstrated that the risk of polymyxin B nephrotoxicity is low, especially when it is conjugated with dextran 70.[42] Amphotericin B also has considerable nephrotoxic potential, but it is rarely administered systemically to horses. Ochratoxins have potential to produce ATN, but ARF caused by ochratoxins has not been documented in horses. Similarly, pyrrolizidine alkaloid poisoning may cause renal disease in horses, but failure is unlikely. Blister beetle poisoning (cantharidin toxicosis) may cause abdominal pain, shock, hematuria, diaphragmatic flutter, dysuria, and renal dysfunction in horses fed alfalfa grown in regions where the beetles are prevalent.[43] One report of renal failure was associated with granulomas, as well as brain involvement, caused by the nematode *Halicephalobus*.[44]

34.2.8 Vasomotor Nephropathy

Any condition that causes sustained, marked hypotension or release of endogenous pressor agents can initiate hemodynamically mediated (vasomotor) ARF. Although poorly documented, vasomotor ARF may be more common than nephrotoxic ARF in the horse. Hemorrhagic shock, severe intravascular volume deficit (e.g., as with enterocolitis), septic shock, and coagulopathy are important risk factors for vasomotor ARF in horses.[45] Another cause may be adverse drug reactions, including those accompanying intravenous (IV) administration of vitamin and mineral products or immunomodulators. The predominant lesion in vasomotor nephropathy is ATN, although diffuse renal cortical or renal medullary necrosis may occur in some cases.

Clinical signs with vasomotor ARF are nonspecific and are more often referable to the primary disease (e.g., hemorrhage or diarrhea). Additional subtle signs, including more marked depression and anorexia than would be expected with the primary disease, with or without signs of mild colic, may increase suspicion of ARF. If sedation for colic signs is deemed necessary, xylazine or detomidine can be administered as long as intravascular volume and blood pressure are not overly compromised. Occasionally, horses with severe ARF may also be ataxic or manifest neurologic signs similar to hepatoencephalopathy.

Oliguria (often manifested as a lack of expected urination in response to fluid therapy) is an important early indicator of vasomotor ARF and production of dilute urine (specific gravity <1.020) that may be discolored (hematuria or hemoglobinuria) may be observed when urine is eventually voided. If urine produced is clear,

microscopic hematuria is usually present and will produce a positive result on reagent strip analysis of urine. Glucosuria may also be detected in an occasional horse with vasomotor ARF as a consequence of severe proximal tubular damage. Although the pathophysiologic relationship to ARF is not well defined, diarrhea and severe laminitis may develop in more serious cases of vasomotor ARF.

34.2.9 Acute Glomerulopathy

Although subclinical glomerular damage likely accompanies some diseases affecting horses, especially immune-mediated disorders (e.g., purpura hemorrhagica), acute glomerulonephritis is a rare clinical problem.[46] A syndrome of arteriolar microangiopathy and intravascular hemolysis causing distention of glomerular capillary loops with fibrin thrombi and accumulation of large amounts of proteinaceous debris in Bowman's capsule has also been described in a few horses.[47] Affected horses presented with oliguric ARF accompanied by hematuria, proteinuria, and intravascular hemolysis, and response to treatment was poor. The cause of the syndrome is not known, although renal lesions resemble those found with the hemolytic-uremic syndrome in humans (caused by toxins of *Escherichia coli*). Bacterial toxins, a consumptive coagulopathy, immune complex deposition, vasoactive amines, and hemodynamic alterations may all be contributors to this rare syndrome in horses.

Acute glomerulopathy should also be considered in horses with severe ARF that do not have a predisposing primary disease leading to vasomotor ARF and that have not been exposed to nephrotoxins. Gross hematuria, proteinuria, and oliguria would support an acute glomerulopathy, and renal biopsy can be pursued to confirm the lesion. Recently, in a case of toxic shock caused by *Streptococcus mitis,* ARF with glomerulopathy was one component of this syndrome.[48]

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34.2.10 Acute Interstitial Nephritis

Acute interstitial nephritis is a rare syndrome of ARF accompanied by rapid elevations in creatinine and clinical signs of uremia. Renal lesions include interstitial edema with a mild inflammatory infiltrate. Although adverse drug reactions (idiosyncratic) may be a cause, the etiopathogenesis of this disease in horses is unknown. In humans, eosinophilic infiltrates in renal biopsy tissue are supportive of adverse drug reaction. Although there are no published reports of the syndrome in horses, I have examined three horses with apparent acute interstitial nephritis. Because of the pronounced interstitial edema that may accompany this disease, treatment with corticosteroids may be of benefit in suspect cases.

34.2.11 Leptospirosis

Acute renal failure attributable to infection with *Leptospira interrogans* serovar *pomona* has been documented in several foals and a stallion over the past decade.[49–52] Fever, partial anorexia, and depression were the presenting complaints, and gross hematuria was observed in one foal. Azotemia and low urine specific gravity (<1.020) without bacteriuria were common laboratory findings, although leptospiruria was detected in one foal. Leptospirosis should be included in the list of possible causes of ARF when an underlying primary disease leading to vasomotor nephropathy is not apparent and there has been no exposure to nephrotoxins. Seroconversion or high serum titers and positive fluorescent antibody test results on urine (air-dried sample on a microscope slide) can be used to establish the diagnosis. Successful treatment has been accomplished with IV fluids and penicillin administration.

34.3 DIAGNOSIS

Acute renal failure should be suspected in patients showing more marked depression and anorexia than would be expected with the primary disease process and in patients that fail to produce urine within 6 to 12 hours of initiating fluid therapy. Rectal palpation in horses with ARF may reveal enlarged, painful kidneys in some cases. Enlargement can be confirmed by renal ultrasonography, which may also reveal perirenal edema, loss of detail of the corticomedullary junction, or dilation of renal pelves.[53–55]

The diagnosis of ARF is confirmed on the basis of history, potential exposure to nephrotoxins, clinical signs, and laboratory findings. The increase in creatinine is often several-fold greater (e.g., up to 5 to 15 mg/dL) than for blood urea nitrogen concentration (BUN) (e.g., up to 50 to 100 mg/dL) resulting in a BUN/creatinine ratio that is often less than 10:1. Hyponatremia, hypochloremia, and hypocalcemia are usually present, and in more severe cases, hyperkalemia, hyperphosphatemia, and metabolic acidosis may also be detected.

In addition to assessment of the magnitude of azotemia and alterations in serum electrolyte concentrations and acid-base balance, urinalysis should be performed on all horses in which ARF is suspected. As mentioned previously, a low urine specific gravity (≤1.020) in the face of dehydration and gross or microscopic hematuria are common findings with ARF. In addition, evidence of more substantial proximal tubular damage, including increased urinary enzyme activity and glucosuria, may be detected in some horses, and significant proteinuria (urine protein/creatinine ratio >2:1; see Chronic Renal Failure) would support glomerular disease. Examination of urine sediment may reveal casts and increased numbers of erythrocytes and leukocytes, and the amount of urine crystals may be decreased. Increased fractional clearances of sodium and phosphorus are also common findings with ARF. It is important to remember that administration of IV fluids to healthy horses will also result in increased fractional clearances of sodium, chloride, and phosphorus.[56] Thus, electrolyte clearances are ideally determined using the initial urine sample voided after admission or a sample collected by catheterization (i.e., before urine substantially altered by fluid therapy).

The most accurate assessment of renal function involves measurement of glomerular filtration rate (GFR). GFR can be determined by performing timed urine collections (inulin and endogenous or exogenous creatinine clearances) or by assessing plasma disappearance of several compounds (sodium sulfanilate, phenolsulfonphthalein, or radiolabeled substances).[57] In a clinical setting, measurement of GFR in cases of ARF is rarely pursued because multiple measurements are required to assess changes in GFR, and prognosis for recovery is more likely related to the duration of decreased GFR rather than the magnitude of the decrease. Further, because of the inverse relationship between GFR and creatinine, changes in GFR can be more practically assessed by daily creatinine measurement.

Glomerular injury and tubular necrosis can be further confirmed by performing a renal biopsy. However, biopsy is rarely indicated in cases of ARF because the diagnosis is usually evident. Further, correlation between light microscopic findings and functional changes in animals with ARF has not been well established; thus, prognosis often depends more on response to treatment than results of renal biopsy. Immunofluorescent (IF) testing and electron microscopic (EM) examination are routinely performed on human renal biopsy samples to assess mechanisms of renal injury and extent of damage to glomerular and tubular basement membranes. If such detailed evaluation of renal biopsy tissue were also performed in horses with ARF, better information regarding etiopathogenesis and prognosis would likely be provided by the pathologist.

At present, renal biopsy is most often indicated in the evaluation of horses with ARF for which exposure to nephrotoxins or another underlying primary disease process is not apparent. However, renal biopsy should be

approached cautiously because life-threatening hemorrhage is a potential complication. Biopsy of the right kidney with ultrasonographic guidance, usually through the seventeenth intercostal space, is the preferred procedure for renal biopsy.[58] Use of proper instrumentation (automatic or spring-loaded biopsy instruments) and adequate restraint (stocks and sedation) are important considerations. Renal tissue collected should be placed in formalin for histopathologic examination as well as frozen (or placed into additional media specified by the testing laboratory) for IF testing and EM examination. Although biopsy of the right kidney alone usually is adequate for assessment of the disease process affecting both kidneys, samples of the left kidney can also be collected by guiding the biopsy instrument through the spleen. Again, ultrasonographic guidance is important when collecting a biopsy from the left kidney or when biopsy of a specific area of either kidney is desired.

34.4 GENERAL PRINCIPLES OF TREATMENT

General principles of treatment of ARF in the horse are similar to those recommended for human patients.[59,60] Initial treatment should always focus on judicious fluid therapy to replace volume deficits and correct electrolyte and acid-base abnormalities. The magnitude of azotemia and serum concentrations of sodium, chloride, potassium, and bicarbonate should be monitored daily. Sodium and chloride replacement are often required in horses with polyuric ARF and can be accomplished by using 0.9% NaCl as the fluid administered or through electrolyte supplementation in grain feedings or as oral pastes. Serum potassium concentration in horses with nonoliguric ARF is often normal, and except for postrenal problems (e.g., obstruction or rupture), therapy intended to lower serum potassium is usually not necessary. Similarly, it is usually unnecessary to correct the mild hypocalcemia that can accompany ARF in horses.

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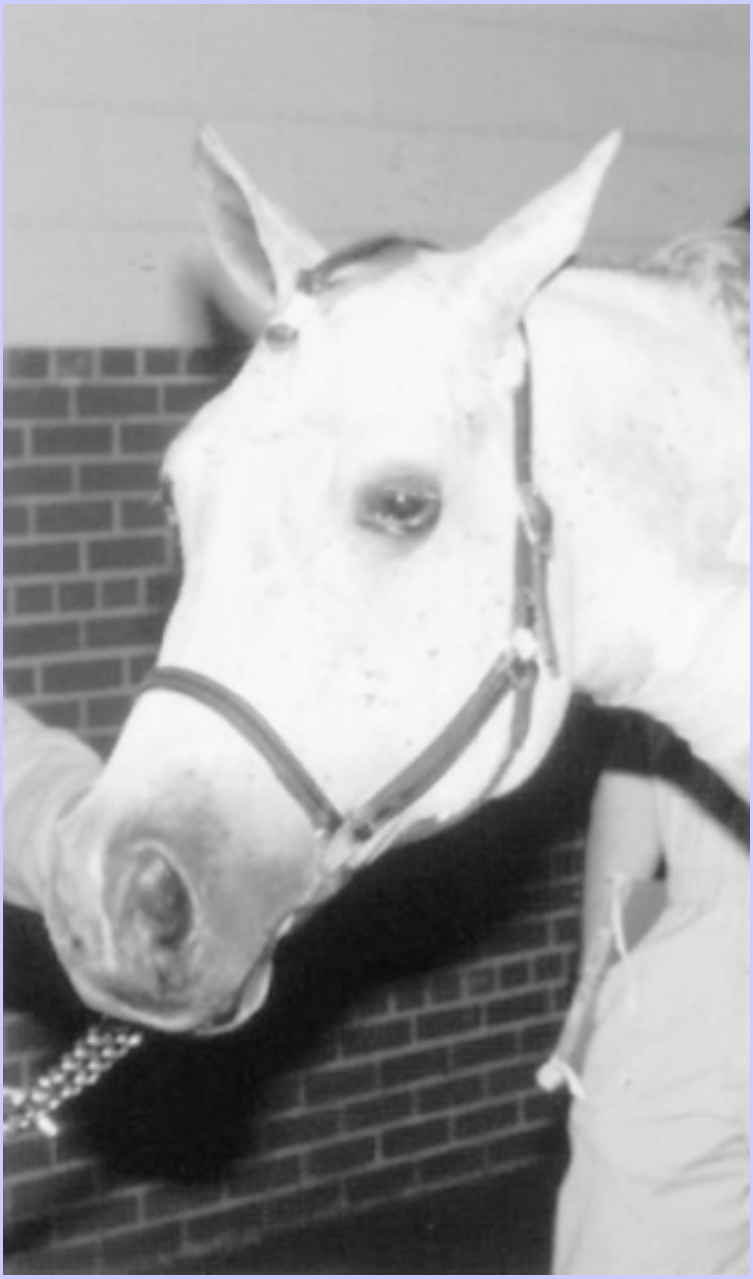
After correction of volume deficits and electrolyte and acid-base abnormalities, an attempt should be made to determine if the animal is oliguric or nonoliguric (polyuric) because the prognosis for recovery appears to be more favorable with nonoliguric ARF. This often becomes apparent by simple observation: oliguric horses fail to produce expected amounts of urine in the initial 12 to 24 hours of IV fluid therapy, and the bedding remains dry, whereas nonoliguric horses repeatedly void moderate volumes of dilute urine during the initial 6 to 12 hours of treatment. Further, edema can develop rapidly in horses with oliguric ARF. In horses with prerenal azotemia rather than intrinsic ARF, creatinine should decrease by at least 30% to 50% within the initial 24 hours of fluid therapy. In contrast, creatinine remains unchanged, or may even increase, with ARF.

In severely ill patients, especially those with vasomotor nephropathy, systemic blood pressure (BP) can be monitored to confirm that fluid therapy has been adequate to restore BP. Some horses may remain hypotensive (systolic BP <80 mm Hg) despite administration of large volumes of IV fluids because fluid may be accumulating extravascularly as edema or a third space fluid. If systemic BP remains low, hypertonic saline, dobutamine, or other pressor agents may be needed to restore BP and glomerular filtration. Fluid and sodium replacement in horses with oliguric renal failure and normal systemic BP must be monitored closely because, as previously mentioned, overzealous fluid administration to horses with oliguric or anuric ARF will result in edema formation, which is often initially noticed in the conjunctiva (Fig. 34-1).

In addition to regular assessment of attitude, vital parameters, packed cell volume, and total plasma protein concentration, monitoring should also include measurement of body weight once or twice daily (patients should not gain weight after rehydration) and comparison of fluid input with fluid (urine) output. Although there is no convenient method of collecting all urine voided by ambulatory foals or mares, urine output can be rather easily quantified in male horses by placing a urine collection device around the abdomen.[61] When desired, monitoring urine output in critically ill foals and mares can be accomplished by use of an indwelling Foley catheter and urine collection bag (closed system), but ascending infection is a risk. Finally, central venous pressure (CVP) can also be

monitored as a more precise measure of fluid balance in critical patients. CVP is measured with a manometer, with the baseline at the level of the right atrium, attached to an IV catheter placed into the anterior vena cava via the jugular vein (normal CVP in horses, <8 cm H_2O).

Fig. 34-1 Severe conjunctival edema from intravenous (IV) fluid therapy in a 3-year-old Arabian with oliguric acute renal failure (ARF). The ARF and a multifocal granulomatous pneumonia occurred after IV administration of an approved immunomodulator.



In horses that remain oliguric after 12 to 24 hours of appropriate fluid and electrolyte replacement and restoration of systemic BP, furosemide at 1 mg/kg intravenously [IV] every 2 hours should be administered. Unfortunately, furosemide treatment is often ineffective in increasing renal blood flow, GFR, and tubular flow in horses with ARF.[60,62] Continuous infusion of furosemide at 0.12 mg/kg/hr, preceded by a loading dose of 0.12 mg/kg IV, was considered superior to intermittent use in one study.[63] If urine is not voided after the second dose, administration of mannitol (1 mg/kg as a 10% to 20% solution) and/or a dopamine infusion (3 to 7 µg/kg/min IV) can be instituted. Dopamine administration should only be performed in a hospital setting in which heart rate and BP can be monitored frequently to avoid development of tachycardia and hypertension. Use of dopamine for selective renal vasodilatory and natriuretic actions has recently been called into question because most studies in humans have not demonstrated prevention of ARF in high-risk patients or improved outcome in those with established ARF.[64] Further, the drug may precipitate serious cardiovascular and metabolic complications in critically ill patients. If these treatments are successful in converting oliguria to polyuria (may require 24 to 72 hours), they can be discontinued, but maintenance of urine production must be monitored closely over the next few days. Fortunately, the majority of horses with ARF resulting from ATN are nonoliguric rather than oliguric, and administration of furosemide, mannitol, or dopamine is not needed in most of cases of nonoliguric ARF.

When this treatment approach to oliguria remains unsuccessful for more than 72 hours, the prognosis becomes grave. One study of horses with colic or colitis found that horses with persistent azotemia after 72 hours of fluid therapy were three times as likely to die or be euthanized as the horses without persistent azotemia.[65] However, dialysis therapy may be a further treatment option in select patients. Hemodialysis has been successfully used to treat two adult horses with myoglobinuric ARF[66,67] and a neonatal foal with oxytetracycline-induced ARF.[41] Peritoneal dialysis has been attempted in a few horses with nephrotoxic-induced ARF; however, omental plugging of the catheter has limited its success, and special dialysis catheters are needed for effective fluid exchange. Pleural dialysis is another option for which fluid exchange is less problematic. Hemodialysis or dialysis would likely be most effective in horses with nephrotoxic ARF, whereas vasomotor nephropathy is best treated by addressing the predisposing condition and instituting appropriate fluid therapy.

After volume deficits have been restored and polyuria has been achieved, patients usually require only continued fluid therapy (0.9% NaCl or another balanced electrolyte solution, 40 to 80 mL/kg/day) to promote a continued decrease in creatinine. Fluid therapy may need to be continued (20 to 40 mL/kg/day) for several days until creatinine returns to the normal range or a steady-state value and the horse is eating and drinking adequate amounts. Supplementation with oral electrolytes (1 to 2 oz NaCl twice daily) will also promote greater fluid intake and diuresis. Potassium supplementation (1 oz KCl twice daily) may also be required because the diuresis also results in kaliuresis. When horses remain anorectic during treatment, addition of 50 to 100 g dextrose/L fluids can provide needed calories, and if anorexia persists for several days, caloric intake may need to be provided by nasogastric tube feeding or total parenteral nutrition.

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Within the week after fluid therapy is discontinued, creatinine should be measured again to ensure that it has not increased. Occasionally, creatinine may not decrease to below 2 to 3 mg/dL despite continued fluid therapy. As long as the horse is eating and drinking well, IV fluids can be discontinued. In some horses, further recovery will be manifested as a return of creatinine to the normal range within the next couple of months, whereas in other patients a persisting elevation in creatinine indicates a permanent loss of renal function.

34.5 CHRONIC RENAL FAILURE

THOMAS J. DIVERS

Chronic renal failure (CRF) in the horse may be divided by clinical and pathologic findings into two broad categories: primary glomerular disease and primary tubulointerstitial disease.[68,69] However, pathology in one portion of the nephron usually leads to altered function and eventual pathology in the entire nephron. Thus, CRF is an irreversible disease process characterized by a progressive decline in GFR. However, the rate of decline in GFR is variable between affected horses, making the short-term (e.g., months to 2 years) prognosis guarded to favorable while the long-term prognosis remains poor.

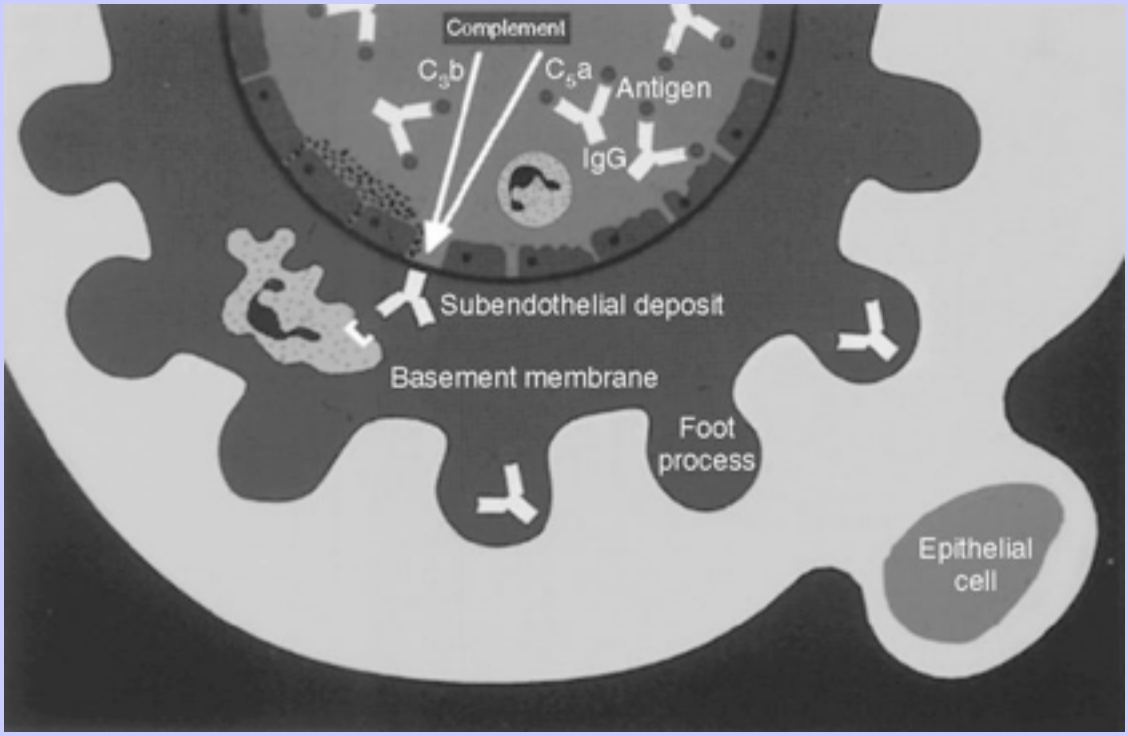
Primary *glomerular* diseases that can lead to CRF in horses include glomerulonephritis, nonspecific glomerulopathy, renal glomerular hypoplasia, and amyloidosis. Primary *tubulointerstitial* diseases causing CRF include incomplete recovery from acute tubular necrosis (ATN), pyelonephritis, nephrolithiasis, hydronephrosis, renal dysplasia, and rarely, papillary necrosis. Collectively, the latter disorders produce pathology categorized as *chronic interstitial nephritis*. Unfortunately, because renal disease is often advanced when horses are first presented for clinical evaluation, the inciting cause leading to CRF may be difficult to ascertain, and end-stage kidney disease (ESKD) may be the pathologic diagnosis. The inciting cause may more likely be discerned from the history (long term) rather than clinical findings at presentation, especially for primary tubulointerstitial diseases. Adjunctive diagnostic evaluation, including laboratory assessment, renal ultrasonography, and renal biopsy, may provide further evidence to document the inciting cause.

34.6 CAUSES

34.6.1 Proliferative Glomerulonephritis

Proliferative glomerulonephritis (GN), indicating increased cellularity of the glomerular tufts consequent to influx of inflammatory cells and proliferation of mesangium, is the most common glomerular disease causing CRF in horses. It is thought to result from deposition of circulating immune complexes along the glomerular capillaries or in situ formation along the glomerular basement membrane (GBM) (Fig. 34-2). Deposition of immune complexes causes activation of complement and vasculitis (type III hypersensitivity response). In one study, deposits of immunoglobulin G (IgG) and complement along the GBM were found through immunofluorescent (IF) staining in a large percentage (22 of 53) of horses at necropsy.[70] However, only 1 of these 53 horses developed CRF. Thus, although immune (antigen-antibody) complex deposition and subclinical GN may be common in horses, progression to CRF appears to be an infrequent occurrence. In this necropsy survey the predominant IF staining pattern was granular (patchy deposits of immune complexes and complement along GBM), but linear deposits were found in two horses. The latter finding was supportive of true autoimmune disease with more diffuse deposition of anti-GBM antibodies (type II hypersensitivity response) along the basement membrane antibody.

Fig. 34-2 Depiction of a subendothelial immunologic reaction suspected to occur in horses with streptococcal antigen-antibody—associated glomerulonephritis.



Streptococcal antigens have been suggested to be an important trigger for development of proliferative GN,[71] and in one horse with CRF, streptococcal antigens were confirmed to be present in diseased glomeruli.[72] Although equine infectious anemia virus is the only other antigen that has been detected in glomeruli of horses with proliferative GN,[73] subclinical GN likely accompanies other chronic infections in horses. It has also been suggested that equine GN may also be associated with either mixed or monoclonal cryoglobulins forming antibody-antibody glomerular depositis.[74] Fortunately, GN in most patients is rarely of clinical significance.

34.6.2 Chronic Interstitial Nephritis

Chronic interstitial nephritis (CIN) and fibrosis may be the most common cause of CRF in horses. Interstitial nephritis (tubulointerstitial disease) usually develops as a sequela to ATN consequent to exposure to nephrotoxins or vasomotor nephropathy. Other causes include drug-induced interstitial nephritis, urinary obstruction, pyelonephritis, renal hypoplasia/dysplasia, and papillary necrosis. Although the majority of horses that develop ARF attributable to these causes recover with apparently normal renal function (they remain nonazotemic), a few may survive with significant loss of renal functional mass and subsequently (often years later) develop signs of CRF attributable to CIN.[75] In horses less than 5 years of age that develop CRF that cannot be attributed to other causes, anomalies of development, including renal hypoplasia, dysplasia, and polycystic kidney disease, should be strongly suspected[69,76–78] (Fig. 34-3).

Fig. 34-3 Yearling thoroughbred with chronic renal failure caused by renal dysplasia. Failure to grow normally and lethargy were the primary complaints.

34.6.3 Pyelonephritis

Bilateral septic pyelonephritis is a rare cause of CRF in horses.[79–81] Pyelonephritis is usually a result of an ascending infection and is often accompanied by nephrolithiasis or ureterolithiasis. Multiparous mares, especially those with a history of dystocia, and horses with bladder paralysis are at greater risk for bacterial colonization of the lower urinary tract and subsequent development of ascending infection. Chronic distention with bladder paralysis compromises the integrity of the ureteral orifices, leading to vesiculoureteral reflux and pyelonephritis. With long-standing bladder paralysis, the ureteral orifices may appear wide open during cytoscopic examination, and in an occasional affected horse, the endoscope can be advanced into the ureter with little resistance. With unilateral pyelonephritis, adequate renal function is usually maintained by the contralateral kidney; however, passage of small uroliths into the bladder can lead to recurrent urethral obstruction. Gram-negative organisms appear to be the most common causative agents, although *Staphylococcus, Streptococcus,* or *Corynebacterium* species may be isolated in some cases, and mixed bacterial infections are not uncommon.

34.6.4 Miscellaneous Causes

Other reported causes of CRF in horses include amyloidosis,[82] neoplasia,[83] focal glomerulosclerosis-like disease,[84] and chronic oxalate nephrosis.[85] One study described CRF caused by polycystic kidney disease in an aged pony with hematuria, which also had hepatic cysts.[86] Renal amyloidosis has been reported only in horses used for production of antiserum.[82] Further, “oxalate nephropathy” in horses is likely a misnomer because the presence of oxalate crystals in renal tissue of horses with CRF is typically a consequence, rather than the cause, of CRF.[85]

34.7 Clinical Signs and Laboratory Findings

The most common clinical sign observed in horses with CRF is weight loss.[69] A small plaque of ventral edema, usually between the forelimbs, is another frequent finding in horses with CRF.[69,87] Moderate polyuria and polydipsia (PU/PD) are usually present at some stage of the disease process, but PU/PD may not be noticed except by the astute owner or trainer.[69] Dysuria is generally not reported unless CRF is caused by pyelonephritis, which may be associated with bladder paralysis, lithiasis, and lower urinary tract infection (UTI). Normal equine urine is rich in crystals and mucus, making a prediction of urine abnormalities on gross observation difficult. However, hematuria or pyuria (gross or microscopic) may be reported in some, but not all, horses with pyelonephritis, urinary calculi, or neoplasia. Often, urine produced by horses with CRF is light yellow and transparent because it is relatively devoid of crystals and mucus. Accumulation of dental tartar, especially on the incisors and canine teeth (Fig. 34-4); melena; and oral ulcers are other findings that may be detected in horses with CRF. Growth in horses with renal hypoplasia, dysplasia, or polycystic kidney disease may be stunted. Although abdominal pain would be expected in horses with obstructive nephroliths or ureteroliths, colic signs are not often reported in horses with lithiasis producing obstruction of the upper urinary tract.[75,88]

Clinicopathologic findings in horses with CRF vary depending on appetite, diet, and the cause and severity of renal damage. Most horses with clinical signs of CRF have moderate to severe azotemia (creatinine usually ≥5 mg/dL). The BUN/creatinine ratio may vary, depending on protein intake, muscle mass, hydration, and degree of azotemia, but is usually 10:1 or greater. Mild hyperkalemia, hyponatremia, and hypochloremia are typically found in horses with CRF. Hypercalcemia, with serum concentrations sometimes exceeding 20 mg/dL, appears to be a laboratory

finding with CRF that is unique to the equid. One early case series of CRF reported six of nine horses to be hypercalcemic[89]; however, others have found a lower percentage to be hypercalcemic.[90] Hypercalcemia in horses with CRF is not a consequence of hyperparathyroidism,[91] and its presence or absence appears to be more closely related to dietary intake than to the magnitude of azotemia. For example, four of four nephrectomized ponies fed alfalfa hay developed marked hypercalcemia,[92] whereas serum calcium concentration remained within the normal range in four of four nephrectomized ponies fed grass hay (although filterable calcium did increase).[68] Similarly, hypercalcemia in horses with spontaneously occurring CRF can resolve within a few days of changing diet from alfalfa to grass hay.[78] Serum phosphorus concentration in horses with CRF is usually normal to decreased, and hypophosphatemia is more often detected with concurrent hypercalcemia. Hypermagnesemia may also be detected in some horses with CRF. Acid-base balance usually remains normal until CRF becomes advanced, but metabolic acidosis is a common finding in horses with end-stage disease.

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Fig. 34-4 Dental tartar caused by chronic azotemia in a 5-year-old standardbred with chronic renal failure.

Many horses with CRF are moderately anemic (packed cell volume, 20% to 30%) as a consequence of decreased erythropoietin production by the diseased kidneys. Those with CRF resulting from GN frequently have hypoalbuminemia and hypoproteinemia, and horses with advanced CRF of any cause may also have mild hypoproteinemia associated with intestinal ulceration. Hyperglobulinemia may be detected in horses with immune-mediated diseases or chronic pyelonephritis. Horses with CRF can also develop hypercholesterolemia and hypertriglyceridemia (hyperlipidemia), and a horse with advanced CRF occasionally may have grossly lipemic plasma.[93]

Urinalysis findings may also vary depending on the cause of CRF. As mentioned, urine collected from horses with CRF is relatively devoid of normal mucus and crystals, making samples transparent. Further, urine specific gravity is typically in the isosthenuric range (1.008 to 1.014), although heavy proteinuria in an occasional horse with GN may produce values up to 1.020. Quantification of urine protein concentration (as for cerebrospinal fluid) is required to assess proteinuria accurately. Urine protein concentration in normal horses is usually less than 100 mg/dL, and the urine protein/creatinine ratio should be less than 1:1.[94,95] With significant proteinuria, urine protein/creatinine ratio is usually greater than 2:1.[72] In the earlier stages of GN, excessive urine protein is primarily albumin, but with progression of glomerular pathology, an increasing amount of globulin is also lost in the urine. Horses with CIN usually do not have significant proteinuria. Hematuria (gross or microscopic) may be present with pyelonephritis, urinary calculi, or neoplasia and can produce trace proteinuria, but urine protein/creatinine ratio usually remains less than 2:1. Although horses with septic pyelonephritis would be expected to have pyuria (>5 leukocytes/high-power field) and significant bacteriuria on sediment examination, these findings are not consistently detected, and a urine sample should be submitted for quantitative bacterial culture in all horses with CRF. Usually, more than 10,000 colony-forming units per milliliter of urine are found with infection, although lower numbers do not always rule out septic pyelonephritis.

34.8 Diagnosis

A diagnosis of CRF is most often made in horses with azotemia and isosthenuria that present with a complaint of weight loss or decreased performance. As discussed earlier, determining the inciting cause of CRF can be difficult because the disease has often advanced to ESKD when horses are initially presented for evaluation. Urinalysis does not often reveal the cause of CRF, except in some horses with pyelonephritis. In theory, assessment of urine protein concentration and urine protein/creatinine ratio should be helpful in separating glomerular disease from tubulointerstitial disease, but in practice, these laboratory measures have not consistently been elevated in horses with histopathologic evidence of glomerulonephritis. However, detection of moderate to heavy proteinuria (urine protein/creatinine ratio >2:1) without hematuria provides support for glomerular disease.

Rectal examination may be helpful in determining the cause of CRF. Horses with pyelonephritis, as well as those with ureteral calculi, often have enlarged ureters that can be palpated dorsolaterally as they course through the retroperitoneal space. Although kidneys of horses with CRF are often small with an irregular surface, these changes are not always apparent on palpation of the caudal pole of the left kidney. The right kidney cannot usually be palpated in the horse unless it is greatly enlarged or displaced caudally by the liver or a mass. Ultrasonographic imaging is useful for evaluating kidney size and echogenicity and may reveal fluid distention (hydronephrosis, pyelonephritis, polycystic disease) or presence of nephroliths.[96–98] Horses with significant renal parenchymal damage and fibrosis often have loss of detail of the corticomedullary junction, and echogenicity of renal tissue may be similar or even greater than that of the spleen. In contrast, intravenous pyelography (IVP) provides little information in adult horses and its use is generally limited to foals less than 50 kg. When hematuria or dysuria accompanies CRF, cystoscopic examination can be helpful in determining the side (right vs. left) from which renal hematuria is originating and further allows assessment of the ureteral orifices and urine flow from each kidney.

As described under Acute Renal Failure, measurement of GFR provides the most accurate assessment of renal function, and repeated measurements at monthly or longer intervals can be useful to monitor rate of progression of CRF. It is also a useful measure to document a reduction in renal function in horses that are thought to have early CRF, before significant azotemia has developed. GFR can be measured by several methods, including urinary clearance of endogenous or exogenous creatinine, inulin, or technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) (all require timed urine collections) or plasma disappearance of sodium sulfanilate,

phenolsulfonphthalein, or radiolabeled compounds (e.g., ^{99m}Tc-DTPA).[78,99–102] Assessment of renal function by nuclear scintigraphic imaging of the kidneys has also been described, but in horses this technique appears to be better for documenting decreased individual kidney function (i.e., with unilateral or asymmetric disease) than for quantitative assessment of GFR.[103,104] In most clinical settings, performing a 24-hour endogenous creatinine clearance is the most practical and economical method for measuring GFR. The major challenge is application of a urine collection device for collection of all urine produced. Once urine has been collected, a well-mixed sample is submitted to the laboratory, along with a sample of serum obtained during the collection period, and GFR is estimated by the following standard clearance formula:

$$\mathrm{GFR\,(mL \cdot kg^{-1} \cdot min^{-1})} = \left\{ \left([\mathrm{Cr}_{urine}] \Big/ [\mathrm{Cr}_{serum}] \right) \times \mathrm{UF} \right\} \Big/ \mathrm{bwt}$$

where *UF* is urine flow (mL • min^{-1}) and *bwt* is body weight in kilograms.[100] GFR in horses with normal renal function ranges from 1.5 to 3.0 mL • kg^{-1} • min^{-1}, and values less than 1.0 mL • kg^{-1} • min^{-1} are indicative of a decrease in GFR. Although repeated measurement of endogenous creatinine clearance provides useful information about the rate of decline in GFR in horses with CRF, simply measuring creatinine and assessing body condition at monthly or longer intervals are the most common methods used to evaluate the progression of CRF in affected horses.

The inciting cause of CRF can be confirmed in some horses by renal biopsy. As discussed under Acute Renal Failure, renal biopsy should be approached cautiously and pursued only if findings are likely to change treatment or prognosis. Treatment for CRF consists of supportive care, and the long-term prognosis is poor; therefore, renal biopsy is rarely indicated in horses with CRF. Further, most horses have rather advanced CRF at the time the disease is initially detected, and biopsy results in these patients may not provide useful information regarding the inciting cause.

34.9 Treatment

Treatment of horses with CRF is most likely to produce improved renal function if there is an acute, reversible component exacerbating CRF (i.e., acute on chronic syndrome). Similar to ARF, sudden exacerbation can be caused by exposure to nephrotoxins or vasomotor nephropathy secondary to diseases producing hypovolemia (e.g., diarrhea or sepsis causing volume depletion). Ascending urinary tract infection or obstruction can also exacerbate CRF. If an acute component is detected, it should be corrected rapidly (as described for ARF) with the goal of minimizing further loss of functional nephrons. In addition, surgical removal or fragmentation of stones may be indicated in horses with calculi thought to be disrupting urine flow.

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In horses with relatively stable CRF, management changes should be kept to a minimum and, when necessary, made gradually. Treatment of horses with stable CRF consists of supportive care: providing sufficient fluids, electrolytes, and nutritional support.[105] Water should be available at all times, and salt can be provided freely as long as edema or hypertension is absent. If edema develops, salt should be restricted, even in the face of hyponatremia. In addition to creatinine, serum electrolyte concentrations and acid-base balance should be measured regularly (e.g., monthly or longer intervals). If serum sodium and chloride concentrations are decreased, 60 to 120 g (~2 to 4 oz) of salt may be added to the feed, provided edema is not present. If metabolic acidosis is detected (e.g., blood pH <7.35 or serum bicarbonate concentration <20 mEq/L) and the patient is not edematous, sodium bicarbonate ($NaHCO_3$) powder (100 to 200 g/day) or a mix of $NaHCO_3$ and salt should be added to the diet. The goal of supplementation with salt and $NaHCO_3$ is to maintain serum electrolyte concentrations and acid-base balance within reference ranges. However, the effect of electrolyte supplementation on progression of CRF is

unclear because high-salt diets may actually hasten the decline in GFR and exacerbate proteinuria in human patients with CRF.[106]

Although no adverse effects of hypercalcemia in horses with CRF have been documented, decreasing calcium intake (e.g., replacing alfalfa or other legume hays with grass hay) may result in a return of serum calcium concentration to the normal range. The hypophosphatemia that usually accompanies hypercalcemia in horses with CRF may prevent mineralization of soft tissues. There appears to be no need for vitamin D supplementation in horses with CRF but regular administration of vitamin B complex, and anabolic steroids may be helpful to stimulate appetite. If appetite remains good, anabolic steroids may further limit muscle wasting and may increase packed cell volume (PCV). Attenuation of anemia in human and canine patients with CRF by administration of recombinant erythropoietin has been one of the most significant advances in management of CRF because it has eliminated the need for blood transfusions, improved exercise capacity, and decreased morbidity associated with the uremic syndrome.[107] In an occasional horse with advanced CRF, marked hyperlipemia may develop, and administration of heparin (40 to 100 IU/kg subcutaneously [SC] twice daily) may stimulate lipoprotein lipase and decrease plasma triglyceride concentration.[108] However, this treatment is not without risk because it may cause a further decline in PCV and potentiate bleeding tendencies in a uremic patient. NSAIDs and corticosteroids are best avoided in horses with CRF attributable to primary tubulointerstitial disease. If these drugs are essential for treatment of a complicating problem, they should be used judiciously.

Treatment of CRF consequent to GN appears to be even less rewarding than treatment of CRF caused by tubulointerstitial disease (CIN). Immunosuppressive therapy has been of limited benefit in slowing the progression of the disease and may even hasten weight loss. For patients with significant edema, treatment with diuretics may result in transient improvement, and plasma transfusions may be of temporary benefit to horses with edema and hypoalbuminemia.

As CRF progresses, partial anorexia and lethargy lead to more rapid loss of body condition. Thus, nutritional management aimed at maintaining body condition is probably the most important aspect of supportive care of horses with CRF. Increasing carbohydrate (grain) intake and adding fat to the diet are recommendations to increase caloric intake. Fat can be added by feeding corn oil (up to 16 oz/day) or a commercial fat supplement. Increased intake of omega-3-fatty acids (e.g., available in linseed oil or flaxseed oil) has been demonstrated to slow the progression of renal failure in experimental models, but potential benefits in spontaneously occurring CRF are less clear.[109,110] Over the past two decades, restricting dietary protein intake by human and veterinary patients with CRF was thought to have beneficial effects[111]; however, the current recommendation is to provide adequate amounts of dietary protein and energy to meet or slightly exceed predicted requirements while maintaining a neutral nitrogen balance.[112] In horses with CRF, adequacy of dietary protein intake can be assessed by the BUN/creatinine ratio; values greater than 15:1 suggest excessive protein intake, and values less than 10:1 may indicate protein-calorie malnutrition. Finally, an important but often overlooked aspect of nutritional management of horses with CRF is provision of a highly palatable diet. Feeding smaller meals more frequently and varying the diet (e.g., offering various types of concentrate feeds as appetite may vary from day to day) are helpful methods to increase food intake.

Additional treatments for CRF in human patients include antihypertensive agents including diuretics, β-adrenergic blockers, and angiotensin-converting enzyme (ACE) inhibitors.[113] Use of ACE inhibitors may have an additional benefit of limiting proteinuria.[114] Currently, little is known about the roles of systemic or intrarenal hypertension in progression of renal disease in horses, and there are no reports of potential benefits of use of antihypertensive medications in horses with CRF. Finally, efforts are under way to examine the roles of mediators of inflammation

in development of renal fibrosis, with the hope that future specific interventions may be developed to limit the progressive interstitial fibrosis that occurs in all patients with CRF.[115]

Horses with end-stage CRF often develop oliguria and uncontrollable metabolic acidosis. At this stage, CRF can only be managed by hemodialysis or peritoneal/pleural dialysis. However, pursuit of either hemodialysis or peritoneal dialysis in horses with CRF is impractical because, even when successful, dialysis prolongs the life of the patient for only a short time.

34.10 Prognosis

The progressive loss of nephron function that is characteristic of CRF precludes successful long-term treatment in horses. However, many horses with early CRF may be able to continue in performance or live as a pet for months to a few years. In general, as long as creatinine remains less than 5.0 mg/dL and the BUN/creatinine ratio is less than 15:1, affected horses seem to maintain a reasonably good attitude, appetite, and body condition. However, once creatinine exceeds 5.0 mg/dL, the rate of progression of CRF appears to accelerate, and signs of uremia (e.g., anorexia, poor hair coat, loss of body condition) become more apparent over a few weeks to months. Although this threshold value for creatinine is a useful figure for offering an initial prognosis for most horses with CRF, it is important to remember that progression of CRF is highly variable between affected animals. Thus, each case must be handled on an individual basis, with the emphasis on maintenance of body condition until humane euthanasia may become necessary.

34.11 URINARY TRACT INFECTIONS

THOMAS J. DIVERS

Urinary tract infections (UTIs) can be anatomically divided into two categories: (1) those affecting the upper urinary tract (kidneys and ureters) and (2) those involving the lower urinary tract (bladder and urethra). Lower UTI in horses usually results from anatomic or functional causes of abnormal urine flow, especially bladder paralysis (see Urinary Incontinence). Although recognized less frequently, upper UTI is often a more serious, potentially life-threatening problem. In horses, UTI is also frequently accompanied by urolithiasis and partial obstruction. With the exception of single, large cystoliths (that predispose affected horses to lower UTI), it is often difficult to determine whether development of nephroliths, ureteroliths, multiple small cystoliths, and urethroliths was a predisposing cause or a consequence of UTI. The pathophysiology, diagnosis, and management of equine UTI has recently been extensively reviewed.[116]

34.12 RISK FACTORS AND CAUSES

The most common risk factors for development of UTI in horses are bladder paralysis, concurrent urolithiasis, and urethral damage (e.g., foaling trauma in mares, neoplasia or habronemiasis in stallions and geldings). The shorter urethra and its location near the anus also increase the risk of lower UTI in healthy females. For example, silent lower UTIs and pyelonephritis, resulting from infection with bacteria shed from the GI tract, can develop in prepubertal girls and during pregnancy or after menopause in adult women.[117] This increased risk at certain times in women has been further attributed to a lack of estrogen, a hormone that appears to be important for production of glycosaminoglycans that cover uroepithelial surfaces and inhibit attachment of bacteria.[118] Whether fillies or pregnant mares are at increased risk for UTI has not been studied. However, horses with bladder paralysis (detrusor dysfunction) or decreased urethral sphincter tone (from trauma or neurologic disease) are clearly at greater risk of

UTI than horses with normal detrusor and urethral sphincter function. Finally, because bladder catheterization cannot be performed in a sterile manner because of normal bacterial flora in the vestibule and distal urethra, contamination of the lower urinary tract is an accepted risk of this procedure. Nevertheless, development of lower UTI is an unlikely complication of bladder catheterization in otherwise healthy animals because host defense mechanisms, including urine flow, are highly effective in eliminating contaminating bacteria. However, when urethral or bladder mucosa has been damaged or when urine stasis (bladder paralysis) is present, bladder catheterization has a greater risk of producing UTI.

In a group of horses with neurologic bladder dysfunction complicated by UTI, *Escherichia coli, Staphylococcus* species, *Corynebacterium* species, and *Pseudomonas aeruginosa* were the microbes isolated most frequently.[119] In my experience, *E. coli, Proteus mirabilis, Klebsiella* species, and *Enterobacter* species are the most common pathogens isolated from individual horses with UTI. *P. aeruginosa* can cause lower UTI in some horses, but it can also be isolated from the urethra of many clinically normal horses. Gram-positive organisms are less frequent causes of UTI in horses, although *Staphylococcus* and *Corynebacterium* species are occasionally identified pathogens.[120] In horses with abnormal urine flow (e.g., with uroliths) or instrumentation of the urinary tract (e.g., indwelling bladder catheters, ureteral stents), UTI with *Enterococcus* species (formerly *Streptococcus faecalis*) may also develop. Similarly, lower UTI with *Candida* species develop commonly in recumbent neonatal foals receiving broad-spectrum antibacterial therapy.

34.12.1 Clinical Findings

Clinical signs with UTI usually reflect the location, severity, and duration of the infection. Lower UTI is typically characterized by recognizable disturbances in urine flow but seldom causes signs characteristic of a systemic infection (e.g., fever, weight loss). Dysuria, stranguria, pollakiuria, and incontinence are consistent with lower UTI. Urine scalding of the perineum may develop with chronic UTI in mares (but should not be confused with estrus), and the sheath opening and dorsal aspects of the hindlimbs may be coated with urine crystals or blood in affected stallions and geldings. Gross hematuria may be observed if urinary calculi are present or if bladder or urethral mucosa has been eroded. Hematuria of bladder origin typically produces hematuria throughout urination, but gross discoloration of urine is most obvious at the end of urination. Hematuria caused by renal hemorrhage was a major component of pyelonephritis reported in seven horses.[121] In an occasional horse, gross pyuria may also be observed as passage of mucopurulent debris in otherwise clear urine. Horses with upper UTI are more likely to have signs characteristic of a systemic infection (e.g., fever, weight loss). However, because UTI is typically accompanied by concurrent lower UTI, dysuria may also be present. As an example, recurrent urethral obstruction with small uroliths may be the presenting complaint for chronic upper UTI.

Rectal examination may help confirm a predisposing cause of lower UTI (e.g., enlarged and atonic bladder, cystic calculi, accumulation of sabulous urine sediment, bladder mass). Chronic cystitis also usually leads to bladder wall thickening; however, this change is not easily detected by rectal palpation. Although ureters are usually not found during rectal examination of the normal horse, careful palpation of the dorsolateral aspects of the caudal abdomen (retroperitoneal space) usually reveals enlarged ureters in horses with upper UTI. With pyelonephritis, palpation may further reveal kidneys that are either enlarged or shrunken and misshapen.

34.12.2 Diagnosis

A diagnosis of UTI is based on clinical signs and laboratory analysis of blood and urine samples. With lower UTI, results of a complete blood count (CBC) and serum biochemical profile are usually within reference ranges,

whereas CBC results with upper UTI often support a systemic inflammatory response. With chronic upper UTI, increased total protein and globulin concentrations are often detected, and when the UTI is bilateral, azotemia may also be present. Detection of greater than 20 organisms and more than 10 white blood cells (WBCs) per high-power field on sediment examination of a urine sample collected during midstream voiding or via bladder catheterization is highly supportive of UTI, and growth of 10^4 or more organisms per milliliter of urine confirms the diagnosis.[122,123] When evaluating a horse for possible UTI, urine samples collected should be examined and processed for bacterial culture within 30 minutes after collection, or they should be refrigerated because bacteria can continue to proliferate when urine is stored at room temperature.[122]

Detection of azotemia, low urine specific gravity, and WBC casts in urine sediment are indicative of bilateral upper UTI, especially when accompanied by signs of systemic illness. Ultrasonographic examination of the kidneys is useful for detecting abnormal renal size, shape, or consistency in horses with upper UTI.[121,124–126] Endoscopic examination of the lower urinary tract is another useful tool for evaluating the integrity of urethral and bladder mucosa, detecting small uroliths, and assessing urine flow from each ureteral orifice.[127,128] With long-standing cystitis, especially when bladder paralysis is the underlying cause, ureteral orifices may become dilated (and appear wide open), allowing for vesiculoureteral reflux and development of ascending pyelonephritis. When unilateral pyelonephritis is suspected on the basis of ultrasonographic findings and absence of azotemia, catheterization of each ureter to collect urine samples from each side of the upper urinary tract can be helpful to document unilateral disease. Ureters may be catheterized by passing sterile polyethylene tubing through the biopsy channel of the endoscope during cystoscopy, or this can be accomplished in mares by directing blunt-ended catheters (e.g., 8-Fr polypropylene) through the urethra into each ureteral orifice.[129]

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34.12.3 Treatment

Treatment of UTI consists of proper antimicrobial therapy and correction, if possible, of predisposing anatomic or functional causes. Selection of the appropriate antimicrobial agent is best determined by prior knowledge of the following:

- Susceptibility patterns of the causative agent(s)
- Concentration of the antibiotic in renal tissue and urine
- Activity of the antibiotic at different pH values
- Ease of administration
- Toxicity
- Expense
- Compatibility with other antimicrobial drugs

Recommended antimicrobial agents for treatment of UTI in horses are discussed next. It should be emphasized that in vitro resistance to a particular antibiotic may not preclude successful treatment with the drug, as long as high concentrations are achieved in urine. Similarly, in vitro susceptibility does not always guarantee a successful response to treatment. For example, *Enterococcus* species are routinely found to be susceptible to trimethoprim-sulfa combinations; however, this pathogen is inherently resistant to these combinations in vivo.[130]

34.12.4 TRIMETHOPRIM/SULFONAMIDE COMBINATIONS

Trimethoprim-sulfonamide combinations have been highly successful in treating lower UTIs in some species.[131–133] Although sulfonamides alone can be effective in treating many lower UTIs,[134] addition of trimethoprim improves antibacterial spectrum without a prohibitive increase in expense or toxicity.[135] When selecting a trimethoprim-sulfonamide combination for treatment of horse with a UTI, metabolism of the sulfonamide should be considered. For example, sulfamethoxazole is largely metabolized to inactive products before urinary excretion, whereas sulfadiazine is excreted largely unchanged in urine.[136]

34.12.5 PENICILLIN AND AMPICILLIN

Penicillin, administered parenterally, is effective for treating upper or lower UTIs caused by susceptible *Corynebacterium, Streptococcus,* and some *Staphylococcus* species.[137] Ampicillin has also been used successfully for treatment of both upper and lower UTIs in animals and human patients.[131,138] Although many isolates of the Enterobacteriaceae family demonstrate resistance to ampicillin in vitro, this drug is highly concentrated in urine, and many organisms that are resistant in vitro may be killed in the urine of treated animals.

34.12.6 GENTAMICIN AND AMIKACIN

Gentamicin and amikacin, which can be nephrotoxic, should be reserved for treating lower UTIs caused by highly resistant organisms or acute, life-threatening upper UTIs caused by gram-negative organisms. Pharmacokinetic studies in adults and foals are available.[139,140] Potentiated penicillins (ticarcillin or ticarcillin/clavulanic acid) may be considered as an alternative to aminoglycosides in horses with severely compromised renal function (e.g., creatinine >3.0 mg/dL).

34.12.7 CEPHALOSPORINS, TETRACYCLINES, AND CHLORAMPHENICOL

Cephalosporins, tetracyclines, and chloramphenicol are frequently and effectively used for treatment of UTIs in other species.[138] Cephalosporins are concentrated in urine. Ceftiofur has broad-spectrum antimicrobial activity and could be selected when urinary pathogens demonstrate resistance to trimethoprim-sulfonamide combinations or penicillin. Tetracycline and chloramphenicol are predominantly metabolized in the liver with variable excretion in bile. However, when acceptable serum concentrations are achieved, excretion of active drug into urine may be high enough that either drug may be effective for treatment of UTIs caused by susceptible organisms.[141,142]

34.12.8 OTHER ANTIMICROBIAL AGENTS

Nitrofurantoin has an impressive in vitro spectrum, demonstrating activity against most common gram-negative organisms, including *Salmonella*.[126] The drug is inexpensive, is easily administered as an oral suspension, and achieves high concentrations in urine. Although this antimicrobial agent has not been well studied in horses, adverse effects and acquired resistance appear to be uncommon. However, nitrofurantoin does not attain high concentrations within renal parenchyma; thus, efficacy in treating upper UTI would be questionable. Further limitations of nitrofurantoin usage include decreased antimicrobial activity at an alkaline pH, and increased risk of toxicity has been described in other species as GFR falls (e.g., with CRF). Because urine concentration and

antimicrobial activity of nitrofurantoin after oral administration have not been well substantiated in horses, use of this antibiotic should be reserved for select cases in which specific susceptibility of a gram-negative organism has been demonstrated, or when expense precludes selection of another antibiotic for long-term therapy.

It is not unusual to find highly resistant organisms in urine of horses with chronic UTIs, especially those with bladder paralysis that have been repeatedly catheterized and have received a variety of antibiotic agents. In some cases the organisms may be highly resistant to all drugs approved for use in the equine. I have successfully treated a few adult horses and a yearling with UTI with enrofloxacin (2.5 mg/kg orally [PO] every 12 hours) without apparent adverse effects. Potential cartilage damage in younger horses should be considered and discussed with the owner before treatment with enrofloxacin would be pursued.

When treating UTIs in horses, antimicrobial therapy should be continued for at least 1 week for lower UTIs and for 2 to 6 weeks for upper UTIs. Ideally, a midstream-voided urine sample should be submitted for bacterial culture 2 to 4 days after initiation of therapy and again 1 to 2 weeks after treatment has been discontinued. If the UTI recurs and the same organism is isolated, a focus of upper UTI should be suspected. Ultrasonographic or nuclear scintigraphic examination of the kidneys should be considered in such cases to rule out a nephrolith or other parenchymal disease. Cystoscopy and ureteral catheterization can also be pursued to evaluate for unilateral or bilateral infection of the upper tract. In contrast, recurrence of UTI with a different pathogen suggests an anatomic or functional cause of abnormal urine flow as a predisposing cause of recurrent lower or upper UTI.

34.12.9 URINARY INCONTINENCE

ELIZABETH A. CARR

Urinary incontinence in the horse can result from urolithiasis, congenital anomalies or defects of the lower urinary tract, trauma, neoplasia, neurologic diseases accompanied by bladder dysfunction, and decreased urethral tone. Bladder and urethral calculi frequently result in transient incontinence secondary to cystitis or partial obstruction. Ectopic ureter and other congenital malformations of the urinary tract generally produce incontinence from birth, although development of incontinence in adult horses has been described.[143–146] Traumatically induced incontinence may develop after breeding injury or dystocia in mares or in both genders after sacral or spinal injury.[147] Incontinence has also been speculated to develop with long-standing lumbosacral or lower back problems that make it difficult for horses to posture to urinate. Over time, incomplete bladder emptying allows crystals normally present in equine urine to accumulate in the ventral aspect of the bladder. This crystalloid sediment becomes heavy and in some cases quite firm and further prevents complete bladder emptying. This condition, which has been termed *sabulous urolithiasis,*[148] can accompany bladder paralysis of any cause but may also be able to produce myogenic bladder dysfunction in the absence of an underlying neurologic problem. Horses with neoplasia of the lower urinary tract can also present with incontinence, but other complaints (e.g., stranguria or hematuria) are usually reported as well.

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Neurologic disorders that often result in bladder paralysis and incontinence include equine herpesvirus (EHV) myelitis, cauda equina neuritis, and sorghum toxicosis. These diseases, along with other problems affecting gray matter of the sacral segments (e.g., an occasional horse with equine protozoal myelitis), result in loss of lower motor neuron function, whereas lesions of the lumbar or higher portions of the spinal cord result in loss of upper motor neuron function. Lower motor neuron damage leads to loss of detrusor function and overflow incontinence. A large, easily expressed bladder is found on rectal palpation. Initially, upper motor neuron disease is characterized by increased urethral resistance, leading to increased intravesicular pressure before voiding can occur. Voiding may occur as short bursts of urine passage with incomplete bladder emptying, and rectal examination may reveal a turgid bladder that is small to increased in size. Although upper motor neuron signs

are initially different from those of lower motor neuron disease, incontinence is usually not recognized until overflow incontinence develops as a result of sabulous urolithiasis and progressive loss of detrusor function. The latter progression can explain why bladder paralysis and incontinence may occasionally be found in horses with other neurologic diseases, such as cervical stenotic myelopathy, equine degenerative myelopathy, and even viral encephalomyelitis. Presence of other signs associated with lower motor neuron dysfunction (e.g., loss of anal or tail tone) or upper motor neuron dysfunction (e.g., ataxia) may aid in differentiating the inciting cause of bladder paralysis. Despite many possible causes, the prognosis for recovery from incontinence resulting from bladder paralysis is generally poor because sabulous concretions and UTI quickly complicate the problem.

A final syndrome of incontinence caused by decreased urethral sphincter tone has been reported in a few mares.[149,150] This condition has been attributed to hypoestrogenism because incontinence improved after treatment with exogenous estrogen.

34.12.9.1

Diagnosis

In addition to taking a complete history and performing physical and neurologic examinations, it is helpful to observe the incontinence or any attempts made by the animal to urinate. Rectal palpation, transrectal ultrasonography of the bladder, and endoscopy of the lower urinary tract are useful to rule out uroliths, neoplasia, and congenital anomalies as causes of incontinence. Although most affected horses remain nonazotemic (unless significant obstruction or bilateral pyelonephritis has developed), laboratory analyses of blood and urine, including a quantitative urine culture, should be performed in all horses with incontinence because UTI is a common sequela. Urethral and bladder pressure profiles can be used to assess urinary sphincter and detrusor muscle function. Normal values for both mares and geldings have been reported.[151–153] When an underlying neurologic problem is suspected, cerebrospinal fluid (CSF) collection and analysis may also be of value.

A review of 21 horses presented to Michigan State University's Veterinary Teaching Hospital between 1995 and 2000 with a primary complaint of incontinence revealed that 15 horses had bladder paralysis, three had urolithiasis, and one foal had bilateral ureteral ectopia. Another horse had incontinence of undetermined cause that appeared to respond to treatment with phenylbutazone. The remaining horse had a urachal diverticulum, hydroureters, cystitis, pyelonephritis, an atonic bladder, and urethral sphincter dysfunction that was supported by an abnormal urethral pressure profile. Of the 15 horses with bladder paralysis, four developed the problem after foaling, two of which had dystocia. Fat necrosis around the urethra and bladder neck was found postmortem in one of the latter mares. Bladder paralysis was attributed to equine protozoal myelitis (EPM) in two horses and to EHV myelitis, cauda equina neuritis, and cervical stenotic myelopathy in one horse each. One horse had segmental neuronal degeneration in the lumbosacral and caudal spinal cord, and another horse had histopathologic evidence of denervation atrophy of the detrusor that was attributed to prior spinal cord trauma. An underlying neurologic disease causing bladder paralysis could not be determined in the remaining four horses. Although originally presented for evaluation of acute-onset severe spinal ataxia and weakness, another mare developed signs of an upper motor neuron bladder dysfunction (squirts of urine and a turgid bladder on rectal palpation) during hospitalization. Bladder function returned to normal as the neurologic disease improved over 2 weeks.

34.12.9.2

Treatment

Treatment for incontinence varies with the underlying cause. Removal of calculi and appropriate antimicrobial therapy are effective treatments for urolithiasis. Surgical correction is generally needed for treatment of

congenital anomalies, but owners should be discouraged from using affected animals for breeding. EHV myelitis and EPM carry the most favorable prognoses for recovery, although bladder paresis may persist for several weeks. Removal of sabulous crystalloid material (by bladder lavage through a catheter or by cystotomy) and temporary placement of an indwelling bladder catheter are indicated in cases of recent onset of bladder paresis, to prevent continued distention and further damage to the detrusor. Antimicrobial treatment, ideally based on urine culture results, is also indicated in all horses with bladder paralysis.

Bethanechol (0.25 to 0.75 mg/kg SC or PO every 8 to 12 hours), a parasympathomimetic agent that appears to have a somewhat selective effect on smooth muscle of the GI tract and bladder, has been recommended for improving detrusor tone and strength of contraction in horses with bladder paralysis. However, response to treatment has usually been disappointing, perhaps because of long-standing paralysis before incontinence is recognized. Use of phenoxybenzamine (0.7 mg/kg PO four times daily), an α-adrenergic blocker that decreases urethral sphincter tone, has also been recommended in combination with bethanechol in cases with upper motor neuron bladder dysfunction. In horses with evidence of urethral sphincter hypotonia, the sympathomimetic agent phenylpropanolamine (1 mg/kg PO every 8 to 12 hours) has also been used, but a successful response has not been reported. Dosing regimens for these autonomic drugs have been extrapolated from other species because no pharmacokinetic data are available for the equine species.

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In general, treatment with these autonomic drugs has largely been ineffective in controlling incontinence resulting from bladder paralysis, and the long-term prognosis for recovery is usually poor. On a more positive note, treatment of a few mares with urethral sphincter hypotonia with estradiol cypionate or benzoate (5 to 10 μg/kg intramuscularly [IM] every other day) has been effective at resolving incontinence as long as detrusor function was normal. Estrogen may modulate the effect of norepinephrine on α-receptor activity in the urethral sphincter, thereby improving urethral sphincter tone. Of further interest, incontinence in two mares with partial detrusor dysfunction was also reported to improve after treatment with estrogen,[150] although the mechanism by which estrogen would improve detrusor function is not clear.

34.12.10 ECTOPIC URETER

THOMAS J. DIVERS

Although rare, ectopic ureter is the most frequently reported developmental anomaly of the equine urinary tract. Of the cases reported, almost 90% have been fillies, and the primary complaint is urinary incontinence and perineal dermatitis (urine scalding).[154–157] However, this gender distribution may reflect easier recognition of urinary incontinence in females rather than a true gender predilection. In the male, intermittent urine dripping from the end of the penis is less easily recognized; further, urine entering the pelvic urethra may pass retrograde into the bladder.

34.12.10.1 Diagnosis

Ectopic ureter should be suspected in young horses with incontinence observed shortly after birth. Renal function is usually normal, but the affected ureter may be extremely dilated. In young foals (e.g., <50 to 75 kg) an excretory urogram (after IV administration of contrast agent) or pyelography (after percutaneous injection of contrast agent into renal pelvis via ultrasonographic guidance) may aid in diagnosis of ectopic ureter.[157,158] Unfortunately, most patients are not presented until they are too large for this procedure to be performed (Fig. 34-5). Ultrasonographic examination may reveal mild dilation of the renal pelvis on the affected side. Vaginoscopic and cystoscopic examinations should also be pursued in older foals to determine whether the

problem is unilateral or bilateral, and when unilateral, to determine which ureter is ectopic. In the latter case, cystoscopic examination should reveal urine entering the bladder from only one normal ureteral opening, located at either 2 or 10 o'clock in the bladder neck. Urine can be seen squirting from normal ureteral openings every 20 to 30 seconds. Observation of normal bouts of voiding, in addition to incontinence, further supports a unilateral problem. To determine the location of the opening of the ectopic ureter, visual examination of the vestibule and vagina (using a blade speculum) should be performed initially to look for intermittent urine flow from the area of the urethral papilla. Ectopic ureteral openings are usually not apparent unless urine flow is seen. Intravenous administration of dyes including sodium fluorescein (10 mg/kg IV; yellow-green color), indigotindisulfonate (indigo carmine, 0.25 mg/kg IV; blue-purple color), azosulfamide (2.0 mg/kg IV; red color), or phenolsulfonphthalein (1.0 mg/kg IV; red color) to discolor the urine may aid in location of ectopic ureteral openings.[154,155]

Fig. 34-5 Urine scalding in an 8-month-old thoroughbred filly with a left ectopic ureter. The filly recovered after a nephrectomy.

34.12.10.2 Treatment

If the ectopic ureter is unilateral, creatinine is normal, and ultrasonographic examination of the opposite kidney appears normal, the preferred treatment may be surgical removal of the kidney on the affected side and ligation of the ureter. Nephrectomy may produce an increase in creatinine (0.5 to 1 mg/dL) for a few days, but creatinine returns to the prenephrectomy value within a week. If both ureters are ectopic, which is not unusual, implantation of the distal ureters into the bladder neck should be attempted. Several surgical techniques have been described, but complications can include ascending infection, resulting from dilated ureters, and development of adhesions.[154–157]

34.12.11 NEOPLASIA

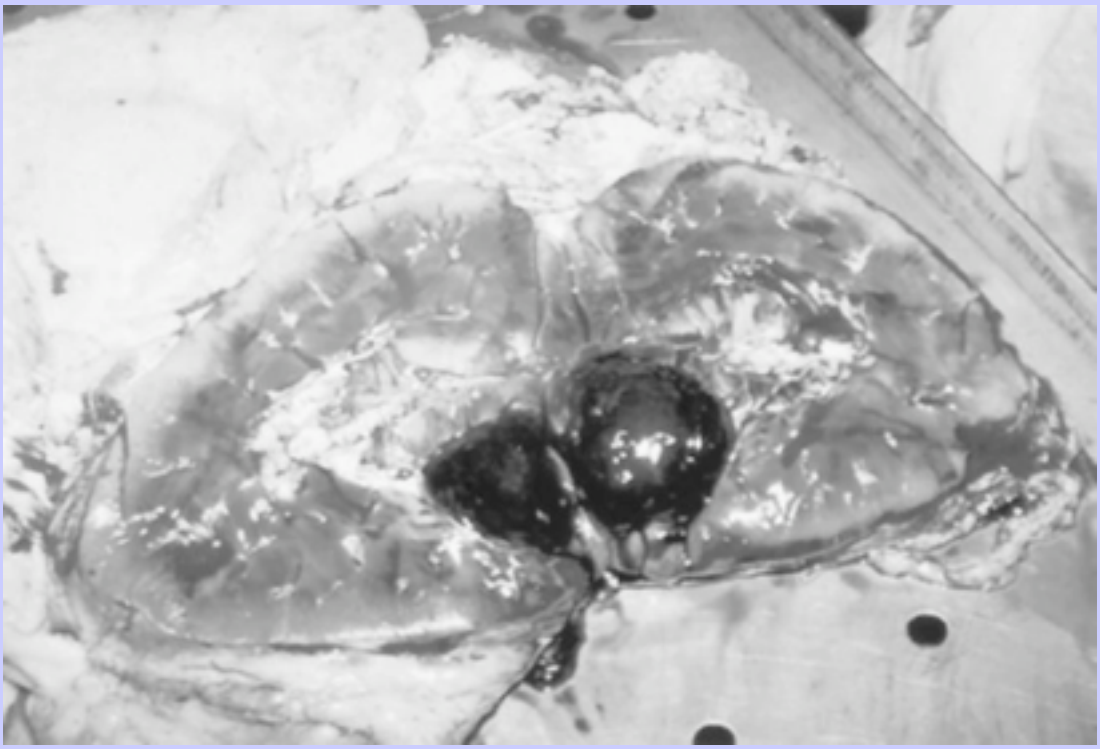
THOMAS J. DIVERS

Neoplasia of the urinary tract is rare in horses. Primary kidney neoplasms include renal cell carcinoma and nephroblastoma, with the former being the most common tumor of the kidney.[159] Renal cell carcinoma (or adenocarcinoma) occurs more frequently in older horses, but nephroblastomas may be detected in young horses. Squamous cell carcinoma is the most common bladder tumor, but horses may also develop transitional cell carcinoma.[160,161] Fibromatous polyps may also occur in younger horses, but bladder tumors usually develop in middle-age to older horses. Adenoma, lymphosarcoma, hemangiosarcoma, and melanoma may also involve the kidneys and, on rare occasions, the bladder.[162,163]

34.12.11.1 Clinical Signs and Diagnosis

Clinical signs in horses with renal neoplasia include hematuria, weight loss, and recurrent colic. Sudden death may occur if the neoplasm hemorrhages into the abdomen or thorax. Renal tumors may result in marked enlargement of the kidneys such that both left and right kidneys may be found on rectal palpation. In other cases, tumors may be small, circumscribed lesions within a kidney (Fig. 34-6) that cannot be felt during rectal palpation. Small tumors may also be difficult to visualize on ultrasonographic examination. The diagnosis is based on history, clinical signs, and ultrasonographic findings (Fig. 34-7). Affected horses usually are not azotemic, but mild anemia may be detected when gross hematuria is observed. Although neoplastic cells are unlikely to be found in urine, cytologic examination of urine sediment is warranted. Nephroblastoma usually remains limited to the kidney, but renal cell carcinomas typically metastasize to the liver and lungs. Thoracic radiographs are helpful in detecting pulmonary metastases. With ultrasonographic guidance, the tumor can usually be biopsied and a definitive diagnosis established.

Fig. 34-6 Cut section of the left kidney from a 25-year-old horse with chronic weight loss, hematuria, and severe anemia. The kidney appeared normal, except for a small, 4 × 5—cm carcinoma with surrounding hemorrhage.



In addition to hematuria and weight loss, horses with bladder tumors may also present with pollakiuria and stranguria. With bladder tumors, a mass can usually be palpated on rectal examination, but it should not be confused with a cystolith or accumulation of sabulous concretions in the ventral aspect of the bladder. Horses with gross hematuria may be mildly anemic but usually are not azotemic. Other than hematuria and associated proteinuria, urinalysis results are often unremarkable; however, with bladder tumors, cytologic examination of urine sediment is more likely to reveal neoplastic cells than with renal tumors.[160,164] A diagnosis of bladder neoplasia may be confirmed by cystoscopic examination and biopsy (Fig. 34-8).

Fig. 34-7 Sonogram of the left kidney area of a 19-year-old horse with chronic hematuria. A 26 × 20 × 19—cm echocavitated mass (renal carcinoma) originates from the left kidney.

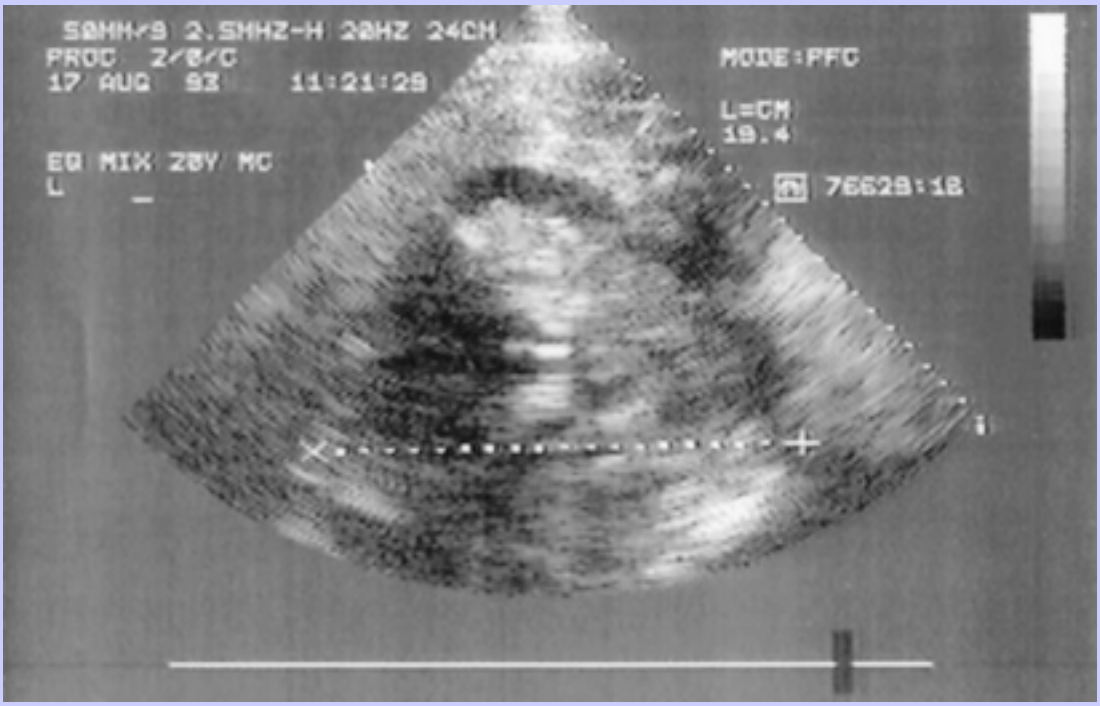
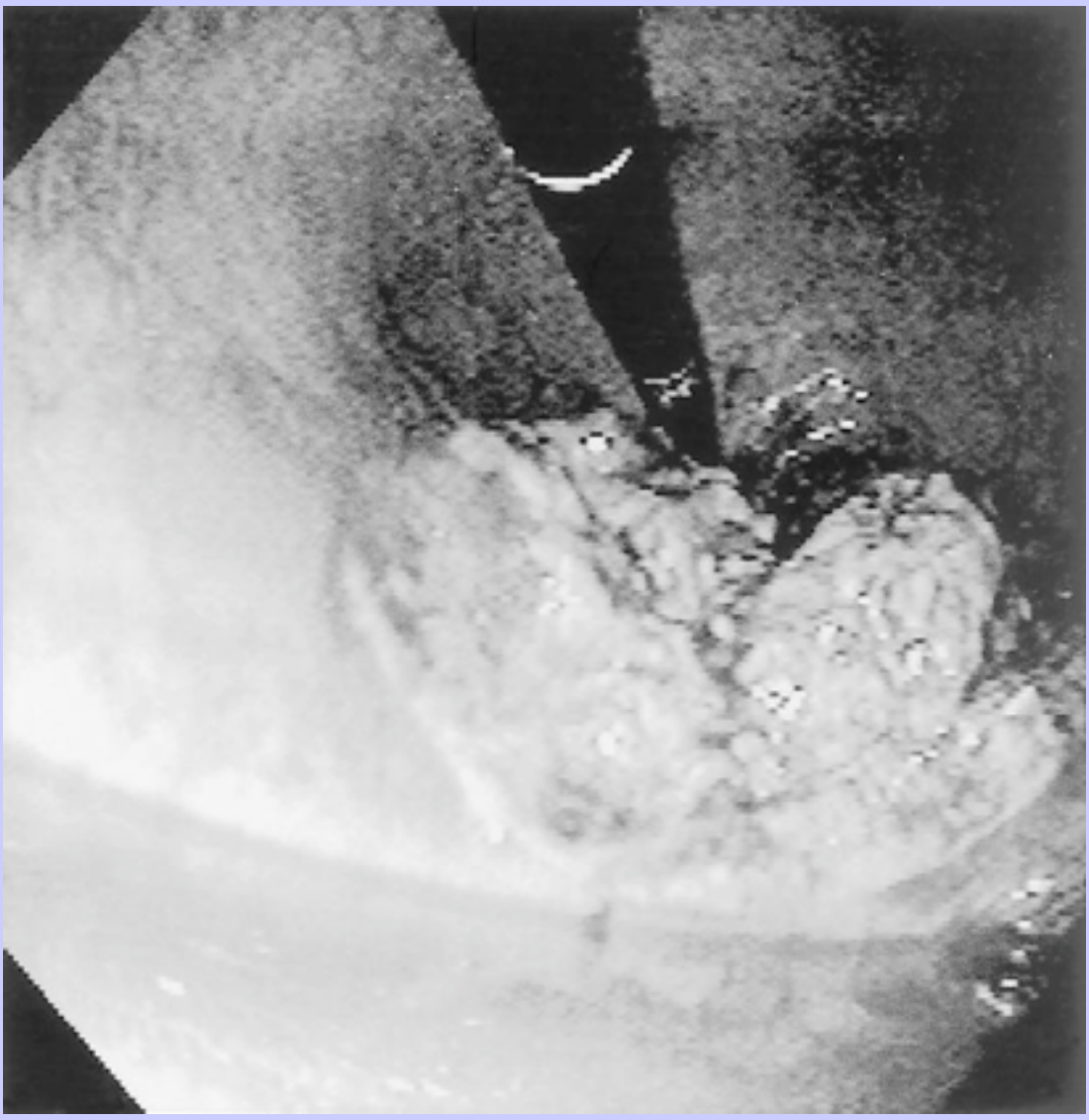


Fig. 34-8 Cystoscopic image of a squamous cell carcinoma of the bladder causing intermittent hematuria in a 14-year-old warmblood mare. The endoscope has been passed beyond the tumor and retroflexed to provide a view directed caudally; a pool of urine is in the foreground, and the tumor can be seen in the ventral aspect of the bladder neck.



In addition, tumors may metastasize, and the initial signs may be as varied as a lameness[165] or an ulcerated mass on the premaxilla.[166] Tumors can also metastasize to the lung.[167]

Multiple myeloma involving the kidney resulted in hypercalcemia and a high serum parathyroid hormone—related protein concentration.[168] Hypoglycemia was the chief clinical sign in a 6-year-old horse with renal cell carcinoma, which was producing insulin-like growth factors.[169]

34.12.11.2 Treatment

The treatment of choice for unilateral renal neoplasia is nephrectomy. Unfortunately, most cases of renal cell carcinoma have metastasized by the time the diagnosis is made, and surgical intervention is of little benefit to horses with disseminated disease. Thus, careful evaluation for metastatic disease should be pursued before contemplating a nephrectomy. Treatment of bladder tumors includes surgical excision and/or topical chemotherapy using either 5-fluorouracil or triethylenethiophosphoramide.[160]

34.12.12 UROLITHIASIS AND OBSTRUCTIVE DISEASE

THOMAS J. DIVERS

34.12.13 RENAL AND URETERAL CALCULI

Renal and ureteral calculi can produce partial or complete obstruction of one or both sides of the upper urinary tract. Nephroliths usually develop within or adjacent to the renal pelvis, and obstruction can lead to hydronephrosis. Most ureteroliths likely originate as nephroliths that pass into the ureter, where they become lodged and enlarge over time. Ureteral stones have a propensity to lodge in the distal ureter and can sometimes be palpated rectally dorsal and lateral to the bladder neck. Occasionally, small nephroliths may pass all the way down the ureter into the bladder; unlike their human counterparts, affected equine patients are rarely recognized to manifest renal colic.[170,171] Renal and ureteral calculi are most often composed of calcium carbonate crystals; calcium phosphate stones may occasionally develop. Although usually not recognized clinically, a nidus of damaged tissue (e.g., interstitial inflammation, infection, or fibrosis; area of medullary crest necrosis adjacent to renal pelvis) is likely necessary for initiation of stone formation. Anomalies of development (e.g., renal hypoplasia, dysplasia, polycystic disease) or prior exposure to nephrotoxins could also provide a nidus for stone formation.

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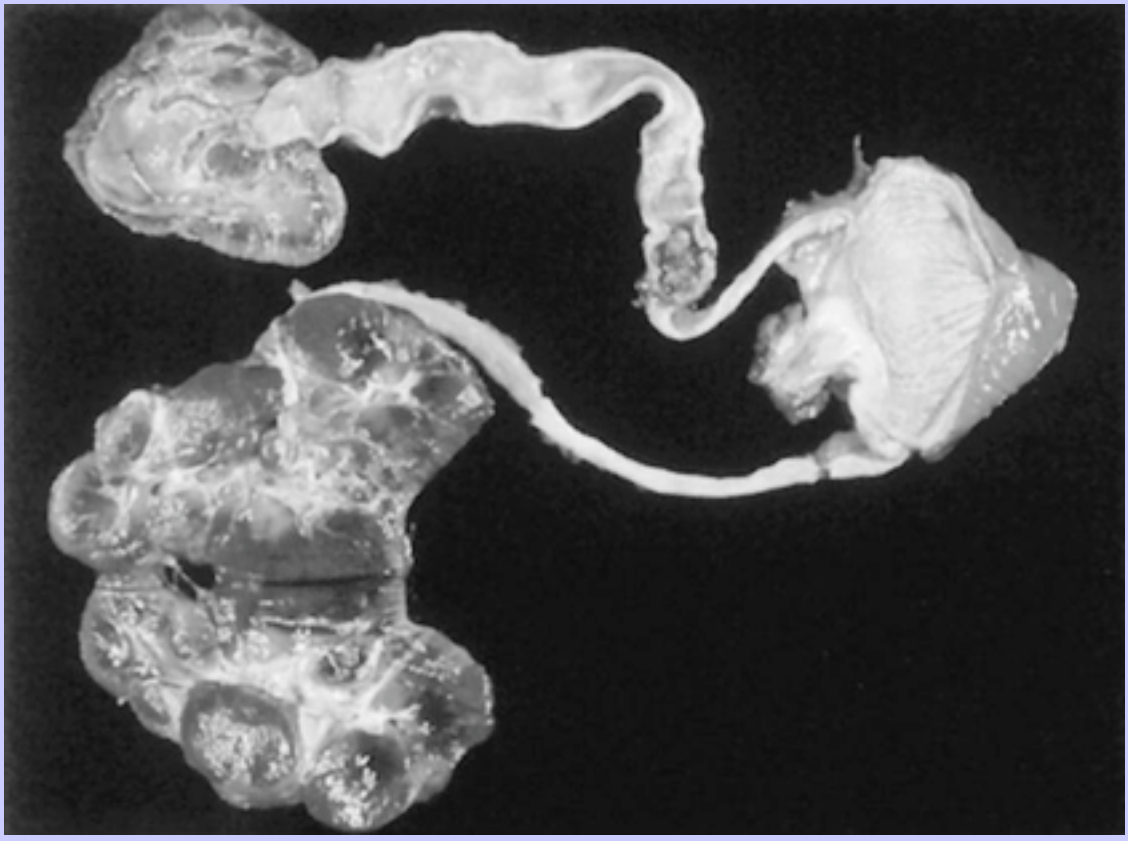
Bilateral nephrolithiasis and ureterolithiasis has been best described in a series of young adult racehorses, and development of subclinical medullary crest necrosis as a result of NSAID use was a suggested risk factor[172]; this was also seen in a 2-year-old gelding.[173] When both sides of the upper tract are affected, the condition typically progresses to CRF before horses are presented for evaluation (Fig. 34-9). As described for CRF, the most common presenting complaint is weight loss, but polyuria and poor performance may be earlier complaints in competitive horses. Establishing a diagnosis of urolithiasis causing unilateral upper tract obstruction is more challenging because clinical signs are mild (recurrent colic) or nonexistent and azotemia is usually absent. In fact, unilateral upper tract stones may be detected as incidental necropsy findings in horses of all ages. In horses with clinical signs, careful rectal palpation may reveal a turgid ureter and presence of a ureterolith. When passed from the upper tract into the bladder, small uroliths may be voided without problem or may cause urethral obstruction in males. Horses with repeated bouts of urethral obstruction should be thoroughly evaluated for presence of upper tract disease.

In horses with bilateral disease leading to CRF, azotemia and isosthenuria are present. As already mentioned, azotemia is usually absent with unilateral obstruction. With either scenario, gross hematuria is uncommon unless stones have been passed into the bladder or urethra, but urinalysis usually reveals pigmenturia, and microscopic hematuria is confirmed by examination of urine sediment. Although UTI usually is not present with upper tract obstruction consequent to lithiasis at the initial evaluation, it may develop with catheterization or other instrumentation used for relief of the obstruction. Thus a quantitative urine culture should be considered part of the minimum database, especially if pyuria or bacteriuria is detected on sediment examination. Transabdominal ultrasonography is a valuable tool for detection of nephroliths, dilation of the renal pelvis (or complete hydronephrosis), and fibrosis (increased echogenicity) within the kidney.[174–176] However, small nephroliths (<1 cm in diameter) occasionally can be missed despite a complete ultrasonographic examination. Transrectal ultrasonography is also useful for detection of ureteral dilation and lithiasis.

Fig. 34-9 Urinary tract removed from a 5-year-old standardbred with chronic renal failure caused by intermittent or persistent obstruction by renal and ureteral stones. Note the location of the ureteral obstruction near the bladder. This is the most common site for the obstruction to occur.



If upper urinary tract obstruction is diagnosed before development of more severe azotemia (creatinine >5.0 mg/dL), surgical removal is recommended. A nephrotomy and/or ureterotomy may be required.[170,172] When equipment is available, electrohydraulic lithotripsy is the preferred technique for removal of ureteral stones.[177] This procedure involves passing an endoscope into the ureter until the stone can be seen, then advancing a lithotriptor through the biopsy channel of the endoscope until the end touches the ureterolith (Fig. 34-10, *A*). An irrigating solution is pumped through the endoscope to distend the distal ureter, and an electrical impulse delivered by the lithotriptor causes a shock wave at the surface of the stone. Because the majority of calcium carbonate stones are inherently fragile,[178] fragmentation by lithotripsy is usually rapid (Fig. 34-10, *B*), and remaining fragments are flushed distally by further infusion of irrigating solution (Fig. 34-10, *C*). Before surgical intervention is pursued, both kidneys should be thoroughly evaluated for evidence of other stones because upper tract lithiasis is often bilateral.

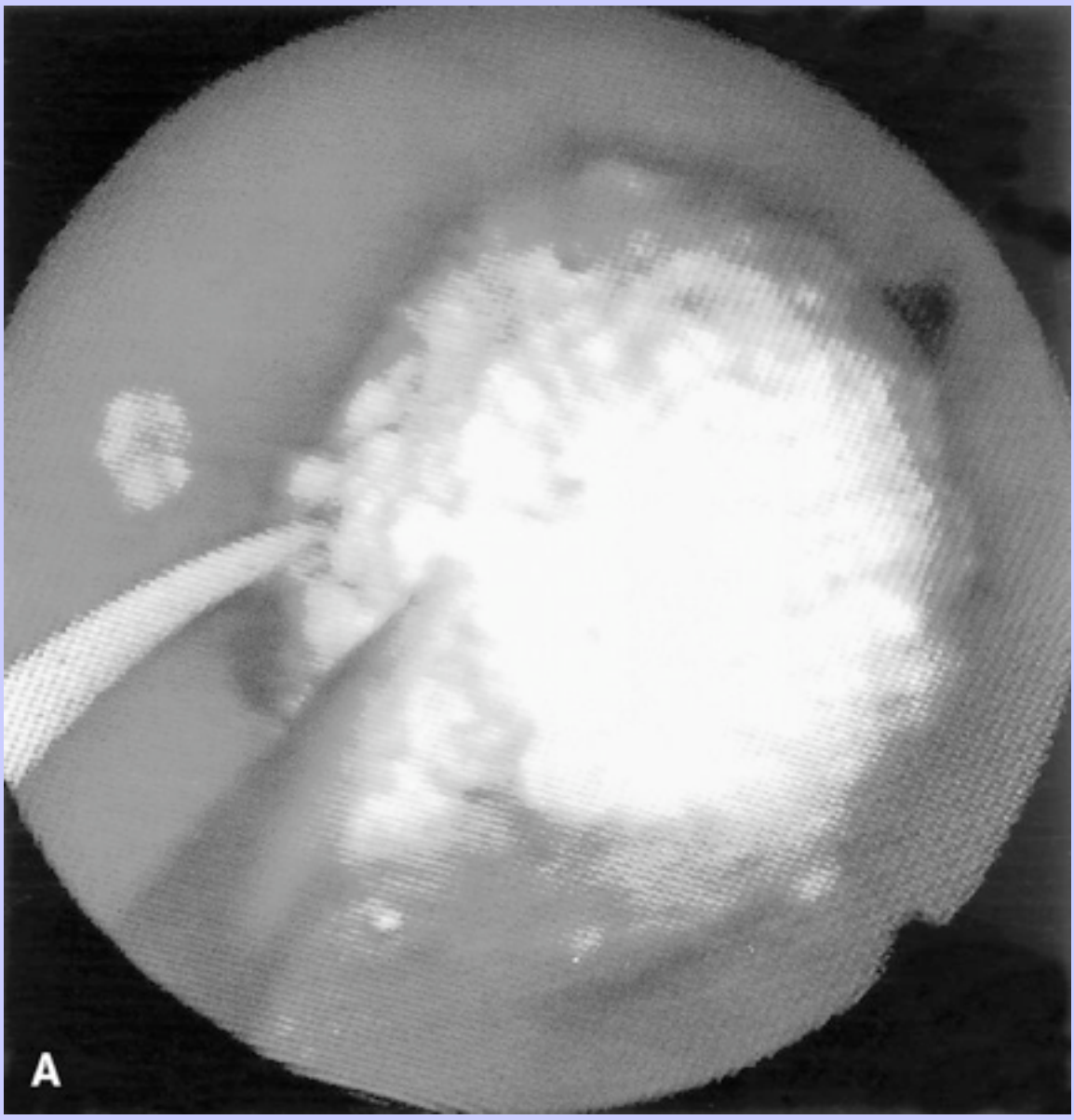
In addition to intermittent signs of mild colic, unilateral nephroliths may occasionally cause intermittent or persistent gross hematuria. In the absence of azotemia and evidence of disease of the contralateral kidney, unilateral nephrectomy is the treatment of choice for obstructing nephroliths and remains a reasonable alternative to lithotripsy for treatment of unilateral ureteroliths[179] (Figs. 34-11 and 34-12).

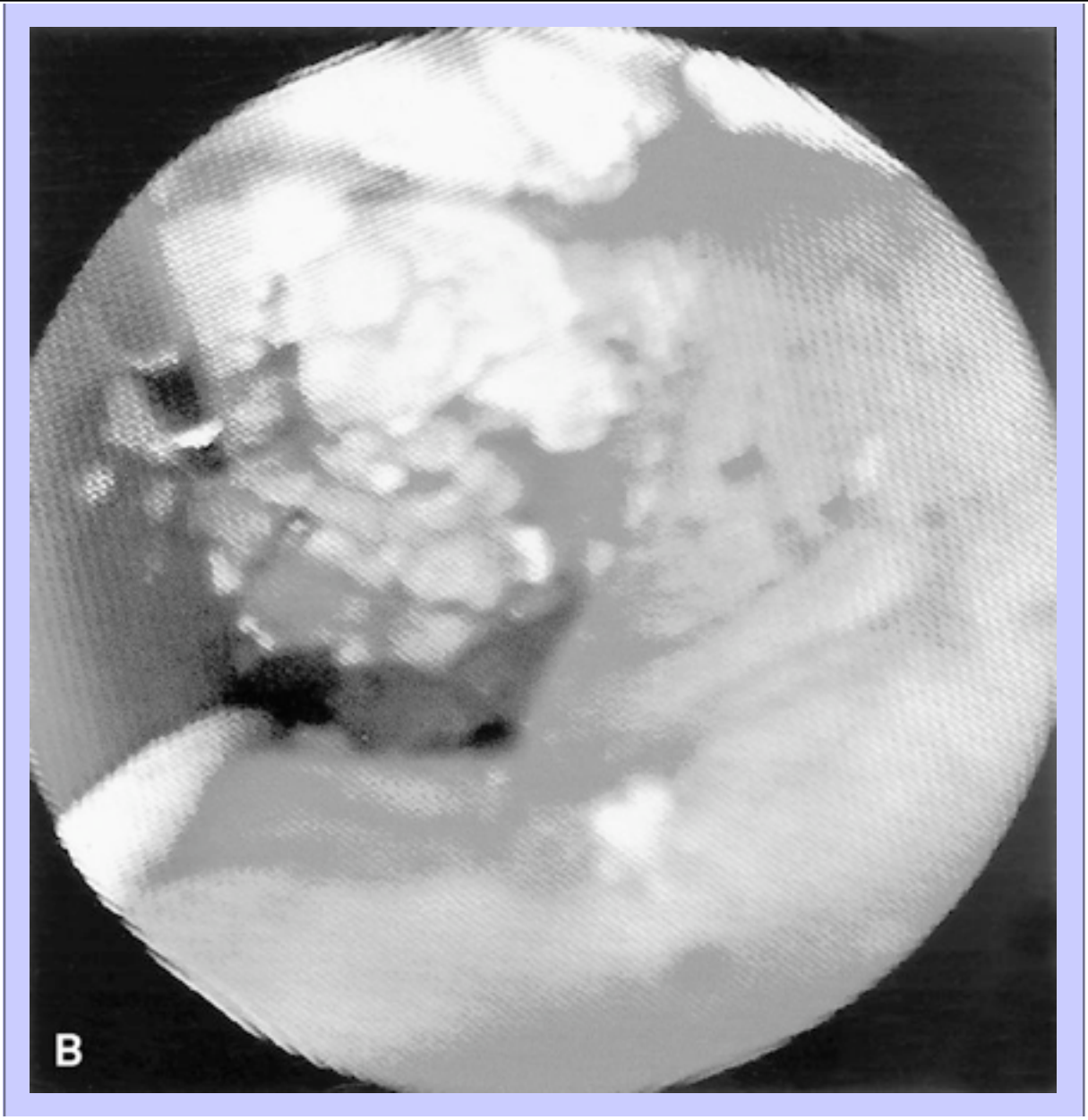
34.13 CYSTIC CALCULI

Although occurrence is rare compared with other species, cystolithiasis is the most common form of urolithiasis in horses, and intact males appear to be at greater risk.[171,180] Calculi that develop in the bladder are usually single, large spiculated stones composed of calcium carbonate crystals.[178,180,181] Less often, stones are a mix of calcium carbonate and calcium phosphate crystals; these stones often have a smooth surface and are more resistant to fragmentation.[182] Risk factors for development of bladder stones in horses are not well understood, but anatomic defects (e.g., diverticuli) or suture material persisting from prior bladder surgery may predispose horses to cystic calculi. Although bacteria can often be detected by culture of the center of equine calculi, their role in stone formation is unclear.[171] Considering that normal equine urine is rich in calcium carbonate crystals, it is surprising that cystoliths are not more common in horses than in ruminants or small animals. Their low occurrence can likely be attributed to the large amount of mucus that is also present in horse urine. Mucus, produced by glands in the renal pelvis and proximal ureter, appears to act as a lubricant to prevent adherence of crystals to uroepithelium.

The most common clinical sign exhibited by horses with cystic calculi is hematuria after exercise. Pollakiuria, stranguria, or incontinence may also be observed. Less frequently, dysuria may be caused by accumulation of urine sediment in the ventral aspect of the bladder. This condition, sabulous urolithiasis, usually develops as a result of bladder paralysis.[183] Urinary incontinence is usually present in horses with sabulous urolithiasis, and prognosis is guarded to poor because of underlying detrusor dysfunction.

Fig. 34-10 Endoscopic images of a ureterolith completely obstructing the left ureter. **A**, Immediately before electrohydraulic lithotripsy. **B**, After partial fragmentation. **C**, After complete removal. White instrument is a ureteral stent placed to facilitate passage of the ureteroscope, and gray instrument (in **A** and **B**) is the lithotriptor touching the surface of the ureterolith.

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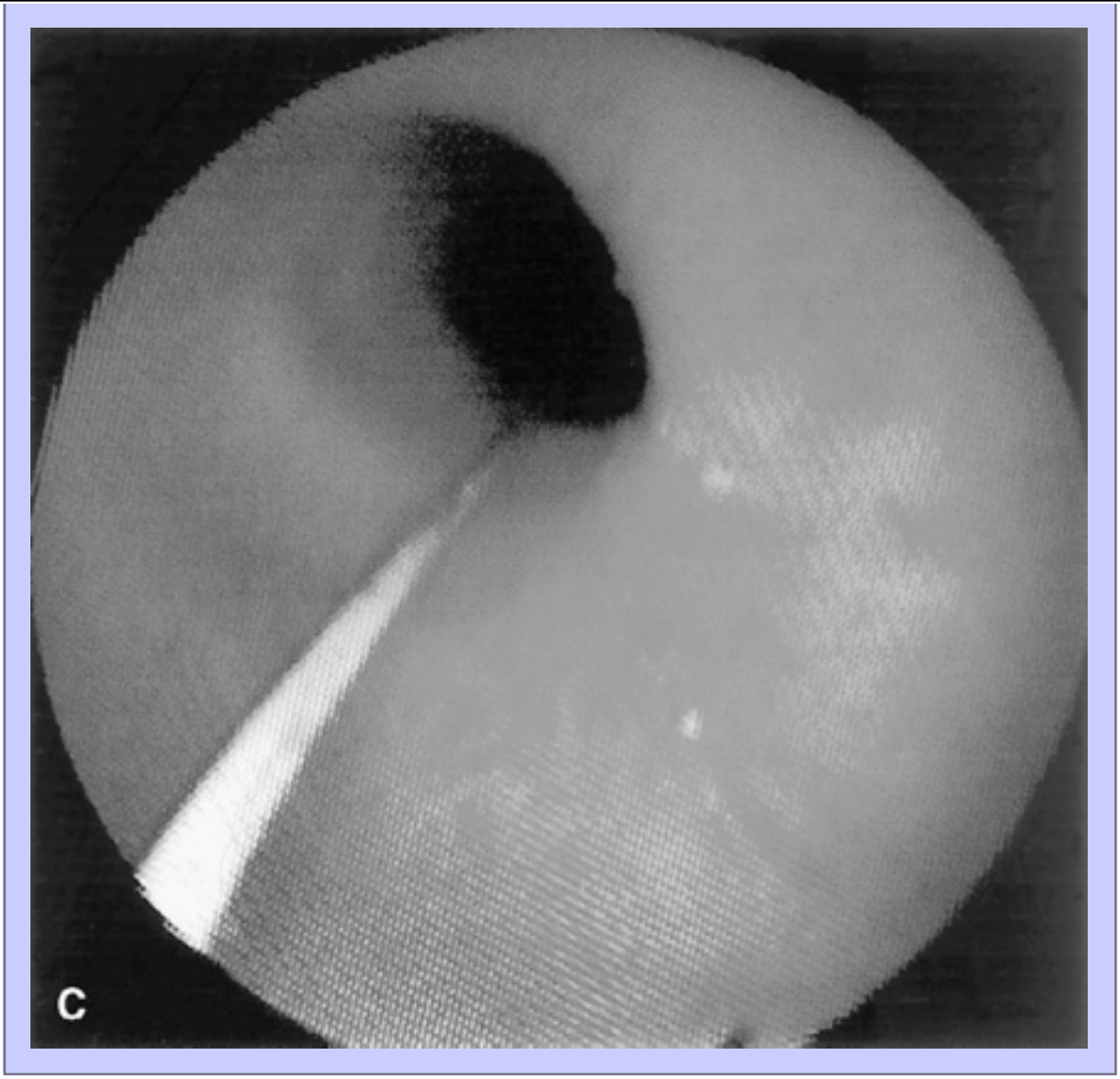
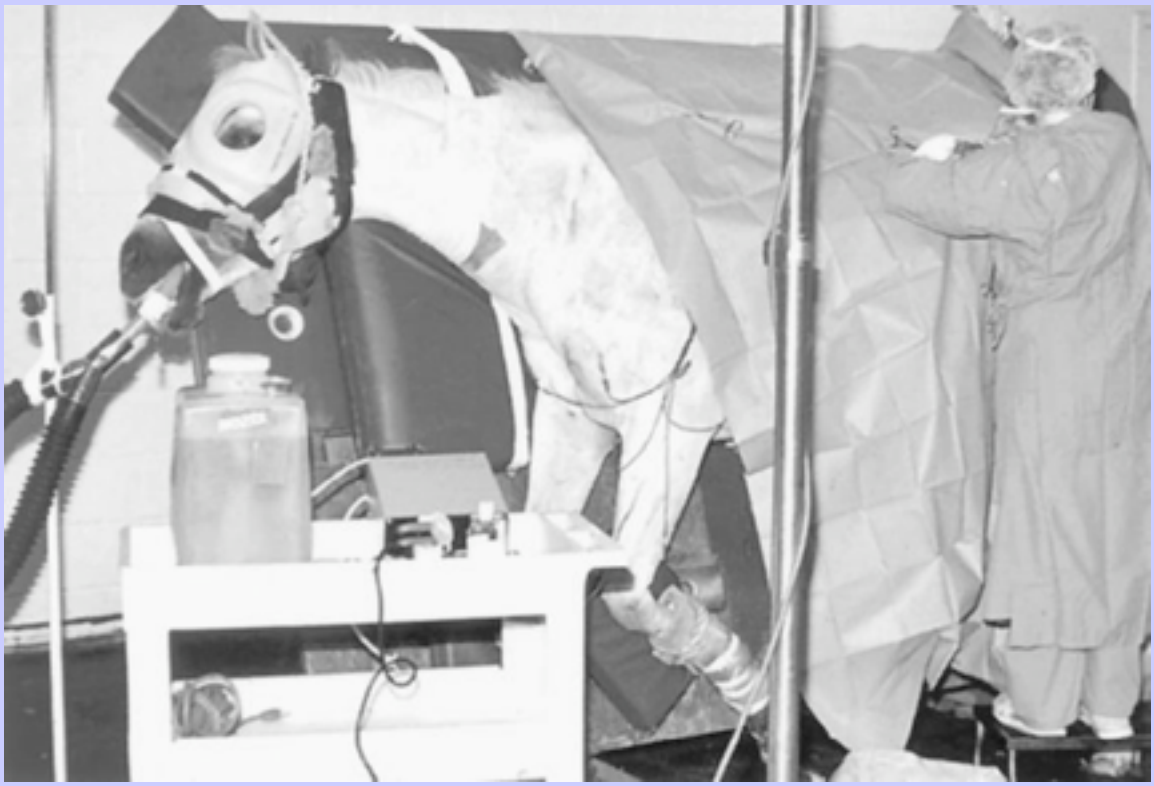


Presence of a cystolith can be confirmed by rectal examination. It is important to remember that most bladder stones can be palpated with only the hand and wrist in the rectum. As a result of frequent urination, the bladder is usually small, and cystic calculi can be missed if the examiner passes quickly beyond the calculus during the rectal examination. Careful palpation may also allow discrimination between soft-tissue masses of the bladder (neoplasia) and sabulous urolithiasis. With the latter, firm sediment is usually palpated well over the pelvic brim in the ventral aspect of a distended bladder. Manipulation of the bladder is accompanied by incontinence, and sabulous uroliths may be indentable when palpated after the bladder has been emptied via catheterization. Although rarely needed to confirm the diagnosis, ultrasonographic examination of the entire urinary tract should be considered because calculi may be present in multiple locations. Because UTI can sometimes accompany cystolithiasis, urinalysis and a quantitative urine culture are warranted during the initial evaluation of all horses with bladder stones.

Fig. 34-11 Left kidney of a 12-year-old thoroughbred that presented with a complaint of intermittent hematuria. Right kidney appeared normal on ultrasound examination, and renal function was normal.

Fig. 34-12 Left kidney shown in Fig. 34-11 was removed with the horse anesthetized but strapped to the surgery table in an upright position. This is the preferred surgical position for nephrectomy or nephrotomy in adult horses.



Treatment of cystic calculi usually consists of surgical removal accompanied by a 7- to 10-day course of postoperative antibiotic treatment. Cystotomy can be performed via celiotomy or a pararectal approach (Gäkel's operation) or the stone can be removed after fragmentation with a lithotriptor passed via a perineal urethrotomy.[182,184,185] In mares, urethral sphincterotomy after epidural anesthesia with xylazine has been advocated as a practical method for stone removal. However, with sedation and epidural anesthesia, manual distention of the urethra often allows several fingers or a small hand to be passed into a mare's bladder, and depending on size, the stone can be retrieved intact or after fragmentation. Placing the cystolith into a sterile rectal sleeve or surrounding it with a similar smooth plastic material allows easier removal of spiculated stones and fragments. If available, electrohydraulic or pulsed-dye-laser lithotripsy may be the least traumatic method of fragmentation and removal of bladder stones in both genders; however, success may be limited by the ability to lavage all stone fragments from the bladder.[186–190]

Historically, risk of recurrence after surgery has been considered low; however, in a series of 68 cases of urolithiasis (at all levels of urinary tract), 12/29 horses (41%) with follow-up had recurrence 1 to 32 months after surgery. Recurrence was more common with perineal urethrotomy than cystotomy and was attributed to the former's inability to remove all fragments completely by lavage.[171] This relatively high recurrence rate indicates

that postoperative management changes are warranted to decrease risk of future stone formation. Changing from a legume to a grass hay is the most practical recommendation to decrease urinary calcium excretion. Urinary acidification with ammonium chloride (50 to 200 mg/kg/day PO) or ammonium sulfate (200 to 300 mg/kg/day PO) has also been recommended to decrease the amount of urine crystals in equine urine.[190,191] Unfortunately, these ammonium salts are rather unpalatable and should be administered as two or three doses daily for effective urinary acidification. Further, the actual benefit of urinary acidification in horses has never been established, and recurrence may be more likely related to inadequate mucus secretion or persistence of damaged uroepithelium in the upper or lower tract. A more practical recommendation may be to administer 2 to 4 oz of salt in the feed daily to increase water consumption and urine flow. The increase in urine flow is accompanied by a decrease in urine pH to near-neutral values.

34.14 URETHRAL OBSTRUCTION

Calculi, neoplasms, congenital anomalies, and preputial edema and inflammation may all produce partial or complete obstruction of the urethra. Urethral calculi are most often calcium carbonate stones that lodge in the pelvic urethra in stallions or geldings,[192] and the most common neoplasm causing urethral obstruction is squamous cell carcinoma of the penis.[193] Preputial edema and inflammation may develop as a consequence of trauma or parasitism (habronemiasis). In addition, overweight horses may develop recurrent preputial inflammation and infection associated with fat deposition in the sheath. Horses with the latter condition may fail to drop the penis during urination, and urine scalding within the sheath is likely a contributing factor to recurrent inflammation.

Complete urethral obstruction usually causes moderate to severe signs of colic, and an enlarged, turgid bladder is detected on rectal palpation. Careful palpation of the urethra below the anus may reveal the location of an obstructing urolith or frequent contraction of the urethralis muscle. Rarely, postrenal ARF may develop, or the bladder may rupture. Partial urethral obstruction is usually accompanied by dysuria, incontinence, and urine scalding of the hindlimbs. A diagnosis of urethral obstruction is based on clinical signs, rectal examination findings, external examination of the penis and prepuce, and passage of a catheter or endoscope through the urethra to the bladder.

Treatment of urethral obstruction usually involves surgery. Urethral calculi can be removed either by a subischial urethrotomy over the site of obstruction or by hydropulsion through the urethrotomy incision. Excessive tissue trauma should be avoided because it may increase the risk of urethral stricture and recurrent urolithiasis. Laboratory assessment of fluid and electrolyte status is important for correction of dehydration, azotemia, and electrolyte alterations that may develop with sweating (caused by pain), bladder rupture, or anuria. With squamous cell carcinoma, aggressive surgical resection of involved tissues is warranted with larger lesions, whereas smaller lesions may be amenable to treatment with 5-fluorouracil ointment. However, because recurrence rate of squamous cell carcinoma of the penis and prepuce is 20% or greater,[193] surgical removal should be initially considered in all affected horses. Detrusor function may be decreased if bladder distention had been ongoing for several days, and an indwelling bladder catheter (closed system) or treatment with bethanechol (0.25 to 0.75 mg/kg SC or PO every 8 to 12 hours) may help with recovery of detrusor function.

34.15 IDIOPATHIC RENAL HEMATURIA

HAROLD C. SCHOTT II

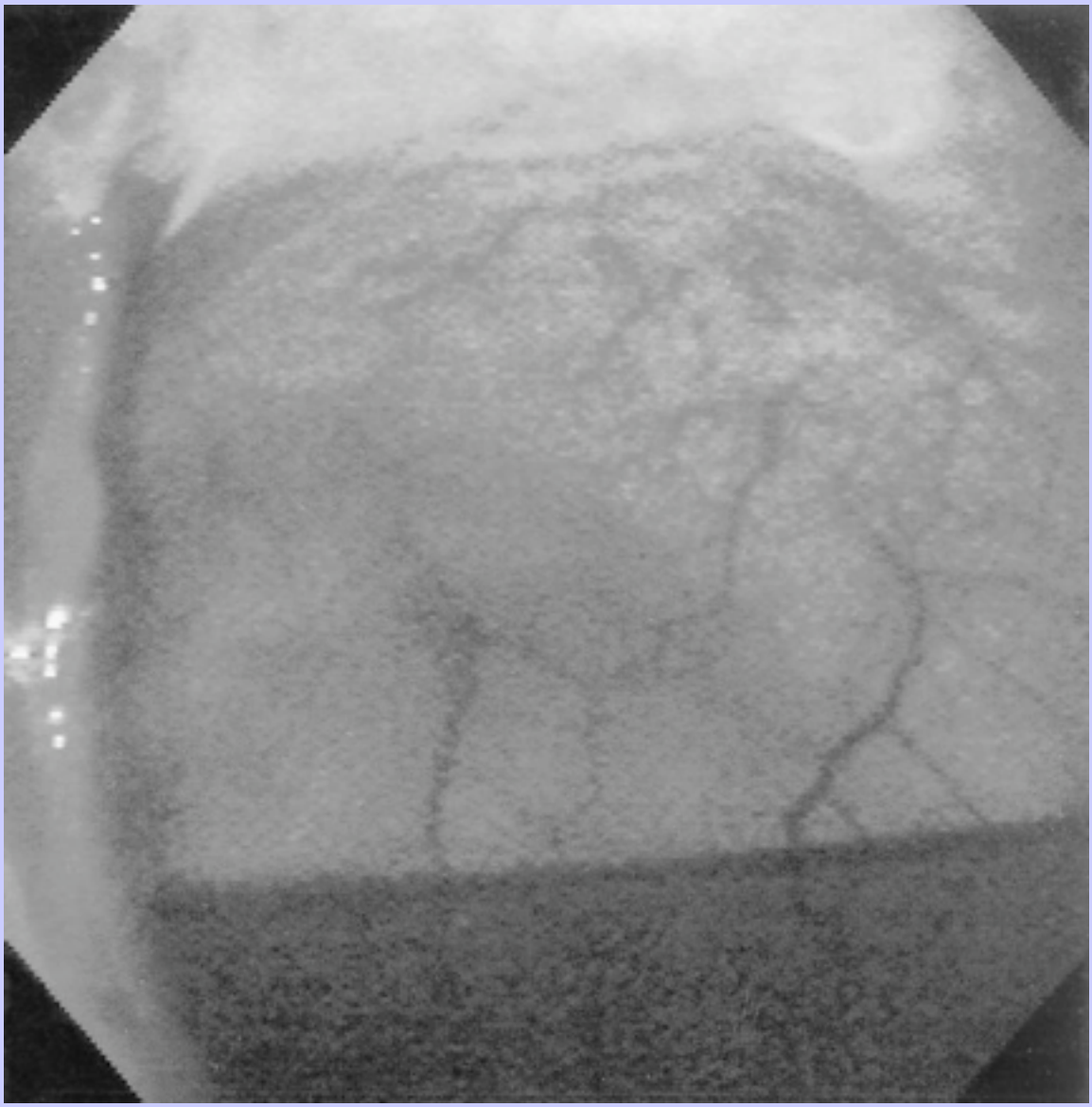
Idiopathic renal hematuria (IRH) is syndrome characterized by sudden onset of gross, often life-threatening hematuria.[194] Hemorrhage arises from one or both kidneys and is manifested by passage of large blood clots in

urine. Endoscopic examination of the urethra and bladder usually reveals no abnormalities of these structures, but blood clots may be seen exiting one or both ureteral orifices. Although a definitive cause of renal hemorrhage may be established in some horses (e.g., renal adenocarcinoma, arteriovenous or arterioureteral fistula),[195,196] the disorder is termed *idiopathic* when a primary disease process cannot be found. Both genders, a wide age range, and several breeds of horses (including a mammoth donkey and a mule) have been affected. However, more than 50% of animals with IRH have been Arabians.

Use of the term *idiopathic renal hematuria* to describe this syndrome of horses was adopted from its use in human patients and dogs with severe renal hemorrhage.[197–201] *Benign essential hematuria* and *benign primary hematuria* are other terms that have been used to describe less severe hematuria that is not associated with trauma or other obvious causes of hematuria. In humans and dogs, hematuria is more often a unilateral than a bilateral problem, similar to what has been observed in the few affected horses. The pathophysiology remains poorly understood, but macroscopic hematuria has been associated with immune-mediated glomerular damage (e.g., acute postinfectious glomerulonephritis, membranoproliferative glomerulonephritis, IgA nephropathy or Berger's disease), thin basement membrane nephropathy, and the loin pain—hematuria syndrome in human patients.

Although hematuria and pigmenturia can accompany several systemic diseases in horses,[202–205] patients affected with IRH appear to have spontaneous, severe hematuria in the absence of other signs of disease. Although one report suggested that severe renal hemorrhage was caused by pyelonephritis,[206] supportive data were lacking. In cases that I managed, neither UTI nor lithiasis has been detected, and the magnitude of hematuria often resulted in the need for repeated blood transfusions. As with hemorrhage associated with guttural pouch mycosis, the syndrome may produce episodic hemorrhage. Initially, hemorrhage is noted by finding a large amount of clotted blood in stall bedding or in the pasture. However, other client complaints (e.g., depression, anorexia, weight loss) are typically absent. Examination may reveal dried blood at the end of the penis or in the sheath of males or on the vulvar lips and between the hindlimbs of mares. In both genders, neoplasia of the external genitalia or urinary tract is an important differential diagnosis, and in mares, varicosities in the area of the vestibulovaginal sphincter also must be considered, especially in multiparous mares. When blood is not detected in the sheath or vulvar areas, further evaluation may be unrewarding because the renal bleeding may cease spontaneously. Bleeding has anecdotally been attributed to cystitis and pyelonephritis, in the absence of positive urine culture results, because hemorrhage stops during a course of antimicrobial therapy. More likely, spontaneous resolution has occurred. Further, the magnitude of hematuria is considerably greater with IRH than with most UTIs; pyuria is absent; and urine culture results are negative. In my experience, one or two initial episodes of hemorrhage are followed by a more severe hemorrhagic crisis within months to 2 years after observation of the initial bleeding episode. Of interest, renal colic has been notably absent in the history of affected horses.

Fig. 34-13 Cystoscopic image of a 19-year-old Arabian mare with idiopathic renal hematuria. A large blood clot can be seen exiting the left ureter, whereas the right ureteral opening appears normal.



34.15.1 Diagnosis

A diagnosis of IRH is made by exclusion of systemic disease, other causes of hematuria, and alterations in hemostasis. Physical examination may reveal tachycardia, tachypnea, and pale membranes consistent with acute blood loss. Rectal palpation may reveal an enlarged, irregular bladder resulting from the presence of blood clots. Azotemia is uncommon. Endoscopic examination is important to document that hematuria is originating from

the upper urinary tract and to determine whether hemorrhage is unilateral or bilateral (Fig. 34-13). Repeated examinations may be required to answer the latter question. Ultrasonographic imaging is necessary to rule out nephrolithiasis or ureterolithiasis and may occasionally reveal a distended vascular space or renal vascular anomaly as the cause of hematuria. Renal scintigraphy can be a useful technique in affected horses, providing semiquantitative information about renal function when a nephrectomy is being considered. Renal biopsy and IF staining may assist in documenting immune-mediated glomerular injury, but the significance of such results is not well understood at this time.

34.15.2 Treatment

Treatment for IRH consists of supportive care for acute blood loss, including blood transfusions. Medications intended to promote hemostasis (e.g., α-aminocaproic acid, formalin) have also been administered, but their efficacy has not been validated. Because the condition may be self-limiting in some patients, supportive care is warranted. With severe and recurrent hematuria of unilateral renal origin, a nephrectomy may be indicated, but owners should be warned that there is a risk of hematuria developing in the contralateral kidney. In my experience, risk of contralateral renal bleeding appears to be greater in the Arabian breed.

34.16 URETHRAL HEMORRHAGE

HAROLD C. SCHOTT II

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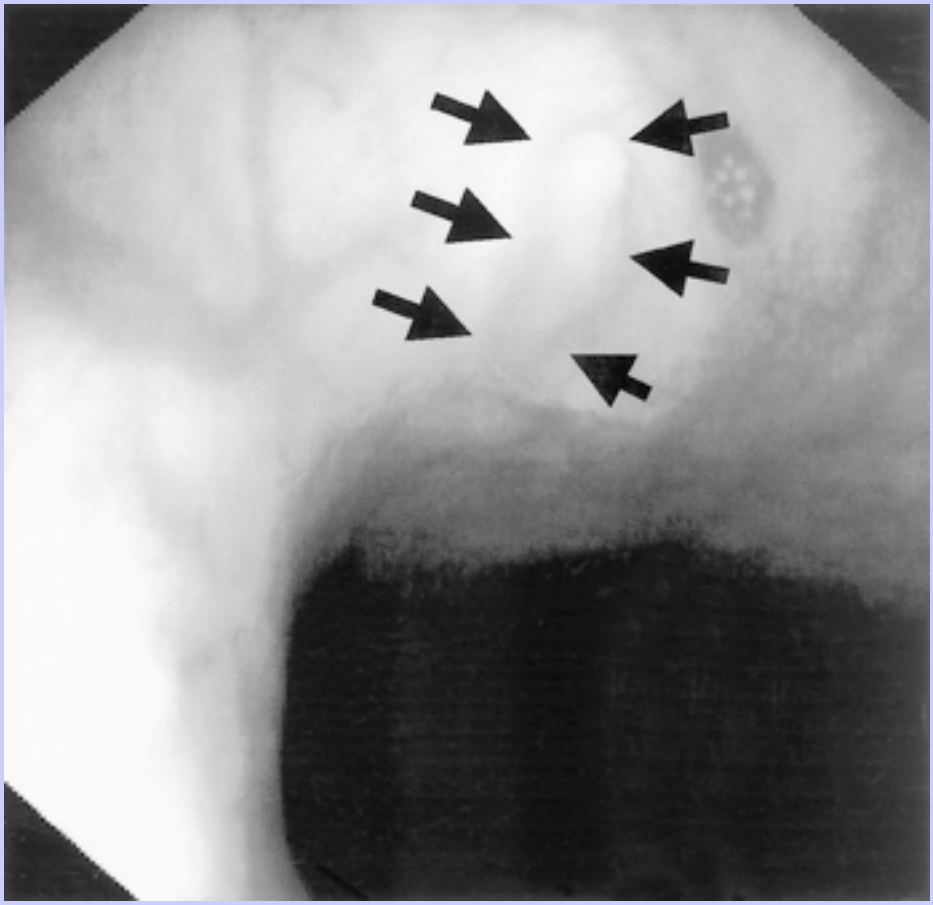
Although a recognized cause of hemospermia in stallions, defects or tears of the proximal urethra at the level of the ischial arch are a more recently described cause of hematuria in geldings.[207–209] Urethral defects typically result in hematuria at the end of urination, in association with urethral contraction. Affected horses generally void a normal volume of urine that is not discolored. At the end of urination, a series of urethral contractions results in squirts of bright-red blood. Occasionally, a smaller amount of darker blood may be passed at the start of urination. In most cases the condition does not appear painful or result in pollakiuria. Interestingly, the majority of affected stallions with hemospermia and geldings with hematuria have been quarter horses or quarter horse cross-breeds that have been free of other complaints.[210,211] Treatment with antibiotics for a suspected cystitis or urethritis has routinely been unsuccessful, although hematuria appears to resolve spontaneously in about 50% affected horses. Because the defects are difficult to detect without use of high-resolution videoendoscopic equipment, previous reports of urethral bleeding have been attributed to urethritis or hemorrhage from “varicosities” of the urethral vasculature. However, vasculature underlying the urethral mucosa becomes quite prominent when the urethra is distended with air during endoscopic examination, especially in the proximal urethra (to the point that blood can be seen flowing in the submucosal vasculature). Thus it would be logical to suspect that hemorrhage could arise from an apparent urethritis or urethral varicosity, although these problems are poorly documented in horses.

Examination of affected horses is often unremarkable, and laboratory analysis of blood reveals normal renal function, although mild anemia can be an occasional finding. Urine samples collected midstream or by bladder catheterization appear grossly normal. Urinalysis may have normal results, or an increased number of red blood cells (RBCs) may be found on sediment examination, a finding that would also result in a positive reagent strip result for blood. Bacterial culture of urine yields negative results. The diagnosis is made with endoscopic examination of the urethra, during which a lesion is typically seen along the dorsocaudal aspect of the urethra at the level of the ischial arch. External palpation of the urethra in this area is usually unremarkable but can assist in localizing the lesion because external digital palpation can be seen through the endoscope. With hematuria of several weeks' duration, there is little evidence of inflammation; rather, the lesion appears as a fistula communicating with the vasculature of the corpus spongiosum penis (Fig. 34-14).

Although the pathophysiology of this condition remains unclear, it has been speculated that the defect is the result of a "blowout" of the corpus spongiosum penis (cavernous vascular tissue surrounding the urethra) into the urethral lumen.[209] Contraction of the bulbospongiosus muscle during ejaculation causes a dramatic increase in pressure in the corpus spongiosum penis, which is essentially a closed vascular space during ejaculation. The bulbospongiosus muscle also undergoes a series of contractions to empty the urethra of urine at the end of urination; thus the defect into the urethra may develop by a similar mechanism in geldings. Once the lesion has been created, it is maintained by bleeding at the end of each urination, and the surrounding mucosa heals by formation of a fistula into the vascular tissue. An explanation for the consistent location along the dorsocaudal aspect of the urethra at the level of the ischial arch has not been documented but may be related to the anatomy of the musculature supporting the base of the penis and an enlargement of the corpus spongiosum penis in this area. Further, a narrowing of the lumen at the distal extent of the ampullar portion of the urethra may also contribute to the location of the defects. An anatomic predisposition in quarter horses has not been documented but could be speculated based on an apparent increased risk in this breed.

Fig. 34-14 Endoscopic image of the proximal urethra of a gelding with hematuria at the end of urination. A urethral defect can be seen *between the arrows* along the caudal aspect of the urethra as it passes dorsocranially over the pelvic brim.



Because hematuria may resolve spontaneously, no treatment may be initially required. If hematuria persists for more than a month or if significant anemia develops, a temporary subischial "incomplete" urethrotomy has been successful in some affected geldings. After sedation and epidural or local anesthesia, a catheter is placed in the urethra and a vertical incision made into the corpus spongiosum penis but not into the urethral lumen. The surgical wound requires several weeks to heal, and moderate hemorrhage from the corpus spongiosum penis is apparent for the first few days after surgery. Hematuria should resolve within a week after this procedure. Additional treatment consists of local wound care and prophylactic antibiotic treatment (typically a trimethoprim-sulfonamide combination) for 7 to 10 days.

34.17 POLYURIA AND POLYDIPSIA

HAROLD C. SCHOTT II

Polyuria and polydipsia (PU/PD) are defined as urine output in excess of 50 mL/kg/day and fluid intake of more than 100 mL/kg/day.[212,213] These values equate to production of 25 L of urine and consumption of 50 L of water for a 500-kg horse. It is important to remember that urine production and water consumption vary with age, diet, workload, environmental temperature, and GI water absorption.[214,215] For example, urine production increases by 50% to 100% when the diet is changed from a grass to a legume hay.[216] Similarly, horses in heavy exercise, stabled in hot climates, or with chronic diarrhea may have a water intake in excess of 100 L/day yet produce normal volumes of urine. The major causes of PU/PD in horses include renal failure (discussed previously), pituitary adenoma (Cushing's disease), and primary or "psychogenic" polydipsia. Less common causes include excessive salt consumption, central and nephrogenic diabetes insipidus, diabetes mellitus, sepsis/endotoxemia, and iatrogenic causes (e.g., sedation with α_2-agonists, corticosteroid therapy, diuretic use).[213]

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34.18 POLYURIA/POLYDIPSIA WITH CUSHING'S DISEASE

Pituitary adenoma and the resulting syndrome of hyperadrenocorticism (Cushing's disease) is common in older horses.[217] Although the most consistent clinical sign is hirsutism, PU/PD may be reported in some horses. For example, in one review of 17 horses with Cushing's disease, PU/PD was found in 13 (76%).[218] However, in another series of 21 cases, PU/PD was not a historical complaint in any of the affected horses.[219] This discrepancy can be explained by the fact that PU/PD associated with Cushing's disease is generally of lesser volume than that observed with psychogenic polydipsia or diabetes insipidus.

Cushing's disease may lead to PU/PD by several mechanisms. First, polyuria may be the result of an osmotic diuresis. The renal threshold for glucose in horses (~150 to 175 mg/dL) appears to be lower than in small animals.[220] When plasma glucose concentration exceeds the renal threshold, the resultant glucosuria can lead to an osmotic diuresis. Although often implicated as the cause of PU/PD in horses with Cushing's disease, glucosuria was found in only one of five affected horses in one report.[219] Further, horses with hyperglycemia and glucosuria may still be able to concentrate their urine in response to water deprivation.[221] A second mechanism implicated in the development of polyuria is antagonism of the action of antidiuretic hormone (ADH) on the collecting ducts by cortisol. Although frequently cited as the mechanism of polyuria in canine hyperadrenocorticism, experimental evidence to support this mechanism is lacking in both dogs and horses. Further, there is considerable species heterogeneity in the effects of corticoids on ADH activity, and in some species a primary dipsogenic effect may be more important. Next, growth of the adenoma may lead to impingement on the posterior pituitary and hypothalamic nuclei (located immediately dorsal to pituitary gland), the sites of ADH storage and production, respectively.

Decreased ADH production and release would result in central diabetes insipidus as a third mechanism for polyuria.[217] Therefore, PU/PD seen in some, but not all, horses with pituitary adenomas is likely the combined result of several mechanisms.

34.19 PSYCHOGENIC POLYDIPSIA

Although rare, primary or "psychogenic" polydipsia is probably the most common cause of PU/PD in adult horses for which clients will have a primary complaint of excessive urination.[215,222] Horses with this problem are generally in good body condition and are not azotemic. Further, the magnitude of polyuria is typically dramatic, with owners reporting that horses drink two to three times more water than their stablemates, and stalls can be flooded with urine. In some horses, primary polydipsia appears to be a stable vice that reflects boredom, whereas in other cases it may develop after a change in environmental conditions, stabling, diet, or medication administration. Anecdotally, it has been reported to be more common in southern states during periods of high temperature and humidity.

The diagnosis of primary polydipsia is made by exclusion of renal failure and hyperadrenocorticism. In addition, other factors (e.g., salt supplementation, medication administration) must be excluded. Diabetes insipidus is excluded by demonstrating urinary concentrating ability after water deprivation.[223,224] Urine specific gravity should exceed 1.025 after water deprivation of sufficient duration (12 to 24 hours) to produce a 5% loss of body weight. In horses with long-standing polyuria, the osmotic gradient between the lumen of the collecting tubule and the medullary interstitium may be diminished (medullary washout). In these horses, ADH activity may not lead to an increase in urine specific gravity to values greater than 1.020. Consequently, in horses with primary polydipsia of several weeks' duration that fail to concentrate their urine after 24 hours of water deprivation, a modified water deprivation test may be tried. This is performed by restricting water intake to approximately 40 mL/kg/day for 3 to 4 days. By the end of this period, urine specific gravity should exceed 1.025 in a horse that has had medullary washout. If urine specific gravity remains in the isosthenuric range (1.008 to 1.014), the polyuric horse should be further evaluated for early CRF in which urine concentrating ability may be compromised before the onset of significant azotemia. In theory, this could occur when two thirds to three fourths of functional nephrons have been lost. Subtle signs of decreased performance and mild weight loss would also support early renal failure.

Management of horses with primary polydipsia is empirical. Because this is a diagnosis of exclusion, once it has been established that the horse does not have significant renal disease, it is safe to consider restricting water intake to meet maintenance, work, and environmental requirements of the horse. In addition, steps should be taken to improve the attitude of the horse by reducing boredom. Increasing the amount of exercise and turning the horse out to pasture are possible options, along with providing a companion or diversions in the stall. Also, increasing the frequency of feedings or the amount of roughage in the diet may increase the time spent eating and thereby reduce the habitual drinking.

In an occasional case of primary polydipsia, PU/PD may be attributed to excessive salt consumption and is manifested by an increased fractional sodium clearance.[214] Such "psychogenic salt eaters" appear to be less common than "psychogenic water drinkers" because the former would have to consume a substantial amount of salt to develop polyuria. In fact, salt intake may have to exceed 5% to 10% of dry matter intake before PU/PD becomes apparent.[225,226] Successful management consists of limiting water intake and preventing access to excess salt.

34.20 DIABETES INSIPIDUS

Diabetes insipidus (DI) may occur because of inadequate secretion of ADH (neurogenic DI) or decreased sensitivity of the epithelial cells of the collecting ducts to circulating ADH (nephrogenic DI).[212,213,227] With both forms of DI, dramatic PU/PD may be reported, and affected animals fail to concentrate urine in the face of water deprivation.

In human patients, neurogenic DI is the more common form of DI, with both hereditary and acquired forms described.[227] Two well-documented equine cases of neurogenic DI have been described.[228,229] Neither animal could concentrate urine in response to water deprivation, but administration of exogenous ADH resulted in an increase in urine specific gravity and decrease in urine volume. In a Welsh pony in which the condition was considered idiopathic, the absence of an increase in plasma ADH concentration after water deprivation further supported a diagnosis of neurogenic DI.[228] Acquired neurogenic DI secondary to encephalitis was confirmed histologically in the other horse.[229]

Nephrogenic DI is most often a familial disorder in humans, with an X-linked semirecessive mode of inheritance. [227] Therefore the disorder is carried by females and expressed in male offspring. Nephrogenic DI has been described in sibling thoroughbred colts, suggesting that an inherited form may also occur in horses.[230] These colts could not increase urine specific gravity in response to water deprivation, although they did show appropriate increases in plasma ADH concentration. A lack of response to exogenous ADH administration further confirmed resistance of the collecting ducts to ADH. Nephrogenic DI can also develop in association with drug therapy or a variety of metabolic, infectious, or mechanical (postobstruction) disorders. Anomalous or neoplastic disorders resulting in structural deformation of the kidneys are other potential causes of nephrogenic DI.[227]

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After determining that an equine patient with PU/PD is not azotemic, the initial diagnostic test to differentiate DI from primary polydipsia is a water deprivation test.[228,229] However, horses with suspected DI should be monitored closely during water deprivation because affected horses will continue to excrete excess water in the face of water deprivation. As a result, they may become substantially dehydrated (10% to 15%) within the first 12 hours of water deprivation. When a patient fails to concentrate urine during water deprivation, neurogenic DI can be differentiated from nephrogenic DI by measuring plasma ADH concentration or by administration of synthetic ADH (as illustrated by the cases previously described). Currently, equine ADH cannot be measured at commercial laboratories, but synthetic ADH (60 IU every 6 hours IM or SC) can be administered in combination with monitoring urine specific gravity.

Treatment of DI is directed at managing PU/PD. With neurogenic DI, hormone replacement therapy with desmopressin (dDAVP, a potent ADH analog administered as eyedrops) has been a successful treatment in small animal patients.[231] However, this treatment has not been described in horses and may be cost prohibitive. With nephrogenic DI, hormone replacement therapy is ineffective, and the only practical form of treatment for many years has been to restrict sodium and water intake and to administer thiazide diuretics. The latter treatment may reduce polyuria by 50% in human and canine patients.[227,232] Thiazide diuretics inhibit sodium reabsorption in the distal tubule (diluting segment of nephron) and increase solute delivery to the collecting duct, but the mechanism by which such therapy benefits patients with nephrogenic DI is not well understood. Administration of prostaglandin inhibitors or amiloride may also decrease polyuria in patients with nephrogenic DI. The former agents probably work by decreasing renal blood flow and GFR, whereas amiloride, a sodium channel blocker, is thought to act similar to the thiazide diuretics.[216] No reports have documented the use of these treatments in horses.

34.21 DIABETES MELLITUS

Diabetes mellitus (DM) is a state of chronic hyperglycemia usually accompanied by glucosuria. The resultant osmotic diuresis is an occasional cause of PU/PD in horses and was described to result in a water intake in excess of 80 L/day in one report.[233] Type 1, or insulin-dependent, DM results from of a lack of insulin, which in human patients is usually attributable to viral or autoimmune disease. Individuals with type 2, or non-insulin-dependent, DM have normal to high insulin concentrations, but their tissues are insulin insensitive. The most common cause of equine type 2 DM is Cushing's disease, in which elevated plasma cortisol concentration appears to antagonize the effects of insulin. Although uncommon, there are a few reports of both type 1 and type 2 DM that were not caused by a pituitary adenoma and that resulted in PU/PD as one of the presenting complaints.[233–235]

34.22 SEPSIS/ENDOTOXEMIA

Polyuria and polydipsia have been described in horses with sepsis or endotoxemia, although other clinical signs (e.g., fever, abdominal pain, weight loss) predominate.[236] The mechanism of PU/PD is unclear but may result from endotoxin-induced prostaglandin production. Prostaglandin E_2 (PGE_2) is a potent renal vasodilating agent that can antagonize the effects of ADH on the collecting ducts.[237] Some horses with chronic gram-negative bacterial infections (e.g., peritonitis, pleuritis) may have low-grade or intermittent endotoxemia as a mechanism for PU/PD, similar to the polyuria observed with canine pyometra.[238]

34.23 IATROGENIC POLYURIA

A final cause of PU/PD may be iatrogenic as a result of several treatments. The most obvious iatrogenic cause is fluid therapy, for which polyuria is a desired response. Polyuria has also been observed with exogenous corticosteroid administration, although the mechanism remains unclear. Humans and dogs appear to experience a potent thirst response to exogenous corticosteroids; thus, polydipsia may be an important cause of the polyuria observed. In horses receiving chronic dexamethasone treatment for immune-mediated disorders, profound glucosuria (2 to 3 g/dL) may be observed and could lead to an osmotic diuresis. Finally, a transient diuresis or polyuria accompanies sedation with the α_2-agonists xylazine and detomidine.[239] Although these agents also cause transient hyperglycemia and occasional glucosuria, a more likely mechanism for the polyuria is existence of α_2-adrenoreceptors on collecting-duct epithelial cells. Activation of these receptors is another mechanism by which the action of ADH can be antagonized.[240]

34.24 RENAL TUBULAR ACIDOSIS

MONICA ALEMAN

Renal tubular acidosis (RTA) is a syndrome characterized by abnormal renal tubular function, which results in a hyperchloremic metabolic acidosis.[241–243] Hyperchloremia develops as a result of enhanced renal conservation of chloride consequent to bicarbonate loss. RTA can be categorized as *primary* (genetic or idiopathic) or *secondary* when attributed to an underlying disease process or drug administration. Drug-induced RTA has been documented in human patients after administration of amphotericin B, trimethoprim-sulfamethoxazole, outdated tetracyclines, gentamicin, cephalosporins, carbonic anhydrase inhibitors, lithium carbonate, and other organic compounds.

Three types of RTA have been described: I (distal), II (proximal), and IV (hyperkalemic distal).[241–243] Types I and II have been reported in dogs, cats, and horses. Type I develops when distal tubular excretion of hydrogen ions (H^+) becomes compromised, and affected patients are unable to produce acidic urine. Type II results from decreased proximal tubular bicarbonate resorption and subsequent loss of bicarbonate in the urine. Because H^+ ions are normally excreted as bicarbonate is reabsorbed in proximal tubules, acidosis with both type I and type II RTA results from decreased H^+ excretion. Type II RTA often is a self-limiting problem but may be accompanied by more widespread proximal tubular dysfunction, leading to defective resorption of glucose, amino acids, phosphate, potassium, sodium, calcium, magnesium, uric acid, and other organic acids. The latter disorder is known as *Fanconi's syndrome;* as with RTA, it may be a primary (inherited) problem or can develop secondary to kidney, metabolic, and autoimmune diseases or drug administration.[241–243] Although there are no well-documented reports, Fanconi's syndrome likely develops in an occasional horse as a sequela to nephrotoxic or vasomotor ARF. To date, type IV, or hyperkalemic distal, RTA has only been described in human patients.[242]

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Renal tubular acidosis is a sporadically occurring metabolic disorder in horses.[244–247] There is no obvious breed or gender predilection, and to date, no evidence indicates that RTA is an inherited condition in horses. Typically, affected horses present with profound depression and anorexia and may have a history of poor performance, weight loss, and signs of abdominal pain. Vital parameters are generally within normal ranges, and horses do not appear clinically dehydrated. Hematologic and clinical chemistry findings are usually within reference ranges, with the exception of electrolyte concentrations and acid-base balance. A profound metabolic acidosis (plasma bicarbonate concentration <13 mEq/L and venous blood pH <7.25) and hyperchloremia (serum chloride concentration = 105 to 120 mEq/L) are characteristic for horses with RTA. A compensatory decrease in carbon dioxide partial pressure (P_{CO_2}) is also observed in most horses with RTA. Hypokalemia (and total body potassium depletion) may occur in horses with RTA because of the combined effects of anorexia and ongoing loss of potassium in urine, especially in patients with type II RTA, in which bicarbonaturia further increases urinary potassium excretion.

Mild to moderate azotemia may be detected in horses with RTA, especially when they are dehydrated at presentation. Affected horses may also have evidence of renal tubular damage detected on urinalysis (e.g., pigmenturia, glucosuria, abnormal sediment), and urine specific gravity may be low. Despite profound metabolic acidosis, urine pH is generally neutral to alkaline. If pursued, renal biopsy results generally support tubulointerstitial disease (CIN).

Differentiation of type I from type II RTA in human and canine patients is most easily accomplished by assessing urine pH; it remains neutral to alkaline with type I and should be neutral to acidic with type II.[241–243] Most horses with RTA have had neutral to alkaline urine; however, because herbivores normally have alkaline urine, this distinction may be less useful in horses with RTA. A few reports have described horses with acidic urine,[246,248,249] supporting type II RTA, but urine pH values near neutral are difficult to interpret. Assessment of all laboratory abnormalities (Table 34-1), along with additional testing (e.g., ammonium chloride challenge, urinary ammonium concentration) may allow further discrimination between type I and type II RTA.[249,250] However, this distinction may not be entirely necessary because the approach to treatment and the prognosis are similar for both types of RTA in horses.

Treatment of RTA consists primarily of IV and oral administration of sodium bicarbonate. Response to treatment appears to be largely dependent on the rate of $NaHCO_3$ administration. For initial correction of acidosis, IV $NaHCO_3$ must be administered aggressively, and large amounts (3000 to 9000 mEq) are often required to return plasma bicarbonate concentration to values above 20 mEq/L. Half the estimated bicarbonate deficit is generally

replaced with IV $NaHCO_3$ over 6 to 12 hours, and the remaining deficit is replaced with a combination of IV and oral $NaHCO_3$ (initial oral dose: 100 to 150 g twice daily; 1 g contains ~12 mEq $NaHCO_3$). Close monitoring of serum electrolyte concentrations and acid-base balance is required to adjust the rate of IV $NaHCO_3$ replacement. Marked improvement in attitude and appetite usually accompanies correction of the acidosis, but unfortunately, relapse after discontinuation of IV therapy can occur. Continued oral administration of $NaHCO_3$ (baking soda) for months to years may be required for maintenance of a normal acid-base status in individual horses.

Table 34-1 Classification of Type I and Type II Renal Tubular Acidosis

	Distal or Type I	Proximal or Type II
Acidosis	Severe	Self-limiting
Hypokalemia	Severe	Mild to moderate
Serum phosphate	Normal	Low
Urine pH	Neutral to alkaline	Neutral to acidic

Because potassium excretion is proportional to the bicarbonate delivery to the distal tubule, initial correction of acidosis with $NaHCO_3$ promotes kaliuresis and may exacerbate potassium depletion, especially when horses have been anorectic for several days. Therefore, concurrent supplementation with IV or oral potassium chloride is usually also necessary during initial correction of the acidosis. Complications associated with rapid correction of acidosis have not been described, but transient diarrhea may develop if large quantities of $NaHCO_3$ (>200 g) are given by nasogastric tube to horses that are completely anorectic.

Recurrence of metabolic acidosis also can occur when oral $NaHCO_3$ is discontinued. Relapses can be immediate or delayed for weeks to months, especially in horses that have RTA with evidence of renal damage. Reinstitution of $NaHCO_3$ supplementation usually corrects the metabolic abnormalities and accompanying depression and anorexia. The short-term prognosis for horses with RTA is good, and although the long-term prognosis has not been well documented, several horses have been reported to recover completely.[244–246]

34.25 BLADDER RUPTURE IN ADULT HORSES

THOMAS J. DIVERS

On rare occasions, bladder rupture may occur in adult horses. The problem often develops in association with urethral obstruction, foaling, or prolonged recumbency.[251] As azotemia develops, affected horses become depressed and inappetent. Clinical signs may not be apparent for several days, or stranguria may be observed, depending on the cause of the rupture. Abdominal distention is not as apparent in adult horses as in foals.

The diagnosis is based on history, rectal examination findings, laboratory results, and findings on ultrasonographic or cystoscopic examination. Postrenal azotemia develops within 24 hours after rupture and is accompanied by hyponatremia and hypochloremia. Unlike uroperitoneum in neonates, hyperkalemia is not a consistent finding. Transabdominal ultrasonographic examination of the abdomen reveals a large amount of peritoneal fluid (Fig. 34-15); abdominal fluid is easily recovered on abdominocentesis, and peritoneal fluid creatinine is twofold or greater than that of serum. Detection of calcium carbonate crystals on cytologic examination of peritoneal fluid is also diagnostic for uroperitoneum. Endoscopic examination of the bladder should allow determination of the

location and extent of the bladder tear. Rarely, uroperitoneum may also develop in some horses without full-thickness disruption of the bladder wall, and it is difficult to establish definitively the cause of uroperitoneum in these cases.

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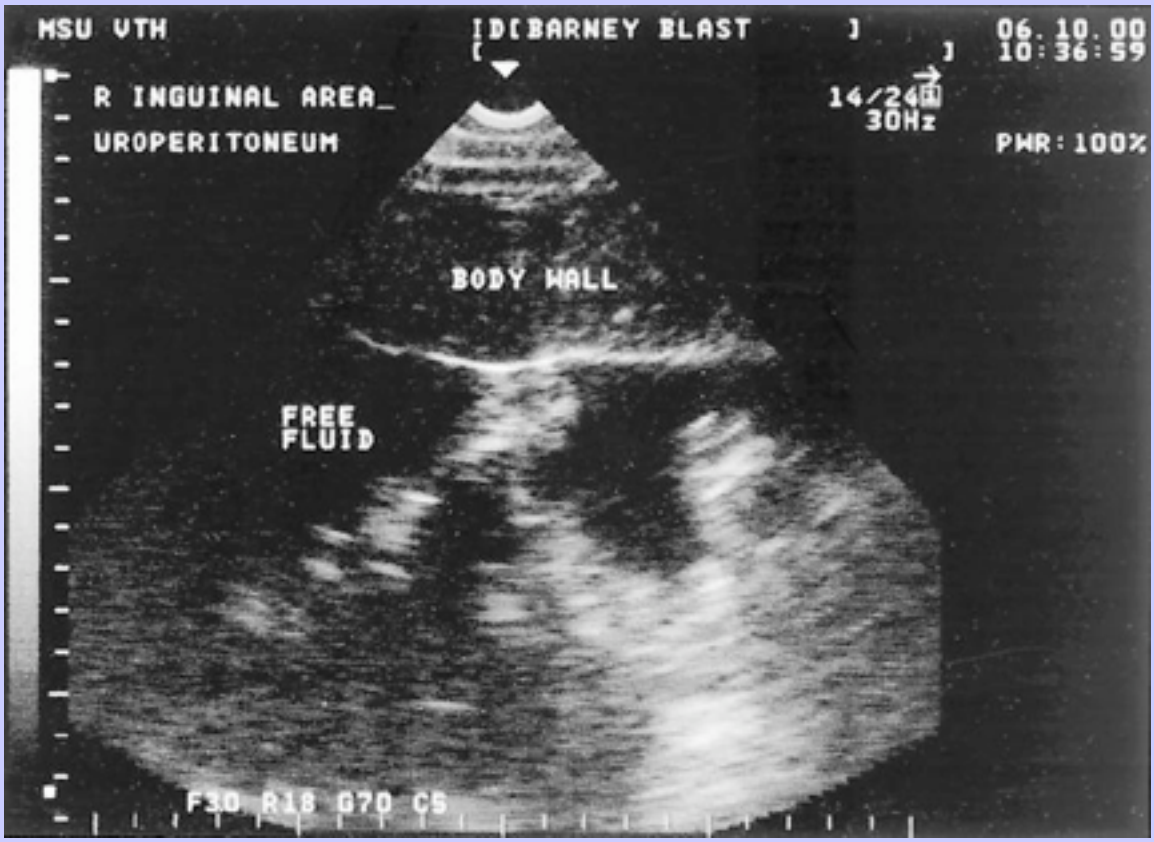
Fig. 34-15 Transabdominal ultrasonographic image of the right inguinal area of an adult horse with a ruptured bladder. A large amount of free hypoechoic fluid is apparent.



Surgical repair is indicated in horses with large tears in the ventral half of the bladder. In patients with small dorsal tears or incomplete tears, use of an indwelling bladder catheter (closed system) to keep the bladder small may allow the tear to heal without surgery.[252] Before surgery, IV fluids should be administered to correct dehydration, along with broad-spectrum antibiotics as prophylaxis against sepsis. If the abdomen is distended, urine accumulated in the abdomen should be removed (e.g., by placement of chest tube or other large catheter through ventral abdominal wall) before anesthesia is induced, to avoid further compromising respiration.

34.26 URINARY SYSTEM DISORDERS IN THE FOAL

THOMAS J. DIVERS

Umbilical disorders of the neonatal foal, including patent urachus, urachal infections, and omphalitis, are discussed in Chapter 19.

34.27 UROPERITONEUM

34.27.1 Bladder Rupture

The most common disorder of the bladder of otherwise healthy newborn foals is bladder rupture.[253–255] It is more common in colts, and clinical signs include repeated posturing to urinate and stranguria during the first 2 days of life. As urine accumulates in the abdomen, depression and abdominal distention typically develop between days 2 and 4. Repeated posturing and stranguria can easily be misinterpreted as tenesmus associated with meconium impaction (Fig. 34-16). Further, affected colts may continue to void small volumes of urine. Thus, establishing a diagnosis of a ruptured bladder can initially be challenging until more obvious signs of uroperitoneum (e.g., decreased nursing, abdominal distention) develop.

Laboratory findings in foals with uroperitoneum include hyponatremia, hypochloremia, hyperkalemia, and azotemia.[253–256] An occasional foal may also develop intermittent fine muscle tremors or a cardiac arrhythmia resulting from these electrolyte alterations, especially hyperkalemia. Transabdominal ultrasonographic examination usually reveals a large quantity of free fluid in the abdominal cavity, and peritoneal fluid creatinine/serum creatinine ratio greater than 2:1 confirms uroperitoneum.[253–256]

Fig. 34-16 A 2-day-old foal exhibiting stranguria caused by a ruptured bladder. Note the caudal position of the hindlegs, suggesting that the foal is straining to urinate rather than defecate. Differentiating between stranguria and tenesmus (meconium impaction) is not always easy.

Treatment of bladder rupture includes surgical closure of the defect, supportive care, and broad-spectrum prophylactic antibiotics for 3 to 7 days postoperatively.[253,254,256,257] An emergency surgical procedure is usually not required, and in most cases, surgery should be postponed for several hours until electrolyte abnormalities are partially corrected (most notably correction of hyperkalemia to a serum concentration <6.0 mEq/L). This can usually be accomplished by IV administration of 1 to 3 L of a 0.9% NaCl/5% glucose solution. Treatment with insulin should be avoided unless hyperkalemia is causing significant electrocardiographic (ECG) abnormalities and response to initial fluid therapy is poor. With marked hyperkalemia or abdominal distention causing respiratory embarrassment, slow drainage of urine from the abdomen (e.g., by chest tube or similar catheter) may be necessary before induction of anesthesia. Despite significant azotemia in some affected foals, use of aminoglycoside antibiotics is generally safe because the azotemia is postrenal rather than reflecting intrinsic renal disease. In most cases, placement of a urinary catheter to maintain an empty bladder for the initial 2 postoperative days is not necessary. However, uroperitoneum may recur after surgery in an occasional foal as a result of ongoing leakage from the bladder tear. When this complication occurs, it can usually be managed conservatively by placement of an indwelling bladder catheter (closed system) for 3 to 5 days. Rarely, a second celiotomy may be required.

34.27.2 Urachal Urine Leakage

Uroperitoneum may also develop in foals with urachal infection or ischemia. Affected foals are often septicemic or hospitalized for treatment of prematurity, hypoxic-ischemic encephalopathy, or botulism, and uroperitneum is recognized later (e.g., after 5 to 10 days of treatment).[257,258] Prolonged recumbency and bladder distention are likely risk factors. The umbilicus of many affected neonates appears normal during the first 2 days of life but, in some cases, may subsequently become patent. Urine leakage through the umbilicus may or may not be accompanied by leakage into the abdominal cavity or subcutaneous tissues of the abdominal wall. In other affected foals the umbilicus remains normal, and all urine leakage accumulates into the abdominal cavity. When monitored, inappropriate weight gain (e.g., >2 kg in 24 hours) is another common finding in hospitalized neonates that develop uroperitoneum.

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Laboratory abnormalities typical for uroperitoneum may be found in affected foals but are not consistently abnormal because these patients are often being treated with IV fluids. Correction of the problem includes surgical removal of the diseased urachus, closure of the bladder apex, and continued supportive care for the primary disease. The prognosis for a successful outcome for these foals is not as favorable as for simple bladder rupture because they often have a degree of peritonitis (increasing risk for adhesions), and uroperitoneum is often only one of several complications of the underlying disease.[257,258]

In an occasional foal the urachus may also rupture more distally than usual and lead to subcutaneous accumulation of urine, ventral abdominal swelling, stranguria, signs of colic, and distress.[259] The swelling may be differentiated clinically from a hematoma or septic omphalitis because it may enlarge quickly and often becomes cold. Ultrasonographic examination and/or local aspiration of fluid and measurement of creatinine (twofold or greater than in serum) confirm the diagnosis. Prompt surgical removal of the leaking urachus is indicated.

34.27.3 Ureteral Defects

Ureteral defect(s) or disruption may also lead to development of uroperitoneum in both male and female foals.[260–263] Stranguria is usually absent, and urine initially accumulates in the retroperitoneal space, but with time the

retroperitoneal tissue ruptures, causing uroperitoneum. Affected foals may not be presented until 5 to 10 days of age because urine accumulation is slower than with a ruptured bladder. Clinical signs include decreased nursing, depression, and mild colic, and in fillies an external bulging of the vagina may be observed. Laboratory findings are typical for uroperitoneum, and with significant hyperkalemia, intermittent muscle fasciculations may be also noted.

If urine accumulation remains localized to the retroperitoneal space, ultrasonographic examination of the lower abdomen may be normal, but a large amount of retroperitoneal fluid will be detected around the kidney and upper flank (within retroperitoneal space) on the affected side(s). In addition, the renal pelvis may be mildly dilated.[264] If the peritoneal membrane is ruptured, physical and ultrasonographic examination findings are similar to those seen with a ruptured bladder, but careful ultrasonographic examination may also reveal a full bladder or concurrent retroperitoneal fluid accumulation. As with a ruptured bladder the ratio of retroperitoneal or peritoneal fluid creatinine/serum creatinine is greater than 2:1. In small foals (e.g., <50 to 75 kg), excretory urography (after IV administration of contrast agent) or pyelography (after percutaneous injection of contrast agent into renal pelvis with ultrasonographic guidance) may be useful for localizing the ureteral defect(s).

One or both ureters may be involved, and during surgical exploration, one or more defects can usually be found in the proximal half of the ureter, often near the renal pelvis. During surgery the defects can be localized by placing a catheter into the ureter through a cystotomy and injecting dye (e.g., Evans blue, methylene blue). Successful correction of unilateral and bilateral defects can be accomplished by placing a stent in the affected ureter(s) for 7 to 10 days.[260,261]

A report describing bilateral ureteral defects adjacent to the renal pelves provided histopathologic evidence that the lesions were traumatic in origin, rather than developmental anomalies.[263] The foal in that report had previously been kicked by its dam. The editor has also seen three foals with similar ureteral defects, all of which also had multiple rib fractures. Ureteropelvic junction injuries and proximal ureteral tears are a recognized complication after blunt abdominal trauma in human patients.[265] Taken together, these observations suggest that many ureteral defects in foals may more likely be traumatically induced at foaling, rather than being developmental anomalies.

34.28 CYSTITIS

Cystitis is rare in foals but can develop in recumbent premature or neonatal foals being treated with broad-spectrum antibiotics. Voided urine may have a characteristic flocculent consistency. When cystitis is suspected, the bladder should be catheterized and a urine sample submitted for urinalysis and quantitative culture. UTIs with *Candida* species are fairly common in recumbent neonates. Specific antimicrobial therapy is not usually necessary for *Candida* cystitis as long as systemic antibiotics can be discontinued. If antibiotic therapy continues, dissemination of the yeast infection can spread to other sites (e.g., joints).

34.29 SERUM CREATININE ELEVATIONS IN NEWBORN FOALS

During the first 1 to 3 days of life, creatinine concentration in newborn foals is often 30% to 40% higher than in their dams.[266] The cause is unclear but likely related to an inability of creatinine to equilibrate rapidly across placental membranes. As supportive evidence, creatinine concentration of normal amniotic fluid (that contains fetal urine) at term is approximately 10 mg/dL (and may exceed 30 mg/dL in some mares).[267] This transient increase in creatinine, which may occasionally exceed 20 mg/dL in premature foals, has been called a “spurious” elevation, but

this term should be discontinued because creatinine is truly increased. When an elevated creatinine level is detected in an otherwise healthy foal (that has also been observed to urinate normally), there may be no cause for alarm. However, if creatinine does not decline rapidly after birth or remains greater than 2.5 mg/dL on day 3 of life, peritoneal or retroperitoneal accumulation of urine, renal hypoplasia, or other causes of renal failure should be considered. Unlike creatinine, BUN values in foals are typically low (<10 mg/dL) after day 2 and remain low for the first several months of life. This finding can be attributed to the anabolic state of the growing foal.

Urinalysis results in normal neonatal foals are also different from those in adult horses. Specifically, normal foals may have marked proteinuria for 1 to 2 days after birth resulting from filtration of small—molecular-weight proteins absorbed with colostrum. Next, water intake on a predominantly milk diet (~250 mL/kg/day, compared with intake of 50 mL/kg/day of water by adults) is high in foals. As a result, after day 2 of life, urine is hyposthenuric (specific gravity, 1.002 to 1.006) and remains that way for several months. Finally, urinary enzyme activity and sodium and chloride clearances may be greater than adult values, and urine pH is neutral to acidic in foals.[268]

34.30 ACUTE RENAL FAILURE

Acute tubular necrosis is the most common pathologic lesion causing ARF in neonatal foals. Many cases develop during or after episodes of diarrhea, likely caused by poor perfusion (vasomotor nephropathy). Surprisingly, the diarrheal disease in some affected foals does not appear to be serious, but they may develop ARF. Similar to adult horses with ARF, the prominent clinical signs are depression and development of edema. Abnormal laboratory findings include azotemia, hyponatremia, hypochloremia, and hypocalcemia. Foals are more likely to develop significant hyperkalemia and hyperphosphatemia than adult horses with ARF. A urine specific gravity less than 1.018 and microscopic hematuria are usually also found in foals with ARF. Urine output of sick neonates should be monitored closely because they may become oliguric to anuric 12 to 24 hours before significant depression or azotemia is recognized. In addition, fluid retention during incipient ARF is another cause of inappropriate weight gain (e.g., >2 kg in 24 hours), which can often be detected before obvious edema develops.

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Nephrotoxicity, most often from administration of aminoglycoside antibiotics or tetracycline, is another important cause of ARF (usually nonoliguric) in neonatal foals. As in adult horses, the recent change to once-daily aminoglycoside dosing appears to have decreased the incidence of hospital-acquired ARF in foals. However, it is important to remember that sick neonates are often more critically ill than many adult horses treated with aminoglycosides. Premature foals appear to be at even greater risk of nephrotoxicity than term foals. Judicious fluid therapy to correct dehydration and maintain blood pressure is an important precaution. Although there is a general impression that amikacin may be less nephrotoxic than gentamicin in foals, little supportive data exist. Regardless of which aminoglycoside antibiotic is selected, monitoring trough concentrations (<2 mg/mL for gentamicin; <4 mg/mL for amikacin) is warranted to decrease the risk of aminoglycoside toxicity in high-risk neonates. Dosage adjustment may be necessary in seriously ill neonates or premature foals because renal clearance may be decreased.[269]

The principles of treatment of ARF in neonates are essentially the same as those for adult horses (see earlier discussion). However, greater attention must be paid to monitoring responses to fluid therapy, including twice-daily measurement of body weight. Although foals that have a bout of ARF in the neonatal period would seem at greater risk of developing CRF later in life, no long-term follow-up study has corroborated this speculation.

34.31 SEPTIC RENAL DISEASE IN FOALS

Multifocal renal abscesses or infarct may be a complication of neonatal septicemia and can lead to ARF. *Actinobacillus equili* is the most common pathogen causing renal abscesses, but affected foals often die or are euthanatized because of overwhelming sepsis before clinical signs of ARF develop. Foals 2 to 4 days of age appear to be at greatest risk of developing acute *Actinobacillus* septicemia; when this problem is suspected, IV therapy with penicillin and gentamicin (at prolonged dosage) is recommended (see Chapters 18 and 20).

34.32 RUMINANT RENAL SYSTEM

34.32.1 ULCERATIVE POSTHITIS AND VULVITIS

DAVID C. VAN METRE

Ulcerative posthitis and vulvitis (enzootic balanoposthitis, pizzle rot, sheath rot) is an ulcerative bacterial infection of the mucous membrane and surrounding skin of the prepuce and vulva of small ruminants. The causative organism, *Corynebacterium renale,* inhabits the mucosal surface of the prepuce and vulva in low numbers. It proliferates and induces disease under conditions of high urea concentration in urine, which typically result from excessive dietary protein content. Losses result from debilitation caused by pain, incapacitation of breeding animals, loss of breeding soundness, and deformation of external genitalia. Venereal spread is possible.

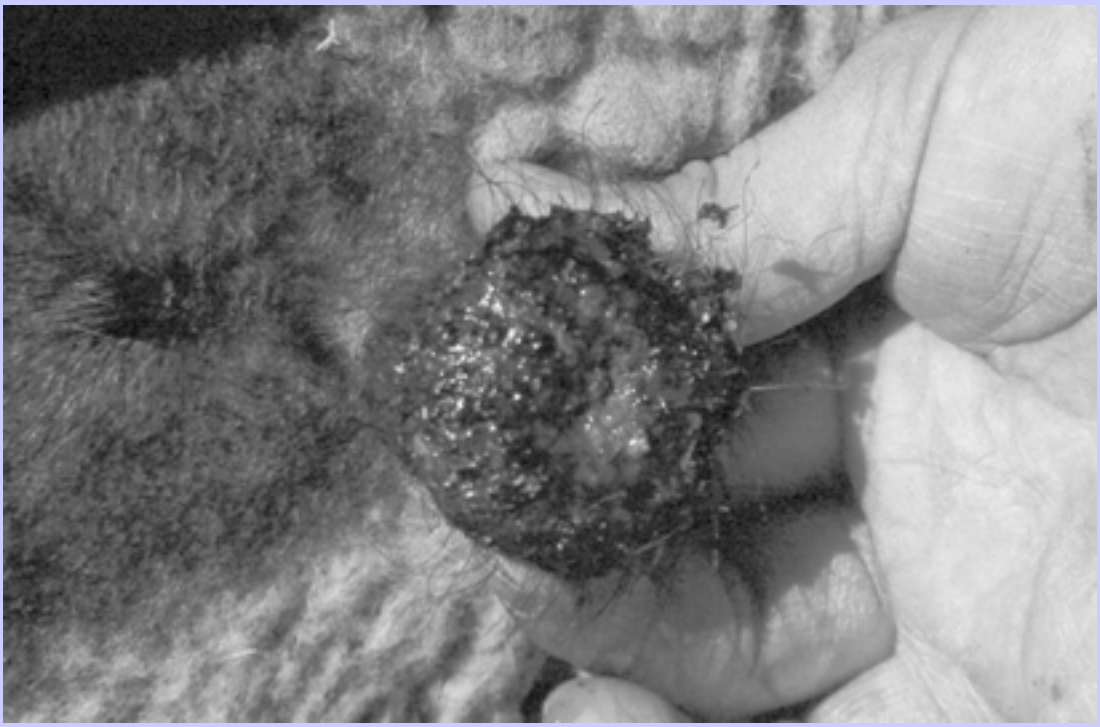
34.32.1.1 Clinical Signs

In rams, bucks, and wethers the infection begins as a moist ulcer, usually at or near the mucocutaneous junction of the prepuce. The ulcer surface is soon covered with a thin, loose, brown to red, malodorous scab (Fig. 34-17). If the scabs are removed, little or no hemorrhage will occur from the underlying tissue.[1] Focal swelling is often noticeable at the cranial aspect of the prepuce, and the area is usually painful on palpation.

If unchecked, the infection may spread along the mucosal surface inside the prepuce, creating the more serious internal form of ulcerative posthitis. In such cases the entire prepuce may be swollen and elongated. Affected animals often show dysuria, and goats may vocalize during voiding. Weight loss may occur in chronic cases. As local inflammation progresses, ulceration of mucosal surfaces may result in fibrous adhesions between the penis and prepuce. Severe inflammation of the glans penis may cause stricture of the urethral process *(pizzle)* and restriction of urine egress. Impairment of breeding soundness may result from admixing of blood or exudate into the ejaculate, penile adhesions, cicatricial scarring of the preputial orifice, or suppurative urethritis; pain may limit libido as well.

Ulcerative lesions of similar appearance can develop on the vulva and perineum of affected ewes and does. Gross vulvar enlargement may be noticed from a distance. Dysuria may result from involvement of the urethral orifice. The fibrosis and contracture that develop in chronic, severe cases may distort normal vulvar conformation to the point of impairing copulation or partuition.

Fig. 34-17 Ulcerative posthitis in a Suffolk ram.



34.32.1.2

Differential Diagnosis

Ulcerative dermatosis (lip and leg ulcer) is a dermatitis of sheep caused by an unclassified poxvirus related to the parapox virus of contagious ecthyma.[2] Infection with this agent may manifest as balanoposthitis and vulvitis, and the crusted ulcers that develop closely resemble those induced by infection with *C. renale*. Removal of the crusts overlying ulcerative dermatosis lesions may reveal a granular lesion that bleeds readily. The genital form of ulcerative dermatosis occurs most often in the fall breeding season in the western United States. Ulcers on the lips, nares, coronets, and interdigital spaces may also be present.[2] Contagious ecthyma *(orf)* occasionally affects the genitalia and perineum, although lesions are much more frequently found on the lips, face, and udder. These lesions are raised, appear proliferative, and are covered with a thick, durable scab. Urolithiasis must be considered strongly in the differential diagnosis of any dysuric male or castrated male small ruminant. Although rare in small ruminants, preputial trauma, particularly if resulting from entrapped grass awns, can cause preputial swelling, pain, and exudation within the preputial cavity. External ulcerative lesions would not be expected in such cases.

Caprine herpesvirus 1 (CHV-1) was isolated from aborted fetuses in three separate California goat herds.[6] A buck on the premises had shallow, red, irregularly shaped ulcers in its prepuce that tested positive for CHV-1 on polymerase chain reaction (PCR). Biopsy of the ulcers revealed intranuclear inclusion bodies within the stratum spinosum of the preputial epithelium.

34.32.1.3

Pathophysiology

C. renale is an aerobic, gram-positive, pleomorphic, club-shaped bacterium that is a normal inhabitant of the skin and external genitalia of small ruminants.[3,4] This organism is capable of surviving in wool and scabs from lesions for as long as 6 months and can survive freezing temperatures in lesion exudate.[5] *C. renale* is capable of hydrolyzing urea. Experimental diversion of urine flow has demonstrated that the presence of urine is required for both induction of and maintenance of lesions on the genitalia.[3] The organism proliferates on the genital mucosal surface in response to elevated urinary concentration of urea. Diets high in crude protein or nonprotein nitrogen increase the urinary urea content and are required for development of the disease.[1,5] *C. renale* hydrolyzes urea to ammonia, which causes ulceration of the prepuce and surrounding skin.

34.32.1.4

Epidemiology

This condition appears to be more common in males and wethers than in females.[1] Lambs under 6 months of age can occasionally be affected,[5] but given the relatively short lifespan of market lambs, the disease is most often recognized in rams, Angora wethers, and pet wethers. Although all breeds are susceptible, higher rates of this disease are found in Merinos and Angoras.[1,7] Because of the dense wool and hair coat of these breeds, urine soaking near the preputial orifice may increase the local concentration of urea. Seasonal differences in the incidence of the disease are thought to reflect shearing schedules and changes in the availability of high-protein diets.[1]

Because the organism is part of the normal skin and genital flora, disease can occur in isolated individuals under proper dietary conditions. However, the disease is contagious, because transfer of necrotic debris from the ulcers of affected animals can induce the disease in normal animals.[1,5] Venereal transmission of the disease has been documented. Several months may pass between the exposure of ewes to infected rams and the development of vulvitis in ewes.[5]

34.32.1.5

Treatment and Prevention

Affected animals should be isolated to limit venereal or contact transmission. Wool or hair should be removed from the skin surrounding the prepuce or vulva, and a topical antibiotic may be applied. Caustic antiseptic solutions should not be used. Treatment with systemic antibiotics is indicated for advanced cases or for outbreaks, in which handling of several animals for topical therapy is not feasible. Penicillin is the antibiotic of choice, although tetracycline has provided favorable results. Treatment should continue until the lesions have dried and acute inflammation has subsided.

Reduction of protein and nonprotein nitrogen intake is crucial for successful treatment of affected animals and for prevention of additional cases.[1,5] Dietary crude protein levels of 16% to 18% (or higher) predispose sheep and goats to ulcerative posthitis and vulvitis.[1] Reduction of dietary protein alone may result in satisfactory cure if the lesions are early in development. Shearing, especially at the time of highest protein intake, may be efficacious in reducing disease incidence.[5] Incorporation of grass hay feeding into a program of legume pasture grazing may help limit protein intake.

Surgical treatment of advanced cases has been described.[8] The procedure involves resection of ventral preputial tissue to allow for normal urine flow and, less often, successful return to breeding.

34.32.1.6 Prognosis

Response to treatment is optimal early in the infection, before deformation of the prepuce and vulva as a result of fibrosis. The chances for full recovery without recrudescence are poor if dietary protein intake is not reduced. Complete recovery of breeding soundness is unlikely in animals with internal ulcerative posthitis.

34.33 UROLITHIASIS

JENNIFER M. MACLEAY

Urolithiasis is a common metabolic disease occurring in most mammalian species. Uroliths cause disease through trauma to the urinary tract and obstruction of urinary outflow. Calculi (uroliths) most often lodge in the urethra, although obstruction of the bladder trigone, ureters, or renal pelvis can also occur. Sequelae to urinary tract obstruction include urethral perforation and rupture, urethral stricture, bladder rupture, ureteral rupture, hydroureter, hydronephrosis, and rarely, rupture of the kidney(s). Urolithiasis can occur in outbreaks or as an endemic problem in group-housed animals or as an individual disorder in animals kept as pets. A definitive diagnosis of urolithiasis in a single animal suggests that all males in the population are at risk for the disease, because of the importance of dietary and environmental factors in its pathogenesis.[9]

34.33.1 HISTORICAL FINDINGS

The clinical signs of urolithiasis can vary; duration, extent (complete vs. partial), and location of the obstruction determine the historical and examination findings. The early clinical signs can be remarkably subtle and may include anorexia, depression, and mild bloat. A history of colic and straining to urinate or defecate may be provided, and novice owners often mistake stranguria for constipation or tenesmus. To aid in the diagnosis, suspected cases can be placed in a dry, unbedded stall to allow for assessment of urine output.

34.33.1.1 Acute Urethral Obstruction

34.33.1.1.1 Clinical Findings

Impacted calculi lead to urethral trauma and progressive bladder distention, resulting in strangury and abdominal pain. Affected animals may be restless, tread, swish their tails, and or grind their teeth. Goats and camelids may vocalize. Stranguria is manifested as repetitive bouts of stretching and contraction of the abdominal muscles. Straining may induce secondary rectal prolapse; therefore, urethral obstruction should be investigated as the primary disease in cases of rectal prolapse. Rarely, affected calves develop a visible dilation of the urethra at the midline of the perineum proximal to the obstruction.[10] Tachycardia, tachypnea, and mild bloat secondary to ruminal stasis are more common findings. Anuria occurs if urethral obstruction is complete, whereas urine may dribble in cases of partial obstruction. If a urine sample can be collected for dipstick analysis, proteinuria and occult hematuria are frequently detected. Crystals or blood may be found on the hairs of the preputial tuft; in cases of anuria the hairs are dry. Fever is usually absent.

The lumen of the bovine urethra narrows at the distal aspect of the sigmoid flexure, near the level of insertion of the retractor penis muscles.[11,12] Calculi most frequently become lodged at this site in cattle,[11–14] and pain or focal swelling over this area may be appreciated. Rectal examination (digital rectal examination in small ruminants) often reveals pulsation of the pelvic urethra. In cattle, bladder distention is palpable rectally except in cases of complete obstruction complicated by rupture of the urethra or bladder.

Abdominal palpation is useful in affected small ruminants, small camelids, and pot-bellied pigs. The examiner should place the fingertips of each hand into the ventral flank on each side of the abdomen. While slowly pressing the fingertips toward midline in the caudal abdomen, the examiner may encounter an orange- to grapefruit-sized, firm, spherical structure, which is the distended bladder (Fig. 34-18). Severe bladder distention will not be palpated in cases of incomplete urethral obstruction or bladder rupture.

The urethral process (pizzle) is the most common site of calculus impaction in sheep and goats and should be examined in suspected cases of urolithiasis.[14,15] Sedation or general anesthesia facilitates extrusion of the penis for examination. Because of its diuretic effect, xylazine may exacerbate bladder distention and is not recommended. Diazepam (0.1 mg/kg IV slowly) or acepromazine (0.05 to 0.1 mg/kg IV or IM) have been used successfully, either as sole agents or in combination with butorphanol (0.05 to 0.1 mg/kg IV). Alternatively, in hemodynamically stable individuals, it is possible to induce light general anesthesia with isoflurane.

Fig. 34-18 Palpation of the bladder of a Barbados wether.

An adjunct or alternative to sedation is administration of epidural anesthesia, which provides greater patient comfort and eliminates muscular resistance to penile extrusion. One milliliter of 2% lidocaine per 5 kg of body weight is injected into the epidural space at the lumbosacral junction.[16] Lower dosages may provide sufficient anesthesia. The total dose should not exceed 15 mL of 2% lidocaine in any small ruminant, regardless of size.[16] If cerebrospinal fluid (CSF) is obtained, one half of the epidural lidocaine dosage can be administered as a true spinal block. Hindlimb motor blockade, potentially lasting for several hours, is expected with either epidural or true spinal anesthesia at this site.

To exteriorize the penis, the sheep or goat is propped up on its rump. The examiner can then exteriorize the penis by pushing the sigmoid flexure cranially from the base of the scrotum while pulling the sheath caudally. Small towel clamps or Allis tissue forceps can be used to apply traction to the penis. In many cases, preputial mucosa must be carefully grasped and extruded before the penis can be reached with a second pair of forceps. The urethral process can then be inspected and palpated for the presence of discrete uroliths or sandlike grit within the lumen. If the urethral process is obstructed, it can be amputated with scissors or a scalpel blade (see Surgical Treatment).

34.33.1.1.2

Differential Diagnosis

Tachycardia, colic, bloat, and anorexia are characteristic of gastrointestinal (GI) obstruction, but auscultation and percussion of the abdomen, abdominal succussion, rectal examination, and abdominal ultrasonographic examination should differentiate this condition from acute urethral obstruction. Goats with grain overload will occasionally vocalize and show signs of colic.[17] Encephalopathies, salmonellosis, coccidiosis, and proctitis from rectal prolapse or trauma frequently cause tenesmus. Additional signs of primary neurologic or GI dysfunction should be evident with these diseases.

Although rare in male ruminants, primary urinary tract infection (UTI) may result in dysuria and pollakiuria. Bladder distention is uncommon with UTI, and large numbers of white blood cells (WBCs) and bacteria are present in the urine sediment. Occasionally an animal with urolithiasis successfully voids the obstructing urolith(s). The resultant traumatic urethritis might cause dysuria, but the rate and ease of urination typically improve over time and with antiinflammatory treatment.

In younger animals, it is important to consider congenital abnormalities, such as ectopic ureter(s), pelvic displacement of the urinary bladder, and urethral duplication. Congenital abnormalities may be manifest at birth or not until later, depending on the level of observation and whether the defect results in obstruction, partial obstruction, or constant urine dribbling.

34.33.1.2

Urethral Rupture

Urethral rupture is a common complication of urethral obstruction in cattle. The wall of the obstructed urethra undergoes pressure necrosis, causing leakage of urine into the subcutaneous tissue of the perineum and ventral abdomen. Sequelae include cellulitis, penile adhesions (possibly creating phimosis), and urethral stricture. Erection failure secondary to vascular obstruction of the corpus cavernosum of the penis has been reported as a sequela to urethral obstruction and rupture in a goat.[18]

34.33.1.3 Clinical Findings

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Affected animals are frequently depressed and inappetent and have bilaterally symmetric, pitting edema in the ventral perineum, inguinal region, prepuce, and ventral abdomen (Fig. 34-19). Swelling of the abdominal wall may extend as far forward as the axillae. The affected areas are initially warm and painful on palpation. As necrosis progresses, the tissues become cool, dark, nonpainful, and potentially gangrenous. A fistula may develop to allow urine to escape. Fever may occur if tissue necrosis and sloughing are extensive. Rectal examination in steers and bulls reveals a small bladder.

Fig. 34-19 Urethral rupture in a Holstein steer. Tissue swelling from urine accumulation may extend to the sternum and axillae.

34.33.1.4 Differential Diagnosis

Ventral abdominal swelling is found with umbilical or scrotal hernias with or without concurrent subcutaneous infection. These conditions can be differentiated from urethral rupture by careful palpation of affected tissues and through ultrasonography to identify defects in the body wall or presence of bowel in the swelling. Pain and heat are more pronounced in local infection than in urethral rupture. Aspiration of subcutaneous fluid with cytologic examination is helpful in identifying primary infectious processes. In bulls, penile hematomas may cause localized swelling of the prepuce in the prescrotal region and caudal sheath; unlike urethral rupture, however, the swelling does not involve the ventral abdominal wall. Aspiration of a suspected penile hematoma is not recommended because of the risk of iatrogenic infection.

34.33.2 Rupture of the Bladder (Water Belly)

In all ruminants and camelids, prolonged bladder distention secondary to urethral obstruction may result in pinpoint perforations, tears, or necrosis of large areas of the bladder wall. In cows, bladder rupture may also occur as a rare complication of dystocia.[19,20] Rupture of a urachal remnant may also result in uroperitoneum.[21] The dorsum of the bladder fundus is the most common site for rupture,[14] but rupture in other bladder regions does occur.[22]

34.33.3 Clinical Findings

Relief of bladder distention causes cessation of stranguria. Bilateral distention of the ventral abdomen develops within 1 to 2 days after rupture and is accompanied by worsening clinical signs of depression, anorexia, weakness, dehydration, and shock. Ballottement of the abdomen may elicit a fluid wave. Rectal temperature may be normal,[23] but shock may result in hypothermia. The animal's breath may smell like ammonia. On rectal or abdominal palpation, the bladder is small or not palpable. Ultrasonography of the abdomen reveals a large volume of free fluid and a collapsed or partially filled bladder. Abdominocentesis yields a large volume of blood-tinged fluid. The fluid may or may not smell like urine and can be warmed to aid in detection of the urine smell. Measurement of creatinine in the fluid can be used to confirm a diagnosis of uroperitoneum (see Clinical Pathology). On occasion, urine translocation into the thoracic cavity can occur, presumably by passage across the diaphragm. Uremia and dehydration result in debilitation and eventual death if medical and surgical treatments are not provided.

34.33.4 Differential Diagnosis

Seepage of urine across the bladder wall and into the abdominal cavity may occur in cases of severe bladder distention; in such cases, rupture is often imminent. Ventral abdominal distention may develop with diffuse peritonitis, vagal indigestion, or ascites secondary to liver fibrosis, caudal vena caval thrombosis, or hypoproteinemia. Marked peritoneal cavity effusion may be found in cases of mesothelioma. These conditions are differentiated from bladder rupture through rectal examination, ultrasonography, cytologic and chemical analysis of peritoneal fluid, evaluation of serum chemistry, and abdominal exploratory surgery.

34.34 Chronic Partial Urethral Obstruction

An uncommon form of urolithiasis, chronic partial urethral obstruction occurs if calculi impair but do not completely obstruct urine outflow.[24] Chronic retention of urine elevates fluid pressure within the urinary tract lumen, potentially leading to hypertrophy of the bladder wall, hydroureter, and hydronephrosis. Azotemia, progressive renal failure, and uremia are evident in cases that develop hydronephrosis.

34.35 Clinical Findings

Affected animals have been termed “dribblers” because of their characteristic slow or intermittent urine flow during voiding.[25] Lethargy, reduced appetite, and thin body condition are evident if renal failure has developed. On rectal examination the bladder may be small, and thickening of the bladder wall may be palpable.[24]

34.36 Differential Diagnosis

Urine dribbling may also occur in animals with neurologic disease caused by previous urethral trauma (stricture formation), congenital anomalies of the urogenital tract, chronic infection, or neoplasia. Contrast urethrography may be used to identify the presence of strictures or anomalous structures. Small ruminants with the internal form of ulcerative posthitis may dribble urine. In such cases, characteristic preputial lesions are present. Tumors of the urinary tract, although rare compared to urolithiasis, may cause gradual obstruction in cattle, small ruminants, and camelids.

34.37 Ureterolithiasis and Nephrolithiasis

34.37.1 Clinical Findings

Cattle with acute ureteral obstruction may show severe colic with stretching, kyphosis, treading, collapse, and vocalization.[25] Signs of distress may be less severe or even absent if obstruction is intermittent or incomplete.[26] Enlargement of the blocked ureter may be palpated rectally, and if the left ureter is obstructed, enlargement of the left kidney may be appreciated. Azotemia is most severe if the obstruction is bilateral. Rarely, pyelonephritis is the inciting cause of ureteral obstruction, because necrotic debris and calculi may be released into the ureter from the infected renal pelvis. Pyelonephritis can also be a consequence of ureteral[26] or renal[27] calculosis. With ureteral or renal rupture, uroperitoneum or retroperitoneal accumulation of urine may occur.

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34.37.2 Differential Diagnosis

Signs of abdominal pain or colic can result from GI or urinary tract obstruction in ruminants and camelids. Auscultation and percussion of the abdomen, rectal examination findings, ultrasonography, or radiography may allow for differentiation of GI obstruction from ureteral or renal obstruction. Cases of ureteral or renal calculosis without colic may show nonspecific signs of illness, and serum chemistry, urinalysis, and ultrasound examination may be useful for definitive diagnosis.[26]

34.37.3 Ancillary Diagnostic Tests

34.37.3.1 ULTRASONOGRAPHY/RADIOGRAPHY

A presumptive diagnosis of urolithiasis can usually be made through historical and physical examination findings. Ultrasonographic or radiographic evaluation of the urinary tract may allow for confirmation of a diagnosis.[28–31] In cases of prolonged urethral obstruction (≥48 hours) or urethral obstruction with severe azotemia, it is prudent to perform ultrasonographic examination of the kidneys before consideration of surgical treatment. Detection of severe hydronephrosis warrants a poor prognosis for recovery.

Ultrasonographic evaluation of the bladder of pot-bellied pigs, small ruminants, and camelids is most easily accomplished through transabdominal scanning with a 3.5- or 5.0-MHz sector-array probe, directed caudodorsally from the inguinal area. Both kidneys of small ruminants and camelids and the bovine right kidney can be examined from the right paralumbar fossa.[28] In cattle, transrectal examination of the pelvic urethra, bladder, ureters, and left kidney is performed with a 7.5-MHz linear-array probe. Marked distention of

the bladder, thickening of the bladder wall, and echogenic material within the bladder lumen may be seen with acute urethral obstruction. A large volume of free fluid in the abdomen is characteristic of uroperitoneum and is suggestive of existing or impending rupture.

Radiographic examination of the urinary tract is limited to thin, pot-bellied pigs, camelids, small ruminants, and young cattle. Radiodense calculi in the bladder may be most easily detected with lateral views of the abdomen, taken with the animal in lateral recumbency with the hindlimbs pulled caudally. Positive-contrast urethrography allows for detection of radiolucent urethral calculi, urethral stricture, or urethral rupture. After catheter placement about 5 cm into the penile urethra, injection of a volume of 10 to 30 mL of water-soluble contrast media has been used with success in adult bucks and rams. Accidental introduction of bubbles may complicate interpretation of urethrograms; to avoid this problem, the catheter should be completely filled with contrast material before insertion. Injection should be performed slowly with minimal pressure to avoid iatrogenic urethral rupture.

34.38 CLINICAL PATHOLOGY

34.38.1 Acute Urethral Obstruction

Hematologic and serum chemistry findings may be unremarkable in ruminants with acute urethral obstruction uncomplicated by urethral or bladder rupture.[15] Hyperglycemia and a stress leukogram may be present. With time, hemoconcentration and azotemia develop secondary to reduced water intake. Azotemia is severe in cases of hydronephrosis. Hematuria and proteinuria are consistent abnormalities, whereas crystalluria is a variable finding.[32] Pyuria is present with traumatic urethritis, cystitis, or secondary bacterial infection.

34.38.2 Bladder Rupture

Bladder rupture and accumulation of urine in the abdomen result in more profound alterations in hematologic and serum biochemical parameters. Urine osmolality is normally two to three times that of extracellular fluid (ECF), and ruminant urine contains higher concentrations of urea, creatinine, and potassium but lower concentrations of sodium and chloride than ECF.[23,33] Therefore, movement of water, urea, and electrolytes occurs along diffusion gradients, resulting in hyponatremia, hypochloremia, hyperphosphatemia, uremia, and hemoconcentration.

Serum potassium concentration in ruminants with bladder rupture may be more variable, depending on appetite and time before diagnosis. Potassium values tend to be normal or low in cattle with bladder rupture, even if uroperitoneum exists for several days.[23] Anorexia may contribute to hypokalemia or normokalemia in these cases, and aldosterone release secondary to volume depletion results in dramatic increases in salivary potassium excretion, providing an alternative route of potassium excretion in affected cattle.[19] Once in the GI tract, potassium absorption may be diminished by ileus and preferential absorption of sodium over potassium.[20] Alkalosis, which occurs secondary to hypochloremia, may also serve to reduce ECF potassium concentration by encouraging movement of potassium intracellularly.[23]

Although only a small fraction (≤10%) of phosphorus excretion in the ruminant is urinary,[20] hyperphosphatemia may occur secondary to uroabdomen. Potential mechanisms for hyperphosphatemia include phosphorus diffusion from the urine into the ECF, reduced glomerular filtration, and tissue hypoxia causing breakdown of

organic phosphate compounds in cells.[23,34] In addition, reduced salivary flow from anorexia may limit phosphorus excretion in the saliva, contributing to phosphorus retention.[20] Anorexia, ileus, and a competitive effect of hyperphosphatemia may contribute to reduction in serum calcium concentration in cases of uroabdomen.[23]

Chemical analysis of peritoneal fluid is a useful means of documenting uroabdomen. Creatinine is a relatively large, polar molecule that does not readily move back into the ECF space despite its high concentration in the abdomen. Therefore, peritoneal fluid creatinine can be compared to serum creatinine concentration, with a peritoneal fluid/serum ratio of 2:1 indicating uroabdomen.[23]

Uroabdomen is often associated with a chemical peritonitis. However, experimentally induced bladder rupture did not cause peritonitis in steers, even after several days of uroperitoneum.[23] Nonetheless, WBC count and blood fibrinogen levels may increase in cases of ruptured bladder, possibly reflecting more extensive tissue necrosis and inflammation in natural cases. With uremia, impairment of blood coagulation may become an important clinical consideration. Reduced platelet aggregation and alteration of coagulation factor function occur in uremic patients of other species.[34] Bleeding diathesis and elevation of partial thromboplastin time (PTT) have been reported in azotemic cattle.[35]

34.38.3 Urethral Rupture

Leakage of urine into the subcutaneous space produces hematologic and serum biochemical alterations that are similar but less severe than those seen with bladder rupture.[33] The muscles and subcutis holding the urine do not possess as large a surface area as the peritoneal cavity. Therefore, less rapid and less extensive fluxes of water, ions, and waste products occur.[33] Tissue necrosis and secondary infection may result in neutrophilia, leukocytosis, and hyperfibrinogenemia.

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34.38.4 Chronic Partial Obstruction

Hyponatremia, hypochloremia, hypocalcemia, hyperphosphatemia, and severe azotemia with isosthenuria suggest extensive nephron damage caused by hydronephrosis.[24]

34.38.5 Necropsy Findings

When the urethra is opened along the sagittal plane, hemorrhage and necrosis of the urethral mucosa are evident at the site of obstruction. Particular attention should be paid to examination of the distal urethra in camelids, the urethral process in sheep and goats, and the sigmoid flexure in cattle. Calculi may be relatively large, discrete mineral aggregates or very fine and sandlike. Calculus material should be collected for analysis of mineral composition. Occasionally, no calculi can be found in the urinary tract, but mucosal trauma and necrosis of the bladder or urethra persist.

Urethral rupture is characterized by the subcutaneous accumulation of urine in the inguinal area, prepuce, and ventral abdomen and hemorrhage at the site of the urethral defect. In cases of bladder rupture the abdominal cavity is filled with a large volume of blood-tinged fluid. Defects in the bladder wall vary in size and location, and necrosis of large areas of bladder wall may be present.[22] In rare cases the bladder wall is intact but obvious

uroabdomen exists, suggesting transmural seepage of urine. Hydronephrosis, hydroureter, and bladder wall hypertrophy may be present in animals with chronic partial urethral obstruction.[24]

34.38.6 Treatment and Prognosis

34.38.6.1 SALVAGE

Steers and feeder lambs may be sent for immediate slaughter if urethral obstruction is diagnosed before development of azotemia or urinary tract rupture.[36]

34.38.6.2 MEDICAL TREATMENT

Medical treatment of urolithiasis is aimed at relief of the obstruction and correction of any fluid and electrolyte abnormalities. The antispasmodic effect of certain tranquilizers may facilitate passage of a urethral obstruction.[9] Relaxation of the retractor penis muscle, which results in straightening of the sigmoid flexure, is another means by which these drugs may facilitate passage of calculi.[13] In small ruminants, however, medical treatment with intravenous (IV) fluids, nonsteroidal antiinflammatory drugs (NSAIDs), or tranquilizers alone has not met with much success, and surgical intervention is recommended.[15,37]

34.38.6.3 SURGICAL TREATMENT

Surgical treatment of urolithiasis is dictated by economic considerations, intended use of the animal, available facilities and equipment, and status of the patient. Removal or bypass of the obstruction and restoration of urine output are the goals of surgical treatment. The prognosis for both short-term and long-term survival will vary according to the patient's status and the surgical procedure chosen. Acute renal failure is an occasional sequela to urinary tract obstruction and should be considered in the prognosis.

34.39 PREOPERATIVE CONSIDERATIONS

Ruminants and camelids with urinary tract obstruction, particularly those with uroperitoneum, often require preoperative stabilization of hypovolemia and correction of electrolyte abnormalities, particularly if surgery is to be performed under general anesthesia or with the animal restrained in recumbency. Fluid therapy should be guided by analysis of serum electrolyte concentrations. An initial bolus of hypertonic (7%) saline followed by physiologic (0.9%) saline solution can be used to correct intravascular volume deficits, hyponatremia, and hypochloremia. Calcium salts can be added to the fluids if indicated. Empirical supplementation of IV fluids with potassium should be avoided because the potential for hyperkalemia always exists. Hyperkalemia can induce fatal cardiac dysrhythmias, and this effect is augmented by concurrent hyponatremia.[38] Administration of dextrose, sodium bicarbonate, and/or insulin (regular insulin at 0.25 to 0.4 U/kg IV slowly, SC, or IM) reduces serum potassium concentration by promoting movement of potassium from the extracellular to the intracellular space. Blood glucose should be closely monitored when insulin is administered. Uremic animals undergoing IV fluid therapy may develop pulmonary edema,[39] so attention must be paid to respiratory rate, auscultatory findings, and respiratory effort during fluid therapy. Slow drainage of urine from the abdominal cavity reduces pressure on the diaphragm and slows the progression of metabolic derangements caused by uroperitoneum. In long-standing cases of uroabdomen, urine may also be present in the thorax, further warranting close observation of respiratory function

during anesthesia. Thoracocentesis to remove thoracic urine is indicated if respiratory function is compromised; otherwise, abdominal drainage usually induces resolution of thoracic urine accumulation.

Although bacterial infection is not considered to be a common primary cause of urolithiasis, secondary UTIs may develop after surgical intervention. Loss of the flushing effect of urination, urinary mucosal damage, impaired host cellular defenses secondary to uremia, and indwelling urinary catheter placement may contribute to the development of ascending UTI. Perioperative antibiotic therapy is therefore prudent, with due consideration of withholding times in animals intended for slaughter. Postoperative antibiotic therapy is discussed later.

34.40 SURGICAL OPTIONS

Surgical options include amputation of the obstructed urethral process, penectomy, perineal urethrostomy, prepubic urethrostomy, urethrotomy, cystotomy, tube cystostomy, and bladder marsupialization. Urethral catheterization and retrograde flushing have been used to dislodge urethral calculi and restore urine flow in a ram.[40] However, successful clearance of the urethra is rarely achieved,[15] and retrograde flushing under pressure may result in urethral rupture. Retrograde passage of a catheter may allow for localization of the urethral obstruction, potentially guiding further surgical treatment. Passage of a catheter into the bladder of ruminants and camelids is difficult because of the presence of a urethral recess located near the ischial arch.[41]

In sheep and goats, *amputation of an obstructed urethral process* is a simple procedure that may at least temporarily restore urethral patency. The urethral process can be removed without detrimental effects on breeding soundness.[42] Success rates for initial restoration of urine flow after urethral process amputation range from 37.5%[32] to 66%.[15] However, recurrence of urethral obstruction is extremely common, and urethral patency is often maintained for only hours to days before reobstruction occurs.[15,32] Therefore, urethral process amputation is palliative and may provide enough time to allow feeder lambs to survive until slaughter. For pet wethers, rams, and bucks, recurrence of urinary tract obstruction appears to be probable if this is the only procedure performed.

Penectomy is an option for animals intended for slaughter. *Perineal urethrostomy* is a surgical option for ruminants not intended to be used for breeding. In small ruminants, postoperative stricture of the stoma or recurrent obstruction with additional calculi is a long-term risk.[15,43] *Ischial urethrostomy* with placement of a Foley catheter into the bladder has been used as a treatment for urolithiasis in heavy feedlot steers[44] and bulls.[12] If urethral damage is not severe, this procedure allows the breeding ability of bulls to be maintained.[12]

Prepubic urethrostomy has been reported in a sheep and a goat.[45] In this procedure a midperineal penectomy is performed. The perineal segment of the penis and pelvic portion of the urethra are dissected free from the surrounding soft tissue using perineal and ventral celiotomy incisions, respectively. Bilateral ileal and ischiadic osteotomies may be required to free the pelvic urethra. The urethral mucosa is then sutured to the skin of the caudoventral abdomen to create a long-lasting stoma.

Urethrotomy (removal of obstructing calculi and primary closure of urethra) is another option.[12,14] The calculi may be located, crushed with a towel clamp, and flushed from the urethral lumen, eliminating the need for a urethral incision.[12,14] Urethral stricture, adhesions resulting in phimosis in breeding males, and reobstruction with additional calculi are long-term complications.

Cystotomy allows for maintenance of breeding soundness and removal of additional calculi from the bladder. In small ruminants and camelids, bidirectional (normograde and retrograde) flushing is used to restore urethral

patency.[15,32] Even if the urethra is successfully cleared of calculi, traumatic urethritis may cause significant postoperative dysuria in these animals. Therefore, some surgeons prefer also to perform a tube cystostomy to allow for rest and healing of the irritated urethra.[46] If the urethra cannot be cleared at surgery, the tube cystostomy allows for the urethra to rest, and spontaneous elimination of calculi often occurs. Alternatively, a percutaneous tube cystostomy could be performed under ultrasound guidance.

Tube cystostomy allows urine to exit the bladder through a temporary Foley or other type of suprapubic catheter, which is anchored in the bladder lumen and exits the ventral abdomen.[37,47] Urethral patency is apparently restored when calculi are spontaneously expelled from the urethra, dissolved, or refluxed into the bladder, at which time the catheter can be removed. In cases of urethral rupture where patency of the entire urethra is the preferred outcome, tube cystostomy is often the sole feasible option.[46] Primary repair of the urethral defect is rarely successful because of swelling and maceration of the damaged mucosa.

Contrast medium can be introduced into the bladder through the catheter to monitor urethral patency, locate urethral obstruction, or identify urethral rupture.[29] In a goat with a tube cystostomy, 30 mL of a commercially available urinary lavage product containing citric acid, glucono-delta lactone, and magnesium carbonate (hemiacidrin; Renacidin, Guardian Laboratories, Hauppauge, NY) was infused through the cystic catheter and left in the bladder for 30 minutes four times daily for 3 days.[48] This solution is acidic (pH 3.85) and was used to facilitate dissolution of calculi.

Spontaneous resolution of urethral obstruction with tube cystostomy may take several weeks or longer; a mean time of about 11 days in small ruminants has been reported.[37,47] To judge when removal of the catheter is appropriate, the cystic catheter can be clamped shut and the animal observed for urination through the urethra.

Complications of tube cystostomy have been reported to be as high as 50% with surgically placed tube cystostomies and 100% with percutaneously placed cystic catheters.[49] The primary complication is a dislodged catheter, the replacement of which necessitates a second surgery. Risk of tube dislodgement appears to be less when 18 to 20 French tubes are used, when the tube has a balloon to retain the catheter in place (Foley-type catheter), and when a purse-string suture is used in the bladder wall.[47,49] Other complications encountered include tears of the bladder, leakage of urine into the abdomen, adhesions of the bladder to intestine or body wall, and obstruction of the catheter.

In cases of bladder rupture, the urine should be drained from the abdominal cavity, and a surgical procedure should be performed to divert urine to the exterior. If primary repair of the bladder defect is desired, a laparotomy and cystotomy or tube cystostomy can be performed with the animal under local[22] or general[50] anesthesia. Primary repair of the bladder defect is not always necessary, however, because spontaneous sealing of the bladder with fibrin or omentum can occur. Depending on the size and location of the bladder defect, daily or continuous abdominal drainage may need to be performed until spontaneous sealing occurs. Tears are more likely to seal spontaneously if they are located on the dorsal aspect of the bladder[51]; however, it is generally difficult to know the location of the bladder defect without performing a laparotomy. Abdominal drainage may be combined with perineal urethrostomy or penectomy.[12–14] Alternatively, a catheter can be secured in the bladder by a small abdominal incision[52] or an ischial urethrotomy.[12,44]

In *bladder marsupialization* the apex of the bladder is exteriorized using a small paramedian incision, and the seromuscular layer of the bladder is circumferentially secured to the abdominal wall. A cystotomy is performed, and the bladder mucosa is secured to the skin, creating a permanent opening for urine drainage from the bladder to

the exterior.[53] Advantages of bladder marsupialization include decreased hospitalization time and expense for the owner. However, complications include chronic urine scalding, stricture formation, reobstruction, and bladder prolapse. Failure of bladder marsupialization was reported to be 33% in one study.[49]

Ureteral calculi may be removed by *ureterotomy*.[14] *Nephrectomy* may be performed in unilateral cases of obstructive nephrolithiasis.[54] If unilateral nephrectomy is under consideration, measurement of BUN, serum creatinine, and urine specific gravity, with or without a biopsy of the apparently unaffected kidney, should be performed to evaluate remaining renal function.[55] Normal urine specific gravity, BUN, and serum creatinine indicate that the majority of nephrons in the remaining kidney are functional.

Multiple small stab incisions into the skin and subcutaneous tissue along the ventral abdomen may facilitate urine drainage in cases of urethral rupture. These are allowed to heal by second intention.

34.41 POSTOPERATIVE CONSIDERATIONS

Continued assessment of hydration, urine output, and serum urea nitrogen, creatinine, and electrolyte concentrations is indicated after surgery. Postobstruction diuresis has been reported in ruminants[40] and may result from tubular damage, accumulation of urea or natriuretic factors, or preoperative fluid therapy.[56] Induction of modest diuresis through fluid therapy after surgery may help to reduce azotemia and accumulation of blood clots and bacteria in the urethra.

Antimicrobial therapy with an antibiotic that achieves high urine concentrations (e.g., penicillin, ampicillin, sulfonamides) is warranted; the duration of therapy depends on the surgical procedure chosen, residue withholding considerations, and whether UTI exists at surgery. For tube cystostomy, antimicrobial therapy is recommended while the tube is in place and for at least 1 week after the tube is removed.[37] Antimicrobial therapy should be maintained for at least 3 weeks after surgery in animals with active UTI.

Prompt initiation of preventive dietary and environmental management is critical for the long-term success of any surgical procedure for urolithiasis (see Prevention). In animals intended for slaughter, at least 30 days is often required for resolution of tissue damage from urethral or bladder rupture.[44]

34.41.1 Epidemiology

34.41.1.1 GENDER

Obstructive urolithiasis in ruminants and camelids is almost exclusively a disease of males and castrated males. Urinary calculi appear to develop to a similar degree in female ruminants. However, most calculi can pass through the relatively short, distensible urethra of the female, making urethral obstruction uncommon.[57]

Calculi form to a similar extent in the urinary tracts of bulls and steers. Because of the trophic effect of testosterone, the urethral diameter of yearling bulls is approximately 25% greater than that of yearling steers. Urethral obstruction therefore is more common in steers.[11] A similar predisposition for urethral obstruction may exist for wethers relative to buck goats.[49] However, because many wethers are kept as pets, factors such as diet, environment, and age are likely to differ compared with bucks. Specific gender risks in camelids and

pot-bellied pigs is not well described; in commercial pigs, urolithiasis is generally associated with husbandry problems such as improper calcium/phosphorus ratio in the ration and inadequate water availability.[58]

34.41.1.2 SEASON

The incidence of urolithiasis increases in the late fall and winter in North America.[57] Limited water availability, increases in the silica content of range grasses, and a larger population of susceptible animals (young, growing males) during this time of year may be responsible for this trend. In warmer climates, urolithiasis is more frequently a problem in the arid months of the year, underscoring the role of water intake in the pathogenesis of the disease.[57]

34.41.1.3 AGE

Cattle of various ages may develop obstructive urolithiasis. The tendency for this disease to be seen in younger ruminants may be the result of dietary influences, because younger animals are more often fed concentrates for weight gain and eventual slaughter than are mature males kept for breeding. In addition, because relatively fewer mature males are kept for breeding, the apparently increased prevalence of urolithiasis in younger animals may simply reflect the greater numbers of younger males and castrated males at risk.

34.41.1.4 SILICA UROLITHIASIS

Estimates of annual death losses in steers in western North America range from 3%[44] to 5%.[57] Deaths and treatment costs attributable to silica urolithiasis in cattle have been estimated to cost Canadian ranchers $500,000 to $1 million per year (1981 Canadian dollars).[57] Silica urolithiasis is a very common subclinical condition in certain areas. For example, in western North America, silica calculi can be found in the urinary tracts of 50% to 80% of range cattle, with urinary tract obstruction occurring in a variable percentage of these animals.[57,59]

34.41.1.5 PHOSPHATIC UROLITHIASIS

In one study the prevalence of urolithiasis was 0.5% and 0.35% for two Colorado lamb feedlots.[60] The calculus types in these lambs were not identified and are assumed to have been phosphatic calculi. Urolithiasis was the fifth most prevalent cause of death on each feedlot.[60] In beef feedlots, death losses from urolithiasis have been estimated at 0.6%.[61]

34.41.2 Pathophysiology

34.41.2.1 MECHANISMS OF CALCULOGENESIS

Multiple factors influence the development of urinary calculi, but of primary importance is the development of high urinary concentrations of soluble, ionized minerals *(crystalloids)* that aggregate to form insoluble crystals. Supersaturation of urine with a calculus-forming crystalloid is a prerequisite for urolith development.[62] However, supersaturation alone is not solely responsible for urolith initiation because normal urine is

typically supersaturated with a variety of calculogenic ions.[63] Urine contains variable concentrations of mucopolysaccharides, ions, and organic acids, which act as intrinsic inhibitors of crystallization. Through physical and electrochemical interactions, these compounds maintain calculogenic minerals in a colloidal suspension. Calculus formation is initiated if supersaturation of urine with appropriate crystalloids exceeds the protective capabilities of the crystallization inhibitors. The crystalloids are rendered insoluble and precipitate out of the aqueous phase of urine. Calculi enlarge as further mineral precipitation takes place on the crystal surfaces. Dietary, environmental, and management influences interact to determine the degree of supersaturation of urine with calculogenic minerals. Dehydration, with resultant concentration of urinary minerals, would appear to be a potential contributing factor in the development of all types of uroliths.

Mucoproteins, which make up a variable fraction of most uroliths, may act as templates (matrices) on which calculogenic ions could initiate crystallization.[62] Urine mucoproteins may reduce the solubility of certain crystalloids or may be passively incorporated into developing uroliths.[64,65] Estrogenic substances in the diet may promote urolithiasis by increasing urinary mucoprotein concentration.[65,66] This was of particular concern in the past, when diethylstilbestrol (DES) was used as a growth promoter in sheep and cattle in North America.[66]

The solubility of some calculogenic crystalloids is influenced by urinary pH. Struvite (magnesium ammonium phosphate), calcium phosphate, and calcium carbonate uroliths are less soluble in alkaline urine, whereas calcium oxalate solubility is not affected by changes in urine pH within the physiologic range.[63,67–69] The effect of urinary pH on silica calculi is debatable,[70] but recent findings show a trend toward reduction in formation under conditions of mild aciduria.[71]

Primary UTI is considered an uncommon cause of ruminant urolithiasis.[68] Purulent debris within the urinary tract may serve as a nidus for crystal development, and bacterial ureases may increase urinary pH, thereby reducing the solubility of certain crystalloids. Pyelonephritis, with presumed secondary urolithiasis, has been reported in cattle.[26] Urolithiasis may be considered as both a rare cause[27] and a rare consequence[26] of UTI.

Although rare, vitamin A deficiency has been incriminated as a contributory factor for urolith development.[68] Metaplasia of urinary tract epithelium may create nidi for calculogenesis through desquamation of cells or altered cell surface characteristics.

Feeding patterns may influence the formation of urinary calculi. In ruminants, providing a ration in one or two feedings per day induces antidiuretic hormone (ADH) release soon after feeding, resulting in a marked but transient decline in urine output and an increase in urine concentration.[14,57] These changes in urine composition can be limited through ad libitum feeding.[9] Water hardness (dissolved mineral content) has not been considered a significant factor in ruminant urolithiasis.[57]

34.41.2.2

PHOSPHATIC UROLITHIASIS

Ruminants consuming rations high in phosphorus, such as grain-based feedlot rations, typically develop struvite calculi[9,68,72–75] or calcium phosphate (apatite) calculi.[58,76] Rations where the calcium/phosphorus ratio favors phosphorus are particularly prone to cause outbreaks of urolithiasis.[58,75] Increased dietary phosphorus levels result in increased concentration of phosphate ion in ruminant urine.[72] Because calcium opposes phosphorus absorption from the gut, urinary excretion of phosphate is augmented by low dietary

levels of calcium relative to phosphorus.[68,72,73] The interaction of magnesium with calcium and phosphorus is less clearly understood,[72] but experimental increases in dietary magnesium levels to 0.6% of dietary dry matter induced calcium phosphate and struvite urolithiasis in calves.[74] 956 957

Pelleting of rations has been associated with an increased incidence of phosphatic urolithiasis.[9] Ruminant saliva is rich in phosphorus, and the GI tract is the primary route of phosphorus excretion in ruminants.[20] In theory, ruminants feeding on pelleted rations produce less saliva, which would reduce GI phosphate losses and increase urinary phosphate excretion.[9]

34.41.2.3

SILICA UROLITHIASIS

Silica urolithiasis is primarily a problem of sheep and cattle grazing native rangeland grasses of western North America. The silica fraction of these grasses tends to increase with maturity and may continue to increase even after growth ends. In some areas, 4% to 8% of total grass dry matter may be silicon compounds.[57] A fraction of dietary silica, as unpolymerized silicic acid, is dissolved in the ruminal fluid of the grazing animal, absorbed, and excreted in the urine. In sheep and cattle on range, water intake is usually intermittent. During periods of water deprivation, avid water and sodium resorption by the kidneys results in the formation of highly concentrated urine. Silicic acid may be concentrated to such an extent that it polymerizes to a less soluble form, polysilicic acid. Polysilicic acid, in turn, forms large micelles in solution that quickly become insoluble when bound to urinary mucoproteins.[64] The resultant calculi are usually composed of about 20% mucoprotein, 75% silicon dioxide, and variable amounts of calcium oxalate and calcium carbonate.[57]

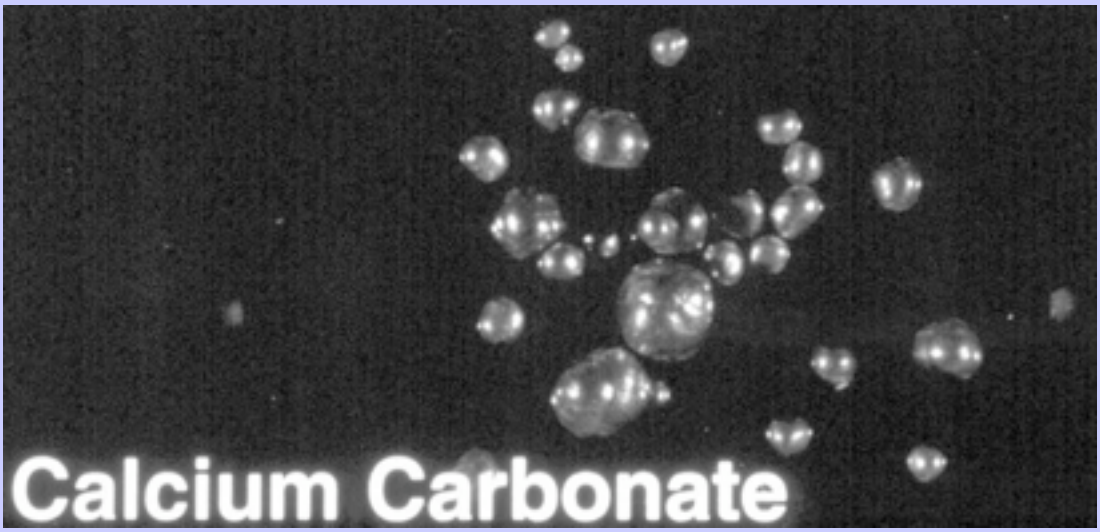
Dietary deficiencies of copper and zinc have been identified as contributory factors in silica urolith formation in rats.[77] The incidence of silica urolithiasis can be increased by feeding sheep rations that have a high calcium/phosphorus ratio (~2.8:1) and induce more alkaline urine.[71,78] It is important to note that a high calcium/phosphorus ratio in the diet can help to prevent one type of urolith (struvite) but may be a contributory factor for another (silica). This underscores the importance of both ration and urolith mineral analyses in the formulation of preventive measures for this disease.

34.41.2.4

CALCIUM CARBONATE UROLITHIASIS

Calcium carbonate calculi have a characteristic round shape and golden color and are often present as multiple calculi scattered throughout the lower urinary tract (Fig. 34-20). These calculi are common in sheep grazing lush, rapidly growing clover pastures in Australia.[69] These forages are rich in calcium and low in phosphorus and magnesium and have high oxalate content. In the gut, oxalate avidly binds calcium and makes it unavailable for absorption. With gradual introduction of oxalate-rich diets, ruminal bacteria efficiently metabolize oxalate to bicarbonate.[69,79] Thus, microbial metabolism of oxalate in the rumen may increase the availability of dietary calcium.[80] These factors may combine to increase urinary calcium excretion and alkalinize urine, thereby promoting calcium carbonate calculogenesis. Calcium carbonate urolithiasis has been reported in northern California.[81] Although many of the animals in this report had a history of being fed alfalfa hay, the relationship, if any, between alfalfa feeding and calcium carbonate urolithiasis remains unclear.

Fig. 34-20 Calcium carbonate calculi.



34.41.2.5 CALCIUM OXALATE UROLITHIASIS

Oxalate is an end product of glycine and ascorbic acid metabolism and is a normal constituent of urine.[62,69] In humans, inherent defects in oxalate metabolism and calcium homeostasis contribute to calcium oxalate urolithiasis.[62] Dietary and metabolic factors that influence formation of this urolith type have not been elucidated in ruminants. Poisoning by oxalate-containing plants is not considered a common cause of calcium oxalate urolithiasis.[68] Given its very low solubility, calcium oxalate crystals are often present in normal urine[68] and may be incorporated into other uroliths as a trace component.

34.41.3 Prevention

A preventive approach to a urolithiasis problem begins with a search for risk factors associated with the diet, management, and the environment. Whenever possible, ration analysis and mineral analysis of the urolith(s) should be performed to identify causative dietary factors accurately. Consult Box 34-1 for analysis laboratories. If uroliths are not obtained, ration analysis and a thorough dietary history may provide a strong suggestion of the urolith type. In light of the central role of urinary supersaturation in calculogenesis, the ultimate aim of preventive measures should be reduction of urinary concentration of calculogenic mineral ions. In addition, the urine should be diluted to such an extent that the calculogenic ions are less prone to precipitate. Dilution of urine is achieved through increased salt and water intake.

34.41.3.1 DIETARY MANAGEMENT

34.41.3.1.1 Phosphatic Urolithiasis

Prevention of phosphatic calculi requires adjustment of the dietary calcium/phosphorus ratio to a level of 2:1 or greater.[72] The magnesium content of the ration should be maintained at recommended levels. Abandoning pelleted feeds and increasing the quantity of long-stem forage in the ration may increase salivary flow and fecal phosphate excretion.[9]

34.41.3.1.1.1 Box 34-1 Urolith Analysis Laboratories

34.41.3.1.1.1.1 URINARY STONE ANALYSIS LABORATORY

Department of Medicine and Epidemiology

School of Veterinary Medicine

University of California at Davis

Davis, CA 95616

1-530-752-3228

34.41.3.1.1.1.2 DR. CARL OSBORNE

Department of Small Animal Clinical Sciences

College of Veterinary Medicine

University of Minnesota

1352 Boyd Avenue

St. Paul, MN 55108

1-612-625-7744

34.41.3.1.1.1.3 UROLITHIASIS LABORATORY

PO Box 25375

Houston, TX 77265-5375

1-800-235-4846

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Addition of salt to feedlot rations has proved effective in several studies. Sodium chloride, fed at a level of 3% to 5%, reduces the incidence of urolithiasis without adverse effects on feed intake or weight gain.[64] Cattle consuming such rations show variable increases in water intake and urine output, implying that some

of the beneficial effect of salt feeding results from diuresis.[57,82] Other studies show minimal effect of this level of salt supplementation on urine volume, and one investigator has suggested that the preventive effect is caused by interruption of crystal development by chloride ion in urine.[66] Nonetheless, it is prudent to anticipate increased water intake after salt supplementation is initiated.

Ammonium chloride supplementation, fed at a level of 0.5% to 1% of ration dry matter, also reduces the incidence of struvite urolithiasis.[82,83] Ammonium chloride may increase the solubility of magnesium ammonium phosphate crystals through a modest reduction in urinary pH. The pH of the urine is likely to be influenced by the relative concentrations of strong cations (sodium and potassium) and strong anions (chloride and sulfate) of the entire ration, a relationship termed the *dietary cation-anion difference*.[84] Thus the efficacy of ammonium chloride in reducing urinary pH and therefore reducing struvite urolithiasis may vary among different livestock operations because the concentration of these cations and anions may vary among rations.[81]

34.41.3.1.2

Silica Urolithiasis

Restriction of dietary silica intake in ruminants grazing native grasses is not feasible; thus dietary management is limited to salt (sodium chloride) supplementation. However, loose salt or lick salt is unlikely to be ingested in sufficient quantities to affect water intake.[85] Sodium chloride supplementation of palatable creep feeds, at a level of 15% of dry matter, is an effective measure for range calves.[57] Creep feeding should begin at 4 months of age or earlier. Initially, lower salt concentrations may be required for young calves to become accustomed to the feed. The feeders should be located near a reliable source of palatable water.

Ammonium chloride supplementation (1% of dry matter) has been demonstrated to significantly reduce silica urolith development in lambs.[78] In the same study, reduction of the dietary calcium/phosphorus ratio from 2:1 to almost 1:1 resulted in a trend toward reduced silica calculi formation. The role of copper and zinc deficiencies in ruminant silica urolithiasis remains to be determined.

34.41.3.1.3

Calcium Carbonate Urolithiasis

This type of urolith has been frequently recovered from small ruminants fed alfalfa hay.[81] Because of this and the risk factors identified in Australian sheep, reduction of dietary calcium levels could be beneficial. This may not be possible for sheep grazing legume pastures. Ammonium chloride supplementation may be an effective preventive measure because calcium carbonate is more soluble in acidic solutions.[69]

34.41.3.2

WATER MANAGEMENT

Maximizing water intake is an important aspect of urolithiasis prevention, regardless of the urolith type involved. Cleaning of water containers should be a regular practice. Water palatability may also be improved through provision of shade for water containers during the summer. Dark liners (with sun exposure) or heaters will warm water during the winter. Automatic waterers should be checked regularly for proper function. Shallow containers capable of rapid refilling provide higher rates of water turnover, resulting in less stagnation.

In operations involving multiple animals or large pastures, placement of multiple watering sites might allow for more frequent intake. This is especially true for sheep, whose banding instinct usually prevents individuals from traveling alone to distant watering sites.

34.41.3.3

URACHAL DISORDERS

ROGER W. ELLIS

Abnormalities of the umbilicus and umbilical remnants, including the urachus, are frequently encountered disease conditions of neonatal calves. Infections of the umbilicus, urachus, and umbilical vein or arteries *(navel ill)* are often associated with localized or systemic bacterial infections acquired from environmental contamination at birth. The association of umbilical abnormalities with calfhood morbidity and mortality has been established.[86] Of the umbilical structures, the urachus is most frequently involved.[87,88] Occasionally, more insidious and chronic conditions of the urachal remnant are observed in older calves and mature cattle. Internal abscessation, adhesions, sepsis, peritonitis, uroperitoneum, cystitis, and intestinal strangulation have all been reported.[89–94] Urachal fistulas or acquired patent urachus, although often observed in foals, is infrequently reported in cattle.[95]

34.41.3.3.1

Pathogenesis

Subsequent to bacterial infections of the urachus of the neonate, the inflammatory response within the abdomen precipitates development of fibrinous adhesions between the urachus and surrounding viscera, including the rumen, intestine, uterus, bladder, or ovaries. Abscesses may form in single or multiple locations in the urachal stalk; although uncommon, abscesses involving the apex of the urinary bladder result in concurrent cystitis.[91,94] Urachal fibrosis and adhesions may serve as a means of mechanical interference of bladder emptying, resulting in secondary cystitis from chronic urine retention.[94] Infrequently, the urachal abscess perforates, with subsequent peritonitis, sepsis, or uroperitoneum.[89,90] Most urachal infections involve *Arcanobacterium pyogenes* or *Eschericia coli*; other skin or enteric organisms may be present as well.[96]

Alternatively, the urachus may fail to regress completely, creating a persistent communication between the bladder apex and the pouchlike urachal remnant. The volume of urine retained in the urachal remnant is variable. Animals with this problem may remain asymptomatic for life; however, retention of urine in the urachal “pouch” can predispose the animal to urinary tract infection. Further, rupture of the urachal remnant can occur, resulting in uroabdomen and, if cystitis is also present, septic peritonitis.[89]

34.41.3.3.2

Clinical Findings

Calves with internal urachal abscesses, adhesions, and other sequelae are usually older than 4 weeks of age. A history of umbilical infection during the neonatal period may or may not exist, and external umbilical abnormalities may not be present. Clinical signs may be nonspecific, including fever, lethargy, poor body condition, and poor growth or productivity. Dysuria, pollakiuria, stranguria, and colic may be evident on examination or may be included in the medical history. External palpation of the umbilicus and abdomen in smaller calves may reveal pain and enlarged umbilical remnants, particularly in the caudoventral abdomen along a line from the umbilicus to the pelvic brim. Diarrhea, abdominal distention, and an ached-back

stance may be evident in animals with concurrent peritonitis. Complications from associated septicemia, such as lameness and joint distention, pneumonia, hypopion, and meningitis, are occasionally seen. When infection extends into the bladder lumen, hematuria and pyuria are reliably present.[91,94]

In older animals, spontaneous rupture of the infected urachal stalk may result in the acute onset of peritonitis. If the urachal remnant communicates with the bladder lumen, rupture of the urachus results in uroabdomen. Rupture may occur spontaneously or after abdominal trauma or parturition. Transrectal palpation may allow detection of abnormal bladder size, position, or shape resulting from adhesion of the bladder apex to the urachal remnant. Distention or displacement of bowel may be detected in cases of urachovisceral adhesions.

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A detailed ultrasonographic examination of the interior of the umbilical remnant is warranted. Transrectal and transabdominal ultrasonographic examination of the caudal and ventral abdomen may reveal structures compatible with urachal abscesses. The bladder and other viscera may assume abnormal shape or position as a result of urachal adhesions.[91,97] The luminal contents of the urachal remnant and bladder may appear flocculent in cases complicated by concurrent cystitis. Uroabdomen is characterized by accumulation of echolucent fluid in the abdominal cavity, with variable amounts of fibrin deposition evident.

In cases complicated by urachal infection or peritonitis, laboratory findings of an inflammatory hemogram, including leukocytosis, neutrophilia, hyperfibrinogenemia, and hyperglobulinemia are expected. Urinalysis may be normal or indicative of cystitis if the urinary bladder is involved. Abdominocentesis findings are variable and depend on the presence and extent of peritonitis associated with the urachal lesion. Voluminous, blood-tinged abdominal fluid suggests uroperitoneum, and analysis of the fluid and serum creatinine concentration is indicated (see Urolithiasis).

34.41.3.3.3

Differential Diagnosis

Because of the variable nature of urachal problems, the differential diagnosis will vary according to the organ(s) involved. The general clinical picture may suggest acute, subacute, or chronic infection with involvement of the abdomen and lower urinary tract. Urachal adhesions to the intestine or uterus may result in colic, signs of intestinal obstruction, and postpartum peritonitis or uroabdomen. Concurrent signs involving the lower urinary system might indicate the potential for primary ascending infections, such as cystitis or pyelonephritis. In cases of uroabdomen in males, obstructive urolithiasis is an important differential. Urolithiasis, urethritis, or neurologic disease may be included in differential diagnoses of dysuric animals. Nephritis of hematogenous origin is worthy of consideration in animals showing ill-thrift, colic or an arched back, or abnormal urine.

34.41.3.3.4

Treatment

Ventral midline celiotomy, paramedian celiotomy, or laparoscopy under general anesthesia is recommended to enable complete evaluation of the abdominal cavity.[98,99] Resection of the urachal remnants with careful dissection of adhesions is often required for complete resolution. Resection of the apex of the urinary bladder is necessary if the urachus incorporates or communicates with the bladder. Perioperative and postoperative antibiotic therapy is essential, and appropriate antibiotic selection may be based on culture and sensitivity of the abscess(es) or urine.

34.41.3.3.5 Prognosis

Outcomes of the surgical management are often satisfactory, but recurrence of adhesions should always be considered as a potential outcome. A guarded to poor prognosis is warranted for severe peritonitis or extensive adhesions. Without surgery, medical management with long-term antibacterial therapy would be expected to provide limited success because the structural problems created by adhesions and abscesses are not directly addressed.

34.41.4 EVERSION OF THE BLADDER AND PROLAPSE OF THE BLADDER

DAVID C. Van METRE

Eversion of the bladder is an uncommon event that occurs during or shortly after parturition in cows.[100–104] Forceful straining moves the bladder fundus caudally, eventually turning the bladder inside-out. The bladder is then forced out of the urethral orifice. Prolapse of the bladder is also a rare periparturient event in cattle, more frequently associated with dystocia.[100,101] In this condition a full-thickness tear of the vaginal wall occurs during delivery, allowing the bladder (and possibly other viscera) to be displaced from the abdominal cavity into the vagina.

34.41.4.1 Clinical Findings and Differential Diagnosis

Cows with either eversion or prolapse of the bladder have a smooth, spherical mass within the vagina, usually protruding from the vulva. An affected cow may be alert and ambulatory, but if concurrent hypocalcemia, exhaustion, or peritonitis exists, the cow may be recumbent and depressed. Careful vaginal examination is required to differentiate these two conditions from each other and from vaginal prolapse, vaginal polyps, fat protrusion from a vaginal tear, vaginal neoplasia, fetal membranes, and uterine prolapse. Prevention of straining through epidural anesthesia is essential because expulsive efforts can cause herniation of other viscera through the urethra (bladder eversion) or through the vaginal tear (bladder prolapse).[100] Epidural anesthesia also facilitates cleaning of the area because straining may result in continual fecal contamination of the perineum and vestibule.

34.41.4.1.1 EVERSION OF THE BLADDER

The mucosal surface of the bladder is exposed. The ureteral openings may be visible on its dorsal aspect, although these may be occluded and difficult to see if the wall of the bladder is edematous.[103] Vaginal palpation reveals that the protruding tissue originates from the urethral orifice. With time, constriction of the everted bladder by the narrow urethra may cause venous congestion, edema, thrombosis, and eventual necrosis.[100] Palpation and ultrasonographic examination are required for detection of herniation of other viscera through the urethral orifice and into the interior of the everted bladder. Strangulation of incarcerated bowel may occur.[101,102] Careful fine-needle aspiration of the interior of the eversion has been used to differentiate eversion from prolapse of the bladder. With bladder eversion, aspiration may yield peritoneal fluid, but laceration of herniated bowel is a concern.[100]

34.41.4.1.2 PROLAPSE OF THE BLADDER

The serosal surface of the bladder is exposed. Careful palpation of the vagina reveals that the bladder protrudes from a full-thickness tear in the floor or lateral wall of the vagina. Other viscera may be present in the vagina as well. Fine-needle aspiration yields urine from the bladder lumen.

34.41.4.2 Treatment and Prognosis

34.41.4.2.1 EVERSION OF THE BLADDER

Manual reduction of the everted bladder may not be possible if it is edematous or if other viscera have herniated into its interior. The dorsal aspect of the urethra may be incised to widen the route through which the bladder is to be replaced.[100,101] Laparotomy is required for assessment of the viability of herniated bowel, and subtotal cystectomy may be performed if extensive bladder trauma or necrosis has occurred.[101] The viability of the involved structures is of primary concern for prognosis. Bladder paralysis and rupture are potential sequelae to ischemic damage that develops during eversion.[100] Cystitis and pyelonephritis may develop as well, and antibiotic therapy is warranted if repair is attempted. Animals with chronic conditions may develop hydroureter, hydronephrosis, and renal failure.[104]

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34.41.4.2.2 PROLAPSE OF THE BLADDER

A flexible catheter may be passed into the urethra to remove urine from the bladder, thereby confirming the diagnosis and facilitating bladder replacement. After catheterization and removal of urine, the bladder can be replaced into the abdominal cavity and the vaginal tear can be sutured. Severe contamination of the peritoneal cavity may render attempts at treatment unjustified. Antibiotic therapy is indicated for surgical candidates.

34.41.4.2.3 PELVIC ENTRAPMENT OF THE BLADDER

DAVID C. Van METRE

In pelvic entrapment of the bladder, the apex and fundus of the bladder are displaced caudodorsally into the pelvic cavity, resulting in impaired urine outflow. In one report the condition was diagnosed in two Holstein cows a few days after parturition had occurred, suggesting a potential role of delivery or postpartum straining in bladder displacement.[105] Entrapment of the bladder in a perineal hernia[106] or within a vaginal prolapse[107] may also occur.

34.41.4.2.3.1 Clinical Findings

Bladder emptying is impaired, and the presence of the bladder in the pelvic inlet induces straining. An affected cow may show tenesmus, pollakiuria, and stranguria. On rectal examination a soft, fluctuant mass may be detected beside the vagina.[105] In calves, radiography has been used to demonstrate the pelvic position of the bladder.[108]

34.41.4.2.3.2

Differential Diagnoses

Differential diagnoses include proctitis, vaginitis, retained placenta, bladder paralysis, cystitis, and perivaginal abscess. Needle aspiration of the bladder per vaginum has been used to make a definitive diagnosis,[105] although the danger of uterine puncture should be considered.[107] Ultrasonographic examination can also be useful for definitive diagnosis.[107] Draining the bladder through catheterization or needle aspiration facilitates replacement of the bladder by manipulation per vaginum. However, laparotomy was necessary in one cow to reset the bladder because of the development of fibrinous adhesions between the bladder and vagina.[105] In cases of bladder entrapment within a vaginal prolapse, complete correction of the prolapse usually restores the bladder to its normal position.[105]

34.41.4.2.4

ENZOOTIC HEMATURIA

DAVID C. Van METRE

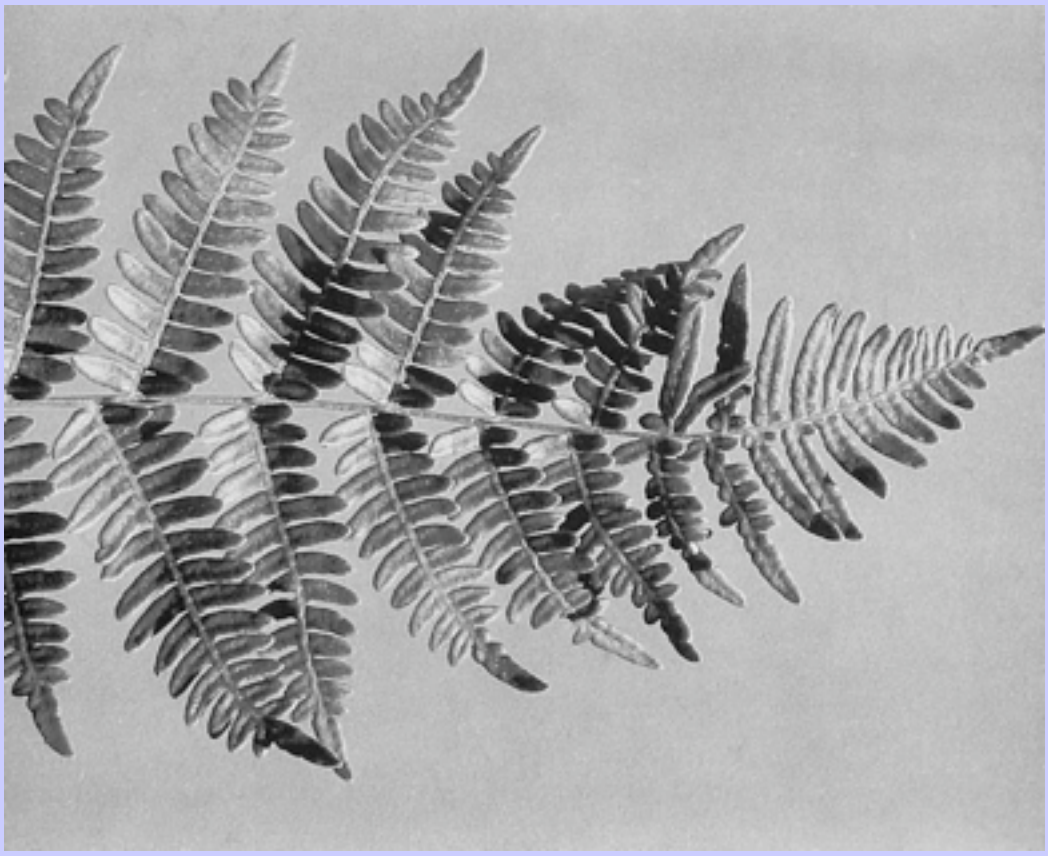
Enzootic hematuria is a disease of chronic or intermittent hematuria in cattle and sheep and is associated with chronic ingestion of bracken fern *(Pteridium aquilinum)*[109–115] (Fig. 34-21). A different fern species, *Cheilanthes sieberi,* may induce this disease in Australian cattle.[109,111] Hemorrhagic cystitis is the initial consequence of exposure to the toxic compound(s) in the plant. With continued ingestion of bracken fern, cattle develop bladder neoplasms of epithelial, mesenchymal, or mixed origin. Bladder infection with bovine papillomavirus type 2 is involved in carcinogenesis.

34.41.4.2.4.1

Clinical Findings

In most cases, several animals are affected in a group that is grazing a particular pasture or being fed a particular type or cutting of hay. Protracted, possibly intermittent, hematuria is the first clinical sign detected in most animals.[109] Blood clots may be voided on occasion. Chronic blood loss eventually results in tachycardia, tachypnea, exercise intolerance, pale mucous membranes, and a decline in productivity and body condition. Bladder wall thickening and bladder tumors may be palpated per rectum. Proliferative changes or overt neoplasia of the bladder may cause dysuria, pollakiuria, and rarely, obstruction of the bladder trigone. Occasionally, blood clots may cause urethral obstruction. Depending on the magnitude and duration of bracken fern ingestion, hematuria may last for months to years before severe debilitation or death occurs. Ultrasonographic examination of the urinary bladder of affected animals may reveal bladder thickening and an irregularly shaped bladder wall. In an Indian study, affected cattle showed a bladder wall thickness of 4 to 5 mm (normal, 1 to 2 mm).[110]

Fig. 34-21 Bracken fern *(Pteridium aquilinum)*.



The syndrome of enzootic hematuria is quite different from acute bracken poisoning, which occurs after ingestion of large quantities of bracken fern (approximating the animal's body weight), usually over 1 to 3 months.[111,112] Acute bracken poisoning manifests as an acute coagulopathy or fulminant septicemic crisis associated with severe bone marrow suppression. Clinical signs include fever, profound weakness, epistaxis, hyphema, dysentery, and petechial hemorrhages of the mucosal surfaces and sclera.[111] Acute bracken poisoning is further described in Chapter 54.

34.41.4.2.4.2

Clinical Pathology

Severe anemia is often seen on hematologic examination of cattle and sheep with enzootic hematuria. Evidence of a regenerative response may not be present if bone marrow suppression is severe. The platelet, segmented neutrophil, and lymphocyte counts may be reduced.[111–113] Urinalysis reveals hematuria, proteinuria, and variable pyuria.[109]

34.41.4.2.4.3

Differential Diagnosis

Examination of serum for evidence of hemolysis and analysis of sediment from a freshly voided urine sample for intact red blood cells allow for differentiation of hematuria from the hemoglobinuria found in hemolytic diseases. Icterus, also characteristic of ruminant hemolytic disorders, is not found in cases of enzootic hematuria. Hematuria may be evident in urinary tract infection, but pyuria and bacteriuria are marked, and anemia, if present, is usually mild. Simultaneous involvement of several animals is uncommon with urinary tract infection but common in enzootic hematuria. Hematuria may be evident in cattle affected by malignant catarrhal fever (MCF). Protracted, severe hematuria is rare in cases of urolithiasis, and anemia is also not expected. Without necropsy, a diagnosis of enzootic hematuria requires documentation of access to bracken fern in animals with characteristic clinical signs and laboratory data.

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34.41.4.2.4.4

Epidemiology

Enzootic hematuria has a wide geographic distribution, with cases reported in North and South America, the United Kingdom, Australia, and several European countries.[109] Bracken fern is found in all areas of the United States except the Great Plains, with most livestock poisonings occurring in the Pacific Northwest and upper Midwest.[112] The plant grows best in well-drained, fertile soils and is often localized in open areas of forests.[114] Sheep and cattle are poisoned by grazing the plant or consuming contaminated hay.[114]

Enzootic hematuria is primarily seen in adult sheep and cattle. In field cases, cattle grazing infested pastures develop hematuria by 2 to 3 years of age.[109,115] Feeding adult cattle 1 to 2 kg bracken fern/head/day led to hematuria within 10 to 15 months in one trial.[109] Papillomas of the bladder occur as early as 1 year after bracken feeding begins, with invasive carcinomas arising 2 to 6 years later.[109,115]

34.41.4.2.4.5

Pathophysiology

All parts of the plant are toxic to sheep and cattle.[111,112] Several compounds in bracken fern possess irritant, mutagenic, immunosuppressive, or carcinogenic activities.[109,113] These include ptaquiloside (aquilide A), quercetin, and a-ecdysone.[116–119] The carcinogenic principles are present in the milk of cows grazing bracken fern.[120,121] Bracken fern compounds may cause recrudescence of latent bovine papillomavirus 2 (BPV-2) infections through immunosuppression. Bladder infection with BPV-2 follows, and mutagenic compounds in bracken fern interact with BPV-2 in the bladder to induce local neoplasia.[109,113,116] Growth of the resultant neoplastic tissue may be enhanced by further exposure to mutagenic bracken compounds.[109,113,116] Similarly, BPV-4 and mutagens from bracken fern may act in synergy to induce neoplasia of the mucosa of the upper GI tract.[116,118,119]

In multiple species, cyclooxygenase 2 (COX-2) is overexpressed in epithelial neoplasms, including those of the urinary bladder origin. Certain types of tumors of urinary epithelium may coexpress COX-1 and COX-2. Bladder carcinomas from cows with enzootic hematuria have been shown to express both COX-1 and COX-2 at a high level relative to normal controls, when evaluated by immunohistochemical

methods.[122] The efficacy of COX-2 inhibitor drugs on cancer prevention or treatment in cattle at risk for bladder tumors remains to be investigated.

Immunosuppression results from reduction in circulating neutrophil and lymphocyte counts. Neutropenia appears to be a reversible phenomenon that results from bone marrow suppression. Neutrophil counts may normalize within 1 to 2 weeks of cessation of bracken feeding. Lymphopenia persists during periods of low-level ingestion.[113]

34.41.4.2.4.6

Necropsy Findings

Tissue pallor from anemia is often appreciated. The bladder wall is thickened and the mucosa hemorrhagic and ulcerated. Microscopic examination of the bladder wall reveals capillary engorgement, intramural hemorrhage, and metaplasia of the bladder epithelium.[111] Several types of bladder tumors and mixed-origin neoplasms may be present. Metastasis of epithelial neoplasms to the regional lymph nodes or other organs can occur.[123] Pharyngeal, esophageal, or ruminal papillomas may be found as well, and carcinomas may develop in these same locations in cattle exposed to bracken fern over several years.[115]

34.41.4.2.4.7

Treatment and Prevention

Treatment of enzootic hematuria is limited to reduction or elimination of bracken fern in the diet. Wooded areas that support growth of bracken fern can be fenced off, and forage improvement may help to limit incorporation of the plant into hay. If such measures are not feasible, a program of early culling may help to avoid low productivity from anemia and neoplasia. Hematuria will cease if bracken feeding is discontinued before the onset of tumor formation.

34.41.4.2.5

URINARY TRACT INFECTION

David C. VAN Metre

Cystitis, ureteritis, and pyelonephritis in ruminants most often result from ascending urinary tract infection (UTI) with *Corynebacterium renale* or *Escherichia coli*.[124] Less common causative organisms include various coliform species[125] and other members of the *C. renale* group.[126] Renal infection via the hematogenous route (suppurative embolic nephritis) is much less common but may result from bacteremia with such agents as *Salmonella* species, *Actinomyces pyogenes,* or in small ruminants, *Corynebacterium pseudotuberculosis*.[127]

34.41.4.2.5.1

Clinical Signs

Cystitis in cattle is typified by dysuria and pollakiuria, with or without gross hematuria and pyuria. During urination the flow rate is often decreased. An affected cow may tread or swish the tail and retain an arched stance after voiding has ceased. Blood, purulent debris, or crystalline material may occasionally be found on the hairs of the ventral commissure of the vulva. Rectal palpation may reveal a thickened, painful bladder. If UTI is limited to the bladder, an affected cow usually does not show generalized signs of infectious disease (e.g., fever, anorexia, depression).[124]

In contrast, cattle with acute pyelonephritis often have a history of an abrupt reduction in feed intake and milk production. Fever, depression, ruminal stasis, scleral injection, and occasional episodes of mild colic accompany the signs of cystitis previously described.[124] With bilateral or left-sided pyelonephritis, renal enlargement, pain, and a loss of normal lobulation of the left kidney may be evident on rectal examination. Transabdominal ultrasonographic examination is useful for evaluation of the right kidney, because the right kidney usually cannot be reached during rectal examination unless it is greatly enlarged.[124] In an adult cow, ultrasound evaluation of the right kidney can be performed using a 3.5-MHz transducer at the twelfth intercostal space. This transducer can also be used to view the left kidney at the dorsocranial aspect of the right paralumbar fossa.[128] Alternatively, the left kidney can be imaged transrectally with a linear-array transducer. Dilation of renal calyces; echogenic, flocculent material within the renal pelvis; abnormal renal shape; and renal enlargement are ultrasonographic findings suggestive of pyelonephritis. Vaginal palpation is usually necessary to detect ureteritis[124]; the ureters may be enlarged and painful when palpated through the vaginal wall.

The clinical signs of chronic pyelonephritis are relatively vague and inconsistent.[124] Weight loss or poor growth rate, anorexia, and reduced milk production are common presenting complaints. Posture and behavior during urination may be normal, although affected calves have been noted to dribble urine, thereby developing phosphatic calculi adherent to the vulvar hairs and urine scald of the perineum and hindlegs. Ulcerative vulvovaginitis may be present as well.[129] Polyuria without gross urine abnormalities 961
may be found in some cases. Diarrhea and pale mucous membranes may also be seen during physical 962
examination. Rectal and vaginal examination findings for chronic pyelonephritis are similar to those of the acute form, although the involved structures may not be painful or enlarged when palpated.

Urinalysis with chemical reagent strips appears to be a sensitive ancillary test for both acute and chronic pyelonephritis. In a study of 15 cases of bovine pyelonephritis, clinical signs suggestive of urinary tract disease were found in only three cows. However, evidence of hematuria or proteinuria was found through routine reagent strip urinalysis in all 15 cases.[124] Further examination and testing of the urinary tract confirmed a diagnosis of pyelonephritis.

34.41.4.2.5.2

Differential Diagnosis

Mild colic may result from a variety of GI disorders, but urinalysis findings are normal in these conditions. Enzootic hematuria usually affects multiple animals in a particular locale, and access to bracken fern is usually demonstrable. Although dysuria and hematuria may be evident in enzootic hematuria, anemia is profound, whereas pyuria and bacteriuria are mild or nonexistent. Urolithiasis may induce colic, dysuria, and hematuria. However, urolithiasis is almost exclusively a disease of male ruminants, and UTI is more common in females. Bladder distention is a common finding in urolithiasis but rarely occurs in UTI. Other conditions that may cause dysuria include vaginitis, vulvar trauma, perivaginal abscesses, and pelvic entrapment of the bladder. Careful assessment of the neurologic system is warranted in cases of UTI to determine if the underlying cause is bladder paresis or incomplete voiding.

34.41.4.2.5.3

Clinical Pathology

Neutrophilic leukocytosis and hyperfibrinogenemia are evident on hematologic evaluation of cattle with pyelonephritis. Hyperglobulinemia may develop if the infection is established for several days. Severe, protracted proteinuria may cause hypoalbuminemia, and the resultant low plasma oncotic pressure may contribute to the development of diarrhea in occasional cases. In chronic pyelonephritis, anemia may result from reduced erythropoietin production, chronic inflammatory disease, and blood loss through the urine.[124]

If azotemia is found on serum chemistry analysis, the clinician must consider renal and prerenal causes before formulation of a prognosis. Pyelonephritis with azotemia and isosthenuria would indicate bilateral renal involvement, lowering the chances for successful treatment.[124]

Urinalysis is required for definitive diagnosis of UTI, but careful collection technique is important for valid conclusions to be made. Concurrent metritis, vaginitis, or posthitis may result in contamination of urine with blood, bacteria, and inflammatory cells, particularly if the rate of voiding is slow. A midstream or end-stream catch is likely to provide the most accurate culture results.[130] Tentative identification of the organism may be obtained through Gram stain of the urine.

Urinary tract infection consistently produces hematuria, proteinuria, and bacteriuria on urinalysis. Quantitative culture of a urine sample allows for confirmation of the diagnosis and identification of the causative organism. Although not present in all cases, leukocyte casts provide definitive evidence of pyelonephritis.[131]

34.41.4.2.5.4

Pathophysiology

Factors involved in ascending UTI include the dose and virulence of the bacterial challenge, the presence of urogenital trauma (e.g., from calving injuries) or abnormal vulvar conformation, obstetric manipulation, bladder catheterization, and urine retention (as occurs with bladder paralysis or urethral obstruction). After cystitis is established, alterations in the contractility and thickness of the bladder wall may promote vesicoureteral reflux, spreading infection into one or both ureters.[132] Hemorrhage, fibrin deposition, and epithelial necrosis may result in intermittent ureteral or renal obstruction, which may be responsible for the episodic signs of colic occasionally seen in affected cows. Once pyelonephritis is established, necrosis of papillary and tubular epithelium leads to accumulation of necrotic debris in the renal pelvis, loss of functional nephron mass, abscess formation, fibrosis, and distortion of renal shape. Renal calculi, particularly struvite uroliths, may occasionally develop in cases of pyelonephritis. Crystal deposition on necrotic debris and the high local pH caused by bacterial urease activity may contribute to calculogenesis.

Corynebacterium renale is a large, pleomorphic, club-shaped bacillus that is aerobic, ureolytic, nonmotile, and gram positive.[126] Pyelonephritis caused by *C. renale* has been reported in a sheep[132] and induced experimentally in goats.[133]*C. renale* is adapted to and maintained in the bovine and ovine urinary tract and is unlikely to be maintained in the external environment for prolonged periods.[126] Subclinical carriers and diseased animals transmit the organism through direct vulvar contact or by splashing urine droplets onto the vulvas of susceptible cows. Iatrogenic transmission through

contaminated obstetric instruments or urinary catheters is also possible. Venereal transmission of *C. cystitidis*[126] and *C. renale*[134,135] from infected bulls may also occur.

Adherence of *C. renale* to urinary tract epithelium appears to be mediated by pili[136] in a pH-dependent manner.[137] Adherence is enhanced under alkaline conditions and inhibited by acidic conditions. This may explain the clinical improvements reported in infected cattle fed salts that promote urinary acidification.[134] Through ureolysis and ammonia production, the organism maintains urine alkalinity, thereby facilitating colonization of the epithelial surface. A serum antibody response develops after renal infection is established, but this response is rarely curative[124] and does not appear to impart resistance to reinfection with *C. renale*.[138]

Ruminant UTI is also frequently caused by *Escherichia coli,* a ubiquitous, gram-negative coliform bacterium.[124] The serotype(s) and virulence factors of *E. coli* involved in bovine pyelonephritis have not been identified. Clinical evidence suggests that UTI results from fecal contamination of the urogenital tract or loss of normal urinary tract defenses.

Congenital defects such as ectopic ureter occasionally result in UTI, presumably from ascending infection of an abnormally positioned ureter. Impairment of bladder emptying, as might occur with bladder adhesions, urachal remnant infection, or diseases of the spinal cord, may promote ascending UTI. Urethral trauma caused by urolithiasis, breeding injury, urogenital papillomas, or catheterization of the urethra may also be conducive to infection.

34.41.4.2.5.5

Epidemiology

An Israeli study found that the prevalence of pyelonephritis on a per-farm basis varied between 0.3% and 2.7%.[139] UTI is much more common in female ruminants than in males because of the relatively short urethral length in females[140] and the potential for urinary tract contamination and trauma during parturition. Seventy-three percent of pyelonephritis cases developed within the first 90 days after calving, suggesting that the postpartum period is a critical time for initiation of UTI.[139] Another study identified reproductive tract abnormalities such as pneumovagina, metritis, and poor perineal conformation in 7 of 15 cows with pyelonephritis.[124]

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In the past, *C. renale* has been regarded as the most common causative organism for bovine pyelonephritis[125]; however, in recent studies from Israel, *E. coli* has been the most frequent cause.[129,141] Once *C. renale* infection exists in a herd, the number of subclinically infected cows increases over time, and the infection becomes difficult to eradicate.[126] Through increased frequency of contact, overcrowded cattle may experience more rapid transmission of infection.

34.41.4.2.5.6

Necropsy Findings

Hemorrhage, ulceration, and fibrin deposition are evident on the epithelium of the bladder and urethra. With chronic infection, polypoid growths may develop in the bladder mucosa; these masses grossly resemble tumors and must be definitively identified by histopathologic examination.[125] One or both ureters may be enlarged, with purulent debris occasionally occluding the ureteral lumen. Pyelonephritis cases may show gross renal enlargement in acute to subacute cases (Fig. 34-22). On sagittal sectioning of

the kidney, viscous, gray, odorless exudate is found within the renal pelvis and extending into the medulla and cortex.[126] A Gram stain of the exudate is useful for differentiation of *C. renale* from *E. coli* infection. Renal abscesses, with gross distortion of renal size and shape, may be seen in cases of chronic pyelonephritis.

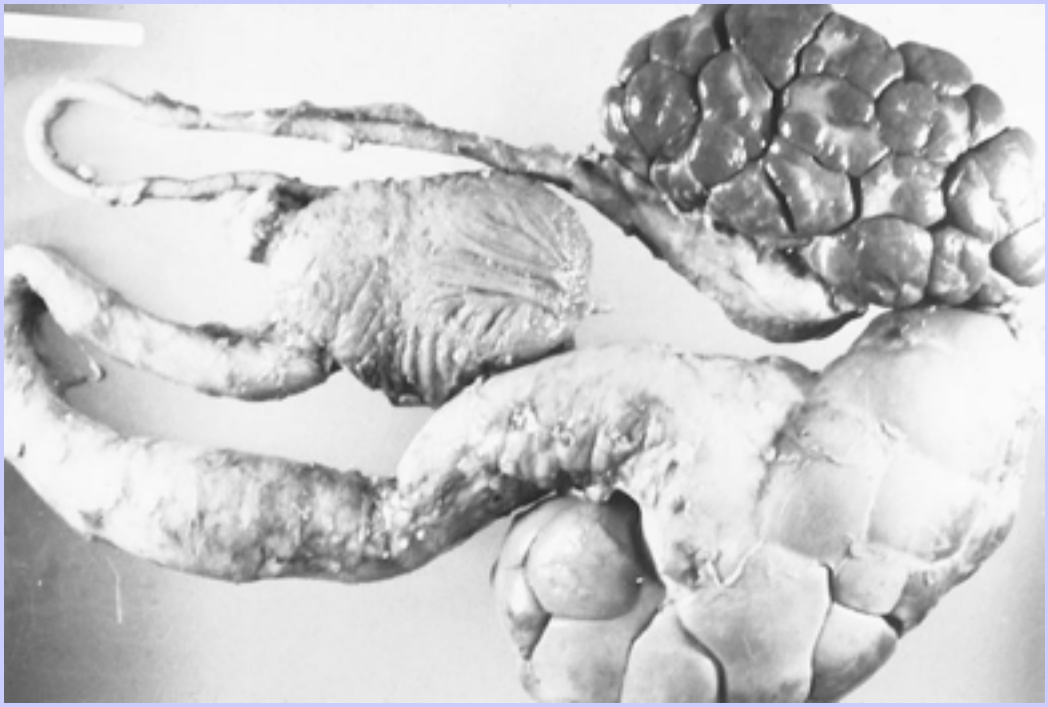
34.41.4.2.5.7

Treatment and Prognosis

Aggressive antibiotic therapy is essential for successful treatment of UTI. Penicillin is the treatment of choice for *C. renale* infection; recommended dosage regimen includes procaine penicillin G (22,000 to 44,000 IU/kg IM twice daily) or ampicillin trihydrate (11 mg/kg IM twice daily).[124] For valuable animals, higher serum and urinary concentrations of penicillin may be achieved with IV administration of sodium or potassium penicillin (22,000 to 44,000 IU/kg every 6 hours) or sodium ampicillin (10 to 50 mg/kg every 8 hours). Treatment should be continued for a minimum of 3 weeks. Subcutaneous injection of antimicrobial drugs may be necessary to limit muscle pain and swelling during the course of treatment. Urinalysis and urine culture should be repeated 1 week after treatment is discontinued to ensure complete resolution. After prolonged therapy with these extralabel dosages of antibiotics, residue withdrawal times for meat and milk must be extended appropriately. In addition, induction of diuresis through oral or parenteral fluid therapy may aid in removing necrotic debris and bacteria from the lumen of the urinary tract.

Urinary tract infection with *E. coli* or other coliforms may also be successfully treated with high doses of penicillin or ampicillin.[124] Achieving high urinary concentrations of these antibiotics may render them effective against many coliforms, even those that show in vitro resistance to the expected serum concentrations of the antibiotic.[124] Repeated assessment of appetite, attitude, rectal temperature, and reagent strip urinalysis is recommended for monitoring cows with coliform UTI that are receiving penicillin or ampicillin therapy. If these parameters do not improve after 96 hours of treatment, another antibiotic should be chosen.[124] Gentamicin (2.2 mg/kg IM twice daily) has been used to successfully treat refractory coliform UTI in a cow, but the nephrotoxicity of the drug and the current prolonged slaughter withdrawal period are important considerations.[124] Trimethoprim-sulfadiazine (15 mg/kg IV once daily)[125] and ceftiofur (3 mg/kg IV twice daily)[142] have also been used with success.

Fig. 34-22 Postmortem specimen of unilateral pyelonephritis and ureteritis in a cow. The affected kidney and ureter are greatly enlarged.



The prognosis for UTI in ruminants depends on the duration of infection, the extent of UTI (cystitis alone vs. unilateral or bilateral ureteritis and pyelonephritis), and the remaining renal function. The chances for successful treatment are improved if treatment is initiated early in the course of infection. In recent reports the combined case fatality and cull rate for pyelonephritis in dairy cattle varied between 18%[124] and 33%[139] for treated cases; however, antibiotic dose and duration varied greatly between these two studies. Cows with pyelonephritis and marked azotemia (BUN >100 mg/dL) were found to be at much greater risk for culling (odds ratio = 60) than nonazotemic cows with pyelonephritis.[139]

34.41.4.2.5.8

Prevention and Control

Isolation of animals infected with *C. renale* is recommended to limit spread of the organism, and disinfection of heavily contaminated areas is advised. Aseptic technique during urogenital procedures and disinfection of obstetric and surgical equipment will limit iatrogenic transmission. In herds using natural service, venereal transmission by subclinically infected bulls may be difficult to control over the long term. An artificial insemination or mass treatment program may be required to prevent further losses from UTI.

34.41.4.2.6

AMYLOIDOSIS

DAVID C. Van METRE

Amyloidosis in cattle is caused by deposition of insoluble protein fibrils in the kidney, GI tract, liver, and adrenal glands. Renal amyloidosis in cattle is characterized as a sporadic, chronic wasting disease. Amyloid deposition in the kidney disrupts the normal glomerular structure, resulting in a protein-losing nephropathy.

34.41.4.2.6.1

Clinical Signs

The most common clinical signs of amyloidosis include chronic diarrhea, weight loss, and poor productivity in mature animals.[143,144] Generalized or ventral edema may be present as a result of hypoproteinemia. Alterations in appetite and attitude may be present, although this may be caused by concurrent disease. Enlargement of the left kidney may be palpated during rectal examination. The enlarged kidneys generally are not painful and maintain normal lobular patterns. Urine may develops stable foam after hitting the ground or being collected and shaken in a container, a result of high urine protein concentration.

34.41.4.2.6.2

Clinical Pathology

Cattle with renal amyloidosis consistently develop marked proteinuria and hypolbuminemia.[143] Serum creatinine and BUN levels may be elevated if renal damage is advanced. In cases of chronic, active inflammatory disease, hyperfibrinogenemia and hyperglobulinemia may occur.[143,144] Polarized light microscopy and electron microscopy have been used to examine urine sediment for the presence of amyloid protein in urine.[145]

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34.41.4.2.6.3

Differential Diagnosis

Amyloidosis must be differentiated from other diseases causing chronic diarrhea, hypoproteinemia, weight loss, and poor productivity. Diseases to consider include Johne's disease, copper deficiency, salmonellosis, bovine viral diarrhea, GI parasitism, and glomerulonephritis. Other than amyloidosis, glomerulonephritis is the only other differential diagnosis routinely displaying prolonged proteinuria. Renal biopsy can be performed to differentiate glomerulonephritis from amyloidosis in the live animal.

34.41.4.2.6.4

Pathophysiology

Amyloidosis of cattle is classified as the reactive (AA) type,[146,147] which is frequently associated with chronic inflammatory disease in domestic animals and humans.[148] Concurrent inflammatory disease, such as traumatic reticuloperitonitis, pneumonia, mastitis, and metritis, have been found in some, but not all, cattle with amyloidosis.[143,144] Serum amyloid A protein (SAA) is synthesized in the liver and is a precursor of amyloid A (AA) fibril in tissues.[149] SAA concentrations increase dramatically in disorders such as trauma, neoplasia, and inflammatory disease. An elevation in SAA is apparently required for an animal to develop active amyloidosis.[148] Elevations in SAA as a result of abnormal catabolism by the reticuloendothelial system may also increase AA fibril formation.[148,150] AA fibrils are resistant to

proteolysis, allowing for their accumulation in tissues over time.[146] Accumulation of amyloid in the glomerulus alters glomerular filtration. A resultant hypoalbuminemia develops, which in turn decreases intravascular oncotic pressure. Diarrhea develops as a result of edema or amyloid deposition in the GI tract.[144] The protein-losing nephropathy and diarrhea result in weight loss. Glomerular filtration rate will be reduced if the glomeruli are obliterated by amyloid deposition. Renal or pulmonary thrombosis may develop as a result of the loss of low—molecular-weight anticoagulants through the compromised kidney.[151]

34.41.4.2.6.5

Necropsy Findings

Renal enlargement with yellow-tan to white discoloration is frequently present. A waxy quality of the renal parenchyma may be appreciated on cut surface of the kidney.[143] Generalized edema resulting from hypoalbuminemia may be present. Some animals will have renal or pulmonary thrombosis.[144] Other inflammatory lesions may be found in other sites. Histologic examination of the kidney may reveal amyloid deposition in the glomerulus, interstitium, and tubule lumen. Immunohistochemical tests using antihuman AA monoclonal antibody can be used for specific demonstration of amyloid in bovine kidney specimens.[151]

34.41.4.2.6.6

Prognosis

Because the lesions of amyloidosis are irreversible, the prognosis for affected cattle is poor. The resilient nature of the amyloid protein results in its persistence in tissues, even if the underlying cause of inflammatory disease is treated successfully. Specific treatment for amyloidosis has not been reported in cattle.

34.41.4.2.7

GLOMERULONEPHRITIS

DAVID C. Van METRE

Glomerulonephritis (GN) is a rare clinical disorder of ruminants that may result from deposition of antigen-antibody complexes in the glomerular basement membrane or from binding of antibody to intrinsic or foreign antigens in the glomerulus. Glomerular injury occurs subsequent to targeting of glomerular tissues by the immune system. Nonimmune mechanisms may be involved in certain forms of the disease.

34.41.4.2.7.1

Clinical Signs

Cattle with GN may have a history of weight loss, poor productivity, and chronic diarrhea.[152,153] Lethargy and generalized edema may be detected on physical examination. Rectal palpation may reveal a mildly enlarged but nonpainful left kidney.[153] GN may be clinically occult in cattle persistently infected with bovine viral diarrhea (BVD) virus[154] and in cattle with fascioliasis.[155] GN has been associated with pregnancy toxemia in ewes; affected animals tend to show clinical signs typical of pregnancy toxemia[156] (see Chapter 33).

Mesangiocapillary GN has been described in Finnish Landrace lambs of specific lineage in Scotland and Canada.[157] The disease is heritable, but the exact mode of inheritance remains unknown. Clinical signs of

this disease begin within hours after birth to 3 months of age. Affected lambs may be dull, ataxic, and appear blind. Fine muscle tremors, colic, and convulsions may also be seen.

34.41.4.2.7.2

Differential Diagnosis

The differential diagnosis for cattle with GN is similar to that for amyloidosis (see preceding section).

34.41.4.2.7.3

Clinical Pathology

Heavy proteinuria, mild anemia, and hypoalbuminemia have been reported in cattle with GN.[152,153] Granular casts, red blood cells, and leukocytes were found in the urine sediment of one affected cow.[152] Azotemia, proteinuria, and ketonuria are found in ewes with GN associated with pregnancy toxemia. Mesangiocapillary GN in Finnish Landrace lambs is characterized by uremia, hypoalbuminemia, proteinuria, hypocalcemia, and hyperphosphatemia.[157]

34.41.4.2.7.4

Pathophysiology

In humans, GN may result from a variety of infectious, toxic, or autoimmune disorders, all of which induce eventual immunologic injury to the glomerulus.[152,158] Antibodies may be directed against host or foreign antigens located in the vascular endothelium, mesangial cells, or basement membrane. In addition, circulating immune complexes may deposit in the glomerulus. The ultimate consequences of antigen-antibody interaction in the glomerulus are activation of complement and chemotaxis of leukocytes, both of which result in direct glomerular injury and increased glomerular permeability.[158]

Filtration of plasma albumin through the damaged glomerulus results in chronic albuminuria, eventually leading to reduced plasma oncotic pressure and generalized edema. Passage of antithrombin III through the damaged glomerulus and into the urine may result in a hypercoagulable state.[159]

Immunohistochemical data suggest involvement of immune-mediated mechanisms for spontaneous GN in cattle[152,153] and sheep,[157] GN associated with persistent BVD infection and fascioliasis in cattle,[154,155] and mesangiocapillary GN of Finnish Landrace lambs.[157] In the last condition a heritable deficiency of the third component of complement has been documented, but the role of this deficiency in GN remains unclear.[156] Glomerulonephritis may also be an incidental histologic finding in animals with acute septic disease.[157]

The clinical and histopathologic characteristics of GN of pregnancy toxemia in ewes resemble those of the preeclampsia syndrome of women.[156] Enlarged glomeruli with reduced blood content in glomerular capillaries are found throughout the renal cortex of affected ewes. The renal lesion in preeclampsic women may result from endothelial injury during disseminated intravascular coagulation (DIC) or an excessive glomerular vasomotor response to angiotensin.[160] The lesion can be reversible in women, but the consequences of this condition in ewes have not been described.

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34.41.4.2.7.5

Treatment and Prognosis

Treatment of GN in ruminants has not been described. Because most cases of GN are advanced at diagnosis, the prognosis is poor. Mesangiocapillary GN in Finnish Landrace sheep is not invariably lethal, and some affected lambs may survive until adulthood.[156]

34.41.4.2.8

HEMOLYTIC UREMIC SYNDROME

DAVID G. RENTER

Hemolytic uremic syndrome (HUS) is classified within the group of thrombotic microangiopathy syndromes.[161] HUS is a set of symptoms characterized clinically by acquired, nonimmune hemolytic anemia, thrombocytopenia, and acute renal failure (ARF).[162] Histologically, HUS is characterized by renal thrombotic microangiopathy.[163] HUS is the most common cause of ARF in young children and infants, with prodromal diarrhea occurring in approximately 90% of cases.[164] Evidence indicates that almost all the postdiarrheal human cases of HUS are caused by enterohemorrhagic (EHEC) or verotoxigenic *Escherichia coli* infections, and that the majority of the cases in the United States are caused by the EHEC serotype O157:H7.[164] Although three horses[165,166] and a heifer[167] have been reported with clinical syndromes similar to HUS, an etiologic agent was not identified in any of these four animals.

34.41.4.2.8.1

Clinical Findings

Horses with clinical signs indicative of HUS have exhibited fever, diarrhea, hematuria, hemoglobinuria, profound azotemia, oliguria, and ventral edema.[165,166] Hematologic findings included leukocytosis, anemia, and evidence of hemolysis.[165,166] The blood smear of one horse revealed the presence of poikilocytes and schistocytes.[166] All three horses were euthanized after unsuccessful treatment of anuria and azotemia with fluid therapy and diuretics. The reported case in a heifer was fatal postparturient HUS demonstrated by severe progressive anuric renal failure, acute hemolytic anemia, and consumptive thrombocytopenia.[167]

In humans, HUS presents as pallor, oligoanuria, edema, seizures (rarely), or generalized hemorrhagic diathesis. In prodromal human cases, this syndrome develops on average 1 week after onset of diarrhea.[162] The classical clinical syndrome of HUS in people includes ARF, hemolysis, thrombocytopenia, and manifestations of DIC.[163] For treatment of HUS in humans, evidence is insufficient to support use of specific therapies, and some treatments, such as certain antibiotics and motility-modifying agents, may be detrimental.[162] Supportive therapy, including fluid/plasma therapy and dialysis, can be of paramount importance.

34.41.4.2.8.2

Pathophysiology and Necropsy Findings

In humans, HUS is the most common life-threatening complication of hemorrhagic colitis (HC) from EHEC infection. The EHEC strains produce the exotoxins Shiga toxin 1 (Stx1) and Shiga toxin 2 (Stx2), also referred to as verotoxin 1 and verotoxin 2.[168] Although *E. coli* O157:H7 is the most widely

publicized, as many as 100 different serotypes of *E. coli* (as well as *Shigella* and other Enterobacteriaceae) can carry the genes for Stx1 or Stx2 and are capable of causing disease.[161]

The EHEC organisms, including serotype O157:H7, are noninvasive but attach to the intestinal mucosa and produce characteristic histologic attaching and effacing lesions. The Shiga toxins (Stxs) released from the bacteria are believed to translocate across the mucosa, where they access the systemic circulation. The Stxs bind to specific glycolipid receptors on the surface of vascular endothelial cells, are internalized by endocytosis, and induce cell death through inhibition of protein synthesis.[161] Activation of the coagulation cascade after exposure of subendothelial collagen may result in thrombosis of small vessels in the kidney and other organs. Oliguric or anuric ARF can result from fibrin/platelet thrombi in renal vessels and glomeruli, fibrinoid necrosis of vessel walls, congestion of glomeruli, and tubular ischemia. Because the coagulation events may be localized to certain organs, the results of laboratory tests of coagulation (e.g., PT, PTT) are not consistently abnormal.[169]

Cattle feces are considered to be the major source of EHEC; however, these bacteria have been isolated from the feces of many other asymptomatic species, including humans. EHEC organisms do not generally cause illness in cattle, although they do colonize the bowel. Fecal contamination of ground beef, other food sources, and water is thought to be the primary mode of transmission of the organisms. However, the small infectious dose makes person-to-person transmission a significant problem, especially in day care, nursing home, and outbreak situations.[161]

In the four large animals reported with HUS, the inciting cause was uncertain, and the isolation of EHEC or other Stx-producing organisms was not attempted.[165–167] The heifer had a necrotizing endometritis, but during postmortem examination of the three horses, no focus of infection was identified. Renomegaly, renal infarcts, and scattered petechial and ecchymotic hemorrhages within the renal parenchyma were apparent on gross necropsy. Acute tubular necrosis and fibrin thrombi within the glomerular capillaries were evident on histologic examination.

Although the etiology was not determined, the clinical signs and pathologic lesions reported in the four large animal cases are compatible with a diagnosis of HUS. Based on these reports, the pathogenesis of HUS in large animal animals shares some features of the disease in humans.

34.41.4.2.9

TUBULAR NECROSIS

DAVID C. Van METRE

Tubular necrosis (TN), or *tubular nephrosis,* is the disease condition that results from a variety of toxic, infectious, or hemodynamic insults to the kidneys. Compounds identified as nephrotoxins for ruminants are listed in Box 34-2. Hemodynamic causes of TN include diseases that reduce renal perfusion (blood loss, endotoxic shock) or that occlude the renal vasculature (DIC, renal vein thrombosis). Bilateral bacterial infection of the kidneys may result in ARF or chronic renal failure (CRF) as a result of destruction of nephrons by bacterial toxins and the host inflammatory response. Renal infection may be established by ascending UTI or by hematogenous infection of the kidneys. Depending on the nature and duration of the primary insult, widespread dysfunction or necrosis of tubular epithelial cells may produce reversible renal injury, ARF, or CRF.

34.41.4.2.9.1

Clinical Signs

The clinical signs of ARF in ruminants are nonspecific and usually are not indicative of overt urinary tract dysfunction. Depending on the inciting cause, anuria, oliguria, or polyuria may exist. Cattle with ARF frequently are presented for evaluation of poor appetite, diarrhea, or epistaxis.[170] Depression, nasal discharge, ileus, melena, and mild free-gas bloat may also be present. If a concurrent septic condition exists, fever, tachycardia, and scleral injection may be present. The saliva may have a strong ammonia smell. Muscular weakness, even recumbency, may result from the acid-base and electrolyte imbalances and intravascular volume depletion that occur with severe acute TN. Rectal palpation findings are usually unremarkable, although renal enlargement and perirenal edema may be found in occasional cases. Table 34-2 lists clinical criteria that may facilitate diagnosis of TN caused by nephrotoxins. If untreated, CRF may ensue, usually producing weight loss in addition to the signs just listed. In such cases a reduction in size of the left kidney may be appreciated on rectal palpation of affected cattle.

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34.41.4.2.9.1.1

Box 34-2 Nephrotoxic Agents

34.41.4.2.9.1.1.1

METALS

Arsenic

Mercury

Cadmium

Chromium

Lead

Zinc

Copper (secondary to hemolysis)

34.41.4.2.9.1.1.2

ANTIMICROBIALS

Aminoglycosides

Tetracyclines

Sulfonamides (rare)

Ionophores

Amphotericin B

Polymyxin B

34.41.4.2.9.1.1.3 ANALGESICS

Nonsteroidal antiinflammatory drugs (NSAIDs)

34.41.4.2.9.1.1.4 PLANTS

Amaranthus retroflexus (pigweed)

Lilium species (Easter lily)

Quercus species (oaks)

Philodendron species (philodendron)

Pinus ponderosa (Ponderosa pine; nephrosis occurs in conjunction with hepatocellular damage and abortion)

Xanthium species (cocklebur)

Cestrum diurnum (day-blooming jessamine)

Oxalate-containing plants: *Rumex* (curly dock), *Beta* (beets) *Rheum rhaponticum* (rhubarb), *Halogeton glomeratus* (halogeton), *Sarcobatus vermiculatus* (greasewood), *Oxalis* species (soursob), *Chenopodium album* (lamb's-quarters), *Salsola pestifer* (Russian thistle)

34.41.4.2.9.1.1.5 ENDOGENOUS

Hemoglobin

Myoglobin

Calcium oxalate

34.41.4.2.9.1.1.6

MISCELLANEOUS

Ethylene glycol

Vitamin C (parenteral form) overdose

Pentachlorophenol

Mycotoxins: ochratoxin, citrinin, fumonisin (high doses)

Cholecalciferol-based rodenticides

Parenteral vitamin D overdose

Renal (uremic) *encephalopathy* is a syndrome of brain dysfunction associated with renal disease. It is characterized by signs of intracranial disease, such as altered behavior or sensorium, weakness, motor dysfunction, and convulsions, which may resolve on restoration of normal renal function or improvement of clinical parameters of renal disease. The pathogenesis of renal encephalopathy is complex and incompletely understood; neurologic function appears to be impaired by alterations in the extracellular fluid content of acids, phosphorus, amino acids, or certain hormones. Alteration in neurotransmitter balance or release within the central nervous system (CNS) may also be involved. Renal encephalopathy appears to be a rare complication of renal failure in ruminants, as reported in two cows and a goat.[171–173]

34.41.4.2.9.2

Differential Diagnosis

Formulation of a differential diagnosis for a ruminant with TN may be difficult because of the nonspecific nature of the clinical signs and the variety of primary disease conditions that may predispose cattle to secondary TN. Coagulopathies and pulmonary abscesses are common causes of epistaxis in ruminants. The differential diagnoses for diarrhea are listed in Chapter 7. Female ruminants with advanced pregnancy toxemia may be depressed, azotemic, inappetent, and recumbent. Recumbent cattle should be evaluated for musculoskeletal injury, mastitis, metritis, peritonitis, spinal cord disease, and metabolic diseases. Cattle with TN are frequently misdiagnosed with milk fever because a temporary improvement in muscular strength may be seen in cattle with TN after treatment with calcium salts.

34.41.4.2.9.3

Clinical Pathology

Elevation in BUN and creatinine levels occurs with clinical TN, and the azotemia is confirmed to be of renal origin by detection of isosthenuria on measurement of urine specific gravity. Proteinuria, hematuria, and granular casts may be found on urinalysis. Hypochloremia and metabolic alkalosis, resulting from abomasal atony or chloride loss in the urine, are often found in ruminants with ARF.[170,174] Hyponatremia occurs after sodium loss in the urine. Because the kidney is the primary organ controlling magnesium excretion in ruminants, hypermagnesemia may occur in TN, particularly under conditions of high

magnesium intake.[170,175] Hyperphosphatemia results from reduced phosphorus excretion in saliva during anorexia, reduced urinary phosphorus excretion, and tissue hypoxia.[176,177] Hypocalcemia is also common in TN in ruminants because of reduced calcium intake, GI stasis, urinary losses, and the competitive effect of hyperphosphatemia.[170] Metabolic acidosis may develop in juvenile ruminants with TN and concurrent diarrhea.[177,178]

Fractional clearance (fractional excretion [FE]) of sodium has been used to help document renal failure in cattle.[178] Values of 0% to 4% have been described in normal cattle; age, ration, and metabolic status may affect FE values.[178] When applying this test, it is prudent to compare the patient's FE value for sodium to that of an age-matched herdmate in a similar physiologic state and on a similar ration. The normal values for several urinary diagnostic indices in healthy calves have been reported.[179]

34.41.4.2.9.4 Pathophysiology

34.41.4.2.9.4.1 ISCHEMIC AND HYPOXIC INJURY

Reduced blood flow to the kidneys most often occurs during generalized loss of vascular volume, as seen with marked blood loss, septicemia, endotoxemia, or severe dehydration. Oliguria or anuria is seen initially, and urine output varies after IV fluid therapy. These conditions may also cause infarction of the renal cortex and renal vein thrombosis.[170] Severe ruminal gas distention may impair renal perfusion.[170] Prolonged, severe ischemia may destroy the tubular basement membrane, thereby preventing tubular epithelial cell regeneration.[180]

34.41.4.2.9.4.2 TOXIC INJURY

The high metabolic demands of renal tubular epithelial cells render them susceptible to toxins that disrupt cellular enzymes. The injury caused by most nephrotoxins is compounded by dehydration, which concentrates the toxin in the tubular filtrate, slows toxin clearance, and if severe, reduces renal perfusion. Because some nephrotoxins are therapeutic agents, it is vital that the veterinarian monitors appetite, body weight, water intake, urine output, routine urine chemistry, serum drug concentration, and serum creatinine concentration during administration of these agents. Young or elderly patients, patients with preexisting renal insufficiency or sepsis, those receiving other potentially nephrotoxic drugs, and patients on prolonged or high-dose therapy with these agents warrant the closest attention.[181]

Table 34-2 Clinical Characteristics of Acute Toxic Nephrosis Caused by Common Nephrotoxins

Nephrotoxin	Clinical Findings*
Aminoglycosides	Usually nonoliguric, ototoxicosis possible; hematuria, glucosuria, proteinuria, increased serum trough concentration of drug
Tetracycline	Hematuria, glucosuria, proteinuria; possible hepatocellular enzyme elevation
Ionophores	Diarrhea, dark urine, dyspnea, cardiac dysrhythmias; elevated CK, AST, and indirect bilirubin
Ethylene glycol	Anuria or oliguria, tachypnea, ataxia, weakness; hemolysis, increased anion gap, increased serum osmolality, increased osmolar gap, acidosis, calcium oxalate crystalluria
Oxalate-containing plants, vitamin C	Hindlimb ataxia or paresis, apprehension, salivation; hypocalcemia, calcium oxalate crystalluria, aciduria, increased renal cortical echogenicity on ultrasonogram
Oak, acorns	Hemorrhagic diarrhea, ascites, hydrothorax, subcutaneous and perirenal edema; hyperfibrinogenemia, increased hepatic enzymes
Myoglobin	Muscle stiffness and weakness, dark urine; elevated serum CK and AST, positive reactions for blood and protein on urine chemistry strip, hemolyzed serum not present
Hemoglobin/methemoglobin	Icteric to pale mucous membranes, tachycardia, tachypnea, red or brown urine; positive blood and protein reactions on urine chemistry strip, anemia, elevated serum total protein, hemolyzed serum (hemoglobin only)
Arsenic	Colic, hemorrhagic diarrhea, ataxia; elevated blood and liver arsenic levels

CK, Creatine kinase; *AST,* aspartate aminotransferase.

* Many general clinical characteristics of acute tubular necrosis are also present. See Clinical Signs and Clinical Pathology.

34.41.4.2.9.5

Treatment and Prognosis

In cases of toxic nephroses, the animal should first be removed from the toxin source, or treatment with a nephrotoxic drug should be discontinued. *Rumenotomy,* with removal of toxic material, is most beneficial if performed soon (within 24 hours) after the animal has ingested a nephrotoxin. Activated charcoal (2 to 4 g/kg PO) may bind the agent in the gut lumen. The use of magnesium sulfate or other magnesium-containing laxatives should be avoided in such cases because severe hypermagnesemia may result in animals with concurrent compromise of renal function. If an animal is exposed to a potentially harmful quantity of a nephrotoxin, prophylactic diuresis through fluid therapy is warranted. In such cases, if the veterinarian were to wait for azotemia to appear before initiating fluid therapy, significant (>75%) loss of nephron function would occur before medical intervention.

The cornerstone of treatment of TN is restoration of adequate renal perfusion and urine production. This is most effectively achieved through IV administration of isotonic, sodium-containing fluids, with calcium and potassium supplementation as indicated. If cost or facilities make IV fluid therapy impractical, repeated administration of water and electrolytes by stomach tube is an option. A small-bore stomach tube can be passed through the nasal cavity into the rumen and secured to the animal's halter to allow one person to administer fluids repeatedly without the need for repeated tube passage. Placement of a small rumenostomy or securing in place a nasogastric tube allows one person to administer fluids repeatedly with relative ease. Administration of IV or oral fluids at 1.5 to 2 times the adult maintenance level of 60 mL/kg/day may be adequate to induce diuresis. The patient should be monitored for chemosis or labored or rapid respiration, which may be indicative of overhydration. Fluid therapy should be continued until azotemia resolves, at which time the patient's voluntary fluid intake can be assessed. Oral supplementation of potassium and calcium salts may be necessary in some cases, because it is often not possible to add adequate yet safe levels of these salts to IV fluids in cases of refractory hypokalemia and hypocalcemia, respectively.

Restoration of urine production is necessary in anuric or oliguric animals. If fluid therapy does not promote diuresis, furosemide (1 mg/kg IV or IM) may be administered. Repeated administration (every 1 to 2 hours) may be necessary to induce urine production in oliguric or anuric patients. With repeated use of furosemide, the patient's serum sodium and potassium concentrations must be monitored. Mannitol (0.25 g/kg IV) or dopamine (2 to 5 µg/kg/min IV) may be required to initiate urine flow if the previous measures are unsuccessful.

Lesions that occlude tubular blood flow (renal vein thrombosis, DIC) warrant a poor prognosis, whereas renal failure resulting from toxic causes carries a more favorable prognosis with early diagnosis and aggressive therapy. Return of appetite and progressive reduction in BUN and serum creatinine levels are positive prognostic indicators.[182] Prolonged supportive treatment (2 to 3 weeks) may be necessary to allow for regeneration of tubular epithelium in cases of acute TN.

34.41.4.3

LEPTOSPIROSIS

ROBERT J. CALLAN

Leptospirosis is a complex disease of both animals and humans caused by pathogenic species of *Leptospira*.[183–189] Pathogenic *Leptospira* species persist as chronic infections of the renal tubules of the maintenance host species, often causing little or no disease. Transmission to incidental hosts results from direct contact with urine from an infected maintenance host or through environmental and feed contamination with infected urine. Infection in the incidental host can cause acute disease in multiple organ systems, including the kidney, liver, and CNS, as well as result in abortion or reproductive failure. This discussion focuses on *Leptospira* infection and disease of the renal system of ruminants.

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Leptospira is a diverse genus of motile, gram-negative, obligate aerobic, tightly coiled spirochetes approximately 0.1 to 0.3 µm in diameter and 6 to 20 µm in length.[183–185] The bacteria can survive in the environment for up to 6 months.[183,184,190] *Leptospira* species prefer a warm, moist environment with a pH of 7.2 to 8.0. Survival is short under dry conditions or at temperatures below 10°C.[183] *Leptospira* does not survive freezing in the envrironment.[191]

Before 1989, *Leptospira* was divided into the pathogenic species, *L. interrogans,* and the nonpathogenic saprophytic species, *L. biflexa*. The current taxonomy and classification of *Leptospira* use a complex system of both serologic and genetic characteristics.[184,185] Serologic classification is based on antigenic grouping of the lipopolysaccharide (LPS) and other outer surface antigens using the cross-agglutinin adsorption test (CAAT). More than 240 serovars are characterized. Antigenically related serovars are combined into larger serogroups, and serovars may also be further characterized into serotypes. Seventeen genomospecies have been identified based on DNA sequence heterogeneity.[184,185]

34.41.4.3.1

Epidemiology

Leptospirosis is predominantly observed under conditions where livestock come in direct or indirect contact with urine from an infected maintenance host (Table 34-3).[183–185,190] The prevalence of infection within a maintenance host population tends to be high (30% to 50%); in such populations, infection is often spread between animals by direct contact.[183] Transmission to incidental hosts is generally by contact with the environment, feed, or water that is contaminated with urine from an infected maintenance host. Transmission can also occur from contact with an infected fetus or uterine discharge. Survival of the bacteria in the environment and the incidence of infection in animals are increased in regions with warm, humid climatic conditions. The seasonal incidence is higher during the summer or fall in temperate regions and during the rainy season in warm-climate regions.[184] Environmental conditions that contribute to moist surroundings and foot abrasions may contribute to *Leptospira* transmission, particularly in housed dairy cattle.

Cattle are the primary maintenance host reservoir of *L. interrogans* serovar *hardjo* (type hardjopragitno) and *L. borgpetersenii* serovar *hardjo* (type hardjo-bovis). *L. interrogans* serovar *hardjo* (type hardjopragitno) is isolated primarily from cattle in the United Kingdom, and *L. borgpetersenii* serovar *hardjo* (type hardjo-bovis) is observed worldwide. Cattle can also serve as maintenance or incidental hosts for *L. interrogans* serovar *pomona* and *L. interrogans* serovar *grippotyphosa*.

Serovars *hardjo, pomona,* and *grippotyphosa* are most often implicated in renal infection of cattle.[192] Although data are scarce, renal disease caused by leptospirosis in small ruminants appears to be uncommon.[191,193] Sheep may serve as subclinical carriers of serovar *hardjo*.[187,194] Some serovars of *Leptospira* have zoonotic potential, and humans are always considered an incidental host.[183–185,188]

Table 34-3 Current Nomenclature, Maintenance Host, and Incidental Hosts for Common *Leptospira* Isolates in Ruminants

Genomospecies	Serovar	Maintenance Host	Incidental Hosts
L. interrogans	*Canicola*	Dogs	Cattle
L. interrogans	*Pomona*	Swine, opossums, skunks, racoons	Horses, cattle, sheep, goats, dogs
L. interrogans	*Icterohaemorrhagiae*	Rats	Dogs, cattle, swine
L. interrogans	*Bratislava*	Pigs, mice, horses	Dogs, cattle, horses
L. interrogans	*Hardjo* (type hardjoprajitno)	Cattle	Sheep, goats
L. borgpetersenii	*Hardjo* (type hardjo-bovis)	Cattle	Sheep, goats
L. borgpetersenii	*Ballum*	Mice	—
L. kirschneri	*Grippotyphosa*	Raccoons, muskrats, squirrels	Cattle, sheep, horses, dogs

An abattoir study of more than 5000 cattle in the United States identified approximately 2% renal carriers of *L. interrogans*.[192] Serovar *hardjo* was the most common renal isolate, followed by serovar *pomona* and serovar *grippotyphosa*. A study of Texas slaughterhouse cattle detected *Leptospira* species in 36% of urine samples by PCR. The seroprevalence for serovars *pomona* and *hardjo* was 22% and 15%, respectively.[195] A national survey showed 49% seroprevalence for *L. interrogans* serovars in cattle, with the highest seroprevalence found in cattle from southeastern, south-central, and Pacific Coast states.[196] Because contact with urine from infected animals is a means of transmission within cattle populations, high stocking density or confinement may increase the rate of infection in a herd.

In general, infection of cattle with the host-adapted serovar *hardjo* rarely results in acute, severe disease. If present, signs of disease are usually mild in acutely infected cattle and may simply present as cases of undifferentiated fever. Persistent, latent urogenital infection usually follows acute infection, with most overt losses attributable to adverse effects on reproduction.[188,197–199]

Acute, severe renal disease is more characteristic of incidental (also termed “accidental”) infection of cattle, particularly calves, with a non—host-adapted serovar of *Leptospira*. However, exceptions to this generalization do occur because host immunity and virulence of the organism are variable.[187,188]

34.41.4.3.2

Clinical Findings

Serovar *hardjo* is host-adapted to cattle, and many infections are asymptomatic or result in nonspecific reproductive failure or abortion. *Leptospira* serovar *hardjo* infection of cattle may produce chronic interstitial nephritis of variable severity, but overt renal dysfunction is rarely observed.[200] Chronic infection of the genital tract of cows and bulls is common.[189,201] Protracted shedding of the organism in the urine

often results, possibly lasting for the life of the animal.[200,201] Infertility, stillbirth, abortion, and birth of weak calves are typical clinical manifestations of infection with serovar *hardjo* in cows.[189,198,202,203] The fetus can be infected in utero, and if it survives the acute infection, it may be born persistently infected.[183] Fever, agalactia, and mastitis may occasionally occur, and the resulting syndrome has been termed the "milk-drop syndrome"[187] or "flabby udder."[188] The udder is uniformly soft, and the milk may be yellow- or red-tinged and thick.

In contrast, infection with the non—host-adapted serovars can result in severe systemic disease, hemolytic anemia, hepatitis, interstitial nephritis, and tubular nephrosis in calves and less often in adult cattle.[189,200] Meningitis is a rare manifestation.[193] Agalactia and mastitis often occur in lactating cows, and pregnant cows may abort. Urine shedding of non—host-adapted serovars by infected cattle can persist for weeks to months.[188,189,203] Renal lesions result from direct damage to the vascular endothelium during leptospiremia, hypoxia from endothelial damage and hemolysis, tubular epithelial damage from hemoglobin, and interstitial nephritis.[183,184,200] Some *Leptospira* serovars, particularly *pomona,* produce hemolysins that can cause acute intravascular hemolysis and anemia in cattle.

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Clinical signs associated with acute infection may include fever, anorexia, lethargy, decreased milk production, petechiation, hemolytic anemia, and hemoglobinuria. Oliguria may be seen with interstitial nephritis or hemoglobinuric nephrosis. Elevated creatinine caused by pre-renal or renal causes may be observed on serum chemistry analysis. Examination of the urine may show proteinuria, pyuria, and cellular or granular casts in cases of nephritis. Hemoglobinemia and hemoglobinuria may be observed in patients with leptospire-induced hemolysis and can occasionally result in hemoglobinuric nephrosis.

34.41.4.3.3

Pathophysiology

Contaminated feed and surface water, wildlife, rodents, and domestic animals are potential sources of pathogenic serovars for cattle.[183,184,187,188] Leptospires penetrate external mucosal surfaces and scarified or macerated skin. The bacteria multiply locally during an incubation period that can last 2 to 20 days.[183,184] After the incubation phase, the organism enters the bloodstream through the lymphatics or by direct penetration into the blood vessel. Leptospiremia results in dissemination throughout the body and infection of multiple organs. This bacteremic phase lasts 4 to 7 days. Fever and other systemic signs are often present in clinically affected animals. Humoral antibodies can be detected at the end of the bacteremic phase. Opsonizing antibodies are generated and aid in clearing infection from most tissues in the host.

During the convalescent phase, leptospires may become localized in the mammary gland, kidney, or genital tract, where they appear to be protected from the immune response.[183,204] Depending on the virulence of the serovar involved, chronic renal infection may create few histologic changes, mild interstitial nephritis, or diffuse, severe, lymphocytic interstitial nephritis with fibrosis.[193] Nephritis may persist long after the host immune response has cleared the organism. Chronic infection of the kidney or reproductive tract allows for transmission of the organism in urine, uterine and vaginal secretions, placenta, fetal tissues, and semen.[187,189,201,205] Shedding in the urine may last for weeks to months with non—host-adapted infections. Renal shedding of host-adapted serovars can persist for months to years. The bacteria reside in the lumen of the renal proximal tubules, where they are protected from phagocytes and humoral antibodies. The bacteria do not stimulate a systemic immune response while localized in the proximal tubule lumen, and thus serum antibody titers can decline and become negative even though the kidney is infected and shedding bacteria.

Multiple potential virulence factors may contribute to leptospirosis.[184,185] Leptospiral LPS and outer membrane proteins are believed to contribute to the development of interstitial nephritis. However, leptospiral LPS has different biochemical properties that make it less toxic than other gram-negative lipopolysaccharides. Motility is an important pathogenic mechanism and contributes to invasion and dissemination of the bacteria. As many as 50 genes are related to leptospiral motility.[185] Pathogenic *Leptospira* strains produce chemotaxis proteins, and some strains exhibit chemotaxis toward hemoglobin. Adherence to cells is in part conferred by fibronectin-binding protein present on the surface of pathogenic strains but not on nonpathogenic strains. Leptospiral immunoglobulin-like protein A (LigA) may also be involved in attachment and invasion. Additional proteins that may contribute to virulence include hemolysins, sphingomyelinase C, sphingomyelinase H, and hemolysis-associated protein 1 (HAP-1).[184,185]

34.41.4.3.4

Diagnosis

The microscopic agglutination test (MAT) is the most widely used serologic test for the diagnosis of leptospirosis in cattle. The MAT detects antibodies to specific serovars, but cross-reactivity occurs between related serovars, particularly within the same serogroup. Thus, an infection with one strain may result in increased MAT titer to multiple serovars. Serum antibody enzyme-linked immunosorbent assay (ELISA) tests have been developed for research but have not yet been adopted in the routine clinical diagnostic setting for animals.[206–209]

An elevated serum antibody titer is observed after the bacteremic phase and is suggestive of *Leptospira* infection when associated with concurrent clinical signs. However, interpretation of a single titer is problematic in vaccinated animals or when endemic exposure is suspected.[189,204] A fourfold increase in MAT titer between acute and convalescent serum samples, or conversion from a negative titer to a titer of 1/100 or greater, supports a diagnosis for both host-adapted and non—host-adapted serovars. However, vaccinated animals may have a diminished serologic response after challenge and renal colonization with *L. borgpetersenii* serovar *hardjo*.[210] Serologic detection of persistent infection with serovar *hardjo* can be difficult because paired serum titers may be increasing, static, decreasing, or undetectable at examination (e.g., at abortion).[189,204] It is generally recommended to consider the serovar with the highest titer as being the infecting strain. However, recent studies demonstrate that serologic antibody titers may not accurately predict the infecting strain in humans because of cross-reaction between different serovars within the same serogroup.[211] Consultation with a clinical immunologist affiliated with the laboratory performing the MAT is recommended for accurate interpretation of results.

Leptospira shedding in urine and semen can be detected by multiple tests, including urine culture, phase-contrast microscopy, darkfield microscopy, fluorescent antibody (FA), polymerase chain reaction (PCR), nucleic acid hybridization, and immunoblot.[192,204,205,212–214] Urine cultures are often unrewarding because of the fastidious nature of the organism, and conclusive results may not be obtained for up to 6 months.[205] Both FA and PCR assays are typically used by veterinary diagnostic laboratories to identify *Leptospira* species from urine samples. Neither of these tests will determine the infecting serovar. The sensitivity of detecting *Leptospira* shedding can be improved by performing two tests on a single sample.[205,214] Evaluation of serovar-specific antibody titers from positive animals may aid in identification of the infecting serovar.

Second-voiding urine samples collected after the administration of IV furosemide are recommended for urine testing.[191,215] Furosemide is administered at 0.5 to 1.0 mg/kg IV or IM, and the first-voided urine is discarded. A second urine sample is then collected after cleaning the vulva of gross debris. Approximately 10 mL of urine should be collected and stored on ice (not frozen) for transport to the diagnostic laboratory. Urine from 10 to 15 adult animals should be tested when evaluating a herd for endemic *Leptospira* serovar *hardjo* infection.

Biopsy or necropsy samples of renal tissue may be treated with Warthin-Starry or Levaditi silver stains for microscopic examination.[193] Immunoperoxidase staining was shown to be more sensitive for identifying *Leptospira* species in kidney and liver of naturally infected cattle than Levaditi silver stain.[216]

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34.41.4.3.5

Treatment and Prognosis

Treatment of acute leptospirosis caused by non—host-adapted serovars should focus on the elimination of the bacteria, systemic support, and diuresis if renal involvement is observed. In vitro susceptibility has been demonstrated for several antibiotics that could be used in food-producing ruminants, including ampicillin, amoxicillin, penicillin G, erythromycin, tetracycline, tylosin, and tilmicosin.[203,217–219] Oxytetracycline (10 to 15 mg/kg IM twice daily) and dihydrostreptomycin (12.5 mg/kg IM twice daily) have been recommended for treatment of acutely infected cattle.[191] Nephrotoxicosis is a potential concern with this dosage of oxytetracycline in cattle with preexisting renal disease, and dihydrostreptomycin is not currently available for use in cattle in the United States. Penicillin (25,000 IU/kg IM twice daily) and sodium ampicillin (20 mg/kg IM twice daily) have been suggested for treatment, but the efficacy of these regimens in cattle remains unproved.[191] In humans, doxycycline (100 mg every 12 hours for 7 days) has been shown to reduce the duration and severity of illness.[184]

Intravenous or oral fluids and nonsteroidal antiinflammatory drugs (NSAIDs) may be indicated for systemic support. In animals with severe hemolysis, blood transfusion may be considered. Renal diuresis should be established in animals with hemoglobinuria or evidence of ARF from pigment nephrosis or interstitial nephritis. The prognosis for renal disease caused by leptospirosis is influenced by the virulence of the serovar involved, host immunity, and the extent of renal lesions. Cases with renal azotemia warrant a guarded prognosis because more than 75% of nephrons are affected in such cases, and chronic interstitial nephritis and fibrosis may occur after treatment of the acute disease.

Chronic renal infection with *Leptospira* serovar *pomona* in cattle can be eliminated with a single injection of dihydrostreptomycin (25 mg/kg IM), although spontaneous clearance of this serovar often occurs in cattle.[191,203] Conflicting data exist on the efficacy of this treatment in clearing renal infection with serovar *hardjo*.[220,221] Long-acting oxytetracycline (20 mg/kg IM or SC, two doses 10 days apart) has been recommended to treat chronic leptospiral infections or reduce the risk of introduction of infected animals into a herd.[187] Oxytetracycline (20 mg/kg IM once), ceftiofur (2.2 mg/kg IM every 24 hours for five treatments), and tilmicosin (10 mg/kg SC once) have been shown effective in clearing renal shedding of *L. borgpetersenii* serovar *hardjo* from experimentally infected cattle.[222]

34.41.4.3.6

Prevention

Draining or fencing off standing water may reduce transmission. Maintaining a dry, clean environment may also help reduce exposure and infection. Limiting rodent and wildlife contact with cattle and their feed and water is often difficult to accomplish, but it reduces the potential for transmission of non—host-adapted leptospires.[189] For host-adapted *Leptospira* serovar *hardjo,* it is necessary to prevent or eliminate the renal carrier state in infected cattle in order to reduce transmission.

Vaccination is regarded as an effective means of preventing losses from leptospirosis. Conventional pentavalent (*L. canicola, grippotyphosa, hardjo, icterohaemorrhagiae,* and *pomona*), whole-cell, inactivated leptospiral vaccines are recommended in calves and adult cattle as an aid to prevent clinical disease caused by *Leptospira* species. However, these conventional pentavalent vaccines may not consistently prevent renal colonization and shedding after challenge with host-adapted *L. borgpetersenii* serovar *hardjo* (type hardjo-bovis).[223,224]

A monovalent *L. borgpetersenii* serovar *hardjo* (type hardjo-bovis) vaccine (Spirovac, Pfizer Animal Health, New York) is licensed for the prevention of *Leptospira* serovar *hardjo* infection, including reproductive and renal tract colonization, and urinary shedding for up to 12 months. This vaccine stimulates an immune response characterized by IgG_1 and IgG_2 agglutinating antibodies, as well as antigen-specific T-cell production of interferon gamma (IFN-γ).[210,225–227] The strong IFN-γ response is consistent with induction of a type 1 immune response and may be responsible for antibody class switching to IgG_2, which is a more potent opsonin than IgG_1.[225] Combination pentavalent *Leptospira* vaccines have been developed that also promote high *L. hardjo* antibody titers, in addition to the other serovars contained in the vaccine (Vira Shield 6+$L5^{HB}$, Novartis Animal Health US, Greensboro, NC; Vista 5 L5 SQ, Intervet, Millsboro, Del). Because *Leptospira* species are largely extracellular pathogens, the relevant protective immune response appears to be antibody-mediated neutralization and opsonization during leptospiremia.[184,185] There is no indication that cytotoxic immunity is a relevant immune response for protection or resolution of leptospirosis.

Although these vaccines help prevent colonization and shedding of *leptospira* serovar *hardjo* from the kidney, they are not effective in resolving current renal infection and elimination of the carrier state. Thus, vaccination at an early age followed by annual boosters is recommended to prevent initial renal colonization. Renal shedding in previously infected animals can be resolved by antibiotic treatment, and vaccination can be used to prevent future colonization.

34.41.4.4

CONGENITAL DEFECTS

DAVID C. Van METRE

Most severe congenital defects of the urinary tract of ruminants manifest at an early age, although occasionally defects remain clinically occult until adulthood.[228] Congenital defects of the urinary system should be considered in the differential diagnosis for a young animal with renal disease or abnormal urination. However, tubular necrosis caused by severe volume depletion, nephrotoxins, and infectious diseases are much more common. If a congenital defect of the urinary tract is identified, a careful examination of other body

systems should be performed; 73% of lambs with urogenital defects were found to have one or more defects in other organ systems.[229] Urogenital defects in ruminants are described in Chapter 51.

34.41.4.4.1 Renal Defects

Renal cysts are considered to be a common bovine renal defect[230] and have been described in sheep[229] and a goat.[231] These fluid-filled cavities in the renal parenchyma are usually of no clinical significance unless they are large or numerous (polycystic kidneys).[228,230] *Renal agenesis* was found to be the most common renal defect in lambs, with hydronephrosis and renal dysgenesis occurring less frequently.[229] A retroperitoneal, perirenal *pseudocyst* (a fluid sac lacking an epithelial layer) has been reported in a ram with acute abdominal pain.[232] Pseudocysts typically develop as outpocketings of the renal capsule and can develop as a result of renal trauma, urinary tract obstruction, or vascular or lymphatic anomalies.

Renal oxalosis is a metabolic disease of beefmaster calves that is suspected to have an inherited basis. The calves show weakness, lethargy, and anorexia within days to several weeks of age. Alopecia over the head, neck, and extremities; dehydration; and diarrhea may also be seen. Evidence of renal failure is found on serum chemistry analysis. An inherited abnormality of glycine or glyoxalate metabolism may generate high levels of endogenous oxalate, which readily complexes with calcium. As a result, calcium oxalate crystals accumulate in the renal tubules, obstructing outflow of the tubular filtrate. Exposure to oxalate-containing plants and ethylene glycol must be ruled out in all cases of renal oxalosis.[233]

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34.41.4.4.2 Ectopic Ureter

Ectopic ureter is a rare congenital defect in which one or both ureters terminate in an abnormal location. An ectopic ureter may terminate in the urethra, vagina, or cervix or caudal to the bladder trigone in females. In males the ectopic ureter usually terminates in the urethra, vas deferens, or seminal vesicles. Urinary incontinence is the most common presenting complaint for affected animals.[234] Urine dribbling results in scalding of the perineum and medial surfaces of the hindlimb in heifers, and scalding in males is usually located on the prepuce and ventral abdomen. Occasional episodes of normal micturition may be seen. UTI, polycystic kidney(s), and hydronephrosis may exist concurrent to ectopic ureter(s).

Definitive diagnosis requires IV contrast urography or endoscopic examination of the urinary tract. Options for surgical correction include transposition of the ectopic ureter(s) or, in the case of unilateral involvement, ipsilateral nephrectomy. The latter option is valid only if the contralateral kidney is functional, as determined by blood chemistry, and structurally normal or near normal, as determined by ultrasonography or IV pyelography. The use of affected animals for breeding should be discouraged.

34.41.5 NEOPLASIA

DAVID C. Van METRE

Other than those associated with ingestion of bracken fern, primary neoplasms of the urinary tract of ruminants are rare. In a North American abbatoir survey, primary tumors of the bladder were detected in 0.05% of more than 21,000 cattle examined, with cases of papillomas, adenomas, and transitional cell carcinomas identified in the sample population.[235]

Renal carcinoma has been described in cattle,[236,237] and nephroblastoma has been documented in a ewe and an aborted lamb.[238] Renal involvement may be seen in occasional cases of lymphosarcoma in ruminants. Single cases of lymphoma involving the urinary bladder of a cow[239] and a goat[240] have been reported.

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35 Chapter 35 Diseases of the Nervous System

Mary O. Smith

Consulting Editors

Lisle W. George

35.1 CEREBROSPINAL FLUID

Cerebrospinal fluid (CSF) is partly derived from and in equilibrium with the extracellular fluid that bathes the brain and spinal cord parenchyma.[1–3] CSF has been shown to act as a "sink" for brain extracellular fluid,[4] and its composition is an indicator of the state of the intrathecal milieu. CSF is produced by a combination of ultrafiltration of plasma and active secretion.[5] The sites of CSF production are the choroid plexuses of the lateral, third, and fourth ventricles; the ependymal lining of the ventricular system; the pia arachnoid; and the meningeal blood vessels. The CSF in the ventricular system flows caudally and diffuses out of the lateral apertures in the fourth ventricle. It then circulates around the brain and the spinal cord. Circulation of CSF is achieved through regional pressure changes caused by spinal motion and pulsations of blood vessels. Resorption of CSF occurs from both the cranial cavity (75%) and the spinal canal (25%).[6] Some resorption of brain CSF occurs at the arachnoid villi associated with large veins and sinuses, but recent studies have shown that most resorption occurs at the cribriform plate, into nasal lymphatics.[7,8] Resorption of spinal CSF occurs into the lymphatics associated with spinal nerves.

The predominant direction of CSF flow in the spinal canal is caudal; thus, changes in CSF caused by lesions within the nervous system occur predominantly caudal to lesions. CSF can be collected from the cisterna magna when the site of interest is the brain, whereas it should be collected from the lumbar subarachnoid space when the lesion is in the spinal cord. In large animals, however, the risks associated with the general anesthesia required for cisterna magna tap are considerable, so lumbar puncture is usually the most suitable technique for CSF collection in these species, regardless of the site of the lesion.[9,10]

35.1.1 COLLECTION OF CEREBROSPINAL FLUID

35.1.1.1 Lumbosacral Spinal Tap

Collection of CSF from the lumbosacral cistern is preferred for most large animal patients and is always done when the lesion is located in the spinal cord. Because the predominant flow of CSF is caudal, fluid collected from the cisterna magna reflects only changes within the brain and the most cranial parts of the spinal cord. However, fluid collected from the lumbosacral site is altered by either brain or spinal cord disease. Once a neuroanatomic diagnosis has been made, therefore, the site most suitable for collection can be chosen.

For collection of CSF by lumbosacral puncture, the animal is lightly sedated, and the skin of the dorsal midline over the junction of the sixth lumbar (L6) and first sacral (S1) vertebrae is surgically prepared (Fig. 35-1). A variety of standard sedative protocols are suitable, although xylazine has been shown to reduce CSF pressure.[11] Correct placement of the spinal needle is more easily achieved with the animal standing. The proper anatomic site for insertion of the spinal needle is between the dorsal spinous process of L6 cranially

and S1 caudally and the two tuber sacrales laterally. The overlying skin forms a depression that can be recognized by palpation, although this may be difficult in well-muscled horses. The correct site for needle placement can also be located by determining (1) the dorsal midline at the “highest point” of the quarters or (2) the point where a line drawn between the caudal aspects of the two tuber coxae intersects the midline.

The skin is anesthetized with 2% lidocaine, and a 1-cm incision is made with a No. 15 scalpel blade. A 6- to 9-inch, 18- to 20-gauge spinal needle is inserted perpendicularly through the incision and advanced until the tip punctures the lumbosacral cistern (a 3½-inch needle can be used in small ruminants, foals, and most cattle). A “snapping” sensation sometimes is felt as the needle passes through the interarcuate ligament. The patient may reflexly contract the tail, anus, and gluteal muscles. Some patients, particularly horses, may respond with violent motor activity. For this reason, a lumbosacral spinal tap performed on a conscious horse should be done only when the animal is restrained in stocks; people have been severely injured when this rule was not followed. The average depth of insertion is 17.64 cm (7 inches) in horses, 8.26 cm (3⅓ inches) in ponies,[10] and about 7.5 cm (3 inches) in adult cattle.

The spinal needle is advanced gently to the floor of the spinal canal. Passage of the needle through the terminal spinal cord or the cauda equina does not cause subsequent neurologic abnormalities. When the needle is seated in the spinal canal, very gentle negative pressure can be applied by withdrawing spinal fluid into a series of 3-mL syringes. If frank blood is obtained, the tip of the needle probably is in one of the ventral vertebral sinuses. The needle should be withdrawn a few millimeters and a clean syringe attached to the hub. Compression of the jugular vein causes engorgement of the ventral vertebral plexus, which increases CSF pressure in the lumbosacral cistern. Failure of the CSF to flow from the needle after compression of the jugular vein could indicate incorrect needle placement or an obliterative lesion of the thoracolumbar spinal cord.

35.1.1.2

Cisterna Magna Tap

General anesthesia is required for a cisterna magna tap. After the patient has been anesthetized, the dorsal area of the neck overlying the atlantooccipital joint is surgically prepared. The patient's head is held flexed at a right angle to the neck, with the sagittal plane of the head parallel to the floor or table on which the patient is lying. The head must not be allowed to move while the needle is inserted. The needle is inserted at 1 to 2 cm caudal to a point corresponding to the intersection of the dorsal midline and a line drawn between the cranial aspects of the wings of the atlas. This point usually is 6 to 9 cm (2½ to 3½ inches) from the poll (Fig. 35-2). A 3½-inch, 18-gauge spinal needle is inserted perpendicular to the skin and aimed toward the nose. The needle is advanced slowly with the stylet seated. After the needle has been advanced a few millimeters, the stylet is removed and the hub of the needle examined for CSF flow. The stylet is replaced if it is dry and CSF is not spontaneously dripping from the hub, and the needle is advanced another few millimeters and checked again for CSF flow. Entry of the tip of the needle into the cisterna magna may be accompanied by the sensation of “popping” through a tissue plane or by a sudden decrease in resistance to the advancement of the needle. In other cases, however, no such sensation is perceived, thus the precaution of checking for CSF flow every time the needle is advanced a few millimeters.

Fig. 35-1 Close-up view of landmarks for a lumbar cistern puncture in a horse. The large dark ovals *(A)* represent the position of the two tubers sacrale. The smaller curved lines *(B)* represent the respective caudal and cranial aspects of the L6 and S1 dorsal spinal processes. The dotted line represents the optimum area for placement of a skin stab.

Fig. 35-2 View of the ideal area for a cisterna magna cerebrospinal fluid tap in a cow. The two lines *(a)* represent the wings of the atlas. The large spot in the center *(b)* is the optimum area for needle insertion. It is essential to prevent head movement by use of anesthesia and restraint.

In most large animals the needle is seated at approximately 5 to 8.75 cm (2 to3½ inches). While advancing the needle, the heel of the hand should be held firmly against the animal's neck to minimize the possibility of spinal cord injury. The mean depth of insertion is 6.16 cm (2½ inches) in horses[10] and 5.08 cm (2 3½ inches) in cattle. In a cisterna magna tap, the needle entry site is close to the cervical spinal cord and the brainstem. To minimize the danger of central nervous system (CNS) damage during a cisterna magna tap, the animal should be adequately anesthetized and ventilated, because an increased partial pressure of carbon dioxide (P_{CO_2}) results in elevated intracranial pressure.[12] Removal of fluid from the cisterna magna is contraindicated in a patient with increased intracranial pressure because a possibly fatal herniation of the brain through the foramen magnum and under the tentorium cerebelli may occur. Signs of increased CNS pressure include a moderate to marked decrease in mentation, mydriatic pupils, opisthotonos, extensor rigidity, ventrolateral strabismus, and papilledema.

Ultrasonography can be used as an aid to needle placement for collection of CSF from both the atlantooccipital cistern and the lumbosacral subarachnoid space.[13,14] In the authors' experience, however, CSF collection can usually be effected without such assistance.

35.1.1.3

Myelography

Contrast material for myelography is injected into the cisterna magna in large animal patients. Withdrawal of CSF before injecting the contrast medium is unnecessary, and reinjection of CSF after it has been withdrawn is inadvisable. The turnover of CSF is rapid and under strict homeostatic control; therefore, withdrawal of CSF through a spinal tap does not have deleterious effects that require its replacement.[15–17] In horses undergoing myelography, two spinal needles can be placed, one at the lumbosacral space and one into the cisterna magna. As the contrast medium is injected through the needle in the cisterna magna, CSF is allowed to drain freely from the lumbar needle. This technique facilitates injection of large volumes of contrast material but is not absolutely necessary to obtain a good-quality myelogram.

35.1.2

ANALYSIS OF CEREBROSPINAL FLUID

The color of the CSF should be noted as it flows from the hub of the spinal needle. Blood can originate from the tapping procedure (iatrogenic hemorrhage) or from a traumatic CNS lesion. Iatrogenic hemorrhage is unevenly mixed in the CSF and disappears as the fluid drips from the needle. Fluid collected immediately after placement of the spinal needle tends to be mildly contaminated with blood even when this is not apparent grossly. Successive aliquots usually are less contaminated, so the later aliquots are most suitable for cellular and protein analysis.???[18] Blood resulting from CNS hemorrhage is evenly mixed with CSF even after a large amount has been removed. Hemorrhage that has occurred days earlier may have a brownish rather than red discoloration. Prior hemorrhage also results in *xanthochromia,* a yellow discoloration of the CSF. Xanthochromia can be observed in the CSF for at least 10 days after the introduction of blood. Xanthochromic samples do not contain bilirubin.

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Fig. 35-3 Black cerebrospinal fluid from a lumbosacral tap of a gray horse with paraparesis. The animal had a melanoma that infiltrated the caudal spinal rootlets.

Other abnormalities may be noted in CSF. For example, a black discoloration is diagnostic of a melanoma (Fig. 35-3). Foamy CSF denotes a protein concentration greater than 200 mg/dL, and turbid CSF usually denotes cell counts exceeding 400 mg/dL.

The normal values for CSF are presented in Table 35-1. Cell counts should be determined in a noncentrifuged specimen as soon as the sample is collected, using a hemacytometer. Automated methods for counting cells are

not suitable for CSF because the very low numbers of cells in CSF compared to blood result in erroneous counts. Morphologic examination of cells from CSF is most suitably done on cytospin preparations in an appropriately equipped laboratory, but sedimentation and membrane filtration techniques for CSF cell preparations have been described.[19,20] Normal CSF from large animals contains fewer than six white blood cells (WBCs) per deciliter. Some reports have documented occasional WBC counts greater than 40 cells/dL in the CSF of normal horses.[21] Although suggested to correct for the effects of iatrogenic blood contamination, various "correction factors" are inaccurate and should not be used.[18,22]

Table 35-1 Normal Range of Values in Cerebrospinal Fluid for Large Animals[1,4,5]

Component	Unit	Equine	Bovine	Ovine	Caprine
Specific gravity		1.004–1.008	1.004–1.008	NA	NA
Refractive index		1.3343–1.3349	1.3343–1.3349	NA	NA
Protein	mg/dL	5–100	20–40	8–70	24–40
White blood cells (WBCs)	WBCs/dL	0–6	0–3	0–5	0–7
Glucose	mg/dL	30–70	35–70	48–109	45–87
Sodium	mEq/L	140–150*	132–144*	145–157*	NA
Potassium	mEq/L	2.5–3.5	2.7–3.2	3–3.3	3
Creatine kinase	IU/L	0–8	2–48	NA	NA
Magnesium	mEq/L	NA	1.7–2.7	NA	NA

NA, Result not available.

* Cerebrospinal fluid (CSF) sodium is the same as serum or plasma sodium when measured with ion-specific electrodes. When other measurements are used, the CSF sodium is usually higher than plasma sodium.

The refractive index of normal CSF is less than 1.335. The protein concentration of CSF in normal adult ruminants is less than 50 mg/dL and in normal horses less than 100 mg/dL, although reference values vary with the techniques used for protein measurement; reference values should be established for each laboratory.[23] Nephelometry is usually used for measurement of CSF protein in commercial laboratories. Protein electrophoresis has been performed on CSF to identify particular patterns associated with specific diseases;[24] however, conflicting results limit the clinical application of this technique.[25]

Studies of the specific and relative quantities of albumin and immunoglobulins, particularly IgG and IgM, have been stimulated by the increasing importance of immunologic testing of CSF for diseases such as equine protozoal encephalomyelitis. Reference values for a number of parameters have been established.[26] The most important of these parameters are *albumin quotient,* a measure of blood-brain barrier (BBB) permeability, and *IgG index,* a measure of intrathecal production of IgG.[27] The formulae for these parameters are as follows:

$$\text{Albumin quotient} = (\text{CSF albumin} / \text{Serum albumin}) \times 100$$

$$\text{IgG index} = (\text{CSF IgG} / \text{Serum IgG}) \times (\text{Serum albumin} / \text{CSF albumin})$$

Reference values must be established for each species. An elevated albumin quotient indicates BBB leakage or contamination of CSF with blood, with possible introduction of immunoglobulins from serum. An elevated IgG index indicates intrathecal production of IgG and may support a diagnosis of infectious disease of the CNS. The usefulness of these parameters is influenced by a number of other variables, including the immunoreactivity of blood.[28] Therefore, clinical interpretations must be made with great caution.

The concentrations of glucose and protein in the CSF of newborn foals are almost twice those found in the CSF of adults, but they approximate adult normal values by 2 weeks of age.[29] In contrast, calves between 1 and 2 months have lower protein concentration and higher leukocyte numbers in CSF than adult cattle.[30] The reference values for CSF proteins of normal horses and cattle are presented in Table 35-2.

Neural tissue contains the BB isoenzyme of creatine kinase (CK), which increases after damage to the nerve cells.[31,32] The molecule does not cross the BBB, so CK in the CSF originates from neural tissue. Contamination of CSF with dura or fat, however, falsely elevates the CK concentration. Some have suggested that CK is an accurate marker and a prognostic indicator for CNS disease, but other studies have not supported this conclusion, and measurement of CK, although interesting, has limited clinical utility.[31,33,34]

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Table 35-2 Protein Composition* of Cerebrospinal Fluid in Horses and Cattle[3–5,10]

Factor	Horses	Cattle
Albumin	22.6–67.9* (55.1)	8.2–28.7 (15.7)
Total globulin	3.8–20.1 (10.5)	NA
Total alpha	0.51–12.8 (0.46)	9.7–24.3 (14.7)
$Alpha_1$	0.18–10.6 (0.48)	NA
$Alpha_{2a}$	0.1–0.76 (0.31)	NA
$Alpha_{2bc}$	0.23–1.44 (0.59)	NA
$Beta_1$	0.38–3.36 (1.59)	1.875–8.85 (3.8)
$Beta_2$	0.27–1.31 (7)	NA
Gamma	0.27–3.03 (1.35)	2.45–8.85 (4.8)

NA, Result not available.

* Range of values for protein concentration is expressed in mg/dL; numbers in parentheses are mean values.

The normal CSF concentration of glucose is approximately 80% of that in blood. A decline in the ratio of CSF to serum glucose occurs in animals with bacterial meningitis because of increased use of glucose by inflammatory cells.

Measurement of the sodium concentration of the CSF may be helpful for diagnosing salt poisoning in cattle. In animals that do not have salt poisoning, this value is always less than 160 mmol/L; in animals with salt poisoning, the concentration usually is greater than 180 mmol/L.

35.1.3 TESTING CEREBROSPINAL FLUID FOR SPECIFIC DISEASES

Testing CSF for antibodies to a variety of infectious agents is now possible, as discussed later for specific diseases.

Measurement of neurotransmitters and several biomarkers for CNS injury is currently available in the experimental setting.[35] Studies of these substances aid our understanding of CNS physiology and pathology. Large animal species frequently are used as experimental models in such research, thereby enhancing our knowledge of CSF in health and disease in these species. Quantitation of neuropil-specific proteins (e.g., glial fibrillary acidic protein, neurofilament proteins), a variety of cytokines, nitric oxide metabolites, and neurotransmitters (e.g., nociceptin) is proving useful in elucidating the mechanisms of CNS injury and, in some cases, quantitating its severity.[36,37] Although these tests are not yet commercially available, this may change in the future, facilitating the clinician's ability to determine the prognosis for patients with CNS injury or disease.

35.2 DISEASES PRODUCING CORTICAL SIGNS

35.2.1 MAEDI-VISNA VIRUS INFECTION (OVINE PROGRESSIVE PNEUMONIA VIRUS INFECTION; ZWOEGERZIEKTIE)

35.2.1.1 Definition and Etiology

Maedi-visna virus, or ovine progressive pneumonia virus (OPPV), infection is a chronic disease of sheep caused by a retrovirus (subfamily Lentivirinae).[38–49] Visna virus is closely related to the many lentiviruses that cause immunodeficiency and neurologic disease in other species; these viruses include equine arteritis virus, caprine arthritis-encephalitis virus, and simian, feline, and human immunodeficiency viruses.[50,51] Caprine and ovine lentiviruses constitute a single virus group, termed the *small ruminant lentiviruses* (SRLVs), which can readily cross between species.[52–54] These agents are enveloped ribonucleic acid (RNA) viruses that contain reverse transcriptase.[55,56] The respiratory aspects of the viral infection are discussed in Chapter 31.

35.2.1.2 Clinical Signs

Neurologic disease caused by maedi-visna virus is relatively rare.[51] Nervous system signs may be characteristic of a diffuse encephalitis and include ataxia, twitching of the facial muscles, conscious proprioceptive deficits, normal gait along a straight path, staggering or stumbling when turned or forced to perform a complex maneuver, circling, and blindness. Coma, convulsions, and hyperexcitability may be seen in terminal stages. Other sheep have gradually progressive limb weakness and ataxia, often worse in the rear limbs; myelitis may be the sole clinical manifestation of maedi-visna.[56,57] Some sheep merely show emaciation without neurologic signs. The time between the onset of clinical signs and death may be as long

as 1 to 2 years. Because of the slowly progressive nature of OPPV infection and the high probability that affected sheep eventually will develop chronic disorders of the nervous, musculoskeletal, mammary gland, or respiratory system, the presence of antibody in the serum usually is considered evidence of active infection.[58,59]

35.2.1.3

Clinical Pathology

The CSF of affected animals is characterized by pleocytosis, with the cell counts per deciliter ranging from 1012 to 1478 for animals infected for 1 month and 4 years, respectively.[60] The protein concentrations of CSF range from 50 to 100 mg/dL for 30 days after infection. Antiviral antibody and virus can be detected in CSF specimens. The CSF/plasma ratio of immunoglobulin G (IgG) in the CNS is normal (<0.2) during the first month after infection but rises to over 0.4 after 1 month.[61]

35.2.1.4

Pathophysiology

The lesions of maedi-visna virus infection are partly induced by the host's inflammatory response. Experimental immunosuppression of infected sheep ameliorates the severity of the clinical signs and reduces the pathologic lesions of the cerebral cortex without altering the amount of viral shedding.[62,63] The virus is immunosuppressive. Viral infections usually lead to a variety of secondary bacterial infections.[64] Spread of OPPV within the tissues and secretion of the virus may be facilitated by concurrent diseases, such as *Brucella ovis*.[65] The chronic viremia may be caused by repeated antigenic changes of the virus; by intermittent expression of proteins by persistent proviral deoxyribonucleic acid (DNA) in cells; or by protection of the virus in circulating immune cells. Natural resistance to maedi-visna virus infection may be mediated partly by a nonimmunoglobulin inhibitory substance that is present in ovine plasma.[64]

35.2.1.5

Pathology

Gross lesions of visna infection are seen only rarely, when inflammation and malacia are extensive. In such cases, areas of yellowish tan discoloration are present in white matter.[66] The microscopic lesions of visna are predominantly those of a diffuse, nonsuppurative, perivascular inflammation throughout the neuraxis, affecting white matter in particular, although gray matter also is involved. The lesions include demyelination, gliosis, lymphocytic choriomeningitis, round cell infiltration of the choroid plexus, and focal necrotic areas that are infiltrated by macrophages.[67,68] Inflammatory lesions are predisposed to develop in a periventricular location, including around the central canal of the spinal cord.

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After exposure to the virus, sheep develop an asymptomatic infection for as long as 6 weeks. During this time the virus can be isolated from the brain and other tissues; later the virus can be isolated from peripheral blood neutrophils but not from tissue homogenates, indicating that replication of the virus occurs in circulating cells during this stage of the infection.[69] Once the disease has been recognized, the affected sheep should be culled or slaughtered. Rigid control measures that may be partly successful[46] are discussed in Chapter 31.

35.2.1.6

Diagnosis and Epidemiology

Spread of maedi-visna virus occurs through ingestion of infected milk by neonates, through in utero transmission, and horizontally within a herd. Recent data suggest that the role of colostrums and milk in the spread of disease may be less important than previously thought, and that seropositivity in young lambs may be caused by colostral antibodies rather than true seroconversion by the lambs.[48,70] Low prevalence of the virus within herds managed extensively rather than intensively further supports the belief that horizontal transmission is the most important mode of infection.[71]

The diagnosis of visna infection is made initially by recognition of the clinical neurologic disease in groups of animals in which the pulmonary form of the disease also is present. Agar gel immunodiffusion (AGID) testing has been superceded by more accurate enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) tests.[51,72–75] The diagnosis and epidemiology of maedi-visna virus infection are discussed in detail in Chapter 31.

35.2.1.7

Treatment and Prevention

No effective treatment for maedi-visna virus infection is available for field use, although the disease has been used as an animal model system for the study of drugs effective against lentiviruses.[76,77] Prevention is based on herd hygiene and culling of affected animals. Recently, a novel vaccine strategy using a plasmid encoding for viral envelope glycoproteins has shown some promise, although routine clinical use of such vaccines is probably many years away.[78]

35.2.2

CAPRINE ARTHRITIS-ENCEPHALITIS VIRUS INFECTION (INFECTIOUS LEUKOENCEPHALOMYELITIS)

35.2.2.1

Definition and Clinical Signs

The caprine arthritis-encephalitis (CAE) virus belongs to the retrovirus group and is closely related to the virus that causes maedi-visna and ovine progressive pneumonia in sheep ("small ruminant lentiviruses").[79] The systemic manifestations of the disease are thoroughly discussed in Chapter 38. The leukoencephalomyelitis form of CAE is predominantly seen in young goats but may occur in goats as old as 22 years.[80] The clinical signs of leukoencephalomyelitis include ataxia, paraparesis, paraplegia, tetraparesis, tetraplegia, hemiparesis, hemiplegia, head tilt, nystagmus, tremors, torticollis, trismus, salivation, depression, coma, and opisthotonos.[81–87] The neurologic deficits may be either symmetric or asymmetric. Goats with high cervical spinal cord lesions (L1 to L4) are recumbent and unable to raise their heads from the floor. They may show resistance to passive neck flexion. Vision and pupillary light reflexes may be diminished.[83,85] The specific gait disturbances depend on the areas of the spinal cord involved. Signs of neurologic dysfunction may range from paraparesis to tetraplegia. The spinal reflexes range from hypertonia and hyperreflexia to hypotonia and hyporeflexia.[81–86] This diversity of signs is related to the variable location of lesions in the central nervous system (CNS).

Other clinical signs also are variable. In one study, affected goat kids remained afebrile, whereas in another study, 61% of affected animals had rectal temperatures ranging from 38.9° C to 41.3°C (103.6° F to 106.4°F).[81–86] Other signs that could be associated with systemic viral infection include enlarged joints, vague and shifting leg lameness, weight loss, and tachypnea without significant auscultatory abnormalities.

The major differential diagnostic considerations for the neurologic form of CAE include listeriosis or chlamydial and mycoplasmal infections. The CAE virus causes neurologic lesions in numerous regions of the CNS, whereas the lesions of listeriosis are generally restricted to the brainstem. Mycoplasmal infections typically affect kids ranging from 1 to 6 months of age, and affected animals develop polyserositis. They are systemically ill, and the joints are hot, grossly swollen, and painful. Goats with a mycoplasmal infection show extreme pain when the neck is passively flexed because of meningeal and vertebral articular inflammation. Fluid from the body cavities of goats with mycoplasmal infection has a high protein concentration and an increased number of polymorphonuclear cells.

35.2.2.2

Diagnosis

Previously, an AGID test was used for the diagnosis of CAE, but this has been superseded by ELISA and PCR tests.[88,89] The virus also may be cultured from infected tissue.[90] One study has reported an increase in total plasma protein and hypergammaglobulinemia in affected goats.[82] The results of other hematologic and blood chemistry analyses are normal. The changes in the CSF are characteristic only of a chronic granulomatous inflammation. Specific changes include an increased protein concentration and pleocytosis.[91] Cell counts in the CSF of affected goats range from 5 to 1800/dL, and the protein concentration ranges from 0 to 700 mg/dL.[80]

35.2.2.3

Pathogenesis

Being a member of the retrovirus group, the CAE virus contains RNA-dependent DNA polymerase. When inoculated into goats, the virus causes a chronic infection characterized by demyelinating encephalomyelitis, arthritis, and interstitial pneumonia. The pathologic changes resemble those of an autoimmune process and are probably caused by interactions between the host's immunologic responses, denatured myelin, and the virus.[92] Macroscopic pathologic changes in the CNS of naturally infected goats include cloudiness of the meninges and tan discoloration of the white matter.[81] Microscopic changes include disseminated perivascular accumulations of mononuclear cells, demyelination originating in the subependymal region, astrocytosis, and mononuclear leptomeningitis.[81,85,88,92,93] The inflammatory foci are predominantly composed of macrophages containing material that tests positive on periodic acid—Schiff (PAS) staining. Neuronophagia and neuronal necrosis are not seen.[93] Lesions are most severe in the periductular, periventricular, and submeningeal regions of the white matter. Spinal cord lesions are most frequently observed in the thoracolumbar segments.[80]

35.2.2.4

Treatment

No treatment is available for goats with leukoencephalomyelitis. Control measures are discussed in Chapter 38.

35.2.3 BORDER DISEASE (HAIRY SHAKER LAMBS; HYPOMYELOGENESIS CONGENITA)

35.2.3.1 Definition and Etiology

Border disease is a congenital infection of sheep and goats caused by a noncytopathic togavirus (genus *Pestivirus*).[94] The border disease agent is antigenically similar to the bovine viral diarrhea (BVD) and hog cholera viruses. Once introduced into a flock, the border disease virus causes a devastating syndrome characterized by abortion, infertility, and deformed lambs. The virus infects naive ewes during pregnancy and causes a variety of fetal malformations, including early embryonic death, abortion and stillbirth, and small, malformed lambs. A seroprevalence rate as high as 29% has been seen in a newly infected flock; however, lambs infected in utero become immunotolerant and remain viremic.[95] In an infected flock the incidence of fetal malformations and abortions declines over time because of the growing population of ewes with persistent active immunity. Adult sheep that become infected with the border disease virus develop an inapparent, short-lived viremia and become immune to reinfection.

35.2.3.2 Clinical Signs

The severity of clinical signs in affected lambs varies. Changes are most marked in newborn lambs infected in early gestation (before 50 days). The central nervous system (CNS), skin, and skeleton are the most seriously affected. The hairs of congenitally affected lambs are coarse, straight, and elongated and stand out from the body like a halo.[96] The coat is abnormally pigmented and may have a dark-gray appearance or hyperpigmented spots that are especially prominent over the top of the neck.[97] The combination of pigmentary abnormalities and long, coarse hair shafts gave rise to the descriptive term “steel wool coat.” Animals that survive shed the abnormal hairs at 9 to 12 weeks of age and replace them with normal hair fibers. Affected lambs also have a short, thickened body, shortened legs, smaller orbital size, and doming of the frontal bone.[98,99] Arthrogryposis occasionally may be seen. Some infected lambs show neurologic symptoms such as ataxia and uncontrollable tremors. The tremors are coarse, involve the trunk and head, and disappear when the animal is asleep.[100,101] The lambs often are alert and appetent but initially need assistance to stand and nurse. Some animals walk normally but hop on the rear limbs when forced to run. Over time the lambs become stronger but continue to show impaired locomotion for months. The CNS signs usually disappear by 20 weeks of age, but the animals appear stunted. Affected animals have greatly decreased viability compared with uninfected herdmates and may die suddenly without showing premonitory symptoms. Aside from neonatal death losses, economic burdens imposed by the viral infection include low birth weights, diminished weaning weights, lowered carcass quality, and infertility.[99,102]

Abortions that occur 9 to 106 days after inoculation are seen in 30% of experimentally infected sheep.[97,98,103] In field outbreaks the average gestational age of the aborted fetus is 63 days. Teratogenic effects are most often observed when lambs are infected at 50 to 90 days of gestation.[104] Fetal mummification occasionally may be seen.

The border disease virus is also pathogenic in goats.[105] As in sheep, inoculation of pregnant does results in fetal mummification and abortion. The spinal cords of infected kids are hypomyelinated, but the characteristic hair changes usually observed in sheep fetuses are not seen in goat kids.

The border disease virus has low pathogenicity for cattle. Abortions can be induced in cows inoculated with the virus at approximately 50 days of gestation, and affected calves have cerebral cavitations.[106] The condition is not recognized as naturally transmitted to cows.

35.2.3.3

Diagnosis

Identification of the viral antigens in tissues using fluorescent antibody tests is the most accurate method of diagnosing border disease. Tissues that most consistently contain viral antigens are those of the abomasum, pancreas, kidneys, thyroid, and testicles.[107,108] Serodiagnostic methods, including serum neutralization (SN), AGID, and complement fixation tests, have been developed.[109] In most cases the BVD virus has been used as the indicator antigen. Serodiagnosis of infected lambs is difficult because the lambs tend to be immunotolerant and therefore do not develop strong serologic responses. Sheep infected as adults develop SN titers ranging from 1:20 to 1:320, whereas the SN titers of animals with congenital infections are consistently below 1:10.[103] The presence of viral antibodies in the CSF suggests border disease virus infection.

35.2.3.4

Pathophysiology

Hypomyelination probably is caused by a combination of virus-induced degeneration of the oligodendroglial cells (dysmyelinogenesis), persistent viral infection, and diminished secretion of the thyroid hormones L-3,3′, 5′-triiodothyronine and thyroxine.[110] A deficiency of these hormones probably results in a lowered concentration of 2′,3′-cyclic nucleotide-3′-phosphodiesterase, which contributes to the hypomyelination. The diminished production of thyroid hormones is thought to be related to direct inhibition of the thyroid gland, because the pituitary activity of these lambs appears to be normal. Hypomyelination appears at approximately the same time as specific antiviral delayed-type hypersensitivity, indicating that an immunopathologic event may be partly responsible. Morphometric measurements of the spinal cords of lambs infected in utero show a permanent reduction of both white and gray matter in a cross-sectional area as a result of the decreased myelin content.[111] Depressed blastogenic activity of lymphocytes, a decrease in T4 helper cell function, and an increase in T4 suppressor cell function have been demonstrated in affected lambs between 4 and 7 months of age, indicating a viral immunosuppression.[112–114] Such immunosuppressed lambs succumb to parasitism, diarrhea, and bronchopneumonia.

35.2.3.5

Epidemiology

Border disease is transmitted both vertically and horizontally.[112,115] The agent can efficiently infect sheep through the intact mucous membranes. The major reservoir in infected herds is the asymptomatic, congenitally infected seronegative animal.[95,116] Sheep exposed to the virus as adults develop antibody responses and are able to clear the infections within weeks. Asymptomatically infected animals may shed the virus through the placenta, infected offspring, saliva, respiratory secretions, urine, or feces.[103,112] In one seroepidemiologic study of infected ewes in the western United States, lambs were more often seropositive than ewes.[95] A large percentage of the seropositive lambs were born to seronegative ewes, indicating the presence of a large amount of virus cycling from asymptomatic carriers. Strain-related differences appear to exist in viral pathogenicity.[117]

35.2.3.6 Necropsy Findings

The macroscopic changes associated with border disease virus infection are hydranencephaly, porencephaly, microcephaly, cerebellar hypoplasia, abnormal curvature of the ribs, brachygnathia, doming of the frontal bones of the skull, narrowing of the distance between the orbits, a decrease in orbital size, shortening of the crown-to-rump and diaphyseal lengths, retention of secondary hair fibers, and abnormal skin pigmentation.

Microscopic changes in lambs with congenital infection include hypomyelinogenesis and hypercellularity of the white matter with abnormal-appearing glial cells.[118] The CNS shows dysmyelinogenesis, secondary demyelination, and a nodular periarteritis. Viral antigen can be demonstrated in the adventitia of the CNS arterioles.[110] The microscopic lesions of the placenta include endothelial swelling, thrombotic occlusion of the vessels, and fibrinonecrotic cellular debris in the fetomaternal space.[118]

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35.2.3.7 Treatment and Control

In herd situations, blood cultures and examination of skin biopsies by fluorescent antibody tests should be performed concurrently to identify carriers.[106] The SN test is not a reliable indicator of infection. Noninfected pregnant sheep should be kept separated from others in the flock for the first 60 days of gestation to ensure that in utero infections do not occur.

35.2.4 ENCEPHALITIC INFECTIOUS BOVINE RHINOTRACHEITIS VIRUS INFECTION

35.2.4.1 Clinical Signs

Two herpesviruses, bovine herpesvirus type 1 (BoHV-1) and type 5 (BoHV-5), have been associated with encephalitis in cattle.[119] BoHV-1 infection typically results in an acute upper respiratory tract disease characterized by fibrinonecrotic white plaques of the nasal, pharyngeal, and tracheal mucosa and abortions (see Chapter 31). Other clinical conditions associated with infectious bovine rhinotracheitis (IBR) infection include epizootic conjunctivitis (Chapter 39) and infectious balanoposthitis or vulvovaginitis (Chapter 43). Infection with BoHV-5, in contrast, usually results in meningoencephalitis with few or no respiratory signs. BoHV-1 infections also can result in meningoencephalitis, but much less frequently. The clinical signs of this encephalitis include depression, mild nasal and ocular discharge, conscious proprioceptive deficits, head pressing, aimless circling, bellowing, salivation, bruxism, paralysis of the tongue, head tilt, nystagmus, convulsions, blindness, coma, and death.[120,121] The seizure activity is characterized by a tonic-clonic convulsion with violent spasms or tremors of the head, with all four legs flexed and the head in opisthotonos.[120,121] Rectal temperatures of 41° C to 42°C (106° F and 107°F) have been reported.[122] The case-fatality rate of encephalitic IBR is almost 100%; however, recovery occurs in rare case. In experimental infection, signs develop 1 to 2 weeks after infection.

Differential diagnoses for encephalitic herpesvirus infections in cattle include almost all encephalitic, encephalopathic, and neurotoxic diseases of cattle, including rabies, polioencephalomalacia, salt poisoning, and lead toxicity. Accompanying respiratory disease raises the index of suspicion for herpesvirus. A rising serum neutralizing antibody titer in surviving animals can be used to confirm infection, although this does not distinguish between BoHV-1 and BoHV-5. Specific diagnosis is usually made at necropsy using a

number of modalities, including virus isolation, immunohistochemistry, and PCR.[123–125] Many of these tests do not distinguish between BoHV-1 and BoHV-5; more specific PCR and restriction fragment analysis techniques can differentiate between these two virus types.[126]

35.2.4.2

Epidemiology

Bovine herpesviruses cause disease in cattle worldwide, although the encephalitic form of infection is relatively rare in the United States. Epidemiologic factors that appear to favor dissemination of herpesviruses among cattle include a high stocking rate, repeated introduction of animals from diverse backgrounds, and mass weaning of calves at a time when the passively acquired anti-IBR antibodies are waning.[120] BoHV-1 may survive in the environment for up to a month; cooler ambient temperatures and higher humidity promote virus survival.[127] Calves less than 6 weeks old are most susceptible, but infection and resultant neurologic disease also have been described in adult cattle.[121,122,128–134] Animals that survive the disease become persistently infected; virus survives in the nasal and tracheal muscosa and the trigeminal ganglion. Reactivation and virus shedding may occur during periods of stress.[127–129,132] Although clinical disease caused by reactivation of latent virus is usually mild and may go unnoticed, shedding of virus during such episodes provides a source for infection of in-contact animals. The viruses grow in the nasal and pharyngeal mucosa. Brain involvement results from centripetal spread along the sensory neurons of the trigeminal and olfactory nerves.[132] Hematogenous dissemination to the brain is believed to be relatively unimportant.

35.2.4.3

Pathophysiology

Encephalitic IBR infections cause a nonsuppurative meningoencephalitis that is widely distributed in the gray matter of the brain. Pathologic abnormalities affect predominantly the forebrain, although all areas of the brain can be involved. Findings include marked perivascular cuffing with mononuclear cells, diffuse gliosis, neuronal degeneration and chromatolysis, hemorrhage, edema, necrosis, and neuronophagia. White matter lesions include myelitis with mononuclear cell infiltration and demyelination. Extensive lymphocytic meningoencephalitis is seen. Intranuclear inclusion bodies are rarely seen in bovine herpesvirus encephalitis. The virus usually can be isolated from brain homogenates of affected calves.

35.2.4.4

Treatment and Control

No adequate therapy exists for the encephalitogenic form of BHV-1 infection. Treatment is symptomatic and supportive and should include oral or intravenous fluid support, nonsteroidal antiinflammatory drugs (NSAIDs), antibiotics in animals with respiratory signs, and nursing care. Diazepam or phenobarbital may be used for seizure control when necessary (Table 35-3). Animals with severe clinical signs may be euthanized for humane reasons.

Vaccines that protect against BoHV-1 also may prevent BoHV-5 infection because of the close antigenic relationship between the two viruses.[128] Modified live intranasal vaccines may be most effective in preventing clinical disease and also can reduce shedding of virus by infected animals. In some European countries, eradication programs that employ testing and culling of infected animals have been successful in eliminating BoHV-1. Bovine herpesviruses can be spread through fomites and by aerosol transmission for up to 4 miles (6.4 km).[127] Strict biosecurity procedures are therefore essential to developing and maintaining virus-free herds.

35.2.5 BOVINE SPONGIFORM ENCEPHALOPATHY ("MAD COW" DISEASE)

CHRISTINE F. BERTHELIN-BAKER

35.2.5.1 Definition and Etiology

Bovine spongiform encephalopathy (BSE) is a transmissible spongiform encephalopathy (TSE) of cattle that was first described in 1987 in Great Britain (GB).[135] The TSEs are a group of slowly progressing, invariably fatal neurodegenerative diseases that can affect humans and animals. They are also called "prion diseases" because of the accumulation of prion in the central nervous system (CNS). Since the "prion hypothesis" was first formulated in 1982 by Stanley Prusiner, prions have been widely accepted as the etiologic infectious agents of the TSEs.[136] The prion is an isoform (PrPSc) of the normal prion protein (PrPc), a host-encoded membrane protein that does not carry any nucleic acid. PrPSc replicates by inducing a posttranslational conformational change in the normal protein PrPc to form the abnormal prion PrPSc.[136–138]

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Table 35-3 Recommended Drug Dosages for Treatment of Cerebrocortical Disease

	Dose	Route	Frequency
ANTICONVULSANT DRUGS			
Valium	0.01–0.4 mg/kg	IV or IM	Twice daily or as needed
Pentobarbital sodium	2–10 mg/kg	IV	Three times daily
Phenobarbital	Loading dose 20 mg/kg	IV	One time
	Maintenance dosage 1–4 mg/kg	IV, PO, or IM	Divided twice daily
ANTIINFLAMMATORY OR ANTIEDEMA DRUGS			
Methylprednisolone	1–30 mg/kg	IV	One time
Dexamethasone	1–4 mg/kg	IV or IM	Twice daily
Mannitol	0.25–0.5 g/kg 20% solution	IV	Twice daily
Furosemide	1 mg/kg	IV, IM, or SC	Twice daily
Flunixin meglumine*	1 mg/kg	IV or IM	Twice daily
Phenylbutazone†	2–4 mg/kg	IV or PO	Twice daily
Dimethyl sulfoxide (DMSO)	1–2 g/kg	IV	Twice daily
Acetylsalicylic acid (aspirin)	7–10 g/500 kg	PO	Twice daily

IM, Intramuscular; *IV,* intravenous; *PO,* oral; *SC,* subcutaneous.

*	Monitor for signs of gastric or abomasal bleeding (fecal occult blood).
†	An initial loading dose of 10 to 20 mg/kg, followed by 2.5 to 5 mg/kg daily to every other day thereafter has been recommended for cattle. Because of the prolonged plasma half-life in ruminants, serial administration of the drug should be accompanied by careful monitoring of renal function and gastrointestinal bleeding.

35.2.5.2

Clinical Signs

Video clips of various clinical signs of BSE are available on the Internet.[139] As with all TSEs, BSE has a long incubation phase. It occurs mostly in 4- to 6-year-old cattle (age range, 20 months to 18 years). The clinical signs of BSE are usually insidious in onset.[140,141] They may be precipitated by stressful situations such as transportation, concurrent illnesses, or states of increased metabolic consumption, such as late pregnancy and parturition.

The detection of clinical signs of BSE and the array of clinical signs reported are influenced by how closely the cattle are being observed and the handlers' awareness of the insidious and nonspecific nature of the clinical signs. Subtle early behavioral changes are unlikely to be observed in large herds. Cattle may become apprehensive, stay apart from their herdmates, and become fearful of their handlers. As the disease progresses, cattle often become extremely excitable, especially when restrained or placed in confined quarters or an unfamiliar environment. BSE cattle may refuse to move through previously familiar doorways and become impossible to restrain. Unprovoked aggression is less frequently seen. Hyperesthesia is most marked around the head and neck. A light touch on the hindlimbs may induce violent, “ballistic,” and often repetitive kicking, which may also be observed during milking. Animals may overreact, startle, or “panic” in response to sudden visual, tactile, or auditory stimuli. The startle reaction may be gauged by a hand test (punching fist abruptly toward the animal's head without touching it), flashlight test, a hand clap, or a loud metallic “bang.” Normal animals rarely startle in response to such stimuli, or they may startle once or twice when the stimulus is repeated. BSE cases will frequently startle in a violent and repeatable fashion, with no habituation to a repeated stimulus. In some cases the response may escalate to an extreme “aberrant” startle, with head shaking and seizure-like head bobbing, which may be followed by violent turning, running around, and falling.[139]

Other possible clinical signs of BSE include ptyalism, increased head rubbing, muscle fasciculations, and excessive vocalization. Other behaviors seen in BSE may include frequent and repetitive head tossing, licking of the nostrils, yawning, flehmen, head tossing and head butting, and restlessness.[139,142] A relative bradycardia (≤60 beats/min) may be observed in animals when a tachycardia is expected because of their hyperexcited state. Affected animals often lose weight and have reduced milk output. Ataxia and tremors are seen in more advanced cases. Tremors most often involve the head and neck and may become generalized, especially with exercise. Ataxia is most marked on turns, when going over steps, or on uneven terrain; it may also be accentuated with exercise. BSE animals may become recumbent and unable to feed if the disease is left to run its course. Recumbency may also be triggered by an intercurrent illness or an injury during a fall. The clinical signs of BSE may be more difficult to recognize in animals that have become recumbent than in less advanced cases,[143] and systematic targeted surveys of “fallen stock” have allowed for the detection of previously unsuspected cases of BSE in various countries.[144]

35.2.5.3

Pathophysiology

The exact function of the prion protein is unknown, as are the mechanisms of neurodegeneration and CNS dysfunction in TSEs.

The presence of BSE infectivity in extraneural tissues has not been identified in natural BSE cases. In pathogenesis studies of cattle orally inoculated with BSE, infectivity was detected during the incubation period in the distal ileum from 6 months after challenge and in the CNS from 32 months after challenge (clinical signs first observed at 36 months).[145] Similar studies in sheep revealed infectivity within Peyer's patches by 4 months after experimental inoculation and in a wide range of tissues, including the CNS, by 16 months after inoculation.[146] PrPSc was detected in lymphoid tissue (Peyer's patches) of the distal ileum and in the bone marrow during the clinical phase of the illness.[147] Mice bioassays were negative for infectivity of milk, placenta, tonsils, and lymph nodes from BSE-affected and incubating animals. However, the more sensitive cattle bioassay showed that tonsils do carry small amounts of infectivity.[148] The full results of cattle bioassay studies have not yet been published.

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35.2.5.4

Epidemiology and Zoonotic Potential

BSE may have derived from feedstuffs containing rendered carcasses of scrapie-infected sheep, or it might have been a preexisting sporadic and rare disease unrecognized in the bovine population. The BSE epidemic was traced to the recycling of BSE-infected carcasses into cattle feed, which occurred mostly in the 1980s in the United Kingdom (UK).[149] Cattle in other countries were affected as a result of the importation of infected feedstuffs or cattle, followed by later recycling the agent in their own rendered ruminant feedstuffs.

Bovine spongiform encephalopathy has predominantly affected dairy cattle because of their longer lifespan and more intensive feeding and wider use of concentrate than beef cattle. From 1986 to August 2006, a total of 179,140 cases of BSE were confirmed in GB. These cases have been distributed among 35,411 farms, representing about 60% of the farms holding adult cattle.[150,151] The cattle cohorts born in 1986 to 1989 had the highest incidence of BSE cases, and the peak of the outbreak occurred in 1992, when 36,680 cases were detected through scanning of suspect clinical cases (passive surveillance) in GB. A sustained and sharp decrease in the number of cases has occurred each year since 1992. In 2005, only 39 BSE cases were detected through passive surveillance (of 186 animals investigated), and another 164 (of 547,366 cattle tested) were detected through active (targeted) surveillance programs in GB.[151] The decline in the GB epidemic is directly related to the successive bans on the feeding of ruminant-derived meat and bonemeal to cattle. The initial 1988 ban took effect in 1989 in the UK and has been tightened and refined since then. Similar bans have been adopted by many countries around the world. A map of countries that have reported home-born or imported cases of BSE and the number of cases reported each year is available and regularly updated on the website of the Office International des Epizooties (OIE).[152]

No clear genetic predisposition to BSE has been demonstrated in cattle, unlike for scrapie in sheep. Calves born from dams in the later stages of the incubation of BSE are at most 10% more likely to develop BSE than their herdmates. This may be a result of an unidentified genetic predisposition or a low degree of vertical transmission. Mathematical modeling of the rate of reduction in the number of BSE cases in response to the initial feed bans introduced in the UK showed that vertical and lateral transmission of BSE, if they do occur, do so at a very low rate that could not sustain an outbreak of BSE. At the turn of the century, mathematical

modeling experts had initially predicted that BSE would be eradicated from the UK by the year 2005.[150] This prediction is being revised, especially because a previously unrecognized BSE phenotype has been identified in Italy, France, and Germany.[153,154]

Since the onset of BSE epidemic, new TSEs have occurred in domestic cats, various exotic species, and humans.[151] Strain typing in mice showed that these new TSEs were caused by the BSE agent.[155,156] A new variant Creutzfeldt-Jakob disease (vCJD) was first identified in 1996 in the UK, where it has affected 162 people to date.[157] Other countries have detected vCJD cases (two in United States) in people who had lived in the UK between 1980 and 1996, when the strictest measures were enforced to prevent human infections. France, Italy, Republic of Ireland, The Netherlands, Portugal, Spain, and Saudi Arabia have detected vCJD cases in residents who never traveled to the UK. The emergence of vCJD has put worldwide emphasis on the prevention and detection of TSEs in animals. The route of infection of people by BSE has not been clearly traced, but it is generally accepted that the consumption of food that included cattle nervous system was the main cause of vCJD in people. Successive "Specified Risk Materials" bans have been enforced to prevent contamination of human food with nervous system from ruminant animals.

35.2.5.5

Diagnosis

No in vivo test is available for the diagnosis of BSE. Clinical suspicion can be confirmed only by postmortem examination. The diagnosis of BSE is based on microscopic brain examination or tests that identify prion in brain or spinal cord tissue.[135,153,154,158] Rapid prion tests include Western blot, paraffin-embedded tissue (PET) blot, and ELISAs.[159–162] Rapid tests have enabled the detection of BSE though surveillance in targeted at-risk populations, such as fallen cattle.

Histopathologically, BSE is characterized by neuronal degeneration and intraneuronal vacuolation in specific brain areas. The vacuolation is accompanied or preceded by the accumulation of PrPSc.[149,163,164] The uniformity of the pathology among affected cattle along the UK epidemic and in various other countries has generally supported the theory that all BSE cases were caused by a single strain of TSE agent, which has been defined by its specific BSE histopathologic phenotype.[149,164–167] Since 2004, atypical BSE cases have been described in Italy, France, and Germany.[153,154,168] Further studies are ongoing to determine whether these cases reflect the existence of a previously unidentified strain of BSE.

35.2.5.6

Differential Diagnosis

Nervous system diseases that could be confused with BSE include viral encephalopathies (pseudorabies, rabies, Borna encephalitis, bovine immunodeficiency virus encephalitis), listeriosis, polioencephalomalacia, lead poisoning, CNS parasitic migration, brain tumors and abscesses, and vitamin A deficiency. Hepatic encephalopathy and other metabolic imbalances may also be confused with BSE. Because of the insidious nature of BSE, affected cattle may appear to recover coincidentally with blanket therapy for suspected metabolic imbalances and later relapse. This must be kept in mind whenever therapy for metabolic imbalances initially appears to be successful but is followed by one or more relapses.

35.2.5.7

Treatment and Prognosis

BSE is always fatal, and no treatment is available.

35.2.5.8 Control

Various measures have been taken to protect public health by removing potentially infected animals and tissues from the food chain. The disposal of BSE-infected tissues and the sourcing of bovine tissues and body fluids for the preparation of medicinal products must take into account the extreme resistance of TSE agents. All TSE agents remain infectious after exposed to a wide range of inactivating treatments and environmental changes, such as autoclaving, rendering, storage for months to years, exposure to ultraviolet light, freezing, thawing, prolonged boiling, and incubation with formalin.[169–172] Because of the public health risk, the carcasses of animals suspected of having BSE should be incinerated.

In countries that have had an outbreak of BSE, the complete exclusion of ruminant tissues from ruminant feed has aided progress toward eradication of BSE, as previously noted. In the UK the initial feed ban of 1988 was found to be insufficient and was reinforced by successive measures. The 1996 ban on feeding mammalian meat and bonemeal to all farmed animals was introduced to prevent contamination of ruminant feed at feed mills and down the supply chain to the farm. Because of the long incubation period of BSE, there is a lag time in the effect of feed control measures, and the full effect of such measures can be assessed only when all animals born after a feed ban reach 4 to 8 years of age.

35.2.6 SCRAPIE

35.2.6.1 Definition and Etiology

Scrapie naturally affects sheep, goats, and mouflons. It is the oldest known TSE. It has affected sheep in various countries for more than 250 years. Strain typing in mice has demonstrated the existence of a variety of scrapie agents, none of which are identical to the agent of BSE.

35.2.6.2 Clinical Signs

Video clips of various clinical signs of scrapie are available on the web.[139] Most animals with scrapie are 1 to 5 years old. The clinical course varies but is typically slow and may last several months. Shepherds who work closely with their sheep can best recognize the early signs of scrapie. Early behavioral changes are often accompanied by weight loss. Scrapie cases may stay apart from the flock and become nervous and restless.[173] Pruritus of increasing intensity is a common feature; sheep may rub on fixed objects, scratch with their horns or hooves, and bite or lick at themselves excessively. The head, withers, flanks, back, rump, base of the tail, and lower limbs are typically affected, showing secondary wool loss, dermatitis, and skin infections or excoriations.[173,174] Head and face rubbing and shaking may also cause corneal chemosis or aural hematomas. When scratching the pruritic areas (mostly the back and rump), the animal may display a “scratch reflex” (or “nibble reflex”), which may include reflex nibbling, lip licking, and rhythmic head movements. This reflex is often but not always present in scrapie cases. It may also be observed in other CNS diseases and in pruritic skin diseases, especially ectoparasitism.

Other clinical signs of scrapie include bruxism (tooth grinding) and ptyalism. Less frequently, rumen fluid (cud) may leak through the nostrils or the mouth. Tremors may start with the head and generalize to the whole body. As the disease progresses, some sheep with scrapie may develop signs of apathy, exercise intolerance, and ataxia. The most severe and advanced cases may show convulsions, collapsing episodes, and

stupor. If scrapie is left to run its course, death may occur during a convulsion or as a result of starvation. The clinical signs of scrapie in goats are broadly similar to those in sheep.[174–178] Scrapie has been identified in fallen stock, especially in flocks that are not closely supervised.

35.2.6.3

Pathophysiology

The exact mechanism of CNS degeneration in TSEs has not been identified. The oral route is the most likely route of entry of the scrapie agent,[179,180] which probably enters the gastrointestinal (GI) tract and is transported to peripheral lymphoid tissue.[181,182] Follicular dendritic cells are infected early in the disease course, and there may be an interface between the lymphoreticular system and the nervous system.[183] Transport to the CNS likely occurs along the vagus nerve from the GI tract.[184] PrPSc has been identified by immunocytochemistry in the GI tract (in Peyer's patches and in autonomic plexuses) and in various lymphoid tissues of sheep with scrapie.[185,186] Replication of the agent takes place in lymphoid tissues, including the spleen, but circulating lymphoid cells do not appear to be involved in scrapie replication.[181,182,187]

35.2.6.4

Epidemiology

Scrapie occurs endemically in sheep flocks worldwide.[188–190] Sheep are the natural host of scrapie, but the infection can be maintained in goats that have no direct contact with sheep, indicating both lateral and vertical transmission of the agent in that species.[174,175,188,191] Scrapie cases occur sporadically in infected flocks. Only one or a few animals are affected at any given time. Outbreaks with up to 40% of animals affected in a flock have been linked to the use of infected vaccines[192] or to the introduction of scrapie by an infected animal in a previously uninfected and genetically sensitive flock. The route of natural infection is presumed to be oral. The route of excretion and the means of transfer of the agent between sheep are unknown.[179] Lambing time is known to be a particularly high-risk period for infection for the young. The contamination of pastures with infected placentas is likely to be an important reservoir of the infectious agent in nature.[173,193,194]

Although there is no known breed predisposition to scrapie, the genetic makeup of the host controls differences in susceptibility and resistance to scrapie in various breeds.[172,195,196] The molecular basis of this resistance is largely controlled by the PrP gene.[197] The gene responsible originally was thought to determine the incubation period of scrapie and was called *sip*. This gene is now known to be the prion protein gene. Polymorphisms at three codons of this gene appear to be the main determinants of the susceptibility of sheep to scrapie.[198,199] According to current evidence, the genotype $VV_{136}RR_{154}QQ_{171}$ (or $AA_{136}RR_{154}$ QQ_{171} in some breeds) is most susceptible, and the genotype $AA_{136}RR_{154}RR_{171}$ is totally resistant.[200] The potential relevance of other polymorphisms and other genetic factors is unknown. Selection of scrapie-resistant sheep flocks may be based on pedigree, phenotypic expression of the disease,[172] or genetic testing to select sheep of “resistant” PrP genotypes.[200] Studies are ongoing to determine whether “genetic resistance” may confer resistance to disease but not resistance to infection, in which case some genotypes of sheep could act as asymptomatic carriers of scrapie.[151]

35.2.6.5 Treatment and Prognosis

Scrapie is a fatal and irreversible disease for which there is no known treatment.

35.2.6.6 Diagnosis and Pathology

35.2.6.6.1 IN VIVO DIAGNOSTIC TESTS

Immunohistochemistry may show PrPSc in biopsies of tonsils or nictitating membranes, allowing for diagnosis of infection in live animals that are incubating or in the clinical phase of scrapie.[201–203] However, these tests may be negative in scrapie cases, and their interpretation requires a high degree of experience. Further research is in progress to increase the sensitivity of PrPSc tests. Newer tests also are being developed to detect PrPSc in blood and cerebrospinal fluid (CSF).[204–206]

35.2.6.6.2 DIFFERENTIAL DIAGNOSIS

Nervous system diseases that could be confused with scrapie include pseudorabies, rabies, Borna encephalitis, listeriosis, polioencephalomalacia, lead poisoning, parasitic migration in the CNS (coenurosis), brain tumors, brain abscess, maedi-visna virus infection, vitamin A deficiency, pregnancy toxemia, and other metabolic imbalances. When pruritus is the only clinical sign, skin diseases such as psoroptic and sarcoptic mange, ringworm, myiasis, pediculosis, and atopy may be considered as differential diagnoses. Because of the insidious nature of the illness, animals with early scrapie may initially appear to respond to blanket treatments. This must be kept in mind whenever specific therapy for another suspected illness appears initially to be successful but is followed by relapse. When therapy of an alternate condition fails, the final diagnosis must rely on detailed examination of appropriate postmortem samples.

35.2.6.6.3 POSTMORTEM DIAGNOSIS

Microscopic examination of the brain and spinal cord is the classic diagnostic method for scrapie. It is possible only when tissues are collected soon after death, before autolytic changes take place. Neuronal vacuolation and PrP deposits are found in specific brain nuclei.[207–212] In autolyzed tissues, PrPSc can be identified by immunohistochemistry testing, Western blot tests, or ELISA.[160,161,212–214] 981 982

35.2.6.7 Control

Because there is no effective treatment for scrapie, control measures designed to prevent the spread of the disease are especially important. Scrapie is a reportable disease. Eradication measures vary from country to country.[149,215] Animals suspected of having scrapie are slaughtered and destroyed. Contaminated pastures or paddocks may be left empty of livestock, but the scrapie agent is unlikely to be inactivated in the environment. Contaminated stalls, corrals, and sheds should be disinfected with sodium hypochlorite diluted at 4% available chlorine. In the United States and Canada, scrapie-affected and related animals are destroyed and their flocks quarantined.[215] Lines of sheep genetically resistant to the development of clinical scrapie

have been selected.[216] These sheep do not develop the clinical signs of scrapie, but they may have a chronic asymptomatic infection that could spread to sheep of susceptible genotypes.[172,216,217]

35.2.6.8 PUBLIC HEALTH CONSIDERATIONS

Although scrapie has been endemic in various areas of the world for more than two and a half centuries, epidemiologic studies have not shown any correlation between the incidence of Creutzfeldt-Jakob disease in humans and that of scrapie in sheep.[218] It is nevertheless wise to take precautions to minimize the potential for human exposure to scrapie because some sheep could have been infected by BSE, which would be identical to scrapie in any infected flock.[219] In a study of BSE orally transmitted to sheep, the clinical signs of BSE were identical to those of scrapie.[220]

35.2.7 MURRURUNDI DISEASE AND SEGMENTAL AXONOPATHY OF MERINO SHEEP

Murrurundi disease occurs in the sheep of New South Wales.[221] The condition is a spongiform encephalopathy that has some similarities to scrapie, humpyback, and Coonabarabran disease; however, the three conditions are pathologically differentiable. Murrurundi disease occurs in sheep between 1 and 5 years of age. The initial clinical sign is posterior paraparesis, with progression to paraplegia after several months. No wool breakage occurs in affected animals. Microscopic changes include multiple cytoplasmic vacuolation of the neurons and chromatolysis of Nissl substance. The cause of the disease is unknown.

A similar condition has been described in Merino sheep that developed progressive paraparesis between 1 and 4 years of age.[222] Axonal spheroids within white matter tracts of both the brain and spinal cord were the main pathologic feature of this disease.

35.2.8 HUMPYBACK DISEASE

Humpyback disease affects Merino wethers of Australia. The neurologic signs of the condition are not usually observed until the sheep are gathered for shearing. The affected animals lag behind the flock and show posterior ataxia. They may fall or stand quietly with the head lowered and the back arched; thus the common name of the condition. The clinical signs include rear limb ataxia, stiffness of the rear limbs, knuckling of the fetlocks, arched back, and recumbency. After resting for several minutes, affected sheep arise and travel for a short distance but soon are immobilized again. Eventually the disease leads to recumbency and death. Affected animals worsen over several years.[223] Wallerian degeneration of the spinal cord is the major pathologic change seen in affected sheep; however, the severity of microscopic changes do not correlate well with the clinical signs. The cause of the condition is unknown.[224,225]

35.2.9 EQUINE HERPES MYELOENCEPHALOPATHY

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Eight types of herpesvirus affect horses, donkeys, and possibly other equids.[226,227] Of these, equine herpesvirus type 1 (EHV-1) is clinically important because it sometimes is associated with neurologic disease.[226] EHV-1 is

more frequently associated with reproductive disorders, neonatal diseases, and respiratory disease.[226,228,229] Equine herpesvirus type 4 is primarily associated with respiratory disease and is discussed extensively in Chapter 31.[228] Equine herpes myeloencephalopathy results from ischemic damage to the spinal cord, not from viral infection of neurons.[226] Single individuals may be affected, but outbreaks involving several horses in the same environment have been reported; such involvement of multiple animals raises the index for suspicion of EHV-1.[230–232]

35.2.9.1

Clinical Signs

Acute onset of ataxia and tetraparesis of variable severity most often characterizes the neurologic form of EHV-1.[229,233] Signs usually appear between 6 and 10 days after infection.[229] The severity of clinical signs can range from subtle neurologic deficits to complete recumbency. Other signs also may be seen, including nasal discharge, limb edema, colic, ocular lesions, and anorexia.[226,228–231,233] The animal may be febrile at presentation, but most are normothermic.[226,229] Pyrexia is the most consistent premonitory sign before the onset of neurologic disease, although not all pyrexic horses will develop myeloencephalopathy.[232,234] Coughing and nasal discharge sometimes accompany the neurologic deficits or may have been present in the preceding 2 weeks.[231]

The neurologic signs reflect damage to the white matter of the spinal cord and include ataxia, paresis, conscious proprioceptive deficits, urinary incontinence, flaccid tail and anal tone, and diminished perineal sensation.[226,229,233] Hindlimbs are more severely affected, and deficits usually are symmetric. Bladder atony and dysuria frequently occur, and the associated dribbling of urine leads to secondary perineal scalding. Anal sphincter tone also is diminished, which may result in a distended rectum.

Cranial nerve deficits, including seizures, blindness, and vestibular signs, have been reported with EHV-1 infection.[231] Ocular lesions also may be present, such as mydriasis, hypopyon, uveitis, and optic neuritis.[226,229,235,236]

The clinical signs typically stabilize within 48 hours, although progression varies. Some patients continue to deteriorate and eventually die or are euthanized. Most horses begin to improve within the first 5 to 7 days and ultimately make a full recovery, although the recovery may take months. A patient that does not become recumbent has a much better prognosis.[233,235]

35.2.9.2

Diagnosis

A tentative diagnosis can be made based on characteristic neurologic signs, the history, and supporting findings on the physical examination. A cerebrospinal fluid (CSF) analysis that shows an increase in protein and a normal or slightly increased nucleated cell count (albuminocytologic dissociation) is the classic CSF change seen with EHV-1 infection.[226,229,237] Cerebrospinal xanthochromia may also be seen.[233] The protein level may be normal, which does not necessarily rule out EHV-1. Occasionally, early in the disease the CSF may be normal or may show only mild abnormalities; CSF protein concentration in the normal range does not rule out EHV-1.[226] 982 983

A fourfold or greater increase between acute and convalescent virus neutralizing (VN) antibody titers is consistent with a diagnosis of EHV-1 infection.[237] VN titers usually are the easiest and most economic to

perform. Because they rise quite rapidly and reach a level much higher with natural infection compared with vaccination, a fourfold rise in the VN titer may not be seen, especially if collection of the acute sample was delayed.[226,235] A single titer of 1:256 or higher is highly suggestive of recent infection.[229,237] The titer of VN antibodies does not correlate with protection against infection or with reduced viremia.[238] Complement fixation (CF) titers decline quite rapidly after infection, requiring sample collection early in the course of the disease. A titer higher than 1:16 is consistent with recent infection.[237] It is important to know which assay the diagnostic laboratory uses, because interpretation of the results differs depending on the test performed.

Viral isolation attempts from the buffy coat of an ethylenediamine tetraacetic acid (EDTA) tube and nasopharyngeal swabs may yield a positive result for EHV-1 for approximately 10 to12 days after infection.[226] It is critical that samples be handled appropriately and transported to the laboratory as soon as possible. A viral transport medium is necessary and should be available from the diagnostic laboratory. Viral isolation from the CSF is unrewarding because there does not appear to be direct viral infection of neurons.[233]

35.2.9.3

Pathophysiology

An apparent immune complex vasculitis and thrombosis in arterioles of the spinal cord lead to segmental spinal cord ischemia. Although the lesions are characteristic of a type III (Arthus) hypersensitivity, an immune-mediated pathogenesis has not been conclusively demonstrated.[229] However, the theory of an immune-mediated pathogenesis is supported by the finding that horses vaccinated within the previous 12 months were shown to be 9 to 14 times more likely to develop the neurologic form of EHV-1 infection.[229] The vasculitis may be the result of viral infection of the CNS endothelium by circulating infected leukocytes.[233] The CNS vascular endothelium appears to be the primary site for infection, and the development of neurologic disease may depend in part on the endotheliotropism of the virus. Viral replication within neural tissue has not been definitively demonstrated.[226,229]

35.2.9.4

Epidemiology

Herpesvirus infection is enzootic in the horse population. Infection usually occurs through the respiratory or intestinal epithelium after the animal comes in contact with the virus in fluids from an abortion or in ocular, nasal, or respiratory tract secretions.[229,235] Most horses become infected before 1 year of age. As with most herpesvirus infections, the virus is capable of evading the horse's immune system and can develop latency.[229,235,239] Sites considered likely for latency are the lymphoid tissue and the trigeminal ganglion.[239,240]

Equine herpes myeloencephalopathy is rare, but cases have been reported worldwide.[229] The existence of a neurovirulent form of the virus has been suspected, but the differences in the strains isolated from neurologic syndromes are not significant enough to warrant additional classification.[226] However, equine herpes myeloencephalopathy outbreaks have been reported, lending support to the idea of a neurovirulent form.[230,233,235] During outbreaks, the virus appears to be spread readily, and both morbidity and mortality can be high.[234]

Animals of any age or gender are susceptible; pregnant or lactating mares are most often affected.[226,229] Risk factors for the development of neurologic signs include female gender, older age, and fever. A higher prevalence of neurologic disease was found in standardbred, Hispanic breeds, and draft horses in one study

of multiple outbreaks of herpesvirus myeloencephalopathy.[229] Foals are rarely affected with the neurologic form of EHV-1 infection. There appears to be some seasonal variation because more cases are seen during the spring and winter months.[232] Stress-associated recrudescence of latent infections and shedding without clinical signs are important in the development of equine herpes myeloencephalopathy in a closed population. The virus may be shed for 3 weeks or longer after infection. A morbidity rate of up to 90% and a mortality rate of up to 40% have been reported.[229,233] There are no reports of equine herpes myeloencephalopathy associated with any modified live virus vaccine currently approved for use in horses.[175] Frequent vaccination (up to four times a year) may render animals more susceptible to neurologic manifestation of EHV-1 infection.[234]

35.2.9.5

Necropsy Findings

Gross and histologic lesions are not always limited to the CNS.[226,233] Ocular lesions have been reported, including hypopyon, iritis, and chorioretinitis. Cystitis and scrotal edema may be present.[226,229] Focal areas of hemorrhage may be found throughout the brain and spinal cord parenchyma and meninges. Vasculitis of the small arteries and veins of the spinal cord white matter and of the gray and white matter of the brain results in ischemic lesions in the CNS.[241,242] Equine herpesvirus is infrequently isolated from the CNS during a postmortem examination.[230,237] Polymerase chain reaction (PCR) and direct immunofluorescence assay in situ can be performed on CNS tissues obtained postmortem to confirm the presence of the virus.[230]

35.2.9.6

Treatment

Supportive care is the most important aspect of treatment for equine herpes myeloencephalopathy.[226,229,233,237] Measures include bladder decompression twice a day for horses with bladder atony and urinary incontinence, evacuation of the rectum, enteral or parenteral nutritional support, and administration of intravenous or oral fluids. The horse may require support in a sling.

Administration of antiinflammatory drugs soon after the onset of neurologic signs may be beneficial. Corticosteroids have been used because of the possible immune-mediated pathogenesis, but no objective data are available evaluating the efficacy of this treatment. Dexamethasone (0.05 to 0.1 mg/kg IV) can be given every 12 to 24 hours for 3 to 5 days, with the dosage then tapered for 1 to 3 days.[237] The possibility of viral reactivation is unlikely at the recommended dosage.[229] Dimethyl sulfoxide (DMSO; 0.25 to 0.1 mg/kg by slow IV infusion) every 12 to 24 hours is routinely used when treating neurologic disease, although its efficacy has not been documented.[226]

Use of antibiotics should be considered if the horse is recumbent or has urinary tract involvement, or if respiratory tract signs are present. Antiviral agents, particularly acyclovir, have been recommended based on their use in humans for herpes simplex virus encephalitis. There is insufficient evidence to recommend the use of antiviral agents for EHV-1 infection in horses.[237]

35.2.9.7

Prevention

Currently, no prophylactic measures for or methods of preventing equine herpes myeloencephalopathy are available. The vaccines currently used to prevent EHV-1 respiratory and abortion syndromes do not claim to

prevent equine herpes myeloencephalopathy. Findings in vaccinated horses naturally exposed to EHV-1 during disease outbreaks are mixed regarding protection against myeloencephalopathy.[232,238] Vaccination may reduce the incidence of the other EHV-1—related diseases and thereby reduce exposure to the virus and the risk of developing equine herpes myeloencephalopathy. A recent study concluded that modified live virus vaccine provided significantly better protection against EHV-1 myeloencephalopathy than a killed vaccine,[238] although the duration and robustness of such protection are not yet clear. Vaccination in the face of an outbreak is controversial[226]; viremia may be reduced or prevented as a result of vaccination, but an increase in antibody levels may be partly responsible for, or may play a role in the development of, the neurologic form.

Management practices may reduce the risk of introducing or disseminating EHV-1 infection. Such practices include isolating all new arrivals for at least 3 weeks and maintaining distinct herd groups based on age, gender, and occupation. Pregnant broodmares should be kept apart from the general population as much as possible. Minimizing stress may reduce the likelihood of recrudescence of a latent infection.

35.2.10 PSEUDORABIES (AUJESZKY'S DISEASE, MAD ITCH, BULBAR PARALYSIS)

CHRISTINE BERTHELIN-BAKER

LISLE W. GEORGE

35.2.10.1 Definition and Etiology

Pseudorabies is caused by an encapsulated DNA virus, suid herpesvirus type 1 (Su-HV1), a member of the genus *Varicellovirus*, subfamily Alphaherpesvirinae, family Herpesviridae.[243,244] This virus is able to infect the CNS and other organs (e.g., respiratory tract) of virtually all mammals except humans and most primates. Domestic and feral swine are the natural hosts and may become latent carriers. The virus can also infect cattle, sheep, cats, dogs, and goats as well as wildlife (e.g., raccoons, opossums, skunks, rodents) and rarely, horses.[245–248] In domestic and wild ruminants, pseudorabies is an acute and usually fatal encephalitis.

35.2.10.2 Clinical Signs

The incubation period ranges from 90 to 156 hours, and the illness may last 8 to 72 hours, although some affected animals have been found dead without any observed clinical signs.[249,250] The initial clinical sign is usually a manifestation of paresthesia, with acute and severe pruritus inducing self-trauma, dermal abrasions, swelling, and alopecia.[249] Other signs may include fever, bellowing, bloat, feet stamping, excessive salivation, chewing of the tongue, ataxia, circling, nystagmus, and strabismus.[251–253] Aggression may be seen, but most affected animals become depressed. As the disease progresses, there may be twitching, hyperesthesia, tenesmus, spasmodic kicking, excessive licking of the nostrils, continuous mastication, sweating, vocalization, semicoma, coma, convulsions, opisthotonos, hyperpnea, tachypnea, and slow irregular respiration.[254] The clinical signs of pseudorabies in cattle closely resemble those of rabies, polioencephalomalacia, salt poisoning, meningitis, lead poisoning, hypomagnesemia, and enterotoxemia.

35.2.10.3

Clinical Pathology

The Aujeszky's disease virus (ADV) can be isolated from the pharyngeal or nasal secretions of affected animals and can be easily cultured from infected nervous tissues. Strains of ADV are antigenically distinct from other herpesviruses but share common antigens with the infectious bovine rhinotracheitis (IBR) virus. Heterospecific antibodies to the IBR virus may cross-neutralize the pseudorabies virus and confound serologic tests. For virus culture, tissues should be collected from sensory ganglia or the sensory parts of the spinal cord. Segments serving the pruritic sites should be collected preferentially because these areas contain the highest concentration of virus.

35.2.10.4

Pathophysiology

Ruminants are susceptible to pseudorabies infection after intradermal, subcutaneous, intranasal, or oral exposure to the virus. After subcutaneous, oral, or nasal infection, the virus spreads centripetally to the CNS by axonoplasmic transport. During the acute infection the virus may be present in the nasal mucosa, secretions, and saliva.

35.2.10.5

Epidemiology

Aujeszky's disease has a worldwide distribution and, although cases occur only sporadically, is an economically important disease because of the regulatory quarantine and other restrictions imposed on animals from affected herds (it is a reportable disease). Outbreaks have occurred in cattle in the United States, Europe, Australia, New Zealand, Latin America, and South America. Until recently, Aujeszky's disease was endemic in the United States, but it now has been successfully eradicated from domesticated swine. As of December 2006, all states are classified as free of pseudorabies in domesticated swine (OIE status V), although ADV remains present in feral pigs in parts of the United States.

The viral infection in cattle is perpetuated partly by the occurrence of latent infections in pigs, which can be recrudesced by stressful conditions.[255] Occasional spillover of the virus from swine into ruminants occurs because of the proximity of the two species in many livestock operations.[250,256] The natural routes of transmission include nose to nose, fecal oral, and venereal.[245,257] Indirect transmission usually occurs by inhalation of aerosolized virus. The virus may travel via aerosols up to 2 km (1.2 miles) in certain weather conditions and may survive up to 7 hours in nonchlorinated well water; for 2 days in anaerobic lagoon effluent and in green grass, soil, feces, and shelled corn; for 3 days in nasal washings on plastic and pelleted hog feed; and for 4 days in straw bedding. It is inactivated by drying, sunlight, and high temperatures (≥37°C). Dead-end hosts, such as dogs, cats, and wildlife, can transmit the virus between farms, but aside from feral swine, these animals survive only 2 to 3 days after becoming infected. Sheep have also been infected by modified live virus vaccines targeted for use in swine.[258,259]

Latency of the viral infection in ruminants is not an important mechanism for perpetuation of an outbreak; most animals die within 48 hours of disease onset and may shed ADV in their saliva, oral secretions, and mucous membranes for only up to 6 days after infection, and direct spread of the virus between infected and uninfected cattle is unlikely.[256] Wild mammals such as raccoons may play a role in pseudorabies survival and transmission; rats, however, develop transient infections and do not appear to transmit or perpetuate the virus.[260–262] The pseudorabies virus may survive in contaminated meat products for up to 7 weeks. The role

of this prolonged survival in perpetuating outbreaks in ruminants is unknown. Differences in virus pathogenicity for cattle have been correlated with the type of syncytium formation in tissue cultures.[262] The role of these strain differences in the perpetuation and dissemination of the disease is unclear.

35.2.10.6 Necropsy Findings

The macroscopic changes that occur in animals infected with the pseudorabies virus are alopecia, edema, and hemorrhage at the pruritic site. The neuropathologic changes include perivascular cuffing, interfascicular edema, nonsuppurative encephalitis, gliosis, neuronal degeneration, and eosinophilic intranuclear (Cowdry type A) inclusion bodies. The lesions are most pronounced in the dorsal nerve rootlets and the dorsal horn.

35.2.10.7 Treatment

There is no treatment for pseudorabies, which is usually fatal in livestock, although rare recoveries have been reported.[252]

35.2.10.8 Prevention

The most effective method of preventing pseudorabies virus infection in ruminants is eliminating their exposure to swine. Contaminated pens can be disinfected with 10% sodium hypochlorite solution, quaternary ammonium compounds, tamed iodine, or phenolic compounds.[263] At least 5 minutes of contact time should be allowed before the disinfectant is rinsed from the contaminated surfaces. Fumigation with formaldehyde for 6 hours effectively kills the virus, as does 360 minutes of contact with ultraviolet light.

35.2.11 ALPHAVIRUSES

MAUREEN LONG

E. PAUL GIBBS

Vaccination has reduced the size and number of outbreaks of eastern equine encephalitis (EEE), western equine encephalitis (WEE), and Venezuelan equine encephalitis (VEE) in horses from thousands of cases in the United States to several hundred annually.[264] Nonetheless, these diseases are important because of the resulting mortality or permanent deficits after infection in horses, and because horses are in important part of the surveillance network for arboviruses that also affect humans. Reporting of infection with EEE and WEE in horses is a requirement of licensed veterinarians in most U.S. states, and VEE is considered a foreign animal disease and also has federal reporting requirements.

35.2.11.1 Etiology

Togaviruses are single-stranded, linear, positive-sense RNA viruses with an envelope that makes them susceptible to drying and ultraviolet light. EEE, WEE, and VEE viruses are the most frequently isolated togaviruses from epidemics of encephalitis in horses and humans in the Western Hemisphere.[265] The first recorded epidemic of EEE in horses occurred in Massachusetts in 1831; the virus was first isolated from a

horse in 1933.[265] It was soon determined that epidemics of encephalitis in horses in North America were caused by different alphaviruses with regional geographic biases.[266,267]

The virus is composed of a nucleocapsid within the envelope that has icosahedral symmetry consisting of peplomers arranged as trimers.[265] Viral species are differentiated by hemagglutination inhibition (HI) activity and neutralizing specificity.[267–269] The common group-specific antigenic determinants are still mainly defined by serologic techniques, such as fluorescent antibody, complement fixation, and ELISA.[270–274] Genetic sequencing has application in molecular epidemiology.[275–277]

For WEE virus, WEEV and Highlands J virus (HJV) constitute the two main subgroups.[278–281] WEEV predominates west of the Mississippi River, whereas HJV is primarily detected east of the Mississippi.[282,283] Both these viruses are capable of causing encephalitis in horses, with HJV likely less pathogenic for mammals.[282,283] Other subtypes of WEE virus have been identified in the United States, and most WEE infections in western states are likely the result of infection with one of the several antigenic variants of the actual WEE subtype, although minimal disease has been reported in humans and horses in the last decade.

The organization of VEE is much more complex. Six distinct subtypes (I through VI) and numerous varieties of viruses (designated by letter) within these subtypes are classified within the VEE virus complex.[284–288] The “epidemic types” of VEE virus (types IAB, IC, and IE) are responsible for the large outbreaks of encephalitis in horses in the Western Hemisphere in the past 20 years.[289,290] “Endemic types” of VEE virus are considered to be of low pathogenicity for equids under most circumstances.[291,292] These include type ID and IF variants from Central America and Brazil, respectively; type II (Everglades) virus found in Florida; three known variants of type III (Mucambo) virus; type IV (Pixuna) virus; type V (Cabassou) virus; and type VI virus.

35.2.11.2 Epidemiology

The classic life cycle of equine alphaviruses involves transmission between birds or rodents and mosquitoes.[274] In some cases, other domestic and wild animal species, especially species exotic to North America such as the emu, have been affected during these outbreaks.[293] Understanding the antigenic and genetic relationships among the viruses in the WEE complex has proved more challenging than for the viruses in the EEE and VEE virus complexes. WEE virus is a member of the WEE antigenic complex that includes several Old World viruses in addition to the New World viruses previously described. Phylogenetic analyses of isolates from North and South America indicate that regional WEE lineages appear to evolve independently for several years to a few decades (e.g., genotypes in South America are apparently absent from North America).[283,294–296] However, relatively homogenous genotypes of WEE are dispersed across both North America and South America. This contrasts with EEE and VEE viruses, in which certain virus genotypes appear to be restricted to either North America or South America. WEE virus has been reported in several countries in South America (Argentina, Guyana, Ecuador, Brazil, and Uruguay), but only in Argentina has it been associated with human disease and significant epidemics in horses.[281,297–299]

35.2.11.2.1 EASTERN EQUINE ENCEPHALITIS

Although designated as an “eastern” virus, EEE has a wide geographic distribution. It is found as far north as eastern Canada. Infection in the United States is primarily seen in the southeastern states, but it has been

detected in all states east of the Mississippi River and also in a number of western states. In recent years, intense focal activity has been reported in Wisconsin, Ohio, Massachusetts, and New Hampshire.

In the United States, most reported cases of EEE in horses occur in the northern parts of Florida and the Carolinas. Several hundred equine cases are confirmed each year, despite the widespread availability of vaccines.[300,301] In Florida, most horses that succumb to EEE are not vaccinated or have only received a primary vaccination series, although 17% to 30% of EEE-positive horses have had at least one primary series.[301] These horses are less than 3 years of age and are stock-type horses. There is no gender predilection.

In North America, EEE virus is perpetuated in a sylvatic cycle between avian hosts (passerine birds) and mosquitoes, primarily the ornithophilic mosquito, *Culiseta melanura*.[302] It is likely other mosquitoes, such as *Culex erraticus,* are important in nonavian forms of transmission, as demonstrate by recent studies in Alabama.[303] Indigenous passerine birds do not develop disease but develop sufficient titer viremia to allow transmission to feeding mosquitoes, with recent evidence showing cardinals to be efficient and important local reservoir hosts in the Southeast.[304,305] Secondary-vector or epidemic-vector mosquitoes feed on both birds and mammals and are likely biologic vectors precipitating mammalian disease. These mosquitoes probably transmit EEE to horses, humans, and other vertebrate species, yet these particular clinically affected mammalian hosts do not develop levels of viremia sufficiently high to allow further transmission of the virus by mosquitoes and are considered “dead-end” hosts.

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Culiseta melanura, a temperate breeding species of mosquito, does not readily breed in southern Florida and the Caribbean, and EEE is not an endemic disease in this relatively focal region.[306] As such, sporadic reports or small epidemics of EEE disease are reported in horses in these areas, likely through migratory influx of viremic birds providing occasional sources of virus for secondary vectors. Apparently, these secondary vectors can initiate short-term outbreaks but cannot maintain the disease endemically.

35.2.11.2.2

WESTERN EQUINE ENCEPHALITIS

Historically, large outbreaks of WEE have been described in horses. The virus was first identified in association with a large epizootic in the San Joaquin Valley of California in 1930. Approximately 6000 horses were affected, with a case-fatality rate of 50%.[307] Over the last decade, there have been limited, sporadic reports of WEE in horses, likely reflecting vaccination and protective immunity gained by subclinical exposure.[308,309]

Culex tarsalis is the primary vector that maintains WEE virus in an enzootic cycle with birds, especially nestling passerines.[276,310] *C. tarsalis* population abundance is favored by a rapid increase in temperature after a cool, wet spring, resulting in the rapid melting of snow and flooding of rivers.[311] This species of mosquito also has a predilection for irrigated lands as breeding sites.[312] Other ornithophilic mosquitoes become infected as the summer progresses, and the infection eventually spills over to other types of birds, mammals, and possibly reptiles and amphibians. Most, if not all, of these infections are inapparent.

At least two variants of WEE virus (Fort Morgan and Buggy Creek) have been isolated in western North America and are transmitted between birds by swallow nest bugs *(Oeciacus vicarius)*.[313] The third variant, HJV, found east of the Mississippi River, has been isolated from horses dying of encephalitis, but information is limited on actual annual occurrence of disease.[282,283,313,314]

35.2.11.2.3

VENEZUELAN EQUINE ENCEPHALITIS

VEE virus is one of the most important human and veterinary pathogens in the New World.[290] The virus has been responsible for large outbreaks of disease in both humans and horses over large geographic areas. The first recognized outbreak of VEE occurred initially in equids in Colombia and then in Venezuela in 1935 and 1936, although it is speculated to have been active in this area since 1920.[315] Documentation of human disease occurred in a Columbian outbreak in the 1960s, when an estimated 50,000 to 100,000 equids (horses, mules, and donkeys) died and 250,000 humans were affected (mainly an influenza-like disease, but some cases of encephalitis and death). It is uncertain whether a 1969–1971 epidemic, first reported in Ecuador with subsequent spread to Central America, Mexico, and Texas, was related to the outbreak in Colombia or was caused by the use of an incorrectly inactivated subtype IAB strain vaccine.[316,317] VEE has the potential to spread rapidly within an equine population, with a case-fatality rate approaching 90% in some areas. After a long period without any evidence of clinical disease in horses, geographically extensive outbreaks have occurred in Chiapas (1993), southern Mexico, Venezuela and Colombia (1995), and in Oaxaca, Mexico (1996).[290,318–320] These outbreaks resulted in the demise of large numbers of horses, mules, and donkeys, and an estimated 75,000 to 100,000 human cases of disease occurred. Although the cause of these severe cyclic disease occurrences is still a matter of intense research, it can be assumed that severe epizootic VEE may continue to occur, with interepizootic periods of one to two decades.

Key to understanding the epidemiology of VEE is recognition of the differences in the basic biology of two transmission cycles, enzootic and epizootic, of this virus.[290] Certain strains of virus are found only in the enzootic cycle, usually subtypes I-E, II, III, and IV. These tend to be of low pathogenicity for equids and do not result in high levels of viremia in horses. The enzootic cycle centers around sylvatic rodents such as spiny and cotton rats, which have high natural infection rates and can develop viremia high enough to transmit VEE to mosquitoes.[321,322] Even opossums, bats, and shorebirds likely are important in dispersal of enzootic virus.[323] The subgenus *Culex* mosquito, *Melanoconion (Culex) cedecei,* is likely to be the most important vector of enzootic VEE.[324] This vector resides in tropical forests and swamps and feeds on small forest mammals at night, with activity peaking with high ambient temperature and rainfall.

Epizootic VEE viruses, primarily of the subtypes IAB and IC, occur intermittently.[325,326] These viruses are associated with variable but often high equine mortality (20% to 85%).[327] Efficient amplification with transmissible viremia by equids is the hallmark of epizootic VEE. Humans typically develop a flulike illness, with 4% to 14% exhibiting neurologic signs and symptoms.[323] Case-fatality rate for humans is approximately 1%. Several other species of mammals, including domestic rabbits, small ruminants, and dogs, develop potentially fatal clinical disease after VEE virus infection.[327] More than 100 species of birds have been either virologically or serologically associated with transmission of epidemic VEE virus. Birds may develop viremia as high as $10^{8.0}$ $TCID_{50}$/mL of blood.

The importance of equine infection in maintenance of epizootic VEE is evidenced by the observation that human disease has never been demonstrated in the absence of equine disease.[328] All mammalian hosts are capable of developing a high-titer viremia of approximately 10^5 to 10^7 plaque-forming units (PFU)/mL for up to 5 days, but the horse is likely to be the most important mammalian host in terms of vector capacity.

[290] In contrast with EEE and WEE, where horses are not considered to be a major source of virus for the vector, in VEE epidemics, horses are the most important amplifiers of virus activity.

Several species of mosquitoes from at least 11 genera have been determined to be naturally infected with epidemic strains of VEE virus.[329] Virus has also been isolated from *Culicoides* species (Ceratopogonidae) and blackflies (Simuliidae), but it is not known whether insects in these families are capable of biologic transmission of VEE virus.[299] During an epidemic, dogs regularly become infected and may be capable of virus amplification.[330] In addition, ticks, including the species *Ambylomma cajennense* and *Hyalomma trancatum,* may be capable of viral transmission.[290]

Several theories exist regarding the source of IAB and IC strains and how they persist in the environment between outbreaks.[290] Isolates that are virulent for horses do not appear to be transmitted in the interepizootic period.[331] Mutation of enzootic strains may allow the emergence of highly pathogenic virus and initiation of epizootics with this change in vector emphasis and equine morbidity.[332] This has been identified as the source of four epizootics. Some of these epizootics may have occurred secondary to the use of a modified live vaccine derived from the IAB strain.[317]

35.2.11.3 Pathogenesis

The virus genome is 9.7 to 11.8 kilobases in length and encodes both nonstructural and structural proteins.[333] 986
Alphaviruses replicate to high titer in the cytoplasm of infected cells and exit the cell by the budding of 987
preassembled nucleocapsids through the plasmalemma.[334] They cause cytopathic effects in a wide range of vertebrate cells in vitro. Virulence of VEE virus depends on systemic virus load rather than specific neurovirulence.[335,336] Both EEE and VEE have efficient intracellular replication and are pathogenic when inoculated intracerebrally.[337] Studies in mice demonstrate that neural invasion is likely to occur secondary to vascular infection or invasion through the olfactory epithelium.[338] In young mice, there is intense replication in osteoclasts of developing bone, possibly explaining why young animals and humans are much more susceptible to severe disease.

The regional lymph node is presumed to be the site of primary viral replication after the bite of a mosquito infected with EEE, WEE, or VEE virus.[264] The reticuloendothelial system is a major target in epidemic VEE infections. The viruses cause encephalitis after hematogenous or neuronal spread. Immunity, after both inapparent infection and clinical disease, as caused by EEE, WEE, and VEE, is long lasting in all species. Horses infected with EEE and WEE do not excrete infectious virus, and recovered animals are not persistently infected with virus.

35.2.11.4 Clinical Findings

Different strains of EEE, WEE, and VEE viruses may differ in their virulence not only for horses, but also for humans, certain domestic and wild animals, birds, and laboratory animals.[328] Clinical observations during epidemics of VEE indicate that the disease is generally less severe in donkeys (burros) and mules.[339] None of these viruses appears to cause clinical disease in their reservoir hosts indigenous to North and South America. Many human and equine infections, apart from those caused by highly virulent strains, are

subclinical. When disease does occur, broad differences exist in the clinical manifestations produced by the three virus complexes in horses and humans.

Eastern equine encephalitis and epidemic VEE viruses are generally more neuroinvasive than WEE and endemic VEE viruses. Children and young animals of all susceptible species are more likely than adults to develop clinical signs referable to infection of the central nervous system.[264,301,323,340,341] The incubation periods of EEE, WEE, and VEE vary from 2 to 3 days to, rarely, as long as 3 weeks. Inapparent infections in horses may or may not be accompanied by fever. In clinical cases, pyrexia is the first clinical manifestation of infection. Temperature has usually abated or is only moderately elevated by the time signs of encephalitis become evident. Neurologic signs are variable, but obtunded mentation, ataxia, paralysis, anorexia, and ultimately stupor occur in clinical cases. Irregular gait, grinding of teeth, incoordination, circling, staggering, head pressing, and hyperexcitability are also observed; clinical signs are progressive in nature. Severely ataxic animals may stand by leaning against walls or other objects and sometimes stand with their hindlegs crossed. Partial or even total blindness may be evident. In severely depressed horses the head hangs low with drooping ears, and the eyelids may be slightly swollen and partly closed, while the lips are flaccid and the tongue may protrude from the mouth. The profound depression associated with these virus infections give rise to the common name of “sleeping sickness.” Esophageal paralysis, as manifested by repeated unsuccessful attempts to drink, has also been described.

The course of disease in severely affected horses varies between 2 and 14 days. Almost all horses with EEE encephalitis die, regardless of the quality and intensity of clinical care. Horses with disease caused by VEE or WEE are more likely to survive than those with EEE-induced disease. At terminal stages, horses become recumbent, become comatose, and frequently exhibit seizure activity.

35.2.11.5

Diagnosis

Clinical signs and antemortem clinicopathologic findings are not specific for alphavirus infection. Viral and other encephalitides can cause abnormal cerebrospinal fluid (CSF), which usually consists, in the horse, of a moderate mononuclear pleocytosis with an increased CSF protein. Eastern equine encephalitis is unique in that acute infection frequently results in a neutrophilic pleocytosis. Because there is a high mortality rate associated with this disease, identification of a neutrophilic pleocytosis indicates probable EEE infection and offers the veterinarian a chance to prognosticate regarding the horse's survival.

It is paramount to obtain a definitive diagnosis for clinical signs of encephalitis in the horse, to justify and institute effective control measures, because of the risk of these viruses to the health and well-being of both humans and equine livestock. The viruses of EEE, WEE, and VEE frequently, but not always, can be isolated or detected after death in brain material of diseased horses by the use of cell cultures (e.g., Vero cells), intracerebral inoculation of suckling mice, and by detection of specific nucleotide sequences using reverse-transcriptase polymerase chain reaction (RT-PCR) technology.[342,343] Blood is an inappropriate specimen for virus recovery because no circulating organism is usually present when neurologic signs become apparent. In an epidemic situation, however, it may be possible to isolate the virus from nonencephalitic horses in the affected group, particularly if they have increased body temperature. The cytopathic or lethal effects of the virus in cell cultures or experimental animals can be inhibited by the use of specific antisera, and in this way the virus involved may be specifically identified.

Currently, there are no reliable antemortem diagnostic tests to detect virus in clinically affected horses, and serology provides the mainstay of presumptive antemortem diagnosis. The demonstration of specific IgM antibody (dilution of 1:400) suggests recent infection.[344] The detection of IgM antibody in CSF (if available)

is even more conclusive. Rising antibody titers to EEE, WEE, or VEE viruses in the sera of horses that survive can be detected by testing of acute-phase and convalescent-phase sera. Even in endemic areas, it is not possible to diagnose/differentiate EEE, WEE, or VEE in the horse with any certainty based on clinical signs and epidemiologic circumstances.

Rabies, hepatic encephalopathy, and equine protozoal myeloencephalitis are the major diseases that must be considered in the differential diagnosis in the Western Hemisphere. Other diseases that should be considered are equine herpesvirus 1 infection of the central nervous system, leukoencephalomalacia (a neuromycotoxicosis caused by the ingestion of maize infected with *Fusarium moniliforme*), and ataxia resulting from cervical vertebral malformation.

35.2.11.6

Pathologic Findings

In horses, brain lesions are thought to be the direct result of viral replication and are characterized by necrotizing encephalitis with neuronal dysfunction.[345] There are no consistent gross lesions in horses that die of EEE, WEE, or VEE. Histologically, neuronal necrosis with neurophagia, marked perivascular cuffing with both mono- and polymorphonuclear leukocytes, and focal and diffuse microglial proliferation are evident. The lesions are more pronounced in the gray matter than in the white matter of the brain. Lesions are most marked in the cerebral cortex, thalamus, and hypothalamus, whereas the spinal cord is mildly affected. More frequent and severe lesions are usually present in the cervical spinal cord than in lumbar cord segments.

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35.2.11.7

Treatment

No known antiviral medications have demonstrated reliable activity against alphaviruses, and treatment of disease in affected horses is supportive. The survival rate for EEE infection is low compared with other infectious encephalitides. In most cases, horses die 3 to 5 days after onset of signs.

Corticosteroids should be considered as a component of therapy for horses with neurologic signs consistent with viral encephalitis and neutrophilic CSF. If administered early, corticosteroids (to reduce brain edema) and intravenous fluids may aid recovery. In human patients, treatment with methylprednisolone at 1000 mg/100 kg is often recommended. Administration of flunixin meglumine (1.1 mg/kg every 12 hours IV) or other antiinflammatory medications to horses with EEE does not often result in the dramatic response frequently observed in horses with West Nile virus. Mannitol (0.25 to 2.0 g/kg every 24 hours IV) may assist in the control of brain edema. Detomidine hydrochloride (0.02 to 0.04 mg/kg IV or IM) is effective for prolonged tranquilization.

Intravenous immunoglobin therapy has been used in people for its proposed anticytokine effect. Interferon-alpha (IFN-α) is a relatively common therapy. The recommendation for IFN-α therapy is based on anecdotal reports in the human and veterinary literature. Limited information regarding efficacy in the horse is available.

35.2.11.8

Prevention

The alphaviruses are not stable in the environment and are easily inactivated by common disinfectants. Mosquito control and immunization of horses are both important in control of EEE and VEE epizootics. Vector control can be achieved through reducing the breeding activities of mosquitoes by implementing appropriate water management systems, although this can be difficult in extensive areas.[346,347] The

widespread dispersal (usually achieved by aerial spraying) of insecticides has been used successfully, although several critical factors need to be considered before embarking on such a step. Concern over indiscriminate spraying of insecticides can be mitigated in some circumstances if the biology of the mosquito vector is well known. For example, in northern Florida, where EEE is endemic, treating the pools of water in which *Culiseta melanura* breeds with a larvicide is often practical and economically feasible on those farms with valuable horses. Swamps with soil types that support the breeding of *C. melanura* can often be recognized by the nonentomologist by the presence of the loblolly bay tree *(Gordonia lasianthus);* this broadleaf evergreen tree grows to a height of about 30 feet (9 m) and can easily be recognized by its white magnolia-like flowers and serrated leaf.[264,300,301] Risk assessment can be assisted by geographic mapping of large areas where mosquitoes breed by using thematic mappers, such as those on orbiting satellites.

Immunization of horses has proved highly effective as an adjunct to other control measures, particularly in outbreaks of VEE in which horses may serve as a source of infection for mosquitoes.[348,349] Currently, bivalent vaccines (usually consisting of formaldehyde-inactivated virus) are commercially available against EEE and WEE. These vaccines require a primary and a secondary immunization schedule about a month apart, followed by biannual boosters. The vaccines are not particularly effective in protecting foals and yearling horses, for unknown reasons.[350]

The 1969–1971 VEE epidemic in Central America and the southern United States was controlled partially by immunizing large numbers of horses with an attenuated VEE virus strain, TC-83.[348,349] This vaccine strain was produced by serial passage of an epidemic variant in guinea pig cell cultures. Because of concerns over the presence of low-level viremia in some horses and the possible transmission of vaccine virus between horses by mosquitoes and reversion to virulence, inactivated vaccines against VEE are now available for use in horses. These vaccines are not widely used in North America because they compromise the international movement of horses for competition and breeding.

Outbreaks of VEE might be completely prevented if sustained and widespread vaccination with live attenuated VEE vaccines was performed in Central and South America.[290] Public health and animal industry officials should consider maintaining vast quantities of the live attenuated TC-83 vaccine. The use of the formalin-inactivated vaccine (usually marketed as a multivalent antigen) is discouraged in VEE endemic areas because of the need for multiple vaccinations (and thus delayed onset of protection), short-lived immunity to VEE, lack of long-term compliance from agricultural officials and the horse-owning public in endemic locales, and concern of limited response to the live vaccine in horses immunized recently with a killed product.

Surveillance for encroachment of alphaviruses in new geographic locales is also paramount to control. Most southern U.S. states have encephalitis testing programs that offer subsidized testing for horses with suspected viral encephalitis. Enhanced passive surveillance for alphaviruses should be undertaken when environmental conditions are favorable. For example, hurricanes were implicated in the VEE outbreak in Mexico in 1995. Given that the United States has experienced intense hurricane activity in 2004 and 2005, enhanced surveillance for epizootic VEE should logically be undertaken.

Alphaviruses are pathogenic for people but require a vector for infection. The horse does not develop a sufficient level of viremia with EEE and WEE to act as a reservoir or amplifying host for these viruses. In contrast, horses are considered the most important species for amplification of virus in epizootic VEE. Therefore, control measures should be implemented to limit new exposure of horses in locales that are undergoing epizootic VEE. This includes restriction of horse movement; clinically normal horses may be viremic, and the disease can be translocated. Horses should be vaccinated and sprayed frequently with

permethrin-based products. Mosquito abatement efforts should be pursued. Blood and tissues from VEE horses should be handled as infectious and biohazardous materials, with tissues from EEE and WEE horses handled as such.

35.2.12 MISCELLANEOUS AND FOREIGN EMERGING VIRUSES CAUSING NEUROLOGIC SIGNS

Since the encroachment of West Nile virus (WNV) in 1999 into North America, the potential for emerging foreign disease with widespread impact has been realized. Given the opportunity, many other viral infections could become established in new countries as a result of the globalization of the horse industry. Because of its close genetic relationship to WNV, Japanese encephalitis is one of the most likely candidates. The reader is directed to the WNV section; these diseases are highly similar, and prognostication would be the same. What is unknown at this time is the effect that widespread WNV vaccination will have on the severity of a North American outbreak. The list in Table 35-4 is not exhaustive and includes only the more frequently reported causes of viral encephalitis.

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Table 35-4 Miscellaneous Emerging Viruses that Cause Neurologic Disease

Name	Classification	Transmission	Country of Origin
Getah/Ross River	Alphavirus	Mosquito	Japan, Hong Kong, Se Sia, Korea, India, Australia, and South Pacific
Borna	Bornaviradae	Direct contact	Germany, Northern Europe
California serogroup	Bunyaviridae	Mosquito	Africa, Europe, Asia, North America, South America
Equine encephalosis	Orbivirus	*Culicoides*	Africa: South, Kenya, Botswana
Hendra/Nipah	—	Direct contact	Africa: South, Kenya, Botswana

35.2.12.1 Getah/Ross River Viruses

The Semliki Forest complex of the Togaviridae are widespread throughout their geographic range, either in the Orient (Getah) or South Pacific (Ross River).[351,352] Although closely related, there is little overlap of these viruses. As with the North American alphaviruses, these viruses are transmitted by mosquitoes (*Aedes*, *Anopheles*, and *Culex* species).[353–360] With Getah virus (GV) the reservoir is not known, although swine appear important in its transmission to mosquitoes.[360–363] Other feral species are not firmly established. With Ross River virus (RRV), marsupials are important reservoirs.[364] With GV, horses might develop sufficiently high viremia to transmit virus, but this is unlikely with RRV.[365–367] Many animals have been found to be seropositive to GV, including ruminants, and seroprevalence in horses varies from less than 10% to over 90%.[360,368–370] RRV is endemic in horses and widespread, with seroprevalence ranging from 50% to 80% in Australian horses.[351,371–373]

Getah virus is likely more pathogenic in horses than RRV.[365,368,369] Clinical signs include pyrexia, edema of the limbs, and stiff gait. Horses may also develop urticaria and submandibular lymphadenopathy. The course of GV disease is 7 to 10 days. With RRV, horses also develop fever, lameness, swollen joints, inappetence, generalized stiffness, and even colic.[351,371,373] High rates of mortality are not a feature of either virus.

Serologic detection of antibody is the mainstay of diagnosis of these viruses, although a vaccine against GV complicates diagnosis.[374–376] RRV can be isolated from the blood of horses during the disease course. Pathologic changes associated with these viruses are seldom described because of their low mortality. Horses primarily develop perivascular inflammation in the brain.

Treatment is supportive; no antiviral is specific for alphaviruses. A vaccine for GV is available in Japan.

35.2.12.2

Borna Disease

Borna disease is a cause of encephalitis first reported in horses in Borna, Germany, in the nineteenth century, with identification in other Northern European countries, such as Switzerland, Liechtenstein, and Austria.[377] Unconfirmed outbreaks have been reported in the Middle East and Japan.[378] The Borna disease virus (BDV) is linked to other regions through serologic testing and identification of antibodies in horses from Turkey, Israel, Iran, and the United States.[379–382] Other species noted with clinical signs of BDV include small ruminants, cattle, rabbits, cats, and dogs.[383]

The etiologic agent of Borna disease is a nonsegmented, negative-sense, single-stranded RNA virus of the order Mononegavirales, family Bornaviridae.[384–386] The viruses of Borna disease and Near Eastern encephalitis are indistinguishable. Importantly, with complete sequencing of the genome, several distinct virus clusters occur geographically.[381,387,388] In Germany, Borna has endemic foci centrally and south.[377,381,385] Subclinical exposure in horses is between 10% and 20%, with seroprevalence as high as 50% in stables with disease.

The Borna disease virus is shed through nasal and lacrimal secretions and in the urine of infected animals, so direct contact is suspected.[383,385,389] BDV is resistant to drying and other adverse environmental conditions. Outbreaks in horses in the Middle East may represent transmission from a dense population of infected wild birds, and recurrent outbreaks in Germany have been thought to originate from birds that have migrated from the Near Eastern countries.[377,381,385] Most outbreaks in horses occur in the early spring or autumn.

It is assumed that BDV enters the horse though intranasal infection and migrates to the brain transaxonally.[383,390,391] Direct replication occurs in neurons and glial cells, with spread to peripheral nerves and retina. Infection with BDV is persistent, and Borna disease has a slow onset thought to be caused by chronic inflammatory reaction in the brain. The lesion resembles that of lymphocytic choriomeningitis virus (LCMV) infection, in which the virus induces a cell-mediated response that disrupts and replaces functional aspects of the neuropil.

The clinical signs of Borna disease in large animals are similar to those of the other equine encephalitides.[377] In moderate to severe cases, horse die 1 to 4 weeks after onset of disease. In mild cases, recovery can be spontaneous; however, a chronic disease can occur with recurrent exacerbations. Typical clinical signs include ataxia, head tilts, muscle fasciculations, hindlimb paresis, and localized cutaneous hyperesthesia or

hypoesthesia. Aggressive behavior may be noted. In ruminants the clinical signs include head tremors, hyperesthesia, ataxia, anorexia, propulsive walking, coma, and convulsions.

For antemortem diagnosis, antibodies to the agent may be found in the serum and CSF of most infected animals by ELISA, indirect fluorescent antibody (IFA), and Western blot.[377,382] Some work indicates that CSF antibodies are more likely to be found in clinically affected horses than normal horses. There is often a mononuclear pleocytosis with high protein concentration. Enhanced-sensitivity PCR techniques have demonstrated virus in the CSF and peripheral mononuclear cells.[392] The criteria for diagnosis include a horse with neurologic abnormalities testing antibody positive for BDV in serum or CSF, or a horse with neurologic signs and appropriate histopathologic changes.[377,383]

Pathologic abnormalities resemble those of a viral encephalomyelitis, and confirmatory diagnosis is by immunohistochemistry (IHC), virus isolation, and detection of viral nucleic acids.[389,392–395] The characteristic microscopic lesion of Borna disease is the Joest-Degen inclusion body in the neuronal nucleus, but this is not always observed. Virus is detectable easily with monoclonal or polyclonal antibodies. Histopathologic changes are those of a typical polioencephalomyelitis, with a particular loss of neurons in the hippocampus. There is involvement of the gray matter of the olfactory bulb, basal cortex, caudate nucleus, thalamus, hippocampus, and medulla oblongata.

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No antiviral agents are available for BDV, and use of the amantadine sulfate (developed for treatment of influenza infection) is controversial.[396–398] Likewise, vaccination as a protective strategy is controversial. It is widely assumed that a modified live vaccine would offer more protection; however, the live vaccine available until the early 1990s in Germany was removed from the market because of questionable efficacy.[396]

Controversy also surrounds the zoonotic potential of BDV. Mental health patients, in particular schizophrenics, have been associated with infection through serologic testing.[399–401] However, normal unaffected humans have also been found to be antibody positive. Thus the causality of this virus and the neurologic dysfunction, mainly characterized by altered behavior and perception in people, remain to be firmly elucidated.

35.2.12.3 Hendra/Nipah Viruses

In 1994 an outbreak of a previously unreported illness occurred in horses and humans in Hendra, a suburb of Brisbane, Australia.[402,403] A single mare brought into a stable died 2 days after arrival. In the following 2 weeks, 17 horses at the same facility developed respiratory and neurologic signs; several died or were euthanized. Two people that had close contact with the original mare also developed a flulike illness; one survived, but the other died from multiorgan involvement and cardiac arrest. Originally classified as a morbillivirus, Hendra virus was found to be similar to Nipah virus, was isolated from tissues of affected horses and people, and was believed to be the etiologic agent, as proved by development of similar disease in healthy horses after challenge with tissue homogenates from affected animals.[402,404,405] Nipah virus primarily causes respiratory disease in pigs and respiratory and neurologic disease in humans.[404,406] Infection of horses with Nipah virus has been indicated by serologic testing only in a few horses and in the brain of one horse. These two viruses occupy a new genus, *Henipavirus,* family Paramyxoviridae, subfamility Paramyxovirinae, order Mononegavirales.

These viruses are primarily bat viruses (genus *Pteropus,* fruit bat), with approximately half the bats testing positive in an endemic focus, whereas other mammalian hosts are comparatively seronegative.[407,408] Transmission is thought to be by direct contact of horses, likely with secretions such as urine, aborted fetuses, and other reproductive fluids.[407–409]

The predominant clinical signs of equine hendravirus infection are those of respiratory disease: tachypnea, dyspnea, frothy nasal discharge, tachycardia, fever, anorexia, and death.[405,410] Signs of neurologic disease that may accompany the respiratory signs include dullness and ataxia.

Sera from infected horses are positive for antibodies to the virus.

After infection by direct contact, Hendra/Nipah virus appears to localize in the respiratory tract epithelium.[404,405,411,412] Experimentally, however, infections can occur by all routes, resulting in respiratory shedding of the virus. As with other paramyxoviruses, there is widespread dissemination of the virus in lung, liver, kidney, lymph nodes, and blood after infection. Infection primarily involves the vascular endothelial cells with pulmonary edema, although CNS pathology is similar to that caused by distemper or measles.

The infection results in an interstitial pneumonia with focal necrotizing alveolitis, subpleural edema, and syncytium formation in the vascular endothelium.[403,410]

Treatment is supportive and symptomatic care only. No specific agents have been shown to combat the Hendra/Nipah viruses.

35.2.12.4

California Serogroup Diseases

Bunyaviruses are mainly mosquito-transmitted viruses and are found worldwide. Some of these viruses are known to be transmitted by *Culicoides* flies as well.[361,413–427] Approximately 12 serotypes of these viruses, collectively known as the California serogroup, have been isolated in North America, South America, Africa, Europe, and Asia. The viruses have various names, depending on location or host and possibility for equine infection, including snowshoe hare, Jamestown Canyon, Cache Valley, and Main Drain. Transmission is mainly by *Aedes* mosquitoes.

Clinical signs are consistent with encephalitis and include ataxia, weakness, stiff neck, head pressing, and dysphagia. Systemic signs include tachycardia and fever. Horses that recover generally do so in 1 week.

35.2.12.5

Encephalosis

Th virus for encephalosis is closely related to bluetongue virus and African horse sickness (AHS) virus and is an *Orbivirus*.[428,429] *Culicoides* species transmit this virus to horses of South Africa, Kenya, and Botswana.[429–432] Because this virus is morphologically similar in cell culture to AHS virus, correct identification of this virus sometimes is not made. There is widespread subclinical exposure of this virus to horses throughout endemic regions, and several different serotypes exist.

Although subclinical disease is the most likely manifestation of encephalosis, the virus was originally named for isolation from a horse with typical signs of encephalitis.[433] In addition to signs of acute encephalitis,

horses will demonstrate systemic signs of fever, depression, and facial edema. Cardiac failure has been described, and pregnant horses may abort.

Correct testing that is group specific for encephalosis virus, but not for AHS or bluetongue virus, should be performed on serum from affected horses.[428,434–437] Final, definitive diagnosis is difficult even postmortem; cerebral edema, enteritis, cardiac myodegeneration, and fibrosis are seen.

There is no recognized treatment or prevention for encephalosis.

35.2.13 WEST NILE VIRUS

West Nile virus (WNV), one of more than 70 single-stranded RNA viruses in the *Flavivirus* genus of the family Flaviviridae, causes encephalitis in humans and other mammals and encephalomyelitis in equids.[438] Flaviviridae viruses contain many important veterinary and human pathogens, with at least half of these members classified as "zoonotics."[439] Historically and currently, investigations of these viruses have resulted in some of the most important scientific landmarks in human and veterinary health.

The Flaviviridae are composed of positive-sense, single-stranded RNA, measuring approximately 50 nm with a spherical, enveloped virion.[439–441] Most of the virus is composed of three structural proteins consisting of the icosahedral capsid (C), premembrane (prM) and membrane (M), and envelope (E).[442–444] The E protein is the immunodominant protein and consists of the neutralizing epitopes. There are three domains, with domain II involving virus binding in the brain and III important for vector and host virulence.[445,446]

The nonstructural proteins, seven in number, are essentially involved in synthesis of RNA.[447,448] The glycoprotein NS1 is essential for virus function and appears important for cell activation as part of viral synthesis.[449–451] NS1 also is found on cell membranes of infected cells and must interact with the other NS proteins for function.[449–451] NS3 is highly conserved between flaviviruses; at the N-terminal, it encodes a serine protein with sequences consistent with the trypsin superfamily, and at the C-terminal, it encodes RNA helicases and triphosphatases.[452] The NS4b protein appears to block host antiviral cytokines.[453] The NS5 protein is essential for viral replication by forming the "cap" at the 5′ end of a genome.[443,453,454]

West Nile virus is thought to infect the cell through glycoprotein receptors that are likely highly conserved in respective hosts.[439–446] This is further supported by the ability of WNV to infect and replicate in many cells. After binding, the viral membrane fuses with endosomal vesicle membrane, and the nucleoprotein is released into the cytoplasm. Alternating periods of replication and translation of viral proteins occur, and immature virions, still with the prM, accumulate in vesicles and are transported through the host secretory pathway, where the E and prM proteins are modified. The virus-laden vesicles are transported to the plasma membrane and released by exocytosis. Mammalian cells release progeny virus within 10 to 12 hours after infection.

35.2.13.1 Epidemiology

The life cycle of WNV consists of transmission by hematophagous mosquitoes to an avian host; with amplification occurring in both these hosts.[455] For maintenance, the virus must be cycled between biologic vectors, and presumably, vertical transmission occurs within the vector for season-to-season maintenance.[456]

Passerine birds are likely the most important nonvector reservoir hosts. Horses and humans are dead-end hosts because they do not amplify the virus in quantities sufficient to infect mosquitoes.

Other modes of transmission include oral infection of both avian and mammalian hosts, most notably predator birds and felids. Birds can shed WNV both orally and cloacally.[457–461] Virus is high enough in the blood of humans to be borne through blood and organ contamination by subclinical WNV-positive donors and can be transmitted vertically through placenta and milk.[462–468]

Initial manifestations of WNV disease occurred in humans and were characterized as flulike or febrile illness.[438] Subsequent outbreaks of illness were focal and sporadic, with children more susceptible to actual disease.[455] In endemic areas, most humans and horses demonstrate increased risk of spontaneous seroconversion with age.[457,461,469,470] In the last decade, WNV outbreaks began increasing in both frequency and severity, with neurologic disease and higher mortality in birds, horses, and humans. Before 1999, WNV caused focal intense outbreaks in horses in the Middle East and Europe.[461,470–472] The first year the virus occurred in New York, several dozen cases of equine WNV occurred by 2001. The outbreak spread westward and reached epizootic proportions, infecting large numbers of immunologically naive horses.[473–475]

Equine disease in the United States caused by WNV peaked in 2002 with the report of 15,257 cases that year (U.S. Department of Agriculture [USDA], 2003). Birds have developed natural immunity to WNV, so relatively fewer human and equine cases have been reported, especially in the Northeast and Southeast. However, overt WNV clinical disease still occurs. There were 3000 human cases and 119 human fatalities from WNV reported to the Centers for Disease Control and Prevention (CDC) in 2005. The average number of equine cases has been about 1000/year. As of January 2006, the official CDC count of equine WNV was more than 23,000 U.S. cases (Jennifer Lehman, personal communication). Horses with clinical signs of WNV disease reportedly have a 28.4% to 38% mortality rate.[473,476,477]

By 2005, WNV had been identified in all the 48 continental U.S. states.[478] Canadian provinces reporting disease include Quebec, Ontario, Manitoba, Saskatchewan, and Alberta, with New Brunswick and Nova Scotia reporting evidence of WNV-positive birds.[479] In Latin America, serologic evidence of WNV has been detected in the Dominican Republic, Mexico, Guadeloupe, El Salvatore, Puerto Rico, Cayman Islands, Jamaica, Belize, and Cuba.[461,470,480–484] The incidence of equine and human disease appears low for Central America, South America, and the Caribbean compared with the United States.[485] A decrease in the virulence of the North American strain has been reported, however, and other flaviviruses occur in Central and North America. Cross-protective immunity may also account for the decreased incidence in these locales.

The *Culex* mosquito is considered the most important vector of WNV in North America, although the virus has been detected in more than 60 species of North American mosquito.[461,462,486–489] *Culex pipiens*—positive pools are most frequently detected in the northeastern United States, with *Cx. tarsalis* constituting the majority of positive pools in the West, and *Cx. quinquefasciatus* and *Cx. nigripalpus* in the Southeast.[486,490–503] In the Southwest, epidemics in 2004 were associated, in decreasing frequency, with *Cx. quinquefasciatus*, *Cx. tarsalis*, and *Cx. pipiens*.

Little is known regarding the actual vector of transmission to the horse itself. Blood meal analysis supports *Cx. pipiens* as primarily avian feeders, whereas mammalian feeders include mainly *Anopheles quadrimaculatus, Coquillettidia perturbans,* and *Aedes albopictus*. Recent analysis of *Cx. quinquefasciatus* has detected both human and bird feeding, and *Cx. salinarius* reportedly has widest range of host feeding.[504]

Culex mosquitoes require a blood meal of approximately 10^5 to 10^7 PFU/mL of virus for 30% to 100% of mosquitoes to obtain infection with WNV, respectively.[505] Experimental infection of horses by mosquito transmission studies is accomplished with *Aedes aegypti* and *A. albopictus*.[506,507]

In ticks, transtadial transmission has been inconsistently documented in *Ixodes* species.[508,509] Under experimental conditions, *Carios capensis* transmitted WNV to ducklings, and *Ornithodoros moubata* transmitted WNV to mice.[509,510]

More than 300 species of birds have been reported "WNV positive" in the United States, with 16 new species identified during the 2005 season.[511] Passeriformes and Charadriiformes obtain the highest titers with the longest persistence and viremia, and tissue levels can consistently exceed 10^8 PFU/mL.[460] The house sparrow is considered the most important amplifying host.[460] Although susceptible to fatal infections, corvids develop very high viremia and still are likely efficient reservoirs.[457,459,460,512] Corvid susceptibility to WNV is notable in the North American outbreak. Early studies with the Egyptian WNV strain, however, produced high mortality in crows.[513,514]

With its vector requirements, WNV in horses and humans is seasonal in temperate regions (with expected year-round activity in subtropical regions).[497,504,515,516] Late September and October are times of peak incidence of disease, with July representing the start of intense WNV activity. Temperature-dependent spatial modeling supports these disease dynamics, with risk increasing from 25% in late August to more than 75% by the second week of September.[517–519] A drop in ambient temperature usually results in a rapid decrease in reporting activity.[520,521]

Age is a factor in susceptibility to neuroinvasive disease, as reported for both people and horses.[461,472,522–525] Although men are more frequently affected with neuroinvasive disease, there appears to be no breed or gender predilection in the equine. In fact, in one study examining outcome parameters, female horses were 2.9 times more likely to die than male horses with neurologic signs.[522–524] This may reflect pasture-associated exposure with broodmares or longer lifespan due to reproductive value.

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Multiple free-ranging and domesticated mammals, including the big brown bat, little brown bat, eastern chipmunk, eastern gray squirrel, eastern striped skunk, white-tailed deer, and brown bear, have demonstrated spontaneous seroconversion to WNV.[461,492,505–511,526] Neurologic disease has been diagnosed in WNV-positive gray squirrels and fox squirrels, and febrile disease has been described in cats.[527,528] Oral infection has been induced in experimental infection of cats. Both farmed and free-ranging alligators can obtain extremely high viremia and may be an important reservoir in the Southeast.[526] In farm-raised alligators, cloacal shedding has been demonstrated, with oral infection likely. Serologic evidence of infection has been demonstrated in domestic dogs. Llamas have been reported to develop neurologic disease.[529,530]

35.2.13.2 Pathogenesis

The syndrome of WNV in the horse consists of neurologic signs, with abnormalities in mentation, the spinal cord, and cranial nerves, primarily of the midbrain and hindbrain.[474,531–540] Virus localization in the motor neurons of the thalamus, medulla, and pons likely accounts for changes in behavior.[532,541,542] Change in consciousness occurs frequently, likely caused by lesions in the midbrain and rostral pons affecting the

reticular formation.[540,543] The reticular formation projects to the thalamus, which in turn sends diffuse projections and is the source of cholinergic stimulation to the entire cerebral cortex.[540] Thus, disturbances of the reticular formation and the midbrain may induce the behavioral changes observed, which range from aggression to somnolence.* Spinal deficits are characterized as multifocal, asymmetric, with weakness and ataxia likely reflecting direct infection of the spinal cord, interruption of motor tracts in the hindbrain, and loss of fine motor control through infection of the large nuclei of the thalamus and basal ganglia.[546,547] Loss of fine motor control is evidenced by involuntary skin and muscle fasciculations, tremors, and hyperesthesia, and a predilection for the basal ganglia likely results in Parkinson-like syndrome. Infection in the pons and medulla oblongata can explain clinical deficits of cranial nerves (CNs) VII, XII, and IX.[548]

It is unknown how WNV invades the central nervous system (CNS); WNV is proposed to cause minimal viremia, with replication in the lymph nodes, followed by invasion into the CNS across the blood-brain barrier.[446] Alternatively, there may be transaxonal transmission.[438,519] In rodent models the virus is capable of invading the CNS after peritoneal challenge, demonstrating a primary predilection for neural tissues.[549,550] Viremia occurs 3 to 5 days after experimental challenge and lasts 24 to 72 hours, with dissemination into the CNS at 4 to 6 days after inoculation. Intrathecal infection of horses results in clinical signs 7 to 10 days after inoculation. WNV directly infects nerve cell bodies, and in rodents, initial replication occurs in the basal ganglia, with dissemination later to cortex, cerebellum, and hippocampus. The large neurons of the ventral or anterior horns are infected late in infection, and in mammalian hosts, neuronal viral load is low. As noted earlier, cell lysis occurs with viral replication, but WNV also induces apoptosis in neurons, which likely accounts for most of the pathophysiology.[549,551]

* References 532, 534, 538, 541, 542, 544, 545.

35.2.13.3

Clinical Findings

When infected with lineage type I WNV, horses develop neurologic disease, whereas infection with lineage type II viruses is subclinical in nature.† Both systemic and neurologic abnormalities are observed in horses. Systemic clinical signs occur initially and include a mild to moderate increase in rectal temperature (38.6° C to 40°C; 101.5° F to 104.0°F), anorexia, and depression. Presenting complaints can be insidious and can manifest as abdominal pain or lameness, including a bizarre gait, as in rabies infection in the horse. The occurrence of neurologic symptoms is frequently sudden and progressive, and the exact course of disease in any one animal is unpredictable. The most unique manifestations of equine WNV encephalomyelitis are changes in personality and development of fasciculations. Periods of hyperexcitability and apprehension are common and can be severe, to the point of aggression. Change in personality is manifest by a quiet horse becoming hyperexcitable and an abnormally aggressive horse becoming submissive. Some horses develop attention deficits, even with bouts of sleeplike behavior during activity, resembling cataplexy or narcolepsy. Fasciculations, although not pathognomonic, are so notable that many clinicians base their preliminary diagnosis on their occurrence. These tremors usually involve the face and neck muscles but can involve all four limbs and the trunk so that normal activities such as walking, eating, and interaction with handlers and other horses are interrupted. Rapid blinking of eyelids is common (and stimulated with a penlight), and horses likely are photophobic.

One of the initial signs of motor abnormality is bradykinesia, characterized as a short, slow-stilted gait described by observers as “lameness,” with laminitis being a common differential at this stage. Spinal abnormalities are characterized by ataxia and paresis that can be highly asymmetric or can involve only one or both forelimbs or hindlimbs. Cranial nerves are frequently abnormal, with weakness of the tongue, muzzle

deviation, and head tilt most common. The tongue abnormalities can also be associated with dysphagia and choking. Abnormalities of the cauda equina also occur and consist of stranguria and rectal impaction. All these clinical signs are variable, and after initial signs abate, about one third of clinically affected horses experience an increase in severity of clinical signs within the first 7 to 10 days of onset. Overall, about 30% of the horses progress to complete paralysis of one or more limbs. Most of these horses are euthanized for humane reasons or die spontaneously.

In many horses, clinical signs generally improve within 3 to 7 days of displaying onset. After 3 to 5 days, horses that are recovering or stabled may exhibit a sudden recurrence of signs. Clinical signs may be of short duration, or horses may become suddenly recumbent and either die or recover only with prolonged treatment. Horses that become recumbent often need aggressive supportive care. Once the horse has demonstrated significant improvement, full recovery within 1 to 6 months can be expected in 90% of patients.[554] Residual weakness and ataxia appear to be the main problems; however, personality changes were reported as well.[554] In humans, some patients have experienced long-term inflammation of the meninges, and others have experienced the long-term loss of the use of one or more limbs. In addition, mild to moderate, persistent fatigue on exercise and chronic headache have also been noted.

† References 473, 531, 533, 534, 537, 552, 553.

35.2.13.4

Diagnosis

In general, complete blood count (CBC) and serum biochemistry profiles of WNV horses are normal.[531] Horses may present with a mild absolute lymphopenia, elevated muscle enzymes, and hyponatremia, which has also been described in humans with viral encephalitis. Cerebrospinal fluid cell counts are normal to elevated and mononuclear in nature, with protein levels also normal to elevated.[555]

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Confirmation of WNV infection with encephalitis in horses begins with assessment of whether a horse meets the case definition based on clinical signs occurring in an area in which WNV has been confirmed in the current calendar year in mosquito, bird, human, or horse.[473] Serologic testing relies on the development of immunoglobulin M (IgM) and neutralizing-antibody responses in acute-phase serum, as tested by an IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA) and neutralization testing (NT), respectively. In serologic confirmation of flaviviruses and most arboviruses, the neutralization format is considered the “gold standard” because of the specificity of neutralizing antibody generated in response to these viruses. Until fall 2001, a positive IgM titer of 1:400 or higher and a plaque reduction neutralizing-antibody test (PRNT) titer of 1:10 or higher on a single serum was considered confirmatory for serodiagnosis of WNV encephalomyelitis in a horse exhibiting appropriate clinical signs. Since 2001, reliance on the PRNT for serologic confirmatory diagnosis in horses has diminished because of the availability of WNV vaccination for horses. Vaccination induces formation of neutralizing antibody and likely confounds interpretation of the PRNT. Most diagnostic laboratories use MAC-ELISA for confirmation of WNV disease (because consistently detected IgM rarely occurs after vaccination) in the horse, and the sensitivity and specificity of this test are approximately 81% and 100%, respectively.[556]

Other means of confirmation include postmortem detection of WNV by PCR, culture, and IHC in CNS tissues. Several methods of WNV nucleic acid testing in equine tissue have been described, including nested PCR targeting the E protein, which demonstrated sensitivity for relatively low viral load, and real-time PCR. The E-protein target appears less sensitive; however, the NS5 target has detected WNV nucleic acids in CNS tissues, heart, and intestine of clinically affected horses.

35.2.13.5

Differential Diagnoses

Even if WNV is suspected based on time of year and vaccination history, other infectious CNS diseases should be considered in the differential diagnoses, including alphaviruses, rabies virus, equine protozoal myeloencephalitis (EPM), equine herpesvirus type 1 (EHV-1), botulism (less likely), and verminous meningoencephalomyelitis *(Halicephalobus gingivalis*, *Setaria*, *Strongylus vulgaris)*. Alphaviruses, rabies, *H. gingivalis* infection, hepatoencephalopathy, and leukoencephalomalacia are rapidly progressive cortical signs characterized by behavioral alterations, depression, seizure, and coma. The appearance of seizure and coma is rare in WNV horses but can occur. Cranial nerve signs in EEE and WEE are also common, including head tilt, pharyngeal/laryngeal dysfunction, and paresis of the tongue. The incidence of WEE in horses is fairly low in the United States, but mortality and severity of clinical signs would more closely resemble WNV. Differentiation from rabies is problematic because clinical signs in horses with rabies frequently include ataxia, weakness, or gait abnormalities. Although there are periods of somnolence, blindness, and some cranial nerve deficits, WNV horses appear to become rapidly recumbent or stabilize over several days, as opposed to rapid deterioration with EEE, rabies, and *H. gingivalis*. Spinal disease caused by EPM is a more difficult differential if horses with WNV are not febrile and do not exhibit excessive muscle fasciculations. Noninfectious causes to consider include hypocalcemia, tremorigenic toxicities, hepatoencephalopathy, and leukoencephalomalacia.

Serum titers should be evaluated for recent exposure to other encephalitides, including EEE, WEE, and EHV-1. An IgM-capture format is appropriate for EEE and WEE, but for the NT format, paired titers are necessary in vaccinated horses. Because WNV can present with asymmetric weakness and ataxia, Western blot testing for EPM should also be performed on CSF.

35.2.13.6

Pathologic Findings

Flaviviruses cause polioencephalomyelitis (inflammation of gray matter), with lesions that increase in number from the diencephalon through the hindbrain and frequently increase in severity caudad in the spinal cord.* Gross pathologic findings are limited in WNV infection in the horse. The meninges may be congested. Small to moderate-sized foci of hemorrhagic discoloration can be observed in the brain and spinal cord. The most common areas observed in the brain include the basal ganglia, rostral colliculus, and both pons and medulla. The most common sign of spinal changes appears in the lumbar cord. Edema and softening of tissues are also common.

Histopathologic changes are consistent with viral infection and neural cell death. The basal ganglia, thalamus, pons, and medulla have the highest numbers of lesions, characterized by two to several cell layers of mononuclear perivascular cuffing. Predominantly confined to the gray matter, there are also collections of mononuclear cells within the parenchyma (gliosis). By contrast, this is limited in the cortex and cerebellum. Neuronal damage includes chromatolytic neurons and neuronophagia. In long-standing disease, areas of neuronal dropout may be seen. In the spinal cord, there is perivascular cuffing, gliosis, and damaged neurons. The inflammation associated with the neuropil is confined mainly to the gray matter.

* References 532, 534, 536, 537, 539, 542, 557.

35.2.13.7

Treatment

To date, no antiflavivirus compounds are marketed. Therapy is supportive for these infections, although several experimental inhibitors of RNA virus replication are under development.[558–563] Accurate assessment of the direct effect of any pharmacologic intervention in WNV disease is difficult because horses can begin the recovery process within 72 hours of onset of clinical signs. Flunixin meglumine (1.1 mg/kg every 12 hours IV) early in the course of the disease appears to decrease the severity of muscle tremors and fasciculations within a few hours of administration. To date, much of the mortality in WNV horses results from euthanasia of recumbent horses for humane reasons rather than spontaneous fatality. Recumbent horses are mentally alert and frequently thrash, sustaining many self-inflicted wounds and posing risk to personnel. Therapy of recumbent horses is generally more aggressive and may include dexamethasone sodium (0.05 to 0.1 g/kg every 24 hours IV) and mannitol (0.25 to 2.0 g/kg every 24 hours IV). Detomidine hydrochloride (0.02 to 0.04 mg/kg IV or IM) is effective for prolonged tranquilization. Low doses of acepromazine (0.02 mg/kg IV or 0.05 mg/kg IM) provide excellent relief from anxiety in both recumbent and standing horses. Until EPM is ruled out, prophylactic institution of antiprotozoal medications is recommended. Other supportive measures may include oral and intravenous fluids and antibiotics for treatment of infections that frequently occur in recumbent horses (wounds, cellulitis, and pneumonia).

Interferon-alpha is a relatively common therapy,[560,564,565] based on differences in genetic loci to immune response elements that induce nonspecific immunity in mice. The success of IFN-α rests on anecdotal reports in the human and veterinary literature. Intravenous WNV-specific immunoglobulin therapy has also been described, and in a blind controlled placebo trial with low numbers of animals, the risk for development of recumbency was lower. Otherwise, outcomes and severity were the same. In human therapy, high-dose glutamate has been pursued to prevent neuronal cell death.[566] Another experimental investigation in mice involves β-lactam inhibitors that stimulate GLT1, a chemical that activates glutamate.[567,568]

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35.2.13.8

Prevention

Initial epidemiologic studies indicated a point source for WNV infection, demonstrating that the outbreak could be controlled by vaccination.[474,476,477,544] Presently, three vaccines are licensed for prevention of WNV viremia in the United States. Vaccination before the mosquito season is optimal. Two of these vaccines, a killed product and a recombinant product based on the canarypox vector, require an initial injection followed in 3 to 6 weeks with a booster injection.[569] Most manufacturers recommend more frequent vaccination in areas with year-round mosquito seasons. However, the recently licensed third vaccine demonstrated 12 months of immunity against severe intrathecal challenge with WNV. Limited information is available regarding long-term immunity with the other vaccines, given that the duration of immunity was tested using the mosquito model of WNV infection, which results in seroconversion and viremia as a measure of efficacy. Horses that have recovered from clinical WNV have long-term immunity against WNV and should not require immunization.

West Nile virus is a zoonotic in that a bird reservoir maintains the virus in an endemic life cycle in the environment, with transmission by mosquito to humans. There is little risk of disease by direct contact with a horse. However, the ecology of horse pastures and stables with standing water, a high degree of biologic debris, and “bridge” vectors that feed on mammalian populations pose a risk to people. The same type of management tactics for prevention are important for humans, except that there is no vaccine and deet-based

products are recommended for protection. The North American epidemic of WNV has demonstrated new modes of transmission involving blood-borne and occupational risks. Blood-borne transmission can occur between a viremic host and accidental needle injection. In addition, occupational infection has occurred through necropsy of avian hosts. Veterinarians and horse owners should institute personal protection with appropriate clothing, gloves, and eye protection when coming in contact with animal tissues during the arbovirus season.

35.2.14 OVINE ENCEPHALOMYELITIS (LOUPING ILL)

35.2.14.1 Definition and Etiology

Louping ill is an acute, fatal encephalomyelitis of sheep that occasionally infects humans, wild ruminants, horses, and cattle.[570–572] The disease has been reported in England, Scotland, Ireland, Norway, Turkey, and Bulgaria.[573–575] The etiologic agent of louping ill is a neurotropic, single-stranded RNA virus (flavivirus) that is transmitted by primarily the tick *Ixodes ricinus*, as well as by *Rhipicephalus appendiculatus, Ixodes persulcatus,* and *Hemaphysalis anatolicum*. Most outbreaks occur in swampy areas with dense populations of infected ticks and wild animals. Infection through blood contamination of hypodermic needles, other fomites, and blood products has been reported.[576] Minor genetic variations occur among viruses from different geographic areas, forming four subtypes.[577] A similar disease of sheep in Spain is caused by a genetically distinct flavivirus.[578]

35.2.14.2 Clinical Signs

Sheep develop central nervous system (CNS) disorders. Infection in horses often is asymptomatic.[579] The initial clinical signs of louping ill include fever, anorexia, depression, constipation, and generalized muscular tremors. The ensuing signs are characteristic of CNS disease and include ataxia, conscious proprioceptive deficits, head tremors, hypermetria, and hyperexcitability. The hypermetria results in a characteristic “bunny hopping gait,” which gives the disease its name. Further progression of clinical signs is associated with cerebrocortical dysfunction; these signs include head pressing, hyperesthesia, recumbency, convulsions, coma, and death. Survivors have residual neurologic deficits. The duration of the illness is approximately 12 days.

35.2.14.3 Clinical Pathology

Both hemagglutination inhibition and complement fixation tests can be used to detect virus in infected animals.[576] High levels of virus-specific IgG and IgM can be detected in the cerebrospinal fluid (CSF) of affected animals.[580] Viremia peaks at approximately 3 days after inoculation and disappears by 7 days. Because animals usually are not viremic at the time the nervous system lesions develop, virus recovery is best done from the brain or spinal cord. Isolation of the louping ill virus from the CSF is difficult.

35.2.14.4 Pathophysiology

Ticks become infected when feeding on a viremic host. The virus survives in the salivary glands of the tick and can overwinter here, being transmitted to a new host when the tick becomes active the following year.[576]

After inoculation into susceptible sheep, the louping ill virus migrates into the regional lymph nodes and spleen and then replicates. Viremia occurs 6 to 20 days after the invasion of the lymphatic tissues.[571] Viral replication in the brain causes nonsupportive inflammation and neuronal degeneration.[571] Rapid antibody production is associated with recovery.[581] Concomitant infection of sheep with the agent of tick-borne fever *(Erlichia phagocytophila)* results in a greater level of viremia and increased mortality from the louping ill virus.[582]

35.2.14.5

Epidemiology

Louping ill principally affects yearling sheep in the spring. Maternal immunity wanes when lambs are about 3 months old. Infection develops weeks to months after sheep have been placed on pastures infected by *Ixodes ricinus*. In any outbreak the prevalence of clinical louping ill is low, but the seroprevalence of antibodies in adult sheep in endemic areas is high, indicating a continuous, low-level exposure to the virus, and many animals are asymptomatically affected. Factors such as climate, tick population, and immune status of the flock all play a role in the severity of an outbreak.[576] The case-attack rate may reach 60% of the population, whereas the mortality rate is low, rarely exceeding 15%. The degree of susceptibility of neonatal lambs and adult sheep is similar. Adults tend to be more heavily parasitized by the host ticks and thus play a major role in virus survival and transmission.[583] Pigs, cattle, horses, and red deer also become infected with the virus and can develop similar clinical disease. The seroprevalence rate of the virus in horses from one endemic area was 10%.[579] Milk from infected goats can reach titers high enough to infect suckling kids.[584]

Sylvatic cycles of virus transmission occur in which viral amplification takes place through certain wild mammals and red grouse.[570,585,586] The hare, in particular, appears to play a major role in the propagation and persistence of virus in the red grouse population.[587,588] Certain other small mammals, such as field voles, however, do not have a role in this cycle of virus persistence.[589] In the case of grouse, it has been demonstrated that the host can be infected by ingesting the infected tick, rather than by being bitten by the tick.[590]

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Mild occupational infections can occur in shepherds, veterinarians, and laboratory workers who cultivate the virus. The louping ill virus probably is maintained on pastures through infected sheep because grouse populations become unstable and die out whenever the virus is introduced.[591] The high incidence of louping ill in the spring and summer months probably corresponds to the peak activity of ticks. The virus may persist for long periods in the arthropod vector, but it is unclear if transovarial transmission of the agent occurs. *Ixodes ricinus* is a three-host tick with a life cycle of 3 years. The ticks do not walk, and dissemination over a range requires animal transport. After a blood meal, the tick molts and then rests on vegetation until the next meal, approximately 12 months later. The activity of the ticks tends to increase greatly in the spring whenever the ambient temperatures are above 7°C (43°F).

35.2.14.6

Necropsy Findings

Gross lesions are absent at necropsy. The histologic lesions of louping ill include perivascular cuffing with mononuclear cells and neutrophils, gliosis, neuronal necrosis, and mononuclear cell meningeal inflammation.[592,593] Microscopic lesions are most severe in the Purkinje cells, the motor nuclei, and the ventral horn cells. The forebrain is spared.[594] Virus in tissue can be detected by virus isolation, IHC, and RT-PCR.[576,595,596]

35.2.14.7 Prevention

There is no treatment for louping ill encephalitis, but supportive care should be provided.

A formalin-inactivated vaccine given in the last trimester has been recommended for preventing louping ill.[597] A single dose of the vaccine provides responses that are protective for at least 2 years. Colostral antibody titers higher than 1:40 are considered protective.[583] Other methods of preventing the disease include frequent acaricidal dipping of sheep and clearing of pastures to reduce the population of infected intermediate hosts.

Louping ill has not been detected in the United States, but it is a reportable disease. Any suspicion of this disease should be reported to state and federal authorities. The disease also has a zoonotic potential; infection of humans can occur through tick bites, infected sheep or goat milk, or fomites.

35.2.15 RABIES

CHRISTINE BERTHELIN-BAKER

LISLE W. GEORGE

35.2.15.1 Definition and Etiology

Infection with rabies virus results in severe and usually fatal neurologic disease. Most mammals are susceptible and are infected through bites from other animals during or near the clinical phase of illness. The rabies virus and other highly neurotropic “rabies-related” viruses belong to the genus *Lyssavirus,* family Rhabdoviridae. (bullet-shaped RNA viruses). Wildlife provides a natural reservoir for rabies, and each rabies strain is maintained in particular reservoir host(s). Although they can readily cause rabies in other species, wildlife-adapted strains of rabies usually die out when passed into species to which they are not adapted. Other, “rabies-related” lyssaviruses can cause a neurologic disease identical to rabies. They include the Lagos and Duvenhage viruses of bats in parts of Africa, the Mokola virus of rodents and shrews in Africa, and the European and Australian bat lyssaviruses.[598–600]

35.2.15.2 Clinical Signs

Livestock cases of rabies have been reported mostly in cattle and occasionally in horses, sheep, and goats.[600,601] Rabies should be included in the differential diagnosis of any unexplained acute, rapidly progressive encephalitis, especially in the presence of autonomic instability, dysphagia, hydrophobia, paresis, or paresthesia.[600,602,603] The incubation period ranges from a few days to 6 months, depending on the pathogenicity of the inoculum and the distance from the site of inoculation to the brain. The shortest incubation periods are seen in animals bitten on the head, whereas the longest incubations have been reported after bites on the extremities of the pelvic limbs.

The disease is usually fatal after a clinical course of 1 to 8 days. Occasionally, an animal may be found dead without any previously observed clinical sign. Early clinical signs of rabies in livestock may be nonspecific sensory and behavioral changes, including anorexia, restlessness, depression, separation from the herd, and mild ataxia. Rumination may stop. Horses often appear colicky. Affected animals may repeatedly attempt to mount inanimate objects or show regional paresthesia with pruritus. Rubbing of the pruritic area results in

loss of hair or wool and skin ulcerations. As the disease progresses, animals may become hyperexcitable, fearful, or enraged *(furious rabies)* or mentally depressed *(dumb rabies)*. Furious and dumb states may alternate in the same animal. Cattle rabies frequently manifests as dumb rabies with flaccid paraparesis, tetraparesis, and tetraplegia *(paralytic rabies)* as the disease progresses.

In an experimental study, all cattle and sheep infected with the rabies virus exhibited excessive salivation and behavioral changes, and the majority also displayed tremors, bellowing, aggression, hyperesthesia, and pharyngeal paresis/paralysis.[600] Tetraplegic animals may show frantic motor activity of the legs and bellow when stimulated. Animals with dumb rabies are depressed, inappetent, and usually febrile (>39.4°C [103°F]) and may have a drooped head and neck, ptosis, flaccid facial musculature, profuse salivation, yawning, repeated nibbling motions with the lips, tenesmus, paraphimosis, odontoprisis, head pressing, circling, wide-base stance, difficulty rising, and falling episodes. Other clinical signs associated with dumb rabies include flaccidity of the tongue, tail, anus, and urinary bladder and blindness, strabismus, and nystagmus.

The first clinical sign of paralytic rabies in horses may be an unexplained ataxia or shifting leg lameness, soon followed by paraparesis or paraplegia.[604] Spinal reflexes and tone in the affected limbs may be decreased or absent. Most affected animals become recumbent in 3 to 5 days. Initially the recumbent animal may be able to eat and drink with help, but it soon becomes anorectic and develops encephalopathic signs, followed by coma and generalized seizures[605,606] (Fig. 35-4).

Fig. 35-4 Ten-month-old mixed-breed calf with terminal rabies virus encephalitis. The calf is comatose and showing opisthotonos.

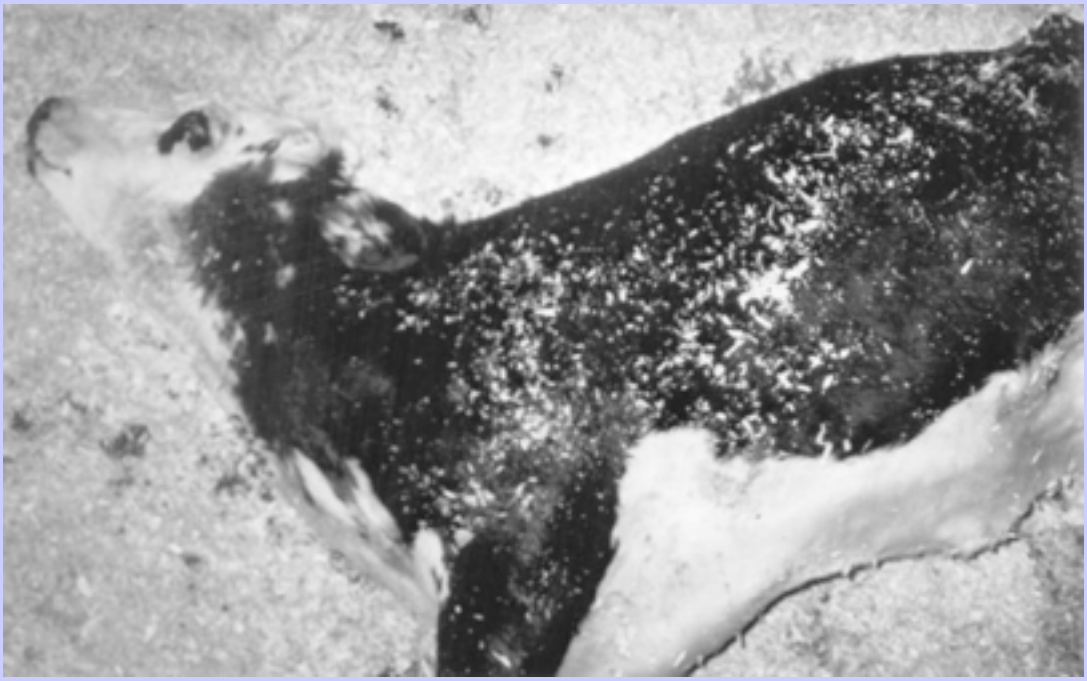

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Table 35-5 Occurrence of Particular Clinical Signs of Rabies in Horses

Clinical Signs	Frequency of Occurrence
Ataxia, paraplegia	11/21
Lameness	5/21
Pharyngeal paralysis	2/21
Recumbency	21/21
Colic	2/21
Hyperesthesia	17/21
Tail and anal paralysis	12/21
Fever	11/21

From Green S et al: Rabies in horses: 21 cases, *J Am Vet Med Assoc* 200:1133, 1992.

Regardless of the clinical manifestations, rabies is rapidly progressive and fatal disease leading to cardiorespiratory failure, and death usually occurs within 10 days. In all disease forms of livestock, the clinical signs rapidly worsen over 1 to 3 days, until the patient becomes recumbent and comatose. Animals may develop a pharyngeal-laryngeal paralysis resulting in stertorous breath sounds, inability to drink (thus the common name of "hydrophobia"), and accumulation of frothy saliva at the commissures of the lips.[607]

One summary of 21 cases of rabies in horses enumerated the frequency of particular clinical signs seen as the presenting complaint (Table 35-5). Rabies can only be differentiated from other encephalitic disorders by specific postmortem tests or virus isolation, which is usually not possible before death occurs. In horses the clinical signs of rabies often are indistinguishable from other encephalopathies, such as hepatoencephalopathy, leukoencephalomalacia, togaviral encephalitis, equine herpesvirus type 1 (EHV-1), protozoal and other meningoencephalomyelitides, and space-occupying masses. In ruminants, rabies may resemble herpesv.irus, thromboembolic meningoencephalomyelitides, nervous ketosis, grass tetany, polioencephalomalacia, nervous coccidiosis, or even focal spinal cord or peripheral nerve diseases. Most horses die of fatal encephalopathy within 5 days of the onset of signs; but cases lasting as long as 14 days have occasionally been observed.[608]

35.2.15.3

Clinical Pathology

There is no valid antemortem test to diagnose rabies in livestock. Rabies usually remains immunologically and serologically silent throughout the incubation and clinical phase of the illness.[244] Clinicopathologic tests are not specific for rabies but may help rule out other, more common diseases. The CSF may be normal or may show moderate mononuclear pleocytosis (5 to 30 cells/μL) and increased protein (60 to 200 mg/dL), occasionally with neutrophils, eosinophils, or xanthochromia reported.

35.2.15.4

Pathology and Postmortem Diagnosis

Rabies causes a nonsuppurative meningoencephalomyelitis. Microscopic changes include brain edema, meningeal congestion, focal areas of hemorrhage, perivascular cuffing, gliosis, neuronophagia, and neuronal degeneration. These changes are most severe in the dorsal root ganglia and can be seen in most CNS regions.

A definitive diagnosis of rabies may be based on the finding of Negri bodies (not always present, especially in cases euthanized early in the disease course) or through a positive direct or indirect fluorescent antibody (DFA, IFA) test conducted on fresh smears of CNS tissues (thalamus, hippocampus, brainstem, pons, medulla, cerebellum).[609–611] If these tests are negative or inconclusive and there has been human exposure, additional testing can be done using intracerebral inoculation of mice with CNS tissue from the suspect case. An antigen-capture enzyme immunodiagnostic technique has been developed for salivary gland specimens, to capture antigen onto solid phase using purified polyclonal antibodies. The specificity and sensitivity of this method are similar to the direct immunofluorescence test, but it has not gained widespread clinical use in the United States.[609] The DFA test on brain tissue has become the standard by which the value of other rabies tests is evaluated.[610] In cases of human exposure, the local public health parties should always be contacted before sample collection and submission. The diagnostic pathologist will usually accept the refrigerated head (or even whole body for small animals and bats), or refrigerated brainstem and cerebellum collected through the foramen magnum in mature cattle and horses. Care should be taken to prevent any human exposure to body fluids and CNS tissue of any animal with rabies on the list of differential diagnoses, especially in areas where rabies is known to be present in any domestic or wildlife species; open wounds or small healing sores may provide portal of entry for the rabies virus.

35.2.15.5

Pathophysiology

The structure of the rabies virus capsid proteins is similar to that of the neurotoxins of cobra venom and acetylcholine.[612] After subcutaneous or intradermal inoculation, the rabies virus replicates locally. After several days, it binds to the acetylcholine (and other) receptors of the peripheral nerves and then migrates retrogradely to the CNS through peripheral nerves, spinal rootlets, and the spinal cord. After entry into the nerve cell rootlets, the virus travels to the brain along nerve tracts and into CSF. From there it spreads centrifugally along the rootlets of the cranial nerves to the salivary glands and the nasal epithelium. Shedding of the virus in the nasal secretions and saliva may precede the onset of clinical signs but not the presence of virus in the brain, where it needs to replicate before it can reach the salivary and nasal secretions. Therefore, whenever an animal bites a person, the attacking animal can always be sacrificed and tested for the potential of rabies virus transmission, and it not necessary to wait for disease progression before testing an animal for rabies, as recommended earlier when Negri bodies were the main diagnostic test for rabies. In humans, most cases become apparent within 1 to 3 months of infection, but up to 10% of cases have had incubation periods in excess of 6 months, extending to several years in rare cases.[598] The rabies virus replicates in the cell bodies (gray matter) of the CNS. Dysfunction of these neurons results in behavioral changes and variable abnormalities of the cranial and the peripheral nerves, with multifocal loss of lower motor neuron and autonomic function. Death results from cardiorespiratory paralysis as the virus infects the brainstem medullary centers.

35.2.15.6

Epidemiology

Rabies is a reportable zoonosis that has been detected worldwide, with some exceptions (especially islands). It does not presently occur in Scandinavia, United Kingdom, Ireland, Australia, New Zealand, or Iceland.[598] The disease is endemic in other parts of the world, including the United States, Canada, and Europe, but remains epizootic in Central and South America, Africa, and parts of Asia, especially where a tropical climate and a high population of infected feral mammals favor viral propagation and transmission.[599,601] The rabies virus is shed in the saliva and does not survive when dried or exposed to ultraviolet (UV) light. The most common method of viral transmission to domestic animals is through the bite of an infected feral or wild mammal. Humans and laboratory animals have also developed fatal infections after respiratory exposure to viral aerosols. Low levels of rabies virus are also shed in the milk of infected animals and may occasionally infect offspring nursing infected dams.[613,614] Laboratory animals, foxes, and skunks also can be infected experimentally by ingestion of infected tissues from rabies cases.[613,614] The consumption of thorny bushes may also have caused horizontal transmission of rabies in an outbreak in African Kudu.[600] In the United States, survival of the virus in the wild may depend on cycling of infections in skunks, bats, or raccoons, which also are common sources of livestock infections.[615,616]

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Certain strains of rabies virus have low virulence in skunks and bats, resulting in asymptomatic carriers serving as reservoirs. The rabies virus is also transmitted directly among bats through aerosols in caves. The bats may die off from rabies during periods of high viral contamination. In the United States the most common wild reservoirs are foxes in Alaska and along the border of Mexico, raccoons in the East, and skunks in the central and western regions.[601] Mandatory vaccination of dogs has virtually eradicated canine rabies from developed countries, where rabies transmission from domestic dogs to livestock is rare.[598,617] Island nations have been able to remain free of rabies by imposing a 6-month quarantine on imported dogs and cats. In South America, rabies outbreaks in cattle often result from vampire bat bites, causing up to 50,000 cattle deaths annually. Human rabies cases may result from bites inflicted by infected pets, feral dogs and cats, bats, or wildlife. Cases resulting from contact with infected cattle or horses are rare.[601,617,618]

Animal rabies cases are most common in late summer, possibly because wild animals give birth to offspring during the early spring, and young animals become infected and then spread the disease as they expand into new territory under pressure from selective forces (e.g., predation, starvation, hunting).

The various strains of rabies virus are maintained in different hosts. Serial passage of virus from field cases (“street rabies virus”) into laboratory animals can produce a modified, “fixed virus” with loss of virulence for the field hosts and increased virulence for the laboratory species. Such fixed strains have been used in the preparation of vaccine viruses.

35.2.15.7

Prevention

Although widespread rabies vaccination of livestock is neither economically feasible nor justifiable on public health grounds, vaccination of valuable livestock, or animals that travel or are in regular contact with humans (e.g., petting zoos, animal shows) should be considered, especially in or near rabies epizootic areas. A list of licensed rabies vaccines for the protection of animals against rabies is regularly updated by state veterinary authorities.[619]

The disposition of livestock that have been bitten by rabid animals depends on the animal's vaccination history, local and national regulations, and the value of the bitten victim. In the United States and Canada, the disease must be reported to the state public health department. Management of exposed livestock must be coordinated with public health officials. Any livestock bitten by a wild animal should be considered to have been exposed to rabies, regardless of the availability of the biting animal for testing. If a bitten horse had been vaccinated before the bite, it should be revaccinated immediately and kept under observation for 90 days. Other exposed, unvaccinated animals with a low economic value should be euthanized, or if the animal is very valuable, the bite wound may be washed with copious amounts of water and iodine or quaternary ammonium disinfectants, after which the animal should be quarantined for at least 6 months and the brain examined if it dies.[619,620]

Vaccination of animals shortly after rabies virus infection is not recommended because it is less effective than prophylactic vaccination. In one study, postinoculation vaccination of experimentally infected sheep had no effect on the incubation period, clinical signs, or mortality rate. Moreover, the antibody titers of the vaccinated animals had no predictive value for protection.[621,622] Whenever human exposure to rabies virus is suspected, the suspected animal must be euthanized and its brain examined for evidence of infection. A vaccinated or valuable animal may be quarantined for 6 weeks under veterinary supervision, and the brain must be examined if it develops clinical signs suggesting rabies during that period. The World Health Organization (WHO) publishes and regularly reviews its recommendations for vaccination and prophylaxis in humans after exposure or suspected exposure to the rabies virus.[599]

Control of rabies by immunization of susceptible wildlife using baits containing modified live vaccines has been successful in certain cases.[601,618,623,624] Such approaches may provide a means for large-scale immunization of wildlife or feral animal populations for eventual eradication of the disease.

35.2.16 SPORADIC BOVINE ENCEPHALOMYELITIS (BUSS DISEASE; POLYSEROSITIS; *CHLAMYDIA PECORUM* INFECTION)

Sporadic bovine encephalomyelitis (SBE) is caused by *Chlamydia pecorum,*[625] which produces a disseminated vasculitis and serositis. The disease was first reported in the United States in 1940.[626] A similar but not identical viral disease occurs in cattle in Australia and has been named “bovine ephemeral fever.”[627–630] SBE occurs in Czechoslovakia, Hungary, and Japan.[631–634] Nonsuppurative meningoencephalomyelitis also has been described in a study of cattle in Switzerland; a variety of pathologic patterns were found in those animals, and neither chlamydiae nor other common neurotropic organisms (rabies virus, Borna disease virus, tick-borne encephalitis virus) were identified as etiologic agents.[635] Outbreaks of SBE are rare, but the case-attack rate in an epizootic ranges from 5% in adults to 25% in calves. The mortality is highest in calves and approximates 31% for all age-groups.[636]

Infected cattle shed the organism in urine, feces, nasal secretions, and milk. It also can be found in the feces of asymptomatic calves exposed to clinically affected herdmates. However, the most common mode of transmission of the chlamydial agent is unknown. The agent tends to remain endemic on a single farm, and sporadic outbreaks of disease may occur only on those premises. The pattern of these outbreaks varies, from a few cases annually to acute, recurrent epizootics with high case-attack rates that subside after 3 to 4 weeks. Sheep and goats are resistant to the bovine agent.

35.2.16.1

Clinical Signs

Affected animals show signs of a multisystemic disease. The initial clinical signs in cattle are fever (39°C to 41.5°C [102.1° F to 106.7°F]), anorexia, depression, and stiffness. The cattle also may show signs of a respiratory disease characterized by nasal discharge, dyspnea, and cough. These animals occasionally have a painful response to percussion of the hoof, as well as swelling of the coronary band or polyarthritis and tenosynovitis.[626] Auscultatory abnormalities may include high-pitched wheezes and crackles over the lung fields or pleural and pericardial friction rubs. Because of the fibrinous peritonitis and pleuritis, the clinical signs in some affected animals may resemble those of hardware disease. These animals may grunt or groan when sudden pressure is applied to the xiphoid region. Some animals may respond to soft percussion of the xiphoid region by striking or kicking at the examiner. There is an initial diarrhea. Progression of the disease is related to development of the meningoencephalitis and is characterized by ataxia and conscious proprioceptive deficits, circling, head tilt, opisthotonos, hyperesthesia, stiff neck, convulsions, and coma. Animals may die after 4 to 10 days.

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35.2.16.2

Diagnosis

The detection of elementary bodies in the exudate cells of pleural and peritoneal effusions is highly suggestive of SBE. The chlamydial agent can be cultured from the blood and body fluids of early infections in guinea pigs inoculated intraperitoneally with fresh tissue specimens and held for 6 to 7 days. Inoculation of embryonated eggs is a less sensitive diagnostic technique than animal inoculation. The causative organism has been identified as a distinct species, *Chlamydia pecorum,* by means of DNA analysis, immunologic assays, and serology.[635]

35.2.16.3

Pathogenesis and Pathologic Lesions

The mode of infection and the genesis of pathologic lesions are unknown in natural cases. Growth of the chlamydiae in the arteriolar endothelium causes vasculitis, hemorrhage, edema, and accumulation of fluid in the body cavities. Diffuse fibrinous pleuritis, peritonitis, and meningitis also are seen. Microscopic changes include perivascular mononuclear cell infiltration and neuronal degeneration. The lesions all are composed of networks of neutrophils and mononuclear cells enmeshed in fibrin. Some of the inflammatory cells contain elementary bodies.

35.2.16.4

Treatment

Early cases of SBE can be treated with oxytetracyclines (20 to 50 mg/kg/day for a minimum of 7 days). Efficacy is indicated by a reduction of fever within the first 24 hours of treatment. The chlamydial agent is also susceptible to penicillin and erythromycin, but the clinical efficacy of these drugs is unknown.

35.2.16.5

Control

There are no known effective control measures for the prevention of SBE. The chlamydial agent is susceptible to a number of disinfectants, including 2% sodium hydroxide (NaOH), 5% cresol, and 0.3% quaternary ammonium compounds.

35.2.17 *MORBILLIVIRUS* ENCEPHALOMYELITIS OF CATTLE

A nonhemagglutinating paramyxovirus *(Morbillivirus)* has been isolated from a calf with encephalitis. The disease was first described in Germany, but subsequent cases have been identified in Switzerland.[637] The German *Morbillivirus* organism is serologically related to the subacute sclerosing panencephalitis virus of humans but is unrelated to the parainfluenza virus of cattle. The clinical signs of *Morbillivirus* infection include pharyngeal paralysis, anorexia, salivation, hyperexcitability, intentional head tremors, aggressiveness, coarse muscle fasciculations, cutaneous analgesia, tonic-clonic seizures, dysphonia, and bellowing. The pathologic lesions include a diffuse, mononuclear cell encephalitis, perivascular cuffing with mononuclear cells, microglial cell proliferation, astrocytosis, neuronal loss, neuronophagia, and intraneuronal intranuclear (Cowdry type A) inclusion bodies.

35.2.18 BOVINE NECROTIZING ENCEPHALOMYELOPATHY

A neurologic disorder affecting Angus calves in Australia has been reported. Approximately 1% of the calves were affected, starting at 2 to 6 weeks of age.[638] The varied signs included nystagmus, strabismus, and wide-base stance with or without proporioceptive deficits, later progressing to recumbency with muscle tremors, bruxism, hyperesthesia, opisthotonos, and death 4 to 7 days after onset. Biochemical changes included increased hemoglobin concentration, neutrophilia, hyperglycemia, and elevated serum creatine kinase (CK) and aspartate transaminase (AST), but biochemical data were available for only two animals. At necropsy, small malacic foci 1 to 2 mm in diameter were observed in the medulla oblongata. Histologically, symmetric degenerative lesions were found in multiple brainstem nuclei, with variable involvement of the spinal cord gray matter and thalamus. The neuropil in affected areas exhibited pallor, edema, and spongiform change. There was central chromatolysis in neurons, cytoplasmic eosinophilia, nuclear margination, and necrosis. Mild inflammatory changes in the form of gliosis, infiltration of gitter cells, and endothelial hypertrophy were observed. Axonal spheroids were numerous.

This disease has been likened to Leigh's disease, inherited subacute necrotizing encephalomyelopathy, in humans. A heritable disorder was suspected because evidence indicated the herd was inbred, but pedigree analyses were not performed. Differential diagnoses included other heritable metabolic disorders, including lysosomal storage diseases, bovine cerebellar atrophy, and encephalomalacia caused by the endotoxin of *Clostridium perfringens* type D.

No treatment is currently available for bovine necrotizing encephalomyelopathy, but investigation into breeding practices and limiting inbreeding would be advisable.

35.2.19 MENINGITIS (SUPPURATIVE MENINGITIS; BACTERIAL MENINGITIS)

35.2.19.1 Definition and Etiology

Meningitis can occur either from direct extension of infectious agents into the calvarium or from hematogenous infection. Causes of suppurative meningitis include direct extension of pyogenic infections into the calvarium from infected skull fractures,[639] osteomyelitis from sinusitis or otitis, osteonecrosis caused by thermal cauterization during dehorning[640] or by improper placement of trephination holes, cribriform plate fractures, and extension from infected coccygeal vertebrae. In horses, septic meningitis is a common

sequela to surgical removal of progressive ethmoidal hematomas and also has been reported as a consequence of local spread of infections of the paranasal sinuses, nasal cavity, periocular tissues, and submandibular lymph nodes.[641]

Centripetal migration of *Cryptococcus neoformans* along peripheral nerve rootlets results in suppurative meningoencephalitis.[642,643] Other bacteria that can cause suppurative meningitis include *Streptococcus zooepidemicus* in foals and goats[644]; *Streptococcus suis* and *Streptococcus equi* in foals[645]; *Actinomyces* species in horses; *Escherichia coli, Pasteurella, Streptococcus, Staphylococcus pyogenes, Mannheimia,* and *Arcanobacterium (Actinomyces) pyogenes* in calves; and *Globicatella sanguinis* in lambs.[646–649] Embolic showers to the central nervous system (CNS) also occur in cases of left-sided endocarditis. *Pseudomonas aeruginosa* mastitis of cattle and goats may terminate with septicemia and meningitis. In adult animals, previous surgical procedures may result in sepsis and subsequent meningitis.[650] Management or environmental factors may predispose to outbreaks of meningoencephalitis within groups of animals, as occurs when inadequate colostrum is supplied to neonates, or when contamination of the water supply occurs, as reported in an outbreak of amebic meningoencephalitis in cattle.[651]

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Suppurative meningitis of hematogenous origin is common in neonates (see Chapter 18). Gram-negative bacteria, *E. coli,* and *Salmonella* species are the dominant organisms involved in neonatal infections. One survey reported a 43% prevalence of septic meningitis in necropsied calves.[652] Deficient passive transfer of colostral antibodies to the neonate predisposes to hematogenous meningitis (see Chapter 53). *Mycoplasma mycoides* subsp. *mycoides* is a common cause of meningitis in goat kids. Underlying immunodeficiency disorders may predispose to the development of suppurative encephalitis in mature animals.[653]

35.2.19.2

Clinical Signs

The earliest clinical signs of meningitis are usually those of systemic illness, such as diarrhea, fever, and anorexia, accompanied by stiff neck and hyperesthesia.[654,655] Passive manipulation of the head and neck causes sudden extension and hypertonicity of the limbs. Slight tactile stimulation of the skin may result in strong spasmodic extension of the limbs, fasciculations of the underlying musculature, or even generalized frantic motor activity. The patient's behavior may vary from extreme depression to hyperexcitability or mania. Animals may display trismus and may vocalize when the head and neck are flexed. Tetraparesis, hyperreflexia, and a tendency to circle or fall toward one side may be noted. A subtle intentional head tremor often is observed in foals. Dysfunction of one or more cranial nerves may result in facial muscular tremors, nystagmus, facial palsy, blindness, anisocoria, or strabismus. These deficits are inconstant. Progression of the clinical signs is associated with a decreased sensorium, propulsive walking, coma, seizures, and status epilepticus. Evidence of infection elsewhere may be apparent, such as swollen joints, omphalophlebitis, or hypopyon.[647]

The clinical signs of purulent meningitis closely resemble those of metabolic encephalopathies, including hypomagnesemia, hypoglycemia (which may occur simultaneously with septic meningitis in neonates), and encephalomalacias (e.g., salt poisoning). The onset of clinical signs may be delayed in horses with *Cryptococcus neoformans* meningitis.[642]

35.2.19.3

Clinical Pathology

Septic meningitis should be differentiated from metabolic encephalopathies by measurement of the plasma concentrations of sodium, glucose, and magnesium and by laboratory evaluation of hepatic function. Diagnosis of meningitis is based on examination of the cerebrospinal fluid (CSF; for normal values, see Table 35-1). The CSF of animals with meningitis may be turbid and white to amber in color, may foam when shaken, and may clot. Xanthochromia may be observed in some specimens. The white blood cell (WBC) counts in CSF of calves with purulent meningitis are typically greater than 100 neutrophils/μL (mean count, 4004 WBCs/mL), and protein concentrations range from 20 to 270 mg/dL.[654] The differential cell counts in the CSF are either predominantly neutrophilic or mononuclear, with fewer neutrophils. The concentration of glucose in the CSF often is less than 50% of the corresponding concentration in the blood. Because of the lack of opsonic and bactericidal activity in the CSF, bacteria can proliferate to high titers and are often observed in Gram-stained smears of CSF. One study showed intracellular bacteria in 10 of 22 calves with meningitis.[656] Abnormalities in the blood are inconsistent and reflect secondary conditions such as septicemia, diarrhea, or overaggressive fluid therapy. These changes could include leukocytosis, left shift, toxic changes in the hemogram, hyperkalemia, respiratory acidosis, hypoglycemia, and hyponatremia or hypernatremia. Evidence of bacteremia and sepsis may be found in peripheral blood.

35.2.19.4

Pathophysiology

Because there is little bactericidal or opsonic activity in the CSF, animals are highly susceptible to meningeal infection by low numbers of bacteria. Bacterial proliferation in the CNS results in production of bacterial endotoxins, cytokines, and other products of inflammation that damage the neural parenchyma. Vascular sequelae of infection may include thrombotic or hemorrhagic infarcts. After several days, inflammation of the arachnoid trabeculae and choroid plexus can result in decreased CSF absorption and hypertensive hydrocephalus.[647]

35.2.19.5

Necropsy Findings

The meningeal vessels appear to be congested, and the meninges are swollen, opalescent, and petechiated. The CSF is cloudy or amber and may contain fibrin clots. In cases associated with bacteremia, a fibrinopurulent iridocyclitis may be observed. Microscopic changes of CNS tissues include infiltration by neutrophils and lymphocytes, endarteritis of the meningeal vessels, choroiditis, scattered leptomeningeal hemorrhages, and bacterial colonies around the blood vessels of the meninges and the brain parenchyma.

Concomitant pathologic lesions, including omphalophlebitis, septic arthritis, anterior uveitis, and panophthalmitis, result from dissemination of the septic process. These lesions may be helpful in differentiating meningitis from metabolic encephalopathies. When meningitis occurs secondary to trauma, the site of organism entry may be detectable. Fungal meningitis caused by *C. neoformans* often is accompanied by granulomatous lesions of the lips, nasal mucosa, and peripheral nerves.

35.2.19.6

Treatment

Treatment of bacterial meningitis is difficult, and the mortality rate is high. Early recognition and treatment are essential for adequate recovery. Antimicrobial sensitivity tests performed on isolates from CSF may

provide valuable information on ideal drugs. However, these tests frequently are unavailable because of the difficulty in isolating primary pathogens from CSF in most cases of purulent meningitis. Because prompt treatment of meningitis is critical, antibiotic therapy usually must be based on the Gram-staining characteristics of sedimented bacteria and the initial 24-hour cultures.

Domestic animals have a well-defined blood-CSF barrier, and antibiotics that reach high plasma concentrations may not necessarily reach bactericidal concentrations in the brain. To ensure an adequate antibacterial efficacy, antibiotic concentrations in the CNS should range from 10 to 30 times the minimum inhibitory concentration (MIC) of the infecting bacteria.[656–664] Antibiotics that are inherently bactericidal tend to produce superior responses compared with agents that are primarily bacteriostatic. The major factors influencing CSF penetration of an antimicrobial agent are the lipid solubility, degree of ionization, and molecular weight of the drug. In general, broad-spectrum drugs with a nonpolar basic character tend to have the greatest CNS penetration and efficacy for treatment of meningitis. Antibiotics tend to diffuse into CSF to a greater extent when it is inflamed. Box 35-1 shows the relative penetrability of antibiotics and antimicrobials into the CSF.

Antibiotic treatments should be administered by intravenous (IV) routes to attain maximum peak blood and CSF concentrations and should be continued for 14 days or longer. Table 35-6 presents the recommended dosages for each of the antibiotics.

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Selection of antibiotics should be based on the results obtained from Gram-stained smears and cultures of the CSF or from other infected areas. Penicillin G is a polar acidic drug that has limited distribution into the CSF. Because of this and the predominance of gram-negative CNS infections in livestock, penicillin alone is a poor choice for initial therapy of uncharacterized purulent meningitis.[665–670] Nevertheless, administration of very high IV dosages of penicillin may be effective for the treatment of meningeal infections by highly susceptible bacteria such as *Streptococcus* or *Haemophilus* organisms. In these cases, low but therapeutic concentrations of the drug can be achieved in the CSF. In humans, IV dosages of 250,000 U/kg daily are required to achieve CSF penicillin concentrations ranging from 0.3 to 0.8 µg/mL.[665] For infections caused by gram-positive bacteria with intermediate susceptibility to penicillin, multiple daily IV dosages of ampicillin (15 to 20 mg/kg) may be useful.

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35.2.19.6.1

Box 35-1 Expected Penetration of Antibiotics and Antimicrobial Drugs into Cerebrospinal Fluid

35.2.19.6.1.1

Good Penetration

Minocycline

Doxycycline

Erythromycin

Sulfonamides

Chloramphenicol*

Metronidazole*

Quinolones

Ceftiofur

Cefotaxime

Moxalactam

Pyrimethamine

Isoniazid

Trimethoprim-sulfonamide

* Intravertebral and intervertebral.

35.2.19.6.1.2

Poor Penetration

Cephaloridine

Gentamicin

Tetracycline

Penicillin G

Kanamycin

Streptomycin

Neomycin

* Prohibited in food-producing animals in the United States.

Table 35-6 Recommended Drug Regimens for Treatment of Bacterial Meningitis in Livestock

Antibiotic or Antimicrobial Drug	Dose, Route, and Frequency	Indication, Comments
Trimethoprim-sulfadiazine	30 mg/kg sulfa PO twice daily	Staphylococci, *Klebsiella,* some coliforms; long-term medication; not for use during acute crises
Chloramphenicol*	100–200 mg/kg PO four times daily *or* 100–200 mg/kg IV six times daily	Staphylococci, streptococci, *Klebsiella, Actinobacillus, Corynebacterium,* some coliforms
Third-generation cephalosporins (moxalactam, ceftriaxone, cefotaxime)	40 mg/kg IV four times daily	Staphylococci, streptococci, coliforms, *Klebsiella, Actinobacillus, Bordetella, Salmonella, Pseudomonas, Corynebacterium;* expensive
Isoniazid	5–20 mg/kg PO two times daily	*Arcanobacterium pyogenes, Rhodococcus equi;* long-term oral therapy is indicated; combine treatments with penicillin, ampicillin, or erythromycin
Erythromycin (cattle only)	10 mg/kg IM two times daily	Streptococci, some anaerobes, *Arcanobacterium pyogenes, Rhodococcus equi;* do not administer to horses or small ruminants; give to cattle only for 3 days; expect severe muscular swelling
Penicillin G, sodium	22,000–240,000 IU kg slow IV four times daily	Some staphylococci, streptococci, anaerobes, *Pasteurella, Haemophilus, Arcanobacterium pyogenes, Rhodococcus equi;* rapid IV infusion may be acutely fatal to small ruminants
Ampicillin, sodium	15–20 mg/kg IV four times daily	Some staphylococci, streptococci, anaerobes, *Pasteurella, Haemophilus, Arcanobacterium pyogenes, Rhodococcus equi;* safer for small ruminants than IV penicillin G
Ticarcillin/clavulanate	44–50 mg/kg IV four times daily	Staphylococci, streptococci, anaerobes, *Pasteurella, Haemophilus, Actinomyces, Rhodococcus equi, Klebsiella,* coliforms
Tetracycline (100 mg/mL concentration)	6–12 mg/kg IV two times daily	Some coliforms, staphylococci and streptococci, *Pasteurella, Haemophilus, Actinomyces, Rhodococcus equi* limited spectrum of activity
Amikacin sulfate	6.6–7.5 mg/kg IV or IM two times daily	Coliforms, *Klebsiella, Pasteurella, Haemophilus*
Metronidazole*	22–25 mg/kg/day PO or IV	Anaerobes

Data regarding predicted susceptibility of bacteria to specific antimicrobials can be found in Prescott JF et al: *Can Vet J* 25:289, 1984.

IM, Intramuscularly; *IV,* intravenously; *PO,* orally.

* Use prohibited in food animals in the United States.

Meningitis caused by the Enterobacteriaceae should be treated with aminoglycoside antibiotics or third-generation cephalosporins. Although aminoglycoside antimicrobials are highly effective against gram-negative pathogens and are bactericidal, their efficacy for the treatment of purulent meningitis is diminished by their polar basic characteristics and low attainable CSF concentrations. The aminoglycosides used most often for the treatment of bacterial meningitis include gentamicin (3 mg/kg IV or IM three or four times daily) or amikacin (6.6 mg/kg IM three or four times daily).[671]

Because of the difficulties associated with aminoglycoside penetration into the CSF and antimicrobial resistance, intrathecal therapy with preservative-free aminoglycoside antibiotics has been recommended for gram-negative meningitis. Intrathecal or intraventricular gentamicin (1 mg daily in smaller animals, 0.05 mg/kg in larger animals) has been recommended for treatment of *P. aeruginosa* meningitis.[672] The safety of the procedure has been questioned, however, on the basis of reports of increased mortality in experimentally treated rabbits and in children with naturally acquired infections.[672,673]

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The third-generation cephalosporins moxalactam, cefotaxime, ceftiofur, and ceftazidime have a high efficacy against gram-negative CSF pathogens and penetrate the blood-CSF barrier better than penicillins or aminoglycoside antibiotics.[674–676] They also are resistant to inactivation by the β-lactamases of the gram-negative bacteria and retain activity in purulent debris. Because of these characteristics, the cephalosporins often are preferred over the aminoglycoside antibiotics for treating gram-negative CNS infections. The recommended dosage for ceftiofur is 5 to 10 mg/kg IV or IM one to three times daily.[647] Fluorinated quinoline antibiotics have a reproducible penetration into the CNS. In laboratory animals, data show that the drugs reached CSF concentrations of 4 to 8 mg/L.[677] The recommended dosage of enrofloxacin for bacterial meningitis is 5 mg/kg IV twice daily. Experimental animals have been given dosages as high as 50 mg/kg for some types of infections.

When the quinoline antibiotics or third-generation cephalosporins are too costly, trimethoprim-sulfonamide (TMS) combinations may be an effective substitute for horses.[678–682] TMS has good penetration into the CSF and may be useful for horses, foals, and preruminant calves, lambs, and kids. The drug is not useful for treating ruminating animals. In the ruminant the half-life of parenteral trimethoprim is short (60 minutes) compared with that of sulfonamide (11 hours). The short half-life of trimethoprim in the ruminant largely results from ruminal excretion and inactivation of the drug. TMS has a higher efficacy in preruminants and horses because the half-life of trimethoprim is significantly longer than in the adult ruminant. The recommended dose is 5 mg/kg/day based on IV trimethoprim given two or three times daily.[647] Combinations of ampicillin with third-generation cephalosporins or TMS may broaden the antibiotic spectrum.

Patients should be observed closely for the first 3 weeks after the start of therapy because clinical improvement is associated with decreased permeability of the blood-CSF barrier and reduced CSF concentration of the chemotherapeutic agent.[646,665–667] Bacteria remaining in the CNS may regrow as a result of the lowered antibiotic concentration, and clinical signs of meningitis may return after a period of initial improvement.[667] This recurrence of signs after 3 to 4 days of seemingly successful therapy should indicate the necessity for an increased antibiotic dosage or a change in the type of antibiotic.

Although chloramphenicol has a nonpolar character and good lipid solubility, it is bacteriostatic and does not reach bactericidal concentrations in the CSF. Its efficacy for the treatment of gram-negative meningitis is

limited. Because of this and the current regulatory restrictions imposed by the U.S. Food and Drug Administration (FDA), chloramphenicol cannot be recommended for the treatment of purulent meningitis in large animals, especially ruminants. The tetracyclines do not appreciably cross the blood-brain barrier and also cannot be recommended for the treatment of bacterial meningitis except for certain highly susceptible infections such as *Haemophilus somnus*.

Table 35-7 Suggested Anticonvulsant Drug Regimens for Treatment of Seizures in Horses and Cattle

Drug	Dose, Route, Frequency	Comments
Diazepam (Valium)	0.01–0.2 mg/kg IV every 30 minutes as needed to control convulsions	Effective for rapid control of status epilepticus; poor choice for long-term therapy because of cost and short plasma half-life
Phenobarbital	12–20 mg/kg IV initial dose, dilute in saline over 30 minutes 11 mg/kg PO once daily (horses)	Begin treatment in convulsive neonates with intravenous (IV) drips; for long-term administration, give orally; monitor trough plasma concentrations of phenobarbital Therapeutic concentrations range from 15 to 40 µg/mL
Pentobarbital	2–20 mg/kg IV (~2 mL/5 kg body weight); repeat every 4 hours as needed for control of status epilepticus; not good for long-term control of sporadic seizures	Must administer slowly and monitor depth of anesthesia carefully to prevent respiratory arrest; control of convulsions in adult horses and cattle often occurs at lower IV dosages; use IV catheter for repetitive administrations

Cryptococcal meningitis of horses has been treated by 100 to 150 mg of IV amphotericin B in 4000 mL of 5% glucose, repeated every 48 hours for 23 days. One horse improved with this treatment but relapsed. Flucytosine (Ancobon, Hoffman LaRoche) was recommended as an alternative treatment.

Concomitant administration of dexamethasone sodium phosphate or an NSAID may improve recovery from purulent meningitis. The choice of steroid versus nonsteroidal drug has not been established for large animals. Supportive therapy for animals with suppurative meningitis should include protection from self-inflicted trauma, sedation, amelioration of pain, fluid therapy, and anticonvulsants.

Convulsions can be controlled by diazepam (Valium) or phenobarbital at respective IV dosages of 0.01 to 0.4 mg/kg[671] and 20 mg/kg (Table 35-7). For IV phenobarbital, the drug should be diluted in saline and administered slowly over 30 minutes. Repeated doses (1 to 9 mg/kg) are given three times daily.[683] After administration of 9 mg/kg to horses, plasma concentrations of phenobarbital range from 11.6 to 53 µg/mL.[684] Phenobarbital distributes slowly in the fat deposits. Because this could lead to drug accumulation, the trough drug concentrations should be measured frequently. The maximum desirable trough phenobarbital concentration is 40 µg/mL, and the minimum therapeutic level is 15 µg/mL.[683,685] After initial sedation, long-term control of convulsions in horses can be maintained by oral diphenylhydantoin (2.8 to 16 mg/kg three times daily) or IV phenobarbital (11 mg/kg once daily).[685–687] The trough plasma concentration of diphenylhydantoin should also be measured repeatedly during continuous drug therapy; the maximum

desirable trough level is 10 to 20 µg/mL,[686] and optimum plasma concentration is 5 to 10 µg/kg. Primidone is metabolically activated to phenobarbital. Because it is more expensive than phenobarbital, however, primidone is not usually administered to large animals.

The concentration of plasma immunoglobulins should be measured in neonatal patients with bacterial meningitis. Neonates with a plasma protein concentration less than 4.5 g/dL or an IgG concentration less than 500 mg/dL should be given 1 to 2 L of plasma from a normal adult.

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Nonsteroidal antiinflammatory drugs (flunixin meglumine or phenylbutazone) are useful analgesics in animals with suppurative meningitis; Table 35-7 lists suggested dosages and routes of administration. Good nursing care is essential. Parenteral fluid therapy should be administered to animals that are unable to drink. Fluid dosages should be selected to replace insensitive water losses and existing deficits (40 to 80 mL/kg daily; balanced electrolytes). The blood pH, serum osmolality, and plasma concentrations of glucose, sodium, potassium, and magnesium should be closely monitored during the antimicrobial therapy and measured repeatedly in animals having seizures.

35.2.20 PITUITARY ABSCESSES

Pituitary abscesses occur sporadically in ruminants. *Arcanobacterium pyogenes* is the most frequently isolated bacterium, but *Corynebacterium pseudotuberculosis,* as well as *Streptococcus, Staphylococcus, Actinomyces, Bacteroides, Fusobacterium, Acinetobacter, Pasteurella, Pseudomonas,* and *Actinobacillus* species, occasionally have been isolated.[688] Pituitary abscesses are rare in horses.

The clinical signs of pituitary abscess occur suddenly and progress for 7 to 10 days before the affected animal dies.[688] The initial signs are ataxia, head-neck extension, wide-base stance, inappetence, depression, head pressing, and recumbency.[688–690] Most affected animals have asymmetric deficits of one or more cranial nerves, resulting in dysphagia, blindness, anisocoria, absent pupillary light reflexes, mydriasis, flaccid tongue, nystagmus, facial paralysis, facial hypalgesia, ventrolateral strabismus, or head tilt.[688,691] Approximately 50% of the affected animals have bradycardia (pulse rate <60 beats/min).

The CSF protein concentration in affected cattle ranges from 70 to 502 mg/dL, and nucleated cell counts range from 6 to 12,640/µL (6% to 84% neutrophils).[688] The antemortem diagnosis is based on the observation of bradycardia, blindness, and nonresponsive pupils in conjunction with evidence of pyogenic inflammation in the CSF.

Some authors have postulated that the infectious agent gains entry to the sella turcica hematogenously and then localizes in the rete mirabile, which is the complex of blood vessels encircling the pituitary gland.[688] A direct relationship exists between the complexity of the rete mirabile and the incidence of pituitary abscessation in different mammals. The horse and dog lack a well-defined rete and correspondingly have a low risk for developing a pituitary abscess, whereas the situation is reversed in cattle. One study reported that 55% of cattle with a pituitary abscess had pyogenic foci in other organ systems or in the sinuses, teeth, or soft tissues of the face,[688] indicating that the abscesses may result from a retrograde bacterial embolization through branches of the facial veins.

Ataxia is caused by interruption of extrapyramidal motor nuclei in the brainstem by the expanding abscess. Extension of the abscess into the communicating retroorbital rete may result in exophthalmos. Extradural extension of the abscess along the brainstem causes sequential loss of the cranial nerve function, with the

nerves closest to the pituitary gland the first to become dysfunctional. Bradycardia may be caused by interference with diencephalic cardioacceleratory centers. In animals that survive for several weeks, the abscess may extend into the dura mater and cause a suppurative meningoencephalitis.

Animals ranging in age from 9 months to 12 years have been affected, but most cases occur between 2 and 5 years of age.[692] Pituitary abscess appears to have a slightly increased prevalence in castrated and intact males.[688] A high incidence of pituitary abscessation has been related to infections that developed in bulls after insertion of a nose ring. Prophylactic administration of penicillin and attention to aseptic procedure during insertion of the ring can reduce disease incidence.[690] Because of the high mortality rate associated with pituitary abscesses, treatment usually is not attempted.

35.2.21

BRAIN ABSCESSES

Because of the high incidence of strangles, *Streptococcus equi* is the most common cause of brain abscesses in horses.[693] *Arcanobacterium pyogenes* is a common cause of brain abscesses in cattle by means of extension of a sinus infection through the calvarium. Brain infections of cattle with *Bacteroides* species have also been reported.[694] The neurologic dysfunction caused by brain abscesses typically has a slower onset and is more asymmetric than that caused by meningitis, probably because most abscesses initially are extradural. However, acute onset of signs also can occur.[693] Forebrain abscesses compress the cerebral cortex, causing a caudal displacement of the brain and functional loss of one or both occipital lobes. Because of the high proportion of crossed fibers in the optic nerve decussation, unilateral cortical abscesses result in vision loss in the contralateral eye. Increased CNS compression by the mass results in ipsilateral mydriasis caused by interference with the oculomotor nerve. Further increases in the size of the lesion cause more generalized cortical signs, including blindness, propulsive walking, circling, head tilt (toward the lesion side), depression, coma, head pressing, or sudden unexplained mania. Abscesses at the base of the brain may cause additional abnormalities of cranial nerve function, including vestibular disease (Figs. 35-5 and 35-6).[693] Ophthalmoscopic examination may reveal papilledema in the ipsilateral eye. Advanced imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI), may be helpful for antemortem diagnosis when these modalities are available.[695,696]

Fig. 35-5 Severely obtunded bull that developed a brain abscess from extension of a frontal sinusitis. The abscess extended to the base of the brainstem and affected cranial nerves V and XII, resulting in dropped jaw and tongue paralysis. The bull also was severely depressed, blind, and ataxic and had facial analgesia.

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Fig. 35-6 Head pressing in a pony caused an abscess in the right cerebral hemisphere. Courtesy Dr. R.H. Whitlock.

In later stages, animals may assume lateral recumbency and display a decerebrate posture characterized by hypertonicity, hyperreflexia, opisthotonos, coma, and convulsions. At this stage the disease is difficult to differentiate from septic meningitis. CSF findings in animals with brain abscesses are variable, ranging from normal to very abnormal, with high protein concentration and marked pleiocytosis.[693,697] Treatment of brain abscess includes antibiotics and supportive care (see Meningitis in this chapter). In one clinical report a brain abscess in a horse was localized with CT scanning and successfully drained through a craniotomy.[695]

35.2.22 MYCOTIC ENCEPHALITIS

Reports of a horse and a calf infected systemically with a phycomycete described recumbency and coma. Pathologic CNS changes consisted of cerebellar and occipital cortical infarction.[698,699] The CSF changes included a greatly increased Pándy test (for elevated CSF protein concentration) and an increased WBC count (79/µL). The cell population in the CSF was composed of 81% mononuclear cells and 19% neutrophils.

35.2.23 BRAIN TRAUMA

35.2.23.1 Definition and Etiology

Because of their size, behavior, and relatively thin calvarium, horses are more susceptible to head trauma than other livestock. Traumatic injuries of horses most often result from kicks, sharp blows, or falling over backward.[700] Blows to the poll of the horse, particularly associated with falling over backward, are very common and result in fracture or displacement of the basisphenoid, occipital, and petrosal bones and the basioccipital and basisphenoid sutures.[701–703] Young horses are particularly prone to this type of injury, probably because of their more fractious nature and tendency to react strongly to restraint, as well as to lesser strength of the immature skull.[703] The basisphenoid and basioccipital bones form a part of the foramen lacerum and the jugular foramen. Fractures around these foramina may result in dysfunction of CNs IX, X, and XII.[704] Hematomas form at the fracture site and extend into the membranous labyrinths and basilar areas of the brain, where they cause vestibular and occipital cortex dysfunction. Basilar region fractures carry a much more guarded prognosis than trauma at other sites.[703] Blows to the forehead result in depression fractures of the dome of the calvarium and trauma to the underlying cerebrum.

Skull fractures occur in cattle from blows to the top of the calvarium. Most skull fractures are located in the center of the frontal bones, where the internal and external plates of the frontal sinus are fused into a single-layer dorsal wall of the cranial vault. This position can be located on the skull as the imaginary cross found by intersecting lines drawn between the medial canthus of the eye and the horn of the opposite side. Injuries in this area compress the frontal and parietal lobes of the cerebral cortex. The pressure changes result in loss of sensorium, sensory deficits, blindness contralaterally, or convulsions.

In young goats and horned sheep under 4 to 6 months of age, the calvarium can be inadvertently opened by removal of excessive bone during disbudding or dehorning. In goats, cerebrocortical burns can occur from overapplication of a hot iron or caustic dehorning paste. Cortical necrosis caused by bacterial infections after dehorning of calves has also been described.[705]

35.2.23.2 Clinical Signs

The clinical presentation of cerebral trauma depends on the area of the brain damaged, the extent of the lesion, and the duration of the injury.[706] Lesions of the cerebral cortex and thalamus are characterized by variably altered mentation, circling, head pressing, pacing, aimless wandering, and cortical blindness (blindness with normal eyes, pupillary light reflexes, and oculomotor reflexes). Seizures also may result; however, occurrence of a seizure does not necessarily indicate a poor prognosis.[703] Compression of the midbrain results in decerebrate rigidity caused by loss of the reticulospinal tracts. In more severe cases of midbrain compression, abnormal breathing patterns may be observed, together with hyperreflexia, tetraplegia, and absence of pupillary reflexes. Compressive lesions of the mesencephalon in the region of the oculomotor nucleus result in mydriatic pupils on the ipsilateral side of unilateral brainstem lesions. Medulla oblongata compression is characterized by serial dysfunction of cranial nerves, severe disturbance of consciousness, and abnormal respiratory rhythm. Involvement of the long motor and sensory pathways to the limbs can occur with brain injuries at any level and results in ataxia and paresis, which may be worse on the

side contralateral to the injury in the case of cerebral cortex, thalamic, and midbrain injury, or on the ipsilateral side in the case of traumatic damage to the medulla or cerebellum.

Basioccipital fractures of horses result in asymmetric signs of vestibular disturbance, including horizontal or rotary nystagmus, ipsilateral ventrolateral strabismus, contralateral dorsomedial strabismus, head tilt, and contralateral blindness. Horses that remain ambulatory lean or circle toward the side of the lesion. Additional signs of this syndrome include dysphagia, facial paralysis, conscious proprioceptive deficits, recumbency, depression, and coma. Horses that are recumbent struggle violently. Fracture of the petrous temporal bone may cause profuse bleeding from the ipsilateral nares, external ear canal, and guttural pouch.

Brain trauma caused by overaggressive dehorning in goats results in depressed sensorium, loss of menace response, increased extensor tonus on the contralateral side, ipsilateral mydriasis, sluggish pupillary reflex, and loss of conscious proprioceptive responses. The clinical syndrome may be delayed by several days in cases of cortical burns or trauma caused by caustic paste and may be complicated by brain abscess or bacterial meningitis.

35.2.23.3

Pathology and Pathogenesis

The pathogenetic events leading to cerebral edema and increased intracranial pressure (ICP) are complex. Trauma to the head results in a variety of abnormal physical forces exerted on brain tissue, including 1003
acceleration-deceleration, shearing, compressive, tearing, and rotational forces.[706–708] The consequence of 1004
direct physical insult to brain tissue that occurs immediately on impact is considered *primary* traumatic brain damage.[707] Such physical insult results in axonal injuries that may be immediate (primary axotomy), such as axonal tearing, or occur many hours after the initiating event (secondary axotomy).[708] Trauma activates neuronal mechanoreceptors, causing cellular depolarization that spreads outward from the site of impact. Together with direct axonal injury, this may underlie initial signs of concussion, including loss of consciousness.[706,708] Processes that follow the initial mechanical trauma and further exacerbate injury are considered *secondary* brain damage.[707] Intracranial hemorrhage or loss of vascular integrity and cerebral edema occur after concussive blows to the head. Hemorrhage after head trauma may be epidural, subdural, subarachnoid, or intraparenchymal.[707] Displacement of the neural tissue is caused by cerebral swelling or hematoma formation. The increased pressure is transmitted to the CSF and interferes with normal vascular flow, resulting in cerebral hypoxia and interneuronal and intraneuronal edema. Diminution of cerebral perfusion results from a combination of increased ICP, disruption of the vascular architecture, and decreased systemic blood pressure. The net result is reduced oxygen delivery to the brain, a tissue that relies on aerobic glycolysis for the production of energy. Interruption of energy production within the brain results in failure of tissue homeostasis. Breakdown of the blood-brain barrier further contributes to brain swelling and loss of intracranial homeostasis.

In addition to gross damage to tissue, brain trauma results in a complex series of biochemical events that disrupt cellular integrity.[706,709] One of the most important is the depletion of adenosine triphosphate (ATP), the main energy store within neurons. This results in dysfunction of cell membrane ionic pumps, permitting influx of sodium (Na^{+}) and calcium (Ca^{++}) into the cell. Influx of these ions activates a number of secondary pathways within the cell, including the kinin, arachidonic, complement, and xanthine-oxidase pathways. Activation of these pathways results in the production of a variety of substances that are deleterious to cellular function, including oxygen free radicals, vasoactive mediators, cytokines, nitric oxide, excitatory

neurotransmitters, and enzymes. Together, these contribute to a destructive cascade of events that further damages cell integrity.[709]

When brain swelling becomes severe, the respiratory centers are depressed, resulting in hypoxemia and acidosis. The extra carbon dioxide diffuses into the brain, and water follows, which further swells the CNS. Acidosis and hypoxemia also worsen the vascular leakage and hypoxemia. Extreme swelling of the cerebral cortex results in herniation through one or more anatomic sites of the calvarium. Four forms of brain herniation have been described in large animals.[710] These include cingulate gyrus herniation ventral to the falx cerebri, herniation of parts of the temporal cortex ventral to the tentorium cerebelli (caudal tentorial herniation), caudal cerebellar vermis herniation through the foramen magnum, and herniation of the rostral cerebellar vermis ventral to the tentorium cerebelli (rostral tentorial herniation). Compressed tissue becomes hypoxemic and edematous. Compression of the CNS causes more hypoxia, prompting a dramatic and rapid deterioration.

35.2.23.4

Clinical Pathology

Clinical pathologic variables noted after head trauma include nonspecific changes consistent with a stress response, such as mild neutrophilia, lymphopenia, and hyperglycemia, as well as those resulting from systemic trauma, such as elevated serum CK.[703] Hyperglycemia has been associated with more guarded prognosis in people with head injuries, possibly from deleterious effects on cerebral vasculature.[711] In one study of horses that had head trauma, only elevated packed cell volume (PCV) was shown to be associated with a more guarded prognosis.[703]

Collection of CSF from the atlantooccipital cistern is generally contraindicated in head trauma, especially if signs of increased CNS pressure, uncontrolled hemorrhage from the ears or the nose, or dorsal sagittal sinus fractures are observed. Clinical signs that may suggest the presence of increased ICP include dull mentation (especially if this is worsening over time), mydriasis, blindness, or papilledema. The CSF changes that occur from traumatic injuries are characteristic. For the first 24 hours, blood is admixed evenly in the CSF. Iatrogenic hemorrhage from the tapping procedure can be differentiated from that caused by trauma because in the former case, the CSF is irregularly streaked with blood; CNS hemorrhage usually results in an even admixture of blood through the CSF. During the first 24 hours, the protein concentration and WBC count of CSF are elevated and are in the approximate ratio as that of peripheral blood. By 48 hours after the traumatic episode, the amount of blood in the CSF decreases, and when centrifuged, the cell-free CSF appears xanthochromic. WBC counts of the CSF are only marginally increased by 24 hours after hemorrhage, and the protein concentration may range from 500 to 1000 mg/mL (albuminocytologic dissociation). Thereafter, the protein concentration gradually decreases, and the xanthochromia disappears by 14 days after the acute hemorrhage. The number of mononuclear inflammatory cells gradually increases as parts of the CNS degenerate. The CK level of the CSF is elevated (10 to 100 IU/dL) for approximately 1 to 2 days after the acute traumatic episode.

35.2.23.5

Diagnostic Imaging

Radiography or more advanced imaging studies (CT, MRI) are the primary modalities for definitive diagnosis of skull fractures. It should be remembered, however, that significant brain trauma can occur in the absence of skull fracture and that this is a common situation. Radiography has the advantages of being widely available and relatively simple to perform, requiring restraint or only mild sedation in most situations.

However, false-negative findings are common, especially in cases where the bony lesion may be particularly difficult to identify, as with basilar bone fractures in horses.[703] While basilar fractures may be difficult to identify, other radiographic changes such as soft tissue densities in the tympanic bullae due to hemorrhage, or gas opacities adjacent to the basilar region, may support this diagnosis.[711a] CT is the technique of choice for the diagnosis of bony lesions and for acute intracranial hemorrhages, whereas MRI facilitates diagnosis of a variety of pathologic changes within the brain parenchyma. These advanced imaging techniques have limited availability, are costly, and usually require general anesthesia. Clinical findings and historical information may form the sole bases for diagnosis in many cases.

35.2.23.6

Treatment

The treatment of brain trauma remains one of the most controversial areas of clinical neurology in all species. Opinions differ widely and evidence in the scientific literature is often contradictory. Treatments that show promise in rodent models of head injury often are disappointing in clinical trials.[711b] Successful treatment depends largely on early recognition and initiation of therapies that maintain cerebral and whole body homeostasis. General medical principles for treating CNS trauma include (1) establishment of proper respiratory function, (2) support of blood pressure and maintenance of cerebral perfusion and oxygenation, (3) control of seizures, (4) nutritional and fluid support, and (5) protection from decubitus and self-inflicted damage. Many treatment modalities recommended for head-injured large animals are based on anecdotal reports and are not supported by rigorous scientific studies. It is reasonable, however, to apply the principles of head trauma management established in other species, including humans, to the management of larger mammals that sustain similar injuries. Immediate treatment involves establishment of a patent airway and administration of oxygen via mask, endotracheal tube, or nasal catheterization. In cases of severe upper airway obstruction, emergency tracheostomy may be indicated.[711c] Aggressive intravenous crystalloid therapy is indicated to establish and maintain a normal systemic blood pressure and to ensure that the brain receives adequate blood supply, with use of colloids or blood products as necessary. Principles of fluid therapy and treatment of shock are described in Chapter 34.

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Administration of dexamethasone, methylprednisolone, mannitol, or dimethyl sulfoxide (DMSO) has been recommended for controlling CNS pressure caused by edema. The clinician should bear in mind that little or no scientific data exist to support the use of corticosteroids or DMSO in the treatment of CNS trauma, and that these drugs may have deleterious effects that outweigh any potential benefits. Doses listed below are largely anecdotal and are included because of the continued widespread tendency to use these agents, despite lack of evidence that they are effective. Studies of the use of corticosteroids in people with head injuries are ongoing, and the pendulum of opinion continues to swing between positive and negative.[711d] An empiric recommendation for the treatment of horses is administration of dexamethasone at 0.1 to 0.25 mg/kg by slow IV injection every 4 hours for 1 to 4 days or, for mature animals, 100 to 1000 mg of methylprednisolone by slow IV injection.[716] Similar dosages could be used in ruminants.

Data supporting the use of methylprednisolone sodium succinate for treatment of acute spinal cord injuries in people comes from the National Acute Spinal Cord Injury Study (NASCIS). A dose of 30mg/kg bodyweight given by intravenous infusion within 8 hours of injury has been recommended, followed by a second and third dose (15 mg/kg each) given intravenously 2 and 6 hours later and a subsequent infusion of 2.5 mg/kg/hr for the next 48 hours.[717] The use of a similar treatment for head injuries does not yet have good scientific support. In addition, the methodology and results of the NASCIS study have been called into question. The potential deleterious effects of such high doses of corticosteroids in large animal species include enhanced

susceptibility to infection, muscular weakness, renal potassium and calcium loss, abortion in ruminants, and laminitis in horses. These adverse consequences of corticosteroid use probably outweigh its uncertain benefits. Table 35-8 presents a list of antiedema drugs often administered to large animals with traumatic brain disease.

Table 35-8 Recommended Drug Dosages for Treatment of Cerebrocortical Edema

Drug	Dose	Route	Frequency
Methylprednisolone	30 mg/kg	IV	Once
	15 mg/kg	IV	2 and 6 hours after 30-mg/kg dose
	2.5 mg/kg/hr	IV	Constant infusion, begin 6 hours after 30-mg/kg dose
Dexamethasone	1–4 mg/kg	IV or IM	Twice daily
Mannitol	0.25–2 g/kg	IV (20% solution)	Twice daily; monitor plasma osmolality; keep below 350 mOsm/L
Furosemide	1 mg/kg	IV, IM, or SC	Twice daily; monitor plasma, calcium, and potassium
Flunixin meglumine*	1 mg/kg	IV, IM, or SC	Twice daily
Phenylbutazone* (horse)	2–4 mg/kg	IV	Twice daily
Phenylbutazone† (cow)	10–20 mg/kg	PO	Initial dose
	2.5–5 mg/kg	IV	Alternate days
Dimethyl sulfoxide (DMSO)‡	0.5–2.5 g/kg	IV (20% solution)	Twice daily
Acetylsalicylic acid	31.2–62.4 g/500 kg	PO	Twice daily

IM, Intramuscular; *IV,* intravenous; *PO,* oral; *SC,* subcutaneous.

* Monitor patient for gastrointestinal bleeding.

† Half-life of phenylbutazone in plasma of the cow is prolonged. Continuous use of the drug in cattle should be accompanied by careful monitoring of renal function and gastrointestinal bleeding.

† Doses of DMSO ranging from 0.5 to 1 g/kg are most often used. Use only in a well-ventilated area. If intravascular hemolysis develops, dilute DMSO to 5% final concentration. DMSO may be toxic for pregnant humans, and therapeutic efficacy may be limited.

The use of the osmotic diuretic mannitol has regained favor in the treatment of head trauma in humans.[711d] Intravenous administration of a 20% solution of mannitol (1 g/kg) or oral administration of glycerol (20 mL/kg) has been used for the treatment of increased ICP in large animal species. The physiologic activity of mannitol for lowering the CSF pressure may be related more to its vasoconstrictive effects than its activity as

an osmotic diuretic. Response to the treatment may occur as early as 1 hour after administration. Mannitol is expensive and usually only economically justifiable for use in neonates. If response to the initial mannitol dosage is noted, additional treatments should be given every 4 to 6 hours for the first day. Mannitol should be administered through blood administration filter sets to minimize the occurrence of microcrystalline emboli. The drug should not be given to animals with active CNS hemorrhage, because diffusion of mannitol into the center of a newly forming hematoma exerts an osmotic effect, enlarges the size of the lesion, and further attenuates the nervous system tissues. Active CNS hemorrhage can be recognized by the presence of unclotted blood in the nose or ears, or parietal bone fractures that lacerate the dorsal sagittal sinus. Despite this provision, administration of mannitol is probably justified in an animal with rapidly worsening and potentially fatal deterioration in neurologic status, even in the likely presence of intracranial hemorrhage.

Intravenous use of DMSO has been recommended for the reduction of increased CSF pressure in large animals. The drug is administered IV at 0.5 to 4 g/kg twice daily.[701,712,718,719] DMSO is diluted fivefold to tenfold in saline (10% to 20% solution) to minimize the hemolytic and hyperthermic effects. In horses, administration of 5L of 10% DMSO in a balanced electrolyte solution has been shown to have minimal deleterious clinical or clinicopathologic effects.[719a] Higher doses (solutions >20%) have been reported to have a number of adverse side effects such as intravascular hemolysis, colic, diarrhea, muscle tremors, and collapse.[719b] The use of DMSO for cerebral trauma is controversial, and benefits may be species specific. For example, anecdotal reports of benefit have been shown for horses, but controlled experiments in dogs have shown limited clinical benefit when treating experimental CNS trauma.[714]

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DMSO has several beneficial pharmacologic actions, including free-radical scavenging, interference with neutrophil chemotaxis, prevention of microthrombi, increased penetration of corticosteroids and antibiotics into the brain, and vasodilation.[720] A major effect of the drug is probably caused by its diuretic action, which is greater than that of furosemide. In experimental situations, administration of DMSO to animals with experimentally induced CNS lesions resulted in more rapid neurologic recovery than treatment with urea, corticosteroids, or mannitol.[720] The adverse effects of DMSO include muscular fasciculations, intravascular hemolysis, hemoglobinuria, and sweating.[719] Deaths have been reported in laboratory animals after intraperitoneal injections of 10 mg/kg and in dogs after IV dosages of 2.5 mg/kg.[721–723] The median lethal dosage of DMSO in large animals is unknown. The drug is teratogenic when administered to pregnant laboratory animals.[722,723] When the drug is administered IV, approximately 70% of the dosage is excreted through the respiratory tract.[724] These data indicate that DMSO should be administered only in well-ventilated areas. Exposure of pregnant women and animals should be avoided. In cattle, DMSO is excreted rapidly and is essentially completely cleared from the plasma by 5 days.[724] A low-level residue of DMSO may persist in the fat tissues for at least 20 days. When administered IV to horses at 1.0 and 0.1 g/kg, the biologic half-life of DMSO is 8.6 and 9.8 hours, respectively.[719]

Depression fractures of the frontal and parietal bones may be reduced surgically. Lacerations of cerebral tissue can be treated surgically with gentle cleaning and debridement of contaminated and devitalized tissue.[725] Such procedures require general anesthesia. Prognosis in animals with exposed and contaminated brain tissue is very guarded, so expectations should be realistic before such intervention is undertaken. Surgical repair of skull fractures in horses using intrafragmentary wires or bone plates may be indicated to improve functional and cosmetic outcomes.[725a,725b]

Convulsions may be controlled initially by IV administration of diazepam (Valium), phenobarbital, or pentobarbital. The recommended dosages and mode of administration of these drugs are presented in Table

35-7. Good nursing care is essential. These drugs are usually highly protein bound in plasma and can be displaced or functionally altered by other drugs. All anticonvulsant treatments should begin at the lowest possible dosage, which can be increased daily or every second or third day until the seizures have been controlled. If seizures cannot be controlled without causing depression or ataxia, a second anticonvulsant is added. The dosage of the second drug is increased gradually until the seizures stop. This combination treatment is continued for 2 to 4 weeks. Thereafter, the dosage of the first anticonvulsant is tapered until it is discontinued. If seizures reappear, the dosage of this drug is increased until the seizures disappear again. The trough blood concentration of all anticonvulsants is checked monthly. The suggested therapeutic trough concentration of phenobarbital ranges from 15 to 40 µg/mL of plasma and that of diphenylhydantoin from 5 to 20 µg/mL. Any attempt to withdraw anticonvulsant therapy should be done gradually over a 4-week period.

Horses with recurrent convulsions should not be ridden or used for sporting purposes. Infrequent seizures generally do not justify anticonvulsant treatment, and economic considerations often limit the amount of drug therapy that is possible. Status epilepticus can be treated with IV diazepam in 5-mg doses until seizures are controlled or by titrated doses of phenobarbital or pentobarbital. Mares with estral-related seizures may be treated with an ovariectomy.

35.2.24 TRAUMATIC OPTIC NERVE BLINDNESS OF HORSES

Severe blunt trauma to the skull of young horses may result in a rapid caudal displacement of the brain and avulsion or stretching of the peripheral optic nerve. The condition often follows basisphenoid fractures or nonfracturing blows to the poll region (see preceding section). The clinical signs include blindness, loss of pupillary reflexes, and pupillary dilation. Ophthalmoscopic changes in the retina include pallor of the optic discs, reduction in the number and caliber of the retinal vessels, and linear peripapillary pigment disruptions. The condition is permanent.[726]

35.2.25 NERVOUS COCCIDIOSIS

35.2.25.1 Definition and Etiology

Nervous coccidiosis is a neurologic syndrome of calves and yearling cattle, sheep, and goats that is associated with enteric infections by *Eimeria* species. The condition is most often seen in western Canada and the northwestern United States and is especially prevalent in feedlots. The incidence of nervous coccidiosis is highest in the winter months. In contrast to enteric coccidiosis, mortality from nervous coccidiosis can be as high as 72%.[727] The pathogenesis of the encephalopathy may be related to the elaboration of a labile neurotoxin by the parasite.[728] The clinical signs and history of nervous coccidiosis are similar to those of other neurologic diseases that affect the function of the cerebral cortex.

35.2.25.2 Clinical Signs

The onset of the nervous system signs is usually preceded by diarrhea, tenesmus, and hematochezia. Some calves with severe diarrhea develop prolapsed rectums. Initial signs of CNS dysfunction include depression, incoordination, twitching, and hyperesthesia. As the clinical signs worsen, the animal becomes recumbent and develops numerous cerebrocortical signs, including opisthotonos, periodic tremors, horizontal nystagmus, frothing at the mouth, bellowing, snapping eyelids, and muscular fasciculations.[729–732] Blindness

is rarely seen. Stimulation of the patient may precipitate a tonic-clonic seizure.[729–732] The animal may die after 1 to 5 days of encephalopathy. Convulsive calves may regain consciousness but relapse a week later.[733]

35.2.25.3 Clinical Pathology

Fecal flotations from the patient and herdmates show a large burden of coccidial oocysts. Fecal egg counts of affected animals may range from 5000 to 4 million/g. To exclude the possibility of other neurologic diseases, blood should be collected for measurement of electrolytes (calcium, magnesium, potassium). The acid-base status, plasma glucose, and blood lead concentrations should be measured. Acute meningitis and salt poisoning may be ruled out by CSF analysis. The plasma vitamin A concentration should be measured in any animal that has not had exposure to green forage. Polioencephalomalacia, ethylene glycol poisoning, lead poisoning, rabies, petroleum distillate poisoning, and clostridial enterotoxemia should be considered as possible differential diagnoses.

35.2.25.4 Pathophysiology

The pathogenesis of the encephalopathy is unknown. The nervous form of coccidiosis cannot be transmitted to mice by injection of CSF from infected calves; however, a heat-labile neurotoxin has been identified in the serum of calves with nervous coccidiosis.[728] The encephalotoxic activity is precipitable with 30% ammonium sulfate and may have an apparent molecular weight of 300,000 kD.[734] The coccidia do not directly invade the CNS.

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35.2.25.5 Epidemiology

Nervous coccidiosis occurs most frequently in feeder cattle, but dairy and pastured beef calves, lambs, and kids also may be affected occasionally. In one epidemiologic survey the prevalence of nervous coccidiosis was 0.3% of the calves that were affected with the intestinal form of the disease. Nevertheless, outbreaks with a large percentage of calves developing CNS disease have been reported.[729] In western Canada, nervous system signs have been reported in 21% of herd outbreaks of intestinal coccidiosis.[735] Approximately 90% of all cases of nervous coccidiosis occur in January, February, and March.

35.2.25.6 Necropsy Findings

No macroscopic lesions are seen in the CNS of calves with nervous coccidiosis. The microscopic lesions of the brain are mild and nonspecific and include edema, congestion, and occasional shrunken neurons. Parasitic invasion of the ileum, cecum, and colon results in lesions in these organs.

35.2.25.7 Treatment and Prevention

Treatment should include 2 to 4 mL/kg of a commercially available calcium gluconate solution that contains magnesium, given subcutaneously. The coccidial infection should be treated with sulfamethazine (110 mg/kg PO for 5 days, or 1 pound/100 gallons of drinking water), or amprolium (50 mg/kg/day PO for 7 days). Diazepam, sodium pentobarbital, or phenobarbital may be used to control tonic-clonic convulsions (see Table 35-3). Slow IV administration of 50 to 100 mL of a 10% magnesium sulfate solution may also be useful as a sedative. The response to treatment is poor and the case-fatality rate is high (~90%) in calves that

develop tonic-clonic seizures. Specific chemotherapeutic regimens and methods of preventing intestinal coccidiosis are described in Chapter 49.

35.2.26 SPOROZOAN INFECTIONS OF RUMINANTS (*SARCOCYSTIS* INFECTION)

35.2.26.1 Definition and Etiology

The three recognized species of *Sarcocystis* that infect cattle—*S. cruzi, S. hominis,* and *S. hirsuta*—are sporozoan parasites with definitive hosts of dogs, primates, and cats, respectively.[736,737] Three other *Sarcocystis* species—*S. capricanus, S. ovicanus,* and *S. tenella*—have definitive hosts in dogs and secondary hosts in goats and sheep.[738]

When a carnivore ingests flesh from an infected cow, *Sarcocystis* cysts in muscle are broken down by digestive enzymes, and motile bradyzoites are released. The bradyzoites infect the intestinal mucosal cell and differentiate into sexual stages called microgametes (male) and macrogamonts (female). The gametes fuse to form an oocyst, which is shed onto pastures as sporocysts. When eaten by a ruminant, the sporocysts hatch in the proximal small bowel and penetrate into the medium-sized mesenteric arteries, where they enter endothelial cells and form sporozoites. The sporozoites then mature in three successive waves. Each wave of development spreads downstream. The third-generation merozoites finally enter the soft tissues and encyst as sarcocysts. The total period of development in the ruminant requires 10 weeks. The life cycle is completed whenever a carnivore ingests uncooked meat containing viable sarcocysts. Chronic illness in the cow occurs during the maturation of the cyst in the muscles, at approximately 9 weeks after infection.

35.2.26.2 Clinical Signs

Most cases of *Sarcocystis* infestation are asymptomatic in both definitive and secondary hosts. However, if a large number of sporocysts are ingested by a nonimmune ruminant, clinical illness may develop. Clinical signs in cattle usually begin between 9 and 11 weeks after ingestion of infectious sporocysts. These signs include fever (>39.5°C [103.5°F]), anorexia, weight loss, symmetric lameness, and diarrhea. Neurologic signs include ataxia, muscular weakness, tremors, hyperexcitability, hypersalivation, recumbency, tonic-clonic seizures, leg biting, blindness, opisthotonos, and nystagmus.[739,740] Cattle may lose the hair of the tail switch (“rat tail”). Sheep may show a wool break.[736–749] Animals with chronic infections may develop edema of the limbs, poor weight gain, muscular atrophy, and pallor.[736–752] Second-trimester abortions may occur in cattle and small ruminants beginning 28 days after ingestion of infectious sporocysts.[743] The fetuses may appear either normal or autolyzed. Lactating cows may have reduced milk production.[752]

35.2.26.3 Clinical Pathology and Pathogenesis

Prolonged prothrombin times may be observed in some infected animals[736]; however, the activated clotting times and bleeding times are normal. The concentrations of plasma lactate dehydrogenase, alanine transaminase, sorbitol dehydrogenase, and blood urea nitrogen are increased. The packed cell volume (PCV) and the serum protein concentration are decreased. During early infection there is a marked normocytic, normochromic anemia that is characterized by 75% reduction of the blood hemoglobin concentration and reduced PCV.[753–755] The anemia is thought to be caused by extravascular hemolysis.[756]

Antibodies to solubilized freeze-dried *Sarcocystis* antigens have been detected by indirect hemagglutination, enzyme-linked immunosorbent assay (ELISA), and an agar gel immunodiffusion (AGID) test.[757–759] Immunoglobulin M (IgM) responses first occur by 3 to 4 weeks after infection and peak by 11 to 15 weeks.[757–759] The concentrations of *Sarcocystis*-specific IgG begin to rise by 5 to 6 weeks and peak after 11 weeks postinfection, with peak seroreactivity occurring by 39 days after infection. Background titers of normal cattle range from 1:54 to 1:486, and titers of infected cattle often exceed 1:10,000. There is no serologic cross-reactivity between *Sarcocystis* and *Toxoplasma gondii,* despite their physical similarities.[751]

35.2.26.4

Pathophysiology

The pathogenesis of *Sarcocystis* is poorly understood. Pathologic changes in the skin and muscle and in serum chemistry probably are related to a combination of parasite-directed immunologic responses and diffuse vasculitis. Although toxins have not been identified, rabbits die acutely after parenteral administration of purified bradyzoites. The clinical signs exhibited by the inoculated rabbits resemble endotoxic shock. Other studies have indicated that chronic infections result in increased concentrations of somatostatin and decreased concentrations of somatomedin.[760] Abortions probably occur because of luteolysis that results from the increased concentrations of prostaglandin $F_{2\alpha}$, caused by vascular infection by the parasite.[761]

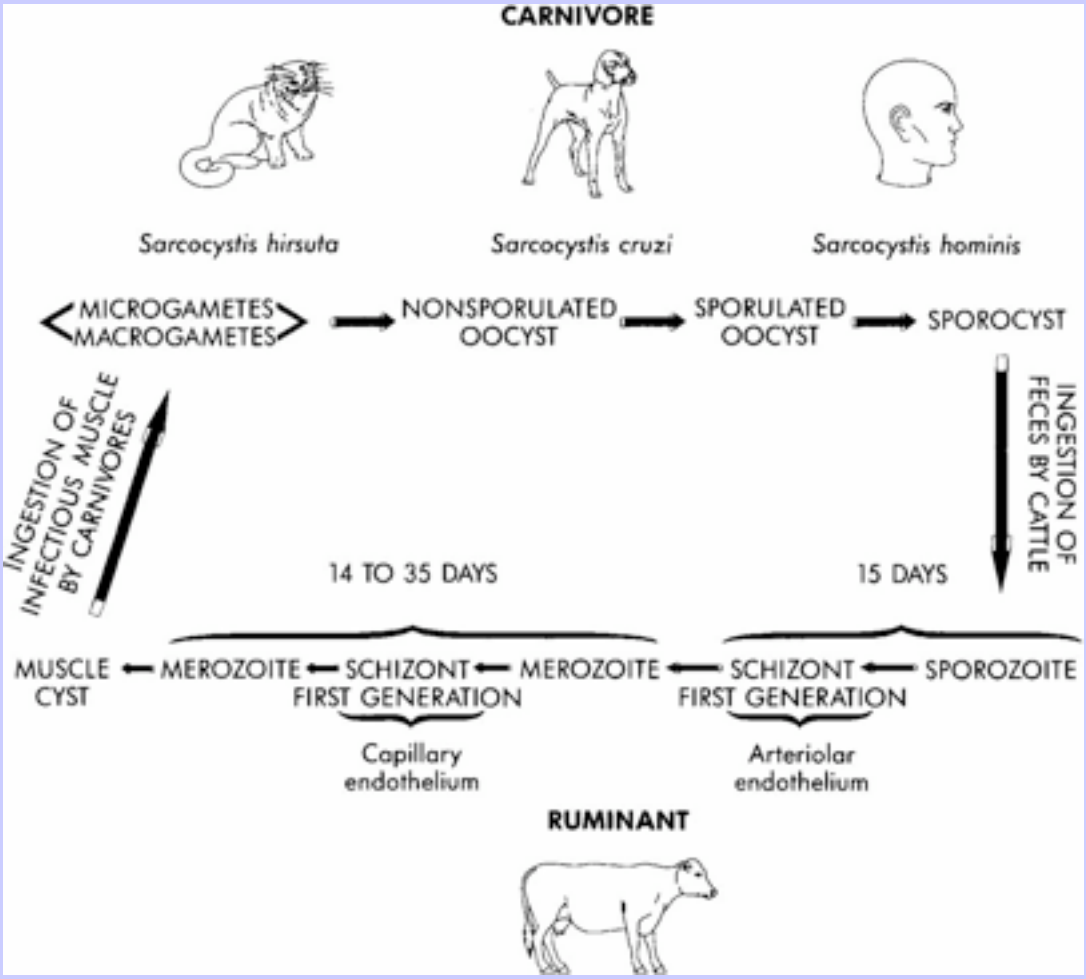
35.2.26.5

Epidemiology

Estimates of infection rates range from 70% to 98% in cattle in the United States.[736] When infected flesh is eaten by carnivores, the encysted sporozoites complete their life cycle[736] (Fig. 35-7). The prepatent period of the parasite in the carnivore (primary host) ranges from 9 to 45 days. The primary host may shed the sporulated oocysts in the stool for as long as 2 months after a single infection. The oocysts withstand freezing but are rapidly killed by sunlight and drying.[736] Reexposure of previously infected canids results in a large fecal output of sporocysts. Ingestion of approximately 250 g of infected meat by a dog can result in an output of 100 to 6000 sporocysts per gram of feces. Wild canids are even more susceptible than domestic dogs and may serve as a major mechanism for propagation of *Sarcocystis* in range cattle in the western United States.

1007
1008

Fig. 35-7 Life cycle of *Sarcocystis* parasite.



Most *Sarcocystis* infestations of cattle are asymptomatic; however, the disease may become clinically apparent with sudden, overwhelming exposure to the parasite in a nonimmune animal. Such conditions occur whenever there is an opportunity for extensive scavenging of ruminant carcasses by carnivores and contamination of feed bunks or pastures with infected carnivore feces.

The economic burden of *Sarcocystis* infection is unknown. One author has estimated an annual loss of $95 million in the United States alone.[736]

35.2.26.6

Pathologic Lesions

The pathologic lesions of the CNS are similar for all species of sporozoans; they include granulomatous meningoencephalomyelitis, focal malacia, perivascular cuffing, neuronal degeneration, and gliosis. The changes are generally most severe in the cerebellum and midbrain but can occur anywhere in the CNS,

including the spinal cord. The pathologic diagnosis is based on finding meronts and merozoites in the affected sections of neural tissue.[762,763]

Pathologic lesions elsewhere include hemorrhages on the sclera, serous surfaces, and muscles; fluid in the body cavities; and lymphadenopathy. The muscles have alternating light and dark stripes. Macroscopic changes may not be evident in animals with chronic sarcocystosis.[741,742] If changes are not evident, postmortem diagnosis is based on the finding of intravascular schizonts or intramuscular hemorrhages without significant inflammation. Ultrastructural examination of affected areas of CNS shows an intracellular colony with rosette orientation of agents in the cytoplasm of infected astrocytes.

35.2.26.7 Treatment

Feeding monensin (100 mg/kg daily for 30 days) during the incubation period is prophylactic; however, the efficacy of the drug in symptomatic cattle is unknown. For maximum effectiveness, monensin should be administered continuously for 2 to 5 weeks after exposure. Treatment of infected sheep with salinomycin (1 to 2 mg/kg) also has been recommended.[764] Administration of amprolium (100 mg/kg once daily for 30 days) may reduce the severity of *Sarcocystis* infection[765] but may not completely eliminate the clinical disease.

35.2.26.8 Control

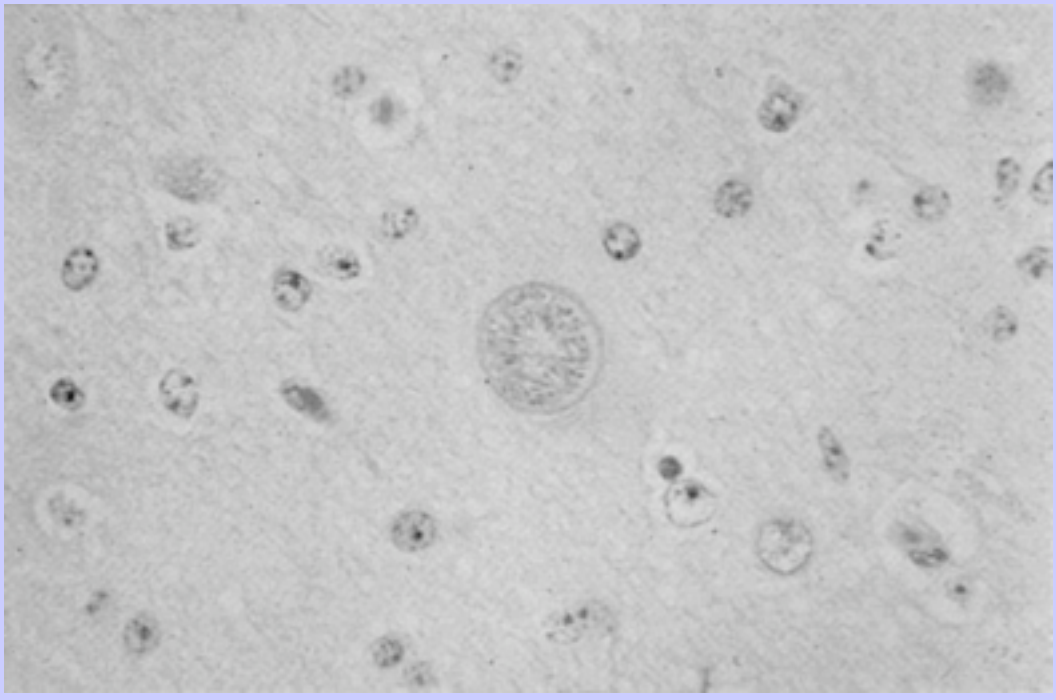
The best method of controlling *Sarcocystis* infection is to protect the food supply of ruminants. Scavenging of carcasses by carnivores should also be prevented by deep burial or incineration. Feed bunks should be kept clean and raised approximately 1 to 3 feet (30 to 90 cm) off the ground. All carnivorous pets that have access to the feed or pastures should be fed cooked meat or processed dry food. In range pasture situations, prophylactic feeding of monensin or elimination of predatory or scavenging carnivores may be necessary.

35.2.27 NEOSPORA INFECTION OF CATTLE (PROTOZOAL ABORTION)

35.2.27.1 Definition and Etiology

A cyst-forming protozoal parasite that closely resembles *Neospora caninum* has been identified in aborted fetuses from cattle in California. The condition is predominantly a disease of dairy cattle; however, sporadic abortions can occur in beef cows.[766–768] The predominant clinical sign of a *Neospora*-like agent is a midterm to late-term abortion (3 to 8 months of gestation). Fetal lesions consist of a focal nonsuppurative necrotizing encephalitis, nonsuppurative myocarditis and myositis, and mononuclear cell infiltrates disseminated in other tissues. Occasionally, calves are mummified. The agent appears to have been responsible for as many as 24% of all abortions in northern California dairy cattle.

Fig. 35-8 Calf with congenital *Neospora* infection of the central nervous system *(left)* and a tissue cyst containing *Neospora* tachyzoites *(right)*.



Occasionally, however, a nonfatal infection may occur in the fetus. In this case the fetus is born with neurologic dysfunction (Fig. 35-8). The clinical signs of neurologic disease vary because of the randomly widespread distribution of the parasite within the CNS. Affected calves are often unable to stand and suckle and have abnormal spinal reflexes. Flexural contractions of the forelimbs, domed skull, and torticollis have also been reported in spontaneously occurring cases.[769,770] The calves are usually born with the CNS signs, which initially are mild but then progress after birth. Pathologic lesions associated with the fetal infection include focal areas of brain discoloration, focal cavitation with cyst formation, and reduction of gray matter. Microscopic changes in the CNS of affected calves include nonsuppurative inflammation of the gray and white matter, demyelination, perivascular cuffing, focal lymphocytic meningitis, and neuronal necrosis. Changes in other tissues include nonsuppurative myocarditis, myositis, and hepatitis. Protozoa can be seen in microscopic sections of the stained tissues.

Neospora organisms have been isolated in pure form using cultured cells.[771] Antibodies have been produced by intubation of laboratory animals, and the agent can be identified microscopically using immunoperoxidase staining on the fixed tissues. The CSF changes in affected calves range from normal to mild pleocytosis.[772] Similar conditions have been described in sheep[773,774] and goats.[775,776]

35.2.28 EQUINE PROTOZOAL MYELOENCEPHALITIS (*TOXOPLASMA*-LIKE AGENT; PROTOZOAL ENCEPHALOMYELITIS; SEGMENTED MYELITIS)

35.2.28.1 Definition and Etiology

Equine protozoal myeloencephalitis (EPM) is a multifocal, progressive disease of the central nervous system (CNS) that is primarily caused by infection with *Sarcocystis neurona*.[777] Recently, another protozoan parasite, *Neospora caninum/N. hughesi,* has been implicated as a cause of EPM in six cases.[778–783] The condition has mostly been reported from many U.S. states, Canada, Panama, Brazil, and Argentina.[784–790] Several reports of the disease in countries other than those in the Western Hemisphere were primarily in horses that originated from the Americas.[791–794] More recently, there have been reports of horses in France that developed neurologic deficits with positive *S. neurona* antibody titers that were native to France and had not resided in the United States.[795,796] Young standardbred, thoroughbred, and quarter horses are most often affected, although horses of any breed may develop the disease. There does not appear to be a gender predilection for EPM, and any age may be affected.[797] The risk would appear to be higher in young horses, but horses as old as 30 years have developed the condition.[797]

The parasite produces inflammation and necrosis of the brain, brainstem, and spinal cord. Under light microscopy, the structure of the EPM agent resembles that of *Toxoplasma gondii,* but comparative electron microscopic analyses of the three agents show differences. The *Sarcocystis* agent of horses has been grown in explant cultures of monolayered bovine monocytes.[787,798] Antibodies in the sera or cerebrospinal fluid (CSF) can be detected using these specimens as probes of immunoblots of the cultured parasites. Sera from clinically affected cases recognized eight *S. neurona*—specific antigens,[799] several of which are the basis for current diagnostic testing. DNA analysis has been very important in characterizing and classifying *S. neurona*. Using a random primed polymorphic DNA assay (RAPD), a unique sequence of base pairs was identified that distinguished *S. neurona* from eight related coccidia, specifically two *Sarcocystis* species, one

Toxoplasma species, and five *Eimeria* species.[800] This research demonstrated that unique DNA sequences could be successfully used as a species-specific probe for *S. neurona,* and that these probes permitted differentiation of *S. neurona* from other coccidia of equines.[800]

35.2.28.2 Clinical Signs

Descriptions of clinical signs of horses diagnosed with EPM may vary greatly because the organisms that cause this disease can affect any CNS tissue. Therefore, any horse exhibiting neurologic abnormality could be diagnosed with EPM.

Clinical signs recognized in the earliest studies of this disease still characterize neurologic abnormalities in horses with EPM. Early workers described horses with EPM as having an asymmetric ataxia and associated muscle atrophy.[801,802] Horses may have a sudden onset of clinical signs, or disease may progress slowly over several months.[801] Vague, intermittent lameness that is nonresponsive to therapy may be caused by EPM, and encephalitic signs typified by asymmetric cranial nerve deficits may also be seen in affected horses.[801] Gait abnormalities in horses with EPM include ataxia, tetraparesis, knuckling, circumduction, and crossing over. The abnormalities may be asymmetric. Depending on the location of the lesion in the spinal cord, areflexia, hyporeflexia, or hyperreflexia may be seen. Infections of the myelencephalon may result in head tilt, facial paralysis, circling, nystagmus, dysphagia, facial paralysis, and apparent blindness, with or without abnormal pupillary reflexes. Parasitic invasion of the ventral spinal rootlets or the radicles of the maxillary branch of the trigeminal nerve may result in neurogenic atrophy of the tongue and masticatory muscles (Fig. 35-9). This is often accompanied by focal areas of desensitization. Regional sweating ("strip sweating") may be observed if the sympathetic tracts of the spinal cord are affected. Although EPM is typified by the presence of asymmetric, multifocal neurologic abnormalities, horses with EPM may have focal or symmetric signs.

Fig. 35-9 Unilateral atrophy of the tongue in a standardbred horse with protozoal myeloencephalitis. Atrophy also may occur in many other muscle groups of the head and the limbs. Courtesy Dr. R.H. Whitlock.

Cerebral signs are rarely seen in horses with EPM. However, three horses with EPM presented to Ohio State University Veterinary Teaching Hospital displayed seizure activity and evidence of cortical electrical activity abnormalities on electroencephalographic (EEG) examination.[803] Horses with cerebral neurologic signs often have a poor prognosis. However, seizure activity in horses with EPM may be treatable. Visual deficits and behavioral abnormalities have been reported in horses with EPM.[804] Head shaking was also reported in a recent case series describing three horses diagnosed with EPM.[805] Head shaking resolved in these horses after treatment for EPM. Recently, urinary incontinence and incoordination have been reported in three horses diagnosed with EPM. Resolution of the clinical signs were mixed in those cases.[806]

Differential diagnoses of the most common neurologic diseases of horses that resemble EPM include equine degenerative myelopathy (EDM), cervical spinal injuries, cervical vertebral stenosis or malformation (CVM), equine herpesvirus type 1 (EHV-1), and equine lower motor neuron disease (ELMND).

Another disease has become the number-one differential for EPM over the last 7 years. West Nile Virus (WNV) was first reported in the United States in 1999; however, the number of equine cases has increased consistently from 25 in 1999 to greater than 14,000 in 2002.[807] Almost all the equine cases in 1999 had been diagnosed with EPM first before a definitive diagnosis of WNV was determined.[808] Asymmetric neurologic deficits with profound weakness and ataxia make it difficult to differentiate WNV from EPM.

35.2.28.3

Clinical Pathology

A Western blot (WB) analysis for the diagnosis of EPM has been described and commercially marketed.[799] Macrophage-cultured *S. neurona* is used as the antigen. After electrophoresis the blots are probed with suspect CSF or serum. Reactions are seen as bands developing on the blotted membrane. The sensitivity and specificity of WB has been reported as 89% based on 295 postmortem examinations.[809] However, these figures are likely based on more severe cases. Although promising, exhaustive examinations of the sensitivity and specificity of the test in clinical cases are not yet available. Recent research suggests that the sensitivity is excellent, but the specificity in current clinical cases is much lower than originally reported.[810] There is no apparent serologic cross-reactivity between the parasites of EPM (*S. neurona* and *N. caninum*) and *T. gondii*. Use of the WB for antibody to *S. neurona* differs depending on the prevalence of the disease in the population studied.[811] If the test is applied in the normal horse population, where the prevalence of EPM is likely less than 1%, the predictive value of a positive test is extremely low (<8%) based on the 89% sensitivity and specificity. However, given the presence of neurologic signs, the prevalence increases dramatically (50% at Ohio State), leading to a positive predictive value of about 90%. This suggests the test should not be applied in normal horses. A recent report demonstrates that the specificity of WB was much lower than originally reported.[812] Another report attempted to demonstrate increased specificity for WB for *S. neurona* antibody detection by blocking the reaction using *Sarcocystis cruzi* antibody.[813] However, a double-blind investigation indicated that this increased specificity is questionable (William J.A. Saville, unpublished data).

Several new diagnostic tests are still measures of reactivity to antigens. Initially, a recombinant surface antigen (SAG1) protein was discovered, and an ELISA test was developed to test horses for *S. neurona* exposure.[814] However, no mention of controlled environment or heat-treated feed in this study makes it difficult to interpret the results. Further development of an ELISA test using a recombinant baculovirus-expressed SAG1 antigen was completed by others.[815] This test was able to detect both naturally and

experimentally infected horses and other species. Another diagnostic test was developed using direct agglutination, the *S. neurona* agglutination test (SAT).[816] In mice the sensitivity of SAT was 100% and the specificity 90%.[816] In California an indirect fluorescent antibody (IFA) test was developed for detection of *S. neurona* antibody.[817] This test was compared with two currently commercially available WB tests, and the results suggested that the IFA was better than either WB test with regard to specificity.[817] Further evaluation of the IFA using both naturally and experimentally infected horses resulted in likelihood ratios that would be useful in diagnosing EPM.[818] The one concern regarding this test is that it may cross-react with horses recently infected with *Sarcocystis fayeri,* another common parasite infecting U.S. horses.[819] Further research with the IFA suggests that using this test on CSF of horses has no benefit if used on the serum in the diagnosis of EPM.[820]

More recently, it has been reported that surface antigens (SAGs) of *S. neurona* are similar to the SAGs of *T. gondii*.[821] The SAGs of *S. neurona* were named SnSAG1 through SnSAG4.[821] Recombinant proteins were developed to the four SnSAGs to produce a set of ELISAs for detection of antibodies to the SnSAGs.[822] Testing these ELISAs with confirmed cases of EPM serum and CSF samples suggested that the SnSAG2, SnSAG3, and SnSAG4 assays would be good tests in the diagnosis of EPM.[822] The ELISA to the rSnSAG1 demonstrated poor sensitivity (68.2%) and specificity (71.4%), likely because of the differences in strains of the parasite, some of which do not express antibody to SAG1.[822] There was also no cross-reactivity when testing horses infected with *S. fayeri* or *Neospora hughesi*.[822] The most recent test developed for diagnosis of EPM has been the *S. neurona*—specific IgM-capture ELISA.[823] This test was developed using samples from previous experimental infection studies performed at Ohio State University.[823] The IgM titers developed and peaked between weeks 2 and 3 postinoculation (PI), and the IgM response waned by 7 weeks PI.[823] The IgM test is still a measure of exposure; however, it indicates an acute infection and therefore may be useful in the early diagnosis of EPM.[823] Further evaluation of this diagnostic test is needed using large numbers of field tests.

Regardless of the tests developed in the past few years, they are primarily still tests of exposure, so diagnosis of EPM is problematic.[824] Therefore, antibodies in serum or CSF must be accompanied by asymmetric neurologic deficits followed by rule-outs of other possible causes of the neurologic deficits.[824]

One of the difficulties in diagnosing EPM is caused by the large number of horses that have detectable quantities of antibody to *S. neurona* in the CSF for several months after therapy, or in horses that do not exhibit neurologic signs. *S. neurona*—specific IgG found in the CSF is assumed to be produced locally because the blood-brain-barrier (BBB) should prevent large molecules from freely entering the cerebrospinal space. However, antibody detected in the CSF could have been produced systemically if the BBB is compromised by disease or if peripheral blood contaminates the spinal fluid during sampling. To help determine whether IgG in CSF was produced locally or resulted from peripheral blood contamination, a series of tests were modified from those used in human patients with neurologic diseases. The albumin quotient (AQ) and the IgG index are calculated using concentrations of albumin and IgG found in serum and CSF of the patient.[825] The AQ is a measure of BBB integrity, and the IgG index is a measure of intrathecal antibody production.[825] Some reports suggest that horses with EPM usually have a normal CSF albumin concentration and a normal AQ, but the IgG index is usually elevated.[826] It has been suggested that these indices, specifically an elevated AQ, can be used to distinguish true-positive WB tests in horses with EPM from false-positive tests resulting from blood contamination during sampling.[826] False-positive results

caused by blood contamination may alter the AQ and the IgG index by increasing the albumin and IgG concentrations in the CSF.[826] It has also been recommended that the CSF indices may be used to monitor the response to therapy for EPM by identifying a decrease in the IgG index that would mark a decrease in intrathecal antibody production over time. However, small numbers of horses were used in the initial evaluation of these tests, with some inconsistencies in the reported results. Although the IgG index did decrease in 9 of 12 (75%) horses treated for EPM, 3 of 12 horses demonstrated an increase in the IgG index.[827] The reliability of the CSF indices has been questioned by others.[828,829] One controlled investigation suggests the CSF indices are inconsistent, therefore, if used, they should be interpreted with caution.[810]

Polymerase chain reaction (PCR) is available to aid in diagnosing EPM.[830,831] The sensitivity and specificity of PCR testing of CSF has been reported to be 83% and 100%, respectively, when histologically confirmed cases of EPM were used to validate the assay.[832] However, other research suggests that the sensitivity of PCR may be only about 40%.[833] PCR requires that parasite DNA be intact. A strong inflammatory response favors enzymatic degradation of parasite DNA, and this process may affect sensitivity of the PCR test. Therefore, PCR may be useful early in the course of the disease and in chronic cases.[832] In addition, PCR analysis of CSF may be insensitive because the parasite is most frequently found in tissues and not floating freely in the CSF. Therefore, parasite DNA may not be present in CSF, even when adjacent tissue is infected.[833] *Toxoplasma gondii* infections are difficult to detect in people for the same reasons.[834] A recent study of clinical cases found that PCR alone was not useful for antemortem diagnosis of EPM based on the low sensitivity (12/151).[829]

Sarcocystis neurona DNA has been detected in blood samples. The presence of DNA in blood samples is thought to indicate recent ingestion of *S. neurona* sporocysts and subsequent infection. However, it is not known how long detectable amounts of DNA remain in the blood stream after infection.[832] Controlled investigations of PCR testing in horses with neurologic deficits as well as in normal horses are required to define the usefulness of this procedure.

Cerebrospinal fluid analysis has been used to aid in determining the etiology of neurologic diseases in the horse. Early studies suggested that horses with EPM had mildly elevated CSF protein concentrations, increases in numbers of mononuclear cells, and mild elevations in CSF enzyme activity (creatine kinase, CK; aspartate transaminase, AST).[835] Two early studies reported marked elevations in the CSF CK activity in horses diagnosed with EPM.[836,837] However, more recent studies suggest that neurologic disease of horses cannot be reliably differentiated based on CSF leukocyte counts, CK activity, AST activity, or protein concentration.[810,838,839]

Several serologic tests have been developed for detection of *Neospora caninum* antibodies in animal species.[840] The three methods currently used are ELISA, IFA test, and direct agglutination test.[840] However, these antibody tests are only measures of exposure to the organism. New diagnostic tests for *N. hughesi* used in experimentally infected equines included a whole-parasite ELISA, a recombinant-protein ELISA, a modified direct agglutination test, and an IFA test, which showed the most consistent results.[841] However, a recombinant NhSAG1 ELISA has been developed that suggests, with a sensitivity of 94.4% and a specificity of 95%, it may be an excellent diagnostic test for *N. hughesi* infections in horses.[842]

35.2.28.4

Pathogenesis and Pathologic Changes

Little is known about the pathogenesis of EPM. It is assumed that the horses ingest *S. neurona* and that the course of infection and disease is then similar to that observed in other host species infected with *Sarcocystis* species. Because the sporocysts of *S. neurona* are passed in the feces of the opossum, infective oocysts likely are introduced into the feed and water supply of intermediate hosts. Once ingested, the sporocysts excyst and release sporozoites, which penetrate the gut and enter arterial endothelial cells of various organs. Meronts develop and rupture the host cell, releasing merozoites into the bloodstream. This is probably followed by a second round of merogony throughout the body. In most *sarcocystis*-like diseases, this process results in the formation of sarcocysts in the muscle. Subsequent ingestion of the infected muscle tissue by the predator or definitive host completes the life cycle. Sarcocysts of *S.neurona* had not been found in affected horses, indicating that the horse is likely an aberrant, dead-end host.[843] However, a recent report suggested that the horse may develop *S. neurona* sarcocysts and therefore may be a natural intermediate host.[844] The fact that 1011
this has been seen only once in the literature is troublesome, and the inability to fulfill Koch's postulates is 1012
also a problem. Horse muscle fed to naive opossums has failed to produce sporocysts after numerous attempts (William J.A. Saville; unpublished data).

Little is known about the life cycle of *N. caninum* or *N. hughesi* in horses. Recent reports have demonstrated that the definitive host of *N. caninum* is likely the dog.[845] At present it is not known if the dog is the definitive host of *N. hughesi*. The dog is the definitive host and also can be an intermediate host, which is similar to *T. gondii* in cats.[840] Unlike EPM caused by *S. neurona,* tachyzoites have been found in horse tissues, as well as tissue cysts in two horses reported to have EPM caused by *Neospora*.[840] In addition, one case of neosporosis in a foal was determined to have been congenitally infected.[780] Congenital infections have not been demonstrated in horses infected with *S. neurona*.

Sarcocystis neurona has been recovered from CNS lesions in several horses and subsequently propagated in culture in the laboratory.[846] When administered to horses parenterally or introduced through the epidural space, cultured merozoites have not induced clinical disease in the horse.[846] The merozoite stage of *Sarcocystis* species is not known to be transmissible to other animals.[846] However, nude mice have been inoculated intraperitoneally with cultured merozoites and subsequently developed evidence of *S. neurona*—associated encephalitis.[847] These mice were immunosuppressed strains, and intraperitoneal injection would not likely be the normal route of infection with *S. neurona* in horses. A better mouse model has recently been developed by feeding sporocysts from feral opossums to interferon-γ knockout (IFN-γ/KO) mice.[848] These procedures in IFN-γ/KO mice also help to differentiate *Sarcocystis* species that are excreted in opossum feces; at least three species appear to be present.[848] The mechanism by which the merozoites enter the CNS is currently unknown. The organism likely enters the CNS through infected leukocytes or through the cytoplasm of endothelial cells.[846] Recent research may help in confirmation of this speculation. When co-cultured with equine peripheral leukocytes, *S. neurona* merozoites penetrated the cells within 5 minutes after starting the culture.[849] This may be the mechanism for entering the CNS. In addition, a microneme protein for host cell invasion has been documented.[850]

There have long been anecdotal reports that the parasite may create immune suppression in the horse. One report demonstrated a strong association between health events and development of clinical signs of EPM.[797] Earlier reports suggested that nitric oxide is important to resistance to intracellular parasites, decreased nitric

oxide was reported in horses with experimental and naturally occurring cases of EPM.[851] Another report indicated that decreased levels of transforming growth factor beta (TGF-β) in CSF of horses may be important in development of EPM.[852] Two recent reports found a decrease in IFN-γ production in lymphocytes from EPM-positive horses compared with negative horses.[853,854] Other studies have corroborated these findings.[855] Two reports in mice suggest that protection against *S. neurona* infections requires CD4 and primarily CD8 cells.[856,857] This phenomenon has been demonstrated in *T. gondii* infections as well.[856,857]

Much more research is needed to elucidate the mechanisms and pathogenesis of *S. neurona* infections in horses.

35.2.28.5

Life Cycle of Sarcocystis neurona

Most specific details regarding the life cycle of *S. neurona* are currently unknown, although recent research has demonstrated that the opossum is likely the definitive host. The geographic distribution of opossums is similar to the geographic distribution of EPM, and areas with lower seroprevalence of *S. neurona* appear to coincide with regions outside the natural range of opossums.[858] Further evidence that the opossum is the definitive host for *S. neurona* was obtained by experimental induction of EPM.[859] When sporocysts from feral opossums were fed to horses, neurologic disease developed.[859] This study has been repeated by other research groups.[860–865] However, induction of clinical EPM by feeding *Sarcocystis falcatula* sporocysts was not successful.[866] More recent work has demonstrated at least three species of *Sarcocystis* sporocysts in feces from the opossum.[867] Other studies suggest that four species of *Sarcocystis* sporocysts may be present in opossum feces.[868,869] Development of DNA probes that distinguish *Sarcocystis* species will better enable researchers to characterize sporocysts from opossum feces, using additional induction studies to help develop a reliable equine model for EPM.

Several recent studies have induced experimental infection in horses with *S. neurona* sporocysts. Initially, in a University of Kentucky study, naive foals were infected with 1×10^6 to 4×10^7 sporocysts orally, which resulted in mild to moderate neurologic deficits. The sporocysts were collected from wild-caught opossums, cleaned, and administered by nasogastric intubation. Unfortunately, the parasite was not cultured from the CNS tissues, resulting in the inability to fulfill Koch's postulates.[859] At the University of Florida, three studies used sporocysts detected using molecular DNA probes.[869] One study administered 1×10^6 *S. neurona* sporocysts and another 5×10^5 sporocysts orally once daily for 7 consecutive days.[864,865] Both studies resulted in mild to moderate neurologic deficits, and no parasite was detected.[864,865] In another Florida study, sporocysts characterized as *S. falcatula* were administered to horses, with no development of neurologic signs and no seroconversion.[866] This study corroborated that the opossum excreted more than one *Sarcocystis* species of sporocysts.[866] Recently, a study at Ohio State University attempted to infect horses using 8×10^4 *S. neurona* sporocysts with three different treatment groups.[863] All nine horses in the infected groups developed neurologic signs; however, the most severe signs (mild to moderate) were seen in horses in the transport stress group. Unfortunately, as in the Kentucky study,[859] Koch's postulates were not fulfilled in the Ohio study.[863]

The previous studies attempted to mimic stress using dexamethasone, but the clinical signs were less severe, and the horses' clinical signs appeared to improve.[859,863,864] In addition, regardless of the dose of sporocysts administered, some horses demonstrated an improvement in their clinical signs with no treatment. These results suggest that horses are capable of clearing large numbers of these organisms. Those findings may explain the high number of CSF antibody-positive horses with no evidence of neurologic deficits. Equally troubling, after orally inoculating horses with 1×10^8 *S. neurona* sporocysts, clinical signs of neurologic deficits were readily detectable; however, no parasite was found in the CNS at 7 or 14 days postinfection (PI) (W.J.A. Saville and J.P. Dubey, unpublished observations). In the natural intermediate host, the raccoon, *S. neurona* was readily detectable in the CNS 7 days PI.[870]

Additional infection studies have been attempted in horses. A horse with severe combined immunodeficiency disease (SCID) received characterized sporocysts of *S. neurona* orally. Although a parasitemia was detected in this horse, the first detection of the parasite in an experimentally challenged horse, the horse did not develop evidence of neurologic dysfunction. This suggests that development of clinical signs of EPM requires an intact immune system, which also supports anecdotal evidence that EPM is a neuropathologic disease in horses.[860,871]

Studies at Ohio State University (OSU) have further characterized *S. neurona* infection in horses. The infectious sporocysts were produced using laboratory-raised opossums and infected raccoons and the life cycle as previously reported.[870,872] The second trial was done to determine the effect of sporocyst dose on development of clinical signs of EPM.[862] Horses in the group that received 1×10^6 sporocysts seroconverted earlier and developed more consistent clinical signs than those infected with lower doses of sporocysts. Horses were transported a second time and developed worsening clinical signs after residing at the Veterinary Teaching Hospital at OSU.[862] Therefore, another trial was carried out testing the effect of a second transport after infection with sporocysts immediately on arrival at the first study site.[861] The results demonstrated more significant clinical signs in the horses not transported a second time, refuting the hypothesis from the 2002 study. Neither the 2002 study nor the 2004 study resulted in detection of the parasite in the tissues of infected horses. Another study, in 2005, demonstrated that *S. neurona* could be detected in the blood of an experimentally infected, immunocompetent horse.[873] The horse had been infected daily for 98 days, and *S. neurona* was detected from the blood of one of six horses tested, demonstrating that the parasite could be detected in immunocompetent, experimentally challenged horses.[873] Because of the lack of parasite detection in equine infection models at most sites, researchers at OSU decided to attempt culture early in the infections rather than at the end of the infection period. Eight naive horses negative for antibody to *S. neurona* were included; six were infected with sporocysts derived from laboratory production using the opossum-raccoon cycle, and two were control animals.[874] Parasite was cultured from mesenteric lymph node, liver, and lung at 1, 2, and 7 days PI; 2, 5, and 7 days PI; and 5, 7, and 9 days PI, respectively.[874] Although no parasite was detected in CNS tissue, evidence of infection was present at 7 and 9 days PI.[874] This recent OSU study was able to fulfill Koch's postulates and shows evidence that the parasite can invade the tissues very quickly after ingestion, as demonstrated in previous studies in two different species of animals.[844,848,870] Further work needs to be done to examine an equine model for the disease.

Unlike most *Sarcocystis* species, *S. neurona* may aberrantly infect a large number of intermediate hosts. Although the full range of intermediate hosts for *S. neurona* has not yet been identified, several species of animals and birds have been reported to exhibit symptoms similar to those seen in horses with EPM. Several reports indicate that an *S. neurona*—like organism infected and caused neurologic disease in dogs, sheep,

cats, mink, raccoons, a striped skunk, a golden hawk, Pacific harbor seals, sea otters, chickens, a Grant's zebra, Canada lynx, and a Fisher.[875–888] The harbor seals and sea otter had evidence of sarcocysts in the muscle that were *S. neurona* positive.[878,879] This seems to be the first evidence for potential *S. neurona* sarcocysts to date, although the significance of this finding was not well understood. This positive reaction to anti—*S. neurona* antibody could be caused by cross-reactivity to other *Sarcocystis* species. A recent report indicates that *S. neurona* cycles normally between the opossum and various intermediate host species. Even though the opossum is the definitive host and does shed the parasite in its feces, the opossum does not develop antibodies to *S. neurona*.[889] Sarcocysts are found in the muscles of five species: infected domestic cats *(Felis domesticus),* nine-banded armadillos *(Dasypus novemcinctus),* striped skunks *(Mephitis mephitis),* raccoons *(Procyon lotor),* and sea otters *(Enhydra lutris nereis)*.[872,890–893] It was thought that the domestic cat was only a laboratory intermediate host, but studies in Missouri and Ohio suggest that the cat is a natural intermediate host as well;[895,894] this also seems to hold true for the striped skunk.

Recently, the life cycle of *S. neurona* has been completed in the laboratory.[892] Previous reports of serum prevalence of antibodies to *S. neurona* in striped skunks suggest that they are likely a natural intermediate host as well.[896] When muscle from wild-caught raccoons and road-killed armadillos was fed to laboratory-raised opossums, it resulted in shedding of sporocysts infective for ponies, horses, and IFN-γ/KO mice.[872,891] High seroprevalence of *S. neurona* antibodies in armadillos tested (100%) from three states and raccoons (57%) tested from four states supports that these two species are natural intermediate hosts.[891,897] After ingestion of the infected muscle, opossums shed sporocysts in their feces. Small numbers of sporocysts were found after feeding sea otter muscle, but the sporocysts were infective for IFN-γ/KO mice.[890] The role of the sea otter as a natural intermediate host is likely limited because it is a marine mammal. Results of these life cycle studies demonstrate that many species may be potential intermediates hosts for *S. neurona*. This wide host range is atypical for *Sarcocystis* species. This host range behavior is similar to that of *T. gondii,* which is phylogenetically close to *S. neurona*.[898,899]

Based on the number of intermediate hosts determined so far, a number of isolates of *S. neurona* are postulated to exist. Recent work found that there are differences between South American and North American isolates.[900,901] Also, evidence indicates that the U.S. group could be divided into northern and southern U.S. groups, which suggests geographic groupings. Other work has demonstrated differences in the SAG1 gene in different isolates of *S. neurona*, with 73% to 100% sequence similarity.[902] This is in contrast to the SAG1 gene of *Neospora* species, with 96% to 98% similarity.[902] These differences in the isolates was confirmed when monoclonal antibodies developed against immunodominant proteins of *S. neurona* failed to detect all isolates.[903]

Based on the estimated numbers of opossums in North America, the poor survival rate of these animals, and the small areas in which they travel, *S. neurona* may be transmitted by routes other than direct contact with opossum feces. Experiments performed by researchers in the 1980s indicate that some transmission may occur through birds.[904] In experiments attempting to characterize the life cycle of *S. falcatula,* birds were apparently infected by aerosol spread.[904] Vector transmission was also demonstrated by the recovery of sporocysts after budgerigars, canaries, white mice, and chickens were fed opossum feces.[905] The recovered sporocysts were then fed to budgerigars to assess the viability of the sporocysts. Four of six budgerigars died, demonstrating that the sporocysts were viable. These experiments suggest that sporocysts might be transmissible between intermediate hosts. Considering the apparent wide range of natural and aberrant intermediate hosts for *S. neurona* and *S. falcatula,* transmission of infectious organisms between intermediate

hosts implies that control of disease caused by these organisms may be extremely difficult. Insects such as flies and cockroaches may also be transport vectors for *S. neurona*. Early work demonstrated that flies and cockroaches may act as transport vectors for *T. gondii*.[906,907] In addition, fatal pulmonary disease developed in psittacine birds fed cockroaches after the cockroaches had been fed opossum feces.[908] Although this suggests that insects may play a role in transmission of *S. neurona*, further investigation is necessary to determine which insects are actually involved in its life cycle.

Stress may play a role in the development of EPM,[843,899] but limited evidence is available to support this hypothesis. The severity of EPM may be related to the size of the infective dose, immune competency of the host, and the environmental stresses to which the horse is exposed.[846] A similar association between immunosuppression and disease has been documented in other species with EPM-like symptoms. For example, recent mouse models have been developed for EPM using nude mice and IFN-γ/KO mice, both of which are immunocompromised strains.[847,848] Raccoons have been identified that were concurrently infected with a *Sarcocystis*-like protozoan and canine distemper virus (CDV).[884,909] Interestingly, CDV is known to 1013
be immunosuppressive and has often been associated with cerebral toxoplasmosis in dogs, foxes, and 1014
raccoons.[909] Immunocompromised people are often infected with *T. gondii,* and stress plays a major role in the recrudescence of the clinical signs of *T. gondii*—associated encephalitis.[910] Infections with either *N. caninum* or *T. gondii* can cause T-cell hyporesponsiveness to the parasite antigen. It has also been demonstrated that an intact T-cell response, specifically, appropriate interleukin-12 (IL-12) and IFN-γ production, is necessary for resistance against either *N. caninum* or *T. gondii*. The parasite may therefore facilitate further infection by compromising host immune responses.[911] Recent evidence suggests that neuropeptides called neuroimmune proteins (NIPs) are released from the CNS when an animal is stressed, which may lead to suppression of lymphocyte production and function.[912] Stress leads to high circulating glucocorticoid concentrations, which are also immunosuppressive.[912] The combination of high resting concentrations of glucocorticoids and an increase in NIP release may result in immunosuppression and facilitate development of clinical disease in horses infected with *S. neurona*. Recent evidence from a controlled investigation at OSU demonstrated that health events before diagnosis of EPM were strongly associated with the disease.[797] Transport stress and induction of the disease in an experimental equine model provide supporting evidence that stress may play a role in the pathogenesis of EPM.[863] It has long been known that transport is a stressor in horses and other species.[913–917] Horses are transported year-round to equestrian events in the United States, sometimes across the country and to other countries. Further controlled investigations are needed to examine the role of stress in the development of clinical signs of EPM in horses.

35.2.28.6

Diagnosis

The diagnosis of EPM has been difficult because of a lack of understanding regarding its pathogenesis and the variety of clinical signs. Postmortem examination was the first method used to diagnose EPM definitively, and many still consider it the “gold standard” for diagnosis. Grossly, the CNS lesions identified postmortem are described as multifocal areas of hemorrhage to light discoloration of the brain or spinal cord.[843] Histology often reveals a marked mononuclear perivascular cuffing with necrosis and loss of neurons, with infiltration of monocytes, lymphocytes, some eosinophils, and rarely, neutrophils.[802,835] Protozoan organisms can be seen in some of the lesions but are often difficult to detect.[835] Difficulty in detecting the organisms increases if the animal has been treated with antiprotozoal medications.[918] Immunohistochemical

staining techniques can be used to identify parasites definitively in situ.[919,920] Postmortem examination is also the definitive diagnostic test for EPM caused by *N. caninum (N. hughesi)*.[840] Inmmunohistochemistry is also a useful tool for identification of the *Neospora* organisms.[840] However, a significant problem with this diagnostic method is that, by definition, it cannot be applied in horses antemortem and therefore cannot be applied to most clinical cases. A reliable diagnostic test that can be used for antemortem diagnosis is needed to better understand EPM and appropriately manage horses with this disease.

35.2.28.7

Epidemiology

Little is known about the epidemiology of EPM, although more and more knowledge is being accumulated about this disease.

A small study from one county in Pennsylvania indicated that the seroprevalence was approximately 45% of the horse population (95% confidence interval, 36.3% to 54.3%), and prevalence increased with age.[921] Another report found an overall seroprevalence of 45% among horses in Oregon, with differences in seroprevalence among geographic regions.[858] In Oregon the seroprevalence ranged from 22% in the eastern arid region of the state to 65% in the coastal region. A third study reported a 53.6% prevalence of serum antibodies to *S. neurona* in Ohio horses.[922] The Ohio study demonstrated an increase in prevalence with age of the horse, and greater prevalence in southwestern Ohio versus northeastern Ohio. The geographic differences in Ohio may have been related to climatic differences and freezing days in various regions of the state.[922] These studies suggest that in many areas of the United States, approximately 50% of the horses may have serum antibodies to *S. neurona*.[923] Another study suggested horses are exposed to *S. neurona* in the eastern half of the United States at a rate 10% to 15% higher than the exposure rate in the western half of the country.[832] More recently, antibodies to *S. neurona* were found in 33.6% of various equid serum submitted to a laboratory in Colorado. As previously reported, the prevalence increased with age; prevalence was 26% in horses age 1 to 5 years versus 37% in 10-year-old horses.[924] Seroprevalence was lowest during the colder months, as reported previously. Another report on seroprevalence of *S. neurona* in horses demonstrated 27% in California, 28% in Florida, 54% in Missouri, 0% in Montana, and 0% from New Zealand.[925] A Michigan study indicated a seroprevalence of 60%, with lower rates in colder areas, which corroborates earlier findings.[926] Another study tested two populations of horses for *S. neurona* antibodies: the wild horse population in Wyoming and horses from western Canada.[927] Using the WB test yielded 18 of 276 Wyoming horses positive and 0 of 243 Canadian horses. These results are difficult to interpret in the Wyoming horses because of the range of the opossum; the Canadian results fit with its range. Two recent reports suggest that the seroprevalence of *S. neurona* antibody in horses in Argentina and Brazil are 35.5% and 35.6%, respectively.[784,785] Another recent study examined *S. neurona* exposure in Brazilian horses using an rSnSAG4 ELISA, resulting in a seroprevalence of 69.6%.[928] Another study examined American-born horses exported to India for *S. neurona* exposure.[929] Of the 86 horses tested in this study, 42 were still positive, even though some of the horses had been in India for 13 years. This work suggests that antibody to *S. neurona* has an extremely long half-life, or that chronic infection occurs with this parasite.

These results suggest that exposure to *S. neurona* is common, but that geographic differences may exist.

Little work has been performed regarding the prevalence of antibody to *N. caninum/N. hughesi* in horses. However, recent work found a seroprevalence of 23.3% in sera examined from two U.S. horse slaughterhouses and a lack of antibody detection in Argentina and Brazil.[784,785,930] Because of the low

numbers of horses involved, these studies may not reflect the true prevalence of *N. caninum/N. hughesi* antibody in horses. A more recent study found seroprevalence to *Neospora* of 2% to 3% in Missouri and California.[925] Antibodies to *N. caninum* were found in 31.1% of Wyoming horses.[927] However, testing of the Brazilian horses using the rNhSAG1 ELISA demonstrated a seroprevalence rate of 2.5% for *N. hughesi*.[928] Based on these varying results, More work is needed regarding *N. caninum/N. hughesi* exposure.

No formal studies on the incidence or prevalence of EPM in the United States have been done until recently. Based on the number of cases diagnosed postmortem at the University of Kentucky, the incidence of EPM may be increasing.[846] The number of samples submitted for immunoblot analysis suggests that several hundred new cases of EPM might be diagnosed in the United States each year.[846] The estimated incidence of EPM based on accessions to the University of Kentucky diagnostic laboratory was 1% or less of all horses each year.[843] The number of U.S. cases has only recently been enumerated by the U.S. Department of Agriculture (USDA), which provide a baseline for future reference. Based on the USDA study, the average incidence of EPM was 14 ± 6 cases per 10,000 horses per year.[931] The incidence was examined based on primary use of the horse in the operation, and the lowest incidence was found in farm/ranch horses (1 ± 1 cases/10,000 horses/year). Incidence in pleasure horses increased to 6 ± 5 cases/10,000 horses/year. A marked increase followed in breeding horses (17 ± 12 cases), racing horses (38 ± 16 cases), and competition/show horses (51 ± 39 cases). The racing horses did not include horses at racetracks. These estimates reflect a similar incidence of EPM as previously reported, if not lower, and provide a baseline for the future.

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Regarding the incidence of neosporosis in horses, no controlled investigations have been performed. There have been six reports of neosporosis in horses caused by *N. caninum (N. hughesi)*.[778–783] However, only four cases were in horses with neurologic signs, one was in an aborted fetus, and one was related to an intestinal problem.

Equine protozoal meningoencephalitis has been reported from a number of U.S. states, as well as from Canada, Mexico, Panama, Argentina, and Brazil.[784–790] EPM has also been reported in England among horses imported from the eastern United States.[794] EPM was diagnosed in an 8-month-old Arabian horse in South Africa that had been imported from the United States approximately 5 months before the onset of signs.[793] The most recent report was a California horse that developed clinical signs of EPM after 10 months in Hong Kong.[792] An American-born horse developing EPM has also been reported in Japan.[791] Neurologic disease has been reported in horses in France, both American-born horses and horses native to France.[795,796] EPM is thus primarily a disease of the Western Hemisphere.

Several authors have suggested prevalence of disease may be high among standardbred horses.[801,802,918,932] However, two of these authors also suggested that this apparent predilection may be caused by the environment in which horses were kept rather than breed characteristics.[801,918] Another case series reported that disease was most common in thoroughbreds.[788] A controlled investigation into risk factors for development of EPM did not find a breed predilection, but occupations such as racing and showing demonstrated increased risk compared with breeding and pleasure horses.[797] This finding was corroborated by the recent National Animal Health Monitoring System (NAHMS) study.[931]

Early reports on EPM suggested that young horses had an increased risk of disease.[788,802,918] A consistent theme among reports was that at least 60% of the affected horses were 4 years old or younger. An OSU study

also found increased risk in young horses, although increased risk was seen in horses older than 13 years as well.[797]

Historically, EPM has been reported as a "sporadic" disease; more than one case is rarely reported on farms.[801,933] In reports of EPM cases from Panama, all affected horses were stabled at the same location, although this is not a common occurrence.[787] Also, an outbreak was reported on a farm in Kentucky.[934] An Ohio study suggested an increased risk for EPM if the disease was previously diagnosed on the farm (>2.5 times higher), which suggests clustering of cases may occur.[797]

Several other risk factors for development of EPM have been reported. The Ohio study found an increased risk if opossums were seen on the farm and with the presence of woods on the farm, seasonal effect, or a health event before development of clinical signs of EPM.[797] The seasonal effect increased the risk of EPM as the temperature increased, with the highest risk in the fall.[797] Risk decreased if a creek or river was present on the farm and if the feed was kept protected from wildlife access.[797] The NAHMS study found an increased risk if opossums were seen (vs. never seen) on the premises and even higher risk if the opossums were seen frequently.[931] Risk also increased with increased numbers of horses, purchased versus homegrown grain, use of wood chips or shavings as bedding, presence of rats and mice on the premises, and increased human population density. A lower risk was seen when woods were within 5 miles of the premises and when surface water was used as the primary drinking source. As in the Ohio study, the highest risk for disease was in the fall of the year. It is difficult to explain some of the findings from these studies, but management apparently plays a role in development of clinical EPM.

Recent results demonstrate that transplacental transmission of both *S. neurona* and *N. hughesi* is unlikely. After following horses at three breeding farms in California and one farm in Kentucky, investigators concluded that there was no detectable risk of transmission of either parasite.[935]

35.2.28.8

Treatment and Prognosis

Because of the slow development of a consistent equine model for induction of EPM, and because clinical patients require medication due to the severity of the disease, treatment regimens have evolved empirically. Until recently, recommended therapy had not changed since EPM was originally identified. However, recent use of liquid combination therapies with questionable stability resulted in a lack of response and consistently longer duration of treatment. This has led to the development of novel treatments.

The standard therapy for horses with EPM is a combination of sulfadiazine and pyrimethamine, both antifolate medications. Based on the description of the pathologic lesions of EPM and identification of organisms that resemble *T. gondii,* the first recommendations for treatment of EPM were extrapolated from therapy used to treat toxoplasmosis in humans.[936,937] Numerous changes have since been made with regard to dosage and duration of the therapy.[896,933,938,939] Most recommendations were empirically based on clinical impressions rather than controlled clinical trials.[896] More recently, some therapeutic recommendations have been based on pharmacokinetic data.[940,941] One study tested pyrimethamine, trimethoprim, sulfonamides, and combinations of these drugs against *S. neurona* merozoites in tissue culture.[942] Pyrimethamine was demonstrated to be completely inhibitory and coccidiocidal at 1.0 μg/mL. The same was true for trimethoprim at 5.0 μg/mL. None of the sulfonamides alone had activity at 100 μg/mL. Sulfonamides (5.0 or 10.0 μg/mL) in combination with pyrimethamine (0.1 μg/mL) improved activity against

S. neurona.[942] However, these findings are based on in vitro studies, and further work is needed in controlled clinical trials in horses. Controversy surrounds the duration of therapy required to treat horses with EPM effectively; initially, recommendations were based on clearing of specific IgG from the CSF, as indicated by a negative WB. However, many horses remain CSF positive for antibody to *S. neurona* for months after therapy. Many clinicians have adopted the recommendation that the medications be continued at least 2 weeks after resolution of signs or 4 weeks after a plateau of the clinical signs. Current recommendations for the pyrimethamine/sulfadiazine combination is 20 mg/kg of sulfadiazine once or twice daily and pyrimethamine at 1 mg/kg daily orally for at least 150 to 180 days. Horses with EPM are often treated for long periods with medications that act by inhibiting folate metabolism. Some suggest that complete blood counts should be monitored for signs of folic acid deficiency in horses treated for EPM. Potential side effects of treatment with antifolate medications include bone marrow suppression, anemia, colitis, and even teratogenesis. Most of the anemias are mild and improve after withdrawal of the medication. One other side effect of trimethoprim-sulfamethoxazole and pyrimethamine, a commonly used combination in the past, is its effect on reproductive function in pony stallions.[943] Although it may not affect semen quality, testicular volume, sperm production efficiency, erection, or libido of healthy stallions, it may induce changes in copulatory form and agility and alter the pattern and strength of ejaculation.[943] Therefore, caution should be used when treating stallions for neurologic disease believed to be EPM.

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Recently, triazine derivatives have been used to treat EPM. Two of these drugs, diclazuril and toltrazuril, were originally designed for use as herbicides and have been used in other countries in the prophylaxis of coccidiosis in poultry and swine. The response to therapy in horses with EPM was slightly better than the response documented for the standard therapy.[944] The pharmacokinetics of both diclazuril and toltrazuril have been demonstrated.[945] Currently, diclazuril is only available as a ration premix, so large volumes must be given daily. Another disadvantage is the poor palatability of diclazuril in its present form. One advantage to use of these compounds is an appreciably shorter duration of therapy. Diclazuril is administered at 5 mg/kg for a minimum of 28 days.[946] Recent in vitro testing for activity of diclazuril against *S. neurona* has been demonstrated.[947] Diclazuril may need to be administered by nasogastric tube daily.[946] Toltrazuril is another coccidiostat becoming increasingly popular because of its ease of use and good absorption orally in horses.[948] Toxicity studies of toltrazuril in horses at 50 mg/kg for 10 days resulted in mild anorexia and depression.[949] The current recommended dose is 5 to 10 mg/kg for a minimum of 28 days.[946] Further in vitro evidence indicates that ponazuril, a metabolite of toltrazuril, is effective against *S. neurona*.[950]

Nitazoxanide (NTZ) is another novel treatment recently used in the treatment of EPM. NTZ is a 5-nitrothiazole with a broad spectrum of activity against bacterial, protozoal, and helminthic parasites.[946] It has been shown to kill *S. neurona* in cell culture.[946] Toxicity studies showed that when horses were given two times the recommended dose, they became lethargic after 1 week of daily dosing.[946] When horses were given NTZ at four times the recommended dose, they became significantly ill, with one death.[946] At present, the suggested dose schedule is 25 mg/kg once daily for the first week and 50 mg/kg once daily for the next 23 days.[946] Two of these three new EPM medications, Marquis and NTZ, have been approved by the U.S. FDA.

The prognosis for horses diagnosed with EPM is similar regardless of the treatment used. Most reports suggest an approximate improvement rate of 70% when using the standard therapy,[804,951,952] but earlier work suggested the success rate of therapy was about 50%.[939] Less than 25% of affected horses may return to their original function, although little objective information exists on this issue.[804] A recent study with

diclazuril resulted in approximately 75% improvement in horses severely affected with EPM.[944] In the diclazuril study, approximately 30% of the horses (11/36) treated either returned to their original level of performance before EPM diagnosis or improved their level of performance.[944] An efficacy study of 70 horses given NTZ found 63% of the horses met the criteria for success after treatment.[946] A growing concern is the percentage of horses which have a relapse in clinical disease after cessation of therapy. Some horses will relapse days, weeks, or even months after cessation of therapy, but the mechanism of relapse is unknown.[896] Relapse may be caused by recrudescence of a truly latent stage of the parasite, presence of a small, persistent focus of infection, or perhaps reexposure to the parasite.[896] Anecdotal estimates of the relapse rates range from 10% to 28% of treated horses.[804,951,952] In a controlled study performed at OSU, relapse rates were 19%, close to previous anecdotal reports.[953] The relapse rate using diclazuril for the treatment of EPM was less than 5%.[944]

Identification of protein activity in *S. neurona* merozoites has demonstrated two potential targets for therapy, including serine protease and enolase.[954,955] In the future, better treatments might be developed against certain proteins to remove or reduce relapse rates and improve the resolution of clinical signs of EPM.

Before recognition of EPM, corticosteroids were widely recommended for treatment of neurologic diseases in horses. However, corticosteroids should be used with caution in horses with suspected EPM because the host immune response to the organism could be adversely affected.[789,794,936,937] NSAIDs and DMSO have also been routinely used in the treatment of horses with EPM since the mid 1980s.[794,804]

Because antibody to *S. neurona* persists in CSF for long periods in some horses with EPM, and because some horses may not mount a sufficient immune response to clear the organism, immune stimulants (nonspecific T-cell—stimulating compounds) have been recommended.[804] Unfortunately, no controlled trials have examined the efficacy of these treatments.

Supplementation with folic acid, folinic acid, and brewer's yeast has been recommended for treatment of presumed folic acid deficiency, particularly in pregnant mares.[794,939] However, folic acid supplementation has been discouraged by other investigators because of poor absorption and the potential for toxic effects on bone marrow activity.[804] Toxicity has also been reported in newborn foals born to mares that were treated for EPM with antifolate medications and concurrently supplemented with folic acid.[956] These foals showed evidence of bone marrow aplasia and hypoplasia, renal nephrosis or hypoplasia, and skin lesions. Another case report involved an adult horse being treated for EPM.[957] A cause-and-effect relationship between folic acid supplementation and these developmental abnormalities has not been conclusively demonstrated. At present, however, folic acid supplementation should not be used, particularly in pregnant mares, until controlled clinical trials can be performed to corroborate or refute these findings.

Use of additional supplements, such as vitamin E and thiamine, that may facilitate healing of nervous system tissue have been recommended for treating horses with EPM.[804,951] However, clinical trials have not been performed to establish the efficacy of this supplementation.

35.2.28.9

Prevention

Based on the proclivity for transportation to equestrian events and the nature of the horse business, prevention of clinical cases of EPM will be difficult. A complicating factor is that the parasite is widespread

throughout much of the United States. A killed—*S. neurona* vaccine was developed and released on a conditional license in 2000. The vaccine has been shown to induce both humoral and cell-mediated immunity in the horse.[958] However, efficacy of the vaccine to prevent EPM using an equine model have not been completed to date. Because development of other parasite vaccines is extremely difficult, efficacious vaccines most likely will not be developed for many years.[949–962]

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Based on age as a risk factor for the disease, close monitoring for evidence of neurologic disease in high-risk age-groups (young horses, old horses) may help detect EPM early. The seasonal risk for EPM should raise the index of suspicion that it may be the cause of the clinical signs when horses are presented for neurologic disease in the warmer months. This seasonal risk factor is compounded by many major horse competitions occurring in the fall. Therefore, monitoring of horses subsequent to transport and competition may be helpful. Access to feed and water by wildlife (opossums) and pests (mice, rats) should be restricted by using rodent-proof containers, which may help to prevent some cases of EPM. Forages should also be protected from wildlife access by keeping the forages in enclosed facilities to prevent access to opossums.[797] Some research suggests that preventing bird access to facilities may help to prevent some cases of EPM, although it is not known what role birds may play in its pathogenesis. Ingesting sporocysts may result in passage through the intestinal tract of birds and may be infective for other species of wildlife or horses.[904,905] Horses may develop EPM after some other health event, as confirmed by a recent controlled investigation.[797] Therefore, monitoring of broodmares close to foaling and horses that develop a major illness or injury is important because it may assist in the early diagnosis of EPM cases.

Focusing prevention on manipulation of risk factors for the disease, such as keeping opossums out of the feed and water, is very important. However, one also must consider the intermediate host's role in EPM. As discussed previously, several species of mammals have been reported to act as natural or laboratory intermediate hosts in the life cycle of *S. neurona*.[872,891–893] These animals are not a threat unless they are dead. Therefore, veterinarians should encourage horse owners to pick up dead cats, armadillos, skunks, and raccoons on their property. It is important to dispose of the carcass so that opossums cannot eat them and excrete more infectious organisms to infect horses. Picking up these carcasses should be done carefully with an inverted plastic garbage bag, plastic gloves, or some other instrument.

These protozoan parasites are extremely difficult to kill in the environment. A recent study tested the most common disinfectants used in veterinary medicine, including povidone-iodine, chlorhexidine, formalin, two different strengths of NaOH, and high-temperature steam.[963] The *S. neurona* sporocysts thrived on the disinfectants and the lower concentration of NaOH. At the higher concentration of NaOH, the parasites did not survive the treatment, however, most barn materials could not withstand this agent. The parasite could not withstand temperatures of 60°C (140°F) for 1 minute or higher temperatures for shorter periods. Therefore the only alternative for cleaning horse facilities is use of steam.

Recently, medications to prevent development of clinical signs in IFN-γ/KO mice and in horses were attempted. The first study used pyrantel tartrate, a daily anthelmintic prophylactic treatment, and concluded that it does not prevent *S. neurona* infections in mice.[964] A similar study in horses tested for seroconversion in serum and CSF and days to seroconversion.[965] There was no difference in the groups receiving and those not receiving pyrantel. Another study used the triazine-derivative anticoccidial diclazuril;* mice treated before or up to 7 days after infection did not develop clinical signs, and no parasites were recovered from the mice.[966] This study suggests that anticoccidial drugs may be useful in the prevention of *S. neurona* infections in animals. A second triazine derivative, ponazuril, was tested in IFN-γ/KO mice.[967] A single dose prevented

abnormal neurologic signs and death, depending on when it was administered. This further corroborates the potential for prevention of EPM using anticoccidial drugs. In a further study on prevention of EPM in horses, two dose ranges of ponazuril were administered daily based on the recommendations for treatment; 71% of horses given 2.5 mg/kg and 40% given 5 mg/kg developed neurologic deficits.[968] Seroconversion was decreased in the 5-mg/kg group compared with the controls. Therefore, this study needs to be repeated to attempt other doses of ponazuril for prevention of clinical signs of EPM, because coccidiostats may be one method of prevention useful in the future.

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35.2.29

BABESIA ENCEPHALITIS (BABESIOSIS; PIROPLASMOSIS; TEXAS CATTLE FEVER; TICK FEVER; REDWATER)

Parasitemia of cattle caused by the protozoans *Babesia bovis, Babesia argentina,* and *Babesia bigemina* usually is subclinical but results in devastating economic losses worldwide.[969] The disease is transmitted to cattle by the cattle fever ticks *Boophilus annulatus, Boophilus microplus,* and *Boophilus decoloratus*. Babesiosis occurs in the Americas, Europe, Africa, Asia, and Australia. Ticks acquire *Babesia* infection from an infected animal and then pass the agent to their offspring through the ovaries. The protozoan is passed to susceptible cattle by nymphs and adults. Most infections result in intravascular and extravascular hemolysis and kidney and liver failure. A small proportion of *Babesia* infections cause acute encephalitis.[970,971] The CNS signs begin suddenly and include fever (41.7°C [107°F]), anorexia, depression, ataxia, conscious proprioceptive deficits, mania, convulsions, and coma. Sudden death occasionally is observed. The nervous system signs are accompanied by engorgement of the scleral vessels, icterus, proteinuria, and hemoglobinuria. Encephalopathic diseases that closely resemble babesiosis include rabies, coccidiosis, polioencephalomalacia, lead poisoning, infectious bovine rhinotracheitis virus encephalitis, theileriasis, heartwater disease, salt poisoning, and chlorinated hydrocarbon toxicity.

The pathogenesis of the CNS signs is unclear; however, possible causes include capillary thrombosis and infarction, disseminated intravascular coagulation (DIC), anoxic encephalopathy, and direct invasion of the CNS by the parasite. Thrombi are disseminated throughout the CNS. Expression of parasite proteins on the surface of infected red blood cells (RBCs) facilitates binding of RBCs to capillary endothelial cells.[972] The proclivity of *Babesia*-infected RBCs for binding to brain capillaries, particularly those in the cerebellum, is supported by the high incidence of parasite-positive RBCs found in the brains of infected cattle.[973] These findings and the observation of increased prothrombin and partial thromboplastin times, thrombocytopenia, and decreased fibrinogen concentrations suggest that DIC may play a role in the pathogenesis of the CNS disease.[974–976] Vascular blockage in the CNS, caused by severe sludging of RBCs within brain capillaries, appears to be central to the pathogenesis of neurologic disease in infected animals.[977] Studies of *Babesia ovis* in sheep, in which neurologic disease did not occur, failed to demonstrate RBC blockage of brain capillaries.[978] This further supports the belief that CNS vascular pathology is key to the development of neurologic signs in bovine babesiosis.

Babesia encephalitis is a reportable disease in the United States. Suspect cases should be referred to the appropriate state and federal authorities.

35.2.30 *EHRLICHIA (COWDRIA, RICKETTSIA) RUMINANTIUM* INFECTION (HEARTWATER DISEASE)

35.2.30.1 Definition and Etiology

Ehrlichia ruminantium is a rickettsial parasite that causes a fatal encephalitis in goats, sheep, and cattle.[979] The disease originated in sub-Saharan Africa and has spread to cattle in the West Indies (Guadeloupe, Antigua, and Marie Galante),[980] where it has become an economically important tick-borne disease of cattle. *E. ruminantium* is transmitted by *Amblyomma* ticks.[981,982] Although a number of *Amblyomma* species have been implicated in the transmission of heartwater disease, the most important agents are *A. hebraeum* and *A. variegatum*. The intermittent feeding behavior of the tick makes it particularly resistant to treatment with acaricides. *Amblyomma* ticks require three separate blood meals to complete their life cycle. The gravid females fall from the host and lay the eggs in rotting vegetation, particularly in areas where the hosts are bedded for the evening. Recently hatched larvae crawl onto foliage and await a host. After their first feed the larvae detach, molt into nymphs, and await a second host. After refeeding the nymphs detach and molt into adults. The adults remain under rotting vegetation until they are activated by carbon dioxide exhaled by a large mammal. They are further attracted to the host by pheromones from male ticks that remain permanently attached to the host. Animals that do not have male tick infestations are poor attractants for nongravid females. Once attached to the proper host, the females seek the male, breed, feed, and fall from the host when it lies down for the evening. Ticks that feed from *Ehrlichia*-infected hosts develop ovarian infections and transmit the agent to their offspring. This serves to perpetuate the agent over successive seasons.[983]

Many species of vertebrates, including snakes, iguanas, lizards, and birds, are reservoirs for *E. ruminantium* because these animals may serve as the first two hosts for the *Amblyomma* tick.[984] A vector-wildlife cycle facilitates the survival of *E. ruminantium* even when domestic livestock are absent from the environment.[985]

35.2.30.2 Clinical Signs

Animals with the peracute form of *E. ruminantium* infection die suddenly without premonitory signs. The acute form of the disease is characterized initially by fever, anorexia, depression, and respiratory distress. Cyanosis also may be noted. Nervous system signs, which may appear within a few days, include hyperesthesia, snapping closure of the eyelids, rapid extension of the tongue, behavioral changes, muscular fasciculations, hypermetria, ataxia, conscious proprioceptive deficits, and head pressing. As the disease progresses, the animals become recumbent and comatose. Convulsions may occur terminally. These episodes are characterized by opisthotonos, nystagmus, chewing movements, and frothing at the mouth. Mild forms of the disease are characterized by transient diarrhea, malaise, and fever, with no CNS involvement. The mortality rate in sheep ranges from 6% to 80%. Animals that recover are immune to reinfection for at least 58 months.[986] Losses may reach 60% of susceptible cattle and 40% of goats. The mortality rate among Angora goats may exceed 90%.

35.2.30.3 Pathophysiology

After inoculation into a ruminant, the rickettsial agent infects reticuloendothelial cells and proliferates by binary fission within membrane-bound vacuoles.[987,988] Release of the parasite from degenerating

macrophages and neutrophils causes successive waves of parasitemia that infect endothelial cells and cause vasculitis.[988,989] In the cell the developmental stages of the *Ehrlichia* organism resemble those of chlamydia and include elementary, reticulate, and intermediate bodies, which can be differentiated microscopically.[990] Nervous system lesions may be caused by permeability changes in the cerebral capillaries. Changes in the other soft tissues include hydropericardium, hydrothorax, and subcutaneous edema.[979]

Except for Angora goats, which are highly susceptible to *Ehrlichia* infection, animals reared in indigenous areas usually have a high level of immunity and do not succumb to the infection.[991] Animals that survive the initial infection become asymptomatic but remain rickettsemic for as long as 223 days (sheep), 246 days (cattle), and 8 days (goats). Calves under 3 weeks of age, lambs under 8 days of age, and kids under 6 weeks of age are inherently resistant to *E. ruminantium* infection, regardless of the amount of colostral protection they have received.[992,993]

35.2.30.4 Necropsy Findings

Pathologic changes of heartwater disease include hydropericardium, hydroperitoneum, hydrothorax, pulmonary edema, perirenal edema, hemorrhages in the pleura and peritoneum, and hemorrhagic enteritis. Microscopic changes include microgliosis, necrotizing vasculitis in the brain, hemorrhage, edema of the neuropil, microcavitation, and focal necrosis of the granular layer of the cerebellum. In clinical cases the parasite can only be definitively diagnosed by biopsy of the cerebral cortex or by collection of the cortical tissues at postmortem examination.[994] Simple techniques for collection of such biopsy specimens have been described.[995–997] Squash preparations of the biopsied material should be stained with either methyl green pyronine or Giemsa stain before microscopic examination of the tissues.[998,999] A cloned DNA probe that identified *E. ruminantium* DNA has been developed, but the clinical usefulness of the test is unknown.[1000]

Diagnostic tests developed to identify infected livestock include an indirect fluorescent antibody (IFA) test using infected bovine aortic endothelial cells for indicators, several ELISAs, and tests using PCR methodology.[1001–1004] Of these, PCR is the most accurate.

35.2.30.5 Treatment

The administration of oxytetracycline (6 to 10 mg/kg IV twice daily for 3 or 4 days) may be beneficial for treatment of the early stages of the disease. The long-acting formulation of oxytetracycline also is effective, but for best results it should be administered as soon as the animal becomes febrile. Addition of dimethyl sulfoxide (DMSO) to the treatment regimen may be helpful: DMSO improved respiratory function in *E. ruminantium*—infected sheep, although it reduced their appetites.[1005] Treatment usually is futile if the first dose of oxytetracycline is administered after the onset of neurologic symptoms.[1006] Despite the depository nature of the long-acting formulation, two or more doses 48 hours apart are needed to achieve a good clinical response. Cattle should be re-treated if they develop a fever after the first dose has been administered.[1007] Animals with nervous system signs frequently die despite intensive antibiotic therapy. Angora goats are highly susceptible to heartwater disease. In South Africa, Angora producers routinely treat all animals every 14 days during the summer with oxytetracycline. Nevertheless, the number of deaths caused by heartwater disease is directly related to the number of antibiotic treatments administered. Animals that remain essentially tick free never develop adequate immunity to the *Ehrlichia* organism.

A small degree of tick infestation and exposure of the animals to low numbers of the agent, combined with judicious oxytetracycline therapy, would seem to favor the development of immunity over time.[1008] One method of immunization uses a controlled infection of a virulent strain (Onderstepoort Ball 3 strain) of the *Ehrlichia* organism and treatment with long-acting oxytetracycline (800 mg per adult goat) at the beginning of clinical disease and 10 days later.[1009] Vaccination with this isolate produces immunity against exposure to homologous but not heterologous strains of *Ehrlichia*.[1010–1012] More recent strategies have included vaccines utilizing inactivated organisms, live attenuated organisms, and fragments of *E. ruminantium* nucleic acid, but none has had great success.[1013–1017]

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35.2.30.6 Prevention and Control

Control of ticks on cattle pastures is the most desirable means of controlling heartwater disease. Complete eradication of the ticks in most regions of sub-Saharan Africa is neither possible nor desirable. Cattle that are reared in areas where *Ehrlichia* infection is endemic develop acquired immunity over time. In these areas the ticks should be sufficiently abundant to permit a low level of heartwater infections in most cattle, yet not so populous as to introduce severe, overwhelming infections. Integrated methods for tick control have been recommended. These include exclusion of wildlife from paddocks, artificial induction of host resistance to ticks, application of insecticidal ear tags, and conventional acaricide application. Application of insecticides as the sole method of tick control has not proved highly effective. Resistance to the acaricides may develop with prolonged use. The dips are expensive and frequently are used at improper concentrations. Moreover, some species are not highly attracted to ruminants unless other ticks are already attached. Treatment of these animals would be ineffective and wasteful. A novel osmotic pump loaded with ivermectin that delivers 60 µg/kg/day kills *Amblyomma hebraeum* and reduces the number of fertile eggs shed. Data on the efficacy of the drug under field conditions have not been published.

35.2.31 CEREBRAL THEILERIASIS (TURNING SICKNESS; DRAAISIEKTE; EAST COAST FEVER; CORRIDOR DISEASE; JANUARY DISEASE; TROPICAL FEVER)

35.2.31.1 Definition and Etiology

Cerebral theileriasis is an encephalitic disease of cattle caused by the piroplasma parasites *Theileria annulata* and *Theileria parva*.[1018,1019] Theileriasis is seen mainly in Africa (Kenya and Tanganyika) and India, where it is characterized by a high mortality rate and is known as East Coast Fever. *Theileria sergenti* is found in Korea and Japan. *Theileria mutans,* a parasite of cattle in the southwestern United States, is relatively nonpathogenic.[1020] A mild form of theileriasis, locally called “January disease,” occurs in cattle in Mozambique. This condition is caused by the subspecies *Theileria parva bovis*. Corridor disease is caused by *Theileria parva Lawrence,* and *Theileria annulata* is the cause of Mediterranean Coast fever or tropical theileriasis. Other species associated with cerebral theileriasis include *Theileria mutans* and *Theileria taurotragi*.[1018]

East Coast fever probably originated in buffalo in eastern Africa and later spread to cattle. Spread of the disease to southern Africa probably occurred through introduction of infected cattle from eastern Africa. European breeds of cattle *(Bos taurus)* develop a more severe disease than do comparably infected Indian breeds *(Bos indicus)*. Both types of cattle appear to be equally susceptible to infection, but differ in their

ability to control the course of disease.[1021] *Theileria* organisms are transmitted to susceptible cattle by the ticks *Hyalomma anatolicum, Hyalomma lusitanicum,* and *Amblyomma hebraeum.*[1022]

Trypanosoma species manipulate the immune system both to evade destruction and to promulgate infection. Organisms escape the host immune response by altering immune system activation so that infected cells avoid recognition and destruction.[1023–1025] Clonal expansion of infected lymphocytes is promoted, and these cells disseminate throughout the body.[1026]

35.2.31.2 Clinical Signs

The clinical signs of *Theileria* infections include lymphadenopathy, nasal discharge, lacrimation, tachycardia, fever, subcutaneous edema of the face, gangrenous dermatitis, sloughing of facial skin, dyspnea, pallor, CNS disorder, and emaciation.[1027] The neurologic syndrome is characterized by ataxia, hypermetria, conscious proprioceptive deficits, depression, head pressing, hyperesthesia, blindness, nystagmus, circling, and aggressiveness. Terminally the animals become recumbent and develop opisthotonos, tonic-clonic seizures, and coma. In rare cases the parasite may localize in the spinal cord. The CNS signs result from vasculitis and lymphocytic inflammation of the brain.[1028–1030] Clinically recovered animals become persistently infected.

35.2.31.3 Necropsy Findings

The postmortem lesions of theileriasis include capillary engorgement, scattered punctate hemorrhages on the surface of the brain, thrombosis of the meningeal vessels, hemorrhage in the cerebral ventricles, pulmonary edema, peripheral lymphadenopathy, and infarctions of the kidney and spleen. The brain of affected animals appears to have a yellow hue.[1030] Microscopically, blue cytoplasmic inclusion bodies (Koch's blue bodies) are seen in the lymphocytes adjacent to the hemorrhagic areas.

The nervous form of theileriasis is difficult to diagnose definitively because the parasite is only sporadically visible in sections of nervous tissue from the infected animals. Parasitemia occasionally can be detected by microscopic examination of blood smears from infected calves. Reliable blood tests currently are not available. Biopsy of the cerebral cortex has been recommended as a confirmatory test for the disease. The CSF of affected animals is normal or has an increased protein concentration ranging from 1400 to 12,452 mg/dL, with normal numbers of white blood cells.[1029]

35.2.31.4 Treatment

Parvaquone (Clexon),* 10 to 20 mg/kg intramuscularly (IM) in two injections 48 hours apart, and buparvaquone (Butalex),† at a single dose of 2.5 mg/kg, are approximately 90% effective for the treatment of theileriasis.[1031] Some studies have found buparvaquone to be the most effective treatment.[1032,1033] Parvaquone can be combined with furosemide, which improves survival of cattle that develop pulmonary edema, a common consequence of theileriasis.[1034] Menoctone (10 mg/kg IV or IM) also is curative. Single doses were effective, but repeating the treatment daily for 5 days eliminated posttherapeutic recrudescence.[1035] The disease is exotic to the United States.

* Coopers Animal Health, Mundelelin, IL.

† Burroughs-Wellcome, United Kingdom.

35.2.31.5 Prevention

Prevention of *Theileria* infection has largely been based on the use of live attenuated vaccines, which produce a solid, cell-mediated immunity.[1036] These vaccines are used in an "infection and treatment" manner, whereby vaccination must be combined with administration of long-acting tetracyclines.[1037] Recent efforts at vaccine development have focused on the creation of subunit vaccines, using a variety of *Theileria* antigens. While promising, more work is still needed.[1038–1041] Use of vaccines, however, is still not on a large scale.

The napthoquinones are the preferred chemotherapeutic agents in vaccinated animals and include parvaquone, halofunginone lactate,* and buparvaquone (see Treatment).

* Terit, Hoescht, Germany.

35.2.31.6 Control

Tick control is vital. Weekly spraying with coumaphos and insertion of ear tags impregnated with cypermethrin (Decum)† have been effective for controlling ticks and preventing *Theileria* infections in calves in Tanzania. The calves became infected with *Theileria parva* by 3 months after the tags were removed. Woodford[1042] suggested that the intensive tick control could minimize the incidence of theileriasis until the calves could be successfully vaccinated. However, inadequate or incorrect application of products and tick resistance to chemicals present challenges to effective tick control.

† Decum Tearina, United States.

35.2.32 CEREBRAL TRYPANOSOMIASIS (SLEEPING SICKNESS)

35.2.32.1 Definition, Etiology, and Clinical Signs

Trypanosomiasis is a hemoprotozoan disease of African cattle that also infects the central nervous system (CNS). The disease is transmitted to cattle by the bite of the tsetse fly (*Glossina* species). The agents that infect cattle include *Trypanosoma vivax, Trypanosoma congolense,* and *Trypanosoma brucei*. An especially severe neurologic form of the disease has been caused by the inoculation of cattle with *T. congolense,* followed 1 year later by infection with *T. brucei,* or by simultaneous inoculation with the two agents.[1043] The encephalitic signs develop 2½ to 5 months after infection and include ataxia, conscious proprioceptive deficits, knuckling, depression, circling, and head pressing. Some animals may show signs of behavioral change, lose the herd instinct, and develop hyperesthesia and constant repetitive movements. Other signs associated with progression of trypanosomiasis are semicoma, coma, recumbency, opisthotonos, and intermittent tonic-clonic convulsions, which occur 2 to 3 days before death. Affected animals are emaciated, anemic, and icteric at death.[1044]

Experimental infection with trypanosomes causes a marked fever (as high as 40.5°C [105°F]). Other common nonneurologic signs are anemia, petechiation of the mucous membranes, occult fecal blood, melena, and epistaxis. Chronic weight loss without other clinical signs may be seen in some animals.

Hematologic abnormalities include anemia, hypoalbuminemia, hyperbilirubinemia, and increased plasma concentrations of aspartate transaminase and urea nitrogen.

Acutely infected animals may develop a thrombocytopenia and prolongation of the prothrombin and partial thromboplastin times, indicating that DIC may be responsible for the vascular changes that occur before death. The anemia is characterized by increased mean corpuscular volume and mean corpuscular hemoglobin, with increased serum iron concentrations early in the infection.[1045,1046] One study did not demonstrate a change in the concentration of white blood cells or protein in the CSF of animals with the encephalitic form of trypanosomiasis.[1043] However, another study showed significant alterations in cattle infected with *T. bruceii*.[1047] These included an increase in total protein (range, 37 to 44 mg/dL) and pleocytosis (range, 0 to 3060 mononuclear cells/μL). The abnormalities in the CSF may be present in infected cattle not currently displaying clinical neurologic signs. Antitrypanosomal antibody may be found in the CSF of affected cattle using IFA tests.

35.2.32.2

Pathology

The pathologic lesions of trypanosomiasis are a nonsuppurative encephalomyelitis, serosanguineous pericardial fluid, serosal hemorrhages, pulmonary edema, centrilobular coagulative necrosis, splenomegaly, necrotizing myocarditis, and glomerulonephritis.[1048] Macroscopic lesions of the CNS include subtle thickening and grayish discoloration of the meninges. The meningeal vessels are congested. Microscopic lesions of the CNS include mild to moderate diffuse meningoencephalitis, plasmacytic and lymphocytic perivascular cuffing, nodular gliosis, and mononuclear choroiditis. The pathogenesis of the encephalitis is not understood.

Trypanosomes may be cultured from the blood and CSF of infected cattle. The number of hematogenous parasites is highest in animals with a dual infection by *T. congolense* and *T. brucei*. The clinical diagnosis of trypanosomiasis may be confirmed by inoculating blood or CSF specimens into laboratory mice and observing the recipients for parasitemia with direct darkfield examination of the patient's blood. Identification of motile trypanosomes in the buffy coat zone of a microhematocrit capillary tube using darkfield illumination apparently is the most accurate of all diagnostic methods. Trypanosomes can be differentiated by their morphologic features, manner of attachment to erythrocytes, and type of motility.[1049] Species-specific antibodies can be detected in serum using either an antigen-capture ELISA or an IFA test in which the column-purified trypanosomal antigen is fixed with acetone or formalized saline. Titers of 1:200 to 1:2000 were consistent with acute infection. The test is not typically used for field diagnosis of trypanosomiasis.[1050,1051] Infected cattle develop acquired resistance to homologous but not heterologous isolates of trypanosomes.

35.2.32.3

Treatment and Control

Of the drugs available for the treatment of trypanosomiasis, isometamidium chloride* is most often used. The recommended dosage ranges from 0.25 to 1 mg/kg IM; a single dose of 1 mg/kg exerts a protective effect for up to 6 months.[1052] The higher dosage (1 mg/kg) was required to obtain increased weight gain and prevent recurrent infection. The treatment was particularly effective when combined with weekly surveillance, followed by treatment of confirmed infected animals.[1053] Side effects of isometamidium include tachycardia, salivation, lacrimation, pollakiuria, muscle fasciculations, convulsions, diarrhea, and in

rare cases, death. The drug apparently does not cause abortion in pregnant cows or otherwise affect the calf.[1054]

Other drugs used include suramin sodium,[†] diminazene aceturate[‡] (7 mg/kg), quinapyramine sulfate and homidium chloride[§] (1 mg/kg). These drugs provide residual protection from reinfection for approximately 2 months; however, recurrent infection and resistance, especially to diaminazene, have been reported.[1055–1058] Combinations of these drugs (e.g., diaminazene followed by isometamidium) reduce the number of resistance-related therapeutic failures. Relapses also undoubtedly occur because many of the chemoprophylactic drugs are unable to penetrate the blood-brain barrier in sufficient concentrations to eliminate the parasite in the CNS tissues.

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Because of the variable responses to treatment and the ability of *Trypanosoma* organisms to develop drug resistance, all control programs must include methods of controlling the tsetse fly.[1057] Current recommendations for fly control include application of insecticides with residual pyrethroids. Several methods of pyrethroid application have been investigated, including inclusion in a visual baited target (deltamethrin)[1059] or application of a pyrethroid pour-on formulation (Bayticol pour on, 10 mL/100 kg).[*] Both methods have been highly effective for reducing the tsetse fly population and trypanosome infection rates. Animals can be dipped in Deltamethrin dip every 2 weeks. A single application of the chemical has residual activity for as long as 52 days; however, to ensure maximum killing, application every 14 days is recommended. Because the tsetse fly prefers to feed from the ventral torso or the legs, insecticide-impregnated ear tags have been ineffective for preventing infection.[1060] Other fly control methods include aerial spraying with endosulfan, ground-based spraying with 4% dichlorodiphenyltrichloroethane (DDT), or use of scented insecticidal traps.[1059] However, cost and environmental concerns have limited the usefulness of these techniques.

Selection of resistant lines of cattle is possible. The taurine N'Dama and West African shorthorn breeds have innate resistance to trypanosomiasis and are the sole breeds of cattle in areas of tsetse fly range.[1061] Resistant breeds of small ruminants include the Djallonke, Red Maasai, Blackhead Persian, and East African sheep and goats.[1062] Imported breeds of livestock usually cannot be maintained, even in areas of low tsetse fly risk, without intensive drug therapy.[1063]

* Samorin, May & Baker; Trypamidium, Specia.

† Naganol, Bayer Ag Division, Animal Health, Shawnee Mission, KS.

‡ Berenil, Hoescht, Germany.

§ Novidium, May & Baker.

* Bayer AG, Germany.

35.2.33

POLIOENCEPHALOMALACIA (CEREBROCORTICAL NECROSIS)

CHRISTOPHER CEBRA

GUY LONERAGAN

DANIEL GOULD

35.2.33.1

Definition and Etiology

Polioencephalomalacia (PEM) is a common and important neurologic disease of ruminants[1064,1065] with a worldwide distribution. An animal with clinical manifestations of PEM often is referred to as having “polio” or being a “sleeper” or “brainer.”

Polioencephalomalacia is a descriptive term for histologic lesions[1064,1066] that may arise from a variety of etiologies. Literally, the name means softening or necrosis (malacia) of regions of the gray matter (polio) of the brain (encephalo). Thus a definitive diagnosis of PEM requires appropriate histologic examination of brain tissue. The possible etiologies of PEM include (but are not limited to) excessive sulfur consumption,[1067–1069] presumably manifested through elevated ruminal sulfide production;[1070,1071] altered thiamine metabolism;[1072] so-called salt poisoning or water deprivation;[1073] amprolium administration;[1074–1076] the molasses-urea diet;[1077] and lead intoxication.[1078]

35.2.33.2

Clinical Signs

PEM appears to manifest both subacutely and acutely.[1064,1071] In the subacute form, signs may develop within hours or over several days. In the early stages of the disease, the affected animals detach from the herd or flock, become anorectic, and stagger. They often appear blind, walk with the head held erect, and demonstrate a slight hypermetric gait. Occasionally, affected animals are excitable and charge around their enclosure, which may present a significant hazard to the veterinarian and animal handlers. Other early signs of PEM can include diarrhea, hyperesthesia, and muscle tremors, which are most obviously observed as ear flicking or facial twitching. Progression of the condition is associated with cortical blindness, head pressing, opisthotonos, dorsomedial strabismus, miosis, repetitive chewing, profuse ptyalism, and odontoprisis[1064,1068,1079–1081] (Figs. 35-10 and 35-11). Despite the defective menace response, the animals usually have normal palpebral reflexes. Affected animals may also develop a variable nystagmus, strabismus (Fig. 35-12), and head tilt. The rectal temperature is normal unless excessive muscular fasciculations have developed. The pulse and respiratory rates are usually increased. An odor of hydrogen sulfide may be detected on the breath if the PEM is associated with excessive sulfur consumption.

Although most of these animals respond favorably to aggressive therapeutic intervention, clinical signs may progress to recumbency, tonic-clonic convulsions, and death. In facilities with certain types of fencing, such as cables, affected animals may push or press with such force that they die of asphyxiation.

Fig. 35-10 Feedlot steer with clinical manifestations of polioencephalomalacia. The steer has adopted a sawhorse posture.

Fig. 35-11 Calf with advanced signs of polioencephalomalacia showing abnormal head posture and depressed sensorium.

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Fig. 35-12 Abnormal pupillary angle associated with strabismus in a calf with polioencephalomalacia. Because the calf's head is tied upward, the eye has rotated ventrally, although this is actually dorsomedial strabismus.

In the acute form of PEM, animals are found recumbent and comatose.[1064,1071] These animals often experience episodic tonic-clonic convulsions, and they remain recumbent and hypertonic between seizures. The prognosis is poor for acutely affected animals or those with advanced subacute manifestations. Survivors may remain irreversibly decorticated and are culled because of poor performance, chronic anorexia and ataxia, or blindness. However, mildly affected animals may remain as productive members of the herd.

Because the clinical manifestations of PEM may be subtle and nonspecific, they can be confused with other disorders. PEM often is temporarily associated with lactic acidosis that develops after consumption of

excessive amounts of readily fermentable carbohydrates. Animals with lactic acidosis may appear ataxic and obtunded in addition to having a foul-smelling, watery stool and a distended, fluid-filled rumen. Concurrent PEM may not be diagnosed, or producers may confuse PEM for lactic acidosis or primary ruminal tympany in acutely affected animals that have remained laterally recumbent for some time.

The major differential diagnoses for PEM include enterotoxemia type D (focal symmetric encephalomalacia form), *Haemophilus* meningoencephalitis (thrombotic meningoencephalitis), coccidiosis with nervous system involvement, listeric meningoencephalitis, vitamin A deficiency, ethylene glycol poisoning, locoism, rabies, and infectious bovine rhinotracheitis encephalitis (calves only).

35.2.33.3

Clinical Pathology

Although a definitive diagnosis depends on histologic confirmation, a presumptive diagnosis may be made antemortem based on the history and clinical signs or on a definitive diagnosis in herdmates of affected animals. If a diagnosis of PEM is made, either presumptive or definitive, attention should be focused on identifying the likely causes so that exposure of herdmates to etiologic agents can be mitigated or eliminated. The investigation may proceed at the animal, herd, and environmental level to identify evidence supportive of sulfide toxicity, thiamine deficiency, lead toxicity, or water deprivation—salt toxicosis.

Sulfide concentrations in the ruminal fluid and gas cap in experimentally induced sulfur-associated PEM have been shown to be high.[1082,1083] However, unpublished data supported a finding of a decrease in gas cap sulfide concentrations in naturally developing PEM associated with increased sulfur consumption.[1084] This probably is caused by the rapid metabolism of sulfate to sulfide in the rumen and resultant absorption or eructation of hydrogen sulfide (H_2S). Animals with naturally developing PEM are likely to have been anorectic for some time, resulting in a decrease in oxidized and reduced forms of ruminal sulfur.

Estimation of the rumen gas cap H_2S concentration in clinically healthy penmates of affected cattle is an effective chute-side diagnostic procedure that can indicate excessive sulfur consumption.[1071] This method provides real-time results that may aid direction of further animal and environmental investigations. In short, an area in the left paralumbar fossa is prepared for ruminocentesis. An 18-gauge, 3½-inch spinal needle is inserted through the body wall and into the rumen gas cap. A modified gas sampler is attached to the spinal needle by means of an extension set, and a known amount of gas is drawn through an H_2S detector tube.[1083] It is important to adjust the values to account for any dead space of the sampling instrument, such as the extension set and other modifications. H_2S concentrations greater than 1000 ppm are indicative of excessive sulfur consumption.[1085]

Appropriate blood samples may be analyzed for lead concentration and possibly estimation of thiamine status. Thiamine status generally is evaluated using one of several available methods, including determining the total blood thiamine concentration using a thiamine-dependent *Lactobacillus* bioassay.[1086] The erythrocyte thiamine pyrophosphate concentration may be measured by high-performance liquid chromatography (HPLC).[1087] The value of estimating all phosphorylation forms of thiamine (free, diphosphate, and triphosphate) is questionable. Table 35-9 shows the reference ranges for the total thiamine concentration in normal and affected cattle.

Another method of evaluating thiamine status is determining erythrocyte transketolase activity. This is a sensitive and specific measurement of active thiamine status.[1088] Transketolase catalyzes the reaction

between xylulose-5-P and ribose-5-P to form sedoheptulose-7-P and 3-phosphoglyceraldehyde in the pentose phosphate pathway. Normal mean transketolase activity has been reported to range from 0.301 to 2.9 mmol pentose/hr/10^9 RBCs (mean, 0.782). Transketolase assays often are reported as the mean thiamine pyrophosphate effect (Table 35-10). This test compares the specific activity in the active (holoenzyme) and inactive (apoenzyme) forms with the activity of the two forms after addition of thiamine to the homogenates. A large increase in specific transketolase activity after addition of the thiamine pyrophosphate suggests thiamine deficiency. Theoretically, in animals with thiamine-associated PEM, the concentration of holoenzyme is decreased, and that of the apoenzyme is increased. Thiaminase may be detected in the rumen and feces of affected animals, but the value of this assay is questionable.[1072,1087,1089,1090] If thiamine deficiency is identified in an affected animal, caution should be used in interpreting the results because a period of anorexia may result in a decrease in ruminal de novo synthesis;[1092,1091] thus, affected animals may have a thiamine deficiency that develops secondary to PEM.

Changes in CSF of affected animals usually are vague. They include mild pleocytosis (5 to 50 WBCs/dL) with vacuolation and increased protein concentrations (>50 mg/dL).[1072,1093]

Electrophysiologic studies of affected animals show a normal latency and decreased amplitude of the late peaks of the visual-evoked potentials. These changes reflect a decreased population of neurons capable of responding to the photic stimulation.[1094] Electroencephalographic (EEG) changes in some animals include constant high amplitude (50 to 60 mV) and slow activity (1 to 4 Hz). Another change is diffuse lowered activity, which is consistent with diffuse necrosis.[1095]

Table 35-9 Mean Concentration of Thiamine in Tissues*: 95% Confidence Intervals in Clinically Normal Cattle and Sheep and in Patients with Polioencephalomalacia

Tissue	Species	Normal	Polioencephalomalacia
Liver, wet	Cattle	2.81 ± 0.515	0.613 ± 0.102
	Sheep	2.07 ± 0.474	0.421 ± 0.06
Liver, dry	Cattle	11.1 ± 2.11	2.51 ± 0.428
	Sheep	7.34 ± 1.73	1.42 ± 0.197
Heart, wet	Cattle	2.81 ± 0.46	0.549 ± 0.118
	Sheep	3.1 ± 0.432	0.581 ± 0.093
Heart, dry	Cattle	13.18 ± 2.12	2.45 ± 0.558
	Sheep	13.5 ± 1.75	2.44 ± 0.416
Brain, wet	Cattle	1.4 ± 0.248	0.301 ± 0.061
	Sheep	1.21 ± 0.101	0.592 ± 0.111
Brain, dry	Cattle	7.67 ± 1.52	1.8 ± 0.366
	Sheep	5.81 ± 0.566	3.22 ± 0.558

From Edwin EE et al: Diagnostic aspects of cerebrocortical necrosis, *Vet Rec* 104:4, 1979.

* Values given in µg/g (ppm).

Table 35-10 Mean (and 95% Confidence Range) Values of Erythrocyte Transketolase as Percentage of Thiamine Pyrophosphate Effect in Erythrocytes of Normal Cattle and Sheep and in Patients with Polioencephalomalacia

Species	Normal (%)	Polioencephalomalacia (%)
Cattle	15	172
	(2–114)	(120–247)
Sheep	23	122
	(12–41)	(96–158)

From Edwin EE et al: Diagnostic aspects of cerebrocortical necrosis, *Vet Rec* 104:4, 1979.

Environmental investigations should include evaluation of all practical feed and water sources for sulfur concentrations or the possibility of lead contamination. The diet should also be checked for molasses and urea content.

35.2.33.4 Pathogenesis

The fundamental lesion with PEM appears to be neuronal edema with secondary compartment syndrome. In most cases the edema is postulated to result from adenosine triphosphate (ATP) depletion and insufficient function of the sodium-potassium pump. With salt intoxication, aberrant accumulation of intraneuronal osmolar substances, followed by mass movement of water into neurons, offers a different pathway to cerebral edema. In either case, the bony calvarium limits expansion, and neuronal swelling leads to pressure necrosis. Additional neuronal dysfunction independent of edema and compartment syndrome cannot be ruled out.

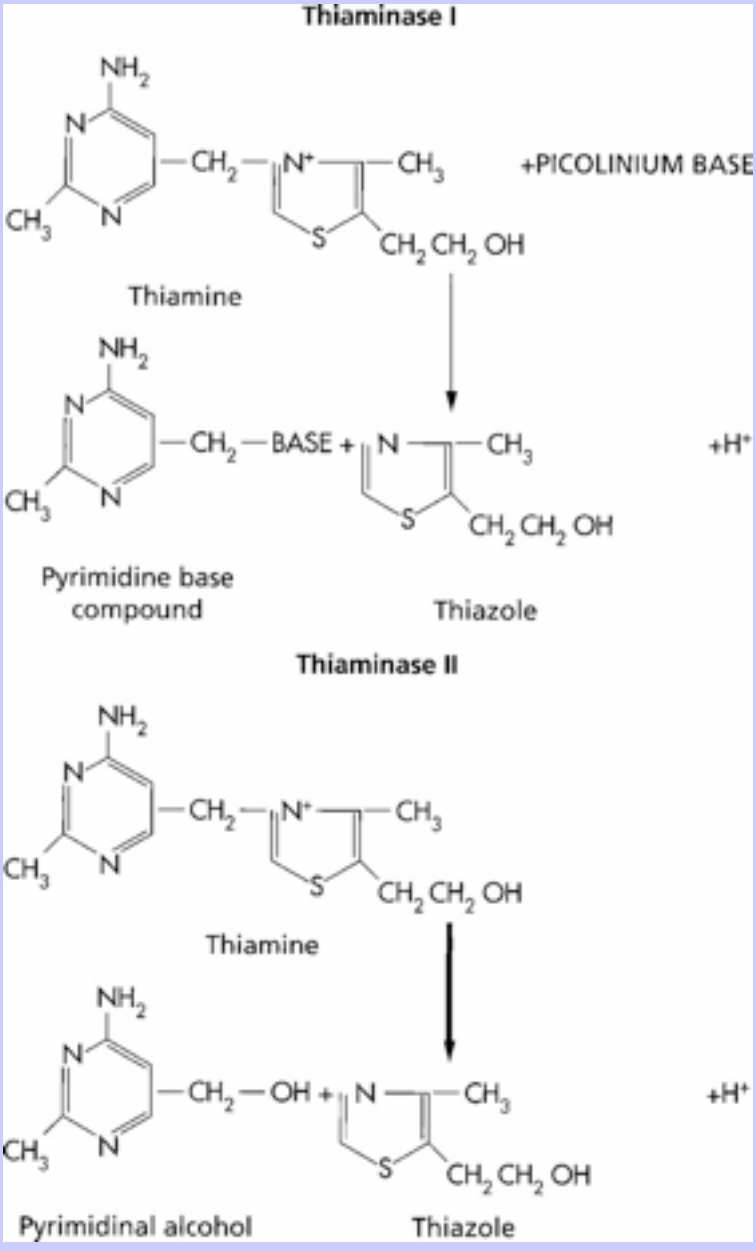
The brain is susceptible to PEM because of its high energy and oxygen requirements. Brain tissue is only about 2% of body weight but accounts for 20% to 30% of body glucose utilization and 20% of oxygen utilization in adults.[1096] More than 85% of glucose used by the brain is energy substrate, and the blood-brain barrier prohibits the switching to many alternate energy substrates. Compared with liver or muscle, the brain has relatively small glycogen stores, only about a 10-minute supply. It is entirely dependent on circulating oxygen, and under normal conditions, the extracellular fluid contains approximately 100 times as much glucose as the oxygen required for complete aerobic glycolysis. Thus, oxygen delivery or utilization is much more rate limiting for ATP production under most circumstances than glucose availability,[1097] and factors that inhibit oxygen utilization (e.g., H_2S, lead) could have profound effects on neuronal ATP production.

One intriguing but controversial theory on cerebral energy metabolism could further explain the high neuronal susceptibility to ATP depletion. By this theory, glucose is reduced anaerobically to lactate in astrocytes.[1098] This lactate diffuses into neurons, which are then absolutely dependent on aerobic glycolysis for ATP production. Even if this theory is false, it is unlikely that anaerobic glycolysis alone could meet neuronal ATP needs.

Much of the early work on PEM focused on the importance of thiamine (vitamin B_1, thiamin, aneurin). In adult ruminants, thiamine is produced by rumen microbes at a rate that is marginally faster than the rate of consumption; very little is stored.[1099] Preruminants depend on dietary thiamine. Thiamine compounds play several important roles in the glycolytic pathways. Thiamine pyrophosphate (thiamine diphosphate) is an important coenzyme for transketolase, the rate-limiting enzyme in the hexose monophosphate pathway (pentose phosphate shunt) of glycolysis, and the α-ketoacid dehydrogenases of the Krebs cycle. The role of thiamine in the hexose monophosphate pathway was long thought to be key in the development of PEM, but this pathway actually accounts for less than 3% of cerebral glycolysis.[1100] It is unlikely that impairment of this pathway alone could lead to such severe disease. However, decreased function of the Krebs acid cycle through inactivity of the α-ketoacid dehydrogenases could probably cause the necessary reduction in ATP production. Thiamine triphosphate may also play a role in neuronal function independent of its enzymatic function.

The dependence of ruminants on microbial thiamine production has lead to investigation of factors that might decrease production, absorption, or function. The mechanisms proposed include ruminal production of bacterial thiaminases, production or ingestion of inactive thiamine analogs, ingestion of preformed plant thiaminases, decreased intake of preformed thiamine by preruminants, impaired absorption or phosphorylation of thiamine by rumen bacteria, increased fecal excretion of thiamine, and decreased ruminal production of thiamine diphosphate. The most frequently reported inactive thiamine analog is amprolium.[1074–1076] Two types of bacterial thiaminases have been described. Thiaminase I, which is produced by *Bacillus thiaminolyticus* or *Clostridium sporogenes,*[1101] catalyzes the cleavage of thiamine at the methylene bridge between the pyrimidinyl and the thiazole ring. A basic cosubstrate is required to combine with the pyrimidinyl derivative to form a new compound[1102] (Fig. 35-13). Many common feedlot medications, including benzimidazoles, levamisole, and promazines, appear to be able to serve as this cosubstrate.

Fig. 35-13 Enzymatic cleavage of thiamine by thiaminase I and II. Thiaminase I attaches a picolinium base to the pyrimidine ring structure, whereas thiaminase II catalyzes the hydrolysis of thiamine at the methylene bridge. (From Edwin EE, Jackman R: A rapid radioactive method for determination of thiaminase activity and its use in the diagnosis of cerebrocortical necrosis in sheep and cattle, *J Sci Food Agric* 25:357, 1974.)



Several plants also appear to make a thiaminase similar to thiaminase I. These include bracken fern *(Pteridium aquilinum)*[1103,1104] horsetail *(Equisetum arvense),*[1104] and Nardoo fern *(Marsilea drummondii)*.[1105] Of these, only the Australian Nardoo fern has been strongly linked to outbreaks of PEM. Thiaminase II is produced by *Bacillus aneurinolyticus,* which proliferates in response to excessive grain intake.[1106] The enzyme catalyzes the hydrolysis of the methylene bridge between the two ring structures of the thiamine molecule. The specific relationship of this thiaminase to the clinical syndrome of PEM as seen in the field is unclear.

Complete correlation has not been established among production of ruminal and fecal thiaminase, tissue and plasma concentration of thiamine, and development of clinical encephalopathy.[1089,1107] Some affected animals may show normal amounts of thiamine in the plasma but have greatly decreased levels in the erythrocytes and other tissues, supporting the diversity of causes of PEM.[1108]

Dietary sulfur and sulfates are an important factor in the development of many cases of ruminant PEM. Beef cattle require 0.15% to 0.20% sulfur on a dry matter basis.[1109] Sources of sulfur include elemental sulfur,[1067] feed additives such as gypsum and ammonium sulfate,[1068,1110] feedstuffs such as corn-processing by-products,[1109] cruciferous crops,[1111,1112] molasses,[1077] and fertilizers. Water can be an important contributor to sulfur intake, usually in the form of sulfates.[1070,1113,1114]

There are two primary metabolic pathways of sulfur in the rumen.[1114–1119] The *assimilatory pathway* involves reduction of sulfate to sulfides and incorporation into sulfur-containing organic compounds such as cysteine and methionine.[1117] These are ultimately incorporated into microbial crude protein. The *dissimilatory pathway* is an energy-producing pathway in which microorganisms use sulfate as a terminal electron acceptor, similar to how mammals use oxygen.[1120] The end product is liberated sulfide ion. At a ruminal pH of 5.2, 97.2% of sulfide ions are in the form of H_2S and move freely to the rumen gas cap.[1116,1121] H_2S is readily absorbed and transported to the liver and oxidized to sulfate.[1121,1122] Some H_2S may be lost through eructation,[1082,1121] but the significance of this route has been questioned.[1123] Excess sulfur is excreted in the urine and large intestine[1124,1125] or recycled to the rumen.[1126,1127] A period of adaptation is required for maximum H_2S production after exposure to sulfur.[1118,1124,1127–1129]

Because sulfur and sulfate demonstrate low cellular toxicity, it is unlikely that sulfur-associated PEM results from a sulfate or sulfur toxicity. However, sulfides are highly toxic.[1130–1132] Sulfur-associated PEM is more likely to occur secondary to a sulfide toxicity.[1069,1071,1082]

It has been proposed that the pathogenesis of sulfur-induced PEM involves inhibition of cytochrome-*c* oxidase, an enzyme in the electron transport chain; this chain is important for regenerating the intermediaries of aerobic glycolysis and the final round of ATP production. With oxygen availability already limiting aerobic glycolysis in the brain, inhibiting the electron transport chain could have a profound effect on neuronal ATP production.

For highly toxic sulfide to reach the brain, it must escape hepatic oxidation. This might be achieved by two mechanisms. A surge in ruminal sulfide generation usually follows a period of adaptation to high-sulfur diets. This may overwhelm the hepatic detoxification capacity. As an alternative possibility, cattle inhale the majority of eructated ruminal gas.[1133] These inhaled gases can contain high amounts of H_2S, and if absorbed

via the pulmonary route, the H_2S would completely bypass the hepatic circulation. However, this concept has been questioned.[1134]

In feedlot cattle, a summer peak in PEM cases was associated with consumption of water containing 2500 mg/L of sulfate.[1070] The total sulfur intake of these steers was estimated to be 0.6% on a dry matter basis during the hottest days of the year. Most PEM cases occurred between 15 and 35 days after arrival in this feedlot. In another investigation, 11% of weaners consuming a diet containing 0.9% sulfur on a dry matter basis developed clinical manifestations of PEM.[1071] Lesions were confirmed in one steer that died. Addition of gypsum (calcium sulfate) to feeder steer rations at a final concentration more than 2% organic sulfate results in a significantly greater risk of developing PEM. The addition of sodium sulfate (0.6% to 0.8%) to diets may induce PEM within 11 days.[1082,1128,1135,1136] High sulfur concentrations in well water in combination with accumulation in forage has been traced to an outbreak of PEM in Canada.[1071] One survey described an outbreak of cerebrocortical necrosis in cattle eating diets containing 7200 mg/kg of sodium sulfate.[1114]

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The recommended maximum tolerance level of sulfur is 0.4% of dry matter intake.[1109] Other effects of excessive sulfur intake are decreases in feed intake and weight gains. Accurate diagnosis of sulfur toxicity requires measurement of sulfur in all food and water sources. Sulfur from water must be included when calculating total sulfur intake. One third of the molecular weight of sulfate is sulfur. Therefore, if an animal drinks 30 L of water a day containing 2000 mg/L of sulfate, this contributes 60,000 mg of sulfate, or 20 g of sulfur. Furthermore, if this animal consumes an average of 10 kg of dry matter daily at 0.15% sulfur, the feed or forage contributes 15 g of sulfur, making the total sulfur intake 35 g, or 0.35% on a dry matter basis. Water therefore may be a substantial source of sulfur.

Some have suggested that sulfides result in thiamine destruction, thereby directly implicating a thiamine deficiency in the pathogenesis of sulfur-associated PEM. Rumen thiamine production was slightly reduced by the inclusion of excessive sulfur in the ration.[1137] However, the authors deemed the reduction clinically insignificant. Apparently, sulfur-associated PEM occurs independent of thiamine status.

PEM induced by feeding of molasses and urea is thought to be related to the high sulfur content of the molasses and to the depletion of propionate and other glucogenic precursors induced by the foodstuff.[1077] It is not considered to be caused by an underlying thiamine destruction. The tissue thiamine concentrations of animals with molasses-related PEM are normal,[1138] and signs are preventable by concomitant feeding of glycerol, which is converted to glucose in the rumen. Outbreaks of PEM in range cattle have been associated with ingestion of the plant *Kochia scoparia*.[1139,1140] The pathogenesis of this condition is unknown; however, some have suggested that the plant has the capacity to accumulate sulfur in the forage.[1114]

Some cases of PEM cannot be linked to either problems with thiamine or sulfur toxicosis. Other compounds, such as lead, affect electron transport in a manner similar to sulfides and therefore also impair ATP production. Water intoxication creates a similar histologic lesion, but the pathogenesis of edema relates more to the generation of osmotic compounds and fluid shifts with rapid fluctuations of blood and neuronal osmolality.

35.2.33.5

Epidemiology

PEM has a worldwide distribution. The condition is seen both in individuals and as herd outbreaks. In one instance, approximately 2000 of 2200 sheep grazing were clinically affected with PEM.[1067] No predilection by gender or breed is seen, although anecdotal reports suggest that heifers are less likely to develop PEM than steers in a feedlot environment. The condition affects cattle, sheep, goats, deer, camels, and camelids.[1068,1074,1141–1144] Although PEM is seen predominantly in animals that eat a high-concentrate supplement, the condition also can occur in unsupplemented animals on pasture. The inciting cause of PEM can be identified in some cases.

One report from the United States indicated a predominance of cases in the summer in range cattle.[1064] The age range for susceptibility to PEM has been reported as 3 weeks to 5 years in sheep, 3 weeks to 8 years in cattle, and 2 months to 2½ years in goats. The peak age of incidence is 18 months or younger in cattle and sheep, but this depends on the production system.[1064,1071,1145] The incidence of PEM has been reported as high as 90% in some sheep flocks, with mortality of 1% to 10%.[1067] The incidence of PEM is high in sheep exported by sea from Australia to the Middle East. In these cases the underlying disturbance was thought to be associated with a thiamine deficiency caused by a lack of rumen synthesis secondary to the shipboard conditions.[1146]

35.2.33.6

Necropsy Findings

In cases of sulfur-associated PEM, rumen contents may have an odor of H_2S. In other cases there may be evidence of grain overload, coccidiosis, or respiratory disease. Some of these lesions relate to management conditions, but may also relate directly or indirectly to PEM. The macroscopic pathologic brain lesions of PEM include cortical swelling, softening, flattening, and yellowish discoloration of the gyri. Necrotic areas of the cerebral cortex autofluoresce under ultraviolet light (365 nm).[1147,1148] Severe cases show herniation of the cerebellum through the foramen magnum or the occipital cortex under the tentorium cerebelli. Animals necropsied months after recovery may show cerebral atrophy and submeningeal cortical cysts. The major microscopic lesion is a diffuse laminar necrosis. Other changes include intracellular and intercellular edema, neuronal necrosis, gliosis, and neuronophagia.[1066,1080]

35.2.33.7

Treatment and Prognosis

Regardless of the underlying cause, animals with the subacute form of PEM often respond favorably to parenteral administration of thiamine hydrochloride. These animals may remain blind and may have depressed sensorium for weeks or months.[1149] Thiamine should be administered at 10 to 20 mg/kg IM or subcutaneously (SC) three times daily. In severe cases, IV administration of the first dose might be warranted. If given IV, thiamine should be diluted in 5% dextrose or other isotonic fluid and administered slowly to avoid adverse reactions. If no improvement occurs initially, the treatment should be continued for at least 3 days. In some patients, recovery may take as long as 7 days, but most patients show improvement by 24 hours. A single administration of sodium dexamethasone at 1 to 2 mg/kg IM or IV or 1 g/kg of mannitol in a 20% solution IV may be beneficial in reducing cerebral edema. Anecdotal reports indicate that feedlot animals that have recovered from PEM are at increased risk of respiratory disease; therefore,

prophylactic antimicrobial administration may be indicated. Convulsions may be controlled with phenobarbital, pentobarbital, or diazepam. Specific dosing regimens are listed in Tables 35-7 and 35-8.

Animals with the acute form of PEM usually have more severe cortical and deep gray matter lesions than animals with the subacute form.[1071] These animals generally do not respond to therapeutic regimens. Ruminants with PEM secondary to the molasses-urea diet do not appear to respond to treatment with thiamine. They may respond more favorably to parenteral administration of glucose or enteral or parenteral administration of a glucose precursor.

35.2.33.8 Prevention and Control

Thiamine supplementation may not prevent outbreaks of PEM. Ultimately, the best way to prevent outbreaks is to manage the dietary intakes of susceptible animals appropriately. Ruminants should be allowed an adequate period of adaptation to high-concentrate rations. All feedstuffs and water sources should be carefully analyzed on a routine basis with an estimate of total sulfur intake. If excess sulfur consumption is a factor, steps should be taken to remove sources such as high-sulfur hay, ammonium sulfate, and molasses. If the excess sulfur intake is unavoidable, steps can be taken to limit its effects. Older members of the cow herd could be used to graze the high-sulfur pastures, and younger, more susceptible animals could be kept to lower-sulfur pastures or given hay supplementation. Personnel should be trained so that animals with PEM can be identified early in the disease and treated appropriately.

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Thiamine may be supplemented (3 to 10 mg/kg of feed) in rations in which the concentrate/fiber ratio is high, but this has little or no effect in preventing PEM. Other recommendations for preventing PEM include addition of brewer's yeast to the ration and gradual adaptation of ruminants (at least 2 weeks) to high-concentrate diets. If present as a feed-limiting additive, gypsum should be removed from the diet. Elimination of supplementation and rotation of pastures have been sufficient for controlling some outbreaks.[1145] Supplementation with cobalt in trace-mineral salt mixes may be necessary in deficient areas.

35.2.34 THIAMINE DEFICIENCY OF HORSES

Horses may develop thiamine deficiency when fed diets that contain thiaminases. Common sources of thiaminases are bracken fern *(Pteridium aquilinum),* horsetails *(Equisetum arvense),* and amprolium (400 to 800 mg/kg). The clinical signs of thiamine deficiency are ataxia, conscious proprioceptive deficits, heart block, bradycardia, blindness, weight loss, dysuria, hypothermia of the extremities, and periodic muscular fasciculations. Terminally, affected horses develop convulsions. Electrolyte changes include hyperkalemia, hyperphosphatemia, hyperglycemia, and decreased glucose tolerance. Parenteral thiamine is effective treatment.[1150,1151]

35.2.35 SALT POISONING

35.2.35.1 Definition and Etiology

Salt poisoning is a common CNS disease of livestock. Salt-rich solutions ingested over time can cause production-related losses and even death. Ingestion of water containing more than 7000 mg/L of total dissolved salts is likely to result in acute salt poisoning.[1152,1153] Water that contains less than 3000 mg/L of total dissolved salts is considered safe for consumption. Salt poisoning can be associated with water

deprivation.[1152,1154,1155] Provided that access to free water is constantly available, animals may tolerate as much as 13% dietary salt intake.[1156] The total dietary salt concentration should never exceed 4%.

The acute toxic dose of oral sodium chloride (NaCl) for cattle and horses has been reported as approximately 2.2 g/kg body weight and for sheep about 6 g/kg.[1156] With water restriction, the toxic dose of salt is considerably less, and poisonings have resulted from ingestion of 0.9% NaCl in water-restricted cattle.[1157] Chronic toxicity can occur at lower dietary salt levels than acute toxicity. Ingestion of water with salt concentrations above 1% uniformly results in toxicosis if no other source of ion-free water is provided.[1158,1159]

Ingestion of water containing 0.7% salt lowers the fertility of females,[1159] and water containing 0.25% salt suppresses milk production in cattle.[1160] Dairy calves have been poisoned by daily feeding of 4 L of milk replacer containing 2.6% NaCl.[1161] Animals are most susceptible to salt poisoning during the summer because of the increased insensitive loss of water at that time. Salt poisoning in ruminants is most frequently a syndrome of "water intoxication": a period of restricted access to low-salt water, followed by unrestricted access to water.[1152,1154,1155]

35.2.35.2

Clinical Signs

Rapid ingestion of large amounts of salt causes gastrointestinal and neurologic signs.[1158,1161–1166] These include mucohemorrhagic diarrhea and colic, head-neck extension ("star gazing"), blindness, aggressiveness, hyperexcitability, psychomotor seizures (paddling and loss of consciousness), vocalization, ataxia, proprioceptive deficits, head pressing, constant chewing movements, nystagmus, muscle twitching, and coma. Death occurs as a result of respiratory failure. Before the onset of neurologic signs, cattle with chronic salt toxicosis may appear to be depressed and dehydrated. Table 35-11 summarizes the spectrum of clinical effects associated with different levels of salt intake.

Excessive salt intake also may interfere with productivity in the absence of acute neurologic signs. In one study, cattle were given either tap water (196 ppm of dissolved salts) or saline (2500 ppm NaCl), and their milk production was measured.[1160] Cows given tap water had a greater fluid intake and a significantly greater lactational persistence and daily milk production than did cows given saline. The serum concentrations of sodium and potassium were normal in the animals fed saline.

The clinical diagnosis of salt poisoning depends on the demonstration of exposure to toxic concentrations (>7000 ppm or 0.7% of sodium), the presence of water deprivation, or the determination of serum or cerebrospinal fluid (CSF) sodium concentrations greater than 160 mEq/L. CSF/serum sodium ratios greater than 1 also suggest salt poisoning. The serum sodium concentration may vary, depending on whether the patient had recently been given ion-free water before measurement. Some animals with acute neurologic lesions may be normonatremic if they have recently drunk to repletion with ion-free water, whereas others that have not had ion-free water may be hypernatremic. The CSF sodium concentration in salt-poisoned animals is consistently elevated and may exceed 200 mEq/L.[1162] Ruminal sodium concentrations above 0.36% to 0.5% or brain sodium concentrations above 150 mEq/g or 1800 ppm[1167] also suggest salt poisoning in cattle.[1162,1163,1168] Rapid intake of low-sodium water during the rehydration phase of the disease may cause intravascular hemolysis with resultant hemoglobinuria; such findings raise the index of suspicion of salt poisoning.[1153]

Table 35-11 Effects of Different Salt Concentrations in Drinking Water on Performance in Cattle

Salt Concentration (mg/L or ppm)	Clinical Effect
<1000	No effect
1000–3000	Temporary diarrhea; reduced milk production
3000–5000	May reduce milk production and feed intake; may produce reproductive failures (failure to conceive)
5000–7000	Conception failures (abortion, infertility), reduced appetite
7000	Unsafe, especially in hot weather; may produce encephalopathic signs, abdominal pain, mucoid diarrhea, thirst, salivation, polyuria, central nervous system signs; include knuckling, blindness, convulsions, coma, and abdominal pain

From McCoy CP, Edwards WC: Sodium ion poisoning in livestock from oilfield wastes, *Bovine Pract* 15:152, 1980.

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The concentration of acetylcholinesterase in plasma and RBCs is decreased in animals that have been ingesting excessive salt (>0.49% of diet).[1169] The decrease is first seen after 4 months of continuous ingestion of the high-salt diet.

35.2.35.3

Pathophysiology

The pathogenesis of salt poisoning involves the deposition of sodium ions in the CNS parenchyma and the CSF, which occurs either acutely from ingestion of a large quantity of salt or chronically after long periods of reduced water consumption. The ionic sodium accumulates in the CSF and neurons by passive diffusion. The resulting hyperosmolality reduces energy-dependent sodium transport mechanisms and the anaerobic glycolytic pathways.[1170] These mechanisms normally provide energy by which the sodium ion is removed from the cell cytoplasm.[1165] The thirst receptors are triggered in response to the hyperosmolality. The animal is permitted to drink ion-free water to repletion, and the fluid is absorbed from the gastrointestinal tract, resulting in expansion of the extracellular fluid and a return to normal plasma osmolality. Water then diffuses from the blood into the relatively hyperosmolar CSF and neurons, resulting in CNS edema, increased intracranial pressure, and acute encephalopathy. If the patient has had sudden access to a large quantity of salt, the hyperosmolality in the intestine results in saline catharsis and diarrhea.

35.2.35.4

Epidemiology

Animals are tolerant of high dietary salt levels if they have concomitant access to fresh drinking water. Feedstuffs that are common sources of excessive salt include whey, saline-preserved fish or fish meals, bakery by-products, and certain milk replacers.[1171] Confined calves may be poisoned by improperly formulated milk replacers or oral electrolyte replacements.[1162,1171] Cattle eagerly ingest large amounts of oil well sludge, which is a potential source of salt for cattle in the western and southwestern United States.[1166,1172,1173] Brine is used extensively as a flush during the drilling of oil wells. Effluents from drilling rigs

may contain as much as 100,000 ppm of salt. The effluents are also contaminated by heavy metals and magnesium salts, which complicate the clinical syndrome of salt poisoning. Concurrent neurologic disease may predispose animals to reduced water intake, as occurred in a group of goats with locoweed (*Oxytropis* species) poisoning who became water deprived because of reluctance to move to a water source. They developed clinical and pathologic evidence of salt poisoning when moved subsequently to an area where water was easily available.[1154] Salt poisoning caused by water restriction may occur either inadvertently from freezing of water sources in northern climates or from intentional water restriction of veal calves.[1162] Ingestion of brackish or tidal water is a cause of salt poisoning in cattle pastured on the coastal regions of the world.

35.2.35.5

Necropsy Findings

The pathologic changes of salt poisoning include cerebral edema and softening and flattening of the cortical gyri. Microscopic lesions include laminar cortical necrosis, poliomalacia, and occasionally, meningeal or perivascular infiltration of eosinophils. Perivascular infiltration of eosinophils is not as reliable an indicator of salt poisoning in ruminants as in pigs because most affected ruminants show perivascular cuffing of mononuclear cells.

35.2.35.6

Treatment

Treatment of animals affected by salt poisoning is difficult. Many animals die even after intensive medical treatment. Prognosis depends on severity of clinical signs at the start of treatment: animals that already have significant cerebral edema have a guarded prognosis. Therapy should be aimed at limiting the ingestion of nonionic water and attempting to remove intracellular solutes slowly from the brain while simultaneously controlling cerebral edema and attendant CNS signs. To prevent brain swelling and herniation of the brain through the foramen magnum or the tentorium cerebelli, slow reduction of the CSF and plasma sodium is imperative. Slow intravenous (IV) administration of normal or hypertonic saline is the mainstay of treatment.

Adult cattle should receive normal or hypertonic saline intravenously (IV) at maintenance rate (7% body weight in adult cattle, 10% in neonates).[1153] Slight underestimation of fluids is preferable to excess fluid administration. Serum sodium should be monitored regularly and correction effected over 24 hours or longer. Oral fluids can be introduced gradually toward the end of the first day of treatment; salt should initially be added to oral fluids to make them isotonic to blood. When IV replacement is not feasible, isotonic to hypertonic oral fluids should be administered at a maintenance level divided into four to six feedings daily. Access to low-salt water is gradually allowed after 3 to 4 days. Any worsening of clinical signs is an indication to increase the salt level in fluids and may require IV mannitol (0.5 to 2.0 mg/kg as a 20% solution) or oral glycerin (1 mL/kg diluted 50:50 with water) to reduce cerebral edema.[1153]

In calves, treatment can be accomplished by administration of hypertonic saline concomitantly with feeding of 2 to 4 L of fresh milk daily. First, the plasma sodium concentration is measured, and the calf then is given 1 to 2 L of a hypertonic saline solution IV. The molar strength of the sodium ion in the IV fluid should be equal to or slightly greater than that of the plasma. If the hypotonicity of the whole milk is not counterbalanced by treatment with hypertonic saline, the CNS will rapidly expand as a result of absorption of free water. The plasma electrolyte concentration is measured twice daily. If the plasma sodium concentration declines too rapidly, 1 L of hypertonic saline solution is infused over several hours. The concentration of sodium in this fluid should be greater than the most recent plasma sodium measurement and less than the beginning plasma sodium concentration. If the calf develops nervous twitching, salivation, head-neck

extension, stiff forelimbs, or convulsions, 0.5 to 1 g/kg of mannitol is immediately infused IV. A blood administration set is used to filter insoluble mannitol crystals. The calf should have no access to fresh water.

The use of solutions containing 5% glucose is dangerous and probably contraindicated because this represents ion-free extracellular fluid, which can exacerbate brain edema. Administration of corticosteroids (dexamethasone, 0.4 to 0.8 mg/kg by slow IV injection twice daily for 2 to 3 days) may be helpful in animals with acute cerebral edema. However, potential benefits should be weighed against the possibility of inducing extrarenal sodium retention. If the neurologic signs diminish and the plasma sodium level returns to normal, the animal may be given fresh ion-free drinking water. Thiamine (10 mg/kg by slow IV injection) may be a useful adjunctive therapy.

35.2.35.7 Control

Cattle should be fenced away from polluted ponds and oil wells. Cattle on coastal pastures should have access to fresh well water. The total daily dietary salt intake should not exceed 4% of dry matter intake. Drinking water must contain less than 7000 ppm of sodium unless the dietary sodium load is reduced correspondingly. Oral rehydrating fluids for calves should be dissolved in strict accordance with the manufacturer's recommendations and should not be administered for longer than 3 consecutive days.

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35.2.36 VITAMIN A DEFICIENCY

35.2.36.1 Definition and Etiology

Vitamin A (retinol) is found in green plants and can be synthesized by the small intestinal mucosal cells from plant carotenoid precursors. Precursors of vitamin A are usually fed in cattle rations as β-carotene or as retinoids (retinyl palmitate or acetate). Carotenoid in forage is converted to retinol in the liver and gut. Vitamin A deficiency occurs primarily in growing ruminants in feedlots. Deficiency develops under these conditions because the growing animal has a higher requirement for the vitamin, and feedlot-reared animals may have limited access to succulent plants. The vitamin is labile in foodstuffs and is essentially depleted after several years of storage. Diets that are naturally low in vitamin A include cereal grains, beet pulp, and cottonseed hulls. Conditions in which the immune system is challenged, as when exposure to pathogens is high, also increase the requirement for vitamin A.

The clinical signs of vitamin A deficiency in cattle are related to increased intracranial pressure and ill-thrift caused by secondary infections. Signs include intermittent convulsions, depression, and blindness. The usual dietary or management conditions that favor the vitamin deficiency include grazing on dry pastures or cereal grains other than corn, exclusive feeding of cereal grains that have been stored at high temperature and humidity, or prolonged feeding of mineral oil as a preventive for frothy bloat.

35.2.36.2 Clinical Signs

The neurologic signs of vitamin A—depleted animals are age dependent. Signs in deficient calves include anorexia, ill-thrift, blindness, diarrhea, and pneumonia. The syndrome in adults is characterized by “star-gazing” posture, blindness, diarrhea, anasarca, nystagmus, strabismus, exophthalmos, loss of pupillary light reflexes, and intermittent tonic-clonic convulsions. The seizures last for only a few minutes and are followed by partial recovery.[1174–1176] Animals may die during seizures. Stimulation of the animals frequently

precipitates seizures.[1177,1178] Death often is preceded by hyperesthesia and coma.[1174,1175,1179] Inadequate vitamin A supplementation of calves is associated with unthriftiness, intermittent fevers, and a higher incidence of diarrhea.[1180] Vitamin A—deficient adults appear to be in good body condition unless parasitism or some other nutritional deficiency is superimposed on the low vitamin A intake.[1174,1181] Secondary factors that can influence the appearance of the animals include concomitant nutritional deficiencies, parasitism, and pneumonia.

The ocular changes of vitamin A deficiency are characteristic. The pupils become dilated and unresponsive. As papilledema develops, the optic disc becomes pale and its borders become indistinct, particularly in the upper quadrants,[1174,1176,1182] giving the appearance of an inverted heart. The swollen disc may cast a shadow on the adjacent retina. The color of the disc becomes faded. In advanced cases the disc may become atrophic and appear dull, gray, flattened, and smaller than normal. The retinal blood vessels become tortuous or appear to be occluded as they course over the disc. Retinal detachment and subretinal hemorrhages are possible.[1174] Corneal changes are an uncommon clinical finding.[1174,1175]

Reproductive disturbances can occur, including malformed fetuses, abortions, loss of libido, testicular degeneration, and decreased sperm counts. Calves born to vitamin A—deficient dams are blind, have domed foreheads and thickened carpal joints, and are weak at birth.[1183]

Vitamin A deficiency can be clinically differentiated from polioencephalomalacia (PEM) and salt poisoning by comparing the menace response with the pupillary light reflex. Calves with lead poisoning and PEM generally have intact pupillary light reflexes because of the proper functioning of the mesencephalon and optic nerves, whereas vitamin A—deficient cattle have absent pupillary light responses because of retinal degeneration and constriction of cranial nerve II at the level of the optic foramen.

35.2.36.3 Clinical Pathology

Assay of vitamin A and carotene concentrations in the plasma and feed is the most direct method of diagnosing the dietary deficiency. The concentration of plasma vitamin A and β-carotene in normal animals ranges from 25 to 85 μg/dL and 150 and 397 μg/dL, respectively.[1175] Plasma concentrations of vitamin A—deficient and β-carotene—deficient animals usually are less than 7 and 70 μg/dL, respectively. Papilledema first occurs when plasma concentrations of the vitamin fall below 18 μg/dL.[1184] Ataxia and blindness occur when the serum vitamin A concentration ranges from 4.87 to 8.88 μg/dL.[1177] The hepatic concentration of vitamin A and carotene in normal calves ranges from 60 to 200 and from 4 to 800 μg/g of tissue, respectively. In deficient calves the hepatic concentrations of the vitamin A and carotene nutrients range from 2 to 14 and from 0.5 to 32 μg/g, respectively.[1181,1184] There are no consistent changes in the blood chemistry analysis or the hemogram of deficient animals. Increased CSF pressure (>200 mm Hg) may occur; however, standardization of the measurement for all forms of anesthesia and methods of measurement is difficult.[1185] Changes in the CSF of vitamin A—deficient animals include a mononuclear cell pleocytosis (40 to 50 nucleated cells/dL) and an increased protein concentration (140 mg/dL).[1186]

35.2.36.4 Pathophysiology

Vitamin A is responsible for the regeneration of rhodopsin in the retina and the maintenance of tissue integrity. The vitamin has effects on osteoblasts and osteoclasts, epithelial tissues, the choroid plexus, and

reproductive tissues. The arachnoid villi and the retina are most sensitive to a deficiency of the vitamin. Vitamin A deficiency causes a thickening of the dura mater, resulting in diminished CSF absorption from the arachnoid granulations and the nerve rootlets. Narrowing of all the bony foramina of the skull occurs in immature animals, although bone remodeling does not occur in adults. The combined effects cause an increase in CSF pressure.[1181] In severe cases the brain may herniate through the foramen magnum. Closure of the optic foramen may lead to transection of the optic nerve. The high CSF pressure is transmitted into the optic nerves and results in papilledema.

Three causes of blindness have been associated with vitamin A deficiency. Nyctalopia is presumably caused by the decreased formation of vitamin A aldehyde in the regeneration of the visual pigment rhodopsin; this type of blindness usually is reversible. Degenerative changes in the outer retinal layers also cause blindness; this is reversible if treated in the early stages. The third cause is associated with stenosis of the optic foramen and compression of the optic nerve; this condition is irreversible.[1187] An experimental study has shown that humoral immune function also is impaired in sheep with vitamin A deficiency. The pathogenesis of this condition is unclear.[1188]

35.2.36.5

Epidemiology

The vitamin A requirement of all species ranges from 40 to 110 IU/kg daily.[1189–1191] The minimum recommended daily dose of vitamin A for growing calves up to 1 year of age, for pregnant sheep, and for growing horses is 40 IU/kg. Pregnant cattle and pregnant or lactating horses require 40 to 50 IU (13.76 to 17.2 µg/kg) of vitamin A daily.[1189] Lactating cattle require 80 IU (27.5 µg/kg) of vitamin A daily. Horses are susceptible to vitamin A deficiency, but the condition is rarely seen in that species. This is thought to be the result of differing conditions of management rather than an inherent resistance to the deficiency. The daily dietary requirement for carotene is 0.12 mg/kg.[1189] Pasture forage, silage, and properly cured hay (<1 year old) contain large amounts of carotene. Common constituents that have low concentrations of vitamin A are sorghum, brewer's grain, and wheat straw.

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Livestock are protected from short-term deprivation of vitamin A by their ability to accumulate the vitamin in the liver; however, it is estimated that the intake required to initiate storage is at least three times the minimum daily intake.[1189] Vitamin A—replete cattle fed a diet devoid of vitamin A require approximately 180 days before they begin to show clinical signs. During that time the cattle grow and fatten normally and show no adverse effects. Offspring born to these animals may show severe deficiencies. Papilledema and blindness develop rapidly after the hepatic stores are depleted.[1189] An interesting sexual dimorphism in susceptibility to dietary deficiency of vitamin A was found in one study of feedlot cattle; although all cattle were fed the same deficient diet, only steers had clinical signs.[1190]

Vitamin A deficiency may be categorized as a primary or a secondary condition. Primary deficiencies of vitamin A develop in cattle confined in drylot corrals or pasture on dry grass forage for prolonged periods or when cattle are kept indoors and fed unsupplemented, vitamin-depleted cereals and dry forage in which the activity of carotene has been destroyed. Also, there is a seasonal difference in the concentration of vitamin A in feedstuffs. For example, cattle grazed on green pastures are consistently replete with the vitamin, whereas those grazed on dry pastures at the end of summer may become marginally deficient. Approximately 80% of the vitamin A concentration of hay is lost during field curing.[1192]

Destruction of carotene is hastened by many environmental and physical factors, including heat, sunlight, trace mineral supplements, and humidity. In one study, exposure of nine different supplements to trace minerals in a humidified atmosphere (60% relative humidity) at 28°C (82.2°F) resulted in depletion of 47% to 92% of the total vitamin A after 1 week of incubation.[1193] Improper storage has been implicated as the cause of the depletion of vitamin A in one field case.[1189] Other factors that affect the stability of vitamin A in feedstuff include pelleting and exposure to rancid fat in the feed. The addition of gelatin to vitamin premixes has been recommended to stabilize the vitamin A activity in feed.[1184,1194]

Secondary deficiencies of vitamin A result from interference with vitamin absorption, inhibition of the conversion of β-carotene to retinol (vitamin A) in the small intestine, or an increased requirement in the face of limited vitamin intake. The conversion of carotene to retinol is impaired in vitamin A—deficient patients.[1179] Sheep may be more resistant to vitamin A deficiency because they convert β-carotene more efficiently than cattle.[1179] Extensive destruction of preformed vitamin A by microflora appears to occur in the rumen and the abomasum.[1194–1197] Microbial destruction, fever, lactation, high ambient temperatures, and inadequate dietary energy may increase the daily requirement for vitamin A.[1198] Females are slightly more resistant to the vitamin deficiency than males, presumably because of the interconversions of estrogenic hormones into vitamin A.

Secondary deficiencies of vitamin A may be caused by impaired vitamin absorption, which may occur from long-term feeding of mineral oil. Ingestion of highly chlorinated naphthalenes (X disease) causes severe vitamin A deficiency as a result of interference with the conversion of carotene to vitamin A. Some in vitro evidence indicates that a high level of dietary nitrates inactivates intraruminal vitamin A by oxidation. This may not be clinically important, however, because studies performed in vivo failed to show a greater requirement for the vitamin when animals were fed subtoxic doses of nitrates.[1197–1202] Other factors that can affect availability of vitamin A or the requirement for the vitamin include diets with low forage content, high proportion of corn silage to hay in the diet, increased exposure of animals to pathogens, and periods where immunocompetence is reduced (e.g., peripartum period).[1191] Challenges to the immune system increase the requirement for vitamin A.

35.2.36.6 Necropsy Findings

The major pathologic changes in the fundus of vitamin A—deficient calves include papilledema, small flame-shaped hemorrhages around the optic disc, venous congestion in the area of the swollen optic disc, degeneration of the retinal ganglion cells, focal retinal thinning, and fusion of parts of the retina to the choroid plexus.[1182] Other changes associated with vitamin A deficiency include doming of the frontal bones, enlargement of the carpi, cerebellar and cerebral compression, partial transtentorial herniation of the cerebellum, cystic dilation of the hypophyseal cleft, focal ruminal hyperkeratosis, and increased keratinization of the squamous epithelium of the penile and the preputial mucous membrane.[1203,1204] Corneal ulceration and clouding have been observed in the eyes of calves with naturally occurring deficiencies.[1175,1185] Vitamin A deficiency also can cause anasarca, squamous metaplasia of the salivary ducts, degeneration of the germinal testicular epithelium, degenerative changes in the intestinal epithelium in lambs, and reduction in intramuscular fat in cattle.[1204–1206]

Microscopic changes in the CNS include attenuation of the optic nerve with necrosis and demyelination. Focal accumulations of phagocytic cells containing lipofuscin and hemosiderin are present in the necrotic

area. The optic nerve is attenuated along its entire length. Gliosis and focal vacuolization of the nerve also are seen, as is a focal loss of granular and molecular layers and Purkinje's cells in the cerebellum. The meninges are thickened by fibrosis and mononuclear cell inflammation. The microscopic changes in the bones include wider than normal spacing of the central canals and reduction of osteoclastic lacunae.

35.2.36.7 Treatment and Control

Cattle with severe blindness caused by damage to the retina or optic nerves do not regain their vision when treated with vitamin A; however, cattle with acute encephalopathy and simple papilledema may respond favorably after a short period of vitamin supplementation.[1189] Affected cattle should receive 440 IU/kg (1 IU = 0.4 µg) of vitamin A parenterally and then 6000 IU/kg parenterally every 50 to 60 days until the diet has been enriched. High-dose oral therapy is important because carotene and oil suspensions of vitamin A are not efficiently used when administered by parenteral injection.[1207] Administration of large doses orally is important because conversion of β-carotene to vitamin A is inhibited in deficient calves. The recommended concentration of vitamin A in milk replacers for preruminant calves is 11,000 IU/kg dry matter.[1180]

Prophylactic dietary supplementation of vitamin A should be considered in all cattle that lack access to green feed. Dietary supplements could include leafy, freshly cured hay, green pasture, or 0.5 to 2 kg of alfalfa meal daily. Concentrate feeds formulated with exogenous, stabilized vitamin A are commercially available. 1029
Vitamin A powder* may be added to the drinking water at a rate of 425,000 U/50 gallons. This treatment 1030
should be continued for as long as the dietary deficiency exists. The recommended vitamin A requirements in cattle are 80 IU/kg for growing animals and 110 IU/kg for adult animals (including pregnant and lactating cows). Recommended concentrations (IU/kg dry matter) of vitamin A in feed are 2200 IU for feedlot cattle, 2800 IU for pregnant cows, and 3900 IU for lactating cows.[1191]

Subclinical deficiencies in ewes have been treated with a vitamin-mineral premix containing 0.3 to 0.27 kg iodine, 20.6 kg zinc, 7.9 kg copper, and 1644.5 million IU vitamin A per ton of feed. Addition of this premix to the diet of a group of sheep increased their productivity, as measured by viability, birthweight and rate of gain of lambs, and amount and quality of wool.[1208]

* Vitamin AD 5000, Butler, Inc., Dublin, OH.

35.2.37 HYDROCEPHALUS AND HYDRANENCEPHALY OF RUMINANTS

35.2.37.1 Definition and Etiology

Hydrocephalus/hydranencephaly is a common occurrence in large ruminants. It is underdiagnosed because many of the affected animals die of complications, and the primary condition is overlooked during clinical and pathologic examinations. One study reported that 97 of 155 calves with CNS lesions had hydrocephalus.[1209] Hydrocephalus may be classified as hypertensive or normotensive.[1210]

35.2.37.1.1 NORMOTENSIVE HYDROCEPHALUS (HYDRANENCEPHALY)

Normotensive hydrocephalus that develops as a result of a failure of cell growth or cellular necrosis is called *hydranencephaly*.[1210] Most cases of hydranencephaly in domestic livestock are caused by in utero infection of the fetus by the bluetongue, bovine viral diarrhea (BVD), akabane, Cache Valley, aino, or

border disease virus.[1209,1211–1217] The pathogenesis and epizootiology of the multisystemic virus infections bluetongue and BVD are discussed in detail in Chapter 32. The neurologic effects of border disease virus infection are discussed earlier in this chapter.

The loss of neurons results in flexural contractions of the limbs (arthrogryposis) and inability to nurse. The calves appear blind and are unaware of their surroundings. They usually are unwilling to stand and display a weak suckle. They may exhibit a dysphonia, which resembles a bark. Neonates that are unable to nurse are deprived of colostrum and die of septicemia by 4 days after birth.

35.2.37.2 Akabane Virus Infection

The akabane virus is a member of the Sindbis serologic subgroup of the Bunyaviridae family of the Arboviridae.[1211] It has been isolated from cattle in Africa, Japan, Israel, Korea, and Australia.[1212–1217] The host range of akabane virus includes sheep, cattle, and goats. Infection of pregnant, nonimmune dams results in hydranencephaly or arthrogryposis of the fetus.[1218] The disease is thought to be transmitted to the cow by various *Culicoides* species. Experimentally infected calves develop porencephaly and encephalitis when exposed to the akabane virus between gestational days 62 and 96.[1219] Studies in naturally infected cattle showed that infection of calves between days 76 and 104 of gestation resulted in hydranencephaly or porencephaly, whereas infection between days 103 and 174 of gestation resulted in arthrogryposis.[1220] Lambs are susceptible when exposed to the virus on gestational days 30 to 36.[1217] Fetuses that survive the in utero infection are born with arthrogryposis. The CNS lesions apparently are the result of a direct necrotizing effect of the virus on the developing neurons. The pathologic changes of the CNS in experimentally infected calves and lambs are similar to those of naturally acquired infections.[1214,1217] Adults occasionally abort when infected by the virus but do not develop clinical disease.

A syndrome of arthrogryposis, facial deformities, kyphoscoliosis, hydranencephaly, and hypoplasia of multiple regions of the brain and spinal cord has been described in Corriedale sheep in Australia. Although resembling the disorder caused by congenital akabane virus infection, breeding trials supported an autosomal recessive inheritance for the disease.[1221]

35.2.37.3 Aino Virus Infection

The aino virus causes stillbirths, premature calving, and congenital malformations, including arthrogryposis, cerebellar hypoplasia, and hydranencephaly, in calves of Japan and Australia.[1222–1224] Aino virus is antigenically and biologically distinct from akabane virus, but the clinical syndromes of fetal infection by the two viruses are indistinguishable.

35.2.37.4 Chuzan Virus Infection

Hydrocephalus, hydranencephaly, and cerebellar hypoplasia have been attributed to infection of pregnant cattle with the Chuzan virus.[1225–1227] This virus is a relative of the akabane and aino viruses and is classified as a new member of the Palyam subgroup of the genus *Orbivirus*. The virus has been isolated from *Culicoides oxystoma,* which may serve as the major vector. The clinical signs are characteristic of hydrocephalus.

35.2.37.5

Cache Valley Virus Infection

A flock outbreak of arthrogryposis, myositis, hydranencephaly, and a variety of other brain malformations (micrencephaly, cerebellar hypoplasia, porencephaly) in newborn lambs in the southwestern United States was attributed to in utero infection with the Cache Valley virus (family Arboviridae).[1228,1229] Cache Valley virus was first isolated from mosquitoes from Utah and has since been isolated from caribou, horses, sheep, and cattle elsewhere. Antibodies have been found in white-tailed deer in the southwestern United States, but the role of this mammal in the survival of the virus and the transmission of the disease to livestock is unknown.[1230] In one survey of sheep in the western United States, the seroprevalence for the Cache Valley virus was 19.1%.[1228] Vectors for the virus include *Anopheles, Aedes, Culex,* and *Coquellettidia* mosquitoes.[1231] Infection before 30 days of gestation may cause embryonic death, whereas infection between days 30 and 52 causes fetal malformations.[1231]

35.2.37.6

Bluetongue Virus Infection

The bovine fetus is most susceptible to the development of hydranencephaly from bluetongue virus when the dam is infected at approximately 125 days of gestation.[1232,1233] Abortions occur when nonimmune dams are infected at other times of gestation. Serotype 11 or serotype 17 of the virus is most frequently isolated from calf and lamb neonates in field epizootics.[1233] Calves infected in utero may develop one or more associated birth defects, including hydranencephaly, arthrogryposis, brachygnathia, prognathia, and excessive gingival tissue. In vitro studies have not supported the role of infected calves as reservoirs for the virus.[1234] Similar abnormalities and fetal deaths have been reported following vaccination of pregnant ewes with live attenuated virus.[1235] (See Chapter 32 for additional information.)

35.2.37.7

Bovine Viral Diarrhea Virus Infection

Hydranencephaly, hydrocephalus, and cerebellar hypoplasia have been associated with fetal infection of cattle with the BVD virus.[1236–1239] Precolostral serum antibody titers for the virus in affected calves vary; some titers range from 1:32 to 1:256, but other calves may have persistent viremias yet no demonstrable antibody. The BVD antibody titer in CSF may range from 1:4 to 1:32. The virus can be isolated from approximately 12% of affected calves.

35.2.37.8

Other Infectious Agents

A single case of hydrocephalus in a calf aborted at 7 months of gestation was associated with necrotizing encephalitis caused by *Neospora caninum*.[1240]

35.2.37.8.1

HYPERTENSIVE HYDROCEPHALUS

An increase in CSF volume that results from compressive or obstructive lesions in the ventricular system or from decreased CSF absorption is called hypertensive hydrocephalus.[1210] Obstructive lesions of the ventricular system trap the CSF in the ventricles, causing an increase in CSF volume and pressure. Ischemia and CNS degeneration result from the high CSF pressure. The sites of obstruction most often

include the lateral apertures, mesencephalic aqueduct, lateral ventricles, interventricular foramina, and fourth ventricle. The obstructions may be either congenital or acquired. Causes of acquired obstructive hydrocephalus include cerebral abscess, cholesteatoma (equines), equine infectious anemia, *Coenurus cerebralis* infestation, pachymeningitis, and lymphosarcoma. Hypertensive hydrocephalus also may be caused by acute inflammatory disease such as meningitis and vitamin A deficiency. In these diseases the increased pressure is the result of impaired CSF resorption.

35.2.37.8.2

CONGENITAL HYPERTENSIVE HYDROCEPHALUS

Congenital hypertensive hydrocephalus is a hereditary condition seen in Hereford, Charolais, Ayrshire, Dexter, Holstein, and Jersey calves.[1241–1243] The condition also has been recognized in Arabian foals.[1244]

At least six forms of congenital hypertensive hydrocephalus (types I through VI) have been identified in cattle.[1245] Type I is a communicating hydrocephalus that is unrelated to dwarfism and apparently has a hereditary basis.[1241] The mode of inheritance is thought to be a single autosomal recessive character. In highly inbred herds the prevalence of heterozygotes may exceed 20%. Pathologic lesions of this form of hydrocephalus included cranial doming and enlargement of the cerebral cortex and the choroid plexus. All affected calves die by 5 weeks of age.

Type II occurs in Herefords and is characterized by dorsal kinking of the mesencephalon and stenosis of the sylvian aqueduct, without cranial doming. Ventricular dilation is less than that described for type I hydrocephalus.

Type III also occurs in horned Hereford cattle. This type is similar to type II, except that cerebellar hypoplasia, microphthalmia, and muscular degeneration are observed. These are not characteristics of the type II hydrocephalus.

Type IV occurs in white shorthorn calves. The disease is considered to be heritable through either an autosomal recessive gene or a dominant gene with incomplete penetrance. Affected animals develop an obstructive hydrocephalus, microphthalmia, and scoliosis of the thoracolumbar spinal column. Ocular lesions associated with the disease include persistent pupillary membranes, retinal detachment, retinal dysplasia, vitreous hemorrhage, and hypoplasia of the optic tracts. A misshapen sylvian aqueduct apparently causes the fluid accumulation.

Type V is a form of hydrocephalus with congenital achondroplasia that has been reported in Dexter and Jersey calves. The disease is considered to result from a recessive genetic trait. The calves are either aborted or stillborn. Animals that survive to term have arrested development of the nasal bones and maxillae. Anasarca, achondroplasia, kyphosis, and cleft palate also are seen.

Type VI is a form of internal hydrocephalus of Holstein-Friesian calves. The animals are born dead or die shortly after birth. The pathologic abnormalities include fluid enlargement of the lateral ventricles with normal cranial development.[1244] The condition is thought to be hereditary.

35.2.37.9

Clinical Signs

Hydrocephalic animals often are born dead or are weak and die shortly after birth. The most obvious signs in animals that survive include failure to bond to the dam, depression, diminished learning ability, partial failure of suckling, droopy head and ears, muscular fasciculations, head tremor, conscious proprioceptive deficits,

blindness, ventrolateral strabismus, nystagmus, dysphonia, tongue flaccidity or paralysis, retention of food material in the cheeks and lips, limb spasticity, hyperreflexia, psychomotor seizures, recumbency, and coma. Occasionally, doming of the calvarium or protrusion of fluid-filled cystic structures through an open fontanelle is seen.[1246] Affected neonates often do not ingest sufficient amounts of colostrum and frequently die of septicemia.

In virally induced cases of hydranencephaly, associated skeletal deformities may be observed, including abnormally curved ribs, kyphoscoliosis, flexural deformities of the limbs, domed skulls, and brachygnathia. Patients with hydrocephalus caused by compressive lesions around the ventricular system may show unilateral or bilateral signs of increased intracranial pressure. The clinical signs of unilateral lesions include head tilt (toward the lesion side), ipsilateral mydriasis, and contralateral menace deficit. Signs of hydrocephalus in foals are similar to those in calves. The cause of the condition in horses is unknown.

Antemortem diagnosis of brain malformations has been facilitated by CT and MRI. However, these techniques are rarely warranted or available for use in large animal species. A more practical technique for using ultrasonographic imaging, transorbital echoencephalography, has recently been described and has proved effective for the diagnosis of hydranencephaly.[1247]

35.2.37.10 Clinical Pathology

The diagnosis of hydrocephalus in calves and lambs is typically based on the presence of characteristic clinical signs and a domed skull. Whenever hydranencephaly is suspected, blood should be collected for virus isolation, serologic testing, and quantitative immunoglobulin determination. Presuckle serum samples from bovine fetuses that have been infected by the akabane or bluetongue virus in the latter part of gestation may be seropositive. Immunologically competent calves that are infected with the bluetongue virus have serum neutralization indices ranging from 2.5 to 4.[1230]

35.2.37.11 Necropsy Findings

The pathologic lesions of hydranencephaly are similar regardless of the etiologic agent. They include microcephaly, cerebellar hypoplasia, hydrocephalus, hydranencephaly, and porencephaly of the cerebral and the cerebellar cortex. Microscopic lesions of hydranencephaly include segmental loss of dorsolateral ventricular ependyma, thinning of the periventricular white matter, porencephalic cysts, and nonsuppurative meningoencephalitis. Lesions in other parts of the CNS may include loss of ventral horn cells in the spinal cord and demyelination in the spinal cord. Nonsuppurative inflammatory changes may be seen in cases caused by viral infections. Polymyositis has been described in affected calves; however, it is unclear if these lesions are caused by viral infection or occur secondary to the denervation. The skeletal deformities associated with virally induced hydranencephalies include rigid extension or contraction of one or more limbs (arthrogryposis), abnormally curved ribs, domed skull, thickening of the calvarium, kyphoscoliosis, and brachygnathia.

35.2.37.12 Treatment

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1032

Except for one report of successful surgical intervention in a calf with a meningocele, no satisfactory therapy is available for the treatment of hydrocephalus or hydranencephaly in large animals.

35.2.38 AMMONIATED FORAGE TOXICOSIS (COW BONKERS)

Exposure of poor-quality forage to anhydrous ammonia improves the nutritional density of the material and reduces certain toxic fungal metabolites, specifically the prolactin-like toxins of the endophytic fungus *Acremonium coenophialum*.[1248] Ammoniation increases dry matter intake, enhances digestibility, and increases the relative value of the protein content of the feed. However, overammoniation of the forage, at a rate exceeding 3% of the forage on a dry matter basis, may result in toxicosis. Studies now suggest that several dialkylimidazoles may be responsible for the neurotoxic effects of ammoniated feedstuffs, superseding previous theories that 4-methylimidazole is the primary neurotoxin.[1249,1250] Ammoniated foodstuffs containing high levels of molasses are more toxic than similarly treated grass hay. The toxin may be concentrated in milk; consequently, calves suckling from normal-appearing dams may show clinical signs of intoxication.

Affected animals are hyperesthetic and ataxic. At rest the animals assume a sawhorse stance, but when excited, they become hyperactive, appear to be blind, and circle propulsively. Other clinical signs include vocalization, dysphonia, and walking or running into objects. The periods of frenzy may result in recumbency and convulsions. The spasmodic episodes last for 15 to 20 minutes. Afterward the animals rest quietly, with occasional muscle tremors. Repeated occurrences of the mania may be precipitated by loud noises or other frightening experiences. The concentrations of ammonia in the cerebrospinal fluid (CSF) and blood may be increased. In one report, blood and CSF concentrations of ammonia were 8.16 and 1.05 μg/mL, respectively. Levels of interleukin-6 (IL-6) are elevated in the CSF of affected calves, but not in the systemic circulation.[1251] IL-6 is hypothesized to play a key role in ammoniated forage toxicosis. Although specific treatments have not been identified, one report indicated that affected calves benefited from acepromazine (0.045 mg/kg IV) and thiamine (1.14 mg/kg IM).[1252]

35.2.39 LEAD POISONING

35.2.39.1 Definition and Etiology

Lead poisoning in ruminants is characterized by an acute encephalopathy. In contrast, lead poisoning in horses is characterized by chronic polyneuritis. Blindness, ataxia, and depressed sensorium are significant clinical signs in cattle, sheep, and goats, whereas in horses the poisoning is associated with weight loss, dysphagia, and secondary aspiration pneumonia. Cattle most often are poisoned because of their tendency to lick or chew on foreign objects, their access to lead-containing materials, and their propensity to drink contaminated petroleum distillates.[1253]

35.2.39.2 Clinical Signs

The signs of lead poisoning in ruminants are characteristic of central nervous system (CNS) derangement. During the first stages of lead poisoning, affected cattle stand alone and are depressed.[1254] They may show hyperesthesia, muscular fasciculations, and rapid, spastic twitching of the eyelids or other facial muscles. Progression of the disease is associated with ataxia, conscious proprioceptive deficits, blindness, head pressing, odontoprisis, coma, and convulsions.[1255,1256] Despite the blindness, the pupillary reflexes usually are normal. Some animals may display episodic running, hyperesthesia, and bellowing. Others may die suddenly without premonitory signs. The more acute and severe the toxicity, the more acute, severe, and

excitatory are the clinical signs.[1257] Animals with subacute or chronic lead poisoning have signs that are less excitatory and more indicative of CNS depression and have a longer clinical course. Affected cattle may accumulate frothy saliva at the commissures of the lips. Gastrointestinal (GI) signs of bloat, diarrhea, rumen atony, and colic occur in about 60% of lead-poisoned cattle, and the presence of such signs increases the index of suspicion for lead toxicity versus other causes of cerebral dysfunction.[1258] Other substances ingested with the lead may contribute to GI disturbances. The clinical signs of lead poisoning in horses include weight loss, lack of coordination, laryngeal or pharyngeal paralysis, dysphonia, roaring, conscious proprioceptive deficits, loss of anal tone, facial paralysis, and difficulty with mastication.[1259] Aspiration of pharyngeal debris caused by dysphagia may result in pneumonia. Fine muscular tremors occur intermittently. The poisoned animals die in psychomotor seizures. Horses with lead poisoning are emaciated at death.[1260]

In cattle, lead produces microscopic changes of the myocardium that result in arterial hypertension (120 to 150 mm Hg) and electrocardiographic abnormalities. These electrical changes, which occur by 30 days after exposure, include increased duration and amplitude of the P wave (0.16 second and 0.06 mV, respectively), prolongation of the PR interval (0.14 to 0.16 second), decreased QT interval (0.32 second), and inverted T wave in lead II.[1261]

35.2.39.3

Clinical Pathology

Diagnosis of lead poisoning is based on measurement of increased blood and tissue concentrations of lead. Tissue levels of lead in naturally poisoned cattle can reach 20 to 100 ppm in the liver, 30 ppm in the kidneys, and 5000 ppm in bone. Reported reference blood lead concentrations vary considerably, ranging from 0.05 to 2.5 ppm.[1255,1256,1262] Suggested toxic ranges also vary considerably among laboratories. Reference values from earlier colorimetric studies are consistently higher than those from later tests using spectrophotometry.[1263] Modern techniques usually report 0.3 ppm as the maximum normal blood lead concentration. When interpreting the results of a lead measurement, consideration of the reference ranges obtained with similar methodology is essential. Table 35-12 compares the lead concentrations of various tissues of experimentally poisoned and control calves. Heparin is the anticoagulant of choice when collecting blood for lead measurement because it does not chelate the lead. The lead concentration of ruminal fluid from acutely poisoned cattle ranges from 0 to 11,875 ppm.[1255]

Livestock that are chronically poisoned with low concentrations of lead may have a normal blood lead concentration but a high concentration in the bone. In these cases the poisoning can be diagnosed by administration of calcium disodium ethylenediamine tetraacetic acid (EDTA), which solubilizes the bone lead stores and increases the concentration of lead in the plasma. The soluble lead-EDTA complexes are excreted in the urine. The urinary lead concentration may rise by 40-fold over pretreatment levels within a few hours. Table 35-13 shows the lead concentrations in the urine and blood of naturally exposed horses and the temporal changes that occur after treatment with calcium disodium EDTA (75 mg/kg). In cases of chronic lead poisoning, radiographs of the abdomens of smaller patients may reveal lead-containing radiodense foreign material in the GI tract.[1264] “Lead lines” also may be present in the long bones of young animals chronically exposed to lead.

Table 35-12 Mean Lead Concentration (and Range) in Calf Tissues after Exposure to Different Dosages of Lead Acetate for 7 to 20 Days

	Dosage of Lead Administered		
Tissue	**Control ± SD**	**2.7 mg/kg (ppm) ± SD**	**5 mg/kg (ppm) ± SD**
Bone	0.22 ± 0.07	49.2 ± 14.15	54.92 ± 20.15
	(0.18–0.32)	(30–75.34)	(32.63–105.81)
Kidney	0.11 ± 0.02	49.49 ± 32.54	88 ± 19.5
	(0.09–0.13)	(20.72–90.36)	(51.55–114.24)
Liver	0.13 ± 0.04	19 ± 11.76	30.51 ± 11.67
	(0.09–0.18)	(5.42–29.96)	(15.13–54.98)
Cerebrum	0.07 ± 0.02	0.66 ± 0.16	0.81 ± 0.27
	(0.06–0.1)	(0.54–0.89)	(0.5–1.18)
Blood	0.03 ± 0.01	0.47 ± 0.29	1.57 ± 0.62
	(0.03–0.04)	(0.3–0.9)	(1.08–3.21)

Data from Zmudski J et al: Lead poisoning in cattle: reassessment of the minimum toxic oral dose, *Bull Environ Contam Toxicol* 30:435, 1983.

SD, Standard deviation.

Table 35-13 Urine and Blood Lead Concentrations* in Horses with Chronic Lead Poisoning before and after Intravenous Treatment with Calcium Disodium EDTA†

Tissue	Status	0 Hours	6 Hours	16 Hours	24 Hours
Urine	Poisoned	0.1–1.2	3.8–4.6	1.1–5.5	1.1–0.05
Urine	Normal	0.04–0.05	0.11–0.17	0.05–0.06	0.03–0.05
Blood	Poisoned	0.2–0.25	0.3–0.47	0.3–0.37	0.3–0.37
Blood	Normal	0.15–0.2	0.2–0.3	0.2–0.25	0.1–0.2

From Knight HD, Burau RG: Chronic lead poisoning in horses, *J Am Vet Med Assoc* 162:781, 1973.

* Values given in ppm; numbers reflect the range of observations.

† Dosage of 75 mg/kg body weight.

When blood lead concentrations are normal in chronically poisoned animals, measurement of free erythrocyte porphyrins and erythrocyte concentrations of α-aminolevulinic acid (ALA) are the preferred

methods of diagnoses. The concentration of porphyrins is increased in the blood, urine, and feces of animals with lead poisoning. The reference range of blood porphyrin concentrations in normal calves is 21.6 ± 11.6 to 45.6 ± 10.3 μg/dL for whole blood and 113 and 142.8 ± 32.4 μg/dL for erythrocytes.[1256,1265,1266] In chronically exposed, asymptomatic cattle, the free erythrocyte porphyrin concentrations are frequently greater than 2000 μg/dL. A field test has been developed for determining blood porphyrins.[1266]

Reference ranges for ALA dehydrase are 45.8 ± 20.6 U, whereas activities ranging from 28 to 33 U have been reported in naturally exposed calves.[1260] The urinary concentration of δ-ALA is increased and range above 500 μg/mL.[1261,1267,1268] Measurement of ALA in the erythrocytes is more reliable than measurement in urine.[1269]

Environmental sources of lead can be detected by direct measurement of the lead concentration of the soil or pasture forage. Forage from toxic pastures contains more than 30 ppm of lead, and in some cases the level may exceed 300 ppm.[1268,1270]

The hematologic abnormalities of lead poisoning are subtle. Most poisoned livestock have a normal hemogram. If present, lead-related changes are characteristic of a hemolytic anemia with an inappropriately large-bone marrow response. The morphologic abnormalities of erythrocytes include anisocytosis, poikilocytosis, polychromasia, hypochromia, Howell-Jolly bodies, metarubricytes, and basophilic stippling.[1255,1271] The shape changes begin within hours after ingestion of the lead and peak by 100 days.[1255,1271] Blood changes do not occur in all cases of the disease and are not necessarily specific indicators of lead poisoning in cattle, in which elevated blood lead may be present without hematological abnormalities.[1272] However, hematologic abnormalities tend to be more consistent in chronic lead toxicity and in lead-poisoned horses.

Lead toxicity has a variety of effects on endocrine function in cattle. Elevated levels of serum T_3, T_4, estradiol, and cortisol have been demonstrated in cattle with elevated blood lead levels.[1273] Parameters of liver function also are affected; serum alanine and aspartate transaminase (ALT and AST) levels are increased, whereas serum lipids, total protein, and albumin are decreased.

In poisoned animals the concentrations of protein and WBCs in CSF are increased, ranging from 50 to 100 mg/μL of protein and 5 to 50 mononuclear cells/mL, respectively. Such changes are relatively nonspecific and found with other causes of polioencephalomalacia.

35.2.39.4

Pathophysiology

Lead enters the body through the GI tract or less often through the respiratory tract. Metallic lead and the sulfide form are less well absorbed than the acetate, phosphate, carbonate oxide, and hydroxide salts. Metallic lead is poorly absorbed and causes toxicity only when a lead foreign body becomes entrapped in the stomach for prolonged periods. Interaction between lead and other minerals may occur. For example, high levels of dietary calcium reduce the GI absorption of lead. Concomitant exposure to lead and cadmium results in a worsening of the clinical signs of lead poisoning.[1274]

Acute toxic single doses of lead range from 200 to 600 mg/kg for calves and 600 to 800 mg/kg for adults.[1275,1276] Although intestinal absorption of lead is relatively inefficient, significant amounts can cross into the blood if sufficient quantities are ingested. Approximately 1% to 2% of the total oral dose of lead is absorbed

by 24 hours.[1255] Increases in the blood lead concentration are observed as early as 3 hours after dosing. Most of the lead absorbed from the digestive tract (90%) is bound irreversibly to erythrocyte proteins, resulting in a low lead concentration in the plasma but higher concentrations in whole-blood specimens.[1277] At the end of the erythrocytes' lifespan, the cell-bound lead is metabolized from the erythrocyte proteins and deposited in the bone as the triphosphate salt. A smaller amount of dissolved lead is deposited into the soft tissues as the diphosphate. A portion of the soft tissue lead is excreted through the GI tract via the secretions (pancreatic juices, bile) and direct diffusion. The half-life of blood lead in adult cattle is extremely variable and unpredictable, ranging from 48 to 2507 days in one study.[1278] Phenotypic or genotypic factors may affect metabolism and storage of lead; for example, beef cattle store more lead in the liver than the kidneys compared to dairy cattle.[1279] The variable time for clearance of lead has an obvious implication for public health, because all carcasses of animals suspected or known to be exposed to lead must be tested before being cleared for human consumption.[1280]

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Lead also crosses the placental barrier and accumulates in fetal bone, liver, and kidneys, but does not substantially accumulate in milk. Infertility, abortions, and fetal malformations may result from exposure to lead.[1257] The concentration of lead in milk from lactating cattle fed a daily dose of 13 mg of lead acetate remains less than 5.9 parts per billion (ppb).[1281] In one study a logarithmic relationship between blood and milk lead concentrations was found. At blood concentrations below 3.6 µg/dL, milk lead concentrations were 0.8 µg/mL. However, cattle with higher blood lead levels (4.8 µg/dL) had exponentially greater concentrations in milk (2.2 µg/kg).[1282] Lead cannot be detected in milk by 7 months after exposure.[1283]

The toxic effects of lead include inhibition of free sulfhydryl groups found in many enzymes, interference with zinc-containing metalloproteins, and steric inhibition of enzyme activity.[1271] Enzymes of heme synthesis are particularly susceptible to injury. These include δ-ALA dehydratase and ferrochelatase. Interference with ferrochelatase inhibits the formation of heme from protoporphyrin, resulting in a buildup of unmetabolized porphyrins, including protoporphyrin I, uroporphyrins, and coproporphyrins. The last two molecules are excreted in the urine and feces, respectively.[1254] Protoporphyrin I is retained in the erythrocyte.

Interference with the activity of ALA dehydrase may be partly responsible for the brain damage associated with lead poisoning. The enzyme δ-ALA dehydrase combines two molecules of δ-ALA into a single porphobilinogen molecule. This enzyme is exquisitely sensitive to lead. Inhibition of the enzyme leads to accumulation of ALA, which is excreted into the urine. Concentrations of the synthetic product porphobilinogen in the erythrocytes are reduced.[1266,1267,1269,1284]

Because of the interference with heme metabolism and the altered function of other erythrocyte proteins, the erythrocyte half-life is shortened, which may result in a normochromic, normocytic anemia in a small proportion of chronically poisoned animals.[1284] Iron is not adequately used and is stored in sideroblasts in the bone marrow.[1266] Lead also interferes with the activity of pyrimidine-specific 5′-nucleotidase.[1285] Loss of activity of this enzyme results in basophilic stippling.

After absorption, lead rapidly enters the brain at a dose-dependent rate. The lead deposition in the CNS results in acute cerebellar hemorrhage and edema from capillary dysfunction.[1277] Abnormalities of brain cerebroside content and catecholamine metabolism have also been described in animals with lead poisoning; however, the role of these changes in the pathogenesis of the clinical signs is unknown. The pathogenesis of lead encephalopathy is multifactorial. Encephalitic signs probably originate from a combination of decreased

microvasculature, cellular necrosis, brain swelling, neurotransmitter dysfunction, and decreased glucose uptake by the brain.[1286]

The molecular effects of lead on the myocardium are unknown. Hypertension caused by chronic poisoning is thought to result from an inhibition of sodium-potassium adenosine triphosphatase or an alteration of the juxtaglomerular apparatus.[1261]

Ingestion of lead also results in aberrations of other minerals. For example, long-term exposure to lead results in competitive inhibition of selenium uptake, thereby diminishing the absorption of selenium by as much as 26%.[1276] If selenium intake is marginal, lead toxicosis could manifest as an outbreak of white muscle disease. Lead-induced selenium deficiency may contribute to the pathogenesis of myocardial disease and immune system dysfunction.

35.2.39.5

Epidemiology

Sources of lead are legion, including lead arsenate defoliants, batteries, used motor oil, linoleum, roofing felt, paint, machinery grease, caulking compounds, improperly compounded mineral supplements, and foliage near lead smelters and battery-recycling plants.[1254,1260,1268,1287–1293] Blood lead levels of animals residing in highly contaminated urban environments may be significantly greater than those of their rural-dwelling counterparts, and high lead levels have been reported in grasses growing near busy roadways, but the clinical significance of these findings is unclear.[1290,1294,1295] Contamination of preserved feeds, such as silage, can occur before or during processing or during storage. Factors that can increase the likelihood of ingestion of lead-contaminated foodstuffs include lack of alternative feed, hunger, and phosphorus deficiency.[1257] The single lethal dose of lead for cattle is estimated to range from 220 to 600 mg/kg for calves, 600 to 800 mg/kg for adult cattle, and 400 mg/kg for goats.[1257,1275] Poisonings from cumulative intake are associated with substantially lower daily doses. Although cattle can detect fairly low levels of lead on pasture and have an aversion toward contaminated herbage, continued exposure may lessen this aversion, making animals more prone to ingest contaminated material.[1296] Lead poisoning has been induced in cattle by feeding 5 to 6 mg lead/kg body weight/day for 3 years or 6 mg/kg of lead (lead acetate) for 7 days.[1268,1297] Lead poisoning has been reported in cattle exposed naturally to 6 to 7 mg/kg/day of lead on foliage and in calves given oral lead acetate at 2.7 to 20 mg/kg/day.[1297] The interval for development of clinical signs ranges from 5 to 20 days and is related to the dose and the ionic form of lead administered.[1297] Ensiling of contaminated forage results in percolation and concentration of lead at the bottom of the silo.[1298]

The toxicity of lead is apparently influenced by dietary factors. Calves on a milk diet are more susceptible to lead poisoning than calves fed hay and grain.[1262] There appears to be a direct correlation between high levels of vitamin D and enhanced lead absorption, which may explain the greater occurrence of the poisoning during the summer. Elevated copper concentrations in forage, such as may be found in pastures fertilized using pig slurry, may potentiate accumulation of lead in animals consuming it.[1299]

The estimated cumulative toxic dose of lead for horses is 2.9 mg/kg/day.[1300] Poisonings have been reported in horses grazing pastures contaminated with 320 to 440 ppm of lead from a metal smelter; this amounted to a daily intake of 2 g (~6.4 mg/kg). Metallic lead and the “galena” (insoluble sulfide salt) are less toxic than the acetate and carbonate lead salts.[1301]

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35.2.39.6

Necropsy Findings

The macroscopic brain lesions of lead poisoning are mild and include brain edema, congestion of vessels of the cerebral cortex, and yellowish discoloration and flattening of the cortical gyri. Lesions tend to be most severe in the occipital lobes. Microscopic changes in the brain include capillary prominence, endothelial cell swelling, edema of the Purkinje cell layer of the cerebral cortex, laminar cortical neuronal necrosis, and edema of the white matter.[1302] The lesions are predominantly located on the tips of the gyri. Whether these lesions are caused by a direct effect of lead on the neurons or from vascular damage is unclear.[1277] Intranuclear acid-fast inclusion bodies in the renal tubular epithelial cells have been described in experimentally poisoned cattle. Chronic lead exposure also may interfere with normal functioning of the immune system, resulting in an increased susceptibility to infections.[1303]

35.2.39.7

Treatment

Therapy for lead poisoning should include removal of the lead from the digestive tract, chelation therapy with calcium disodium EDTA, and fluid and nutritional support of the patient. Treatment with calcium disodium EDTA (calcium versenate) has been shown to be superior to treatment with penicillamine or dimercaprol (BAL). The EDTA chelates osseous but not soft tissue—bound lead.[1274] After chelation the unsaturated bone stores reequilibrate with the lead remaining in the soft tissues. In cases of acute lead poisoning, several days are required before reequilibration results in a decreased blood lead concentration. The dose of calcium disodium EDTA is 66 mg/kg/day, divided into several doses daily for 3 to 5 days.[1304] After five daily treatments, a 2-day nontreatment period is recommended to reequilibrate the soft tissue and bone lead. After the 2 days' rest, daily treatments are given for another 5 days. The decision to continue therapy with EDTA should be based on the results of posttreatment blood lead analyses and renal function tests. Another recommendation is for administration of two IV injections of calcium disodium EDTA (110 mg/kg per dose) given 12 hours apart for 2 days.[1305] Therapy then is withheld for 2 days, after which the EDTA treatments are reinstituted for 2 more days. The comparative efficacy of this regimen is unknown.

The EDTA also chelates other divalent cations. Consequently, prolonged administration of the drug results in trace-mineral deficiencies, especially of zinc. For this reason, after prolonged EDTA therapy, oral supplementation with zinc should be considered to prevent the development of parakeratosis.

Meso-2,3,-dimercaptosuccinic acid may be a more effective agent for lead chelation, particularly when it comes to removing lead from soft tissue.[1306] However, experience with this drug is still limited. There appears to be no advantage to using this drug in conjunction with calcium disodium EDTA.

Reports have indicated that thiamine therapy is an effective adjunctive treatment with EDTA in cases of acute lead poisoning of cattle.[1275,1307,1308] Administration of 2 mg/kg thiamine daily was more effective than treatment with disodium EDTA (62 mg/kg twice daily for 4 days) or thiamine plus disodium EDTA in inducing remission of clinical signs of experimentally induced lead poisoning.[1309] For clinical treatment of lead poisoning, thiamine dosages of 500 mg for small ruminants and 1 g for cattle weighing 300 kg or 5 mg/kg have been recommended.[1307] Administration of daily doses of thiamine (100 mg/calf/day or 5 mg/kg) has protected experimentally exposed calves from clinical signs of lead poisoning and reduced lead deposition in the soft tissues.[1308,1310,1311] The nature of the protective effects of thiamine is unclear. Apparently, either

lead interferes with thiamine synthesis, or the tissue distribution and deposition of lead are reduced by the formation of rapidly excreted lead-thiamine complexes.

In ruminants, ingested lead is best removed from the digestive tract by means of a rumenotomy.[1275] Magnesium sulfate laxatives are administered concomitantly to form insoluble lead sulfides. Because of the possibility of additional lead absorption from the GI tract, oral administration of chelators is contraindicated.

Patients that respond slowly to chelation and thiamine therapy should be given supportive care. These measures should include provision of 40 to 80 mL free water/kg/day for maintenance, oral hyperalimentation, and administration of diazepam or phenobarbital for convulsions (see Table 35-9).

35.2.39.8

Prevention and Control

Toxic pastures can be made safe by removing contaminated forage. This is best done by cutting, baling, and burying native grasses; burning the stubble; and applying agricultural lime at the rate of 1 ton per acre where the lead concentration of topsoil exceeds 175 ppm.[1266] In the case of negligent poisonings, vigorous attempts at laboratory confirmation of the clinical diagnosis should be made. The source of the lead should be established, and the affected animals should be carefully documented. In the United States, insurance liability responsibilities may be covered under homeowner or farm insurance.

35.2.40

TOXICITY FROM GASOLINE, PETROLEUM DISTILLATES, AND RELATED PRODUCTS

Ingestion of natural gas condensate or petroleum distillates can cause neurologic disease in livestock. Affected animals appear to be anesthetized and fail to respond to auditory or visual stimuli. The clinical signs of petroleum distillate poisoning include depression, ataxia, diarrhea, recumbency, coma, semicoma, absent menace response, decreased palpebral reflex, and muscular hypotonia. Constituents of petroleum and related products cause pathology in many organs, including the lungs, kidney, liver, and digestive tract. Thus a variety of clinical signs, such as dyspnea, coughing, and bloat, may be present in poisoned animals, in addition to neurologic abnormalities.[1312,1313] The feces and digestive tract contents have a strong odor of petroleum or gasoline. Some animals may die suddenly without premonitory signs. Animals in poor condition or suffering from chronic illness are at greatest risk of toxicity.[1314]

Necropsy findings in poisoned animals include diffuse serosal hyperemia of the bowel and forestomachs and diffuse serosal ecchymotic hemorrhages. The lungs are firm and mottled, especially in the middle and cranial lobes. These pulmonary changes may be associated with moderate amounts of serofibrinous pleural exudates. Microscopic changes in poisoned animals include myocardial degeneration and necrosis, enteritis, mild renal tubular degeneration, and granular eosinophilic casts. Affected livers develop periacinar fatty degeneration and periportal infiltrations of lymphocytes and plasma cells.

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Gas chromatography of the intestinal contents usually reveals peaks of aromatic hydrocarbons. For identification of the source of hydrocarbons, gas chromatographic profiles of the environmental specimens can be compared to those of the rumen liquor. Several oxidative biochemical activities of circulating neutrophils are reversibly depressed in animals exposed experimentally to crude oil or diesel fuel. This effect is dose dependent and may provide a method for determining exposure to oil and petroleum products and for tracking recovery.[1315]

In early cases of petroleum distillate poisoning, removal of the hydrocarbons by means of a rumenotomy should be considered. Treatment usually is futile when the animal becomes recumbent and unresponsive.[1316]

35.2.41 ETHYLENE GLYCOL TOXICOSIS (ANTIFREEZE POISONING)

Antifreeze poisoning occurs primarily in ruminants.[1317,1318] When ingested, ethylene glycol is enzymatically converted to a number of acidic intermediate compounds, especially glycolic acid, which is further metabolized to oxalic acid. This acid combines with calcium in the kidneys to precipitate as calcium oxalate. Ruminants are thought to be more resistant to the toxic effects of ethylene glycol than monogastric animals because of their ability to metabolize large quantities of oxalate in the rumen. The acute toxic dose of ethylene glycol for adult ruminants ranges from 5 to 10 mL/kg, whereas that for preruminant calves is 2 mL/kg.

Animals that have ingested sufficient amounts of ethylene glycol become ill by 3 to 4 days after ingestion. Clinical signs of ethylene glycol toxicity include blindness, progressive hindlimb ataxia, salivation, depressed sensorium, nystagmus, tonic-clonic seizures, and status epilepticus. Pupillary reflexes usually are intact. Hemolytic anemia and hemoglobinuria occasionally may be seen.[1317] The clinicopathologic changes of ethylene glycol toxicosis include azotemia (448 mg/dL), increased serum creatinine, hypophosphatemia, hypocalcemia, acidosis, hyperosmolality, and increased γ-glutamyl transaminase.

The pathologic lesions include slight swelling of the kidneys and pulmonary edema. Oxalate crystals can be demonstrated by microscopic examination of the kidney tissues using polarized light. Ethylene glycol can be detected in the rumen for at least 4 days after ingestion. Mass spectrometry of body fluids may show increased urinary and ocular fluid concentrations of glycolic acid (4.3 μg/mL and 2.3 μg/mL, respectively).

Treatment with 20% ethanol at a rate of 50 mL/hr has been recommended but is unsuccessful in advanced stages of the disease. Some have suggested that ruminants also be given an oral dose of activated charcoal, but the effect of this treatment on long-term survival is unknown.[1318]

35.2.42 NARDOO FERN POISONING

Sheep that graze extensively on the Nardoo fern *(Marsilea drummondii)* develop a condition that is indistinguishable from polioencephalomalacia (PEM). Death losses of 2200 of 57,000 sheep have been reported.[1319] The clinical signs are indistinguishable from those of PEM. Neuronal necrosis, malacia, perivascular cuffing, vacuolation of the neuropil, vascular dilation and endothelial hypertrophy, and gliosis occur in the central nervous system. The condition responds to a single subcutaneous injection of thiamine (200 mg). The fern is thought to contain a form of thiaminase I.

35.2.43 *HELICHRYSUM ARGYROSPHAERUM* POISONING

Both naturally occurring and experimental poisoning of sheep and cattle in South Africa by plants of the genus *Helichrysum* results in blindness and a variety of CNS signs.[1320,1321] The clinical signs of intoxication include progressive tetraparesis, depression, nystagmus, mydriasis, blindness, intentional head tremor, and star-gazing attitude. Older sheep may develop lens cataracts 2 to 3 months after eating the plants. The case-attack rate ranges from 1% to 29%. Plants are toxic only in the flowering stage. *Helichrysum* species have been shown to

contain substances that bind at the γ-aminobutyric acid (GABA)—benzodiazepine receptor, suggesting a mechanism for toxic effects on the nervous system.[1322]

Pathologic findings include widespread status spongiosus of brain white matter, particularly in subependymal areas and in the cerebellar peduncles and brainstem.[1321] Myelin edema is present in some cases. Edematous swelling of the optic nerve causes compression of the nerve in the optic canal, with secondary damage to nerve axons and myelin. The toxic principle in *Helichrysum* plants also causes a primary retinopathy in some animals.

Other members of the *Helichrysum* genus are being studied for a variety of medicinal properties, including antiviral, antioxidant, antiinflammatory, and free-radical scavenging activities.[1323–1325]

35.2.44 FLATPEA *(LATHYRUS SYLVESTRIS, LATHYRUS COLLIS)* POISONING

Ingestion of flatpea *(Lathyrus sylvestris, Lathyrus collis)* results in a CNS disorder. The condition may be seen by 5 days after consumption of a diet composed of 50% flatpea vines. Toxicosis has been induced in sheep ingesting forage of 35% flatpea vines.[1326] Livestock can develop a tolerance for the plant through rumen microbial detoxification. Nevertheless, acclimatized animals can be rendered susceptible by treatment with monensin or by a change in rumen microflora.[1327]

The toxic constituent of the plant, 2,4-diaminobutyric acid, is known to inhibit ornithine transcarbamylase, an enzyme responsible for urea detoxification. Consequently, the blood ammonia concentration in clinically affected animals ranges from 189 to 263 mmol/mL (normal, 108 to 185 mmol/mL). Diaminobutyric acid also interferes with the uptake of GABA and inhibits GABA transaminase activity.

The clinical signs of flatpea intoxication are depression, muscular tremors, and spasmodic torticollis. Affected animals become recumbent and are reluctant to rise. When stimulated to move, they display circling, head pressing, and odontoprisis. The urine may appear dark brown. The clinical disorder often culminates fatally in a seizure. During the interictal periods the animals may rest, rise, and resume normal behavior and gait. Treatment is empiric and supportive and could include 1 to 2 L of vinegar orally, IV diazepam, and removal from the offending forage.

Lathyrus sylvestris is a leguminous plant with a high protein content that might be an adequate substitute for alfalfa in areas where the latter grows poorly.[1328] *L. sylvestris* harvested in the vegetative state has been fed to lambs in combination with alfalfa and as a sole diet without ill effect.[1329] Similarly, when fed as part of a mixed silage in which the concentration of diaminobutyric acid was approximately 1%, *L. sylvestris* produced an acceptable weight gain in cattle without signs of toxicity.[1330]

35.2.45 LEUKOENCEPHALOMALACIA (MOLDY CORN DISEASE; EQUINE ENCEPHALOMALACIA; PESTA DE CEGARE; PEN YAN DISEASE; MOLDY CORNSTALK DISEASE; BLIND STAGGERS)

35.2.45.1 Definition and Etiology

Leukoencephalomalacia (LEM) is an intoxication of horses caused by ingestion of corn contaminated with the fungus *Fusarium moniliforme*.[1331–1335] Fumonisin toxins (B1, B2, and B3) produced by *F. moniliforme*

interfere with sphingolipid metabolism, disrupting endothelial cell walls and basement membranes.[1336] Although all three substances are toxic, fumonisin B1 is believed to be mainly responsible for LEM.[1337] Outbreaks of multifocal neurologic signs and hepatic disease occur in groups of horses exposed to tainted feedstuffs.

35.2.45.2 Clinical Signs

The clinical signs of LEM occur suddenly. Occasionally, animals die acutely, without other overt signs,[1338] but most horses show a variety of neurologic signs before death. These include somnolence, flaccidity of the facial and pharyngeal muscles, muscle fasciculations over the neck and withers, ataxia, conscious proprioceptive deficits, head pressing, mania, facial desensitization, pharyngeal paralysis, blindness, seizures, and a tendency to circle or lean to one side.[1338,1339] Most animals die while convulsing.[1331] The few horses that recover usually have permanent neurologic dysfunction. Hepatic involvement occurs in many cases, as evidenced by elevated serum liver enzymes, although hepatic failure is uncommon. Signs of liver disease include icterus, petechiation on mucous membranes, and swelling of the muzzle or lips. Gastrointestinal disease caused by fumonisin toxins has been reported and may manifest as signs of colic.

Unique constellations of clinical signs may predominate within any one outbreak of the disease. Fumonisin toxins cause a variety of clinical syndromes in other species, but horses appear to be particularly susceptible and can show signs when exposed to toxin concentrations as low as 5 to 10 ppm, almost 10 times less than the concentration needed to cause mild signs of inappetence and decreased weight gain in cattle.

35.2.45.3 Clinical Pathology and Diagnosis

Fumonisin toxicosis has no unique clinicopathologic findings, therefore antemortem diagnosis relies on recognition of the clinical signs with a history of exposure to moldy corn. Specific changes in the cerebrospinal fluid (CSF) of affected horses have not been reported. Serum liver enzymes (aspartate transaminase [AST], γ-glutamyltransferase [GGT], sorbitol dehydrogenase [SDH]) and bilirubin may be elevated. Nonspecific changes in serum chemistry associated with dehydration (increased hematocrit, prerenal azotemia) and recumbency (elevated serum creatine kinase [CK]) also may be present. Anemia, leukocytosis, and leukopenia all have been reported, but none is a consistent finding.

Differential diagnoses include craniocerebral trauma, the arboviral encephalitides, hepatic encephalopathy, equine protozoal myeloencephalitis, Theiler's disease, and botulism.

35.2.45.4 Epidemiology

Leukoencephalomalacia occurs worldwide.[1333,1340] Corn becomes contaminated during growth rather than in storage, and climatic factors that stress the plants, such as drought, excess moisture, or heat, contribute to the likelihood of mold development. Most cases of equine disease occur during the winter and early spring.[1332,1338] In experimental studies the toxic dose of infected corn ranged from 5 to 15 kg (10 to 30 lb), but the amount of corn required to cause the disease is likely to vary considerably depending on the amount of toxin in the grain.[1334] A direct link between the onset and severity of clinical signs and the dose of toxin has not been established in naturally occurring cases, but experimental data suggest a dose-related effect.[1341] Repeated exposure to the toxin, rather than a single large dose, seems to be associated with the development of clinical signs.[1342] Experimental studies with infected corn demonstrated an onset of clinical signs on the

ninth day after the beginning of the feeding period. Older animals develop clinical signs of LEM more rapidly than younger animals and thus appear to be most susceptible to the effects of the mycotoxin.[1334]

The rates of disease in exposed horses vary widely, from 14% to 100% in some reports.[1343–1346] Ruminants apparently are more resistant than horses to the effects of the neurotoxin, but this is not a complete resistance because camels and water buffalo have died after ingesting toxic corn. Diplodiosis, a similar neuromycotoxicosis of cattle caused by ingestion of *Diplodia maydis,* occurs in Africa; however, the toxicologic relationship between these conditions is unknown.

35.2.45.5

Pathology

The major pathologic features in the central nervous system (CNS) result from the vascular damage caused by fumonisin toxins, including liquefactive necrosis and degeneration or malacia of the white matter of one or both cerebral hemispheres.[1347,1348] The size of the lesions may vary from 0.5 cm in diameter to complete necrosis of the entire cerebral cortex.[1331] Flattening of the cortical gyri, enlargement of the cerebral cortex, vascular congestion, cortical softening, yellowish discoloration of the white matter, hemorrhage, and cavitation of the cerebral cortex may be present[1331,1338,1340] (Fig. 35-14). A gelatinous fluid can be seen in many of the cavitary lesions.[1338] Hemorrhage in the CNS also has been reported.[1343] Lesions in the visceral organs, including hepatic congestion, centrilobular hepatic necrosis, hemorrhagic enteritis, and cystitis are found in some horses. The relationship between these lesions in the CNS and those in the liver, urinary bladder, and GI tract is unknown.

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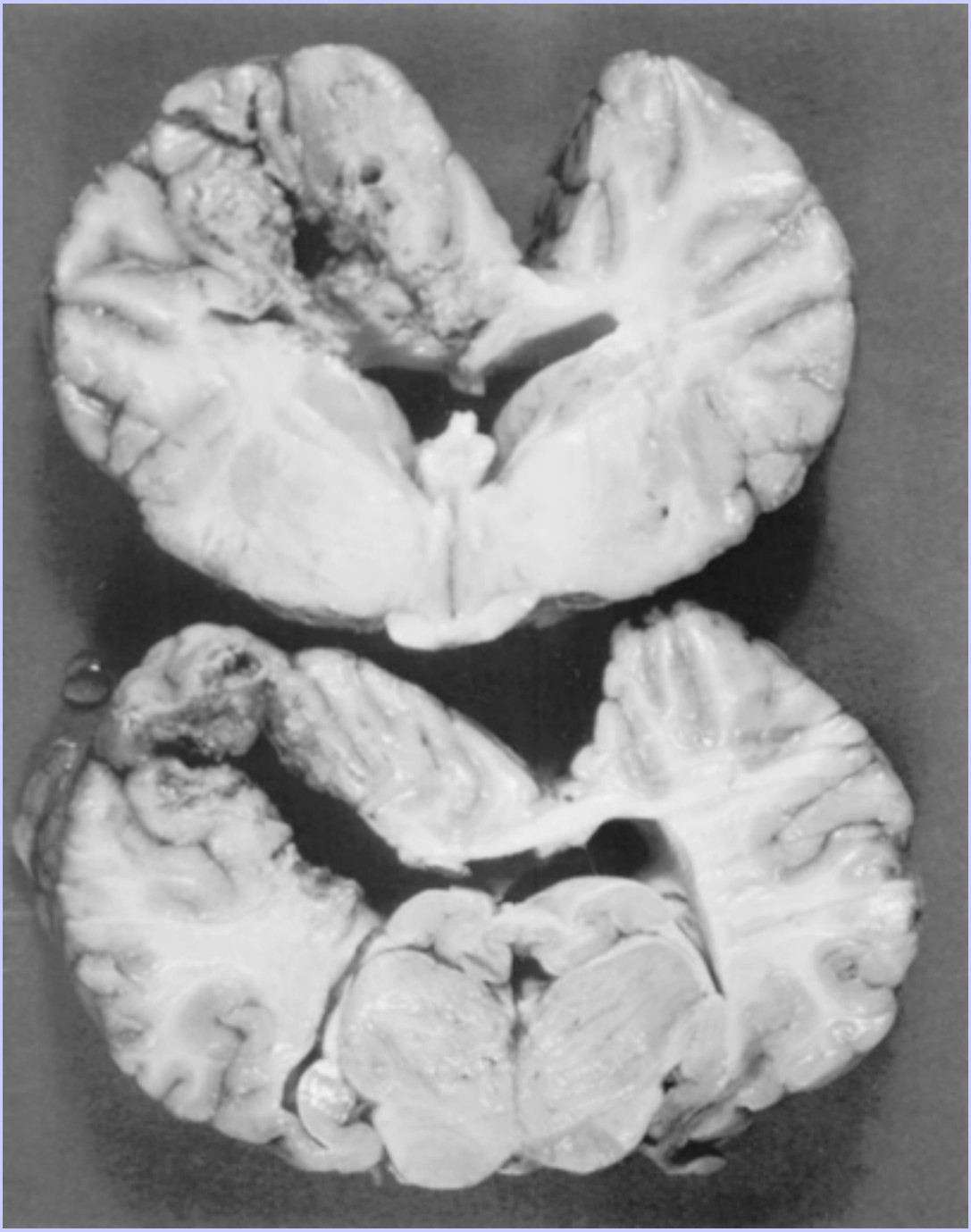
Fig. 35-14 Characteristic appearance of a malacic lesion in the brain of a horse that died of moldy corn poisoning. Courtesy Dr. R.H. Whitlock.



35.2.45.6 Treatment

There is no known specific treatment for LEM, but successful treatment of horses was reported using antiinflammatory medications such as dimethyl sulfoxide (DMSO) (1 g/kg given as 10% solution by slow IV infusion once daily for 3 days) or flunixin meglumine (0.25 to 1 mg/kg), as well as antibiotics and supportive care (thiamine, 5 g IV every 12 hours).[1349] In other cases, survivors usually have permanent neurologic dysfunction.

35.2.46 BLUE-GREEN ALGAE TOXICOSIS

35.2.46.1 Definition and Etiology

Ingestion of stagnant pond water containing certain species of blue-green algae may result in a peracute intoxication of livestock. Blue-green algae poisoning is characterized by convulsions, ataxia, bloody diarrhea, and sudden death.[1350–1353] Although often a fatal toxicity, some affected animals can make a full recovery.[1351,1354] The algal toxins have been responsible for high losses of livestock and illness in humans and for deaths of domestic dogs.[1355,1356] The algal toxins may also be responsible for occasional die-offs of fish and aquatic birds. Toxic algal species include *Microcystis aeruginosa, Anabaena flos-aquae, Aphanizomenon flos-aquae, Anacystis cyanea, Gloeotrichia echinulata, Nodularia sphaerocarpa,* and *Oscillatoria agardhii*. Of these, the first three are most toxic.[1357] Blue-green algae poisoning most often results in sudden death. Affected animals rarely move far from the source of the toxin. Some of the algae produce hepatotoxins, and animals develop liver failure, diarrhea, and photosensitivity. The development of toxic stands of blue-green algae requires specific environmental conditions, including a water pH above 6, organic pollution, and a water temperature ranging from 15° C to 30°C (59° F to 86°F).

35.2.46.2 Clinical Signs

Clinical syndromes of blue-green algae poisoning in livestock may be separated into acute and chronic forms. Acutely affected animals may show signs resembling those of milk fever,[1354] including muscle tremors, reluctance to rise or move, ataxia, cold extremities, weak rapid pulse, mydriasis, muscle tremors, salivation, colic, rumen atony, mild bloat, pallor, increased capillary refill time, vomiting, ataxia, conscious proprioceptive deficits, and bloody diarrhea. Some of the toxins are absorbed through the oral mucosa. Consequently, the full range of clinical signs, culminating in death from respiratory arrest, can occur within minutes of ingestion of the toxic water. If clinical signs are seen before death, affected animals tend to be afebrile but have significantly increased pulse and respiratory rates. Many animals die suddenly without premonitory symptoms.[1358,1359] The deaths often occur in the vicinity of the pond, and dead animals may be covered by the green scum.

In the chronic form of blue-green algae intoxication, affected animals show ataxia, depression, anorexia, hemorrhagic diarrhea, icterus, and photosensitization, which occur secondary to hepatic necrosis.[1359] Death from respiratory arrest and circulatory shock may occur within 2 to 72 hours after the toxin is ingested.

35.2.46.3 Clinical Pathology

The diagnosis of blue-green algae poisoning depends on recognition of a relationship between livestock deaths and ingestion of pond water, identification of toxic algae in the pond water, recognition of hepatic disease in chronically affected animals, and elimination of the possibility of similar clinical conditions, such as cyanide or acute poisoning. Diseases that kill animals suddenly should be considered as differential diagnoses (see Chapter 14). Blue-green algae poisoning should be considered whenever a group of cattle simultaneously develop marked massive hepatic necrosis.

The vegetative cells of the algae can be identified by microscopic examination of rumen contents. The intestinal contents should be split. Half the contents should be placed in 10% neutral buffered formalin for microscopic analysis, and the other half should be refrigerated (not frozen) for mouse bioassay tests or chromatographic identification of the toxin using high-performance liquid chromatography (HPLC).[1360] The blood of animals poisoned by microcystin, the toxic principle of *Microcystis aeruginosa,* shows changes characteristic of hepatic necrosis, including increased concentrations of bilirubin, AST, GGT, alkaline phosphatase (ALP), and arginase. The animals may be secondarily hypocalcemic, which complicates the clinical picture.[1354]

35.2.46.4 Pathophysiology

Blue-green algae grow more slowly than other algae in cold water; therefore, highly flushed systems cannot achieve a toxic bloom. The blue-green algae can fix atmospheric nitrogen dissolved in the water, and they have intracellular gas vesicles that accumulate the nitrogen when photosynthesis decreases. If mixing occurs because of the wind, the amount of light reaching the algae decreases because of the turbulence. The buoyancy of the cells increases because of decreased photosynthesis. At night the winds become calmer, and the algae lose their ability to regulate density. The cells float to the surface of the water and form a scum, which is concentrated on the leeward side. For these reasons, poisonings tend to occur in the period of stable weather just after a frontal system has passed.

Direct ingestion of the toxicant is necessary to cause clinical signs. No significant level of toxin was detected in milk of cows fed the toxin experimentally, so calves are not exposed through their dams' milk.[1361]

All species of blue-green algae probably produce toxins, which can be classified into the following three groups:

- *Aphanizomenon, Oscillatoria,* and *Anabaena* species. *Aphanizomenon* produces two alkaloid toxins that have a structure resembling that of saxitoxin, the agent of paralytic shellfish poisoning. Toxins from *Anabaena* species are named anatoxin-a and anatoxin-a(s) and are structural analogs of cocaine. Toxins from *Oscillatoria* species resemble those of *Anabaena;* they can be absorbed unchanged through the mucous membranes and kill by depolarizing blockade of the neuromuscular junction.[1358,1359,1362–1364]

- Peptide hepatotoxins. These substances are produced by strains of *Microcystis, Oscillatoria,* and *Anabaena* algae. Microcystin-LR is the most frequently isolated hepatotoxin.[1365–1369] On a weight basis, this toxin is 20 times more active than cyanide or strychnine. A single intraperitoneal injection of 1 to 2 µg in a mouse is lethal. At least nine structural variants of microcystin have been identified.

These toxins act exert their toxic effects on mitochondria.[1370] The toxins can cross the placenta and cause lesions in the fetus.

- Lipopolysaccharides. These substances may be produced by most species of blue-green algae.

35.2.46.5 Necropsy Findings

The pathologic lesions of blue-green algae poisoning are either severe centrilobular hepatic necrosis in animals that die of the chronic poisoning or generalized petechiation and body cavity effusions in animals that die peracutely.[1358]

35.2.46.6 Epidemiology

Blue-green algae intoxication occurs worldwide and affects mammals, birds, and fish. The bloom is most abundant during the late summer and early autumn when warm, sunny conditions favor algal growth. Growth is most abundant in ponds with an alkaline pH and in high concentrations of nitrogen, phosphates, carbonates, or organic matter. Release of the toxin is associated with death of the algae and production of a “rotting fish” odor. Most poisonings occur on the leeward side of the pond, where the algae are concentrated by the action of the prevailing wind. Ingestion of approximately 1080 to 1500 mL of heavily contaminated water can be fatal for cattle.[1350] Toxicity varies daily and in different parts of the pond or lake.

35.2.46.7 Treatment

Therapy for blue-green algae poisoning is symptomatic and usually unsuccessful. Experimentally poisoned calves have not recovered, even after 30 hours of artificial respiration, although recovery of cows naturally intoxicated has been reported.[1351,1363]

35.2.46.8 Prevention

Methods for control of the disease include restriction of access to infested ponds and treatment of the pond with copper sulfate or algacides.[1352] Prevention of blue-green algae poisoning depends on the proper construction of farm ponds and the prophylactic treatment of the water with bluestone (copper sulfate) to achieve a final concentration ranging from 0.5 to 1.0 ppm in acid water and 1.5 to 2.0 ppm in alkaline water. The bluestone is either dissolved in water and sprayed over the pond or dragged through the pond in a burlap sack in lanes that are 5 to 10 feet apart.[1352] This amounts to 1.22 kg/acre foot in alkaline water. Cattle should be fenced from the pond for several days after the copper sulfate treatment. The treatment should be repeated whenever the toxic bloom recurs. To prevent algal bloom without application of copper sulfate, farm ponds should be constructed so that they are 80 × 20 feet in length and width and 10 feet in depth. Surrounding drainage areas should be fenced from the livestock. Water should be pumped from the pond to the cattle in polyethylene pipes and delivered into raised water troughs. The water for the troughs should be pumped from the center and bottom of the pond.

35.2.47 NITROFURAZONE TOXICOSIS

Nitrofurazone is an antimicrobial that has been fed to cattle for the treatment and control of respiratory or gastrointestinal diseases. Treatment of food-producing animals with the nitrofurans currently is prohibited by the U.S. FDA. Nervous system signs of nitrofurazone toxicosis occur after 1 to 3 weeks of continuous feeding at dosages exceeding 15 to 30 mg/kg.[1371,1372] Lower dosages (7.1 mg/kg) reduce feed intake but do not result in neurologic signs. The nitrofurans inhibit enzymes of the oxidative glycolytic pathways and are thought to interfere with brain metabolism of carbohydrates.

Clinical signs of nitrofurazone toxicosis include hyperirritability, propulsive running, muscular tremors, blindness, convulsions, and death. At lower doses the convulsions may appear intermittently, but as the condition progresses, the signs become continuous.

35.2.48 INTRACAROTID DRUG INJECTION

35.2.48.1 Definition and Etiology

Intracarotid drug injection is common in horses because the jugular vein and the common carotid artery are closely apposed in the caudal third of the neck. The condition is rarely seen in cattle because the omohyoideus muscle lies between the carotid artery and the jugular vein in the posterior part of the neck. Hypertonic or caustic drugs, including phenothiazine tranquilizers, chloramphenicol, chloral hydrate, barbiturate anesthetics, phenylbutazone, calcium gluconate, sodium iodide, and chloramphenicol, cause cortical necrosis when injected into the carotid artery.[1373,1374]

35.2.48.2 Clinical Signs

The onset is peracute. When the drug is injected into the carotid artery, the animal recoils backward and falls over. Some horses strike or rear violently or run wildly without regard to obstructions. Other animals fall down and become comatose without showing severe motor activity. Severely affected animals may die after a variable period, but others regain their footing and recover completely. Residual neurologic deficits may occur in surviving animals. These deficits include contralateral blindness, facial hypalgesia, head tilt (toward the side of the lesion), and a largely contralateral, conscious proprioceptive deficit. If the injection has damaged the ascending vagosympathetic pathways, the animal may display Horner's syndrome, with signs that include ptosis, miosis, and enophthalmos. Horses with Horner's syndrome also sweat profusely over the head and neck of the ipsilateral side, whereas cattle with the syndrome fail to sweat on the planum nasale on the ipsilateral side of the lesion.

35.2.48.3 Pathophysiology

The CNS lesions are caused by vascular endothelial damage. Intracarotid drug injection results in intense vasospasm and profound alterations of the blood-brain barrier (BBB). The vascular damage causes endothelial cell swelling, increased vascular permeability, mural necrosis, hemorrhage, intercellular edema, and thrombosis.[1373]

35.2.48.4 ### Necropsy Findings

Pathologic lesions include diffuse cerebral edema and brain swelling. Microscopic lesions include arteriolar hyalinization, hemorrhage, edema, necrobiosis, and status spongiosus. Vacuolation of the neuropil, perivascular hemorrhage, fibrin, and edema are also seen.

35.2.48.5 ### Treatment

No effective treatment exists for an accidental intracarotid drug injection. Violent horses should be placed in a padded stall, sedated with diazepam, and treated with dexamethasone (1 to 2 mg/kg). Administration of mannitol or other osmotic diuretics should be avoided in the first 24 hours because of active bleeding in the CNS and loss of the BBB. Administration of a hypertonic dehydrating agent at that time may result in distribution of the osmotically active drugs into the CNS parenchyma, resulting in a large increase in intracranial pressure. Although most animals eventually recover from the effects of an intracarotid injection, fatalities have been reported.[1373–1375]

35.2.48.6 ### Prevention

Intracarotid injection of drugs is best prevented by the use of large-bore needles or catheters for intravenous injections. This allows better visualization of pulsating oxygenated blood when the carotid artery has been accidentally punctured. In the horse, venipunctures should be performed in the anterior one third of the jugular furrow because the artery and vein are separated by the omohyoideus muscle in this area. Needles should be inserted into the vein while they are separated from the syringe.

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35.2.49 ## COENUROSIS (SHEEP GID; *COENURUS CEREBRALIS* INFESTATION; *TAENIA MULTICEPS* INFESTATION)

35.2.49.1 ### Definition and Etiology

Coenurosis is caused by invasion of the CNS by *Coenurus cerebralis,* the intermediate stage of the tapeworm *Taenia multiceps*. The adult worms live in the intestine of domestic dogs and some wild carnivores, where they shed eggs into the feces. Ruminants eat the eggs from contaminated pastures. The eggs hatch in the small intestine of the ruminant, and the larval stages travel through the blood to the CNS, where they mature into *C. cerebralis*. The life cycle is completed when the ruminant dies and the brain is eaten by a scavenging carnivore. *Coenurus* cysts then develop into sexually mature adults in the bowel of the carnivore host.

Many animals, including sheep, goats, cattle, horses, wild ruminants, and humans, are susceptible to *C. cerebralis* infestation.[1376–1378] Outbreaks of coenurosis may occur in previously uninfected sheep that are suddenly exposed to contaminated fecal matter from carnivores. Cases initially occur as early as 2 weeks after the sheep are exposed and continue for as long as 4 months.

35.2.49.2

Clinical Signs

Signs can occur acutely, during the migratory phase of the larval stage in the intermediate host. Lambs 6 to 8 weeks old are most often affected by this form and develop fever, dullness, and mild neurologic deficits.[1379] Occasionally, acute encephalitis occurs, leading to sudden onset of severe neurologic signs and death within a few days. More frequently, the clinical presentation of coenurosis is that of a space-occupying brain lesion; signs include depression, anorexia, ataxia, unilateral or asymmetric loss of vision, facial hemiplegia, head tilt, circling, high-stepping forelimb gait, and hyperesthesia. When the spinal cord is the site of cyst development, hindlimb ataxia and paresis to paralysis is the main clinical sign.[1380] As the disease progresses, the sheep assume lateral recumbency and become comatose.[1381,1382] In advanced cases the calvarium directly over the parasite enlarges and softens.[1378]

35.2.49.3

Pathophysiology

Lesions of the CNS may result from three separate pathogenic mechanisms. These include encephalitis from invasion of the CNS by large numbers of larvae, hypertensive hydrocephalus resulting from interference with CSF drainage, and development of large cerebral cysts that increase intracranial pressure. Full development of the *Coenurus* cyst requires 6 to 7 months. Mature cysts may reach 5 cm in diameter and displace the bones of the calvarium.

35.2.49.4

Necropsy Findings

In the acute form of coenurosis, the main finding is coagulation necrosis and inflammation associated with the pathway of the larval form as it migrates through the CNS.[1383] This may be visible grossly as yellow to red tracks through the brain parenchyma. Coagulation necrosis and surrounding inflammatory cells, such as degenerate granulocytes, macrophages, and histiocytes, are found microscopically. The mature cysts, up to 7 cm in diameter, are thin walled and contain clear fluid or, occasionally, purulent fluid. Protoscolices, up to many hundreds, can be visualized microscopically within the cysts, which are surrounded by severe and mainly nonsuppurative inflammation. The cysts deform and compress the underlying brain tissue.

35.2.49.5

Diagnosis

The combination of a characteristic clinical syndrome and location in an endemic area supports a presumptive diagnosis. Radiographs in the lateral and posteroanterior planes may detect radiolucent areas in the calvarium. The optimum diagnostic views in the posteroanterior projection occur whenever the base of the nose is level with the upper margin of the orbit. Computed tomography (CT) effectively demonstrates the presence of cysts but rarely is practicable in large animal species.[1384]

35.2.49.6

Treatment

Praziquantel,* 50 to 100 mg/kg orally daily for 3 to 5 days, is effective for the treatment of coenurosis in sheep that do not yet have neurologic signs.[1380,1385] Concomitant administration of a nonsteroidal antiinflammatory drug (NSAID) or dexamethasone may enhance the posttreatment survival rate.

The cyst can also be removed surgically,[1386] with success rates as high as 90% reported.[1387] A craniotomy is performed over the site of the cyst. Approximately 70% of the cysts are located extradurally and can be removed easily with minimal dissection. The other cysts are located on the surface of the pia arachnoid, in which case the dura mater is incised. The cyst usually bulges from under the incised dura and can be removed. When the cyst is located in the cerebral cortex, ultrasound probes placed on the surface of the brain may be used to locate the pocket of fluid.[1388–1390]

* Droncit, Miles Laboratories, Shawnee, KS.

35.2.49.7 Prevention

In endemic areas the carcasses of affected animals should not be fed to dogs, and dogs in endemic areas should be treated repeatedly with a vermifuge to minimize the possibility of pasture contamination. Appropriate management practices have virtually eliminated this disease from North American sheep flocks. Lyophilized antigens from in vitro—cultured larvae have protected sheep; however, this preparation is not commercially available.

35.2.50 CEROID LIPOFUSCINOSIS

35.2.50.1 Definition and Etiology

Ceroid lipofuscinosis is a lysosomal storage disease that has been reported in South Hampshire, Swedish Landrace, and Rambouillet sheep, Nubian goats, Devon cattle, and horses.[1391–1396] The disease is known to be inherited as an autosomal recessive trait in many cases[1397] and is believed to be so in others.[1396] It is characterized by the intracellular accumulation of abnormal autofluorescent lipopigments in lysosomes of neurons and other cells throughout the body. The storage material has been shown to consist predominantly of the subunit *c* of mitochondrial *c* synthase.[1398,1399] The mechanism of neuronal dysfunction is hypothesized to be mediated by N-methyl-D-aspartate (NMDA) receptor excitotoxicity.[1400] Affected animals display progressive ataxia and postural abnormalities, blindness due to retinal involvement in many cases, sensory depression, and terminally, coma. Lesions seen on CT scans include enlargement of the lateral ventricles and reduced thickness of the cerebral cortex.[1401]

Gross pathologic lesions in the CNS may include moderate enlargement of the lateral ventricles, flattening of cerebral gyri, and a yellow to brown discoloration of the brain parenchyma. Accumulation of protein storage material in neuronal lysosomes is evident on microscopic examination and is accompanied by neuronal necrosis and astrocytosis, which may be severe. The lesions sometimes have a lamellar appearance.[1400] The disease is ultimately fatal, and no practical method of treatment is currently available.

35.3 CITRULLINEMIA

Citrullinemia is a rare genetic defect of Holstein calves that has been reported in Australasia, Europe, and India.[1402–1404] The genetic defect has been found in one carrier bull in the United States.[1405] The mutation responsible has been traced to offspring of a North American sire named Greyview Crisscross and his son Linmack Kriss

King.[1406] Approximately 8% of all bulls used for artificial insemination in Australia are heterozygous for the gene, but the gene prevalence appears to be much lower in the United States.[1405,1407]

Citrullinemia is caused by a defect of argininosuccinate synthetase, an enzyme that processes citrulline in the pathway for the formation of urea. The condition is fatal. Affected calves are normal at birth but become clinically depressed by 24 hours after birth. By 2 to 3 days after birth, affected calves show head pressing, drooling of saliva, bellowing, muzzle twitching, tongue protrusion, and odontoprisis. Convulsions are first seen at 1 to 4 days of age, and death rapidly follows.

The diagnosis may be made by observing an increased concentration of citrulline in the plasma. The concentration of citrulline in normal calves is 0.16 mM and in affected calves is greater than 1.5 mM by the third day after birth. The plasma arginine concentration is decreased to less than 0.02 mM at death.[1408] There is a marked hyperammonemia because of the inactivity of the hepatic ornithine-citrulline cycle. The brain concentrations of the transmitter amino acids glutamate, aspartate, and GABA are decreased. Affected calves also have a reduced affinity of postsynaptic glutamate NMDA receptors in the brain.[1409] The genetic deficit has been traced to the insertion of a chain termination codon for arginine in the argininosuccinate synthetase genome, which causes a complete loss of enzymatic activity. A PCR test for detection of heterozygotes has been developed.[1407] Microscopic brain alterations include astroglial edema and mild to severe spongiform changes in the deep laminae of the cerebral cortex.[1410]

35.4 BRAIN TUMORS

Nervous system tumors of ruminants include medulloblastoma, ependymoblastoma, neurofibrosarcoma, angioblastoma, meningioma, meningeal hemangioma, neurofibroma, schwannoma, choroid plexus papilloma, pituitary adenocarcinoma, primitive neurectodermal tumor, and reticulosis.[1411–1415] Central nervous system (CNS) tumors of horses include pituitary adenomas, microgliomas, medulloepithelioma, choroid plexus papilloma, ependymoma, neurofibroma, meningioma, meningeal carcinoma, and reticulosis.[1411,1416–1420] Secondary tumors that invade the CNS include melanoma, lymphosarcoma, adenocarcinoma, squamous cell carcinoma, hemangiosarcoma, and osteoma.[1411,1420–1424] Of these, lymphosarcoma is most often encountered.[1425–1427] Metastatic invasion to the CNS occurs either by vascular routes or by extension along the peripheral nerve rootlets.[1428] Local extension from adjacent tissue, such as the paranasal sinuses, also can occur.[1421]

Clinical signs of BRAIN TUMORS vary with the location and include abnormalities of gait (ataxia, paresis, hypometria/hypermetria), seizures, altered mentation (especially dullness), facial paresis or paralysis, facial anesthesia or analgesia, dysphagia, head tilt, strabismus, nystagmus, and loss of the menace reflex.[1421,1428–1430] Migration of facial tumors (squamous cell carcinomas) into the cranial vault through the cranial nerve foramina may also result in facial swelling, exophthalmos, Horner's syndrome, or asymmetric airflow through the nares.[1427] Pituitary adenomas of aged horses (see Chapter 41) rarely cause neurologic disease, but they secrete melanocyte-stimulating hormone, which stimulates the adrenal cortex and causes Cushing's disease. Some tumors are discovered as incidental findings at necropsy.

Antemortem diagnostic tests include radiographs of the skull (for tumors that spread locally and some metastatic tumors), and electroencephalography (EEG) to elucidate brain dysfunction.[1421] Where available, CT or MRI can greatly facilitate diagnosis, but limited availability and considerations of cost restrict their use in most cases.[1428,1430–1432]

Treatment of BRAIN TUMORS in horses and livestock is generally not feasible because of limitations of cost, nursing care challenges after craniotomy, lack of access for large animals to radiation therapy, and considerations of safety for personnel handling animals with significant neurologic deficits. Palliative treatment, such as corticosteroids, may reduce clinical signs temporarily in some animals. Euthanasia is the choice for most large animals with BRAIN TUMORS.

35.5 CHOLESTEROL GRANULOMAS

Cholesteatomas are common lesions in the brains of older horses and frequently are incidental findings at necropsy. Cholesteatomas usually are found in the lateral ventricles.[1433] They may form secondary to chronic hemorrhage into the choroid plexuses, but their exact pathogenesis is unknown. Clinical signs of cerebral dysfunction, such as seizures, result only when the masses grow large enough either to obstruct CSF flow from the lateral ventricles or to attenuate the surrounding neuropil directly. Antemortem diagnosis of cholesteatomas in horses can be done by CT scanning of the brain.[1434] Cholesteatomas appear grossly as brownish nodular thickenings in the choroid plexuses or less often as large masses filling the ventricle. Light microscopy reveals abundant cholesterol crystals interspersed with empty clefts, hemosiderin, and an inflammatory reaction consisting of both macrophages and giant cells. There is no specific treatment for cholesteatomas, and relief of clinical signs should be symptomatic, including anticonvulsants as appropriate.

35.6 EPILEPSY

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Epilepsy is a condition of recurrent seizures not attributable to other neurologic or metabolic disorders.[1435] A seizure (ictus) may be *generalized,* involving the entire cortex and accompanied by loss of consciousness, or *partial* (focal), involving a limited cortical region with no loss of conscious. Partial seizures may in turn become generalized. Seizures may result from trauma, infection, tumors, electrolyte disturbances, or cerebral swelling. Some seizures are idiopathic. Seizures may be preceded by a prodromal aura, usually consisting of a stereotypic sensory disturbance and followed by a postictal depression of variable duration. Seizures in very young or old animals frequently are not of epileptic origin.

Seizure activity results from the synchronization of large aggregates of neurons that are driven, at least in the case of partial seizures, by abnormal epileptic neurons in a seizure focus that recruit increasing numbers of connected neurons.[1436] Generalized epileptic seizure activity may result from subcortical pacing neurons acting through the excitatory amino acid system.[1437] These neurons probably depend heavily on aspartate and glutamate for facilitation.[1438]

Microscopic abnormalities of the brain may be detectable in focal epilepsies but usually are not in generalized epilepsies. Hippocampal degeneration is a well-recognized pathologic change in humans with some forms of epilepsy and has been described in a single cow with seizures. It was not clear in this report, however, whether the hippocampal changes were the cause or the consequence of the seizures.[1439]

Status epilepticus, a condition of repetitive seizures with little or no intervening recovery that requires immediate emergency treatment, may be the first detected clinical manifestation of epilepsy. Status epilepticus may result if antiepileptic medication is abruptly discontinued.

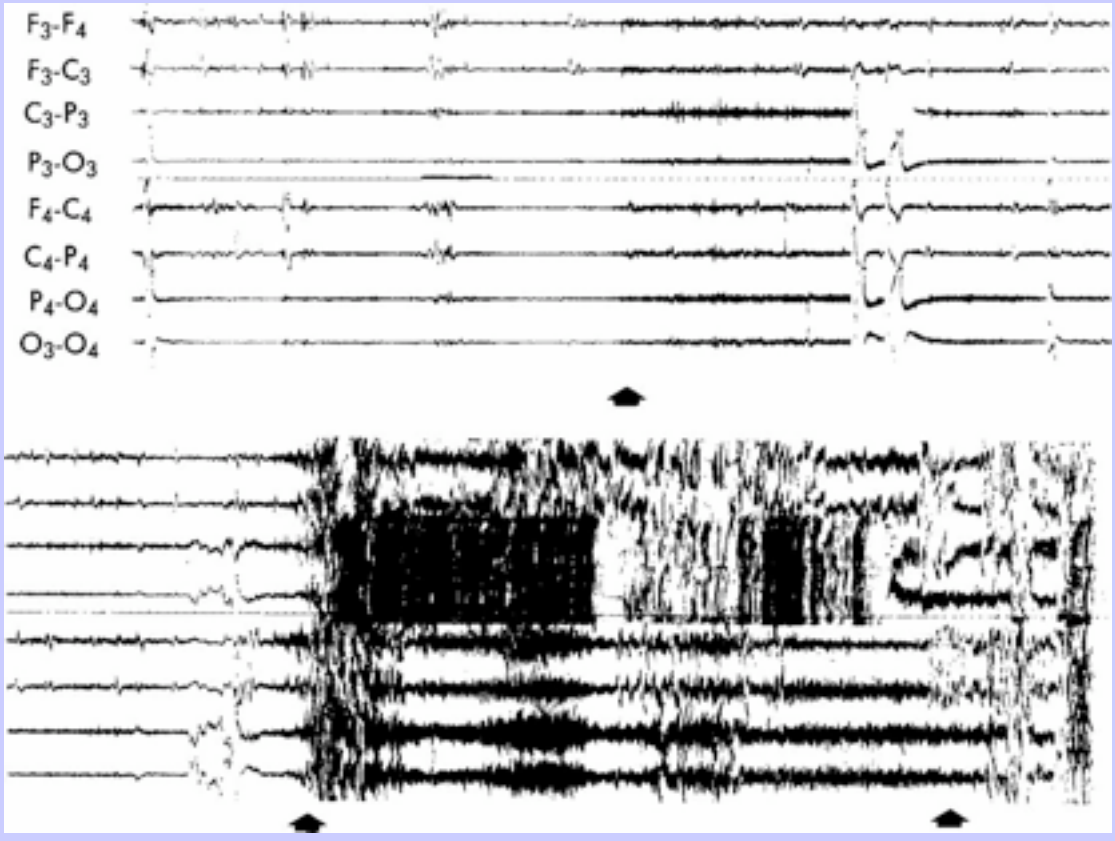
35.6.1 Clinical Signs

Generalized seizures may consist of muscle contractions that are tonic, clonic, or alternating between tonic and clonic. Affected animals may fall and display various autonomic signs, such as salivation, urination, and defecation. During the seizure there may be dorsiflexion of the head and neck and rotation of the eyes. Postictal depression may last minutes to days. Blindness lasting minutes to weeks may be present postictally.[1440] Partial seizures may consist of tonic or clonic contractions of isolated muscle groups without loss of consciousness. Seizure disorders have been described in Romagnola,[1441] Swedish Red,[1442] Brown Swiss[1443] Hereford,[1444] Angus,[1445] Brahman,[1446] and crossbred[1447] cattle. A recent study in Angus cattle suggests that the previously described epilepsy may, in fact, be a cerebellar disease, with episodes of severe cerebellar dysfunction, rather than a true seizure disorder of cerebral origin (see also Bovine Familial Convulsions and Ataxia).[1448] Attacks in a 6-month-old Brown Swiss bull were prompted by undue excitement and declined in number with age.[1449] Young progeny exhibited similar attacks, suggesting that the trait was transmitted as an autosomal dominant genetic character.

Epilepsy has been poorly documented in horses but occurs in Arabians and in some ponies.[1450] There is anecdotal evidence of the existence of the condition in Paso Fino horses of the western United States. A condition known as “benign epilepsy” is seen in foals of many breeds, especially Arabians, but unlike true epilepsy, is usually outgrown. The condition in Arabians is termed “juvenile idiopathic epilepsy.” It occurs in animals of Egyptian lineage, is responsive to antiepileptic drugs (AEDs), and usually resolves by 1 to 2 years of age.[1440] Idiopathic epilepsy in mares has been associated with elevated levels of estrogen.[1451]

An epileptic condition in an 8-year-old Hereford cow has been described.[1444] The seizures began at 6½ years of age. Tonic-clonic convulsions could be elicited by administration of pentylenetetrazol at doses of 4 mg/kg, which was well below the convulsant dose for normal animals. EEG showed high-frequency spike bursts, spike and wave, and polyspike and sinusoidal wave abnormalities (Fig. 35-15). No microscopic abnormality could be found in the CNS of the affected animal. Partial epilepsy has been described in a 5-year-old Nubian goat with a 3½-year history of episodic convulsions. Between episodes the goat appeared to be healthy. The seizures appeared more often at times of peak endogenous plasma estrogen concentrations and could be induced by administration of ketamine. The clinical signs included repetitive tremors of the forelimbs and hindlimbs, head tremors, and mastication without loss of consciousness. The postictal depression lasted for several hours.[1452]

Fig. 35-15 Electroencephalographic (EEG) recording of a tonic-clonic seizure in an epileptic cow elicited by injection of pentylenetetrazol (6 mg/kg IV, marker on time channel). High-frequency EEG changes began at the *first arrow*, the convulsion began at the *second arrow*, and vocalization began at the *third arrow*. Electrodes: left and right frontal (F_3, F_4), central (C_3, C_4), parietal (P_3, P_4), and occipital cortex (O_3-O_4). Calibration: 10 sec and 1 mV; recording bandwidth: 1 to 75 Hz. From Strain GM, Olcott BM, Turk MAM: *J Am Vet Med Assoc* 191:833, 1987.



The EEG evaluation of seizure disorders may be performed using evocative drug challenges with pentylenetetrazol, ketamine, or other seizure-inducing agents and established techniques, but care must be taken to prevent injury to the animal. Although EEG may be of some value in investigation of epilepsy and other brain disorders,[1453] the need for sedation or anesthesia in large animals, combined with the paucity of data available for comparison, limits its usefulness.

Because of the rarity of epilepsy in large animals, specific drug therapies have not been established; however, Table 35-9 presents several drugs that could be administered. These drugs usually are highly protein bound in plasma and can be displaced or functionally altered by other drugs, including tetracycline and chloramphenicol. Because of these potential interactions, these agents should not be used concomitantly with the anticonvulsants.

All anticonvulsant treatments are begun at a low dose, which is increased daily or every second or third day until the seizures have been controlled. If seizures cannot be controlled without causing depression or ataxia, a second anticonvulsant is added. The dose of the second drug is gradually increased until the seizures stop. This combination treatment is continued for 2 to 4 weeks. Thereafter, the first anticonvulsant is tapered until it is discontinued. If seizures reappear, the dose of this drug is increased until they disappear again. After 1 month the trough blood concentration of all anticonvulsants is monitored. Therapeutic trough concentration of phenobarbital is 15 to 40 µg/mL of plasma and for diphenylhydantoin 5 to 20 µg/mL. Any attempt to withdraw anticonvulsant therapy should be made gradually, because rebound seizures may occur with too rapid withdrawal. Dosage recommendations have been established for potassium bromide in horses.[1454] A loading dose of 120 mg/kg daily for 5 days, followed by 90 mg/kg once daily, results in serum concentrations in the range found to be effective for seizure control in other species. However, the efficacy of potassium bromide for seizure control in large animals has yet to be established.

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In many animals, epilepsy may be incurable because of its genetic basis. In these cases, treatment is rarely indicated. Horses with epilepsy should not be ridden or used for sporting purposes. Specific methods of control, other than breeding selection against affected animals, are unavailable.

Mares with estral-related seizures may be treated with an ovariectomy. All ruminants experiencing seizures should also immediately be treated with thiamine (10 to 20 mg/kg IM or SC three times daily, or diluted in 5% dextrose or isotonic fluid and given slowly IV) in case the seizural problem is caused by polioencephalomalacia (see previous discussion). The plasma sodium, magnesium, potassium, and calcium levels should be measured in all animals experiencing seizures of unknown origin. Infrequent seizures generally do not justify anticonvulsant treatment, and economic considerations often limit the amount of drug therapy possible. Status epilepticus can be treated with IV diazepam in 5-mg doses until the seizures are controlled or by titrated doses of phenobarbital or pentobarbital.

35.7 NARCOLEPSY AND CATAPLEXY

GEORGE M. STRAIN

MARY SMITH

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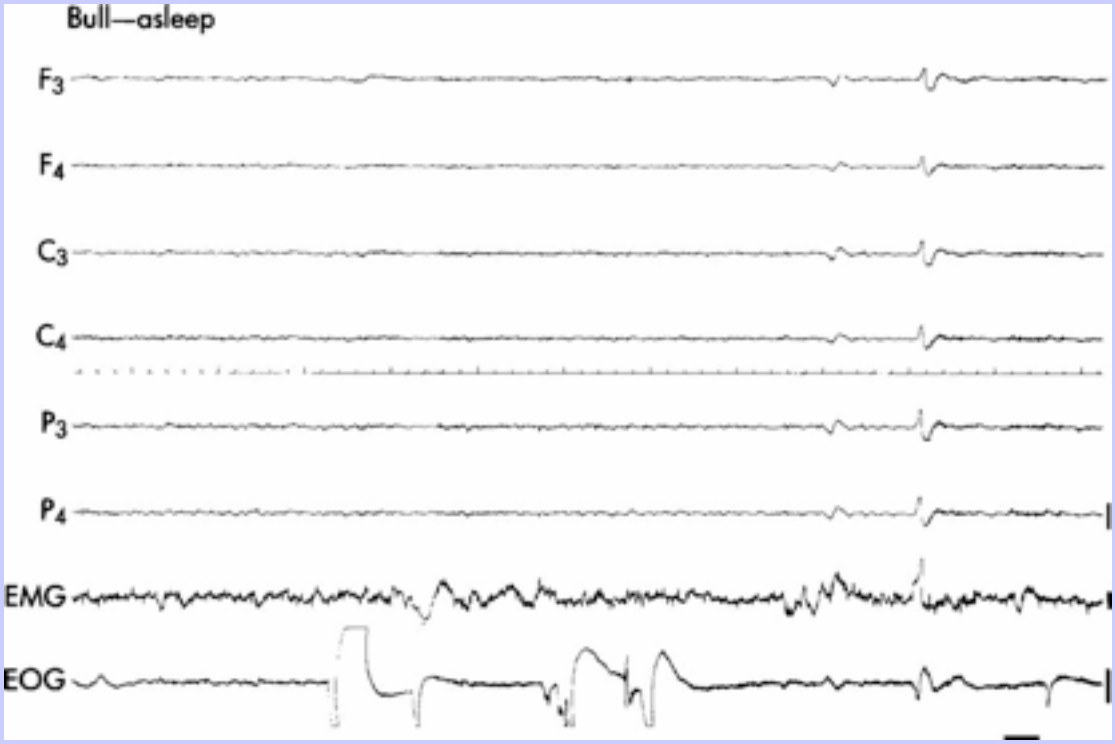
35.7.1 Definition and Etiology

Narcolepsy is a CNS disorder characterized by excessive daytime sleepiness, episodes of muscular weakness (cataplexy), and rapid eye movement (REM)–onset sleep.[1455–1457] Narcoleptic attacks differ from convulsions in that they do not involve tonic-clonic muscular activity.[1455] *Cataplexy,* a sudden episode of paralysis of the voluntary muscles, frequently is induced by stimulation of the patient and can range from atonic, areflexic paralysis of all nonrespiratory muscles to weakness of facial neck and forelimb muscles. Episodes of cataplexy last seconds to minutes. Environmental factors that can stimulate cataplectic attacks include active restraint,

feeding, or changing the stall environment, grooming, or saddling horses in preparation for work.[1455,1458–1460] Excessive daytime sleepiness and REM-onset sleep are difficult to document in large animals, so cataplexy is the most frequently recognized manifestation of sleep disorder in these species.[1461] The disorder is considered an intrusion of aspects of REM sleep into the waking stage, especially the active descending paralysis of skeletal muscle. This intrusion results in indistinct boundaries between wakefulness and REM and non-REM sleep. Cataplectic attacks result from sequential activation of pontine α_1-adrenergic and muscarinic cholinergic systems. The numbers of muscarinic and dopaminergic receptors also are increased.[1456,1462]

Fig. 35-16 Electrophysiologic examination of a narcoleptic Brahman bull. The electroencephalogram shows low-voltage, high-frequency waves in all leads (i.e., left and right frontal [F_3, F_4], central [C_3, C_4], and parietal [P_3, P_4]). The electrooculogram *(EOG)* shows bursts of activity characteristic of rapid eye movement (REM) sleep, and the electromyogram *(EMG)* reflects data from extrinsic ocular muscles.



Attacks of narcolepsy and cataplexy are considered a paradoxic form of sleep because the EEG is characteristic of an alert, awake animal, but the REM is characteristic of deep sleep.[1455] Both neonatal-onset and adult-onset syndromes have been described in horses.[1463] Narcolepsy has been reported in quarter horses, a Shetland pony, thoroughbreds, Morgans, Paint horses, Arabians, Appaloosas, standardbreds, Welsh ponies, Suffolk sheep, Spanish fighting bulls, a Guernsey bull, and a Brahman bull.[1459,1464–1468] A familial occurrence has been reported in American miniature horses.[1469]

35.7.2 Clinical Signs

The clinical signs of narcolepsy include staggering, drooped head, kneeling posture, flaccidity of the lips, closure of the eyes, loss of the menace reflex, stertorous breathing, and proprioceptive deficits. During severe narcoleptic attacks the animal assumes lateral recumbency and appears comatose. The sensorium returns to normal after a time. In the periods between attacks, the patient appears normal.

The EEG changes of narcolepsy and cataplexy have been reported in cattle.[1464] The waveforms vary between low-voltage high-frequency (LVHF) and high-voltage low-frequency (HVLF) patterns, with LVHF corresponding to the actual period of narcoleptic attack (Fig. 35-16). The normal EEG sleep patterns of the horse are usually unavailable, so the technique has limited application for diagnosis of the condition in equine species.

Cataplexy can be induced by IV administration of centrally acting cholinomimetics such as physostigmine salicylate (0.05 to 0.1 mg/kg) or α_1-adrenergic blockers such as prazocin (0.02 to 0.06 mg/kg), but attacks cannot be evoked in all animals. Signs can be reversed for several hours by antimuscarinic drugs such as atropine sulfate (0.02 to 0.1 mg/kg IV once for acute signs). Diagnostic drugs must be used with caution because of possibly inducing colic, especially in horses. Pathologic lesions have not been reported in narcolepsy of large animals. In humans, narcolepsy can be caused by lesions in the rostral brainstem.[1455]

35.7.3 Treatment and Prevention

The tricyclic antidepressant imipramine can be used to treat narcolepsy or cataplexy. Lifelong treatment is required, which must be considered when deciding whether to treat affected large animals. Side effects of imipramine in horses can be serious, including tachycardia, muscle fasciculations, sensitivity to noise, and hemolysis.[1470] Such side effects can occur even when the blood level of imipramine is below the therapeutic range. This drug must be used with caution, and oral dosage in horses should not exceed 2 mg/kg; lower doses should be used when possible.[1457] Results of oral imipramine therapy are inconsistent[1457]; duration of effect is about 5 hours.

35.8 HEAD SHAKING IN HORSES

JOHN E. MADIGAN

Head shaking in the horse is a well-recognized problem that shows no predilection for age, breed, or gender.[1471–1482] Some horses head-shake at rest, whereas most manifest head shaking shortly after the onset of exercise. Head shaking may be vertical, horizontal, or both and often is accompanied by agitation. Suggested causes have included middle ear disorders, ear mites, *Trombicula autumnalis* (harvest mite) larval infestation, cranial nerve abnormalities, ocular disease, guttural pouch mycosis, dental abnormalities, maxillary sinus mass, and allergic vasomotor rhinitis. Finding a specific cause has been difficult, with most cases termed “idiopathic” head shaking. The disorder can occur at any time, but a spring and early-summer pattern is typically reported, although some cases start in the fall and winter.[1480] The research group at University of California, Davis, suggests that neuropharmacologic alterations associated with photoperiod mechanisms, leading to optic trigeminal summation (similar to photic sneezing in humans), may explain the spring onset of head shaking. In many horses, sneezing,

snorting, and nose rubbing accompanies head shaking. Most horses continue head shaking for many years, experience periods of remission, and often resume head shaking at the same time each year.

Examination of horses with head shaking includes a complete physical examination; ophthalmic, otoscopic, neurologic, and dental examinations; endoscopic examination of nasal passages, pharynx, and guttural pouches; radiography of the skull, and a complete blood count and chemistry panel. No abnormalities are usually noted in these examinations.[1483]

Intraorbital neurectomy eliminated head shaking in three to seven horses in one study.[1484] These results would seem to support that some cases of head shaking are caused by a tingling (or other uncomfortable sensation) in the muzzle area. It is postulated that light may play a role in stimulating the response, and that exercise may lower the threshold for onset in some horses.[1483] It is important to note that infraorbital neurectomy has several complications and is not indicated for the treatment of head shaking. The infraorbital branch of the trigeminal nerve is just one branch from that nerve, and it is believed the problem may reside higher up, at the trigeminal ganglia area.

The etiology of head shaking usually is not known. Most horses show no physical abnormalities on comprehensive physical examination, and no lesions have been seen at necropsy. The symptoms in these horses may best be explained by the presence of neuropathic pain involving the trigeminal nerve. Neuropathic pain is a burning, tingling, itching, or electric-like pain that can be intermittent or continuous. Symptoms include sharp, quick movements of the head; occasional striking at the face with a front hoof; excessive snorting and rubbing of the head on objects; carrying the head very low during exercise; and dragging the nose in the dirt. These behaviors could be manifestations of neuropathic pain. The cause of the assumed dysfunction of the trigeminal nerve is not known. The average age of onset of head shaking is 9 years, and most affected horses are geldings, although about 10% to 20% are mares. Often a period of inactivity precedes the onset of head shaking, which can occur quite abruptly.[1485]

Cyproheptadine, 0.3 mg/kg orally twice daily, has been used with some success for idiopathic head shaking.[1483] Cyproheptadine, a type I histamine and serotonergic (5-hydroxytryptamine) blocking agent, was chosen for treating head shaking in horses because of serotonin's role in pain sensations in humans,[1484] and because of photoperiod-induced increases in serotonin in the CNS in the spring. Side effects are few, but mild colic and lethargy have been reported. The drug cannot be used in show or performance horses because it is not an approved medication. Cyproheptadine appears to be effective only when the horse has an adequate blood level of the drug; therefore, it often is not possible to treat a horse and then withdraw the medication before a show and have the head shaking controlled during the event.

Other medications (e.g., corticosteroids, antihistamines, NSAIDs), chiropractic therapy, and acupuncture have not been successful. A few horses respond to a heavy hair net or a dangling device that makes contact with the nose area or upper forehead (Fig. 35-17). This type of contact may prevent the nerve from "firing," similar to blocking a sneeze by placing a finger under the nose and applying pressure. In a review of therapies for head shaking in horses, a nose net device was reported to be successful in approximately 30% of cases.[1486] Box 35-2 lists other treatments used by the author.

Fig. 35-17 Head shake device.

35.8.1

Box 35-2 Treatments and Medications for Horses with Head Shaking*

35.8.1.1

PHYSICAL METHODS

If light is a trigger, consider having the horse wear an ultraviolet (UV) light–blocking sun shade–type fly mask from Guardian Mask, San Diego (http://www.horsemask.com/Main.html).

If the horse is only bothered during exercise, use nose net or other device that attaches to or dangles from over the nostril and muzzle area (e.g., German dangling device); in one stuidy, 30% of head shakers respond.[1486]

The ear covering and forehead "dangling" material.

35.8.1.2

DRUGS TO CONTROL NEUROPATHIC PAIN

Cyproheptidine, 0.3 mg/kg twice daily orally.

Carbamazepine, 1 to 4 g either twice daily or four times daily alone or in combination with cyproheptidine.

Hydroxyzine (Atarax), 400 mg twice daily orally.

Fluphenazine (Repositol), 2 mL IM per horse. Repeat as needed every month or sometimes every 4 months. Use only unopened; if opened, can use refrigerated drug with no discoloration.

Clonidine, 0.0025 mg/kg (0.3-mg tablets); give 4 to 6 tablets orally twice daily to a 500-kg horse.

Phenobarbital, 97.2 mg/tablet; give 16 tablets orally twice daily to 500-kg horse.

35.8.1.3

OTHER TREATMENTS

Lower protein in diet to about 8%. Allow mild weight loss and continue exercise.

Alteration in photoperiod for seasonal head shakers that begin in spring and stop in late fall or winter. Give 12 to 15 mg melatonin orally starting November 1 every day at 5PM. Can try starting in midseason, but not as effective. This resets seasonal clock. Give this dose year-round. Horse may not shed and may need body clipping.

35.8.1.3.1 Combination

Cyproheptidine, standard dose.

Add magnesium supplement: Quiessence (double dose daily).

Spirulina wafers orally.

35.8.1.3.2 Magnesium

Magnesium is an electrolyte that calms nerves by increasing the stimuli needed for depolarization. Supplementing the diet with magnesium may help decrease the stimulation of the trigeminal nerve. One commercial formulation of magnesium, Quiessence, contains 5 g of magnesium per ounce. Feed 2 oz once daily and increase to 4 oz once daily if there is no improvement in the head shaking. Quiessence is available online (http://www.foxdenequine.com/quies.htm).

Have the veterinarian measure the horse's serum magnesium level in about 2 weeks and check it once monthly to ensure it is not high.

35.8.1.3.3 Spirulina

Spirulina is another supplement that may help decrease stimulation of the trigeminal nerve. Administer dose according to the label on the bottle. Spirulina is available online (http://www.springtimeinc.com/ShowView/product/112/1).

35.8.1.3.4 Melatonin

Give 15 mg (average horse) or 18 mg (larger horse) of melatonin orally (five or six 3-mg tablets) every day at 5 PM. Vitaminshoppe is one source for melatonin (http://www.vitaminshoppe.com). Twin Labs is a health food or supermarket brand of melatonin that has good bioavailability. This switches the horse's photoperiod back to winter and sometimes stops the head shaking that starts in the spring.

* There are no clinical controlled trails for these treatment options at this time. None of these suggestions are specific recommendations for an individual horse. Some clients have used these treatments and medications with some degree of success for horses with head shaking. All medications have potential side effects. Owners should always consult directly with their veterinarian before giving any medications to their horse.

35.9 DISEASES PRESENTING PRINCIPALLY WITH BRAINSTEM AND CRANIAL NERVE DYSFUNCTION

LISLE W. GEORGE

35.10 LISTERIOSIS (CIRCLING DISEASE; SILAGE DISEASE; *LISTERIA MONOCYTOGENES* INFECTION)

35.10.1 Definition and Etiology

Listeriosis is an acute meningoencephalitis caused by the gram-positive bacterium *Listeria monocytogenes*. The disease has a worldwide distribution but occurs most often in temperate climates. Listeriosis typically affects ruminants, fowl, and humans but is rare in horses. The prevalence of listeric meningoencephalitis in infected herds does not usually exceed 1% of the adult animals at risk.[1487]

Clinical forms of listeriosis include septicemia of neonates, abortion, neonatal death, ophthalmitis, septicemia and diarrhea of ewes, and neurologic disease.[1488] Usually, only one clinical form is recognized during an outbreak, and only one serovar can be isolated from the clinically affected animals. Neurologic listeriosis may manifest as a multifocal brainstem disorder, as a diffuse meningoencephalitis, or as a spinal cord myelitis. The condition usually affects individual animals but occasionally can affect several members of a herd.[1489] Asymptomatic intramammary infections apparently occur and may be responsible for outbreaks of listeriosis in humans. Repeated intramammary inoculation of 10^6 to 10^7 colony-forming units (CFUs) of *L. monocytogenes* into cattle resulted in 500 to 50,000 CFUs of *Listeria* in the milk for as long as 12 months.[1490]

35.10.2 Clinical Signs

The neurologic signs of listeriosis in adults reflect dysfunction of the caudal brainstem, cerebellar peduncles, or spinal cord.[1491] Signs common to most *Listeria* infections of the central nervous system (CNS) include fever, anorexia, depression, conscious proprioceptive deficits, head pressing, and centrally located cranial nerve deficiencies. Depressed consciousness is the result of lesions of the reticular activating system. Conscious proprioceptive deficits are caused by interference with the descending motor pathways and the ascending proprioceptive fibers in the brainstem and may precede or accompany cranial nerve dysfunction. The fever occurs early in the disease course and often disappears after 3 to 5 days. Head pressing and propulsive walking or compulsive circling are caused by lesions of the basal ganglia.

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Cranial nerves (CNs) V through XII usually are dysfunctional in listeric animals. Patients with loss of the trigeminal nerve (CN V) show dropped jaw or asymmetric jaw closure and facial analgesia or anesthesia. Facial analgesia is best detected by stimulation of the nasal septum with a pencil or piece of straw. Animals with lesions of CN VI exhibit a medial strabismus on the ipsilateral side of the lesion. Animals with lesions of CN VII have ptosis, loss of menace response, absent palpebral reflex, drooped ear, loss of levator nasolabialis muscle function, and decreased lip tone (Fig. 35-18). Small ruminants with CN VII loss have a deviated philtrum. The paralysis of the orbicularis oculi muscle results in exposure keratitis and, in chronic cases, panophthalmitis.[1492] The loss of levator nasolabialis function is best detected by observation of the muscular

contraction on the dorsum of the nose during inspiration. Loss of lip and cheek muscle tone is best detected by observation of drooling of saliva from the ipsilateral side of the mouth and by palpation of the lips and nostrils.

Animals with CN VIII lesions display a nystagmus that changes as the position of the head is altered. Other signs include a head tilt toward the side of the lesion and a tendency to circle or fall to the lesion side. The nystagmus may be horizontal, vertical, or rotatory and usually is inconstant. Goats may lie on their backs with the head curved toward the trunk and tilted with the lesion side toward the ground. If the spinal reflexes can be tested, the affected animals show a mild to moderate hypertonia and hyperreflexia in the limbs opposite the side of the lesion. Lesions of the cerebellar peduncles (juxtarestiform body) may cause paradoxic vestibular signs in which the head tilt and circling are directed away from the side of the lesion and proprioceptive deficits are on the same side as the lesion.[1493] This should be suspected whenever the head tilt is directed toward the side opposite that of the other dysfunctional cranial nerves. Animals with acute loss of CNs IX, X, and XII develop stertorous breathing and dysphagia. Animals with dysfunctional CN XII have paresis or paralysis of the tongue. With unilateral lesions the tongue protrudes from the side of the mouth ipsilateral to the lesion. Progression of listeriosis is associated with decreased consciousness, coma, and convulsions.

Fig. 35-18 Clinical appearance of the neurologic form of listeriosis in a Charolais bull. Note the dropped right eye and ear and the drooling of saliva from the right side of the mouth. Courtesy Dr. W.D. Wilson.

Lambs may selectively develop spinal myelitis without brainstem disease. This condition results in flaccid paraparesis or hemiparesis without attendant signs of brainstem dysfunction.[1494] The clinical signs of myelitis include tetraparesis, tetraplegia, paraparesis, paraplegia, conscious proprioceptive deficits, and recumbency. The sensorium and appetite are normal in some affected animals and greatly depressed in others.[1495]

35.10.3 Clinical Pathology

The clinical signs of multifocal brainstem disease with fever in a ruminant are suggestive of listeriosis, *Haemophilus somnus* infection (cattle), or aberrant parasite migration. Examination of the cerebrospinal fluid (CSF) should be helpful for confirming a diagnosis of listeriosis, but the cell and protein concentrations of the specimens do not correlate with the severity of the clinical signs or the prognosis. The protein concentration in the CSF may be over 40 µg/dL, and the CSF white blood cell (WBC) counts may be more than 12 mononuclear cells/µL.[1487,1496,1497] Many cattle with advanced signs of listeriosis develop metabolic acidosis as a result of salivary bicarbonate loss.

35.10.4 Pathology

Pathologic confirmation of listeriosis is based on identification of multifocal microabscesses in the brainstem and isolation of *L. monocytogenes* from infected brain tissue. The agent is only rarely isolated from CSF and is best recovered from refrigerated nervous tissues. Enrichment of the *Listeria* organisms may be accomplished by refrigerating slices of brain at 4° C (39.1° F) for 3 months while culturing the tissues weekly. In contrast to septicemic listeriosis of monogastric animals, peripheral monocytosis is not observed in infected ruminants.

35.10.5 Pathophysiology

Listeria organisms produce a hemolysin, listeriolysin-O, a thiol-activated toxin (molecular weight, 58 kD) that is correlated with pathogenicity. The molecular role of the toxin in dissemination of the infection and in cell death is not known.

It is unclear whether infection of the brain by *L. monocytogenes* occurs hematogenously or by ascent from the cranial nerve rootlets.[1498] Morphologic studies of naturally occurring cases of encephalitic listeriosis have demonstrated the bacterium in the axons of the trigeminal nerve rootlets, indicating a possible centripetal migration.[1498,1499] Similar findings have been reported in animals infected experimentally.[1500] Younger animals may be susceptible because eruption of the permanent teeth may expose trigeminal nerve rootlets. A model for experimental induction of listeriosis by inoculation of the bacterium into the pulp cavity of sheep has been described.[1501] Infection of the CNS without bacteremia has been detected, indicating that centripetal migration of the bacterium is possible.[1502] Some investigators consider axonal migration as an unlikely mode of pathogenesis because of a lack of nutritional dependency of *L. monocytogenes* for nervous tissue and the ready ability to produce multifocal brain microabscesses by intravenous (IV) inoculation of the bacteria into susceptible hosts.[1498,1503]

35.10.6 Epidemiology

L. monocytogenes has 16 major serologic types based on comparison of somatic and flagellar antigens. Most clinical infections are caused by serovars 1/2a, 1/2b, 4a, and 4b. *Listeria ivanovii,* usually associated with abortions in sheep, also has been classified as *L. monocytogenes* serovar 5. The serovar 1/2 (a and b subtypes) is most prevalent in livestock. The 1/2b subtype appears to be exclusively related to encephalitic infections, whereas other subtypes, including 1/2a, can be associated with any of the clinical forms of listeriosis.[1504] The pathogenicity of serovar 1/2a is hemolysin dependent. Serogroup 1/2 (a or b type) is most often isolated from feedstuffs. Serovar 4b is responsible for most infections in humans.[1505]

The case-attack rate in ruminants may reach 9% but rarely is greater than 2%.[1506] Listeriosis occurs sporadically in weaned lambs confined to a drylot and appears in only a small proportion of the lambs at risk. The encephalitis usually occurs from 4 to 32 days after weaning and at 6 to 12 weeks of age. Between 0.7% and 1.6% of all lambs at risk may develop the infection.[1507] In untreated cases the fatality rate is almost 100%.[1491] The survival rate in treated animals is considerably higher than in untreated patients. The disease in sheep and goats tends to be more acute and results in a higher case-fatality rate than in cattle. Occasional outbreaks of listeriosis may occur in sheep without access to silage.[1491,1508] In these cases the source may be the feces of carrier animals or rotting vegetation on the pastures or feed bunks. During an outbreak of listeriosis, the bacterium can be isolated from the feces of a large percentage of normal animals.[1509] It is unclear whether this high rate of asymptomatic infections represents a true carrier state or is simply the result of a high environmental contamination by nonpathogenic isolates.[1509] The agent infects the udder but rarely causes clinical mastitis. In sheep, excretion of the bacterium in the milk is greatest during the immediate postlambing period.[1510,1511]

Listeria monocytogenes can survive for long periods in the environment and in asymptomatic carriers. The bacterium can multiply at low environmental temperatures and is resistant to environmental influences. *L. monocytogenes* is shed in the feces of asymptomatic carriers, especially at the end of pregnancy and at lambing. Once in the environment, the bacterium can survive for 2 years in dry soil. It is resistant to freezing and thawing in the soil but does not survive for more than 1 to 2 weeks in properly preserved silage. The bacterium proliferates in rotting vegetation in which aerobic conditions exist and the pH is above 5.4.[1512–1514] Common sources of contaminated forage include spoiled silage at the ends of trench silos, decaying forage at the bottom of feed bunks, or rotting hay at the periphery of hay stacks.[1512,1515] The incidence of listeriosis may be increasing because of the greater use of trench silos and bulk handling methods that result in a greater amount of spoilage than in conventional upright silos. Although *L. monocytogenes* can be isolated from silage with a pH below 4, fewer bacteria are found in well-preserved forage.[1516]

A selective enrichment medium has been developed for identifying and enumerating the *Listeria* organisms in silage. This medium permits semiquantitative enumeration of *Listeria* bacteria in 10 g of silage. Hemolysin production is measured by overlaying the colonies with bovine blood agar and reincubating the plates. Using this method, outbreaks of listeriosis have been correlated with silage containing 1 million *Listeria* organisms and more than 1 million enterobacteria per gram of silage. The pH of such silage characteristically is above 7.8.[1517]

There is a significant public health concern about *Listeria* contamination of milk products. The 4b serotype of *L. monocytogenes* is most often responsible for infections in humans.[1518] Outbreaks have been traced to

ingestion of pasteurized milk, cole slaw, and soft, ripened cheese. The occurrence in cheese has led to concerns that the bacterium may survive the pasteurization process[1519]; however, heat resistance by *Listeria* organisms does not appear to be a significant factor in milk-related human exposures. One study indicated that intracellular *Listeria* bacteria survived after exposure to temperatures as high as 73.9° C (165° F) for 16.4 seconds. Complete killing of the *Listeria* organisms required temperatures as high 76.4° C (169.5° F) for 15.4 seconds. These temperatures exceeded the minimum temperatures required by the U.S. Food and Drug Administration (71.7° C [161° F] for 15 seconds).[1520] The public health implications of these findings are unclear.

35.10.7 Pathologic Lesions

The lesions of listeric meningoencephalitis are most common in the pons and the trapezoid bodies, but they can be located anywhere in the brainstem. Neurologic structures most often affected include the reticular formation and CNs V and VII to X. Macroscopic lesions are limited to mild meningeal congestion and clouding of the CSF. Microscopic lesions include perivascular cuffing with mononuclear cells, multifocal asymmetric brainstem microabscesses, and mononuclear cell meningoencephalitis.[1521] The microabscesses are composed predominantly of neutrophils. Other microscopic changes include degeneration of the neuropil and neuronophagia. To enhance the speed and accuracy of pathologic diagnosis, a peroxidase-antiperoxidase method has been developed for use with formalin-fixed nervous tissue. The test detects degraded bacterial proteins, as well as intact bacteria in the suspect tissue. Bacterial antigen is exclusively located in areas of malacia or in the microabscesses.[1522]

35.10.8 Treatment

The recovery rate is best if treatment is administered early in the disease course. Animals that are recumbent, comatose, or convulsive rarely survive despite intensive antibiotic and supportive therapy. In most cases, treatment must be administered for a prolonged period because recovery may take as long as 1 month. *L. monocytogenes* is susceptible to most of the common antimicrobial drugs. Recommended treatment is either oxytetracycline, 10 mg/kg intravenously (IV) twice daily, or penicillin G.[1492] Specific recommendations for penicillin therapy include an initial dosage of 40,000 IU/kg (IV potassium penicillin G) three or four times daily for 7 days and then 22,000 IU/kg (procaine penicillin) intramuscularly (IM) once daily for 14 to 21 additional days.[1492]

The plasma concentrations of bicarbonate and potassium should be measured and specific corrective fluid therapy administered. Maintenance fluids also may be administered by gavage. Good footing and nursing care are helpful in the short term but may not influence the overall recovery rate.[1523]

35.10.9 Prevention

Serologic responses to flagellin and listeriolysin-O develop after oral administration of virulent *L. monocytogenes* and correlate with protection against listerial bacteremia.[1502] Cell-mediated immune responses also are important in protection against virulent challenge. Vaccines of attenuated or killed bacteria have been used successfully to protect sheep and goats. Although these vaccines reduce the incidence of listeriosis in vaccinated flocks, they are not commercially available in the United States.

Although the case-attack rate of listeriosis is low, occasional epizootics may occur in cattle, sheep, or goat herds, invariably associated with high rates of environmental contamination. In such cases the hay and silage should be examined culturally for *L. monocytogenes*. Rotten vegetation should be discarded, and cattle should be fenced from contaminated areas.

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35.11 THROMBOEMBOLIC MENINGOENCEPHALITIS (*HISTOPHILUS SOMNI [HAEMOPHILUS SOMNUS]* INFECTION; SLEEPER CALVES)

35.11.1 Definition and Etiology

Thromboembolic meningoencephalitis (TEME) is a fulminant neurologic disease of cattle that arises from septicemia caused by the pleomorphic, nonencapsulated, gram-negative bacterium *Histophilus somni* (formerly *Haemophilus somnus*).[1524] The disease was first reported in Colorado in 1956,[1525] but characterization of the etiologic agent, *H. somni,* was not completed until 1960.[1526] The disease is economically significant for livestock owners. One study in feedlots of western Canada indicated that the average economic loss from TEME resulted in 15 sick animals and five deaths annually, amounting to $3190 in lost revenue.[1527] In addition to TEME, disease syndromes that have been associated with *H. somni* infection include pneumonia, infertility, metritis, vulvitis, orchitis, conjunctivitis, otitis, and mastitis.[1528–1530] The bacterium has been isolated from unthrifty calves, but its causative relationship to that syndrome is unclear.

Cross-agglutination, complement fixation tests and countercurrent immunoelectrophoresis have shown the existence of common surface antigens among isolates of *H. somni*.[1531] Nevertheless, differences in the susceptibility of heterologous isolates of *H. somni* to antibody and complement have been identified.[1532] Isolates from septicemic animals are serum resistant, whereas those from preputial or vaginal mucosa of healthy animals tend to be serum susceptible.

35.11.2 Clinical Signs

Only the neurologic syndrome (TEME) is discussed here. Descriptions of other clinical syndromes of *H. somni* infection are discussed in Chapters 31, 39 and 43. The neurologic signs of TEME occur peracutely and may be preceded for 1 to 2 weeks by a dry, harsh cough and dyspnea.[1533] Death may occur within 36 hours after the onset of neurologic signs. The initial signs of TEME are fever (40° C to 41.6° C; 104° F to 107° F), anorexia, depression, and ataxia.[1534–1536] In addition to depression, affected animals show a number of conscious proprioceptive deficits, including knuckling, circumduction, crossing over, and interference.[1536] Affected animals may fall while attempting to walk. Signs specifically associated with lesions of the cerebellum and caudal brainstem include head tilt, nystagmus, strabismus, blindness, muscular tremors, opisthotonos, coma, and convulsions.[1537] Auscultatory abnormalities in the chest include harsh bronchovesicular sounds and pleural friction rubs. Localization of the bacterium in the joints or lungs may result in lameness, joint swelling, and fluctuant swellings over the joint surface. Other signs observed in some animals include retinal hemorrhages, hyphema, and hypopyon.[1535,1538]

After recovery from the pneumonia, some affected animals may develop pleuritis, necrotic laryngitis, and weight loss.[1539] Some symptomatic animals and as many as 10% of inapparently infected cattle may develop suppurative arthritis of the hock and the stifle joints.

35.11.3 Clinical Pathology

Examination of CSF may be helpful in substantiating a clinical diagnosis of TEME. Specific CSF changes characteristic of hemorrhage include high erythrocyte counts, xanthochromia, and increased concentrations of protein (>100 mg/dL) and neutrophils (>500 WBCs/μL). In untreated cases of TEME, the bacterium may be isolated from pleural fluid, lung sections, aspirated tracheal exudate, urine, blood, and preputial washings. The bacterium can be isolated from 25% to 34% of all fatally infected cattle.[1537] *Histophilus* organisms die rapidly on swabs or transport media, so specimens should be inoculated directly onto a growth medium as soon as they are collected from the patient.[1530] The inoculated medium should be incubated in an atmosphere containing 5% carbon dioxide. Isolation of *H. somnus* from joint fluid and CSF usually is unsuccessful.[1540] The kidneys and brain should be collected at postmortem examination because these tissues contain the highest concentrations of *H. somni*.[1540]

Initial changes in the peripheral WBC count include neutropenia, left shift, and toxic changes in the neutrophils. A test for serum agglutinins has been developed. Cattle that develop acute TEME invariably have antibody titers greater than 1:400 and show a fourfold increase by 2 to 4 days after infection.[1541] Serum agglutination titers greater than 1:1024 are seen in convalescent cattle; lower titers may be seen with inapparent infection or vaccination.[1542]

35.11.4 Pathophysiology

Infection of cattle by *H. somni* probably occurs through the respiratory tract. Bacterial proliferation in the lungs and other soft tissues by serum-resistant isolates results in bacteremia. Circulating *Histophilus* organisms are phagocytosed by neutrophils but are not killed. Blood-borne bacteria also adhere to and may be phagocytosed by the cells of the vascular endothelium. The infected endothelial cells then degenerate and desquamate, exposing the subendothelial collagen and initiating the blood-clotting cascade and thrombosis.[1543] Death of neutrophils in the tissues is thought to enhance the tissue damage.[1544,1545] The sites of the body most affected by the thrombosis are the brainstem, spinal cord, synovial membranes, pleura, and lungs. Although the name “thromboembolic meningoencephalitis” implies the presence of disseminated coagulopathy, only local thrombus formation likely occurs at the specific vascular lesion. Immunologic mechanisms may play a role in the vascular lesion. Thrombosis occurs most often in animals with high levels of specific agglutinating antibodies and is not seen in colostrum-deprived calves with *H. somni* septicemia, indicating the importance of antigen-antibody complexes for the development of vasculitis.[1546]

Cattle probably develop immunity to *H. somni* infection; however, the presence of serum antibodies does not always confer substantial protection against challenge exposure by virulent bacteria.

35.11.5 Epidemiology

Most cattle develop *Histophilus* infection by inhalation of contaminated respiratory secretions from carrier animals. Although TEME occurs most frequently in feedlot cattle,[1536] outbreaks in the western United States and Canada have been reported in both pasture and dry-lot environments.[1534,1547] The disease occasionally may occur in adult cattle.[1527] Outbreaks of the neurologic form of TEME tend to occur in the winter months, after shipment or overcrowding, or after additions to the herd in the previous 7 months. Outbreaks usually are

preceded by a poorly defined respiratory infection.[1527] In feedlot outbreaks the disease frequently is restricted to herdmates in a single pen or pasture.

Transmission of *H. somni* from asymptomatic carriers to uninfected calves may be enhanced by concomitant infection with infectious bovine rhinotracheitis virus.[1535] The anatomic site of bacterial infection in the carrier animals is unknown. *Histophilus* organisms can be readily isolated from the vaginal and urethral epithelium and from urine, the preputial cavity, and accessory sex glands, but the relationship between these isolates and those found in TEME is unknown.[1548] Although random bacteriologic surveys of cattle indicated that 71% of bulls may have *H. somni* in the preputial orifice, the concentration in the nasal secretions and upper respiratory tract epithelium in cattle with TEME is low.[1548] Consequently, some investigators have suggested that the urogenital tract may constitute the primary colonization site in chronically infected cattle.[1548] Differences exist in serum susceptibility of isolates from the CNS and from the urogenital tract.[1532]

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The seroprevalence rate may be as high as 100% in some endemic herds and may range from 25% to 56% in herds in which the CNS disease is uncommon. In comparison, the case-attack rate of TEME ranges from 2% to 7.4%.[1549] Repeated annual outbreaks can occur in some herds. Estimates of the proportion of carrier animals in feedlots range from 3.2% to 8.8%.

35.11.6 Necropsy Findings

Cattle with the neurologic lesions do not tend to develop fibrinous pneumonia. Macroscopic pathologic lesions of the CNS include disseminated multifocal hemorrhages and 0.1-cm to 0.3-cm infarctions in the spinal cord, brainstem, and cerebral cortex. Bacterial colonies frequently are observed in thrombosed blood vessels and the surrounding infarcted tissues. Ocular lesions are characterized by conjunctivitis, multifocal retinal hemorrhages, and areas of retinal edema. The CSF is cloudy and xanthochromic. A focal fibrinous meningitis is seen, and suppurative otitis may be seen in some cases.

The earliest microscopic lesion of TEME is a vasculitis that progresses to septic infarction and abscessation. The lesions usually are found in the CNS but in severe cases may be disseminated throughout the body.

Nonneurologic lesions of *H. somni* infection include suppurative arthritis, synovitis, suppurative pleuritis, and bronchopneumonia. Changes associated with the bronchopneumonia include infarction, cranioventral pulmonary consolidation, and hemorrhagic interstitial pneumonia. Simultaneous pulmonary infections with *H. somni* and *Pasteurella multocida* result in particularly severe pathologic changes.[1550] These lesions include ecchymotic to petechial hemorrhages over the serous surfaces, purulent exudate in the joints, and ulceration of the laryngeal and tracheal mucosa with pseudodiphtheritic membrane formation.[1551]

35.11.7 Treatment and Prognosis

During an outbreak, cattle must be examined frequently and should be treated when the neurologic signs first appear. *H. somni* is susceptible to many antibiotics and antimicrobial drugs. Drugs that have been reported to be effective for the treatment of TEME include tetracyclines, penicillin, aminoglycosides, and ampicillin. Parenteral oxytetracycline is regarded as the most cost-effective treatment for infected commercial cattle; dosage is 10 mg/kg of a conventional formulation given IV twice daily for 3 days or 20 mg/kg of a long-acting formulation given IM every other day for three treatments. After oxytetracycline therapy, daily treatment with procaine penicillin (10,000 to 20,000 IU/kg IM) should be continued until complete recovery is observed. Some

advocate the addition of chlortetracycline (2.2 mg/kg) to the feed for 10 successive days.[1552] This method of mass therapy for a TEME epizootic is considered more efficacious than vaccination when the mortality is less than 2%.[1552]

35.11.8 Prevention and Control

Antibody responses protective against respiratory challenge have been generated by vaccinating cattle with anionic, heat-stable proteins derived from the bacterial cell wall.[1553] In comparison, cattle vaccinated with cationic cell wall proteins developed precipitating antibodies but were not protected against challenge exposure.[1553] Bactericidal antibodies may constitute important mechanisms for host resistance against *H. somni*.[1545,1550] Vaccination of cattle with commercial products affords substantial protection from experimentally induced *H. somni* septicemia and neurologic disease[1533,1554] for as long as 95 days after vaccination.[1533] (See Chapter 48 for more information about vaccines.)

Mass prophylactic treatment of affected cattle with a parenterally administered, long-acting oxytetracycline formulation may be efficacious for preventing TEME in cattle that have been stressed and exposed to carrier animals.[1555] Oxytetracycline feed additives also may be useful for preventing *H. somnus* infection.[1551] One field study indicated that administration of modified live virus vaccines for infectious bovine rhinotracheitis and bovine viral diarrhea on arrival at a feedlot significantly increased the incidence of TEME.[1550] Such data indicate that modified live virus vaccines should be administered cautiously to cattle exposed to *H. somni*.

35.12 BACTERIAL OTITIS MEDIA-INTERNA OF RUMINANTS

Otitis media-interna is a common disease of cattle and sheep. The condition usually occurs as a sequel to severe respiratory infections caused by *Pasteurella haemolytica, Pasteurella multocida, Corynebacterium pseudotuberculosis, Pseudomonas aeruginosa, Histophilus somni,* or *Mycoplasma* species.[1556–1561] Bacterial ear infections are common in feedlot-reared lambs. The incidence may range from 2.9% to 12% of all animals raised under those conditions, and in these animals the condition usually is subclinical.[1556–1565]

Suppurative bacterial otitis is characterized by thickened mucosae of the vestibular membranes and accumulation of thick fluid in the labyrinths. The infection enters the ear through the eustachian tube. The tympanum may be intact in sheep.[1559] In calves, however, it usually is ruptured, and a clear, yellow, proteinaceous fluid is discharged through the external ear canal; the fluid then accumulates at the base of the ear.[1558,1566] In chronic cases of bacterial otitis, invasion of the local bone of the skull may result in bone remodeling and hyperostosis.[1561]

Vestibular disease results from infections that extend into the inner ear. Patients with vestibular signs display heat tilt (toward the side of the lesion), continuous horizontal nystagmus (fast phase away from the side of the lesion), and a tendency to stumble or fall toward the side the lesion. Head shaking with development of an aural hematoma may precede the clinical vestibular signs. Animals may become recumbent[1561] and lie with the lesion side toward the ground; if turned, they return to the same position. If the lesion involves the cerebellar peduncles, the animal develops paradoxic signs. In this case the head tilt is away from the lesion side, the fast phase of the nystagmus is toward the lesion side, and the patient circles away from the lesion side. Many animals with otitis media also develop facial nerve dysfunction, which results in ptosis, drooped ear, and flaccid lips and nostrils. In small ruminants, facial nerve paralysis results in deviation of the philtrum toward the normal side. Deviation of the philtrum does not occur in cattle because of the large amount of connective tissue surrounding the planum

nasale. Sheep with *Pseudomonas* otitis may develop necrotizing dermatitis of the ear canal. Some affected sheep also develop signs of cortical or brainstem disease, including unilateral blindness and contralateral mydriasis. These signs occur when the infection extends from the middle ear into the meninges. 1049 1050

Although the clinical signs of peripheral vestibular disease are characteristic, it is important to differentiate this condition from that of central vestibular disturbance. Animals with peripheral vestibular disease usually are appetent, alert, and aware of their surroundings and do not have a significant deficit of postural placement. The nystagmus of these animals is constantly horizontal. In comparison, animals with central vestibular disturbances are systemically depressed, have a nystagmus that varies in direction, and show marked conscious proprioceptive abnormalities.

Treatment of bacterial otitis with oxytetracycline (6 mg/kg IM or IV daily or 20 mg/kg of long-acting formulation IM every other day) or procaine penicillin (40,000 IU/kg IM daily) may be effective. Drug therapy should be continued for several weeks to prevent relapses. Treatment is very effective in obtaining a complete cure in animals with acute otitis but is less so in the chronic form. Otic instillation of aminoglycoside antibiotics is contraindicated. Lincomycin (6.5 mg/kg) and spectinomycin (10 mg/kg) have been used successfully when oxytetracycline or trimethoprim-sulfonamide therapy has failed.[1558] Other drugs that have been beneficial for the treatment of otitis include ampicillin, gentamicin, and enrofloxacin. Animals that do not respond should be examined for an abscess or squamous cell carcinoma invading the calvarium or osteomyelitis of the petrous temporal bone.

35.13 EAR MITE INFESTATIONS OF RUMINANTS

The ear mite of cattle is *Raillietia auris,* and that of small ruminants is *Psoroptes cuniculi*. Cattle that become infected with the ear mite develop a hearing impairment. Severe infestations perforate the tympanum and result in vestibular disease, facial paralysis, and ataxia.[1567–1570] Infected sheep and goats shake their heads vigorously and develop aural hematomas.[1571] Infestation of cattle can be recognized by observation of ulceration and purulent debris in the auditory canal next to the tympanum. In cattle, mites may be entrapped between the plug and the tympanum and may not be visible during an otoscopic examination. All infested cattle have pus and ulceration of the ear canal.[1572] A foul-smelling discharge on the side of the face under the ear canal may be seen in some affected animals. Chronically affected cattle develop a hearing loss for high-frequency sounds.

The psoroptic ear mite of small ruminants does not spread over the remainder of the body. The accumulation of purulent debris and swelling of auricular tissues block the transmission of sound to the tympanum.

Ear mite infestations in cattle are common and in some herds may affect most of the adults. One U.S. study reported a prevalence rate of 66% (29 of 44 cattle).[1567] The biologic importance of the infestation may be related to changes in the herding or mothering behavior of range cattle. The economic significance of the infestation is unknown. The parasite can complete a full life cycle by 8 days.

Ear mites have been successfully treated in goats using ear drops containing rotenone[*] once daily for 5 to 10 days. Good clinical responses can be obtained in cattle with the same treatment. Fenthion (Spotton,[†] 0.2 mL) drops also have been used successfully. In cases of parasitic otitis in which the discharge has been inspissated, lateral resection of the ear canal should be considered to establish adequate ventral drainage.[1573] The addition of nicotine to final concentrations of 2 ppm in dip tanks containing 0.25% toxaphene has been 95% effective in some outbreaks.[1574] Plunge-dipping in diazonon, propetamphos, or flumethrin, pour-on preparations of synthetic pyrethroids, and oral dosing with ivermectin all are ineffective.[1574] A single subcutaneous (SC) injection of

ivermectin at 0.2 mg/kg has been shown to be an effective treatment for *P. cuniculi* otitis in both sheep and goats.[1574,1575]

The life cycle of the mite involves two free-living stages, the proto and the deuto nymphs. These forms molt in the vegetation and reinfest cattle as they graze or bed during the evening.[1576] Therefore, tilling the soil of the infested pastures or re-treating cattle every 14 to 21 days with insecticide should be considered as part of an eradication scheme.

A recent report of neurologic dysfunction in a cow with *Raillietia* infestation highlights the importance of thorough evaluation before diagnosis.[1577] This cow also had listeriosis, the more likely cause of the neurologic signs.

* Ear Mitecide, Vedco Laboratories or Phoenix Pharmaceutical, St. Joseph, MO.

† Miles laboratories, Shawnee, KS.

35.14 SPACE-OCCUPYING LESIONS OF CRANIAL NERVES IN CALVES

LISLE W. GEORGE

An epizootic disease of Groningse Blaarkop calves characterized by facial paralysis and vestibulocochlear disease has been identified.[1578] The calves showed drooped ear, loss of vision with normal pupillary reflexes, head tilt, dorsolateral strabismus, circling, and depression. One calf had a mild fever, dysphagia, and mandibular paralysis. The CSF contained a high WBC count and an increased total protein level. The disease was caused by multifocal space-occupying lesions that surrounded the cranial nerves at the entrance of the calvarium. The microscopic lesions consisted of granulomatous inflammation of the nerves at the internal acoustic meatus and the facial canal. The inflammatory cells in the lesions consisted of histiocytes, lymphocytes, multinucleated giant cells, and plasma cells. The specific etiologic agent was not identified. The granulomas did not contain acid-fast bacilli, fungal elements, or *Listeria monocytogenes*. The microscopic appearance of the lesions and their location in the nervous system were similar to cauda equina neuritis in horses. The disease in the calves was nonprogressive, and some of the calves recovered, which differentiates the calf disease from the progressively fatal cauda equina neuritis in horses.

35.15 PERIPHERAL VESTIBULAR DISEASE OF HORSES

35.15.1 Definition and Etiology

Vestibular disease of horses is an acute, asymmetric condition with one of several causes: extension of pyogenic bacterial infections from the guttural pouch, polyneuritis equi, viral labyrinthitis, and traumatic skull fractures.[1579–1581] Idiopathic labyrinthitis probably represents an acute viral inflammation of the vestibular system that is severe,[1580] but spontaneous recovery is common. Lightning strike also has been suspected as the cause of vestibular signs in horses.[1582]

Vestibular disease may also be caused by pyogenic inflammation of the petrous temporal bone or membranous labyrinths. Staphylococci, streptococci, and *Aspergillus* species have been isolated from cases of suppurative otitis in horses.[1579,1583] Two forms of suppurative otitis media-interna have been identified.[1579,1583] In the least severe form, the pyogenic inflammation localizes in the petrous temporal bone but does not spread into the

calvarium or rupture the tympanum. This infection results in vestibular signs. This mild form of otitis media-interna also causes dysfunction of CNs VII and VIII.

35.15.2 Clinical Signs

The clinical course of peripheral vestibular disease may be chronic with acute exacerbations. Recovery is common with appropriate therapy. The more severe form occurs when the pyogenic inflammation extends outward into the temporohyoid joint and stylohyoid bone.[1583] The inflammatory process fuses the tympanohyoid joint, which fractures during strong contractions of the muscles of the pharynx and neck. The fracture line extends into the calvarium, resulting in hematoma formation in the CNS. Pyogenic agents from the original septic site may then gain access to the CNS and cause meningitis. The clinical signs are peracute, and mortality is high. Extension of the fracture lines along the cranial vault and osteomyelitis result in dysfunction of CNs VII and VIII and the cerebrum. Affected horses show a rapid deterioration in mental status immediately after the initial onset of clinical signs. Involvement of the temporohyoid bone can be recognized on radiographic examination of the head and pharynx. The radiographic changes include thickening and pathologic fracture of the stylohyoid bone and tympanosclerosis.

Early clinical signs may appear to be unrelated to the CNS. The horse may appear to be uncomfortable and may shake the head or rub the affected ear for 2 to 3 weeks before the onset of vestibular signs. Otorrhea is not usually observed. The neurologic signs appear suddenly. Horses with mild disease develop ataxia, head tilt, facial paralysis, and nystagmus. The nystagmus is not changed by movement of the head (rapid phase away from the side of the lesion). There also is a ventrolateral strabismus on the side of the lesion. The affected animals circle or more often lean against the stall walls for support. Frequently, a mild conscious proprioceptive deficit is worse on the affected side. Horses with severe calvarium fractures fall and become recumbent. They lie with the side of the lesion facing the floor. Because of the proximity of the facial nerve to the vestibular apparatus in the petrous temporal bone, most affected horses also show signs of facial palsy, including drooped ear and lips, drooling of saliva, ptosis, exposure keratitis, and deviation of the philtrum toward the opposite side of the lesion (Fig. 35-19). If extensive bleeding into the calvarium has occurred, the animal becomes blind in the eye contralateral to the side of the hematoma. Pressure in the cerebral cortex may result in mydriatic pupils on the ipsilateral side. Lesions located central to the geniculate ganglion denervate the lacrimal glands and result in keratitis sicca.

Horses with lesions of the peripheral vestibular system remain appetent and alert. In comparison, animals with vestibular disease accompanied by petrous temporal bone fractures and meningitis tend to be depressed, febrile, and inappetent. Animals that develop septic meningitis secondary to a temporal bone fracture show rapid deterioration of mental status, rigidity, or flailing of the limbs with mild stimulation, stiffness of the neck, hyperesthesia, fever, otorrhea, and dysphagia.[1584]

35.15.3 Diagnosis and Treatment

Ancillary diagnostic measures for vestibular disease in horses include skull radiographs and endoscopic examination of the guttural pouch to exclude the possibility of tympanosclerosis, fractured hyoid bone, or fungal otitis. Otic examination in the horse in difficult because of the external ear anatomy in this species and the resistance of horses to this type of examination. Chemical restraint and the use of video otoscopy can facilitate both otoscopic examination and the sampling of material from the external ear for microscopic examination and culture.[1585] The rate of tear secretion may be tested with a Schirmer tear test strip. The normal rate of tear secretion is approximately 21 mm/min, whereas deficient tear production is less than 17 mm/min.

Brainstem auditory-evoked response testing may help to establish the localization of vestibular signs as peripheral in origin rather than central.[1586]

Fig. 35-19 Head tilt and right-sided facial paresis in a horse with peripheral vestibular disease. Courtesy Dr. W.D. Wilson.

Antibiotic treatment of peripheral vestibular disease should include high doses of penicillin (20,000 to 40,000 IU/kg IV four times daily) or, as an alternative, a third-generation cephalosporin or trimethoprim-sulfonamide combination. The alternative drugs should be considered when infection by penicillin-resistant bacteria is suspected. One study reported clinical improvement in patients treated with chloramphenicol (10 mg/kg orally four times daily).[1583]

Patients with early cases of vestibular disease may benefit from treatment with nonsteroidal antiinflammatory drugs (NSAIDs). Administration of corticosteroids in the acute stages of the disease may ameliorate the clinical signs, but the beneficial antiinflammatory effects of these drugs should be weighed against the potential for nonspecific immune suppression and ultimate extension of pyogenic foci into the CNS along cracks in the calvarium.

Affected horses should be kept in a quiet, heavily bedded stall with good footing. Exposure keratitis may be treated by performing a tarsorrhaphy or by repeatedly administering petrolatum ophthalmic-lubricating ointments. Horses with keratoconjunctivitis sicca may be treated with 0.25% pilocarpine eyedrops four times daily.[1587]

Horses that recover after long-term antibiotic therapy should be used cautiously because subtle neurologic deficits that interfere with coordinated motor activities could precipitate catastrophic accidents. Relapses may occur in some seemingly recovered patients.

35.16 EXOPHTHALMOS AND STRABISMUS OF CATTLE

LISLE W. GEORGE

A heritable exophthalmos and strabismus of Jersey, Holstein, Brown Swiss, and shorthorn cattle has been described.[1588–1591] The defect is characterized by protrusion of the eyeballs and anteromedial rotation of the eye around the axis (cross-eyed). The defect does not become evident until the animals are over 6 months of age. Affected animals have defective vision and show difficulty walking in unfamiliar environments. Both genders are affected. The condition in Holsteins is thought to be related to a decreased number of nerve cells in the abducens motor nucleus.

35.17 NIGROPALLIDAL ENCEPHALOMALACIA (YELLOW STAR THISTLE POISONING; RUSSIAN KNAPWEED POISONING)

35.17.1 Definition and Etiology

Nigropallidal encephalomalacia is a disease of adult horses characterized by facial dystonia, variable ataxia, mild depression, and food retention in the mouth. The disease is caused by ingestion of large quantities of the plants *Centaurea solstitialis* (yellow star thistle) or *Centaurea repens* (Russian knapweed).[1592–1595]

35.17.2 Clinical Signs

The signs appear suddenly but always after long-term ingestion of large quantities of the plants. Characteristic signs of nigropallidal encephalomalacia common to all cases include weight loss, mild to moderate depression,

conscious proprioceptive deficits, yawning, lowered head, protruding tongue, tremor of the tongue and lips, and facial hypertonicity when feed is offered. The facial hypertonicity causes a retraction of the lips, resulting in a fixed grimace with the mouth and lips held half-open (Fig. 35-20). The patient may display constant chewing movements, and prehension, mastication, and deglutition of food are uncoordinated and inefficient. Affected horses can grasp food in their incisors but are unable to chew adequately and propel the food to the back of the mouth. Food retained in the mouth and cheek pouches may protrude from the commissures of the lips. Affected animals may attempt to drink by immersing their muzzles deeply into the bucket to force the water into the back of the pharynx. Once the food or water is in the posterior part of the pharynx, the animal is able to swallow. Affected animals die of starvation or dehydration. Horses that appear to be depressed usually can be aroused by mild stimulation. Motor and sensory deficits include hypertonicity, ataxia, conscious proprioceptive deficits, and occasionally hypermetria. There also may be a transient tendency to walk propulsively or to circle. Occasionally the animals are hyperexcitable. After several days the signs stabilize, and the disease does not progress. Affected animals usually do not recover.

Fig. 35-20 Characterisitc facial expression of a horse with nigropallidal encephalomalacia. When the animal is offered feed, the marked dystonia of the facial muscles, caused by loss of upper motor neuron inhibition, becomes obvious. Courtesy Dr. G.P. Carlson.

35.17.3 Diagnosis

The CSF of affected horses may show increases in WBC count (75/dL).[1594] There are no characteristic changes in the complete blood count (CBC) or the serum chemistries. Magnetic resonance imaging (MRI) was used to make an antemortem diagnosis in one horse with nigropallidal encephalomalacia.[1596]

35.17.4 Pathophysiology

The toxic principle in the plants has been isolated and chemically characterized. The toxic molecule is called *repin,* a sesquiterpene lactone with high affinity for neural tissue.[1597–1600] Long-term feeding of alcoholic extracts containing repin to monkeys has resulted in collapse, convulsions, and death.[1601] Studies in rats suggest that repin exerts its neurotoxic effects by inhibiting dopamine release.[1600] Additional neurotoxic compounds, including aspartic and glutamic acids, also have been isolated from *Centaurea* plants.[1602]

35.17.5 Necropsy Findings

At necropsy, sharply demarcated areas of yellowish malacia are visible grossly in the substantia nigra and globus pallidus (extrapyramidal system). Lesions are bilaterally symmetric in more than 50% of cases but are asymmetric in a substantial proportion of affected animals. Lesions in other brainstem nuclei are found in a small number of animals.[1593,1603] Microscopic lesions include neuronal necrosis, vacuolation with gliosis, liquefactive necrosis, and cavitation in well-developed lesions.[1597]

35.17.6 Epidemiology

Nigropallidal encephalomalacia has been reported in horses of the United States, Australia, and South America. Yellow star thistle is a common plant in unirrigated pastures in the arid regions of the western United States. The plant is resistant to the effects of saline or alkaline soil conditions and has a minimum moisture requirement. Russian knapweed belongs to the sunflower family and grows predominantly on flood plains, where it can extract deep subterranean moisture. In the United States the plants tend to remain green during the dry months, so most poisonings occur during the summer or late autumn. Most horses are reluctant to eat *Centaurea* plants unless other vegetation is unavailable, but some develop a craving and selectively seek it out. Horses that develop nigropallidal encephalomalacia usually are being fed a poor-quality, high-roughage diet. Affected horses range from 4 months to 10 years of age (median, 2 years).[1597] The case-attack rates of yellow star thistle poisoning range from 3% to 31% of horses on infested pastures.[1597] Feeding studies have reported 1052
that as much as 59% to 200% of the body weight of yellow star thistle and 59% to 63% of Russian knapweed 1053
must be eaten over 3 to 11 weeks to cause clinical disease.[1593,1597] Continuous protracted exposure to the weeds seems to be important for expression of clinical disease. The dried plants retain their toxicity.

35.17.7 Treatment and Prevention

There is no known treatment for the poisoning. Prevention is best aimed at correcting the nutritional problem by daily supplementation with 10 to 15 lb of alfalfa hay and by not pasturing horses in areas where the thistle grows.

35.18 RUPTURED RECTUS CAPITIS VENTRALIS MUSCLES (TRAUMA TO CRANIAL NERVES IX, X, AND XI)

LISLE W. GEORGE

Traumatic avulsion of the rectus capitis ventralis muscle is seen exclusively in equids. The condition causes dysphagia. The muscle is ruptured when horses fall over backward and hyperextend the neck and head. Tearing of the tendinous insertion of the muscle damages CNs IX, X, and XI. The clinical signs include mild transitory epistaxis, laryngeal hemiplegia, dysphagia, and pharyngeal paralysis. Endoscopic abnormalities of the pharynx and larynx include mucoid discharge from the guttural pouch, pharyngeal and laryngeal paralysis, atonic proximal esophagus, and food particles in the trachea and bronchi.

Radiographic examination of the head and neck may be helpful for substantiating a clinical diagnosis. The radiologic lesions include irregular radiopaque lesions in the guttural pouch and fracture of sclerotic occipital and petrous temporal bones. These cases usually are associated with a preexisting mycotic lesion that results in bone weakness and pathologic fractures. The neurologic lesion usually is reversible, but affected horses may die of aspiration pneumonia before neurologic resolution.[1604]

35.19 HORNER'S SYNDROME

35.19.1 Definition and Etiology

Horner's syndrome results from interruption of ocular sympathetic pathways. Sympathetic fibers originate from neuronal cell bodies located in the mesencephalic tectum. Axons descend to the first to third thoracic (T1 to T3) segments of the spinal cord, where they enter the gray matter, synapse, and exit through the ventral spinal nerves. From there the nerves pass through the cervicothoracic and middle cervical ganglia (stellate ganglia) and ascend in the cranial vagosympathetic trunk.[1605] The nerves enter the cranial ganglion in the petrous temporal bone, where they synapse. The postganglionic fibers are distributed to the sweat glands of the head, ciliary muscles, periorbital smooth muscles, and periarteriolar musculature. Fibers of the vagosympathetic trunk or the cranial cervical ganglion can be injured as they pass through the neck or over the caudodorsal aspect of the guttural pouch.

Specific causes of Horner's syndrome include mycotic guttural pouch infections; traumatic lesions of the basisphenoid area; cervical trauma; abscesses, tumors, or space-occupying lesions in the anterior aspect of the thorax[1606,1607]; periorbital abscesses or tumors; parotid duct obstruction and inflammation[1608]; esophageal rupture; and complications associated with surgical ligation of the carotid artery. Intracranial lesions involving the central components of the sympathetic pathway in the ipsilateral brainstem are rare but have been reported as a consequence of metastatic neoplasia.[1609] Horner's syndrome also has occurred after IV injection of certain drugs, including xylazine, vitamin E or selenium, and phenylbutazone.[1610–1612] Horner's syndrome has also been seen in horses with polyneuritis equi (cauda equina neuritis) syndrome and equine protozoal myeloencephalitis of the cervical spinal cord.[1613,1614] Tumors that have resulted in Horner's syndrome include sclerosing respiratory epithelial carcinoma, squamous cell carcinoma, and melanoma.[1606,1607,1610,1615,1616]

35.19.2 Clinical Signs

The clinical signs of Horner's syndrome in horses vary but include miosis, enophthalmos, ptosis, regional hyperthermia, excessive sweating on the ipsilateral side of the face, congested mucous membranes, inspiratory stridor, and dermatitis caused by chronic sweating. Ptosis may be detected by palpation of decreased eyelid tone. The palpebral reflex and the menace response are normal. Facial sweating often disappears 6 to 14 days after sympathectomy. If concomitant damage to the cervical sympathetic nerves is present, sweating of the skin of the neck also may be seen. This is not observed in animals with lesions solely in the tectotegmentospinal pathway. Regional hyperthermia is caused by vasodilation, which results from deficient vasomotor tonus. Sweating is thought to be caused by vasodilation and increased cutaneous blood flow.[1617,1618] Increased sweating can be induced by β_2-agonists, including IV clenbuterol (200 µg) or isoprenaline (2 mg) or local application of 10% phenylephrine.[1619] Dysfunction of adjacent neurologic structures may result in simultaneous facial nerve paralysis and laryngeal hemiplegia. Bilateral Horner's syndrome has been reported in a horse with metastatic neoplasia affecting the sympathetic innervation of the head bilaterally.[1616] This horse had a mixed pattern of both preganglionic and postganglionic denervation caused by widespread metastases at multiple sites along the nerves.

In contrast to the disease in horses, cattle do not sweat on the planum nasale of the affected side. This can be explained by the mediation of normal sweat gland secretion by α-adrenergic receptors in the bovine.[1618] The other signs seen in cattle are similar to those in horses. The clinical signs of experimentally induced Horner's syndrome in sheep and goats are limited to a mild ptosis.[1618] Retrobulbar tumors may cause Horner's syndrome, but in these cases the eyeball proptosis results from the excessive retrobulbar pressure.[1615]

35.19.3 Diagnosis

The specific site of the denervation of the ocular sympathetic system usually can be located by pharmacologic testing.[1605] Hydroxyamphetamine (1% solution) instilled into the eye will result in release of norepinephrine from intact postganglionic sympathetic neurons, causing pupillary dilation, but no response when the postganglionic neurons are damaged. A positive response to this test indicates a preganglionic sympathetic lesion, and a lack of response indicates a postganglionic lesion. In animals with a postganglionic lesion, topical administration of 0.1 mL of 1:1000 epinephrine solution directly activates the iris musculature and produces mydriasis by 20 minutes, whereas the onset of dilation occurs at about 40 minutes in animals with preganglionic lesions. Similarly, 2.5% to 10% phenylephrine solution will produce pupillary dilation in an eye with a postganglionic sympathetic lesion, but not in a normal eye. The increased sensitivity to these direct-acting sympathomimetics in animals with postganglionic sympathetic lesions results from the phenomenon of "denervation supersensitivity," with numbers and sensitivity of norepinephrine receptors in the iris muscle increasing over days to weeks after postganglionic nerve injury. A positive response is therefore expected only after the nerve lesion has been present for at least several days. Parenteral administration of 1 mL of 1:1000 epinephrine solution causes affected horses to sweat profusely over the affected side of the face.[1610] However, this test does not differentiate between preganglionic and postganglionic lesions.

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The guttural pouches of horses and the pharynx of all patients should be examined endoscopically to exclude the possibility of pharyngeal or laryngeal paralysis or guttural pouch disease. The jugular furrows should be palpated for swellings. Insertion of a nasogastric tube during palpation may be helpful for detecting subtle lesions on the left side of the neck. Radiographs of the cervical vertebrae should be obtained to exclude spinal

cord disease. The thorax should be examined using auscultation and percussion and, if indicated, radiographs taken. The gait and proprioceptive responses should be examined to evaluate the function of the spinal cord. The skin temperature may be measured using thermography[1607,1620]; on the affected side it is 1° C to 2.5° C (33.4° F to 37.5° F) higher than normal.

35.19.4 Treatment

The treatment for Horner's syndrome depends on the underlying cause of the denervation. Except for Horner's syndrome related to IV injection of xylazine, the neurologic signs often are irreversible, even if the primary cause of the condition has been eliminated. When xylazine is administered IV, the condition disappears spontaneously. The situation differs from inadvertent perivascular drug injections, in which permanent neurologic sequelae may occur. The necrotizing effects of perivascular drug injections can be minimized if treatment is administered immediately. These treatments should include aseptic infusion of large volumes of saline at the perivascular injection site and systemic administration of NSAIDs or dexamethasone, or both. Abscesses should be drained, and fungal infections of the guttural pouch should be treated as described in Chapter 31.

35.20 GUTTURAL POUCH MYCOSIS, NEUROLOGIC SIGNS (DAMAGE TO CRANIAL NERVES IX THROUGH XII)

35.20.1 Definition and Etiology

In one retrospective survey, mycotic infections of the guttural pouch were the third most common disease of the upper respiratory tract of horses.[1621] The clinical signs occur because fungal infections in the medial part of the pouch extend dorsally and damage CNs IX through XII and the internal carotid artery. Mycotic guttural pouch infection usually occurs in older animals; however, horses as young as 3 months have been affected.[1622]

35.20.2 Clinical Signs

Initially the horse may display head shaking and unilateral nasal discharge. Additional clinical signs are nasal catarrh, dysphagia, head shyness, head shaking, roaring, dysphonia, protrusion of the tongue from the mouth, and epistaxis[1622–1624] (Fig. 35-21). Other clinical signs include parotid pain, abnormal head posture, facial sweating, shivering, Horner's syndrome, colic, hemiparesis to hemiplegia of the tongue on the affected side, and facial paralysis.[1622–1628] Epistaxis may be fulminant and life threatening. The abnormal head posture is characterized by a tendency to hold the head in extension or lower to the ground than normal. Atrophy of the brachiocephalicus and trapezius muscles occurs secondary to denervation of the accessory spinal nerve. Horner's syndrome occurs secondary to damage of the cranial cervical ganglion and sympathetic trunk. The sensorium is intact unless aspiration pneumonia develops or the fungus embolizes into the brain.[1629,1630] Occasionally, affected horses die peracutely as a result of exsanguination from a ruptured internal carotid artery. Endoscopic examination of the larynx of affected horses may reveal dorsal displacement of the soft palate, inability to swallow, and unilateral or bilateral laryngeal hemiplegia. Mycotic guttural pouch infection can be definitively diagnosed by endoscopically identifying the characteristic fungal mass in the dorsomedial compartment (Fig. 35-22). Radiographic examination of the pouches shows a poorly defined border of the pouch in the abnormal area. Extension of a mycotic infection from the guttural pouch to the brain through the internal carotid artery has been reported.[1630] The infection caused disseminated necrosis and hemorrhage that

was most severe in the thalamus, cerebral cortex, and hippocampus. The clinical signs were fever (38.3° C; 100.9° F), epistaxis, dysphagia, laryngeal hemiplegia, pharyngeal paralysis, circling, unilateral blindness, mydriasis, facial paralysis, and apprehension.

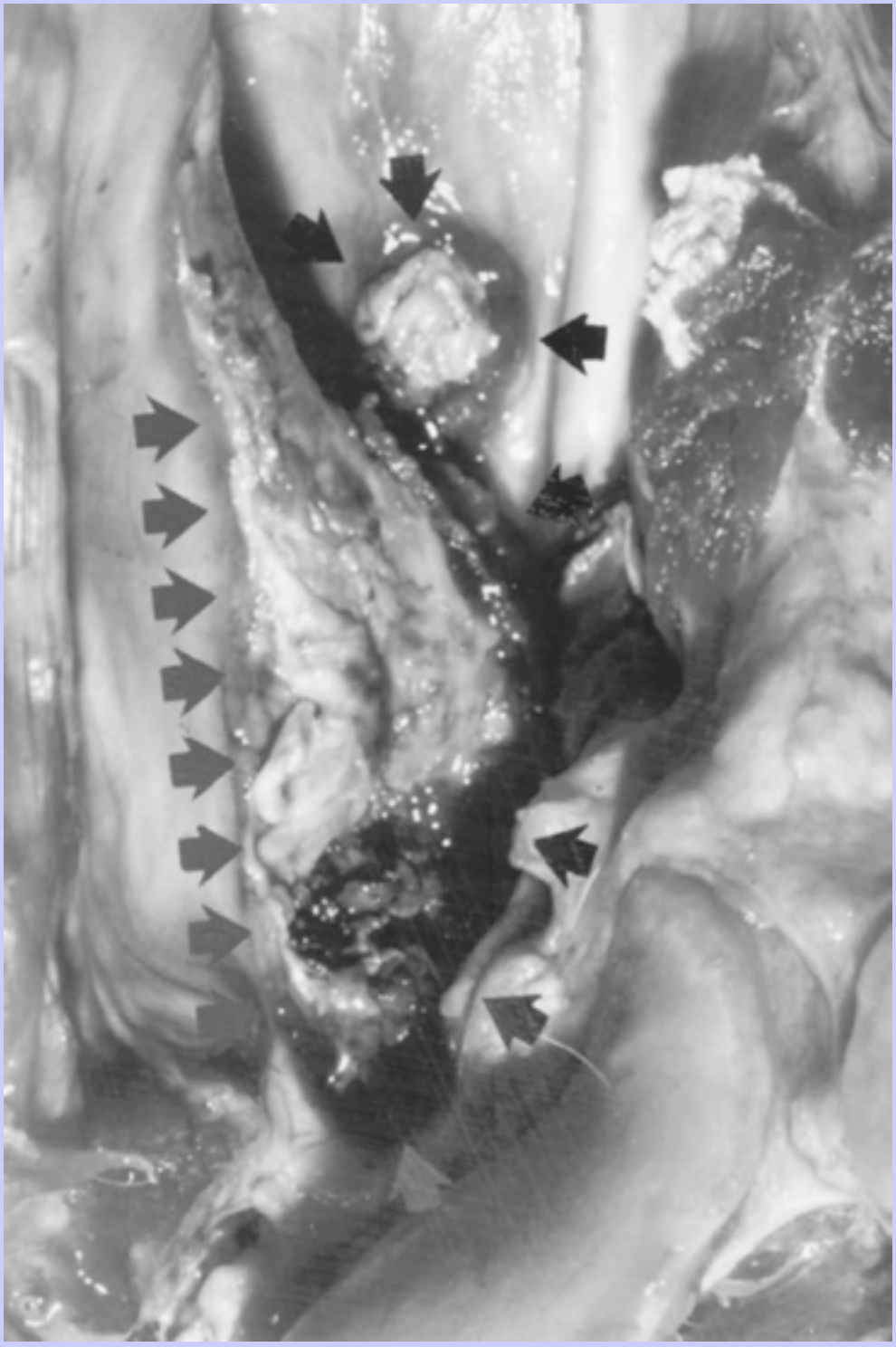
Fig. 35-21 Regurgitation of food material from the nose of a dysphagic horse with pharyngeal paralysis. The horse had a mycotic infection of the guttural pouch.

35.20.3 Pathophysiology

The guttural pouch is separated into two compartments by the stylohyoid bone and the occipitohyoideus muscle. CNs IX through XII and the internal carotid artery are located in the dorsomedial aspect of the medial compartment and are susceptible to damage from mycotic infections. Extension to the cranial nerves occurs because of inflammation and direct destruction of these structures by the fungal elements. Pathologic studies have shown swelling of the myelin sheaths and Schwann cells. Some sections demonstrate necrosis of the nerves and invasion by fungal elements.[1631]

In chronic infections the fungal lesion may extend into the tympanic bulla and cause vestibular disease. Extensive growth of the lesion also results in temporomandibular osteoarthropathy and fusion of the temporomandibular joint or osteoarthritis of the atlantooccipital joint. Excessive muscular force on the fused joint can result in avulsion fractures of the petrous temporal bone and calvarium. Hemorrhage or spread of infection into the vestibular apparatus and calvarium results in acute vestibular disease, cerebral hemorrhage, and septic meningitis (see Peripheral Vestibular Disease of Horses). In rare cases, fungal elements may reach into the lateral compartment, invade the wall of the internal maxillary artery, and affect the facial nerve. Facial nerve paralysis also has been observed and results from abscessation of the parotid lymph nodes secondary to a fungal guttural pouch infection.[1623] In other rare cases, Horner's syndrome may be caused by mycotic lesions in the cranial cervical ganglion. The syndrome also may occur iatrogenically during surgical ligation of the external carotid artery.[1632] Occasionally, the mycotic infection may extend into the brain and cause encephalitic signs.[1629]

Fig. 35-22 Appearance of a mycotic lesion in the dorsomedial compartment of the guttural pouch. Arrows outline the mycotic plaque.



35.20.4 Treatment

Before the onset of neurologic disturbances, the internal carotid artery may be occluded using a ligature or by insertion of a balloon-tipped catheter.[1633] During the exploration the fungal mass is debrided surgically. The surgical procedure is effective for preventing fatal epistaxis but may not reduce the potential for progression of the infection, resulting in nerve deficits or extension of the infection to the CNS. Some studies have shown excellent resolution of the mycotic lesion in horses that underwent carotid artery occlusion with or without additional antifungal therapy,[1634–1636] but in other animals the lesion may progress despite complete arterial occlusion.[1628] Moreover, optic neuropathy and blindness of the ipsilateral eye are common postsurgical sequelae.[1637] Neurologic signs may be permanent, although improvement or recovery over many months has been reported in some horses.[1636] Affected horses often are euthanized for humane reasons. (See Chapter 31 for treatment of guttural pouch mycosis.)

35.21 DISEASES PRODUCING TREMORS AND ATAXIA; CEREBELLAR DISEASES

35.21.1 CEREBELLAR HYPOPLASIA CAUSED BY CONGENITAL BOVINE VIRAL DIARRHEA VIRUS INFECTION

A complete discussion of bovine viral diarrhea–mucosal disease (BVD-MD) can be found in Chapter 32. BVD virus infection of susceptible pregnant cattle from 90 to 170 days' gestation results in abortion or stillbirth, hydranencephaly, or cerebellar hypoplasia in the fetus.[1638,1639] These signs are also seen in calves born to susceptible dams vaccinated during gestation with a modified live BVD vaccine.[1640] The BVD virus infects the developing germinal cells of the cerebellum and kills Purkinje's cells in the granular layer, resulting in necrosis and inflammation.[1641] Such cerebellar lesions tend to be most severe by 21 days after inoculation of the susceptible pregnant dams.[1638] The microscopic lesions include necrosis of the external germinal cells, focal parenchymal hemorrhages, and folial edema. After infection the acute inflammatory responses subside by 42 days, when the microscopic changes include cavities ranging from 1 to 7 mm in diameter, thinning of the neuropil, atrophy of the cerebellar folia, axonal torpedoes, and mild reactive astrocytosis. Calves infected with vaccine virus between 90 and 118 days' gestation may develop hydrocephalus and hydranencephaly.[1642]

The signs of cerebellar dysfunction usually are present at birth and include truncal ataxia, falling backward, opisthotonos, base-wide stance, coarse intentional head tremors, hypermetria, hyperreflexia, and nystagmus or strabismus (Fig. 35-23).[1643,1644] If severely affected, the animal may be unable to stand or lie in sternal recumbency. Excitatory stimuli in these animals precipitate wild oscillations and side-to-side movements of the head, which can be mistaken for convulsions. The affected calves may have a deficient menace response and appear to be blind, especially with concomitant hydranencephaly or microphthalmia. The neurologic condition rarely improves after birth. Other fetal changes that may be induced by the BVD virus include thymic atrophy, retinal degeneration, corneal opacity, failure to grow, and abortion.[1638,1643] The diagnosis of cerebellar hypoplasia is based on identification of the specific clinical signs and the recognition of BVD antibodies in precolostral blood specimens. The virus may be cultured from the blood of some affected calves. Viral antigen has been detected in the spleen, kidneys, and lymph nodes of aborted fetuses.[1644] The virus cannot usually be isolated from immunocompetent calves after antiviral antibody responses develop but may be recovered

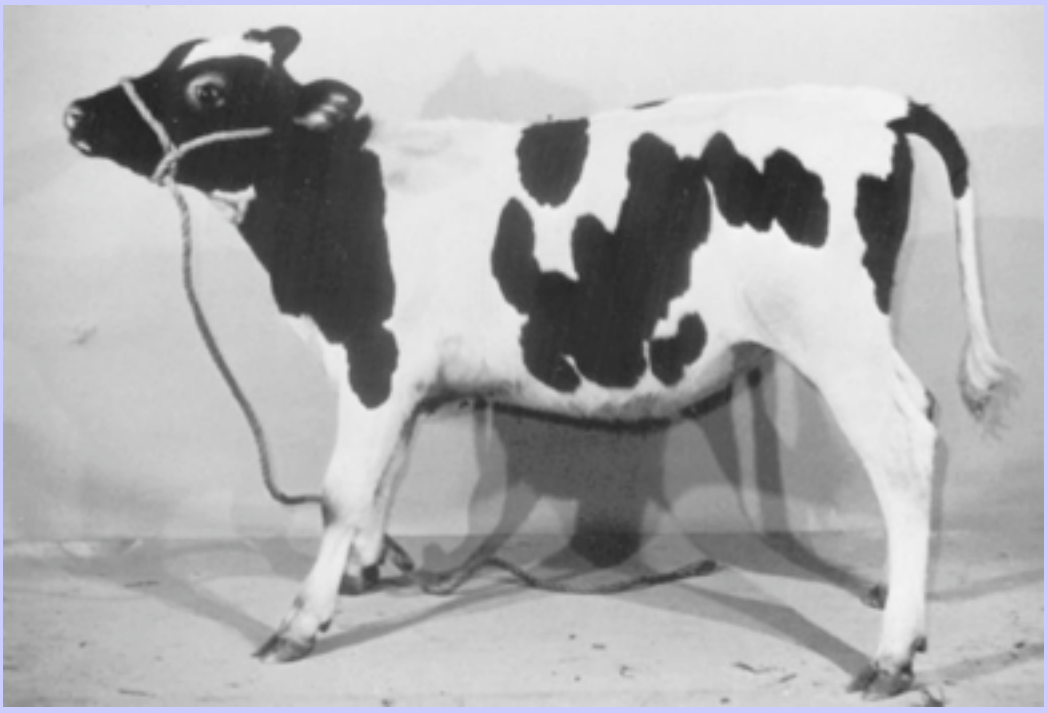
repeatedly from immunoincompetent, seronegative calves. Bluetongue virus may also occasionally cause cerebellar lesions in calves and lambs.

Fig. 35-23 Characteristic head position and base-wide stance of a calf with cerebellar hypoplasia.

35.22 CEREBELLAR ABIOTROPHY OF CATTLE

Abiotrophy is defined as a degeneration of formed elements of the nervous system.[1645] Cerebellar abiotrophy has been described in Holstein, Angus, and Limousin calves. The condition has been reported in the United States, Canada,[1646–1648] Australia,[1649,1650] and the United Kingdom.[1651] In Holstein calves a recessive mode of inheritance is suspected, which can be traced to a single sire. The etiology of the condition in other breeds of cattle is uncertain. Some calves are affected from birth,[1651] whereas others are normal at birth but develop signs at 3 to 9 months, or show signs intermittently, especially when stressed by factors such as inclement weather.[1649,1650] Severely affected animals may be in lateral recumbency and unable to rise. Nystagmus and opisthotonos are often seen in these calves. During the physical examination, signs of cerebellar dysfunction may be observed (Fig. 35-24), including intentional head tremors, base-wide stance, hypermetria, hyperesthesia, hyperreflexia, and lack of menace with preservation of eyesight. The clinical condition of affected animals may remain static or progress slowly until the animals become recumbent and unable to rise. Two calves showed gradual resolution of clinical signs when moved to a new location[1650]; thus environmental factors may play some role in the clinical development of the disease. The pathophysiology of the disease is unknown. There are no macroscopic abnormalities of the cerebellum of affected calves. The microscopic pathologic changes of abiotrophy include noninflammatory focal loss of Purkinje's cells and cerebellar nuclear neurons, with gliosis in the Purkinje and molecular cell layers. Swellings within Purkinje cell axons also have been described in some cases.[1650] The variable pathology described in affected animals suggests that bovine cerebellar atrophy may be several similar but slightly differing disorders rather than a single entity.

Fig. 35-24 Characteristic head posture and stance of a calf with cerebellar abiotrophy. Courtesy Dr. R.H. Whitlock.



35.23 HEREDITARY HYPERMETRIA IN SHORTHORN CATTLE

A neurologic disease characterized by symmetric cerebellar signs was reported in 15 shorthorn cattle of Brazil. The animals were affected at birth, and the clinical disorder was not progressive. The affected animals had no pathologic changes in the central nervous system that differentiated the condition from cerebellar hypoplasia and cerebellar abiotrophy. Examination of the relatives of the affected animals indicated a familial distribution. Pedigree analysis suggested an autosomal recessive mode of inheritance.[1652]

35.24 CEREBELLAR MALFORMATIONS OF AYRSHIRE AND JERSEY CALVES

Cerebellar malformations have been reported in two Ayrshire calves from Great Britain.[1653] The calves appeared to be normal at birth but displayed characteristic signs of cerebellar dysfunction by 24 hours of age. A similar condition has been reported in Jersey calves.[1654,1655] The clinical signs included opisthotonos, base-wide stance, truncal ataxia, hypermetria and hypertonia of all four limbs, and head tremors. Lesions in the calves were present in the cerebellum and the pons; some animals also developed hydrocephalus. The cause of these abnormalities was not definitely determined but was presumed to be a hereditary condition. The relationship of this disease to BVD virus infection is unclear.

35.25 BOVINE FAMILIAL CONVULSIONS AND ATAXIA

Bovine familial convulsions and ataxia is a disease of Angus cattle characterized by multiple tetanic tonic-clonic convulsions and a spastic ataxia that persists for several months.[1656–1658] A similar condition has been reported in a 9-month-old Charolais calf in the United States, in polled Hereford calves in Australia, and in Angus crossbred calves in Canada.[1659–1661] The disorder is believed to result from a defective autosomal dominant gene with incomplete penetrance, although some affected animals did not have a close relationship to blood lines believed to carry the trait.[1658]

35.25.1 Clinical Signs

The onset of clinical signs ranges from 2 to 3 hours after birth to 3 months of age. Calves may be born dead at or near term or may be aborted. Some aborted calves have a dorsiflexion of the spine. Most affected calves are born alive and rapidly develop intermittent signs of cerebellar dysfunction with multiple “tetaniform seizures” that last 3 to 12 hours. Two forms of seizures have been described. One form is characterized by a generalized stiffness and inability to protract the legs, elevation of the tailhead, and head-neck extension with mild head tremor. The animals are hyperesthetic. A more severe form is characterized by lateral recumbency, loss of consciousness, opisthotonos, hypertonicity, tonic-clonic seizures, and trismus. Animals may improve greatly if supported during the tetaniform activity. The frequency of the seizures declines over several months, but animals are left with a permanent ataxia characterized by cerebellar signs. The attacks may be precipitated by sudden, violent auditory, olfactory, visual, or tactile stimuli. These could include driving by dogs, shipment, flashing lights, loud sounds, or painful tactile stimulation. These features of the attacks, combined with a lack of electroencephalographic (EEG) evidence of seizure activity in the cerebrums of affected calves, suggest that these episodes may be exacerbations of cerebellar signs rather than true seizures.[1662] There is no response to treatment with electrolytes, mineral supplements, or B-complex vitamin injections. Seizure-like activity can be controlled by administration of barbiturates or inhalational anesthetics.

Most animals improve when turned out to grass pastures, but episodic relapses associated with excitement may occur for as long as 2 years. Affected animals gradually recover and by 2 years of age either show only mild cerebellar signs or are completely normal. There are no specific diagnostic tests for the disease.

35.25.2 Pathology

The gross appearance of the brain is normal. Microscopic lesions are restricted to the cerebellar cortex and include swelling and vacuolation of Purkinje's cells, chromatolysis, loss of neurofibrils, and formation of axonal torpedoes. The axonal structures have been defined as “argyrophilic axonal swellings.” They are located in the granular layer of the lingula, uvula, and adjacent parts of the vermis. An early report stated that these lesions were not seen in affected animals under 6 weeks of age, but a more recent study found lesions in affected animals of all ages.[1661,1663]

35.25.3 Diagnosis

Diagnosis is based on the presence of typical clinical signs, particularly when several related animals are affected. Differential diagnoses include cerebellar hypoplasia caused by congenital BVD virus infection, hypomyelinogenesis, congenital brain malformations affecting structures in the caudal fossa, congenital storage diseases, and the various cerebellar abiotrophies described in cattle.[1662] Imaging studies (e.g., CT, MRI) are expected to be within normal limits.[1662] Definitive diagnosis can be made only on histologic examination postmortem.

35.25.4 Treatment and Control

There is no known treatment for bovine familial convulsions and ataxia. Affected animals can be fattened and slaughtered but should not be used as breeding stock because the disease is genetically transmitted. Elimination of carrier animals from the breeding population will effectively control the propagation of this disease.

35.26 CEREBELLAR ABIOTROPHY (HYPOPLASIA) IN ARABIAN HORSES

Cerebellar abiotrophy occurs in purebred Arabian or Arabian crossbred horses.[1664–1669] Clinical signs may be present at birth or may develop after several weeks to months of postnatal life. Signs most frequently develop between 2 and 4 months of age and almost always occur before 6 months of age. The disease was initially reported as a cerebellar hypoplasia, but most descriptions suggest that the degeneration begins postnatally, prompting classification of the condition as an abiotrophy.[1670] Some investigators have suggested, however, that the clinical and pathologic course of the disease is not always consistent with a progressive postnatal degeneration of the nervous system.[1666]

The signs of cerebellar abiotrophy appear suddenly and range from subtle ataxia to complete diffuse cerebellar dysfunction. Head tremor is usually present and may occur in either a vertical or horizontal direction. Some horses show no progression of signs, whereas others progress slowly, followed by a plateau. The initial clinical sign in most foals is mild conscious proprioceptive deficits. As the deficits worsen, affected animals show hypertonia and stiff, hypermetric gaits accentuated by stimulation. In the most severe cases the animal may rear and fall over backward when suddenly startled. More severely affected foals have marked intentional head tremor, truncal ataxia, and hypermetria of all four limbs, often more pronounced in the forelimbs. These deficits are exaggerated

by turning the animal sharply, by having the foal step up and down a curb, or by walking the foal on an incline. Most affected animals have a decreased to absent menace response despite normal visual acuity and facial nerve function; however, two affected foals with normal menace responses have been described.[1665,1667] Rotary nystagmus occurs in rare cases.

Diagnosis generally is made on the basis of typical clinical signs in an Arabian horse under 6 months of age. Differential diagnoses include head trauma (particularly associated with basisphenoid bone fracture) and atlantooccipital malformation. With head trauma, other evidence of trauma and signs of vestibular dysfunction often are present. Foals with atlantooccipital malformation are ataxic and somewhat weak but do not have intentional head tremors. Muscular strength is preserved in cerebellar abiotrophy. Cerebrospinal fluid (CSF) analysis usually is normal, although CSF creatine kinase occasionally is elevated.

The major histologic finding is a degeneration and loss of Purkinje's cells in the cerebellum accompanied by gliosis and thinning of the molecular and granular layers of the cerebellum. Evidence indicates that apoptosis may be the primary mechanism underlying Purkinje cell death in Arabian horses with cerebellar abiotrophy.[1671] Mineral deposits in the thalamus also are found in horses with cerebellar abiotrophy, but their significance and relationship to the cerebellar changes are unknown.[1669]

The cause of cerebellar hypoplasia in Arabians is unknown, but there is a familial pattern of occurrence. One survey has reported an 8% prevalence rate in one family of 36 foals and a 6% rate in another family of 67 foals.[1664] Two of four full-sibling colts from a mare were affected.[1664] Pedigree analysis of 19 affected animals showed a high degree of relationship between the patients.

No effective treatment exists for cerebellar abiotrophy of Arabian foals. Occasional animals are reported to have shown gradual mild improvement, with considerable resolution of the head tremor. They remain unsafe for riding, however, and are not suitable as breeding stock because the disease probably is inherited. Owners of affected foals should be counseled about the probable heritability of the disease and should be encouraged to discontinue use of the parent lineage as breeding stock.

35.27 FAMILIAL ATAXIA IN HEREFORD CALVES

A central nervous system (CNS) disorder characterized by lateral recumbency, ataxia, incoordination, pupillary dilation, and abnormal head posture has been reported in Hereford calves.[1672] The disease occurred at 24 hours of age. The pathologic lesions could be differentiated from those of hereditary neuraxial edema and familial convulsions and ataxia of Angus cattle. The lesions in the Hereford calves included hypomyelination of the cerebellum, cerebral cortex, medulla, and midbrain and vacuolation of the white matter. No necrosis of the CNS or inflammatory lesions was seen, and the neurons of the cerebellum appeared to be normal. The cause of the condition was not identified, but the dams were highly related, and a genetic etiology was postulated.

35.28 MICROGNATHIA AND CEREBELLAR HYPOPLASIA IN ANGUS CALVES

Micrognathia was observed in Angus calves of a small herd in western Missouri. These animals were born dead. The calves had severe brachygnathia and cerebellar hypoplasia. Other somatic changes included hepatomegaly and patent foramen ovale. A pedigree analysis indicated that an autosomal recessive genetic trait derived from a common ancestor may have been responsible for the condition.[1673]

35.29 STORAGE DISEASES AND INBORN ERRORS OF METABOLISM

Storage diseases and inborn errors of metabolism are characterized by intraneuronal accumulation of indigestible metabolic products. The material accumulates in the cells because of a deficient activity of one of several lysosomal catabolic enzymes. Neurons have a long lifespan and are rich in gangliosides and glycolipids, which are continuously degraded and resynthesized. In normal animals the metabolic products are internalized by the intraneuronal lysosomes and are degraded into constituent amino acids, monosaccharides, fatty acids, alcohols, and simple lipids by acidic catabolic enzymes. Disturbances of ganglioside metabolism result in accumulation of the degraded by-products in the neurons and other cells.[1674] Overloading of the lysosomes by the undigested material produces profound neurologic dysfunction.

Storage diseases can be classified as either genetic or acquired. Acquired storage diseases are caused by ingestion of plants that contain specific inhibitors of one or more lysosomal catabolic enzymes. Genetic storage diseases are caused by the production of an inactive lysosomal enzyme. One such storage disease is ceroid lipofuscinosis, described earlier.

The genetic storage diseases are named according to the metabolic by-product that accumulates in the lysosomes. When tissues of affected animals are sectioned, processed, and examined microscopically, the metabolic storage product is dissolved from the tissue sections by the normal dehydrating and fixative agents. The spaces that contain the product appear as intraneuronal vacuoles when examined by light microscopy. Special fixation and staining procedures may be used to preserve and identify the metabolic product.[1674]

35.30 α-MANNOSIDOSIS (PSEUDOLIPIDOSIS)

α-Mannosidosis is a genetic defect of the enzyme α-mannosidase that is inherited as an autosomal recessive trait in Angus, Murray Gray, Simmental, Galloway, and Holstein cattle.[1675] At least two different mutations in the gene coding for α-mannosidase occur in different breeds of cattle and have been characterized in Angus and Galloway breeds.[1676] In animals deficient in α-mannosidase, the final cleavage between *N*-acetylglucosamine and mannose cannot occur, and the oligosaccharide accumulates in the lysosomes of the macrophages, neurons, and reticuloendothelial cells.[1674] Other abnormalities of glycoprotein metabolism occurring in affected animals may be the result of the multiple functions that have been ascribed to α-mannosidases.[1677]

The clinical signs first appear by 1 week to 15 months of age. Affected calves tend to be less well developed than age-matched herdmates.[1678,1679] The first symptom usually is a mild ataxia of the pelvic limbs that develops after exercise. Other signs include mild intentional head tremor, hypermetria, base-wide stance, and unwarranted aggressiveness.[1678] When galloping, the rear limbs are overflexed, and the animal's hindquarters appear to be sunken. The nervous system signs become much worse when the animals are excited. Most patients develop diarrhea, become recumbent after 3 to 4 months, and die shortly thereafter. A few affected animals survive for as long as 4 years. The neurologic signs of these animals remain constant, but they usually fail to grow normally. Other clinical manifestations in calves include premature delivery, abortion, stillbirth, and superior brachygnathia. Mannosidosis in Galloway calves is associated with somatic abnormalities such as arthrogryposis, hydrocephalus, and hepatic and renal enlargement.[1675,1680] Phenotypic variations affect the severity and onset of the neurologic signs.

The concentration of α-mannosidase in the plasma can be measured with an enzymatic assay. Heterozygotes have less activity than genetically normal animals; however, occasional overlapping between the phenotypes of homozygotes and heterozygotes can confound attempts at classification. Three isoenzymes of α-mannosidase exist, but only one form is inactive in diseased animals. A delay in separation of the plasma from the cells or the use of serum for enzymatic assays results in a leakage of other isoenzymes from tissue compartments and uncertainty in interpretation of the results. In most cases, two populations of animals usually are evident, the homozygous normal and the heterozygote. The mean plasma concentration of α-mannosidase in heterozygotes is 6.6 nmol/min/mL, whereas the mean plasma enzyme activity in homozygotes is 29.1 nmol/min/mL. The test is most accurate at detecting heterozygotes over 18 months of age.

The brain enzyme activity of heterozygotes ranges from 0.03 to 0.05 IU/g of tissue; the reference range of enzyme activity is 1.8 to 3.1 IU/g. Heterozygotes also may be detected by measuring the relative concentration of α-mannosidase and hexosaminidase in purified peripheral blood neutrophils. This test has been recommended for confirmation of a carrier animal whenever the plasma mannosidase assay is questionable.

35.30.1 Pathology

The diagnosis of a clinical case of mannosidosis can be substantiated pathologically by observation of cytoplasmic vacuolation in the neurons of the cerebrum, cerebellum, brainstem, and spinal cord.[1675] There is also a mild to marked internal hydrocephalus. The microscopic appearance of the brain of affected calves is characterized by vacuolation of the neurons and astrocytes and by reactive astrocytosis.[1675] The vacuolation is not restricted to the nervous system, however, and can be seen in Kupffer's cells, pancreatic exocrine cells, fibrocytes, and macrophages of the spleen and lymph nodes.[1681] The vacuoles are lined by a single membrane and are thought to be part of the Golgi apparatus.[1681] Associated neuronal changes include axonal swelling and spheroids.

Because of the hereditary nature of the disease, the ancestry of affected animals should be traced, and the biochemical phenotypes of related individuals should be tested. Both biochemical and molecular testing facilitate early detection of carrier animals, enabling their elimination from breeding programs.[1682] Although bone marrow transplantation has been shown to correct the defect in the feline and murine models of α-mannosidosis,[1683–1685] there is currently no effective and practical treatment for α-mannosidosis of cattle.

35.31 β-MANNOSIDOSIS

β-Mannosidosis is an autosomal recessive genetic trait of Anglo-Nubian goats and Salers calves. Mannosidosis in goats has a worldwide distribution, with reported cases occurring in Australia, Canada, and the United States.[1686–1690] The frequency of the condition is estimated at 1 in 2000 births of purebred Salers calves. The disease is seen in both the red and the black phenotype of Salers. The gene encoding for β-mannosidase has been characterized in both cattle and goats.[1691,1692] A single base mutation in the complementary DNA (cDNA) coding for the enzyme results in premature termination of translation. PCR-based tests have been used to identify β-mannosidosis carriers of both species.[1692,1693]

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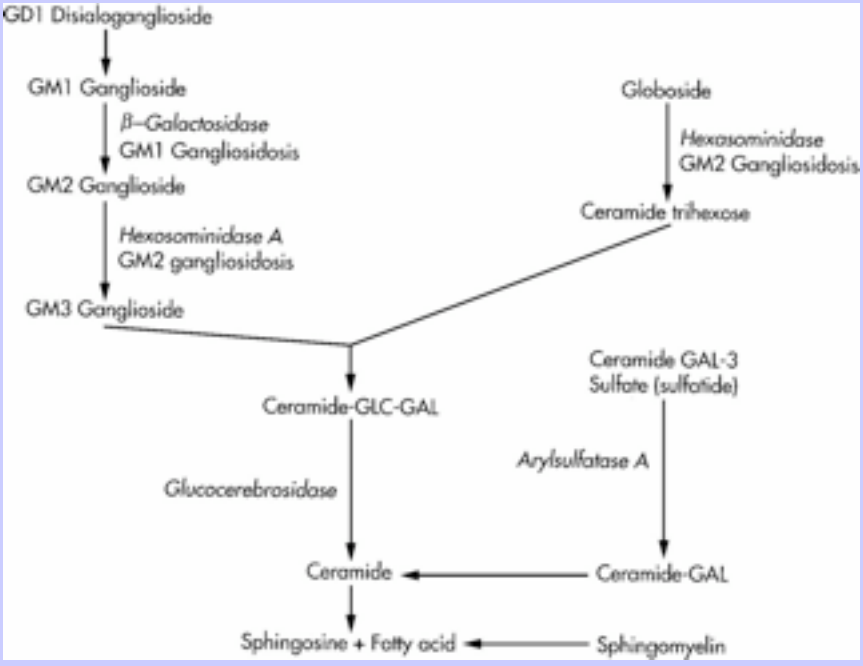
The lesions of mannosidosis have been identified in aborted fetuses and fetuses in utero, and clinical signs are often present at birth.[1694–1698]

The clinical signs in goats include recumbency at birth, deafness, shortened sternum, narrowed palpebral fissures, decreased muscle mass, intentional head tremor, carpal contractures, pastern joint hyperextension, thickened skin, shortened head, excessive gingival tissue, short curled ears, and domed skull.[1686,1699] Numerous ocular changes are seen, including pendular nystagmus, ventrolateral strabismus, thickened immovable eyelid, hazy vitreous humor, ptosis, and Horner's syndrome.[1700] The head movements are described as wide circular motions that culminate with the animal in lateral recumbency. Pupillary and corneal reflexes are intact, and the affected animals appear to have some vision. Compared with goats, affected calves respond to aural and visual stimuli. Other neurologic abnormalities include recumbency, depression, loss of suckle reflex, spontaneous chewing activity, head tremors, depression, and nystagmus.

The diagnosis of β-mannosidosis is based on observation of characteristic microscopic lesions in the central nervous system (CNS), demonstration of decreased tissue β-mannosidase activity, and demonstration of mannose-based oligosaccharides (Nanβ1-4G1cNAc and Manβ1-4G1cNAcβ1-4G1cNAc) in the CNS.[1701] The concentration of serum thyroid hormones is decreased.[1702] Some affected calves have concomitant colisepticemia or bovine viral diarrhea (BVD) infection.

In contrast to α-mannosidase, β-mannosidase has no isoenzymes.[1703] The mean concentration of β-mannosidase in the plasma of normal goats ranges from 66 to 222 nmol/hr/mL of plasma.[1695] There is no detectable β-mannosidase activity in the plasma of affected goats, and the activity in heterozygotes is intermediate between these ranges. The plasma concentrations of β-mannosidase in heterozygotes range from 43 to 64 nmol/hr/mL. These tests cannot be interpreted rigidly because there is significant variability among assays, storage conditions, and different age-groups of cattle.[1690]

Fig. 35-25 Catabolic pathways for gangliosides. Relevant enzymes and diseases caused by enzyme deficiencies are *shown in italics*.



In addition to the CNS abnormalities, cardiomegaly, thyromegaly, and pathologic fractures have been described in affected goats. Calves show a cerebral ventricular dilation and green discoloration of the renal cortices. Microscopic pathologic changes in the CNS include hypomyelination, axonal spheroids, and foamy-appearing neuronal cytoplasm.[1703] The heat shock protein ubiquitin has been detected in the CNS of affected calves.[1704] Cytoplasmic vacuolation also is present in the visceral organs.[1705,1706] Although in utero bone marrow or stem cell transplantation may offer hope for alleviation of the disease in the postnatal animal, no practical treatment exists for animals with β-mannosidosis.[1698]

35.32 GENERALIZED GLYCOGENOSIS (GM1 GANGLIOSIDOSIS; β-GALACTOSIDASE DEFICIENCY)

Generalized glycogenosis is a rare heritable defect of Holstein cattle and several breeds of sheep.[1707–1712] Generalized glycogenosis results from deficient activity of β-galactosidase, resulting in accumulation of the GM1 ganglioside, asialo-GM1, and neutral long-chain oligosaccharides in the tissues[1708] (Fig. 35-25).

A combined deficiency of β-galactosidase and α-neuraminidase has also been described.[1713] This condition is thought to result from a defect of the structural gene of β-galactosidase. The loss of α-neuraminidase occurs because of an inability of the βα-galactosidase molecule to dimerize with α-neuraminidase, leading to deactivation of both molecules.

The clinical signs of all forms of β-galactosidase deficiency are similar. Affected animals tend to show lethargy and anorexia by 1 month of age. The head and neck are held low and rigidly extended. The animals are depressed, stiff, and ataxic, have a base-wide stance, appear to be blind, and eventually become recumbent. The animals tend to fall whenever the head is moved. The blindness is the result of dysmyelination in the optic nerve, which can be detected by observation of numerous small white spots on the retina. None of these signs are pathognomonic for the disease, so biochemical testing or lectin histochemistry to characterize the stored carbohydrates in affected cells is needed for specific diagnosis.[1714,1715]

The genetic disorder is thought to be caused by an autosomal recessive gene. A biochemical test for β-galactosidase using centrifugally purified bovine neutrophils has been described.[1708] Animals with fewer than 3 IU of heat-stable activity are considered deficient. In herds in which GM1 gangliosidosis has already been substantiated, observation of slowness in feeding and lack of alertness has proved to be diagnostically significant.

Pathologic changes of GM1 gangliosidosis are present in the fetus as well as postnatally and include neuronal enlargement, vacuolation, accumulation of granular material in the nerve cells, spheroids, and loss of neurons without gliosis.[1716,1717] The material stains strongly with periodic acid–Schiff (PAS)/alcian blue, Sudan black, and oil red O. The vacuolar contents are composed of complex lipopolysaccharides, including β-galactose, *N*-acetylneuraminic acid and *N*-acetylgalactosamine.[1718]

No treatment is currently available for this disease. Strategies such as in utero bone marrow transplantation or stem cell transplantation may hold promise for the future, but are unlikely to become a viable option in large animal species.[1719]

35.33 BOVINE GENERALIZED GLYCOGENOSIS (TYPE II GLYCOGENOSIS; POMPE's DISEASE)

Generalized glycogenosis results from a dysfunction of α-glucosidase. The condition occurs in shorthorn and Brahman cattle[1720–1722] and is controlled by a single recessive allele.[1723] Several different mutations are described within the bovine α-glucosidase gene and are specific to the breeds.[1724] Two separate clinical entities have been described: the cardiac (infantile) form and the late-onset form. Clinical signs of the infantile form are first seen at about 2 to 3 months of age and include growth failure, weakness, hyperesthesia, muscle tremors, ataxia, conscious proprioceptive deficits, and recumbency.[1723] The cardiac (infantile) form is characterized by right-sided heart failure at 3 to 5 months of age. Brahman calves with the late-onset form die at age 8 to 9 months, whereas affected shorthorn calves may survive for more than a year. The tissues of affected cattle contain only 2% to 5% of the normal α-glucosidase activity.[1723,1725] The concentration of glycogen in the liver and muscles is increased.

The pathologic lesions of the CNS in both forms are similar to those of cattle with α-mannosidosis, including cytoplasmic swelling and foamy cytoplasm in the CNS neurons. Lesions are found in the myocardium and skeletal muscle. These include vacuolation and swelling of Purkinje's cells and myofibers.[1726] Because of a gene dilution effect, the activity of α-glucosidase in peripheral blood lymphocytes can be used to detect asymptomatic heterozygotes.[1727] However, the test result may be falsely positive if the animals are ingesting seeds of *Castanospermum australe* (Moreton Bay chestnut trees). The seeds of this tree have an α-glucosidase antagonist. Hematopoeitic chimerism in twin animals, on the other hand, can result in normal levels of enzyme activity in animals that are heterozygote carriers for the disease.[1728] Enzymatic methods for detecting carriers have now been superseded by DNA testing of leukocytes or hair root samples.[1729]

35.34 GLOBOID CELL LEUKODYSTROPHY (KRABBE'S DISEASE)

Globoid cell leukodystrophy has been reported in polled Dorset sheep.[1730] The genetic defect is the result of a lack of galactocerebrosidase, which produces a high concentration of galactocerebroside in myelin. The clinical signs are seen by 4 months of age. Affected animals show depression, hypersensitivity, conscious proprioceptive deficits, slight tremor of the head and neck, exaggerated patellar reflex, incoordination, and tetraplegia. The activity of the tissue galactocerebrosidase can be measured to substantiate the clinical diagnosis. Differential diagnoses include other heritable disorders, such as neuropathy and abiotrophy of the cerebellum and swainsonine (locoweed) toxicity (see later).[1731]

35.35 NEURONAL LIPODYSTROPHY

Neuronal lipodystrophy occurs in Angus and Beefmaster calves and in sheep.[1732–1734] The biochemical lesion of the condition is unknown. The clinical signs are first seen at about 10 months of age and include depression, blindness, ataxia, circling, coma, and tonic-clonic convulsions. The pathologic lesions include neuronal vacuolation with eosinophilic and sudanophilic inclusions. The inclusions are cytoplasmic and perinuclear and are located in the axonal and dendritic zones. As with other neurovisceral storage diseases, the inclusions are bound by a single membrane. Involvement of the spleen and lymph nodes also can be demonstrated. The mode of inheritance is unknown. There is no effective treatment for the disease.

35.36 SHAKER CALF SYNDROME

Shaker calf syndrome is an inherited neurodegenerative disorder of newborn horned Hereford calves.[1735] The condition is characterized by recumbency, fine tremors of the neck and hindlimbs, and hypermetria. The amplitude and frequency of the tremors are increased by stimulation. Other clinical signs include aphonia, loss of fine motor control of the tongue, hyperesthesia, exaggerated spinal reflexes, and hypertonia. Most affected calves die of starvation by 5 days of life; however, one case of remission followed by relapse after 2 weeks has been described. The cause of the disease is unknown. Limited breeding trials indicate a 12.5% inbreeding factor in affected calves, suggesting a hereditary etiology. The pathologic lesions include a neurofilamentous neuronal degeneration of multiple cell groups of the central nervous system (CNS) and of ganglion cells of the peripheral and autonomic nervous systems. The spinal cord is most severely affected. Neuronal degenerative changes include distention of axons and dendrites by a faintly fibrillar material, neuronophagia, and reactive gliosis. Wallerian degeneration of the spinal rootlets, spheroids, and empty fiber tracts in the spinal cord are noted. The pathologic appearance of the tissues differs from that of calves with hereditary neuraxial edema.

35.37 MAPLE SYRUP URINE DISEASE (SPONGIFORM ENCEPHALOPATHY)

Maple syrup urine disease (MSUD) is a hereditary spongiform encephalopathy characterized by severe CNS disturbance in newborn Hereford and polled shorthorn calves.[1736] The disease has been reported in Australia and Canada and may have occurred in the United States.[1737] The biochemical lesion is a deficiency of branched-chain 2-oxo acid dehydrogenase, which results in accumulation of the 2-oxo acids 4-methyl-2-oxopentanoate, 3-methyl-2-oxobutanoate, (S)-(S-KMV), and (R)-3-methyl-2-oxopentanoate, as well as their precursors leucine, valine, isoleucine, and alloisoleucine.[1736,1738,1739] The urine becomes highly viscous, discolored, and malodorous because of the excretion of these substances through the kidneys. The buildup of the transamination product of isoleucine, α-keto-β-methylvaleric acid, probably gives the urine the odor of burnt maple syrup. Branched-chain α-keto acids have been shown to inhibit energy production in the brain and to cause morphologic changes and death of astrocytes in vitro.[1740,1741] High levels of leucine are directly neurotoxic.[1742] Pyruvate is a vital constituent of the Krebs cycle, which is important for the production of transmitter amino acids. The CNS hyperactivity probably is related to a decrease in GABA-mediated inhibitory transmission. The genetic defect in polled shorthorns and polled Herefords has been shown to be a thymidine-to-cytidine transition in the cDNA coding for a subunit of the branched-chain amino acid dehydrogenase, resulting in a substitution of leucine for proline.[1743] PCR testing now can be used to detect both affected and carrier animals. A protocol for genotyping cattle for both MSUD and inherited neuraxial edema has been used to estimate the frequency of the alleles responsible for these diseases in Australian cattle (0.01 to 0.02).[1744]

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Affected calves are born normal but are depressed by 2 to 3 days. They also are febrile (39.5° C to 42° C; 103.1° F to 107.6° F). They initially show ataxia and depression and become recumbent by the second to third day of life. At that time they show hyperesthesia, opisthotonos, muscular rigidity, myoclonic limb jerks, nystagmus, repetitive head tremors, stimulus-induced tetanic spasms, blepharospasm, generalized decrease of spinal reflexes, and convulsions. The urine has the characteristic color and odor reminiscent of burnt maple syrup. The calves usually die by 5 to 10 days of age. The presence of ketoacids can be detected by mixing urine with dinitrophenylhydrazine and observing a faint-yellow precipitate.[1745]

The clinical presentation of MSUD differs from that of hereditary neuraxial edema.[1737] Calves with neuraxial edema have extensor rigidity but tend to be bright and alert, whereas MSUD calves have rigid extensor tonus and

obtundation. These differential features appear to be significant because the original reports of hereditary neuraxial edema likely included calves with MSUD[1746] (see following section).

Spongiform changes caused by intramyelinic vacuolation are present in the brains of affected calves in both white matter and gray matter.[1747] MSUD can be definitively diagnosed by measuring the ratio of isoleucine, leucine, and valine to α-aminobutyric acid in fixed tissues and finding increased concentrations of these amino acids or their corresponding branched-chain 2-keto acids in urine or blood.[1747] Heterozygotes have normal blood and urine levels of both amino acids and keto acids. PCR analysis of DNA extracted from hair root samples can identify both homozygote affected animals and the clinically normal heterozygote carriers of the disease.[1748–1750] Pharmacologic dosages of thiamine are beneficial for treatment of MSUD in some human patients, probably by increasing mitochondrial thiamin diphosphate, which promotes the activity of the branched-chain α-keto acid dehydrogenase complex.[1751] However, there is no known effective treatment for MSUD in calves.[1736,1737]

35.38 HEREDITARY NEURAXIAL EDEMA (CONGENITAL MYOCLONUS; DODDLER SYNDROME)

Neuraxial edema is an inherited neurologic disease of newborn calves. Polled and horned Herefords and Hereford-Friesian crossbred cattle are affected.[1752–1759] An autosomal recessive genetic trait is thought to be responsible for the condition. The disease is well defined clinically and pathologically[1756,1759]; however, some investigators have reported a disease of polled Hereford calves that has similar neurologic signs but does not result in status spongiosus or CNS edema. These calves had a high frequency of bilateral slippage of the capital femoral epiphysis, subluxation of the femoral head, and acetabular articular cartilage fractures.[1757] The authors named the condition “congenital myoclonus” to differentiate it from hereditary neuraxial edema. Calves with congenital myoclonus have a shorter-than-normal gestational length.

The earliest reports of hereditary neuraxial edema also described two clinical forms in which some calves were bright, alert, and responsive and others had a severely depressed sensorium. Subsequent studies suggested that the calves with systemic depression probably had MSUD (see previous section) and those with normal sensorium had hereditary neuraxial edema.

The clinical signs of hereditary neuraxial edema include hyperesthesia and myoclonic discharges of skeletal musculature that occur spontaneously or in response to tactile, visual, or auditory stimuli. The calves are stillborn or are affected at birth. Affected calves are of normal size but are unable to rise; they lie quietly without lifting the head.[1752–1755] These calves develop marked extensor tonus and clonic spasms of the limbs and head when stimulated. During the spasm the animals become transiently apneic and remain dyspneic for several minutes.[1756] The spasms are less severe after repeated stimulation. Between spasms the patients can stand with assistance, but the proprioceptive responses are greatly altered, and the animals fall when support is withdrawn.[1755] The sensorium and suckling reflexes are unaltered when the calves are not in a spasmodic episode. Some authors have reported that vision and cranial nerve function are unimpaired, but others have reported nystagmus in some calves.[1752,1756] Administration of anticonvulsant drugs does not ameliorate the clinical signs. Pathologic lesions usually are not seen in the CNS of affected calves.[1753] The condition has an autosomal recessive mode of inheritance. The defect lies within the postsynaptic glycinergic receptors in the inhibitory interneurons of the spinal cord.[1760] A protocol for genotyping cattle for both inherited neuraxial edema and MSUD has been used to estimate the frequency of the alleles responsible for these diseases in Australian cattle (0.01 to 0.02).[1744]

35.39 INHERITED MYOCLONUS OF PERUVIAN PASO FOALS

Inherited myoclonus is a disorder of Peruvian Paso foals that is characterized by myoclonic contractions of the musculature in response to auditory or tactile stimuli.[1761] These contractions are sustained with repeated stimulation. Some animals are ambulatory but have a “rabbit hopping” gait. Some animals are recumbent. If assisted, the foals can rise and walk, and the animals are not depressed. Analeptic drugs and tranquilizers are ineffective for controlling this condition. Inherited myoclonus is associated with a specific deficiency of spinal glycine receptors, which are responsible for synaptic inhibition in the CNS. Glycine is a major inhibitory transmitter and works through the Ia afferent neurons in the ventral columns and the Renshaw cells. Loss of the receptors results in uninhibited synaptic transmission.

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35.40 CONGENITAL ENCEPHALOMYELOPATHY IN QUARTER HORSES

Congenital encephalomyelopathy has been described in quarter horse foals.[1762] The condition occurred in three foals born to two different mares and three unrelated stallions. The condition was seen at birth, and clinical signs include recumbency and coarse tremors of the hindlimbs. When assisted into a standing position, the hindquarters bounced off the ground. The forelimb function appeared normal; however, the patellar reflexes were exaggerated. Affected foals are bright, alert, and responsive and have intact pain perception. There are no macroscopic CNS lesions. Microscopic lesions include spongiform degeneration and axonal swelling of the white matter of the medulla, spinocerebellar tracts, and spinothalamic tracts. The lesions extend through the entire length of the ventral funiculi of the spinal cord.

35.41 LOCOWEED POISONING (ACQUIRED MANNOSIDOSIS, *ASTRAGALUS* And *OXYTROPIS* POISONING; LOCOISM; SWAINSONINE TOXICITY; *IPOMOEA* And *SIDA CARPINIFOLIA* TOXICITIES)

35.41.1 Definition and Etiology

Chronic ingestion of a variety of different plants worldwide can result in an acquired neurovisceral storage disease. These include plants of the *Astragalus* and *Oxytropis* genera (locoweeds) in the western United States, Canada, and Australia; *Ipomoea* (shrubby morning glory) in Mozambique; the darling pea in Australia (*Swainsona* species), and *Sida carpinifolia* in Brazil (Table 35-14).[1763–1770] Horses are most susceptible to intoxication, but cattle, sheep, goats, and deer also can be affected.

Conditions that promote locoweed poisoning are hot, dry weather and a scarcity of alternative forage. Horses may be more prone to graze on locoweed than cattle, particularly when other green forage is scarce, and may increase their consumption over a single season.[1771] Chronically exposed livestock can become habituated and feed selectively on the plant over successive grazing seasons.[1772]

The following toxic components have been identified:

- Locoine, swainsonine n-oxide, and indolizidine alkaloids, which interfere with the activity of α-mannosidase and of Golgi mannosidase II.[1764,1765,1773,1774]

- β-Galactosidase and β-glucosidase.[1775]
- Aminonitrile, a compound that caused abortion and teratogenesis.
- Miserotoxin, a compound that causes a respiratory disease complex.
- Selenium accumulation (selenium toxicity may contribute to the neurotoxicity and fetal deformities).

Oxytropis and *Astragalus* plants are legumes that have herbaceous stems and alternate pinnately compound leaves. [1776] The fruits are characteristic leguminous pods that contain kidney-shaped seeds with pods marked by characteristic longitudinal grooves.[1776] The plant is eaten because it is the first vegetation available in the spring. The *Oxytropis* and *Astragalus* species found in the United States are listed in Table 35-14. Symptoms do not usually develop in cattle until 3 weeks after the animals first begin grazing the plant and may not occur until long after ingestion of the plant has stopped. The toxicity of the locoweed may vary from year to year and even within one season.[1771] Despite its relative unpalatability, some sheep may become habituated to the plant and selectively eat forage containing up to 20% *Astragalus* plants.[1772]

Table 35-14 Species of *Astragalus* and *Oxytropis* Found in Western United States

Scientific Name	Common Name
Oxytropis sericea	White locoweed, point locoweed
Oxytropis lambertii	Purple locoweed
Oxytropis campestris	Yellow locoweed
Astragalus argillophilus	Half-moon locoweed
Astragalus bisculatus	Two-grooved milk vetch
Astragalus earlei	Earles locoweed
Astragalus lentiginosus	Speckled, spotted locoweed
Astragalus mollissimus	Wooly locoweed
Astragalus mothoxys	Sheep locoweed
Astragalus wootnii	Wooton locoweed

From Knight AP: *Compend Cont Educ (Pract Vet)* 9:F418, 1987.

35.41.2 Clinical Signs

Experimentally and naturally poisoned horses show clinical signs by 2 to 3 weeks after continuous ingestion of locoweed.[1769,1771] The clinical signs include ataxia, conscious proprioceptive deficits, and depression, with alternating periods of frenzied or manic activity. There is sometimes a high-stepping, stringhalt-like gait.[1777] At rest the horses show intentional head tremor, flaccidity of the nose and lips, repetitive movements with the lips and tongue, and dysphagia.[1777] The clinical signs worsen when affected horses are handled or transported.

Signs in goats are similar, including ataxia, hypermetria, hyperesthesia, and muscle tremors.[1766] Forcing the head backward can result in falling, nystagmus, opisthotonos, seizures, and tetany.[1778] Tranquilization usually is ineffective for controlling the apparent hyperexcitability. Horses that survive locoweed poisoning retain an altered behavior. Abortions, stillbirths, and neonatal deaths can occur in all species exposed to these toxic plants, regardless of whether the dams have clinical signs of neurologic disease.[1764,1766–1768]

Neurologic signs in adult cattle include conscious proprioceptive deficits, hypermetria, weakness, depression, dull staring eyes, and loss of herding instinct. Heavy losses from abortions or malformed calves have also been described. The indolizidine alkaloids are secreted in the milk and may cause unthriftiness and weak suckling behavior in calves. Calves that have been exposed to the toxin in utero are weak and fail to thrive. Some may have flexural contractions of the limbs and lateral rotation of the carpus.[1779–1782] Ingestion of locoweed by certain cattle at high altitudes may result in the development of cor pulmonale.[1779,1780] Many cattle with mild signs of locoweed poisoning recover completely by 60 days after removal from the offending pastures. Ruminants with advanced chronic intoxication apparently have permanent loss of neural tissue.

Poisoned sheep have a star-gazing attitude and appear to be blind, nervous, and stiff. The normal flocking behavior is absent.[1765] Affected sheep may exhibit ptyalism. Testicular atrophy has been reported in rams.[1783] Affected animals have intercurrent pyogenic infections such as pneumonia, keratoconjunctivitis, and foot rot. This is thought to be related to the immunosuppressive effect of the plants on the T lymphocytes.[1784] Depression and reluctance to move induced by locoweed toxicity may predispose animals to other problems, such as water deprivation.[1785]

35.41.3 Clinical Pathology

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Microscopic examination of stained blood smears may reveal the presence of vacuolation in the cytoplasm of 1063
the lymphocytes. These changes are found in the majority of lysosomal storage disorders, but might be considered diagnostic of locoweed poisoning in animals with characteristic clinical signs and historical evidence of exposure. Serum concentrations of alkaline phosphatase (ALP) and aspartate transaminase (AST) may be helpful markers for toxicity; elevated concentrations were detected in sheep exposed to swainsonine in *Oxytropis sericea*.[1786] Definitive diagnosis can be established by assaying sera from affected animals for α-mannosidase and swainsonine.[1787]

35.41.4 Pathology

The microscopic abnormalities of the soft tissues of acutely poisoned animals are similar to those of the inherited lysosomal storage diseases of cattle, including cytoplasmic vacuolation of neurons, particularly Purkinje's cells, and cells in various other tissues.[1766,1777] Paraffin-embedded tissues can be examined using lectin histochemistry to characterize the stored material within the vacuoles.[1766,1788] Vacuolation of renal tubular epithelial cells may occur as early as 4 days after the start of daily feeding of 0.34 kg of locoweed to horses and may be present in animals exposed to toxic plants but clinically normal.[1766,1789] Pulmonary lesions associated with chronic ingestion of locoweed that may predispose to high-altitude disease (brisket disease) in cattle (see Chapter 31) include alveolar emphysema, bronchiolar constriction and hypertrophy, and interlobular edema and fibrosis. Pyloric or gastric ulcers have been reported in affected cattle.[1782,1789] Placental edema, fetal ascites, and hydrops allantois have been described in exposed pregnant cattle.

35.41.5 Treatment

There is no known effective long-term therapy for locoweed poisoning. Animals remain affected for a prolonged period after removal from the plants and may be permanently afflicted. Some recommend either tranylcypromine (60 mg PO), a monoamine oxidase inhibitor, and protryptyline (60 mg PO) or reserpine (3.125 g/500 kg IM once or 1.25 mg PO per animal once daily) for treatment of chronically affected animals.[1790] However, the efficacy of these treatments is unknown. Addition of a mineral supplement and a natural clay (clinoptilolite) to the diet of cattle ingesting locoweed did not prevent toxicity.[1791]

35.41.6 Prevention

Nonaddicted livestock normally do not eat locoweed if other forage is available. The intoxication may be prevented by supplemental feeding during the early spring and late summer. One report has described conditioning aversion to locoweed in horses using lithium chloride administered simultaneously with grazing of *Oxytropis sericea*.[1792] Whether this is a practical management tool in large numbers of animals has yet to be determined.

35.42 GRASS STAGGERS

Grass staggers is caused by a number of related products of plant or fungal metabolism. These compounds appear to have universal activity at the γ-aminobutyric acid (GABA) receptor of the internuncial neurons; therefore, intoxication causes clinical signs characteristic of released inhibition. The structural backbone of these toxins permits the molecules to bind to GABA receptors, thereby inactivating them. Some associated plant or fungal toxins also induce other physiologic effects, including agalactia, fever, and low productivity, because of a prolactin-like effect.

35.43 RYEGRASS STAGGERS

35.43.1 Perennial Ryegrass Staggers

Ingestion of toxic stands of perennial ryegrass *(Lolium perenne)* results in ataxia and tremors in horses, cattle, and sheep. The condition is recognized in livestock of New Zealand, Australia, Northern Europe, United States, South America, and Great Britain.[1793–1808] The case-attack rate may reach 100%, but the mortality rate is typically less than 50%.[1802] Conditions that favor toxicity include late seasonal growth, ambient temperatures over 23° C (73.4° F), and closely grazed pastures. For these reasons, the disease is seen exclusively between June and September in the Northern Hemisphere and between December and June in the Southern Hemisphere. The condition may appear 5 to 10 days after grazing on highly toxic pastures. For a pasture to develop toxicity, the ryegrass must constitute a majority of the forage growth.

Perennial ryegrass produces tremorgenic toxins when infested with the endophytic fungus *Acremonium loliae* or *Acremonium coenophialum*. The fungal infection confers resistance to the Argentine stem weevil, so there is a selective pressure for toxigenic cultivars. Strains of *Acremonium*-resistant ryegrass have been propagated but are difficult to maintain because of the devastating effects of the stem weevil infestation. The chemicals produced by *Acremonium*-infected plants are classified as indole terpenes. These compounds are chemically

related to the fungal tremorgens, penitrem A and fumotremogen. A number of separate toxic compounds have been isolated, including lolitrems A and B, paxilline, and peramine. Paxilline is a biosynthetic precursor of lolitrem B, which is related chemically to peramine. Peramine has the major antagonistic effects against the Argentine stem weevil. The lolitrems have the greatest tremorgenic effect on livestock.[1809] Concentrations of more than 2000 ppb of lolitrem B in forage or 1.68 mg/kg of forage have been associated with toxicity for sheep and cattle, respectively.[1810] The concentration of lolitrem varies seasonally in the same grass, and toxic pastures may become nontoxic over the course of the grazing season.[1811]

A relationship also exists between the frequency of poisonings and the proportion of plants infested by the *Acremonium* fungus. Infection rates below 25% are associated with sporadic cases, whereas plots containing 90% infection rates are associated with large outbreaks of staggers. Intoxication is most common on dry pastures where the perennial ryegrass is growing slowly under relatively low ambient temperatures. The *Acremonium* fungus can be identified by microscopic examination of boiled leaves. The fungus is in greatest prevalence in the summer and is found in the uppermost part of the leaf. To identify the fungus, the ryegrass leaves are immersed in a stain containing 0.06 g aniline blue in 50 mL of lactic acid in 250 mL of distilled water, 50 mL of glycerine, and 50 g of phenol. The mixture is boiled 5 minutes and mounted in lactophenol (20 g phenol, 16.7 mL lactic acid, 40 mL glycerine, and 20 mL water). For biologic assay of lolitrem, chloroform: methanol extracts of suspect plants are injected into mice. The recipients are then examined every few hours for tremors.

The endophyte-infested grasses also produce ergovaline or other ergopeptine alkaloids that exert prolactin-like activity. The resulting clinical signs are diarrhea, fever, tachypnea, and reduced weight gain.

High-peramine, low-lolitrem cultivars of *Lolium*[*] have been propagated. Such cultivars have partial protection against the stem weevil but do not cause staggers in pastured animals.[1812]

* Nui Endosafe, Dairying Research Corp., Hamilton, New Zealand.

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35.43.2 Annual Ryegrass Staggers

Annual ryegrass toxicity is caused by corynetoxin, which is manufactured in the seed heads of annual ryegrass *(Lolium rigidium)* and related grasses. The seed head is infested by the nematode *Anguina agrostis (Anguina funesta)*. The parasitic infestation forms a gall that becomes secondarily infected by the bacterium *Clavibacter toxicus (Corynebacterium rathayii)*.[1813,1814] The *Corynebacterium* organisms produce corynetoxin; this neurotoxin has been purified using high-performance liquid chromatography (HPLC) and can be detected using an enzyme-linked immunosorbent assay (ELISA). The structure of corynetoxin is similar to that of the antibiotic tunicamycin.[1815] The corynetoxin is a glycolipid that inhibits the synthesis of lipid-linked oligosaccharides and blocks protein glycosylation.[1816,1817] Bacterial proliferation in the gall results in the formation of a yellow to orange exudate, which contains the toxin. The toxic material usually leaks out over the seed but occasionally remains encapsulated within the gall and cannot be detected by external examination. Galls that have a normal external appearance are toxic if the interior of the defect maintains a deep-orange color. Loss of color is associated with a decrease in the amount of toxicity. A method of evaluating toxic pastures based on enumeration of contaminated seed heads and ELISA to detect corynetoxin has been developed.

Outbreaks of staggers may occur in animals grazing the same pasture for months because the toxin is not inactivated by the rumen microflora, and daily doses may accumulate in sheep for as long as 9 weeks.[1818] Thus,

repeated exposure leads to an accumulation of the toxin and delayed onset of clinical disease. Also, the concentration of the toxin increases in the seed heads during the summer and is greatest as the plant dries and the seeds ripen.[1819,1820] Finally, toxic ryegrass may occur only in patches in the pastures, and the grazing patterns of the animals is altered by changes in the climatic conditions, the growth of the ryegrass, or introduction of new sheep. This could explain why outbreaks occur shortly after onset of inclement weather or after introduction of new sheep to the pastures.

Pathologic changes associated with annual ryegrass staggers include hemorrhage in the cerebellum, liver, and spleen. Ultrastructural changes include swelling of the capillary endothelial cells, dilation of the endoplasmic reticulum in the endothelial cells, mitochondrial degeneration, swelling of the astrocytic end feet, protein leakage across the blood-brain barrier, pyknosis and death of granular cell nuclei of the cerebellum, and changes in the neuropil adjacent to the damaged capillaries. These changes indicate that the toxin may access the central nervous system (CNS) by damaging the blood-brain–cerebrospinal fluid (CSF) barrier. CNS neurons could be affected because of vascular damage or direct activity of the toxins.[1821]

35.43.3 Clinical Signs and Pathologic Lesions

The clinical signs of annual and perennial ryegrass staggers are similar. For both disorders the case-attack rate usually is high, but mortality varies and can range from 0% to over 90%. The clinical signs may occur within 48 hours to several weeks after cattle are introduced to toxic pastures. The animals appear normal at rest but tremble when they are excited. The gait is stiff, and limbs are hypermetric. There are fine and coarse tremors of all major muscle groups, especially those of the shoulder and flank areas. The tremors worsen as the animal becomes excited. Other clinical signs include intentional head tremor, truncal sway, and base-wide stance. With continued stimulation, affected animals kneel and then fall over. While down, animals have stiff extension of the legs with occasional flailing and may display opisthotonos or convulsions. Frothy exudate from the mouth also has been described. After approximately 10 to 20 minutes of struggle, the animal recovers, stands, and walks back to the herd or flock. New cases and deaths can continue for as long as 1 week after the animals have been removed from the toxic pasture.

35.43.4 Differential Diagnosis

Grass staggers is easily recognized by clinical signs. The specific plant involved must be identified by examination of the pasture forage. Tremorgenic diseases of adult cattle are common throughout most of the world. In addition to ryegrass pastures, tremorgenic plants include *Swainsona luteola* and *Swainsona galegifola; Solanum dimidiatum* and *Solanum fastigiatum; Astragalus* species; red buckeye; *Phalaris* species (canary and reed canary grass); *Eupatorium rugosum* (white snakeroot); *Cynodon dactylon* (Bermuda grass); Dallis grass infested with the fungus *Claviceps paspali; Polypogon monospeliensis* (annual beard grass); *Pennisetum clandestinum* (kikuyu grass); and the mycotoxins of *Penicillium cyclopium*.[1820] Hypomagnesemia has been reported to cause cerebellar degeneration under some circumstances. The storage diseases (α- and β-mannosidosis, generalized glycogenosis, globoid cell leukodystrophy, neuronal lipodystrophy) may also be important differential diagnoses for ataxic animals with tremor and cerebellar signs.

35.43.5 Treatment

There is no specific treatment for grass staggers. If the animals are removed from toxic pastures as soon as signs are first seen, the mortality rate is low despite the high number of affected animals. Several months may

elapse before the neurologic signs resolve completely. Treatment with high doses of magnesium chloride has been recommended, although others have shown it to be ineffective for controlling the muscular spasms.[1822] Pastures may lose toxicity after rain and growth of new grass. In subtropical regions, cattle should not be introduced to toxic pastures until the late fall or winter, when less toxic growth becomes abundant.

35.43.6 Prevention

Ammoniation of dried feed has been recommended as a method of reducing the toxicity of hay. This treatment simultaneously increases the digestibility and protein equivalency of the forage.[1823] For preventing annual ryegrass staggers, high-risk pastures can be identified by visually examining seed heads for infected galls. ELISA is sufficiently sensitive to identify one infected seed gall per 100 g of dried seed heads and also can accurately predict toxicity in pastures.[1824] The most practical strategy for controlling annual ryegrass toxicity is to break the nematode's life cycle by killing the ryegrass for two or three growing seasons. Otherwise, pastures remain perpetually toxic. Integrated control measures that have been recommended for prevention of annual ryegrass toxicity include applying herbicides in the spring, seeding the pastures with legumes, burning the infected pasture grasses during early autumn, and applying ryegrass-selective herbicides in the summer months, combined with heavy winter grazing.[1825]

Prevention of perennial ryegrass staggers using endophyte-free cultivars has been recommended. Such resistant biotypes of ryegrass lack resistance to the Argentine stem weevil and consequently are less productive than other biotypes. The most convenient solution has been to minimize exposure of the animals until fall rains stimulate less toxic pasture growth. Newer cultivars containing fewer tremorgens may be useful in the future.

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35.44 BERMUDA GRASS STAGGERS

Bermuda grass *(Cynodon dactylon)* occasionally may become toxic for livestock.[1228] Cattle are most susceptible, followed by sheep, goats, and horses. Although the nature of the toxic principle in Bermuda grass is unknown, several factors, including sooty mold (*Pullularia* species), endogenous basic alkaloids, and leaf hopper infestation, have been associated with toxic pastures.[1826]

Animals may develop clinical signs as early as 36 hours after consuming toxic forage. Experimentally poisoned goats have developed clinical signs 8 days after being fed 772 g/head/day of toxic hay.[1826] The toxin survives drying. Hay that is cut from offending pastures may remain toxic for as long as 9 years.[1827] The pharmacologic nature of the toxin is unknown; however, the sclerotia of *Claviceps purpurea* have been identified on the seed heads of toxic pastures.[1828] Pastures that are toxic remain so for successive seasons unless the vegetation is burned off and the ground is tilled and reseeded.

The clinical signs of Bermuda grass intoxication occur suddenly, usually simultaneously, in several animals in the herd. In some cases, most of the animals on a single pasture may be affected, whereas animals on an adjacent pasture remain normal. The clinical disease is indistinguishable from ryegrass staggers (see preceding sections). The electroencephalograms of affected animals are normal, indicating that the biochemical lesion is below the cortical level.[1829] The mortality rate is low, and deaths usually occur from self-inflicted trauma. Affected animals recover 2 days to 2 months after removal from the pasture. Tremors may be controlled using intravenous diazepam (0.1 to 1.0 mg/kg two or three times daily as needed).

35.45 KIKUYU GRASS POISONING

A nervous system disease characterized by depression, ataxia, drooling of saliva, and ruminal distention occurs in cattle and sheep of northern New Zealand that are grazing kikuyu grass *(Pennisetum clandestinum)*.[1830]

35.46 DALLIS GRASS STAGGERS (*PASPALUM* STAGGERS; *CLAVICEPS PASPALI* TOXICITY; NERVOUS ERGOTISM)

Ingestion of Dallis grass infected with the ergot fungus *Claviceps paspali* produces a tremorgenic disease similar to that of Bermuda and ryegrass staggers. Other *Paspalum*-type grasses that may become toxic include Argentine bahia grass *(Paspalum dilatatum)* and water couch grass *(Paspalum distichum)*. Horses are susceptible to the toxin, but the condition occurs most often in cattle. The disease has been recognized in the United States, Great Britain, Australia, and New Zealand.[1831–1835]

Claviceps paspali first attacks the pistil of the grass flower and replaces the ovary with fungal tissue. The fungus secretes a sticky fluid, the "honeydew," which contains a large number of spores but little toxin. The fluid hardens into a mature sclerotia containing large amounts of toxin. Toxic stands of Dallis grass can be recognized by the presence of numerous small, reddish brown or black sclerotia measuring 3 to 5 mm in diameter on the seed head of the plant. The fungus produces a number of neurologically active agents. Some of the products resemble lysergic acid diethylamine (LSD) in structure and activity, whereas others may act as dopaminergic agonists. Animals apparently develop a craving for the infested seed heads and graze them selectively. The toxin remains active in cured hay. Toxin production is greatest when there is a wet period after formation of the seed heads. Mowing the toxic pastures and removing or burning the infested seed heads are effective for preventing further outbreaks of the disease. If the amount of rainfall diminishes after mowing, the new growth usually is nontoxic.

The clinical signs of Dallis grass staggers are similar to those described earlier for ryegrass, including coarse and fine muscular fasciculations, head tremors, spastic hypermetric gait, and falling. The clinical signs are exacerbated by fright or external stimulation. Clinical diagnosis is made by visible detection of the toxic agent in the feed or by using thin-layer chromatography (TLC). Animals recover spontaneously within 1 to 3 months after being removed from the pasture.

35.47 CANARY GRASS STAGGERS (*PHALARIS* STAGGERS)

Cattle or sheep that graze on certain *Phalaris* species of canary grass *(P. arundinacea, P. tuberosa, P. acquatica, P. angusta, P. caroliniana, P. brachystachys)* grown under specific environmental conditions may develop neurointoxication.[1836–1841] *Phalaris* poisoning has been reported in Australia, New Zealand, South Africa, Norway,[1842] South America,[1843] and the United States,[1844] where the plant can be found in Virginia, Colorado, Oregon, Florida, Texas, Georgia, Mississippi, Alabama, and California.[1845] The case-attack rate may reach 80%,[1839] and the mortality rate ranges from 4% to 40%.[1837,1839] Acute deaths may occur as early as 4 to 12 hours after commencement of grazing on a toxic pasture.[1837,1840] Animals usually recover by 8 days after removal from offending pastures, but signs can persist for as long as 1 month after removal, and relapses can occur for up to 5 months.[1836,1837,1840]

Continuous exposure to low concentrations of alkaloid (<0.001% of dry matter intake) over 40 days has resulted in severe toxicosis in sheep on a drylot.[1846]

The toxic principles of canary grass are tryptamine alkaloids (dimethylated indolealkyl amines), which are found in one or more *Phalaris* species *(P. tuberosa, P. minor,* and *P. arundinacea*).[1839] The most potent of the toxins is the alkylamine 5-methoxydimethyltryptamine. Intravenous doses of this compound as low as 0.1 mg/kg can cause severe neurologic signs in sheep in 16 seconds.[1841] The toxins competitively inhibit the initial step in the breakdown of serotonin by monoamine oxidase and act on midbrain and medullary nuclei via presynaptic serotonin type 1 cholinergic receptor sites. The overall activity of the toxin is to enhance response to excitatory inputs.[1847]

The dynamics of toxin production have been examined.[1848] The concentration of alkaloid in the plant is increased by a reduction of light intensity (shade) but not by a decrease in length of the daylight.[1848] If light intensities are high, the grass is unlikely to be toxic unless soil nitrate levels are also high.[1848] Rapid growth of the grass also favors the formation and accumulation of toxin. Other factors that enhance the toxicity of a pasture include fog, humidity, or rain, followed by sunny, warm weather or sunshine on nitrogen-fertilized pastures.[1848] Although there is no specific age-related susceptibility to the toxin, only weaned animals tend to be affected during an outbreak. Many outbreaks occur when hungry sheep ingest large amounts of toxic grass over a short period.[1837] The disease has also occurred 3 to 5 days after a rainfall has ended a period of drought.[1843]

Electromyographic studies have indicated that the tremors and spasms probably originate from the spinal cord and the peripheral nervous system. Excitation leads to increased muscle tone and extensor rigidity.[1849]

There are at least two distinct clinical forms of the intoxication: acute death from cardiovascular collapse and a more chronic nervous form.[1838] The cardiovascular form of the disease occurs by 12 to 72 hours after animals are placed on a toxic pasture.[1838,1840] Affected animals die suddenly from heart failure while being herded off toxic pastures. Animals also may be found dead with the head fixed in opisthotonos and the legs in rigid extension. The ground surrounding the limbs is disturbed, indicating that the animal died in convulsions. Signs associated with cardiac collapse include acute dyspnea, cyanosis, pounding heart sounds, irregular heart rate with alternating periods of extreme tachycardia (170 to 240 beats/min), and then bradycardia.[1841,1846]

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The nervous form of the disease is more prolonged and occurs after repeated exposures of 2 to 33 weeks' duration. Signs may be delayed for as long as 4 months after removal from the toxic grass.[1844] The clinical signs include hyperexcitability, exaggerated responses to auditory or tactile stimuli, fine muscular fasciculations (particularly of masseter muscles), licking of the lips, wrinkling of the facial muscles, repetitive chewing, inability to swallow, flaring of the nostrils, ptyalism, nystagmus, intentional head tremor, ear and tail twitching, base-wide stance, reduced menace response, and deficient pupillary reflexes.[1841,1849] The gait of affected sheep is described as stiff legged, with both hindlimbs moving in unison (“rabbit hopping”). Affected sheep buckle at the knees and assume sternal recumbency with the hindquarters elevated. They then fall into lateral recumbency and flail wildly while attempting to stand.[1838] Poisoned cattle also show incoordination and repeated stabbing movements with the tongue and are unable to grasp the forage. They salivate profusely and drop feed from the mouth. Eventually the animals die of starvation. There may be an increased protein concentration (40 to 100 mg/mL) and white blood cell count (4 to 50 mononuclear cells/dL) in CSF of affected animals.[1836] Animals may survive the initial signs but have neurologic symptoms for as long as 10 months.[1850]

For confirmation of a diagnosis, the amount of tryptamine alkaloids in suspect grasses can be measured. Alkaloid concentrations greater than 30 to 50 mg/100 g dry weight of forage are considered toxic for sheep.[1848,1849]

The pathologic lesions in the CNS of affected animals include focal, demarcated, greenish or slate-gray discoloration in the pons, medulla, and corticomedullary junction of the kidney; intracytoplasmic accumulations of greenish brown pigment in the dorsal root ganglia and medullary nuclei; neuronal loss; focal gliosis; and swelling of the axonal sheaths in the ventromedial aspect of the spinal cord.[1836,1839] The pigment is thought to originate from metabolism and deamination of the toxic alkylamines but is not thought to play a direct role in the development of the neurologic deficits.[1845,1849] Other lesions in cattle that have died acutely include ulcerative abomasitis, jejunitis, and ileitis; subcapsular renal hemorrhage; and ecchymoses of the pericardium and epicardium.

Administration of cobalt to animals on toxic grass pastures is protective. The biochemical function of cobalt is thought to be related to increased ruminal inactivation of the toxins. Weekly administration of 28 mg of cobalt to each animal is recommended to prevent clinical signs in exposed sheep.[1844,1845,1850–1852] This dosage is much higher than that delivered by standard supplementation. Additional recommendations include removal of affected animals from the offending pasture, sedation with a phenothiazine tranquilizer, and administration of sodium pentobarbital or diazepam to convulsive sheep. *Phalaris* plants may also contain potentially toxic concentrations of nitrate or cyanide. In any outbreak of suspected *Phalaris* toxicosis with acute signs of sudden death, cyanide and nitrate poisonings should also be considered.[1853]

To prevent *Phalaris* poisoning, animals should be removed from the toxic grasses. The concentration of dimethylindolealkyl amines may be reduced by curing the forage as hay. Ensiling the canary grass does not reduce the amount of toxins.[1854]

35.48 *PENICILLIUM CYCLOPIUM* (TREMORGEN) INTOXICATION

Ruminants that ingest toxic species of *Penicillium* develop clinical signs that are indistinguishable from those of Dallis, ryegrass, *Phalaris,* and Bermuda grass staggers.[1855–1858] The tremors are caused by mycotoxins,[1858] which can be classified into four major groups: the aflatrem-paxilline group, verruculogen-fumotremogen group, territrem group, and tryptoquivaline group. Of these, the most important fungal tremorgens are aflatrem, penitrem A, fumotremogen B, and verruculogen. Verruculogen and fumotremogen B can be isolated from cultures of *Penicillium estinogenum*. Penitrem A is elaborated from *Penicillium nigricans, Penicillium anitellum, Penicillium cyclopium, Penicillium clavigerum,* and *Aspergillus canescens*. Verriculogen has also been identified in pure cultures of *Aspergillus fumigatus*.[1859,1860]

Ingestion of moldy cornstalks constitutes the most common source of fungal tremors in livestock. The fungi proliferate in the corn but do not produce tremorgens until the stalks touch the ground. After production at or near the soil surface, the toxins translocate in plants through root absorption.[1858]

The pathophysiologic mechanisms by which mycotoxins affect the CNS are unknown, but there is increased release of the transmitter amino acids aspartate, glutamate, and γ-aminobutyric acid in the corpus striatum, indicating the presence of a reversible biochemical lesion.

Diagnosis is based on the clinical signs, demonstration of the mycotoxin in the feed, and identification of the fungal elements in the feces. There is no specific treatment for the intoxication. Affected animals recover

completely when they are removed from infected pastures. The diagnosis of tremorgenic fungal intoxication is difficult. The mycelial elements survive degradative conditions in the gastrointestinal tract and can be isolated from the feces of intoxicated animals. Penitrem A and verriculogen can be demonstrated in the forage by TLC or mouse assay.

35.49 TREMORGENIC NEUROTOXICOSIS FROM *ASPERGILLUS CLAVATUS*

Ingestion by cattle and sheep of fodder contaminated by the fungus *Aspergillus clavatus* can result in ataxia, weakness, and tremors, similar to signs caused by ingestion of other neurotoxic molds.[1861,1862] Clinical signs include ataxia, knuckling, muscle weakness and tremors that may be exacerbated by handling, hypersalivation and drooling, altered behavior, loss of appetite, reduced milk production, muscle spasms, recumbency, opisthotonos, and death. Cases have occurred worldwide, linked to feeding sprouted grains and the by-products of beer production, both of which provide an environment for growth of the mold. Factors that can encourage mold growth include high ambient temperature and high humidity.[1861] Hematologic changes include evidence of dehydration, moderate neutrophilia, hypochromasia, and microcytic erythrocytes. Changes in clinical chemistry include elevated creatine kinase (possibly from recumbency), AST, γ-glutamyltransferase, and glutamate dehydrogenase activity. The toxicity of *A. clavatus* is attributed to a variety of tremorgenic neuromycotoxins, including patulin, tryptoquivaline, tryptoquivalone, nortryptoquivalone, cythochalasin E, cythochalasin K, escladiol, and clavatol.[1862]

35.50 DISEASES PRODUCING SPINAL CORD OR PERIPHERAL NERVE SIGNS

35.50.1 CERVICAL VERTEBRAL STENOTIC MYELOPATHY (WOBBLER SYNDROME; CERVICAL STENOTIC MYELOPATHY; CERVICAL VERTEBRAL INSTABILITY)

BONNIE R. RUSH

35.50.2 Clinical Signs

Cervical vertebral stenotic myelopathy (CVSM) is a common cause of symmetric spinal ataxia in horses. Neurologic gait deficits are caused by spinal cord compression by stenotic and malformed cervical vertebrae.[1863] A neurologic examination is performed to assess the symmetry of deficits and the severity of weakness, ataxia, and spasticity.[1864] Gait analysis is performed at the walk; neurologic deficits can be accentuated by circling, elevation of the head, and maneuvering over obstacles and inclines. Ataxia or proprioceptive loss is manifested by circumduction of the hindlimbs, posting (pivoting on the inside hindlimb during circling), and truncal sway. In most cases, pelvic limb ataxia is more pronounced than forelimb deficits. Moderately to severely affected horses have lacerations on the heel bulbs (wobbler heels) and medial aspect of the forelimbs from overreaching and interference. Stumbling and toe dragging indicate weakness. The hooves of horses with prolonged clinical signs of CVSM are chipped, worn, or squared at the toe. At rest, affected horses may have a base-wide stance and may demonstrate delayed responses to proprioceptive positioning. When prompted to back, horses may stand base wide, lean backward, drag their hindlimbs, and step on their hindfoot with a forelimb. The musculature of the neck may appear disproportionately thin compared to the rest of the body, and in some horses, prominent articular processes of the fifth and sixth cervical vertebrae may be evident.[1865]

Occasionally, weakness and stumbling are more pronounced in the forelimbs. This is usually observed in horses with stenosis of the caudal cervical vertebrae (C6-C7) caused by compression of the cervical intumescence. Alternatively, arthropathy of the caudal cervical vertebrae may produce cervical pain and forelimb lameness from peripheral nerve compression, without producing clinical signs of spinal cord compression.[1866] Affected horses typically travel with a short cranial phase of the stride and a low foot arc of the forelimbs and may stand or travel with their head and neck extended. Rarely, diskospondylosis of the cervical vertebrae will produce a short-strided gait and cervical pain, with or without spinal ataxia. Horses with diskospondylosis or arthropathy of the caudal vertebrae may demonstrate increased rate and depth of respiration with cervical manipulation because of pain.

The condition has been reported in most light and draft breeds.[1867] Thoroughbreds are particularly predisposed to CVSM, which affects approximately 2% of the population. Between 10% and 50% of thoroughbreds have characteristic developmental malformations of the cervical vertebrae without spinal cord compression.[1868,1869] Male horses are more frequently affected than females. Most horses with CVSM are 6 months to 3 years of age at presentation. Nonetheless, age (≥4 years) does not preclude a diagnosis of CVSM; spinal cord compression caused by vertebral abnormalities is routinely diagnosed in adult horses, including geriatric horses.

The onset of neurologic gait deficits is typically insidious, with progression of ataxia for several weeks, followed by stabilization (plateau) of clinical signs.[1867,1870] Owners may report a traumatic incident with the onset of clinical signs of CVSM. The event may be the result of mild neurologic deficits, with the injury exacerbating the clinical signs of spinal cord compression. Asymmetric ataxia and paresis may be occasionally observed in horses with dorsolateral compression of the spinal cord by proliferative, degenerative articular processes and periarticular soft tissue structures.

35.50.3 Pathophysiology

CVSM appears to be a manifestation of developmental orthopedic disease. Developmental disease of the appendicular skeleton, such as physitis, joint effusion, osteochondrosis, and flexural limb deformities, occurs more often in young horses with CVSM.[1871] A direct cause-and-effect relationship between osteochondrosis and CVSM has not been identified; however, the association between the frequency of occurrence of osteochondrosis and CVSM indicates that the two conditions have a similar pathophysiology.

The etiology of osteochondrosis and CVSM appears multifactorial, consisting of genetic and environmental influences. It is unlikely that CVSM is heritable by simple mendelian dominant recessive patterns.[1872] The mode of inheritance more likely involves multiple alleles and variable penetrance, which determine genetic predisposition to CVSM. A high plane of nutrition, micronutrient imbalance, rapid growth, trauma, and abnormal biomechanical forces probably contribute to the development of CVSM in genetically predisposed animals.

Dietary copper, zinc, and carbohydrates are thought to play a role in the pathogenesis of osteochondrosis and CVSM. Low dietary copper (12 ppm) and high dietary zinc (1000 to 2000 mg/kg of dry weight) concentrations cause osteochondrosis in foals, whereas copper supplementation (55 ppm) reduces the incidence of osteochondrosis of the axial and appendicular skeleton.[1873,1874] Copper supplementation does not eliminate developmental orthopedic disease, suggesting the existence of other etiologic factors. Excessive carbohydrate in the diet is hypothesized to contribute to the pathogenesis of osteochondrosis through endocrine imbalance.[1875,1876]

Spinal cord compression can be dynamic or static in horses with CVSM.[1870,1877] *Dynamic compression* occurs because of vertebral instability and causes intermittent spinal cord compression during ventroflexion of the neck; compression is relieved when the neck is in the neutral position. Pathologic changes most often observed in horses with dynamic compression are instability between adjacent vertebrae, malformation of the caudal vertebral epiphysis (caudal epiphyseal flare), and malformation or malarticulation of the articular processes. Osteochondrosis of the articular processes is not always present at the site of spinal cord compression in horses with dynamic compression.[1870] The intervertebral sites most frequently affected by dynamic compression are C3-C4 and C4-C5.

Static compression is defined as continuous spinal cord impingement regardless of cervical position. It occurs predominantly in the caudal cervical region, C5-C6 and C6-C7. Static compression is exacerbated by thickening of the dorsal lamina, hypertrophy of the ligamentum flavum, and degenerative joint disease (DJD) of the articular processes. Both static and dynamic compression are associated with narrowing of the vertebral canal from C3-C6, regardless of the site of spinal cord compression, indicating that generalized vertebral canal stenosis is an important factor in the pathophysiology of CVSM.[1878]

Histopathologic examination of the spinal cord identifies myelin degeneration (ventral and lateral funiculi), malacia, focal neuronal loss, and fibrosis at the sites of compression. Wallerian degeneration occurs in ascending white matter tracts cranial to the affected site and in descending tracts distal to the site of spinal cord compression.[1879]

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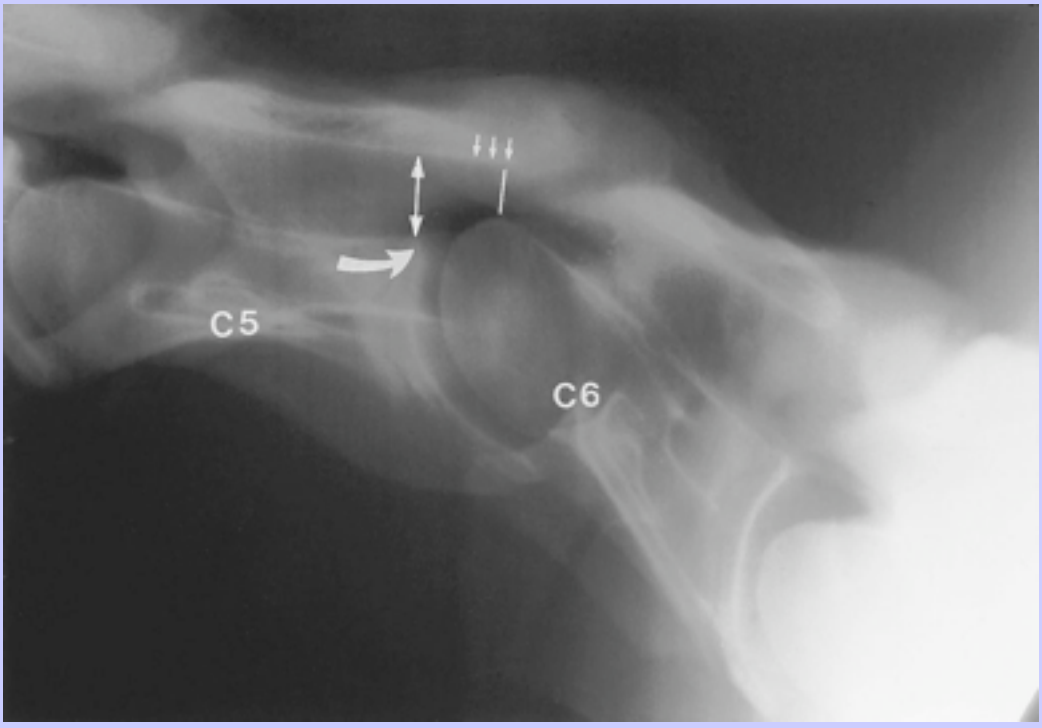
35.50.4 Diagnosis

Radiographic examination and cerebrospinal fluid (CSF) analysis are indicated in horses with symmetric tetraparesis and ataxia to differentiate CVSM from other spinal cord disorders. The most important differential diagnoses for horses with symmetric tetraparesis and ataxia include equine herpesvirus myeloencephalitis, equine protozoal myeloencephalitis, equine degenerative myeloencephalopathy, and spinal cord/vertebral trauma. Cytologic CSF findings usually are unremarkable in horses with CVSM. When CSF findings are abnormal, the alterations are consistent with acute spinal cord compression, such as mild xanthochromia and mild increases in protein concentration.

Survey radiographs of the cervical spine are obtained in standing, sedated horses. Cervical radiographs are evaluated by subjective assessment of vertebral malformation and objective determination of vertebral canal diameter.[1878] The five categories of cervical malformation subjectively assessed in horses with CVSM are DJD of the articular processes, subluxation between adjacent vertebrae, flare of the caudal physis of the vertebral body, abnormal ossification patterns, and caudal extension of the dorsal laminae[1878,1880] (Figs. 35-26 and 35-27). Although the presence of characteristic vertebral malformations supports the diagnosis of CVSM, subjective evaluation of survey radiographs does not reliably discriminate between horses affected and those unaffected by CVSM.[1868,1878] DJD of the articular processes of the caudal cervical vertebrae is the most common and severe malformation observed in affected horses.[1878] However, degenerative arthropathy occurs in 10% to 50% of nonataxic horses and is the most common and severe vertebral malformation in horses without CVSM.[1869,1878] Subjective evaluation of degenerative arthropathy of the articular processes may lead to a false-positive diagnosis of CVSM.[1868]

The vertebral canal diameter is objectively assessed by determining the sagittal ratio.[1876] The *sagittal ratio* is obtained by dividing the minimum sagittal diameter of the vertebral canal by the width of the corresponding vertebral body. The minimum sagittal diameter is measured from the dorsal aspect of the vertebral body to the ventral border of the dorsal laminae, and the vertebral body width is measured perpendicular to the vertebral canal at the widest point of the cranial aspect of the vertebral body (Fig. 35-28). The sagittal ratio eliminates error caused by magnification because the vertebral canal and vertebral body are in the same anatomic plane. The sagittal ratio should exceed 52% from C4 through C6 and 56% at C7 in horses weighing more than 320 kg. The sensitivity and specificity of the sagittal ratio for identification of CVSM-affected horses are approximately 89% for vertebral sites C4 through C7.[1881] Accurate measurement of the sagittal ratio requires a precise, lateral radiograph of the cervical vertebrae. Oblique views yield indistinct margins of the ventral aspect of the vertebral canal, resulting in erroneous values for minimum sagittal diameter and vertebral body width. *Intervertebral ratios* have been suggested to improve the ability to identify the site of spinal cord compression.[1882] This measurement is obtained by determination of the minimum distance from the craniodorsal aspect of the vertebral body to the caudal aspect of the vertebral arch of the immediately rostral vertebra. This value is divided by the width of the vertebral body. Reference values for this technique have not been published.

Fig. 35-26 Survey radiograph of fifth *(C5)* and sixth *(C6)* cervical vertebrae. Bony malformations include flare of the caudal physis (*curved arrow,* C5), caudal extension of the dorsal lamina (*small arrows,* C5), and subluxation and malalignment of the C5-C6 articulation. *Solid line,* Intervertebral canal diameter of C5-C6 articulation; *double-headed arrow,* intravertebral canal diameter of C5.



The semiquantitative scoring system developed by Mayhew et al.[1880] should be used in foals under 1 year of age to assess cervical radiographs for diagnosis of CVSM. The scoring system combines objective measurement of the vertebral canal diameter and subjective evaluation of vertebral malformation. Stenosis of the vertebral canal is assessed by determining the intervertebral and intravertebral minimum sagittal diameters. These values are corrected for radiographic magnification by dividing them by the length of the vertebral body (see Fig. 35-26). Foals that measure below the mean are assessed 5 points, and foals that measure 2 standard deviations (SD) below the mean or fall below the mean at multiple sites are assessed 6 to 10 points (Table 35-15). Cervical vertebral malformation is determined by subjective assessment of five categories: encroachment of the caudal epiphysis of the vertebral body dorsally into the vertebral canal; caudal extension of the dorsal lamina to the cranial physis of the next vertebra; angulation between adjacent vertebral bodies; abnormal ossification of the physis; and DJD of the articular processes. The maximum score allotted for each category of bony malformation is 5 points. A total score of 12 or higher (maximum, 25) confirms the radiographic diagnosis of CVSM. Stenosis of the vertebral canal and malalignment between adjacent vertebrae are the most discriminating parameters in this semiquantitative scoring system to differentiate CVSM-affected foals from normal foals.

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Fig. 35-27 Survey radiograph of fifth and sixth cervical vertebrae. Degenerative joint disease, bony proliferation, and a facet fracture *(arrows)* can be seen on the articular processes of the C5-C6 articulation.

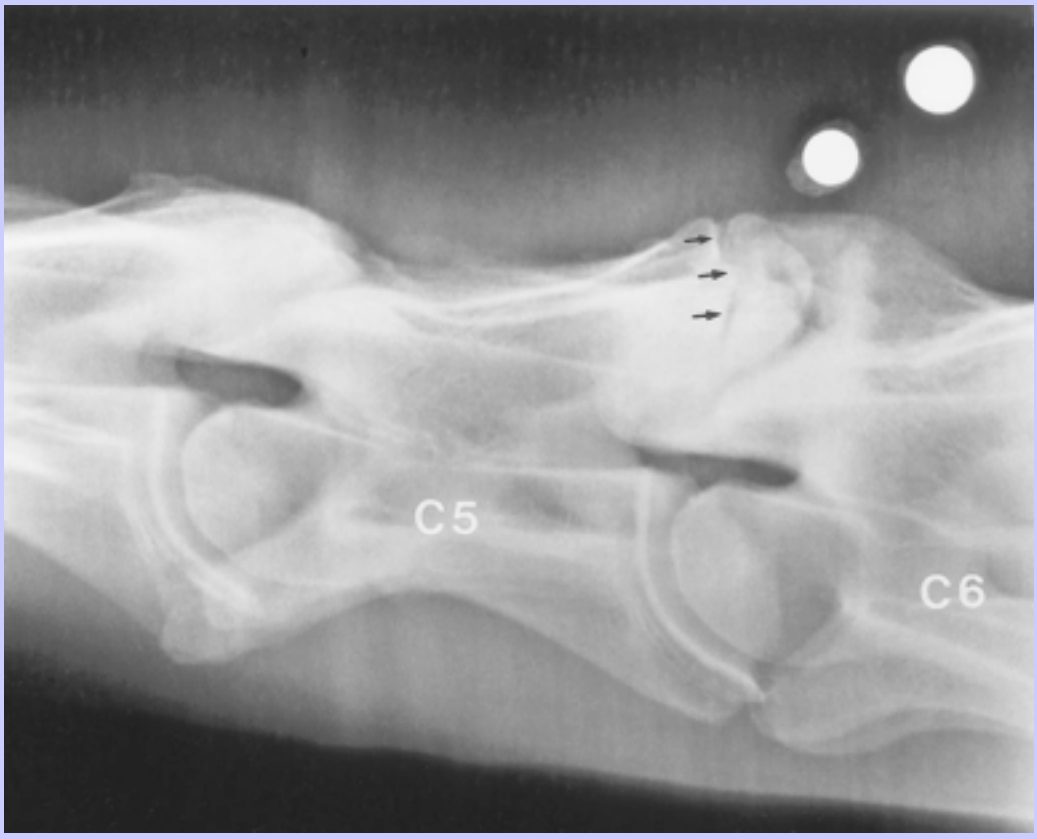
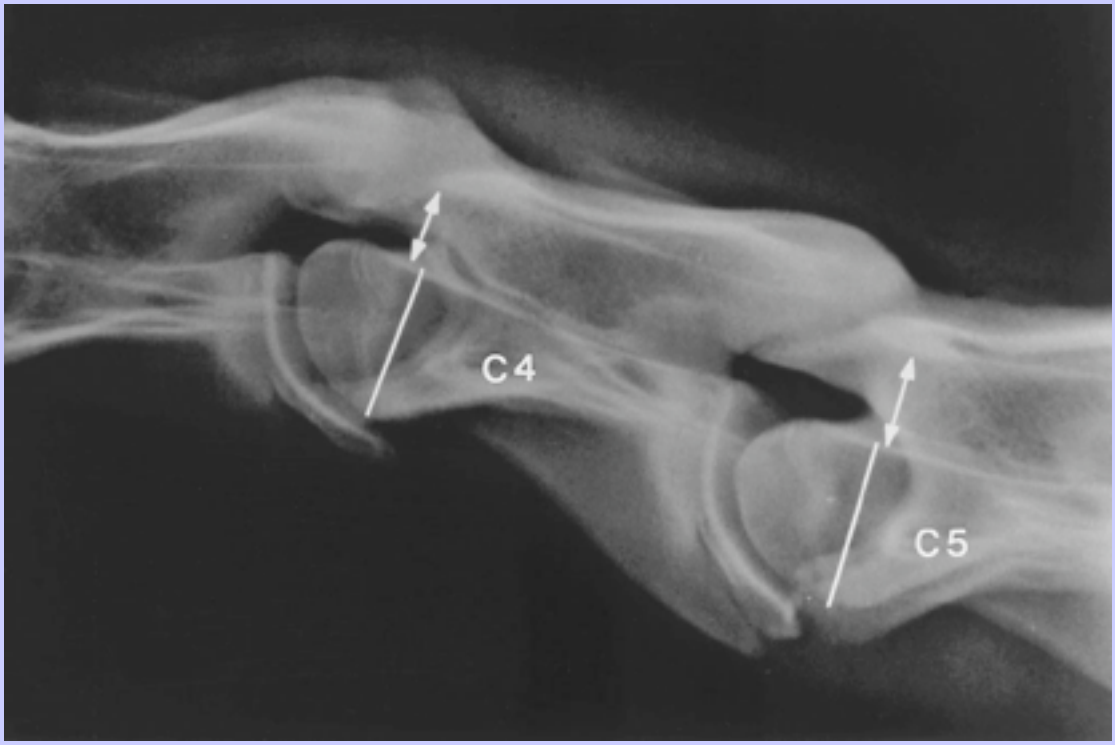


Fig. 35-28 Survey radiograph of fourth and fifth cervical vertebrae. The sagittal ratio is determined by dividing the minimum sagittal diameter *(double-headed arrows)* by the width of the corresponding vertebral body *(lines)*.



Survey radiographic examination of the cervical vertebrae determines the likelihood of spinal cord compression. Myelographic examination is required for definitive diagnosis of CVSM, identification of the location of affected vertebral sites, and classification of compressive lesions. The clinician should use radiographic interpretation to classify the patient into one of the following categories:

1 Low sagittal ratio (<48% at C4 to C6), moderate to severe bony malformation; myelographic examination to identify sites of spinal cord compression and to classify lesions as static or dynamic.

2 Marginal sagittal ratio (48% to 56%), mild to moderate bony malformation; myelographic examination to confirm or rule out CVSM.

3 High sagittal ratio (>56%), minimal bony malformation; other differential diagnoses pursued.

Table 35-15 Mean Minimum Sagittal Diameters* and Corrected Minimum Sagittal Diameters of Cervical Vertebrae in Foals without Neurologic Disease

Cervical Vertebral Site	Minimum Sagittal Diameter (mm) ± SD	Corrected Minimum Sagittal Diameter (%) ± SD
C2	23 ± 1	18 ± 1
C2-C3	28 ± 4	33 ± 2
C3	20 ± 1	24 ± 2
C3-C4	25 ± 2	30 ± 2
C4	20 ± 1	24 ± 2
C4-C5	25 ± 2	31 ± 2
C5	21 ± 1	25 ± 2
C5-C6	26 ± 3	34 ± 3
C6	21 ± 1	27 ± 2
C6-C7	31 ± 5	46 ± 5
C7	23 ± 1	35 ± 2

SD, Standard deviation.

From Mayhew IG et al: Diagnosis and prediction of cervical vertebral malformation in thoroughbred foals based on semi-quantitative radiographic indicators, *Equine Vet J* 25:435, 1993.

Myelographic examination is performed under general anesthesia with the patient in lateral recumbency.[1883] The landmarks for cisternal puncture at the atlantooccipital site are the cranial border of the wings of the atlas, the caudal border of the occipital protuberance, and the dorsal midline. The poll region is aseptically prepared and the head flexed at a 90-degree angle to the cervical vertebral column. The spinal needle (3½-inch, 18-gauge needle with stylet) is introduced and directed toward the lower jaw. The needle is advanced until the dura mater is penetrated, which often produces a "popping" sensation. Clear CSF should drip rapidly or flow from the hub with successful placement of the needle. An equal volume (20 to 40 mL) of CSF is removed before injection of a contrast agent. From 20 to 40 mL of contrast medium produces sufficient positive-contrast opacity to identify spinal cord compression in adult horses.[1883] The bevel of the spinal needle is directed caudally, and contrast medium is injected at a constant rate over 5 minutes. The head and neck are elevated under a wedged platform for 5 minutes at 30 to 45 degrees to facilitate caudal flow of the contrast medium. Iohexol (350 mg iodine/mL) and iopamidol (370 mg iodine/mL) are the most popular nonionic, water-soluble contrast media used for equine myelographic studies.[1884–1886] These second-generation agents cause less neurotoxicity and meningeal irritation than metrizamide.[1887]

It is difficult for investigators to agree on myelographic criteria for definitive diagnosis of CVSM. In many cases the site of compression (or lack thereof) is obvious, and all recommended criteria would produce the same result. However, there is a population of horses for which myelographic interpretation is more difficult. Many reports recommend a 50% or greater decrease in the sagittal diameter of the dorsal contrast column, paired with

obliteration of the ventral contrast column.[1883] The decrease in the sagittal diameter of the contrast column is determined by comparing the value at the intervertebral space to a midvertebral site cranial or caudal to the suspected intervertebral space. The 50% reduction should be interpreted conservatively, given the propensity for false-positive diagnosis; a 70% reduction may be more reliable.[1882] Some investigators prefer to use a diagnostic criterion of less than 2 mm of dorsal contrast column (or smaller) to reduce false-positive results on myelographic studies, but this criterion will increase the risk of false-negative diagnosis. Most recently, a 20% reduction in dural diameter (height of dural sac) at a given intervertebral junction, compared with the dural diameter at the level of the midvertebral body, has been suggested as the most reliable indication of spinal cord compression.[1882]

A complete myelographic examination should include neutral and stressed (flexed and extended) views of the cervical vertebrae.[1863,1883] Horses with dynamic spinal cord compression show obliteration of the dorsal and ventral contrast columns during ventroflexion of the neck (Fig. 35-29), whereas spinal cord compression is not apparent with the neck in the neutral position. Static vertebral canal stenosis is characterized by constant spinal cord compression regardless of cervical position (Fig. 35-30). In some cases of static compression, ventroflexion of the neck stretches the ligamentum flavum and relieves spinal cord compression, whereas hyperextension exacerbates compression. In horses with obvious sites of spinal cord compression on neutral myelographic views, excessive flexion and extension of the neck should be avoided while obtaining dynamic views to prevent exacerbation of spinal cord injury.

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Fig. 35-29 Myelographic examination of C3 through C6 with the cervical spine in ventroflexion. Dynamic instability and spinal cord compression are present at the C3-C4 and C5-C6 articulations. The ventral contrast columns are obliterated, and the dorsal contrast columns are narrowed (to less than 2 mm) at C3-C4 and C5-C6 *(arrows)*.

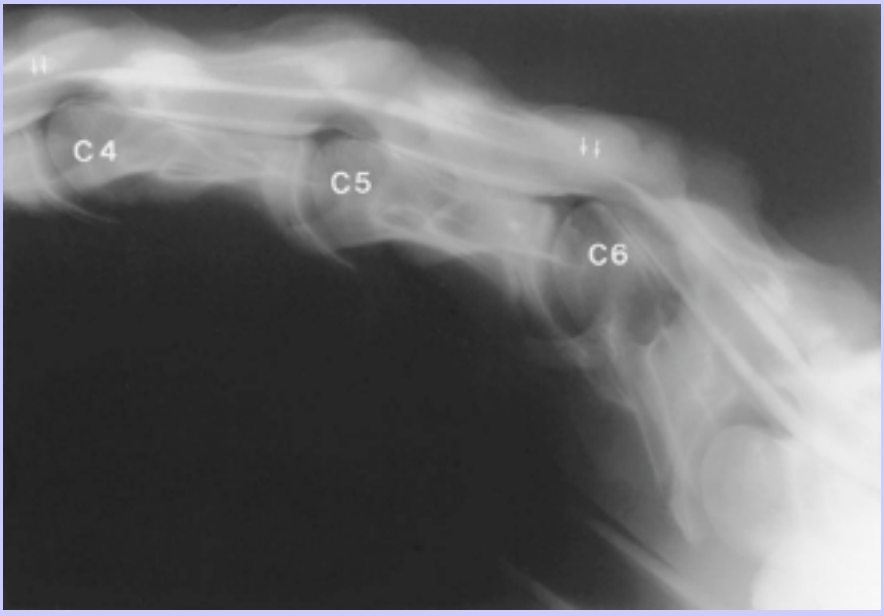
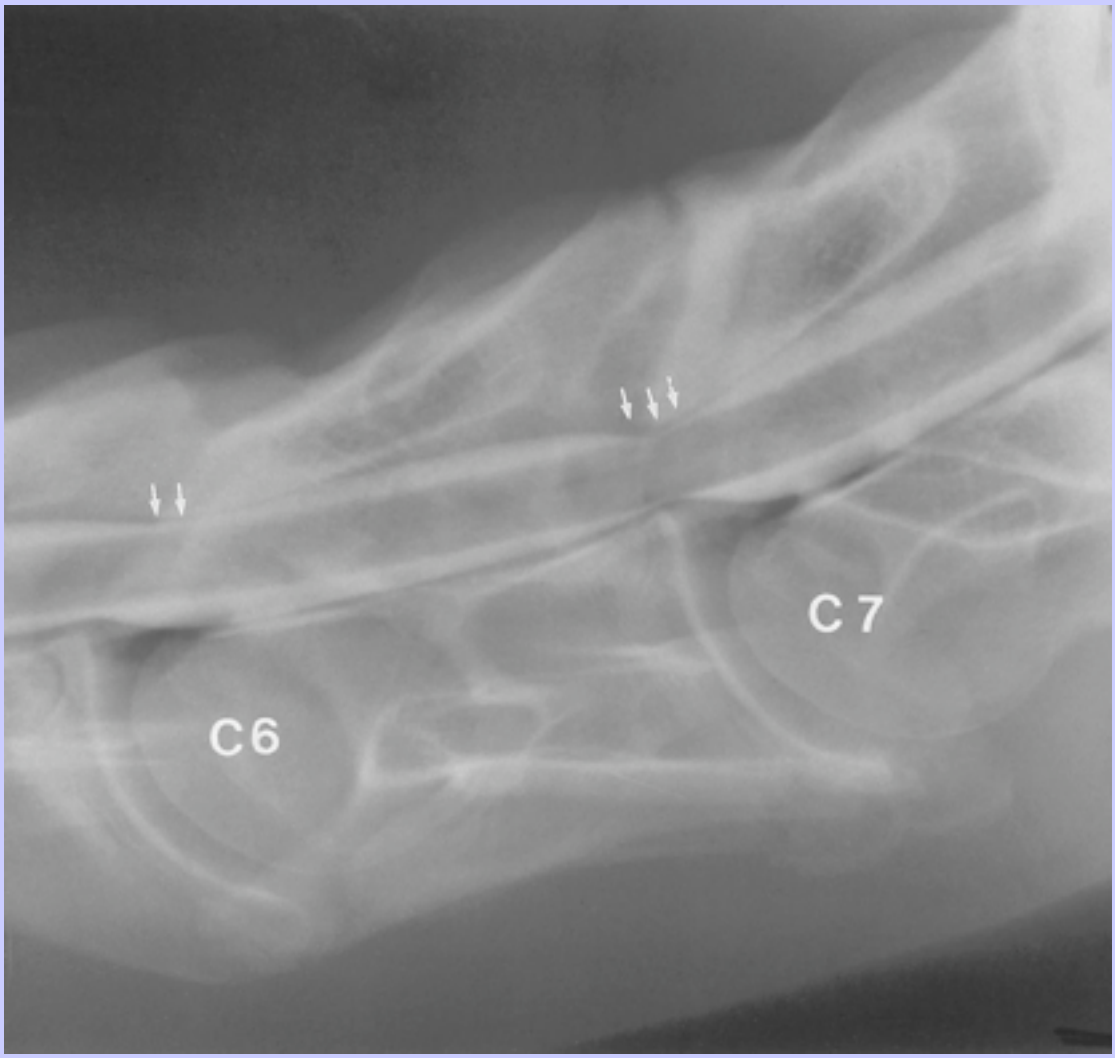


Fig. 35-30 Myelographic examination of C5 through C7 with the cervical spine in neutral position. Static spinal cord compression is demonstrated by obliteration or narrowing (to less than 2 mm) of the dorsal and ventral contrast columns at C5-C6 and C6-C7 *(arrows)*.



Horses should be monitored for 24 hours after the myelographic procedure for depression, fever, seizure, and worsening of neurologic status.[1888] Worsening of neurologic status after myelography may result from spinal cord trauma during hyperflexion, iatrogenic puncture of the spinal cord, or chemical meningitis. Administration of phenylbutazone (4.4 mg/kg PO every 24 hours) 1 day before through 1 day after myelographic examination attenuates fever and depression associated with chemical meningitis.

35.50.5 Treatment

Conservative management of CVSM-affected horses consists of administration of antiinflammatory therapy (glucocorticoids, dimethyl sulfoxide [DMSO], and nonsteroidal antiinflammatory drugs [NSAIDs]) and exercise restriction. Antiinflammatory therapy alone may reduce the edema associated with spinal cord compression; however, full recovery is unlikely without dietary or surgical intervention.

The most successful conservative treatment option for CVSM-affected foals (<1 year of age) is the "paced diet" program.[1889] This program is designed to correct endocrine imbalance associated with high-carbohydrate diets. After a carbohydrate meal, high serum insulin and low serum thyroxine concentrations promote cartilage proliferation and retention without promoting maturation. This dietary program is restricted in energy and protein (65% to 75% of National Research Council [NRC] recommendations) but maintains a balanced vitamin and mineral intake (minimum 100% of NRC recommendations). Vitamins A and E are provided at three times the NRC recommendations, and selenium is supplemented to 0.3 ppm. Roughage is provided by pasture or low-quality grass hay (6% to 9% crude protein). Solitary stall confinement is recommended to minimize repetitive spinal cord compression from dynamic instability.

Horses with cervical pain and forelimb lameness caused by cervical vertebral arthropathy may benefit from intraarticular administration of corticosteroids and chondroprotective agents.[1870,1890–1892] Arthrocentesis of the cervical vertebral articulations (facets) is performed with ultrasound guidance using a 6-inch, 18-gauge spinal needle in the standing, sedated, or recumbent horse.[1893] The cranial facet of the caudal vertebrae will appear superficial to the caudal facet of the cranial vertebrae. The articular space is accessed at the cranioventral opening of the articular facet, which is angled approximately 60 degrees from the ultrasound beam. The needle should be introduced 5 cm cranial to the facet and inserted at a 30-degree angle to the skin surface. Joint penetration should be confirmed by aspiration of synovial fluid. If the neck is extended, the transverse process of the cranial vertebrae may obscure the path to the articulation. Intraarticular triamcinolone (6 mg/joint) or methylprednisolone (100 mg/joint) has produced a positive clinical response in approximately 50% of horses with arthrosis of the articular processes. An antimicrobial agent (e.g., amikacin, 250 mg) can be administered prophylactically with intraarticular corticosteroids or chondroprotective agents. The goal of intraarticular antiinflammatory therapy should be to improve cervical mobility, reduce cervical pain, and eliminate forelimb lameness. It is unlikely that intraarticular therapy will significantly improve clinical signs of spinal ataxia.

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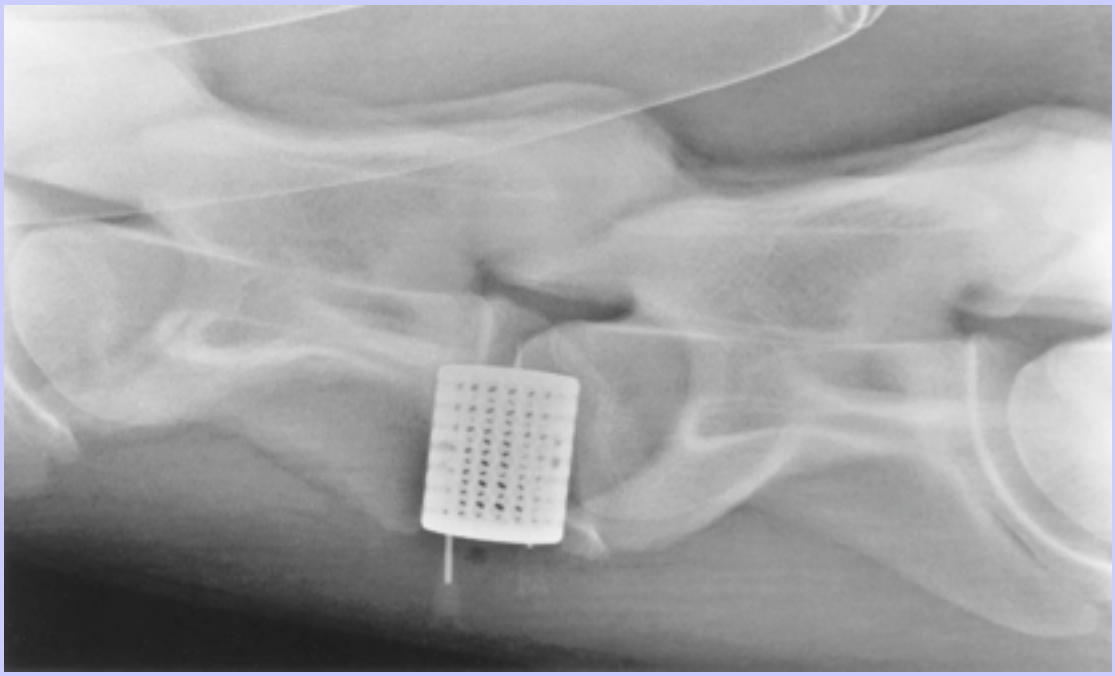
Fig. 35-31 Intraoperative radiograph of third and fourth cervical vertebrae during cervical vertebral interbody fusion. The stainless steel basket is placed in the ventral aspect of the vertebral bodies, spanning the intervertebral disk and vertebral endplates, at the C3-C4 articulation.



Surgical intervention is the most widely reported treatment for CVSM and is indicated to stop repetitive trauma to the spinal cord.[1894–1897] The goals of surgical intervention are to stabilize the cervical vertebrae and decompress the spinal cord. Cervical vertebral interbody fusion (ventral stabilization) provides intervertebral stability for horses with dynamic spinal cord compression. The affected cervical vertebrae are fused in the extended position to provide immediate relief of compression and prevent repetitive spinal cord trauma (Fig. 35-31).

Dorsal laminectomy (subtotal Funkquist type B) is performed to decompress static lesions by removing portions of the dorsal lamina, ligamentum flavum, and joint capsule at the compressed site.[1895] This procedure provides immediate decompression of the spinal cord; however, fatal postoperative complications may occur.[1896] Interbody fusion in horses with static compression causes remodeling and atrophy of the articular processes, resulting in delayed decompression of the spinal cord over weeks to months.[1898] Decompression is immediate with dorsal laminectomy. Because of the relative safety of interbody fusion, however, some surgeons believe it is the technique of choice for both dynamic and static compressive lesions.[1896]

Cervical vertebral interbody fusion improves the neurologic status in about half the horses with CVSM, with some horses returning to athletic function.[1894,1896] An improvement in one or two neurologic grades of five is

expected. The most important patient factor for determining the postoperative prognosis is the duration of clinical signs before surgical intervention; horses with clinical signs for less than 1 month before surgery are more likely to return to athletic function than those with clinical signs for longer than 3 months.[1896] In addition, the number of compressive sites, severity of the compression, and severity of postoperative complications contribute to the long-term prognosis.[1870] Subtotal laminectomy and cervical vertebral interbody fusion for static compression of the caudal cervical vertebrae are associated with fatal postoperative complications, including vertebral body fracture, spinal cord edema, and implant failure.[1896]

Postoperatively, horses should be maintained on strict stall rest for 3 weeks and fed from a hay net to minimize motion at the surgical site. Intraarticular injection of the intervertebral articulations with corticosteroids immediately after surgery may lead to more rapid decompression.[1870] The duration of convalescence and rehabilitation after cervical vertebral interbody fusion is approximately 6 to 12 months. An individualized exercise program, determined by the projected use of the horse and the animal's neurologic status, should be designed to promote muscular strength. Extended exercise at slow speed, including ponying and lunging on inclines, is recommended during rehabilitation. A neurologic examination should be performed to determine the horse's ability to return to athletic function after surgery. It is unlikely that significant improvement in neurologic status will occur beyond the 1-year postoperative period.[1896]

35.51 EQUINE DEGENERATIVE MYELOENCEPHALOPATHY

35.51.1 Definition and Etiology

Equine degenerative myeloencephalopathy (EDM) is a symmetric, noncompressive spinal cord disease of young horses characterized by demyelination in the dorsal funiculi of the cervical spinal cord and in the brainstem.[1899] A similar disorder in which lesions are found only in the gracile and cuneate nuclei of the medulla oblongata also has been described, termed *neuraxonal dystrophy* to differentiate it from the more common EDM.[1900] Signs most often develop in horses less than 1 year of age (mean, 5 months), but onset of signs can occur as late as 12 years.[1899,1901] The incidence of EDM in Arabian horses is disproportionately high.[1899] The disease has been recognized in zebras, donkeys, Welsh ponies, and horses of the Przewalski, thoroughbred, standardbred, Appaloosa, quarter horse, Paso Fino, Paint, Haflinger, Norwegian Fjord, Trakehner, Hanoverian, and Morgan breeds.[1902–1909] EDM has also been observed in Mongolian wild horses.[1903]

The disease may be related to a dietary deficiency of vitamin E, but EDM also has a familial pattern of distribution. These observations suggest a genetic etiology, but the mode of inheritance is not clear.[1910]

35.51.2 Clinical Signs

Affected horses show a symmetric proprioceptive (sensory) ataxia characterized by knuckling, stumbling, circumduction, abduction, interference, abnormal limb protraction, spasticity, hypermetria, and inability to turn sharply or lift the inside forefoot during sharp turns. When the animal is forced to turn sharply in a circle, the inside hindfoot pivots instead of lifting off the ground. Affected animals appear clumsy and cannot stop rapidly from a gallop. When stopped suddenly, they step on the rear of the forelimbs and end in a dog-sitting posture. Affected animals usually have severe conscious proprioceptive deficits that can be detected by postural placement tests. Some patients are unable to back or move easily down an incline. They may fall or stumble

when light pressure is applied to the tuber coxae or withers. Signs are often more severe in the hindlimbs than in the forelimbs; in some cases, signs are only apparent in the hindlimbs.[1911]

Other clinical signs that may be observed with EDM are deficits of the local cervical and cervicoauricular reflexes, absence of response to the "slap test"[1912] (see Chapter 8), and paralysis of the laryngeal adductor muscles. Absence of these findings, however, does not completely exclude a cervical spinal cord disease.[1913] In rare cases, animals with EDM may present in acute recumbency without a prior history of neurologic disease (M.O. Smith, unpublished data).

The most important differential diagnoses for EDM are cervical stenotic myelopathy ("wobbler syndrome"), equine herpesvirus myeloencephalopathy, and equine protozoal myeloencephalitis.

35.51.3 Clinical Pathology and Radiographic Findings

EDM is best differentiated from cervical stenotic myelopathy by plain and contrast radiographic examination of the spinal column. The cervical spinal canal, CSF protein concentration, and white blood cell count of horses with degenerative myeloencephalopathy are normal. Serologic testing and CSF analysis is indicated to rule out herpesvirus and protozoal myelopathies. The acute clinical course of herpesvirus myelopathy and the presence of signs such as cranial nerve involvement and lower motor neuron lesions in protozoal disease help to differentiate these entities from EDM. The plasma vitamin E concentration may be below the reference range (300 to 1050 µg/dL) in some unsupplemented affected horses.[1903,1904] For analysis, optimal methods of blood collection include collection of unhemolyzed blood in a clot tube and storage in an upright position in a refrigerator. The refrigerated specimens should not be allowed to contact rubber stoppers and should not be stored for longer than 72 hours unless the red cells are removed and the plasma is gassed with nitrogen and frozen at −16° C (3.2° F). The concentration of vitamin E in specimens handled in this manner remains constant for at least 3 months.[1914]

35.51.4 Pathophysiology

Some suggest that EDM is associated with a low plasma concentration of vitamin E from 6 weeks to 10 months of age.[1904,1915,1916] Oral absorption of vitamin E does not appear to be deficient in affected horses.[1916] Vitamin-replete, clinically normal horses have a plasma concentration ranging from 1.7 to 9.5 µg/mL; vitamin E concentration is approximately 2 µg/mL higher in the spring and summer than in winter. Horses fed diets that lack fresh green forage have a low plasma concentration of vitamin E. Such diets include poor-quality, sun-baked hay and pelleted rations. In one study testing vitamin E supplementation, the case-attack rate declined from 40% to 10% in the first year after supplementation, and the severity of disease in subsequent foal crops was diminished. Moreover, supplementation of five affected horses with 6000 IU vitamin E daily improved their neurologic condition. Horses' susceptibility to development of low vitamin E concentrations also appears to be age related. Foals sired by affected stallions tend to have lower plasma α-tocopherol concentrations than those sired by normal stallions. These lower concentrations are first noted by 6 weeks of age, but the differences disappear by 10 months. The causes of the differences in the two groups of animals are unknown. An alternative explanation for the role of vitamin E in EDM is a defect in vitamin E absorption, transportation, or metabolism.[1980] The nature of such a defect has yet to be elucidated.

Vitamin E deficiency is apparently not the sole etiologic factor in EDM, however, because one report documented normal vitamin E levels in the sera of 40 affected horses examined at a veterinary hospital.[1917]

Subsequent epidemiologic studies indicated that risk factors for the disorder include heredity, application of insecticides on foals, exposure to dirt lots without pasture, and exposure to wood preservatives. Access to green pasture had a protective effect on foals.[1916] This study may indicate that the changes in the central nervous system are related to the patient's inability to respond adequately to oxidative stress such as phenols, anthelmintics, and insecticides. The key role of vitamin E as an antioxidant may explain the link between the disparate etiologies proposed for EDM.

The deficiency occurs most often in related horses, suggesting a genetic predisposition.[1900,1916] The importance of heredity in the development of EDM is supported by studies in a number of breeds, including Appaloosa, Haflinger, and Morgan horses.[1900,1907,1918] A higher incidence has been documented in both foals sired by certain stallions and foals born to mares that already produced an affected foal.[1901,1904] However, the mode of inheritance is not clear.

Recent studies have indicated that a defect in axonal transport of proteins, particularly certain proteins vital to synaptic function, may be a key mechanism in the pathogenesis of EDM.[1919]

35.51.5 Pathology

The microscopic lesions are present throughout the spinal cord, involving both white matter and gray matter, and are most pronounced in the dorsal spinocerebellar tracts.[1903] These lesions include diffuse axonal degeneration of ascending and descending spinal cord funiculi and prominent myelin loss. Gliosis and astrocytosis develop in response to myelin breakdown. Horses with acute, rapidly progressive disease have evidence of active myelin destruction and vaculoation, whereas those with a more gradual course of disease have prominent astrogliosis. Considerable accumulation of lipofucsin-like pigment has been reported in some affected horses.[1909] The form of EDM termed neuraxonal dystrophy (e.g., in Morgan horses) is characterized by lesions almost entirely confined to the lateral caudate nucleus in the medulla. Because of the clinical signs in these horses, however, it is suspected that subtle lesions may be present within the spinal cord.

35.51.6 Treatment and Control

EDM is a chronically progressive disorder, although the clinical signs may stabilize after 2 to 3 years of age. The signs are irreversible, and most patients eventually are euthanized because they present a hazard to other livestock and humans.

Some improvement of clinical signs has been reported in horses treated with vitamin E. The current recommended vitamin E level for horse feed is 80 to 100 IU/kg/day.[1920] In suspected cases of EDM, supplementation with 6000 IU of D,L-α-tocopherol acetate in feed is recommended, a level that appears to be safe. This dose should be mixed with 60 mL corn oil and fed in 1 L concentrate ration daily.[1920] Once clinical signs are present, the prognosis for complete recovery is guarded to poor. Supplementation has been recommended for foals at risk of developing the disease (e.g., family history of EDM) and foals maintained on poor-quality pasture.[1904,1916]

35.52 EQUINE MOTOR NEURON DISEASE

THOMAS J. DIVERS

In 1990 an acquired neurodegenerative disease of adult horses was first described.[1921] The equine disease appeared similar to one form of human motor neuron disease, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). Equine motor neuron disease (EMND) is the only naturally occurring animal model for ALS. Experimental studies have revealed that the disease occurs secondary to chronic vitamin E deficiency and oxidative neuronal cell injury.[1922] Reports of this disorder are now almost worldwide.

35.52.1 Clinical Signs

Affected animals are adults with a mean age of 9 years (range, 2 to 23 years).[1923] Clinical signs vary depending on the stage or duration of the disorder; therefore the signs are best summarized by dividing the disease into subacute and chronic forms. A subclinical form also occurs, although these cases cannot be currently diagnosed antemortem.

35.52.1.1 SUBACUTE FORM

Horses develop acute onset of trembling, fasciculations, lying down more than normal, frequent shifting of weight in the hindlegs, and abnormal sweating. Head carriage may be abnormally low. Appetite and gait often are not noticeably affected, but some horses have a ravenous appetite. The owner may mention that the horse had been losing weight (loss of muscle mass) for a month before the other signs appeared.

35.52.1.2 CHRONIC FORM

The trembling and fasciculations subside, and the horse's condition stabilizes, but with varying degrees of muscle atrophy. In some cases the atrophy is so severe that the horse looks emaciated. In other cases, muscle mass and fat deposition show noticeable improvement. The tailhead frequently is in an abnormally high, resting position.

35.52.1.3 SUBCLINICAL FORM

Experimental research has proved that horses maintained on prolonged diets low in vitamin E may have subclinical disease. This could have significant implications because unknown to the rider or owner, the affected horse would have diminished strength. Pathology of EMND without clinical signs specific for the disease has also been found in a few yearlings with equine degenerative myeloencephalopathy.

35.52.2 Clinical Pathology

Horses with acute or subacute EMND have mild to moderately elevated levels of creatine kinase (CK) and aspartate transaminase (AST). The serum vitamin E is low (<1 μg/mL) in almost all acute and subacute cases. Levels of α- and γ-tocopherol are low in the gray matter of affected horses. Superoxide dismutase (SOD) activity in red blood cells also is severely decreased, believed to result from increased consumption of SOD. Other clinicopathologic abnormalities may be present in particular individuals, including elevated serum γ-glutamyltransferase (GGT) activity; low vitamin A, β-carotene, and ascorbic acid levels; and high liver iron and spinal cord copper levels. Many horses have abnormal glucose absorption, and some have enhanced glucose utilization.[1924] This supports the observation that many horses have ravenous appetites and that most have normal fat deposition at necropsy.

The protein CSF level is elevated in almost half of affected horses, and intrathecal immunoglobulin G (IgG) is increased in many cases. Increased IgG is thought be a response to neuronal death rather than a primary pathophysiologic event.

35.52.3 Pathophysiology

The sites of lesions in EMND are the ventral horn cells (lower motor neurons) of the spinal cord gray matter; the nuclei of cranial nerves V, VII, and XII; and the nucleus ambiguous; all undergo noninflammatory degeneration. Neurogenic atrophy occurs in muscles innervated by degenerate neurons, particularly those with predominantly type 1 myofibers, which have a higher oxidative requirement than type 2 fibers and thus are more susceptible to oxidative damage. The dysfunction and death of motor neurons is an oxidative disorder, presumably caused by vitamin E deficiency and the resulting inability to protect against oxidative (prooxidant) stress. Clinical signs occur when approximately 30% of the motor neurons are affected.[1925] Some of these neurons may regain function with vitamin E treatment, which may explain why some horses do not have continual progression of clinical signs, as occurs in ALS in humans. Human motor neuron disease, although an oxidative disorder, is more complex that EMND, and the causes have yet to be determined.

35.52.4 Pathology

Gross lesions are limited to pallor of the medial head of the triceps brachii and vastus intermedius muscles. Severe atrophy is present in these muscles and many others, including the sacrocaudalis dorsalis medialis muscle of the tail, which shows severe denervation atrophy and fibrosis. Scattered areas of myofiber necrosis are present in many muscles. A pigment retinopathy[1926] and deposition of lipopigment in the spinal cord vasculature are found in horses with EMND, apparently related to similar pigment depositions in other species with vitamin E deficiency. A vitamin E–supplemented diet may result in resolution of pigment deposition in the spinal cord vasculature but not the retina.

35.52.5 Epidemiology

EMND is a sporadic disease, with only single animals in a barn usually affected, although a few outbreaks of the disease have been reported. All breeds of horse can be affected, as can ponies. The apparent prevalence of EMND in certain breeds probably reflects the prevalence of the breed in specific populations of horses, and no familial or heritable predisposition has been identified. Affected horses usually are housed in facilities with little or no access to pasture for more than a year before signs appear.[1923,1927] The diet of affected animals in North America is deficient in green foodstuffs and frequently consists of pelleted or sweet feed and poor-quality grass hay, without alfalfa or other sources of vitamin E supplementation.[1928,1929] In the United Kingdom a few horses with EMND have been on pasture, have no laboratory or necropsy evidence to support malabsorption, but are deficient in vitamin E.[1930] The explanation for this remains elusive. No other management practices, such as worming and vaccination regimens, insecticide use, amount of exercise, or type of bedding, have been related to development of the disease. The highest prevalence of EMND in North America occurs in the northeastern United States and Canada, although sporadic cases have been reported across the continent. This regional distribution is believed to relate to the frequency of predisposing management practices in high-incidence areas rather than other environmental factors.

35.52.6 Diagnosis

The diagnosis of EMND can be made from the following observations and testing:

1 Epidemiologic information.

a Previous cases in the stable.

b Historic information that suggests the horse might have been without green forage for an extended period (with a few exceptions in the United Kingdom).

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2 Clinical signs (see earlier section).

3 Measurement of plasma vitamin E and muscle enzyme levels.

35.52.6.1 MUSCLE OR NERVE BIOPSY

Biopsy of the sacrocaudalis dorsalis muscle is the invasive test of choice, with almost 90% sensitivity and specificity.[1931] The biopsy specimen should be placed in 10% formalin for laboratory submission. A positive result is the finding of characteristic abnormalities, including denervation atrophy of myofibers and scattered myofiber necrosis. Biopsy of the spinal accessory nerve is more technically demanding but is a more sensitive test in chronic cases.[1931,1932] Nerve biopsy requires general anesthesia, whereas muscle biopsy can be performed using a local block in the sedated horse.

Differential diagnoses for EMND include equine protozoal myeloencephalitis, colic, laminitis, botulism, and tying-up.

35.52.7 Treatment

Oral vitamin E supplementation at 5000 to 7000 IU daily may result in improvement in some clinically affected horses, although full recovery is unlikely. This therapy cannot reverse the neuronal death, and all affected horses are permanently weakened. Use of a source of pure vitamin E is preferable to a multi–vitamin-mineral supplement. Natural vitamin E products are preferred over synthetic products, but both will raise serum levels.

35.52.8 Prevention

All horses without green forage (grass of good quality or green hay) for prolonged periods (>1 year) should be routinely tested for the plasma vitamin E concentration and supplemented with vitamin E. If this were a standard policy, most if not all cases of EMND could be prevented.

35.53 SPINAL FRACTURES AND LUXATIONS AND SPINAL CORD TRAUMA

35.53.1 Definition and Etiology

Vertebral fractures are relatively common causes of spinal cord injury in food animals. In horses with various neurologic disorders, however, spinal fractures represented only about 3% of cases in two studies.[1933,1934]

Because of differences in management, temperament, and regional spinal strength, the pathogenesis and predominant anatomic location of spinal injury sites differ among the livestock species.

35.53.1.1

HORSES

In a U.K. study examining 26 horses with spinal fractures, 16 had cervical fractures, 17 had thoracic fractures, five had lumbar fractures, and four had sacrococcygeal fractures.[1935] The vertebrae most often injured were C1, T12, and L5.[1935] Horses with lesions of the thoracic dorsal spinous processes did not show neurologic deficits, whereas a high proportion of horses that had lesions in the lumbar and cervical spine had ataxia or other associated neurologic deficits. Stress fractures of the lumbar vertebral laminae may be common in racehorses, frequently are undiagnosed during life,[1936] and should be considered in the differential diagnoses for poor performance and hindlimb lameness in at-risk animals.

35.53.1.2

RUMINANTS

Fractures of the vertebral column in ruminants may result from abnormal bone mineralization. The common sites of spinal fractures in calves are C2 to C4, T10 to T13, and L3 to L6 vertebrae. Spinal fractures are especially common in 3- to 6-month-old ruminants as a result of nutritional deficiencies, including vitamin D, calcium, and copper. Differentiation of nutritional osteodystrophies from traumatic vertebral fractures is essential, because different preventive measures must be taken for the two conditions. Traumatic cervical vertebral fractures of cattle and small ruminants may be caused by injuries sustained in falls, roadway accidents, butting of other animals, predation, or squeeze chutes.[1937,1938] Spontaneous fractures of vertebrae weakened by developmental defects (hemivertebrae) or spinal abscesses also are common problems in calves. Rarely, pathologic fracture may result from weakening of bone caused by bacterial osteomyelitis.[1939] More often, bacterial infection is a sequela to spinal fracture.

Traumatic luxations or fractures of the atlantooccipital and atlantoaxial joints of pygmy goats may occur when the horns are held during restraint.

Fractures of the lumbosacral spine of cattle are frequently caused by slipping in cemented areas.[1937] Many of the spinal fractures occur during mounting by herdmates exhibiting estral behavior. Thoracolumbar fractures may occur in calves during correction of a dystocia, particularly epiphyseal slippage at the middle to caudal thoracic vertebrae.[1940,1941] The occurrence of spinal fractures during assisted delivery is mainly related to the excessive traction and rotational force used.[1942] Luxation of the sacroiliac joint in the dam may occur with the use of excessive force during manual extraction of a calf. Traumatic lumbar vertebral fractures occur secondary to chronic ankylosing spondylosis in mature bulls and rams.[1943]

Trauma to the spinal cord without spinal fracture can result in concussive damage to the cord, including shearing forces and hemorrhage within the neuropil. Hemorrhage and inflammation around the cord can result in space-occupying lesions that cause clinical signs similar to those resulting from spinal fractures. Prognosis for recovery is generally more favorable with blunt trauma than spinal fractures, although outcome depends on the severity of the injury.

35.53.2 Clinical Signs

The clinical presentation of a spinal fracture varies, depending on the site of the traumatic lesion, severity of the spinal cord compression, and involvement of specific anatomic tracts.

35.53.2.1 CERVICAL SPINE

Acute vertebral fractures are painful, and the patient usually shows some distress in the early stages. Goats may bleat or cry when the spine is manipulated. Horses groan and, if recumbent, thrash wildly. Cattle and sheep may lie on their sides and groan. Animals with noncompressive cervical lesions maintain a stiff neck ("weather vane" attitude), refuse to lower the head, and eat from the ground while kneeling. To prehend food, they often keep the head away from the ground and extend the tongue. These animals have stiff necks and resist passive flexion of the head.[1944] Similar signs may be seen with meningitis. Forelimb lameness with or without obvious neurologic deficits may be the presenting complaint when fractures are fairly stable and cause minimal disruption to the spinal cord.[1945,1946] Cervical fracture should be a differential diagnosis for unexplained forelimb lamenesses.

Animals with severe lesions may be recumbent. Depending on the amount of pain and the secondary complications associated with the disease, the sensorium varies from bright, alert, and responsive to depressed and painful. Recumbent animals may not be able to lift the head from the floor if a high cervical lesion (C1 to C4) is present.[1947] Crepitation may be palpable in some cases. Luxation of the atlantooccipital joint results in asymmetry of the wings of the atlas. These animals often have a wry neck as a result of the twisting forces on the displaced atlas.[1948] Patients with mild lesions of the cervical spine may be able to stand and show varying degrees of ataxia and conscious proprioceptive deficits. Specific gait abnormalities include circumduction, interference, knuckling, incomplete limb protraction, crossing over, and excessive body sway. Animals with high partial cervical lesions may show hypalgesia of the entire body. Bilateral, severely compressive lesions of the cervical spine can result in rapid death from respiratory paralysis if neurologic injury causes paralysis of the phrenic nerve. If the spinal cord lesion is above the C6 segment (C6 to C7 vertebrae), the muscular tone and spinal reflexes (panniculus, triceps, and biceps) are normal to increased in all limbs. If the lesion is located at the C6 to C8 segments, forelimb reflexes are diminished or absent and hindlimb reflexes normal to increased. The panniculus response may be absent on one or both sides of the body if the lesion affects the C8 segment, the origin of the lateral thoracic nerves.

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Conscious pain perception in the limbs often is diminished or absent, depending on the amount of damage in the sensory spinal cord tracts. In long-standing cases in which the ventral rootlets or motor neurons of C6 to C8 have been destroyed, the muscles of the neck and forelimbs may become atrophic. Regional or strip sweating may be observed in some horses. The anal tone and tail tone are normal. The bladder may be distended, but the tone of the urethral musculature is normal.

35.53.2.2 THORACIC SPINE

Animals with thoracic trauma have an attitude similar to those with cervical lesions, except that thoracic limbs are normal. Animals with severe spinal cord lesions intermittently lie on their sides and then arise to assume a dog-sitting posture. When lying in sternal recumbency, animals hold the hindlimbs extended rather than in the normal tucked-up position. The spinal reflexes of the forelimbs are normal. A crossed extensor reflex may be observed in the hindlimbs. Depending on the amount of damage to the sensory tracts,

conscious perception of pain in the hindlimbs may be decreased or absent. The tail and anal tones are normal. The bladder is distended, but the tone of the urethral sphincter and penis is normal. Animals with acute lesions of the thoracic spine (<2 days' duration) may display Schiff-Sherrington syndrome.[1949] Forelimb postural reactions are normal but muscular tone is increased, resulting in a stiff forelimb gait. Postural reactions in the hindlimbs are decreased to absent, with normal to hyperreflexic myotactic reflexes (see Chapter 8). Schiff-Sherrington syndrome is rare in large animals. Most animals with thoracic injury have normal to exaggerated spinal reflexes and hypertonia of the rear limbs.

35.53.2.3

LUMBAR SPINE

Animals with lumbar injury have an attitude, gait, and posture similar to those with thoracic lesions. Fig. 35-32 shows the characteristic posture of a calf with a fracture at the L6 vertebra. Fig. 35-33 illustrates myelographic findings of cord compression at L6. The forelimbs are normal. Lesions at the L1 to L3 spinal cord segments result in normal or hypertonic and hyperreflexic hindlimbs. Conversely, hypotonia and hyporeflexia of the hindlimbs may be seen in animals with lesions at segments L4 to S2.[1950] Marked spasm of the longissimus dorsi muscle has been described in horses with a lesion between the T11 and T12 segments.[1951] Lesions of segments L4 to L6 result in cutaneous desensitization of the medial surface of the rear leg and diminished or absent patellar reflex because of dysfunction of the femoral and saphenous nerves. Lesions of segments L6 to S2 result in desensitization of the hindlimb and diminished withdrawal (flexor) reflexes. The panniculus response is absent when the skin posterior to the lesion is stimulated. Damage to the spinal rootlets may cause regional swelling. Tail tone and anal tone are normal. The bladder is distended, but the sphincter tone is normal.

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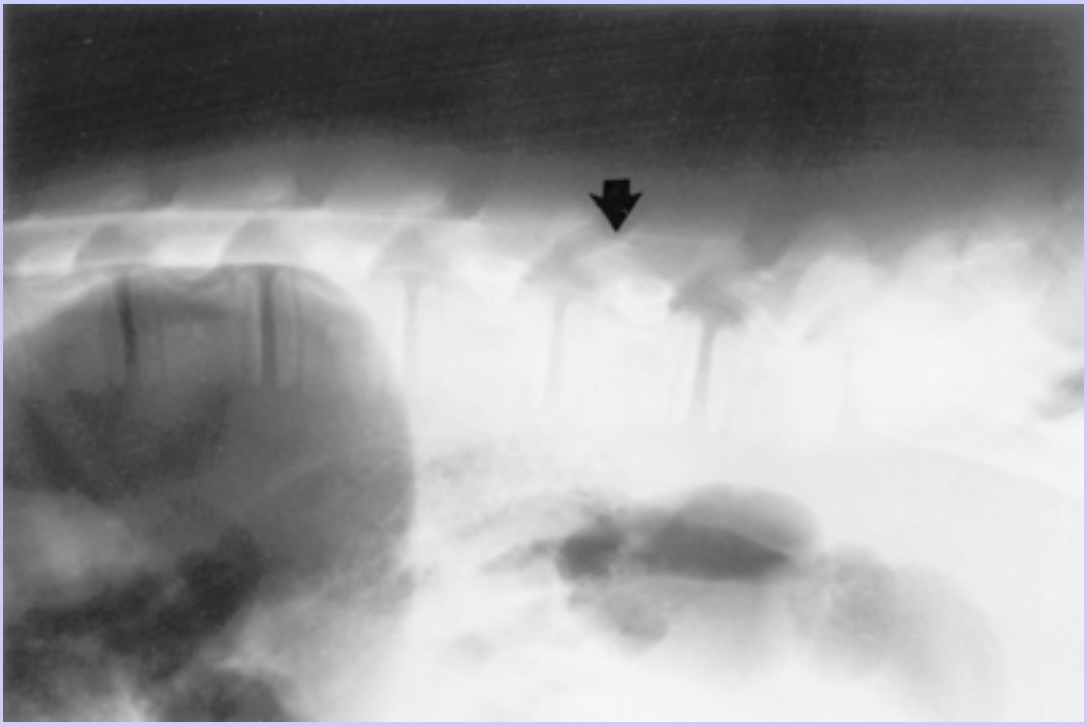
Fig. 35-32 Characteristic posture of a calf with a compressive fracture of the sixth lumbar (L6) vertebra and hematomyelia. The calf was fed a diet of grass hay and corn and developed nutritional osteodystrophy. Courtesy Dr. R.H. Whitlock.

Fig. 35-33 Myelogram of a calf with nutritional osteodystrophy showing a mild compression fracture of the L6 vertebra and complete obstruction of dye flow posterior to L5 *(arrow)*.



35.53.2.4 SACROCOCCYGEAL SPINE

Lesions of spinal cord segments S1 to S2 result in decreased conscious proprioceptive responses of the rear limbs[1952] and diminished flexor reflexes of those limbs. Anal tone is diminished to absent, and the bladder is distended and hypotonic. The patient is incontinent because of atonia of the urethral sphincter, and urine scalding may be seen over the perineum. The tail is flaccid and paralyzed. The anal sphincter is dilated, and the rectum is filled with dry fecal matter. There may be palpable abnormalities of the pelvis or sacrococcygeal joint. Crepitus of the pelvic bones may be noted when the animal is moved.

35.53.3 Clinical Pathology and Radiographic Findings

Radiography is the usual method of diagnosing a spinal fracture. In young horses, slipped physeal plates are often seen in the atlas.[1951,1953] Shortening of the lumbar vertebrae is consistent with either an oblique overriding fracture of the vertebral body or a compression fracture.[1950,1953] Abnormally shaped vertebrae may signify an anomalous vertebral arch. Myelographic examination may detect stenosis in segments distant from the fracture site.[1954]

Examination of cerebrospinal fluid (CSF) collected through a lumbosacral puncture may be useful for ancillary diagnosis of a spinal fracture. Fracture-induced changes in the CSF may be classified as either acute (0 to 1 day) or chronic (>1 day). The acute changes include diffuse blood contamination, a high red blood cell (RBC) count, a normal to high white blood cell (WBC) count, and a high protein concentration. The CSF changes in patients with more chronic injuries include a normal to slightly increased WBC count, normal to increased RBC count, increased protein concentration, and xanthochromia. These changes are not pathognomonic for spinal fracture, however, so should be interpreted with caution.

35.53.4 Pathology and Pathophysiology

Neurologic dysfunction after spinal trauma is similar to that of brain trauma and is a result of both immediate and secondary events. Immediate causes of injury include shearing forces that result in tearing of tissue, hemorrhage, and impingement of bone fragments on the spinal cord, particularly when the fracture is unstable. Trauma initiates a cascade of secondary biochemical events that further injure nervous system tissue, including adenosine triphosphate (ATP) depletion, which deprives cells of their ability to maintain their ionic environment through the action of sodium-potassium ATPase pumps. Rapid intracellular accumulation of calcium and sodium ions causes cytotoxic edema and neuronal depolarization. Release of the excitatory neurotransmitter glutamate and activation of the arachidonic acid and xanthine oxidase pathways further compound cellular damage. Other injurious substances generated after traumatic injury include nitric oxide, oxygen free radicals, lactic acid, arachidonic acid metabolites, and a variety of cytokines. Local vasogenic reflexes, mostly mediated by α-adrenergic receptors, result in decreased blood flow in the gray and white matter. Platelets aggregate in the hypoperfused capillaries and form microthrombi and infarcts. Regional ischemia caused by hypoperfusion results in lipid peroxidation of the axons, myelin degradation, and demyelination.[1955]

35.53.5 Treatment and Prognosis

It is important to recognize that the radiographic appearance of a spinal fracture is not a reliable prognostic indicator, because the vertebral components are likely to be in a different position from that at the time of injury. Not all vertebral body fractures result in neurologic disease. The prognosis is best judged on the basis of repeated neurologic examinations. Provided the animal is not suffering inhumanely and the pain can be adequately controlled, repeated neurologic examinations should be made over the first several hours. The longer the patient remains recumbent and neurologically impaired, the more unfavorable the prognosis.

The mainstay of immediate treatment of spinal injuries is maintaining whole-body homeostasis, particularly the maintenance of cardiovascular integrity and blood pressure.[1956] Ischemia local to the spinal cord plays a key role in development of the injury, but global cardiovascular failure compounds this effect. Most recoveries from spinal cord contusion occur spontaneously and are not appreciably influenced by drug administration. Some recommend treating acutely affected animals with DMSO (0.25 to 1 g/kg IV in 5% dextrose as a 40% DMSO solution) and dexamethasone (0.1 to 0.2 mg/kg four times daily for 2 to 4 days), but supportive data from controlled studies are not available. Analgesics or tranquilizers should be administered with care to ambulatory patients that have thoracolumbar spinal lesions because an ataxic patient may slip and worsen the spinal cord contusion. If signs of pain are severe, NSAIDs or narcotic analgesics may be administered. Epidural catheterization can be an effective method for delivery of analgesics over several days in animals with severe pain.[1957] In animals with pelvic lesions, the bladder should be evacuated either by manual palpation per rectum or by insertion of a catheter and use of a closed urinary drainage system. Attention to aseptic procedure during

catheter maintenance may reduce the number of iatrogenic bacterial infections. The urine should be cultured and examined repeatedly. Bladder infections should be treated with an appropriate antibiotic. In animals with paralysis of the rectal musculature, the feces should be removed manually. Lubricants (1 to 2 quarts of warm detergent or methylcellulose) may be administered with an enema.

If the spinal fracture appears stable and the animal can stand with assistance, the patient may be placed in a water tank and supported for prolonged periods. Goats are most amenable to treatment for spinal fractures, whereas adult horses and cattle may present insurmountable nursing problems and should be euthanized if they are unable to rise after several days or have intractable pain. Slings are commercially available or can be fashioned from canvas or burlap and wool or cotton. The time spent in the sling varies, depending on the animal's temperament and degree of neurologic dysfunction. Some horses become frantic while suspended in the device and cannot be supported without the risk of severe injury to the patient and the handlers. The sling should not be used for recumbent animals that cannot support themselves while harnessed. Such animals can sustain severe (even fatal) respiratory compromise or secondary myositis. Nevertheless, daily slinging of animals with mild neurologic signs may reduce secondary medical complications and facilitate recovery.

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Recumbent cattle should be floated in a tub of warm water. Watertight tubs for use with large cattle are commercially available* (see Down Cows at end of chapter).

Cervical fractures and luxations of small ruminants may be stabilized by incorporation of the head, neck, and anterior thorax in a fiberglass cast. The cast should extend from the middle part of the thorax to the tip of the nose. The feed and water supply of all animals with cervical fractures should be placed so that the animal can reach it without bending the neck. Surgical methods for stabilization of cervical fractures have been described in horses. The effectiveness of such treatments for restoration of neurologic function after traumatic injury or fracture of the spinal column is variable, but good results may be achieved when presurgical signs are mild and the repair is stable.[1958–1961]

Fractures of the dorsal spinous processes, transverse processes, and some small, oblique fractures of vertebral bodies may produce minimal instability of the spine. Such injuries may respond well to conservative treatment, such as stall confinement. Bone sequestra can result in the formation of draining tracts, however, and may require surgical removal to facilitate healing.[1962]

The dietary intake of copper, molybdenum, and calcium should be measured in cattle. If the daily intake is inadequate, the minerals should be fed in supplements. Animals with metabolic bone disease should not be restrained because of the risk of inducing additional pathologic fractures.

* Aqualift, Kirby Manufacturing, Merced, CA.

35.54 ANKYLOSING SPONDYLITIS OF HOLSTEIN BULLS

Ankylosing spondylitis is an inflammatory disease of joint tissue associated with fusion of lumbar vertebrae in Holstein bulls. Approximately 4% of all Holstein bulls used for artificial insemination are culled each year because of spondylitis.[1963] The clinical onset of the condition is insidious. The first signs of the disorder are a stilted gait, reluctance to move, and dragging of the toes of the rear limbs. Affected bulls are slow to mount teaser dummies for collection. The condition is progressive, and over several months the animals develop paraparesis and ataxia. With mounting, the ankylosed area of the spine may fracture, leading to acute recumbency. Pathologic changes associated with the condition include calcification of the ventral vertebral ligaments between the T11 and L3 vertebrae. The condition appears to be hereditary. All bulls with the condition possess the class I major

histocompatibility complex (MHC) BoLA A8 phenotype. In comparison, the phenotypic frequency of BoLA A8 in the general population of normal Holstein bulls is only 44%.[1964]

35.55 SPINAL ABSCESSES

35.55.1 Definition and Etiology

Most abscesses of the spinal cord originate from a preexisting vertebral body osteomyelitis. The bone usually is infected hematogenously. Extension of bacteria from the lungs, the heart, or a septic injection site is common. Neonates frequently develop vertebral abscesses secondary to septicemia.[1965,1966] Bone lesions may develop from sequestra broken from fractured vertebrae. Epizootics of spinal abscesses can result from injection of contaminated vaccines or mineral supplements near the spinal column. Similarly, spinal abscesses may be seen along with other diseases in groups of animals that are immunocompromised, such as cattle with bovine immunodeficiency virus infection.[1967] Infectious agents isolated from spinal abscesses of ruminants include *Corynebacterium pseudotuberculosis, Aracanobacterium pyogenes, Mannheimia haemolytica, Staphylococcus aureus,* and *Fusobacterium necrophorum*.[1965,1968–1970] Agents typically found in vertebral infections of foals include β-hemolytic streptococci, *Salmonella* species, *Actinobacillus equuli, Escherichia coli, Rhodococcus equi,* and *Klebsiella pneumoniae*.[1970–1974] Agents less often associated with vertebral body osteomyelitis of horses and cattle include *Mycobacterium bovis, Mycobacterium avium, Aspergillus* species, *Eikenella corrodens,* and *Brucella abortus*.[1975–1977] In rare cases, septic arthritis of the atlantooccipital joint may result from extension of a mycotic guttural pouch lesion.[1978,1979]

If the infectious agent remains localized in the vertebral body, the patient usually shows signs consistent with a transverse myelopathy. If the infection erodes through the dura mater, the animal develops signs of septic meningitis. If the bone infection is extensive, the vertebrae may fracture suddenly, resulting in signs characteristic of spinal trauma.

35.55.2 Clinical Signs

The neurologic deficits of animals with vertebral body abscesses without pachymeningitis are similar to those described previously for spinal fractures.[1969] Animals with mildly compressive cervical abscesses show a characteristic “weather vane” attitude, appear stiff, and are reluctant to eat food from the ground.[1969,1971,1972] Ruminants with this lesion hold the neck in extension and attempt to prehend the food with the tongue while the head is held more than 30 cm (12 inches) from the ground.[1969] Additional signs of spinal abscess include heat, pain, swelling, or crepitus over the affected areas and associated signs of bacteremia. Abscesses in the thoracolumbar spine cause hindlimb weakness and ataxia of variable severity, from mild gait abnormalities to complete recumbency. Stud males may be unable to breed because of weakness and pain.[1980] Animals with pachymeningitis show characteristic signs of meningeal inflammation such as hyperesthesia, intermittent spasmodic muscle contractions, and recurrent profuse sweating[1971,1975] (see earlier section on meningitis). Differential diagnoses include trauma, aberrant parasite migration, tumor and pathologic fractures, hemorrhage into or around the spinal cord (e.g., postanesthetic myelopathy), myopathies, caprine arthritis-encephalitis, and fibrocartilaginous embolism.[1981] Spinal abscesses can be mistaken for other painful conditions, such as orthopedic disorders or traumatic reticuloperitonitis.[1982]

35.55.3

Clinical Pathology and Radiographic Findings

Radiographs are the best method for obtaining a definitive diagnosis of spinal abscessation. A random pattern of hyperlucency and increased bone density characteristic of osteomyelitis is seen in the affected vertebrae, with or without adjacent soft tissue mass lesions indicative of abscessation[1976,1983] (Fig. 35-34). Diskospondylitis usually results in detectable osteolysis in the intervertebral joints.[1971] Occasional cases of extradural abscesses without radiographic evidence of osteomyelitis have been described in calves and lambs.[1331] Nuclear scintigraphy can be used when the bone lesions are not well defined in plain film radiography.[1977] In addition, myelography can be used to detect the specific site of the spinal cord compression.

A complete blood count (CBC) may indicate the presence of a chronic inflammatory focus. Specific changes in the CBC include hyperfibrinogenemia, neutrophilia, monocytosis, nonresponsive anemia, and left shift. The plasma globulin levels are increased in adults but may be increased or decreased in neonates, depending on the adequacy of colostral immunoglobulin transfer.

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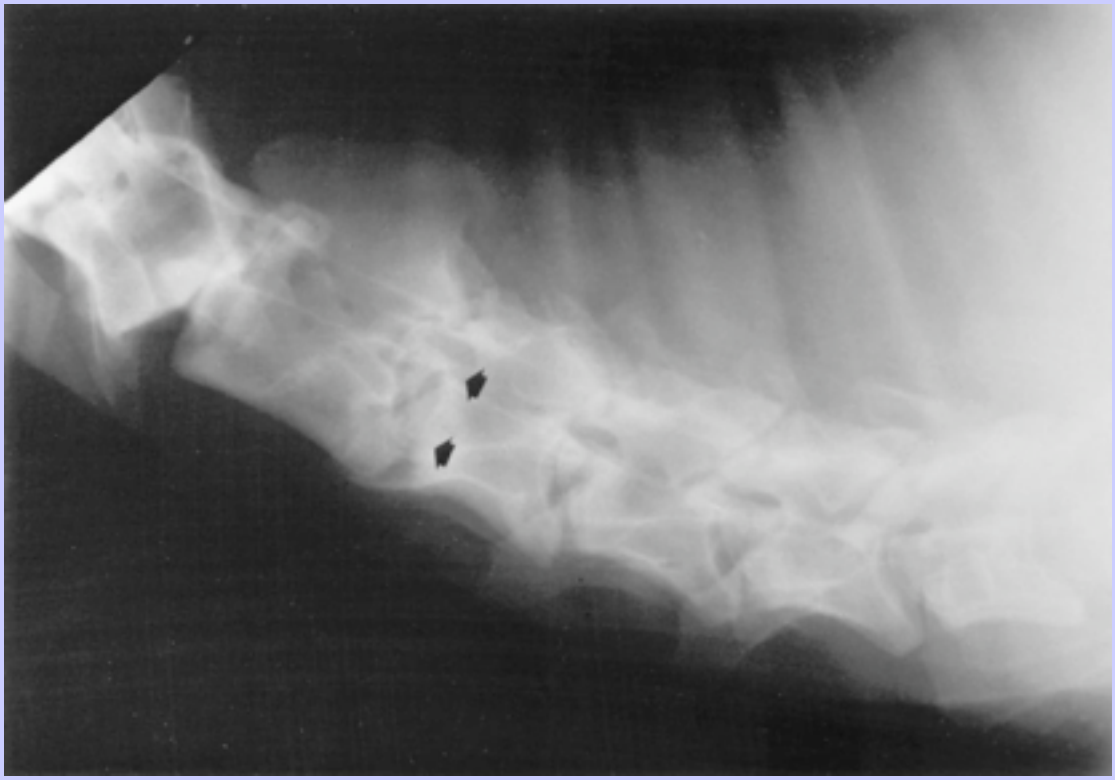
Fig. 35-34 Cervical radiograph of a sheep with osteomyelitis and diskospondylitis at the C2-C3 intervertebral space *(arrows)*. The sheep recovered fully after application of a full-length cast of the head, neck, and trunk and after continuous therapy with parenteral penicillin G for 1 month.



The changes in the cerebrospinal fluid (CSF) depend on the location of the abscess in the nervous system tissue and the meninges. Changes are present in CSF caudal to the lesion, but not cranial to the lesion; thus, CSF should be obtained by lumbar puncture and not cisternal puncture.[1981] In most cases the abscess does not infiltrate through the pachymeninges, and the CSF is normal or shows xanthochromia and mild increases in the protein concentration (60 to 120 mg/dL), with mild to no increase in nucleated cell count.[1984] The CSF of animals with pachymeningitis contains high numbers of WBCs (>100 neutrophils/dL) and a greatly increased protein concentration (>200 mg/dL). The CSF may clot after collection because of high concentrations of fibrinogen. Bacteria may be observed in a Gram-stained smear of CSF sediment. Horses with spinal brucellosis may have a rising serum agglutination titer or one above 1:160.[1975] Because of a high number of nonspecific reactions in equine sera, titers below 1:40 are considered nondiagnostic.[1985] Horses with spinal tuberculosis may be identified by an intradermal skin test using purified protein derivative or tuberculin.[1976]

35.55.4 Pathophysiology

Hematogenously derived abscesses arise because of embolization of septic thrombi into the metaphyseal arteries. These vessels have a sluggish blood flow because they become tortuous as they approach the physis. The metaphyseal vessels communicate with the ventral vertebral plexus, which in turn drains into the post cava, the portal vein, and the pulmonary veins. The ventral vertebral plexus does not have valves; blood flow reverses with an increase in abdominal or pleural pressure. Regurgitated blood from infected sites in the body cavities showers the vertebrae and spinal cord with bacteria.[1968,1977]

35.55.5 Necropsy Findings

The most common sites of involvement are the costovertebral and intervertebral articulations and the vertebral body epiphyses.[1986] Lumbar vertebrae frequently are involved. The bone is uneven, deformed, and softened. The abscessed area is interspersed with calcified trabeculae and pockets of necrotic debris. Sequestration of necrotic bone may be seen in some cases. The meninges may be adherent to the abscessed site, and occasionally a fistulous tract may be seen from the center of the abscess pocket to the subarachnoid space. In other cases the abscess is compartmentalized away from the CSF, but the proliferating bone impinges on the spinal cord.

35.55.6 Treatment and Prevention

If spinal abscessation is recognized early, prolonged antimicrobial therapy generally is effective. Selection of the appropriate antimicrobial agents should be based on the results of cultures from the patient's blood, urine, feces, and CSF. When bacteriologic culturing is inconclusive, a broad-spectrum antimicrobial should be chosen. Amikacin (7.5 to 10 mg/kg IM four times daily) or gentamicin (1 mg/kg IM three times daily) combined with potassium penicillin G (10,000 IU/kg IV three or four times daily) should be administered. After 1 or 2 weeks of this therapy, a trimethoprim-sulfonamide combination (2 to 3 mg/kg trimethoprim, 10 to 15 mg/kg sulfadiazine PO twice daily) in horses or procaine penicillin G (10,000 to 20,000 IU/kg SC or IM daily) in cattle can be administered for 2 to 3 months.

Small ruminants with cervical diskospondylitis may show a good response after 2 to 4 weeks of procaine penicillin G (10,000 IU/kg IM twice daily). Phenylbutazone, flunixin meglumine, or aspirin may be administered for pain relief. Immobilization of the head and neck in a fiberglass cast extending from the thorax to the nose may provide support to smaller patients with a cervical abscess. Surgical drainage of the abscess and

curettage of the necrotic bone may be feasible in smaller animals with sufficient economic value to justify the procedure.[1974,1987] Surgical intervention in adult cattle and horses is usually difficult because of the size of the epaxial musculature and the inaccessibility of the spine in large animals.

35.56 SPINAL TUMORS

With the exception of lymphosarcoma, spinal tumors in domestic animals are rare. Tumors reported to invade the spinal cord of horses include lymphosarcoma, plasma cell myeloma, meningioma, ependymoblastoma, fibrosarcoma, schwannoma, melanoma, carcinoma, angioma, angioblastoma, ganglioglioma, and neurofibroma.[1988–1999] The most common tumor of the spine of ruminants is lymphosarcoma, but others, such as embryonal neuroectodermal tumors, have been reported.[2000,2001]

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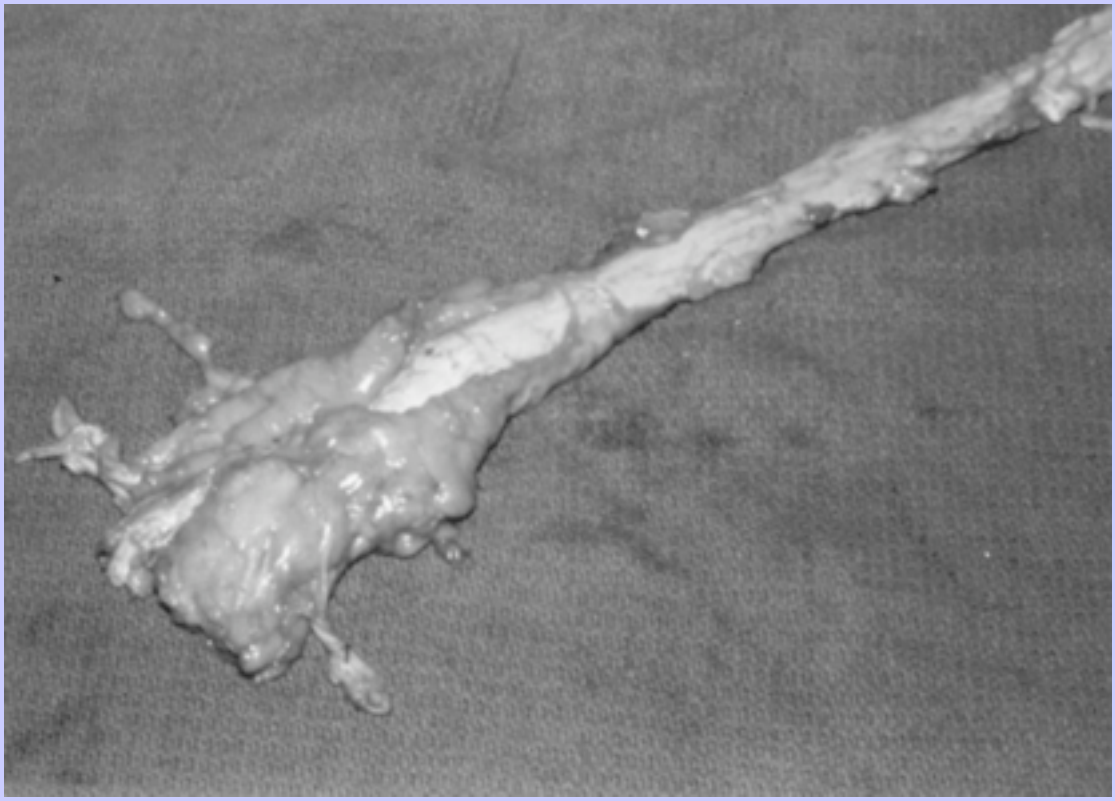
35.56.1 Clinical Signs

The clinical signs of tumorous invasion are indistinguishable from those described previously for spinal fractures. The onset of the neurologic dysfunction varies. Some neurofibromas, melanomas, and lymphosarcomas invade centripetally along the peripheral nerve rootlets. These patients develop slowly progressive dysfunction of the peripheral nerve or spinal cord, which eventually leads to tetraplegia or paraplegia (Figs. 35-35 and 35-36). In rare cases the onset of tetraplegia in cattle with a neurofibroma or lymphosarcoma may be peracute and unaccompanied by prodromal neurologic symptoms. Lymphosarcoma has a predilection for the lumbar segments of the spinal cord and the cauda equina in cattle over 5 years of age. A diagnosis of tumorous spinal invasion should be considered in cases of progressive neurologic disease characterized by flaccid tail and anus, dysuria, urine scalding, distended bladder, perineal analgesia or anesthesia, and paraparesis. Although most animals with spinal tumors are mature to older adults, immature animals can be affected rarely, mainly by embryonal tumors.[1994,1999–2001]

Fig. 35-35 Characteristic appearance of a paraplegic cow with lymphosarcoma of the L6 to cauda equina spinal rootlets and the cauda equina. Courtesy Dr. R.H. Whitlock.

Fig. 35-36 Spinal cord from a cow with lymphosarcoma. The mass is an accumulation of neoplastic lymphocytes that surround the spinal rootlets, filum terminale, and cauda equina.



35.56.2 Clinical Pathology

Examination of CSF may be useful when the tumor has infiltrated the cauda equina and is located in the lumbosacral cistern. In these cases, tumor cells may be biopsied as the needle is inserted into the lumbosacral space. In other cases the CSF may be normal, or albuminocytologic dissociation can be expected (elevated CSF protein with normal to mildly elevated nucleated cell count) with or without variable degrees of hemorrhage and xanthochromia. After necropsy, various immunohistochemical techniques can be used to identify the tumor type when routine histologic examination is insufficient.[2000,2001]

35.56.3 Treatment

There is currently no treatment for most spinal tumors of large animals. One study reported survival of 57 days after three treatments with L-asparaginase at 10,000 IU/mm^2. The body surface area was estimated using the following formula:

$$\text{Surface area } (m^2) = \text{Body weight}(g)^{2/3} \times 10^b \Big/ 10^4$$

where 10^b is a constant that is routinely used for the calculation of surface area in dogs.

The nearly 2-month period of survival allowed the investigators to successfully superovulate the cow. When treating food animals with L-asparaginase, the benefits of the antimetabolite drug must be weighed against the potential for teratogenicity of the fetus, toxicity for humans, and the certainty of relapse in the patient.[2002]

35.57 CEREBROSPINAL NEMATODIASIS

Migration of nematodes and insect larvae through the central nervous system (CNS) can cause acute CNS disease in all species of domestic livestock. The condition occurs in most countries. Parasitic agents that have been reported in the CNS of horses include *Micronema deletrix, Hypoderma lineatum, Hypoderma bovis, Strongylus vulgaris, Draschia megastoma, Setaria* species, and hydatid cysts.[2003–2028] In cattle the condition is caused principally by *Setaria* species and *Hypoderma bovis*. Small ruminants that share pastures with the white-tailed deer may become infected with the meningeal worm *Parelaphostrongylus tenuis*.[2013–2015]

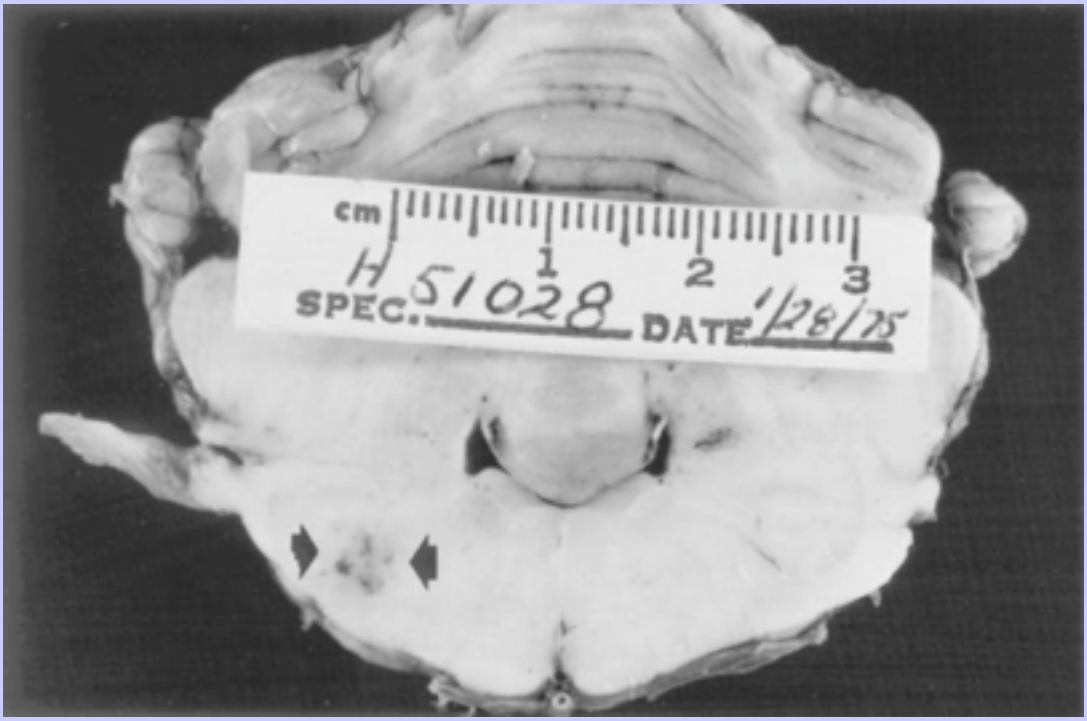
These parasites can attack any region of the CNS, but most clinical cases result from lesions of the brainstem and spinal cord. The clinical signs are similar for all parasitic CNS infestations and include tetraplegia/tetraparesis, paraplegia/paraparesis, asymmetric conscious proprioceptive deficit, hyperreflexia/areflexia, anesthesia or analgesia of dermatomes, and neurogenic atrophy. Cranial nerve deficits may be seen if the parasites migrate through the brainstem. The following sections discuss specific parasitic syndromes in livestock.

35.57.1 HORSES

35.57.1.1 *Strongylus vulgaris* Migration

Migration of *S. vulgaris* in the CNS causes two major clinical syndromes: acute embolization of parasitic emboli and slow perivascular migration of living parasites in the CNS. The two forms have a common pathogenesis. Aberrantly migrating fourth-stage or fifth-stage larvae in the intima of the aorta or left ventricle damage the endothelium, stimulate the clotting cascade, and cause formation of a thrombus that often contains the parasitic larva.[2020] Embolization of the thrombus to the brain results in fulminating encephalitic signs.[2009] As the embolus is degraded, the parasite migrates from the blood vessel into the CNS, resulting in the progressive brainstem disease. The cranial brainstem (diencephalon) is most often affected. The thrombosis and migration are accompanied by multifocal infarction, edema, hemorrhage, and necrosis[2007] (Fig. 35-37). Microscopic findings include linear tracts of hemorrhage lined by neutrophils, macrophages, eosinophils, and reactive glial cells. Anesthesia of the hindquarters has been described in some affected horses.[2010] Donkeys are also susceptible to the aberrant migration.[2029] CSF changes associated with *S. vulgaris* migration in equids include xanthochromia, refractive index over 1.3353, protein concentration ranging from 32 to 550 mg/dL, and increased WBC count (42 to 10,000/μL). The differential counts range from 70% to 80% neutrophils, 12% to 19% mononuclear cells, and 1% to 2% eosinophils.

Fig. 35-37 Parasitic lesions in the brainstem of a horse. The *arrows* indicate the major lesion, but other, smaller lesions are distributed over the entire brainstem. Courtesy Dr. R.H. Whitlock.



35.57.2 ## *Hypoderma lineatum* and *Hypoderma bovis* (Warble Flies)

Hypoderma lineatum and *H. bovis* are parasites that typically affect cattle but occasionally migrate aberrantly in the horse. Warble flies hatch from pupae in the early spring and mature during the summer. The flies deposit the eggs of *H. lineatum* on the lips, where they hatch and are swallowed. The ingested worms burrow through the intestine and along the adventitia of blood vessels until they reach the CNS.[2008] The flies deposit the eggs of *H. bovis* on the legs, where they hatch and burrow into the skin. The subcutaneous parasites then migrate as first-instar larvae to the spinal column, where they penetrate the epidural space along the peripheral nerves.[2004] Peroneal nerve paralysis from a local parasitic invasion has been reported in a pony.

35.57.3 ## Micronema deletrix

Micronema deletrix is thought to be a free-living rhabditid nematode that gains access to the CNS by penetration through the skin of the face and the lips, gums, and tongue.[2005,2006] The parasites migrate into the brain through the vascular system and cause diffuse encephalitis. Nematodes are found in the tunica adventitia and tunica media of blood vessels.[2005] Clinical signs of *M. deletrix* depend on the localization of the parasite. Spinal cord invasion is apparently less common than migration through the brainstem, cerebellum, thalamus, forebrain, and deeper layers of the cerebral cortex. Clinical signs include asymmetric ataxia, loss of conscious

proprioception, depression, behavioral changes, propulsive walking, head pressing, head tilt, circling, nystagmus, recumbency, convulsions, and coma. Affected animals may have granulomatous masses in the nares, pharynx, and maxilla. These could be helpful in formulating a differential diagnosis when parasitic migration is suspected. CSF changes in affected horses include pleocytosis (25 to 80 nucleated cells/μL), a normal to high protein concentration (69 to 114 mg/dL), and xanthochromia.[2003] The cellular types were mostly lymphocytes and macrophages ranging from 78% to 91% of the nucleated cells. Eosinophils were observed in the CSF of one horse.

35.57.4 Draschia megastoma

Draschia megastoma has been found in the brainstem of a horse from the southern United States.[2011] The adult worm is embedded in a pyogranulomatous lesion of the equine stomach, and the eggs are shed into the stomach. They hatch in the small intestine to form first-stage larvae, which are passed in the feces and ingested by the larvae of *Musca* flies. The third-stage larvae migrate to the mouthparts of the fly and are deposited on the mucous membranes of the host as the fly feeds.

35.57.5 Setaria

Setaria parasites are common filarid parasites of cattle that migrate aberrantly when they infect horses, sheep, or goats. These parasites have a worldwide distribution, and clinical cases are especially common in India and the Orient, where the common name for the disease is “kumri” (weak back).[2025] There are at least four *Setaria* species, of which *S. equina, S. digitata,* and *S. labiatopapillosa* are most common. The parasite is found in the connective tissues and peritoneal cavity of cattle, where it produces circulating microfilariae. Mosquitoes and possibly other bloodsucking insects become infected by the microfilariae and thus transmit the parasite.[2024] The parasite has a predilection for the spinal cord in horses. The clinical signs of reported cases include hypotonic tail, bladder paralysis, ataxia, and conscious proprioceptive deficits.[2012] Changes in the CSF associated with *Setaria* infestation include xanthochromia, pleocytosis (25 to 84 cells/dL), and a slightly increased protein concentration (~114 mg/dL). The cells of one horse contained a small proportion of eosinophils and basophils, but this finding was inconsistent with other reports.[2003]

35.57.6 SHEEP AND GOATS

35.57.6.1 Setaria

The infection caused by *Setaria* species in sheep and goats is similar to that described previously for horses.

35.57.7 Parelaphostrongylus tenuis

Disease caused by *P. tenuis* occurs predominantly in sheep and goats of the northeastern United States and western Canada.[2013,2016,2018,2019] The case-attack rate ranges from 10% to 59%.[2014] The disease appears to be spreading because of the increased range of the primary host, the white-tailed deer. Migration of the parasite in the CNS of deer is relatively innocuous, but aberrant migration occurs in domestic small ruminants. The result of this migration is severe signs of spinal cord and brainstem disease.[2014] The life cycle of the worm is complex. Adult worms are found in the cranial subarachnoid space, venous sinuses, and spinal subarachnoid

space of the deer, where they reproduce.[2015] Eggs are deposited into the venous blood and migrate into the lungs, where they embryonate. The larvae penetrate into the airways and are coughed into the pharynx, swallowed, and passed in the feces. They then penetrate into snails and slugs. Sheep and goats are infected when they eat the snails. After ingestion by the ruminant, the larvae penetrate the gastrointestinal wall and enter the CNS by migration along the nerve rootlets. Because of the complex life cycle of the parasite and the indirect life cycle in invertebrate hosts, the neurologic disease in sheep and goats is seen exclusively in late fall and winter. The pathologic lesions of the CNS of affected animals include asymmetric irregular tracts of disrupted necrotic tissue with macrophage infiltration. Coiled larvae occasionally may be seen in the tissues of some affected animals and may be excreted in the feces; however, these are difficult to distinguish from the larvae of *Müllerius* worms.

The clinical signs of *P. tenuis* infection are acute. In untreated animals the disease is progressive. The CSF of animals with *Parelaphostrongylus* infection contains increased concentrations of protein (56 to 157 mg/dL), RBCs (300 to 41,000/µL), and WBCs (17 to 700/µL). The differential cell counts contain a large number of eosinophils (7% to 97%).[2030]

35.57.8 CATTLE

35.57.8.1 Hypoderma Bovis

After hatching, the larvae of *H. bovis* burrow through the skin and migrate along the peripheral nerves to the spinal canal. When the larvae reach the spinal canal, they lie dormant for 2 to 3 months in the epidural fat. Most of the larvae lodge in the lumbosacral part of the spinal cord; very few are found in the cervicothoracic region. If the larvae are killed while lodged in the epidural fat, the host mounts a marked inflammatory response. The swelling and inflammation caused by the dead worms results in spinal cord disease. In clinical practice these signs most often occur by 2 days after administration of a systemic organophosphate grub treatment.[2027,2028] Other drugs that kill *Hypoderma* larvae in the spinal cord could cause a similar problem. In most of North America the grub is located in the epidural space between the months of July and October.

The clinical signs of hypodermiasis include stiffness of the rear limbs, ataxia, paraparesis/paraplegia, hemiparesis/hemiplegia, or tetraparesis/tetraplegia. The conscious proprioceptive responses are greatly altered in the affected limbs. Reflex activity varies, depending on the level of the lesion in the spinal cord.

The CSF changes of hypodermiasis vary. Because of the epidural location of the grub, most affected animals have normal CSF values. If pressure changes induce vascular damage, CSF changes might include mild xanthochromia and slight increases in WBCs and the protein concentration.

35.57.9 Setaria digitata

Infection of the spinal cord of cattle by *S. digitata* has been described in India.[2017]

35.57.10 Diagnosis of Parasitic Infestation of Central Nervous System

Parasitic myeloencephalopathy must be considered in all cases of acute asymmetric disease of the spinal cord, cerebellum, or brainstem. Identification of eosinophils in the CSF may be helpful; however, this pattern is not seen in every neuroparasitic diseases. For example, *Hypoderma* infestations often are extradural, and CSF

changes reflect only increased pressure. The CSF of horses with acute *S. vulgaris* migration could be normal or could show xanthochromia, increased concentrations of RBCs or WBCs, and increased protein concentration.[2009]

35.57.11 Treatment

Although severe reactions often are associated with death of the CNS parasites, administration of parasiticides in conjunction with heavy antiinflammatory therapy is recommended. Such treatment prevents further migration of the parasite yet mitigates the host inflammatory responses.

The recommended treatment for neural *S. vulgaris* infection is either thiabendazole (440 mg/kg PO daily for 2 days) or mebendazole (30 mg/kg daily for 2 days). Horses should also be given a combination of corticosteroids and NSAIDs for 10 days after administration of the parasiticides.

Some experts speculate that ivermectin may be a valuable broad-spectrum treatment for all CNS parasitic infections. The drug has a prolonged plasma half-life after parenteral or oral administration (2.7 days) and may exert an antiparasitic effect for as long as 14 to 21 days after subcutaneous administration.[2031–2033] Although ivermectin diffuses across the blood-brain barrier, the plasma concentrations after oral administration are low, and the drug should be administered parenterally to achieve optimum efficacy. Unfortunately, significant side effects occur (0.92% overall adverse reaction rate) after parenteral administration to horses.[2034,2035] Consequently, until ivermectin is proved to be effective by pharmacologic and clinical studies, alternative parasiticides should be considered for initial treatment of parasitic CNS disease in horses.

35.57.11.1 HYPODERMA BOVIS

Systemic organophosphate insecticides formulated for oral administration or pour-on application have been recommended for eliminating *H. bovis* from the CNS. These one-time formulations include crufomate (75 mg/kg as 13.5% Ruelene), trichlorfon (40 mg/kg PO), famphur* (13.2% 1 fluid ounce per 90 kg body weight, not to exceed total dosage of 4 oz for cattle), ronnel (100 mg/kg PO for cattle or horses), and ivermectin 0.5% solution (1 mL/10 kg). Although ivermectin kills the cattle grub in the subcutaneous tissues, its safety and efficacy in the treatment of clinical neurologic disease are uncertain.

It is important to remember that the treatment of affected animals with any of the systemic parasiticides may aggravate neurologic disturbances through release of toxic factors or the development of local immunologic responses to the dying worms.[2019,2036] Concomitant treatment with corticosteroids (e.g., dexamethasone, 0.1 to 0.25 mg/kg IV every 6 hours) 1 day before and 5 days after treatment is recommended to reduce the inflammation. Dying cattle grubs also release a systemic toxin that lowers blood pressure and causes acute dyspnea and collapse. The systemic toxic effects of the dying grubs can be ameliorated by concomitant administration of phenylbutazone (4 mg/kg IV or PO twice daily in horses; 10 mg/kg IV or PO once every 36 hours in cattle), aspirin (100 mg/kg PO two or three times daily for cattle), or flunixin meglumine (1 to 2.2 mg/kg IV twice daily for horses or cattle). Naproxen (10 mg/kg IV twice daily for horses) may be a useful alternative to phenylbutazone therapy.

Hypoderma infestation can be controlled by prophylactic administration of the pour-on insecticides before worms have migrated into the nervous tissues. The appropriate time for application of the grubicide depends on the time of pupation and the emergence of adults. In most of North America the flies emerge by May, and the larvae reach the nervous tissues by November. Therefore, prophylactic treatment of cattle or horses with

organophosphorus compounds should be completed by August or September in warmer climates and October in colder areas.

* American Cyanimid, Wayne, NJ.

35.57.11.2 PARELAPHOSTRONGYLUS TENUIS

A number of drugs, including levamisole (7 mg/kg PO in a single dose), diethylcarbamazine (40 to 100 mg/kg twice in 72 hours), and thiabendazole (250 to 440 mg/kg PO on 2 consecutive days), may be effective for eliminating *P. tenuis* from the CNS.[2013,2037] Ivermectin has been administered to some affected goats, but only one of three treated animals recovered.[2030] The lack of response to ivermectin was related to its poor distribution in the CNS. Administration of ivermectin to animals before exposure protects them from larva migrans for 7 to 14 days.[2038] All patients treated with anthelmintics should be given corticosteroids and NSAIDs concomitantly.

35.57.11.3 *SETARIA* SPECIES

Administration of a single dose of diethylcarbamazine (80 to 100 mg/kg PO) may be effective against migrating *Setaria* larvae and adults. The drug also has been shown to be effective in preventing infection in sheep and goats when given at 20-day intervals (40 mg/kg PO) during the vector season. The efficacy of diethylcarbamazine in the treatment and prevention of *Setaria* infection in horses is unclear. As with therapy for other parasitic nervous system infections, patients should be given corticosteroids and NSAIDs concomitantly with the parasiticide therapy.

35.58 FIBROCARTILAGINOUS EMBOLIZATION

Fibrocartilaginous embolization has been described in horses, lambs, and a calf.[2039–2044] The clinical signs are those of an acute to peracute onset of myelopathy that usually is asymmetric. Paresis to paralysis of the limbs caudal to the lesion occurs, as does hyperreflexia (if the lesion is above the brachial or lumbosacral intumescences) or hyporeflexia to areflexia (if the lesion is in an intumescence). Differential diagnoses that should be considered include traumatic injuries and, in horses, equine herpesvirus infection. Other types of myelopathy usually have a more gradual onset and less acute course. Lambs may develop diffuse tremors that resemble the truncal ataxia of cerebellar disease. The index of suspicion is increased by ruling out other causes of myelopathy, but definitive diagnosis usually is only made at necropsy. There is no effective treatment for the condition, and affected large animals have not recovered. In dogs, however, in which a similar or identical condition is common, partial to complete recovery over several weeks to months is common and might be anticipated in some milder cases in large animals, particularly when the signs are the upper motor neuron type.[2045,2046]

The emboli are believed to originate from the nucleus pulposus of the intervertebral disks and can be identified histologically using an alcian blue stain.[2042] The exact cause of the embolization and the associated mechanisms are unknown. Pressure changes or lesions associated with degenerative arthropathy might result in herniation of disk material into the marrow cavity of a vertebral body. From there the material is hypothesized to enter the basivertebral veins and pass retrograde along the valveless basivertebral plexus to the spinal veins, where it gains access to the vertebral arterial circuit. The manner in which the material enters the arteries is unknown, but some authors have postulated the presence of arteriovenous shunts in the vertebral vasculature.[2039] Other mechanisms proposed to explain embolization include herniation of nucleus pulposus into persistent or anomalous embryonic

vasculature, into neovasculature formed at the site of a chronically degenerated intervertebral disk, or through the vertebral endplate via Schmorl's nodes into the marrow cavity of the vertebrae and then into the vascular system. Sudden increases in pressure within the disk, such as may occur during exercise or from trauma, may play a role in the formation of emboli. Once the material has embolized, the neurologic signs are related to swelling, infarction, necrosis, and hemorrhage of the neuropil. The emboli occur exclusively in the brainstem, spinal cord, and cerebellum. The CSF of affected animals has been reported to be normal,[2040] but mild pleocytosis and elevations in the protein concentration could be expected in CSF obtained caudal to the lesion in some cases.

35.59 POSTANESTHETIC MYELOPATHY AND ENCEPHALOPATHY

A sudden-onset myelopathy has been described in several horses and in a calf after anesthesia.[2047–2050] Most of the horses were young and in dorsal recumbency during anesthesia. The calf described with a similar syndrome was severely hypotensive during anesthesia. Paraparesis, ataxia, recumbency, or paraplegia occurs immediately after anesthesia or within a few days. Other reported signs include hypalgesia and scoliosis. Lesions occur mainly in the thoracolumbar spinal cord, although the cervical spine may be involved, and consist of malacia predominantly within gray matter (poliomyelomalacia), with severe hemorrhage in the spinal cord parenchyma (hemorrhagic myelomalacia) in some cases.

Rare cases of postanesthetic encephalopathy have been described in horses.[2051,2052] Clinical signs included dementia, pacing and circling, cortical (“central”) blindness, ataxia, hypermetria, and recumbency. The onset of signs ranged from a few hours after recovery to several weeks later. The major pathologic finding in affected horses was cerebrocortical necrosis, particularly in regions of the cortex supplied by terminal arterial branches (“watershed zones”).

Although the pathogenesis of postanesthetic myelopathy is incompletely understood, it likely results from compromise of the vascular supply to the spinal cord caused by hypotension or pressure from the abdominal viscera on the great veins (caudal vena cava, azygous vein) resulting in venous stasis. Similarly, systemic hypoxia, hypovolemia, and hypercapnia may underlie postanesthetic encephalopathy.[2052] Factors suspected to increase the risk of postanesthetic encephalopathy include positioning in dorsal recumbency during anesthesia, multiple anesthesias, endotoxemia, and shock. Differential diagnoses for myelopathy include orthopedic conditions such as limb fractures, spinal fracture, and myopathy secondary to recumbency. Differentials for encephalopathy include numerous metabolic, infectious, and toxic disorders. Prognosis for recovery in both conditions is poor. The risk of these complications probably can be reduced by supporting adequate blood pressure and ventilation in patients under anesthesia and avoiding placing patients in dorsal recumbency whenever possible.

35.60 OCCIPITOATLANTOAXIAL MALFORMATION

Occipitoatlantoaxial malformation appears to consist of a spectrum of cervical spinal abnormalities rather than a single specific anatomic defect.[2053] It occurs in cattle, sheep, goats, and horses.[2054–2056] At least five different types of defect have been reported in horses, as follows[2057–2064]: 1083 1084

1 A heritable condition in Arabians characterized by symmetric atlantooccipital fusion, atlantalization of the axis, and hypoplasia of the atlantal wings.[2058,2062,2065] A similar disorder has been reported in an Arabian-cross colt.[2066]

2 A nonfamilial disease of quarter horses with spinal lesions similar to the lesions in Arabians.[2067,2068]

3 Asymmetric malformations of the occipitoatlantoaxial area in Morgan horses and standardbred foals.[2053]

4 Atlantal duplication in Arabian and Arabian crossbred horses.[2069,2070]

5 Asymmetric occipitalization of the atlas and symmetric atlantalization of the axis.

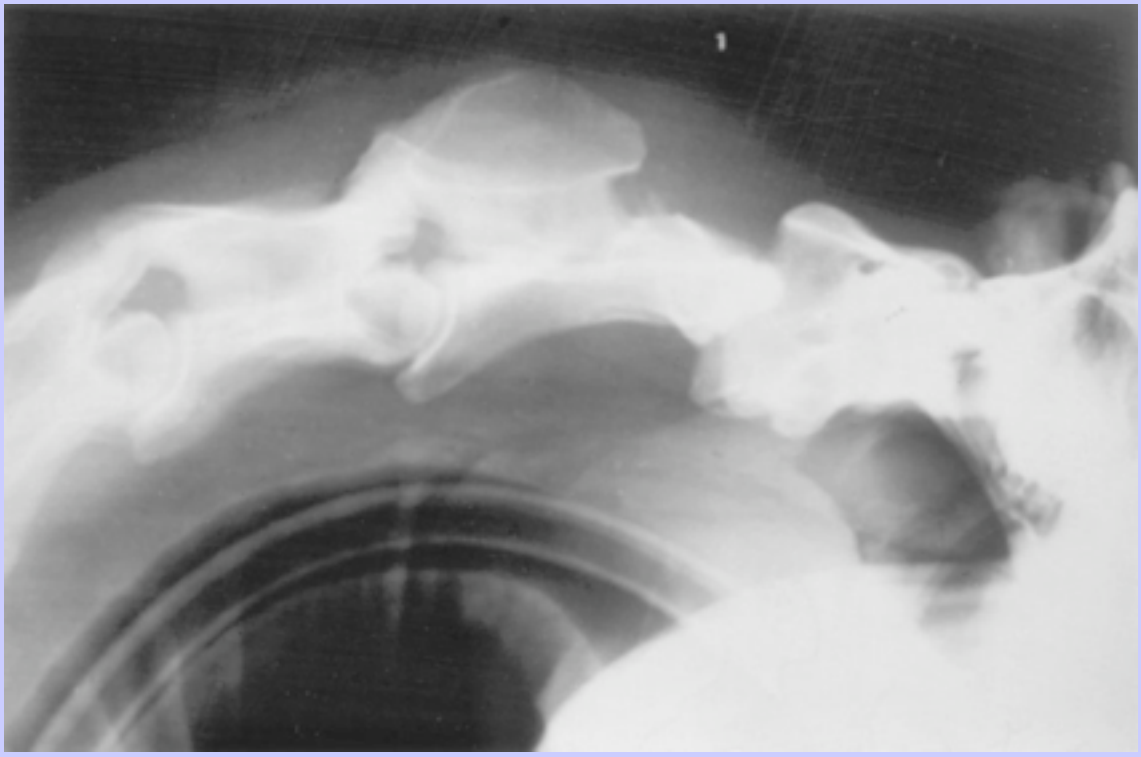
Macroscopic pathologic lesions common to the five forms include loss or flattening of the occipital condyles, asymmetric flattening of the articular surfaces of the axis, and shortened dens. The pathogenesis of the vertebral defects is unknown, but the disease has been shown to be heritable in the Arabian horse.[2071]

The clinical signs vary considerably and range from normal neurologic function with or without torticollis to brainstem compression, sudden unexpected death, and stillbirth.[2053] In typical cases, signs of tetraplegia or tetraparesis begin at or shortly after birth and progress at a variable rate. Foals may become suddenly tetraplegic, appear to stabilize for several days, but then die suddenly.[2062] In rare cases, horses may not show nervous system signs until 3 years of age.[2061]

The signs are symmetric in most affected animals and include conscious proprioceptive deficits, tetraplegia, hyperreflexia, and hypertonia. Some affected animals may show a reluctance to move the neck and head and resist vigorously when the proximal cervical area is passively flexed. A clicking, creaking, or crepitation may be palpated over the cervical spine when the head is moved.[2053,2057] Animals with asymmetric bone lesions often show torticollis, whereas patients with symmetric lesions hold their heads in extension and frequently display the "weather vane" attitude. Neurologic deficits may not be seen despite moderate torticollis.

The bone lesions are readily apparent on radiographic examination (Figs. 35-38 and 35-39), and computed tomography (CT) can further elucidate the anatomic abnormalities.[2067] Affected animals may show subluxation of the atlantoaxial joint, ventral displacement of C2 in relation to C1, nonunited ossification center of the dens, shortened or elongated dens, shortened transverse process of the atlas, fusion of C1 with the occipital condyles, atlantal duplication, and deviation of the basilar bone.[2072] In sheep, additional malformations of the cervical vertebrae have been seen concomitantly.

Fig. 35-38 Lateral radiographic view of a 2-month-old foal with occipitoatlantoaxial malformation. The atlas is occipitalized, and the axis is subluxated dorsally. The odontoid process of the dens is hypoplastic and is not anchored to the floor of the atlas. Courtesy Dr. W.D. Wilson.



Some suggest that treatment could include surgical fusion of the atlantoaxial joints, with or without a laminectomy.[2058,2061,2073–2075] Laminectomy alone has been used to alleviate spinal cord compression and clinical signs caused by occipitoatlantoaxial malformation.[2076] However, long-term results of surgical intervention have been poor, with neurologic deficits persisting. Closed reduction of the luxated atlantoaxial joint has been similarly unsatisfactory.[2067,2077] Arabian horses should not be treated because of the hereditary nature of the disease in that breed.

35.61 SYSTEMIC NEUROAXONAL DYSTROPHY

Systemic neuroaxonal dystrophy is seen in purebred Suffolk sheep.[2078] The animals are born normal but show a hindlimb ataxia beginning at 1 to 5 months of age. The disease is progressive, and eventually the animals become recumbent and either die or are euthanized after 8 to 10 weeks. Pedigree analyses have indicated that an autosomal recessive trait may be responsible for the condition. The pathology of this disease is characterized by numerous focal axonal swellings in gray matter and adjacent white matter, particularly in areas of the spinal cord and brainstem involved in conscious proprioception (dorsal and intermediate horn gray matter in spinal cord, various

nuclei in medulla and caudal midbrain). A condition that is clinically and pathologically similar to systemic neuroaxonal dystrophy has been described in 4- to 7-month-old Merino lambs.[2079]

35.62 WEAVER SYNDROME (BOVINE PROGRESSIVE DEGENERATIVE MYELOENCEPHALOPATHY)

Weaver syndrome is a progressive hereditary CNS disease of 5- to 10-month-old Brown Swiss and Angler cattle.[2080,2081] The disease has been reported in the United States, Canada, Denmark, and Switzerland. The incidence of weaver syndrome in some countries may be as high as 563 per 100,000 registered Brown Swiss cattle.[2082,2083] The disease affects both genders, but males are affected more often than females.[2082]

Fig. 35-39 Dorsoventral myelogram of a foal with occipitoatlantoaxial malformation showing spinal compression and attenuation of the contrast column at the C1-C2 vertebral junction *(arrow)*.

Affected animals develop clinical signs between 5 and 8 months of age. The animals are easily pushed around by herdmates and show marked proprioceptive deficits when forced to move. The clinical signs worsen until the animals become recumbent by 18 to 36 months of age.[2080,2084,2085] The pelvic limbs are most severely affected. Specific signs include weakness, ataxia, conscious proprioceptive deficits (circumduction, crossing over, interference, knuckling), muscle tremors, and recumbency. In early stages, attempts to move rapidly may result in cessation of movement of gait in the hindlimbs while the animal continues to pull with the forelimbs, causing the hindlimbs to be pulled too far caudally. Some animals may show varying degrees of hypermetria ("goose stepping" gait) in the limbs. The spinal reflexes and cranial nerve function are normal. Anestrus in females and aspermatogenesis of affected bulls have been described.[2085] The disease is progressive and leads to irreversible recumbency. The sensory nerve conduction velocity is reduced in affected calves, but motor nerve conduction velocity is normal. Electromyograms and electroencephalograms are normal in affected calves.[2086] The CSF of affected cattle may show an increased concentration of protein (0 to 127 mg/dL) and creatine phosphokinase (2 to 89 mg/dL).[2087]

Except for muscular atrophy of the pelvic limbs (in long-standing cases), the small ovaries, and hypoplastic testicles, macroscopic lesions are not seen.[2082,2088,2089] Although severe muscular changes are not observed, ultrastructural studies of muscle from affected cattle support the hypothesis that myopathic changes are a significant feature of bovine myeloencephalopathy.[2090,2091] The primary microscopic abnormalities include degeneration of the rubrospinal spinocerebellar tracts, particularly in the ventral funiculi of the thoracic spinal cord. The lesions include axonal degeneration, vacuolation of the white matter, spheroids, phagocytosis of myelin debris, gliosis, and status spongiosus.[2082] Axonal swellings have been observed in the brainstem nuclei and medulla oblongata. An ultrastructural study has shown a reduction of the height of the paramembranous densities of the synaptic junctions of affected cattle,[2092] indicating impairment of transmitter releases, dysfunction of the synaptic endplates, or losses of specific cell populations from the motor cortex. Other ultrastructural changes include axonal swelling and vesiculation, swelling of the mitochondria of the Schwann cells, and membrane-bound vesicles.[2085,2093] Cerebellar lesions include degeneration and loss of Purkinje's cells and swelling of Purkinje cell axons.[2088]

The disease is thought to be transmitted by a simple autosomal recessive trait. Apparent association between the weaver condition and genetic predisposition for high milk yield would favor retention of weaver carriers in situations of intense genetic pressure for production.[2094] A genetic test is available for this disease.[2095] Carrier bulls identified by the American Brown Swiss registry are designated by the suffix "W" as an integral part of their registry name.[2096]

35.63 PROGRESSIVE SPINAL MYELINOPATHY OF BEEF CATTLE

Spinal myelinopathy of beef cattle has been reported in Australia.[2097] The condition occurs mainly in animals of the Murray Grey breed and is inherited in an autosomal recessive manner.[2098] Most of the affected animals are unable to stand at birth. Less severely affected calves usually exhibit severe conscious proprioceptive defects. The muscular tone of the hindlimbs is increased. The condition is progressive, and affected animals die or are euthanized by 12 months of age.

The pathologic changes are restricted to the spinal cord white matter, with swollen axons, dilated myelin sheath, wallerian degeneration, and ballooning of the axonal sheaths. There is mild chromatolysis. The animals have normal hepatic copper concentrations, indicating that the condition is not related to enzootic ataxia.[2097]

35.64 BOVINE SPINAL MUSCULAR ATROPHY

Bovine spinal muscular atrophy (SMA) is a heritable disorder of Brown Swiss cattle, certain breeds derived from the Brown Swiss (e.g., Braunvieh, Red Swiss), and Holstein-Friesians.[2099–2103] Most affected calves appear normal immediately after birth but within a few weeks develop severe weakness and rapidly progressive muscle atrophy, particularly affecting proximal musculature. Calves deteriorate rapidly; most become recumbent and develop bronchopneumonia. SMA is characterized pathologically by degeneration of motor neurons in the ventral horn of the spinal cord gray matter (equivalent to human anterior horn cells). Pathology is most severe in the brachial and lumbosacral plexuses but occurs throughout the spinal cord. Abnormalities include neuronal loss, swelling and accumulation of phosphorylated neurofilaments, and neuronophagia.[2104] These findings suggest that neuronal degeneration in SMA is a consequence of necrosis rather than apoptosis.[2102,2104] Sensory neurons are unimpaired.[2099,2105] The SMA-determining gene has recently been mapped to chromosome 24 in Brown Swiss cattle, similar to the equivalent gene in humans.[2106,2107] Bovine SMA is inherited as an autosomal recessive trait.[2099] Although this condition resembles weaver syndrome, the two diseases can be differentiated clinically. Signs of spinal muscular atrophy usually are first seen between 2 and 5 weeks of age. Calves with weaver syndrome first show signs at 5 months of age. The degree of muscular wastage is much greater in calves with spinal muscular atrophy than with weaver syndrome.[2108] SMA also must be distinguished from the dysmyelination described in Braunvieh and Brown Swiss–Braunvieh calves (see next section).

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35.65 SPINAL DYSMYELINATION OF BRAUNVIEH AND BRAUNVIEH-CROSS CALVES

A congenital spinal condition characterized by dysmyelination of the dorsal tracts of the spinal cord has been described in Braunvieh–Brown Swiss crossbred calves.[2109] Test matings have shown that the disease is inherited in an autosomal recessive manner.[2110] Calves are recumbent from birth. They have a coarse tremor of the head, neck, and body when stimulated and generalized muscular atrophy. Necropsy findings included deficient myelin production and demyelination of the dorsal sensory tracts of the spinal cord. The neurons of these calves are normal, which differentiates the condition from weaver syndrome and spinal muscular atrophy. A similar condition was described in purebred Braunvieh calves; recumbency from birth, opisthotonos, and muscular spasticity with increased reflexes were present in affected calves.[2111] Bilaterally symmetric reduction of myelin was found in the spinal cord.

35.66 MYELOPATHY IN HOLSTEIN-GIR CALVES

A single report describes a myelopathy in Holstein-Gir calves in Brazil.[2112] Calves were normal at birth but developed quadriparesis and ataxia at about 3 months of age, becoming recumbent within 1 to 2 weeks after onset of signs. All died from respiratory complications within a few weeks. Nervous system lesions were confined to the spinal cord in all except one calf examined; findings were consistent with a dying-back neuropathy. Lesions were broadly symmetric bilaterally and not limited to any specific tracts within the cord. In one calf, small glial nodules were found in the basal nuclei and medulla. Both male and female calves were affected, and all were offspring of a single Holstein bull, supporting a genetic but not sex-linked basis for this disorder.

35.67 NEUROPATHY, MYOPATHY, AND GLOMERULOPATHY OF GELBVIEH CATTLE

A disorder affecting peripheral nerves, spinal cord, kidneys, and muscles has been described in a small number of Gelbvieh calves.[2113,2114] Animals present with progressive ataxia, stiffness, and weakness at a few weeks of age to slightly over 1 year old. Signs may start in the rear limbs but progress over weeks to months to affect all limbs. Animals may become recumbent but remain bright, with a good appetite. Muscle atrophy is frequently observed, as are flaccid paresis, hyporeflexia, and decreased anal tone.[2114] Hypalgesia to analgesia may be present in affected limbs. Signs of cranial nerve dysfunction are rare. Proteinuria is the most consistent abnormality of clinical chemistry, whereas other changes, such as neutrophilia and elevated serum creatine kinase, are variable and may relate to secondary problems (e.g., muscle damage when recumbent). Histologic alterations include degenerative changes in peripheral nerves and spinal cord (particularly dorsal columns), renal lesions described as "interstitial nephritis" or "glomerulopathy," and variable myopathic changes (e.g., necrosis, fibrosis, atrophy). Vascular lesions also have been described.[2113] Controversy surrounds the relative severity and importance of neuropathy, myelopathy, and myopathy, but all agree that all these tissues are involved and that renal lesions are prominent. Studies of potential toxicities or nutritional deficiencies within affected herds tend not to support these etiologies, but rather suggest that this is a heritable disorder. The exact mechanism of inheritance and the molecular basis for this disease have not been elucidated. No treatment has been described, and the prognosis appears to be poor. Prevention likely would involve changes in breeding management.

35.68 PROGRESSIVE ATAXIA OF CHAROLAIS CALVES

Progressive ataxia occurs in purebred and crossbred Charolais calves of both genders between 6 and 36 months of age.[2115–2120] The condition has a worldwide distribution. Affected calves develop posterior paresis and become recumbent by approximately 2 years of age. The disease is thought to be caused by a recessive genetic defect. Preliminary studies to locate the defect in the gene coding for myelin basic protein have been reported.[2121] The clinical signs begin with posterior ataxia and end in lateral recumbency. Other neurologic signs of progressive ataxia include stiffness of the neck, aggressiveness, dragging of the rear toes, stumbling, and loss of conscious proprioception (abduction, knuckling, circumduction, abnormal leg placement at rest).[2122] In the initial stages of the disease, the gait deficits worsen with exercise and improve after a period of rest. Muscular tremors or a jerking movement of the limbs and tail may be seen when the affected animal attempts to rise.[2117,2123] Some animals may be found down acutely and primarily show signs of central vestibular disturbance.[2122] Head bobbing may be observed, but affected animals have no other signs of brain involvement. Difficulty in assuming and maintaining a urination posture and prolonged pulsatile micturition are characteristic abnormalities in affected animals.[2115,2119,2124] The major pathologic lesion is eosinophilic plaques in the white matter of the brain. Plaques also extend into the white matter of the cerebellar folia and peduncles. Ultrastructural changes include hypertrophy of oligodendrocytes and dysmyelination.[2125] These lesions, which have been characterized as an oligodendrogial dysplasia, are almost unique to this particular disease of Charolais cattle, although similar pathology has recently been described in dogs.[2126]

35.69 SPASTIC PARESIS (ELSO HEEL)

Spastic paresis is characterized by marked asymmetric spasticity and hypertonia of the rear limbs. The etiology is uncertain; it may be genetic. Breeds in which the condition has been recognized include the Holstein, Brahman, Angus, shorthorn, Charolais, Simmental, Red Danish, crossbred shorthorn, Gelbvieh, Ayrshire, polled Hereford,

Hungarian red spotted, Kankrej, Belgian blue, and other rare European breeds.[2127–2139] The clinical signs of this condition are clinically similar to inherited periodic spasticity (see next section), except that spastic paresis is seen in young animals (onset at 3 weeks to 1 year of age) and occurs at all times when the animal stands.[2127–2130] In comparison, inherited periodic spasticity occurs in adults in episodic fashion, with normal gait between episodes. Spastic paresis has been recognized in pygmy goats.[2140]

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35.69.1 Clinical Signs

Spastic paresis is characterized by intermittently increased extensor tonus in the pelvic limb as the animal attempts to walk.[2127,2131,2136,2141] The gastrocnemius and superficial digital extensor muscles are spastically contracted in all calves, whereas the biceps femoris, adductor, quadriceps, semitendinosus, and semimembranosus muscles are less often affected.[2128,2131,2141,2142] The extensor tone is normal when the calf is recumbent and relaxed but becomes excessive when the animal stands and attempts to bear weight. The excessive extensor motor activity results in an inability to flex the hock during protraction of the pelvic limb. To prevent the toes from dragging, the limb is circumducted, resulting in a pendulum-like motion.[2142] At rest the limb is held stiffly abducted and is repeatedly circumducted. The foot is held off the ground, and the gastrocnemius muscles appear to be underdeveloped. The tail is elevated from the ischiorectal fossa as the animal attempts to move. Eventually there is atrophy of the hindquarters. The spasticity is progressive, and affected animals experience difficulty rising and grazing. If untreated, the animals are stunted and usually are culled.

The excessive pull of the extensor tendons produces radiographically detectable changes in the bones of the hock, including osteoporosis, lipping of the dorsal aspect of the tibial epiphysis, plantar displacement of the proximal part of the tibial diaphysis and epiphysis, and excessive straightening of the tuber calcis.[2127,2128,2143]

The etiology and pathogenesis of spastic paresis are unknown. Some investigators have documented the presence of subtle demyelinating lesions of the red nucleus but were unclear about the contribution of these changes to the clinical syndrome.[2132,2134] Changes observed in affected calves include nonsuppurative encephalitis and reduced concentrations of dopamine and 5-homovanillic acid in the cerebrospinal fluid.[2144] There are no histologic or biochemical alterations of the myofibrils.[2145] Neuropharmacologic studies have indicated that the disease may be related to overstimulation of the gamma motoneurons of the spinal cord.[2146] A genetic basis for the disease has been postulated because affected offspring tend to have a common paternity[2127,2130,2132]; however, breeding experiments and progeny evaluation of cattle have not demonstrated heritability. The condition has been seen in female calves only, in one case, and occurred in a single year; calves with the same parentage born in previous and subsequent years were not affected, and calves in the same environment but with different parentage were unaffected.[2139] This suggests that a conjunction of environmental and genetic factors may determine disease pathogenesis. Consequently, some authors do not recommend culling a bull merely because an offspring has developed the condition,[2147] whereas others disagree with this recommendation.[2148]

35.69.2 Treatment

Surgical techniques for correction of the spasticity include sectioning of the spinal afferents at segments L4 through L6, neurectomy of the tibial nerve rootlets supplying the medial and lateral heads of the gastrocnemius

muscle, and superficial digital flexor tenotomy proximal to the tuber calcis.[2129,2141,2149–2151] The tenotomy procedure is performed by incising proximal to the tuber calcis and transecting the superficial head of the gastrocnemius tendon completely (this tendon twists around the superficial digital flexor tendon from medial to lateral, coursing distally) and partly nicking the superficial digital flexor tendon.[2150,2152]

To perform a tibial neurectomy, an incision is made in the groove separating the heads of the biceps femoris. The tibial nerve is identified as the more caudal of the branches off the ischiatic nerve. Some surgeons have recommended a concomitant sectioning of the caudal cutaneous sural nerve.

Success rates of 82% for the neurectomy technique and 40% for the tenotomy procedure have been reported.[2149,2153] Although recurrences may be common, some authors found high rates of sustained improvement over several months with the neurectomy technique.[2149] Results are poorer when animals under 2 months of age are treated.

Despite the reported success of these procedures, these treatments are not routinely performed in most countries because of the possible heritability of the condition and the need for specialized instruments and general anesthesia. Administration of lithium gluconate (4 g/100 kg IM daily for 10 to 30 days) is reportedly efficacious when used to treat calves in the early stages of spastic paresis.[2135]

35.70 INHERITED PERIODIC SPASTICITY (CRAMPY SYNDROME; STRETCHES; BARN CRAMPS; KRAMPFIGKEIT)

Inherited periodic spasticity is seen frequently in Holstein, Ayrshire, Jersey, Brown Swiss, and Guernsey cattle of either gender.[2154] Beef cattle are rarely affected. The condition is thought to be transmitted by a single autosomal recessive factor.[2155] Affected cattle are normal until they reach 3 to 7 years of age, when they develop marked muscular spasms of the hip and upper limb.[2154] An earlier onset was reported in a Hereford bull.[2156] The disease is mild for the first 2 to 3 years but progressively worsens over time. Eventually, affected animals are culled early because of weight loss or chronic foot problems. Specific pathologic changes are absent at necropsy.[2157]

35.70.1 Clinical Signs

During the attack the leg may be held spastically in flexion, but more often it is held in rigid extension. The attacks are episodic, which differentiates them from the spasms of spastic paresis. The two diseases are otherwise similar in appearance. Each spasm is accompanied by kyphosis, which initially lasts 15 to 30 seconds and often is terminated by a fine tremor in the hindquarters or the digit. The intensity and duration of the spasms progressively increase over time. Both hindlimbs are affected. During a spasm the animal usually extends or flexes only one leg at a time. Some animals with advanced disease arch the neck and back dorsally and lift the contralateral forelimb during an attack.[2154] At first the signs appear to typify a response to a painful focus, and affected animals may be misdiagnosed as having laminitis, colic, or peritonitis. Gait and proprioceptive responses appear normal.

35.70.2 Treatment

There is no specific treatment for periodic spasticity, although mephenesin has been recommended, at a total 3-day dosage of 100 to 120 mg/kg orally. Although the pharmacologic effect of mephenesin lasts only 6 to 8

hours, severe symptoms were reportedly reduced for as long as several months after a single course of therapy.[2158] Methocarbamol also has been recommended, but reports of efficacy are anecdotal only.

35.71 DODDLER SYNDROME (HEREDITARY LETHAL SPASMS)

Doddler syndrome is a rare congenital lethal trait of Jersey cattle.[2159] The calves are down but appear bright and alert and usually are able to suckle. When stimulated, they develop severe intermittent spasms of the head and neck and convulsions. The animals can stand with assistance but are very ataxic and fall easily. They have a severe head tremor when forced to stand. The signs improve when the animal is allowed to rest but worsen again with restimulation.[2160] Calcification of multiple neurons and small vessels in the brainstem and cerebellum is observed at necropsy. The condition probably is inherited as a lethal autosomal recessive trait.

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35.72 CONGENITAL VERTEBRAL ANOMALIES (SPINA BIFIDA; BUTTERFLY VERTEBRAE; HEMIVERTEBRAE; ARNOLD-CHIARI SYNDROME)

A large number of spinal deformities have been reported in domestic livestock, including the following:

- *Spina bifida*. Failure of closure of a vertebral neural arch; spina bifida usually occurs concomitantly with one of the forms of myelodysplasia.[2161,2162]
- *Spina bifida cystica*. Spina bifida associated with a cerebrospinal fluid cyst at the site of the bony defect.
- *Hemivertebra*. A unilaterally incomplete vertebral segment; spina bifida and hemivertebrae have been described in calves, and spina bifida also has been reported in sheep and foals.[2161–2170]
- *Arnold-Chiari syndrome*. A complex disorder that occurs in lambs and calves[2171] and is characterized by a number of pathologic changes, including herniation of cerebellar tissue through the foramen magnum, caudal overgrowth and displacement of the brainstem, internal hydrocephalus, polymicrogyria of the cerebral cortex, malformation of the base of the skull, and enlargement of the foramen magnum. The strong correlation between the occurrence of spina bifida and Arnold-Chiari syndrome of calves indicates that the pathogenesis of the two conditions may be interrelated.[2161,2171]

Animals with spina bifida may be asymptomatic or may show paraparesis and paraplegia or tetraparesis and tetraplegia. If the spina bifida is associated with syringomyelia, the calves may have a peculiar “rabbit hopping” gait. The clinical signs often are present at birth or develop in the first 2 postnatal months.[2168,2172] Kyphoscoliosis and abnormalities of the rib cage may be seen at birth in some animals.[2168] The skin over the abnormal vertebrae may be smooth and hairless. When examined microscopically, this tissue resembles meninges or ependyma.[2162,2163]

Spina bifida and hemivertebrae are easily diagnosed by examination of plain radiographs. The specific site of central nervous system stenosis can be detected by performing a myelogram. The etiology of spina bifida is unknown, but some suggest that it may have either genetic[2163–2165] or toxic etiologies.[2173,2174]

Arthrogryposis occurs secondary to the spinal cord changes. Spina bifida and myelodysplasias are not the only causes of arthrogryposis, however, and clinicians should attempt to differentiate between these and other diseases that interfere in utero with motor neuron development in the spinal cord. Nongenetic arthrogrypotic conditions of

cattle include perosomus elumbis, hydranencephaly, manganese deficiency, and ingestion of lupines or *Nicotiana glauca* (40 to 60 days of gestation).[2175–2179]

(See also Chapters 51 and 52.)

35.73 MYELODYSPLASIAS (SYRINGOMYELIA; SPINAL DYSRAPHISM; HYDROMYELIA)

The following types of myelodysplasia occur in livestock[2180–2182]:

1. *Spinal dysraphism*. A general term denoting arrested development of the spinal cord before complete differentiation of gray and white matter; the areas of agenesis form longitudinal cystic structures instead of differentiated nervous tissue.
2. *Syringomyelia*. Longitudinal canalicular cavitations of the spinal cord.
3. *Hydromyelia*. Abnormal dilation of the central canal.
4. *Diastematomyelia*. Duplication of the gray matter at one or more segments.
5. *Rachischisis*. Complete failure to close the neural tube; the central canal remains open and communicates with the integument.
6. *Meningocele*. Herniation of the dura mater through a spinal column defect.
7. *Meningomyelocele*. Herniation of the meninges through a spinal column defect and a concomitant myelodysplasia.

Myelodysplasias are most often seen in Charolais calves, in which the condition is associated with palatoschisis and arthrogryposis.[2180,2183] The condition has also been recognized in 5-month-old thoroughbred foals and an Arabian foal.[2184,2185]

The neurologic deficits of myelodysplasia are difficult to differentiate from other spinal diseases unless the disorder is accompanied by spina bifida. Clinical recognition of myelodysplasia usually is based on the historical findings of paraplegia in a newborn calf without radiographic evidence of spinal fractures and with no myelographic evidence of spinal cord compression.

35.74 COYOTILLO POISONING (TULLIDORA TOXICITY, BUCKTHORN FRUIT POISONING)

Ingestion of the fruit of the coyotillo plant, *Karwinskia humboldtiana,* by domestic animals produces a stiff stilted gait, hypotonia, and hyperreflexia to areflexia.[2186,2187] The condition occurs in the southwestern United States. The neurotoxin identified in and purified from the plant is called “tullidora” toxin, after another name for the plant itself.[2188] Goats are susceptible to the effects of the intoxication. Daily doses of the fresh plant amounting to 0.04% to 0.05% of the body weight are sufficient to produce neurologic signs by 60 days. The intoxication results in a peripheral polyneuropathy characterized by degenerative changes in both axons and myelin.[2188,2189] Higher dosages may result in neuroaxonal dystrophy characterized by axonal swelling and gliosis. Experimental studies in small animals have revealed that the plant toxin exerts effects both on the Schwann cell and peripheral motor neurons, but not on sensory neurons.[2190] It induces a reversible inflammatory polyneuropathy with segmental demyelination and also decreases fast axonal transport.[2191,2192]

35.75 CYCAD PALM POISONING (*ZAMIA*PARALYSIS)

Ingestion of the palm cycad *Cycas circinalis* L., *Bowenia serrulata, Macrozamia lucida,* and *Cycas media* is associated with the development of posterior paresis in cattle and sheep.[2193–2195] The condition is seen exclusively in the tropics. The toxic principles of the cycad palm are glycosides and methylazoxymethanol (aglycone). The clinical signs include curvature of the spine, elevation of the tailhead, paraparesis, and paraplegia. The anal sphincter and tail tone are normal. Cattle develop ataxia by 50 days after feeding of the plant (3.9 kg wet weight total intake). The cerebrospinal fluid of affected cattle is normal. The pathologic lesions include demyelination, spheroids, and cavitation of the spinal cord white matter. Changes relating to hepatic disease have also been reported.[2196] These lesions included coagulative centrilobular hepatic necrosis, icterus, and petechial hemorrhages on the serous surfaces. Poisoning by *Macrozamia reidlei* can cause death from hepatic failure without signs of neurologic disease.[2197]

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35.76 ACQUIRED TORTICOLLIS

Primary acquired torticollis with or without neurologic disease occurs in all species of domestic livestock. Causes include fracture or subluxation of the cervical vertebrae, basilar skull fractures, dystrophic muscle degeneration, unilateral cicatricial muscular contracture from injections, lupinosis, traumatic rupture of the cervical muscles, hydranencephaly, asymmetric neurodegeneration, and congenital vertebral deformity.[2198–2202] Calves with torticollis have a deviated head and neck. One study hypothesized that physical constraint of late in utero development by narrow tips of uterine horns caused acquired torticollis and a variety of other deformities, such as head scoliosis and limb malformations, in more than 200 foals.[2203] Draft horses may be predisposed to this problem, which frequently results in severe dystocia in horses. Provided the spinal cord is intact, no neurologic deficits result.

Treatment of traumatic torticollis should be directed at reducing the edema, relieving pain, and immobilizing the damaged structures. Muscular tears may be treated by incorporating the head, neck, and proximal thorax in a fiberglass cast. Ancillary supportive treatment may include dexamethasone (0.04 to 0.08 mg/kg daily for 2 to 3 days), methocarbamol (8 mg/kg IV daily for 5 days), and NSAIDs (e.g., phenylbutazone PO or IV or flunixin meglumine IV for 3 to 5 days after injury). A method of surgical correction of cervical muscle contractures using a muscle-splitting procedure has been described[2204]; however, this seems unnecessary because most animals recover with only medical treatment. When torticollis is the cause of equine dystocia, delivery of the foal by cesarean section often is followed by rapid and complete anatomic and functional recovery.[2203]

35.77 TETANUS (LOCKJAW)

35.77.1 Definition and Etiology

Tetanus is characterized by muscular rigidity and death from respiratory arrest or convulsions. The disease is caused by the exotoxins produced by the anaerobic, spore-forming, gram-positive bacterium *Clostridium tetani*. Tetanus has a worldwide distribution, and all species of domestic livestock are susceptible. The bacterium is typically isolated from the bowel contents of herbivores, but fecal contamination is considered to be only partly responsible for soil contamination.[2205] The agent also can be found in dirt with no documented contact with domestic livestock. This indicates that *C. tetani* should be considered a primary soil contaminant. Tetanus

usually is a disease of individual animals; however, herd outbreaks of tetanus after tail docking or castration have been described.[2206,2207] During outbreaks of tetanus, *C. tetani* can be isolated from the feces of a large proportion of the cattle, indicating that in some cases the disease may be caused by proliferation of *C. tetani* in the patient's gastrointestinal tract.[2206,2207]

35.77.2 Clinical Signs

The incubation period of tetanus varies and depends on the size of the wound, the redox potential in the contaminated tissue, the number of bacteria inoculated, and the host's antitoxin titer. In most susceptible animals the signs occur from 2 weeks to 1 month after the bacterial inoculation. During the first 24 hours, horses may develop intractable colic, and ruminants may bloat.[2208] The first signs in some animals may be a vague stiffness and lameness of the infected limb, which are related to a local effect of the absorbed toxin (localized tetanus). By 24 hours, generalized spasticity usually is evident. Affected animals display a stiff gait and an extended head posture.[2209] The hypertonia is most evident in the antigravity muscles. Thus the limbs are held in a characteristic posture that resembles the legs of a sawhorse (sawhorse stance). The lips are retracted toward the poll, and the ears are pulled slightly down and caudal. The tail is elevated from the ischiorectal fossa. There is excessive muscle tone of all facial musculature. The jaws are clamped tightly shut (trismus), and the legs are held rigidly extended.

Muscular spasms can be elicited by auditory, ocular, or tactile stimulation. The limbs and head are very resistant to passive flexion. Retraction of the eye and a rapid flashing of the third eyelid across the cornea occurs after a menacing gesture or a slap over the neck.[2208,2210] This sign is more consistently observed in horses than in ruminants. Aspiration pneumonia may develop as a result of impaired deglutition. Severely affected animals become recumbent and lie on their side with the head and legs in full extension and the ears held almost parallel to the thoracic spinal cord (Fig. 35-40). Progression of the disease is associated with increased tonic muscular activity, which results in pyrexia in all species and profuse sweating in horses.[2207,2211] Frothy saliva accumulates at the commissures of the lips because the animals are unable to swallow, and respiratory incursions whip the mucinous saliva into a foam. The respiratory muscles (diaphragm and intercostals) are affected, and the animals develop hypoxia. Ventrolateral strabismus and dilated, fixed pupils may occur in advanced tetanus of cattle. Animals die while in a terminal convulsion. Death is attributable to hypoxemia and heart failure secondary to systemic hypertension and aspiration pneumonia. Survivors begin to show some improvement after 2 weeks, but the clinical signs may persist for as long as 1 month, and lameness may be permanent.

35.77.3 Clinical Pathology

There are no reliable clinicopathologic tests for confirmation of a diagnosis of tetanus. Attempts should be made to culture *C. tetani* from the suspected site of entry.

35.77.4 Pathophysiology

In horses, puncture wounds of the foot or the soft tissues are the most frequent sites of infection, whereas dairy cattle are infected most frequently through the uterus. Other sites for growth of *C. tetani* include lesions induced by elastrator bands, tail docking, dehorning, bull rings, or infected umbilical stalks.[2212] Proliferation of *C. tetani* in the forestomachs of normal cattle may produce sufficient concentrations of toxin to result in clinical

signs.[2213,2214] Outbreaks of tetanus have been correlated with ingestion of millet. This diet has been postulated to promote the growth of *C. tetani* in the large bowel[2215] and probably accounts for the lack of visible wounds in some animals affected with tetanus.[2206,2210]

Fig. 35-40 Characteristic appearance of tetanus in a lamb. This condition developed subsequent to application of an elastrator band to the scrotum.

When inoculated into the anaerobic site, *C. tetani* spores germinate into the vegetative form. Factors that enhance the sporulation and growth of *C. tetani* include necrotic tissue, pus, concomitant bacterial infection, and foreign bodies. Spores inoculated into the tissues are highly resistant to normal host defenses and may remain dormant for months or years before developing into the vegetative state. The production of the tetanus toxins occurs at the end of the logarithmic growth phase of the vegetative form and is governed by a plasmid-associated gene.[2216,2217] The bacterium produces at least three toxic proteins: tetanospasmin, tetanolysin, and a nonspasmogenic toxin. Tetanolysin promotes the spread of the infection by increasing the amount of local tissue necrosis.[2211]

Tetanospasmin is a lipoprotein exotoxin that diffuses from the site of production into the vascular system, where it is distributed hematogenously to the presynaptic part of the motor endplates. Once bound to the nerves, the toxin is internalized and transported to the central nervous system along the axons of the alpha motoneurons through the membrane-bound smooth endoplasmic reticulum.[2209,2218,2219] After reaching the ventral horn of

the spinal cord, the toxin crosses the synaptic cleft to presynaptic inhibitory interneurons (Renshaw cells) in the intermediate gray column.[2220] Tetanospasmin probably inhibits the release of glycine and γ-aminobutyric acid (GABA) from the Renshaw cells, resulting in disinhibition of the gamma motoneurons. The inhibition of these cells results in hypertonia and muscular spasms.

The *nonspasmogenic toxin* is thought to produce overstimulation of the sympathetic nervous system. Systemic hypertension seen in tetanus can be related to excessive catecholamine production by the adrenal medulla. Other physiologic changes identified in humans and laboratory animals include increased plasma cortisol concentrations and neuromuscular blockade. Whether these changes are caused by the effects of the toxin or these are secondary changes occurring in response to a painful and life-threatening problem is unclear. There are no characteristic postmortem lesions associated with tetanus.

35.77.4.1

Treatment

The six general medical principles for treating tetanus in large animals are as follows:

1 Provide muscular relaxation.

2 Ensure good footing.

3 Eliminate the infection.

4 Neutralize the unbound toxin.

5 Maintain hydration and nutritional status.

6 Establish active antitoxic immunity.

35.77.4.1.1

Provide Muscular Relaxation

The patient should be sedated and placed in a quiet, darkened stall. Drugs are administered that may reduce the muscular spasms. These include promazine (0.5 to 1 mg/kg IV) or acetylpromazine (0.05 to 0.1 mg/kg IV) given at 4- to 6-hour intervals. Predictable muscular relaxation may be obtained inexpensively by concomitant IV administration of acetylpromazine (0.06 mg/kg) and 5% sodium pentobarbital (2 to 4 mL/50 kg). An IV catheter may be placed to minimize treatment-associated stimulation. Mephenesin (10 to 20 mg/kg IV three times daily) and guaifenesin have also been recommended. These drugs interfere with the internuncial neurons of the spinal cord that participate in reflex muscle activities. They do not have a high therapeutic efficacy for tetanus. Diazepam (0.01 to 0.4 mg/kg IV two to eight times daily) effectively reduces muscular spasms in large animals by enhancing GABA, but prolonged administration to a large ruminant or horse is expensive because of the short duration in the plasma and CNS. In addition to its enhancement of GABA, diazepam is efficacious because of its glycine-mimetic effects.[2208] Packing the ears with cotton to minimize auditory stimulation also can help reduce muscle spasms.

35.77.4.1.2

Ensure Good Footing

Excellent footing is essential. Tetanic animals have difficulty rising because of increased spasms and muscular tone. The stall should be bedded deeply in shavings or straw to minimize decubital ulcers.

Horses and small ruminants that cannot stand should be supported in a sling, provided they do not become frantic while suspended.

35.77.4.1.3

Eliminate the Infection

Because *C. tetani* grows in nonvascularized sites, the infection is best eliminated by surgical debridement of the affected area. Concomitant infiltration of penicillin G around the wound and parenteral administration of potassium penicillin G (22,000 IU/kg three or four times daily) or procaine penicillin G (22,000 IU/kg IM twice daily) also may be beneficial.

35.77.4.1.4

Neutralize the Unbound Toxin

Before the tetanus antitoxin has bound to the nerve cells, it is susceptible to neutralization with antitoxin. Although administration of antitoxin to animals several days after the onset of clinical signs seems to have little benefit in horses, increased survival rates have been documented in human patients who have received high dosages of tetanus antitoxin in the early phase of the disease. Infiltration of the area with 3000 to 9000 IU of tetanus antitoxin may effectively neutralize toxin that has not yet reached the peripheral vasculature. Although specific dosages have not been determined for domestic animals, suggested doses range from 1000 to 5000 IU/500-kg animal to 1000 to 5000 IU/kg.[2221–2223] The limited therapeutic benefits of intravenous antitoxin must be compared to the cost of the biologic, the potential side effects of hepatic necrosis (see Chapter 33) or anaphylaxis, and the economic value of the animal.

Some claim that administration of 50 mL antitoxin (1000 IU/mL) intracysternally to horses resulted in stabilization of the clinical signs. However, this treatment did not reverse the condition.[2224] The antitoxin is administered after slow removal of 30 mL of cerebrospinal fluid (CSF). Although a survival rate of 77% has been claimed,[2224] the study failed to consider several cysternally injected horses that died of intercurrent diseases. When all cases were considered, there appeared to be no statistically significant difference between cysternally injected horses and conventionally treated controls. Complications of this procedure included iatrogenic CSF infections, anesthesia-related deaths, and sepsis from indwelling catheters. Because of severe reactions to intrathecal equine serum in ruminants, intrathecal administration of equine-origin tetanus antitoxin is contraindicated.

35.77.4.1.5

Maintain Hydration and Nutritional Status

The patient's hydration and food intake should be monitored daily. The food should be placed off the ground in an elevated feed bunk or hay net to allow easier access. Intravenous fluids should be administered as needed to correct dehydration and electrolyte abnormalities. Alimentation with a nasogastric tube may be attempted in anorectic horses, but severe adverse reactions to this procedure in some tetanus patients may limit its usefulness. A rumenostomy in anorectic cattle relieves the chronic ruminal tympany and provides a convenient means of administering oral fluids and feed.

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35.77.4.1.6

Establish Active Antitoxic Immunity

The concentration of tetanus toxin necessary to cause neurologic symptoms is less than that required to stimulate an active immunologic response. Affected animals should be immunized with tetanus toxoid at the time of treatment and given a second dose 1 to 2 months later. Concomitant injections of tetanus

antitoxin and toxoid should be made at different sites of the body and should not be admixed before administration.

35.77.4.1.7

Prognosis

The mortality rate may reach 50% in cattle and 80% in horses. The rate of progression of clinical signs is indirectly related to the prognosis. Animals that survive for longer than 7 days have a fair to good chance of complete recovery.

35.77.4.1.8

Prevention

Because cattle appear to be more resistant to tetanus than horses and small ruminants, they are not routinely immunized against the disease unless outbreaks have occurred previously. Colostral antibodies may interfere with the active immunization of neonates. One report indicates that most foals from immunized dams (82.9%) lose passively acquired specific antitoxic antibodies by 4 months of age. However, other studies suggest that passive immunity may last as long as 6 to 12 months of age. Because some animals have low titers and others have high, persistent titers, a general recommendation might include vaccination of livestock at 2, 3, and 6 months of age, followed by a booster after 1 year. To ensure protective levels of colostral antibodies, mares, does, or ewes should receive an annual booster dose of the toxoid 1 to 2 months before the anticipated date of parturition. One study indicated that tetanus prophylaxis was not cost-effective for sheep, but vaccination recommendations would differ, depending on the economic value of the animal at risk.[2225]

Acute hepatic necrosis of horses (Theiler's disease) has been associated with administration of certain lots of commercially prepared tetanus antitoxin (see Chapter 33) 1 to 3 months previously. Such findings indicate that administration of tetanus antitoxin should be limited to unvaccinated horses with tetanus-prone wounds. The recommended doses of tetanus antitoxin are 1500 IU subcutaneously (SC) or intramuscularly (IM) for adult horses or cattle[2226] and 500 IU SC or IM for sheep and goats. Tetanus toxoid should be administered concomitantly. The antitoxin and the toxoid should not be mixed in the same syringe and should be administered at different sites of the body; a second toxoid dose should be given in 1 month.[2226,2227] Previously immunized horses with tetanus-prone lesions should be given a booster dose of tetanus toxoid and should not be given antitoxin. Foals from unvaccinated dams should receive 1500 IU of tetanus antitoxin at birth.[2226]

Tetanus toxoid is effective, but not all horses develop protective immunity. Historical information citing a previous vaccination should not completely exclude the possibility of tetanus.[2228]

35.78

TRIARYL PHOSPHATE POISONING (CHRONIC ORGANOPHOSPHATE POISONING; DYING-BACK AXONOPATHY)

Ingestion of lubricants containing triaryl phosphates causes a neurologic disturbance of livestock characterized by a delayed neuropathy resulting in incoordination and paralysis. Common sources of the triaryl phosphate esters include turbojet lubricants, hydraulic oils, industrial solvents, plasticizers, and automotive brake fluid. Chronic organophosphate poisoning also occurs in some families of sheep after treatment with organophosphorus anthelmintics.[2229] At least six different phenotypes of sheep have been identified with respect to their ability to

metabolize carboxylic acid esters.[2230,2231] These are designated as Esa/a, Esa/b, and Esa/c (high-enzyme groups) and Esa/c, Esb/b, and Esc/c (low-enzyme groups). This genetically determined inability to inactivate organophosphates governs the appearance of demyelination after administration of therapeutic dosages of the drugs.

Triaryl phosphates have few effects on the glial cells,[2232] but they have profound neurotoxicity for the longest axons.[2233] These fibers degenerate first at the distal, nonterminal areas. The degenerative lesions then spread proximally from the terminal nerve rootlets into the spinal cord until the cell body dies (dying-back axonopathy). Dosages of triaryl phosphate ranging from 5 to 10 g/kg cause paralysis by 19 to 36 days after exposure.[2234] Cats may be poisoned by a single topical application of tri-*o*-cresyl phosphate ester at 1000 mg/kg or by daily application of 1 to 100 mg/kg,[2235] and massive topical exposure may cause toxicity in livestock. The poisoning may be cumulative because in some outbreaks, compounds containing as little as 0.4% tri-*o*-cresyl phosphaester have been found in toxic materials. Animals belonging to the low-enzyme groups are much more susceptible than their high-enzyme herdmates.

35.78.1 Clinical Signs

The onset of slowly progressive neurologic signs occurs about 10 days to a few months after exposure.[2236–2238] The clinical signs of chronic organophosphate intoxication are rough hair coat, bloat, dyspnea, muscular weakness, and incoordination of the rear legs. The animals may slip on their hindlimbs and assume a dog-sitting posture. The limbs are circumducted and lack normal conscious proprioceptive responses. Affected animals become recumbent, attempt to rise, but do so incompletely and fall. Muscular tone and flexor reflexes may be normal, or flaccid paralysis may be evident.[2237] The tail, bladder, and rectum often are paralyzed, and affected animals show signs of incontinence, constipation, and perineal scalding. Slight ventrolateral strabismus has been described, and some animals have been reported to become mute.[2238,2239] Most animals retain a normal appetite and sensorium during the development of the paralysis. Electromyographic changes in experimentally poisoned animals include increased insertional activity, positive sharp waves, and fibrillation potentials in the muscles of the hindlimb, consistent with denervation of affected muscles.[2240] Organophosphate-induced neuropathy also has been reported in horses, where the most striking clinical sign was bilateral laryngeal paralysis.[2241,2242] Degeneration similar to that caused by delayed organophasphate toxicity in other species was most severe in the recurrent laryngeal nerves, but milder changes were present in other peripheral nerves.

35.78.2 Pathology

Laboratory confirmation of the condition usually is based on histopathologic detection of a dying-back axonopathy in the peripheral nervous tissues. Clinical pathologic parameters usually are normal. The RBC cholinesterase is low or undetectable at clinical onset but may return to normal concentrations by the time the animals display profound paralysis. The specific concentration of cholinesterase depends largely on the type of organophosphate and the patient's genetic ability to metabolize the toxic compounds. Whole-blood cholinesterase concentrations in haloxon-treated esterase A–deficient animals remain significantly lower than in controls for at least 27 days after administration of 375 mg. In comparison, the enzyme concentrations in the plasma of normal sheep do not decrease after drug treatment.[2243] Cholinesterase levels in exposed animals are not predictive of the later onset of delayed neurotoxicity.[2238]

Macroscopic lesions are not usually seen. Microscopic lesions are found exclusively in the central nervous system, and their severity appears to be dose dependent. The lesions begin distally and progress retrograde along the long, unsynapsed proprioceptive and motor tracts. The dorsospinal, cerebellar, gracile, and cuneate tracts are most susceptible to the effects of the toxins.[2240] Specific lesions include demyelination, internodal axonal swelling, and wallerian degeneration. There also is a vacuolation of the large neurons of the ventral motor nucleus of the spinal cord. The mechanism of neurotoxicity is unknown, but alteration of a cell membrane protein found in neurons and some other cells has been implicated.[2243–2245] This protein has been designated a "neuropathy target esterase" and is thought to be "aged" by phosphorylation induced by the toxicosis.

Newer compounds in the triaryl phosphate group are less capable of causing delayed neurotoxicity, which offers some hope that the incidence of this type of toxicity may decline in the future.[2245] Delayed organophosphate toxicity is not treatable and is irreversible.

35.79 MOTOR UNIT AND CAUDA EQUINA DISEASES

MARY O. SMITH

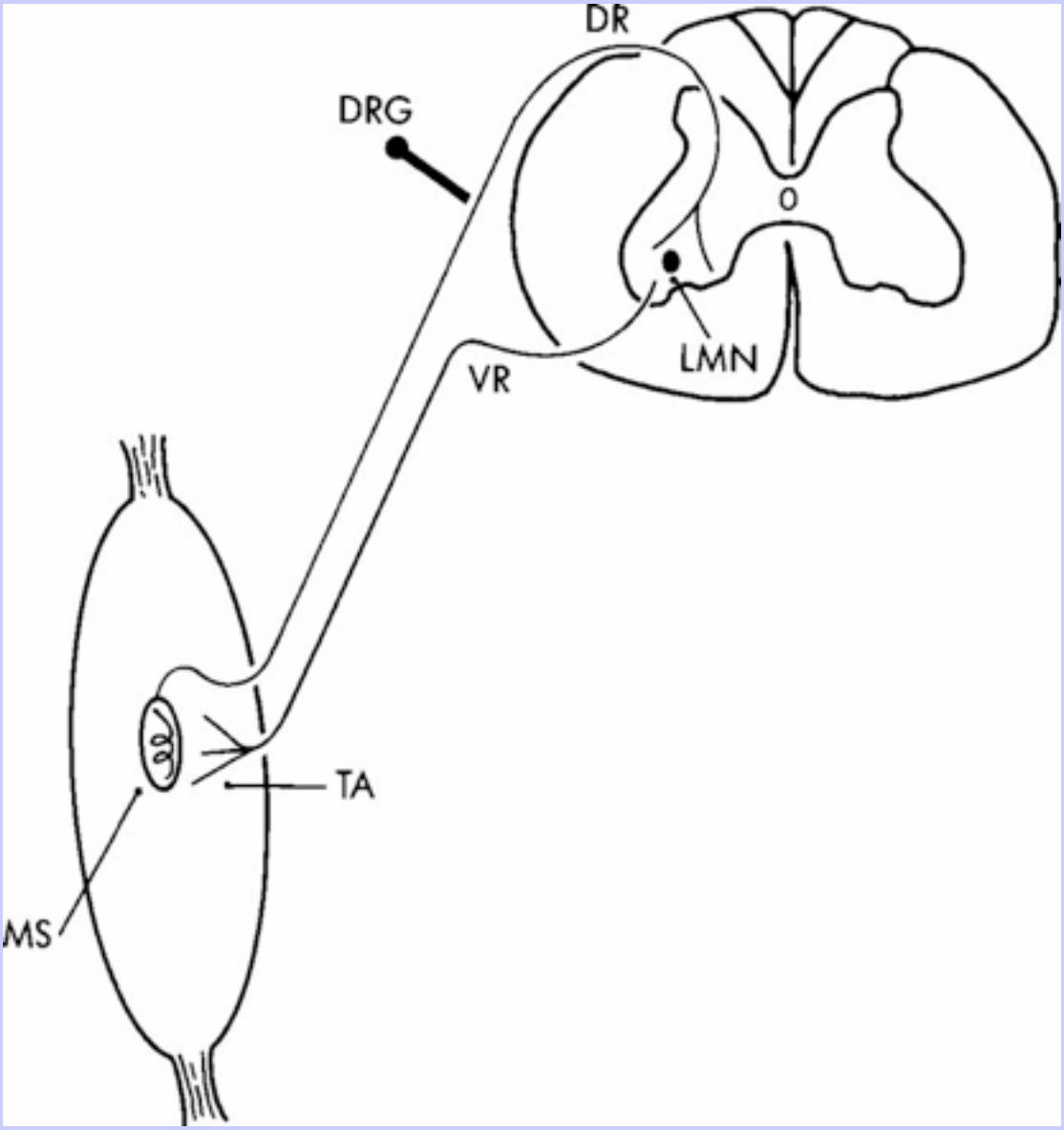
35.80 ELECTROMYOGRAPHY AND NERVE CONDUCTION TESTING IN MOTOR UNIT DISEASE

A number of electrodiagnostic techniques are now applied to the diagnosis of neurologic disease in animals. They are particularly useful when clinical signs of generalized weakness, muscle atrophy, tremors, or obscure lameness are present. Electromyography (EMG) and peripheral nerve conduction testing (NCT) are of great value for diagnosing diseases that affect the motor unit, for assessing the prognosis, and for determining the effects of therapy. EMG and NCT are simple, relatively noninvasive techniques that provide objective information on the functional status of the nerves and muscles that cannot be determined by other means.

35.80.1 Motor Unit

The motor unit is the smallest functional unit of the peripheral motor system. It comprises a single motoneuron and all the myofibers innervated by that motoneuron.[2246] In muscles in which precise control of movement is necessary, each motoneuron innervates only a few muscle fibers, whereas in large postural muscles in which fine control is not required, a single motoneuron innervates many hundreds of muscle fibers. The cell body of the alpha motoneuron lies in the ventral horn of the spinal cord or, in the case of cranial nerves, in cranial nerve nuclei in the brainstem. The myelinated axon of the motoneuron runs within the ventral root to the spinal nerve and peripheral nerves and finally terminates in small, unmyelinated terminal arborizations (Fig. 35-41). Enlargements of the ends of the terminal arborizations form the presynaptic components of the neuromuscular junctions. The postsynaptic part of the neuromuscular junction consists of a specialized region of the muscle fiber membrane. When acetylcholine release from the nerve terminal is sufficient to provoke an action potential in the myofibers, all the myofibers of the motor unit respond equally, an "all or nothing" response. Motor unit disease (lower motoneuron disease) may result from damage to any one of the following: the alpha motoneuron cell body or axon, the Schwann cells that form the myelin sheath of the alpha motoneuron, the neuromuscular junction, or the muscle fiber.

Fig. 35-41 Components of the motor unit. *DR,* Dorsal root of spinal nerve; *DRG,* dorsal root ganglion; *LMN,* lower motor neuron; *MS,* muscle spindle; *TA,* terminal arborizations of lower motor neuron axon; *VR,* ventral root of spinal nerve.



Although they are not part of the motor unit, the neurons that provide the sensory supply to the skeletal muscles may be involved in motor unit diseases in animals. Dysfunction of the peripheral sensory nerves causes clinical signs similar to those seen with motor unit disorders, even when all the components of the motor unit are normal.[2247] The cell bodies of sensory neurons lie in the dorsal root ganglia or in the sensory nuclei of cranial nerves. Their axons extend centrally to synapse with lower motoneurons and interneurons in the spinal cord and

brainstem and extend distally in peripheral nerves to the stretch receptors in the muscle spindles of skeletal muscles and to proprioceptors in joints (see Fig. 35-41).

35.80.2 Instrumentation

The recording of the electrical activity of nerve and muscle cells requires an electrode system, an amplifier, and a device to display the recording. An electrical stimulator is needed for NCT. A variety of computer-based units are now available for EMG and NCT, with a range of specifications to supply the different needs of investigators and clinicians. The components of a system may be purchased individually, but most clinicians prefer to use a complete unit. Portable units make this technology easy to use in the field, not only in hospital situations. EMG units offer a range of specializations to improve signal amplification while minimizing interference, including high- and low-frequency filters, common mode rejection (to reduce 60-Hz interference from nearby electricity sources), and signal-averaging capabilities to facilitate the recording of nerve action potentials. Data can be stored in the computer memory for later transfer to disc or other external memory and to create paper printouts. An audioamplifier is a useful addition to the system, because many of the potentials recorded by EMG produce characteristic sounds when converted to an audible signal. It is often easier for an experienced electromyographer to make a diagnosis by listening to the audio EMG than by trying to follow a series of rapidly changing potentials displayed on the cathode ray oscilloscope (CRO) screen. Programs that can analyze data (e.g., motor unit potentials) and filters that facilitate the study of periodic motion (gait) are now available.[2248–2250]

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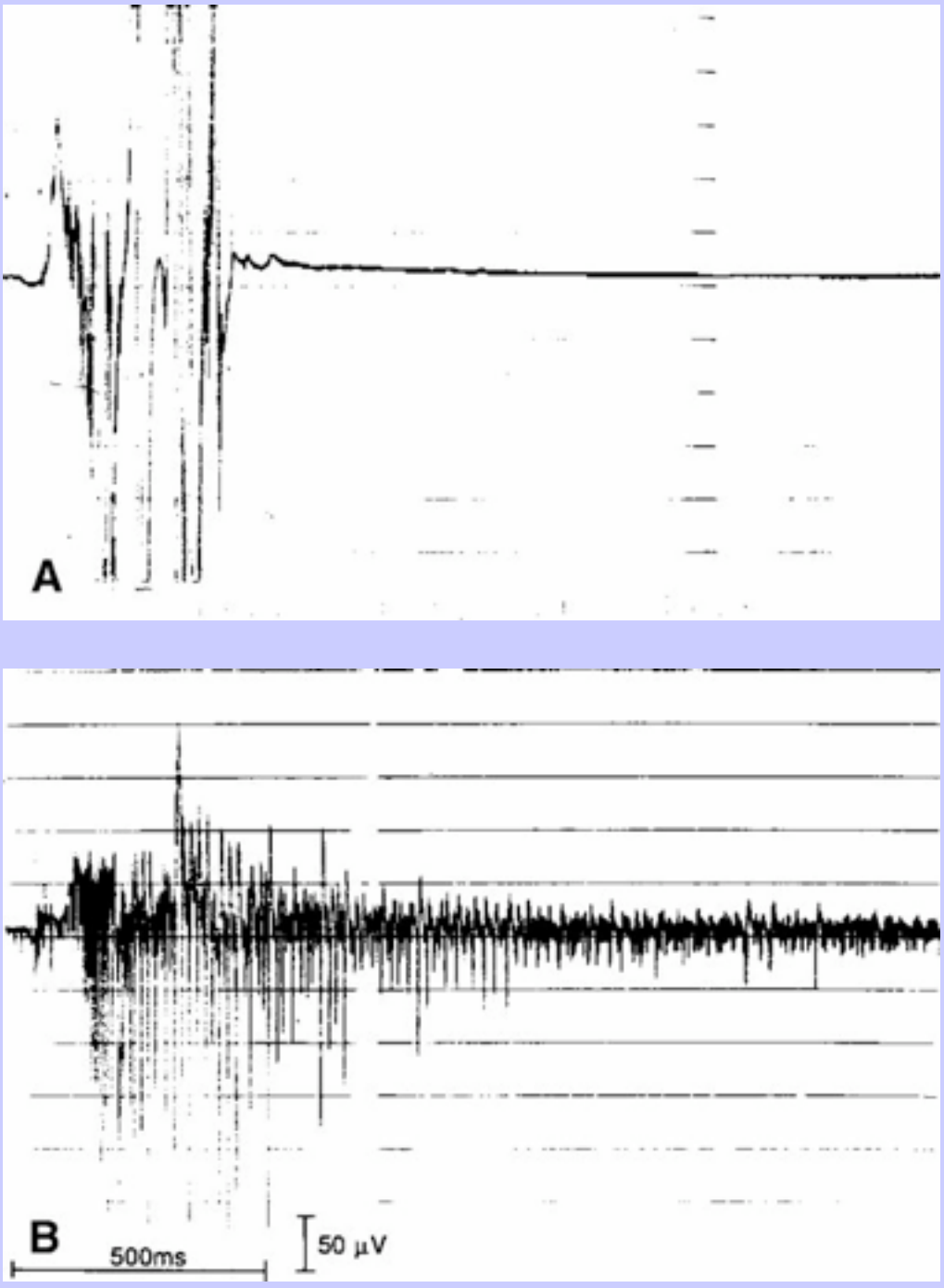
For recording, three electrodes are required: an active or exploring electrode, a reference electrode, and a ground electrode. A number of different arrangements are possible, but the coaxial needle electrode is typically used. The central wire of the coaxial electrode is the active component, and the surrounding hollow needle is the reference component. The wire is insulated from the needle along its length by a material such as Teflon, except at its tip, where it is exposed. This type of electrode is particularly suited to use in large animals because it minimizes the problem of poor electrical contact encountered with surface electrodes and does not seem to cause undue discomfort. For similar reasons, a subcutaneous needle electrode usually is chosen for the ground electrode, which is placed a short distance from the recording and reference electrodes, usually over a bony prominence. Surface electrodes can be used to study activity in muscles during exercise, both to determine the presence of disease and to direct training exercises where development of particular muscles is desired.[2251,2252]

35.80.3 Electromyography

Electromyography usually can be performed in a conscious animal, although some restraint is necessary, such as placing the animal in stocks and administering a sedative agent. General anesthesia may be necessary for EMG in extremely fractious animals, but not without significant risks, particularly when animals are weak and may have difficulty rising after anesthesia. Caudal epidural anesthesia may offer a safer alternative when examination of hindquarter muscles alone is deemed adequate for evaluation.[2253] Common sedatives such as xylazine and acepromazine do not interfere with EMG. An electromyographic examination should include testing of many muscles over the whole body, focusing on those thought to be involved in the disease process. The recording electrode must be inserted into four or five sites in each muscle tested to ensure that focal abnormalities are not missed.

Electromyography alone usually does not provide a definitive diagnosis of the disease process present. EMG does help to localize the lesion and provides information that can then be used in selecting further diagnostic modalities (e.g., NCT) and the most suitable site for muscle or nerve biopsy.

Fig. 35-42 Electromyogram insertion activity. **A,** Normal: insertion activity ends abruptly when movement of the exploring electrode stops. **B,** Abnormal: insertion activity persists after the exploring electrode is at rest.



35.80.4 Normal Muscle

35.80.4.1 INSERTION ACTIVITY

Insertion of the recording electrode into a muscle or its movement in the muscle results in a burst of electrical activity that stops abruptly when movement of the electrode stops (Fig. 35-42). It is accompanied by a harsh, crackling sound. This “insertion activity” is the result of direct stimulation of muscle fibers by the moving electrode.

35.80.4.2 ELECTRICAL SILENCE

When the electrode is motionless in a normal resting muscle (one that is not actively contracting), no electrical activity is seen on the electromyograph. The electron beam of the CRO traces a straight line, and the audio electromyograph is silent. Electrical silence is the normal state in resting muscle except in the endplate zone.

35.80.4.3 MOTOR UNIT ACTION POTENTIAL (MUAP)

An MUAP is the electrical activity of a single motor unit (Fig. 35-43). Only the activity of the fibers lying within approximately 1 mm of the electrode tip is recorded.[2254] MUAPs may be observed during EMG of normal active muscle. The parameters of an MUAP vary with the motor unit that produced it, with the type of electrode arrangement and electromyograph used, and with the position of the electrodes in relation to the electrical event itself. The important characteristics of the MUAP are the amplitude, duration, and number of phases. Normal MUAPs are biphasic or triphasic with amplitudes of 500 to 3000 μV and durations of 3 to 15 msec.[2254,2255] In very active muscles, many MUAPs are superimposed, producing “interference patterns.” This may be observed in the limb muscles of a standing animal.

35.80.4.4 MINIATURE ENDPLATE POTENTIALS (MEPPS)

The neuromuscular junctions of the myofibers of one muscle tend to lie in a band across the midpoint of the muscle fibers; this region is called the endplate zone. The spontaneous release of quanta of acetylcholine from the nerve terminal at a neuromuscular junction results in local electrical responses in the muscle fiber. This activity can be recorded when the recording electrode lies close to the neuromuscular junction in the endplate zone (Fig. 35-44). MEPPs are monophasic-negative potentials having amplitudes of 10 to 20 μV and durations of 0.5 to 1 msec.[2256] MEPPs are local electrical responses in the muscle fiber that are not propagated throughout the whole fiber and thus do not result in fiber contraction. MEPPs are present even in resting muscle and are normal. MEPPs may be absent in disorders in which acetylcholine release is lacking from the nerve (neuropathies), in those with an abnormality in transmission across the neuromuscular junction (junctionopathies), and in some myopathies. MEPPs cannot be detected when the recording electrode is not close to a neuromuscular junction.

Fig. 35-43 Motor unit action potentlals. **A,** Normal: amplitude is approximately 550 µV. **B,** Abnormal: amplitude is decreased by approximately 200 µV.

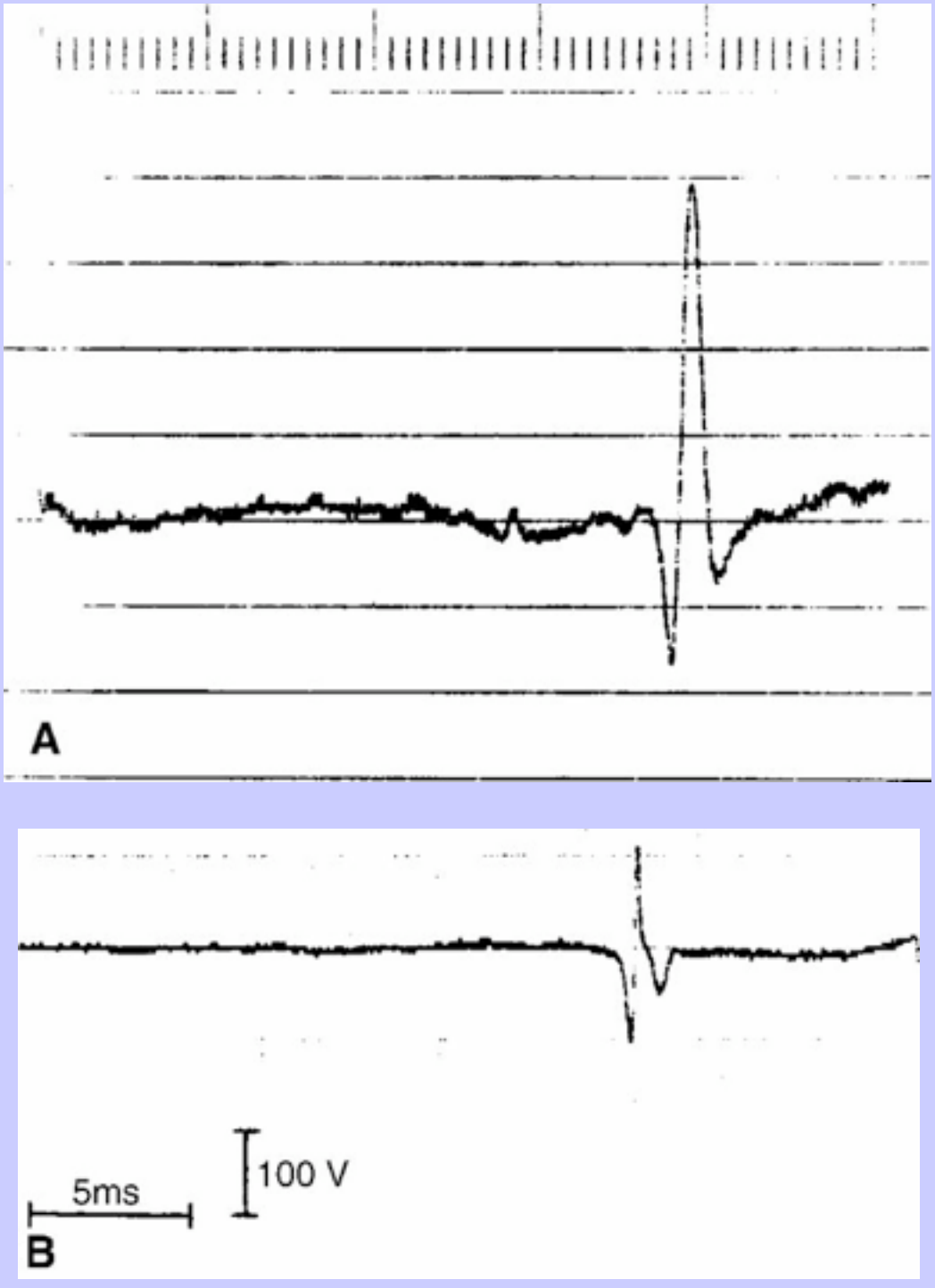


Fig. 35-44 Miniature endplate potentials (MEPPs). MEPPs are a normal electromyographic finding.

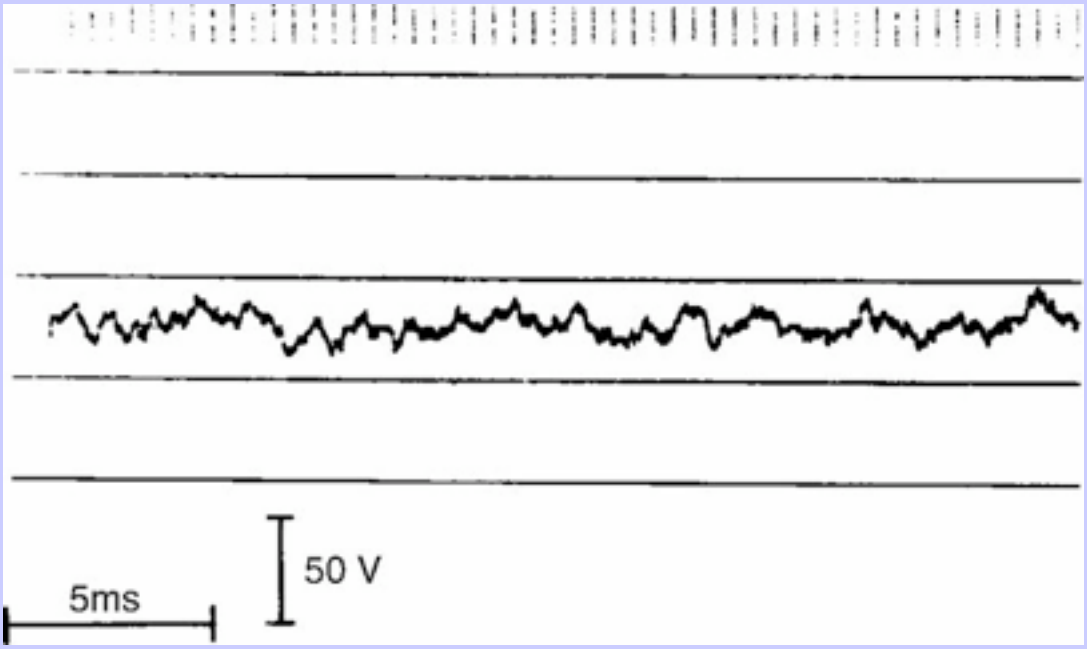
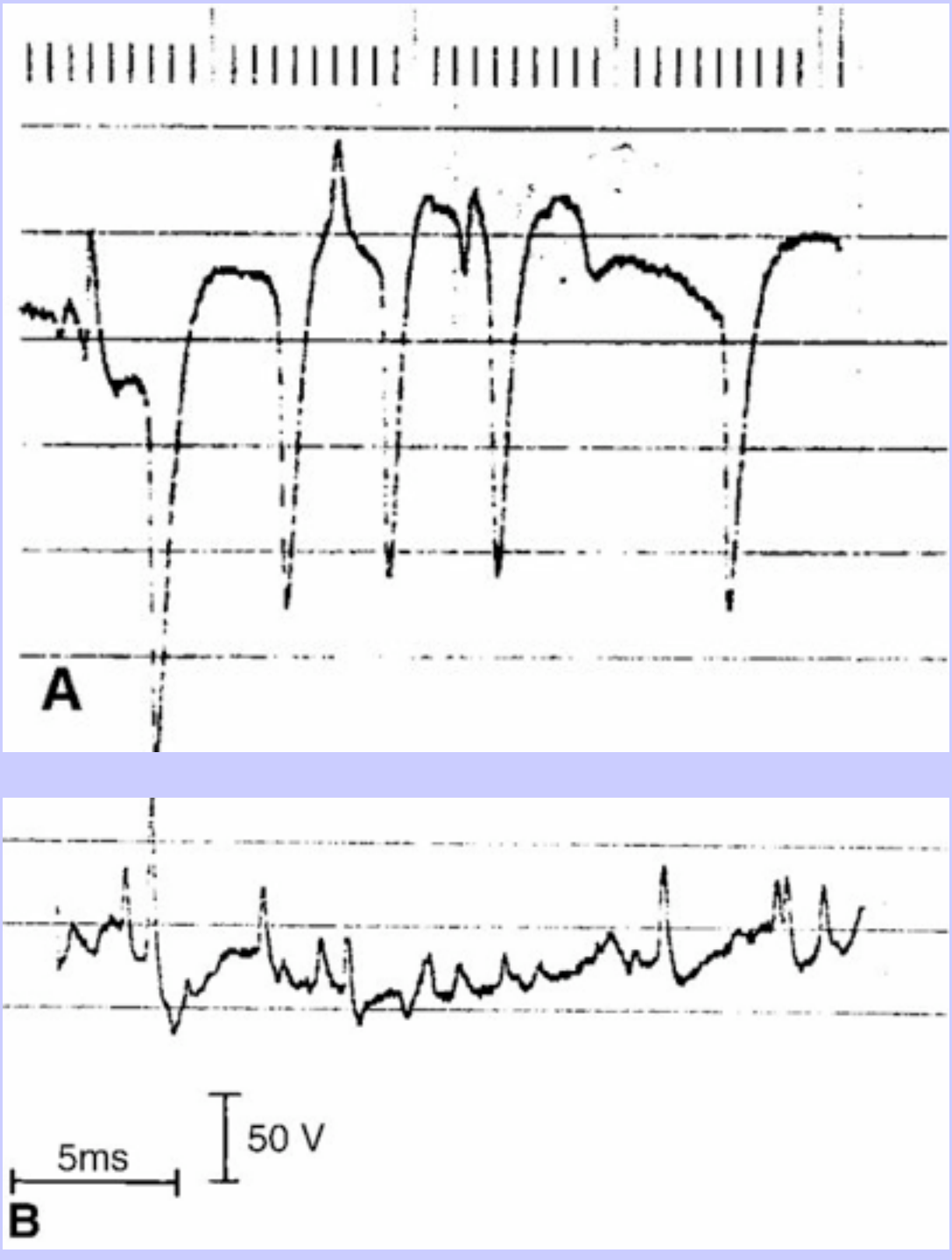


Fig. 35-45 Abnormal electromyographic potentials. **A,** Positive sharp waves. **B,** Fibrillation potentials.



Age of the patient has been shown to have an effect on EMG findings, even in animals that are clinically healthy. Insertional activity, spontaneous activity, and motor unit morphology all have been shown to differ in elderly horses (>18 years old) compared with young and adult horses, with the elderly horses displaying a greater amount of EMG activity usually considered to indicate muscle pathology.[2257] This factor must be taken into account when interpreting EMG findings.

35.80.5 Abnormal Muscle

35.80.5.1 INSERTION ACTIVITY

In both neuropathic and myopathic diseases, insertion activity may be prolonged or occasionally reduced (see Fig. 35-42). Either of these findings is evidence of abnormality. Abnormalities in EMG recordings caused by neuropathic disease do not begin to appear until approximately 5 days after the onset of the neuropathy.

35.80.5.2 MOTOR UNIT ACTION POTENTIALS

In both myopathies and neuropathies, changes in the characteristics of MUAPs occur. These include reductions in amplitude, polyphasia, temporal dispersion, and even absence of MUAPs.

After damage to some nerve fibers, others may undergo collateral sprouting, where new terminal arborizations grow and innervate denervated myofibers. The net result of this process is an increase in the size of the motor unit. The MUAPs of these large motor units have correspondingly larger amplitudes and thus are called giant MUAPs (see Fig. 35-43).

Quantitiative analysis of MUAPs adds another level of sophistication to EMG examination.[2248,2250] Characteristics of MUAPs in healthy horses include amplitude, duration, and number of phases turns within the MUAP. Changes in these characteristics are found when either myopathy or neuropathy are present.[2258]

35.80.5.3 FIBRILLATION POTENTIALS AND POSITIVE SHARP WAVES

These activities result from the electrical activity of single muscle fibers (Fig. 35-45). The muscle activity may be spontaneous or the result of mechanical stimulation of the fiber by the electrode. It is thought that the occurrence of spontaneous individual fiber contraction is a manifestation of an increase in the excitability of the muscle fiber membrane. Fibrillation potentials and positive sharp waves occur in both neuropathies and myopathies. The presence of either activity is not pathognomonic for the type of pathologic condition present.

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Fibrillation potentials are biphasic spikes with an initial positive phase. Their peak-to-peak amplitude is less than 1 mV and their duration less than 5 msec.[2256] Fibrillation potentials are recorded when the recording electrode lies a short distance from the muscle fiber whose activity is being recorded.

Positive sharp waves have an initial positive phase with amplitude of up to 1 mV and duration under 5 msec, followed by a negative phase with lower amplitude and a duration of 10 to 100 msec.[2256] They are recorded when the recording electrode tip lies close to the electrically active myofiber.

In addition to EMG changes induced by primary myopathic and neuropathic disease, electrolyte disturbances such as hypocalcemia and hypomagnesemia also have been shown to result in EMG abnormalities, both inducing spontaneous muscle activity and altering the waveform characteristics of MUAPs.[2259] Therefore, a complete history, physical examination and serum chemistry are essential for correct interpretation of EMG findings.

35.80.6 Nerve Conduction Testing

Nerve conduction studies usually require that the animal be sedated or under general anesthesia, because the procedure is somewhat painful. Routinely used sedatives and anesthetic agents do not interfere with the results of testing. Two stimulating needle electrodes, the anode and cathode, are placed on or close to the nerve to be stimulated. A short pulse of current is applied to the nerve. A compound nerve action potential (CNAP) is evoked in the nerve by the applied current and is propagated along the nerve in the same manner as a naturally occurring action potential. Either the CNAP is recorded directly from the nerve itself, or the compound muscle action potential (CMAP) evoked in the muscle innervated by that nerve is recorded. To ensure that all the nerve fibers are stimulated, the stimulus intensity is varied to determine the maximum stimulus (i.e., the current that just evokes the maximum CNAP or CMAP). A supramaximum stimulus (150% to 200% of the maximum stimulus) is applied when making recordings.[2255,2260]

35.80.6.1 MOTOR NERVE CONDUCTION (MNC)

MNC is determined by stimulating a mixed peripheral nerve such as the radial or median nerve and recording the CMAP evoked in a muscle innervated by that nerve. By recording the CMAP evoked by stimulating the nerve, only the activity of the alpha motoneurons in that nerve is evaluated. The latency between the application of the stimulus and the onset of contraction of the muscle can be broken down into three components: the time for conduction of the action potential in the nerve, the time for neuromuscular transmission, and the time for conduction of the muscle action potential from the neuromuscular junction to the vicinity of the recording electrode. By stimulating the nerve at two or more points, the latter two variables can be eliminated from the calculation and the velocity of conduction of the nerve action potential between the stimulus points determined.

35.80.6.2 SENSORY NERVE CONDUCTION (SNC)

SNC is determined by stimulating a purely sensory nerve peripherally (e.g., palmar digital nerves)[2260] and recording the CNAP from the same nerve at a more proximal point. Because the amplitude of the CNAP is relatively small, usually less than 1 mV, the technique of signal averaging is used; the responses to repeated stimuli are recorded and electrically averaged, eliminating background electrical activity that otherwise would obscure the evoked potential.

Physiologic alterations in nerve conduction must be differentiated from pathologic changes. Cooling of the nerve results in a slowing of conduction velocity.[2261] Therefore it is important to monitor limb temperature when doing NCTs to avoid erroneous interpretation of results. Heating pads and lamps can be used to maintain normal temperature. Conduction velocity of the action potential in the nerve is proportional to fiber diameter. In ponies and dogs, nerve conduction velocity is faster in the proximal portion of the nerve because of the greater diameter of the proximal regions of peripheral nerves.[2262] SNC velocity is slower in horses

than in ponies because of distal tapering of peripheral nerves.[2261] Nerve conduction velocity is slower in young and aged dogs than in mature adults.[2263] This finding is probably true for all species.

Specific techniques for peripheral nerve testing in the horse have been described, and normal values for both MNC and SNC velocities have been determined for a number of peripheral nerves.[2260,2261,2264] Nerve conduction velocity, amplitude, and waveform characteristics all provide valuable information on the functional status of the nerve. In pathologic conditions, changes in nerve function occur that depend only on the nature of the pathologic process in the nerve, not on its etiology.

35.80.6.3

SLOWING OF NERVE CONDUCTION

Reduction in the velocity of nerve conduction is the result of segmental demyelination, which may occur in sensory or motor fibers or both. Demyelination may be present as the sole pathologic change or may be accompanied by other neuropathologic processes. No pathologic significance has been attributed to increased conduction velocity; it is the result of technical error.

35.80.6.4

INCREASED TEMPORAL DISPERSION

Increased temporal dispersion of an action potential also results from segmental demyelination and differences in the rate of conduction in individual nerve fibers. For example, if some fibers are normal and some are undergoing demyelination, increased dispersion of the action potential is recorded, whether a nerve or a muscle action potential. In this case, because some nerves are normal, the nerve conduction velocity calculated will be normal.

35.80.6.5

REDUCTION IN AMPLITUDE

The amplitudes of the CNAP and the CMAP depend on the number of functional neurons stimulated. The CMAP also depends on the number of functional myofibers in the motor unit and on the functional integrity of the neuromuscular junctions. Because different complements of neurons are present in different nerves and in the same nerve in different animals, and also because the size of muscles themselves varies, it is not possible to determine absolute parameters for the amplitude of CNAP or CMAP. However, qualitative evaluations of amplitude can be made. Reduced amplitude of nerve action potentials is seen as a result of primary axonopathy (wallerian degeneration), junctionopathy (e.g., botulism), and nerve conduction block in some demyelinating diseases.[2265] Reduction in the amplitude of the CMAP also may be caused by primary muscle disease, resulting in a reduction in the number of functional myofibers.

35.80.6.6

POLYPHASIA

In cases of collateral sprouting, the resulting larger motor units are distributed more widely in the muscle. Some of the nerve terminal arborizations are longer than others; therefore the nerve action potential does not arrive at all the neuromuscular junctions at the same time. A polyphasic waveform in the CNAP results.

Electromyography and NCT are valuable aids to the diagnosis of motor unit disease in animals. Although they provide considerable information about the nature, extent, and progress of pathologic changes, they do not define the etiology of those changes. Further diagnostic procedures, such as muscle or nerve biopsy, CSF analysis, and serologic testing, are required to arrive at a specific diagnosis.

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35.81 BOTULISM (SHAKER FOALS; FORAGE POISONING)

ROBERT H. WHITLOCK

35.81.1 Definition and Etiology

Botulism spores are ubiquitous in the soil in most areas of the United States and cause isolated occurrences of botulism in humans, animals, birds, and fish.[2266] The clinical signs of botulism result from the effect of the neurotoxin, an exotoxin produced by *Clostridium botulinum,* on the myoneural junction, leading to progressive muscular weakness.[2267–2272] Seven neurotoxin types have been identified: A, B, C, D, E, F, and G.[2273,2274] In North America, horses are most often affected by type B botulism (>85% of cases) and occasionally by types A and C toxins.[2275,2276] Types A and B botulism are associated with forage or hay and do not involve an animal carcass. Type A cases have been reported in California, Utah, Idaho, Oregon, and Ohio, but almost never in the mid-Atlantic region.[2275] Type C toxin is typically associated with a decomposing carcass,[2276] feeding poultry litter,[2277] or situations where ravens or crows feed on a decomposing carcass, then transport toxin to the feed buckets or feed troughs of horses.[2277,2278]

Type D botulism occurs more frequently in South America and South Africa and has been linked to phosphorus-deficient cattle chewing bones of decaying carcasses to restore their phosphorus stores.[2279,2280] Feeding poultry litter to cattle in North America,[2281,2282] Europe, Israel,[2283–2285] and Australia[2286] has been associated with type D botulism, often in massive outbreaks.[2287–2294] More recently, type D botulism was confirmed in a group of beef cattle in Canada being fed bakery waste,[2295] then later in dairy cattle in Canada.[2296]

Recently, types C and D botulism have been reported in Switzerland horses.[2297] Type E botulism in humans[2273,2274] is typically associated with fish, but rarely reported in animals. Birds that eat fish with type E botulism have recently been reported in areas surrounding lakes Erie and Ontario.[2298] Types F and G have rarely been reported in humans.[2274]

Clinical botulism occurs by one of three routes: (1) ingestion of the preformed toxin (the most common form in cattle and adult horses), (2) ingestion of spores, leading to toxicoinfectious botulism (shaker foal syndrome), and (3) wounds contaminated with botulism spores and subsequent production and absorption of the neurotoxin. Wound botulism occurs in horses, most often in castration sites,[2299] umbilical hernia repairs (typically with hernia clamps), or deep puncture wounds that occur with injections of counterirritants.[2300] Horses are much more susceptible to botulinum toxin than cattle. If botulinum-containing forage is fed to both horses and cattle, the horses will develop clinical signs first, and usually more horses will be affected than cattle.[2301] This likely results from degradation of toxin by the rumen microbes,[2302] whereas horses have more time to absorb the toxin from the intestinal tract before the toxin reaches the colon, the site of microbial degradation.

35.81.2 Clinical Signs in Foals (“Shaker Foal Syndrome”)

The owner's chief complaint is often that the foal is found lying down more than normal. When forced to rise, it stands for a few moments, develops generalized muscle tremors (“shaker foal syndrome”), then drops to the ground, usually in lateral recumbency.[2303,2304] Some foals present with colic, whereas others present with pneumonia or respiratory distress.[2305] Closer physical examination usually reveals a well-nourished foal that is bright, alert, and has normal vital signs and normal clinical pathologic findings, which help to differentiate botulism from other diseases. Affected foals often drool milk from their mouth when suckling the mare. Decreased tongue tone is evidenced by the tongue being easier to pull from the mouth than normal and the foal slowly retracting the tongue when released.[2306] Mild mydriasis and weak eyelid tone may be detected in most foals. Progressive symmetric myasthenia, along with the absence of fever and other signs of systemic disease leading to recumbency, remains the predominant clinical sign. Constipation and ileus are consistent findings.[2307] As the disease progresses, the heart rate and respiratory rate increase, which may progress to inhalation pneumonia and terminate in respiratory failure. A small proportion of foals will stabilize at a certain level of neuromuscular weakness and then gradually recover over 10 to 14 days with intensive nursing care. Although botulism may occur at any age, the peak age of occurrence is 4 weeks, with 70% of cases occurring between 2 and 6 weeks of age.[2308]

35.81.3 Clinical Signs in Adult Horses History

Generalized muscle weakness (myasthenia) and dysphagia are typically the first clinical signs of botulism in adult horses detected by an alert horse owner. Astute individuals may detect subtle early signs of botulism, including changes in the horse's attitude (slight depression) and decreased exercise tolerance. This is especially true after a few cases of botulism have occurred on their premises.[2309] Other early signs include slowness to eat, with reduced ability to swallow hay and water. Colic may be the initial clinical sign, presumably from ileus and accumulation of gas.[2310–2313] Occasionally, the pain will be severe enough that an experienced clinician recommends general anesthesia with surgical intervention, later to determine the pain was attributable to botulism. Draft horses have reduced work capacity, leading to progressive weakness, dysphagia, and recumbency. Some owners may not seek veterinary attention until the horse is recumbent.

35.81.3.1 PHYSICAL EXAMINATION

35.81.3.1.1 Decreased Tongue Tone

Characteristic early signs of botulism include reduced tongue strength. Assessment of tongue strength is best done by keeping the jaws closed with the left arm under the jaw, then placing the hand on the top of the nasal bones. The tongue is gently retracted with the other hand through the interdental space and allowed to hang down, then slowly released. Most normal horses quickly retract the tongue into the mouth after release with one or two “tugs” or attempts to retract the tongue.[2310] The strength of the normal tongue retraction response varies significantly from horse to horse and must be considered when assessing tongue strength in a suspect horse. In more advanced stages of the disease, but before recumbency, the horse will retract the tongue very slowly, if at all (Fig. 35-46). This procedure, the “tongue stress test,” if done properly, represents one of the earliest and most sensitive clinical signs of botulism in horses.

35.81.3.1.2

Botulism Grain Test

The horse is offered 8 ounces of sweet feed in a large, flat feeding tube on the ground. The horse is timed and observed for ability to consume the feed. Most normal horses will consume an 8-oz cup of grain (sweet feed) in less than 2 minutes, often in less than 1 minute.[2313] In outbreaks of equine botulism, owners should be taught to perform the grain test and the tongue stress test to detect early signs of botulism and allow early treatment of affected horses. As the ability to retract the tongue diminishes, the time required for the horse to eat sweet feed increases. Grain mixed with some saliva often falls out of the mouth through the horse's lips while eating. This creates a row of grain in the feed tub and a ring on the horse's lip. This is very characteristic of botulism and is one of the earliest clinical signs[2313] (Fig. 35-47).

35.81.3.1.3

Dysphagia

Horses with beginning dysphagia may eat hay but have difficulty swallowing it. Inability to swallow water occurs after the loss of the ability to swallow hay. Horses seem to respond differently to the inability to drink water; many refuse to attempt to drink, whereas others immerse their muzzles under the surface of the water. Decreased tongue strength and dysphagia typically occur before onset of obvious muscle weakness. Recumbent horses with botulism are very difficult to assess with regard to swallowing ability because the struggle to stand takes priority over eating and drinking. During an outbreak of botulism in a herd of horses, if one horse is recumbent, it is always advisable to assess tongue tone on the other horses to detect early cases of botulism.

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Fig. 35-46 Horse with very weak tongue. The tongue may hang over the lips for several seconds, up to a minute or longer in severe cases. This test is not specific for botulism, but is characteristic, and with other compatible clinical signs, strongly suggests botulism.

Fig. 35-47 **A,** Abnormal “grain test,” showing sweet feed mixed with saliva falling out of the side of the mouth. **B,** Note the trail of grain on the bottom of the bucket.

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70 hrs post toxin injection.
40hrs post antitoxin injection (vaccinated).
B

35.81.3.2

OTHER SIGNS AND PROGRESSION OF DISEASE

Decreased eyelid and tail tone may be detected in affected horses; however, the variation in tail tone from horse to horse makes this assessment problematic. Moderately affected horses walk with a shuffling gait, occasionally dragging their toes, and show evidence of muscle weakness. As the disease progresses, the dysphagia becomes more complete and the myasthenia more obvious, often with muscle tremors leading to recumbency and difficulty rising. Although the rate of progression can vary and is toxin dose dependent, clinical signs of botulism are always symmetric and gradually progressive, often leading to recumbency, followed by death from respiratory paralysis or euthanasia for humane considerations.

Vital signs, including capillary refill, are normal in the early stages of the disease. Once the horse is recumbent, both the heart rate and respiratory rate increase in proportion to the intensity of the struggle to rise and severity of the disease. Borborygmal sounds are gradually diminished as affected horses eat less. In the early phases of type C botulism, the character of the respiratory effort changes; the respiratory rate does not increase, but the expiratory effort becomes more exaggerated, with a prolonged abdominal lift. This unusual respiratory effort rarely occurs with other types of botulism, which helps to differentiate type C from types A and B in horses.[2298]

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Moderate mydriasis is an early sign that persists for several days, with a sluggish pupillary response to light persisting for up to several weeks. Muscle trembling and inability to lift the head are two additional but inconsistent signs of type C botulism. The muscle trembling often starts in the triceps and extends to other large muscle groups. As the disease progresses, some horses have increased difficulty lifting their heads, and their head carriage becomes lower and lower. Massive edema of the muzzle and face may interfere with breathing, primarily in type C botulism. Supporting the head in a sling several hours at a time may result in some relief. Affected horses, when treated with botulism antitoxin, gradually regain strength to lift their heads over 7 to 14 days.[2313]

During examination of 40 horses with type C botulism in a California outbreak, dysphagia was not readily apparent or detected.[2314] The absence of dysphagia in these horses with confirmed type C botulism is unexplained. Horses in Canada,[2311] a Florida foal,[2315] and horses with experimentally induced type C botulism[2298] all had evidence of dysphagia. Some California horses that recovered from botulism had unusual prominent muscle atrophy of the supraspinatus and gluteal muscles. The atrophy was still apparent after 2 months but had healed by 5 months in four of the seven surviving horses.[2314] This previously unreported type of muscle atrophy also has not been reported since this case.

The higher the dose of botulinum toxin present at the neuromuscular junction, the more rapid is the progression of the clinical signs and the poorer the prognosis for survival. Low levels of toxin (10^3 mouse lethal dose [MLD] units) result in a more gradual onset of clinical signs, which progress over 5 to 10 days and exhibit reduced severity of signs. Mildly affected horses may only have transient dysphagia and recover with minimal treatment. Larger doses of toxin (10^8 MLD units) result in peracute, rapidly progressive illness. These horses may become recumbent within 8 to 12 hours of the first detectable signs. In herd outbreaks of equine botulism, cases may continue to develop up to 14 days after removal of the suspect feed source.

Adult recumbent horses are more difficult to manage medically than foals and therefore also have a worse prognosis for survival (<15%). Once an adult horse is recumbent as a result of botulism and unable to rise, the prognosis for recovery is poor, despite the most intensive care, including mechanical ventilation.[2300]

Some horses, however, quickly learn to adjust to their muscular weakness and do not object to being recumbent. These horses may stabilize at a certain point and gradually improve over time, but may develop massive decubital sores, even when bedded deeply with straw. Terminally ill horses paddle their legs in an intermittent struggling manner and die of respiratory distress from paralysis of the diaphragm. Euthanasia is recommended when horses are recumbent, unable to rise, and have respiratory compromise.

35.81.4 Clinical Signs in Cattle

35.81.4.1 HISTORY

Most clinical cases of botulism in cattle occur as a herd outbreak, whereas botulism in horses most frequently occurs as a single case. In cattle the veterinarian is usually called to evaluate several down cows that may have initially responded to treatment for hypocalcemia, but then relapsed.[2316] These downer cows are often not associated with recent parturition. Multiple cattle in a herd with clinical signs similar to milk fever and evidence of progressive muscular weakness typify many outbreaks of botulism in cattle. Affected cattle are anorexic and hypogalactic and may develop paraparesis, which leads to recumbency. Affected cows have decreased strength and frequency of rumen contractions and firm feces.[2317]

Further investigation of the herd outbreak usually finds a point source of botulinum toxin. Recent feeding of small grain silage such as barley, ryelage, oatlage or wheatlage stored in large plastic bags is often present 3 to 4 days before onset of clinical signs. In some outbreaks the plastic covering the forage may be damaged, allowing mold and spoilage to occur, which may lead to anaerobic conditions with botulism spores producing toxin. Ryelage and haylage stored in plastic bags or in long plastic tubes are major risk factors for botulism in cattle.[2318] Corn silage is rarely associated with botulism; however, spoiled corn silage with a pH above 5.0 has been reported as a source of botulism for cattle.[2318]

Occasionally, the incorporation of an animal carcass during the silage-making process may lead to an outbreak of botulism. Cats, dogs, and poultry carcasses are typical sources that lead to type C botulism. In one California outbreak, feed contaminated with a cat carcass was responsible for the death of more than 420 adult cattle in 1 week.[2276] Poultry litter containing decomposing chicken carcasses may also predispose cattle to either type C or D botulism.[2282,2285,2286,2319] Repeated occurrences of types C and D botulism in beef cattle have occurred in West Virginia, Arkansas, and other states where feeding poultry litter–based rations is common.[2316]

35.81.4.2 TONGUE TEST

Reduction in tongue strength has been reported as the most important clinical sign of botulism in cattle.[2320] A tongue stress test assesses three aspects of tongue muscular strength. First, insert your right hand and fingers through the interdental space while your other arm and hand keep the jaws closed. Assess the tongue muscular tone by reaching back in the mouth and putting pressure on the base of the tongue. Normally, the tongue is firm and relatively turgid. Softness and lack of tongue turgor indicate weakness. Second, grasp the tongue and pull it out the side of the mouth to test lingual strength. Normally, it not easy to grasp or pull the tongue out of a cow's mouth. Third, with the jaws held closed, slowly release the tongue from your grasp, allowing it to hang out of the side of the cow's mouth. Normally, when the tongue is pulled out of the side of

the mouth with the jaws closed, most cows quickly retract the tongue back into the mouth. If the tongue rests limply over the lip, even for a few seconds, this is very abnormal and suggests a very weak tongue.

In herds experiencing a botulism outbreak, some cattle in herds experiencing botulism will appear normal but have decreased tongue strength and reduced jaw tone; these affected cows are early in their clinical course. Rating the tongue strength of all the exposed animals allows treatment decisions regarding which cows are candidates for prophylactic treatment with botulism antitoxin. Tongue weakness is not specific for botulism, but is characteristic. Reduction in tongue strength has been considered as the most important clinical sign in cows with botulism.[2320] Rarely do cows with botulism protrude their tongue spontaneously.

If tongue strength is normal, another cause for the weakness should be considered. Decreased lingual strength may occur with listeriosis and other causes of hypoglossal nerve injury. In cases of botulism, tongue weakness is symmetric and often associated with dysphagia and progressive muscle weakness, with several animals typically involved in the same herd. During a herd outbreak of type D botulism in Ontario, the tongue test was assessed as normal, and affected cows did not have evidence of dysphagia.[2296]

35.81.4.3

JAW MOVEMENT AND MUSCLE TONE

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In addition to tongue strength, one should also assess the masseter muscle strength by lateral movement of the mandible. Masseter muscle strength is best assessed by grasping the mandible in the area of the symphysis, then moving it laterally to determine tone of the masseter muscles. In cattle with botulism, little resistance is encountered, and the jaw seems very loose compared to normal cattle. Cows with listeriosis may also have weak masseter muscles.

35.81.4.4

PUPILLARY RESPONSE AND DYSPHAGIA

Botulism-affected cattle have pupils that tend to be dilated and poorly responsive to light. The animals may drool saliva because of their inability to swallow. These cattle rarely develop severe acidosis, as may occur with listeriosis. Often, botulism-affected cattle appear to prehend hay or grass, chew, and then swallow. However, on closer examination, the affected cow continually chews the same cud for hours without swallowing. Examination of the pharynx or oral cavity may reveal evidence of chewed hay cud or a forage bolus resulting from the inability to swallow.

Drooping ears have been reported in cows with botulism,[2320] but as with tail weakness, this sign is subjective. Additionally, pricking the skin with a needle often results in no or minimal response. Botulism-affected cattle are dull, depressed, lethargic, and often become dehydrated because of the inability to swallow. They closely resemble cattle with milk fever, except with botulism, multiple cows are involved at the same time. Animals may show muscle tremors and truncal ataxia, even to the point of dribbling urine, before becoming recumbent. They remain in sternal recumbency in the initial phases and in the more advanced stages become laterally recumbent with evidence of respiratory failure.

35.81.4.5

CLINICAL COURSE

As with horses, the rate of progression of clinical signs in cattle after ingestion of toxin-contaminated forage is toxin dose dependent. Typically, cattle that absorb a moderate amount of botulinum toxin exhibit evidence of weakness 24 to 48 hours before becoming recumbent, then are unable to rise for 2 to 3 days before death.

Low toxin concentrations may not yield any clinical signs for 7 to 10 days or longer after toxin ingestion.[2316] Massive concentrations of toxin may lead to clinical signs within 12 to 24 hours of ingestion, but this is rare.

Animals with clinical evidence of botulism should have minimal physical activity. This includes not standing the animal up frequently or hauling in a truck long distance. Physical activity adversely affects the progression of clinical signs. Physically active cattle or cattle that are stimulated to walk some distance are more likely to be affected by lower doses of toxin. The physical activity results in depletion of acetylcholine reserves and may exacerbate muscle weakness, leading to recumbency within 12 to 24 hours, which results in a poorer prognosis for survival.

Most cattle that progress quickly to recumbency after botulinum toxin absorption die as a result of respiratory failure, dehydration, or other complications of recumbency. Cattle with a more gradual progression of clinical signs before becoming recumbent are often able to eat, drink, and swallow and may recover. Typically, down cattle affected with botulism that recover will be down for 5 to 10 days and then gradually regain sufficient muscular strength to rise again. In the author's experience, in a typical herd outbreak, many cattle will have subclinical signs, such as a weak tongue and decreased jaw tone, possibly mild dysphagia, and will never become recumbent. These animals should have a detectable antibody response to botulinum toxin 3 to 4 weeks after recovery from subclinical botulism.[2321–2324] The clinical course ranges from 2 to 30 days, depending on the dose of toxin absorbed and treatment provided. In cattle, 30% to 50% mortality rates are most common.

35.81.5 Other Large Animal Species

Type C botulism has been reported in bighorn sheep in California[2325] and in sheep in South Africa associated with feeding poultry litter.[2326,2327] The later report indicates the importance of sampling both the rumen and the cecal contents for botulinum toxin testing, because in this case the rumen samples were negative but the cecal contents were positive for preformed toxin.

35.81.6 Differential Diagnosis

35.81.6.1 DIAGNOSTIC RULE-OUTS FOR HORSES

Differential diagnoses for horses include any disease associated with muscular weakness and dysphagia, equine protozoal myelitis (EPM), rhinopneumonitis (spinal cord myeloencephalopathy),[2328] West Nile virus, white muscle disease, azoturia, eclampsia, guttural pouch mycosis, leukoencephalomalacia (moldy corn poisoning), eastern and western equine encephalitis, yew poisoning (*Taxus* species), rabies, white snakeroot poisoning, yellow star thistle toxicosis, hypocalcemia, organochlorine toxicosis, and pharyngeal ulceration. EPM with brainstem involvement is one of the most difficult diseases to differentiate from early botulism. However, most horses with EPM have asymmetric neurologic deficits, which rarely occur with botulism. Ionophorous antibiotics (monensin, salinomycin, narasin) may produce signs of profound muscular weakness similar to those seen in botulism, but dysphagia and the absence of increased muscle enzymes distinguish botulism. The absence of systemic signs of illness also helps the practitioner differentiate botulism from sepsis and more generalized infectious diseases.

Hyperkalemic periodic paralysis (HYPP) should be included in the diagnostic rule-out list for myasthenic quarter horses. HYPP, a dominant inheritable condition of quarter horses, is characterized by episodes of

muscular fasciculations, weakness, myotonia, and recumbency.[2329] These episodes are associated with hyperkalemia attributable to a defect in sodium channels. Electromyographic examination, plasma potassium, and demonstration of a DNA marker help confirm HYPP.[2330]

35.81.6.2 DIAGNOSTIC RULE-OUTS FOR CATTLE

Most herd outbreaks of botulism involve several cows at the same time in all stages of lactation. Hypokalemia and hypocalcemia resemble botulism but are easy to differentiate, because most cases of hypocalcemia occur in the periparturient period, and hypokalemia is most common in early lactation. Listeriosis almost always has localized cranial nerve involvement, which is not present with botulism cases. Organophosphate toxicosis results in sailosis, nervousness, and constricted pupils, not mydriasis as occurs with botulism. Spinal cord compressions, as may occur with lymphosarcoma or vertebral body abscess, are single-animal diseases and not herd problems.

35.81.7 Clinical Pathology and Diagnostic Approach

Laboratory support for a diagnosis of botulism requires one of the following: (1) demonstration of preformed toxin in the patient's serum or gastrointestinal (GI) contents or in a wound; (2) demonstration of *Clostridium botulinum* spores in the GI contents or feed materials, with compatible clinical signs; or (3) the detection of an antibody response to *C. botulinum* in patients recovering from suspected botulism. A definitive diagnosis may be obtained by demonstration of preformed toxin in plasma or GI contents, but this is rarely possible in adult horses. Preformed toxin has been identified in about 30% of GI contents of shaker foals, but rarely in adult horses. Finding botulinum spores in the intestinal or rumen contents, with clinical signs compatible with botulism, is strongly supportive of botulism because botulinum spores are rarely detectable in the rumen or GI contents of normal cattle or horses.

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Botulinum toxin is relatively stable in tissues or plasma frozen at −20° C (−4° F) for several weeks. The mouse bioassay, the most sensitive test for botulism currently available, requires a minimum of 5 mL of plasma or serum from an affected animal as early in the clinical course as possible. Detection of toxin in the serum is likely only in animals with peracute onset and rapidly progressive clinical signs (onset to death in less than 48 hours). The serum (1 mL) is injected into two ICR Swiss Webster mice. If clinical signs of botulism occur in the mice (“wasp waist”), four additional mice are injected with the suspect serum. Two of the mice receive either a monovalent or a polyvalent botulism antiserum, depending on the history, along with the test serum. If mice are protected by a specific antitoxin, the test is definitive for the presence of botulinum toxin of that type.[2329] Unfortunately, because horses are very susceptible to botulinum toxin, the level of circulating toxin in an affected horse is often below the threshold of detection of the mouse bioassay. Few reports have demonstrated preformed toxin (type B) in plasma (or serum) from an acutely affected foal or horse.[2330,2331]

A tentative diagnosis may be based on the presence of botulinum spores and toxin in feedstuffs recently consumed by animals having clinical signs compatible with botulism.[2301] Spores of *C. botulinum* type B are found in the feces of approximately 34% of adult horses (three fecal samples per horse) with clinical signs compatible with botulism. *C. botulinum* toxin and spores can be found in the feces of approximately 20% and 70%, respectively, of foals affected with botulism. Spores are rarely detected in fecal samples from normal foals or adult horses.[2310] The presence of neutralizing botulinum antibody is a recently recognized indicator of botulism in nonvaccinated animals.[2321–2324] The polymerase chain reaction (PCR) for the detection of botulinum neurotoxin gene type B was reported to be more sensitive than the mouse bioassay in a natural case

of type B botulism in Australia.[2332,2333] At present, however, this technique remains a research tool that is not readily available for routine diagnostic purposes. In the author's experience, electromyographic evaluation has not been very rewarding to confirm a diagnosis of botulism in horses.[2301]

Typically, botulism is a diagnosis by exclusion, ruling out other diseases that may result in similar clinical signs. Both hematologic and routine plasma biochemical findings in early to moderate cases of botulism show few abnormalities. Hyperglycemia is often present[2334] and expected in cases of botulism, because elevated blood glucose is expected in many life-threatening diseases of cattle. If significant abnormalities are present, a disease other than botulism should be strongly considered. The gradual progression of clinical signs over 1 to 4 days, including dysphagia, decreased tongue tone, and muscular weakness leading to recumbency, is fully compatible with botulism.

35.81.8 Pathophysiology

Botulinum toxin acts primarily presynaptically at the peripheral cholinergic neuromuscular junction by blocking the evoked release of acetylcholine.[2268] The three steps involved in the neuromuscular blockage are (1) a primary step in which toxin heavy chain binds rapidly and irreversibly to receptors on the presynaptic nerve terminal, (2) an internalization process involving receptor-mediated endocytosis of the toxin light chain, and (3) a final blocking step to prevent the release of acetylcholine from the vesicle,[2272] leading to a flaccid paralysis. Once toxin is bound at the motor endplate, improved neuromuscular function is achieved only by the regeneration of new endplates; thus the prolonged time of a week to 10 days for clinical improvement after antitoxin therapy. Each neurotoxin serotype has its own specific receptor, an endopeptidase,[2335,2336] which may explain differences in species susceptibility to different toxin types. (For more detail about the neurotransmission, see Dasgupta.[2269])

Toxicoinfectious botulism occurs in foals and was initially reported as “shaker foal syndrome.” Foals may ingest botulinum spores with their food material as “normal” contaminants. The spores then produce toxin in vivo in the GI tract, resulting in neurologic disease.[2303,2304,2315] Toxin is detectable in the feces of approximately 30% of shaker foals, but only in the acute clinical phase of the condition.[2310] Normal intestinal flora of adult horses, humans, and other animals inhibit intraintestinal growth of botulism spores, limiting the occurrence of toxicoinfectious botulism to neonates.[2337] In human infants less than 6 months of age, *C. botulinum* may colonize the GI tract, which lacks competing microbial microflora. After their ingestion, botulism spores vegetate to produce botulinum toxin, which may be detectable in the stool for several weeks.[2338]

Most cases of type B equine botulism are associated with spores in the hay and rarely with commercial grain contaminated by decomposed animal carcasses. Commercial feeds (grains) are seldom proven to be the source of botulism toxin for horses. The origin of botulism affecting only one or two horses on a farm is often not identified. When several horses are involved, the source is typically found to be the forage, as in outbreaks in California (hay cubes),[2314] Ohio (contaminated wheat fed to work horses),[2295] North Carolina (baled alfalfa hay),[2309] England (big baled hay),[2330,2339] Sweden (big bale ensilage),[2340] and Australia (oaten chaff).[2341] Silage and hay contaminated with type B botulinum toxin and spores are the typical sources of exposure for horses.[2310] Hay stored in plastic bags or tubes has become a common factor in many outbreaks of botulism in the United States and England.[2342,2343]

Conditions of low acidity (pH >4.5), low oxygen, and high water content favor spore germination and toxin production. Small-grain forage, such as ryelage, oatlage, wheatlage, and barley,[2344] frequently provides these conditions and is a major risk factor for bovine botulism. The small-grain forages have a narrow window of harvest; if harvested too early or too late, fermentation is inadequate, and the pH remains high, helping botulism spores to vegetate, producing botulinum toxin. Spoiled hay or poorly fermented silage also represents potential sources of botulism exposure for horses.[2281] Silage with high pH (>4.5) is a well-known source of botulism for horses and is not a recommended equine feed because horses are much more susceptible to botulism toxin than cattle.[2301]

35.81.9 Necropsy Findings

Typically, no obvious gross or histologic lesions are associated with botulism in most species. Myositis or aspiration pneumonia may be present in some foals and adult horses because the deglutition reflex is abnormal. Patches of edema among the cervical muscles of an adult horse suggest type C botulism because some horses are unable to lift their head when affected with this toxin type.

35.81.10 Treatment and Prognosis

Equine botulism is usually fatal unless affected animals are promptly treated with specific antitoxin.[2310] In a series of 91 foals, yearlings, and adults with presumed type B botulism, none was treated with antitoxin and only two of the foals survived.[2345] On the other hand, a recent report of 30 foals affected with botulism had a survival rate of greater than 98% when treated with antitoxin.[2346] Neutralization of circulating toxin with a specific or multivalent botulinum antiserum should be the first and immediate therapeutic objective. Every hour between initial examination and antitoxin treatment results in a poorer prognosis for survival. Only one dose of antitoxin is needed because the half-life of botulinum antitoxin of equine origin is about 12 days in normal horses. Unfortunately, the antitoxin has no effect on the toxin after binding to the cell receptor; thus the importance of immediate treatment.[2269] Once an adult horse is recumbent, the prognosis for survival is greatly reduced, with less than 15% survival. Because the prognosis for survival in recumbent horses is poor, these animals should not be treated with antitoxin, unless the owners are fully appraised of the poor prognosis, the extensive nursing care that will be required, and the huge financial costs of an attempt to save these recumbent animals.

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The recommended dose of antitoxin is 200 mL (30,000 IU) for a foal and 500 mL (70,000 IU) for an adult horse. A single dose of antitoxin should provide passive protection for more than 60 days. Horses with mild, slowly progressive disease may survive without antitoxin, as long as the patient is confined to a stall to restrict muscular activity as much as possible. Frequent attempts to force the horse to rise are also contraindicated to avoid further depletion of acetylcholine stores and exacerbation of the clinical signs. Antimicrobials may be given for specific secondary complications (e.g., aspiration pneumonia). If antimicrobials are used, those that may potentiate neuromuscular weakness should be avoided (e.g., aminoglycosides).[2347,2348] Metronidazole, often effective against anaerobic bacteria,[2349] is not effective against botulism and has predisposed laboratory animals and human patients to develop botulism.[2350] Mineral oil is often recommended as a cathartic for horses with ileus to prevent impaction colic. Parasympathomimetics (e.g., neostigmine) and 4-aminopyridine are countraindicated for the treatment of botulism in animals.[2310]

Most equine patients cannot swallow, so supportive alimentation is required. A high-quality protein slurry composed of 4 lb of alfalfa meal and up to 12 L of water should be administered twice daily by nasogastric tube using a bilge pump to support a 1000-lb horse. Hydration should be monitored by daily determinations of packed cell volume (PCV) and total plasma protein (TPP). Alfalfa meal gruel with adequate water was shown to maintain dysphagic horses for more than 2 weeks.[2313] Expensive mixtures of electrolytes and semipurified nutrients are not necessary for oral alimentation.[2351] If the horse or foal is recumbent, it should be fed in a sternal position and supported during gastric emptying. Recumbent foals are prone to developing ileus and may accumulate a large amount of fluid in their stomach, which must be relieved by nasogastric intubation. Additionally, recumbent male horses require bladder catheterization several times daily because they are unable or unwilling to urinate. If not catheterized, severe cystitis or bladder necrosis may result. Because most animals continue to attempt to eat, muzzling may be necessary to prevent aspiration of food or bedding, which can lead to aspiration pneumonia.

Foals often require intragastric feeding with either mare's milk, goat's milk, or a commercial milk replacer (Foal-Lac; Borden) through an indwelling nasogastric tube (Levin Tube, 16 Fr, 1.27 m; Davol). Additional therapy often includes histamine receptor (H_2) blockers such as ranitidine or cimetidine, along with sucralfate to help prevent gastric ulcers, which occur frequently in shaker foals.[2308] Ophthalmic lubricating ointments (Lacri-Lube; Allergan Pharmaceuticals) are often needed to prevent corneal abrasions that may result from decreased eyelid tone. Recumbent foals must be turned frequently to help prevent decubital ulcers and muscle necrosis. Parenteral antibiotics (e.g., potassium penicillin, ceftiofur sodium) are indicated to help reduce secondary infections, especially inhalation pneumonia. Approximately 50% of foals with botulism will require supplemental oxygen, and 30% will require mechanical ventilation.[2352] In foals requiring mechanical ventilation, 87.5% survived.[2352]

Recovery from botulism depends on toxin dose and the resulting severity of the clinical disease. Dysphagic horses that are able to stand will gradually regain the ability to swallow over 3 to 7 days. The more complete the dysphagia, the longer is the time required for recovery. An occasional horse will remain dysphagic for more than 2 weeks. Most adult horses are able to eat hay and swallow grain and water by 7 to 10 days after treatment with antitoxin. Return to full strength often takes more than 1 month. Very few adult horses that become recumbent and are unable to rise for 24 hours recover unless they are provided meticulous nursing care. Decubital ulcers and secondary respiratory problems are the major complications. Recumbent foals are usually able to stand after 7 to 10 days of intensive nursing care.[2308]

35.81.11 Prevention

A toxoid for *Clostridium botulinum* type B, BotVax B, is available from Neogen Corporation (Lexington, Ky). Three doses of vaccine 1 month apart are required to successfully immunize horses according to current recommendations.[2353] Alternatively, three vaccinations given at 10-day to 12-day intervals may provide protective antibody after 3 weeks, if necessary for emergency situations (e.g., outbreaks).[2354] Annual revaccination of pregnant mares 4 to 6 weeks before foaling is highly recommended. Horses from an endemic area should be revaccinated annually. The colostrum from vaccinated mares receiving boosters 6 to 8 weeks before foaling should contain adequate antibody to protect the foal for 8 to 12 weeks.[2355] Foals vaccinated with toxoid in the first few days of life should be immunoresponsive and should develop antibodies to the toxoid, even in the presence of passive antibody.[2354] Foals or weanlings given only two doses of toxoid may not be protected.

Botulism toxoid is considered highly efficacious when administered properly and is regarded as one of the safest and most effective vaccines for horses. Occurrence of clinical botulism in fully immunized horses has not been reported. No multivalent vaccine or licensed type C toxoid for horses is available in North America at this time. However, horses have been vaccinated and immunized with a type C toxoid approved for use in mink. This vaccine has been used for several years in endemic type C areas, such as southwestern United States.

35.82 POLYNEURITIS EQUI (NEURITIS OF CAUDA EQUINA; CAUDA EQUINA NEURITIS)

35.82.1 Definition and Etiology

The etiology of polyneuritis equi in horses is unknown. Inflammatory changes occur in various nerve roots, particularly those of the cauda equina and cranial nerves. All nerve roots may be affected to a greater or lesser degree, which has led to the use of the term *polyneuritis equi* as a more descriptive name for the condition than its previous name of "cauda equine neuritis."[2356–2358]

The disease usually occurs in adult horses,[2356–2361] although it has been described in a yearling filly.[2359] No breed or gender predilection has been noted.[2360]

Several hypotheses have been proposed for the cause of this disease. The lesions it causes bear some histopathologic resemblance to experimental allergic neuritis of rats, coonhound paralysis of dogs, and Guillain-Barré syndrome in humans, all of which are suspected of having an autoimmune basis.[2361,2362] Other proposed etiologies include a hypersensitivity reaction after systemic infection, aberrant migration of helminth larvae, and association with equine herpesvirus type 1 (EHV-1) and equine viral arteritis (EVA) infections.[2359,2360,2363–2365] However, conclusive evidence supporting any of these theories is lacking.

35.82.2 Clinical Signs and Differential Diagnosis

The clinical signs of polyneuritis equi reflect the involvement of the lower motoneurons and sensory neurons at the level of the nerve roots. In the initial stages of the acute form, horses show signs of hyperesthesia, particularly around the tailhead, and rub and chew at this area.[2361] Sometimes pain is apparent, and horses become apprehensive of handling.[2366] The condition can progress to hypoesthesia or anesthesia of the affected areas.[2356,2357,2363] In the chronic form a gradually progressive paresis of the tail, bladder, rectum, and anal sphincter develops, which may terminate in paralysis.

Common signs include weakness or paralysis of the tail.[2367,2368] The anus may be hypotonic or atonic and distended.[2356,2366–2369] Fecal retention or incontinence is sometimes a feature.[2356,2357,2363,2366,2370] Urinary incontinence occurs in many horses because of involvement of parasympathetic fibers in the sacral nerves and is the lower motoneuron type (i.e., bladder is atonic, distended, and easily expressed manually). In severe cases, overflow incontinence develops, and urine dribbling may cause vaginal hyperemia and scalding of the perineum in mares and scalding of the thighs in animals of either gender.[2356,2357,2363,2367–2371] Retention of urine predisposes to urinary tract infections.[2369] In males the penis may be relaxed and protruding, with decreased sensation in the perineal skin.[2356,2357,2369] Impotence resulting from incomplete erection and inability to achieve intromission was the presenting complaint in one stallion with polyneuritis equi.[2372] The preputial skin, which derives its innervation from spinal cord segments L2 to L4 through the genitofemoral

nerve, usually retains normal sensory function.[2373] When the nerve roots of the lumbosacral enlargement of the spinal cord are involved, hindlimb weakness with ataxia is seen.[2360,2361,2363,2366] Weakness and ataxia have been observed in all four limbs of some horses.[2357,2361,2367,2370] The gait may be stiff,[2366,2369] and denervation atrophy of muscles may result.[2366]

Cranial nerves can be involved. The signs depend on the individual nerves affected and the severity of the disease. The motor branch of the trigeminal nerve is reported to be most often involved, resulting in atrophy of the temporal and masseter muscles, with drooling and dysphagia.[2367,2370,2371,2374] Involvement of the facial nerve results in unilateral or bilateral facial paralysis, which can cause keratitis and corneal ulceration.[2361,2363,2367,2370,2374] Head tilt and other signs of cranial nerve dysfunction may also occur.[2357,2367,2374]

Any disorder that affects the cauda equina may cause similar signs. These include instabilities of the caudal spine caused by luxations or fractures, EHV myelitis, sorghum intoxication, and infectious diseases that involve the cauda equine, as well as some primary diseases of the lower urinary tract.[2375–2377]

35.82.3 Clinical Pathology

Cerebrospinal fluid (CSF) may have a mononuclear and neutrophilic pleocytosis, sometimes with more than 100 cells/μL.[2359] The CSF protein concentration usually is moderately to markedly increased.[2360,2370,2374] Electromyographic abnormalities occur in polyneuritis equi as a result of denervation of affected muscles. A recent study suggests that the presence of circulating antibodies to P2 myelin protein may prove to be a useful diagnostic test, but further research is required to confirm this.[2378,2379]

35.82.4 Pathophysiology

The finding that some horses with polyneuritis equi possess antibodies to P2 myelin protein supports the theory that this disease has an autoimmune etiology.[2378,2379] An initial traumatic or infectious insult might cause the release of autoantigens from nerve tissue and disrupt the blood-nerve barrier so as to permit an autoimmune reaction.[2366] Experimental inoculation of P2 protein in rats produces an antibody response and an allergic neuritis that shares some pathologic features with polyneuritis equi.[2380] However, such autoantibodies may represent an epiphenomenon and may not be central to the pathogenesis of the disease.

35.82.5 Necropsy Findings

The main lesions are in the nervous system. The cauda equina is thickened, discolored, and covered with edematous tissue and fibrous material.[2361,2371,2381] There may be adhesions of the nerve roots or the spinal cord to the meninges and the periosteum of the vertebral canal.[2356,2369] Subdural or epidural petechiation and hemorrhage are sometimes seen.[2356,2363,2366]

At the microscopic level the major finding is a granulomatous inflammation that is most intense in the extradural part of the nerve roots. On rare occasions, microabscesses are found at the center of the granulomatous lesions.[2356,2361] The epineuria, perineuria, and endoneuria are thickened and are infiltrated to varying degrees by lymphocytes, plasma cells, lymphoblasts, macrophages, giant cells, eosinophils, and in rare cases, neutrophils.[*] Intraneural inflammation, necrosis, and endoneurial thickening can obliterate nerves.

2356,2363,2366 Axonal degeneration and demyelination are present.2361 Often, myelinated axons are absent in the affected nerves. Mildly affected nerves have axonal swelling and ballooning of myelin sheaths. Nerve bundles are separated by large amounts of fibrous tissue. There is minimum to moderate evidence of nerve regeneration. 2361

Lesions can also be found in the spinal cord itself, having occurred secondary to the nerve root lesions, such as wallerian degeneration in the dorsal columns and axonal reaction in the ventral horn cells.2366 Inflammatory lesions in dorsal root ganglia and in trigeminal ganglia have been found in some horses with this disease.2367

* References 2356, 2361, 2363, 2367, 2368, 2371.

35.82.6 Treatment and Prognosis

Treatment with corticosteroids at antiinflammatory doses early in the course of the disease may be helpful. 2359,2363,2371,2382 However, no therapy has consistently been shown to be effective. Immunosuppressive drugs, such as azathioprine, may be useful in the treatment of polyneuritis equi, but their use for this disease has not been reported.2383 General supportive care should be given, including fluid therapy when necessary, and the bladder and bowels should be manually evacuated. Because of the slow progression of signs in some horses, these animals may be maintained on supportive care for a long time. Because of the severity of the clinical signs, the gradual deterioration, and the poor prognosis, euthanasia usually is the eventual choice.

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35.83 *SORGHUM* TOXICITY

35.83.1 Definition and Etiology

A syndrome of ataxia and cystitis in horses, cattle, and sheep has been linked to the feeding of *Sorghum* species.2384–2389 The underlying mechanism is probably toxic damage to the central nervous system, but the precise toxin responsible is not known. This disease does not appear to be linked to the breed, gender, or age of an animal.2385

35.83.2 Clinical Signs

The first sign observed usually is ataxia of the hindlimbs, usually followed by urinary incontinence. Affected animals have a swaying hindlimb gait and a tendency to knuckle over. Occasionally, affected horses may walk with a hopping gait, in which both hindlimbs are lifted off the ground simultaneously (Fig. 35-48). Signs in horses tend to worsen on backing, and animals may fall or even become recumbent.2385 During an outbreak of the disease in cattle, 3 of 54 affected cows became recumbent, and two of these died.2386 The perineal muscles are relaxed, and urine dribbles from a flaccid, distended bladder.2385,2386 In mares the vulva opens and closes repeatedly; in stallions and geldings the penis is relaxed and protrudes from the prepuce.2385 Paresis of the tail may be present in both horses and cattle. Loss of skin sensation over the hindquarters has been described in a cow, suggesting involvement of both sensory and motor nervous pathways.2386 Head shaking, ataxia, weakness, recumbency, opisthotonos, and death have been reported in sheep, and mortality can approach 50%. 2384

Cystitis in affected animals may be severe and occurs secondary to urine retention. Dribbling of urine onto the skin of the perineum and hindlimbs results in scalding of the skin and dermatitis. Pyelonephritis is a common sequela to chronic cystitis and may be fatal.[2385,2387] Sometimes the clinical signs may be chronic; in one outbreak, horses had been showing signs for as long as 3 years.[2385]

Abortion in mares, arthrogryposis as a congenital deformity of foals and lambs, and neurologic abnormalities in newborn lambs also have been linked to the feeding of *Sorghum* plants.[2384,2385]

35.83.3

Clinical Pathology

Diagnosis of sorghum toxicity is made by the presence of typical clinical signs in association with a history of feeding *Sorghum* plants. No specific diagnostic test is available. Cystitis and pyelonephritis are identified by typical findings on routine urinalysis, serum biochemistry, and urine culture.

Fig. 35-48 Characteristic “rabbit hopping” gait of a horse with lathyrism. This horse was believed to have eaten sweet peas (*Lathyrus* species). Horses may also simply show ataxia and paraparesis. Courtesy Dr. G.P. Carlson.

35.83.4 Pathophysiology

The precise nature of the toxic substance in *Sorghum* plants that causes this syndrome is unknown. Most *Sorghum* species are cyanogenetic plants that contain hydrocyanic acid at potentially toxic concentrations.[2389] Chronic exposure to cyanide has been suggested as the cause of the neuropathologic changes found in affected animals.[2385] Similarities in the clinical signs of this syndrome and those of neurolathyrism in humans have led to the suggestion that the toxic principle in *Sorghum* plants may be a lathyrogen-like substance.[2390]

35.83.5 Epidemiology

The cyanide content of *Sorghum* plants is increased by drought or freezing and also is higher in new shoots and wet plants.[2389,2390] In one survey of the disease in horses, most cases occurred during the wet season and involved young, growing plants.[2385] The period of grazing before the onset of signs ranges from 1 week to many months.[2385,2386]

35.83.6 Necropsy Findings

Wallerian degeneration, swelling of axons and myelin sheaths, and demyelination in a small number of nerve fibers throughout the length of the spinal cord, in the cerebellum, cerebellar peduncles, and the pons have all been described, together with the presence of phagocytic gitter cells.[2384–2386] These changes are not associated with specific tracts.[2386] Ultrastructural studies of brains and spinal cords of affected sheep have revealed that the axonal swelling (spheroids) are composed of aggregates of neurofilaments, mitochondria, vesicular bodies, and dense bodies, enclosed within a thin myelin sheath.[2384]

35.83.7 Treatment and Prognosis

Withdrawal of *Sorghum* plants from the diet of affected animals results in a gradual improvement in the clinical signs over weeks to months, although recovery may not be complete.[2384,2386] Death is a potential sequela, however, and mortality can be high in some cases.[2384] There is no specific treatment for affected animals. Supportive therapy includes antibiotics for treatment of bacterial urinary tract infections.

35.83.8 Control

Avoidance of feeding *Sorghum* plants as a predominant part of the diet or the sole diet is the only method of control. This plant has considerable feed value and should not present a major hazard when used as part of a diversified feeding regimen.

35.84 STRINGHALT (SPRINGHALT; HAHNENTRITT)

35.84.1 Definition and Etiology

Stringhalt is a disorder of unknown etiology that produces a characteristic hyperflexion of one or both hock joints in affected horses. The sporadic form usually affects a single hindlimb and is often associated with traumatic injury, although in some cases no inciting cause is identified. The epidemic form affects both hindlimbs and sometimes the forelimbs. This form also is called *bilateral stringhalt,* rather than "epidemic" stringhalt. Laryngeal paresis from involvement of the recurrent laryngeal nerves also has been described in this form of the disease. This form of stringhalt occurs often as an outbreak in groups of horses grazing poor-quality, weed-infested pastures; it is suspected to have a toxic etiology.

35.84.2 Clinical Signs

Affected horses appear normal at rest but have a characteristic involuntary hyperflexion of the tarsocrural joint when moving. The disorder may be unilateral or bilateral and can vary in severity from a slight exaggeration of normal movement to a motion wherein the rear foot strikes the belly. A grading system has been proposed, with the severity of signs classified from grade I to grade V.[2391] In grade I, mild signs are noted just as the horse begins to move; in grade V, animals are reluctant to move and have a "bunny-hopping" gait when forced to do so. The signs generally worsen on turning or backing and may also be more severe when the animal is frightened, after a period of rest, or in cold weather.[2392–2394] Knuckling of the forelimbs may occur in the epidemic form of the disease, sometimes with evidence of laryngeal weakness in the form of dyspnea or "roaring." Atrophy of muscles in the affected limbs is usually a feature of stringhalt and is most severe in distal limb muscles.

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35.84.3 Clinical Pathology

No abnormal clinical pathologic findings are associated with stringhalt. Electromyography of affected muscles reveals increased insertion activity and abnormal spontaneous activity, such as fibrillation potentials and positive sharp waves, consistent with denervation.[2395,2396] Nerve conduction velocity is slowed in the peroneal nerves of affected limbs, indicating demyelination, and improves as animals recover clinically.[2391]

35.84.4 Pathophysiology

The etiology and pathophysiology of stringhalt are unknown. The sporadic form occurs in individual animals. In some sporadic cases, a history of traumatic injury to the limb, particularly to the dorsoproximal metatarsus, precedes the development of stringhalt by several months,[2397,2398] although in other cases the cause is unknown. Explanations for the development of stringhalt after traumatic injury include tendinous adhesions and alterations in the function of nervous or muscular components of the myotactic reflex in the affected muscles.[2393,2399,2400] Outbreaks of stringhalt among horses in Australia and the United States have been associated with ingestion of certain plants, particularly *Hypochoeris radicata* (catsear), but a causal role for a plant toxin has not been proved experimentally.[2401–2403] Other related plants that have been associated with the development of stringhalt include *Taraxacum officinale* (dandelion) and *Malva parviflora* (cheeseweed mallow).[2394] Lathyrism, a toxicity caused by plants of the *Lathyrus* (flatpea) family, can cause signs similar to stringhalt (see

earlier discussion). Detailed pathologic studies of horses affected by the epidemic form of stringhalt have revealed that the lesion is a distal axonopathy in peripheral nerves that selectively affects large-diameter myelinated axons.[2402,2404] The pathologic changes are widespread and involve nerves of the forelimb and the recurrent laryngeal nerves, as well as those supplying the hindlimbs. Neurogenic myofiber atrophy is present in muscles innervated by the affected nerves, with type II fibers being more severely affected than type I fibers. Recovery in affected horses is presumed to result from axonal regeneration, a process that requires an intact neuronal cell body.[2402]

35.84.5 Epidemiology

The sporadic form of stringhalt occurs in individual animals worldwide and at any time of year. The epidemic form occurs in outbreaks in which several horses in the same location are affected; it has a seasonal incidence, being most prevalent in the late summer or early autumn after a period of very dry weather. Outbreaks have been reported in Australia (thus the alternative name for the epidemic form, “Australian stringhalt”) and in the western United States.[2405,2406]

35.84.6 Necropsy Findings

Lesions are limited to the peripheral nerves and muscles.[2402] There is a loss of large-diameter myelinated fibers in a number of peripheral nerves, especially those innervating the hindlimbs and the recurrent laryngeal nerves. The pathologic changes in the nerves include demyelination, fibrosis, and proliferation of Schwann cells. Longer nerves are more severely affected. Muscles innervated by the affected nerves show evidence of denervation atrophy, particularly of type II myofibers.

35.84.7 Treatment and Prognosis

Individual cases rarely recover spontaneously. Surgical therapy by tenotomy or tenectomy of the lateral digital extensor tendon has been the treatment of choice in sporadic cases, resulting in a guarded to favorable prognosis for recovery.[2392,2393,2407] Conservative treatment using gradually increasing exercise or intraarticular administration of corticosteroids also has been advocated for animals with a history of trauma to the affected limb.[2397,2398] One study found no apparent significant difference in outcome between horses that underwent surgery and those managed conservatively.[2397] Steroid therapy was successful in the one case reported, whereas exercise alone resulted in improvement in two of four horses but complete recovery in only one horse.[2397]

In the epidemic form, most horses recover in weeks to months without treatment.[2401] Because a toxic etiology is suspected, it is usually recommended that the horses be removed from the pasture they were grazing when they developed signs. Administration of phenytoin (10 to 15 mg/kg orally once or twice daily) resulted in clinical improvement and reduced abnormal electromyographic activity within 24 hours of starting therapy and reached full effect by 1 week.[2396,2408] Horses that did not recover spontaneously while receiving phenytoin showed reappearance of signs within a few days. Mild sedation is a possible side effect of this treatment. Other drugs reported to have variable beneficial effects include mephenesin and baclofen.[2409–2411]

35.84.8 Control

Because plant toxicity is suspected as the cause of the epidemic form of stringhalt, control is best effected by not grazing horses on weed-infested pasture and by using weed control and good pasture management where horses are being grazed. Judicious exercise regimens may be helpful in reducing the likelihood of stringhalt in horses that have sustained traumatic injuries to the dorsoproximal region of the metatarsus.[2397]

35.85 TICK PARALYSIS

35.85.1 Definition and Etiology

An ascending lower motoneuron paralysis has been described in horses, sheep, cattle, and goats in Australia, associated with infestation by the tick *Ixodes holocyclus*.[2412–2417] In the United States a similar disease occurs in dogs, humans, cattle, New World camelids, and wild animal species as a result of infestation with several *Dermacentor* species.[2418,2419] A similar problem occurs in small ruminants in Africa, where *Ixodes rubicundus* and *Rhipicephalus evertsi evertsi* are the tick species implicated.[2420]

35.85.2 Clinical Signs

Progressive generalized paresis develops over one to several days, terminating in recumbency. Death from respiratory paralysis may occur in as little as 24 hours in severe cases.[2412] Animals may be found recumbent or may be paraparetic and ataxic in the early stages of disease. When signs are mild to moderate, differential diagnoses include a variety of neurologic and nonneurologic diseases, such as rabies, colic, uterine torsion, trauma, myelopathies, myopathies, and metabolic disorders. These do not usually progress to the profound muscular flaccidity seen in tick paralysis.[2421] Reflex withdrawal from a noxious stimulus and the blink reflex both are reduced to absent, although sensory function appears normal. The major differential diagnosis for fully developed tick paralysis is botulism. Tick paralysis often is fatal when caused by *I. holocyclus,* but animals affected by *Dermacentor* species recover if the ticks are removed before the animals are moribund. Diagnosis is made on the basis of the clinical signs and finding ticks on the affected animal.

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35.85.3 Clinical Pathology

There are no pathognomonic findings in affected animals except for the presence of ticks on the patient. Electromyography in tick paralysis in dogs in North America reveals minimal spontaneous activity and lack of evoked compound muscle action potentials in response to motor nerve stimulation.[2422] Findings in large animals can be expected to be similar. Cerebrospinal fluid is normal in tick paralysis, helping to differentiate it from some, but not all, myelopathies.

35.85.4 Pathophysiology

The cause of tick paralysis is believed to be a neurotoxin in the saliva of female ticks that is inoculated into the host when the tick feeds. Nymphs and larvae also may cause the disease.[2413,2415,2416] In the case of *I. holocyclus* the toxin has been named holocyclotoxin. The toxin elaborated by *Dermacentor* species has been

less well characterized. The pathogenesis of the disease is blockage of transmission at the neuromuscular junction as a result of reduced release of acetylcholine. Mortality is common in tick paralysis caused by *I. holocyclus* despite tick removal.

35.85.5 Epidemiology

The disease occurs worldwide, associated with different tick species in different areas. In North America the region from the Pacific coastal range to the Continental Divide provides especially favorable conditions for the proliferation of *Dermacentor andersoni*.[2418] Tick paralysis in the United States and Canada occurs mainly in the Pacific Northwest and the Rocky Mountains, although the range of the tick species involved covers a much wider area.[2421] The disease tends to be seasonal in North America, with most cases occurring in the spring, when ticks are most active. Smaller animals, such as sheep and New World camelids, are more often affected than cattle, probably because they receive a larger dose of the tick neurotoxin relative to their body size.[2421] Tick factors probably influence disease severity, and genetic variation within *I. holocyclus* may play a role in toxin potency.[2423] A short-lived immunity has been demonstrated in dogs exposed to ticks. Tick paralysis is most common in the early part of the season and in younger animals, suggesting that a similar phenomenon may occur in other species.[2421] The significance of host immunity is supported further by the finding that *D. andersoni* has reduced virulence in hamsters after the ticks are prefed on cattle previously exposed to the same species of tick compared with ticks prefed on naive cattle.[2424]

35.85.6 Necropsy Findings

There are no pathognomonic findings at necropsy, although the presence of ticks should increase suspicion of this disease. Death usually results from respiratory paralysis.

35.85.7 Treatment and Prognosis

Treatment is symptomatic after removal of the ticks, which is essential. Lack of improvement suggests that ticks remain on the animal, except in cases of *I. holocyclus* infestation, where signs persist and may worsen despite removal of all ticks. Spraying or dipping affected animals facilitates tick removal. In small animals, shaving the hair coat may be necessary to ensure detection and removal of all ticks. Areas such as the axillae and groin, in particular, provide good sites of attachment for ticks. The prognosis is good in the case of *Dermacentor*-induced paralysis when tick removal and supportive care are instituted before animals are moribund. Fatalities occur frequently in the case of *Ixodes*-induced paralysis despite removal of ticks. Cooling of the patient has been suggested in treatment of *I. holocyclus* toxicity because anecdotal clinical reports suggest that patients may be more likely to survive when cool. In vitro studies revealed that binding of holocyclotoxin at the neuromuscular junction is reduced in a cooler environment.[2425] However, such an approach may increase risk of severe complications in patients that are paralysed and cannot thermoregulate. A better approach may be to avoid warming the patient excessively.

Administration of hyperimmune serum has been shown to be beneficial in the treatment and prevention of this disease in dogs and in one llama.[2417,2426] Adverse reactions such as anaphylaxis, bradycardia, and hypotension occur in a small number of dogs and cats treated with hyperimmune serum, but these can be avoided by premedication of atropine.[2427] No report of such treatment in other species was found.

35.85.8 Control

Environmental control to reduce tick populations and routine use of acaricides may decrease the incidence of tick paralysis.

35.86 EQUINE DYSAUTONOMIA (GRASS SICKNESS)

Equine dysautonomia, commonly known as grass sickness, is a disorder of unknown etiology that occurs in horses, ponies, and donkeys in Great Britain and northern Europe.[2428–2434] A disease with similar clinical signs ("mal seco") has been described in horses in Colombia.[2435] The major clinical finding is a decrease in or cessation of gut motility. The signs of grass sickness, which are mainly caused by intestinal stasis, include colic, bloat, constipation, inappetence, weight loss, and dehydration. Esophageal dysfunction may be manifested by dysphagia. Paralysis of the urinary bladder occurs in some animals, and in males the relaxed penis may protrude from the prepuce. Significant cardiac functional disturbance has been documented in horses with grass sickness.[2436] The course of the disease varies from peracute with sudden death to chronic; some animals survive for many months despite alimentary dysfunction.[2429,2430,2437] Survival and return to function has been documented in horses midly affected with the chronic form of disease when they received good nursing care.[2437–2441] Risk factors for developing the disease include younger age, male gender, and location on premises that have previously experienced the disease. Dry weather has been identified as a risk factor, but not all studies support meteorologic influences on disease occurrence.[2442] Peak incidence occurs from April to June.[2443]

Histologic examination reveals characteristic degenerative changes in peripheral autonomic ganglia, in the myenteric and submucous plexuses, cardiac ganglia, and in certain central nervous system nuclei, particularly in the medulla oblongata.[2431,2432,2436,2444,2445] A reduction in the number of interstitial cells of Cajal within the gut wall has been demonstrated; these cells are believed to have a "pacemaker" activity, and their depletion may be central to the clinical manifestations of equine dysautonomia.[2446] Furthermore, electrical activity in the gut is decreased in grass sickness, possibly including that of the interstitial cells of Cajal.[2447] Studies of animals that recovered from the disease indicate that the histopathologic changes may be reversible.[2439] Some degree of esophageal dysfunction occurs in all horses with grass sickness.[2434] The histopathology of autonomic ganglia in horses that showed complete clinical recovery from grass sickness was virtually normal, with normal morphology in all four horses studied and normal cells numbers in three of the four horses.[2444]

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Diagnosis rests mainly on clinical presentation; there are no definitive clinicopathologic abnormalities in grass sickness.[2448,2449] A small study demonstrated that the presence of chromatolytic neurons in rectal biopsies might be a useful adjunctive test for diagnosis.[2450]

Evidence for pathology not related to the gastrointestinal (GI) tract was found in a study of motor nerves and skeletal muscle in horses with grass sickness. The investigators found electromyographic evidence of a subtle peripheral neuropathy, which was further supported by mild pathologic changes in both muscle and nerve at necropsy.[2451]

There is mounting evidence for an association between equine dysautonomia and *Clostridium perfringens* type C neurotoxin.[2429,2452–2454] The presence of a neurotoxic factor in the plasma of affected horses was suggested by induction of typical neuropathologic lesions in ponies by intraperitoneal inoculation of plasma and serum from

horses with acute disease. Clinical illness was not observed in the ponies.[2455] Circulating antibodies to *C. perfringens* type C endotoxin have been positively associated with the development of grass sickness.[2456] Growth of the organism in the GI tract (toxicoinfection) is hypothesized to be the source of the botulinum toxin. On the other hand, horses with grass sickness have lower circulating levels of antibodies directed against the surface antigens of clostridia, suggesting that these may have a protective effect against the disease.[2457] This finding also raises the possibility of a vaccine against grass sickness. The number of bacteria, including clostridial species, is significantly increased in the intestines of horses with grass sickness, posing the question as to whether change in GI flora is a cause or a consequence of the disease.[2458]

Treatment of equine dysautonomia is supportive and includes supplementary feeding and fluid therapy. The indirect-acting cholinergic cisapride (0.5 to 0.8 mg/kg orally every 8 hours for 1 week) facilitates release of acetylcholine from the myenteric plexus and increases gut motility in chronic grass sickness. Colic signs may increase shortly after administration of this drug.[2459] Many affected animals die, but recovery has been reported in some chronic cases, as well as in 50% to 70% of chronically affected horses that receive appropriate treatment.[2431] Analgesia with intravenous flunixin meglumine or intravenous or oral phenylbutazone is appropriate in some cases, and diazepam (0.05 mg/kg every 2 hours) may be helpful as an appetite stimulant. Factors associated with a better prognosis include willingness to eat concentrates and milder signs of dysphagia.[2460]

35.87 PERIPHERAL NERVE DISORDERS

LISLE W. GEORGE

Most peripheral nerve disorders of large animals are traumatically induced, but injections, abscesses, tumors, and parasitic invasion of the nerves may occur in rare cases. The following section discusses the peripheral nerves most often damaged in large animals.

35.88 PERIPHERAL NERVES

35.88.1 Suprascapular Nerve

Mechanical damage to the suprascapular nerve results in paralysis of the infraspinatus and supraspinatus muscles.[2461] Early denervation is characterized by a slight outward bowing of the scapulohumeral joint as weight is placed on the limb. Neurogenic atrophy develops after several months, and the scapular spine becomes prominent (Fig. 35-49). The common name for this condition is “Sweeney.”

35.88.2 Brachial Plexus

Damage to the brachial plexus may result in any combination of dysfunction of the biceps and coracobrachialis muscles (musculocutaneous nerve), as well as the pectoral, subscapularis, and triceps muscles.

Lesions of the brachial plexus are caused by trauma to the shoulder, deep penetrating axillary wounds, or traction on the forelimbs of a fetus during relief of a dystocia. Because of their tendency to rear and jump over objects, horses are most susceptible to brachial plexus injuries. The condition may occur in small ruminants after automobile accidents, carnivore attacks, or blows from larger animals.

35.88.2.1

MOTOR DEFICITS

Severe lesions of the brachial plexus result in complete flaccidity of the forelimb. The animals are unable to bear weight. Triceps reflexes are absent. Loss of pectoral nerve function results in abduction of the elbow. Subscapular muscle paralysis results in dropped shoulder.[2462] Musculocutaneous nerve paralysis results in a hyperextension of the elbow at rest and an inability to flex the joint. There is loss of the biceps reflex. The clinical signs of radial nerve paralysis are described next.

35.88.2.2

SENSORY DEFICITS

Avulsions of the brachial plexus result in complete desensitization of the entire forelimb.

Fig. 35-49 "Sweeney" (neurogenic atrophy) of the left supraspinatus and infraspinatus muscles in a Charolais bull. The lesion was caused by trauma related to running through a cattle chute.

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35.88.3 Radial Nerve

The radial nerve is motor to the extensor muscles of the forelimbs. The nerve courses over the lateral aspect of the elbow joint and is vulnerable to traumatic insult at that point. Radial nerve paralysis most often arises from direct trauma to the nerve, during prolonged anesthesia, or during restraint in lateral recumbency with inadequate padding of the forelimb.[2463,2464] Degeneration of the triceps muscles also plays a significant role in many cases of radial nerve paralysis.[2463]

The limb position varies, depending on the location of the lesion in the radial nerve. Lesions at or near the elbow joint result in high radial nerve paralysis, characterized by a dropped elbow, failure of limb protraction with scuffing of the toe, and flexion of all distal limb joints (Fig. 35-50). The foot is knuckled over at rest, and the animal is unable to bear weight on the leg. Lesions of the distal radial nerve result in knuckling of the carpus, fetlock, and pastern joints. The animal can support weight on the affected limb if the metacarpus and distal limb are held in extension. The triceps reflex is depressed to absent. Chronic dysfunction of the radial nerve results in neurogenic atrophy of the extensor muscles of the forelimb. Detectable sensory deficits resulting from radial nerve paralysis tend to be vague and probably vary from patient to patient.

35.88.3.1 “KANGAROO GAIT” IN SHEEP

A bilateral forelimb locomotor disorder of pregnant and lactating female sheep has been reported in Scotland and northern England.[2465] The problem appears to be a bilateral radial paresis and is strongly associated with pregnancy and lactation.[2466] Sheep recover after weaning their lambs or even while still lactating. Sheep kept in lowland areas are more frequently affected than those in hilly areas, although it is unclear whether this results from environmental factors or differing susceptibilities inherent to the different breeds of sheep kept in these areas. Most sheep affected are outdoors grazing, and sheep that are housed, even for part of the day, are less likely to be affected. “Kangaroo gait” occurs most often in the late winter and early spring, when the greatest numbers of sheep are in late pregnancy and early lactation. There is no specific treatment, and most animals recover uneventfully, although signs may recur at later pregnancies. The most common differential diagnosis is lameness caused by the numerous orthopedic conditions of sheep.

Fig. 35-50 High radial nerve paralysis in a horse showing knuckling of the carpus and digit and dropped elbow. Courtesy Dr. R.H. Whitlock.

35.88.4 Femoral Nerve

The femoral nerve is distributed to the quadriceps femoris muscles and the skin of the rear limb extending from the medial thigh to the medial part of the coronet (saphenous nerve). Traumatic overextension of the hip and stifle joint from a fall or other injury or forced posterior delivery can damage the femoral nerve. The clinical signs of femoral nerve paralysis are related to an inability to extend and fix the stifle.[2461] The reciprocal apparatus is unable to fix the hock, resulting in collapse of the limb during weight bearing and constant flexion of all distal digital joints. Chronic lesions of the femoral nerve result in atrophy of the quadriceps femoris muscles and the muscles of the posterior part of the gluteals. The patellar reflex is absent or depressed, and the patella often is displaced laterally. There is analgesia to anesthesia of the medial part of the rear limb extending from the proximal thigh to the medial malleolus of the tibia.

35.88.5 Sciatic Nerve

The sciatic nerve innervates the extensor muscles of the hip, the flexor muscles of the stifle, and most of the muscles of the distal limb.

Sciatic nerve paralysis occurs most often in postpartum cows after forced fetal extraction. Loss of function of the lumbar branches of the nerve most likely plays a major role in the so-called calving or obturator paralysis syndrome.[2467] Injection of irritating drugs into the space between the greater trochanter and the ischial tuberosity may cause a sciatic neuritis. This occurs most frequently in neonates but can occur rarely in adult cattle and small ruminants. Other causes of sciatic nerve damage are pelvic fractures, tumors, or abscesses located along the course of the nerve.

The sciatic nerve innervates most of the musculature of the rear limb, so the motor deficits associated with denervation are profound. At rest the limb is hanging behind the animal. The stifle is dropped and extended (Fig. 35-51). The foot is constantly knuckled. If the limb is positioned properly, the animal usually can bear weight for a limited period because of the normal function of the quadriceps muscles and the action of the reciprocal apparatus. Chronic denervation of the sciatic nerve results in neurogenic atrophy of the caudal thigh muscles and all of the muscles distal to the stifle.

Fig. 35-51 Characteristic posture of a cow with partial sciatic nerve paralysis. The condition pictured here was induced during correction of a severe dystocia. Note the flexion of the hocks, fetlocks, and stifle. These signs differentiate the condition from peroneal paralysis. Courtesy Dr. R.H. Whitlock.

The sciatic nerve divides into the tibial and the peroneal nerves in the distal limb. Therefore, except for the medial part of the thigh and rear limb, there is analgesia and anesthesia of the entire limb distal to the stifle.

35.88.6 Peroneal Nerve

The peroneal branch of the sciatic nerve is distributed to the flexor muscles of the hock joint and the extensor muscles of the digit. The nerve becomes superficial and is exposed to damage as it crosses over the lateral condyle of the fibula.[2468] The condition is typically seen in all species of large animals and is common in postpartum dairy cattle that have been recumbent as a result of hypocalcemia or other causes and in horses because of postanesthetic myopathy. Neurologic deficits of the peroneal nerve result in a hyperextended hock joint and flexion of the fetlock and pastern[2461,2468,2469] (Fig. 35-52). Many cows knuckle at the fetlock even when the foot is flat on the ground, and others may be able to bear weight only when the limb is manually placed in the proper position.

There is desensitization of the skin over the craniolateral aspect of the limb extending from the stifle to the hoof.

35.88.7 Tibial Nerve

The tibial nerve supplies the extensor muscles of the hock joint (gastrocnemius) and the digital flexors.

Tibial paralysis is most often observed in periparturient cattle or neonates that have been given an injection of an irritant drug in the caudal leg at the level of the stifle. Tibial paralysis also is seen in sheep and goats and is a common sequela to dog-bite injuries. With tibial paralysis, the hock is overflexed and is pulled higher than normal when the limb is protracted. The toe does not drag on the ground, and the limb is dropped suddenly perpendicular to the ground at the end of the stride. At rest the pelvis is asymmetric, with the affected side held lower than normal.[2461] Chronic loss of tibial nerve function results in atrophy of the gastrocnemius and digital flexor muscles. There is anesthesia to analgesia of the skin of the caudomedial aspect of the leg.

Fig. 35-52 Calf with peroneal nerve paralysis. Note the flexed fetlock and digit and the hyperextended carpus. This condition was caused by injection of antibiotics into the peroneal nerve on the caudolateral aspect of the leg. Courtesy Dr. R.H. Whitlock.

35.88.8 Obturator Nerve

The obturator nerve supplies motor impulses to the adductor muscles. The nerve is well protected in the equine and small ruminants, and therefore damage is rare in these species. The cow has a shallow acetabulum and a poorly developed round ligament. Consequently, the condition is often seen in peripartum cows. Reports of obturator nerve paralysis of cattle accompanied by knuckling and inability to support weight on the rear limbs probably represent a combination of sciatic and obturator nerve deficits. Coxofemoral luxation is a common complication of obturator paralysis in cattle housed in stalls with slippery flooring. Such luxation can be recognized by the identification of crepitus during passive manipulation of the hip joint. There may be a difference in the length of the rear limbs.

Obturator nerve paralysis is most common in cattle and is almost always a result of dystocia. The nerve injury is located in the pelvis at the level of the obturator foramen. Of all dystocias, 9.2% result in paraplegia.[2470]

The obturator nerve innervates the adductor, pectineus, and gracilis muscles. Only minimum deficits are observed if the cow is placed on a surface that has good traction. Clinical signs of an obturator nerve deficit include a hopping gait when the animal attempts to run and severe abduction or splay-leggedness when the animal is placed on a slippery surface (Fig. 35-53). In severe cases the cow may be sternally recumbent with the rear limbs extending laterally to each side. Experimental studies have indicated that the so-called calving paralysis syndrome is actually a result of a combination of lesions of the lumbar root (L6) of the sciatic nerve and the obturator nerve. Experimental sectioning of the obturator nerve alone does not produce paralysis, provided the animal has a nonslip footing.[2461,2467,2471] Obturator nerve paralysis does not result in a cutaneous sensory deficit.

Fig. 35-53 Cow with obturator nerve paralysis caused by relief of a difficult dystocia. Note the base-wide stance, yet the apparent ease with which the cow is able to stand on the deep bedding. Note also that rope hobbles are being applied to prevent further abduction and possible luxation of the coxofemoral joint.

Damage of one or more peripheral nerves during parturition or milk fever may play a large role in the so-called downer cow syndrome (see later discussion).[2472,2473] The incidence of the condition ranges from 4% to 28% of all cases of milk fever and is associated with a mortality rate ranging from 20% to 67%.[2474–2477]

35.89 PERIPHERAL FACIAL NERVE PARALYSIS

The facial nerve becomes superficial as it courses across the lateral aspect of the mandibular ramus and the masseter muscle. It is most susceptible to blunt trauma or laceration at that site. Horses are most often injured from prolonged recumbency or from trauma caused by a poorly designed halter. Halters with large brass rings in the caudodorsal aspect of the cheek pouch are most likely to result in iatrogenic facial palsy. Similar conditions occur in goats and are caused by excessive pull on neck chains while the animal is being led onto the milk stand or tied with the neck chain. In cattle, facial nerve deficits usually are the result of space-occupying masses at the caudal aspect of the mandibular ramus.

Most animals with facial nerve paralysis caused by trauma recover after 1 to 10 days of treatment, but some animals may require several months before resolution is observed. Occasionally the nerve deficits are permanent. In chronic cases, food should be removed from the cheek pouches twice daily, and the tongue and fauces should be routinely examined for ulcers. If present, oral ulcers should be treated by flushing the mouth.

35.90 TREATMENT OF PERIPHERAL NERVE DISEASES

Medical management of peripheral nerve injuries consists of reducing inflammation in the nerves, relieving musculoskeletal pain, preventing secondary medical complications (e.g., mastitis, fractures, joint/ligament tears), and preventing malnutrition and dehydration. Medical treatment for reduction of neurologic inflammation should be instituted as soon as possible after the injury.[2472] Dexamethasone (0.05 mg/kg IV daily for the first 3 to 5 days after injury) may be beneficial. Plasma concentrations of calcium, magnesium, and potassium should be measured repeatedly, because low levels of these electrolytes may aggravate the muscular weakness, increase the animal's struggling, and enhance the severity of the musculoskeletal lesions. Calcium gluconate can be given empirically to down cows (500 mL SC daily), as may potassium chloride (100 g in 20 L of water given daily by stomach tube). Concomitant administration of phenylbutazone by intravenous injection and application of cold water or ice packs to the affected part also may be beneficial during the first 24 hours after injury. Appendicular pain may be controlled by administration of nonsteroidal antiinflammatory drugs (e.g., banamine, phenylbutazone, or salicylic acid) and/or narcotic analgesics, including Demerol (1 to 2 mg/kg IV) or morphine (0.07 to 0.14 mg/kg IV).

Affected patients should be placed in a dry soil stall that has been deeply bedded. Concrete-floored stalls should be avoided because the poor footing may promote an accidental fall that worsens the musculoskeletal lesions. Recumbent animals should be turned six to eight times daily to prevent decubital ulcers and pressure myopathy. Support of some patients in slings may be useful for minimizing decubitus and maintaining strength in the opposite limbs. Goats tolerate dog slings well, but care must be used when lifting cattle in a hip sling because the device may cause severe contusions of the muscles at the point or attachment to the tuber coxae. The hip sling should not be used repeatedly to support cattle that fail to support weight when lifted. Abduction of the rear limbs may be prevented in cattle by application of a hobble around the metatarsus. The distance between the legs should be approximately 35.6 to 50.8 cm (14 to 20 inches) when the legs are tied together and held abducted. It is important to apply the hobbles with a nontightening bowline knot to prevent strangulation of the foot.

The prognosis is poor for animals with neurologic dysfunctions lasting longer than 2 weeks.

35.91 DOWN COWS (ALERT DOWNERS)

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Down cows, downer cows, or downers are cattle that are recumbent and cannot stand; those that can maintain sternal recumbency while continuing to eat and drink are classified as “alert downers.” Common underlying causes of recumbency in cattle include mastitis (especially coliform mastitis), metritis, musculoskeletal disease (primary musculoskeletal injuries, including fractures and torn muscles/tendons), neuropathies secondary to pelvic trauma (calving paralysis or “obturator” paralysis), spinal cord compression (secondary to lymphosarcoma), and metabolic disease (hypocalcemia, hypokalemia, hypophosphatemia, hypomagnesemia).[2478] Following the initial episode of recumbency, secondary muscle and nerve injury caused by extended periods of recumbency on a firm surface may further exacerbate the recumbency. Heavy cattle down on concrete are particularly susceptible to pressure ischemia of the muscles and nerves and to muscle and ligament tearing secondarily to repeated struggling and slipping. The severity of pressure damage depends on regional anatomic factors and the duration of compression.

Identifying underlying causes for recumbency in downer cattle represents a diagnostic challenge for the practitioner. Assessing prognosis and determining reversibility of the underlying condition are necessary for practitioners to assist producers in making treatment decisions, as well as to conform to laws and abide by ethical norms surrounding humane handling of down animals. The American Veterinary Medical Association (AVMA) Position Statement on Disabled Livestock indicates that nonambulatory animals on the farm are not to be dragged; in cases of irreversible recumbency or extreme distress to the animal, the animal should be humanely euthanized or humanely slaughtered on the farm (where allowed by state law).[2479] Although current U.S. law prohibits dragging of nonambulatory animals under any circumstances,[2480] legislation that would require humane euthanasia of any recumbent animal at a place of commerce has also been proposed (Downed Animal Protection Act).[2481]

Laboratory testing for metabolic causes of recumbency would be ideal in all circumstances, but this is often not feasible or possible. As such, many downer cattle are treated empirically for suspected metabolic abnormalities, and response to treatment aids in establishing the diagnosis. Periparturient downer cows should be treated for hypocalcemia with one or more doses of calcium. Animals that become more alert but that are not standing after one or two doses of calcium are classified as alert downer cows. It is reported that 3.8% to 28.2% of all milk fever cases become alert downers,[2474–2476,2482] with a mortality rate of 20% to 67%.[2474–2477] The incidence of downers (24 hours or longer) was 21.4 cases per 1000 cow-years in Minnesota dairy herds, with a 33% recovery rate.[2483] Fifty-eight percent of downers occurred within a day of calving, and 97% occurred within the first 100 days after calving.[2483]

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Because the pressure damage done to muscles and nerves is aggravated by recumbency, it is desirable to have the animal on soft bedding (e.g., sand,[2484] grass) and to have the animal stand as soon as possible. Eight of 16 normal cows anesthetized for 6 to 12 hours in sternal recumbency with the right hindlimb under the body were unable to stand on recovery and became alert downers.[2485] Those that could stand exhibited swelling and stiffness and peroneal nerve deficits and paresis in the right hindlimb.[2485] These signs are typically seen in cows that have been

recumbent for several hours on a hard surface. As pressure applied to a nerve increases, nerve conduction is impaired and eventually lost.[2486]

Serum creatine kinase (CK) values in experimental downer cows increased, starting at 12 hours and continuing up for the first 48 hours, and then decreased, even though the cow remained down.[2485] The CK values at 12 and 24 hours did not differ statistically for the cows that could rise after anesthesia and the downers. After 48 hours and 96 hours, the downers had higher mean CK values than the ambulatory group, but there was a great range in values.[2485] In another study of downers, aspartate transaminase (AST) levels were greatly elevated on days 4 to 7, even after CK levels fell.[2487] The clinical difference between cows that recovered and those that remained downers was attributed to damage to the sciatic nerve or its branches, particularly the peroneal nerve.[2485] Peroneal nerve damage results in knuckling over at the fetlock. Serum levels of creatine phosphokinase, AST, and lactate dehydrogenase have been examined to determine whether these indices of muscle damage can predict recovery of recumbent dairy cattle. Of the three enzymes, AST has been shown to be most useful in predicting nonrecovery. Dairy cattle with an AST level greater than 171 U/L are 80% more likely not to recover than a dairy cow with an AST level less than 171 U/L.[2488]

Devices that aid and promote standing traditionally include hip lifters (hip clamp), slings, and inflatable bags. Although these devices help less severely affected animals to stand temporarily, they do not allow the animal to stand comfortably for hours and may even cause further trauma in animals that struggle. For these reasons, the use of water flotation has been explored as a tool in the management of downer cows. Rasmussen[2489] first reported on the use of a warm-water flotation system in Denmark in 1982. Commercial flotation systems practical for cows* are marketed in the United States.

For flotation therapy to allow the best chances for recovery, the animal should first be examined to determine that it is a good candidate for flotation, by ruling out fractures, severe spinal cord compression, and severe systemic illness. Identifying and correcting electrolyte disturbances (e.g., hypocalcemia, hypophosphatemia, hypomagnesemia, hypokalemia) are required for successful application of flotation therapy. Once metabolic or systemic illnesses have been addressed and the cow is considered strong enough to stand once supported by water, the cow is placed in the flotation tank as follows: (1) the water tank is positioned near the down cow; (2) the wheels and tongue are detached, and both ends of the tank are removed; (3) a mat is pulled from the tub to a position beside the cow, and the down cow is rolled or slid onto the mat; (4) the mat is winched or otherwise pulled into the tub, and the ends of the tub are put in place; they seal with rubber gaskets and large turnbuckles; and (5) the cow's head is held up a few inches by a rope halter, and a hose is inserted into the tub, which is filled with water as quickly as possible; the water temperature should be 37.7° C to 38.7° C (100° F to 102° F). Cows in lateral recumbency on the mat become sternal when 12 to 24 inches of water fills the tub and usually attempt to stand beginning when the tub is one-half to two-thirds full. If no hot water is available near the cow, or if the tub is not next to dirt or grass suitable for the cow to exit on, the wheels can be put back on and the cow easily trailered to a better location. In addition, it is helpful to have an assistant support the tail or have a means to pull the tail once the cow attempts to rise. This helps the cow maintain a sternal position during early efforts at struggling before the cow is actually standing. Before floatation of lactating cattle at the University of California, Davis, cows are milked and teat ends sealed with a rubber teat sealant; this is removed once the cow is removed from the tank before milking. The sealant is reapplied after milking in preparation for the next flotation.

Once the cow is standing in warm water, it is possible to determine which limb or limbs are paretic or painful by observing which limbs the cow is using to support weight. Most cows calm down and relax in a standing position within 5 minutes. Most will eat hay, and even first calf heifers that have not been handled much seem to be remarkably calmed by the warm water. Unlike horses, cattle do not panic or attempt to jump out. The cow can be

left in the water for 12-24 hours. If the water temperature drops below 35° C (95° F), some water should be released from the discharge valve and replaced with hot water; this is especially recommended in cold weather. When the decision is made to remove the cow from the tub, the water is drained, and the end of the tub facing the dirt, sand, or grass is opened. The cow is encouraged to exit *slowly* into a pen with good footing. Some cows fall as the water is let out, and others collapse once they try to walk. By observing how a cow is ambulating on exit, it is possible to determine whether hobbles should be placed onto the cow before the next flotation. If cows are considered at risk for splaying out while exiting the tank, it is recommended to apply hobbles before placing the cow in the tank.

Careful observation as the cow moves can be very helpful in trying to locate anatomic or functional problems. The animal that collapses can be pulled out on the mat and left on suitable bedding, dirt, sand, or grass until refloated after a period of rest. Advanced planning on location is important for successful use of flotation therapy. Cows that can walk out into a pen may or may not be able to stand by the next day and may need to be refloated. Cows may need to be floated for up to 10 consecutive days before they can arise by themselves. If cases are carefully selected to rule out fractures, severe traumatic stifle injuries, septic arthritis, and spinal cord compression, a recuperative success rate of 46% to 90% can be expected.[2489,2490]

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Flotation is most effective if applied early, before a downer cow develops serious myopathy and neuropathy. Studies have shown that water flotation is practical and effective, even when cattle have been down for 24 hours or longer.[2489] The sooner a postparturient alert downer cow can be floated after onset of recumbency, the shorter the time to stand. In one study of postparturient alert downer cattle treated with flotation therapy, the mean time to stand was shorter for cattle floated within 1 day of going down (mean, 2.8 days to stand) than for cattle floated after being down for 2 or more days (mean, 5.3 days to stand).[2490]

* Aqua Cow Rise System, St. Johnsbury, VT; www.downcow.com.

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36 Chapter 36 Mammary Gland Health and Disorders

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The efficient production of wholesome milk is the primary mission of a dairy farm. Mammary gland health is essential for maximizing milk production and farm profitability. It also ensures the safety and quality of milk and milk products and limits the use of antimicrobial agents on the farm. This chapter discusses the pathogenesis, diagnosis, treatment, and control of mastitis and other mammary gland disorders, with emphasis on dairy cattle.

The large size of new dairy operations, growing emphasis on the well-being of farm animals, and heightened public concern about antimicrobial residues in milk and antimicrobial resistance in pathogens present challenges for today's dairy producers. Competitive markets for high-quality milk and demand for “natural” milk products afford new opportunities. By providing expertise in prevention and treatment of udder health disorders, veterinarians can help producers address these challenges and enhance their opportunities for financial success.

36.1 ANATOMY AND PHYSIOLOGY OF THE MAMMARY GLAND

Knowledge of mammary gland anatomy and physiology is required to fully understand the pathophysiology of mammary gland disorders. The bovine udder comprises four mammary glands, each with its own teat. The milk-synthesizing cells of the mammary gland, called *mammary epithelial cells,* are arranged in hundreds of alveoli, each with a central lumen. In normal lactating glands, tight junctions between the epithelial cells provide an impermeable barrier that prevents molecules and ions from diffusing between blood and milk.

Nutrients required for milk synthesis are delivered to the mammary gland by the circulatory system and transported into the epithelial cells or directly into the alveolar lumen. Major milk constituents, such as casein, lactose, and fat, are synthesized within the epithelial cells and secreted into the lumen, where they combine with other constituents to form milk. A portion of the milk synthesized between milkings (the *cisternal fraction*) drains from the alveoli through a series of progressively larger ducts to be stored in cisterns in the gland and teat; however, most of the milk (the *alveolar fraction*) remains in the alveoli until milk ejection occurs.[1]

When the teats are manipulated at milking time, a neurohormonal reflex, triggered by pressure-sensitive receptors in the teat skin, causes the pituitary gland to release *oxytocin* into the bloodstream.[2] Milk is ejected when myoepithelial cells surrounding the alveoli and adjacent ducts contract in response to binding of oxytocin. When the resistance of the teat canal (also called *streak canal*) is overcome by pressure of milk in the teat or by milking or suckling, milk is expelled through the teat orifice.[2] Activation of the sympathetic nervous system, as occurs during stress or excitement, can inhibit the release of oxytocin from the pituitary gland or the binding of oxytocin to myoepithelial cells, thus preventing milk ejection.[3]

As with cattle, South American camelids (SACs; llamas, alpacas) have four mammary glands, called *quarters*. In contrast, sheep, goats, and horses have only two mammary glands, called *halves*. In horses and SACs, each mammary gland is composed of two distinct lobes.[4,5] Horses and SACs also have relatively small teats and limited cisternal storage capacity compared with ruminants. Otherwise, mammary gland anatomy and physiology are similar among livestock species.

36.2 DEFENSE MECHANISMS OF THE MAMMARY GLAND

A host of physical, cellular, humoral, and chemical defense mechanisms protect the mammary gland against infection. These defense mechanisms enable the mammary gland to resist microbial invasion, inhibit microbial growth, destroy and remove microbes, neutralize toxins, and resist tissue damage during inflammation.

36.2.1 Teat Canal

The teat canal and surrounding musculoelastic tissue provide the primary physical barrier to microbial invasion and also prevent leakage of milk between milkings.[6,7] The teat canal is a narrow, longitudinally folded cylinder lined with stratified squamous epithelium. The tortuous shape of the canal provides physical protection against infection, as does protein-rich *keratin,* which is continually produced by the epithelial cells and lines the canal. Keratin physically plugs the teat canal and traps invading microbes, which are then expelled with sloughed keratin at milking time. Keratin also contains fatty acids and proteins that have bacteriostatic or bacteriocidal effects in vitro,[8,9] although their role in mammary gland defense is uncertain. Loss of keratin greatly increases the risk of intramammary infection.[10]

Management practices and the cow's physiologic state influence teat function and mastitis resistance For example, the integrity of the teat canal is compromised for up to 2 hours after milking while the elastic fibers surrounding the canal recoil and keratin begins to be renewed.[6,11] Therefore, it is recommended that cows be fed after milking, to keep them standing and to minimize exposure to pathogens while the teat canal recovers. When a cow is dried off at the end of lactation, the teat canal does not fully fill with keratin for days to months. A delay in keratin plug formation is associated with an increased risk of intramammary infection.[12,13] When antibiotics are infused into the teat, full insertion of the cannula disrupts the keratin and can transport microorganisms from the teat canal or skin into the teat cistern. Therefore, the “partial-insertion” method of administering antibiotics, whereby the cannula is inserted only 2 to 3 mm into the canal, is recommended.[14] Using the partial-insertion method to infuse antibiotics at dry-off can reduce the incidence of intramammary infection or clinical mastitis during the dry period.[14,15]

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Callosity (hyperkeratosis) of the teat end and abrasion of the teat orifice epithelium increase the risk of intramammary infection.[16,17] Trauma to the teat end compromises teat canal function and predisposes to infection. Trauma can occur when a cow steps on her teat or as a consequence of the milking process. Ineffective pulsation, excessive milking vacuum, or poorly fitting teat cup liners can damage teat tissue during milking.[18] Air admission into the milking cluster, as occurs with liner slips, can cause reverse-pressure gradients that propel bacteria-laden milk droplets up through the teat canal into the teat cistern.[19] Even the shape of the teat end and length and diameter of the teat canal influence infection risk; short, wide teat canals and flat or inverted teat ends predispose to mastitis, as does teat canal protrusion.[7,20,21]

Because of the importance of the teat in mammary gland defense, dairy producers should routinely monitor teat condition and use a combination of genetic selection and management practices to promote teat health and function. *Teat Club International,* a group of researchers, veterinarians, and udder health advisors, has developed a standard method for scoring teat condition; the method and images are published on an educational CD available through the National Mastitis Council (NMC; www.nmconline.org).

36.2.2 Cellular Defense Mechanisms

Once microbes have breeched the teat canal, leukocytes and mammary epithelial cells constitute the next line of defense. Milk from healthy mammary glands contains a low concentration (<100,000/mL) of cells, the majority of which are macrophages. However, when microbes are detected, macrophages and epithelial cells release cytokines and chemokines that trigger an influx of neutrophils.[22,23] The rapidity and extent of neutrophil influx are critical determinants of infection outcome.[24,25] Neutrophils are the predominant cells in mastitic milk, with concentrations often exceeding 1 million/mL during acute infection. Macrophages, lymphocytes, and epithelial cells are present in much lower concentrations, with the total cell concentration referred to as the *somatic cell count* (SCC).

36.2.2.1 NEUTROPHILS

Neutrophils are critical for eliminating mastitis-causing pathogens from the milk. An effective neutrophil response to infection includes four functions: recruitment, phagocytosis, intracellular killing, and apoptosis. Deficiencies in any of these functions can increase the severity or duration of mastitis.

36.2.2.1.1 Neutrophil Recruitment

Neither microbes nor microbial toxins are strongly chemotactic for bovine neutrophils. Therefore, the presence of organisms in the milk does not effectively stimulate neutrophil recruitment.[26] Initial recruitment depends on release of chemotactic factors from macrophages and epithelial cells. Two potent chemoattractants for bovine neutrophils are interleukin-8 (IL-8) and complement factor C5a.[27,28] However, other proinflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and granulocyte-monocyte colony-stimulating factor (GM-CSF), also attract bovine neutrophils and may play a greater role in recruitment than previously recognized.[23]

Circulating blood neutrophils must adhere to the vascular endothelium before migrating into the milk. Vascular neutrophils in the marginal pool loosely bind and roll along the endothelium, using a surface adhesion molecule called CD62L (L-selectin). In response to proinflammatory mediators, endothelial cells express surface receptors that cause neutrophils to upregulate expression of the β_2-integrin adhesion complex CD11b/CD18. The CD11b/CD18 complex firmly anchors neutrophils to vascular and intercellular adhesion molecules (VCAMs and ICAMs). Once bound, neutrophils migrate between the endothelial and mammary epithelial cells into the milk *(diapedesis),* traveling along the chemotactic gradient to the site of infection.[23,29] Both the speed of recruitment and the number of neutrophils recruited influence microbial clearance.[22,26] In fact, the chemotactic responsiveness of neutrophils in vitro can distinguish cows that are “high responders” or “low responders” to intramammary infection and predict the severity and outcome of mastitis.[30]

36.2.2.1.2 Neutrophil Phagocytosis

Neutrophils become activated during diapedesis and chemotaxis. Activation results in upregulation of surface receptors that facilitate phagocytosis. These receptors recognize and bind microbial cell wall components or specific opsonins. Expression of CD14 receptors enables neutrophils to bind bacterial

lipopolysaccharide (LPS) in the presence of LPS-binding protein (LBP); this binding facilitates nonopsonic phagocytosis of gram-negative bacteria.[31] At the same time, soluble CD14 (sCD14) is shed into the milk, where it neutralizes free LPS and binds to epithelial cells, enhancing chemoattractant release.[26] The most important neutrophil receptor for opsonic phagocytosis is the *Fc receptor,* which binds the Fc region of immunoglobulins (Ig), particularly IgG_2 and IgM, enabling the phagocytosis of antibody-coated pathogens.[32,33] Complement component 3b is also opsonic for bovine neutrophils.[28]

Receptor binding stimulates the neutrophil to extend pseudopods and engulf the adhered pathogen into a phagosome. The phagosome fuses with cytoplasmic secretory granules to form an intracellular vesicle (phagolysosome), where degranulation and microbial killing take place. Unfortunately, neutrophils in milk are less efficient at phagocytosing and killing microorganisms than are neutrophils in blood. In milk, neutrophils engulf fat globules and casein, which reduces subsequent pseudopod formation as well as intracellular killing capacity.[26] This may explain why such a large number of neutrophils must be recruited.

36.2.2.1.3

Neutrophil Antimicrobial Systems

Two general antimicrobial systems, designated "oxygen (O_2) dependent" and "O_2 independent," contribute to neutrophil-mediated killing of microorganisms. Ingestion of microorganisms leads to an increase in oxygen consumption and generation of a variety of reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide; these ROS interact to form hydroxyl radical and singlet oxygen, which are strongly bactericidal.[26,29] Myeloperoxidase, which is released from cytoplasmic granules within the neutrophil, stimulates production of other bactericidal species, such as hypochlorite.[34] This O_2-dependent process is called the "respiratory burst" or "oxidative burst." Reduced ROS production by neutrophils in milk is associated with increased severity of *Escherichia coli* mastitis. In fact, cows can be classified as low or high responders to *E. coli* mastitis on the basis of preinfection ROS-generating capacity.[34]

Neutrophil granules contain cationic peptides called *bactenecins* and *defensins,* which have broad-spectrum antibacterial and antifungal activities.[22,35] These proteins, along with lactoferrin, hydrolytic enzymes, and a variety of other substances contained in neutrophil granules, contribute to O_2-independent killing of engulfed pathogens.

36.2.2.1.4

Neutrophil Apoptosis

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Prompt elimination of neutrophils that have completed their antimicrobial functions is necessary to avoid release of cellular contents that can damage host tissue. Neutrophil elimination is accomplished by programmed cell death *(apoptosis),* followed by phagocytosis. Apoptosis fragments the neutrophil into small, membrane-bound bodies that are easily phagocytosed and removed by macrophages.[26,36]

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36.2.2.2

MACROPHAGES AND LYMPHOCYTES

Macrophages are the predominant leukocytes in normal milk but are greatly outnumbered by neutrophils during mastitis. As with neutrophils, macrophages ingest and kill microorganisms.[37] They appear to be particularly important in chronic intramammary infections and during involution (dry-off) of the mammary

gland. Macrophages process and present antigen to T lymphocytes, enabling them to secrete cytokines, activate B lymphocytes, and exert cytotoxic, suppressor, and memory functions.[38] In milk, $CD8^+$ (memory, cytotoxic, and suppressor) lymphocytes predominate over $CD4^+$ (helper) lymphocytes.[39] However, percentages of lymphocyte subclasses change with stage of lactation[39] and are impacted by the presence and duration of intramammary infection.[40] Milk also contains γδ T lymphocytes, which may help regulate the inflammatory response or heal damaged epithelial cells,[29] and natural killer (NK) cells, which are cytotoxic.[38] B lymphocytes recognize specific antigens and differentiate into antibody-secreting plasma cells and memory cells.

36.2.2.3 EPITHELIAL CELLS

Although leukocytes are considered the main defensive cells in the mammary gland, epithelial cells are recognized as mediators of the early, innate immune response to infection. Toll-like receptors, which are found on epithelial cells, recognize conserved bacterial components, such as LPS on gram-negative bacteria or lipotechoic acid on gram-positive bacteria. Binding leads to a cascade of events that causes production and release of proinflammatory cytokines and chemokines.[22,41] Cytokine production is lower and less persistent in response to lipotechoic acid than LPS, which may help explain why gram-positive intramammary infections tend to be more persistent than gram-negative infections.[42] Epithelial cells are also a source of antimicrobial proteins, such as β-defensins. As research continues, additional roles for epithelial cells in mammary gland defense will probably be identified.

36.2.3 Noncellular Defense Mechanisms

36.2.3.1 IMMUNOGLOBULINS

Immunoglobulin concentrations are low in normal milk but rise in response to intramammary infection; the rise partly results from local Ig production but mostly from increased permeability of vascular endothelial cells and mammary epithelial cell tight junctions, which allows an influx of plasma Ig (and other plasma proteins) into milk. Influx of opsonizing Ig (IgM and IgG_2 in cattle) enables efficient phagocytosis of microorganisms by neutrophils.[32,33,43] Nonopsonizing Ig (IgG_1 and IgA in cattle) have other beneficial functions, such as neutralization of bacterial toxins, agglutination of bacteria, and prevention of bacterial adherence to epithelial cells. Immunoglobulins in milk also mediate antibody-dependent cell-mediated cytotoxicity by leukocytes.[38,44]

36.2.3.2 LACTOFERRIN AND OTHER ANTIMICROBIAL PROTEINS

Lactoferrin is an iron-binding glycoprotein produced by mammary epithelial cells and found in neutrophil granules.[45] Lactoferrin concentration is low in normal milk but increases substantially during the dry period and in response to intramammary infection.[22] By sequestering iron, lactoferrin prevents multiplication of iron-dependent microorganisms, such as coliform bacteria.[46] Lactoferrin plays a more general role in mammary gland defense by modulating granulopoiesis, leukocyte trafficking, lymphocyte cytotoxicity, and other immune functions. By disrupting bacterial cell membranes, it is also bactericidal.[22,47]

Lysozyme and lactoperoxidase are other antimicrobial proteins that play more minor roles in mammary gland defense.[38] Xanthine oxidase, found in milk fat globules, catalyses the formation of nitric oxide, which also plays a role in mammary gland defense.[22]

36.2.3.3 CYTOKINES

Cytokines regulate the activity of cells involved in nonspecific and specific immune responses. Many cytokines are produced in response to intramammary infection and influence the signs, severity, and outcome of mastitis. The origins, actions, and interactions of these proteins are too extensive to cover in detail. However, of major importance are the interleukins (ILs), interferons (IFNs), TNF-α, and colony-stimulating factors (CSFs).[48] Macrophages, T lymphocytes, and epithelial cells are the main producers of these cytokines. The cytokines interact with membrane receptors on target cells to stimulate release of leukocytes from bone marrow, enhance recruitment and activation of neutrophils, influence antibody production by B lymphocytes, direct the inflammatory response to infection, and in some cases, induce toxic shock.[29,38] Differences in cytokine profiles elicited by *Escherichia coli* and *Staphylococcus aureus* may help explain why *S. aureus* mastitis is more persistent than *E. coli* mastitis.[48]

Recombinant cytokines (e.g., IL-2, G-CSF, GM-CSF, IFN-γ) have been investigated as preventative[49,50] or therapeutic[27,51,52] agents for mastitis and as vaccine adjuvants.[53] Although these cytokines have been effective in some in vitro and in vivo studies, none has proved sufficiently safe or practical for commercial use.[54]

36.2.4 Defense Mechanisms in the Periparturient Period

Mammary gland defense mechanisms are greatly reduced in the periparturient period, making cows most vulnerable to mastitis at that time. Indeed, both the incidence and the severity of mastitis are higher in the periparturient period than at other times.[29,55–57] Neutrophil functions, particularly chemotaxis and intracellular killing, are impaired in periparturient cows, as is phagocytosis by macrophages. The immunosuppression accompanying parturition is partly caused by a high circulating cortisol concentration, which impairs neutrophil margination and recruitment. Neutrophils of periparturient cows also undergo apoptosis more rapidly than do neutrophils of cows in later lactation, and early onset of apoptosis reduces phagocytic and intracellular killing activity.[26] Low circulating concentrations of insulin-like growth factor 1 (IGF-1) in periparturient cows may reduce neutrophil viability and impair cytokine secretion.[56] Because a cow's ability to resist microbial challenge is reduced during the periparturient period, producers must pay special attention to the housing and management of periparturient cows.

36.3 INTRAMAMMARY INFECTION AND MASTITIS

The importance of mammary gland defense mechanisms in protecting against or limiting the effects of intramammary infection cannot be overstated. When pathogens traverse the teat canal and multiply in the milk, an inflammatory response is initiated, which results in mastitis (inflammation of the mammary gland). If cellular and noncellular defense mechanisms combat the infection rapidly and effectively, mastitis will be mild and transient. However, when defense mechanisms are compromised (e.g., during periparturient period) or when the pathogen is

able to evade normal defenses (e.g., resist phagocytosis or intracellular destruction), severe or chronic mastitis may develop. The intensity of the inflammatory response determines whether mastitis is subclinical or clinical.

With *subclinical mastitis,* the inflammatory process does not result in visible abnormalities in the milk, mammary gland, or cow. However, milk production is reduced and milk composition altered.[58] With *clinical mastitis,* milk from the affected quarter is visibly abnormal, the gland itself may appear inflamed, and the cow may exhibit a drop in milk production and general signs of illness. Although mastitis can develop in response to trauma, the vast majority of mastitis episodes are caused by intramammary infection. It is preferable to promote mastitis resistance and limit exposure to pathogens than to combat mastitis once it has developed. However, episodes of mastitis will occur even in well-managed herds.

36.3.1 Detection of Subclinical Mastitis

36.3.1.1 SOMATIC CELL COUNT

Subclinical mastitis is the predominant form of mastitis in cattle and other livestock. A consistent finding with subclinical mastitis is an increase in the SCC of the milk. The SCC can be measured in milk from an individual quarter (QMSCC) or milk composited from all four quarters (CMSCC). In either case, SCC greater than 100,000/mL is consistent with inflammation (mastitis). However, inflammation is not synonymous with intramammary infection. Milk from cows with intramammary infection usually has an SCC substantially higher than 100,000/mL because of neutrophil recruitment. The CMSCC is lower than the QMSCC because milk from the uninfected quarters dilutes the cells from the infected quarter.

Although intramammary infection is the most important determinant of SCC, SCC can be influenced by stage of lactation and milk production. For example, colostrum and milk produced during the first week after calving often have higher SCC than milk produced later.[59,60] Some investigators have also observed an increase in SCC during late lactation.[59] Findings in early and late lactation may be confounded because intramammary infection is common at those times and milk production is relatively low, which concentrates the cells.[61] Any disease that causes a marked drop in milk production, such as abomasal volvulus or traumatic reticulopericarditis, may cause an increase in SCC because of concentration.

The SCC of milk can be quantified by direct microscopic observation or by use of a Coulter counter. However, most commercial laboratories use a fluoro-opto-electronic (Fossomatic) cell counter, which can accurately measure SCC in preserved or frozen milk.[62] In the United States, many dairies subscribe to monthly CMSCC testing of all lactating cows. The CMSCC is typically reported as linear score (LS), a logarithmic conversion of SCC calculated as follows: $LS = \log_2 (SCC/100) + 3$. Conversion to LS achieves a normal distribution and linear association with milk yield loss (see section on economics).

Because SCC can remain high after intramammary infection resolves and can vary during the course of an infection, the accuracy of a single QMSCC or CMSCC for detecting infection is compromised.[59] A SCC threshold of 200,000 or 250,000/mL is usually recommended for cattle; cattle with SCC below the threshold are assumed to be free of intramammary infection, and cattle with SCC above the threshold are assumed to have intramammary infection. Unfortunately, no SCC threshold is perfect. The lower the threshold, the higher is the sensitivity (more infected glands are detected) and lower the specificity (more uninfected glands are classified as infected). Increasing the threshold improves specificity (more uninfected glands are correctly classified) but reduces sensitivity (more infected glands are missed). The choice of threshold therefore

depends on the purpose of testing. For example, if it is important to identify all infected cows so they can be managed in a certain way (segregated, culled, or treated), a low SCC threshold should be used to select animals for culture so infections are not missed. However, when screening cows to determine the types of pathogens causing high SCC in a herd, use of a higher SCC threshold to select animals for culture will reduce the chance that cultures will yield no growth.

The predictive value of SCC is impacted by the prevalence of intramammary infection in a herd. For example, SCC values above a given threshold are more likely to predict intramammary infections correctly in a herd with a high prevalence of mastitis than in a herd with a low prevalence of mastitis. In contrast, SCC values below a given threshold are more likely to predict healthy glands correctly in a herd with a low prevalence of mastitis than in a herd with a high prevalence of mastitis.[63] Therefore, knowing the approximate prevalence of mastitis in a herd is helpful when interpreting SCC data.

36.3.1.2

CALIFORNIA MASTITIS TEST

A rapid, inexpensive alternative to SCC testing is the California Mastitis Test (CMT). With the CMT, 2 to 3 mL of milk from each quarter of the mammary gland is stripped into individual cups of a hand-held paddle. A reagent is added to lyse the cells and agglutinate cellular proteins, resulting in thickening (gelling) of the mixture.[64] The degree of gelling is subjectively scored using a five-point scale; a score of 0 (negative) corresponds to SCC less than 200,000/mL.[64] Although qualitative, progressively higher CMT scores correspond to progressively higher ranges of SCC.

The CMT is impractical for routine monitoring of mastitis prevalence in a herd but can be a useful tool for screening individuals, such as fresh cows, for possible infection and selecting quarters for culture.[65,66] As with the SCC, the CMT is not a perfect test for intramammary infection. The optimal threshold will depend on the stage of lactation and objective of testing.[60]

Hand-held SCC counters are available for use at cow-side. However, the need for exact SCC quantification (vs. qualitative CMT results) must be weighed against cost to determine if such a purchase is warranted. Advantages of cow-side SCC counters and the CMT are that they provide immediate results and can be used to assess individual quarters, whereas monthly CMSCC provides infrequent data for the cow as a whole. A test strip that simultaneously detects cells and actively respiring bacteria in milk (V Strip 2, GeneBact Animal Health) is available in the United States, but the utility and acceptance of this test remain to be determined.

36.3.1.3

ELECTRICAL CONDUCTIVITY

An alternative method of subclinical mastitis detection is measurement of electrical conductivity of the milk. Electrical conductivity of normal milk is approximately 4.0 to 5.5 ms/cm^2 at 25° C. With mastitis, increases in sodium and chloride concentrations and a reduction in potassium concentration in the milk result in an increase in electrical conductivity.[67] An advantage of electrical conductivity over SCC is that conductivity can be measured automatically while cows are being milked, using sensors in the milking system. It is therefore adaptable to robotic milking systems.[68] Unlike CMSCC testing, which is performed monthly, electrical conductivity can be measured at each milking, thus allowing changes to be detected early. Results can be downloaded and archived on a computer and calculations performed. Mastitis detection can be based

on an absolute increase in conductivity or on interquarter ratios or differences in conductivity, with a combination of absolute and interquarter thresholds being most sensitive.[67]

The median sensitivity of electrical conductivity for detecting intramammary infection in 41 studies was 75% and the median specificity 95%.[67] However, in herds with a low prevalence of mastitis, the predictive value of a single or multiple positive tests can be much less than 60%.[69,70] Variations in electrical conductivity can occur with transient intramammary infections that do not require treatment and for reasons other than mastitis. Therefore, treatment should not be initiated on the basis of electrical conductivity results. As with SCC, electrical conductivity is simply a tool to assist in mastitis detection. Dairy producers must use electrical conductivity data along with other automated data (milk production, milk temperature, milk color, pedometry data) and physical examination findings to identify cows for monitoring or further testing. Although hand-held electrical conductivity meters are available, they generally perform poorly compared with the CMT for cow-side detection of subclinical mastitis.[71]

36.3.1.4 OTHER SUBCLINICAL MASTITIS INDICATORS

A variety of milk compositional changes accompany subclinical mastitis besides the increase in SCC. These include reduced casein, lactose, and α-lactalbumin concentrations; an influx of sodium, chloride, and plasma proteins; increased proteolytic and lipolytic activity; an increase in lactoferrin concentration and enzyme activities; and a rise in pH.[58] As a result of permeability of mammary epithelial cell tight junctions, potassium, lactose, casein, α-lactalbumin, and other mammary gland—derived substances move from milk into plasma. Many of these changes can be used as indicators of subclinical mastitis. Among the more common milk tests are those that detect albumin, sodium, chloride, lactose, or adenosine triphosphate (ATP) concentration; *N*-acetyl-β-D-glucosaminidase (NAGase) activity; antitrypsin activity; or pH; plasma tests detect α-lactalbumin, casein, or lactose concentration.[58,71–75] Milk concentrations of the acute-phase proteins amyloid A and haptoglobin are also used to distinguish healthy quarters from those with subclinical mastitis.[71,75] To date, none of these tests has proved sufficiently more accurate or convenient than SCC, so they are used mainly in research.

36.3.2 Detection of Clinical Mastitis

Clinical mastitis results in obvious abnormalities of the milk, mammary gland, or cow and is easier to recognize than subclinical mastitis. Most episodes of clinical mastitis are mild to moderate in severity. With *mild* clinical mastitis, milk from the affected quarter is abnormal in color, viscosity (watery, thick), or consistency (contains flakes or clots of inflammatory material). In *moderate* cases the affected mammary gland is noticeably inflamed (swollen, firm, warm, red, painful), and milk production may be somewhat decreased. With *severe* clinical mastitis, milk and mammary gland changes are accompanied by systemic illness. Systemic signs may include decreased feed intake or milk production, lethargy, depression, tachypnea, enophthalmos, weakness, recumbency, or low-volume diarrhea that may contain mucus or blood. Physical examination of the cow often reveals fever, tachycardia, decreased rate or strength of rumen contractions, prolonged skin tent or capillary refill time, tacky mucous membranes, or cold extremities.[76–79] Hypothermia may precede death in fatal cases. Occasionally, *gangrenous* mastitis occurs, in which case the skin of the mammary gland or teat may be cold, black, or crepitant, and gas may be expelled when milking the teat.

The severity of clinical mastitis influences the choice of treatment, as well as the prognosis, so efficient detection of clinical mastitis and determination of severity are critical. Detection of clinical mastitis is

accomplished by stripping foremilk onto the floor of the milking parlor at each milking. Milk that is grossly abnormal must be discarded or fed to calves and must not enter the bulk tank. Grossly abnormal milk generally has a very high SCC and altered composition, so immediate exclusion from the bulk tank helps to protect milk quality. Currently, no automated methods reliably detect clinical mastitis in the milking parlor, although such tests are being sought for robotic milking systems.

Milking personnel should routinely check mammary glands for signs of inflammation while cows are in the milking parlor. When cows with abnormal milk or an inflamed mammary gland have reduced milk yield or appear to be systemically ill, they should be examined promptly and systematically to determine mastitis severity and appropriate actions. Relevant farm staff must therefore be trained in assessment of attitude, rectal temperature, hydration status, and ideally, rumen motility.

Resolution of clinical signs is not synonymous with resolution of intramammary infection. Clinical signs may persist for a time after the pathogen has been eliminated, as often occurs with *E. coli* mastitis, or infection may persist after clinical signs have resolved, as with *S. aureus* mastitis. Regardless, clinical mastitis is always followed by a period of subclinical inflammation. If the infection has resolved, SCC usually returns to normal within 2 weeks.[80] Persistent elevation in SCC suggests chronic intramammary infection, which can be accompanied by recurrent bouts of clinical mastitis. Therefore, monthly CMSCC and periodic CMT are useful tools for assessing the likelihood of cure after clinical mastitis.

36.4 CONTAGIOUS VS. ENVIRONMENTAL MASTITIS

Mastitis pathogens have traditionally been categorized as “contagious” or “environmental” based on the primary reservoir of infection and mode of transmission. With the advent of new methods of strain typing, this method of categorization clearly is oversimplistic. Within both pathogen groups are strains that vary in contagiousness. The traditional categorization still provides a reasonable basis for investigating risk factors and initiating control programs in problem herds. However, if control measures do not achieve expected results, strain typing of pathogens can help to identify an atypical reservoir(s) of infection. The next two sections provide general information about the epidemiology and control of contagious and environmental mastitis. Specific pathogens are discussed in more detail in later sections.

36.4.1 Contagious Mastitis

Infected mammary glands are the predominant reservoirs of contagious mastitis pathogens. Transmission occurs when milk from an infected gland contacts the teat of an uninfected gland during the milking process. The teat cup liners of the milking cluster are important fomites if infected cows are milked before uninfected cows. Other fomites include the hands of the milking personnel and towels used to wash or dry the teats of multiple cows. Once pathogens have been deposited on the teat skin, the gland is at risk of infection, especially when teat defense mechanisms are compromised. In some cases, abrupt vacuum fluctuations within the milking cluster (reverse-pressure gradients) can propel contagious pathogens from the milk of an infected gland into the teat canal of an uninfected gland.[19]

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Streptococcus agalactiae and *Staphylococcus aureus* are major contagious mastitis pathogens that cause persistent elevation in SCC and reduction in milk yield. *Corynebacterium bovis* is a minor contagious mastitis pathogen with a lesser impact on SCC and milk yield. Infection with these three pathogens can be controlled by implementing a five-point mastitis control program consisting of (1) postmilking germicidal teat disinfection *(postdipping),* (2) antibiotic treatment of all quarters of all cows at dry-off (“blanket” dry-cow antibiotic

therapy), (3) culling of chronically infected cows, (4) prompt recognition and treatment of clinical mastitis cases, and (5) proper use and maintenance of the milking machine.[81] Together, these measures reduce both the incidence and the prevalence of infection. *Mycoplasma bovis* and other *Mycoplasma* species are usually categorized as contagious mastitis pathogens even though they colonize body sites other than the mammary gland (see section on *Mycoplasma* mastitis). This is because once intramammary infection is established, *Mycoplasma* spreads among cows and glands in a contagious manner.

36.4.1.1 POSTMILKING GERMICIDAL TEAT DISINFECTION

Postdipping is the key to preventing new contagious mastitis infections.[82,83] Postdipping kills pathogens deposited on the teat skin during the milking process before they colonize the teat orifice and invade the gland. A variety of germicides are effective, with iodine-based (0.1% to 1.0%) dips the most common. However, not all products are equally effective. To determine if a particular germicide has been scientifically tested and proven effective, practitioners can consult the *Summary of Peer Reviewed Publications on Efficacy of Pre-milking and Post-milking Teat Disinfectants Published since 1980,* which is updated regularly by the NMC and available in the NMC annual meeting proceedings or at www.nmconline.org

Even teat dips of proven efficacy may fail to control mastitis if they are stored or handled improperly or not used consistently. Each teat of every lactating cow must be dipped after each milking; discontinuing dipping during cold weather or when mastitis appears to be under control is likely to result in reemergence of mastitis. Poor coverage of teats with dip is a common cause of postdipping "failure." In particular, spraying the teats, rather than using a dip cup, often results in incomplete coverage. When investigating a contagious mastitis problem, the postdipping process must be observed, rather than simply questioning the producer.

36.4.1.2 ANTIBIOTIC TREATMENT OF DRY COWS

Blanket dry-cow antibiotic therapy is the most effective way to resolve contagious mastitis infections once they occur.[82] *S. agalactiae* and *C. bovis* are susceptible to the antibiotics marketed for dry cows in the United States; cure rates approaching 100% can be expected. *S. aureus* infections are more resistant to antibiotic treatment for several reasons (see section on *S. aureus* mastitis). However, the cure rate for *S. aureus* mastitis is higher when antibiotics are administered during the dry period than during lactation. Cows with chronic *S. aureus* mastitis, especially mastitis that fails to resolve after dry-cow antibiotic therapy, are candidates for culling. *Mycoplasma* species are resistant to the antibiotics available for use in dry cows in the United States, so blanket dry-cow antibiotic therapy will not reduce the prevalence of infection. To eliminate chronic *Mycoplasma* infections, cows must be culled.

Selective dry-cow antibiotic therapy is an appealing alternative to blanket therapy because it reduces antibiotic treatment of uninfected glands. However, common selection criteria (CMT score, lactation average SCC, clinical mastitis history) are imperfect indicators of infection status. When a high CMT or SCC threshold is used, many infected glands will go untreated. When a low CMT or SCC threshold is used, many uninfected glands will be treated. Even milk cultures fail to detect a portion of chronic infections. Therefore, in herds with a high prevalence of contagious mastitis, or with risk factors favoring contagious mastitis transmission, blanket dry-cow antibiotic therapy is prudent. Selective dry-cow therapy also fails to protect untreated glands against new infections in the early dry period.[84]

36.4.1.3 OTHER CONTAGIOUS MASTITIS CONTROL MEASURES

Individual cloth or paper towels (one per cow) should be used to prepare teats for milking. Milking personnel should wear gloves and wash them frequently. An automated back-flushing system can be installed to disinfect milking clusters between cows. A milking order can be established, in which uninfected cows are milked before infected cows. Milking fresh heifers before older cows is recommended, but in some cases, infected heifers are the main source of infection.[85] Complete segregation of infected cows from uninfected cows is impossible to achieve, even if using culture results or SCC as criteria. However, segregation can have beneficial effects, particularly in herds with *S. aureus* mastitis.[86,87]

In open herds, incoming animals can introduce contagious mastitis pathogens. Purchasing cows from known sources, where historical mastitis information (bulk tank culture results, BTSCC, individual cow SCC) is available, can reduce this risk. Culturing all quarters of all new cows is the best way to screen for contagious mastitis, but this is costly, especially if *Mycoplasma* testing is performed. Negative culture results must be interpreted in conjunction with SCC or CMT values because infections (especially *S. aureus*) can be missed on a single milk culture.

36.4.2 Environmental Mastitis

With environmental mastitis, the predominant reservoir is the environment. Transmission occurs when teats become contaminated with environmental pathogens between milkings or at milking time. Common sources of infection are fecal material, bedding, soil, and contaminated water. Once environmental pathogens have been deposited on the teat skin, the gland is predisposed to infection, particularly when defense mechanisms are compromised. Environmental pathogens can also be transported into the teat canal or cistern if the teat end is not sufficiently disinfected before infusing antibiotics, or when a contaminated infusion preparation or cannula is used. The predominant environmental mastitis pathogens are coliform bacteria and streptococci other than *S. agalactiae* (environmental streptococci). However, many other environmental organisms are capable of causing mastitis.

36.4.2.1 HOUSING AND HUSBANDRY RISK FACTORS

The five-point mastitis control program does not effectively control environmental mastitis. Control requires reducing exposure of teats to environmental pathogens. This is accomplished by frequently removing manure from lots, alleyways, and other cow holding areas; rotating pastures and providing sufficient shelter to minimize congregation of pastured cows; limiting access to wet, muddy areas; avoiding overstocking; using appropriately designed stalls; and managing bedding to control pathogen load. Stall design and bedding comfort impact a cow's willingness to use the stall. If poor stall design or insufficient bedding results in discomfort or injury to the cow or hinders her ability to lunge forward and rise, the cow will choose to rest in a less sanitary location. The same is true for a barn with poor ventilation. Poor sizing of stalls may allow manure and urine to accumulate in the bedding, rather than being deposited in the alley.

Sand is the favored bedding material because it is inorganic and comfortable, as long as the beds are well maintained. However, not all manure handling systems can handle sand, and it is not always readily available. Many organic materials, such as straw, sawdust, newspaper, recycled manure, or rice hulls, are acceptable if stored properly and replaced frequently. However, bacterial concentrations greater than 10^6/g can develop in less than 24 hours, especially if the bedding is contaminated with manure. Mattresses or

rubber mats can be used but must be replaced or repaired when worn and topped with organic bedding material as needed to ensure comfort.

36.4.2.2 UDDER HYGIENE PRACTICES

Because it is impossible to eliminate teat exposure to environmental pathogens, cleaning teats in the milking parlor is an important component of environmental mastitis control. Premilking germicidal teat disinfection *(predipping)* is the preferred method in the United States. To be effective, the teats must be wiped of gross organic material, and the germicide must contact the skin for approximately 30 seconds before being removed with a towel. All surfaces of the teat, including the teat end, must contact the dip and be thoroughly cleaned. Massaging the teat helps to distribute the dip, clean the skin, and stimulate milk ejection.

An alternative to predipping is washing the teats with water containing a sanitizing solution. Only the teats should be washed, keeping the udder dry to avoid droplets of water from pooling on the teat cups and contaminating the teats.

With either method, the teats must be clean and dry when the milking cluster is attached. Dry wiping of the teats without washing or predipping is inferior for removing bacteria. Clipping or flaming of udder hair reduces the amount of fecal material and bedding that adhere to the udder and facilitates cleaning of the teats; however, the effect on mastitis incidence has not been adequately studied. Tail docking has proved ineffective at reducing mastitis risk.[88,89]

Postmilking teat disinfection does not provide a sufficient duration of germicidal activity to protect teats effectively against infection with environmental pathogens between milkings.

36.4.2.3 MANAGEMENT OF DRY COWS

Environmental mastitis can be acquired during the dry period as well as during lactation. In fact, infection risk is increased in the early and late phases of the dry period, when secretions accumulate in the gland and defense mechanisms are compromised. Many of these infections do not manifest as clinical mastitis until early lactation. Housing conditions and management practices for dry and parturient cows should minimize exposure of the teats to pathogens. Individual calving pens that are cleaned between cows are preferable to group pens that are cleaned less frequently.

Antibiotic therapy at dry-off can reduce environmental streptococcal mastitis by resolving existing infections and preventing new infections in the early dry period.[12,84] However, by the late dry period, antibiotic concentrations are too low to protect against environmental streptococcal infection. Antibiotic therapy at dry-off is generally ineffective for resolving or preventing infections caused by coliform bacteria or other environmental pathogens. An alternative or (preferably) adjunct to antibiotic therapy is use of an external or internal teat sealant to provide a physical barrier against pathogen invasion. External teat sealants are applied at dry-off or in the late dry period, but must be monitored for peeling and reapplied as needed.[90] Internal teat sealant is infused into the teat at dry-off and remains in the teat until physically removed after calving.[91]

36.5 PATHOGEN DETECTION

To address herd mastitis problems or develop appropriate treatment protocols for clinical mastitis, it is necessary to identify the responsible pathogen(s). Microbiologic culture of milk is the current “gold standard” method of

pathogen identification. Milk from individual mammary glands (quarter samples) can be cultured, as can composite milk from all four mammary glands (composite samples), pooled milk from particular groups of cows (pooled or string samples), or bulk tank milk; the choice of sample depends on the question being investigated.

For milk culture results to be accurate, milk samples must be collected aseptically, stored and handled properly, and plated on appropriate media. The volume of milk cultured, laboratory methods used, experience of the interpreter, and criteria for defining intramammary infection all influence results.

36.5.1 Sample Selection

36.5.1.1 QUARTER VS. COMPOSITE MILK SAMPLING

Quarter samples are appropriate for identifying the cause of clinical mastitis in affected glands. Although it is best to collect the milk before administering antibiotics, the presence of antibiotics in milk does not preclude culturing. In one study, mastitis pathogens were isolated from 92% of milk samples collected 12 to 24 hours after antibiotic treatment.[92] Quarter samples can also be used to determine if infection has resolved after treatment.

Quarter samples are more sensitive for detecting *S. aureus* infection than are composite samples, although the sensitivity of composite samples increases with the number of infected glands per cow.[93,94] Sampling the cow on more than one occasion (quarter or composite samples) increases the likelihood of detecting glands that intermittently shed *S. aureus*.[95] Quarter samples are also preferable to composite samples for detecting *Mycoplasma* mastitis; a recent study showed that up to 40% of glands infected with *Mycoplasma* species shed less than 100 colony-forming units (CFU)/mL of milk.[96] In contrast, single composite milk samples are acceptable for detecting cows infected with *S. agalactiae* because bacterial shedding is heavier and more consistent.[97]

When screening cows for subclinical intramammary infections, it is less time-consuming and costly to collect composite samples than quarter samples. However, pathogens from infected glands are diluted by milk from uninfected glands, which reduces sensitivity and can lead to false-negative culture results. Also, there is more risk of a composite sample becoming contaminated during the collection process. An alternative to composite sampling is to select quarters for culture using the CMT. The specificity of the CMT is high, especially if using a high threshold (score ≥2), meaning that most CMT-positive samples will yield growth. However, sensitivity is likely to be less than 50% regardless of the threshold, meaning that many infected glands will be missed.[98]

Some producers routinely culture composite milk from cows at calving or select quarters for culture using the CMT. Such culturing provides a general assessment of udder health, which reflects the adequacy of management practices for dry cows and heifers. However, culturing for the purpose of selecting animals or quarters for antibiotic treatment is unlikely to be accurate or economical. The sensitivity and specificity of the CMT for detecting infection in the first week after calving are moderate at best,[60,66] and antibiotic treatment is likely to be beneficial only for streptococcal infections.[99] The costs associated with CMT screening, culturing, antibiotic therapy, and milk discard will probably outweigh the benefits, unless the prevalence of streptococcal mastitis is high.

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36.5.1.2 BULK TANK MILK SAMPLING

Bulk tank milk is cultured to assess the udder health status of a herd, troubleshoot milk quality problems, or evaluate the adequacy of premilking hygiene practices. In the United States, processing plants routinely test bulk tank milk for aerobic bacteria (standard plate count, SPC) and SCC (BTSCC) and may test for psychotrophic, thermoduric, or coliform bacteria. Results of these cultures help to distinguish milk quality problems caused by mastitis from those caused by poor premilking hygiene, contaminated water, improper cooling of milk in the bulk tank, or unsanitary milking equipment.[100] However, processing plants do not routinely speciate aerobic bacteria or test for *Mycoplasma* species. More comprehensive milk cultures are useful for determining the contagious mastitis status of a herd.

Detection of *S. agalactiae, S. aureus,* pathogenic *Mycoplasma* species, or *C. bovis* in bulk tank milk implies there are infected cows in the herd. However, concentrations of these pathogens in bulk tank milk are not indicative of the number of infected cows or glands.[101] The BTSCC should be high if infections are prevalent, but BTSCC cannot be used to predict the prevalence. Failure to detect contagious mastitis pathogens in bulk tank milk, especially *S. aureus,* which is shed intermittently and in relatively low concentrations, does not mean that a herd is free of intramammary infection.[101,102] Also, milk from cows with clinical mastitis is diverted from the bulk tank, which prevents the causative pathogens from being detected. To improve the sensitivity of bulk tank or pooled-milk cultures, at least four samples should be cultured on different days. Culturing of milk filters is less sensitive for detecting contagious pathogens than is culturing of bulk tank milk.[102]

Detection of environmental streptococci, coliform bacteria, or coagulase-negative *Staphylococcus* species in bulk tank milk does not imply a mastitis problem. Although these pathogens may be originating from infected mammary glands, they can also come from teats that are not effectively cleaned and dried before milking. Contaminated teats predispose to environmental mastitis, so when high concentrations of environmental bacteria are found in bulk tank milk, it is important to assess premilking hygiene practices and farm conditions that impact teat cleanliness.

36.5.1.3 POOLED MILK SAMPLING

Culturing pooled milk from a subset of cows, rather than the entire herd, allows screening of specific groups or strings of cows for the presence of contagious mastitis. To accomplish this, the bulk tank is sampled before and after milking the cows in question, and results are compared. Alternatively, aseptically collected milk samples from individual cows may be pooled.

36.5.2 Sample Collection, Storage, and Handling

36.5.2.1 SAMPLING COWS

Teat ends must be thoroughly disinfected before collecting milk, to avoid introducing skin or environmental organisms into the sample. Typical preparation practices include dry-wiping the udder to remove loose debris that could fall into the tube, stripping a few streams of milk from the teat to remove organisms in the teat canal, and scrubbing the teat end with alcohol-soaked cotton swabs or gauze pads; scrubbing should continue until the swabs or pads appear clean. Wearing gloves and dipping the teats in a germicidal solution before

scrubbing the teat ends further reduce contamination risk. The risk of a contaminated sample is lower when milk is collected after milking, but premilking (foremilk) samples are more sensitive for detecting many pathogens.[103]

Milk should be collected in sterile tubes or sterile sealable bags. The tube or bag must not touch the teat. Milk should be directed into the tube or bag at an angle, to avoid placing the tube or bag directly under the teat, where it could become contaminated with falling debris from the udder. The cap of the tube must remain sterile and space left at the top of the tube or bag to accommodate expansion during freezing. When sampling multiple teats, the far teats should be scrubbed before the near teats and the near teats sampled first, to avoid contamination by the sampler's arm or hand. Failure to use aseptic technique can produce culture results that are not interpretable or are falsely interpreted. Samples must be refrigerated at 4° C, held on ice, or frozen until cultured.

36.5.2.2 SAMPLING BULK TANK

Milk should be aseptically collected from the top of the bulk tank using a sanitized dipper. Alternatively, a sterile uterine infusion rod attached to a 60-mL syringe works well. The sample should be collected shortly after the herd is milked and after agitating the milk for 5 to 10 minutes.[104] Bulk tank milk should be placed on ice or refrigerated and cultured within 36 hours of collection; freezing is required if longer storage is necessary.

36.5.3 Selection of Media

The media used for quarter or composite milk samples depends on the pathogen(s) of concern. Blood agar (5%), the most common medium, allows growth of most aerobic mastitis-causing pathogens. Addition of esculin or staphylococcal beta-toxin facilitates identification of streptococci. Clinical mastitis samples are often plated on MacConkey medium, which selects for gram-negative bacteria and facilitates diagnosis of coliform mastitis. Biplates are available that contain both blood agar with esculin and MacConkey agar. A variety of selective media for streptococci and staphylococci are also available. Triplates and quadplates incorporate streptococcal and staphylococcal media along with blood and MacConkey agar. The use of biplates, triplates, or quadplates facilitates pathogen identification by farm personnel.[105] *Mycoplasma* spp will not grow on blood agar and requires special media and enhanced—carbon dioxide (CO_2) incubation conditions. Therefore, if milk samples are to be tested for *Mycoplasma* spp, it is important to notify the laboratory.

Bulk tank milk samples should be plated on a variety of media to facilitate detection and quantification of streptococci, staphylococci, coliform bacteria, and (when of concern) *Mycoplasma* species.

36.5.4 Inoculum Size and Laboratory Methods

The amount of milk plated determines the lower limit of pathogen detection. For example, a 0.01-mL (10-µL) inoculum allows detection of approximately 100 CFU/mL of milk, whereas a 0.1-mL (100-µL) inoculum detects concentrations as low as 10 CFU/mL. With the traditional method of milk culturing, a swab or 0.01-mL loop is used to plate the sample onto one quadrant of a plate; this allows four samples to be cultured per plate. Larger (0.05- or 0.10-mL) inocula increase recovery rates for pathogens shed in low concentrations, such as *E. coli* or *S. aureus*. Other ways to increase recovery are preculture centrifugation,[106] incubation,[94,107,108] or freezing[108] of the milk, or a combination of these methods. The optimal method is pathogen dependent.

Augmented methods are most useful for detecting subclinical *S. aureus* infections and reducing false-negative results for clinical mastitis samples. Some reports suggest that freezing negatively impacts the isolation of *E. coli* from milk,[109,110] but this is not the case in all studies.[111]

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A selective culture system marketed for isolation and enumeration of specific pathogens from food products (Petrifilm plates, 3M, Minneapolis) was more sensitive (88%) than traditional milk culture (66%) for detecting *S. aureus* in milk and provided results within 24 hours. However, this test requires subjective interpretation of color changes, which leads to false-positive results if the person reading the films is inexperienced.[94]

The inoculum volume used for bulk tank milk varies among laboratories. Larger inocula (e.g., 0.1 or 0.2 mL) enhance detection of pathogens that are present in low concentrations. Preculture incubation (95° F for 18 hours) of bulk tank milk dramatically increased detection of *S. aureus* in one study.[112]

36.5.5 Interpretation of Culture Results

Pathogen identification procedures are described in detail in the *Laboratory Handbook on Bovine Mastitis* published by the NMC.[113] In most cases, it is not essential to identify mastitis pathogens to the species or strain level. For routine diagnosis and treatment purposes, it is sufficient to categorize isolates as *S. agalactiae*, other *Streptococcus* or *Enterococcus* species, coagulase-positive *Staphylococcus* species, coagulase-negative *Staphylococcus* species, coliform bacteria, *Corynebacterium* species, *Arcanobacterium (Actinomyces) pyogenes, Bacillus* species, yeast, or "other." Most isolates can be tentatively categorized on the basis of colony morphology, hemolysis pattern, Gram stain results, and catalase testing. Use of blood agar that contains esculin and staphylococcal beta-toxin allows differentiation of *S. agalactiae* from other streptococci and enterococci; alternatively, separate CAMP and esculin tests can be performed. Coagulase testing distinguishes coagulase-positive staphylococci (assumed to be *S. aureus*) from less pathogenic coagulase-negative species. As previously mentioned, use of biplates, triplates, or quadplates can facilitate pathogen categorization.[105] When speciation or further confirmation is desired, a variety of biochemical and nonbiochemical testing methods can be used. *Mycoplasma* isolates must be speciated to distinguish potential mastitis pathogens from incidental, nonpathogenic species.

Deoxyribonucleic acid (DNA) fingerprinting, phage typing, ribotyping, pulse-field gel electrophoresis, multilocus gene sequencing, and other molecular methods of pathogen typing can provide valuable information about the source and spread of infection in herds with mastitis problems. For example, ribotyping identified a cat with chronic sinusitis as the probable source of a herd outbreak of *Streptococcus canis* mastitis.[114] DNA fingerprinting demonstrated that many cows with recurrent episodes of clinical *E. coli* mastitis had chronic infections,[115] challenging the assumption that *E. coli* infections resolve spontaneously shortly after the onset of disease. Typing techniques allow bacterial isolates from potential environmental reservoirs to be compared with those causing high SCC or clinical mastitis[116] and can help identify the source of bacteria in bulk tank milk.[117] As molecular technologies become more affordable, their use in mastitis investigations is likely to increase.

36.5.6 Definition of Infection

No universally accepted criteria exist for defining intramammary infection. Researchers require growth of the same pathogen in at least two of three consecutive milk samples, growth of the same pathogen in duplicate milk samples collected simultaneously, or growth of a pathogen in conjunction with indirect evidence of infection (high SCC, positive CMT, or clinical signs of mastitis). In practice, it is too costly to collect consecutive or

duplicate milk samples. Therefore, diagnosis is usually made on the basis of a single milk culture result; fortunately, most cultures are from cows with clinical mastitis or high SCC, providing indirect evidence of infection.

Confidence in culture results is greatest when a single pathogen is isolated in pure culture. However, co-infections do occur. When three or more colony types are isolated from a given sample, the sample is considered contaminated. However, even in a contaminated sample, growth of a single colony of *S. agalactiae* or *S. aureus* is considered significant.

36.5.7 Alternative Methods of Pathogen Detection

Clinical mastitis episodes caused by gram-positive bacteria are usually treated with antibiotics, whereas antibiotics are not required for many coliform mastitis episodes (see section on clinical mastitis treatment). A variety of nonculture schemes using historical data (e.g., parity, stage of lactation, season of year) and clinical signs (e.g., rectal temperature, rumen contraction rate, appearance of milk) have been developed to distinguish coliform mastitis from mastitis caused by gram-positive bacteria.[118–121] Unfortunately, none of these schemes is sufficiently accurate to be used as a basis for antibiotic treatment decisions. Although veterinary practitioners often believe they can recognize coliform mastitis, one study showed that practitioners correctly identified only 23 of 36 (63%) coliform mastitis episodes and misidentified 32 of 82 (39%) noncoliform episodes.[122] An artificial neural network and a model using inductive inference were only able to accurately classify bacterial pathogens about 60% of the time.[123]

Cow-side tests that detect LPS in milk have been used to identify gram-negative mastitis episodes.[124] However, these tests are not available in the United States. A method that distinguishes gram-positive and gram-negative bacteria in milk by adding a reagent, incubating the mixture in hot tap water for 2 minutes, filtering the mixture through a membrane, and staining the membrane has been described.[125] Unfortunately, the limit of detection of that method was 10^6 CFU/mL or greater for *E. coli* and *S. aureus,* which is too high for many mastitis episodes.

Cows with gram-negative clinical mastitis are more likely to be neutropenic and monocytopenic and to have higher blood hemoglobin concentration than cows with gram-positive clinical mastitis. The sensitivity of the combination of these hematologic parameters for detecting gram-negative mastitis was 93%, and specificity 89%, in one study.[126] If a laboratory is not available or a complete blood count (CBC) is considered too costly, the percentage of segmented neutrophils and monocytes on a blood smear can be used; sensitivity and specificity of differential cell counts were 87% and 71%, respectively.

Polymerase chain reaction (PCR) technology has allowed development of a number of PCR tests for mastitis pathogens. With PCR, pathogens are detected and definitively identified more rapidly than by milk culture. Unfortunately, because PCR primers are specific for particular pathogens, PCR cannot be used to test milk for a wide range of mastitis-causing pathogens. Multiplex PCR overcomes this limitation to some extent. For example, a recently developed multiplex real-time PCR method for simultaneous detection of *S. aureus, S. agalactiae*, and *Streptococcus uberis* correctly identified 96% of quarter milk samples.[127] PCR is also used for detecting *Mycoplasma* mastitis because culture results can take more than a week.[128] Now that techniques have been developed to overcome the inhibiting effects of milk on PCR, PCR testing will likely become more widespread.

36.6 SPECIFIC MASTITIS INFECTIONS

36.6.1 *Streptococcus agalactiae* Mastitis

Herds that conscientiously use the control measures described earlier in the five-point plan can eliminate or greatly reduce *S. agalactiae* mastitis within a few years. However, *S. agalactiae* spreads rapidly when effective control measures are not in place and can cause substantial economic loss. Most episodes of *S. agalactiae* mastitis are subclinical and last for months or years if not treated. Subclinical infection may be interspersed with bouts of mild clinical mastitis, but cows do not become systemically ill.

Streptococcus agalactiae adheres to epithelial cells in the mammary gland and localizes primarily in the ducts. Milk production declines when ducts become blocked with cells and debris and the associated alveoli involute. Early treatment can restore milk production because permanent damage to the gland is minimal. However, tissue damage, fibrosis, and a permanent decrease in milk production can occur if infection becomes chronic. *S. agalactiae*–infected glands tend to shed high concentrations of bacteria and SCC in milk. Even a small number of infected cows can increase the SCC or SPC of bulk tank milk and result in milk quality penalties.[129–131]

Streptococcus agalactiae mastitis should be suspected in herds that have a high or increasing BTSCC or a large or increasing proportion of cows with persistently elevated SCC. Growth of esculin-negative, CAMP-positive streptococci in milk from the bulk tank or from individual cows confirms *S. agalactiae* infection. Composite milk from all cows in the herd must be cultured to determine the prevalence of infection and identify positive cows. PCR is a promising alternative to milk culture.[127,131–133]

36.6.1.1 Treatment

S. agalactiae is highly susceptible to penicillin and other antibiotics marketed for intramammary infusion in the United States. Bacteriologic cure rate typically exceeds 90% after a single course of therapy during lactation[134–136] or at dry-off.[137] Therefore, in herds with prevalent *S. agalactiae* mastitis and high economic loss, it is acceptable to mass-treat (“blitz-treat”). This is accomplished by treating all lactating cows or (preferably) culturing milk from all lactating cows and treating those with *S. agalactiae* infection; all four quarters of each cow are treated. Cows that are close to the end of lactation can be dried off and dry-treated. A small proportion of cases will fail to cure or will be missed on milk culture, so it is essential to institute effective control measures in conjunction with blitz treatment. Although the initial cost of blitz treatment is high, the benefit/cost ratio usually exceeds 2:1 because of an increase in milk production and decline in BTSCC.[135,138,139]

Failure to disinfect teat ends adequately before blitz-treating cows, or use of contaminated antibiotic solutions or infusion equipment rather than commercially available antibiotic tubes, can result in financially devastating outbreaks of environmental mastitis.[140–142] Therefore, veterinarians or other personnel who are trained in aseptic technique should perform the infusions, using commercially available tubes. Systemic antibiotics are not necessary or recommended for treatment of *S. agalactiae* mastitis.[136]

36.6.1.2 Control

Control measures for *S. agalactiae* mastitis are described in the section on contagious mastitis. Postmilking germicidal teat dipping and dry-cow antibiotic therapy are the most important measures. Introduction of infected cows to a herd can lead to rapid spread of *S. agalactiae* mastitis if control measures are not meticulously carried out. Purchasing animals from an *S. agalactiae*–free herd or culturing milk before putting cows in the milking herd can reduce this risk. Vaccines are not available or necessary for control of *S. agalactiae* mastitis.

36.6.2 *Staphylococcus aureus* Mastitis

Most dairy herds have cows with *S. aureus* mastitis, but the prevalence and economic impact vary. As for *S. agalactiae*, most *S. aureus* intramammary infections are chronic and subclinical, with periodic bouts of clinical mastitis. However, clinical *S. aureus* mastitis ranges in severity from mild to gangrenous. Herds with a high prevalence of *S. aureus* mastitis cannot be distinguished from those with a high prevalence of *S. agalactiae* mastitis without culturing milk; in some cases, both pathogens are prevalent. Herds with *S. aureus* or *S. agalactiae* mastitis tend to have a high or increasing BTSCC and a large or increasing proportion of cows with persistently elevated CMSCC; however, *S. agalactiae* mastitis tends to cause higher SCC and a higher bulk tank bacteria count.

Staphylococcus aureus mastitis is presumptively diagnosed by isolating coagulase-positive staphylococci from bulk tank milk or infected glands, particularly if colonies are surrounded by a double zone of hemolysis (complete hemolysis surrounded by incomplete hemolysis). Because certain *S. aureus* strains are coagulase negative[143] and other *Staphylococcus* species (e.g., *S. hyicus*) can be catalase positive,[144] definitive identification requires additional diagnostic testing. Herds typically have a predominant strain of *S. aureus,* with additional strains appearing sporadically.[145] Strains of *S. aureus* differ in contagiousness, virulence, and antibiotic susceptibility, leading to variable responses to treatment and control measures among herds and among cows.[146–148] In some cases, multiple strains of *S. aureus* co-inhabit a gland or cow.[149] Resolution of infection with one strain can be followed by infection with another strain.[150]

Staphylococcus aureus adheres to and invades mammary epithelial cells and interstitial tissue.[151–153] It also resists phagocytosis by neutrophils. Antiphagocytic mechanisms include a capsule that inhibits opsonization and a surface protein (protein A) that binds the Fc portion of host Ig. Leukotoxin production enables some *S. aureus* strains to kill phagocytes.[154] Other mechanisms allow *S. aureus* to survive within leukocytes and epithelial cells and induce apoptosis.[153,155,156] *S. aureus* strains produce a variety of enzymes and exotoxins that damage mammary cells and result in fibrosis and abscess formation.[157] Some strains produce β-lactamase, conveying resistance to antibiotics such as penicillin and amoxicillin. Others convert to L-form or small colony variants, which can persist with antibiotic therapy.[158–160] Certain *S. aureus* strains form adherent colonies surrounded by a biofilm, making them inaccessible to phagocytes and antibiotics[161,162]; biofilm-associated proteins are associated with persistent *S. aureus* mastitis.[161] For these reasons, *S. aureus* intramammary infections seldom resolve spontaneously and are difficult to treat with antibiotics.

36.6.2.1

Treatment

A number of cow factors influence the response of *S. aureus* to antibiotic treatment during lactation or at dry-off.[163] These include parity, stage of lactation, SCC, and quarter.[66,164–166] Older cows (parity >2), cows in early to midlactation, quarters with SCC greater than 1×10^6/mL, and rear quarters have a higher risk of treatment failure compared with young cows, cows in late lactation, quarters with low SCC, and front quarters. Duration of infection and bacterial concentration in milk are also negatively correlated with cure rate.[66,164] Infection in multiple quarters reduces cure rate at the cow level.[164] Because pathogen and cow factors can greatly impact treatment response, blitz treatment should never be attempted, even in herds with a high prevalence of infection. Rather, treatment decisions should be made on a case-by-case basis, considering the cow's history, value, and likelihood of cure.

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Intramammary antibiotics are the mainstay of *S. aureus* mastitis treatment. Beta-lactamase—resistant antibiotics, such as cephapirin, ceftiofur, or cloxacillin, should be used unless isolates are tested for β-lactamase production.[167] Even when β-lactamase—producing *S. aureus* strains are treated with β-lactamase—resistant antibiotics, the cure rate tends to be lower than for β-lactamase—sensitive strains[148]; therefore, β-lactamase testing can be prognostic. Most intramammary antibiotics marketed in the United States are labeled for two or three doses 12 or 24 hours apart. The bacteriologic cure rate associated with a typical 2- or 3-day treatment regimen is very low. Increasing the duration of treatment increases the time above the minimum inhibitory antibiotic concentration (MIC) for the pathogen, which should increase the likelihood of cure. Indeed, a 4-, 5-, or 8-day treatment regimen was superior to a 2-day regimen or no treatment in several studies.[166,168,169] However, even with extended therapy, the cure rate can be less than 50%.[170] Infusing antibiotics per label directions on three occasions, with a withholding period after each treatment period ("3-peat therapy"), avoids extralabel drug use, but cure rates vary widely (14% to 50%) among studies.[171]

Duration of intramammary antibiotic treatment is irrelevant if the antibiotic cannot reach bacteria that are sequestered within cells or abscesses. Inflammation and swelling in *S. aureus*–infected glands can also reduce the distribution of intramammary antibiotics.[172] Concurrent use of systemic antibiotics that achieve effective concentrations in mammary tissue and milk should augment intramammary antibiotic therapy, but few well-designed studies have addressed this question. In one study the cure rate of *S. aureus* mastitis was twofold higher (51% vs. 25%) when six intramammary infusions of amoxicillin were accompanied by three intramuscular (IM) injections of procaine penicillin.[159] A combination of intramammary and systemic antibiotics also appears to be superior to systemic antibiotics alone.[148]

The variability in cure rates observed among herds, regardless of antibiotic treatment regimen, likely reflects cow selection and the strains of *S. aureus* in the herd.[173] Milk from treated cows should be cultured at least twice after the end of the antibiotic-withholding period before cure is presumed; increasing the number of cultures will detect more unresolved infections.[165,174]

36.6.2.2

Control

The five-point mastitis control plan (see contagious mastitis) effectively reduces the incidence and prevalence of *S. aureus* mastitis but does not eradicate it. Some strains persist in the face of excellent milking hygiene practices, necessitating strict segregation, culling, and drying off of infected cows to control an

outbreak.[87] The five-point plan will not necessarily control sporadic infections with nonpredominant strains.[147] Those strains may be harbored outside the mammary gland and require different control measures. New *S. aureus* infections can develop during the dry period, when glands are not being milked,[150] attesting to alternative reservoirs of infection, such as the environment or skin.

Herds that purchase replacement heifers have a higher prevalence of *S. aureus* mastitis and more *S. aureus* strains than do closed herds, illustrating the importance of biosecurity in mastitis control.[145] Because the predominant strains of *S. aureus* differ among herds, even those close to one another,[175] measures that effectively control *S. aureus* mastitis in one herd may fail in other herds in the same geographic area. Cows with resistant *S. aureus* mastitis or a low likelihood of cure should be culled as soon as economically feasible, or segregated and milked last. Alternatives are simply to stop milking the infected gland or to induce cessation of lactation by infusing a disinfectant solution (see treatment of clinical mastitis).

Highly effective vaccines for *S. aureus* mastitis are not available. Commercially available, multistrain bacterins provide variable protection against acute and chronic infection,[176–179] and protection is typically of short duration. Vaccination may enhance the spontaneous cure rate,[176] reduce SCC,[176,179] or reduce the severity or duration of clinical mastitis,[178] but again, results vary. Efficacy likely depends on the relatedness of the *S. aureus* strains in the bacterin to strains present in the herd. Herd-specific autogenous bacterins have generally failed to provide protection,[180,181] possibly because of the components of the bacterin or dosing regimen. In general, *S. aureus* bacterins appear to be more protective in heifers than in cows.

Recently, *S. aureus* vaccines have been used in combination with extended intramammary antibiotic therapy in an attempt to increase bacteriologic cure rate.[171,182] Infected cows are vaccinated before and shortly after antibiotic treatment. Although experimental vaccines appeared promising, use of a commercially available bacterin in conjunction with extended pirlimycin therapy did not enhance the efficacy of pirlimycin therapy[171] and cured less than 50% of infections.[182] Vaccination strategies being investigated include delivery of *S. aureus* virulence-associated antigens in plasmid expression vectors (DNA vaccination),[183] recombinant viral vectors,[183] or microspheres.[184] Better vaccines will likely be available in the future as researchers identify appropriate antigen combinations, adjuvants, and delivery mechanisms.

36.6.3 *Mycoplasma* Mastitis

Mycoplasma species are found in a variety of extramammary body sites of cattle, such as the respiratory and urogenital tracts. Colonized cattle may be asymptomatic or may develop bronchopneumonia, otitis, polyarthritis, or mastitis. In dairy herds with *Mycoplasma* mastitis, otitis media-interna, respiratory disease, or swollen joints may be seen in calves, especially if unpasteurized milk is fed.[185] Cows may or may not exhibit clinical signs other than mastitis. Most *Mycoplasma* intramammary infections are subclinical and chronic, as with *S. agalactiae* and *S. aureus*. However, when clinical mastitis occurs, it often affects multiple glands simultaneously or in succession and fails to respond to conventional antibiotic therapy. Although the milk from cows with clinical *Mycoplasma* mastitis is visibly abnormal, the cows are usually systemically healthy.

The pathogenesis of *Mycoplasma* mastitis is not fully understood. Asymptomatic carrier animals may infect herdmates by shedding the organisms in nasal or vaginal secretions, feces, or milk. Purchased animals are often blamed for introducing *Mycoplasma* mastitis, but outbreaks can occur even in closed herds. Cow-to-cow transmission of intramammary infection is believed to occur through milk-contaminated fomites at milking

time, as with other contagious mastitis pathogens. However, it appears that *Mycoplasma* species can be transmitted from other body sites to the mammary gland, or vice versa, via the bloodstream or lymphatics. For example, experimental intramammary inoculation of *Mycoplasma* species into a single mammary gland was followed by detection of phenotypically identical *Mycoplasma* species in extramammary body sites, blood, and noninoculated mammary glands,[186,187] even when gland-to-gland transmission was prevented by a special milking device.[187] Recently, Biddle et al.[188] found that isolates of *Mycoplasma* species from the milk, mammary gland parenchyma, and supramammary lymph nodes of infected cows all had the same pulse-field gel electrophoresis pattern, and that all cows had at least one extramammary isolate with the same pattern. These findings suggest that cows with *Mycoplasma* mastitis frequently have disseminated infections, and that internal transmission may occur.

Results of bulk tank surveys suggest that less than 10% of U.S. dairy herds have cows with *Mycoplasma* mastitis; however, the economic impact in infected herds can be substantial. Many species of *Mycoplasma* can infect the mammary gland and cause mastitis, but *M. bovis* is isolated most frequently. *Mycoplasma* infection will be missed when milk is cultured unless appropriate media and incubation conditions are used. Freezing of samples reduces the concentration of viable organisms, whereas broth enrichment before culturing can enhance detection of *Mycoplasma* species.[189] Colonies usually take 7 to 10 days to appear, and isolates must be speciated to differentiate pathogenic from nonpathogenic *Mycoplasma* strains. Because of the time required for culture and secondary speciation, PCR-based diagnostic methods have been developed. Recent PCR-based methods have acceptable limits of detection (<100 CFU/mL) and use primers that differentiate among several *Mycoplasma* species.[190] PCR-based methods likely will increasingly replace culture for detection of *Mycoplasma* mastitis.

When pathogenic *Mycoplasma* organisms are isolated from the bulk tank or milk from an individual cow, the herd probably contains more than one infected animal. Pooled milk can be cultured after milking each string of cows to help identify infected groups for further testing. Cows with clinical mastitis and those with high SCC are good candidates for testing but may not include all infected individuals.

36.6.3.1

Treatment and Control

Antibiotic treatment of *Mycoplasma* mastitis is unrewarding, at least with antibiotics that can be used in lactating cows in the United States. Although some intramammary infections may resolve spontaneously, infected cows should be considered permanently infected. Even if repeated culturing of milk from an individual quarter yields negative results, infection might persist in an extramammary site and spread to the mammary gland later. For this reason, some dairy producers cull all cows diagnosed with *Mycoplasma* mastitis. However, even aggressive diagnosis and culling programs may not prevent periodic *Mycoplasma* mastitis incidents if infections persist asymptomatically in extramammary sites. A more economical alternative to aggressive culling is to house and milk infected cows separately, culling only when indicated (e.g., persistent or recurrent clinical mastitis, low production); once a cow enters the *Mycoplasma* string, she should remain there until culled. In one study, *Mycoplasma* species were isolated from bulk tank milk for less than 1 month in 70% of herds, suggesting that producers rapidly identified and managed cows before prevalence could escalate.[191]

Although *M. bovis* bacterins are available in the United States, minimal data have been published to assess their efficacy. Vaccination against *M. bovis* is hindered because of variable expression of a diverse and ever-changing set of genes encoding surface lipoproteins (Vsps).[192]

Mycoplasma species are susceptible to germicides often found in teat dips.[193] Effective premilking and postmilking teat dipping and other measures used to prevent the spread of contagious pathogens in the milking parlor help limit *Mycoplasma* mastitis transmission. Dry-cow antibiotic therapy, however, does not reduce the prevalence of infected mammary glands. Pasteurization of waste milk reduces the risk of *Mycoplasma* transmission to milk-fed calves.[185]

36.6.4 *Corynebacterium bovis* Mastitis

Although highly contagious, *C. bovis* is considered a minor mastitis pathogen because it typically inhabits the teat canal, induces a lesser increase in SCC than other contagious mastitis pathogens, causes subclinical infection, and has little impact on milk yield.[194] *C. bovis* can cause clinical mastitis,[195,196] but the episodes are usually milder than those caused by other gram-positive bacteria or coliform bacteria.[196] As with *S. aureus*, there is often a predominant strain of *C. bovis* in a herd.[197]

Corynebacterium bovis mastitis can be controlled by measures that control other contagious mastitis pathogens.[198] A high prevalence of *C. bovis* mastitis is often attributable to poor teat-dipping practices.[195,199]

There is some evidence that *C. bovis* infection may protect against mastitis caused by major pathogens. For example, in a large case-control study, the odds of infection with a major pathogen were significantly reduced when a gland was infected with *C. bovis* than when a gland was uninfected (odds ratio [OR] = 0.52).[200] However, failure to control *C. bovis* means that contagious mastitis control measures are insufficient and the herd is at risk for an outbreak of *S. aureus, S. agalactiae*, or *Mycoplasma* mastitis should those pathogens be introduced.

36.6.5 Environmental Streptococcal Mastitis

Mastitis-causing *Streptococcus* species other than *S. agalactiae* are referred to as "environmental streptococci." These include *S. uberis, S. parauberis, S. dysgalactiae, S. equinus, S. saccharolyticus. S. salivarius, S. canis*, and others; enterococci, such as *Enterococcus faecalis* and *E. faecium*, and *Aerococcus viridans* are often grouped with the environmental streptococci. These catalase-negative, gram-positive cocci have reservoirs in the environment and act as opportunistic pathogens, whereas the main reservoir for *S. agalactiae* is infected mammary glands. This does not mean that environmental streptococcal mastitis cannot spread contagiously. Indeed, *S. dysgalactiae* is sometimes categorized as a contagious pathogen. Also, *S. canis* and some strains of *S. uberis* have been implicated in mastitis outbreaks that appear to involve cow-to-cow transmission.[114,201,202] Still, environmental streptococcal mastitis is relatively more prevalent and costly in herds that have achieved control of contagious mastitis. Most research on environmental streptococcal mastitis has focused on *S. uberis,* which is considered the most important of these pathogens.[203]

Environmental streptococci are shed in the feces of cattle and are ubiquitous in the environment on dairy farms. Fecal shedding probably accounts for isolation of environmental streptococci from water, soil, plant material, and flies.[116] Infected dogs and cats can carry *S. canis* in their respiratory and urogenital tracts and serve as potential sources of infection for cows.[114,201] *S. uberis* is found in the vagina of cows,[116] but genital tract secretions probably play little role in the transmission of infection compared with feces.

Bedding is considered to be a major source of environmental streptococcal exposure for cows housed in confinement. Environmental streptococci multiply in a wide range of bedding materials, particularly when the bedding is contaminated with feces and urine.[204,205] Straw, in particular, supports the growth of *S. uberis*. However, *S. uberis* mastitis also affects pastured cows and cows in lots that are not bedded. High-traffic races and areas of pastures or lots where cows congregate and defecate harbor *S. uberis* and serve as reservoirs.[116]

Approximately 50% of environmental streptococcal infections are initiated during the dry period.[206] The mammary gland is highly susceptible to environmental streptococcal infection during the early and late stages of the dry period, when mammary secretions accumulate and host defense mechanisms are compromised.[13,207–209] However, infection may develop at any stage of lactation. Infection is accompanied by a rapid influx of neutrophils into the mammary gland and a resultant increase in SCC. Based on experimental inoculation studies with *S. uberis*, the recruited neutrophils are unable to fully prevent bacterial multiplication.[210] Ineffective host response probably explains the prolonged infections and persistently high SCC seen in some cases.

Environmental streptococcal infections often remain subclinical, with the main impact being the increase in SCC. When the prevalence of environmental streptococcal mastitis is high, the increase in BTSCC may result in penalties or loss of quality premium payments.[201,211] In some cases, environmental streptococcal counts in bulk tank milk may exceed the regulatory limit of 100,000 CFU/mL.[117] Although a portion of the environmental streptococci in bulk tank milk come from contaminated teat skin, strain typing has demonstrated identical strains of *S. uberis* in bulk tank milk and infected mammary glands. This suggests that infected cows may contribute to excessively high bulk milk bacteria counts.[117]

Although most environmental streptococcal infections resolve within 30 days, about one third of infections persist for long periods, sometimes more than a lactation. Also, up to 50% of environmental streptococcal infections result in clinical mastitis.[206] Clinical mastitis causes economic loss as a result of discarded milk and treatment costs. Fortunately, most clinical mastitis episodes are of mild to moderate severity and do not result in marked milk production loss or death of the cow.

36.6.5.1

Treatment

Antibiotic treatment of clinical mastitis is an important component of environmental streptococcal mastitis control (see later). Treatment of subclinical mastitis is usually accomplished by intramammary infusion of antibiotics at dry-off. Antibiotic treatment of subclinical mastitis during lactation is controversial and usually discouraged. Milk yield may not increase after treatment of environmental streptococcal mastitis,[212] which limits potential economic benefit. However, effective treatment reduces the duration of high SCC and bacterial shedding, thus improving milk quality. Effective treatment also decreases clinical mastitis occurrence and reduces the risk of transmission to other quarters or cows. When these benefits were considered, partial budget modeling predicted a net profit from treating subclinical environmental streptococcal infections with a 3-day course of intramammary antibiotics.[213]

Alternatives to antibiotic administration for treating subclinical or mild clinical environmental streptococcal mastitis have been investigated. The most common alternatives are no treatment, administration of oxytocin at milking time, and frequent milk-out of the gland(s). Although oxytocin administration resulted in similar clinical and bacteriologic cure rates for mild clinical environmental streptococcal mastitis as did two or three treatments with intramammary antibiotics,[214] the subsequent rate of recurrence and new infections was

higher.[215] Adoption of a nonantibiotic approach to clinical environmental streptococcal mastitis was followed by a marked increase in bulk tank SCC and clinical mastitis in one herd, presumably caused by persistence and spread of infections.[211] Bacteriologic cure rate was increased and recurrence rate decreased in several studies in which intramammary antibiotics were compared with no treatment for mild clinical[216,217] or subclinical[212,216] mastitis. Similarly, intramammary antibiotics resulted in a higher cure rate for mild clinical environmental streptococcal mastitis than did oxytocin administration with or without frequent milking.[217,218] In one study, administering oxytocin in conjunction with intramammary antibiotics reduced the bacteriologic cure rate of experimentally induced *S. uberis* mastitis compared with antibiotics alone, suggesting a detrimental effect of oxytocin.[217] Oxytocin and frequent milking were ineffective at preventing clinical mastitis, even when initiated at the first sign of subclinical *S. uberis* infection.[219]

Susceptibility of environmental streptococci to antibiotics used in commercial intramammary infusion products in the United States varies among species, with *S. dysgalactiae* isolates being more susceptible than *S. uberis*, and enterococci being least susceptible.[220,221] However, in vitro susceptibility does not necessarily predict responsiveness to antibiotic therapy.[222,223] The bacteriologic cure rate associated with a two- or three-dose (on-label) regimen of intramammary antibiotics is usually lower for environmental streptococcal mastitis than for *S. agalactiae* mastitis.[213,215,224,225] Extending the duration of therapy increases the time that antibiotic concentration is above the MIC. Extended duration therapy (5 to 8 days) enhanced the bacteriologic cure rate in studies involving experimental[217,226] and natural[170,225,227] environmental streptococcal infections compared with on-label therapy. However, the economic benefit of extended (8-day) therapy for subclinical environmental streptococcal mastitis was predicted to be less than for 3-day therapy in one model.[213] As for *S. aureus* mastitis, the duration of environmental streptococcal infection and the magnitude of SCC probably influence the likelihood of successful antibiotic treatment, with chronic infections and infections with high SCC being difficult to resolve.[225]

Systemic antibiotic treatment is an alternative to intramammary antibiotic treatment. For example, IM administration of penethamate hydroiodide cured 59% of chronic *S. uberis* or *S. dysgalactiae* infections, versus 0% in untreated cows[212]; clinical mastitis incidence and CMSCC were also reduced by antibiotic treatment. However, systemic antibiotic therapy results in greater total antibiotic use than intramammary antibiotic therapy, and both routes appear to produce similar cure rates.[217] Therefore, intramammary antibiotic therapy is preferred.

36.6.5.2

Control

Control of environmental streptococcal mastitis involves reducing exposure of the teats to feces and fecal-contaminated fomites, such as bedding and soil. This can be accomplished by providing clean, dry, comfortable stalls or resting areas; feeding cows after milking to keep them standing; controlling environmental temperature and humidity; providing sufficient shelter to reduce congregation of cows; avoiding overcrowding; removing manure frequently; and preventing access to high-risk locations such as contaminated ponds. Particular attention should be paid to housing conditions for dry and periparturient cows because of their increased susceptibility. Sand is the preferred bedding material for housed cows, but sand that becomes contaminated with feces and urine can readily support pathogen multiplication.[205] Brisket boards, cow trainers, and other devices used to position cows properly in stalls can reduce contamination of the bedding. Management of bedding is critical to avoid buildup of environmental streptococci. Frequent removal and replacement of organic bedding material are essential because environmental streptococcal

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concentrations can escalate within 24 hours under the right conditions.[204,205] Alkaline and acidifying bedding conditioners may transiently inhibit bacterial growth, but efficacy depends on the type of bedding and declines within 2 to 6 days after application.[228]

If facilities and environmental hygiene practices are appropriate, udders should be relatively clean and dry when cows enter the milking parlor. Cleanliness scoring systems have been developed to facilitate assessment of udder hygiene and monitor changes in hygiene over time.[89,229] Clipping or flaming of udder hair should reduce accumulation of bedding material and feces. However, this practice did not reduce teat skin or milk bacterial concentrations or intramammary infection risk in a herd with excellent premilking hygiene practices.[230] Tail docking, although a seemingly logical procedure for reducing fecal contamination of the udder, does not significantly improve udder cleanliness or reduce mastitis risk[88,89]; clipping of the switch is a more humane alternative to reduce manure on the tail.

Even visibly clean teats should be disinfected before milking to reduce bacteria on the skin and in the bulk tank.[231] Predipping is an effective way to accomplish this, provided gross organic matter is removed first and the germicide contacts the skin of the entire teat for a sufficient time (20 to 30 seconds) before being removed.[231–233] Failure to effectively wipe the teats to remove the dip can result in germicide residues in the bulk tank milk.[234] Washing of each teat with water containing a sanitizing solution is an alternative to predipping, provided the water is clean, excessive wetting of the udder is avoided, and the teats are thoroughly dried using clean towels.[231] Predipping and drying were more effective at preventing experimental *S. uberis* intramammary infections than washing and drying in one study.[232] Thorough cleaning and drying of the teats, with or without forestripping, provide the stimulation and time needed to elicit milk ejection, which minimizes milking time and the risk of milking-induced teat trauma.[235]

Postmilking teat disinfection may reduce environmental streptococci on the teat skin and thereby potentially prevent new infections from developing immediately after milking. However, postmilking teat disinfection does not protect cows against teat contamination or infection between milkings or during the dry period. Dry-cow antibiotic therapy is used to resolve environmental streptococcal infections that are present at dry-off and prevent new infections during the early dry period.[12,84] Unfortunately, antibiotic activity is not sufficient to prevent new infections in the late dry period.[209]

To help protect the teats from environmental streptococcal infection throughout the dry period, an internal teat sealant can be infused into all four quarters at dry-off. This inert material (bismuth subnitrate) remains in the teat cistern, providing a physical barrier against infection until removed after calving. Internal teat sealant used alone reduces new environmental streptococcal infections during the dry period compared with no treatment.[236] New infection rates are similar for quarters treated with teat sealant or antibiotics at dry-off.[237–239] However, the combination of antibiotics and teat sealant is superior for preventing new environmental streptococcal infections during the dry period and is also indicated if the prevalence of infection at dry-off is high.[91,238] External teat sealants are an alternative to internal sealants but are more cumbersome to use because teats must be monitored frequently and the sealant reapplied as needed.[90]

Because of the large number of species and strains of bacteria that cause environmental streptococcal mastitis, vaccination is not a feasible general control measure. Vaccines that specifically target *S. uberis* hold promise[203] but will not replace hygiene as the mainstay of mastitis control.

36.6.6 Coliform Mastitis

Coliform mastitis is a major cause of disease in many well-managed dairy herds, accounting for approximately 30% to 50% of clinical mastitis episodes.[240] Although *E. coli* causes most coliform mastitis episodes, *Klebsiella* species are important contributors on some farms, with *Enterobacter* species isolated less frequently. Other gram-negative mastitis-causing bacteria, such as *Serratia, Pseudomonas, Salmonella, Proteus,* and *Pasteurella,* are discussed later. Coliform mastitis can be distinguished from noncoliform mastitis by culturing milk on MacConkey agar and observing the characteristic pink colonies indicative of lactose fermentation.

As with environmental streptococci, coliform bacteria are shed in the feces and are ubiquitous on dairy farms. A wide variety of strains are capable of causing mastitis.[241] Mastitis develops after teats are exposed to feces or to contaminated bedding, water, or soil. Organic bedding materials, such as straw, wood chips, sawdust, recycled manure, pelleted corncobs, and newspaper, support the growth of coliform bacteria, particularly under warm, wet conditions.[242,243] Sawdust bedding has been implicated in outbreaks of *Klebsiella* mastitis,[244] but *Klebsiella* species can proliferate rapidly in other bedding materials as well. Intramammary infections and clinical coliform mastitis tend to increase during summer.[245] Rainfall, stocking density, frequency of manure removal, and frequency of pasture rotation can also influence the extent of exposure and risk of intramammary infection.

The majority of coliform intramammary infections develop during the early and late phases of the dry period.[208,246] These infections usually remain subclinical until after parturition. Most clinical coliform mastitis episodes that develop during early lactation are the result of infections acquired during the dry period.[208,246] Also, quarters that were infected during the dry period are at higher risk of clinical mastitis in early lactation than are quarters that were not infected.[246] In one study, *E. coli* infection during the late dry period was associated with an increased risk of culling in the next lactation.[209] Although the dry period and early lactation are times of high risk for coliform mastitis, it can develop at any time during lactation, particularly if exposure is high and cows are stressed.

The majority of clinical coliform mastitis episodes are mild, with less than 10% causing systemic illness or a marked drop in milk production.[120,247] However, coliform mastitis accounts for the majority of severe clinical mastitis episodes on most farms.[248] The outcome of clinical coliform mastitis depends on the severity, which reflects the cow's immune response (see later). Systemic signs are better than local signs or a combination of systemic and local signs for predicting coliform mastitis outcome.[249] High or subnormal rectal temperature, reduced rumen contraction rate and amplitude, marked dehydration, and marked depression are associated with increased risk of death, culling, or poor return to milk production.[76,79] Severe neutropenia[79] and high bacterial concentration in the milk[79,250] are also indicative of a poor prognosis. Cows in early lactation cows do not develop neutropenia to the extent observed in later lactation; therefore the leukon is not a good indicator of mastitis severity in early lactation cows.[126,251]

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Once in the mammary gland, coliform bacteria multiply rapidly but do not adhere to or invade the epithelial cells.[252] Therefore, if the cow's immune response is rapid and efficient, infection will be eliminated quickly, with little long-term impact on cow health or productivity. This is what usually happens when healthy cows are experimentally inoculated with *E. coli* and when cows develop coliform mastitis in mid- to late lactation. In such cases, cows are referred to as “mild responders” or “moderate responders.” However, when influx of

neutrophils is delayed or phagocytosis or intracellular killing mechanisms of neutrophils impaired, bacterial multiplication continues, resulting in high bacterial concentrations in the milk and severe clinical disease. This happens most frequently in the periparturient period and early lactation. In such cases, cows are referred to as "severe responders," and prognosis for recovery is worse.[25,55,253,254] Responsiveness does not depend solely on stage of lactation and varies among cows. Indeed, it is believed that cow factors, rather than bacterial factors, are the predominant determinants of coliform mastitis outcome.[252]

As coliform bacteria multiply and die in the mammary gland, LPS (endotoxin) is released from the cell wall. Binding of LPS to host cells results in release of TNF-α, which is largely responsible for initiating the inflammatory cascade that causes the local and systemic signs of coliform mastitis.[255,256] Important contributors to the inflammatory response include prostaglandins,[257] IL-1, IL-6, and IL-8,[25] C5a,[258] nitric oxide,[256,259] and acute-phase reactants.[254] Although LPS concentration in the milk may be high, LPS is usually undetectable or in low concentration in the plasma.[260] This suggests that the fever, tachycardia, reduced rumen motility, and signs of shock that accompany severe coliform mastitis are not a consequence of endotoxemia but of production and absorption of other inflammatory mediators, such as TNF-α. The concentration of TNF-α in milk is positively correlated with coliform mastitis severity, and a high concentration of TNF-α in blood is seen only in severe responders.[25,254–256] Hematologic and plasma biochemical changes that often accompany clinical coliform mastitis include leukopenia (neutropenia, lymphopenia, monocytopenia), hypocalcemia, and reductions in plasma concentrations of zinc, copper, and iron.[126,261]

Bacteremia does not occur during experimental coliform mastitis but develops in 30% to 40% of severely ill cows with naturally occurring clinical coliform mastitis.[77,262] The risk of coliform bacteremia increases with the severity of clinical signs.[262] Also, cows that remain neutropenic for 4 or more days, or that have high metamyelocyte and myelocyte concentrations in their blood, are more likely to be bacteremic than cows with a normalizing leukon.[251] Cows with coliform bacteremia are at greater risk of death or culling compared with nonbacteremic cows.[262]

Most coliform intramammary infections are of short duration, which means that less than 5% of quarters in a herd are infected at a given time.[245,247] However, up to 10% of *E. coli* infections can become chronic. Chronic infections put cows at risk for recurrent clinical mastitis in the affected quarter and for coliform infections in other quarters.[115,263] Clinical mastitis accompanying persistent infections tends to be milder than clinical mastitis accompanying newly acquired infections.[263]

36.6.6.1

Treatment

Antibiotic treatment of subclinical coliform mastitis is considered unnecessary because of a high spontaneous cure rate and short duration of infection. The need for antibiotic treatment of clinical coliform mastitis is debated. Cows with mild to moderate clinical coliform mastitis are often able to combat the infection effectively without antibiotics. Even some systemically ill cows clear the intramammary infection rapidly, making antibiotics unnecessary. However, certain cows (e.g., immunocompromised, severely ill) are likely to benefit from appropriate antibiotic treatment.

Clinical coliform mastitis can be treated with intramammary and systemic antibiotics. Many of the intramammary antibiotics available in the United States, such as pirlimycin, erythromycin, and cloxacillin, are ineffective against coliform bacteria. Even when intramammary antibiotics with gram-negative activity

are used, most studies show no effect on mastitis outcome. For example, intramammary infusion of amoxicillin or cephapirin according to label directions (two or three treatments) did not improve clinical or bacteriologic cure rate of mild clinical coliform mastitis, compared with oxytocin injection.[214] Intramammary infusion of colistin sulfate[264] or gentamicin,[265] both of which have good activity against coliform bacteria in vitro, did not alter the course of experimental *E. coli* mastitis, compared with no antibiotics. However, intramammary antibiotic therapy was beneficial in some studies. For example, a florphenicol-containing product infused on three occasions enhanced the bacteriologic cure rate in cows with experimental *E. coli* mastitis, compared with no antibiotics.[266] In a field trial, intramammary infusion of three doses of cefuroxime was associated with a higher clinical cure rate for *E. coli* mastitis, compared with three intramammary infusions of cloxacillin, which was expected to be ineffective.[267] Benefit/cost ratios were not reported.

Systemic antibiotic therapy has been studied in many experimental coliform mastitis trials and a few field trials. Results of experimental inoculation studies must be interpreted cautiously because cows usually recover rapidly without treatment, making it difficult to determine antibiotic efficacy. Three injections of a potentiated sulfonamide did not alter the course or outcome of experimental *E. coli* mastitis compared with no antibiotics.[264] However, systemic administration of cefquinome for 2 days, with or without concurrent intramammary administration of cefquinome, improved clinical and bacteriologic cure rates and lessened milk production loss in cows with experimental *E. coli* mastitis, compared with intramammary administration of ampicillin and cloxacillin.[268] Also, two injections of enrofloxacin enhanced the rate of bacterial clearance from the mammary gland[260,269] and reduced the decline in milk yield and changes in milk composition[270] accompanying experimental *E. coli* mastitis, compared with no antibiotics. The same enrofloxacin regimen reduced the acute drop in milk yield in cows with experimental *E. coli* mastitis when the cows were also given flunixin meglumine.[271]

Results of field trials are more applicable than results of experimental inoculation trials. However, cows in field trials often receive a variety of supportive treatments and intramammary antibiotics in addition to systemic antibiotics, making it difficult to determine the direct effect of systemic antibiotic therapy. Also, it is often impossible to include an untreated control group. Some field trials have shown no benefit of systemic antibiotic therapy for clinical coliform mastitis. For example, systemic administration of gentamicin did not affect the clinical course of acute coliform mastitis, compared with no systemic antibiotics.[272] Systemic administration of ceftiofur did not improve the bacteriologic cure rate or reduce mastitis recurrence or culling risk in cows with mild coliform mastitis, compared with no systemic antibiotics.[273] On the other hand, systemic administration of ceftiofur to severely ill cows for 5 days reduced the odds of death or culling, compared with no systemic antibiotics.[274] Systemic administration of marbofloxacin for 3 days improved bacteriologic cure rate and resulted in more rapid improvement in appetite, general condition, and milk production, compared with systemic administration of amoxicillin and clavulanic acid.[275] Cows with mild to severe clinical coliform mastitis had a more rapid clinical cure when treated with intramammary (cephapirin) with or without systemic (oxytetracycline) antibiotics, compared with no antibiotics.[218]

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Results of these studies suggest that antibiotics are not necessary or helpful for treating clinical coliform mastitis in many cases. Using antibiotics when they are unnecessary carries a risk of iatrogenic infection, is costly, and should be avoided if possible. However, cows that are unable to efficiently combat infection may benefit from antibiotics. Such cows are likely to be severely ill and have a high concentration of coliform bacteria in their milk. A high bacterial concentration indicates an inadequate neutrophil response. Therefore,

infusion of an intramammary antibiotic with a gram-negative spectrum (e.g., ceftiofur in United States, cefquinome in Europe) or systemic administration of an antibiotic that achieves therapeutic concentrations in milk (e.g., fluoroquinolones in Europe) may aid in killing bacteria and stopping the cycle of bacterial multiplication, LPS release, and worsening inflammation. Severely ill cows may benefit from systemic antibiotics to treat bacteremia and prevent infection of other organs. Unfortunately, fluoroquinolones and cefquinome, the most promising antibiotics for coliform mastitis, cannot be used in the United States; cefquinome is not available, and the use of florquinolones in lactating dairy cows is banned. The only systemic antibiotic labeled for treatment of mastitis in the United States, erythromycin, does not have an appropriate spectrum for coliform bacteria, making extralabel drug use necessary. Ceftiofur is currently the most logical antibiotic for treatment of coliform bacteremia in the United States, because potentiated sulfonamides are banned and there is a voluntary ban on aminoglycoside use in lactating dairy cows. However, the effect of systemic antibiotic administration in bacteremic cows needs further study.

Predicting which cows will be moderate responders and which will be severe responders to coliform infection would facilitate antibiotic treatment decisions. However, although cows can be distinguished on the basis of in vitro neutrophil function tests,[30] there is no practical method for use in the field. Clinical signs, blood leukocyte concentration, milk culture results, and blood culture results are currently the most predictive indicators of outcome, with clinical signs being the most practical.

36.6.6.2

Control

Control measures for coliform mastitis are similar to those for environmental streptococcal mastitis (see earlier discussion). Effort should be focused on reducing the exposure of teats to coliform bacteria during the dry and periparturient periods. Sand is the preferred bedding material because it resists the growth of coliform bacteria better than organic bedding materials.[242,276] Adding lime to the back one third of the stall reduces coliform bacteria in sawdust for 1 day but is ineffective when applied for longer periods.[277,278] The inhibiting effect of acidifying bedding conditioner is also short-lived and depends on the type of bedding used.[228]

In contrast to environmental streptococcal mastitis, intramammary antibiotic treatment at dry-off is considered to be ineffective for resolving or preventing coliform infections during the dry period. This may be a result of the antibiotics (β-lactams and macrolides) available for use in dry cows in the United States.[279] Infusion of internal teat sealant at dry-off reduced the incidence of new *E. coli* infections compared with infusion of antibiotics (cephalonium) in one study.[237] However, the risks of new gram-negative intramammary infections during the dry period and clinical mastitis during early lactation were similar when quarters were treated with teat sealant plus antibiotics (cloxacillin) or antibiotics alone.[91] The benefits of internal teat sealant are more clear-cut for environmental streptococcal mastitis.

One beneficial component of coliform mastitis control is vaccination of cows with a bacterin-toxoid derived from mutant strains of *E. coli* or *Salmonella typhimurium* that lack outer cell wall antigens. These vaccines elicit an antibody response to core LPS antigens, which is believed to facilitate opsonization and phagocytosis of gram-negative bacteria and enhance neutrophil diapedesis into the mammary gland.[280] The core antigen bacterins do not prevent intramammary infection but can reduce the incidence and severity of clinical coliform mastitis[281–284] and improve survivability.[283] The vaccines are usually administered at the end of lactation and during the dry period, to increase resistance during the periparturient period and avoid potential vaccine-induced reduction in milk production.[285] However, the optimal timing and frequency of

vaccination are still being investigated.[286] Vaccines that target receptors for iron-binding proteins on gram-negative bacteria are also being studied but have not yet been sufficiently tested in field settings.[287]

36.6.7 Coagulase-Negative Staphylococcal Mastitis

Coagulase-negative staphylococci (CNS) are the most prevalent bacteria isolated from mammary secretions of lactating cows, dry cows, and prepartum heifers (see section on heifer mastitis). Coagulase-negative staphylococci can also be isolated from teat skin and teat canals and found in the environment. *Staphylococcus hyicus, S. chromogenes, S. haemolyticus, S. epidermidis, S. simulans*, and *S. sciuri* are among the most frequently isolated CNS species, but many others have been cultured from bovine milk; *S. hyicus* is usually grouped with the CNS, even though some strains are coagulase positive.

Although the CNS are usually considered as a group, different species and strains may differ in epidemiology, virulence, and response to treatment. For example, novobiocin-sensitive CNS predominate in intramammary and teat canal infections, whereas novobiocin-resistant CNS are more likely to be found in the environment and on teat skin.[288]

Most CNS infections are subclinical, manifested only by an increase in SCC. However, infections tend to be persistent.[289] Compared with most other pathogens, the increase in SCC with CNS mastitis is much less.[200] In a meta-analysis the geometric mean SCC for CNS-infected quarters was 138,000/mL, compared with 357,000/mL for *S. aureus* and greater than 1 million/mL for *S. uberis* and *E. coli*.[290] For this reason, the CNS (as with *C. bovis*) are referred to as "minor" mastitis pathogens. Several studies suggest that CNS infection protects the mammary gland against infection with major pathogens[291,292] or shortens the duration of infection.[200] However, the protective effect differs for the various major pathogens,[292,293] and some studies have shown no protective effect or even a detrimental effect of CNS infection.[200,294] Therefore, relying on a high prevalence of CNS intramammary infections to protect a herd against major mastitis pathogens is unrealistic.

Coagulase-negative staphylococci can be isolated from the milk of cows with clinical mastitis in both poorly managed and well-managed herds.[295] However, this typically occurs in less than 10% of clinical mastitis episodes, and signs are usually mild. For these reasons, the role of CNS in clinical mastitis is usually downplayed. Care must be taken when collecting milk samples from cows with clinical mastitis to avoid culturing CNS from the skin or teat canal, which could lead to misdiagnosis.

The CNS are often susceptible in vitro to antibiotics in intramammary infusion products in the United States. Antibiotic treatment of clinical mastitis is logical, especially given the persistent nature of many CNS infections. However, controlled trials specifically investigating the efficacy and economics of antibiotic treatment for clinical CNS mastitis are lacking. Infusing intramammary antibiotics at dry-off successfully treats subclinical CNS mastitis. Treatment of subclinical CNS mastitis during lactation is unlikely to be profitable because the potential increase in milk yield after treatment is small.

There are no specific control measures for CNS mastitis. Effective germicidal teat dipping, antibiotic treatment of cows at dry-off, and prompt treatment of clinical mastitis are recommended. Although such practices can reduce the prevalence of CNS mastitis, CNS are still the most prevalent isolates in herds that have adopted these practices. Because of the wide variety of CNS and the limited economic loss associated with CNS mastitis, vaccines are not available.

36.7 OTHER MASTITIS PATHOGENS

Contagious mastitis pathogens, coliform bacteria, environmental streptococci, and CNS are responsible for most mastitis episodes in cattle. However, many other organisms are capable of opportunistically infecting the mammary gland and causing mastitis. Such infections usually occur sporadically, but herd outbreaks can develop in certain circumstances. It is not feasible to discuss all potential mastitis pathogens in detail. Some of the more common opportunistic pathogens are discussed next. In general, mastitis caused by these pathogens is not responsive to antibiotic therapy. Therefore, control depends on identifying and eliminating the source or predisposing factors for infection.

36.7.1 *Arcanobacterium pyogenes* Mastitis

Arcanobacterium pyogenes (formerly *Actinomyces pyogenes* and *Corynebacterium pyogenes*) is the predominant pathogen involved in "summer mastitis," a condition that affects prepartum heifers and nonlactating cows, mainly during summer.[296] In most cases, anaerobic bacteria (e.g., *Peptococcus indolicus, Bacteroides* species, *Fusobacterium necrophorum*) and facultative anaerobes (e.g., *Streptococcus dysgalactiae*) are also involved.[296,297] Summer mastitis occurs mainly in northern Europe and Japan, but cases have been reported throughout the world. It is characterized by a swollen, hard, painful mammary gland containing purulent, foul-smelling secretion. Acutely affected animals may show systemic signs ranging from lethargy and reduced feed intake to high fever, severe depression, abortion, and death. Chronically affected animals may have palpable or draining mammary abscesses. Systemic administration of procaine penicillin G often resolves systemic illness. However, neither systemic nor intramammary antibiotics are effective at eliminating intramammary infection.[298] The outcome of most episodes of summer mastitis is chronic clinical mastitis or a nonfunctional quarter. Therefore, affected cows are often culled.

Horn flies are believed to be responsible for transmitting summer mastitis. Flies that were allowed to feed on summer mastitis—causing bacteria transmitted the bacteria to teats, with subsequent development of intramammary infection[299]; damaged teat skin facilitated infection. However, the occasional occurrence of summer mastitis in winter suggests that other methods of transmission are possible. Because *A. pyogenes* is often found in the environment on farms and on body sites of cattle, teat skin contamination may predispose to infection, as occurs with coliform or environmental streptococcal mastitis, particularly if teat defenses are compromised.

Control of summer mastitis is accomplished by fly control, infusion of mammary glands with antibiotics at dry-off, appropriate environmental hygiene practices and stocking density, prevention and treatment of teat lesions, and prompt recognition and segregation of infected cows. Amputation of the teat, which facilitates drainage of secretions, increases environmental contamination and should not be done unless the cow can be segregated.

A condition similar to summer mastitis occurs sporadically in lactating cows.[297] *A. pyogenes* is usually involved, often in conjunction with other bacteria. Mastitis almost always follows teat injury or teat skin damage. The result is clinical mastitis and a very high SCC. Milk yield loss persists for at least 70 days.[300] The majority of episodes result in a blind quarter or loss (culling, death) of the cow.[297]

36.7.2 *Prototheca* Mastitis

Prototheca species are unicellular algae. These organisms have been isolated from bovine feces, as well as from soil, mud, vegetation, standing water, pond water, drinking water, feed troughs, and barn floors on dairy farms.[301] *Prototheca zopfii* is the main species associated with mastitis. Mastitis can be subclinical or clinical and can occur sporadically, endemically, or as an acute outbreak. Once infected, cows carry *P. zopfii* chronically in milk, mammary tissue, and supramammary lymph nodes, which results in pyogranulomatous inflammation.[302] Infected cows usually have persistently high SCC and reduced milk production. An elevation in BTSCC sufficient to threaten marketability of grade A milk has occurred in some herds.[303] Shedding of *P. zopfii* in milk can be persistent or intermittent.[304] Diagnosis is facilitated by culturing milk on selective media, such as Prototheca Isolation Medium; however, *P. zopfii* does grow on blood agar and can be detected by Gram staining of suspect colonies. Fine-needle aspiration of mammary tissue[305] and antibody testing of whey[306] are alternatives to milk culture but are not typically performed. Most *Prototheca* intramammary infections are probably acquired from the environment, but spread from shedding to uninfected cows at milking time may play a role in transmission.

Prototheca zopfii is resistant to antimicrobial therapy, and infection can persist through the dry period.[304] Therefore, identification, segregation, and progressive culling of infected animals are required to control *Prototheca* mastitis. Culling must be coupled with identification and avoidance of contaminated environmental sites, enhanced cleaning of feed bunks and watering devices, and use of milking procedures that ensure clean teats and minimize contagious spread of infection.

36.7.3 Yeast Mastitis

Yeast can be isolated from feed, bovine skin and feces, and a variety of environmental sites on dairy farms.[307] *Candida* species, *Trichosporon beigelii*, and other species can cause clinical mastitis in individual cows or herds. Yeast infection usually follows intramammary antibiotic treatment or teat skin injury. Outbreaks occur when homemade, multidose infusion products or associated equipment (e.g., needles, syringes, bottles, cannulas) are contaminated or when the teat is not adequately disinfected before infusion.[140,141] In one study, six cows treated with a homemade intramammary antibiotic solution contaminated with *T. beigelii* all developed fever, hypogalactia, and swollen mammary glands within 2 weeks, and two of the six died. When the producer continued to use homemade solutions, an additional 23 cows (over half the herd) became infected, and the herd was dispersed.[140] Yeast can be cultured from towels or teat cup liners used on infected cows, suggesting that contagious transmission may occur.[140,308]

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On blood agar, yeast colonies appear similar to CNS colonies, so it is important to examine the colonies microscopically. Sabouraud dextrose agar with antibiotics is a common alterative medium that selects for yeasts. Yeast infections are not susceptible to antibiotic treatment, and infusion of antibiotics may potentiate infection. Antifungal agents have not been demonstrated to be effective and should not be used. Infection (especially with *Candida* species) often resolves spontaneously within 2 to 4 weeks,[141,308,309] but cows with severe or recurrent clinical mastitis, reduced milk production, or persistently high SCC should be culled.[140] Control of yeast mastitis includes aseptic intramammary infusion procedures; use of single-dose, commercially prepared antibiotic infusion products; segregation of infected cows at milking time; and use of individual rather than shared towels. Feeding contaminated silage promotes fecal excretion of yeast and has been blamed for

outbreaks of yeast mastitis in cows that have not received intramammary infusions.[308] Bulk tank SCC can increase greatly during yeast mastitis outbreaks.

36.7.4 *Pseudomonas* Mastitis

Intramammary infection with *Pseudomonas* species can result in severe clinical mastitis, similar to that caused by *E. coli*.[310] Gangrene develops in some cases.[311] However, chronic subclinical mastitis with periodic bouts of mild clinical mastitis is more common. *Pseudomonas aeruginosa* is the most common *Pseudomonas* species associated with mastitis. Intramammary infection with *P. aeruginosa* can occur sporadically or can affect more than one third of lactating cows in a herd.[312] A high incidence or prevalence of *P. aeruginosa* intramammary infections should trigger an investigation of the water system in the milking parlor. Hoses used to wash teats before milking have been implicated in numerous outbreaks of *Pseudomonas* mastitis.[313] Water from the hoses or the hoses themselves have cultured positive, particularly after water has been sitting in the hoses for several hours. When wash water is contaminated with *Pseudomonas* species, the hoses and nozzles must be replaced, but not without first culturing potential sources of bacteria. For example, water tanks, water heaters, or water lines may need to be replaced or decontaminated to prevent colonization of new hoses.[313] Other steps that can be taken are to flush stagnant water from the hoses before each milking and ensure that iodine concentration in the wash water is 25 ppm.[313] Alternatively, the teats can be predipped rather than washed before milking.

Pseudomonas mastitis has also been attributed to contaminated intramammary infusion products[314] or teat cannulas, inadequate teat end sanitation before drug infusion, contaminated teat wipes,[315] and exposure of cows to stagnant water. Therefore, investigation of a herd problem should include intramammary infusion practices and housing conditions. Once *P. aeruginosa* mastitis is established, it usually persists, and antibiotic therapy is unsuccessful. This is caused in part by production of factors that inhibit host defenses and reduce antibiotic efficacy, such as biofilm.[31] Cows with persistently high SCC or repeated bouts of clinical mastitis are usually culled, but infusing glands with germicide to induce permanent cessation of lactation is another option for cows with a single infected gland.[316]

36.7.5 *Serratia* Mastitis

Serratia mastitis is caused mainly by *S. marcescens* and *S. liquefaciens*. Mastitis can be clinical or subclinical, with the subclinical form predominating. More than 15% of lactating cows can be infected in problem herds, which can cause substantial elevation in BTSCC.[317,318] Although *Serratia* species produce bright-red colonies on blood agar, they are easily outcompeted by other pathogens. Therefore, infection prevalence may be underestimated unless special media and cultural conditions (e.g., incubation at 20° C) are used.[317,318]

Serratia intramammary infections can originate during lactation or the dry period. In one longitudinal study, 48% of *Serratia* infections were acquired during the first half of the dry period and 31% during the second half, with only 21% initiated during lactation.[319] Almost half the infections resulted in clinical mastitis. Cows with clinical *Serratia* mastitis do not exhibit severe clinical signs, such as those accompanying acute *E. coli* mastitis.[319,320] However, *Serratia* infection persists longer than *E. coli*. A mean duration of 55 days has been reported,[319] but many infections persist for 6 to 10 months.[317,321]

Serratia mastitis has been associated with contaminated teat dip or teat dip cups,[322,323] frostbitten teats,[320] contaminated organic bedding material,[317] and dirt packs in cow lots.[318] In some cases the reservoir of infection is never identified.[321] Antibiotic therapy is usually ineffective,[319,320] but some infected quarters eventually self-cure.[319] Cows with repeated bouts of clinical mastitis or persistently high SCC should be culled.

36.7.6 *Nocardia* and *Mycobacterium* Mastitis

Nocardia species occasionally cause sporadic cases or herd outbreaks of mastitis. Infections can be subclinical or clinical, with some clinical episodes being severe or fatal. Fibrosis and draining abscesses may accompany chronic infections. Clinical or subclinical mastitis can also be caused by *Mycobacterium fortuitum*. This organism causes granulomatous inflammation and encapsulated granulomas in the mammary gland.[324] Other rapidly growing *Mycobacterium* species, such as *M. chelonei, M. smegmatis, M. phlei, M. vaccae*, and *M. flavescens,* have been isolated from cows with acute or chronic mastitis.[325–327] *M. avium* subspecies *paratuberculosis,* the causative agent of Johne's disease, does not readily cause mastitis, despite being shed in the milk of infected cows.

Milk culture is required to diagnose and differentiate *Nocardia* and *Mycobacterium* species. *Nocardia* species produce characteristic cottony white, adherent colonies on blood agar, but the colonies may not appear for 72 to 96 hours; the color changes from white to yellowish orange as the colonies age. On the other hand, *M. fortuitum* produces nonadherent, smooth colonies.[324] The other mycobacteria may or may not grow on blood agar.[325,327] With all these organisms, a tentative diagnosis can be made by observing acid-fast rods or gram-positive rods with branching filaments in a milk smear.[324,325]

Nocardia species and mastitis-causing *Mycobacterium* species are saprophytes and therefore may cause intramammary infection when teats are exposed to unhygienic environmental conditions. However, most outbreaks are associated with contaminated intramammary drugs or infusion equipment or poor teat hygiene before infusion.[324,326] Results can be devastating. In one *Nocardia* outbreak, 450 of 3300 cows died, and 500 more were culled.[328] Use of oil-based dry-cow infusion products appears to facilitate growth of *Nocardia* and *Mycobacterium* species. Both types of pathogens cause intramammary infections that persist for months, even through the dry period. Antibiotic therapy is futile. Cows with chronic *Nocardia* mastitis should be culled or the quarter dried off to prevent continued exposure of humans to this potentially zoonotic pathogen.[329] Cows with *Mycobacterium* mastitis are often culled because of chronic mastitis and low productivity. Control of *Nocardia* and *Mycobacterium* mastitis involves proper intramammary infusion practices and general environmental hygiene.

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36.7.7 *Pasteurella multocida* Mastitis

Pasteurella multocida, a normal upper respiratory tract inhabitant of cattle and contributor to the bovine respiratory disease complex, occasionally causes mastitis. Most episodes are sporadic, but herd outbreaks can occur.[330,331] In a recent report a high incidence of clinical mastitis caused by *P. multocida* was accompanied by an increase in BTSCC from approximately 200,000/mL to over 900,000/mL in about 5 months.[330] BTSCC increased partly because milk from cows with clinical mastitis was not diverted from the bulk tank. Hematogenous or lymphatic spread of *P. multocida* from the respiratory tract to the mammary gland has been proposed, and *P. multocida* has been isolated from the blood of cows with severe coliform mastitis.[262]

However, it is unlikely that hematogenous or lymphatic spread is responsible for herd outbreaks. Contamination of teats by nasal secretions (e.g., from nursing calves or intersucking cows), cow-to-cow spread at milking time, or inappropriate infusion practices may contribute to outbreaks.[330] Antibiotic treatment has historically been unrewarding, and infected cows are often culled. However, spontaneous resolution appears to occur in some cases.[330]

36.7.8 Food-Borne Disease Agents

Salmonella species and *Listeria monocytogenes* can cause mastitis. However, mastitis is an uncommon manifestation of these infections. With the exception of *Salmonella dublin*, a cattle-adapted species that is shed in the milk of infected cows, *Salmonella* species or *L. monocytogenes* in bulk tank milk are most likely to originate from unclean teats or fecal contamination of milking units, rather than from the milk itself. Good milking hygiene practices reduce the risk of milk contamination.

36.8 THERAPY OF CLINICAL MASTITIS

In the United States, farm personnel treat most episodes of clinical mastitis. The veterinarian is relied on to develop rational, economical mastitis treatment protocols for farms. Developing protocols is challenging because many factors can influence mastitis treatment decisions for a given cow. These include the severity of clinical signs; the suspected (or known) pathogen; the cow's milk production, stage of lactation, pregnancy status, and previous mastitis history; the cow's genetics and market value (if she can be culled); the price and availability of replacement heifers; the milk-withholding and slaughter-withholding times of drugs; and the anticipated treatment costs. Farm personnel responsible for making breeding and culling decisions must work with those responsible for treating mastitis to ensure that treatment decisions are financially as well as medically sound.

Even when the pathogen causing an episode of clinical mastitis is known and a logical treatment plan instituted, the outcome can vary substantially. For example, one cow with mild *Streptococcus uberis* mastitis might be clinically normal after on-label treatment with intramammary antibiotics and maintain a low SCC for the rest of the lactation. Another cow with the same signs and pathogen might take longer to respond, maintain a high SCC throughout lactation, and experience repeated recurrences of clinical mastitis. Factors responsible for intercow variability include the strain of the pathogen, inoculum dose, duration of intramammary infection at onset of treatment, and the cow's ability to mount an effective immune response. The latter is influenced by stage of lactation, parity, previous exposure to the pathogen, nutritional status, concurrent disease, and a variety of stressors. Treatment failure is often attributed to ineffective drugs when, in fact, cow or pathogen factors or how the drugs are administered may be more important.

For a mastitis treatment program to be successful, the veterinarian and producer must work together to ensure that cows are housed, managed, and fed to promote good immune function (see mastitis control section). Farm personnel must be trained to monitor cows for clinical mastitis and assess mastitis severity. Criteria must be established to assist farm personnel in selecting cows for antibiotic treatment so that time and money are not wasted on infections that are unlikely to respond. Drugs and treatment practices that are banned, ineffective, or potentially detrimental must be avoided for legal, financial, and ethical reasons. Antibiotics must have an appropriate spectrum of activity for the pathogens of concern and must be administered in sufficient doses, by the appropriate route(s), at an appropriate frequency, and for a sufficient duration to achieve the desired outcome. Appropriate supportive treatment practices must be used to promote welfare and assist the cow in responding to infection. Because of a paucity of published data to guide the veterinarian, mastitis treatment protocols are typically developed using a combination of science, personal experience, common sense, and trial and error.

36.8.1 Antibiotic Treatment

Antibiotics can be avoided without adversely impacting the outcome of many clinical mastitis episodes. However, treatment protocols that exclude antibiotic use altogether are likely to have a detrimental effect at both the cow and the herd level. Judicious use of antibiotics should be the goal, rather than complete avoidance. This section discusses some principles and factors to consider when making antibiotic treatment decisions. More specific recommendations can be found in the sections pertaining to each pathogen.

36.8.1.1 CONSIDER THE PATHOGEN

The effectiveness of antibiotic therapy and choice of antibiotic depend on the pathogen causing clinical mastitis. Cows with mild clinical mastitis and no bacterial growth in the milk are unlikely to benefit from antibiotic therapy, as are cows with a low concentration of *E. coli* in the milk. Cows with *Mycoplasma* mastitis or mastitis caused by opportunistic pathogens such as *Pseudomonas aeruginosa, Prototheca zopfii*, or yeast are unlikely to respond to antibiotic therapy. On the other hand, antibiotics can enhance resolution of many streptococcal or staphylococcal mastitis episodes.

Farm personnel can make the most informed antibiotic treatment decisions if milk from each cow is cultured. Some farms have adopted this practice, despite the associated labor and supply costs. Milk is cultured on-farm or at a local veterinary practice or laboratory. Use of biplates, triplates, or quadplates facilitates culturing and allows farm personnel or veterinary staff to identify basic classes of pathogens with minimal training. Results are usually available in 12 to 24 hours. For clinical mastitis episodes of mild to moderate severity, waiting for culture results before beginning treatment does not appear to be detrimental to the outcome.[332] Using this approach allows antibiotic therapy to be targeted to cows with gram-positive infections and can dramatically reduce antibiotic use. If farms do not routinely culture milk from cows with clinical mastitis, it is still important to determine the most frequent clinical mastitis pathogens in the herd to make appropriate treatment and prevention recommendations. It is particularly important to determine if *Mycoplasma* species or opportunistic pathogens that are nonresponsive to antibiotic therapy are contributing to clinical mastitis.

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36.8.1.2 CONSIDER THE COW'S HISTORY

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A small proportion of cows can be responsible for a large proportion of clinical mastitis episodes in a herd. Antibiotic therapy is unlikely to cure infections in glands with repeated bouts of clinical mastitis episodes. The same is true for cows with persistent clinical mastitis or chronic intramammary infection. A number of cow factors, such as parity, stage of lactation, and SCC, influence the outcome of antibiotic treatment for *S. aureus* mastitis (see earlier section) and probably for mastitis caused by other pathogens.

36.8.1.3 CONSIDER THE SEVERITY

Cows with severe clinical coliform mastitis have a guarded prognosis at best. Euthanasia must be considered as an alternative. However, clinical parameters such as rectal temperature, rumen contraction rate, attitude, degree of dehydration, and appearance of the mammary gland can be used to assess the likelihood of a cow returning to production.[249] A producer might be more apt to choose euthanasia over treatment if the chance of recovery is predicted to be less than 10%, versus 50%. If treatment is pursued, clinical parameters can help

determine the likelihood of bacteremia, which is an indication for systemic antibiotic use. As mentioned in other sections, the blood leukocyte concentration and the concentration of coliform bacteria in milk also reflect clinical mastitis severity and outcome. Spending a few dollars on a blood smear to determine that a cow is extremely neutropenic and unlikely to recover is more prudent than spending over $100 on aggressive treatment that fails.

36.8.1.4

CONSIDER THE ALTERNATIVES

Alternatives to antibiotic treatment include (1) euthanizing or culling the cow, (2) drying off the cow or gland, (3) inducing permanent cessation of lactation in the gland, (4) administering supportive treatment alone, or (5) doing nothing. The cow's welfare must be considered when choosing among these options, to minimize pain and suffering. If supportive treatment or no treatment is chosen, the cow should be milked after healthy cows and the milk withheld from sale as long as it is visibly abnormal. If a single gland is dried off, antibiotics should not be infused because this may result in antibiotic residues in milk from the other glands.

Germicides can be infused into the mammary gland to induce cessation of lactation. A single infusion of 120 mL of 5% povidone-iodine solution, or two 60-mL infusions of chlorhexidine diacetate 24 hours apart, induces permanent cessation of lactation.[333,334] Two infusions of chlorhexidine suspension (1 g chlorhexidine in 28 mL base) induced cessation of lactation in one study, but milk was produced by the treated quarter in the next lactation; unfortunately, 40% of treated glands were still infected when lactation resumed.[333] Researchers recommend administering a systemic antiinflammatory agent when inducing cessation of lactation, to limit the inflammatory response and reduce pain.[333] Cessation of lactation should be undertaken only if the infused gland can be clearly recognized by the milking personnel; otherwise, germicide-containing secretions could enter the bulk tank milk.

36.8.1.5

DETERMINE THE DESIRED OUTCOME

The ideal outcome of a clinical mastitis episode is clinical cure (resolution of clinical signs and return to marketable milk), bacteriologic cure (resolution of intramammary infection), and normalization of milk production and SCC. Clinical cure without bacteriologic cure can result in recurrence of clinical mastitis, transmission of infection to other glands, and persistence of high SCC, even if mastitis is caused by environmental pathogens, such as *S. uberis* or *E. coli*.[115,211,218] However, an ideal outcome is unrealistic in some cases (e.g., chronic *S. aureus* mastitis). Survival of the cow and clinical cure without bacteriologic cure may be acceptable outcomes if the intent is to slaughter or cull the cow as soon as possible or keep her until she calves or her milk production declines. Veterinarians can help producers identify appropriate goals for different types of mastitis episodes and tailor treatment recommendations accordingly.

36.8.1.6

INSTITUTE TREATMENT PROMPTLY

Antibiotic treatment is most likely to be effective if initiated early in the course of clinical mastitis. Delaying treatment for more than a few days can allow potentially susceptible pathogens, such as *S. uberis* and *S. aureus,* to become established and evade antibiotics and host defenses. If milking personnel do not strip and examine milk before each milking, mild clinical mastitis episodes may to go undetected until they are difficult to treat.

36.8.1.7

CHOOSE APPROPRIATE ANTIBIOTICS

Fluoroquinolones and potentiated sulfonamides are used to treat clinical mastitis in other countries; however, these antibiotics are banned for lactating dairy cows in the United States and must not be used, regardless of the cow's condition. Antibiotics labeled for treatment of mastitis must be used preferentially, whenever they are likely to be effective. However, extralabel drug use is frequently necessary.

The spectrum of activity must be considered when selecting an antibiotic; for example, certain β-lactam antibiotics, such as procaine penicillin G or amoxicillin, should be avoided when treating mastitis caused by penicillinase-producing staphylococci (see section on *S. aureus* mastitis). Erythromycin, pirlimycin, and penicillin, all labeled for intramammary treatment of mastitis in the United States, are not appropriate choices for coliform mastitis because coliform bacteria are resistant to these drugs. Erythromycin is the only antibiotic currently labeled for systemic administration to cows with mastitis in the United States; extralabel use of an antibiotic with a more appropriate spectrum, such as ceftiofur or oxytetracycline, is warranted for cows with severe coliform mastitis to combat potential bacteremia. When antibiotics are used in an off-label manner, extralabel drug use requirements must be observed,[335] including avoidance of violative residues in milk and meat.

36.8.1.8

REALIZE LIMITATIONS OF ANTIMICROBIAL SUSCEPTIBILITY TESTING

Antimicrobial susceptibility test results should not be used as the main basis for antibiotic selection. In most cases, susceptibility cut-points for zone diameters (for the disk diffusion test) or MIC values are based on antibiotic concentrations in serum or interstitial fluid of people after oral or intravenous (IV) dosing; these are not equivalent to concentrations achieved in milk or mammary tissue after intramammary or systemic dosing.[336] The absolute MIC value is more useful than a result (susceptible or resistant) based on an irrelevant cut-point. However, the reported MIC value may not reflect the MIC in milk because MICs in milk are often higher than in blood.[337] The newest intramammary antibiotics have MIC or disk diffusion cut-points that are relevant to treatment of mastitis, but the cut-points need to be validated in vivo. In at least two recent studies, susceptibility test results (susceptible vs. resistant) had no impact on the outcome (clinical cure, bacteriologic cure) of clinical mastitis episodes.[222,223] However, testing *S. aureus* isolates for penicillinase production facilitates antibiotic selection and prognostication; penicillinase-producing strains are less responsive to treatment even if penicillinase-resistant antibiotics are used.[148]

36.8.1.9

CONSIDER PHARMACOKINETICS AND PHARMACODYNAMICS

The site being targeted (milk, mammary tissue, or blood) influences the antibiotic treatment plan.[338] Streptococci and coagulase-negative staphylococci reside mainly in the milk, so intramammary antibiotic therapy is appropriate for mastitis caused by these pathogens; systemic antibiotics provide little or no additional benefit. On the other hand, with severe coliform mastitis, bacteria may be circulating in the blood, in which case systemic antibiotics are appropriate. With *S. aureus* mastitis and chronic *S. uberis* mastitis, organisms can reside within leukocytes and mammary tissue, as well as in milk, so a combination of intramammary and systemic antibiotics may be beneficial. Unfortunately, most of the systemic antibiotics used in lactating dairy cows in the United States, such as penicillin, ampicillin, sulfadimethoxine, and ceftiofur, do not achieve high concentrations in milk or in leukocytes. Oxytetracycline and macrolide antibiotics attain higher concentrations in milk, but mastitis pathogens are often resistant to these drugs.[338]

Time above the MIC is a critical determinant of efficacy for the antibiotics used to treat mastitis in the United States. Most intramammary antibiotics are labeled for two or three treatments 12 or 24 hours apart. This dosing regimen is highly effective for *S. agalactiae* mastitis but may not provide a sufficient duration of inhibitory antibiotic concentrations for other streptococci or staphylococci. Improved clinical and bacteriologic cure rates have been observed for *S. uberis* and *S. aureus* mastitis when intramammary antibiotics were administered for a longer duration (see sections on *S. aureus* and environmental streptococci). Switching of antibiotic classes after two or three doses, as is frequently done on farms, limits time above the MIC and should be avoided. Although extended antibiotic therapy may constitute extralabel drug use, it is more prudent than using a subtherapeutic treatment regimen.

Veterinarians can use reported MIC values and their knowledge of antibiotic pharmacokinetics and pharmacodynamics to determine if administering a particular antibiotic by a particular route is likely to exceed the MIC of a given pathogen in milk, mammary tissue, or blood. However, even if the likelihood is high, many factors can prevent effective concentrations from being achieved. For example, inflammatory debris in the ducts or microabscesses in the mammary tissue can prevent antibiotics from reaching the organisms. Factors affecting the disposition of intramammary antibiotics used to treat mastitis have recently been reviewed.[339]

36.8.1.10 SUMMARY

Judicious antibiotic use is necessary for successful mastitis treatment programs. Case selection is critically important to avoid unnecessary antibiotic use, which is costly to the producer and of concern to the public. When producers are unwilling or unable to use culture results as the basis for treatment determination, it is probably preferable to treat all cows (that meet selection criteria) with antibiotics than to avoid antibiotics altogether. In one study, cows with clinical mastitis were treated with supportive measures either alone or with antibiotics (extended intramammary cephapirin administration with or without IV oxytetracycline). Environmental (coliform, streptococcal) and bacteriologically negative mastitis episodes predominated, with the majority of episodes being mild. Antibiotic use was associated with higher clinical and bacteriologic cure rates (particularly for environmental streptococcal infections), fewer recurrences of clinical mastitis, less severe disease, lower milk yield loss (mean of 182 vs. 528 kg), and lower cost of mastitis (mean of $201 vs. $295/affected cow).[340] Complete avoidance of antibiotics can result in increased streptococcal mastitis prevalence and reduced milk quality.[211] Antibiotic selection and the timing, dosage, frequency, and duration of treatment impact the outcome. Therefore, antibiotic treatment protocols should be designed with veterinary input and monitored for efficacy. Monitoring requires that farm personnel record the incidence, severity, and duration of clinical mastitis, as well as the treatments administered; SCC data and targeted milk culture results also facilitate assessment of treatment efficacy.

36.8.2 Supportive Treatment

A variety of supportive measures are used in cows with clinical mastitis, often in conjunction with antibiotic therapy. Fluids and electrolytes are administered to combat circulatory and electrolyte disturbances. Steroidal and nonsteroidal antiinflammatory agents are used to reduce pain, inflammation, and fever. Oxytocin and frequent milk-out are used to promote milk ejection and removal of secretions. Dairy producers and veterinarians use many other systemic and local treatments, most of which have not been scientifically evaluated or shown to be effective. This section discusses the most frequently used supportive treatments.

36.8.2.1

FLUID AND ELECTROLYTE THERAPY

Cows with clinical mastitis can develop fluid and electrolyte disturbances as a result of decreased feed and water intake, rumen stasis, ileus, and diarrhea. Severely affected cows, particularly those with coliform mastitis, may develop septic or endotoxic shock; death or organ damage can result from decreased effective circulating volume.

The hydration status of an adult cow is assessed subjectively, by observing skin tent duration on the neck or eyelid and position of the globe in the orbit. Unfortunately, findings can be influenced by the body condition of the cow. Objective criteria for estimating the extent of dehydration have been reported for dairy calves[341] but have not been established for adult cows. Extrapolating from calves, a healthy cow should have a cervical skin tent duration of 2 seconds or less and no recession of the eyeball. Skin tent durations of 4, 6, or 8 seconds and eyeball recession of 2, 4, or 7 mm would correlate with 4%, 8%, and 12% dehydration, respectively. Indicators of reduced peripheral perfusion are cold extremities (ears, tail, fetlocks [only reliable at moderate ambient temperatures]) and a dry muzzle or mouth.[342] Hematocrit and plasma protein concentration are not reliable indicators of hydration status in an individual cow because of the wide range of normal values and the effects of inflammation and stage of lactation on total protein concentration.

Most cows with clinical mastitis, even severe mastitis, have normal acid-base balance or metabolic alkalosis; metabolic acidosis is uncommon and associated with a poor prognosis.[77,343] Therefore, there is no need for routine IV administration of alkalizing agents, such as bicarbonate or lactate. Also, oral products containing magnesium hydroxide or sodium bicarbonate should not be administered.

36.8.2.1.1

Oral Fluid Therapy

Fluids can be administered by the oral (intraruminal) or IV route. The oral route is least expensive and is often adequate for cows with mild to moderate dehydration. Oral fluids should be hypotonic or isotonic and should contain sodium, to create an osmotic gradient between rumen fluid and blood and enable sustained absorption of fluid and electrolytes; hypertonic oral fluids should be avoided.[344] A 600-kg cow that is 6% dehydrated needs to absorb 36 L (~9 gal) of fluid to replace her deficit. This volume can be safely administered orally, but administration of larger volumes of hypotonic fluid might lead to intravascular hemolysis.[345] Oral fluids are not sufficient for cows with severe dehydration because they do not cause rapid resuscitation.

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36.8.2.1.2

Intravenous Fluid Therapy

Ringer's solution, which is an isotonic (isosmotic), mildly acidifying solution that contains physiologic concentrations of sodium, chloride, potassium, and calcium, is the fluid of choice for rapid IV resuscitation of adult ruminants.[344] Isosmotic (0.9%) sodium chloride is an alternative that can easily be constituted using table salt and distilled water in a sterile carboy. However, administration of isosmotic crystalloid solutions is impractical in many situations because of the large volume of fluid required and the need for IV catheterization. A 600-kg cow that is 10% dehydrated requires 60 L (~15 gal) of fluid to replace her deficit.

A practical (although inferior) alternative to isosmotic IV fluid therapy is IV administration of hypertonic (7.2%, 2460 mOsm/L) saline. Hypertonic saline is administered through a large-bore needle at 4 to 5 mL/kg body weight over 4 to 5 minutes, in conjunction with oral administration of water (5 gal). Rapid administration of hypertonic saline is required to effectively create an osmotic gradient that draws fluid from the intercellular spaces and gastrointestinal tract (mainly rumen) into the vasculature. Although hypertonic saline does not have a sustained effect and will not completely correct a large fluid deficit, it rapidly increases plasma volume and improves cardiac output and tissue perfusion. Hypertonic saline has been shown to be safe in cows with endotoxic mastitis.[346,347]

36.8.2.1.3

Electrolyte Therapy

Mild to moderate hypocalcemia often accompanies clinical mastitis, with the odds of hypocalcemia increasing with the severity of mastitis.[79] Affected cows may show muscle tremors or weakness but are seldom recumbent. Calcium supplementation can be by the oral, subcutaneous (SC), or slow IV route, depending on the severity of clinical signs and product used. Other serum electrolytes are variable. Inappetent cows often become hypokalemic, especially if anorexia persists for several days. Hypertonic saline administration also causes a transient reduction in serum potassium concentration. Potassium chloride can be supplemented orally at a rate of up to 240 g divided two to three times daily, with lesser amounts (30 to 120 g) being satisfactory for mild to moderate hypokalemia.[348] Sodium and chloride derangements are usually mild and can be addressed by administering balanced oral or IV fluids or hypertonic saline. Blood glucose concentration is usually normal or high in cows with clinical mastitis, so dextrose should not be administered routinely. However, IV dextrose treatment may be warranted in cows with concurrent ketosis.

36.8.2.2

ANTIINFLAMMATORY AGENTS

Most of the physiologic and pathologic changes associated with clinical mastitis are a result of the inflammatory response to infection. Therefore, it is logical to administer antiinflammatory agents. Also, antiinflammatory agents can reduce the pain associated with clinical mastitis. However, the inflammatory response is necessary for resolving intramammary infection, and antiinflammatory agents can produce detrimental side effects. The potential benefits must be weighed against the potential risks. Some antiinflammatory agents are expensive, making repeated doses cost prohibitive. Many of the agents used in other countries are not labeled for use in lactating dairy cows in the United States. The choice of antiinflammatory agents in the United States is limited to three approved drugs: dexamethasone, isoflupredone acetate, and flunixin meglumine.

36.8.2.2.1

Steroidal Antiinflammatory Agents

Dexamethasone and isoflupredone acetate are inexpensive steroidal antiinflammatory agents that have no milk-withholding requirement. However, each of these agents has potential adverse effects. Dexamethasone can be immunosuppressive and can cause abortion in pregnant cows, especially after 5 months of gestation. Repeated dosing (0.04 to 0.8 mg/kg IM for 3 days) of cows with subclinical intramammary infections resulted in increased bacterial shedding and development of clinical mastitis.[349,350] Isoflupredone acetate reduces plasma potassium concentration,[351] and repeated doses can lead to severe hypokalemia and recumbency.[351–353]

Data on the efficacy of steroidal antiinflammatory agents for treatment of clinical mastitis are limited to experimental mastitis trials. A single, 30-mg IM dose of dexamethasone given at the time of *E. coli* inoculation reduced local signs of inflammation, tachycardia, rumen motility impairment, and 14-day milk production loss, compared with untreated controls.[354,355] A single IM dose of a product containing dexamethasone (0.025 mg/kg) and antibiotics (colistin and ampicillin) reduced fever, improved rumen contraction rate, and shortened the duration of high SCC when given immediately or 2 hours after endotoxin infusion, but not after 4 hours[356]; this implies that delaying treatment may reduce or prevent efficacy. A single, large IV dose of dexamethasone (0.44 mg/kg) given to goats 12 hours after *E. coli* infusion reduced fever and appetite suppression but had no effect on heart rate, rumen contractions, serum biochemical parameters, SCC, milk yield, or histopathologic changes.[357] Isoflupredone acetate (20 mg IV) administered to endotoxin-challenged cows after the onset of clinical mastitis had no beneficial effect on systemic parameters, mammary gland swelling, or milk production, compared with untreated controls.[358]

The relevance of results of experimental mastitis trials to naturally occurring clinical mastitis is questionable. Thus far, published studies do not provide compelling evidence to support the use of steroidal antiinflammatory agents for treatment of clinical mastitis.

36.8.2.2.2

Nonsteroidal Antiinflammatory Agents

A variety of nonsteroidal antiinflammatory drugs (NSAIDs) are used to treat clinical mastitis worldwide. However, only flunixin meglumine is approved for use in lactating dairy cows in the United States. Dipyrone and phenylbutazone are banned, and other NSAIDs can be used in an extralabel manner only if appropriately justified. The NSAIDs are not immunosuppressive, but as with steroids, they carry a risk of abomasal ulceration and renal damage. These complications are not well documented in cattle and presumably are minimized if treatment is of short duration, hydration is maintained, and appetite is restored.

Treatment of cows with flunixin meglumine at 0 and 3 to 5 hours after *E. coli* inoculation abolished fever and improved rumen motility, compared with untreated controls, but had no effect on gland or milk appearance, heart rate, or respiratory rate.[359] Similarly, administration of flunixin meglumine every 8 hours beginning 2 hours after endotoxin infusion reduced fever and improved gland appearance and attitude, compared with untreated controls, but had no effect on milk appearance, heart rate, rumen motility, SCC, or milk production.[360] When administered after the onset of fever and gland swelling, flunixin meglumine (2.2 mg/kg IV) reduced heart rate and rectal temperature and increased rumen motility in cows with endotoxic mastitis but had no effect on milk production or mammary gland inflammation.[361] As with the steroids, the relevance of these trial results to cows with naturally occurring clinical mastitis is uncertain.

The most compelling evidence to support the use of NSAIDs in clinical mastitis comes from field trials. In one trial, cows treated with NSAIDs (ketoprofen, 2 g IM; dipyrone, 20 g IM; or phenylbutazone, 4 g IM) plus systemic antibiotics were 2.8 times more likely to recover (return to ≥75% milk production) than cows treated with antibiotics alone.[362] In two trials, cows treated with antibiotics plus ketoprofen (2 g once daily) were 2.6 and 6.8 times more likely to recover than cows treated with antibiotics alone or in conjunction with a placebo.[363] Meloxicam, although not available for use in U.S. cattle, was shown to reduce pain associated with clinical mastitis.[364] In summary, it appears that NSAIDs can improve well-

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being and outcome in cows with clinical mastitis. However, specific criteria for instituting NSAID therapy and the optimal duration of treatment remain to be determined.

A locally infused antiinflammatory agent (glycyrrhizin) reduced inflammatory changes in the mammary gland and milk of cows with coagulase-negative staphylococcal mastitis, compared with intramammary antibiotics.[365] However, such antiinflammatory agents require additional study in controlled field trials.

36.8.2.3

OXYTOCIN AND FREQUENT MILK-OUT

Oxytocin is administered to stimulate milk ejection and facilitate removal of secretions from mastitic mammary glands. Frequent milk-out (stripping) is performed to increase the frequency of removal of pathogens, toxins, and inflammatory mediators from the mammary gland. Although seemingly logical practices, no solid evidence exists to support their routine use, and some data suggest they can be detrimental. Oxytocin (20 IU IM twice daily for 3 days) at milking time prevented development of clinical mastitis in only two of eight cows experimentally inoculated with *Streptococcus uberis;* once clinical mastitis developed, oxytocin was ineffective at resolving the *S. uberis* infections.[219] When initiated at the onset of clinical *S. uberis* mastitis, oxytocin (80 IU IM, followed by 20 IU IM twice daily) resulted in no clinical or bacteriologic cures by 3 or 6 days.[217] In contrast, clinical and bacteriologic cure rates of 91% and 64%, respectively, were achieved by intramammary antibiotic administration for 6 days. When oxytocin was used in conjunction with intramammary antibiotics, clinical and bacteriologic cure rates at 6 days dropped to 10%, implying a significant adverse effect of oxytocin and stripping. Frequent milk-out (every 4 to 6 hours) in conjunction with oxytocin administration did not shorten the time to clinical or bacteriologic cure or resolution of systemic illness in cows with experimentally induced coliform mastitis, compared with no treatment.[366] When oxytocin administration (100 IU IM twice daily for 1 week) was compared with no treatment (udder massage only) in cows experimentally inoculated with *Staphylococcus aureus*, oxytocin administration reduced bacterial concentrations in the milk but did not improve the bacteriologic cure rate or reduce SCC.[367] Oxytocin administration increases the permeability of mammary epithelial tight cell junctions in a dose-dependent manner, which can alter milk composition in nonmastitic glands, particularly if high doses (≥100 IU) are administered repeatedly.[368]

Oxytocin and frequent milk-out have not been evaluated extensively in the field. In a California study, oxytocin (100 IU IM twice daily for three treatments) at milking time resulted in similar clinical and bacteriologic cure rates, as did two or three treatments with intramammary antibiotics; however, an untreated control group was not evaluated.[214] No overall benefit resulted because the oxytocin-treated cows had a higher recurrence rate of clinical mastitis, particularly environmental streptococcal mastitis.[215] In a Virginia study, frequent milk-out (six times daily) in conjunction with oxytocin administration (20 IU) did not improve clinical or bacteriologic cure rates, time to cure, or return to milk production compared with no treatment.[369] In an Illinois herd, cows treated with supportive therapy alone (oxytocin administration [all cases], frequent milk-out [moderate and severe cases], antiinflammatory therapy [severe cases], and fluid therapy [severe cases]) had lower clinical and bacteriologic cure rates and a higher recurrence rate than cows given antibiotics in addition to the same supportive therapy.[218]

In summary, oxytocin administration and frequent milk-out do not appear to be effective stand-alone treatments for clinical mastitis, particularly mastitis caused by streptococci, and may even be detrimental. In certain circumstances, when a cow clearly will not eject milk or when garget in the milk prevents effective

milk removal, these practices might be of some benefit. Otherwise, unnecessary administration of injections and frequent milking of painful teats should be avoided for welfare reasons.

36.8.2.4 OTHER SUPPORTIVE TREATMENT MEASURES

A wide variety of other nonantibiotic supportive measures are used to treat cows with clinical mastitis. These include udder massage, application of liniments, hydrotherapy of the affected gland, intramammary infusion of fluids, vitamin injections, and homeopathic treatments. In most cases, efficacy has not been scientifically evaluated, or the only studies involved experimentally induced mastitis, making it difficult to extrapolate results to naturally occurring clinical mastitis. Massage and liniment application were of no benefit in resolution of experimental *S. aureus* infection.[367] Intramammary administration of hypertonic saline did not hasten recovery of cows with experimental coliform mastitis.[370] Ascorbic acid (25 mg/kg SC once daily for 5 days) in conjunction with intramammary antibiotic therapy appeared to shorten recovery time and reduce severity of illness in one small field study, compared with intramammary antibiotics alone.[371] Ascorbic acid, 25 g IV 3 and 5 hours after intramammary endotoxin infusion, did not reduce clinical illness but did increase milk production recovery (9% higher).[372] Homeopathy is frequently practiced on organic dairy farms, but controlled clinical trials are difficult to perform because of the individual nature of the treatments; minimal efficacy data are available.[373] Natural antimicrobial substances (e.g., lactoferrin, nisin) and immunostimulants are receiving attention as potential alternatives or adjuncts to antibiotic therapy but need further investigation. Minimizing stress, feeding balanced diets with appropriate concentrations of vitamins and minerals, and maintaining cows in good nutritional condition are logical practices that should enable cows to respond effectively to clinical mastitis.

36.9 MASTITIS IN HEIFERS

Mammary glands of prelactational heifers are often infected with mastitis pathogens. The prevalence of intramammary infection can be as high as 90% to 97% of heifers and 60% to 75% of quarters.[374,375] In a multistate study the prevalence of intramammary infection in heifers at calving averaged 34% of quarters and 63% of heifers, but varied widely by location and herd.[376] Prevalence appears to be highest during the third trimester of gestation.

Coagulase-negative staphylococci are responsible for the majority of intramammary infections in heifers. However, *Staphylococcus aureus* can be isolated from up to 37% of heifers and 15% of quarters,[374] which allows heifers to serve as a reservoir of *S. aureus* for lactating cows. In most herds the prevalence of *S. aureus* intramammary infections in heifers is between 0% and 25%.[85,377] Other pathogens isolated from mammary secretions of heifers before or at calving include environmental streptococci and, occasionally, *Streptococcus agalactiae* and coliform bacteria. The majority of intramammary infections are subclinical, but when clinical mastitis is present at calving, the outcome is often poor, especially if mastitis is caused by *S. aureus*.[378]

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The mechanisms by which the mammary glands of heifers become infected are uncertain. Coagulase-negative staphylococci and *S. aureus* can be isolated from teat skin, teat orifices, and teat canals of prepartum heifers,[379,380] suggesting that intramammary infection follows colonization of the skin and canal. In fact, heifers with teat skin colonized by *S. aureus* before calving tended to be at higher risk of *S. aureus* intramammary infection at calving.[379] On the other hand, isolation of *S. chromogenes* from the teat apex did not increase intramammary infection risk at calving but did increase the likelihood that the heifer would have a low SCC (<200,000/mL).[381] *S.*

aureus was more frequently isolated from heifer body sites, such as udder skin, muzzle, and vagina, and from insects, bedding, water, and the environment in herds with a high *S. aureus* prevalence (>10%) in lactating cows, compared with herds with a low prevalence (<3%).[379]

The feeding of infected milk to calves may facilitate colonization of the oral cavity or muzzle.[379] Intersucking occurs frequently among calves and heifers[382] and may transmit pathogens from the oral cavity or muzzle to the teat skin. However, flies are thought to be more important than intersucking in infection transmission. DNA fingerprinting identified the same *S. aureus* subtypes in horn flies found on heifers as in the mammary secretions and teat canals of the heifers.[383] When flies exposed to a marker strain of *S. aureus* were housed with heifers, the same strain was subsequently isolated from teat skin of the heifers.[384] Teats with visible scabs or lesions have a higher prevalence of intramammary infection than normal teats,[380] and scabs can harbor high concentrations of *S. aureus* and serve as a source of infection for flies.[384]

36.9.1 Treatment

Several studies have investigated the efficacy and cost-effectiveness of intramammary antibiotic treatment in prepartum heifers. One treatment option is to administer an intramammary antibiotic formulated for dry cows to breeding age or primigravid heifers. A dry-cow formulation of penicillin and novobiocin reduced infection prevalence from 98% (prepartum) to 40% (at calving), with prevalence in untreated heifers remaining above 95%.[385] In the same study, *S. aureus* prevalence decreased from 17% to 3% of heifers after treatment, compared with a lesser decrease (26% to 16%) in untreated heifers. When quarters were inoculated with *S. aureus* 12 to 14 weeks before calving, infusion with a dry-cow formulation of cephapirin 1 to 3 weeks later cured all treated quarters, compared with spontaneous cure in only one of nine untreated quarters.[386] The choice of antibiotic appears to be relatively unimportant, because high overall cure rates were observed for five different dry-cow products infused 12 to 14 weeks prepartum.[387] However, the timing of treatment is important, with fewer new infections developing after treatment during late gestation.[387]

The other treatment option is to administer an intramammary antibiotic formulated for lactating cows 7 to14 days before calving. This is generally more practical because heifers are managed more intensively during the close-up period than earlier in gestation. When lactating cow formulations of cloxacillin or cephapirin were infused in this manner, the prevalence of intramammary infection after calving was 18% of heifers and 5% of quarters, compared with 78% of heifers and 45% of quarters in untreated controls.[375] Lactating formulations of penicillin-novobiocin and pirlimycin, administered prepartum, also significantly reduced intramammary infection prevalence in heifers at calving.[388] Treatment 14 days before the expected calving date reduces the risk of violative antimicrobial residues in milk after calving, compared with treatment 7 days before the expected calving date.[389]

Advantages of prepartum antibiotic treatment of heifers include a higher cure rate than with treatment during lactation (especially for *S. aureus*), a reduction in chronic mastitis, a lower SCC in cured quarters, and reduced risk of pathogen transmission to other cows or quarters.[390] Antibiotic-treated heifers produced 531 kg more milk/lactation than untreated heifers in one study,[390] but no difference in milk yield or SCC was found in other studies.[376,391] Prepartum antibiotic treatment is most appropriate for herds with a high prevalence of *S. aureus,* high SCC, or high incidence of clinical mastitis in heifers at calving. Extreme care must be taken to disinfect teat ends thoroughly before infusing antibiotics, to avoid iatrogenic infections. Control measures should focus on fly control and reducing the incidence and prevalence of *S. aureus* intramammary infections in lactating

cows. Feeding milk replacer or pasteurized waste milk may reduce the risk of colonization of calves with *S. aureus* in problem herds, but the impact on subsequent mastitis incidence is uncertain.

36.10 ECONOMIC IMPACT OF MASTITIS

Mastitis is considered the most costly disease of dairy cattle. The costs associated with mastitis are a result of unearned revenues as well as real expenditures. Costs differ for subclinical and clinical mastitis and depend on market prices for milk and cattle, the causative pathogen, and the parity and stage of lactation of the cow.

36.10.1 Subclinical Mastitis

In most prevalence surveys, approximately one third to one half of cows have intramammary infections, with the vast majority of infections being subclinical. Subclinical infection is accompanied by an increase in SCC and reduction in milk yield, the extent and duration of which depend on the causative pathogen and effectiveness of host defense mechanisms. The reduction in milk yield associated with subclinical mastitis is usually estimated by extrapolating from crude SCC or a logarithmic transformation of SCC. The relationship between crude SCC and milk yield loss is nonlinear, whereas logarithmic transformation results in a linear relationship. For example, each twofold increase in crude SCC above 50,000/mL on monthly test day reports was associated with an average reduction in milk yield of 0.6 kg/day for multiparous cows and 0.3 kg/day for heifers.[392] Each unit increase in $\log_{10}$SCC on weekly test day reports was associated with an average reduction in milk yield of 2 kg/day for multiparous cows and 1.3 kg/day for heifers.[393] In the United States, linear score (LS), a $\log_2$-based transformation of SCC that results in scores of 0 to 9, is the usual parameter used. Each unit increase in lactational average LS above 2 results in an average milk yield reduction of 0.7 kg/day or 180 kg/lactation for multiparous cows, with losses for heifers being approximately half.[394] Such associations provide a rough estimate of the magnitude of milk yield loss associated with subclinical mastitis in a herd, but do not accurately estimate milk yield loss in individual cows.

Sometimes, herd milk yield loss is estimated from the SCC of the bulk tank (BTSCC). For example, a decrease in milk yield equating to a loss of at least $100/cow/year was demonstrated in herds with BTSCC greater than 200,000/mL.[395] One problem with using BTSCC to estimate milk yield loss is the dilutional effect of milk from high-yielding cows on BTSCC.[396] 1135 1136

Milk from cows with subclinical mastitis is not usually withheld from the bulk tank. This causes an increase in BTSCC and reduction in milk quality. The milk quality changes associated with subclinical mastitis adversely affect the processing properties, organoleptic qualities, and shelf life of milk and milk products.[397] In the United States, milk processors routinely monitor BTSCC, and dairy producers may be paid premiums for low BTSCC or penalized for high BTSCC. Premium and penalty programs vary widely by location; however, in some cases, penalty payments or unearned premiums account for the greatest loss associated with subclinical mastitis.[398] A substantial economic loss is incurred when BTSCC exceeds 750,000/mL because the milk cannot be marketed as grade A; this BTSCC limit is much higher in the United States than in Canada and other developed countries.[399] High-BTSCC milk also has a greater risk of condemnation because of violative antimicrobial residues.[400–402]

Cows that maintain persistently high SCC, have untreatable intramammary infections, or have low milk production often are culled prematurely. The cost of premature culling depends on the perceived value of the cow, the market prices for culled cows and replacement heifers, and the potential value of the replacement

heifer.[398] A recent retrospective study revealed that cows with lactation average SCC greater than 700,000/mL had more than twice the risk of being culled than cows with SCC of 200,000 to 250,000/mL; the risk tended to be greater in herds with low SCC than those with high SCC.[403] Cows that are not culled sometimes require segregation or special milking procedures that increase labor costs; for example, cows with chronic *S. aureus* or *Mycoplasma* mastitis may need to be milked last or in separate strings.

36.10.2 Clinical Mastitis

Approximately 15% to 20% of cows experience clinical mastitis during the course of a lactation.[404,405] However, the incidence of clinical mastitis varies among herds, from less than 10% of lactations to greater than 50% of lactations. An acute drop in milk production often accompanies the onset of clinical mastitis. Some cows rapidly cease lactating or produce substantially less milk than predicted for the rest of the lactation. Others experience little drop or rapidly return to normal or near-normal production.[406] Average lactational milk yield losses reported for clinical mastitis range from less than 50 kg to 749 kg per lactation, but a loss of 5% of lactational milk production is usually assumed.[406] Milk yield loss is generally higher when clinical mastitis occurs in early to peak lactation than in late lactation, and for multiparous cows than for heifers.[406]

Milk that is visibly abnormal or contains drug residues must be diverted from the bulk tank and withheld from sale. The cost associated with diverted milk is a major component of the cost of clinical mastitis. Actual cost depends on whether the milk is discarded or fed to calves in place of milk replacer, as well as the price of milk and milk replacer and difference in labor associated with the two feeding methods. Failure to detect clinical mastitis and divert milk from the bulk tank adds to the reduction in milk quality caused by subclinical mastitis. Cows with repeated episodes of clinical mastitis produce the majority of diverted milk in some herds.[407]

A small proportion (<5%) of cows with clinical mastitis die or are euthanized because of the severity of their condition. More cows fail to respond adequately to treatment or experience recurrent episodes of clinical mastitis, resulting in premature culling. Mastitis is consistently ranked as one of the top reasons for culling dairy cows. In a national survey, U.S. dairy producers reported that mastitis and other udder problems were responsible for an average 27% of culls[408]; mastitis may also have contributed indirectly to the 19% of cows culled because of low milk production. Neerhof et al.[409] reported that the risk of culling Danish Black and White cows was 1.7 times higher for cows that had experienced clinical mastitis than for those without mastitis. Rajala-Schultz and Gröhn[410] reported similar findings for Finnish Ayrshire cows. In a study examining the effect of mastitis on herd life in two New York dairy herds, the first episode of clinical mastitis caused by *Streptococcus* species, *S. aureus, Staphylococcus* species, *E. coli*, or *Klebsiella* species reduced herd life, with pathogen-associated hazard ratios ranging from 1.19 to 3.18.[411] The hazard of culling for clinical mastitis differs with stage of lactation and increases with age of the cow.[411,412]

The cost of diagnosing and treating an episode of clinical mastitis depends on its severity, the causative pathogen, the treatments administered, the labor required, whether the milk is cultured, and whether a veterinarian is involved. Antibiotic treatment carries a risk of inadvertently introducing antibiotics into the bulk tank and causing violative drug residues, which is costly. However, if antibiotic treatment improves the cure rate and reduces lost milk, SCC, and risk of mastitis transmission, economic losses are reduced.[413] The appropriate selection of cases for antibiotic treatment is critical for optimizing returns and avoiding unnecessary losses, as discussed in other sections.

36.10.3 Effects of Mastitis on Reproduction

One increasingly recognized cost associated with mastitis is reduced reproductive performance. Development of clinical mastitis between days 15 and 28 postpartum delayed the onset of ovarian cyclicity and estrus by approximately 6 days, regardless of the causative pathogen (gram positive or gram negative).[414] Clinical mastitis episodes caused by gram-negative pathogens induced a substantially higher rate of premature luteolysis (47%) than those caused by gram-positive pathogens (8%) and prolonged the follicular phase of the estrus cycle when mastitis occurred at that time.[414] Development of clinical or subclinical mastitis before first service caused increases in days to first service, days open, and services per conception, compared with nonmastitic cows.[415] Induction of *S. uberis* mastitis before ovulation decreased luteinizing hormone (LH) pulses, impaired 17β-estradiol production, and prevented ovulation.[416] Maintenance of pregnancy can be impaired when mastitis occurs shortly after a cow is bred, presumably as a result of embryonic death.[417,418] Cows with LS greater than 4.5 before breeding were 2.4 times more likely to experience early embryonic death than cows with LS less than 4.5.[419] Both experimental and natural clinical mastitis episodes have been reported to induce abortion.[420,421] Together, these findings imply that both clinical and subclinical mastitis caused by a variety of pathogens can be detrimental to reproductive performance and can contribute to economic loss.

36.10.4 Total Cost of Mastitis

The total cost of mastitis is impossible to quantify accurately, varies over time, and is herd dependent. No studies have included all the major categories of economic loss in their calculations.[406] However, imperfect estimates of average costs have been generated and are useful for appreciating the impact of the disease. The cost of clinical mastitis has been estimated at $107 per case[422] and $30 to $50 per cow in the herd.[398] In one herd the cost associated with loss of saleable milk and treatment alone averaged $201 or $295 per lactation, depending on the treatment protocol.[340] The total cost of mastitis has been estimated at $200/cow/year or $1.5 to $2 billion per year nationally.[398,423]

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The economic loss resulting from mastitis is not equivalent to the economic returns available from mastitis control, because it is impossible to eliminate mastitis completely. Also, the costs associated with mastitis control can be substantial. In one survey the cost of mastitis prevention accounted for 50% of the cost for preventing all diseases.[422] Return on investment in mastitis control measures is more important than the absolute cost. Return on investment ranged from −$20 to $275/cow/year in nine studies,[424] depending on the prevalence and type of mastitis in the herd, control measures already in place, efficacy of the control measures to be implemented, and producer compliance.[425,426]

Stochastic modeling has been used to predict return on investment under a variety of scenarios.[426,427] Using one model, mastitis control programs that included antibiotic treatment of all cows at dry-off and preventive measures in the milking parlor (forestripping, cleaning, or predipping of teats and postdipping of teats), with or without antibiotic treatment of lactating cows, yielded positive annual net benefits, regardless of whether the primary pathogens in the herd were contagious or environmental. On the other hand, lactating-cow antibiotic therapy alone was not profitable in any circumstance.[426] Such models can assist in making rational decisions about mastitis control, but results depend on the assumptions used, which are seldom universally applicable.

36.11 MASTITIS CONTROL

Eradication of mastitis is an unrealistic goal. However, mastitis can be controlled by (1) determining the causative pathogens, (2) identifying and reducing the predominant reservoirs, (3) identifying and limiting the main risk factors for transmission, and (4) promoting host defense. Control measures for specific pathogens are discussed in previous sections. Pathogen identification is an essential first step in mastitis control because reservoirs and risk factors differ among mastitis agents. Reducing reservoirs and risk factors can decrease intramammary infection risk, but exposure of teats to pathogens cannot be completely avoided. Therefore, host defense mechanisms are critically important in preventing new infections and limiting the severity and duration of mastitis (see section on defense mechanisms).

Factors influencing host defense against mastitis include teat condition, nutrition, genetics, and stress. Traditional mastitis control measures can be augmented by keeping teats healthy, feeding appropriately formulated diets, selecting for inherent mastitis resistance, and minimizing stress.

36.11.1 Teat Condition

Teat injuries can be avoided through appropriate housing and stall design. Milking machine—associated teat damage can be minimized by providing appropriate pulsation and teat end vacuum and by using properly sized teat cup liners. Premilking teat preparation methods can promote oxytocin release and allow teat cups to be attached after milk ejection, thus minimizing milking time and associated risks to the teats. Teat chapping, which facilitates bacterial colonization, can be avoided by providing protection against adverse weather and using teat dips that condition the skin. Teat cannulas and dilators compromise the teat canal and should be avoided. Intramammary antibiotics should be administered using the partial-insertion method of infusion.[14] Internal teat sealant can enhance physical defense against pathogen invasion during the dry period.

36.11.2 Nutrition

Negative energy balance, or more specifically *ketogenesis,* is a risk factor for mastitis.[428,429] Ketone bodies adversely affect neutrophil function in vitro.[430] Experimental *E. coli* mastitis is more severe in ketonemic cows than nonketonemic cows.[429,431] In one field study, 29% of cows with circulating β-hydroxybutyrate (BHB) concentration of 1400 μmol/L or greater in the week before calving developed clinical mastitis after calving, compared with 9% of cows with BHB concentration less than 1400 μmol/L.[432] In another study, cows with serum BHB concentration of 1000 μmol/L or greater 1 to 3 days after calving were at increased risk of developing clinical mastitis caused by environmental pathogens, compared with cows with BHB concentration less than 1000 μmol/L.[433] Heifers with BHB concentration of 100 μmol/L or greater in milk during the first or second week after calving were more likely to have subclinical mastitis before calving and develop new intramammary infections after calving, compared with heifers with less than 100 μmol/L BHB in milk.[434] These findings suggest that dietary management to minimize ketosis in the periparturient period should reduce the incidence and possibly the severity of mastitis. Ionophore antibiotics also may help to reduce energy-associated mastitis risk. Administering a controlled-release monensin-containing capsule before calving reduced serum BHB concentration in periparturient cows,[435] and feeding monensin after calving reduced clinical mastitis incidence and rate of intramammary infection.[436]

Dietary vitamin and mineral concentrations influence mastitis susceptibility, particularly in the periparturient period when feed intake declines. Vitamin E and selenium have received the most attention because of their synergistic antioxidant actions and beneficial effects on the immune system, especially neutrophil function.[437,438] Heifers fed a selenium-deficient diet before and during their first lactation experienced more severe and persistent *E. coli* mastitis than heifers fed a selenium-supplemented diet.[439] The prevalence of intramammary infection, rate of clinical mastitis, and BTSCC all decline as blood selenium concentration increases.[437,440] Supplementing 1000 or 4000 IU vitamin E/day during the last 2 weeks of the dry period reduced clinical mastitis in the first week after calving by 30% and 88%, respectively, compared with 100 IU/day.[441] Current recommendations are to feed 1000 IU vitamin E/day during the late dry period and early lactation and 500 to 1000 IU/day at other times.[442] The traditional practice of feeding 0.1-ppm dietary selenium may result in blood selenium concentrations that are too low to protect against mastitis; 0.3 ppm is considered advantageous.[441] Rations for U.S. dairy cows often contain suboptimal concentrations of both vitamin E and selenium, which creates an opportunity to improve mastitis resistance through dietary supplementation. In contrast, parenteral injection of vitamin E or selenium provides less consistent beneficial effects.[437,443]

Additional dietary ingredients considered important in immune system function and mastitis resistance are vitamin A, β-carotene,[444] and antioxidant trace minerals and vitamins such as zinc, copper, and ascorbic acid.[445] Ensuring adequate vitamin and micronutrient supplementation should assist in mastitis control. Protein balance, particularly a balance of amino acids such as glutamine, may also be important.[446]

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36.11.3 Genetics

Although mastitis occurrence is largely determined by physiologic and environmental factors, susceptibility is partly attributable to genetic variability. Direct selection against clinical mastitis is difficult because heritability is low (<0.05) and producers do not consistently record clinical mastitis events. Somatic cell count (SCC) is recorded more consistently and has higher heritability (0.10 to 0.30), making it a better selection parameter.[447] Genetic correlation between SCC and intramammary infection is almost 1.0, and correlation between SCC and clinical mastitis is fairly high (0.5 to 0.8), making SCC a reasonable proxy.[448] For instance, daughters of sires that transmit low somatic cell score (SCS) have a lower prevalence of intramammary infection at first parturition and shorter and less severe episodes of clinical mastitis during first lactation than daughters of sires that transmit high SCS.[449,450] Lactation average SCS, clinical mastitis incidence, and duration of clinical mastitis in first lactation are all influenced by predicted transmitting ability (PTA) for SCS, as are total number of lactations, days of productive life, and total days in milk, which means that daughters from sires with high PTA SCS are culled sooner.[451] The concern that breeding for low SCS will increase clinical mastitis susceptibility does not appear to be founded.[452]

Both clinical mastitis and SCC are moderately correlated (0.2 to 0.7) with udder depth and udder attachment, meaning that selecting for high, tightly attached udders should reduce mastitis susceptibility.[448] Clinical mastitis is negatively correlated with body condition score (−0.16) and positively correlated with dairy character (0.27), which suggests that placing more emphasis on body condition and less on dairy character might promote positive energy balance and reduce the risk of ketosis-associated mastitis.[453]

Unfortunately, clinical mastitis is positively correlated (~0.40) with milk production and milking speed.[448] Therefore, selecting solely for increased milk production is detrimental to udder health.[454] This may be the result of shorter, wider teat canals and increased pressure in the teats of high-yielding cows, both of which compromise the barrier function of the teats. Use of bovine somatotropin (rBST), which enhances milk yield, increases the risk of clinical mastitis by approximately 25%.[455] High-yielding cows also have more severe negative energy balance in the periparturient period, when immune function is compromised and mastitis risk is high.[429] Therefore, the economic benefits of higher production and faster milking must be weighed against the economic and welfare costs associated with clinical mastitis.

It may be possible to use immune function measures to select for mastitis resistance. Neutrophil function in vitro and antibody production in response to vaccination in vivo are more heritable than SCS and influence mastitis susceptibility or severity.[448,456] Therefore, immune function testing of sires might be helpful in selecting for cows that can resist mastitis. Differences in alleles of class I and class II major histocompatibility complex (MHC) genes also are associated with clinical mastitis susceptibility or SCC. For example, MHC class I alleles A26 and A7(w50) are associated with mastitis resistance and the class II DRB3.2*24 allele with susceptibility.[448] Similarly, quantitative trait loci for SCS and clinical mastitis are found on almost all chromosomes.[448] Therefore, in the future, producers may be able to use haplotype or quantitative trait loci data to supplement other selection criteria. The challenge will be to develop the most appropriate combinations of criteria to protect udder health without serious detriment to other health or production parameters.

36.11.4 Stress

Mastitis susceptibility is increased in the periparturient period, when stress hormones are high. The role of stress at other times on mastitis susceptibility is not clear. However, because a variety of stressors affect immune function, it is logical that stress avoidance should promote mastitis resistance. Such measures as sprinklers, shades, and tunnel ventilation can help prevent heat stress. Good housing and stall design, appropriate stocking density, and sufficient feedbunk space can reduce housing and social stress. Handling cows calmly and humanely, taking advantage of natural behaviors, can minimize handling stress.

36.11.5 Other Practices That Influence Host Defense

Vaccination of cows against core LPS antigens boosts immunity against gram-negative pathogens and reduces the severity of coliform mastitis. Unfortunately, effective vaccines are not available for most mastitis pathogens. Manipulation of photoperiod (short daylength exposure) during the dry period enhances cellular immune responses in vitro at calving,[457] but the effect on mastitis incidence and severity needs further investigation.

Antibiotic therapy can assist host defenses in resolving mastitis in some cases (e.g., with streptococcal infection). However, several classes of antibiotics often used to treat mastitis, such as β-lactams and tetracyclines, have detrimental effects on neutrophil phagocytosis or killing ability in vitro.[26,458] It is not known if this translates to a negative impact on mastitis outcome in vivo.

36.12 MASTITIS IN SHEEP AND GOATS

36.12.1 Clinical Mastitis

The incidence of clinical mastitis in small ruminants is low (<5% of lactations).[459] In most cases, clinical mastitis is sporadic, but outbreaks occasionally occur. Ewes or does with clinical mastitis can experience severe clinical illness or develop chronic mastitis with abscessation. The reduction in milk yield that accompanies clinical mastitis reduces income on dairy operations and can adversely impact growth or viability of nursing neonates. Dairy producers must divert clinically abnormal or residue-containing milk from sale. Ewes or does that develop clinical mastitis are often culled at weaning or at the end of lactation, if not sooner. Therefore, despite its low incidence, clinical mastitis can still have an adverse economic impact on sheep and goat farms.

Staphylococcus aureus is the most common clinical mastitis pathogen in meat and dairy sheep, as well as in goats.[460,461] *S. aureus* is more likely to cause severe clinical signs or gangrenous mastitis in small ruminants than in cattle, and small ruminants are more likely to develop abscesses in the mammary gland if infection persists. Another important clinical mastitis pathogen of sheep, particularly meat sheep, is *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*).[460] *S. aureus, M. haemolytica*, and coagulase-negative staphylococci are responsible for most clinical mastitis episodes in sheep, with streptocooci, corynebacteria, coliform bacteria, and *Arcanobacterium pyogenes* isolated less frequently.[460] These pathogens also cause clinical mastitis in goats, but *M. haemolytica* is isolated less frequently than in sheep.[459] Outbreaks of clinical mastitis in small ruminants are usually caused by *S. aureus*, streptococci, or opportunistic pathogens, such as *Pseudomonas* or fungi.[459]

When clinical mastitis cannot be explained by bacterial or fungal infection, *Mycoplasma* infection should be suspected. A variety of *Mycoplasma* species can cause clinical mastitis outbreaks in small ruminants. *Mycoplasma mycoides* subspecies *mycoides* (large-colony type) is an important mastitis pathogen in goats in the United States, especially in California.[462,463] *Mycoplasma putrifaciens* is involved in some outbreaks,[464] and *M. agalactiae* is isolated on rare occasions.[465] Does with *Mycoplasma* mastitis often exhibit severe clinical illness and reduced milk yield, in addition to an inflamed udder and visibly abnormal milk; however, subclinical intramammary infections can occur. Adult goats and kids in herds with *Mycoplasma* mastitis may experience polyarthritis and pneumonia, and pregnant does may abort. Morbidity and mortality can be very high, with more than 90% of goats dying or euthanized in some herds.[464]

Clinical mastitis is detected at milking time in dairy sheep and dairy goats but may not be readily apparent in animals that nurse their young. Lethargy, depression, or abnormal gait may be the most obvious sign if the mammary gland is not greatly enlarged. Abnormal gait, which is often mistaken for lameness, occurs when the animal attempts to keep its hindlimb away from the painful gland. Lambs or kids of dams with clinical mastitis may make frequent attempts to nurse but have poor abdominal fill because of the reduced milk production.

Little research has been done on the treatment of clinical mastitis in small ruminants. Ewes or does with severe or recurrent clinical mastitis are often sacrificed rather than treated, and the goal of treatment is often to maintain survival until the animal can be slaughtered or sold. When treatment is performed, practices for bovine mastitis are usually followed. These include intramammary and systemic antibiotics, antiinflammatory agents, and fluid therapy (see section on clinical mastitis treatment). No intramammary or systemic antibiotics are labeled for treatment of mastitis in sheep or goats in the United States, so extralabel drug use is necessary. Beta-

lactam and macrolide antibiotics are often used because of the predominance of staphylococci and (in sheep) *M. haemolytica*.[466] Without efficacy data, it is impossible to make evidence-based recommendations.

Because of the small volume of the ovine and caprine mammary glands, producers often administer one half of the bovine dose when infusing intramammary antibiotics. This is likely to be adequate, provided the pathogen is susceptible, the antibiotic can reach the site of infection, and treatment is continued for a sufficient duration. Depletion of antibiotics from the mammary gland of goats after intramammary infusion is similar to that for cows.[467] However, when using antibiotics labeled for cows, the milk-withholding and slaughter-withholding times should be extended to avoid violative residues.

Economics often drive treatment decisions in small ruminants, but the welfare of the animal must be addressed. Because clinical mastitis in small ruminants is usually caused by gram-positive bacteria, in contrast to the high rate of coliform mastitis in cattle, antibiotics should be administered. Also, analgesics (NSAIDs) are indicated to control pain. Flunixin meglumine administration hastens clinical recovery in both sheep[468] and goats.[469] Neither intramammary nor systemic antibiotics are likely to resolve *Mycoplasma* infection, making euthanasia the most humane option in animals with clinical mycoplasmosis. Euthanasia is also the best option in most cases of gangrenous mastitis; if euthanasia is not performed, it may be necessary to amputate the teat or surgically remove necrotic tissue. Animals with gangrenous mastitis should be segregated to avoid contaminating the environment and transmitting the pathogen (usually *S. aureus*) to herdmates.[470]

36.12.2 Subclinical Mastitis

Subclinical mastitis is more common than clinical mastitis in both sheep and goats. Intramammary infection is identified in 20% to 40% of ewes and does in most surveys.[461,471,472] The prevalence of intramammary infection ranges from less than 10% to more than 90% among sheep flocks[460,473] and less than 10% to more than 60% among goat herds.[461,474] Prevalence increases with parity in goats.[471,475]

Subclinical mastitis is accompanied by reduced milk production and altered milk composition. On dairy farms, this reduces income and adversely impacts the quality of milk and milk products. On farms raising sheep or goats for meat, the weaning weights of nursing animals may be reduced.[476–478]

Coagulase-negative staphylococci (CNS) cause the majority of subclinical mastitis episodes in sheep and goats.[459] Although CNS are considered minor pathogens in dairy cows, this is not the case in small ruminants. Mammary glands infected with CNS, particularly novobiocin-sensitive species, have substantially higher SCC than do uninfected glands.[461,472,474,477] Also, CNS infections in small ruminants usually persist for months. Other subclinical mastitis pathogens of sheep and goats include *S. aureus,* streptococci, enterococci, corynebacteria, and *Mycoplasma* species.[459] Within-herd/flock prevalence of *S. aureus* is typically lower for small ruminants than for dairy cattle.

Subclinical mastitis is most often detected by palpating mammary glands for firmness and abscesses. In meat animals this is done at weaning, breeding, or lambing/kidding. In dairy animals it is done more routinely. Ultrasonograpy can be helpful in detecting abscesses or areas of fibrosis.[479] Although milk culture is the “gold standard” method for diagnosing subclinical intramammary infection, most sheep and goat producers do not routinely culture milk. Indirect diagnostic tests for subclinical mastitis include SCC, CMT, electrical conductivity/impedance, and NAGase activity (see Intramammary Infection and Mastitis). SCC is a more reliable indicator of intramammary infection than CMT,[480] but CMT is more practical. In one trial, electrical

impedance was of no predictive value in sheep and little value in goats.[480] NAGase activity increases with intramammary infection in sheep and goats,[474,481] but more studies are needed to determine the ability of NAGase activity to predict infection accurately.

Somatic cell counts are more likely to be monitored in dairy sheep/goats than meat animals. An SCC threshold of 250,000/mL was suggested for sheep in one report, because 82% of milk samples from uninfected halves had SCC less than 250,000/mL and 91% of samples from infected halves had SCC greater than 250,000/mL.[482] In contrast, the mean SCC for uninfected halves of sheep was 500,000/mL in another study.[480] Thresholds ranging from 500,000/mL to more than 1 million/mL have been recommended for both sheep and goats. The choice of SCC threshold and its value for predicting infection status depend on the prevalence of infection in the flock/herd, as is the case for cattle (see section on mastitis detection). In general, a low SCC is more predictive of a healthy gland than a high SCC of an infected gland.[480,483] SCCs from sequential tests are more valuable than a single test result.

An interesting difference between goats and sheep (or cattle) is that milk secretion in goats is an apocrine process. Anucleated cytoplasmic particles are expelled from the secretory cells into the milk during secretion of milk components. These particles are approximately the same size as somatic cells, average 150,000/mL in goat milk, and they can be mistaken for somatic cells by some counting methods. Therefore, only direct microscopic observation or methods that identify DNA should be used for quantifying somatic cells in goat milk.[484] Another difference between goats and sheep is a higher proportion of neutrophils in normal goat milk. Lastly, the SCC of goat milk increases substantially in late lactation, even in does free of intramammary infection. Counts can exceed 1 million/mL in healthy glands, making SCC an unreliable predictor of intramammary infection in late lactation.[484,485] To explore mastitis prevalence in a goat herd using SCC, goats should be sampled after the postparturient period but before 130 days in milk, to avoid the influence of stage of lactation on SCC.[474]

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Geometric mean SCC values for CMT scores of negative, trace, 1, 2, and 3 are 170,000, 309,000, 760,000, 1,911,000, and 8,819,000/mL, respectively, for dairy sheep and 135,000, 148,000, 359,000, 1,110,000, and 7,505,000/mL, respectively, for dairy goats, showing a clear positive relationship between CMT score and SCC.[480] A CMT threshold of 1 is usually recommended for differentiating infected from uninfected halves. However, the CMT has the same drawbacks as SCC, with low scores (negative or trace) being highly predictive of uninfected glands but high scores being poorly predictive (<45%) of infected glands, unless infection prevalence is very high.[480] Bulk tank SCC is useful for estimating the intramammary infection prevalence in dairy sheep and goats,[459] but the proportion of goats in late lactation must be considered when interpreting BTSCC.

Subclinical mastitis in small ruminants is most effectively treated by infusing antibiotics into the mammary glands at dry-off/weaning. Antibiotic products labeled for dairy cows are used. Antibiotic infusion at dry-off/weaning significantly increases cure rate compared with spontaneous cure. Antibiotic infusion at dry-off/weaning also reduces the incidence of new intramammary infections at parturition and the prevalence of intramammary infection throughout lactation, and results in lower SCC and higher milk yield.[481,486,487] There appears to be little difference in efficacy between a full dose of antibiotic and a half dose, so producers typically split one antibiotic tube between two udder halves. When this is done, the cannula should be swabbed with alcohol before inserting it into the second gland.[486] As in cattle, inadequate disinfection of the teat or poor intramammary infusion technique in sheep and goats can lead to opportunistic intramammary infections. Withholding times for milk and meat must be extended and milk tested for antibiotic residues after parturition if

it is to be sold for human consumption. The risk of antibiotic residues by 5 to 7 days after lambing appears to be negligible.[481]

Other mastitis control measures for small ruminants include culling of chronically infected animals, hygienic housing conditions, and good premilking udder hygiene practices. Contagious ecthyma control will reduce the risk of teat lesions and secondary mastitis. Identification and removal of milk-robbing lambs may reduce spread of pathogens from teat to teat. Control measures for contagious mastitis in dairy cows are recommended for dairy sheep and goats; these include postmilking germicidal teat dipping and use of gloves and individual towels when preparing teats for milking. Apparently healthy goats can carry pathogenic *Mycoplasma* species in their external ear canals, often in conjunction with ear mites,[488] but the importance of the ear as reservoir for *Mycoplasma* mastitis is uncertain.[489]

Heritability of SCS in sheep is .10 to .15, with a negative genetic correlation (−0.35 to −0.11) between SCS and milk yield. Genetic selection for mastitis resistance is practiced in certain breeds in some countries.[459] Identification of regions of the ovine genome involved in mastitis resistance has led to use of quantitative trait loci programs for genetic selection in some countries.[459]

36.12.3 Retroviral Mastitis

Retroviral (lentiviral) infections in sheep (ovine progressive pneumonia, maedi-visna)[490] and goats (caprine arthritis-encephalitis)[491,492] can cause interstitial mastitis. Mammary glands become diffusely and homogenously firm, and milk production declines. Viral infection results in an interstitial accumulation of lymphocytes in the mammary gland. The SCC of seropositive (presumptively infected) goats is higher than the SCC of seronegative goats, but not as high as with bacterial intramammary infection.[492] The increase in SCC in seropositive goats may be caused by an increase in mononuclear cells in the milk or a reduction in milk yield. In contrast, retroviral infection in sheep appears to have little effect on SCC.

Retroviral mastitis should be suspected when the udder is firm but not inflamed and the milk appears normal. A positive serologic test result and other signs of retroviral infection (chronic weight loss, increased respiratory effort, arthritis) support the diagnosis. There is no effective treatment for retroviral mastitis, so affected animals must be culled. Feeding colostrum or milk from affected animals to their offspring can transmit the infection.

36.13 MASTITIS IN BEEF CATTLE

Approximately 15% to 40% of beef cows have intramammary infection in one or more mammary glands in most surveys.[493–495] Coagulase-negative staphylococci are the predominant isolates, but *Staphylococcus aureus* is found in 7% to 10% of samples. Streptococci and corynebacteria are isolated occasionally, as are gram-negative bacteria. Milk from infected glands has significantly higher SCC than milk from uninfected glands,[493] but somatic cell counting is not usually performed in beef herds. Clinical mastitis occurs sporadically and is diagnosed and treated as for dairy cows when economically feasible; most mild clinical mastitis cases probably go unrecognized.

The prevalence and etiologic agents of intramammary infection in prepartum beef heifers are similar to those in lactating beef cows.[493,496] In contrast to dairy cattle, clostridia are the predominant bacteria found in the teat canal of beef cattle, followed by *Bacillus* species and staphylococci.[497]

Several modes of mastitis transmission have been proposed for beef cattle. Flies are believed to serve as vectors for staphylococci. This may explain the higher prevalence of intramammary infection in the front glands of beef heifers than the rear glands, because flies on the front glands are less accessible by the tail. Fly-induced scabs on the teats of beef heifers have been shown to harbor staphylococci.[493] Calves may also serve as vectors by transmitting oropharyngeal organisms to the teats or carrying bacteria-laden milk from teat to teat. Unsanitary housing conditions probably increase the risk of infection with environmental pathogens.[498] As with dairy cows, poor udder conformation and teat injuries may predispose to mastitis.

Several studies have demonstrated numeric or significant decreases (up to 40 kg) in weaning weights of calves from beef cows with subclinical mastitis.[493–495] This probably results from reduced milk production. The adverse effect on weaning weight appears to increase with the number of infected glands.[494] In most cases the cost associated with reduced weaning weight is unlikely to justify antibiotic treatment. Selective intramammary antibiotic treatment at weaning based on CMT reaction has been suggested, but CMT score is unlikely to be an accurate predictor of infection. Sanitary housing conditions, appropriate stocking density, and good fly control should help minimize mastitis risk in beef cattle.

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36.14 MASTITIS IN HORSES

Mastitis is an uncommon problem in horses, partly because of the small size and inguinal location of the udder, which minimizes exposure to environmental pathogens. Little research has been done on the prevalence of subclinical mastitis in horses, but it is not recognized to be a serious problem. In one study, no pathogens were grown from the milk of 11 mares sampled repeatedly during the first 2 months of lactation, and average SCC was less than 50,000/mL at most sampling times.[499]

Clinical mastitis occurs sporadically in lactating and nonlactating mares; signs range from mild to severe. The most common clinical mastitis pathogen is *Streptococcus zooepidemicus,* but a variety of aerobic bacteria have been isolated from the milk of affected mares.[5,500] In a retrospective study of 28 cases, gram-negative bacteria (coliform bacteria, *Pseudomonas, Actinobacillus, Pasteurella*) were isolated from 42% of milk samples.[5] Streptococci and staphylococci constituted most of the gram-positive isolates. Rarely, mastitis is caused by nonbacterial pathogens. For example, one mare developed unilateral mastitis as a component of disseminated coccidioidomycosis.[501] Verminous mastitis has even been reported.[502]

Clinical signs of mastitis in horses include an enlarged, firm, warm, painful mammary gland and edema of the udder and surrounding tissues. The mare resists milking, and secretions are abnormal in appearance (color, viscosity, consistency). About half of all mares with clinical mastitis are systemically ill, with signs such as fever, tachycardia, tachypnea, anorexia, depression, or agalactia. The mare may be reluctant to move or may adopt an abnormal gait to minimize contact between the hindlimb and the painful gland. Sedation or anesthesia is necessary to achieve a thorough examination of the udder and collection of milk in some horses.[500]

Culturing of the milk is required to identify definitively the causative pathogen of equine mastitis and confirm that antibiotic selection is appropriate. However, bacteria can often be observed on cytologic examination of the milk.[5,503] A differential diagnosis for a firm, enlarged, painful mammary gland is adenocarcinoma, particularly if the udder skin is ulcerated and the secretion is serosanguineous.[504] With adenocarcinoma, neoplastic cells may be seen during cytologic examination of the secretion, or a mammary biopsy may be required. Because bacterial mastitis and adenocarcinoma can occur simultaneously, it is important to reevaluate mares that do not respond as

expected to antibiotic treatment. A differential diagnosis for agalactia in mares is fescue toxicosis. With fescue toxicosis, the udder is not inflamed, and mares may sweat profusely, have prolonged gestation, or give birth to weak or dysmature foals.[505]

Treatment of bacterial mastitis in horses consists of intramammary and systemic antibiotics to combat infection; NSAIDs to reduce pain, inflammation, and fever; and fluids to correct dehydration. Hot packing, hydrotherapy, and frequent stripping of the affected gland are empirically justified supportive measures but may be difficult to accomplish. Furosemide can be administered if edema is substantial.

Broad-spectrum antibiotics should be given until results of cytologic examination or culture of the milk are available. Potentiated sulfonamides, or a combination of penicillin and an aminoglycoside, are reasonable systemic antibiotic choices. Because no antibiotics are labeled for intramammary administration in horses in the United States, intramammary infusion products for cattle are used. Infusion products containing ceftiofur, cephapirin, amoxicillin, or hetacillin are appropriate until the cause of the mastitis is determined. A commercial intramammary infusion product is preferable to a homemade solution because the latter carries a greater risk of unintentional contamination. Intramammary infusion of antibiotics can be difficult to accomplish in horses because of the small size of the teat orifice and the presence of two distinct lobes within each udder half. One or both lobes can be infected, so antibiotics must be directed appropriately. Antibiotic treatment should be continued for at least 5 days to avoid relapse.

The prognosis for survival of horses with bacterial mastitis is good; however, milk production may be transiently or permanently reduced. Fortunately, mastitis is usually unilateral, and recurrence is rare.[5] Most mares respond rapidly to antibiotic treatment. Although spontaneous recovery is possible, it is unethical to withhold treatment from a mare that is ill or in discomfort. The prognosis for mammary adenocarcinoma is poor, even with surgical removal of the affected mammary gland(s) and local lymph nodes, because of the high rate of metastasis.[504]

36.15 MASTITIS IN SOUTH AMERICAN CAMELIDS

As with the horse, the udder of South American camelids (SACs) is nonpendulous, has small teats, and is protected from trauma and environmental contamination by its caudal location. Because they are not reared for milk production, SACs are spared the contagious mastitis risks associated with hand or machine milking. Therefore, it is not surprising that the prevalence of mastitis is low. In a survey of 100 llamas, potential mastitis pathogens were isolated from 21% of mammary glands, with 57% of llamas having at least one infected gland; the majority of isolates were coagulase-negative staphylococci.[506] However, isolation of an organism was not associated with an increase in SCC, CMT score, NAGase activity, or pH, which indicates that the organisms were not causing mastitis. None of the llamas exhibited signs of clinical mastitis, and 88% had a CMT score of 0 (negative). The SCC (direct microscopic count) was 300,000/mL or less in all cases. Therefore, CMT and SCC scores for healthy llamas are much lower than for healthy sheep and goats. Low SCC values were also found when milk from 10 llamas was tested weekly for the first 27 weeks of lactation.[507] The NAGase activity and lactoferrin concentration in llama milk is higher than in sheep or cow milk, which may help protect against infection.[508]

Despite a low prevalence of subclinical mastitis, llamas occasionally experience episodes of acute clinical mastitis,[509] most often after birthing. Treatment includes systemic and local antibiotics and antiinflammatory agents. As with the horse, intramammary antibiotic infusion is complicated by the presence of two distinct lobes per mammary gland. Because each lobe has its own teat canal and orifice, both orifices should be cannulated when infusing intramammary antibiotics. The orifices are usually too small to accommodate the cannulas on

intramammary infusion products for cattle; therefore a 3.5 French tomcat catheter is recommended.[4] As with other species, disinfection of the teat end and aseptic infusion techniques are essential to prevent iatrogenic infection. Broad-spectrum antibiotics should be administered until culture results are available, because both gram-positive and gram-negative bacteria have been isolated from mastitic llamas. Systemic antibiotics should be used in conjunction with intramammary antibiotics in llamas that are systemically ill. Pain should be addressed by administering NSAIDs, with fluids administered if needed. Hot packing and frequent stripping of the affected gland are empirically justified treatments that may prove difficult because many llamas resist handling of the udder. Prognosis for survival is good if mastitis is treated early, but milk production may be reduced.

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36.16 UDDER EDEMA

Dairy cattle frequently develop physiologic edema of the udder during the periparturient period. Other large animals are affected less frequently. Physiologic udder edema must be differentiated from *pathologic* edema, which can accompany mastitis and diseases of other body systems. *Physiologic* udder edema is symmetric, is cool to the touch, and pits on palpation. It can be limited to the udder or extend cranially along the ventrum or into the perineal region. In contrast, the edema that accompanies mastitis is more focal, is asymmetric, and is accompanied by abnormal milk and an inflamed mammary gland. Intermandibular and brisket edema, which are often observed in cows with congestive heart failure or severe hypoproteinemia, do not occur in cows with physiologic udder edema.

In most cases, physiologic edema is of little consequence and resolves spontaneously after parturition. However, treatment is recommended if the udder becomes excessively large and heavy, because this threatens the integrity of the udder suspensory apparatus and predisposes to teat injury and mastitis. Severe edema also can hinder ambulation or impair milking or nursing of the teats. If the edematous udder impinges on the skin of the thigh, moist dermatitis and secondary infection may develop, and the skin may slough; this condition is referred to as *udder scald*.

The mechanism(s) of physiologic udder edema is uncertain. Supplementing the ration of prepartum dairy cows with high concentrations of sodium or potassium salts significantly increases the incidence and severity of edema.[510] However, serum biochemical values and fractional clearance of electrolytes are similar in affected and nonaffected cows.[511] Increased capillary hydrostatic pressure (resulting from changes in mammary blood flow and intramammary pressure that occur around parturition) might be involved, as might incompetent valves in the cranial superficial epigastric veins draining the udder. Cows with udder edema have higher blood pressure in the cranial superficial epigastric veins than do unaffected cows, and blood pressure is inversely related to mammary blood flow.[512] Poor udder suspension can also predispose to physiologic udder edema.

First-calf heifers and high-producing cows are at greatest risk of developing udder edema. Other risk factors are not well documented. In a case-control study of heifers in Florida, the risk of udder edema increased as height of the heifer increased, was higher if calving occurred in winter than in summer, and was higher if the fetus was male rather than female.[513] Heifers with udder edema in the first lactation were more likely than unaffected heifers to develop edema in subsequent lactations.[513]

Treatment of udder edema includes preventing excessive salt intake and administering a diuretic. In the United States, furosemide is labeled for use in dairy cows, has 48-hour milk-withholding and slaughter-withholding times, and is the diuretic of choice for treating udder edema. In one study, high cranial superficial epigastric venous pressure in cows with udder edema was reduced by IV administration of furosemide (500 mg), but not hydrochlorothiazide (250 mg) or acetazolamide (500 mg).[512] Repeated administration of furosemide for several

days should be avoided, but if repeated dosing is necessary, cows should be monitored for signs of electrolyte imbalance. Although corticosteroids have been recommended for treatment of udder edema, their efficacy is questionable. Prepartum milking reduces the severity of edema[514] but also decreases colostral immunoglobulin concentration at calving, so an alternative source of colostrum is needed. Increased milking frequency, udder massage, exercise, and hydrotherapy are empirically justified treatments for udder edema. Udder supports are available for cows with excessively pendulous or heavy udders.

36.17 BLOODY MILK

It is not uncommon to observe blood in postpartum mammary secretions. Small vessels may rupture as a result of trauma or in conjunction with udder edema. The milk is usually light pink to red or brown and may contain blood clots. Antibiotic treatment is not indicated. Bloody milk can also accompany severe clinical mastitis or gangrenous mastitis, both of which have a poor prognosis, but physical examination of the animal will identify these conditions.

Bloody milk should be withheld from sale for human consumption. The milk usually returns to normal appearance within 1 week. However, because blood contains natural antimicrobial inhibitors, bloody milk may cause false-positive antibiotic residue test results. The IgG_1 concentration of bloody colostrum is similar to that of normal-appearing colostrum, meaning it is not necessary to discard colostrum simply because it contains blood.[65]

36.18 COLOSTROGENESIS AND COLOSTRAL IMMUNOGLOBULIN TRANSPORT

About 2 weeks before parturition, the mammary gland begins producing colostrum, a process that accelerates as parturition approaches. Colostrum contains an appropriate balance of nutrients for the neonate, as well as substances that provide protection against infection and modulate development of the immune system.[515,516] Of particular importance are colostral immunoglobulins, which are derived predominantly from maternal serum, by selective transport across mammary epithelial cells.[517,518]

In cattle, all immunoglobulin (Ig) isotypes are transported into colostrum,[519] but IgG transport predominates. Mammary epithelial cells express receptors for both IgG_1 and IgG_2 during the periparturient period, but IgG_1 receptors are more abundant and of higher affinity.[518] Preferential transport of IgG_1 results in an IgG_1/IgG_2 ratio of at least 7:1 in colostrum, compared with 1:1 in plasma.[517] The IgG_1 concentration of Holstein colostrum averages 40 to 80 g/L, with substantial variability among cows.[520]

Immunoglobulin G_1 is also the most abundant Ig in the colostrum of sheep and goats, with concentrations averaging 60 to 80 g/L in sheep[521,522] and 40 to 60 g/L in goats.[523] Preferential transport of IgG_1 over IgG_2 has been demonstrated.[523,524] Less is known about colostral Ig isotypes and transport in SACs,[525,526] but mean colostral IgG concentration for llamas and alpacas in one report was 193 g/L,[525] much higher than for small ruminants.

Equine colostrum contains IgGa, IgGb, IgGc, IgG(T), and IgA, but IgGb predominates, as is true for serum. In one study, serum-to-colostrum concentration ratios of these five isotypes were 0.06, 0.12, 0.16, 0.17, and 0.18, respectively, demonstrating that all are greatly increased in colostrum.[527] Total IgG in equine colostrum is highly

variable, with concentrations ranging from less than 10 to almost 400 g/L.[527,528] In contrast to colostrum, IgA is the predominant Ig in equine milk.[527]

Neonatal ruminants are agammaglobulinemic at birth and rely on absorption of colostral IgG_1 across the intestinal epithelium during the first day of life to achieve protective circulating Ig concentrations.[522,529] Foals are also dependent on intestinal absorption of colostral Ig, particularly IgGb.[527] Most dairy calves are hand-fed a fixed volume of colostrum by bottle, bucket, or esophageal feeder.[530] Therefore, the IgG_1 concentration of the colostrum is critical in determining if a sufficient mass (≥125 g/calf) of IgG_1 is fed. Beef calves, small ruminant neonates, and foals usually obtain colostrum by suckling the dam, so both the amount of colostrum suckled and its Ig concentration are critical in determining if a sufficient mass of Ig is ingested.

A number of factors influence colostral IgG concentration. Colostral IgG concentration is typically lower for cows in first or second lactation than cows in third or greater lactation.[65,530] In contrast, colostral IgG concentration was highest in 3- to 10-year-old mares and lower in older mares in one study.[528] In sheep, yearlings had higher colostral IgG_1 concentrations than older ewes.[521] Beef cows typically produce colostrum of higher IgG concentration than dairy cows,[531] and breed differences in colostral IgG concentration are apparent in both ruminants and horses.[521,528,532,533]

Differences in colostral IgG concentrations among species, or among animals within a species, probably result largely from the volume of colostrum produced. Colostral IgG concentration is negatively correlated with colostral volume in dairy cows, meaning that colostrum from high-yielding cows frequently has lower IgG concentration than colostrum from lower yielding cows.[65,530]

Colostral IgG concentration is highest at the first milking after parturition and declines rapidly thereafter, which means that a delay in time to first milking results in a progressive reduction in IgG concentration.[534] The decline in colostral IgG concentration in horses appears to be even more rapid than in cattle.[527] Intramammary infection reduces colostral yield in dairy cows but not colostral IgG concentration.[535]

Direct measurement of IgG concentration in colostrum is time-consuming and costly, so IgG concentration is often estimated from the specific gravity of the colostrum. In cattle, specific gravity is positively correlated with colostral protein concentration and, to a lesser extent, IgG_1 concentration[520,532,536]; the relationship between specific gravity and IgG_1 may differ among breeds of cows.[532] In horses, there is also a positive correlation between colostral specific gravity and IgG concentration.[528] Cattle producers frequently measure colostral specific gravity on-farm, using a commercial colostrometer. Values marked on the colostrometer do not accurately reflect actual IgG_1 concentration,[536] but the colostrometer can be used as a tool to differentiate very poor colostrum from excellent colostrum. Unfortunately, the appearance of bovine colostrum is not indicative of its IgG concentration.[65]

Transfer of colostral Ig to the neonate is discussed in Section Three of this book.

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37 Chapter 37 Diseases of the Hematopoietic and Hemolymphatic Systems

Monica Aleman

Gary P. Carlson

37.1 DISEASES ASSOCIATED WITH BLOOD LOSS OR HEMOSTATIC DYSFUNCTION

DEBRA DEEM MORRIS

Blood loss may be acute or chronic, and the clinical and laboratory manifestations differ widely because physiologic adaptation occurs in the chronic state.

37.2 ACUTE BLOOD LOSS

Common causes for acute blood loss include trauma (e.g., severe lacerations), surgical procedures (e.g., dehorning, castration), and erosion of the carotid artery by guttural pouch mycosis in horses. External hemorrhage is immediately obvious, but hemorrhage into a major body cavity may be occult (e.g., spontaneous rupture of middle uterine artery; splenic rupture resulting from trauma or erosion of major vessel by abscess, aneurysm, or neoplasia). Hemoperitoneum may induce signs of colic, and hemothorax is generally attended by dyspnea. Acute massive blood loss induces hypovolemic shock characterized by tachycardia, tachypnea, cold extremities, pale mucous membranes, muscle weakness, and eventual death resulting from cardiovascular collapse.

Acute blood loss does not initially cause a change in the packed cell volume (PCV) or total plasma protein (TPP), although rapid mobilization of extracellular fluid to maintain circulating blood volume causes the PCV and TPP to decline within 12 to 24 hours. The severity of blood loss may be partially masked by splenic contraction because shock causes activation of the sympathetic nervous system. Icterus is absent, and bone marrow erythroid hyperplasia is delayed by 3 to 4 days. Peripheral signs of erythroid regeneration in horses are limited to mild anisocytosis with a variable increase in mean corpuscular volume. Ruminants show erythrocyte polychromasia, basophilic stippling, Howell-Jolly bodies, and occasionally, nucleated erythrocytes within 4 days of the onset of hemorrhage.

37.2.1 Diagnosis

Diagnosis of acute blood loss is based on clinical signs, evidence of recent hemorrhage, and anemia accompanied by hypoproteinemia. Hemoperitoneum and hemothorax may be suggested by ultrasound and by abdominocentesis and thoracocentesis, respectively.

37.2.2 Treatment

Treatment of acute blood loss should initially be aimed at stopping the hemorrhage. External hemorrhage may be managed by pressure wraps or appropriately placed ligatures; however, it may be inadvisable to attempt to control internal hemorrhage when the patient is a poor risk for general anesthesia and the source of hemorrhage may not be found. Hypovolemic shock should be treated by prompt intravenous (IV) administration of 40 to 80 mL/kg body weight of sodium-containing crystalloid solutions. Studies indicate that a small volume of hypertonic saline (4 to 6 mL/kg of 7.2% sodium chloride) may temporarily reverse the pathophysiologic

sequelae of severe hemorrhagic shock.[1,2] The total volume of necessary crystalloid solution is usually much greater than the volume of blood lost because crystalloid solutions distribute throughout the extracellular space. The clinical response to fluid administration should be evaluated in light of ongoing losses to determine the necessary replacement volume.

If anemia becomes life threatening, whole-blood transfusion must be considered. A PCV less than 20% in an animal with acute blood loss suggests depletion of erythrocyte reserves, and persistent reduction of the PCV to 12% or less over 24 to 48 hours indicates the need for blood transfusion. A low but stable PCV (12% to 20%) does not necessitate transfusion because transfusion should be reserved for cases in which oxygen delivery to the tissues is inadequate to support life. Blood transfusion can only be viewed as a temporary therapeutic procedure because even crossmatch-compatible, allogeneic erythrocytes are removed from the circulation by the mononuclear phagocyte system within 2 to 4 days of transfusion.[3] Horses and cattle display a high degree of blood type polymorphism, and minor antigenic incompatibilities are only delineated by blood typing.[4] Serum antibodies against nonhost erythrocyte antigens (erythrocyte alloantibodies) probably mediate the short lifespan of transfused erythrocytes. Compatibility testing is used to avert life-threatening antigen-antibody reactions caused by major blood group mismatching.

The routine crossmatch involves incubating washed erythrocytes from donor (major) and recipient (minor) with serum from the other. Gross and microscopic examination for clumping demonstrates serum agglutinins in horses. Sensitized cattle erythrocytes do not become clumped in saline solution but do lyse in the presence of rabbit complement, so only a hemolytic crossmatch can be performed in this species. Not all equine erythrocyte alloantibodies act as agglutinins, and hemolysins must be detected by adding complement to the reaction mixture. Pooled rabbit serum must first be absorbed with equine erythrocytes to remove naturally occurring antibodies. The need for special handling and storage of rabbit serum makes hemolytic crossmatch procedures impractical for most veterinarians. These tests are best performed by veterinary hematology laboratories (e.g., Veterinary Genetics Laboratory, School of Veterinary Medicine, University of California, Davis), which usually require serum and whole blood in sodium citrate or acid-citrate-dextrose (ACD) to crossmatch.

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The first transfusion of whole blood to a horse or ruminant that has not been previously transfused or sensitized by immunization or pregnancy is usually well tolerated because natural alloantibodies are of low concentration and weak activity. After incompatible transfusions, alloantibodies develop rapidly, making subsequent transfusions more hazardous.

Blood for transfusion should be collected aseptically into sterile containers containing sodium citrate (2.5% to 4%) or ACD solution and used immediately. The necessary dosage can only be estimated, but in most cases, replacing 20% to 40% of the calculated blood loss is sufficient to maintain life until the bone marrow can respond. A drop in PCV from 36% to 12% in a 500-kg animal (8% body weight blood) represents a loss of 27 L of blood. In this case, 6 to 8 L of whole blood would be therapeutic and easily donated by another 500-kg individual. Blood warmed to 37° C (98.6° F) should be administered through an in-line filter to remove clots. After pretransfusion vital parameters have been recorded, 0.1 mL blood/kg body weight is given over 5 to 10 minutes and the evaluation repeated. If parameters and attitude are unchanged, the transfusion can be continued at a rate not to exceed 20 mL/kg/hr. The recipient should be continuously monitored so that the transfusion can be stopped if adverse reactions occur, such as tachypnea, dyspnea, restlessness, defecation, tachycardia, piloerection, muscle fasciculations, or sudden collapse. Although these signs may not indicate anaphylaxis, severe reactions should be treated with epinephrine (0.01 to 0.02 mL/kg, 1:1000). Mild signs may respond to a slowed transfusion rate or administration of corticosteroids or flunixin meglumine. Because it is often not possible to delineate the cause of transfusion reactions, the safest approach is to discontinue the blood and administer isotonic crystalloid solutions.

The prognosis is good for most cases of acute blood loss if hypovolemic shock is quickly treated and the bleeding stops. The normal bone marrow begins to replace lost cells within 5 days. Sequential analysis of the PCV will be necessary to determine whether blood loss is controlled. Examples of specific disorders follow.

37.2.3 Guttural Pouch Mycosis

See Chapter 31.

37.2.4 Hemoperitoneum in Horses

MONICA ALEMAN

Hemoperitoneum is the accumulation of blood in the abdominal cavity, which can be a life-threatening problem. Causes associated with hemoperitoneum in the horse include trauma, postoperative abdominal hemorrhage, neoplasia, complications from pregnancy and foaling (uteroovarian, middle uterine, and external iliac artery rupture), organ rupture, mesenteric injury, coagulopathies, ovarian hematoma, systemic amyloidosis, and idiopathic causes.[5–11] The underlying cause of hemoperitoneum may be identified in the majority of the cases (78%).[11] Trauma (mainly of spleen, as well as reproductive tract with associated vessels in mares) and neoplasia are the most common causes of hemoperitoneum.[7,11]

A recent retrospective study of 67 horses with hemoperitoneum revealed that thoroughbreds and Arabians were overrepresented breeds.[11] In addition, middle-aged and older horses (>13 years old) were also overrepresented. Females may be overrepresented.[10,11] The most clinical signs include abdominal discomfort, lethargy, hypovolemic shock, pale mucous membranes, prolonged capillary refill time, tachycardia, and tachypnea.[10,11] Other clinical signs are anorexia, reluctance to move, weakness, trembling, cool extremities, and abdominal distention.[10]

Clinicopathologic abnormalities include anemia, neutrophilia, lymphopenia, thrombocytopenia, hypoproteinemia, hypocalcemia, and azotemia.[10] Abnormalities in clotting parameters may be observed, depending on the cause. Hemorrhagic abdominal effusion is characterized by high red blood cell (RBC) count (>2.4 million RBCs/μL), PCV (≥18%), and total protein (≥3.2 g/dL), with a normal to high leukocyte count.[10] Central venous pressure and blood lactate concentration appear to be early indicators of hypovolemia caused by acute blood loss.[12] Swirling fluid and the site of hemorrhage may be evident on abdominal ultrasound.

Primary goals of therapy consist of treating hypovolemic shock, restoring perfusion and oxygen delivery to tissues, correcting fluid deficits, stopping further blood loss, and preventing complications. Blood transfusion should be considered if anemia becomes life threatening. The use of antifibrinolytic and procoagulant agents have been reported in the literature, but controlled studies on its efficacy and safety in the horse with acute blood loss are lacking. Physical activity must be restricted in affected patients.

The short-term outcome is strongly associated with the underlying cause.[11] Horses with neoplasia, uterine artery rupture, mesenteric injury, or disseminated intravascular coagulation (DIC) are a greater risk of death. The survival rate has been reported to range from 51% to 74%.[10,11] Poor short-term outcome was significantly associated with high respiratory rate in one study.[11] Prepartum hemorrhage appears to be associated with a poorer prognosis than postpartum hemorrhage (100% vs. 20% mortality, respectively).[11]

37.2.5 Hemothorax

Hemothorax may occur secondary to trauma (including lung biopsy), neoplasia, and strenuous exercise[13] (see Chapter 31). Hemothorax in neonatal foals may be the result of lacerated lungs and vessels from fractured ribs[14] (see Chapter 19).

37.2.6 Exercise-Induced Pulmonary Hemorrhage

Exercise-induced pulmonary hemorrhage (EIPH) has not been associated as a major cause of blood loss. EIPH is associated with high intensity exercise in horses. An estimated 14% to 75% of racehorses examined by endoscopy have EIPH.[15] Based on bronchoalveolar lavage analysis, a study suggested that 100% of horses performing strenuous exercise have EIPH.[16] EIPH has been reported in various breeds. A recent study reported that the frequency of EIPH is associated with race type, distance, gender, and age. In one study, epistaxis was more common in females, in older horses than in horses less than 2 years old, after steeplechase races than flat races, and with shorter distances (≤1600 m [1 mile] long).[17] Recurrence rate in that study was reported to be 4.64%. The pathophysiology of EIPH is not completely known. For a complete description of this disorder, see Chapter 31.

37.3 CHRONIC BLOOD LOSS

DEBRA DEEM MORRIS

A number of diseases can result in chronic loss of blood that is insidious until clinical signs of anemia develop. Physiologic adaptation to gradually developing tissue hypoxia generally masks signs of anemia until the PCV is less than 15%. Causes for chronic blood loss include bleeding gastrointestinal (GI) lesions, certain renal diseases, hemostatic dysfunction, bloodsucking external parasites, and haemonchosis (especially in goats and sheep). 1145 1146

Gastrointestinal hemorrhage is usually caused by neoplasia (especially gastric squamous cell carcinoma in horses and abomasal lymphoma in cattle), parasitism, or mucosal ulceration (e.g., abomasal ulcers in cattle, nonsteroidal antiinflammatory drug [NSAID] toxicity in horses). Significant hemorrhage may occur in ruminants heavily infested with *Haemonchus contortus* shortly after they are treated with an anthelmintic. Generally, GI hemorrhage is best detected by chemical determination of fecal occult blood because melena rarely occurs in horses, and bleeding abomasal ulcers cannot be excluded in cattle when melena is absent. Because of the low specificity of tests for fecal occult blood, the diagnosis of chronic GI blood loss is usually supported by strong clinical suspicion and ruling out other sources of hemorrhage.

Although renal papillary necrosis (caused by NSAID therapy) and urinary calculi cause hematuria, anemia rarely results. Renal neoplasia or congenital renal vascular anomalies rarely may be associated with chronic blood loss anemia. Other causes of blood loss include idiopathic hematuria and idiopathic recurrent hematuria of Arabian horses.

Disorders of hemostasis may cause internal or external hemorrhage that leads to anemia if enough blood is lost. Qualitative or quantitative abnormalities of blood vessels, platelets, or coagulation factors result in hemostatic dysfunction (see next section). Loss of erythrocyte iron secondary to chronic severe blood loss may result in iron deficiency anemia. Hypoferremia or reduced serum ferritin develops with increased total iron-binding capacity and reduction in marrow iron.

The aim in management of chronic blood loss is to determine the primary cause. Treatment of the anemia itself is rarely indicated. Iron deficiency may be alleviated by oral supplementation with ferrous sulfate, although good-quality forages contain more than adequate amounts of iron. Parenteral iron supplementation as iron dextran should be avoided because it has been associated with anaphylactoid reactions in large animals. Examples of specific disorders follow.

37.3.1 Gastric Ulceration

MONICA ALEMAN

Gastric ulceration in horses is also known as *equine gastric ulceration syndrome* (EGUS). Although EGUS is not an important cause of blood loss, it has a high prevalence among adult horses. Thoroughbred racehorses have the greatest prevalence (82% to 93%), followed by endurance horses (67%), show horses (58%), hospitalized horses (49%), and geriatric patients with abdominal pain (18%).[18–22] Gastric ulcers were found in 66.6% of pregnant and 75.9% of nonpregnant mares in a thoroughbred breeding farm.[23] Clinical signs may include poor hair coat, decreased appetite, poor performance, nervous disposition, abdominal pain, teeth grinding, and salivation. Proposed causes of gastric ulceration include exercise, transportation, grazing deprivation, alternating periods of feeding and fasting, diets with high concentrate content, and confinement. For a complete description of gastric ulceration, see Chapter 32.

37.3.2 Right Dorsal Colitis

Right dorsal colitis (RDC) is an enteropathy associated with administration of NSAIDs, most often phenylbutazone.[24,25] Other proposed factors that predispose to RDC include infection, immune-mediated response, genetics, and stress. The pathogenesis of RDC is unknown. NSAIDs act by inhibiting cyclooxygenase (more inhibition of constitutively expressed COX-1 than inducible expressed COX-2 during states of inflammation), which will cause inhibition of the production of prostaglandin E resulting in hypoxic or ischemic GI mucosal damage and may delay mucosal healing.[25]

Ponies and young performance horses appear to be predisposed to RDC. The clinical signs include inappetence, lethargy, intermittent or episodic colic, diarrhea, and weight loss.

Clinicopathologic abnormalities may include mild anemia, moderate to severe hypoproteinemia with hypoalbuminemia, hypocalcemia, and in some cases azotemia. Although mild anemia may be seen in most cases, horses occasionally present with severe anemia and hematochezia. RDC often develops over days or weeks. (See Chapter 32.)

37.4 HEMOSTATIC DYSFUNCTION

DEBRA DEEM MORRIS

37.4.1 Basic Physiology of Normal Hemostasis

Understanding the pathogenesis and manifestations of hemostatic disorders is based on knowledge of the normal physiologic mechanism of hemostasis. Hemostasis can be viewed as two interrelated components,

coagulation and fibrinolysis (both with their respective inhibitors), which function to stop bleeding from a damaged blood vessel and maintain nutrient blood flow.

Coagulation is mediated by blood vessels, platelets, and blood procoagulant proteins. When a blood vessel is damaged, vasoconstriction occurs, followed by rapid adherence of platelets to subendothelial collagen. Platelet adhesion causes membrane conformational changes that trigger aggregation, contraction, and granule secretion (the basic platelet reaction). Platelet phospholipoprotein (platelet factor 3) provides the necessary surface to catalyze interactions among the activated coagulation proteins that result in thrombin formation. Coagulant proteins are localized to this hemostatic plug because the platelet surface protects them from plasma anticoagulants. Through an incompletely understood mechanism, platelets also prevent spontaneous hemorrhage into the skin and mucous membranes by maintaining "vascular integrity."

Procoagulant proteins circulate in the blood as precursive forms *(zymogens)* that must be altered during coagulation to become active. Numerous communications exist between the traditional extrinsic and intrinsic pathways, although initiating mechanisms remain distinct.[26] The extrinsic system is initiated when lipoprotein *tissue factor* (TF) gains access to the bloodstream. TF is widely distributed in most tissues, including endothelial cells and monocytes, and may be increased or secreted in response to numerous pathologic stimuli, such as bacterial endotoxin. Intrinsic coagulation is initiated when blood is exposed to a negatively charged surface such as activated platelets. Because of reciprocal activation between factor XII and prekallikrein, the intrinsic coagulation pathway stimulates formation of numerous inflammatory mediators (e.g., kinins, complement). Both coagulation pathways culminate in the formation of activated factor X (Xa), by which thrombin is generated. In addition to catalyzing the conversion of fibrinogen to fibrin, *thrombin* promotes platelet aggregation, enhances cofactor activities of factors V and VIII, and activates factor XIII and protein C.[27] Mechanisms to localize coagulation to the site of vascular injury are critical to protect against generalized thrombosis.[28] Plasma anticoagulant proteins include the serpins, which inhibit activated coagulation factors, and the protein C system, which is directed against cofactors V and VIII.[29] *Antithrombin III* (AT III), the main physiologic inhibitor of thrombin and Xa, normally provides 70% of the anticoagulant activity of plasma. Although not absolutely needed, heparin accelerates AT III action by 2000-fold.[30] Activated protein C destroys factors V and VIII, ultimately limiting its own activation, which depends on thrombin and endothelial cofactor, thrombomodulin. Protein S enhances the anticoagulant ability of protein C.

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The *fibrinolytic system* is activated simultaneously with coagulation and functions to prevent tissue ischemia by limiting the extent of fibrin clot formation. Plasmin, primarily responsible for degradation of fibrin, exists in the plasma as the zymogen *plasminogen*. Plasminogen has a high affinity for fibrin, as does *tissue plasminogen activator* (tPA); therefore, clots contain the necessary components to allow lysis from within, and systemic plasmin formation is avoided. *Alpha-2-antiplasmin* (α_2-AP), the main physiologic inhibitor of plasmin, competes with the binding of plasminogen to fibrin, and the clot contains equal amounts of both glycoproteins. Because of this molar balance between α_2-AP and plasminogen, a normal blood clot does not lyse spontaneously, despite fixation of tPA. Physiologic inhibitors of tPA (PAIs) are found in plasma, platelets, and endothelial cells, and platelet-derived PAI also protects a blood clot against premature lysis. Clot lysis is initiated if additional tPA is taken up from the surrounding tissues; stasis upstream from the occluded vessel is a potent stimulus for release of endothelial tPA. Conversion of plasminogen to plasmin allows partial digestion of fibrin and exposure of additional plasminogen-binding sites. When this additional plasminogen is converted to plasmin, the inhibitory effect of α_2-AP is overcome, and clot lysis is accelerated. Plasmin hydrolyzes fibrinogen and fibrin with equal affinity, as well as numerous other procoagulants, and it can activate complement and kininogen. The physiologic actions of plasmin are limited to the fibrin clot by the affinity between the latter and plasminogen and the presence of α_2-AP in blood. Because of multiple interactions between the coagulation and

fibrinolytic systems, the most important factor that determines the rate of fibrinolysis is the rate of fibrin formation.[31]

37.4.2 Inherited Coagulation Disorders

Inherited deficiencies of factors VIII,[32] IX, XI,[33] and prekallikrein[34] have been described in horses. Holstein cattle may have inherent factor XI deficiency.[35] Congenital factor VIII deficiency (hemophilia A) is sex linked and recessive, occurring only in males. Factor XI deficiency in cattle is transmitted as an autosomal recessive trait.[35] The inheritance pattern of the other deficiencies has not been proved.

Clinical signs of clotting factor deficiency reflect the tendency for abnormal hemorrhage from larger vessels (e.g., subcutaneous hematomas; hemarthroses; epistaxis; melena; hematuria; prolonged bleeding after trauma, diagnostic procedures, or surgery). Petechiae are a feature of vascular or platelet disorders and are not caused by clotting factor deficiency. Clinical signs do not always result from inherited clotting factor deficiencies. Cattle deficient for factor XI and horses with prekallikrein deficiency have complete in vivo coagulation competency. Prekallikrein appears to perform an accelerating rather than required role in activation of factor XII.[26] Activated factor XII activates factor XI, which then catalyzes the remainder of the clotting sequence. Factor XII is also capable of activating factor VII in the extrinsic pathway,[26] which may explain why factor XI deficiency does not cause a hemorrhagic diathesis. Values for the coagulant part of factor VIII (VIII:C) or factor IX must be reduced to less than 5% of normal before spontaneous hemorrhage occurs. Less severe deficiencies may result in excessive hemorrhage only after trauma.

The major differential diagnoses for heritable factor deficiencies include the acquired coagulation factor—deficient states, DIC, warfarin toxicosis (horses), moldy sweet clover toxicosis, and acute hepatic disease. The heritable clotting factor deficiencies involve proteins in the intrinsic pathway; thus a prolonged activated partial thromboplastin time (aPTT) is the only hemostatic abnormality. Acquired coagulation factor deficiencies involve proteins in the extrinsic or common pathways as well, causing a trend toward prolongation of both the prothrombin time (PT) and aPTT. The definitive diagnosis of heritable clotting factor deficiency must be based on specific quantitative assays of intrinsic clotting factors. The only possible treatment for heritable clotting factor deficiency is replacement of clotting factors through the administration of fresh plasma. Specific clotting factor concentrates are not commercially available for large animals, and the rarity of specific factor-deficiency states that produce clinical signs makes the development of these products unlikely. Because of the expense of therapy and the potential for complications, the long-term prognosis for horses with hemophilia A or multiple congenital coagulation factor defects is poor. Cattle with factor XI deficiency apparently live a normal life but may be more susceptible to secondary diseases.[35]

37.4.3 Thrombasthenia in Horses

MONICA ALEMAN

37.4.3.1 GLANZMANN'S THROMBASTHENIA

Glanzmann's thrombasthenia (GT) is a rare inherited platelet defect caused by quantitative or qualitative change in the platelet glycoprotein complex IIb-IIIa (integrin $\alpha_{IIb}\beta_3$). These subunits are encoded by separate genes, and in order to form a stable functional complex on the platelet surface, both subunits must be expressed. This complex was recognized as the receptor that mediated platelet aggregation and was termed

the *fibrinogen receptor*. GT has been documented in humans and dogs.[36,37] Clinical signs in these species include purpura, epistaxis, and gingival bleeding. There have been four reports of thrombasthenia in the horse, two of which (4-year-old quarter horse, 7-year-old cross-thoroughbred gelding) were confirmed with various tests, including genetic analysis.[38–41] The prominent clinical sign is chronic, intermittent epistaxis unrelated to exercise. Other signs include petechial and ecchymotic hemorrhages in the nasopharynx.

Mild anemia may be observed. Platelet count, activated coagulation time, PTT, PT, thrombin time (TT), fibrin degradation products (FDPs), and plasma concentrations of von Willebrand (vW) factor antigen are normal. However, gingival bleeding time is prolonged (>60 minutes, control horses <2 minutes), clot retraction test is greatly reduced, and platelet aggregation in response to various agonists (as measured by aggregometry) is greatly impaired. Platelet morphology is normal on electron microscopy. Flow cytometric studies using CD41/CD61 monoclonal antibodies have revealed a reduction in the $\alpha_{IIb}\beta_3$ integrin on platelet surfaces.[40] These findings are the basis for the diagnosis of GT.

Christopherson et al.[41] found a single nucleotide change in codon 41 in exon 2 of the gene encoding integrin α_{IIb} in two affected horses. This mutation would encode a proline instead of an arginine, which would result in an aberrant conformation that would prevent association of α_{IIb} with integrin β_3 with ultimate lack of expression of the complex on platelet surface. Currently, treatment is not available.

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37.4.3.2

HERITABLE BLEEDING DIATHESIS (OTHER THAN GLANZMANN'S THROMBASTHENIA)

Severe bleeding diathesis was reported in a 2-year-old thoroughbred filly presented for prolonged bleeding time after minor insults.[42] The filly's template bleeding time was longer than 120 minutes, versus 5.5 minutes in control horses.[42] Platelet concentration, PT, PTT, antithrombin III, and coagulation factors (vW, VIII, IX, XI, XII) were unremarkable. Platelet-rich plasma (PRP) aggregated normally in response to a range of agonists (adenosine diphosphate, thromboxane A_2) but was slightly prolonged in response to thrombin and collagen.[43] Several integral platelet membrane glycoproteins involved in aggregation and clotting (e.g., GPIb, GPVI, $\alpha_{IIb}\beta_3$) were present in this filly. However, this filly had a reduced prothrombinase activity, production of thrombin, and binding of fibrinogen.[43] The mare's disorder results in decreased platelet aggregation and ineffective clotting. Offspring of the affected mare were also affected.

37.4.4

Acquired Hemostatic Disorders*

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Acquired defects of hemostasis may be divided into those involving blood vessels, platelets, and coagulation factors, although some diseases affect more than one component.

37.4.4.1

VASCULITIS

Vasculitis is a clinicopathologic process that involves inflammation and necrosis of blood vessel walls, regardless of size, location, or cause.[44] Vasculitis in large animals is generally a secondary manifestation of a primary infectious, toxic, or neoplastic disorder and has characteristics of hypersensitivity vasculitis in humans. The predominant involvement of small vessels in the skin (e.g., venules, arterioles) is the hallmark of hypersensitivity vasculitis.

The clinical manifestations of vasculitis include demarcated areas of dermal or subcutaneous edema, which may progress to skin infarction, necrosis, and exudation.[45] Hyperemia, petechial and ecchymotic hemorrhages, and ulceration of mucous membranes are common. Although the skin and mucous membranes are predominantly involved, hemorrhage and necrosis may occur in any organ system, resulting in conditions such as lameness, colic, dyspnea, and ataxia. Subclinical renal disease may also occur. Vasculitis is often accompanied by adverse sequelae such as cellulitis, thrombophlebitis, laminitis, and pneumonia. Characterized vasculitis syndromes with predominant cutaneous involvement in horses include equine purpura hemorrhagica (EPH), equine viral arteritis (EVA), equine infectious anemia (EIA), and equine granulocytic ehrlichiosis (EGE). In addition, for a number of vasculitis syndromes in horses, the cause, pathogenesis, and clinical course are poorly defined.[46,47]

Vasculitis is apparently uncommon in ruminants but may accompany certain septicemic diseases, such as malignant catarrhal fever of cattle and bluetongue of sheep.[48]

Hematologic and serum biochemical findings in vasculitis are determined by the underlying disease, length of illness, organ involvement, and secondary complications. Chronic inflammation may involve neutrophilia, mild anemia, hyperglobulinemia, and hyperfibrinogenemia. Some horses with EPH develop a moderate anemia (PCV, 20% to 25%) thought to be caused by increased erythrocyte destruction.[49] The platelet count is generally normal. Muscle damage may be reflected by increased serum concentrations of creatine phosphokinase (CPK) and aspartate aminotransferase (AST). The creatinine may be elevated, and urinalysis may rarely show trace hematuria or proteinuria if there is glomerulonephritis.

The definitive diagnosis of vasculitis is made by demonstration of the characteristic histopathology of involved vessels. Full-thickness punch biopsies (at least 6 mm in diameter) of skin in an affected area should be obtained and preserved in 10% formalin and Michel's transport medium. Multiple biopsies from different sites may be necessary to reach the diagnosis. The most common inflammatory pattern is neutrophilic infiltration of venules in the dermis and subcutaneous tissue, with nuclear debris in and around involved vessels (leukocytoclasis) and fibrinoid necrosis. Immunofluorescence on biopsies preserved in Michel's medium may reveal immune complexes. Considerable evidence suggests that most vasculitis syndromes are mediated by immunologic mechanisms, that is, an allergic reaction to a microbe, drug, toxin, or protein.[44] In some cases an exogenous stimulus cannot be identified, and an autoimmune pathogenesis is suspected. Immune complex deposition in vessel walls, with subsequent complement activation and chemoattractant production, seems to be the major pathogenic mechanism. Infiltrating neutrophils and macrophages release proteolytic enzymes that cause vessel wall necrosis, with subsequent edema, hemorrhage, and infarction of supplied tissues. Size and physiochemical properties of immune complexes, blood flow turbulence in sites of vessel bifurcation, and hydrostatic forces in dependent areas account for preferential formation of lesions in certain disease states and anatomic locations. Horses and cattle with idiopathic vasculitis may have incomplete response to therapy with an unpredictable, poor prognosis.[48,49]

37.4.4.1.1

Equine Purpura Hemorrhagica (MA, DDM)

EPH is a noncontagious disease of horses characterized by vasculitis leading to extensive edema and hemorrhage of the mucosa and subcutaneous tissue. The disease has been recognized as a sequela to infection or exposure to *Streptococcus equi, S. zooepidemicus, Rhodococcus equi, Corynebacterium pseudotuberculosis,* and other species and to vaccination against *S. equi*.[45,50]

Young to middle-aged horses are usually affected (mean, 8.4 years; range, 6 months to 19 years).[50] The clinical signs usually develop acutely within 2 to 4 weeks of a respiratory infection.[51] The predominant signs are well demarcated subcutaneous edema of all four limbs, lethargy, anorexia, hemorrhages on mucous membranes, fever, and tachycardia. Other signs include tachypnea, reluctance to move, exudation from the skin, colic, and epistaxis.

The predominant laboratory abnormalities include anemia, neutrophilia, hyperproteinemia, hyperfibrinogenemia, hyperglobulinemia, and elevated muscle enzymes. Thrombocytopenia is rarely detected in horses with EPH.

Skin biopsy shows evidence of acute leukocytoclastic or nonleukocytoclastic vasculitis with necrosis of blood vessels. The lesions consist of marked dermal and subcutaneous hemorrhage, protein-rich edema, and multifocal areas of dermal infarction. Small arteries and capillaries are swollen and infiltrated by degenerate or nondegenerate neutrophils. Hyaline thrombi may be observed.[50] Immune complexes primarily composed of IgM or IgA, and streptococcal M protein may be present in capillaries and small blood vessels of horses with EPH, leading to type III hypersensitivity reaction.[52] Deposition of complement in immune complexes in vessel walls may result in cell death. Extensive hemorrhages in the dermis, subcutis, skeletal muscles, lungs, kidneys, spleen, intestinal walls, and blood vessels have been observed on postmortem examination.

Horses with infarctive EPH can present with colic, lameness, muscle swelling, and stiffness.[53] Extensive GI infarction results in severe colic signs. The significant findings in these horses include leukocytoclastic vasculitis and necrosis of various tissues, neutrophilia with a left shift, hypoalbuminemia, and high serum creatine kinase.[53]

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Treatment is initiated to address the primary cause if identified, reduce the immune and inflammatory response, and provide antimicrobial therapy in cases of active infection, or to prevent infection if indicated, provide supportive care, and prevent complications. Horses with known streptococcal infection should receive penicillin (22,000 IU/kg of procaine penicillin G intramuscularly [IM] twice daily, or potassium penicillin G intravenously [IV] every 6 hours) for at least 2 weeks. Hydrotherapy, limb bandages, and light exercise (hand walk) have been helpful in reducing limb edema. Fluids administered through nasogastric tube or IV may be necessary for animals that become severely lethargic and fail to drink or those that develop dysphagia from laryngeal edema. Stridor and dyspnea may indicate the need for tracheostomy. Prolonged treatment with corticosteroids (2 to 4 weeks) has resulted in favorable outcome and low relapse rate. However, some horses may require more than 4 weeks. Depending on severity of clinical signs, proposed dosage is 0.04 to 0.2 mg/kg of dexamethasone (IV, IM, or orally [PO]) once (morning) or twice daily, or 0.5 to 1.0 mg/kg of prednisolone PO once (morning) or twice daily, with a gradual reduction of the dosage.[50] Use of antimicrobials has been suggested throughout corticosteroid therapy to reduce the prevalence of secondary sepsis.[45]

The outcome will depend on early detection, early aggressive treatment, and extent of organ involvement. Skin sloughing, laminitis, cellulitis, pneumonia, and diarrhea may be seen and may significantly prolong convalescence. Although the prognosis has been thought to be fair with early aggressive therapy and supportive care, a recent retrospective study of 53 horses with EPH reported a mortality rate of 7.5%.[50]

* Author(s) of discussions in this section indicated by initials (as listed) after disorder.

37.4.4.1.2

Equine Viral Arteritis (MA)

EVA is an infectious disease characterized by panvasculitis, edema, hemorrhage, and abortion in pregnant mares. EVA is caused by an enveloped, spherical, positive-stranded RNA virus with a diameter of 50 to 70 nm. Equine arteritis virus (EAV) is a non-arthropod-borne virus classified as a member of the new order Nidovirales within the family Arteriviridae.[54] EAV was first isolated from fetal lung collected during an epizootic of abortion in Bucyrus, Ohio.[55] Clinical signs may be absent or may develop 1 to 10 days after infection and include pyrexia, lethargy, anorexia, limb edema, stiffness, rhinorrhea, epiphora, conjunctivitis, rhinitis, and abortion. Edema of several regions may be observed, including periorbital, supraorbital, ventral abdomen, mammary gland, scrotum, and limbs.[56] Other signs include urticarial rash, abortion, respiratory signs, ataxia, mucosal eruptions, submaxillary lymphadenopathy, and intermandibular and shoulder edema. EAV can present as epidemic abortion, with occasional fatalities in foals and adults. In natural exposure, abortion rate varies from less than 10% to more than 60% and can occur from 3 to 10 months of gestation.[57] Infected mares do not become EAV carriers or chronic shedders and do not appear to have fertility problems.

Laboratory abnormalities are variable and not diagnostic for EVA. Experimentally infected mature horses had a consistent leukopenia from neutropenia and lymphopenia.[58] After infection, EAV can be localized in macrophages and lymph nodes within 24 and 48 hours, respectively. Various tissues are affected, but blood vessels are the principal target of EAV. Within vessels, EAV localizes in endothelium, medial myocytes, and pericytes. The virus causes vasculitis with fibrinoid necrosis of tunica media, abundant vascular and perivascular lymphocytic and lesser granulocytic infiltration with karyorrhexis, loss of endothelium, and formation of large, fibrinocellular, stratified thrombi.[56] Body cavity effusion may be seen.

The virus is mainly transmitted through aerosols from respiratory, urinary, or aborted secretions of acutely infected animals. The other route of transmission is through semen from shedding stallion. The virus remains viable in fresh, chilled, and frozen semen.[57] Horizontal transmission by fomites is possible.[59] Natural EAV exposure results in long-term immunity to disease. Mares and geldings eliminate virus within 60 days, but 30% to 60% of acutely infected stallions will become persistently infected, temporarily or permanently shedding virus in the semen.[56] The virus is maintained in the accessory organs of the male reproductive tract (ampullae, vasa deferentia).[57] An outbreak of EVA occurred in the quarter horse population in 2006.[60]

A fourfold or more increase in serum neutralizing antibodies between acute and convalescent samples (3 weeks apart) is required for diagnosis. Stallions with positive titers of 1:4 should be tested for persistent infection by virus isolation from sperm-rich ejaculate.[57] Viral isolation can be attempted from fetal and placental tissues. Semen can be tested for viral shedding by culture, isolation, or polymerase chain reaction (PCR). Identification of carrier stallions is crucial in preventing dissemination of EAV. A modified live

vaccine is available.* Vaccination will result in the development of a serum titer that will be detected on EVA testing and cannot be distinguished from active infection. Horses vaccinated for the first time may temporarily shed the modified virus.

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37.4.4.1.3 Equine Infectious Anemia

See section on hemolytic anemia.

37.4.4.2 *ANAPLASMA PHAGOCYTOPHILA* INFECTION IN HORSES (MA, JEM)

37.4.4.2.1 Definition and Etiology

Equine granulocytic ehrlichiosis (EGE) was first reported in the late 1960s in the foothills of northern California.[61] The disease is caused by *Anaplasma phagocytophila,* formerly known as *Ehrlichia equi* but reclassified in the *Anaplasma* genus based on genetic analysis.[62] Recently, the agent of human granulocytic ehrlichiosis (HGE)—*Ehrlichia phagocytophila*—and *E. equi* have been grouped into a single species and named *Anaplasma phagocytophila*.[62] These organisms are identical based on 16S rRNA gene sequences and have similar morphology, host cell tropism, and indirect fluorescent antibody (IFA) response.[63] Furthermore, injection of infected blood from patients with HGE into horses causes EGE.

The organism is found within vacuoles (1.5 to 5 μm in diameter) in the cytoplasm of infected granulocytes, primarily neutrophils and eosinophils. These vacuoles, or inclusion bodies, are pleomorphic and contain one or more coccibacilli or large, granular aggregates called *morulae*. The organisms are visible under light microscopy as deep-blue to pale-blue gray with Giemsa or Wright-Leishman stains.

37.4.5 Epidemiology

Since the disease was first reported in California,[64] cases have been diagnosed in Colorado, Connecticut,[65] Florida, Illinois, Minnesota, New Jersey, New York, Oregon, Washington, Wisconsin, Canada, Brazil, northern Europe, and Israel. Equine cases occur during late fall, winter, and spring. There is no apparent gender or age predilection. However, EGE appears to be less severe in younger horses. Persistent, chronic, or latent infections and carrier status have not been demonstrated and are unlikely to occur because the presence of *A. phagocytophila* is limited to the acute phase. Therefore, it is also unlikely that infected horses could serve as reservoirs. The disease is not contagious but could be readily transmitted through the administration of infected blood. The vectors of granulocytic ehrlichiosis are *Ixodes pacificus* in California, *Ixodes scapularis* in the East and Midwest (U.S.), and *Ixodes ricinus* in Europe.[66–69] Potential or proposed reservoirs are white-footed mice, chipmunks, white-tailed deer, dusky-footed wood rats, cervids, lizards, and birds.[69]

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37.4.6 Pathogenesis

The pathogenesis of EGE is unknown. Entry of the organism occurs after inoculation from a biting tick and presumed spread by blood and lymphatics. The organism has cell tropism toward neutrophils and eosinophils, where it replicates within vacuoles, forming characteristic morulae. Presumed cytolysis, induction of inflammation, and cell sequestration, consumption, or destruction result in the observed clinical signs and

pancytopenia.[70] Cell-mediated and humoral-mediated immune responses develop in affected animals. Antibody titers peak at 19 to 81 days after the onset of clinical signs, and immunity may persist for a long time (2 years).[71]

37.4.7 Clinical Signs

Signs include reluctance to move, fever ranging from 39.4° to 41.3° C (102.9° to 106.3° F), mild to moderate tachycardia (50 to 60 beats/min), lethargy, decreased appetite, limb edema, petechiation, icterus, weakness, ataxia, and recumbency (reported in one case). Secondary trauma may result from falling in severely ataxic horses. These clinical signs appear to be less profound in younger horses. The presumptive incubation period after natural infection is believed to be less than 14 days. The prepatent period after experimental exposure to infected ticks or inoculation with infected blood is 8 to 12 days and 3 to 10 days, respectively. The disease is self-limiting and nonfatal provided no complications develop. However, affected horses may be predisposed to secondary bacterial, fungal, and viral infections.[61] Abortions and laminitis have not been reported in affected horses.

37.4.8 Clinical Pathology

Laboratory alterations include anemia, leukopenia characterized by granulocytopenia and lymphopenia, and thrombocytopenia. Morulae may be observed within the cytoplasm of neutrophils and eosinophils during the acute phase of the infection.

37.4.9 Diagnosis

The definitive diagnosis is based on the presence of characteristic morulae (minimum of three) within the cytoplasm of neutrophils and eosinophils or positive PCR assay for *A. phagocytophila* in peripheral blood (buffy coat).[72] Morulae may be observed in less than 1% of cells in the initial stages of the infection, up to 20% to 50% of the cells few days later. A-fourfold or greater increase in IFA titer of paired samples confirms recent exposure.[73]

37.4.10 Pathologic Findings

Petechiae and ecchymosis of subcutaneous tissues and edema of the ventral abdomen, limbs, and prepuce are characteristic in infected animals. Proliferative and necrotizing vasculitis, thromboses, and perivascular cuffing in subcutaneous tissue, fascia, kidneys, heart, brain, lungs, ovaries, and testes have been reported.[61,70]

37.4.11 Treatment, Prognosis, and Prevention

The treatment of choice is IV oxytetracycline, 7 mg/kg once daily for 5 to 7 days. Prompt response to treatment is seen within the first 24 hours. Supportive therapy may be necessary in some cases. The disease can be self-limiting in 2 to 3 weeks if untreated. The prognosis of the disease is excellent provided secondary complications are prevented. At present, prevention is limited to tick control.

37.4.11.1

THROMBOCYTOPENIA (DDM)

Thrombocytopenia (platelet count <100,000/μL) can result from one or more of three basic mechanisms: (1) decreased or ineffective platelet production, (2) abnormal sequestration (usually in spleen), or (3) shortened platelet survival (consumption or destruction). Thrombocytopenia causes a hemorrhagic diathesis characterized by multiple sites of small-vessel bleeding. Petechial hemorrhages with or without ecchymotic hemorrhages are generally found on the oral, nasal, or vaginal mucous membranes, as well as on the nictitans and sclera. Epistaxis, melena, hyphema, or microscopic hematuria may occur, but spontaneous hemorrhage is unusual unless the platelet count is less than 10,000/μL. Prolonged bleeding from wounds, injections, or surgical procedures and the propensity to form hematomas after minor trauma are common when the platelet count drops below 40,000/μL. The platelet count below which bleeding occurs varies among individuals and seems to be determined by concurrent diseases.

The interaction of blood platelets with a discontinuous vascular surface constitutes the basis for primary hemostasis. In addition, platelets provide the phospholipoprotein surface necessary to catalyze interactions among the activated coagulation proteins that culminate in fibrin formation. The platelet surface also protects activated clotting factors from destruction by plasma anticoagulants, thereby localizing coagulation to the hemostatic plug. Finally, platelets maintain “vascular integrity” through obscure mechanisms and prevent spontaneous hemorrhage into the skin and mucous membranes. Severe thrombocytopenia produces prolonged bleeding time and abnormal clot retraction without affecting clotting times or plasma fibrinogen.

Persistent life-threatening hemorrhage caused by thrombocytopenia may be treated with a transfusion of compatible fresh whole blood or, preferably, PRP, which may be produced by centrifugation thrombocytopheresis[74] or by centrifugation of freshly collected blood, 3 to 5 minutes at 250 *g*.[75] Blood or plasma must be used immediately and contact with glass prevented to avoid platelet adhesion and activation. Platelet transfusion is a very transient lifesaving measure, and the ultimate prognosis for thrombocytopenia depends on the cause.

Decreased production of platelets may result from replacement of the normal marrow architecture by neoplastic or inflammatory tissue (myelophthisic disease) or from bone marrow aplasia. Both conditions are characterized by peripheral pancytopenia of variable severity and are extremely unusual in large animals. Myelophthisic disease with thrombocytopenia has been described in horses with various forms of myelogenous neoplasia[76–78] and eosinophilic myeloproliferative disorder.[79]

Hypoplastic anemia with leukopenia and thrombocytopenia has been reported in horses and cattle, as discussed later under Aplastic Anemia. Shortened platelet lifespan is by far the most common cause of thrombocytopenia in large animals. Increased platelet consumption accompanies DIC (discussed in the next section) and rare cases of vasculitis. Immune-mediated mechanisms result in platelet destruction.

Immune-mediated thrombocytopenia (IMTP) may be primary (idiopathic) or secondary to drug administration, infections, neoplasia, or other immunologic disorders.[75] This disease is most common in horses and has been reported secondary to EIA,[80] lymphoma,[81] and autoimmune hemolytic anemia.[82] The clinical signs of IMTP include mucosal hemorrhages and the propensity to bleed from small blood vessels. Horses with idiopathic IMTP are usually bright, afebrile, and without overt hemorrhage despite severely reduced platelet numbers. Thrombocytopenia in a horse with obvious primary disease should prompt a thorough hemostatic workup to rule out DIC.

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Alloimmune thrombocytopenia of neonates has been recognized as a spontaneous disease of human infants, piglets, foals, and possibly mule foals.[83] Clinical signs include depression, loss of suckle, a bleeding tendency, blood loss, and rapidly developing anemia because of a profound thrombocytopenia. The condition occurs in multiparous dams, and immunoglobulins may be found in the mare's plasma, serum, and milk that bind to the foal's platelets. Alloimmune thrombocytopenia should be considered in neonates with severe thrombocytopenia when other causes can be excluded, and platelet antibody assays should be used to support this diagnosis. Differential considerations include neonatal sepsis, neonatal maladjustment syndrome, and neonatal isoerythrolysis.

Laboratory findings of IMTP include severe thrombocytopenia (<40,000/μL), prolonged bleeding time, and abnormal clot retraction with normal TT, PT, aPTT, and plasma fibrinogen. FDPs may be mildly increased, and anemia with hypoproteinemia develops if blood loss is ongoing. In most cases of IMTP and other causes of shortened platelet lifespan, megakaryocytic hyperplasia is evident on examination of bone marrow aspirates or biopsies. Megakaryocytic destruction by the immunologic process could induce megakaryocytic hypoplasia, although this is apparently rare in horses.

The definitive diagnosis of IMTP requires demonstration of increased quantities of platelet-associated IgG or C3 or antiplatelet activity in the serum. Unfortunately, methods to detect platelet-associated immunoreactants have not been adapted for horses, although it appears they affect platelet function.[84] Therefore the diagnosis of IMTP must be based on small-vessel hemorrhagic diathesis and severe thrombocytopenia in a horse with normal coagulation times and no other evidence of DIC. Response to therapy (see next section) supports the diagnosis. A tentative diagnosis of IMTP in the horse should prompt a thorough search for an underlying disorder, especially lymphoma.

Platelet destruction in IMTP is apparently mediated by antibodies coating the platelet surface that cause premature platelet removal from circulation by the mononuclear phagocyte system (MPS).[85] In *primary* IMTP the platelet-associated immunoglobulin is directed against a membrane antigen, is usually of the IgG class, is produced in the spleen, fixes complement, and can be absorbed from serum by platelets from a normal individual of the same species. Autoantibodies may attach to megakaryocytes, but the latter are not necessarily destroyed because they do not circulate through the spleen or liver. In *secondary* IMTP the immunoglobulin bound to the platelet surface is part of an immune complex composed of antibody directed against a drug, microbe, or neoplastic antigen that is nonspecifically attached to the platelet Fc receptor. For secondary IMTP to be perpetuated, the foreign antigen must be constantly replenished or difficult to excrete. Drug-induced IMTP generally subsides within a few days of drug discontinuation, although thrombocytopenia secondary to chrysotherapy (gold therapy) may persist for weeks to years. Because gold is occasionally used to treat pemphigus foliaceus in horses, thrombocytopenia should be considered as a potential side effect. The spleen is the major site of platelet phagocytosis because (1) much antiplatelet antibody is secreted locally, (2) more than 30% of circulating platelets are normally stored there, and (3) the stagnant splenic blood flow allows sensitized platelets to pass slowly through a dense network of phagocytic cells. The mean cell life of circulating platelets and the platelet count are inversely proportional to the quantity of platelet-associated IgG.

When any unexplained case of thrombocytopenia is treated, all current medication should be stopped. If a drug is absolutely necessary, it must be replaced by the chemically most-dissimilar substitute. Drug-induced IMTP usually responds within 14 days of drug withdrawal. Most animals with suspected IMTP improve when treated with corticosteroids. Although their precise mechanisms of action are speculative, corticosteroids improve capillary integrity, impair clearance by the MPS, decrease the number and avidity of

macrophage Fc receptors, impair antiplatelet antibody production, impede platelet-antibody interactions, and increase thrombocytopoiesis.

Dexamethasone (0.05 to 0.2 mg/kg IV or IM) given once daily generally results in an elevation in the platelet count within 4 to 7 days. Once the platelet count is greater than 100,000/μL, the dose of dexamethasone can be reduced by 10% to 20% daily, while the platelet count is monitored for a relapse. Occasionally, animals with IMTP are refractory to dexamethasone, in which case prednisolone (1 mg/kg IM twice daily) may be tried. Treatment with corticosteroids can usually be discontinued after 10 to 21 days, provided the platelet count has been normal for at least 5 days.

Most horses with IMTP have a favorable prognosis, and the disease resolves within 14 to 21 days. This suggests that many cases may be secondary, although the initiating cause is rarely found. Chronic or recurrent IMTP requiring prolonged corticosteroid therapy has been reported.[86] Alternative treatment modalities for IMTP are largely unproved in horses because most cases respond to corticosteroids.[87–89]

37.4.11.2

DISORDERS OF COAGULATION FACTORS (DDM)

Normal blood coagulation proceeds in an integrated sequence that can be simplistically viewed as three key reactions: formation of activated factor X, formation of thrombin, and formation of fibrin. Other protein interactions serve to accelerate or inhibit the reaction rate of the coagulation factors.[26] Excessive use or inhibition of these proteins produces a relative deficiency that causes hemorrhagic diathesis. Alterations in the coagulation cascade, including thrombocytopenia and procoagulant and anticoagulant effects, can be observed with snakebite (e.g., rattlesnake) envenomation (see Chapter 54).

37.4.11.2.1

Disseminated Intravascular Coagulation

The most common form of hemostatic dysfunction in large animals is a syndrome known variously as DIC, consumption coagulopathy, defibrination syndrome, or intravascular coagulation fibrinolysis.[90–91] The pathologic process is characterized by widespread fibrin deposition in the microcirculation, with subsequent ischemic damage, and the development of a hemorrhagic diathesis caused by the consumption of procoagulants and hyperactivity of fibrinolysis.[26] Never a primary disease entity, DIC represents an intermediary mechanism of underlying disease. In large animals, DIC has been described in association with forms of localized or systemic septic processes,[91–94] neoplasia,[91] GI disorders,[49,95] renal disease,[95] and hemolytic anemia.[94,96] Diffuse activation of the hemostatic system is particularly prevalent in horses with acute GI disorders that cause colic[31,94,95] and is a likely initiating factor for laminitis.[97,98] Because of the dynamic nature of DIC, clinical manifestations range from diffuse thrombosis leading to ischemic organ failure to severe hemorrhagic diathesis. The most important determinants are the rate of thrombin generation, which depends on the triggering disease, adequacy of fibrinolysis, and functional state of the MPS, which is largely determined by peripheral circulation. Coagulopathy usually occurs in a compensated form in horses and cattle and is rarely accompanied by overt hemorrhage; however, microvascular thrombosis and subsequent ischemia to vital tissues leads to organ malfunction (e.g., renal failure), which contributes to the morbidity and mortality of the primary disease process.

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Renal involvement is common in DIC, which produces ischemic cortical necrosis followed by acute tubular necrosis. Renal disease may be manifested by oliguria, depression, and ileus caused by azotemia and electrolyte imbalances. GI microthrombosis may induce colic as a result of submucosal necrosis and

superficial ulceration. Spontaneous GI hemorrhage caused by DIC may cause melena in ruminants and occult fecal blood loss in horses. Rarely, pulmonary function may be compromised by microvascular thrombosis in DIC, causing tachypnea and variable hypoxemia. Altered consciousness, delirium, convulsions, or coma may follow cerebral microvascular thrombosis, although these signs are not common in large animals with DIC. Although reported in both horses[99] and cattle,[96] microangiopathic hemolysis is rare in large animals with DIC because of their small erythrocyte size.

Digital ischemia frequently accompanies DIC in horses and may play a role in the development of acute laminitis. Laboratory evidence of DIC has been documented during the developmental phase of equine laminitis,[98] and digital microvascular thrombosis occurs in horses that develop laminitis with colic or septic conditions.[97] The tendency for thrombosis of major peripheral veins is another prominent manifestation of coagulopathy in horses. Venous thrombosis occurs in horses and is associated with needle- or catheter-induced intimal trauma, nonsterility during catheterization, blood sampling or treatment procedures, and thrombogenic catheter materials. However, the strong clinical impression remains that severely ill horses with diseases known to induce coagulopathy have a greater tendency toward venous thrombosis. Spontaneous thrombosis of smaller cutaneous vessels also occurs.

As the thrombotic stimulus continues or intensifies, the tendency for hemorrhage develops because of clotting factors and platelet depletion or generation of excessive fibrinolytic by-products (FDPs). Petechial or ecchymotic hemorrhages on mucosae and sclerae and a tendency to bleed from venipuncture or after minor trauma are the principal signs. Spontaneous life-threatening hemorrhage is very rare; however, trauma or surgery may induce uncontrollable hemorrhage. Once signs of blood incoagulability develop, the prognosis is poor.

Horses may develop a chronic, compensated form of DIC with few or no clinical signs. This entity develops in patients with illnesses that produce a low-grade or intermittent procoagulant stimulus that allows used coagulant proteins and platelets to be partially or totally replenished and activated clotting factors and FDPs to be cleared by the MPS. Localized sepsis (e.g., pleuritis), neoplasia, protein-losing enteropathy, and immune-mediated disorders (vasculitis, anemia) are common initiating diseases. This compensated state may become imbalanced by stress, concurrent diseases, or worsening of the primary process, resulting in clinically obvious DIC. Diseases that must be differentiated from DIC include IMTP, warfarin toxicosis (horses), moldy sweet clover toxicosis, and inherited coagulation abnormalities.

Numerous laboratory tests of hemostasis may be abnormal during DIC; however, no one test consistently or specifically provides a definitive diagnosis. Lack of test sensitivity results from the dynamic nature of DIC; laboratory findings are determined by the balance between coagulation and fibrinolytic forces, as well as MPS integrity at blood sampling.

The most widely used hemostatic function tests in large animals include the platelet count, plasma fibrinogen, PT, aPTT, and serum FDPs. Because clinical manifestations of DIC vary widely, clarification of the most frequent laboratory abnormalities in large animals with DIC is hindered by lack of a definitive diagnosis in most cases. A disseminated coagulopathy is manifested by multiple hemostatic abnormalities, and serial analyses should reveal reduced platelet numbers and a trend toward prolongation of the PT, aPTT, and TT. Repeated hemostatic testing is advised when there is strong suspicion for DIC. Serum FDPs are most often elevated by DIC, but they are usually normal in the early or compensated form of the disease. Hypofibrinogenemia is an uncommon manifestation of DIC in large animals and, when present, should strongly suggest concomitant liver dysfunction. Hemostatic function tests are totally unreliable unless blood samples are collected and handled properly.

Criteria used for diagnosis of DIC are extremely arbitrary, and laboratory results must be interpreted in light of the patient's underlying disease. The combination of thrombocytopenia with mild to moderate prolongation of the PT or aPTT strongly suggests DIC. The clinician should seek laboratory assistance when considering the diagnosis of DIC but should appreciate that the findings are often not helpful. Clinical signs and specific situations suggest the possibility of DIC, and laboratory tests are only used to provide support.

Diseases initiate DIC by two major mechanisms: (1) generation of excessive procoagulant activity within the blood and (2) contact of blood with abnormal surfaces. Many diseases act by more than one mechanism to induce the overwhelming stimulus needed to trigger DIC. The nature and intensity of the procoagulant force (which determines the rate of thrombin formation), the concentration of natural coagulation inhibitors, and the functional capacity of the MPS determine (1) whether an individual with a given disease process develops DIC and (2) the clinical manifestations of DIC. Many diseases that produce DIC have the propensity to cause endotoxemia. The intestinal tract in large animals normally contains large quantities of endotoxins, only a small part of which is absorbed through the portal vein and removed by the liver. Conditions that cause intestinal mucosal edema or disruption allow endotoxins to gain access to the peripheral circulation and initiate many morbid sequelae, one of which is DIC. Intestinal strangulating obstruction, thromboembolic infarction, and severe colitis induce mucosal abnormalities, allowing endotoxemia to occur. The proliferation of gram-negative bacteria within tissues and the blood is also accompanied by endotoxemia.

Gram-negative endotoxins are capable of direct factor XII activation. However, most studies indicate that the procoagulant effects of endotoxin are primarily mediated by cytokine production by mononuclear phagocytes.[27,100] After endotoxin stimulation, phagocytes produce a platelet-activating factor (PAF), tissue factor, prostaglandins, interleukins, tumor necrosis factor (TNF), and other mediators with procoagulant activity.[27,101]

The net result of any triggering mechanism for DIC is the exaggerated generation of systemic thrombin, which causes widespread microcirculatory thrombosis. In addition to the cleavage of fibrinogen to produce fibrin monomers, thrombin activates factor XIII to render fibrin more resistant to fibrinolysis, enhances the cofactor activity of factors V and VIII, and induces platelet aggregation and exposure of platelet phospholipid. Circulatory obstruction produces organ hypoperfusion, leading to ischemic necrosis.

The counterbalance fibrinolytic system is also activated by DIC and plasmin contributes to factor consumption by destroying factors V, VIII, XIIa, IX, and XI, in addition to fibrin and fibrinogen. FDPs contribute greatly to the hemorrhagic manifestations of DIC because they have antithrombin activity, interfere with fibrin monomer polymerization, and cause platelet dysfunction.[28] Paradoxically, the combination of consumption and anticoagulation predisposes to hemorrhage at the same time that disseminated thromboses occur.

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The MPS plays a vital role in the pathogenesis of DIC. The tissue-fixed macrophages of the spleen and liver normally remove FDPs and activated clotting factors from the peripheral circulation, and FDPs only increase when their rate of formation exceeds the ability of the MPS to clear them. Shock and hypoperfusion of the liver and spleen or diseases associated with excessive tissue debris that must be removed by the MPS (e.g., sepsis, metastatic neoplasia) reduce the function of the MPS and predispose to or perpetuate DIC.

Therapy for DIC is highly controversial, and the only noncontended modalities are those directed toward identification and treatment of the primary disorder, along with general supportive measures to combat shock and maintain tissue perfusion.[26,88,102,103] Intravenous fluid administration helps to prevent organ dysfunction after microvascular thrombosis and can correct existing acid-base or electrolyte imbalances. Septic conditions should be treated with appropriate antimicrobial agents, and necrotic tissue or purulent exudate removed whenever possible (e.g., immediate surgical intervention to resect nonviable bowel). Flunixin meglumine mitigates the deleterious effects of endotoxin caused by eicosanoids and is used in horses at 0.25 mg/kg IV every 8 hours.[49] Corticosteroids may worsen DIC because they reduce the phagocytic action of the MPS and potentiate the vasoconstrictor effects of catecholamines.

Significant life-threatening hemorrhage is rare in large animals with DIC; however, if it occurs, fresh plasma should be administered (15 to 30 mL/kg) to replace used coagulant and anticoagulant proteins. The use of heparin in DIC has been recommended in various regimens to stall the disseminated microvascular thrombosis that precipitates organ failure; however, its efficacy is still controversial.[88,103] In dogs, minidose heparin therapy (5 to 10 U/kg subcutaneously [SC] three times daily) is often used with blood products in treatment of DIC.[88,102] Efficacy of heparin for DIC in horses is unproven. Heparin in all species can predispose to hemorrhage, thrombosis, and thrombocytopenia[104] and causes anemia and erythrocyte agglutination in horses.[105] If considering heparin therapy, the clinician must ensure there is adequate plasma AT III, which is necessary for heparin action. Because AT III is often depleted by DIC, plasma may be necessary. Clinical trials in humans have not indicated therapeutic benefit of anticoagulants in chronic DIC.

The prognosis for DIC in large animals depends largely on the nature and severity of the underlying disease and how effectively the latter is treated. Once DIC has progressed to the stage at which signs of blood incoagulability predominate, the prognosis generally is extremely poor.

37.4.11.2.2

Warfarin Toxicosis

Horses may develop a hemorrhagic diathesis caused by warfarin toxicosis.[106] Some use this coumarin-derivative anticoagulant to treat horses with navicular disease.[107] Rarely, horses and other animals may be exposed to coumarins used as rodenticides in grains or other feedstuffs. Therapeutic concentrations of warfarin can have a cumulative toxic effect if the diet is altered to contain less vitamin K or if there is concurrent protein-bound drug therapy. The clinical signs of warfarin toxicosis include hematomas, ecchymoses of mucous membranes, epistaxis, and hematuria. The earliest laboratory indication of warfarin toxicosis is a prolongation of PT because the plasma half-life of factor VII is shorter than the other clotting factors.[108] As the disease progresses, the aPTT becomes prolonged, and the animal may develop blood-loss anemia and hypoproteinemia. The diagnosis of warfarin toxicosis is based on a history of exposure, clinical signs of large-vessel hemorrhagic diathesis, and prolonged PT with or without aPTT and with no other abnormalities of the clotting profile.

Warfarin acts through competitive inhibition of vitamin K, which is necessary for liver production of clotting factors II, VII, IX, and X.[107] Factor activity is reduced in the blood at a rate that depends on its individual half-life. In most species, factors VII, IX, X, and XI have increasingly greater half-lives, accounting for the greater sensitivity of PT for the early diagnosis of warfarin toxicosis. After GI absorption, warfarin is highly bound to plasma proteins. Drugs that are normally protein bound (e.g.,

phenylbutazone, chloral hydrate) can enhance the toxicity of warfarin by allowing a greater proportion of the administered drug to be unbound and active.[109] In the same manner, hypoalbuminemia may increase the likelihood of warfarin toxicosis. Corticosteroids and thyroxin can lower the necessary therapeutic dose of warfarin by increasing both the receptor affinity and the clotting factor catabolism. Drugs that induce hepatic microsomal enzyme activity (e.g., barbiturates, rifampin, chloramphenicol) can accelerate warfarin metabolism and reduce therapeutic response to a given dose. Finally, any reduction in hepatic function or content of vitamin K in the diet can precipitate warfarin toxicosis.

Treatment of warfarin toxicosis depends on clinical signs. Warfarin therapy should be stopped if PT exceeds twice the pretherapeutic value. Vitamin K_1 (0.5 to 1 mg/kg SC) must be given every 6 hours until PT is again normal and stable. Significant hemorrhage can be controlled by the administration of fresh plasma to provide necessary clotting factors. If the anemia is life threatening, whole-blood transfusion should be considered. Although warfarin is eliminated rapidly, some potentiated coumarins have a prolonged half-life, requiring a longer course of vitamin K therapy. The prognosis for warfarin toxicosis is good with early diagnosis and prompt administration of vitamin K. It is imperative that vitamin K_3 not be used because it has poor therapeutic action and is highly nephrotoxic for horses.[110]

Prevention of warfarin toxicosis is based on limiting access of livestock to rodenticides and carefully monitoring the therapeutic use of warfarin in horses. The benefits of warfarin in horses are highly controversial, and many question whether advantages outweigh the risks.

37.4.11.2.3

Sweet Clover Toxicosis

Sweet clover (*Melilotus* species) toxicosis is caused by the ingestion of moldy sweet clover hay or silage containing dicoumarol. Natural coumarins in sweet clover can be converted to dicoumarol when hay or silage is improperly cured and mold forms. The toxin persists in moldy hay or silage and is palatable. This disease can occur in all species but is most often seen in cattle fed sweet clover hay in the northern plains states. Early signs include epistaxis and melena, with the development of subcutaneous hematomas and periarticular swellings as the disease progresses. Visible swellings occur at points of trauma (e.g., brisket, tuber coxae, carpi) and are not hot or painful, although they may cause stiffness and disinclination to move. Accidental and surgical wounds cause severe hemorrhage and may precipitate fatal blood-loss anemia.

Clinical pathology in sweet clover toxicosis is similar to that described for warfarin toxicosis, with prolonged PT being the earliest abnormality (detected before clinical evidence of hemorrhage). The platelet count remains normal, which differentiates this syndrome from DIC and bracken fern toxicosis. Other diagnostic rule-outs include mycotoxicosis, and toxicosis from trichloroethylene-extracted soybean meal.[48] In the absence of fever and anorexia, coagulopathy should make moldy sweet clover toxicosis a strong tentative diagnosis in animals with a history of access. Chemical analysis for dicoumarol in suspected feed or in the blood and liver of affected animals aids in the diagnosis[111]; however, the disease cannot be excluded if dicoumarol is not detected.

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The pathogenesis of moldy sweet clover toxicosis is identical to that of warfarin toxicosis. Dicoumarol interferes with hepatic synthesis of clotting factors II, VII, IX, and X by inhibiting vitamin K. Usually the syndrome appears in cattle 2 to 7 days after they ingest the moldy hay. Lower levels of dicoumarol (<70 mg/kg) in feed may prolong the onset of signs for up to 3 months.[48]

The succulent nature of sweet clover creates a high incidence of molding in hay. Grazing the crop is not dangerous. Because of its high forage yield, sweet clover is usually harvested as silage, which should carry less danger of molding when properly cured. The toxic level of dicoumarol in sweet clover feed samples is 10 mg/kg of feed.[111]

Treatment of sweet clover toxicosis involves discontinuing the use of contaminated feed and administering vitamin K_1.[109] Dosages between 1.1 and 3.3 mg/kg should be administered IM; response occurs within 24 hours. Animals with severe blood-loss anemia or ongoing hemorrhage should be treated with plasma or whole fresh blood. Sweet clover toxicosis can be prevented by careful forage preparation, followed by the inspection of hay and silage before feeding. When the disease is suspected, questionable feed should be removed from the diet.

37.5 DISEASES ASSOCIATED WITH INCREASED ERYTHROCYTE DESTRUCTION (HEMOLYTIC ANEMIA)

GARY P. CARLSON

Hemolytic disorders are characterized by an increased rate of red blood cell (RBC, erythrocyte) destruction. Anemia occurs when the rate of RBC destruction exceeds the bone marrow capacity for increased proliferative response. Although intravascular hemolysis occurs in some circumstances, these anemias are primarily caused by an increased rate of extravascular erythrocyte destruction and shortened intravascular lifespan.

Hemolytic anemias are associated with a wide range of systemic disease processes. The mechanisms responsible for the enhanced RBC destruction also vary greatly. Box 37-1 lists differential considerations of possible causal factors for hemolytic anemia in large animals. Clinical manifestations of hemolytic anemia vary with the degree of anemia, rate of RBC destruction, and primary or underlying disease process. Regardless of the cause, however, several common clinical signs are seen in animals with a severe hemolytic anemia, including pallor of the mucous membranes, fatigue, depression, and anorexia. Clinical icterus can be quite variable, depending on the rate of RBC destruction and the ability of the liver to excrete bilirubin. Icterus is a characteristic feature in hemolytic anemia, but intense icterus is noted only after massive RBC destruction and often is transient. With continued low-level hemolytic processes, the liver may be able to excrete bilirubin at a rate sufficient to avoid clinical icterus. Hemolytic icterus must be differentiated from other potential causes, such as liver disease or anorexia, in horses. If icterus is caused by hemolytic processes, clear clinical and hematologic evidence of anemia should exist. Massive intravascular hemolysis may result in an orange to reddish discoloration of the mucous membranes. Modest to marked and often variable febrile responses are frequently encountered in hemolytic anemias caused by infectious agents and during periods of active erythrocyte destruction. With advanced anemia the pulse and respiratory rates are elevated at rest. Death losses may occur, and neurologic abnormalities ranging from bizarre behavior to mania, collapse, and death may be associated with handling animals with a severe anemia.

37.5.1 Box 37-1 Causes of Hemolytic Anemia

37.5.1.1 INFECTIOUS CAUSES

37.5.1.1.1 Parasitic

- Anaplasmosis
- Babesiosis
- Hemobartonellosis
- Eperythrozoonosis
- Theileriasis
- Trypanosomiasis

37.5.1.1.2 Bacterial

- Leptospirosis
- Bacillary hemoglobinuria

37.5.1.1.3 Viral

- Equine infectious anemia (EIA)

37.5.1.2 IMMUNE-MEDIATED HEMOLYTIC ANEMIA

- Autoimmune hemolytic anemia
- Neonatal isoerythrolysis (NI)
- Drug induced: penicillin, trimethoprim-sulfamethoxazole

37.5.1.3 HEINZ BODY HEMOLYTIC ANEMIA

Phenothiazine toxicity

Wild onion poisoning

Red maple leaf poisoning

37.5.1.4 OTHER CAUSES

Severe cutaneous burns

L-Tryptophan—indole intoxication

Water intoxication

Postparturient hemoglobinuria

Copper poisoning

Hemolytic syndrome in horses with liver failure

Erythropoietic porphyria in Holstein cattle

The hematologic manifestations of hemolytic anemia also vary with the rate of RBC destruction, time course of the anemia, and primary or underlying disease process. The anemia may be modest to severe; after the first few days in all species except the horse, there is usually hematologic evidence of enhanced erythropoietic response, manifested by increased anisocytosis, polychromasia, reticulocytosis, and the presence of nucleated RBCs in the circulation. Morphologic abnormalities of diagnostic significance (e.g., intracellular/epicellular parasites, granulocytic inclusion bodies, Heinz bodies, spherocytes, schistocytes, poikilocytes) may be noted on examination of stained blood smears. Responsive anemias often are accompanied by a neutrophilia and regenerative left shift. The bone marrow usually shows an active erythropoietic response with a decreased myeloid/erythroid (M/E) ratio. The serum concentration of haptoglobin is decreased, and serum lactate dehydrogenase (LDH) enzyme activity may be elevated during acute hemolytic episodes. An increase in serum bilirubin concentration, caused primarily by an increase in indirect reacting bilirubin, is a reflection of active RBC destruction. 1154 1155

Specific serologic diagnostic procedures are available for many of the infectious causes of hemolytic anemia. Immunohematologic procedures such as the direct and indirect Coombs' test show that immune-mediated processes contribute to enhanced erythrocyte destruction. The principal mechanisms responsible for increased rate of RBC destruction associated with many of the infectious causes of hemolytic anemia (parasitic, bacterial, viral) are immunologically mediated, and affected animals may be transiently Coombs' positive.

37.6 INFECTIOUS CAUSES OF HEMOLYTIC ANEMIA

37.6.1 Anaplasmosis

GUY PALMER

37.6.2 Definition and Etiology

In veterinary medicine, anaplasmosis traditionally refers to disease characterized by progressive anemia caused by intraerythrocytic infection with *Anaplasma marginale* in cattle and *Anaplasma ovis* in sheep and goats. In addition, *A. marginale* subspecies *centrale* (also known as *Anaplasma centrale*) causes mild disease in cattle and has been used as a live vaccine to induce partial protection against *A. marginale*.

In the recent taxonomic reclassification of the tick-borne bacteria in the genera *Anaplasma* and *Ehrlichia, Ehrlichia equi* (cause of equine granulocytic ehrlichiosis), *Ehrlichia phagocytophila* (the cause of tick-borne fever in sheep, not recognized as a significant disease problem in North America), and the agent of human granulocytic ehrlichiosis (HGE) have been reclassified and unified as a single species, *Anaplasma phagocytophila*.[62] Correspondingly, the disease caused by *A. phagocytophila* in humans is designated as human granulocytic anaplasmosis (HGA) and in horses as equine granulocytic anaplasmosis. In addition, *A. phagocytophila* is an emerging disease of dogs.[112] Although this discussion primarily addresses bovine anaplasmosis and, to a lesser degree, ovine and caprine anaplasmosis, it is important to emphasize that any descriptions of human anaplasmosis are in reference to infection with *A. phagocytophila*. There is no evidence that *A. marginale* or *A. ovis* are capable of infecting humans or any nonruminant mammalian species.

37.6.3 Clinical Signs and Differential Diagnosis

Clinical signs are highly variable, from acute severe disease to subclinical infection, and reflect variation in virulence among pathogen strains and age- and breed-related differences in host susceptibility. Age at the time of initial infection is a primary determinant of host susceptibility. Disease is often mild in calves in the first 6 to 9 months of life and increasingly severe in older cattle. The typical incubation period ranges from 15 to 30 days. Infections in calves are often asymptomatic, but mild lethargy and anorexia may be seen for 24 to 48 hours. In contrast, the early stage of acute anaplasmosis in adult cattle is typified by fever, with rectal temperatures ranging from 39.5° C to 41° C (103° F to 106° F). Within 12 to 24 hours the fever subsides, and the temperature may drop to normal and become subnormal before the animal dies. Anorexia and, in dairy cows, a dramatic decrease in milk production can usually be observed soon after a fever is detected. Concurrently, there is suppression of rumination, dryness of the muzzle, and lethargy. Cattle may stagger or become aggressive as a result of cerebral hypoxia associated with anemia. Care must be taken not to stress severely anemic cattle because this may result in collapse and death. Early, the mucous membranes are pallid, but they may be icteric if an animal has survived for 2 to 3 days past the acute crisis. Constipation is a consistent sign, with the feces dark brown and covered with mucus, and pollakiuria is characterized by dark-yellow urine. Hemoglobinuria does not occur. Abortion may occur when infection occurs late in gestation. If an animal survives the acute crisis, the convalescent period is protracted and depends on the severity of the anemia. Icterus and weight loss are more frequently observed in the convalescent period, which may last for 3 to 4 weeks. Recovered animals remain persistently infected for life and, as described later, are epidemiologically important as a reservoir for ongoing transmission. However, persistent infection is not

associated with any disease or decrease in production status; therefore, no basis exists for a diagnosis of "chronic anaplasmosis." Although *A. ovis* infection in sheep and goats is often asymptomatic, anemia occasionally becomes severe enough to produce signs similar to those seen during *A. marginale* infection of cattle.

Definitive diagnosis of acute anaplasmosis requires identification of *A. marginale*— or *A. ovis*—infected erythrocytes by microscopic examination of blood smears, concomitant with a significant decrease in hematocrit (see next section). The differential diagnosis requires consideration of the diseases that can produce anemia or icterus, including babesiosis, bacillary hemoglobinuria, and leptospirosis. In pastured cattle, hepatotoxic plant poisonings *(Senecio)* and other causes of liver disease that produce icterus must also be considered. Copper poisoning is considered in sheep.

37.6.4 Clinical Pathology and Serology

Because acute bovine anaplasmosis is characterized by anemia, a falling hematocrit is an excellent criterion for prognostic purposes and for determining the severity of infection. The packed cell volume (PCV) drops below 30% when the first clinical signs are observed and may drop precipitously within 24 to 48 hours. Death can occur during this period despite a PCV above 20%. In other cases, PCV may decrease below 10% before death. During this acute phase, *A. marginale* can be detected within the erythrocytes by microscopic examination of blood smears stained with Wright's, new methylene blue, or Giemsa stain. The inclusion is composed of a small morula of two to eight individual organisms, and over 5%, up to 20% to 70%, of the erythrocytes may be infected. Later, after several days of anemia, the percentage of infected erythrocytes decreases dramatically, and evidence of RBC regeneration can be detected. There is anisocytosis, basophilic stippling, poikilocytosis, polychromatophilia, and reticulocytosis.

After recovery from acute disease, cattle and sheep remain persistently infected, with 0.000001% to 0.1% of erythrocytes being infected. These extremely low levels cannot be reliably detected by microscopic examination, and persistently infected animals, which serve as reservoirs for transmission, need to be detected serologically. Serologic diagnosis is most often accomplished through competitive enzyme-linked immunosorbent assay (cELISA),* which provides both high specificity and, unlike the complement fixation test, high sensitivity in detection of persistently infected carrier cattle.[113,114] The cELISA, approved as an official test by the U.S. Department of Agriculture (USDA) and the Office of International Epizootics (OIE), is conducted by most, if not all, state diagnostic laboratories. Currently, negative status with the cELISA is required for importation of live cattle into Canada. Although cattle will seroconvert by cELISA during acute infection, serology generally is of minimal utility in diagnosis of acute anaplasmosis.

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* VMRD Inc., Pullman, Wash.

37.6.5 Pathophysiology

Anaplasma species are naturally transmitted by Ixodidae ticks, most often the genera *Dermacentor* in the mainland United States and *Rhipicephalus* (including tick species previously classified in *Boophilus*) in tropical and subtropical regions worldwide. Although there is strong epidemiologic evidence of transmission by hematophagous flies, under experimental conditions this is very inefficient,[115] and thus the field conditions that allow transmission remain poorly understood. In addition, direct iatrogenic transfer of infected blood (contaminated needles; dehorning, castrating, hormone-implanting, or ear-tagging instruments) can result in transmission. After transmission, sequential rounds of bacterial invasion of mature erythrocytes, replication, and egress result in a progressively increasing, cell-associated bacteremia, with a doubling time of

approximately 24 hours. Clinical signs appear when greater than 1% of erythrocytes are infected and the severity roughly correlates with the percentage of infected erythrocytes. Anemia is at least partly caused by splenic and hepatic macrophage-mediated phagocytosis of both infected and uninfected erythrocytes. This appears to reflect both induction of autoantibodies against the RBC surface and induction of acute-phase reactants, including complement activation, during high-level rickettsemia. The regenerative response to anemia can be vigorous and does not appear to be suppressed by the infection.

Protective immunity appears to require induction of both antibody against the outer membrane proteins and macrophage activation for enhanced phagocytosis and bacterial killing.[116] Although the immune response controls the acute phase of infection, organisms are not completely cleared from the blood because of the emergence of antigenic variants.[117] These variants are responsible for persistent infection, characterized by recurring waves of bacteremia that reflect sequential emergence and then immune control of antigenically variant organisms.

37.6.6 Epidemiology

A. marginale is the most prevalent of the tick-borne infections of cattle worldwide and remains a serious constraint to livestock production in tropical and subtropical regions. However, anaplasmosis is also a significant problem in temperate regions. In the United States, infection is endemic in much of the West and occurs episodically in many historically nonendemic regions; anaplasmosis has been detected in at least 40 states. Canada is considered to be free of endemic anaplasmosis. Endemic regions are maintained by the prevalence of both competent arthropod vectors and persistently infected carrier cattle. These carrier cattle, which are typically asymptomatic, are efficient reservoirs for tick-borne transmission.[115,118] Vector activity varies by region, but outbreaks of anaplasmosis generally occur most frequently in the late spring and summer, when arthropod activity is highest. However, it should be emphasized that the determinants of tick-borne and fly-borne transmission are not well understood, and transmission is often unpredictable. In contrast, iatrogenic transmission can occur at any time and can be controlled by avoiding blood contamination during veterinary medical procedures. Although wild ruminants (e.g., deer, elk, bison) rarely have clinical disease and generally are asymptomatic, persistently infected carriers, their overall importance in the epidemiology of infection is unclear. Currently, wild ruminants are thought to play at most only a minor role in natural transmission.

37.6.7 Pathology

At necropsy, there are no pathognomonic lesions for the diagnosis of anaplasmosis. In acute anaplasmosis the blood is thin and watery and fails to clot readily. Mucous membranes, subcutaneous tissues, and skeletal musculature are pale (anemic pallor). In later stages of acute disease, however, the same tissues exhibit varying degrees of icterus. Splenomegaly is a consistent finding; hepatomegaly and distention of the gallbladder are common but seen less often. Urine is deep yellow, but neither hemoglobinuria nor hematuria occurs. The absence of hemoglobinuria helps differentiate anaplasmosis from other hemolytic diseases (babesiosis, bacillary hemoglobinuria, leptospirosis, onion toxicity, copper poisoning in sheep). Occasionally, petechiae may be found in the subepicardium, subendocardium, and other serous membranes. Detection of *A. marginale*—infected erythrocytes within capillaries of Giemsa-stained histologic sections can be used to confirm a diagnosis of anaplasmosis.

37.6.8 Treatment

Tetracyclines are the antibiotic of choice for treating acute disease, and resistance has not been reported. In acute anaplasmosis, oxytetracycline at 11 mg/kg IV every 24 hours for 3 to 5 days is effective. One to two administrations of long-acting oxytetracycline at 20 mg/kg IM at 72-hour intervals is also an effective treatment. In addition to antibiotic therapy, supportive therapy is important. If the PCV is 12% or lower, whole-blood transfusion may be indicated to prevent death and shorten the convalescent period; 4 to 8 L of whole blood is usually administered to an adult animal. A PCV of 8% or lower indicates an unfavorable prognosis, and death often occurs despite appropriate antibiotic and supportive therapy. Importantly, the oxytetracycline regimen used to treat acute anaplasmosis is not effective in completely clearing the animal of the organism, and recovered animals become persistently infected carriers. Although prior studies showed that long-acting oxytetracycline at 20 mg/kg every 3 days for four successive treatments resulted in clearance, more recent studies using this regimen and variations of this regimen have indicated that clearance is not achieved.[119] If required for exportation, clearance should be confirmed by conversion to seronegative status.

37.6.9 Prevention and Control

Control measures vary depending on the geographic region and type of livestock production system. In endemic regions with high transmission rates, such as those in tropical countries, beef cattle are often allowed to become naturally infected at a young age and remain asymptomatic carriers with minimal risk of later acute disease. In regions with lower transmission rates, live blood-based vaccines may be used to ensure infection of cattle at a young age. This is exemplified by the use of trivalent *(A. marginale, Babesia bovis, Babesia bigemina)* live vaccine in Australia. Similarly, live vaccines based on *A. centrale* or weakly virulent strains of *A. marginale* are typically used in Africa, Asia, and Central and South America. However, these are not licensed for use in the United States, largely because of the risk of transmitting known or newly emergent pathogens contaminating the blood-based vaccine. The exception to this is the licensing of a live vaccine* for use in California. Importantly, these live vaccines should only be used in young animals and are contraindicated for use in older and especially pregnant animals. Killed vaccines are less efficacious and require multiple immunizations, but these can induce at least partial protection against severe morbidity and mortality. Unfortunately, none of the federally licensed killed vaccines previously marketed in the United States are currently available. However, an experimental killed vaccine* has been licensed for use in 14 states and Puerto Rico.

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In the absence of immunoprophylaxis, anaplasmosis is usually controlled by preventing transmission. Although it is difficult to prevent completely the contact of ticks and biting flies with cattle grazing on open ranges or farm pastures, strategic use of acaricides and insecticides can reduce transmission during periods of high vector activity. Periodic spraying for tick control and the use of insecticide-impregnated ear tags or insecticide dust bags for biting-fly control are cost-effective, not only for control of anaplasmosis but also for control of pinkeye and for directly reducing irritation and increasing weight gain. Because blood-contaminated instruments and needles can mechanically transmit infection, appropriate sanitary measures should be implemented when injections or surgical procedures are performed.

Maintenance of an *A. marginale*–free herd in nonendemic areas can be accomplished by quarantine and serologic screening of all additions using the USDA-approved cELISA. Within endemic regions, however, this requires extreme vigilance in screening and prevention of both direct contact and sharing pasture with other domestic and wild ruminants, which may result in vector-borne transmission. The risk of maintaining a fully susceptible herd within an endemic region should not be taken lightly.

Table 37-1 *Babesia* Species (Babesiosis)

Organism	Livestock Affected	Principal Geographic Distribution	Morphology of Organism	Tick Vectors
B. bigemina (B. bovis)	Cattle	Americas, Europe, Africa, Australia, Middle East	4.5 × 2.5 µm (large, round, and pyriform; acute angle)	*Boophilus annulatus, B. decoloratus, B. microplus*
B bovis (B. berbera, B. argentina)	Cattle	Americas, Europe, Russia, Africa, Asia, Australia	2.4 × 1.5 µm (small and more rounded; obtuse angle)	*B. annulatus, B. microplus, Ixodes* species (?)
B. divergens	Cattle	Europe	1.5 × l.4 µm (small, narrow and obtuse angle)	*Ixodes ricinus*
B. major	Cattle	Europe, Russia, North Africa, Middle East	2.6 × 1.5 µm (similar to *B. bigemina,* but smaller)	*Haemaphysalis punctata*
B. jakimovi	Cattle	Asia	2-4.6 × 1.5-2.1 µm (large, round, and pyriform)	*I. ricinus*
B. ovata	Cattle	Japan	4.5 × 2.5 µm (large, round, and pyriform)	*Haemaphysalis longicornis*
B. caballi	Horses	Americas, Europe, Russia, Asia, Africa, Middle East	3 × 2 µm (large, pyriform; acute angle)	*Dermacentor, Hyalomma,* and *Rhipicephalus* species
Theileria equi (B. equi)	Horses	Americas, Europe, Russia, Asia, Africa, Middle East	1-2 µm (small and rounded; Maltese cross is characteristic)	*Dermacentor, Hyalomma,* and *Rhipicephalus* species
B. motasi	Sheep and goats	Europe, Russia, Asia, Middle East	3 × 2 µm (large, pyriform; acute angle)	*D. silvarum* (?), *Haemaphysalis* species, *R. Bursa*
B. ovis	Sheep and goats	Europe, Russia, Asia, Middle East	1.5 × 1 µm (small and more rounded; obtuse)	*I. ricinus* (?), *R. bursa, D. reticulatis* (?)
B. trautmanni	Swine	Europe, Africa, Russia	3.5 × 2 µm (large, narrow, and long; acute angle)	*R. sanguineus* (?), *Dermacentor* species (?), *Boophilus* species, *Hyalomma* species (?)

B. perroncitoi	Swine	Europe, Africa, Asia	0.7-2 µm (small and more rounded)	Vectors unknown

From Kuttler KL: *Foreign animal diseases,* Richmond, Va, 1984, United States Animal Health Association, p 77.

(?), Suspected vector.

* AnaVac, PHL Associates, Davis, Calif.

* Experimental Anaplasmosis Vaccine, University Products LLC, Baton Rouge, La.

37.7 Babesiosis

JERRY L. ZAUGG

Babesiosis is a tick-borne intraerythrocytic disease of domestic and wild mammals and humans caused by protozoan parasites of the genera *Babesia* and *Theileria*. The acute disease is characterized by fever, hemolytic anemia, icterus, hemoglobinuria, and death. Although both morphologic and serologic differentiation is needed for specific identification of the various disease-producing species, all can be categorized as being either "large" or "small" in size. Table 37-1 presents common *Babesia* species (and *Theileria equi*), their usual biologic vectors, and livestock hosts. Babesiosis has a wide geographic distribution, particularly in the tropics and subtropics, largely related to the distribution of vector ticks. Of the different diseases, the economically most important infections of livestock are those of cattle and horses.

37.7.1 BABESIOSIS IN THE BOVINE

JERRY L. ZAUGG

37.7.1.1 Etiology

Known variously by such names as bovine babesiosis, piroplasmosis, Texas fever, redwater, tick fever, and tristeza, the disease may be caused by at least six *Babesia* species (see Table 37-1). Animals other than cattle known to be susceptible to agents of bovine babesiosis include white-tailed deer, American bison, water buffalo, reindeer, and African buffalo. Infections in these other animals are nominal, and except under unusual conditions, such hosts are probably not significant reservoirs.

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Of greatest concern in the Western Hemisphere are the species *B. bigemina* and *B. bovis. Babesia bigemina* is a large species characteristically appearing within mature erythrocytes as nonpigmented, paired, pear-shaped bodies joined at an acute angle. Irregularly shaped, round, or amoeboid forms are also seen. *Babesia bovis* is a small, pleomorphic species often identified as a single round body or as paired, pear-shaped bodies joined at an obtuse angle within mature erythrocytes. Of the two species, *B. bovis* is usually considered the most virulent.

Natural transmission of both species occurs primarily by the feeding of various stages of the one-host ticks of the genus *Boophilus*. Ticks are most often infected transovarially (vertically). The female tick becomes infected by the ingestion of parasites during engorgement. After it drops off the host, the babesial organisms reproduce within the tick's tissues. Some of the reproducing organisms are incorporated within developing tick embryos, and the disease agents are transmitted to new vertebrate hosts by the feeding of ensuing tick larvae, nymphs, or adults. Larval ticks may transmit *B. bovis*, but *B. bigemina* is not transmitted until the

larvae have molted into the nymphal or adult stages. Both *Babesia* species may also be transmitted iatrogenically through blood-contaminated fomites, as described under Anaplasmosis.

37.7.1.2

Clinical Signs

Clinical signs manifest 2 to 3 weeks after tick infestation. The incubation period after blood inoculation may be less than 5 days to more than 3 weeks, depending on the volume of inoculum. Clinical signs of fever (40° C to 42° C, 104° F to 107.6° F), depression, icterus, anorexia, tachycardia, tachypnea, anemia, hemoglobinemia, hemoglobinuria, abortion, and death are seen. Anemia is caused by intravascular destruction of erythrocytes by escaping merozoites after intraerythrocytic reproduction of the babesias by binary fission. In addition, the osmotic fragility of the whole-erythrocyte population increases terminally, such that massive lysis occurs, even though the parasitemia may be less than 1%.[120] Additionally, as also seen with anaplasmosis, an autoimmune condition may result in which the spleen removes damaged and apparently healthy erythrocytes from circulation. Thus, the degree of anemia may exceed that expected with a low parasitemia. The anemia may occur rapidly, with 75% or more of the erythrocytes destroyed in a few days. The exit of *B. bigemina* and *B. bovis* parasites from infected erythrocytes releases two or more parasite-associated proteolytic enzymes into the plasma. These enzymes and other parasite metabolic products are believed to interact with blood components and are responsible for such clinical signs as metabolic acidosis and anoxia. Tachycardia may be dramatic and the heartbeat pronounced.

Cerebral babesiosis, characterized by hyperexcitability, convulsions, opisthotonos, coma, and death, may be observed in cattle infected with either *B. bigemina* or *B. bovis*, but especially with the latter. Central nervous system (CNS) signs are caused by brain anoxia resulting from severe anemia and erythrocyte blockage of cerebral capillaries.

Death is caused by a shocklike syndrome associated with the accumulation of toxins, release of vasoactive substances, and anemic anoxia. Most cases with cerebral involvement are fatal; however, mortality is extremely variable, depending on *Babesia* species involved, susceptibility of the host, and management and environmental stress factors. Many cattle that survive the acute phase recover but become chronic carriers. Other survivors often experience episodes of recrudescence, eventually succumbing to the disease, or they may die as a result of secondary infections contracted during their debilitated state.

Cattle of all breeds are susceptible to babesiosis. However, *Bos indicus* breeds exhibit a definite degree of resistance to both *Babesia* species and the tick vectors.[121] Calves possess a natural immunity to babesiosis. Such immunity was believed to be reinforced by colostral antibodies for calves born to previously infected dams.[122] However, erythrocytes of young bovines may contain factor(s) independent of antibody that provide an innate resistance to severe babesiosis.[123] Thus, calves infected up to the age of 9 months experience a minimum reaction to the disease, becoming asymptomatic carriers. Carriers remain resistant to clinical disease for at least 4 years.[124] The carrier state can be overcome, however, by such stressors as calving, malnutrition, and concurrent disease.[125]

37.7.1.3

Clinical Pathology

Clinical signs observed in cattle in enzootic areas with *Boophilus* ticks may provide sufficient data for a presumptive diagnosis. Other conditions that may exhibit similar signs as babesiosis are anaplasmosis, trypanosomiasis, theileriosis, leptospirosis, chronic copper toxicity, and bacillary hemoglobinuria. The cerebral signs may be confused with rabies and other encephalitides. A positive diagnosis requires

identification of the *Babesia* species on Giemsa-stained thin blood smears, positive serologic tests, or inoculation of splenectomized calves with infective blood. In acute infection, *Babesia* species can usually be detected in smears made from peripheral blood. In chronic cases, numbers of parasitized erythrocytes diminish, becoming so sparse as to make detection difficult. This is especially true with *B. bovis,* which shows a marked tendency to accumulate in capillaries, particularly those of the brain. *B. bovis* may favor capillaries in the brain and kidney because the major energy-producing pathway of *Babesia* appears to be anaerobic glycolysis. The blockage of cerebral and renal capillaries by parasitized erythrocytes results in an anaerobic condition that enables the parasites to absorb preformed substrates by pinocytosis and diffusion through their surface membranes. PCV values drop rapidly from a normal of 35% to below 10% in less than a week after onset of clinical signs.[126] Serum potassium levels decrease in some infected animals, whereas urine potassium levels increase in almost all cases.[127]

Specific anti-*Babesia* antibodies are detectable in cattle sera less than 7 days after infection.[128] Such antibodies also exist for at least 252 days after the disappearance of detectable parasites.[129] The complement fixation (CF) and indirect fluorescent antibody (IFA) tests are the most widely used.[128] The CF test follows the same basic procedure used in anaplasmosis CF testing[130] with a *Babesia* antigen.[131] The test is effective, but approximately 100 days after infection, the CF antibodies drop below a reliable diagnostic level.[128] The IFA test uses the whole intraerythrocytic parasite as antigen rather than an extract and commercially prepared rabbit antibovine γ-globulin conjugated to fluorescein.[128] Other serologic tests include gel precipitation,[132] latex particle agglutination,[133] rapid card agglutination,[134] and enzyme-labeling immunoassay (EIA).[135] The immunologic assays, however, are indirect methods and do not detect the causal organisms in samples obtained from a suspected infected animal. Recombinant DNA techniques using selected clones containing inserts of *Babesia* genomic DNA sequences are now available to be used as specific, highly sensitive DNA or RNA probes to detect the presence of the hemoparasite DNA in an infected animal or a tick vector.[136]

37.7.1.4

Necropsy Findings

Postmortem findings in cattle that die peracutely are characteristic of an acute hemolytic crisis. Such findings include a generalized pallor or icterus throughout the carcass; an enlarged icteric liver; gallbladder distended with thick, dark-green bile; and a greatly enlarged, dark, soft spleen. Hydropericardium and subepicardial/subendocardial petechiation may be seen. The blood is thin and watery. The urinary bladder is frequently distended with dark-red urine. There may be subserosal ecchymotic hemorrhages in abomasal and intestinal mucosa, and the lymph nodes are edematous. The carcass of an animal that dies after a prolonged illness is generally emaciated and icteric. The intermuscular fascia is also edematous. The kidneys are pale and edematous, and the bladder may contain pink-tinged or normal urine. The liver is enlarged and jaundiced, and the bile may contain flakes of semisolid material.

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37.7.1.5

Treatment and Prognosis

After the onset of hemoglobinuria or cerebral signs, the prognosis is poor. Acute cases with PCV values above 12% usually respond well to treatment. The prognosis decreases for cases with PCV values below 10%. Successful treatment depends on early diagnosis and prompt therapy. In addition to specific treatment, supportive therapy such as blood transfusions (4 L of whole blood per 250 kg of body weight), fluids, hematinics, and prophylactic antibiotics are important. However, wild, excitable cattle may best be left alone.

With severe hemolytic anemias, any exertion associated with restraint and treatment may precipitate an anoxic crisis.

The small *Babesia* species are more resistant to chemotherapy and may require increased dosages or additional treatments. The most frequently used, effective, and relatively less toxic specific babesiacides are diminazine aceturate* at 3 to 5 mg/kg; phenamidine diisethionate† at 8 to 13 mg/kg; imidocarb dipropionate‡ at 1 to 3 mg/kg; and amicarbalide diisethionate§ at 5 to 10 mg/kg.[137] Generally, treated cattle become chronic carriers and are resistant to further clinical episodes of the disease. However, treatment of *B. bigemina* may be so effective that sterilization occurs, eventually leaving the animal susceptible to reinfection. Imidocarb has both therapeutic and prophylactic activities. In enzootic areas, its use prevents clinical infection for as long as 2 months but at the same time allows mild, subclinical infections to occur, resulting in premunition immunity.[138,139]

* Berenil (Intervet Inc., St. Millsboro, Del) and Ganaseg (Squibb and Sons de Mexico, Mexico City).

† Lomidine, May and Baker Ltd., Dagenham, England.

‡ Imizol, Pitman-Moore, Middlesex, England.

§ Diampron, May and Baker Ltd., Dagenham, England.

37.7.1.6

Prevention and Control

Eradication of *Boophilus* tick vectors has provided effective control in the United States. Other such projects attempted elsewhere have not been successful because of such diverse reasons as tick resistance to acaricides; ability of some ticks to infest alternate, nonbovine hosts; failure to obtain 100% cooperation of cattle producers; and lack of financial resources to sustain a prolonged program.

Most procedures aimed at reducing tick infestations (acaricide applications [on host or over environment], controlled range burning, cultivation, prolonged pasture rest, use of repellents) are beneficial. Care should be taken to prevent accidental transfer of blood from one animal to another in routine surgery (e.g., dehorning, castration, ear marking, hormone implantation) and vaccination procedures.

The most common form of immunization consists of inoculating live organisms (virulent or attenuated) into susceptible calves to induce a state of premunition. Inoculation of older animals is followed by nonsterilizing chemotherapy as needed to modify clinical effects.[140] Although a premunition approach is useful in endemic areas, it is less desirable in areas with low infection rates because the premunized carriers provide a large reservoir of infection. Some killed adjuvant vaccines have proved successful in limited trials.[141] In vitro cell cultivation techniques have yielded highly immunogenic soluble antigens of *B. bovis*.[142] Subunit vaccines derived from monoclonal technologies were proved effective in protecting against severe clinical disease.[143] The monoclonal antibodies apparently inhibit merozoite invasion of the erythrocytes. Vaccines of such noninfectious material generally do not prevent disease, but they do moderate the effects of infection and do not directly produce carriers.

37.7.2 BABESIOSIS IN THE HORSE

37.7.2.1 Etiology

Babesiosis/theileriosis of equids (piroplasmosis) is a febrile, tick-borne disease caused by *Babesia caballi* and *Theileria equi*. Until recently, *T. equi* was known as *Babesia equi*. However, because the organism more closely resembles members of the genus *Theileria* with its exoerythrocytic (lymphocytic) stages within the vertebrate host, with development of microschizonts and macroschizonts, *B. equi* is now classified as *Theileria equi*[144] (see Table 37-1). *Babesia caballi* is a large species resembling *Babesia bigemina,* which affects cattle. Although *T. equi* is not a member of the genus *Babesia*, for practical purposes it is still considered a "small" parasite, similar to *B. bovis* on stained thin blood smears. However, a unique characteristic of *T. equi* is that the intraerythrocytic parasites divide into four cells to form a Maltese cross.[145]

Equine piroplasmosis is widely distributed throughout the tropics and subtropics and to a lesser extent in temperature regions. The distribution roughly corresponds to those of the tick vectors. Both species are naturally transmitted by ticks of the genera *Dermacentor, Hyalomma,* and *Rhipicephalus. B. caballi* is passed transovarially (vertically) from one tick generation to the next. Transmission of *T. equi* apparently occurs only transstadially (horizontally); one tick stage (larvae or nymphs) becomes infected, and the disease agent is passed to the next vertebrate host in the next tick stage (nymph or adult). Because of the widespread prevalence of potential tick vectors in the United States (*Dermacentor albipictus, D. iteus,* and *D. variablis*), it is unknown why equine piroplasmosis is not a problem in the United States.

37.7.2.2 Clinical Signs

All equids apparently are susceptible to both parasite species. The zebra in Africa is naturally infected with *T. equi* but not with *B. caballi*. Once infected, survivors remain chronic carriers. *T. equi* can be transmitted transplacentally. Clinical features after an incubation period of 5 to 28 days include fever (39° C to 42° C; 102° F to 107.6° F), hemolytic anemia, jaundice, hemoglobinuria, and death. Generalized signs of depression, anorexia, incoordination, lacrimation, mucous nasal discharge, swelling of the eyelids, and frequent lying down are seen. *T. equi* is considered the most pathogenic of the two species and is responsible for a greater incidence of hemoglobinuria and death. *B. caballi* causes a more persistent fever and anemia. Differential diagnoses include equine monocytic ehrlichiosis, equine infectious anemia, liver failure with hemolytic anemia, and other hemolytic anemias of the horse.

37.7.2.3 Clinical Pathology

A fever associated with anemia, jaundice, and hemoglobinuria, with the detection of parasite-infected erythrocytes in Geimsa-stained blood smears, is diagnostic. A significant increase in relative and absolute numbers of monocytes and absence of eosinophils may be observed in horses infected with *T. equi*. Hemoglobinuria is rare in animals infected with *B. caballi,* but urine is often dark yellow. The most frequently used serologic tests are CF and IFA tests. Blood from spleen-intact horses can become CF positive within 14 days after parasite exposure. There is also a cELISA test for *T. equi* and a polymerase chain reaction (PCR) test for both equine diseases. Further, as with the bovine infections, both *B. caballi* and *T. equi* infections can be specifically detected with nucleic acid probes.[136]

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37.7.2.4 Necropsy Findings

Postmortem features are similar to those seen in bovine babesiosis, but jaundice is even more prominent throughout the carcass. There is excessive fluid in the body cavities, especially the pericardial sac. Pulmonary edema is evident. The liver is swollen, and hepatic vessels contain large, yellowish clots. The spleen in enlarged with rounded edges.

37.7.2.5 Treatment and Prognosis

Generally, both *B. caballi* and *T. equi* respond to the same babesiacidal drugs used to treat bovine babesiosis, but *T. equi* is more refractory to treatment than *B. caballi*. If diagnosed early and treated promptly, recovery is the rule. The drug of choice for eliminating the carrier state of infected animals is imidocarb; at 2.2 mg/kg twice in 24 hours, imidocarb is effective against *B. caballi;* 4 mg/kg four times over 72 hours is effective against *T. equi* of Eastern Hemisphere origin.[137] However, donkeys receiving similar treatment died from drug toxicosis.[121] The higher doses of imidocarb often produce transient side effects in horses similar to signs seen in colic. To date, attempts to eliminate consistently the carrier state of *T. equi* of Eastern European origin have been unsuccessful.[146] However, as proposed in 1993,[147] irregular chemical sterilization success has been obtained with concurrent IV buparvaquone* at 4 mg/kg and IM imidocarb at 4 mg/kg.

* Butalex, Coopers Animal Health Limited, Hertfordshire, United Kingdom.

37.7.2.6 Prevention and Control

Control of the tick infestations does much to reduce disease incidence, as does care to prevent blood transfer during such routine surgical procedures as castration. No vaccines effectively prevent equine babesiosis. Premunition (as used in bovine babesiosis) is of limited value in some enzootic areas, but it is not widely practiced because early treatment without sterilization is effective, and the resulting chronic carriers resist further disease challenge.

37.8 Hemobartonellosis (Eperythrozoonosis)

GARY P. CARLSON

Haemobartonella bovis is an epicellular organism that is closely associated with the surface of erythrocytes. It may appear as a rod shape, an ovoid, or in chains with conventional stains. Hemobartonellosis is primarily of academic interest in North America because it is rarely a cause of anemia.[148] The organism has been found in association with other rickettsial diseases and has been experimentally transmitted in splenectomized calves. The agent may be visualized as delicate ovoid, rod, or dumbbell forms arranged in chains or tight groups or randomly distributed epicellularly throughout appropriately stained blood smears.

37.8.1 EPERYTHROZOONOSIS IN CATTLE

The causal agent is *Eperythrozoon wenyoni (Mycoplasma wenyoni)*. Infection is usually latent, producing no clinical signs in normal cattle, but it may become apparent in animals that have been severely stressed by some other systemic disease. The disease can be produced experimentally if infected blood is administered to

splenectomized calves. Even under experimental circumstances, clinical signs consist of mild depression, fever, and modest anemia. The disease in cattle is of little clinical consequence, except for the potential for confusion should the organism be seen on stained blood films. Occasionally, cattle may have swollen and tender teats and legs.[148]

37.8.2 EPERYTHROZOONOSIS IN SHEEP AND GOATS

The causal organism in sheep and goats is *Mycoplasma ovis (Eperythrozoon ovis)*, which appears to be very similar morphologically and serologically to the species found in cattle. The disease can produce more prominent clinical signs in sheep, with profound depression, anemia, and significant death losses in young lambs.[149] Erythrocyte destruction is thought to be caused by intravascular hemolysis and erythrophagocytosis.

37.9 Theileriasis

GARY P. CARLSON

Theileriasis is caused by small hemoparasite of the genus *Theileria* that infects lymphocytes and erythrocytes of ruminants and is most common in tropical and subtropical climates. The organism is spread by bloodsucking arthropods, particularly ticks of the Ixodidae family. *Theileria parva* is the cause of East Coast fever, a highly fatal disease of cattle in Africa. Other members of the genus *Theileria (T. annulata, T. mutans, T. hirci*, and *T. ovis*) tend to be less pathogenic and produce diseases with a wider geographic distribution.[149] *T. cervi* has been seen in North American deer. *T. mutans* has been seen in erythrocytes of both cattle and deer in North America. Theileriosis caused by an agent indistinguishable from *T. buffeli* has been described in cattle from Texas and North Carolina with parasitemia, but clinical signs were not reported.[150] Recently, *T. buffeli* was reported as the cause of a hemolytic anemia in a 6-month-old Simmental calf.[151] There was serologic evidence of a high herd prevalence of *Theileria* infection, and the agent was transmitted to splenectomized calves, which developed mild anemia. The organism produces a brief illness characterized by mild fever, anorexia, and modest anemia, followed by rapid recovery.

37.10 Trypanosomiasis

GARY P. CARLSON

Trypanosomes are flagellated protozoal organisms that can produce a variety of serious diseases of humans and animals, although many are nonpathogenic. Nagana, a disease of cattle in Africa, is caused by *Trypanosoma congolensi. Trypanosoma evansi* is the cause of surra, a disease of cattle in India, and *Trypanosoma equiperdium* produces dourine in horses. In North America, *Trypanosoma theileri (Trypanosoma americanum)* is the only agent reported and is principally of academic interest because it is relatively nonpathogenic. The organism is occasionally seen free in the plasma in small numbers on stained blood films from cattle as a large, flagellated protozoan with an undulating membrane.[149] The organism is best visualized in buffy coat smears, which tend to concentrate it. *T. theileri* rarely produces clinical signs, but occasionally a fulminating parasitemia may develop, resulting in fever, depression, and decreased milk production.

37.11 Leptospirosis

GARY P. CARLSON

Leptospira infections produce disease in several species, including cattle, sheep, swine, horses, dogs, and humans, but the acute hemolytic syndrome associated with these infections is seen most often in calves and lambs. *Leptospira interrogans* serovars *pomona* and *icterohaemorrhagiae* are the serotypes usually involved in the hemolytic syndrome. Clinical signs of the hemolytic syndrome vary but generally include fever, lethargy, icterus, anemia, and petechial hemorrhages. The anemia results, at least in part, from immune-mediated mechanisms. Cold-reacting immunoglobulin M (IgM) antibodies have been implicated in the hemolytic anemia seen in lambs. The degree of anemia is variable but can be severe, with evidence of erythropoietic response apparent in the peripheral blood within 4 to 7 days. A moderate leukocytosis and elevation in plasma fibrinogen are often associated with the hemolytic anemia. The diagnosis is generally made on demonstration of the organism in the urine, PCR, and an increase in serum antibody titer. Discussion of leptospirosis as a reproductive, renal, and ocular problem can be found in other chapters.

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37.12 Equine Leptospirosis

MONICA ALEMAN

Leptospirosis is a bacterial zoonotic disease that is prevalent worldwide.[152] The organism can be readily transmitted between mammalian species (cattle, pigs, horses, dogs, and humans) through infected urine, body fluids, and contaminated soil or water.[153] In horses from North America, infections are primarily caused by *Leptospira interrogans* serovar *pomona kennewicki*.[154] There are various maintenance hosts for this serovar, with the skunk being the most common host. *Leptospira bratislava* has been considered the host-adapted serovar of the horse, although this has been controversial. Some researchers believe this serovar is also pathogenic to the horse, and when the horse is infected, the organism can be shed indefinitely in urine and possibly the reproductive tract.[154]

Leptospira pomona can cause uveitis, placentitis, abortion, stillbirth, renal disease, and hemolysis. Clinical signs include fever, jaundice, anorexia, and lethargy. Leptospirosis is a sporadic cause of abortions, although in endemic areas it may account for 13% of bacterial abortions.[155] In general, abortions occur during late-term gestation. The organism can be found in the placenta, umbilical cord, kidney, and liver of the aborted fetus. *L. pomona* can be shed in urine for up to 14 weeks after infection. *Leptospira grippotyphosa* and *L. hardjo* are serovars also known to cause equine abortions.[154]

Renal disease, tubulointerstitial nephritis, pyuria, and rarely acute renal failure have been reported in horses with leptospirosis. More often, two ocular disorders appear to be associated with *L. pomona* infection in horses: *equine recurrent uveitis* (ERU) and *immune-mediated keratitis*. The immune-mediated response is postulated to result from the cross-reaction between leptospiral antigens and uveal tissue, cornea, lens, vitreous body, and retina.[156] Recent reports have confirmed the presence of live *Leptospira* in the uveal tissue of horses with uveitis through isolation of the organism, positive PCR, or high antibody titer in the aqueous humor.[156]

37.12.1 Diagnosis

Diagnosis of leptospirosis can be challenging because of variable serologic results. Microscopic agglutination titer (MAT) in serum and fluorescent antibody titer (FAT) in infected tissues have been routinely used for diagnosis. The sensitivity and specificity of FAT in tissues of aborted fetuses are almost 100%.[155] In cases of uveitis, high antibody titers in aqueous humor may be found despite variable serum titers, suggesting local

antigenic stimulation.[156] Serum titers of 1:6400 are considered significant and consistent with infection.[157] Serum titers of 1:3200 that are stable for 2 to 3 weeks are not considered significant. Rising titers after 2 to 3 weeks are considered significant, and the patient should be isolated and treated. Other diagnostic modalities are PCR, histology, and bacterial isolation. Recently, Divers[155] isolated genes of two surface proteins of *L. pomona* (immunoglobulin-like proteins A and B) that are expressed only during active infection. These proteins may improve the diagnosis and development of a protective vaccine for leptospirosis.

37.12.2 Treatment

Treatment for leptospirosis has been advocated with ampicillin, amoxicillin, procaine penicillin (22,000 IU/kg IM every 12 hours), oxytetracycline (5 to 10 mg/kg IV every 24 hours, slow in fluids not containing calcium), or doxycycline (7 to 10 mg/kg PO every 12 hours) for 7 days. The inflammatory response in horses with ERU and immune-mediated keratitis has been managed with corticosteroids and cyclosporine, but this may provide only temporary relief. Affected horses tend to develop ocular complications (e.g., cataracts, glaucoma, blindness, intractable pain) that may result in enucleation. The inability to cure many cases of ERU may be caused by the lack of treatment for the possibly active infection. Therefore, treatment should be directed toward controlling the ocular inflammatory response and ongoing infection, if indicated. Systemic antimicrobial therapy may not be successful in ERU cases resulting from an intact blood ocular barrier despite being inflamed.[155]

37.12.3 Prevention

Prevention must be aimed at controlling exposure to shedding hosts, infected animals, and contaminated fomites. Thorough cleaning and disinfection of contaminated areas and proper disposal of infected material are essential measures to minimize exposure. Pregnant mares should be isolated from other animals because bacterial shedding may last several weeks. If abortions occur in endemic areas, it is recommended to test horses for leptospiral antibodies and isolate those horses with a serum titer of 1:6400 or higher.[157] Also, horses with a negative or low titer should be retested in 2 to 3 weeks. Horses with rising titers should be isolated. Attempts to decrease shedding in horses with oxytetracycline, penicillin G, and streptomycin have not been effective. Vaccination is sometimes performed on farms with endemic abortions or high rates of uveitis.[155]

37.13 Bacillary Hemoglobinuria (Redwater)

GARY P. CARLSON

Bacillary hemoglobinuria is an acute hemolytic disorder caused by *Clostridium haemolyticum* (*Clostridium novyi* type D). Also known as “Nevada redwater,” it has been reported as a naturally occurring disease in cattle and has been experimentally produced in sheep. Clinical signs develop rapidly, and death losses are often seen. Affected animals may manifest severe depression, anorexia, fever, hemoglobinemia, and hemoglobinuria. The disease is endemic in certain poorly drained areas of the western United States and is caused by ingestion of infectious spores. The organism finds a favorable environment for development in areas of preexisting liver damage, most often produced by migrating liver flukes. The hemolytic syndrome results from toxins elaborated by the organism, which also produce a characteristic focal liver lesion. The anemia produced may be marked, and both icterus and evidence of erythropoietic response may be seen in animals that survive for more than a few days. (See Chapter 33.)

37.14 Equine Infectious Anemia

BRETT SPONSELLER

Equine infectious anemia virus (EIAV) is an RNA virus, a member of the Retroviridae family, belonging to the *Lentivirus* genus. It has a structure and genome organization similar to other animal and human lentiviruses. Lentiviruses use virally encoded *reverse transcriptase* to convert the RNA genome to a DNA intermediate that is integrated into the host's genome by another virally encoded enzyme, *integrase*. The integrated DNA intermediate, or provirus, usurps the host cell to replicate its genome, manufacture viral proteins, and assemble the virally encoded proteins into virions, which subsequently bud from the cell. Thus, infection by a lentivirus results in a lifelong, persistent infection. EIAV causes the disease, equine infectious anemia (EIA), first described in 1843 by Lignée.[158] In 1904, Carré and Vallée[159] determined that EIA was associated with a filterable agent, making it the first animal disease determined to be caused by a virus.

37.14.1 Serosurveillance and Detection

EIA is a USDA-regulated disease. In 2003 the USDA estimated that serosurveillance of almost 2 million samples cost U.S. horse owners more than $48 million. USDA-accredited laboratories use a testing scheme that detects the presence of serum antibody to the virus. The Coggins' test, developed by Dr. Leroy Coggins in 1970, provided the first efficient serologic test for detection of EIAV-infected animals; it remains a USDA-accepted test.[160,161] In addition, four ELISAs are licensed tests, one of which is a competitive ELISA (cELISA). These ELISAs detect antibody directed at the transmembrane glycoprotein (gp45) and the p26 antigen.[162] All areas in the United States, Canada, and Mexico accept either the Coggins' test or one of the licensed ELISAs when testing for EIA is required for entry. Equids that cross state lines or that attend many equestrian events are required to be seronegative for EIA; however, the required period of seronegativity between tests varies according to the state. No tests are currently approved by the USDA for diagnosis of EIA based on detection of viral nucleic acid.

Serosurveillance can lead to the detection of horses that are infected with EIAV but that otherwise appear healthy. Indeed, most infected horses are inapparent carriers. However, blood transferred from an inapparent carrier to another horse, through instruments (e.g., needles, nasogastric tubes, dental equipment), blood products, or insect vectors (primarily tabanids), can lead to infection with a fatal outcome.

37.14.2 Clinical Findings

The clinical form of EIA is characterized by three defined, temporal stages of disease: acute, chronic, and inapparent. The *acute stage* occurs with the initial burst of viremia and is characterized by high fever, thrombocytopenia, and nonspecific signs of malaise, including lethargy and inappetence. Ecchymoses and petechiae may also be detected on the mucous membranes. During the *chronic stage,* similar clinical features occur during recurrent episodes of viremia, interspersed with periods of clinical quiescence and low viremia. Throughout the chronic stage the clinical episodes tend to diminish gradually in severity and duration. The *inapparent stage* occurs once levels of viremia are immunologically contained and no clinical signs are detected. Horses experiencing clinical disease at any point may develop DIC and die. In addition, episodes of stress, including transportation, racing, and extreme temperatures, may precipitate clinical disease. Furthermore, corticosteroids have been used experimentally to induce recrudescence of clinical disease.[163]

Other chronic manifestations of EIA include the development of dependent edema, weight loss, anemia, and other ill-thrift signs. Rare manifestations that may develop include leukoencephalitis and enterocolitis.[164] The expression of clinical disease, particularly during acute infection, likely involves multiple factors, including inoculating dose, virulence factors of the inoculating viral strain, immune status and immunogenetics of the host, age, and stress. Indeed, clinical disease occurs concomitantly with high-titer viremia. Horses with high-titer viremia pose the greatest risk of transmission to uninfected horses.

Lentiviruses have a DNA-dependent RNA polymerase (reverse transcriptase) that misincorporates nucleotides, resulting in changes in the viral genome.[165] This mechanism allows for generation of viral variants that differ genetically from preexisting ones. As a result, genetic and antigenic variation of epitopes for neutralizing antibody and cytotoxic T lymphocytes allows viral escape from adaptive immune responses.[166,167] Antigenic variation plays a central role in recurrence of clinical disease throughout the chronic stage of infection and thwarts attempts to develop an effective vaccine.[165]

The EIA virus can replicate effectively in monocytes, dendritic cells, and tissue macrophages.[168–170] In addition, EIAV has been shown to replicate in endothelial cells.[171] EIAV replication in endothelial cells may play a role in the development of DIC by viral damage to endothelial cells, with subsequent exposure of subendothelium.[171] This in turn could lead to platelet aggregation and formation of thrombi.[172] In addition, damaged endothelium may result in development of dependent tissue edema by transudation of fluid through compromised small vessels.[171]

37.14.3 Necropsy Findings and Clinical Pathology

Necropsy examination of horses that die of EIA may demonstrate splenomegaly, lymphadenopathy, hepatomegaly, pronounced hepatic lobular architecture, ecchymoses of the mucosa and viscera, dependent subcutaneous edema, and thrombotic disease of small vessels. Histologic findings may include a mononuclear cell infiltrate of periportal regions of the liver, adrenals, spleen, lymph nodes, meninges, and lungs. Hemosiderophages are frequently detected in the spleen, lymph nodes, liver, and bone marrow. Glomerulonephritis from immune complex deposition is often observed.

Clinicopathologic abnormalities vary depending on the stage and severity of infection. During clinical disease, a frequently profound thrombocytopenia develops concurrently with each successive episode of fever. Platelet function of EIAV-infected horses has been demonstrated to be hypofunctional, possibly exacerbating bleeding tendencies and the progression to DIC in clinically affected equids.[173] Anemia from intravascular hemolysis, extravascular hemolysis, and depression of bone marrow erythropoiesis may progressively develop during the chronic stage of infection.[174] During the inapparent stage, horses typically have increased plasma total solids and globulin concentrations, mild anemia, and decreased albumin concentration.[175] Polyclonal B-cell activation is also evident, suggesting chronic antigenic stimulation despite clinical quiescence.[175] Concomitant fever and thrombocytopenia should prompt immediate consideration of EIA. A history of recurring fever is also suggestive of EIA, particularly when other causes of fever have been ruled out.

37.14.4 Prevention, Control, and Regulatory Considerations

It is well recognized that EIAV seroprevalence varies with the region of the United States.[174] States considered at a high risk include Texas, Oklahoma, Louisiana, and Arkansas, whereas the mid-Atlantic area, New England, Alaska, and Hawaii are considered low-risk regions. The remaining states are classified as intermediate-risk areas. Despite regional differences in risk to noninfected horses, sporadic outbreaks do occur. Veterinarians should therefore encourage all horse owners to test for EIAV annually, test new arrivals, and maintain good fly control. In addition, the veterinary community should encourage organizers of equestrian events to require proof of seronegativity of attending horses. 1162 1163

Once a seroreactor is identified, all contact horses are quarantined and undergo testing until two negative test results at 30- to 60-day intervals are obtained for all individuals in the quarantined herd.[162] The required interval is based on the need to allow recently infected horses to seroconvert. Seroreactors may be either quarantined or euthanized, depending on state regulations. Quarantined horses must be at least 200 yards (180 m) from seronegative animals, the distance shown to be sufficient to obviate viral spread by insect vectors. In addition, seroreactors remaining in permanent quarantine need to be identified. A USDA code number followed by the letter A is assigned to the quarantined horse and permanently applied to the horse as a brand or lip tattoo.

Because an eradication program has never been implemented in the United States for EIA, persistence of reservoirs of horses infected with EIAV must be expected. Indeed, the vast majority of horses in the United States are not tested on an annual basis. To encourage horse owners voluntarily to maintain vigorous surveillance testing, the veterinary community needs to educate owners about the consequences of infection by EIAV. Horse owners are often unprepared to deal with the financial and emotional losses associated with detection of a horse seropositive for EIAV.

37.15 IMMUNE-MEDIATED HEMOLYTIC ANEMIA

37.15.1 Autoimmune Hemolytic Anemia

GARY P. CARLSON

37.15.1.1 Definition and Etiology

Autoimmune hemolytic anemia is associated with the production of autologous antibodies directed against the patient's own RBCs. These antibodies combine with complement and antigens on the RBC membrane, leading to the rapid removal of affected RBCs from the circulation and their accelerated destruction. Autoimmune hemolytic anemia occurs rarely as a primary idiopathic disorder[176,177]; more often it is found secondarily associated with some other primary disease process.[176] An idiopathic immune-mediated hemolytic anemia has been reported in a calf[177] and pony.[178]

37.15.1.2 Clinical Signs and Differential Diagnosis

The presenting clinical signs of animals with autoimmune hemolytic anemia are quite variable, depending on the degree of anemia and the primary disease. Animals with marked anemia (PCV <15%) manifest signs typical of those seen in any animal with a severe hemolytic anemia (i.e., depression, pale mucous

membranes, variable icterus, elevated heart and respiratory rate, variable to intermittent fever). Secondary autoimmune hemolytic anemia in horses has been associated most often with some other primary problem, such as purpura hemorrhagica, lymphoma, other neoplasms, protein-losing enteropathy, or chronic bacterial infections.[179,180] Clinical features are typical of the primary problem, with additional findings of a hemolytic anemia. In humans, exposure to a wide variety of drugs has been causally associated with the development of autoimmune hemolytic anemia. A number of studies report an association between procaine penicillin and autoimmune hemolytic anemia in horses.[82,181–185] Autoimmune hemolytic anemia was reported in a 10-year-old horse treated with trimethoprim-sulfamethoxazole.[186] This apparently occurs rarely, perhaps only in specific individuals, but drug history should be ascertained in all animals with an otherwise unexplained hemolytic anemia.

The anemia in cattle with anaplasmosis and babesiosis or in horses with equine infectious anemia, piroplasmosis, or ehrlichiosis is largely the result of an immune-mediated hemolytic process. These diseases are discussed fully elsewhere in this book.

37.15.1.3

Clinical Pathology

The hemolytic process often is rapid and persistent, leading to a pronounced anemia. The hematologic features are those typically expected for a responsive hemolytic anemia. The anemia often is progressive and may become severe, even life threatening (i.e., PCV <10%). Erythrophagocytosis and autoagglutination may be noted on blood smears. Spherocytosis may be difficult to recognize in large animals because of the relatively small cell size and lack of a clear area or central pallor of the erythrocytes from these species. If the process has been present for 4 days or more, hematologic evidence of active erythropoietic response may be seen in the peripheral blood of all species except the horse. This evidence of bone marrow response is a favorable prognostic indicator, even when the anemia is quite advanced. A moderate neutrophilic leukocytosis is a common feature, and thrombocytopenia may be noted in some individuals if the autoimmune process is directed at platelets and megakaryocytes, as well as the erythrocytes.

37.15.1.4

Diagnosis

Documentation of the presence of antierythrocyte antibodies and complement on the RBC membrane is based on the direct Coombs' test. The indirect Coombs' test detects antierythrocyte antibody in the serum. It is important to remember that the Coombs' test is based on species-specific reagents. These reagents are commercially available in the United States for small animals and horses, and not all diagnostic laboratories will have suitable Coombs' reagents for other species. Special procedures may be necessary to adsorb these reagents to avoid nonspecific reactions. Multivalent Coombs' reagent directed against IgG, IgM, and complement is most often used. The Coombs' test usually is conducted at body temperature and also in the cold. A positive reaction at body temperature indicates that the antibodies are primarily IgG. These warm antibodies are associated more frequently with anemia, generally produce a more severe anemia, and tend to be more responsive to corticosteroids than the cold-reacting antibodies. The cold-reacting antibodies detected with the saline agglutination test run at 25° C and 4° C (39° F and 77° F) are primarily of the IgM class. Exposure to a cold environment may be necessary to produce clinical signs associated with cold agglutinin disease. Both the warm-reacting and the cold-reacting antibodies are capable of fixing complement. Unfortunately, the Coombs' test is not always positive in affected animals. Approximately one third of human and canine patients with autoimmune hemolytic anemia have a negative direct Coombs' test, possibly because of low concentrations of antibody or low binding to the RBC membrane. The diagnosis in these patients depends on ruling out other causes of a responsive hemolytic anemia and on the response to

corticosteroid therapy. Direct immunofluorescence with flow cytometry was used to determine the classes of antibody bound to erythrocytes in three horses and 12 dogs with immune-mediated hemolytic anemia. The three horses had surface-bound IgG, including a horse with suspected penicillin-induced hemolytic anemia, a foal with neonatal isoerythrolysis, and a foal with clostridial septicemia.[187] 1163 1164

A substantial proportion of otherwise normal horses have small amounts of cold-reacting Coombs' antibodies, and spontaneous agglutination may be noted in blood sample tubes exposed to the cold. In most cases these cold agglutinins appear to occur naturally and, at low levels, are of little clinical significance. Prior treatment with corticosteroids may inhibit antibody production and could lead to a false-negative Coombs' test.

37.15.1.5 Pathophysiology

Autoimmune hemolytic anemia rarely has been reported as a primary or idiopathic process in large animals; however, immune-mediated anemia occurs more often as a secondary problem (1) in association with certain types of neoplasia; (2) with a variety of viral, bacterial, rickettsial, and protozoal infections; (3) after exposure to certain drugs; or (4) in association with other immune-mediated disorders, such as systemic lupus erythematosus.[188] The initiating factors for this autoimmune disorder are not completely understood but may be related to alterations in the RBC membrane through direct or indirect injury, which elicits an abnormal response by the immune system. The RBC membrane is no longer recognized as “self” and is treated as a foreign antigen. Alternately, changes in the immune system or stimulation by some other antigenic source may result in production of antibodies with a misdirected cross-reactivity with the patient's own normal erythrocytes. Structural and functional changes in the RBC membrane are induced by the antigen-antibody reaction and complement fixation. The complement-fixing IgG or IgM antigen-antibody reaction may produce sufficient RBC damage to result in intravascular lysis of erythrocytes, but more often, affected cells are removed from the circulation at a rapid rate by the reticuloendothelial system of the liver and spleen. Partial phagocytosis of affected cells may result in spherocyte formation. Although the presence of spherocytes on blood smears is a characteristic diagnostic feature in human and canine patients with autoimmune hemolytic anemia, the relatively small size of RBCs of most large domestic animals may make it difficult to recognize spherocytes.

37.15.1.6 Treatment and Prognosis

The approach to treatment of autoimmune hemolytic anemia depends on the causal factors. If the animal has a history of drug therapy, it is advisable to discontinue medication or to change to another class of drug. Patients with primary or idiopathic autoimmune hemolytic anemia may be the best candidates for treatment. Immune-mediated hemolytic anemias secondary to other diseases can only be managed if the primary problem is amenable to treatment. Thus, treatment of an immune-mediated hemolytic anemia in a patient with extensive lymphoreticular neoplasia is likely to be unrewarding, and thorough diagnostic efforts should precede case selection for treatment. Although immune-mediated processes are responsible for hemolytic anemia in a number of infectious diseases, therapy must be directed at the primary agent, and corticosteroids are contraindicated in these diseases. Corticosteroids can cause recrudescence of viremia in horses with EIA, and a negative Coggins' test should be a prerequisite to treatment of horses with an autoimmune hemolytic anemia of undetermined cause.

Treatment of autoimmune hemolytic anemia is directed at providing supportive care and interrupting the immune response responsible for antibody production. This is usually accomplished with systemic

glucocorticoids. For a 450-kg horse, dexamethasone is recommended at an initial dosage of 30 to 40 mg/day given parenterally. This rate is continued for 3 to 5 days, then decreased gradually over 7 to 14 days, depending on the response to therapy; the hematologic response should be closely monitored. If there has been no response in 5 to 7 days, the diagnosis of autoimmune hemolytic anemia should be reviewed, and potential causes of bone marrow suppression should be evaluated. Once the hemolytic process is well under control, oral prednisolone can be given at 400 to 500 mg daily. Human patients and small animals with immune-mediated hemolytic anemia unresponsive to corticosteroids are often treated with cyclophosphamide. There is one report of successful management of a horse with cyclophosphamide and azathioprine when the anemia failed to respond to corticosteroids.[189] Supportive care consists of providing a quiet, restful environment and good nutrition, including vitamin supplementation. Iron- and copper-containing hematinics are generally of little benefit because neither of these elements is lost with hemolytic anemia. Blood transfusion is also of little benefit because it is often impossible to find a compatible donor, and the transfused cells are rapidly removed from the circulation. Blood transfusion should not be administered unless the anemia is life threatening and the immune response can be controlled with corticosteroids.

37.15.2 Neonatal Isoerythrolysis in Horse and Mule Foals

MONICA ALEMAN

Neonatal isoerythrolysis (NI) is the most common alloimmune disease in neonatal foals 7.5 hours to 12 days old (median. 2.5 days).[190] NI is characterized by hemolytic anemia, icterus, and hemoglobinuria. Clinicopathologic abnormalities include anemia, high serum indirect and direct bilirubin concentrations, and sorbitol dehydrogenase activity. NI is caused by a blood group incompatibility between the foal and dam. The foal inherits from the sire and expresses an erythrocyte antigen (alloantigen) that is not present in the mare. The hemolytic syndrome is mediated by maternal antibodies against foal erythrocytes (alloantibodies) absorbed from colostrum. Blood factors associated with NI in horse foals are Qa, Qb, Qc, Aa, Pa, and Dg, and donkey factor in mule foals.[190] The most common antigens are Qa and Aa. Foals with NI may also present with alloimmune thrombocytopenia. (See Chapters 19 and 53.)

37.16 HEINZ BODY HEMOLYTIC ANEMIA

GARY P. CARLSON

MONICA ALEMAN

37.16.1 Definition and Etiology

An acute hemolytic anemia can develop after exposure to a variety of oxidizing agents. These include drugs such as phenothiazine, methylene blue, and acetylphenylhydrazine and plants such as wild or domestic onions, members of the Brassica family (rape or kale), and wilted or dried leaves of the red maple *(Acer rubrum)*.[191–197] Red maple toxicosis (RMT) has been reported in horses, zebras, and alpacas.[195,198–200] Heinz body hemolytic anemia also occurs in sheep on specially formulated diets that are low in molybdenum, which results in chronic copper toxicity, as herd problems in cattle grazing rye grass *(Secale cereale)*[201] or selenium-deficient pastures in Florida,[202] and with selenium deficiency as a contributing factor in postparturient hemoglobinuria of cattle in New Zealand.[203] These agents produce or allow oxidative denaturation of hemoglobin and resultant

aggregation of the protein globin, which appears as Heinz body inclusions within the RBCs. Heinz body anemia has been seen in association with lymphoma in a horse, possibly from failure of the reticuloendothelial system (RES) to remove the Heinz bodies, as reported in horses with EIA.[204]

37.16.2 Clinical Signs and Differential Diagnosis

Clinical signs vary with the species involved, specific toxin or toxic metabolites, amount of toxin ingested, time course of the disease process, and occurrence of complicating secondary factors, such as hemoglobin nephrosis and acute renal failure. Weakness, lethargy, anorexia, and exercise intolerance are the usual presenting complaints, and death losses can occur. Mucous membranes are generally pale with variable to marked icterus. The heart and respiratory rates are generally elevated, but rectal temperature is usually within normal limits. Horses with RMT may be subclinical or may present with lethargy, muddy or cyanotic mucous membranes, tachycardia, inappetence, weakness, colic, icterus, brown discoloration of the blood, and pigmenturia. Rarely, sudden death occurs.[200] Pyrexia and hypothermia have also been documented. Most horses develop clinical RMT during summer and fall. The high mortality rate in horses with RMT may relate to the combination of a rapidly progressive hemolytic anemia and the formation of methemoglobin. Urine output may be reduced, and the urine may be dark because of the presence of hemoglobin, methemoglobin, or bilirubin.

It is not possible to differentiate Heinz body hemolytic anemia from other potential causes of hemolytic anemia without laboratory evaluation. The absence of fever may help to differentiate these anemias from infectious causes of hemolytic anemia. History of exposure to potential oxidizing agents and the fact that these toxic plants may produce death losses or clinical signs in multiple animals at the same time should help to differentiate these cases from autoimmune hemolytic anemia.

37.16.3 Clinical Pathology

Poisoning or intoxication resulting in Heinz body formation usually causes acute and profound anemia. In the early stages a very high percentage of erythrocytes may have Heinz body inclusions. Later, as these cells are removed from the circulation and replaced by young cells from the bone marrow, the relative number of affected cells may decrease greatly. Heinz bodies are round, oval to serrated, refractile granules usually located near the cell margin or protruding from the cell and best visualized with vital stains such as crystal violet or new methylene blue applied to unfixed blood smears. Heinz bodies appear as bluish green inclusions with the new methylene blue stain. Fixing of blood smears with methanol in preparation for staining with the classic Wright's stain interferes with stain uptake, and Heinz bodies appear as a pale area within or projecting from the cell margin and can easily be missed. After the first 3 or 4 days, the anemia is usually associated with hematologic evidence of an active erythrogenic response in all species except the horse. The total plasma proteins usually remain within normal limits, and the Coombs' test is negative. Red maple poisoning also results in depleted RBCs, reduced glutathione, methemoglobinemia, increased osmotic fragility, and modest elevations of liver-derived serum enzyme activities.

The rapid and profound erythrocyte destruction may lead to hemoglobinemia and hemoglobinuria. The development of renal failure secondary to hemoglobin nephrosis is a definite risk in these animals and is reflected by modest to marked increases in the blood urea nitrogen (BUN) and creatinine, as well as changes in the urinalysis.[196,197] These parameters should be monitored in severely affected animals. As with other causes of hemolytic anemia, serum bilirubin, particularly the indirect reacting bilirubin, is elevated.

The clinicopathologic abnormalities of horses with RMT include anemia (PCV as low as 7.5%), eccentrocytes, Heinz bodies, and elevated plasma methemoglobin concentration.[200] Other significant findings consist of inflammatory leukogram and renal insufficiency (75% and 40% of cases, respectively).[200] Mild elevation of serum total bilirubin is observed in most cases, and hemoglobinuria is seen in all affected patients.

37.16.4 Pathophysiology

Heinz bodies are formed by the precipitation of oxidatively denatured hemoglobin. The hemoglobin contained within the RBC is constantly undergoing mild oxidative stress associated with oxygen transport, as well as generation of superoxide radicals and hydrogen peroxide within the cell. A number of reducing mechanisms within the RBC counteract these oxidative processes through production of NADPH and reduced glutathione. The occurrence of Heinz body hemolytic anemia could be viewed as a consequence of exposure to oxidative stresses that simply overwhelmed the cells' reductive capacity. Selenium deficiency results in a decrease in glutathione peroxidase, a selenium-containing enzyme; in special circumstances, selenium deficiency may contribute to Heinz body formation by impeding the ability of the cells to respond to oxidative stress. Substantial species variation in the rate of Heinz body formation relates to the chemical structure of hemoglobin and the efficacy of erythrocyte-reducing mechanisms in the face of oxidative stress.[191] RBCs with Heinz bodies are less deformable than normal cells and are rapidly removed from the circulation by the RES in the spleen, where they are phagocytized and broken down. Old or senescent erythrocytes are thought to be more prone to develop Heinz bodies. Splenectomy or corticosteroid therapy may alter Heinz body clearance mechanisms, allowing significant numbers of affected RBCs to remain in the circulation of otherwise normal animals.

Gallic acid is a strong oxidant present in red maple leaves. Gallic acid has been implicated in the oxidation of hemoglobin, methemoglobin formation, and Heinz body anemia.[195,196,205] Methemoglobin is the result of oxidative change of hemoglobin iron to the nonfunctional ferric state (see discussion of nitrate poisoning, Chapter 54). This is normally prevented by glutathione reductase, ascorbic acid, and reduced glutathione. Methemoglobin cannot load or transport oxygen and, when present in sufficient quantities, results in a brown color of peripheral blood and mucous membranes. An estimation of methemoglobin concentration in a blood sample can be made by comparing the hemoglobin concentration measured by the cyanmethemoglobin method, which measures all forms of hemoglobin, with that measured by the oxyhemoglobin method, which only measures oxyhemoglobin, not other forms such as methemoglobin. Methemoglobinemia and hemolytic anemia have been reported in a mare and her dam in association with decreased levels of RBC glutathione and glutathione reductase, presumably as a result of an inherited enzymatic defect.[206]

37.16.5 Treatment

Treatment primarily involves removal from the source of toxicity and provision of supportive care. Blood transfusion can be very beneficial in severely anemic patients, particularly when there is insufficient evidence of active erythropoietic response. Iron-containing hematinics are of little benefit. Intravenous fluid therapy is indicated in animals with hemoglobinuria or azotemia to reduce the potential for further renal damage. High doses of vitamin C (ascorbic acid, 50 to 100 g IV daily), together with fluids and transfusion, were thought to aid recovery in two horses with red maple poisoning.[207] One report suggests that vitamin C therapy may have little impact on survival of affected horses, and when methylene blue was used to treat the associated methemoglobinemia in two horses, both died.[208] The goal of therapy should be to improve tissue oxygenation

and perfusion and control inflammation and pain (use of NSAIDs). Horses treated with corticosteroids have an increased likelihood of death.[200]

37.16.6 Prognosis

Prognosis in animals with modest anemia and evidence of response is good if the inciting factor can be controlled or eliminated. The mortality rate of horses with experimental or naturally occurring RMT is reported to be 60% to 65%.[208] In animals with rapidly progressive and profound anemia, prognosis is poor unless blood transfusion is undertaken. Complications are associated with hypoxia, hypoperfusion, and inflammation. Horses may develop acute renal failure, colic, pyrexia, and laminitis. A recent retrospective study of 32 horses reported a fatality rate of 59%.[200] It has been proposed that the severity of anemia is associated with mortality, but the previous study showed no such association.[200]

37.17 OTHER CAUSES OF HEMOLYTIC ANEMIA

37.17.1 Intravascular Hemolysis Following Cutaneous Burns

MONICA ALEMAN

Intravascular hemolysis has been reported in horses after severe cutaneous burns affecting more than 25% of their body surface. Plasma on admission showed hemolysis along with abnormal RBC morphology, increased osmotic fragility, hemoglobinuria, azotemia, and hemoglobin pigment nephropathy.[209] The pathophysiology of hemolysis is unclear but suspected to be associated with the production of hydroxyl radicals by complement-activated neutrophils. Abnormal findings reported in humans include intravascular hemolysis, increased RBC osmotic fragility, decreased membrane deformability, RBC crenation, eccentrocytosis, spherocytosis, bud formation, fragmentation, and vesiculation.[210] Presence of these abnormalities depends on the severity of burn trauma.[210] Pseudothrombocytosis has been reported, presumably caused by the incorrect recognition by automatic counters of RBC microvesicles as platelets.[210] Early fluid therapy and free-radical scavengers have been beneficial for the treatment of burns in humans, along with supportive and wound care, control of pain and inflammation, and prophylaxis of sepsis. A recent murine study suggested that the level of plasma free hemoglobin is related to the size and depth of burn injury, which may be difficult to determine in some cases.[211]

37.17.2 L-Tryptophan—Indole Intoxication

GARY P. CARLSON

Experimental studies in ponies have demonstrated an acute hemolytic process associated with orally administered L-tryptophan, which is converted to indole in the GI tract.[212] Intoxication was associated with an acute onset of restlessness, tachypnea, intravascular hemolysis, and hemoglobinuria. At necropsy there was evidence of hemoglobinuric nephrosis and bronchiolar degeneration in some ponies. Similar clinical signs were noted after oral administration of tryptophan at 0.35 to 0.60 g/kg and indole at 0.1 to 0.2 g/kg.[212,213] Intravascular hemolysis was associated with increased osmotic fragility and with Heinz body formation in a few of the experimental ponies.

37.17.3 Water Intoxication

GARY P. CARLSON

Massive water intake may produce marked hypotonicity of the body fluids, with subsequent intravascular hemolysis of erythrocytes.[214] This problem has been described as a naturally occurring entity in milk-reared calves when first given access to unlimited quantities of water.[215,216] Severe neurologic signs may be seen, including depression, convulsions, and coma; respiratory distress, hemoglobinuria, and death losses occur in some cases. Clinicopathologic features include hemolytic anemia, hypoproteinemia, hyponatremia, hypochloremia, hyposmolality, hemoglobinuria, and hyposthenuria. A sudden decrease in serum osmolality is believed to result in osmotic lysis of erythrocytes.[217] Fragility of the erythrocytes to osmotic shock is greatest in calves between 4 and 5 months of age. Treatment is primarily a matter of temporarily restricting water and providing supportive care. Calves with marked hyponatremia (sodium 110 mmol/L) that are manifesting neurologic signs may benefit from hypertonic saline, mannitol, and corticosteroids. The goal of treatment is the restoration of serum sodium to 120 to 125 mmol/L without overcorrection. Death losses can occur in as soon as 2 hours, but most calves recover without long-term adverse effects.

37.17.4 Postparturient Hemoglobinuria

GARY P. CARLSON

A syndrome of intravascular hemolysis, hemoglobinuria, and anemia has been recognized in postparturient dairy cattle worldwide.[218] The disease occurs sporadically, and the incidence is relatively low. Affected animals are most often high-producing multiparous cows that develop clinical signs during the first month after calving.[219] Depression, decreased feed consumption, and decreased milk production are associated with hemoglobinuria, anemia, and icterus. The anemia is often marked and after 4 or 5 days is associated with evidence of a strong erythropoietic response. The precise mechanism causing the intravascular hemolysis has not been fully defined. The condition has been related to the marked hypophosphatemia often found in affected cows and the moderately low phosphate levels in unaffected herdmates. Hypophosphatemia arises from inadequate dietary phosphorus intake in animals grazing phosphorus-deficient soils or fed fodder grown on such soils. Low intracellular phosphate concentration may interfere with energy metabolism, thus affecting cell viability and the ability of RBCs to deal with potential hemolysins, such as saponins from sugar beets or alfalfa. A postparturient hemolytic problem has been described as a herd problem in New Zealand associated with copper deficiency and Heinz body formation[203] (see previous section).

Blood transfusion and supportive IV fluids are indicated in valuable cows with severe life-threatening anemia. Treatment of hypophosphatemia consists of provision of phosphate, initially as sodium acid phosphate ($NaH_2PO_4H_2O$), 60 g/300 mL of water IV, followed by oral phosphorus supplementation. Correction of dietary imbalances is indicated.

37.17.5 Copper Toxicosis

LISLE W. GEORGE

Copper is an essential nutrient for domestic animals, but excessive supplementation can result in toxicity. Copper poisoning is a common intoxication in ruminants. The toxicodynamics and clinical syndromes have been reviewed.[220–222] Lambs are most susceptible to the effects of copper, but poisonings have occurred in adult sheep, goats, and cattle. Merino sheep are more resistant than British breeds to the toxic effects of copper.[223] Cattle have been poisoned by ingesting diets containing 37 mg of copper/kg of feed for 2 years.[224] Cattle fed 12 mg or more of copper/kg have been reported to develop subclinical hepatic disease.[225]

1166
1167

37.17.6 Pathogenesis

Elemental copper is an essential trace mineral that has a narrow therapeutic window. Dietary requirements for growing sheep range between 4 and 6 parts per million (ppm), but toxicity can occur whenever sheep are exposed to diets containing as little as 10 to 20 ppm.[226–228] Phytogenous copper poisoning results from concomitant ingestion of copper at 20 ppm of food, molybdenum, and sulfate. Ingested salts of copper are absorbed through enterocytes by carrier proteins and transported to blood in loose complexes with albumin and amino acids.[229] Ionized copper is approximately 20% of the total plasma copper. Between 70% and 90% of the ionic copper is internalized by hepatocytes, where it is redistributed to bile, packaged in lysosomes in protein complexes, or used for the formation of ceruloplasmin.[229] Accumulation of copper occurs because daily hepatic biliary copper excretion amounts to less than 1% of ingested copper in ruminants.[230] Hepatic storage can buffer high levels of copper intake until the sites become saturated. At that time, hepatocytes die spontaneously or in response to environmental stress or dietary changes. Hepatocyte death causes the release of large amounts of cuprous copper into the blood. Animals that have preexisting hepatitis from pyrrolizidine alkaloids store less copper and are more susceptible to the hemolytic crisis.[223,231]

Free inorganic copper is an oxidant and can participate in Fenton's reaction. Cellular damage is related to the production of oxidative hydroxides and peroxides, but not to copper oxidation. These reactive intermediates are thought to initiate lipid peroxidation and oxidative denaturation of proteins within erythrocytes. Oxidation of heme protein produces Heinz bodies, and oxidation of the hemin produces methemoglobinemia. Oxidized erythrocytes spontaneously lyse intravascularly, or they are sequestered in the spleen and degraded to constituent amino acids. Vitamin E is also denatured. This latter reaction removes a potent antioxidative protective factor and enhances the cellular susceptibility to additional oxidants. Differences in genetic susceptibility to copper poisoning are unknown.

The hemolytic phase of copper poisoning is often initiated by noxious stimuli that could include shipping, hierarchic change, administration of oxidative drugs, starvation, or change of housing.[232] Feeding of high-protein diets has increased the resistance in sheep to the hemolytic crisis; however, the role of extra molybdenum intake in these supplemented animals was unclear.[228,233] The mechanistic relationship between the stressful events and the hepatocyte release of copper is unknown.

37.17.7 Etiology

Sources of copper that have been responsible for copper accumulation in animals include trace-mineralized salt, inappropriately formulated cereal grain mixtures, forages from pastures fertilized by swine or chicken manure,[234] orchard pastures contaminated by copper-containing fungicides, rations containing more than 20% chicken litter, and diets that contain high concentrations of palm kernel oil. Other potential sources of copper accumulation include fencing and copper piping and overdoses of parenterally administered copper salts. In one

recent case at the University of California, Davis, dairy goats were poisoned by supplementation of trace minerals that were formulated for dairy cattle.

The toxic dose of copper for each species is variable and depends on the duration of exposure, the animal's genetics, and the amount of molybdenum being fed. Diets that contain copper/molybdenum ratios greater than 6:1 are more likely to result in copper poisoning than diets with lower ratios. The interaction between the two minerals may occur in the solid phase of rumen ingesta, when insoluble and nonabsorbable complexes of copper, sulfur, molybdenum, and large—molecular-mass protein are formed. The highly complexed copper is unabsorbed and thus not toxic. High dietary intake of zinc and iron also inhibits absorption of copper, and although the precise mechanism of antagonism is unknown, the elements share a competitive affinity for metallothioneine.[235–237] Competition for this protein could alter the storage capacity for copper. Soil sulfates reduce molybdenum absorption by plants, thereby increasing the potential for pathologic accumulation of copper in herbivores.

The respective single toxic doses of copper for sheep and cattle range from 20 to 110 mg/kg and 220 to 880 mg/kg body weight. Most poisonings occur after a long-term, low-dose ingestion of the element. Copper poisoning can occur in sheep after 2 months of daily dosing of 3.5 mg/kg copper, feeding a ration that contains 20 ppm copper for several months, or after a single subcutaneous injection of copper—ethylenediaminetetraacetic acid (EDTA) salt at 2.0 mg/kg.[238] Sheep have been poisoned by subcutaneous injection of 3 to 4 mg/kg copper-calcium EDTA, but remained normal after 6 mg/kg copper methionate.[239] Sheep have died after single injections of 2 mg/kg diethylamine copper oxyquinoline sulfonate.[239] One study that fed 3.7 mg copper/kg daily for 84 days reported peak hepatic copper levels between 258 and 375 mg/kg wet weight by 26 days after the final copper feed.[240] A single dose of 50 mg copper caused acute hemolytic crisis in sheep when treated during midpregnancy. The highest incidence of hemolytic anemia occurred in Welsh sheep, with a lower cumulative incidence in Cheviot sheep.[241] Single doses of copper-calcium ETDA at 25 mg/animal has killed lambs.[242] Cumulative doses of copper ranging between 12.8 and 22 g have produced hemolytic anemia in Suffolk lambs by 42 days.

Goats may show signs of copper poisoning by 144 days after daily feeding of a ration that contains 80 mg copper/kg. Placental transfer of copper occurs, but concentrations in the tissues of lambs are not toxic, even during the hemolytic phase in the dam.

Adult cattle may be poisoned by feeding 5 g copper sulfate daily for as long as 4 months. Calves may be poisoned after 6 to 8 weeks of feeding milk replacer containing 115 ppm copper.[229,243] Horses are resistant to high dietary concentrations of copper and may remain clinically normal after prolonged feeding of diets containing levels as high as 791 ppm. In these horses, hepatic concentrations of copper at the end of the feeding period reached 4000 ppm. Adult ponies treated once with oral copper at 40 mg/kg did not develop hemolytic anemia.

37.17.8 Clinical Signs

Animals that have been exposed to high levels of copper are asymptomatic for weeks until the onset of hepatic necrosis.[244,245] Signs develop rapidly after the onset of hepatic necrosis and reflect coexisting anemia, myopathy, and neurologic, renal, or hepatic disease. Clinical signs include inappetence, lethargy, weakness, recumbency, cool extremities, pallor, and grayish discoloration of the mucous membranes. Affected animals have a greatly increased pulse rate, tachypnea, hypotension, and hypothermia. The pulse amplitude of the

linguofacial artery is decreased. Urine is dark red due to the presence of free hemoglobin products. The animals may have marked petechiation of the conjunctival mucosa. Pregnant animals often abort because of hypoxemia. Feces are dark or have yellowish discoloration, but are normally formed, and do not contain hemoglobin unless secondary abomasal ulceration has occurred. Recumbent patients usually expire without struggling. Exposed ewes that survive copper poisoning tend to have dystocia and dilation failure in subsequent lambing periods.

37.17.9 Pathology

The tissues of hemolyzing animals are pale and icteric. The serous surfaces are covered by petechial and ecchymotic hemorrhages. The liver is often pale and yellow, and the lungs are firm. The kidneys are black and have a metallic sheen because of entrapped hemoglobin. The urinary bladder of copper-poisoned animals is filled with serosanguineous urine. Microscopic changes include hemoglobinuric and tubular nephrosis, as well as necrosis of the splenic follicles and hepatocytes. There is also biliary ductular proliferation and pericholangitis.[240,246] Hepatic necrosis may be detectable by microscopic examination for as long as 412 days after poisoning. Microscopic changes in the brain of poisoned animals include spongy degeneration of the pons and brainstem.

37.17.10 Diagnosis

Normal hepatic copper concentrations in sheep have been reported as 173 ± 130 ppm (mean ± SD) and 129 ± 59 ppm (wet matter) for adults and lambs, respectively.[247] Wet matter hepatic concentrations of copper in poisoned animals were 429 ± 249 ppm. Dry weight concentrations may be greater than 3000 ppm. Hepatic concentrations are usually high before and after the hemolytic episode, but normal hepatic copper concentrations in hemolyzing animals have been reported.[238] The correlation between plasma and hepatic copper concentrations in prehemolytic animals is poor.[248,249] Copper poisoning in animals with normal plasma concentrations and near-toxic liver levels has been reported.[250] Normal plasma copper concentrations range from 13 to 20 μmol/L (0.8 to 1.2 μg/mL).[240] Serum copper concentrations range between 0.60 and 1.50 μg/mL (0.6 to 1.5 ppm). Plasma copper concentrations that range between 2.4 and 20.0 μg/mL (2.4 to 20 ppm) are diagnostic of acute toxicosis.

37.17.11 Clinical Pathology

There are no consistent hematologic changes until 24 hours before the hemolytic crisis, when sudden concentrations of cytosolic hepatic enzymes increase coincidentally with a sharp rise in plasma copper concentration. Plasma copper concentrations fall rapidly after the hemolytic crisis and are often near normal by 4 days posthemolysis.[244] The concentrations of copper within erythrocytes remain high.

Hepatic concentrations of 16 mmol copper/kg of dry matter are the threshold for development of hemolytic anemia. The half-life of copper in the liver of nontreated poisoned sheep has been estimated at 175 ± 91 days, [240] and high copper concentrations in hepatic tissues can be found for as long as 100 days after the initiation of the hemolytic episode.[248]

Kidney concentrations of copper in animals with hemolytic crisis are 15 and 50 ppm for dry and wet weight volumes, respectively. Sheep may have increased plasma concentrations of γ-glutamyltransferase (GGT) and aspartate aminotransferase (AST) for 3 days before onset of hemolysis, and glutamate dehydrogenase may be

increased for as long as 700 days after cessation of copper ingestion.[240,251] Fecal copper concentrations may exceed 10,000 ppm during the hemolytic episode.

Clinicopathologic changes that occur during the acute hemolytic crisis include Heinz body formation; intravascular hemolysis; methemoglobinemia (as much as 5%); decreased PCV; increased concentrations of plasma bilirubin, AST, GGT, alkaline phosphatase, total bilirubin, creatine kinase, creatinine, and plasma urea nitrogen; and increased plasma ceruloplasmin. Urine is dark brown to black and contains high concentrations of protein, blood, and hemoglobin casts. Microscopic examination of urine may detect erythrocytic casts and inflammatory cells.[252] Sheep that survive the hemolytic episode develop reticulocytosis by 4 days after onset of clinical signs.[253]

37.17.12 Treatment

Animals with acute hemolytic syndrome should be treated with insufflated oxygen and vitamin E (three to five daily doses of 3000 IU/dose). If PCV is less than 8%, animals should be given packed, washed homologous erythrocytes. Additional therapy should include D-penicillamine (Cuprimine* at 52 mg/kg daily for 6 days), anhydrous sodium sulphate (1 g/sheep daily for 6 days), and ammonium molybdate (100 mg/sheep daily for 6 days). D-Penicillamine therapy increases urinary copper excretion by 10- to 20-fold.[254] Single-dose therapy with D-penicillamine (28 mg/kg) increases copper excretion, but the effect is transient and insignificant for reducing the total hepatic copper load.[255]

Dietary supplementation with 7.7 ppm ammonium molybdate also results in hepatic copper concentrations that are 40% lower than in unsupplemented controls. Addition of 7 or 15 mg molybdenum for 80 days to experimentally poisoned sheep has reduced hepatic copper concentration in sheep by 34% and 46%, respectively.[256] Copper-poisoned cattle have been successfully treated with oral sodium molybdate (3 g daily) and sodium thiosulphate (5 g daily). When introduced into the sulfur-rich rumen contents, molybdenum salts complex with high—molecular-weight proteins in the solid phase of the digesta.[257] The protein-bound thiomolybdate aggregates strongly chelate copper in insoluble and indigestible complexes. Molybdenum salts also enhance biliary copper excretion and remove copper selectively from hepatic metallothioneine.[235,258,259] For poisoned cattle, top dressing of food with 500 to 1000 mg ammonium molybdate daily for 18 days greatly reduced the amount of hepatic copper.[260]

Parenterally administered ammonium tetrathiomolybdate has been recommended for treatment of acute hemolytic crises caused by copper poisoning. Intravenous administration of ammonium tetrathiomolybdate reduces both lysosomal and cytosolic copper in hepatocytes. The drug has been given at 0.2 mg/kg molybdenum (thiomolybdate), as IV injections of 50 to 100 mg twice weekly for up to 11 weeks, or as three doses of 3.4 mg/kg on alternate days and beginning at the onset of hemolytic crisis.[261–265] Concomitant administration of 36 mg xylazine IV increased copper excretion in bile by as much as 2.25-fold over controls that were treated with thiomolybdate only.[266] The parenteral administration of the thiomolybdate results in transient increases of copper concentrations in blood for as long as 24 hours. Because copper is acid insoluble, the effect is to protect the copper-exposed animals from hemolytic crises and reduce the tissue damage during an hemolytic event.[267,268] Biweekly injection of 100 mg molybdenum as tetrathiomolybdate increased daily hepatic biliary copper excretion by a factor ranging between 150% and 300%.[269]

* Merck Sharp & Dohme, Rahway, NJ.

37.17.13 Prevention

Because of the sporadic nature of the poisoning and lack of signs during the accumulative phase, copper poisoning can be difficult to prevent. Clients should be counseled to purchase concentrates with label claims for the species that are being supplemented. Copper-supplemented salts should be restricted, especially in sheep. Heavily copper-contaminated pastures can be top-dressed with molybdenum phosphate at 113 g per acre. Fencing and plumbing that contain copper sulfate or metallic copper should be removed from the environment. One study controlled the hemolytic crisis and associated mortality from copper poisoning in sheep receiving 36 mg copper/kg daily for 18 months, by subcutaneous (SC) injection of sterile ammonium tetrathiomolybdate containing 3 to 4 mg molybdenum on alternate days for three injections.[264] The sheep in this study were given either IV or SC molybdenum at dosages that amounted to 1.7 and 3.4 mg/kg ammonium tetrathiomolybdate. Addition of ammonium molybdate at 7.7 ppm and sodium sulfate at 4200 ppm reduced liver copper and decreased plasma ceruloplasmin in experimentally exposed lambs.[249]

Feeding of sodium molybdate and sodium sulfate at respective daily dosages of 20 mg and 6 g to experimentally poisoned lambs reduced hepatic copper content after 90 days.[270]

Molybdenum and sulfur protect sheep by converting ingested copper to nonabsorbable thiomolybdate complexes in the rumen. The antagonistic effects are greatest at times of rapid hepatic accumulation of copper. Addition of 3 mg/kg of food (dry matter) molybdenum as tetrathiomolybdate reduced hepatic copper accumulation by as much as 33-fold.[263] Lambs that were fed diets containing 7.7 ppm ammonium molybdate after weaning until 14 weeks of age had reduced hepatic copper and decreased ceruloplasmin concentrations.[249] Cattle can tolerate indefinite periods of feeding copper at dosages less than 0.6 mg/kg daily.[250] Addition of 220 to 420 ppm zinc may be protective against copper poisoning in sheep, but this is not used in clinical situations.[257]

37.17.14 Hemolytic Syndrome in Horses with Liver Failure

GARY P. CARLSON

A fulminant, intravascular hemolytic syndrome has been reported as a near-terminal event in horses with either acute or chronic liver failure.[271] Marked hemoglobinemia and hemoglobinuria are associated with intense icterus. The sclera and conjunctiva often take on a distinctive, deep—reddish orange color. The onset of intravascular hemolysis is sudden and rapidly progressive. The prognosis is highly unfavorable because almost all horses that develop this syndrome die or must be euthanized because of clinical deterioration.[272] Intravenous fluids, corticosteroids, and supportive care do not appear to alter the clinical course or the unfavorable outcome.

The cause of this syndrome has not been determined, but apparently it is not related to a release of hepatic copper stores. The hemolysis appears to be associated with increased erythrocyte osmotic fragility. Human patients with liver cirrhosis develop a hemolytic syndrome associated with alterations in the exchangeable lipoproteins of the RBC membrane. It is not known if a similar mechanism is responsible in horses, but morphologic alterations in the RBCs of these horses resemble the “burr cells” described in human patients.[273] Bile acids and their salts are greatly increased in liver failure and could play a contributing role in the hemolytic process. At necropsy, widespread hemorrhagic lesions that resemble those described for DIC are often present.

[273] DIC and the activation of various mediators may play a role in the terminal stages of this almost invariably fatal process.

37.17.15 "Pink Tooth," Congenital Erythropoietic Porphyria, Toxic Porphyria

GARY P. CARLSON

A rare congenital disorder of hemoglobin production inherited as an autosomal recessive trait has been recognized primarily in Holstein cattle, but it has also been reported in Shorthorns and Jamaican cattle.[274,275] This disorder is commonly called "pink tooth" and is characterized by slow growth rates in calves, photosensitization and exfoliation of nonpigmented skin when exposed to sunlight, reddish brown teeth, and modest anemia. The teeth and bones exhibit a pink fluorescence under ultraviolet (UV) light, and the urine is brownish red because of uroporphyrin. The condition is present at birth, and the metabolic defect in these cattle is a hereditary deficiency of the enzyme *uroporphyrinogen III cosynthetase,* which catalyzes an essential step in the synthesis of the porphyrin structure of hemoglobin.[275] This leads to the accumulation of uroporphyrin and coproporphyrin, which deposit in the teeth, where porphyrin is concentrated in the dentine, bones, and other tissues. Several factors contribute to the variable anemia seen in these cattle. A reduced intravascular RBC lifespan is related to the high concentration of uroporphyrin and coproporphyrin within the cells. Porphyrins may induce hemolysis and also delay maturation of the RBC series in the bone marrow, although there is often evidence of active erythropoietic response in the peripheral blood.[275]

There is no treatment for this inherited disorder, but genetic counseling is advisable. Substantial efforts have been made to reduce the incidence of pink tooth in the Holstein breed. It may be possible to detect carrier animals. Affected cattle have much lower levels of uroporphyrinogen III cosynthetase than normal cattle, and carrier animals have intermediate levels of this enzyme. Despite their rather serious problems, these cattle do reasonably well if housed indoors out of direct sunlight. The principal differential consideration is chronic fluorosis, which also produces brown discoloration of the teeth. However, the teeth of cattle with chronic fluorosis do not fluoresce under UV light.

An additional form of altered porphyrin metabolism, *congenital erythropoietic porphyria,* has been described in humans and cattle.[275] In humans the mode of inheritance is autosomal dominant, whereas in cattle the disorder appears to have a recessive pattern of inheritance and may be sex linked because it is only seen in females. The disease does not produce anemia, porphyrinuria, or discoloration of the teeth. This disorder is caused by a deficiency of ferrochelase (heme synthase), which leads to high concentrations of erythrocyte and fecal protoporphyrins. Porphyria has also been reported in swine, with a dominant pattern of inheritance.[275] There is little effect on the health of the pigs and no photosensitivity, but the teeth have reddish brown discoloration. Although similarities exist with bovine congenital erythropoietic porphyria, the precise defect in swine has not been found.

Finally, animals may develop *acquired toxic porphyrias*. This can occur with heavy metal poisonings, principally lead, but has also been produced experimentally with hexachlorobenzene and other chemicals. Lead inhibits several key enzymes of heme synthesis. Inhibition of aminolevulinate dehydrase leads to an accumulation of aminolevulinic acid, and decreased aminolevulinate dehydrase activity is a sensitive indicator of lead poisoning. Lead also inhibits ferrochelase, leading to marked elevation of erythrocyte zinc protoporphyn IX, the measurement of which provides a means of monitoring lead exposure.[275]

37.18 ## DEPRESSION ANEMIA

GARY P. CARLSON

The most common form of anemia in domestic animals is associated with inadequate erythropoiesis or bone marrow depression. Depression anemia can be caused by (1) deficiencies of vitamins or minerals that are essential for erythrocyte production, (2) systemic disease processes that interfere with normal erythropoiesis, and (3) processes that damage or displace normal bone marrow elements (Box 37-2). Depression anemia is often mild to moderate in severity and generally is only slowly progressive. Depressed erythropoiesis is occasionally associated with processes that also result in blood loss and increased rate of erythrocyte destruction. When this occurs, a profound, rapidly progressive, and potentially life-threatening anemia can develop.

With the possible exception of chronic iron or copper deficiency, depression anemia tends to be normocytic and normochromic. Bone marrow evaluation is an extremely useful diagnostic tool in animals with nutritional deficiencies or when bone marrow damage or dyscrasia is suspected. A thorough clinical evaluation and vigorous application of appropriate diagnostic procedures are necessary to establish a diagnosis of depression anemia and to determine the factors responsible for the anemia.

37.19 ## IRON DEFICIENCY ANEMIA

GARY P. CARLSON

MONICA ALEMAN

Iron is present in most forages and grains. In neonates the major source of iron is colostrum (~0.79 mg/L in mare's milk).[276] Soil, dam's feces, and milk are other important sources of iron.[276] Iron deficiency most often is associated with chronic blood loss as the result of internal or external parasitism, bleeding GI lesions, or hemostatic defects.[149] Dietary iron deficiency is seldom the sole cause of anemia, even in neonates on an all-milk diet, unless they are raised on cement or in barns or hutches with no access to the soil. A modest anemia is anticipated in veal calves. The anemia seen in some young calves during the first few days to weeks of life is apparently the result of congenital iron deficiency,[277] but the causal factors have not been determined. Altered immune functions, high incidences of infection, and reduced growth performance are reported in veal calves on low-iron diets.[278] Alterations in gastrointestinal pH may alter absorption of iron by the small intestine. States of inflammation and infection cause iron sequestration, not deficiency, by the reticuloendothelial system and lactoferrin. Iron deficiency has been well documented in calves and piglets that are housed exclusively indoors or hatches with no access to soil.[279] Absolute iron deficiency anemia is not usually reported in horses.[280–283]

37.19.1 ### Box 37-2 Causes of Depression Anemia

37.19.1.1 #### NUTRITIONAL DEFICIENCY

Iron deficiency

Copper deficiency

Cobalt deficiency

Vitamin B_{12} deficiency

Folic acid deficiency

37.19.1.2 ANEMIA OF INFLAMMATORY DISEASE

Chronic infection

Chronic inflammation

Fractures and severe trauma

Neoplasia

37.19.1.3 ANEMIA SECONDARY TO ORGAN DYSFUNCTION

Chronic liver disease

Chronic renal disease

Chronic gastrointestinal disease

Parasitism (trichostrongylosis)

37.19.1.4 BONE MARROW DAMAGE/DYSPLASIA

Myeloid and megakaryocytic bone marrow hypoplasia in standardbred horses

Bracken fern poisoning

Congenital dyserythropoiesis and keratosis in polled Hereford calves

Trichloroethylene-extracted soybean meal toxicity

Myelophthisic disorders (myeloproliferative disease, lymphoma)

Aplastic anemia

The circulating erythrocytes account for approximately two thirds of the total iron reserves found in the body. The remaining iron stores are distributed in the liver, spleen, and bone marrow. With chronic blood loss anemia, iron depletion is first indicated by decreased marrow iron, which can be appreciated with special staining of the bone marrow with Prussian blue stain for iron. As blood loss continues and iron deficiency progresses, serum iron is decreased, whereas iron binding capacity actually may increase. It is only late in this whole process that iron-deficient erythropoiesis results in the typical microcytic, hypochromic erythrocytes that generally are thought to be characteristic of iron deficiency anemia (decreased PCV, hemoglobin concentration, mean corpuscular volume, and mean corpuscular hemoglobin concentration).[149,192] Other laboratory findings include echinocytosis, keratocytosis, schistocytosis, acanthocytosis, ovalocytosis, hypoferritinemia, and hypoferremia.[280–283] The observed RBC morphologic abnormalities are thought to be caused by oxidative damage. The normal serum iron and iron-binding capacity for most domestic animals is 100 and 300 μg/dL, respectively. There is one report of a neonatal foal that had iron deficiency with refractory anemia and severe abnormal RBC morphology, but no microcytosis or hypochromasia.[283]

Treatment of iron deficiency anemia depends on evaluation of the cause and the correction or resolution of the process responsible for the chronic blood loss. Iron is usually supplied as an oral supplement or as a feed additive, and a variety of commercial preparations are available. Injectable iron dextran intended for use in baby pigs should be avoided in horses and cattle because it can induce an anaphylaxis, especially if administered repeatedly.[284] Iron cacodylate was a safe parenteral iron preparation for use in horses but is no longer readily available. An injectable iron preparation intended for use in horses was reported to result in acute iron overload, massive hepatic necrosis, and severe death losses in a group of young cattle.[285] Iron overload has resulted in acute death losses in neonatal foals fed an iron-containing microbial supplement. Iron accumulation resulting in hemochromatosis with extensive liver damage has also been reported in adult horses, although the mechanism responsible for the iron accumulation has not been explained.[286]

37.20 COPPER DEFICIENCY

GARY P. CARLSON

Copper deficiency can occur as a primary problem in milk-fed animals or in pastured animals in copper-deficient areas. More often, copper deficiency occurs secondarily in association with other trace mineral imbalances (e.g., dietary molybdenum excess) and is influenced by the sulfur and zinc content of the diet. Copper is an essential cofactor for a variety of enzymatic reactions, and copper deficiency produces a constellation of clinical signs related to impairment of these reactions.[287] Clinical signs of copper deficiency are most prominent in young, growing animals and may include reduced growth rate, rough and depigmented hair, diarrhea, osteoporosis with spontaneous fractures, and anemia. In lambs, copper deficiency can produce a demyelinating syndrome known as “swayback” or “enzootic ataxia.” Copper deficiency has also been associated with hemolytic anemia in postparturient dairy cattle in New Zealand.[285]

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Copper plays an important role in the transport of iron from the gut to the marrow and in the incorporation of iron into the heme moiety. The anemia produced by copper deficiency is generally moderate, slowly progressive, and closely resembles iron deficiency in that it is usually a microcytic, hypochromic anemia. Bone marrow evaluation often reveals intracellular accumulations of iron known as *sideroblasts*. This finding indicates that the principal

problem is a function of altered incorporation of iron into the erythrocyte hemoglobin rather than an actual deficiency of iron. Copper deficiency can be documented by measuring serum copper as ceruloplasmin, erythrocyte superoxide dismutase, or the copper content of hair, liver, or kidney. Serum iron tends to be low in animals with copper deficiency. Copper can be supplied as a dietary supplement or as an injectable copper glycinate preparation.

37.21 VITAMIN B_{12} AND FOLIC ACID DEFICIENCY

GARY P. CARLSON

Almost all the vitamins are necessary for normal erythropoiesis, but in ruminants and horses, only deficiencies of vitamin B_{12} and folate have been associated with the development of anemia.[149] These two vitamins play essential roles in DNA synthesis. When deficiencies of both vitamins coexist, as experimentally produced in pigs, a marked macrocytic anemia with hypersegmented circulating neutrophils and giant metamyelocytes and neutrophils in the bone marrow may be found. In ruminants, vitamin B_{12} deficiency has been associated with grazing cobalt-deficient pastures. A macrocytic to normocytic anemia may be noted in these animals. Folate deficiency has been reported as a cause of a mild seasonal decline in erythrocyte parameters in horses.

37.22 ANEMIA OF INFLAMMATORY DISEASE

GARY P. CARLSON

A depression anemia associated with characteristic disturbances of iron metabolism is often found in animals with conditions that result in a chronic inflammatory response.[288,289] These conditions include chronic internal or cutaneous infections, infectious diseases, or immune-mediated processes that result in chronic inflammation, severe traumatic injury or fractures, and active malignant neoplasia. The anemia tends to be mild, slowly progressive, and of itself, of little clinical consequence. Clinical signs relate to the primary disease process; and hematologic features are those of a mild, nonresponsive anemia, often with indications of a chronic inflammatory response (neutrophilic leukocytosis, as well as monocytosis with elevated fibrinogen, total protein, and globulin). Serum iron and iron-binding capacity are decreased, but marrow iron reserves and serum ferritin are increased.[149,289]

Anemia in these animals partly results from a modest decrease in the circulating RBC lifespan, but it is primarily caused by major alterations in iron metabolism and a depressed bone marrow response to the anemia. These alterations represent part of the body's response to inflammation, which includes the release of interleukin and other mediators and the production and release of various “acute phase” proteins from the liver. The body tends to sequester iron from the circulation into storage forms primarily in the liver and bone marrow, where it is retained and is relatively unavailable for erythropoiesis. This general reaction may play a protective role by denying readily available iron to potential bacterial pathogens that require iron for rapid growth and multiplication. Iron supplementation is not indicated for the treatment of the anemia of chronic inflammation, and therapeutic effort should be directed at resolution of the primary disease process.

37.23 ANEMIA SECONDARY TO ORGAN DYSFUNCTION

GARY P. CARLSON

A mild to moderate, nonresponsive anemia can develop in patients with chronic endocrine, hepatic, renal, or GI diseases. These disorders can produce bone marrow depression by (1) reducing the production or absorption processing and the distribution of elements essential for erythropoiesis, (2) allowing the elaboration or accumulation of toxic compounds, or (3) interfering with the production or action of erythropoietin.[290,291] These effects can occur independent of alterations in iron metabolism that characterize the anemia of inflammatory disease.[289] However, should inflammatory processes be responsible for the specific organ damage or dysfunction, the same pattern of anemia as described in the previous section would apply. Specific therapy for the anemia in these patients is not indicated, and resolution of the anemia depends on successful management of the primary disease process.

Internal parasitism, particularly that associated with *Trichostrongylus* species in ruminants, can result in a marked anemia. The anemia in these animals is primarily the result of bone marrow depression, in which failure to absorb iron, copper, and essential amino acids plays a major role.

37.24 MYELOID AND MEGAKARYOCYTIC BONE MARROW HYPOPLASIA

GARY P. CARLSON

Myeloid and megakaryocytic bone marrow hypoplasia was reported in eight young standardbred horses sired by the same stallion.[292] Clinical signs were variable and in individual horses included nonhealing wounds, nonresponive fevers, pleuritis, pneumonia, ataxia, hemoperitoneum, and bleeding into the bowel. Seven horses died or were euthanized. The principal laboratory findings were a variable RBC count from normal to modest to marked anemia, moderate to profound neutropenia, and an intermittent thrombocytopenia in most of the horses. There appeared to be a cyclic variation in neutrophil and platelet counts. A bone marrow microenvironment or growth factor defect is suspected as the cause of this problem because myeloid progenitor cells were present and were able to respond to exogenous growth factors. A familial basis for the disease is suspected.[292]

37.25 APLASTIC ANEMIA

DEBRA DEEM MORRIS

Aplastic anemia is a stem cell disorder characterized by reduced marrow production of all blood components in the absence of a primary disease process infiltrating the bone marrow or suppressing hematopoiesis.[293,294] 1171
Peripheral pancytopenia secondary to marrow aplasia is apparently very uncommon in horses, although idiopathic 1172
hypoplastic anemia has been reported,[295–297] as well as rare cases associated with the use of phenylbutazone.[290,298] Hemorrhagic diathesis caused by thrombocytopenia is often the first indication of disease, manifested by epistaxis, mucosal petechiae, or prolonged hemorrhage after trauma or injections. Pallor may be present, with other signs of anemia (e.g., reduced exercise tolerance) depending on the severity and rapidity by which aplasia progresses. Neutropenia causes increased susceptibility to infections, which may result in intermittent fever or weight loss. The production of lymphocytes is reportedly not impaired; however, absolute lymphopenia can occur in aplastic anemia. Circulating lymphocytes are often highly reactive, producing the suspicion of neoplasia or a preleukemic syndrome.[290]

Marrow aplasia in humans is usually termed *idiopathic,* although some cases are associated with exposure to a drug, chemical, ionizing radiation, or presence of another disease.[294] Marrow failure results from damage to the

hematopoietic stem cell compartment. This may be in the form of DNA damage to stem cells or depletion of later progenitor cells by a cycle-active agent. Some cases of marrow aplasia appear to be immune mediated, either genetically determined or incited by a particular viral infection or drug exposure.

The diagnosis of aplastic anemia is based on the combination of peripheral pancytopenia and bone marrow hypoplasia with fatty replacement. Because the normal erythrocyte lifespan in horses is approximately 140 days and in cattle exceeds 160 days,[299] neutropenia with no left shift and thrombocytopenia are earlier hematologic manifestations.

The major aims in treatment of aplastic anemia are to remove the animal from suspected causative agents and to provide supportive care, in the hope that spontaneous remission will occur. Broad-spectrum antimicrobials are necessary to control infections. Blood transfusions are rarely indicated, and platelet transfusion should be reserved for severe bleeding episodes, which rarely occur. Bone marrow transplantation is used with some success in humans, although graft-versus-host disease poses significant risk. The latter would presumably limit this therapy in horses, and too few horses with aplastic anemia have been studied to give a clear indication of prognosis.

Bracken fern toxicosis in ruminants causes bone marrow depression and subsequent pancytopenia.[48,299] Most field outbreaks of the disease occur in cattle. The toxic effects of the plant are cumulative, and clinical signs occur suddenly 2 to 8 weeks after cattle gain access to the plant. Clinical signs include fever, melena, epistaxis, hematuria, mucosal petechiae, hyphema, and bleeding from the eyes and vagina. Hematology reveals a platelet count less than 40,000/μL and profound leukopenia with essentially no neutrophils present. Death may follow in 1 to 3 days as a result of the combined effects of multiple internal hemorrhages and bacteremia. The aplastic anemia factor in bracken fern has not been identified, although ptaquiloside has been suggested.[299] Necropsy of cattle with bracken fern toxicosis reveals multiple hemorrhages throughout most tissues, necrotic GI tract ulcers, and pale bone marrow. Antibiotics and blood and platelet transfusions may be appropriate but cattle with advanced bracken fern toxicosis (platelet count <50,000/μL; leukocyte count <2000/μL) usually die.

37.26 PARADOXIC ERYTHROID HYPOPLASIA

MONICA ALEMAN

Recombinant human erythropoietin (rhEPO) has been used in racehorses to enhance their athletic activity by stimulating erythrocyte production in the bone marrow. Mild to moderate anemia and paradoxic erythroid hypoplasia based on bone marrow cytology were reported in two standardbred race horses after rhEPO administration.[300] Serum from these horses inhibited the rhEPO-induced activity of mouse bone marrow in vitro. The degree of inhibition was inversely proportional to the amount of exogenous rhEPO added to the serum, suggesting the presence of anti-rhEPO antibodies. Anti-rhEPO antibodies to exogenous rhEPO likely cross-reacted with the horses' endogenous rhEPO. These horses were treated with dexamethasone at adjustable dosages according to response and returned to their usual athletic activity.

37.27 ERYTHROCYTOSIS (POLYCYTHEMIA)

DEBRA DEEM MORRIS

Absolute erythrocytosis is caused by increased erythropoiesis that creates a circulating erythrocyte mass above normal for the species. Relative erythrocytosis caused by hemoconcentration, endotoxemia, and splenic contraction (horses) must be ruled out because these conditions are much more common in large animals than

absolute erythrocytosis. Diagnosis of absolute erythrocytosis is based on persistently elevated packed cell volume (PCV), hemoglobin, and erythrocyte count, without clinical evidence of shock or dehydration and without response to intravenous fluid therapy. Primary erythrocytosis is associated with normal arterial oxygen tension and reduced plasma erythropoietin, whereas secondary erythrocytosis is caused by increased production of erythropoietin.

All disorders characterized by an absolute erythrocytosis share clinical manifestations caused by expanded blood volume and increased blood viscosity. Generalized vascular expansion and venous engorgement cause the characteristic "muddy" hyperemia of mucous membranes. A marked decrease in cardiac output accompanies blood hyperviscosity and ultimately impairs tissue oxygenation, producing the vague signs of lethargy and weight loss. There may be an increase in thrombotic complications such as laminitis and renal failure.

37.28 CONGENITAL ERYTHROCYTOSIS

Familial erythrocytosis, described in cattle[301] and humans,[302] is caused by autonomous erythropoietin production without a demonstrable lesion. Congenital erythrocytosis is thus a form of inappropriate secondary erythrocytosis. Chronic hypoxia should be ruled out by measuring the arterial oxygen concentration. The only way to definitively differentiate secondary erythrocytosis from primary erythrocytosis is by determination of serum erythropoietin.

37.29 ACQUIRED ERYTHROCYTOSIS

37.29.1 Primary Erythrocytosis

Polycythemia vera, an idiopathic myeloproliferative disorder characterized by excessive proliferation of erythroid, myeloid, and megakaryocytic elements, has not been reported in large animals.

37.29.2 Secondary Erythrocytosis

37.29.2.1 PHYSIOLOGICALLY APPROPRIATE ERYTHROCYTOSIS

In domestic animals, absolute erythrocytosis is usually secondary to chronic diseases that produce tissue hypoxia. Chronic tissue hypoxia that attends residence at high altitude, congenital heart defects that produce right-to-left shunting, and some forms of chronic pulmonary disease induce a compensatory increase in plasma erythropoietin that results in absolute secondary erythrocytosis.[303]

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The partial pressure of oxygen (P_{O_2}) in capillaries must be maintained close to 40 mm Hg to ensure adequate off-loading of oxygen to tissues. At elevated altitudes, diminished atmospheric oxygen tension produces a much smaller alveolar capillary P_{O_2} gradient and an inadequate driving force for tissue oxygenation. Erythropoietin production in response to hypoxia causes erythrocytosis to increase the oxygen-carrying capacity of circulating blood. Cattle are most susceptible to the effects of high altitude, and some develop polycythemia at 1800 m (5940 ft) above sea level.[48] Horses develop an increased erythrocyte mass above 2200 m (7260 ft), especially when in training. Sheep are similar to cattle, but goats are apparently least susceptible to elevation hypoxia.

Congenital cardiac disorders that produce right-to-left shunts are a common cause for absolute erythrocytosis in large animals. Tetralogy of Fallot is the most common defect to cause shunting of unoxygenated blood

into the peripheral circulation, although a number of other defects, including the most common ventricular septal defect, may eventually result in right-to-left shunting and secondary erythrocytosis.[304]

Chronic impairment of alveolar ventilation may eventually cause erythrocytosis, although most chronic pulmonic diseases in large animals are not associated with significant hypoxemia. Chronic obstructive pulmonary disease in horses may produce enough ventilation/perfusion mismatching to reduce the pressure of arterial oxygen below normal, but the resultant hypoxemia is insufficient to induce erythrocytosis.

37.29.2.2 PHYSIOLOGICALLY INAPPROPRIATE ERYTHROCYTOSIS

Inappropriate elaboration of erythropoietin (i.e., normal Po_2 and secondary erythrocytosis) may rarely accompany renal, hepatic, or endocrine disorders, especially those caused by neoplasia. Secondary erythrocytosis may accompany nonmalignant renal disorders, in which local intrarenal ischemia is believed to mediate increased erythropoietin production. Paraneoplastic erythrocytosis with normal serum erythropoietin is caused by tumor production of androgenic steroids or a protein with erythropoietin-like action.[305] Increased plasma erythropoietin and secondary erythrocytosis have been identified in horses with hepatocellular carcinoma.[303,306] Erythrocytosis was described in a horse with hepatoblastoma[307] and in another with lymphoma,[308] but serum erythropoietin levels (as measured by a human assay) were normal in both cases. In the horse with lymphoma, erythropoietin gene expression was identified in the lymphoma tissue. Typically, the diagnosis of inappropriate secondary erythrocytosis is based on elevated serum erythropoietin in the absence of hypoxemia. Elevated serum erythropoietin may not be demonstrated because of the nature of the assay or other compounds causing erythrocytosis.

37.30 TREATMENT OF ERYTHROCYTOSIS

When erythrocytosis is not in response to an appropriate physiologic stimulus (e.g., primary erythrocytosis, inappropriate secondary erythrocytosis), phlebotomy to keep the PCV less than 50% is the mainstay of the treatment to control hypervolemia and blood hyperviscosity. Initially, 2 to 4 L of blood may need to be removed every 2 to 3 days, but as iron deficiency supervenes, the frequency of phlebotomy may be reduced. The myelosuppressive drug hydroxyurea, used in humans and dogs with polycythemia vera,[302,309] has not been tried in large animals.

The management of appropriate secondary erythrocytosis is more complex because there is a need for increased oxygen-carrying capacity of the blood. The beneficial effect of expanded RBC mass is ultimately offset by the detrimental effect of increased blood viscosity on oxygen delivery. Oxygen delivery is impaired when the PCV exceeds 60%, although continued erythropoietin output may result in overcompensation. Phlebotomy is indicated when the PCV is greater than 60%, but the optimum PCV for patients residing at high altitudes or those with right-to-left cardiac shunts must be determined by trial and error.

The long-term prognosis for patients with erythrocytosis is determined by the severity and cause of the disorder. Congenital cardiac defects, neoplastic diseases, and chronic organ insufficiency carry a guarded to poor prognosis. Familial or primary erythrocytosis may be managed by phlebotomy, although there are no long-term follow-ups for large animals with these disorders.

37.31 PROLIFERATIVE DISORDERS OF LYMPHOID AND MYELOID SYSTEMS

The lymphoproliferative disorders reported in horses include lymphoma, lymphocytic leukemia, and plasma cell myeloma. The myeloproliferative disorders include myeloid leukemias and malignant histiocytosis.[310] The following sections describe lymphoma, leukemia, and myeloma.

37.32 BOVINE LYMPHOMA

JOHN ANGELOS

MARK C. THURMOND

Bovine lymphoma (lymphosarcoma) is characterized in terms of the frequency of occurrence (sporadic or endemic/enzootic), age at onset, organ involvement, and associated etiologic agent. Sporadic bovine lymphoma occurs as generalized lymphadenopathy in calves (calf or juvenile form), as thymic involvement in cattle between 6 months and 2 years of age (thymic or adolescent form), and as a cutaneous form in cattle between 1 and 3 years of age. Lymphoid tumors of cattle with sporadic bovine lymphoma are of the B-cell or T-cell lineage.[311] The most common form of lymphoma appears endemically in adult cattle more than 2 years of age and is associated with *bovine leukemia virus* (BLV) infection and typically involves multiple organ systems; BLV-associated lymphomas of adult cattle are of the B-cell lineage.[312] BLV is classified in the genus *Deltaretrovirus,* subfamily Orthoretrovirinae, and family Retroviridae.

37.32.1 Sporadic Lymphoma

37.32.1.1 CALF OR JUVENILE FORM

The prevalence rate of juvenile lymphoma is unknown, but this form of lymphoma is rare, and multiple cases may be seen in the same herd. The cause of juvenile sporadic lymphoma is unknown and does not appear to be associated with BLV infection.[313]

The age at onset ranges from 3 to 6 months, but can be seen in calves as young as 1 month or in cattle as old as 3 years. There have been reports of fetal involvement with the calf form.[314] Calves generally present with a history of slight to moderate depression, weight loss, weakness (mainly in older calves and despite good appetite), or lymphadenopathy (mainly in younger calves).[315] The onset of signs can be sudden (within a week).

Physical examination may reveal generalized bilateral enlargement of lymph nodes, particularly the deep cervical and parotid nodes and occasionally the popliteal and hemonodes. Moderate to marked enlargement may be noted for the iliac and mandibular nodes. Rarely, node enlargement is not generalized but is restricted to a regional anatomic site.[313,315] Enlarged nodes tend to be smooth and firm and are not hot or painful. Mucous membranes are usually pale as a result of anemia. Tachycardia, tachypnea, hyperpnea, cough, and harsh respiratory sounds may be evident on auscultation. Less frequently reported signs include fever, ruminal tympany, an enlarged liver, ataxia, and diarrhea.[315]

Hematologic features include a microcytic hypochromic anemia, low hemoglobin concentration (<7 g/100 mL),[316] low PCV (typically mid-20s), and a leukocytosis primarily caused by a lymphocytosis.[313,315–317] Bone marrow examinations may reveal an elevated myeloid/erythroid ratio, with massive neoplastic infiltration in some calves.[316] Affected calves also tend to have low serum globulin and elevated AST. Neoplastic involvement of a variety of organs, including the spleen, heart, kidney, liver, pancreas, uterus, and thymus, may occur.[313,315,316] Less thymic involvement occurs compared with the thymic form of lymphoma; neoplastic tissue is found only as small, microscopic nodules.[316] Subperiosteal neoplastic infiltration may produce spinal cord compression and result in paresis.[316] The disease is rapidly progressive and usually fatal within 2 to 8 weeks of onset.

37.32.1.2

THYMIC OR ADOLESCENT FORM

The thymic form of lymphoma is very rare. The disease is usually seen in cattle 6 to 24 months of age but may occur in newborn calves and cattle up to 4 years of age.[315] Clinical signs are produced by space-occupying lesions in the neck or thorax.[318] Metastatic mammary lymphoma along with thymic lymphoma was reported in a 3-year-old beef heifer.[319] Cattle with thymic lymphoma typically present with brisket enlargement or firm swelling in the presternal area of the brisket, associated with pitting edema.[320] Loss in body condition, rumen tympany, and dysphagia are common. Bloat may occur as a result of inability to eructate ruminal gas as a result of a space-occupying lesion around the esophagus.[318] Although generalized lymphadenopathy is uncommon, enlarged superficial cervical and prescapular nodes are usually observed. The jugular veins are distended and nonpulsating; there may be muffled heart sounds and diminished resonance on thoracic percussion. Tachycardia, dyspnea, coughing, or respiratory distress may be present. Hematologic features are generally unremarkable. Anemia is not a consistent feature, and lymphocytosis is only seen occasionally. The course of the disease from the time of recognition is generally from 2 to 9 weeks, but poor condition may have been present for several months before presentation.[321] The disease is fatal, often as a consequence of bloat.

Although thymic lymphoma is not associated with BLV infection, there has been one report of a BLV-positive 18-month-old heifer with thymic lymphoma. In situ PCR was used to detect the presence of BLV proviral DNA in lymphocytes of the thymus and in liver and kidney epithelium.[322]

37.32.1.3

ATYPICAL FORMS

A 7-month-old Holstein heifer with diffuse swelling over the left thigh, difficult ambulation, and peroneal and tibial nerve deficit had an infiltrative B-cell lymphoma involving the semitendinosus, semimembranosus, and gluteal muscles.[323] This heifer was serologically positive for BLV antibody, but the possibility of maternally derived antibody could not be ruled out. In another case report, the external and internal surfaces of the trachea of an 18-month-old Friesian heifer with cutaneous lymphoid tumors also had extensive lymphoid nodules covering the external and luminal surfaces of the trachea.[324] An 8- to 9-year-old beef cow with weight loss was reported with pleural and pericardial invasion with a lymphoid tumor of T-cell lineage; the animal tested negative for BLV on PCR.[325] Four of 10 cattle 3 years of age or younger diagnosed with sporadic lymphoma had BLV provirus in tumor DNA, as detected by PCR, and a possible role for BLV in some cases of sporadic lymphoma of cattle has been suggested.[326]

37.32.1.4 CUTANEOUS FORM

Cutaneous lymphoma is not as age specific as the other forms of sporadic lymphoma and may affect cattle between 1 and 3 years of age. The history may reveal an initial period of 1 to 3 months during which cutaneous swellings are observed around the anus, vulva, escutcheon, shoulders, or flank. These signs may regress and subsequently recur.[327] Lesions tend to be raised and can be ulcerated. They are generally about 2 to 3 cm in diameter with necrotic centers and may be painful on palpation. Other clinical signs depend on additional organ system involvement of the tumor and may include cardiac insufficiency, with brisket edema extending along the ventral abdomen and jugular pulsation. Pulse and respiration may be elevated as a result of anemia. Hematologic features include anemia and presence of atypical lymphocytes. The mandibular, prescapular, prefemoral, and supramammary lymph nodes are usually enlarged.[328]

At necropsy, a variety of organs may be involved, including heart, brain, skin, spinal cord, liver, lung, kidney, and abomasum. The massive lymphoid infiltration of the skin resembles the clinical manifestations of mycosis fungoides of humans.[314] In a report of a 12-month-old red Holstein heifer with cutaneous T-cell lymphoma, serum activity of lactate dehydrogenase (LDH) was moderately increased despite normal to minimally increased activities of liver and muscle specific enzymes.[329]

37.32.1.5 HEMONODE ENLARGEMENT (HEMAL LYMPH NODE)

A lymphoproliferative condition associated with hemonode enlargement and some generalized lymphadenopathy has been described for cattle infected with a lentivirus[321] that is now called *bovine immunodeficiency virus* (BIV). BIV belongs in the genus *Lentivirus,* subfamily Orthoretrovirinae, and family Retroviridae. BIV has molecular similarity to human immunodeficiency virus (HIV) and is associated with persistent lymphocytosis, lymphadenopathy, central nervous system (CNS) lesions, progressive weakness, and emaciation.[330] Infected calves may develop enlarged superficial nodes *(hemonodes)*, mainly in the cervical region anterior and dorsal to the prescapular lymph node, over the spine of the scapula, in the paralumbar fossa, and dorsal to the prefemoral lymph node. Lymphocytosis may be related to an increase in B lymphocytes. In utero transmission of BIV has also been documented.[331]

37.32.2 Adult Lymphoma (Bovine Leukemia Virus)

The adult or enzootic form of lymphoma is the most common neoplastic disease of cattle and is associated with BLV infection. Rates of lymphoma in cattle vary considerably, probably reflecting variation in BLV infection rates. In 1978 the U.S. condemnation of carcasses because of lymphoma was reported to be 170 per 100,000 head slaughtered.[332] A high condemnation rate, sometimes exceeding 1%, was reported for slaughtered California dairy cows,[333] and about 1.73% of BLV-infected cattle had lymphoma.[334] The rate of cattle condemnations resulting from lymphoma appears to have increased over time.[333]

37.32.3 Epidemiology

The epidemiology of adult lymphoma is not completely understood. Herd size might be positively correlated with a high rate of lymphoma, which may reflect higher rates of BLV infection in large herds or a preponderance of susceptible pedigrees in some of the herds studied.[334,335] Susceptibility to BLV infection is

associated with BoLA type,[336,337] which may explain why higher rates of lymphoma are found in certain families of cattle. The progression of disease to lymphocytosis in some BLV-infected cows may also be influenced by BoLA type, suggesting a possible genetic predisposition to development of lymphoma through the antigens of the major histocompatibility complex (MHC) encoded at closely linked loci. Other potentially contributing factors, including nutrition, concurrent infections, and environmental/meteorologic stressors, have not been explored sufficiently. There is no evidence for a seasonally associated pattern to appearance of clinical lymphoma.[333] Antigenic and molecular evidence for the presence of BLV in mammary glandular epithelium has been demonstrated.[338] The effect of persistent mammary BLV infection on the mammary gland is not completely understood. Although one study identified increased average milk production in BLV-infected versus uninfected cattle,[339] others report negative associations between milk production and BLV status.[340,341]

37.32.4 Economics

The economic importance of adult lymphoma varies according to production type.[341,342] Producers incur losses from lymphoma associated with death of cattle (particularly genetically valuable livestock), loss of milk production, costs of treatment and diagnosis, and premature replacement costs for cattle dying or culled as a result of lymphoma. The latter may partly explain an observed increased rate of culling found for BLV-infected dairy cattle.[339,343] In addition to premature culling and replacement, losses are incurred because of failure to retain salvage value of cows condemned for lymphoma at slaughter.[333] A hidden cost of lymphoma also may be in the perpetuation of BLV-infected cattle through in utero infection of calves born to cows with lymphoma.[344,345]

37.32.5 Diagnosis

Cattle presented with the adult or enzootic form of lymphoma usually are older than 4 years but may be as young as 2 years. Cattle are often presented with a history of loss in condition, an abrupt drop in milk production (over a few days), enlarged peripheral nodes, exophthalmos, or partial to complete anorexia, particularly with regard to grain or concentrates. Because dry cows are not observed as closely as lactating cows and are not monitored for milk yield, lymphoma is less likely to be recognized until they freshen. Subclinical lymphoma may be diagnosed in cows submitted for routine reproduction examinations; other signs may include diarrhea, ataxia, paresis, ketosis, and infertility.

Physical examination often reveals an organ system failure resulting from tumor involvement. Thoracic auscultation may reveal cardiac dysrhythmia, tachycardia, tachypnea, and hyperpnea. Common sites of lymphoid tumor predilection in adult lymphoma include right atrium, uterus, retrobulbar space, abomasum, and spinal cord (epidural space); involvement of rumen, colon, and kidney is also seen. Dependent, pitting edema is common when cervical or supramammary lymph nodes are involved. Involvement of the intestinal lymphatics is often associated with generalized dependent edema anterior to the udder. Peripheral nodes typically found to be enlarged are the prescapular, femoral, and supramammary nodes. Feces may be scant, pasty, or watery and probably reflects the presence of lesions within the GI tract. Melena may be present in animals with ulceration of the abomasum and lymphoid cell infiltration in the abomasal wall. Rectal palpation can be a useful in cases lacking peripheral node enlargement or exophthalmos. Tumor masses palpated in the abdomen typically are multiple and range in size from only slightly enlarged lymph nodes to massive lesions half a meter in diameter. The internal iliac nodes are involved in most cattle with abdominal tumors.

Tumors tend to be firm but not hard and may feel slightly lobulated. Differentiation by palpation of lymphoma tumors from other masses is highly subjective. Carcinomas tend to be of similar consistency but are seldom larger than 15 cm in diameter and are usually associated with intestinal tissue. Lymph nodes of cows with a carcinoma are not usually enlarged unless a secondary infection is present. Melanomas are generally less than 15 cm in diameter and hard, sometimes with protrusions 1 to 2 cm high along the surface. They usually are not found associated with lymph nodes. Masses of fat necrosis tend to be firm and are usually associated with omental tissue. Internal abscesses are often single and associated with the uterus, as a consequence of uterine tear and infection during parturition, or with gluteal muscles of the pelvic ceiling, as a consequence of injection-related infections. Exploratory laparotomy may be indicated as an additional diagnostic tool in difficult cases, particularly in valuable cattle.

The hemogram of cattle with lymphoma often is generally unremarkable. Anemia, characterized as microcytic and hypochromic, may be present in cattle with GI hemorrhage. Fibrinogen levels have been inconsistent in lymphoma, and therefore its measurement may be helpful only in differentiating an abscess. Approximately 30% of cattle with BLV infection develop persistent lifelong lymphocytosis, composed mostly of B cells.[346,347]

Cytology of aspirates of tumors or tumorous nodes may not always be a reliable diagnostic tool, although it can be helpful. Discrimination cannot be made between a normal node responding to an infectious agent and a node involved with neoplastic lymphocytes; in both situations, cells resembling young, poorly differentiated lymphocytes may be present. Examination of nontumorous active lymph nodes may reveal an elevated proportion of large, young lymphocytes that could resemble those of lymphosarcoma. Histopathologic examination of biopsied tumors or nodes may be more useful than aspirates in making a diagnosis. However, cytology and culture of aspirates could be helpful in differentiating a tumor from an abscess. Failed attempts at collection of cerebrospinal (lumbosacral) fluid in cattle with recumbency or hindlimb weakness may be associated with the presence of lymphoid tumors in the vertebral canal; cytologic examination of cells from the collection needle in such cases may reveal abnormal lymphoid cells.

Standard serologic testing for BLV involves identification of antibody against the 51-kilodalton (kD) envelope glycoprotein (gp51). Although BLV diagnosis historically involved the use of the agar gel immunodiffusion (AGID) test, that method has been shown to be less sensitive than the enzyme-linked immunosorbent assay (ELISA).[348] ELISA test kits are available commercially that detect antibodies to gp51 in serum and milk.[*] Diagnosis is also possible by use of PCR to detect BLV nucleic acid,[349–351] as well as by a combined PCR-ELISA that is more sensitive than staining of PCR amplicons with ethidium bromide.[352] ELISA-positive cattle that were not detected by PCR testing have been reported, most likely related to a low number of infected circulating lymphocytes at sample collection.[353] The PCR by itself is considered unreliable for routine detection of BLV in herds with a high prevalence of disease.[354] The ability of PCR to detect a BLV infected animal is improved by means of a nested PCR, which was reported to be effective in diagnosing infection when seroconversion had not yet occurred.[355] The presence of antibodies to gp51 is generally considered to be a prerequisite to a diagnosis of lymphoma, except for cows during the periparturient period, when circulating antibodies may fall below the level detectable by a serologic test.[356] The mere presence of BLV antibodies does not necessarily mean that an animal has lymphoma, which is found in only about 1.7% of BLV-infected cattle.[357] However, serology can be helpful in predicting the chance of lymphoma in cattle seropositive to the gp51 antigen. Sera from cattle with lymphoma generally have high titers to the gp51 antigen (score of 3 or 4 on AGID), compared with those of infected cattle without lymphoma (score of 1 or 2). In addition, cattle that do not have lymphoma tend not to have antibodies to the p24 antigen of BLV, as detected by AGID. The percentage of cattle with histologically confirmed lymphoma but in which lymphoma was not diagnosed by a

gp51-positive and p24-negative test result (false-negative rate of diagnostic test) has been found to be only 0.21%, using the AGID test.[334] Unfortunately, most diagnostic laboratories do not have the capability to perform the test using the p24 antigen.

At necropsy, tumors are found enclosed in a capsular-like tissue that, when sectioned with a knife, results in an eversion of tumor stroma. Cut tumor tissue is cream colored and friable, with little binding structure. Centers of tumors may appear necrotic and mushy, whereas peripheral regions are firmer and pink to white. Histopathology provides the only definitive diagnosis. Tissue should be biopsied by surgical removal of as much of the node (or mass) as possible.

* HerdChek Bovine Leukemia Virus Antibody Test Kits (IDEXX Laboratories, Westbrook, Maine); Bovine Leukemia Virus Antibody Test Kit, ELISA (VMRD, Pullman, Wash); SVANOVIR BLV gp51-Ab ELISA (Svanova Biotech AB, Uppsala, Sweden).

37.32.6 Control

No curative treatment for lymphoma exists. However, supportive therapy may be indicated to reduce discomfort and prolong life long enough to remove valuable ova/embryos or calves or to harvest semen.

Until more information is available on the epidemiology of lymphoma, control and eradication hinge on success of efforts to eradicate BLV from a herd. Presently, no vaccines offer effective protection from BLV infection.[358–361] Control and eradication of BLV require reduction of blood transmission through iatrogenic means and through physical contact among cattle.[362] Transmission associated with physical contact between infected and susceptible cattle can be reduced by segregating infected and noninfected cattle.[363–365] Separation of cattle by 10 feet is preferred, but a single fence may reduce sufficiently the degree of contact necessary for transmission. Transmission after physical contact may be through inhalation of BLV shed in nasal secretions.[366–369] Experimental studies have found that under extreme conditions of blood contamination and mucosal irritation, BLV can be transmitted rectally.[370–374] Under conditions typical of routine palpation during pregnancy examination, however, BLV appearance may not necessarily be transmitted to any measurable degree.[372,374] If potential for rectal transmission is a concern, palpation sleeves may be rinsed or replaced between cows. Although insect transmission of BLV is theoretically possible,[375] as demonstrated experimentally by interrupted feeding of tabanids from cattle with persistent lymphocytosis to uninfected cattle,[376] studies of natural infection have not been able to link flies with new natural infections.[377,378] Several studies have been unable to demonstrate transmission after use of a common needle.[379–381] However, infection after use of a Tb needle dipped in blood of a BLV-infected animal could be prevented by wiping the needle with cotton before injection.[382] Although data have not shown the use of common needles to be an important means of BLV transmission, it would be prudent to use individual sterile needles for treatment, testing, or vaccination.

Transmission of BLV has not been shown in cows inseminated artificially using commercially prepared frozen semen.[383–387] However, infection resulting from the use of an infected bull in natural breeding may be possible.[388–390] Semen of 27 bulls that were BLV PCR positive in peripheral blood had no evidence BLV on PCR.[391] Embryo transfer recipients should be tested for BLV before transfer.[392] Embryo transfer using noninfected recipients offers a means of producing phenotypically preferred cattle from BLV-infected cows and controlling in utero infection,[377,383,393,394] because at harvesting, embryos are not infected.[385] It is possible to produce

transferable in vitro fertilized embryos that are free of BLV provirus from oocytes that are exposed to BLV during maturation, fertilization, or after fertilization, through a washing procedure.[395]

For most herds, control and eradication of the infection would require modification of facilities, alteration of management practices, and serologic surveillance at least annually. Planning a control program should include a cost/benefit analysis to evaluate potential return on the investment. Financial benefit of a BLV control program has been documented in herds in which the prevalence of BLV infection is 12.5% or higher.[396] The selective culling of BLV-infected cattle based on positive lymphocyte BLV antigen expression in vitro was reported to be effective in preventing transmission of BLV infection.[397]

37.33 LYMPHOMA IN HORSES

MONICA ALEMAN

Lymphoma and lymphosarcoma are terms that have been used interchangeably to describe a group of neoplasias originating from the lymphoid system, including nodal lymphoma (lymph nodes) or extranodal lymphoma (thymus, spleen, and mucosal-, conjunctival-, or skin-associated lymphoid tissue [MALT, CALT, and SALT, respectively]). The mucosal-associated lymphoid tissue includes mucous membranes lining the digestive, respiratory, and urogenital systems. Metastasis can occur to other organs, including primary lymphoid tissues such as bone marrow. Based on its embryologic origin, lymphoma is classified as a *mesenchymal neoplasm*. Although the suffix *-oma* indicates a benign neoplasm and *-sarcoma* a malignant mesenchymal neoplasm, the Leukemia and Lymphoma Society determined that lymphoma is the appropriate term because all neoplasms of the lymphatic system in humans are malignant. In veterinary medicine, lymphomas are also malignant, so the term *lymphoma* has been adopted. It is important to emphasize that "lymphoid hyperplasia" is not synonymous with lymphoma. Clonality studies may determine if a specific clone of lymphocytes (B, T, natural killer, and plasma cells) are malignant versus hyperreactive.

Lymphoma is one of the most common malignant neoplasia in the horse. On postmortem examination, prevalence of lymphoma in the horse was estimated to be 2% to 5%.[398,399] In contrast to other species, lymphoma development has not been associated with a viral etiology in the horse. However, virus-like particles in lymph nodes of neonatal foals with lymphoma have been described, although no causal relationship was proved.[400,401] Lymphomas can occur at any age, from an aborted equine fetus to horses 30 years old.[401–403] Typically, age of onset of all forms of lymphomas has been reported as 5 to 10 years; however, a recent study revealed that the mean age of intestinal lymphoma was 16 years.[403,404] There is no apparent breed or gender predilection. The clinical signs vary depending on tumor location but most often include lymphadenopathy, lethargy, weight loss, edema, and pyrexia. Affected lymph nodes tend to be firm, cool, and nonpainful. In one retrospective study of 79 horses with lymphoma, 21 cases had ocular involvement.[405] Paraneoplastic pruritus and alopecia were described in a horse with diffuse lymphoma.[406] Neurologic alterations, lameness, osteolysis, and pathologic fractures have been described as the result of lymphoma.[407–412]

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The hematologic features of lymphoma are varied. However, anemia is a relatively common finding. Anemia is thought to be caused by suppression of erythropoiesis, bone marrow infiltration, blood loss, or immune-mediated hemolytic anemia.[81] There is only one report, in a 9-year-old warmblood mare, involving multicentric lymphoma and persistent paraneoplastic erythrocytosis.[308] Frank leukemia is rare, but when present (reported counts as high as 256,500 cells/μL), neoplastic cells are generally found in the bone marrow.[413] More often the lymphocyte count is within the reference range or low. Atypical lymphocytes may be noted in the blood smears of 20% to

50% of affected horses, especially late in the course of disease.[414–417] A modest neutrophilic leukocytosis with an elevated fibrinogen is often seen. This inflammatory response can cause confusion when trying to differentiate neoplasia from internal abscessation.[418] Serum biochemistry profiles may show internal organ involvement. Serum protein alterations are frequently observed and include hypoalbuminemia, hyperglobulinemia with polyclonal gammopathy (most cases), and decreased albumin/globulin ratio. However, deficiencies in IgG and IgA concentrations were reported in a horse.[419] Neoplastic lymphocytes may arise from reactive B-cell clones producing antibodies responsible for gammopathies and immune-mediated processes (hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia).[81] Although low serum IgM concentrations and hypercalcemia have been reported in a few cases, these are not consistent features of lymphoma in the horse.[179,417,419–421]

Lymphomas in horses have been classified based on anatomic distribution, morphology, and cell lineage.[422–425] Based on its anatomic distribution, the classification of lymphoma in the horse is as follows: multicentric, generalized, alimentary or intestinal, splenic, mediastinal, thymic, and cutaneous forms. The spleen is the organ most frequently affected with lymphoma, and lymphoma is the most common neoplasia of the spleen.[426]

Morphologically, lymphocytes are classified as “small” if their nuclear diameters are 1.5 times or less the diameter of erythrocytes and “large” if their nuclei average twice or more the diameter of erythrocytes.[423] Small-cell lymphoma consists of 60% or more small cells. Large-cell lymphoma consists of 60% or more large cells. A lymphoma designated as “mixed” is a tumor that contains both small and large neoplastic cells of the same immunophenotype.[423]

Immunohistochemical classification of lymphomas has been determined by using monoclonal antibodies, such as BLA36, CD79a (mb-1), and B29 for B-cell lymphomas and polyclonal antibodies to CD3 and CD5 for T-cell lymphomas. All three lymphomas—B cell, T cell, and mixed B and T cell—have been reported in the horse.[423,424] The monoclonal antibody proliferating-cell nuclear antigen (PCNA) has been used to determine the proliferative status of the cells.[423] Frequently, lymphomas are described as T-cell—rich B-cell lymphoma, or vice versa. T-cell—rich, large—B-cell lymphoma is a neoplastic proliferation of large B cells associated with a prominent component of nonneoplastic reactive T lymphocytes that constitutes a significant percentage of the cellular population.[423] The presence of large numbers of nonneoplastic T cells within a B-cell lymphoma could result in an erroneous diagnosis of a T-cell tumor. Neoplastic cells are determined based on large cell size; large, vesicular, and irregularly shaped nuclei with coarse chromatin; atypical mitotic figures; and positive immunostaining to PCNA markers. Nonneoplastic cells are identified by their normal morphology and lack of immunoreactivity to proliferation markers. However, it may not be this simple to differentiate accurately between neoplasia and reactive inflammatory response; clonality assays are required to make this determination. Polyclonality is seen with lymphocytic hyperplasia and monoclonality with lymphoma. Accurate characterization and staging of lymphomas in humans have been critical to establish therapeutic management and prognosis. All forms of lymphomas are considered malignant in the horse.[426]

37.33.1 Multicentric Lymphoma

The multicentric form of lymphoma involves lymph nodes (veterinary oncology terminology: nodal = lymph node; multiple lymph nodes = multinodal = multicentric) regardless of location.[426] Extranodal lymphoid tissue (lymphoid tissue other than lymph nodes) is not involved.[426] However, multicentric lymphoma may metastasize to extranodal areas, in which case it will be classified as generalized (diffuse) lymphoma.[426] In veterinary medicine the terms *multicentric* and *generalized* have been used interchangeably.

37.33.2 Generalized Lymphoma

The generalized form is considered an end-stage lymphoma characterized by involvement of both nodal and extranodal lymphoid tissue.[426] This form is more common than the intestinal (extranodal) and mediastinal (nodal) forms alone. Horses often present with severe lethargy, emaciation, anorexia, generalized lymphadenopathy, and edema because of impaired lymphatic drainage.[404,427] Anemia is common, and hypoproteinemia caused by hypoalbuminemia may be found. Although rare, leukemia is generally associated with this form of lymphoma.[413] In addition to lymphoid tissue involvement, infiltration of tumoral cells has been reported in the spleen, liver, bladder, kidney, lung, heart, nasopharynx, eye, ovary, uterus, brain, and spinal cord.[402,413,420] Multifocal eosinophilic granulomas have been identified in neoplastic lymph nodes, thought to be in response to paraneoplastic interleukin-5 (IL-5) and granulocyte-monocyte colony-stimulating factor (GM-CSF) produced by neoplastic cells.[413]

37.33.3 Alimentary or Intestinal Lymphoma

Alimentary tract lymphoma involves the GI tract, more frequently the small intestine.[424,428] Lymphoma is the most common neoplasia of the intestinal tract in horses.[403] This neoplasia has been reported most often in horses less than 5 years of age. However, a recent retrospective study on intestinal neoplasias revealed that the mean age of horses with lymphoma was 16 years (range, 2 to 30 years), with Arabian horses the most common breed associated with this type of lymphoma.[403] Lymphoma arises from the lymphocytes of the lamina propria (extranodal lymphoid tissue) of the intestinal tract, resulting in diffuse or segmental thickening, focal masses, or scattered crater-like ulcers with raised margins of the intestinal wall.[424,425,428] Lymphadenopathy is generally not present. Metastases to mesenteric lymph nodes, liver, and spleen have been reported.[425] Transabdominal ultrasound may be very useful for the detection of intestinal thickening and cecal lymphadenopathy. These tumors could be of B-cell or T-cell origin. Although most of these tumors are considered to be of B-cell origin, clonality assays recently revealed that T-cell lymphomas are more common than B-cell lymphomas in the intestinal tract.[403] This neoplasia is usually associated with malabsorption, protein-losing enteropathy (hypoalbuminemia), weight loss, edema, abdominal effusion, mild recurrent colic, and diarrhea.[428–431] Affected horses frequently have an abnormal glucose or xylose absorption test, indicating small intestinal malabsorption. Taylor et al.[403] reported that abdominal fluid cytologic analysis was useful for diagnosis of miscellaneous intestinal neoplasia in 38% of cases.

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37.33.4 Thoracic Lymphoma: Mediastinal/Thymic

Lymphoma is the most common thoracic neoplasia in horses and may involve mediastinal lymph nodes, thymus, and lungs.[432,433] Exclusive involvement of mediastinal lymph nodes is called *mediastinal lymphoma,* whereas exclusive involvement of thymus is called *thymic lymphoma*.[426] Prevalence varies from 18% to 29% of all forms of lymphoma.[110,430,434] Primary and secondary (metastatic) mediastinal lymphomas have been reported. Most often, however, the neoplasia results from metastasis.[432] Primary mediastinal lymphoma is usually seen in adult horses (mean age of 10 years, range of 2 to 30 years), although it was reported in a 1-month-old foal with a 1-week history of respiratory distress.[402] Metastasis from primary mediastinal lymphoma often occurs. In the early stages of the disease, minimal clinical signs may be observed. Common signs include

nasal discharge, adventitious lung sounds, pleural effusion, thoracic ventral and limb edema, and regional lymphadenopathy at the thoracic inlet.[430,432] Other signs include cough, pyrexia, pleurodynia, and in some cases, respiratory distress.[432,435] Temperature, pulse, and respiratory rate are often elevated. Dysphagia may be observed in some cases with retropharyngeal lymphadenopathy.[436] High nucleated cells counts of several thousand per microliter, with a large percentage of abnormal lymphocytes, are often evident on pleural fluid cytology; however, collection of multiple pleural fluid samples may be necessary to establish a definitive diagnosis.[435] Some of the cytologic abnormalities include the presence of prolymphocytes, lymphoblasts, nuclear blebbing, indented and cleaved nuclei, amorphous nuclei, altered nuclei/cytoplasm ratio, and mitotic figures.[435] Lymphomas could be of B-, T-, or mixed-cell origin, but T-cell lymphomas are more common.[423,435]

37.33.5 Cutaneous Lymphoma

Cutaneous tumors are confined to the skin-associated lymphoid tissue. Single or multiple, subcutaneous, firm, nonpainful nodules ranging from less than 1 cm to greater than 20 cm in diameter can develop rapidly or slowly, regionally, or over most of the body surface.[437,438] The nodules are usually covered with hair. In some cases the lesions tend to wax and wane spontaneously, or they are associated with hormonal influences, seasonality, and steroid therapy. There is one report of complete regression of cutaneous lymphoma after surgical removal of an ovarian tumor.[439] Because of the waxing and waning response, there is controversy whether this may be lymphoid hyperplasia rather than lymphoma. Depending on anatomic location, lymphomas may cause mechanical lameness and limb edema as a result of vascular and lymphatic obstruction. In most cases, no hematologic abnormalities are present, and generalized lymphadenopathy and internal organ involvement are rare. This type of tumor is usually of B-cell origin. Mycosis fungoides is another form of cutaneous lymphoma in which there is diffuse infiltration of neoplastic T-cell lymphocytes in the epidermis, dermis, and subdermis. This type of lymphoma has been reported in a mare with a vulvar mass that infiltrated the skin of the perineum and ventral abdomen.[440] Cutaneous lymphoma may involve mucocutaneous junctions and carries a poor prognosis if deeper tissues are involved.[440]

37.33.6 Angiotrophic Lymphoma

Also known as *endotheliotrophic lymphoma* and *intravascular lymphangiomatosis,* angiotrophic lymphoma has been described in humans, dogs, and cats.[441–443] There is a single report in horses, in a 12-year-old pregnant thoroughbred mare with anorexia, tachycardia, and mild fever.[444] The significant laboratory abnormalities were profound anemia (PCV of 12%), decreased RBC count, marked anisocytosis, mild lymphopenia, low IgM, and marked erythroid hyperplasia and erythrophagocytosis on bone marrow biopsy. Triglycerides, cholesterol, and total bilirubin were elevated on serum biochemistry. Coombs' and Coggins' tests were negative. Postmortem examination revealed generalized icterus, with moderately enlarged mediastinal and mesenteric lymph nodes. Histologic examination revealed thickened pulmonary alveolar septa and vessels crowded with atypical lymphoid cells with scattered mitoses. Similar atypical cells were evident in renal vessels. The neoplastic cells were determined to be of T-cell origin based on immunohistochemical staining. Angiotrophic lymphoma may represent an antemortem diagnostic challenge because of the lack of circulating neoplastic lymphocytes and identifiable masses.

37.33.7 Chemotherapy for Treatment of Lymphoma

Information about chemotherapy for lymphoma in horses is limited. One protocol used in two pregnant mares with lymphoproliferative disease consisted of a combination of cytarabine (200 to 300 mg/m^2 SC or IM every 7 to 14 days), chlorambucil (20 mg/m^2 PO every 14 days) or cyclophosphamide (200 mg/m^2 IV every 14 to 21 days), and prednisolone (1.1 to 2.2 mg/kg PO every 48 hours).[445] Vincristine (0.5 mg/m^2 IV every 7 days) can be added if no clinical improvement is noticed in the first month of therapy. This protocol was continued for 2 to 3 months, followed by a maintenance protocol consisting of gradual decreases of prednisolone, and extending by 1 week the administration of other chemotherapeutic agents, for the next 2 to 3 months. This was followed by extending the administration interval by another week for 2 to 3 months, for a total of 6 to 9 months.[445] Other protocols include drugs used alone or in combination, such as L-asparaginase (10,000 to 40,000 U/m^2 IM every 14 to 21 days), doxorubicin (50 mg/m^2 IV), vincristine (1.4 mg/m^2 IV), and rituximab (375 mg/m^2 IV). A horse with thoracic lymphoma was treated with cytarabine (170 mg/m^2 IM) 2 weeks apart, alternating with cyclophosphamide (142 mg/m^2 IV) 7 days after each dosage of cytarabine.[435] In addition, the horse received prednisolone (86 mg/m^2 PO every 48 hours) and was discharged 1 month after the initiation of chemotherapy, with instructions to continue prednisolone at the previous dosage for life. Eight months after discharge, the horse was in good health and resumed light exercise. Therapy may be attempted with dexamethasone (0.2 mg/kg IV or PO every 24 hours for 5 days), followed by prednisolone (1 to 2 mg/kg PO every 24 hours). Tapering dosages of corticosteroids is not recommended because this has no therapeutic benefit and may induce drug resistance to corticosteroids and chemotherapy.[426]

Complications associated with chemotherapeutic agents in horses include anorexia, lethargy, thrombosis, arrhythmias, laminitis, bone marrow damage, GI and genitourinary toxicoses, urticaria, and immunosuppression. Anemia, thrombocytopenia, leukopenia, and secondary infections may occur.[446] Successful management of cutaneous lymphomas has been achieved using glucocorticoids such as dexamethasone, prednisolone, and betamethasone. As mentioned earlier, however, controversy surrounds the nature of cutaneous nodules as possible lymphoid hyperplasia and not true lymphomas. Other treatments include autologous tumor vaccine and radiation therapy.[447,448] Although periods of remission have been reported with chemotherapy,[435,445] the long-term prognosis has been poor for most horses.

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37.34 LYMPHOMA IN NEW WORLD CAMELIDS

MONICA ALEMAN

Lymphoma is the most common neoplasia in New World camelids. Two forms of lymphoma, multicentric and generalized, have been reported in alpacas and llamas.[449–456] There is no age or gender predisposition. The reported median age of affected alpacas was 0.8 year, with a range of 0.2 to 2 years.[456] The median age of affected llamas was 5.5 years, with a range of 0.3 to 15 years.[456] However, information from approximately 50 camelids with lymphoma (unreported and reported) revealed a mean age of 4 months and 4 years for alpacas and llamas, respectively.[457] Lymphoma has been diagnosed in alpacas as early as a fetus and 2-week-old cria.[457] The pathogenesis of lymphoma in camelids is unknown at present.

The most common clinical signs are weight loss, palpable masses, lethargy, respiratory signs, and anorexia.[449–453] Other signs are tachycardia, fever, weakness, and recumbency if the CNS is affected.[451,456] The most common clinicopathologic abnormalities include anemia, left-shifted leukogram, hypoalbuminemia, and hyperglycemia. Cerebrospinal fluid (CSF) analysis may yield atypical, immature lymphocytes if the CNS is involved.[456] Liver, kidney, heart, bone marrow, lymph nodes, stomach, and nervous system (extradural and subarachnoid spaces) have been reported to be involved.[449–453,456] Immunophenotyping analysis has been limited to three alpacas; two had T-cell and one had mixed B-cell and T-cell lymphoma.[452,456] Treatment of lymphoma was attempted in a single case but was unsuccessful.[451]

37.35 LEUKEMIA IN HORSES

MONICA ALEMAN

Leukemia is a rare neoplasia of the hematopoietic system that originates from the bone marrow (primary leukemia).[310] A leukemic phase (secondary leukemia) has been rarely reported in horses with lymphoma, in which blood and bone marrow were infiltrated with neoplastic cells.[310,413,415,416] Based on cell of origin, the major forms of leukemia include myeloid and lymphoid leukemias, which can have an acute or chronic clinical course. According to the Leukemia and Lymphoma Society, *acute* leukemias are rapidly progressing disorders that affect mostly primitive or immature cells that lack normal function; whereas *chronic* leukemias progress slowly, allowing some growth and cell maturation, which may preserve limited normal function. Reported leukemias in the horse include myelomonocytic, monocytic, granulocytic, eosinophilic, and lymphocytic forms.[76–79,413,415,458–472] Based on presence and numbers of cells in blood, other terms used are leukemic, subleukemic, and aleukemic leukemias. *Leukemic* leukemia is characterized by an increase in cell numbers in peripheral blood. *Subleukemic* leukemia is defined by an increase in abnormal blast cells in blood, with a total white blood cell (WBC) count within the reference range or low. *Aleukemic* leukemia is characterized by abnormal cells in the bone marrow, but not in peripheral blood.

There is no apparent breed or gender predisposition based on the few reported cases and horses seen at the University of California, Davis.[76–79,413,415,458–472] The age at onset of clinical signs ranges from 2 to 25 years. The most common clinical signs are weight loss, lethargy, anorexia, pyrexia, and lymphadenopathy if associated with lymphoma. Other signs are weakness, ventral edema, exercise intolerance, colic, and recurrent or concurrent infections.

At the initial stages of the disease, the laboratory features may show mild hematologic abnormalities, including one or more of the following: anemia, neutropenia, lymphopenia, thrombocytopenia, hyperproteinemia, and hyperfibrinogenemia. As the disease progresses (days to months), marked leukocytosis (counts up to 270,000 WBCs/μL) and hyperproteinemia will be observed in leukemic leukemias.[413] Thrombocytopenia is a common hematologic feature.[413,468,469,472] Pancytopenia and high blast cell counts (up to 1.6×10^9 cells/μL) were reported in a lactating mare with myeloblastic leukemia.[472] Pancytopenia caused by severe infiltration of leukemic cells in the bone marrow, ineffective hematopoiesis, and myelofibrosis have been reported.[468] Horses with multicentric lymphoma, pancytopenia, severe leukocytosis (more than expected for severe inflammation), or presence of atypical or blast cells in peripheral blood should prompt the collection of a bone marrow aspirate or biopsy. Bone marrow aspirates may have normal to altered myeloid/erythroid ratio (reference range, 0.5 to 3.76), with a

disproportionate number of atypical or poorly differentiated blast or mature cells of certain lineage. A decrease in or absence of megakaryocytes is often observed.

Hyperproteinemia is a consistent finding because of hyperglobulinemia. Serum electrophoresis typically shows a polyclonal increase of β_2- and γ-globulin fractions, and in some cases α-globulin fraction as well. Marked increases in serum IgG and IgA concentrations have been detected in horses with lymphocytic leukemias.[413] Deficiencies in IgA and IgM have been reported in a single horse with chronic lymphocytic leukemia.[465]

Necropsy findings may include mucosal ulceration, edema, thrombosis, and hemorrhages of various organs resulting from intravascular leukostasis (aggregates of leukemic cells in blood vessels), disseminated intravascular coagulopathy, and thrombocytopenia secondary to decreased production of megakaryocytes. Leukemic-induced cell lysis may occur as the result of mediators released by neoplastic cells. Peripheral and internal lymphadenopathy may also be observed. Other pathologic findings are those associated with concurrent disease.

The diagnosis is based on routine blood work, cytologic and histopathologic evaluation of bone marrow, immunocytochemical analysis, flow cytometry, and immunophenotyping.[310] Previously, leukemic cells in peripheral blood and bone marrow were described based on their morphology; however, this may result in leukemia misclassification, especially in acute leukemias, in which mononuclear blast cells constitute the leukemic clone, which may lack specific identifying morphologic features. Numerous cytologic and cytochemical stains have been used to determine the type of leukemia, such as Wright, Giemsa, Sudan black B, peroxidase, periodic acid—Schiff, alkaline phosphatase, acid phosphatase, various esterases, and surface glycoproteins. However, leukemic cells may also lack specific cytochemical properties. Currently, the various types of leukemias are determined by the identification of specific cellular antigens using a panel of monoclonal antibodies and flow cytometry in peripheral blood and bone marrow; examples are B-cell/IgM-positive, B-cell/IgM-negative, CD3/CD4/CD5-positive T-cell, CD3-negative/CD4-positive T-cell, and CD13-positive myeloid leukemias.[413,465,469] Table 37-2 lists the various monoclonal antibodies for specific equine leukocyte antigens.

The prognosis is poor, resulting in death within days to a few months after diagnosis. Treatment of leukemia has been attempted in horses with cytosine arabinoside, cytarabine, and prednisolone, but with little success.[461,469,471] 1179 1180

Table 37-2 Monoclonal Antibodies for Specific Equine Leukocyte Antigens (ELAs)

ELA Marker	Specificity
EqCD2	T cells
EqCD3	T cells
EqCD4	T helper cells
EqCD5	T cells
EqCD8	T cytotoxic cells
EqCD11a/18	Pan leukocyte
EqCD13	Myeloid cells
EqCD44	Pan leukocyte
CD79a	B cells
EqWC1	Large T-cell and neutrophil subsets
EqWC2	T cells and neutrophils
EqWC4	Minor T-cell subset
MHCI	Nucleated cells
MHCII	B cells, macrophages, dendritic cells, and large T-cell subset
IgM	B cells

Data from McClure JT, Young KM, Fiste M, et al: Immunophenotypic classification of leukemia in 3 horses, *J Vet Intern Med* 15:144, 2001.

Eq, Equine; *CD,* cluster of differentiation; *WC,* white cell; *MHC,* major histocompatibility complex.

37.36 MYELOMA IN HORSES

MONICA ALEMAN

Myeloma is a neoplastic proliferation of plasma cells that primarily originate in the bone marrow but may have an extramedullary source.[473] Both forms have been reported in the horse.[474–476] Accumulations of neoplastic plasma cells outside the marrow is called *extramedullary plasmacytoma*.[473] Plasmacytomas can form in several organs and tissues, including the skin. The most common extraosseous sites in horses are lymph nodes, kidneys, spleen, and liver.[474,476,477] Multiple myeloma involves bone marrow at multiple locations and other tissues; and it is the most common form of myeloma in humans.[478] In human medicine, causes of myeloma include chromosomal translocation, irradiation, and chronic antigenic stimulation.[473]

Myeloma is a rare neoplasia of the horse, with only 16 cases reported in the literature, at a median age of 14 years (range, 3 months to 25 years).[474–477,479–489] Almost half these cases were quarter horses, but various breeds, including draft horses and ponies, were represented. There is no apparent gender predilection. The clinical signs

vary with the degree of plasma cell infiltration, extent, and location. The most common clinical signs are weight loss, anorexia, fever, pale mucous membranes, lethargy, limb edema, and recurrent infections.[474–477,488,489] Bone pain as the result of osteolytic disease is the most common early sign of myeloma in humans.[478] Four horses from the literature were reported to have lytic lesions. The clinical signs in these horses included paresis, cervical pain, and lameness.[476,480,482,485]

The laboratory features are anemia, hyperproteinemia caused by hyperglobulinemia, hypoalbuminemia, and proteinuria. Anemia results from reduced erythropoiesis secondary to myelophthisis and infection, blood loss, and paraproteins' osmotic effect. Pancytopenia is observed if myelophthisis develops. Hypercalcemia has been reported in a few cases.[474,476,477] Exception to these features occurred in one gelding with systemic AL amyloidosis and multiple myeloma.[489] This horse had hypoproteinemia, hypoglobulinemia, hypoalbuminemia, and hypocalcemia; thought to be the result of protein-losing enteropathy caused by the severe, diffuse gastrointestinal amyloidosis.[489] Concurrent systemic amyloidosis and multiple myeloma are common in humans but extremely rare in domestic animals, with only one cat and one horse reported in the literature.[489,490] Serum parathyroid hormone—related protein concentration was mildly elevated in one horse with multiple myeloma.[477]

In secretory myelomas the neoplastic plasma cells are responsible for overproduction of a monoclonal immunoglobulin called M protein, or paraprotein. M protein may be fragments (mainly light chains, also called Bence Jones protein) or a complete immunoglobulin. Subclasses of IgG are the predominant paraprotein associated with myeloma in horses.[474,488] Recently, however, three horses were reported to have IgA paraprotein.[476,477]

Plasma cells are relatively sparse in normal bone marrow. The involvement of the marrow is usually focal rather than diffuse, requiring multiple marrow aspirates in some cases to confirm plasmacytosis. The diagnosis of multiple myeloma in humans is based on the presence of at least 10% of plasma cells in the affected tissue, monoclonal protein in serum or urine, and evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions). Renal insufficiency has not been reported in horses with myeloma.[474,476] Bleeding and blood hyperviscosity syndrome are common complications of multiple myeloma in humans[478]; these complications have been reported in four horses.[474,483] In addition, bone nuclear scan studies have been helpful in humans to detect single (monostotic) versus multiple (polyostotic) myeloma.

Median survival after diagnosis in humans is approximately 3 years.[478] Because of poor prognosis or deterioration, most reported horses were euthanized within a few days to months after diagnosis. However, two horses survived for 1 and 2 years, respectively.[484,487] A quarter horse with multiple myeloma was euthanized at age 29 years, 3.5 years after diagnosis, because of deterioration.[476] This horse had weight loss, intermittent limb and ventral edema, recurrent infections, and colic. Serial blood work revealed mild anemia, hyperproteinemia, hyperglobulinemia, hypoalbuminemia, hypercalcemia, and hyperproteinuria.

37.37 LYMPHANGIOMA IN HORSES

MONICA ALEMAN

Lymphangioma is a rare tumor in horses that originates from lymphatic vessels. Morphologically, lymphangiomas are classified into three types: simplex or capillary, cavernous, and cystic.[491] This neoplasia has been described involving cutaneous tissue of the mammary gland, thigh and inguinal regions, pleural cavity, and intestines.[492–

[494] Lymphangioma has only been observed in young horses. The clinical signs vary depending on tumor location. Because of the extent of these tumors, surgical removal has not been possible, resulting in euthanasia.

37.38 OTHER DISEASES OF THE HEMOLYMPHATIC SYSTEM

37.38.1 ANTHRAX

RICHARD L. WALKER

Anthrax is a soil-borne bacterial disease primarily affecting herbivores. It most often presents as an acute septicemia with high mortality. Other animal species, including humans, can be infected. Anthrax occurs worldwide and is noteworthy because of its impact on agriculture and its potential to cause zoonotic infections. The anthrax bacillus has recently garnered increased attention because it is one of the microbes most likely to be used as a bioterrorism agent.

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37.38.2 Etiology

Bacillus anthracis is the etiologic agent of anthrax. In the vegetative form, it is a large, rectangular-shaped, gram-positive rod. Vegetative cells are predominantly found in tissues of infected animals; however, *B. anthracis* exchanges genetic information with other *Bacillus* species in the environment, indicating vegetative cells exist, to some extent, outside animal hosts.[495] Under nutritionally limiting conditions, vegetative cells are induced to form spores. Sporulation is an oxygen-dependent process and does not occur under anaerobic conditions. The spore form of *B. anthracis* is highly stable and resists many chemical and heat treatments, as well as adverse environmental conditions.[496] Spores can survive and remain infectious in the environment for decades.

37.38.3 Pathogenesis

Exposure of animals occurs primarily from grazing contaminated pastures and ingesting spores.[497] Fodder grown in contaminated soil and contaminated animal by-products are other sources for infection. In swine, consumption of contaminated animal by-products in feed is the usual source of infection.

Ingested anthrax spores cross mucosal barriers, are phagocytosed by macrophages, and are transported to regional lymph nodes. As spores convert to their vegetative phase, they are able to avoid the antimicrobial action of the phagocyte and escape into the extracellular environment. The production of plasmid-encoded virulence factors, particularly a poly-D-glutamic acid capsule and a three-component toxin, are key to survival in the host.[497] Production of a capsule is important in evasion of the host's phagocytic defenses. The three components of the toxin are protective antigen (PA), lethal factor (LF), and edema factor (EF). PA attaches to host cells through surface receptors, polymerizes to form a prepore, and binds one or both of the other two toxin components, LF and EF. This entire complex enters the cell by endocytosis. In the endosome the polymerized prepore becomes a functional pore and allows LF and EF to enter the host cytoplasm.[498] The enzymatic effects of EF and LF disrupt host cell functions, including innate and adaptive immune responses.[499] EF increases cyclic adenosine monophosphate (cAMP), leading to tissue edema and suppression of phagocytic capability. LF causes cell death through interruption of signal transduction pathways and increases numerous proinflammatory

cytokines. The result is rapid proliferation of *B. anthracis* in the host and an overwhelming septicemia. Death is caused by toxic shock with hypotension and multiorgan failure.

37.38.4 Epidemiology

As mentioned, anthrax occurs worldwide, and frequency of outbreaks depends on geographic location. Some parts of the world (sub-Saharan Africa, central and southern Asia), with high concentrations of spores in the soil are referred to as "anthrax zones." In the United States, certain states or geographic regions, such as Texas and the plains regions, have more occurrences of anthrax than other areas. Some areas with greater incidence of disease follow old cattle trails, which may have been the primary source for contaminating those environments.[500,501]

Environments favorable for anthrax spores include soils with elevated pH and concentrations of selected cations (Ca^{++}, Mn^{++}) and soils rich in organic material.[497] Droughts followed by heavy rainfall or flooding often precede outbreaks, as do earth-disturbing activities such as excavations. Topography that favors collection of runoff and establishment of temporary water storage areas (seasonal ponds) may promote the concentration of spores.[500,501] Outbreaks usually occur during warmer months of the year.

Bites from bloodsucking insects can spread anthrax organisms from infected septicemic animals through mechanical transmission.[502] Scavenging animals can also disseminate organisms.[501] Carcasses of affected wildlife are an additional source for contaminating environments because they are unlikely to be disposed of properly.

37.38.5 Clinical Presentation

Susceptibility to *B. anthracis* infection depends on the individual animal species. Ruminants (cattle, sheep, and goats) are most susceptible. Because of the often peracute nature of anthrax in ruminants, clinical signs before death may not be observed. If seen, nonspecific clinical signs include fever, depression, respiratory distress, congestion of mucous membranes, and convulsions.[503] In more protracted cases, bloody diarrhea, hematuria, and localized tissue swelling may be observed.

Horses develop an acute intestinal form of anthrax. Associated clinical signs include colic, diarrhea, fever, and depression followed by a fatal septicemia. A more localized form, possibly initiated by insect transmission, typically involves the neck region with massive edema. A dependent edema may result involving the thorax, abdomen, prepuce, or mammary gland.

SWINE are less susceptible to anthrax infection. Oropharyngeal involvement with swelling of the head and neck is the most common presentation.[497] If severe enough, edematous tissue may obstruct breathing and swallowing. Cervical lymph nodes are prominently involved. An intestinal form may present as dysentery. Pregnant animals may abort.

37.38.6 Pathology

Animals that die of anthrax sometimes produce bloody exudates from body orifices and show incomplete rigor mortis. Blood is poorly clotted. Carcasses undergo rapid decomposition. If a carcass is opened, the spleen is frequently enlarged and has a "blackberry jam" consistency. Lymph nodes may be edematous and hemorrhagic. Hemorrhages may be present on the surface of other organs. Signs of enteritis may be apparent. The more

localized edematous form shows regional swelling. In the oropharyngeal form the cervical lymph nodes are edematous and hemorrhagic.[503] Histologically, large numbers of bacilli are observed in most tissues of septic animals. Spleen and lymph node architecture is obscured by the massive hemorrhages.

37.38.7 Diagnosis

Initially, anthrax may be confused with clostridial infections, lightning strikes, plant poisoning (e.g., oleander), other intoxications, or mineral deficiencies. Carcasses of animals with suspected anthrax should not be opened, in an effort to prevent sporulation of vegetative cells and further contamination of the environment. Laboratory diagnosis is necessary for definitive diagnosis of index cases. Diagnosis is made by examining direct blood or tissue smears and performing bacteriologic cultures. Samples that minimize the potential for environmental contamination but still provide good-quality cultures include unclotted blood collected from superficial veins and ocular fluid collected in a sterile syringe using a large-gauge needle. An intact eye can also be removed and submitted to the laboratory for diagnostic evaluation. In the more localized form of anthrax, samples from regional lymph nodes may be required. Because anthrax carcasses undergo rapid putrefaction, and vegetative *B. anthracis* cells are destroyed during the putrefactive process, the time between death and sample collection can substantially affect the recovery rate of *B. anthracis*. As a good safety practice, whenever a case of anthrax is suspected, this should be relayed to laboratory personnel performing the diagnostic testing.

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Examination of direct smears by Gram stain is performed to demonstrate the typical, large, gram-positive, squareended rods found singly or in chains of two to four cells. A polychrome methylene blue (M'Faydean) capsule stain is performed to demonstrate the presence of the *B. anthracis* capsule surrounding organisms observed in direct smears. Frequently it is necessary to distinguish anthrax bacilli from postmortem invading clostridial species, which have more rounded ends and are acapsular when examined with the M'Faydean stain. *B. anthracis* also stains well with common laboratory stains, including Wright and Giemsa stains, and displays morphology similar to that observed on Gram staining.

Isolation of *B. anthracis* is readily made on standard sheep blood agar. Colonies are apparent after as soon as 6 hours of incubation. Typical *B. anthracis* colonies after 24 hours of incubation are large, gray-white, with a bee's-eye texture. Colonies are usually nonhemolytic. Gram stains of young colonies show very long chains (≥10 cells) of large, square-ended, gram-positive rods often described as having the appearance of a row of “railway boxcars.”

Identification of *B. anthracis* isolates is confirmed by demonstrating lack of motility, lysis by a specific bacteriophage (gamma phage), and protoplast formation in the presence of penicillin (string of pearls test).[504] Capsules are demonstrated in culture by growing isolates on bicarbonate agar under an increased CO_2 atmosphere. Spores develop in cultures after approximately 48 hours of incubation. They are centrally located in the cell and do not cause the cell to bulge.

A number of molecular-based and rapid screening tests for detecting *B. anthracis* directly from samples or for identifying individual isolates are available. Most of these are primarily used in bioterrorism surveillance programs. PCR-based assays using primers specific for the capsule and PA genes are useful for differentiating field strains from the vaccine strain. Because of the sporadic nature of the natural disease, molecular-based identification may not be available in all veterinary diagnostic laboratories.

37.38.8 Treatment, Control and Prevention

Any suspected anthrax case should be reported to appropriate local or state veterinary regulatory officials as soon as possible. Because of the peracute nature of many anthrax infections, successful treatment requires early intervention; however, treatment is often unrewarding. Penicillin and tetracycline remain the drugs of choice for treating animals. Treatment should be continued for a minimum of 5 days. Rare *B. anthracis* strains resistant to these antibiotics have been reported.

Carcass management is critical in controlling anthrax outbreaks. Carcasses should not be opened or moved from the area where they are discovered. Carcasses are destroyed either by burning or deep burial. Burning of carcasses is preferred to burial because it is more effective at destroying spores. Any contaminated bedding or soil should be handled similarly.

In the face of an outbreak, regulatory officials will likely quarantine affected premises. All potentially exposed animals should be closely observed for clinical signs that suggest they might be infected. All clinically normal animals should be vaccinated using a commercially available, live, acapsular vaccine strain (Sterne strain).* Prophylactic antibiotic treatment of unaffected herdmates is sometimes practiced; however, the combined use of antibiotics and vaccination in individual animals is not recommended. Because the vaccine is a live attenuated strain, concurrent use with antibiotics may lessen effectiveness of the vaccine. Combined vaccination and prophylactic antimicrobial treatment should be undertaken only after consultation with local veterinary public health or regulatory officials. Vaccination of neighboring herds should be initiated to prevent new infections resulting from either exposure to similar predisposing environmental conditions or through spread from initial outbreak sources. Controlling insects and both avian and mammalian scavengers will aid in preventing dissemination to neighboring premises.[501]

Vaccination is the major prophylactic measure undertaken to protect animals in endemic areas. Vaccination should be performed annually 4 weeks prior to turning animals onto pastures where outbreaks have occurred. A single dose of vaccine is given subcutaneously in the neck. In heavily contaminated areas, a second dose may be given 2 to 3 weeks later to afford better protection. The vaccine manufacturer's recommendations or local regulatory official's instructions should be followed regarding postvaccination market-withholding time for meat and discard time for milk. A minimum 42-day, postvaccination withholding period before slaughter is recommended. Localized swelling may occur at the site of vaccination. Goats and llamas may exhibit serious adverse reactions to the vaccine.

Ensuring that pastures are of good quality so that animals will not graze close to the soil will minimize exposure to spores. Avoiding rough feed that might traumatize mucosal surfaces will also decrease incidence rates. If possible, grazing animals on highly contaminated pastures should be avoided altogether and alternate uses encouraged for the land.

* Anthrax spore vaccine, Colorado Serum Co., Denver, Colo.

37.38.9 Public Health

Anthrax is a zoonotic disease. Humans develop three forms of anthrax: cutaneous, inhalational, and gastrointestinal.[497] Occurrence of the different forms depends on the route of exposure. Naturally acquired anthrax cases in humans in the United States are rare. When they occur, the cutaneous form is most common. Veterinarians are included among at-risk individuals because of the potential for contact with organisms while

handling infected carcasses. If anthrax is suspected, proper personal protective equipment, including physical barriers (e.g., gloves) and respiratory protection, should be used when collecting diagnostic samples and during carcass disposal. Naturally acquired inhalational anthrax in humans is rare because of the relatively high median lethal dose (LD_{50}, 8000 to 10,000 spores) required for infection and because spores carry static charges. These charges result in spores binding to larger particles, making aerosolization of spores more difficult.[500]

Concern about biologic weapons and terrorism has focused the public health community's attention on *B. anthracis* because it is an agent well suited for such use. Dissemination of a powdered form of anthrax spores through the mail in a bioterror attack on the eastern coast of the United States in 2001 demonstrated the effectiveness of *B. anthracis* as a biologic weapon. In that incident, both cutaneous and inhalational anthrax cases in people occurred.[505] *B. anthracis* is now classified as a "select agent," meaning that possession of virulent strains is federally restricted. Any isolation of *B. anthracis*, even from naturally occurring cases, must be reported to appropriate federal regulatory agencies (USDA) and any *B. anthracis* isolates securely stored or destroyed.[506]

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37.39 LYME DISEASE

MONICA ALEMAN

JOHN E. MADIGAN

Lyme disease, also known as *borreliosis,* is one of the most important arthropod-borne bacterial infections in the United States. The disease is caused by the spirochete *Borrelia burgdorferi* and affects humans, horses, dogs, and cats.[507–510] Lyme borreliosis was first identified as a causative agent of an epidemic of juvenile inflammatory arthritis in children and adults in Old Lyme, Lyme, and East Haddam, Connecticut.[511,512] Therefore, medical references usually cite "Lyme disease" when referring to infection with *B. burgdorferi*.

37.39.1 Epizootiology

B. burgdorferi is widely distributed in the Northern Hemisphere. Prevalence of infection or exposure in horses has been reported to be high in the northeastern United States (50%), Midwest, Texas, and California.[513] Lyme borreliosis has been reported extensively in Europe, England, Russia, China, Japan, Southeast Asia, and South Africa.[514] *B. burgdorferi* is transmitted from ticks to humans and animals by ticks belonging to the *Ixodes ricinus* complex.[515] These ticks each feed three times, during the larval, nymphal, and adult stages.[511] The larvae and nymphs feed on wild animals, and adults are found most often on deer.[515] On the East Coast, *Ixodes scapularis* ticks are the principal vector, whereas on the West Coast, *Ixodes pacificus,* the western black-legged tick, is the main vector identified.[516] *I. scapularis* is seen from the Atlantic coast to Oklahoma and Texas.[517] A much higher percentage of *I. scapularis* ticks (12% to 99%) will carry the spirochete compared with *I. pacificus,* in which the maximum number of infected ticks is 4% to 5%.[516,517] *I. scapularis* larval ticks acquire the spirochete principally from *Peromyscus leucopus,* the white-footed mouse, and the nymphal stages are the major transmitters of disease to animals and humans.[518] With *I. pacificus* the California kangaroo rat, *Dipodomys californicus,* and the dusky-footed wood rat, *Neotoma fuscipes,* are the likely enzootic reservoirs of *B. burgdorferi*.[519]

Borrelia burgdorferi is found in many arthropods, but the major route of transmission to animals and humans is believed to be limited to the *Ixodes* species ticks. Experimental studies have demonstrated that ticks may harbor and transmit several pathogens, including the human granulocytic ehrlicheal agent and *B. burgdorferi,* at the same time.[520] Exposure to ticks infected with *B. burgdorferi* produced seroconversion without detectable histopathologic changes except for skin lesions in experimental horses.[521]*B. burgdorferi* is maintained in a 2-year enzootic cycle that involves *Ixodes* species ticks and mammals. Ticks are usually attached for at least 24 hours for *B. burgdorferi* transmission.[521] Birds are frequently infected with *B. burgdorferi* and may be responsible for the spread of the disease to new areas.[515]

37.39.2 Public Health Considerations

Surveillance for Lyme disease was initiated by the U.S. Centers for Disease Control and Prevention (CDC) in 1982, and in January 1991 it became nationally reportable. Cases have been reported from 46 states, and the annual number of Lyme disease cases has increased 18-fold, from 497 to 8803. It is now the most common tick-transmitted disease in the United States.

Borrelia burgdorferi organisms have been recovered from the urine of feral white-footed mice, *Peromyscus leucopus*.[522] Contact transmission has been reported among white-footed mice,[522] further complicating the understanding of transmission. Because of lack of any proof to the contrary, it is generally believed at this time that any potential increased risk to humans from infected animals is attributable to animals bringing ticks into areas of human habitation rather than any animal transmission.[523]

37.39.3 Molecular Biology

Immunochemical analysis of North American strains of *B. burgdorferi* reveal two abundant surface proteins, termed outer surface protein A (OspA, 30 to 32 kD) and outer surface protein B (OspB, 34 to 36 kD).[524] The 41-kD antigen is located on the flagellum and is similar to the flagellar antigens of other spirochetes.[525] All isolates to date have four to nine pieces of extrachromosomal plasmid DNA. Plasmid may code for proteins that are important in pathogenicity because the loss of infectivity of isolates that have been heavily passaged in the laboratory correlates with the loss of particular plasmid in culture.[526] Recent work suggests that *B. burgdorferi* can vary its antigenicity similar to the relapsing fever—causing *Borrelia* (e.g., *B. hermsii)*, although by a different mechanism and by using subtle alterations in the genome.[527]

37.39.4 Clinical Signs

37.39.4.1 EQUIDS

Clinical signs are not specific but may include low-grade fever, stiffness, lameness in more than one limb, muscle tenderness, hyperesthesia, swollen joints, and behavioral changes.[528,529] The most common signs are lameness and hyperesthesia. These signs have been reported more often in performance horses. *Borrelia* may be found concurrently with *Anaplasma phagocytophila* in *Ixodes* ticks, resulting in dual infection in the horse.[520]

Horses from endemic areas have serologic evidence of exposure.[530–533] Attempts have been made to correlate individual cases of arthritis, uveitis, or brain infection with this organism.[532,534,535] Experimental infection has produced seroconversion and shedding of the organism in the urine and seroconversion in contact controls.[536] In the United Kingdom, most seropositive horses do not show clinical signs of disease.[537]

37.39.4.2 RUMINANTS

Although there are some reports in the literature of seropositive animals with arthritis, the evaluation performed on the patients makes it difficult to determine if *B. burgdorferi* was the cause of the signs.[538] It appears at this time that many ruminants are seropositive to *B. burgdorferi* but do not have clinical signs. Whether these tests lack specificity in the ruminant or represent a host-adapted strain of the *Borrelia* organism is unknown.[539] A recent report correlates exposure of *I. scapularis* ticks in dairy cattle with titers to *B. burgdorferi*.[540] An attempt to develop a more specific test in cattle using the 41-kD flagellin antigen has recently been reported.[541]

37.39.5 Diagnosis

A number of diagnostic methods are available, including IFA, ELISA, indirect CF, and Western blot.[535,538] Culture of the organism requires special media (BSK) and is difficult but may be possible from blood, urine, or CSF. Diagnosis of recent or active *Borrelia* infection has been based on high ELISA titers (>300 units kinetics-ELISA [KELA]), positive Western blot, or PCR.[542] In an experimental infection study, *I. scapularis* ticks infected with *B. burgdorferi* were placed in healthy ponies for 7 days. These ponies developed detectable antibody at 5 to 6 weeks.[542] KELA units were elevated at 3 to 4 months postexposure and remained elevated for several months until euthanasia. Western blot became positive at 10 to 12 weeks postexposure.[542] Throughout the study the organism was isolated from the skin where infected ticks were attached. Histopathologic examination revealed lymphohistiocytic nodules in the dermis, lymph node enlargement, and perivascular and perineural lymphocytic infiltrates in the skin, fascia, and perisynovial membranes. PCR was useful for the detection of organisms in the skin, lymph nodes, skeletal muscle, fascia, and synovial membranes. Less often, the organisms were detected in heart, pericardium, kidney, bladder, and meninges.[542] More recently, detection of serum antibodies to *B. burgdorferi* in horses was improved (84% detection) by using an ELISA based on whole-cell and recombinant antigens.[543]

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37.39.6 Treatment

Antibiotic susceptibility of *B. burgdorferi* has been reported but may lack appropriate standardization.[544] *B. burgdorferi* is sensitive to tetracycline and moderately sensitive to penicillin. Amoxicillin, ceftriaxone, and imipenem are highly active against *B. burgdorferi*. Aminoglycosides, ciprofloxacin, and rifampin lack activity.[545] Doxycycline twice daily in humans has been frequently used. Probenecid and ampicillin or amoxicillin also have been used.[544] When CNS involvement is present, ceftriaxone or IV penicillin G has been used. The appropriate duration of therapy is unknown but is related to the stage of infection.

Three different antimicrobials—ceftiofur sodium (2.2 mg/kg/day IM), doxycycline (10 mg/kg/day PO), and tetracycline (5 mg/kg/day IV)—were used for a 28-day period in experimentally infected ponies.[546] High KELA titers and *B. burgdorferi* isolation from skin biopsies confirmed infection. Antimicrobial therapy was initiated 3 months postexposure. Tetracycline was the most effective antimicrobial; it decreased KELA antibody titers (<110 units) during and months after treatment, and bacterial isolation became negative in tissues. However, tissues were still positive for the spirochete on PCR.[546] The efficacy of decreasing titers of tetracycline in the clinical setting has not been highly successful.[547] Proposed treatment for *Borrelia* infection includes tetracycline (6.6 mg/kg IV every 12 hours), doxycycline (10 mg/kg PO every 12 hours), or ceftiofur (2.2 mg/kg IM every 12 hours) for 3 to 4 weeks.[542]

A recombinant outer surface protein A (rOspA) subunit vaccine was shown to be effective in preventing infection in challenged horses with infected ticks.[520,548] Specific recommendations for its use in the clinical setting are lacking.

37.40 TULAREMIA

BRADFORD P. SMITH

Tularemia is an infectious disease of humans, wild animals, livestock, and pets caused by *Francisella (Pasteurella) tularensis*. The organism is a facultative, intracellular, non-spore-forming, gram-negative coccobacillus that survives frozen or in mud and water for long periods (>1 year),[549] but it only survives for hours in carcasses. The natural hosts are rabbits and rodents, and transmission to livestock occurs chiefly through ticks, fleas, deerflies, and other insects.[550] Sheep are the most frequently affected livestock species. Massive epidemics with a high mortality in range sheep have been reported.[550] Humans are stricken with a plaguelike illness when bitten by infected ticks, fleas, or insects and from handling infected rabbits or other infected animal carcasses.[551] Sheep shearers may become infected by bites of parasites from the sheep. Disease in horses has also been documented.[552] Oral infection from contaminated water occurs, so fresh water should be provided.[550]

The disease causes an acute septicemia, with localization and granulomatous lesions in the organs (particularly the liver and spleen). Signs are very nonspecific, as expected with bacteremia, and include fever, anorexia, lethargy, and in some cases cough, rapid respiration, or diarrhea. Stiffness and edema of the limbs may be seen. The course of disease is usually 2 to 14 days.

Agglutination titers in recovered affected sheep range from 40 to 5000. Agglutination titers persist for very short periods (21 days) in horses,[550] probably because they measure mainly IgM. Diagnosis is based on culture of the organism from blood or organs. Diagnosis can also be made by IFA testing or PCR.[553]

Necropsy usually reveals ticks on the carcass. Often, reddened or necrotic areas appear in and under the skin at the site of infected bites. Regional lymph nodes may be swollen and congested. Congestion and edema of the lungs are common. Differentials include other bacteremias such as *Mannheimia (Pasteurella) haemolytica* in sheep, *Histophilus somni (Haemophilus somnus),* in cattle, *Mycoplasma mycoides* subspecies *mycoides* in goats, and anthrax in all livestock. Treatment early in the course of infection is effective. Aminoglycosides, tetracyclines, or cephalosporins all are probably beneficial initially, until results of antimicrobial susceptibility testing are available. Insecticide removal of ticks from affected animals and herdmates is important. No vaccine is currently

available, so insect and tick control in endemic areas remains the major prevention. Because oral infection from contaminated water has also been documented, fresh water should be provided.

37.41 *CORYNEBACTERIUM PSEUDOTUBERCULOSIS* INFECTION

MONICA ALEMAN

SHARON J. SPIER

37.41.1 Definition

Corynebacterium pseudotuberculosis infections occur worldwide and cause external and internal caseous lymphadenitis in sheep and goats; cutaneous excoriated granulomas and mastitic, visceral, or mixed infection in cattle; and ulcerative lymphangitis and external and internal abscesses in horses.[554–557] Subacute to chronic lymphadenitis and pneumonia have been reported in humans handling infected sheep.[558,559] Several zebras in the United States developed severe or multiple internal abscesses and died weeks after being exposed to horses in California.[560] There have been reports of the disease in camels, alpacas, and buffalo.[561–563]

37.41.2 Microbiology

C. pseudotuberculosis infection is caused by a 2-µm, gram—positive, intracellular, nonmotile, pleomorphic rod-shaped, facultative anaerobe.[554,564] *C. pseudotuberculosis* grows well at 37° C on blood agar in 24 to 48 hours, and it forms small, pinpoint-diameter, whitish, opaque colonies that are surrounded by a weak zone of hemolysis. Because of the high content of lipids in the bacterial cell wall, particularly corynomycolic acid, the colonies spatter in a flame can be pushed across the agar surface.[554] The high content of lipids may facilitate survival of the organism in macrophages.[565] Two species-specific biotypes of *C. pseudotuberculosis* have been identified based on differences in nitrate reduction[559] and DNA fingerprinting techniques.[566–568] Strains isolated from small ruminants are nitrate negative, strains from horses are nitrate positive (except for two horses that were nitrate negative), and both strains have been isolated from cattle.[555,559,567,569] From DNA studies the terms “biovar equi” for nitrate-positive and “biovar ovis” for the nitrate-negative strains were proposed.[566] Recent studies revealed that there is more heterogeneity of the isolates of *C. pseudotuberculosis* from small ruminants and from horses[567,568,570] and concluded that nitrate reduction may not absolutely distinguish between the isolates as does ribotyping.[567] On the basis of ribotyping, sheep and goats have specific isolates throughout the world, and horses and cattle have two distinct groups of isolates depending on geographic location, with one from the United States and the other from South Africa and Kenya.[567] Natural cross-species transmission does not seem to occur.[554]

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Corynebacterium pseudotuberculosis produces various exotoxins, including phospholipase D (PLD), sphingomyelinase, inhibitory factor of staphylococcal beta hemolysin, hemolysis factor, dermanecrotoxins, and mouse lethality toxins.[571] PLD and sphingomyelinase are important in the pathogenesis of the disease because they hydrolyze lysophosphatidylcholine and sphingomyelin, respectively, thus degrading the endothelial cell wall and increasing vascular permeability.[572] The synergistic activity of sphingomyelinase with the exotoxin of *Rhodococcus equi* in lysing RBCs in agar forms the basis for the synergistic hemolysis inhibition (SHI) test.[573]

Most recently, molecular characterization of *C. pseudotuberculosis* isolates from four different states (California, Colorado, Kentucky, and Utah) was determined by random-amplified polymorphic DNA (RAPD) PCR.[574] The identity of *C. pseudotuberculosis* in these isolates was confirmed by the presence of the gene encoding the PLD toxin by PCR. Ten distinct genotypes (I to X) were identified. Types IV to VIII and X were isolated only from horses, whereas types III and IX were isolated from horses and cattle. This study also found differences in genotypes among states as follows: California (III, IV, V, VI, IX, X), Colorado (III, VI, VII, IX, X), Kentucky (III, IV, V, VI, VIII), and Utah (III). In horses, types III, VI, and X were isolated from internal abscesses from California and Kentucky, and types III to VI and VIII to X were isolated from external abscesses from one or more states.[574]

37.41.3 Clinical Signs and Differential Diagnosis

37.41.3.1 SHEEP AND GOATS

C. pseudotuberculosis causes caseous lymphadenitis (CLA) in sheep and goats worldwide. CLA is a major cause of poor production, premature culling, and mortality. The two forms of CLA are external and internal abscesses.[575] The infection in small ruminants is primarily characterized by suppuration and necrosis of the large, superficial lymph nodes. *External abscesses* are found more often involving the mandibular, parotid, prefemoral, or prescapular lymph nodes. The exudate present in those abscesses is thick or inspissated and may appear white in sheep and greenish in goats.[554] A breed association with the type of CLA cutaneous lesions was observed in an outbreak in a commercial ram stud in Scotland.[576] The disease is commonly known as “cheesy gland” in Australia. Differential diagnosis should include abscesses caused by other organisms, trauma, seroma, hematoma, foreign body, injection reaction, and less frequently, tumors. Because *C. pseudotuberculosis* infection represents a major herd health problem, culturing of the abscess to determine the causative agent is important. Mastitis occasionally develops.[556]

Internal abscesses can be found in the lungs, kidneys, and mediastinal, bronchial, mesenteric, and lumbar lymph nodes.[575] Chronic weight loss is the most common presenting complaint. Other clinical signs are related to the organ or tissues affected. Other diagnostic procedures may be necessary for the differentiation of internal abscesses as the cause of weight loss. Signs of spinal cord compression by vertebral abscesses have been seen in lambs born in unsanitary conditions.[554] Knowledge of the local prevalence can help in the diagnosis of the infection when uncommon anatomic locations are affected. The prevalence in large breeding operations in endemic areas is estimated at 5% to 10%.

37.41.3.2 CATTLE

The infection in cattle occurs as a herd problem with a sporadic incidence. The most common clinical form affecting cattle is cutaneous excoriated granuloma; other forms include mastitis and visceral and mixed infections.[556] In the most common form the lesions do not occur as abscesses; instead, they appear as ulcerative, exuding granulomatous lesions as large as 20 cm in diameter with necrotic areas that are easily removed surgically, leaving granulation tissue underneath.[554,557] The location of the lesions is usually in the lateral exposed areas of the body: face, neck, thorax, and flanks. The exudate varies from bloody to thick and greenish in color. The lesions heal spontaneously in 2 to 4 weeks and do not appear to cause significant illness or decrease milk production in cattle, as reported in California.[554] However, monthly milk production

was decreased by 6% in Israeli cattle.[557] Prevalence of the infection has been reported as high as 10% in California dairies.[554] Morbidity was reported as high as 35% in Israeli herds.[557] Management problems, such as broken posts or exposed wires, traumatize the skin of cattle, allowing penetration of the organism. Young cattle appeared to be less susceptible to the disease than older cattle in Israel.[557] The differential diagnoses include trauma, foreign body, and other masses (e.g., tumors). Cutaneous lesions and mastitis were seen in 6% and cutaneous lesions with concurrent visceral involvement in 1.6% of the Israeli cases.[557] The rest of the cows (92%) only had the cutaneous form.[557] The most affected organ in the visceral form was the lung.[557] The infection has been reported in bison from Egypt, resulting in severe emaciation and edema in the ventral areas and flanks.[561]

37.41.3.3 CAMELS AND CAMELIDS

Caseous lymphadenitis has been reported in alpacas in South America.[577] A recent study documented five young alpacas (22 days to 14 months old) in North America with CLA or subcutaneous abscesses that developed during late summer and early fall.[563] The alpacas did not appear clinically ill but developed swellings that progressed to abscesses. The abscesses (1 to 3 per alpaca) were located in the submandibular and cervical areas and in one case adjacent to the eye. Abscess excision appeared to be the most effective treatment in those cases. Differential diagnoses include abscesses caused by *Streptococcus* species, *Corynebacterium* species, and *A. pyogenes*.[578] Severe lymphadenitis was reported in camels in Asia.[562] A study on experimental infection of adult alpacas resulted in abscesses at the inoculation site and renal lymph nodes.[579]

37.41.3.4 HORSES

Three forms have been described in horses: ulcerative lymphangitis, external abscesses, and internal abscesses. In a study of *C. pseudotuberculosis* infection in horses from California, ulcerative lymphangitis was diagnosed in 1%, external abscesses in 91%, and internal abscesses in 8% of the cases.[580] There appears to be no breed or gender predilection for development of the infection. Ulcerative lymphangitis appears as a severe cellulitis, in which the lymphatics are affected in one or more limbs, with multiple draining ulcerative lesions. Horses often develop a non-weight-bearing lameness, fever, lethargy, and anorexia. This form of the disease has a worldwide distribution and often becomes chronic, resulting in limb edema, lameness, weakness, and weight loss.[554] The differential diagnosis should include blunt trauma, fracture, foreign body, puncture wounds, nonseptic cellulitis, staphylococcal cellulitis, and other septic cellulitis.

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The median age for horses with external abscesses is 5 years (range, 3 months to 28 years).[580] Young horses appear to be predisposed to infection because 52% of the cases in a large retrospective study were 5 years or younger.[580] Only a low number of cases involved foals under 6 months of age, suggesting that foals born to mares in endemic areas may be protected for several months by colostral antibodies.[580] The external abscesses located primarily in the pectoral and ventral abdominal regions are common in geographically restricted areas of the western United States (Texas, New Mexico, Nevada, California) and Brazil.[554,555,580,581] However, the infection has been diagnosed in other states, such as Arizona, Colorado, Kentucky, Utah, and Wyoming.[574,582] This form of infection is commonly known as “pigeon fever” because of the large size of the pectoral abscesses with the appearance of a pigeon's breast. “Dryland distemper” is another name given in relation to its geographic distribution primarily in the arid areas. Other common

anatomic locations are the prepuce, mammary gland, axilla, inguinal region, limbs, and head. Abscesses involving the head include the ears, eyelids, forehead, and maxillary and mandibular regions.[580] Severe facial suppurative cellulitis and panniculitis with skin sloughing has also been reported.[583] Other, less common areas are the thorax, neck, parotid gland, guttural pouches, larynx, flanks, umbilicus, tail, and rectum. Septic joints and osteomyelitis have been reported.[580]

A large area of edema develops in the area of abscess formation. As the abscess matures, the area becomes hard and painful, and some become very large, particularly in the pectoral area. The abscesses typically have a thick capsule, measuring up to 10 cm, and can cause severe lameness if located in the axillary or inguinal region.[555,580] Maturation can be slow and drainage difficult to establish if the abscess lies deep to muscle. Once drainage is established by spontaneous rupture or lancing, the majority of the cases resolve within 10 to 14 days without complications. The abscesses may contain 5 to 400 mL of thick, tan, purulent exudate.[555] The majority of the horses present with a single abscess rather than multiple abscesses.[580] About 25% of animals develop fever up to 40° C (104° F). Other signs are nonhealing wounds, lameness, ventral dermatitis, and less often, depression, anorexia, mastitis, and other signs, depending on the abscess location.[580]

The vast majority of horses (91.4%) had complete recovery, with no recurrence of infection in subsequent years, implying a long-lasting immunity. However, 8.6% of the infections persisted for more than 1 year or had recurrence as external or internal abscesses.[580] In sheep and goats, humoral and cellular immune responses develop after infection, and macrophages acquire the ability to kill the organism.[558] The case fatality for horses with external abscesses is very low (0.8%).[580] The differential diagnosis for external abscess, particularly pectoral, should include trauma, seroma, hematoma, foreign body, and abscess caused by a different organism.

In a large retrospective study of *C. pseudotuberculosis* infection in the horse, 8% of 538 horses developed internal abscesses.[580] In two different studies, almost half to 63% of horses that had internal abscesses also had concurrent or a history of external abscesses.[580,584] In a study of 30 horses with internal abscesses, a female predilection (70%) was apparent.[584] The mean age is 8 years (range, 10 months to 23 years).[580,584] The most common clinical signs are anorexia, lethargy, fever (up to 41.1° C), tachycardia, and weight loss. Other signs are colic, pale mucous membranes, ventral/limb edema, ventral dermatitis, ataxia, hematuria, nasal discharge, and abortion.[580] The most frequently affected anatomic location is the liver, followed by mesentery, mediastinum, lungs, kidneys, diaphragm, spleen, pericardium, blood, and uterus.[575,584,585] A postmortem examination on an aborted fetus from a mare with pneumonia revealed *C. pseudotuberculosis* abscesses in the liver, lungs, spleen, diaphragm, kidney, and bladder.[584] Bacteremia may also occur. Both single-organ and multiple-organ involvement have been documented.[584] The case fatality for horses with internal abscesses ranges from 30% to 40%.[580,584] The differential diagnosis should include other types of abscesses, such as those caused by *Streptococcus, Actinomyces, Staphylococcus, Rhodococcus equi* in foals, *Coccidioides immitis,* and anaerobes, as well as neoplasia and other causes of weight loss. The clinical signs and differential diagnosis will depend on the location of the abscess.

37.41.3.5 HUMANS

Human infection may result from the consumption of unpasteurized infected milk or milk products, continued close contact with infected animals, handling contaminated equipment, and exposure of wounds

with exudates.[558,586] Human infection has been reported from strains of small ruminants.[558] Transmission from horses to humans has not been reported, but precautions when handling infected horses should be taken. Infection in humans occurs as a subacute to chronic lymphadenitis and pneumonia.[558]

37.41.4 Clinical Pathology and Laboratory Diagnosis

Almost half the horses with external and/or internal abscesses had anemia of chronic disease in one study.[580] Leukocytosis with neutrophilia and elevated fibrinogen are common features of developing bacterial infections, particularly in the case of internal abscesses.[580] Leukocytosis with neutrophilia was seen in 36% and 76% of the horses with external and internal abscesses, respectively.[580] Hyperproteinemia caused by increased globulins was observed in 38% and 59% of the horses with external and internal abscesses, respectively.[580] Similarly, infected cattle and small ruminants had increases in WBC counts.[557,576]

Peritoneal fluid from 93% of the horses with abdominal abscesses was abnormal.[580] The remaining horses with abdominal abscesses and normal peritoneal fluid had abscesses located retroperitoneally in the kidneys without involvement of other abdominal structures. *C. pseudotuberculosis* was isolated in 32% of the samples of peritoneal fluid.[580] Failure to isolate the organism from peritoneal fluid does not rule out the disease. The organisms could be located retroperitoneally, or sequestered within a thick capsule, or suppressed by local factors or nucleated cells.[587]

The ELISA test for the detection of cell wall antigens is reportedly not very accurate in horses.[554,571] ELISA appears to be more useful for detection of infection in sheep.[588–591]

Another useful diagnostic aid is the synergistic hemolysis inhibition (SHI) test, which measures IgG response to the exotoxin in the patient's serum by detecting the highest dilution that will prevent hemolysis of *R. equi* exotoxin—sensitized bovine RBCs when mixed with *C. pseudotuberculosis* exotoxin of a known concentration.[573,592] The IgG response to the exotoxin depends on the chronicity and severity of the infection and antibody availability.[554] It has been reported that a serum antibody titer of 1:128 indicates exposure, whereas 1:512 or higher indicates the presence of infection.[554] Studies in goats have demonstrated that most animals have serum antibody titers that correlate with bacterial culture results.[593] The SHI test can be used in sheep and goats to monitor prevalence and exposure of incoming animals and to detect subclinical infections.[554,592] Only 40% of horses with external abscesses, in which the infection was confirmed by culture, had serum antibody titers of 256 or higher. However, a low SHI titer does not rule out the disease. Possible reasons for lack of titers include (1) acute onset of infection and rapid maturation of the abscess before developing an immunoglobulin response, (2) presence of a thick capsule isolating the organisms and preventing a serologic response, and (3) consumption of antibody during active infection.[554,580] Many horses that are seronegative at drainage of an external abscess seroconvert at a later time. In contrast, almost all horses with confirmed *C. pseudotuberculosis* internal abscesses have SHI titers of 512 or higher.[575,584] The high titers in horses with internal abscesses probably reflect the chronicity of the disease and the resulting prolonged immune stimulation. Prolonged seropositivity has been observed in horses and goats.[580,592,594] The SHI test appears to be a reliable ancillary aid for the diagnosis of internal abscesses in horses.[580,584] Presence of a SHI titer greater than 512 can occasionally be found in horses with external abscesses and exposed herdmates.

Other serodiagnostic tests used in sheep and goats are tube agglutination, complement fixation, and gel immuno-diffusion.[571,595]

A presumptive diagnosis can be made based on the history, local prevalence, time of the year, clinical signs, and characteristics of the exudate.[554] For the diagnosis of internal abscesses, the previous features must be considered, in addition to the presence of an inflammatory leukogram with elevated fibrinogen, serum chemistry abnormalities, abnormal peritoneal fluid or transtracheal wash, positive blood culture, SHI titer of 512 or higher, and ultrasonographic or radiographic evidence of masses.[580,584] The definitive diagnosis is established through the isolation of the organism from abscesses or draining wounds. The organism is readily isolated and grows well in blood agar in 24 to 48 hours, even when contaminant bacteria are present.[580]

37.41.5 Pathophysiology and Epidemiology

C. pseudotuberculosis is a soil-borne organism that survives for months to years, even in direct sunlight at environmental temperatures.[558,596,597] The incidence of infection in horses varies considerably from year to year. External and internal abscesses in horses can present at any time of the year but are seen more often during the fall and early-winter months, with the highest incidence in September, October, and November.[580] However, internal infections are more frequently seen in November through January, 1 to 2 months after the peak number of cases with external abscesses.[584] The largest numbers of equine cases have been observed during the dry months of the year, after heavy rainfall, which may result in optimal breeding conditions for insects.[555,580,581] The seasonal incidence in horses has been associated with the presence of biting insects such as *Haematobia irritans* (horn fly), which causes ventral midline dermatitis from its feeding pattern. Insect vectors involved in the transmission of disease in horses, such as *H. irritans, Stomoxys calcitrans,* and *Musca domestica,* were identified by detecting the PLD exotoxin gene of *C. pseudotuberculosis* in an endemic area.[598] The results of one study suggest that the disease could be transmitted through horse-to-horse contact, vectors, or contaminated soil.[599] Temporal and spatial analysis indicated an incubation period of 3 to 4 weeks in horses. There is no breed or gender predilection[580]; however, a retrospective study indicated a predilection for internal abscesses in females.[584] A case-control study in an endemic area revealed that young adult horses less than 5 years of age had increased risk of infection.[600] Horses housed outside or with access to an outside paddock, or in contact with other horses on pasture, appeared to be at higher risk than stabled horses.[600]

The disease in cattle from Israel occurred during the spring and summer dry season, from March to October, when the housefly population is high.[557] *C. pseudotuberculosis* was isolated from houseflies collected over an Israeli cow lesion.[601] The infection in cattle may spread by direct contact or indirectly by houseflies or fomites.[557] The disease in sheep and goats is not seasonal, and transmission is through contact of exudate from a draining abscess from animal to animal or through contaminated equipment.[555] Lambs born in contaminated surroundings can be infected through the umbilicus, mouth, or inhalation.[554] Sheep that acquire the organism orally or from shearing wounds tend to have parotid, submandibular, prefemoral, or thoracic abscesses.[554] Goats can be infected when wounds are exposed to contaminated milking equipment. The incubation period is long and variable. In experimental infections in small ruminants, the incubation period was 2 weeks to several months.

The pathogenesis of the disease in horses is not clear, but it has been speculated that the organism enters the equine host through skin or mucous membrane abrasions or wounds, as confirmed in sheep.[602,603] Experimentally induced infections in small ruminants revealed that once *C. pseudotuberculosis* gains access through wounds or abrasions, the organisms spread to the subcutaneous or submucosal lymphatics, where they are phagocytosed by macrophages that migrate to the invasion site to engulf the organism.[604] The organism survives intracellularly because of its high content of lipids (e.g., corynomycolic acid), which resist the action of lysosomal enzymes.[564,604] *C. pseudotuberculosis* replicates in the phagolysosome; if large numbers of organisms are engulfed, phagocytic cells die. Experimental inoculation of the organism in sheep revealed a massive infiltration with polymorphonuclear neutrophil leukocytes (PMNs),[605] which are believed to carry the bacteria to regional lymph nodes.[554] A PLD toxin of approximately 31.5 kD, produced by all *C. pseudotuberculosis* isolates, increases the vascular permeability, causing spread of the organism regionally and systemically.[558,593,606] Development of abscesses at secondary locations in horses can occur in up to 25% of the cases.[580] PLD toxin can cause necrosis and thrombosis of the lymphatics and may enhance survival and multiplication of the organism through complement depletion and inhibitory effects on phagocytic cells.[558] The corynomycolic acid and PLD toxin contribute to the inflammation, edema, and pain during abscess development.[607] The profound reaction of these compounds is probably responsible for the thick abscess capsule that develops as phagocytes accumulate in the abscess core. The abscess eventually matures and drains, but if removal of infected material is incomplete, recurrence may be expected, particularly in small ruminants.[554] The development of internal abscesses in horses is unclear but has been postulated to result from hematogenous or lymphatic spread of bacteria from more superficial sites.[554,580,584]

37.41.6 Treatment and Prognosis

Important considerations when treating external abscesses are (1) to allow for the abscess to mature; (2) to establish drainage, then collect and dispose of the infective exudate; and (3) to lavage the wound with an antiseptic solution. In a retrospective study in horses, most external abscesses were incised to establish drainage, and some animals received antimicrobials after drainage in an effort to decrease cellulitis. Many horses received no treatment, and the abscesses broke and drained on its own. Other horses were treated only with antimicrobials. The outcome was successful for 99% of the horses with external abscesses.[580] Horses with abscesses in the axillary region or deep within muscles have considerable pain, necessitating incision and drainage. Ultrasound is useful for the detection of the location of deep abscesses.[584]

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In one report the median resolution time for horses with external abscesses that did not receive antimicrobial therapy before abscess drainage was 18 days, versus 30 days for the horses that received antimicrobials.[580] These data suggest that systemic antimicrobial therapy before abscess drainage in horses with external abscesses may prolong the course of the disease.[580] However, when abscesses recur, drainage and concurrent antimicrobials may improve the chance of resolution. Conversely, long-term (minimum 4 to 6 weeks) antimicrobial therapy is necessary for the treatment of internal abscesses and ulcerative lymphangitis. The median resolution time for horses with internal abscesses treated with antimicrobials was 36 to 42 days, with a maximum duration of 97 days.[580,584] The case fatality for horses with internal abscesses treated with antimicrobials was 30% to 40%, but 100% if not treated.[580,584] In vitro, *C. pseudotuberculosis* is susceptible to almost all common antimicrobials, including penicillin, trimethoprim-sulfonamide, tetracycline, cephalosporin, chloramphenicol, erythromycin, and rifampin.[608,609] Most isolates are resistant to nitrofurans, cycloheximide,

and nalidixic acid.[609] Bacitracin has marked activity against the bacterium.[610] In selecting an antimicrobial, the clinician must consider (1) the intracellular location of the organism, (2) presence of a thick abscess capsule and presence of pus, (3) lengthy course of treatment that may be required, (4) risk of complications (e.g., diarrhea), and (5) cost. Antimicrobial-associated diarrhea was seen in 6% of horses receiving antimicrobials (rifampin, trimethoprim-sulfas, penicillin) for *C. pseudotuberculosis* infection in a retrospective study.[580] Additional therapies include marsupialization of internal abscesses if location allows. NSAIDs such as phenylbutazone or flunixin meglumine may be used to control the pain and fever while waiting for external abscesses maturation.

The prognosis for external abscesses is good. Most resolve in 3 weeks from the day of drainage.[554] The prognosis for horses with internal abscesses and ulcerative lymphangitis is guarded. The prognosis improves if infection is detected early and appropriate therapy administered.

In a bovine study the skin lesions on individual cows healed on average in 23 days after local or parenteral treatment; 17% of severely affected cattle were culled.[557] Simple drainage in small ruminants does not usually result in resolution of the disease and creates potential sources of infection. Dilute iodine solutions can be used for abscess lavage. Complete excision of the abscess under general anesthesia may be necessary to keep the abscess from draining and to prevent the spread of infection to other animals.[554] The treatment of choice in small ruminants is surgical removal of the affected lymph nodes.

37.41.7 Prevention and Control

Even though *C. pseudotuberculosis* infection is one of the most frequently diagnosed infectious diseases in California, little is known about its prevention and control. General recommendations to prevent the spread of the infection are isolation of infected animals, fly control, good sanitation, careful shearing practices, disinfection of contaminated fomites, and careful disposal of bedding. In small ruminant farms the morbidity can reach 100%, with depopulation being the most economic option. Because of the ability of the organism to survive in soil and fomites, the potential for environmental contamination is very high.[596,600]

Immunization trials using whole cells, cell walls, toxoids, and bacterin-toxoid combinations have been performed in the prevention of CLA in small ruminants.[611–615] These vaccines have been shown to provide a high degree of protection, decreasing the number of infected sheep and the number of abscesses per sheep. *Corynebacterium pseudotuberculosis* toxoids are commercially available for sheep and goats.* The use of autogenous bacterin-toxoid in horses resulted in fewer abscesses and less postchallenge pain in experimentally inoculated horses, but did not reduce the incidence of infection in one farm because of a low prevalence of disease.[616] Use of an experimental bacterin-toxoid demonstrated increased SHI titers after two injections; however, the protection remains to be established.[617]

* Caseous D-T (Colorado Serum Co., Denver, Colo.); Glanvac (Australia).

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38 Chapter 38 Diseases of the Bones, Joints, and Connective Tissues

Consulting Editors

Robin M. Dabareiner

38.1 PHYSITIS (EPIPHYSITIS)

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38.1.1 Definition and Etiology

Physitis is a term used to describe a developmental orthopedic condition in which there is a disturbance in endochondral ossification at the physis, or growth plate. Of the developmental orthopedic diseases—osteochondrosis, physitis, subchondral bone cysts, flexural limb deformities, cuboidal bone malformation, acquired angular limb deformities, and juvenile arthritis—physitis is the most common.[1,2] In one study of 1711 Irish thoroughbred foals, 67% had signs of developmental orthopedic disease.[2] The term *physitis* may better be defined as "physeal dysplasia" because typically there is no evidence of an inflammatory process.[3]

Physitis has been seen in growing cattle as a result of copper deficiency and interactions with molybdenum, zinc, and sulfates, as well as in calves raised on slatted floors.[4] Two common antagonists of copper include zinc, which at high levels prevents absorption of copper by the body, and molybdenum, which is found in alfalfa.[5] Other animals in which physitis has been reported include show rams being heavily fed and sheep and goats with pregnancy-associated ephiphysitis.[4]

Physitis typically affects the given physis during its active growth phases. Factors implicated as causing physitis in horses include the following[4]:

1 A genetic component for faster-growing horses and for specific conformation (e.g., upright and pigeon-toed appearance).

2 Overweight foals.

3 Growth spurts in foals.

4 Intake of high levels of carbohydrates, causing hormonal changes and affecting the physis.

5 Improper mineral balance (e.g., copper or zinc deficiency).

6 Excessive or deficient calcium intake.

7 Excessive exercise, especially on hard ground, may cause strain on maturing cartilage.

38.1.2 Clinical Signs

Physitis in horses is seen mainly in three specific locations at certain ages. Foals ranging in age from 3 to 6 months most often have signs of physitis at the distal metacarpal/metatarsal growth plate (with or without involvement of the proximal physis of the first phalanx). Older foals (8 to 24 months) may have signs of physitis at the physis of the distal radius.[6] Less frequently the distal physis of the tibia may be involved. Physitis is characterized by firm swellings that may be warm and painful on palpation. Typically the swellings are medial because of increased weight bearing on this portion of the limb.[6] Foals may or may not be lame. Radiographic changes include a sclerotic, roughened physis with an irregular metaphyseal shape.[2] If the physitis continues, the growth plate may close prematurely, leading to an irreversible angular limb deformity (usually a varus deformity because of decreased growth on medial physis).[6]

38.1.3 Diagnosis

A diagnosis of physitis is usually made by appreciation of the clinical signs, including warm, sometimes painful, firm swellings in the locations previously cited. Physitis at the fetlock may appear to have an hourglass appearance if the proximal physis of the first phalanx is affected. A convex appearance just proximal to the distal tibial and radial physis may be seen early in the disease process.[6] Recently, a quantitative method for detection of physitis was investigated in thoroughbred foals.[2] This method is based on the observation that when the physis is enlarged, both the metaphysis and the ephiphysis are more concave.[7] Results of this study show that epiphyseal concavity may indicate the degree of physeal swelling by using the maximum second derivative value of that contour. Radiographically, physitis is characterized by a growth plate that is irregularly thickened with sclerotic adjacent bone.[2]

38.1.4 Treatment and Prognosis

Treatment of physitis should begin with management changes. Special attention should be given to the nutrition of these foals and weanlings. Ensuring proper balance of minerals, especially calcium and phosphorus, as well as adequate amounts of trace minerals such as copper and zinc, is necessary. Copper is required for successful cross-linking of collagen. When a copper deficiency exists, the cartilage matrix weakens and microfractures occur. Because mare's milk is very low in copper, foals rely on hepatic stores gained during the last trimester of gestation.[5] One study showed that supplementation of mares with copper during gestation significantly reduced radiographic signs of physitis in their foals at 150 days of age. Supplementation of foals did not affect the incidence of physitis in the same study. Based on these results, supplementation of mares during the second half of gestation with copper on farms with a high incidence of physitis may be beneficial in preventing physitis in their foals.[8] A general reduction in energy is needed to slow growth rates and, when necessary, decrease body weight. Total concentrate for nursing foals should be 0.5 to 0.75 kg/100 kg body weight, 1 to 1.5 kg/100 kg for weanlings, and 0.5 to 1 kg/100 kg for yearlings.[4]

Varying degrees of discomfort are associated with physitis. For horses with very painful, warm physes, the judicious use of nonsteroidal antiinflammatory drugs (NSAIDs) is indicated. Exercise restriction, specifically stall rest, is indicated in affected horses. Without exercise restriction, these horses continue to load the physes, which may lead to permanent conformational changes, such as angular limb deformities.

With early detection and treatment, the prognosis for physitis is good for athleticism.

38.2 OSTEOCHONDROSIS

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38.2.1 Definition and Etiology

Osteochondrosis is a developmental orthopedic disease characterized by failure of, or defect in, endochondral ossification that can lead to cartilage flaps, osteochondral fragments, or subchondral bone cysts. It is classified as a *developmental orthopedic disease* (DOD) along with physitis, angular limb deformities, subchondral bone cysts, flexural deformities, incomplete ossification of the cuboidal bones, and juvenile arthritis.[9] *Chondrodysplasia* and *dyschondroplasia* are more descriptive terms because they imply a primary defect in cartilage maturation, but their use is generally reserved for abnormalities of limb and vertebral development. The terms osteochondrosis, osteochondritis, and osteochondritis dissecans have all been used synonymously in discussing the condition. To maintain consistency and avoid confusion, the following designations are used: *osteochondrosis* refers to the disease, *osteochondritis* refers to the synovial inflammatory response caused by the disease, and *osteochondritis dissecans* refers to the condition when a cartilaginous flap is identified.[10]

Osteochondrosis has been recognized in most domestic species, including horses, swine, and less often in cattle, sheep, and goats. The main focus has been in horses because of the economic impact and performance-limiting characteristics of the disease and in swine because of effects on production traits[11] and the development of comparative models for study of the disease.[12]

38.2.2 Clinical Signs and Differential Diagnosis

Osteochondrosis can present with a variety of clinical signs that are frequently recognized in juvenile animals. Effusion of the affected joint with or without accompanying lameness is common. The tarsocrural and femoropatellar joints are most often affected, but the condition can be seen in any joint. Physitis, or inflammation at the physeal plate, in young animals can have a similar appearance, with generalized enlargements adjacent to synovial structures. Osteomyelitis can cause a periosteal reaction that, if located in the area of a joint, can have a similar appearance. Septic arthritis can closely mimic the signs of osteochondrosis, but the associated lameness is often much more severe. Physitis, osteomyelitis, synovitis, and septic arthritis should all be considered in the differential diagnosis of osteochondrosis in juvenile animals. In older animals the clinician should consider synovitis, osteoarthritis, and trauma in the differential diagnosis.

Osteochondrosis is generally diagnosed in horses when they are started into training programs or begin athletic activity. They often present with a complaint of joint effusion that can be acute or insidious. Lameness is usually nonapparent to mild, except in cases with large osteochondral fragments or subchondral bone cysts. Severe cases seem to be more common in the stifle, and associated clinical signs may be present in foals as young as 6 months. Warmblood horses generally present later, at 3 to 4 years of age, because it is common practice to delay training until this stage.

Reports in cattle indicate that young, intact male, purebred animals are most often affected. The typical clinical signs are lameness with associated joint effusion. Osteochondrosis in swine has been associated with a syndrome known as “leg weakness.” Affected animals can show a range of signs, from mild lameness to

inability to rise and inability or refusal to mount.[13] Evaluation of performance data from swine herds can be a useful indicator of osteochondrosis because it has been shown to have a significant effect on production traits.[11,14] Cattle and swine are production animals slaughtered before 2 years of age, so clinical signs may only be recognized in purebred animals used for breeding purposes.

38.2.3 Sites of Predilection

Osteochondrosis can be found in any diarthrodial joint, but sites of predilection exist in all species affected. In horses the stifle and hock are most frequently affected. In the stifle, in order of frequency, the lateral trochlear ridge of the femur, medial trochlear ridge of the femur, trochlear groove, and distal end of the patella are affected.[15] The medial femoral condyle is the site of predilection for subchondral cystic lesions. In the hock, in order of frequency, the distal intermediate ridge of the tibia, lateral trochlear ridge of the talus, and the medial malleolus are affected.[15] Predilection sites in cattle are similar to those in horses, with the hock and stifle most often affected and similar distribution in the joints.[16] Swine show a slightly different pattern, with the medial condyle of the humerus and femur most frequently affected.[14]

38.2.4 Diagnostic Tests

Animals presenting with signs of joint effusion and lameness should undergo a thorough physical examination. Complete blood count (CBC) indicating a septic process along with radiography help differentiate osteomyelitis, septic physitis, or septic arthritis from osteochondrosis. In cases with any indication of a septic process, appropriate cultures should be taken. Horses should be observed in motion along with flexion tests, using local and intraarticular anesthesia to localize the site of lameness. Swine and cattle can be observed in their normal surroundings for signs of lameness. Once localized, the affected joint should be radiographed along with the corresponding joint on the contralateral limb in the tarsocrural and femoropatellar joints because the lesions are often bilateral in nature (Fig. 38-1). If lesions are detected in the metacarpophalangeal or metatarsophalangeal joint, the remaining three limbs should be radiographed because these can occur quadrilaterally.[17]

Lameness and effusion are more reliably seen in cases of osteochondritis dissecans and subchondral bone cysts than in osteochondrosis. Intraarticular anesthesia of the affected joint will alleviate the lameness, localizing the source. After the lameness has been localized, appropriate radiographs of the affected area should be obtained (Fig. 38-2), as well as of the contralateral or quadrilateral limbs, as described previously.

Swine and cattle will often present with signs of lameness and mild joint effusion. Careful physical examination of the restrained animal should allow localization of the affected area and appropriate radiographs to be obtained. As with equine patients, the lesions are rarely unilateral, and corresponding limbs should be radiographed. Reviewing production records of finishing or breeding swine herds may also be of diagnostic value because osteochondrosis has been shown to cause significant reductions in performance and production traits.[11]

Fig. 38-1 Osteochondrosis in the tarsocrural joint of a horse. Note the characteristic osteochondral fragments located at the distal intermediate ridge of the tibia.

The manifestations of osteochondrosis may not be adequately represented by clinical signs and radiographs. Clinical signs of lameness and joint effusion have been shown to precede changes within the joint, and serial radiographs may be needed to diagnose the condition.[18] Also, radiographic abnormalities consistent with osteochondrosis of the distal intermediate ridge of the tibia and lateral trochlear ridge of the femur can return to a normal appearance by 5 and 8 months, respectively, in warmblood foals.[19] Radiographs also often underrepresent the severity or size of the lesion seen at surgery.

38.2.5

Pathophysiology

Endochondral ossification is the process of bone formation that begins with a cartilage scaffold arranged in zones that are gradually replaced by bone. It occurs at the articular/epiphyseal and metaphyseal growth plates and secondary centers of ossification, such as the carpal and tarsal bones. Directly beneath the articular cartilage is a zone of resting chondrocytes that divide to form the next zone, the proliferating chondrocytes. These proliferative cells divide rapidly, organizing into columns perpendicular to the long axis of growth. The cells progress to the hypertrophic zone, where they swell and become vacuolated, and the columns become more organized. The chondrocytes in this zone also become surrounded by increasing amounts of extracellular matrix, which becomes mineralized in the zone of calcification. These columns of chondrocytes are invaded by metaphyseal blood vessels, and bone forms on these calcified cartilage columns, creating the primary spongiosa, which is subsequently remodeled into mature bone.

Fig. 38-2 Osteochondrosis in the femorotibial joint of a horse. Note the large subchondral cystic lesion in the medial femoral condyle, a typical location for these types of lesions.

The exact pathogenesis of osteochondrosis is still undefined. The traditional theory is that the process of endochondral ossification is disrupted, resulting in areas of thickened cartilage. The deeper layers of these retained cartilage plugs do not receive adequate nutrients by diffusion from the synovium, and necrosis of the cells develops. These areas of cartilage have less structural integrity than normal cartilage and are prone to damage. Shear forces acting on the abnormal cartilage can lead to fissure formation. These fissures can then form dissecting cartilage flaps, free flaps, or fragments of cartilage and subchondral bone. When compressive forces predominate on an area of thickened cartilage, it can cause infolding of the cartilage plug. Normal endochondral ossification proceeds around the infolded plug, forming a subchondral bone cyst.

This traditional theory of defective endochondral ossification is still well accepted, but recent literature suggests this may be a simplistic view of a multifactorial condition. Limited reparative responses of bone and cartilage make it difficult to determine whether the origin of a lesion is developmental or traumatic. A recent report failed to distinguish articular cartilage differences in naturally occurring osteochondrosis versus healing osteochondral fragments.[20] Arthroscopic observations of normal-thickness cartilage defects and normal subchondral bone, as well as lesions occurring preferentially at single sites at the limits of articulation, suggest causative factors other than defective endochondral ossification.[17] The development and spontaneous regression of osteochondrosis lesions suggest that the condition is a dynamic process that can be affected by numerous intrinsic and extrinsic factors, and a “window of susceptibility” may exist whereby lesions are repaired and normal articular development proceeds.[21] These findings and observations suggest that multiple pathologic pathways exist and that a single etiologic explanation of osteochondrosis is unlikely.

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38.2.6 Etiology

As with the pathophysiology, the exact etiology of osteochondrosis is unclear and likely multifactorial in origin. Several factors, including biomechanical forces, failure of vascularization, nutrition, growth rate, genetics, and hormones, have been implicated and are likely interrelated in the etiopathogenesis of the disease.

The consistent distribution of lesions at specific anatomic sites within the joint implicate trauma as a causative factor. The bilateral or quadrilateral nature of the disease would indicate that trauma or biomechanical stress is a necessary factor rather than direct cause. It has been established in pigs that microtrauma or disruption of the blood vessels in the developing cartilage canals causes ischemic necrosis, failure of mineralization, and a retained cartilage plug.[22] This mechanism has not been elucidated or studied in horses or cattle; therefore, while offering a plausible explanation, the results cannot be applied across species lines.

Nutritional influences have been extensively studied in relationship to osteochondrosis. The studies have focused mainly on dietary energy levels and mineral composition (copper and zinc). The growth rate of the animal is directly affected by energy intake as well as the genetic predisposition of the animal for growth and size. Animals fed high-energy levels for accelerated growth rates have a much higher incidence of osteochondrosis than those fed for lower rates of growth.[12,23,24] Low copper levels and increased zinc concentrations have both been implicated in the etiology of the disease. Low copper is thought to exert its effect through lysyl oxidase, a copper-dependent enzyme essential in the cross-linking of collagen molecules. Increased levels of zinc antagonize copper and could work indirectly through a similar mechanism. There is conflicting evidence on the causative nature of low copper levels, and lesions seen in copper-deficient animals do not always mimic those of naturally occurring osteochondrosis. More recently, evidence suggests that neonatal copper levels exert a positive effect on the resolution of osteochondrosis lesions but are not directly involved in the pathogenesis of the disease.[25]

Genetics have been shown to be at least partially responsible in the etiopathogenesis of osteochondrosis in different species. Landrace and Yorkshire breeds of swine show a high frequency of osteochondrosis, whereas domestic pigs crossed with wild hogs do not develop the disease.[12] Heritability has also been demonstrated in standardbred trotters in the tibiotarsal and metacarpal/metatarsal phalangeal joints.[26,27] A genetic component may also be related to nutrition levels because an animal must have the genetic capacity for increased growth rates and size while at high planes of nutrition.

Alterations in hormone concentrations have been implicated in the etiology of osteochondrosis, but the mechanisms remain in question. Numerous hormones, such as insulin, somatotropin, and thyroxine, are involved in the process of endochondral ossification. Physiologic or iatrogenic alterations of these hormones or their derivatives could theoretically lead to the development of osteochondrosis. The contribution of these factors to the etiology of osteochondrosis will likely not be elucidated until the molecular mechanisms of endochondral ossification are better understood.

38.2.7 Treatment and Prognosis

The treatment of osteochondrosis should take into account several factors. The clinical signs; severity of the lesion; species, age, intended use, and relative value of the animal; and owner expectations should all be considered. Treatment options include both nonsurgical and surgical management.

Nonsurgical management should consist of rest, controlled exercise, and dietary evaluation. The mineral and carbohydrate levels of the diet should be evaluated carefully and any deficiency or excess corrected. Systemic NSAIDs and intraarticular medications such as corticosteroids, hyaluronic acid, and polysulfated glycosaminoglycans (GAGs) can all be administered, but minimal clinical evidence exists to support their use. In food-producing animals the clinician must take into consideration that these are not approved treatments and that withdrawal times may not be established. Given the nature of the disease, nonsurgical management may provide a favorable outcome only in very young animals with regenerative capacity or in those with very mild lesions and minimal to no clinical signs.

Animals with osteochondritis dissecans are best treated with arthroscopic surgery. Cases with no radiographic evidence of degenerative joint disease (DJD) before surgery and minimal articular damage at arthroscopy carry a favorable prognosis. Animals that show radiographic evidence of DJD before surgery or considerable damage to the articular surfaces at arthroscopy carry a guarded prognosis. Arthroscopic approaches to the joints of cattle have been described, but the procedure is more difficult than in the horse.[16] In select cases, reattachment of large cartilage flaps with absorbable poly-*p*-dioxanone pins may be warranted.[28] Diet evaluation should be included with the surgical patients and appropriate adjustments made.

Treatment of subchondral cystic lesions is still controversial, and many options are available. Nonsurgical management can be attempted and should consist of rest, controlled exercise, and intraarticular injection of corticosteroids along with hyaluronic acid or polysulfated GAGs. The prognosis is guarded except in cases with very narrow openings into the synovial cavity, and alternate treatments should be considered in refractory cases. Cysts can be treated with ultrasonographically or arthroscopically guided intralesional deposition of corticosteroids, bone marrow aspirates, or a combination of the two. Studies are lacking as to the efficacy of this treatment. Arthroscopic debridement and curettage of the cystic lesion is another option, and horses less than 3 years of age carry a better prognosis. Recent investigations show promise for arthroscopic debridement and curettage of lesions followed by packing of the remaining defect either with a cancellous bone graft

covered by a chondrocytic growth factor or with various bone substitutes.[28] Cysts located in the proximal interphalangeal joint are generally nonresponsive to conventional treatment, and arthrodesis of the joint offers the best prognosis.

Treatment of osteochondrosis in food animals is generally limited by the economic value of the animal. Show animals or valuable breeding animals may be treated by any of the methods previously described, and the surgical options will offer a better prognosis than nonsurgical treatment. In production herds, ration evaluation and genetic predisposition may be the only variables that can be addressed. A review of production records and estimates of monetary loss will indicate whether intervention is necessary.

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38.3 ANGULAR LIMB DEFORMITIES

JEFFREY P. WATKINS

38.3.1 Definition, Etiology, and Clinical Signs

Angular limb deformities are deviations in the axis of the forelimbs or hindlimbs in the frontal plane. *Valgus* deformity denotes a lateral deviation of the limb distal to the origin of the deformity; *varus* deformity denotes a medial deviation. The deformity is further described by naming the joint adjacent to the origin of the deformity; for example, carpus valgus describes an angular deformity arising in the carpal region with lateral deviation of the metacarpus (knock-kneed conformation) (Fig. 38-3).

Angular limb deformities may be either congenital or acquired. In general, they are caused by laxity of periarticular supporting structures, incomplete ossification, or asynchronous growth rate. Although the underlying cause of these abnormalities remains undefined, potential causes include intrauterine malpositioning, relative immaturity, hereditary predisposition, rapid growth, dietary imbalances, osteochondrosis, and trauma.[29–31]

Congenital angular deformities frequently are attributed to intrauterine malpositioning and laxity of periarticular supporting structures. They typically originate in the region of the carpus and tarsus, resulting in bilateral valgus deformity. It is also common to identify a “windswept” foaling in which valgus deformity of one limb is accompanied by varus deformity of the contralateral limb. Acquired angular deformities usually occur secondary to asynchronous growth. Additionally, a foal born with incomplete ossification may acquire an angular deformity secondary to crushing of the cartilaginous precursors of the cuboidal bones. A hereditary angular limb deformity of Suffolk, Suffolk crossbred, and Hampshire sheep is known as spider lamb syndrome (see later discussion).

Fig. 38-3 Carpus valgus deviation.

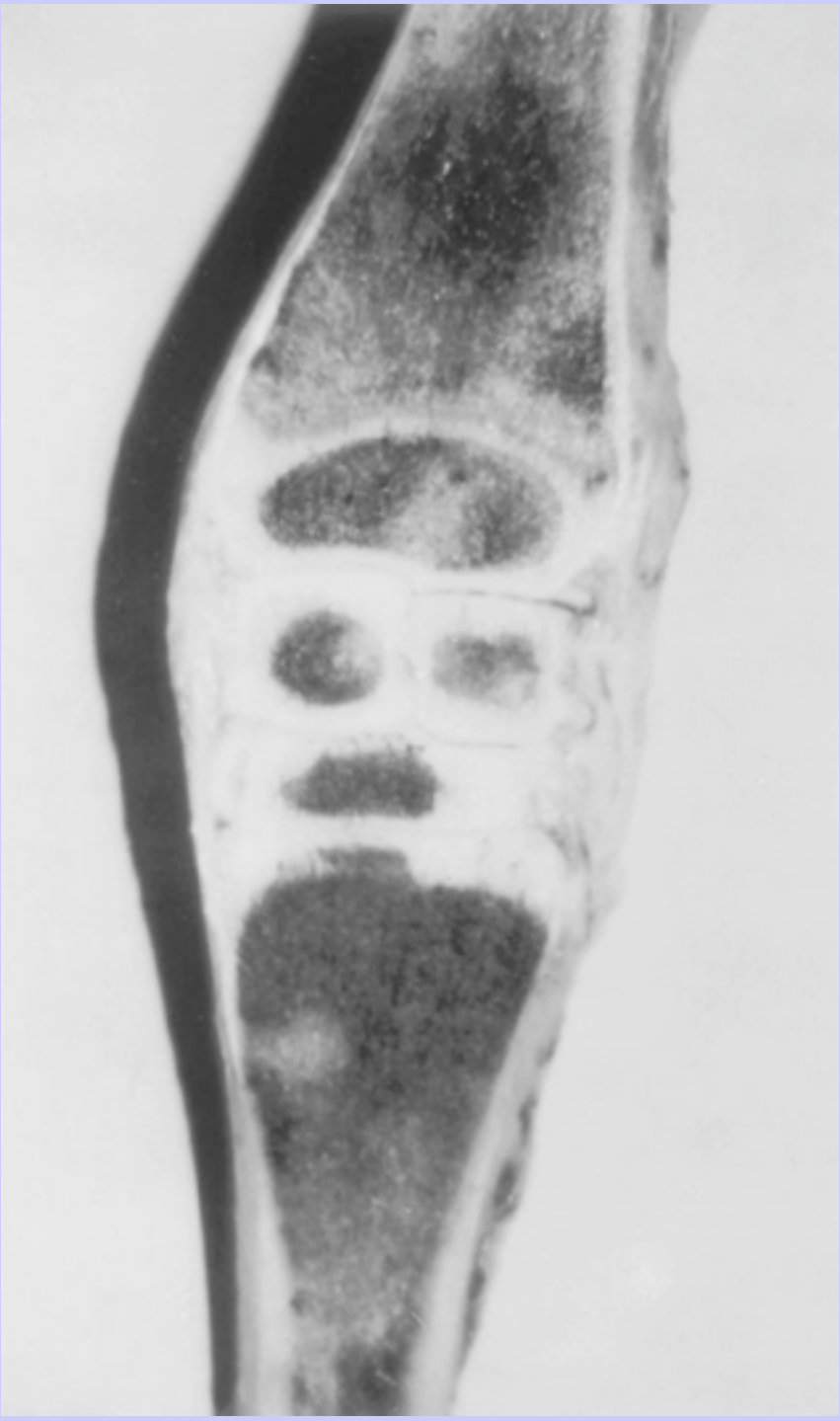
38.3.2 Pathophysiology

Incomplete ossification is an important cause of angular deformities originating at the carpus and tarsus. The epiphyses and cuboidal bones of the carpus (ulnar, third, and fourth carpal bones) and tarsus (central and third tarsal bones) are primarily affected.[29] Ossification of the cartilaginous precursors of these bones occurs in late gestation; prematurity or relative immaturity results in the birth of a foal before these precursors are completely ossified (Figs. 38-4 and 38-5). If laxity of the periarticular supporting structures accompanies incomplete ossification, the deformity is congenital and may progressively worsen with weight bearing. If laxity is not present, the foal may be born with straight legs and may acquire an angular deformity after deformation of the precursors of the cuboidal bones during weight-bearing activity.

Foals can acquire an angular limb deformity as a result of asynchronous growth at the metaphyseal and epiphyseal growth cartilages.[30,31] An important cause of asynchronous growth is trauma to a portion of the growth cartilage of the physis.[32] In many foals this trauma is in the form of nonphysiologic compression of the growth cartilage. Excessive exercise in foals with mild angulation and normal activity in foals with moderate to severe preexisting angular deformity may cause sufficient trauma to the growth cartilage to cause progressive deformity.

Fig. 38-4 Premature foal with incomplete ossification of the cuboidal carpal bones showing marked bilateral carpus valgus.

Fig. 38-5 Specimen from a foreleg of the premature foal in Figure 38-4, cut in the frontal plane. Note the thick cartilage surrounding the centers of ossification of the cuboidal carpal bones.



Asymmetric loading also occurs when severe lameness is present. With the change from a rectangular stance with four weight-bearing limbs to a triangular stance with three weight-bearing limbs, asymmetric, nonphysiologic loading of the weight-bearing limb occurs, which predisposes it to develop an angular deformity. Because compressive forces are concentrated along the medial aspect of the growth cartilages, a varus deformity usually develops in the overloaded limb. Abnormalities of the growth cartilage that affect ossification, such as osteochondrosis, also may be responsible for angular deformities caused by asynchronous growth. Foals with a predisposition for rapid growth or those that are exposed to nutritional imbalances appear to be at greatest risk for developing the disease. Rapid growth also may result in a foal with a large body size disproportionate to its skeletal structures. This condition may cause increased compressive forces, nonphysiologic loading of the growth cartilages, and angular deformity.[32]

Ruminants raised in confinement may experience endochondral dysplasia and angular limb deformities if dietary iron is high or dietary vitamin D is low[33] (rickets). Elevated dietary iron results in elevations in serum phosphorus, which may in turn inhibit 1,25-dihydroxycholecalciferol synthesis by the kidney, resulting in rickets.[33] Pregnancy-associated epiphysitis in primiparous dairy goats[34] also may result in angular limb deformities.

38.3.3 Evaluation and Radiographic Findings

In the evaluation of a foal with an angular deformity, important historical information includes age, onset and progression of the deformity, and intended use of the foal. The foal should be observed carefully while standing and walking to characterize the degree of deformity and determine the presence of compensatory problems or lameness. Physical examination includes careful palpation of the affected limb and a determination of whether the deformity can be corrected by manual manipulation of the limb. If the foal is examined before ossification has progressed, deformities resulting from laxity of periarticular supporting structures and incomplete ossification can be corrected manually. On the other hand, if deformities in foals born with incomplete ossification are left untreated and the cuboidal bones are in a collapsed configuration, or if deformities are the result of asynchronous growth, they cannot be corrected manually.

An arthropathy should be suspected if lameness is present. Collapse of incompletely ossified cuboidal bones may result in deformation of articular surfaces and subsequent DJD. When this occurs in the carpus, the prognosis for athletic performance is guarded to poor. If the cuboidal bones of the tarsus are affected, mild collapse may not adversely affect performance, but with significant collapse, degenerative change is likely. A less common cause of lameness in foals with angular limb deformity is osteochondrosis. The prognosis for athletic performance in foals with osteochondrosis-associated angular limb deformities is guarded, depending on the severity of the cartilage lesions.

The importance of early radiographic evaluation of foals with angular deformity cannot be overemphasized. If a diagnosis of incomplete ossification is delayed, irreparable damage, as described previously, may occur. In fact, a strong argument can be made for radiographic evaluation of all foals shortly after birth before uncontrolled exercise is allowed. Radiographic evaluation is mandatory to determine the degree of ossification in premature foals, twins, foals that appear to be relatively immature at birth, and foals born with angular deformities.

Radiographic evaluation allows the examiner to identify the origin of the deformity and determine its severity. Dorsopalmar views for the carpus and fetlock using 7 × 17–inch film cassettes and a lateromedial view of the tarsus are recommended. In the carpus and fetlock the origin of the deformity may be subjectively determined by two geometric methods (Fig. 38-6). One is to draw longitudinal lines bisecting the long bones above and

below the joint. Where these lines intersect is the *pivot point,* which is considered the origin of the deformity. In addition, the angle of incidence of these lines is an estimation of the degree of deformity. Another method, which the author prefers for the carpus and fetlock, is to draw lines through the joints and adjacent physes. These lines should be parallel to each other and perpendicular to the long axis of the long bones proximal and distal to the affected joint. The origin and degree of deformity are estimated by determining where and by what degree these lines deviate from normal. Both asynchronous growth and incomplete ossification can occur concurrently, which is most easily determined with the latter method of geometric evaluation[29] (Fig. 38-7). Geometric examination to determine the degree of deformity in the tarsus is less reliable because the tibia and third metatarsus are not in the same frontal plane. The severity of the angular deformity in this location is best determined by a careful visual assessment.

Radiographic examination of foals with incomplete ossification reveals a rounded contour to the affected bones instead of their normal angular appearance. The width of the radiolucent cartilage is increased, appearing radiographically as an increase in the width of the joint space (Fig. 38-8). As ossification progresses, the bones may appear wedge shaped or crushed because of deformation of the cartilage during weight bearing. This phenomenon often is noted in the ulnar, fourth, and lateral aspect of the third carpal bones in the forelimb and the central and third tarsal bones in the hindlimb. In severe cases the affected bones may be grossly deformed and appear to be partially extruded from the joint (Fig. 38-9). In the tarsus, lateromedial radiographs are used to determine whether ossification is complete (Fig. 38-10).

Fig. 38-6 Two methods for geometric evaluation of an angular deformity at the carpus. Lines *A* and *B* are drawn through the long axis of the radius and metacarpus, respectively. The angle of incidence is 15 degrees. Lines *a, b, c* and *d* are drawn through the distal radial physis, antebrachiocarpal (radiocarpal), middle, and carpometacarpal joints, respectively. Line *a′* is drawn parallel to line *b*, and line *a″* is perpendicular to *A*. Their angle of incidence is 15 degrees. *Reprinted with permission from* Compend Cont Educ (Pract Vet)*4:S330, 1982*.

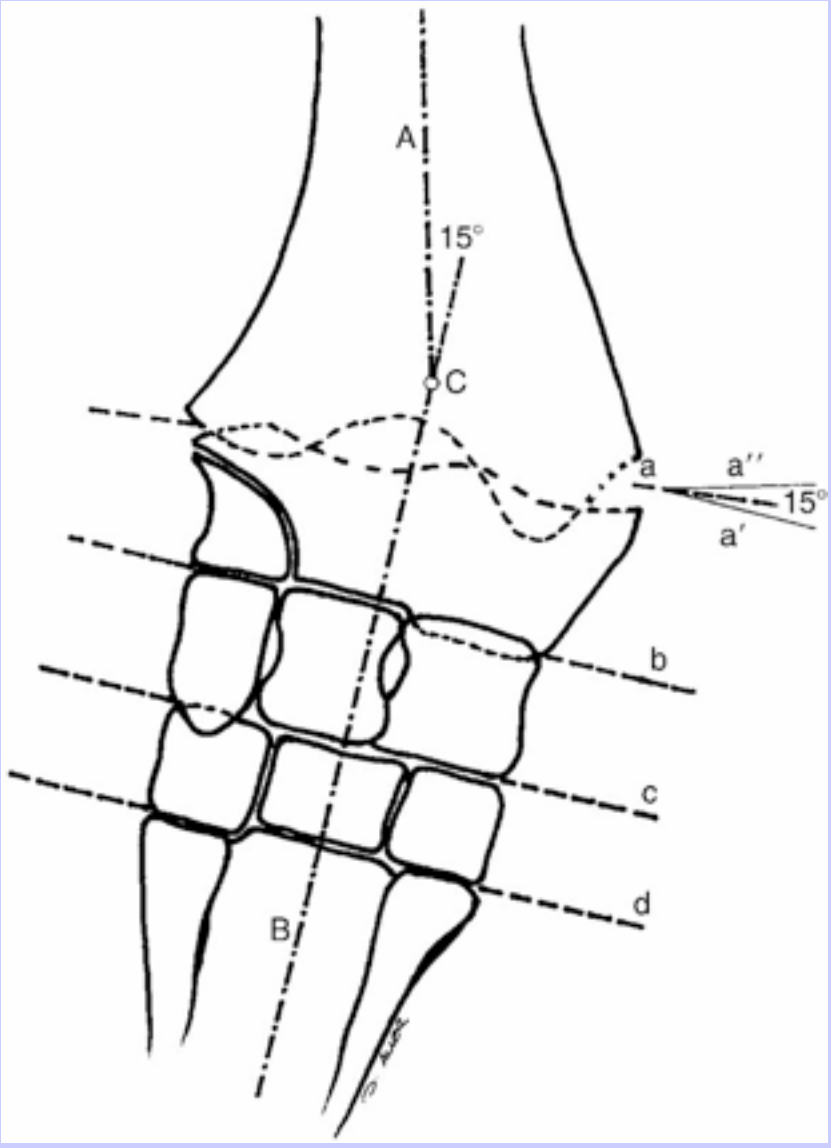


Fig. 38-7 Geometric evaluation of an angular deformity at the carpus caused by a combination of asynchronous growth and incomplete ossification. The pivot point, *c,* identified by lines *A* and *B,* indicates that the origin of the deformity is in the distal radial epiphysis. However, lines *a, b, c* and *d* are not parallel to each other; and lines *a, b* and *c* are not perpendicular to the long axis of the metacarpus and radius. Their orientation indicates that the deformity is in the distal radial physis and the cuboidal carpal bones as well. Note that the sum of angles of *a-a′, b-b′*, and *c-c′* equals the angle of incidence of lines *A* and *B*. *Reprinted with permission from* Compend Cont Educ (Pract Vet) *4:S330, 1982*.

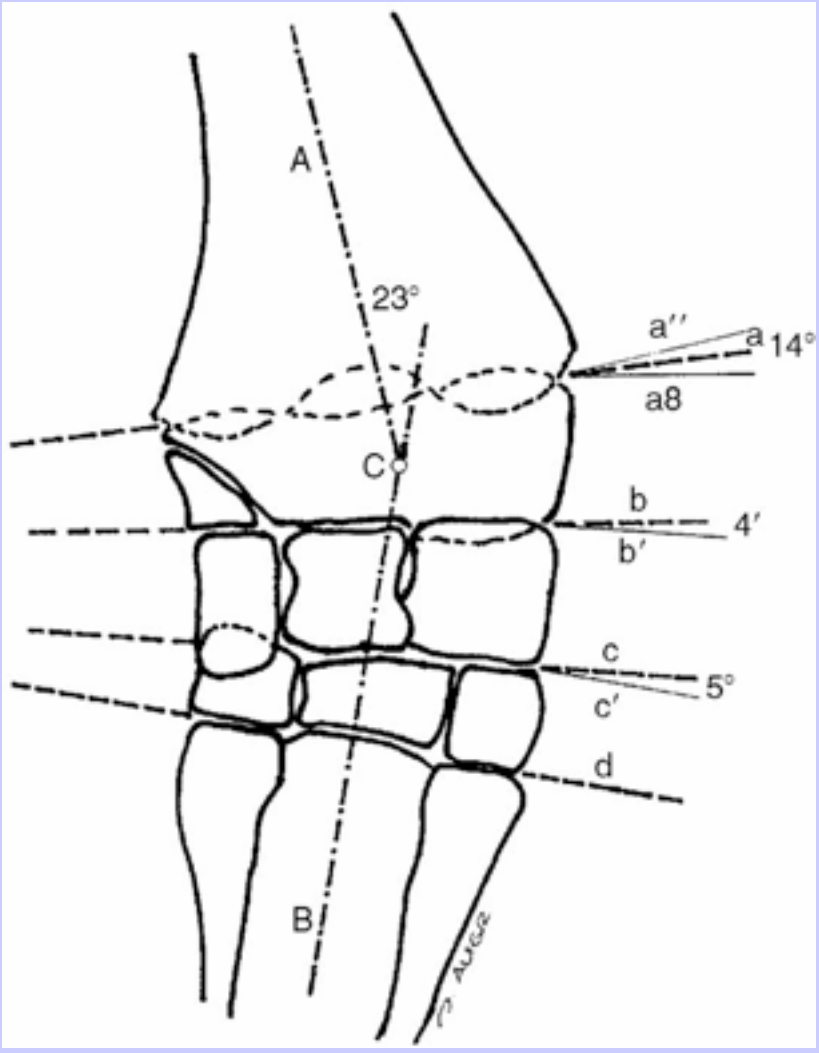
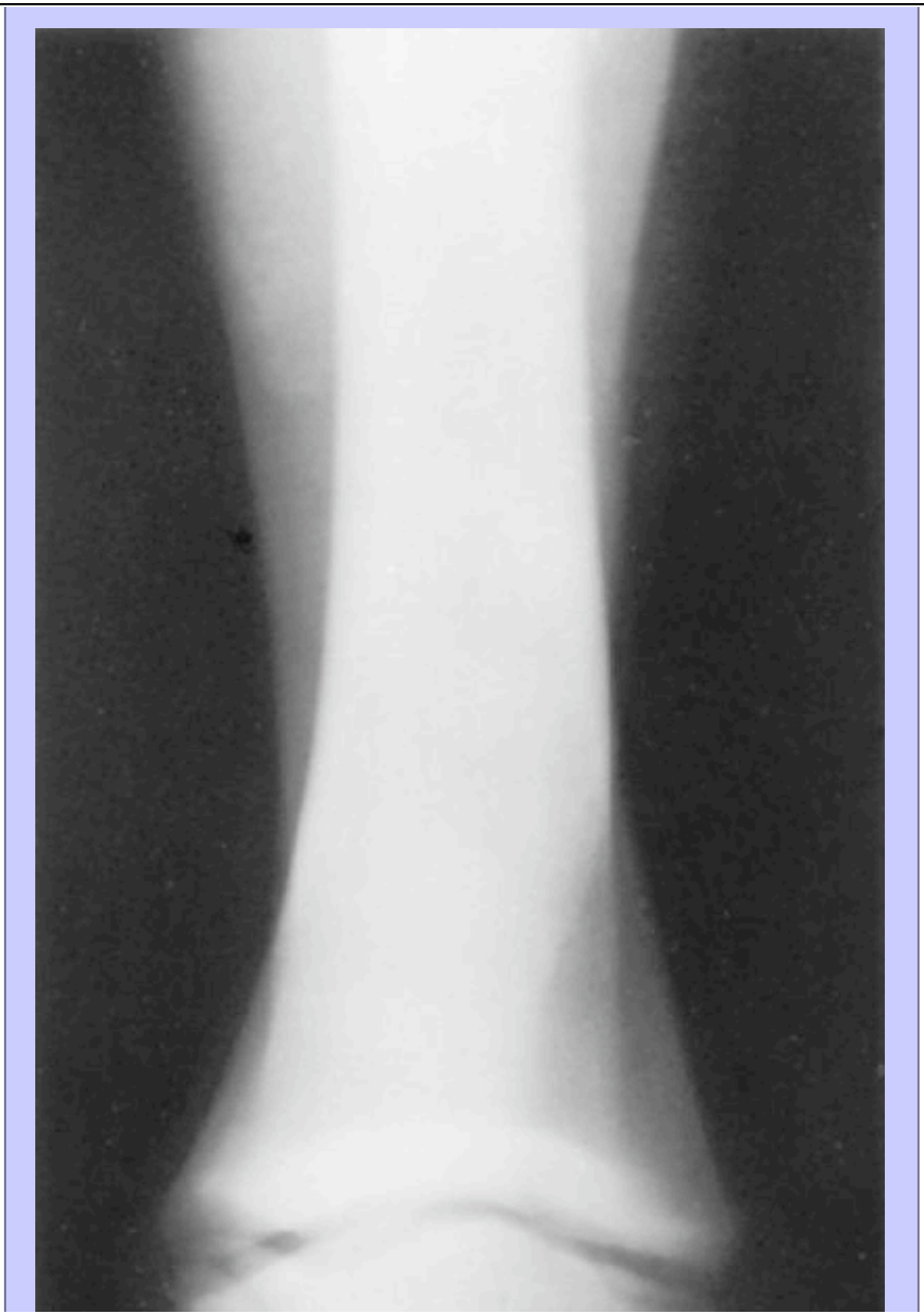


Fig. 38-8 Dorsopalmar radiograph of a foal with mild incomplete ossification of the cuboidal carpal bones. Note the difference in width of the medial aspect, *a,* and the lateral aspect, *b,* of the third carpal bone. Normally, width *a* should be approximately three-fourths the width of *b*.[41] Also note the appearance of an increase in the width of the joint space, *c,* as a result of incompletely ossified joint cartilage.



Radiographic evaluation of foals with angular deformity caused by asynchronous growth may show wedging of the epiphysis (Fig. 38-11), widening of the physis, and sclerosis adjacent to the physis. Geometric evaluation places the deviation in the metaphysis or the epiphysis of the long bone proximal to the affected joint. The joints are parallel each other and are perpendicular to the longitudinal axis of the adjacent long bones.

38.3.4 Treatment and Prognosis

Neonatal foals with an angular deformity should be confined to a stall until clinical and radiographic examinations are completed. If the deformity is 10 degrees or less and radiographs reveal normal ossification, stall confinement with periods of controlled exercise is recommended. This regimen promotes continued development of the supporting structures while minimizing trauma to growth cartilages that could result if the foal were allowed uncontrolled exercise.

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Fig. 38-9 Dorsopalmar radiograph of a foal with incomplete ossification that was not externally supported. Severe deformation and collapse of the fourth and third carpal and proximal fourth metacarpal bones have occurred.

Foals with a congenital angular deformity of more than 10 degrees accompanied by incomplete ossification or ligamentous laxity failing to improve with controlled exercise should be externally supported. If incomplete ossification is present and the limb is not supported in axial alignment, continued weight bearing can cause deformation of the cartilaginous structures. Subsequent ossification results in a permanent deformity of the affected bones (see Fig. 38-9).

Methods of externally supporting the carpus and tarsus vary from the application of tube casts or rigid splints to custom-made orthotic devices. Tube casts have been recommended and used successfully for several years.[29–31] Although tube casts provide the rigid external support needed to maintain axial alignment while ossification progresses, several potential complications are associated with their use. The most serious complication is the potential for coxofemoral luxation when tube casts are used on the hindlimbs. In addition, foal skin is easily traumatized by a poorly fitting cast, and deep ulcerations may occur. Other considerations include the cost of materials and need for constant monitoring to detect signs of a poorly fitting cast. Monitoring the status of a cast requires daily evaluation by a trained individual, and owners are seldom capable or willing to take on this responsibility; therefore hospitalization is recommended. Rigid splints are an alternative method of support. The leg is protected with a padded support bandage, and the splint is applied with nonelastic tape while the limb is held in alignment by an assistant. These splint bandages are changed every third or fourth day. Pressure sores beneath the splint bandage are a concern and must be prevented. A splint for the tarsus may be fashioned from synthetic casting material molded lengthwise over the cranial aspect of a padded bandage centered at the joint. Once the material has dried, the splint is taped to the dorsal surface of the bandage.

Fig. 38-10 Lateral-to-medial radiograph of a tarsus from a foal with incomplete ossification. Note the lack of an angular appearance of the central tarsal bone and incomplete ossification of the third tarsal bone.

Regardless of the means of external support used for the carpus or tarsus, it should not extend beyond the distal metacarpus or metatarsus. Continued weight bearing by the suspensory apparatus of the fetlock helps prevent the development of fetlock hyperextension after removal of the external support. A degree of carpal hyperextension is usually present immediately after removal of external support from the forelimb, and exercise should be controlled until the tendons and periarticular supporting structures regain their normal tone.

Foals with angular deformity resulting from asynchronous growth should also be confined to a stall and allowed only controlled exercise to minimize the magnitude of asymmetric loading at the growth cartilages and encourage spontaneous correction. In these cases, reducing the magnitude of the forces acting asymmetrically at the growth cartilage should encourage compensatory growth to occur and correct the deformity. Additional therapy consists of corrective hoof trimming. Because foals with valgus deformity typically have a toe-out conformation, emphasis in the past has been to lower the lateral hoof wall of the affected limb. If this mode of therapy is vigorously pursued, compensatory varus deformity may develop in the fetlock region. This form of corrective trimming concentrates forces asymmetrically on the medial aspect of the distal metacarpal and proximal phalangeal growth cartilages. Currently, trimming the hoof level and squaring the toe to promote breakover at the toe are recommended. If the lateral hoof wall is to be lowered; only a few millimeters should be removed each week.

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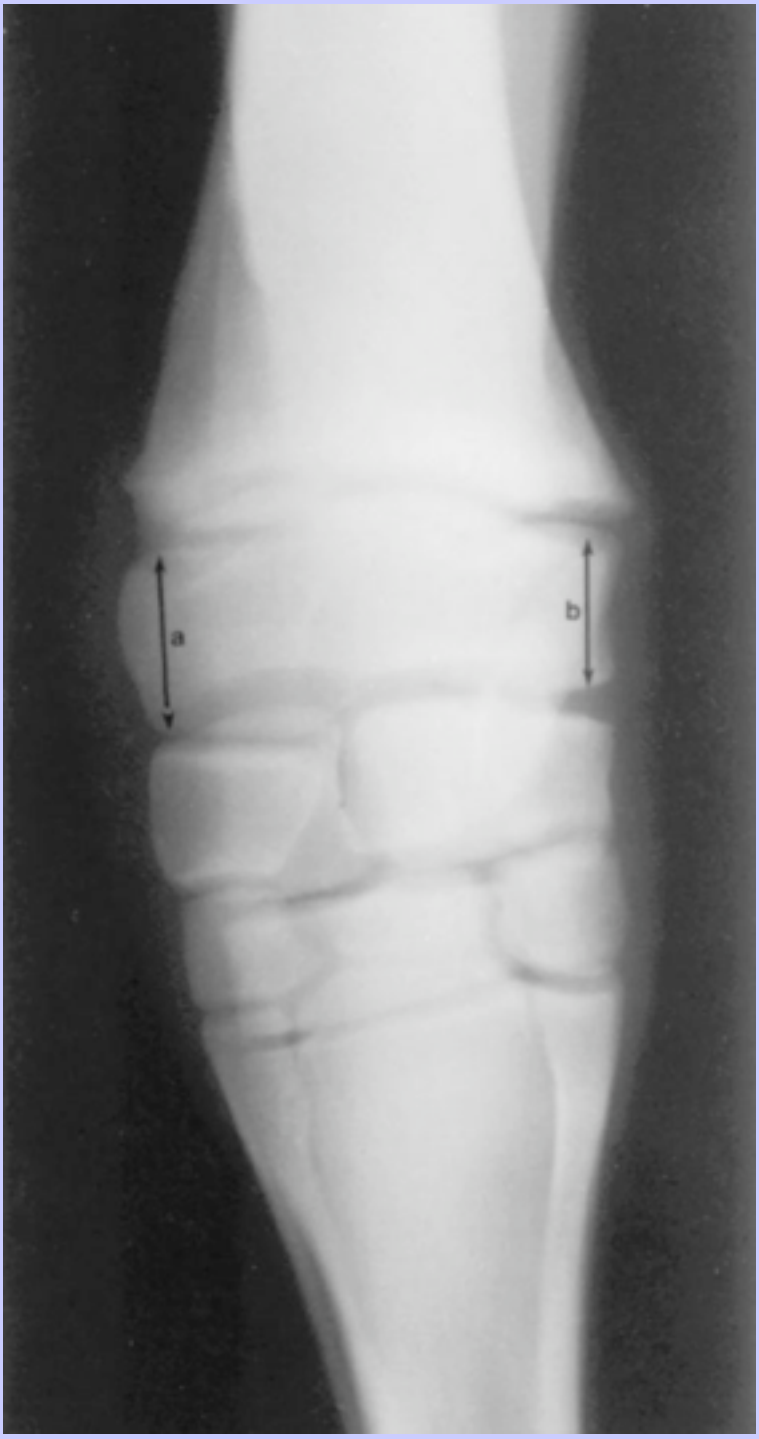
Fig. 38-11 Dorsopalmar radiograph of a foal with angular deformity caused by wedging in the distal radial epiphysis, the result of asynchronous growth of the epiphyseal growth cartilage.



Foals with angular limb deformities that fail to respond to stall confinement are candidates for surgical therapy. Although it was previously believed that animals with angular deformities arising distal to the physis were not candidates for surgical therapy, it has been shown that they can respond favorably to surgery.[35,36]

The decision for surgery should take into account the amount of correction required (degree of deformity) and the age of the foal. The more severe the deformity, the earlier should be the surgical intervention. Timing of surgery should consider the periods of rapid and predictable growth at the physis. The most rapid and predictable rate of growth occurs from birth to 10 weeks of age.[37] In the distal radius, continuous but declining growth occurs until 60 weeks of age. In the distal third metacarpal and metatarsal bones, growth rate slows dramatically by 10 weeks of age and stops shortly thereafter.

Surgical manipulation of physeal growth is intended to alter asymmetrically the elongation occurring at the physis, thereby realigning the axis of the limb. Growth at the physis can be altered surgically in one of two ways: retardation or acceleration. *Growth retardation* is accomplished by bridging the physis with metallic implants. When applied to the convex side of the affected physis, growth is disallowed on the long side of the bone while continued growth on the opposite of the bone brings the limb into alignment. As long as the implants are in place, the effect continues and is limited only by the amount of growth remaining at the physis. If the physis is still active once the limb is aligned, it is extremely important that the implants be removed, or overcorrection will occur. Techniques of transphyseal bridging include stapling, screw and wire implants, the use of a small bone plate, and more recently, a single transphyseal screw. Indications for transphyseal bridging include deformities that present after the period of rapid and reliable physeal growth, severe angulations, and based on the author's experience, deformities of the carpus and tarsus resulting from cuboidal bone malformations.

In the second surgical approach to altering physeal growth, periosteal transection and elevation (stripping) is aimed at promoting *growth acceleration* on the concave side of the bone.[38] Reported advantages include rapid correction without the potential for overcorrection.[35,38] Periosteal transection does not require implants; therefore the likelihood of infection and excessive fibrosis is reduced. Implant failure is not a consideration, and a second surgery for implant removal is not required. The procedure does not require specialized equipment and is technically easy to perform. In one series of foals, correction of the deformity occurred in 22 of 25 limbs treated with periosteal transection.[38] In a second series of 23 foals, 83% had straight limbs and were sound for their intended use at long-term follow-up.[35] The success rate was not affected by the origin of the deformity, degree of deviation, or presence of mild to moderate morphologic changes in the involved bones.[38] Indications include mild to moderate deformities present during the rapid, reliable growth at the involved physis. The periosteum will reestablish itself, so the surgical effect is short-lived, and if correction is not adequate within 4 to 6 weeks, additional therapy is indicated.

38.4 SPIDER LAMB SYNDROME (OVINE HEREDITARY CHONDRODYSPLASIA)

NANCY EAST

By the mid-1980s, multiple reports from all areas of the United States were documenting the occurrence of Suffolk lambs with skeletal abnormalities, commonly called “spiders,” “spider lambs,” “corkscrew lambs,” “monkey lambs,” “crooked lambs,” and “bent lambs” by producers. Simultaneously in several university-owned Suffolk sheep flocks, lambs were born affected with the spider syndrome, and research began to describe and characterize the syndrome.[39]

38.4.1 Definition and Etiology

Spider lamb syndrome is characterized by generalized chondrodysplasia and is apparently a semilethal autosomal recessive trait. Variable expressivity of the trait may occur in the homozygous animal.[40–42] It has been seen in Suffolk, Suffolk crossbred, and Hampshire sheep (Hampshire sheep often have some Suffolk breeding). At this time, no chondrodysplastic lambs from any white-face breeds of sheep have been reported.

38.4.2 Clinical Signs

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Lambs affected with spider lamb syndrome are characterized by overall appendicular and axial deformities, including one or more of the following conditions[40,42]: kyphosis, scoliosis, concavity of the sternum, lateroventral deviation of the maxilla (crooked nose and Roman nose), and angular limb deformities. The limb deformities usually include a "knock-kneed" appearance at the carpus (carpus valgus) and lateral deviation with rotation of the metacarpus or metatarsus (Fig. 38-12). In addition, these lambs show extreme height, fineness of bone, poor muscling, and failure to thrive (Fig. 38-13).

The number and severity of the deformities seen in individual lambs vary widely. Spider lamb syndrome can occur in two types of lambs: those that are obviously abnormal at birth and, more often, those that develop abnormalities at 3 to 8 weeks of age. Lambs that are abnormal at birth may have kyphosis, scoliosis, facial deformities, deformed sternum, and angular limb deformities.[40] Lesions may be present as early as day 100 of gestation but are not detectable by radiographic or ultrasound examination.[42] The lambs may be stillborn or die within a few days of birth because of their inability to stand or nurse. If these lambs are maintained by good nursing care, they fail to gain weight normally and usually die of secondary problems (e.g., scours, pneumonia) by 4 weeks of age. In lambs that are apparently normal at birth but develop angular limb deformities at 3 to 8 weeks of age, one to four limbs may be affected; and close examination may show curvature of the spine and concavity of the sternum. Often these lambs are unusually tall, long necked, fine boned, and poorly muscled. The growth rate of these "spider lambs" decreases after 4 to 8 weeks of age, and the various deformities become more marked until the lambs can no longer walk; chronic bacterial pneumonia and pathologic fractures are common.

Fig. 38-12 Rotation and deviation of front legs (carpus valgus) characteristic of spider lamb syndrome in a 16-week-old Suffolk lamb.

Fig. 38-13 Twin Suffolks (12 weeks old), with normal lamb (78 pounds) at left and lamb with spider syndrome (37 pounds) at right. Note extreme height, narrow chest, scoliosis, kyphosis, and facial deformity of affected lamb.

Attempts to maintain spider lambs for research are rarely successful beyond 6 months to 1 year of age. In Illinois an affected ram lamb was able to breed seven ewes before he died, but in California, two affected ram lambs failed successive semen evaluations from 7 to 12 months of age and were euthanized because of their poor condition.

38.4.3 Diagnosis

Currently, spider lamb syndrome is diagnosed on the basis of appearance, radiographic changes, and pathology (gross and microscopic). Radiographic changes are diagnostic, although serial radiographs may be necessary in some cases. There are widened, irregular growth plates with retained islands of cartilage in the olecranon, sternum, shoulder, long bones, and spine (Fig. 38-14). The most constant radiographic lesion is in the olecranon, which exhibits multiple islands of ossification instead of the uniform, nonmineralized cartilage surrounded by dense bone in a normal lamb.[40,43] The olecranon should be radiographed lateral to medial with the elbow flexed. The changes in the olecranon usually begin by 1 to 3 weeks of age and are progressive.

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Lambs that are stillborn or die in the first week of life may not exhibit radiographic abnormalities in growth plates associated with spider syndrome.

Fig. 38-14 Lateral radiograph of front leg of a lamb with spider syndrome. Note thick, irregular growth plates and multiple ossification centers near the olecranon and distal humerus.

Chromosomal evaluation, hematology, and standard serum chemistry, as well as morphologic and biochemical evaluations of growth plate, have not been abnormal in spider lambs.[42–44] Circulating levels of insulin-like growth factor type I (IGF-I) and its associated hepatic messenger ribonucleic acid (mRNA) are increased in very young spider lambs. The proliferative zone of the growth plate is a major target of IGF-I.[45]

Differential diagnosis includes other diseases that result in congenital defects (scoliosis, kyphosis, and arthrogryposis, often associated with hydranencephaly), including Cache Valley virus, bluetongue virus, lupine ingestion, and the bent leg syndrome.[40,43] The bent leg syndrome is believed to be a dietary problem in young lambs suckling ewes on unimproved pasture; chondrodysplasia of the elbow is not present.

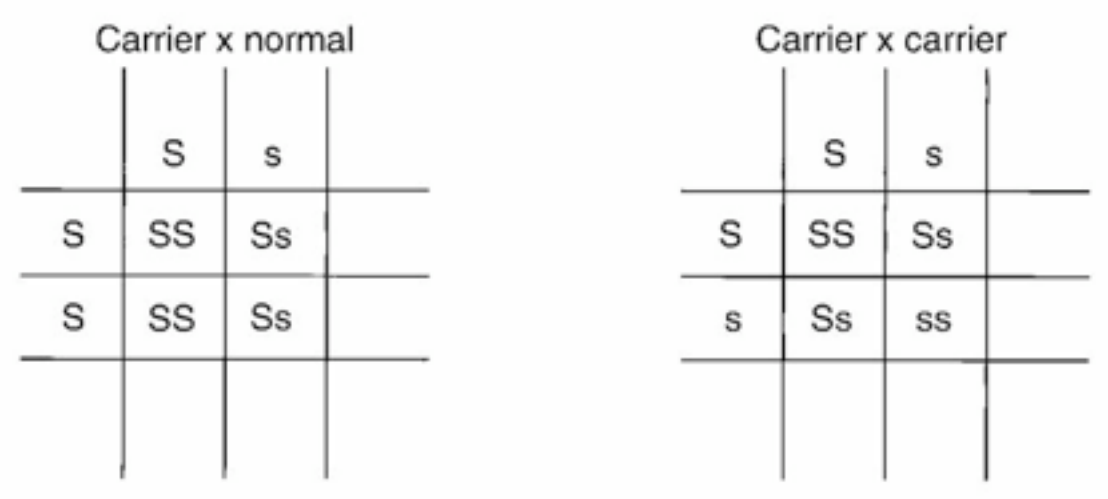
38.4.4 Epidemiology

Limited breeding trials, pedigree analysis of breeding stock producing "spiders," and the wide geographic distribution of spider lambs indicates that the spider syndrome is an inherited defect and is probably an autosomal recessive gene.[41,42] Some workers believe that the selection for very tall sheep within the Suffolk breed resulted in selection for the recessive trait. Affected lambs are double recessive (ss), and both the parents must be carriers (heterozygotes Ss) to produce a spider lamb (Fig. 38-15). Carrier sheep appear to be fairly common within the seed stock of the Suffolk breed and presently can be identified only when they produce a spider lamb. The appearance of a clinically affected lamb may lag years behind the introduction of carrier breeding stock, especially if a carrier ram is crossed into a ewe flock free of the trait. It is important that the diagnosis of a spider lamb is made correctly and with care, particularly in lambs that die before 3 weeks of age, because the condition may be confused with other congenital defects causing scoliosis, kyphosis, and arthrogryposis. Not all lambs suspected as being spider lambs can be confirmed as such.

38.4.5 Necropsy Findings

Gross postmortem examination findings are similar to radiographic changes (generalized chondrodysplasia). Joint cartilage may show erosion, and excess cartilage is evident in thickened, irregular growth plates and in the olecranon. Retained cartilage cores are apparent on the metaphyseal side of affected growth plates. Dysplastic growth plates of spider lamb syndrome are characterized by thickened, proliferative, and hypertrophic zones and a failure to form organized columns. Histologically, chondrocytes exhibit a chaotic pattern of ossification, with chondrocyte proliferation in areas of maturation and loss of normal pattern and direction.[40,44]

Fig. 38-15 Spider syndrome is believed caused by an autosomal recessive trait. This figure illustrates probable mode of inheritance in two possible matings that could produce spider lambs. *SS,* Normal; *Ss,* carrier; *ss,* affected.



38.4.6

Prevention and Control

Carrier rams should be destroyed, but carrier ewes can be used to produce market lambs or to progeny-test rams for the spider trait. Ram lambs produced from carrier ewes must not be used for crossbreeding on commercial ewes of any breed, except for terminal cross-market lambs, because crossbred Suffolk lambs can carry the trait into the commercial sheep industry. A ram can be progeny-tested by breeding to ewes that have produced spider lambs or by breeding to its own daughters. If a ram produces 16 normal offspring from matings with known carrier ewes or 32 normal offspring from mating with his own daughters, the probability that he is a carrier is less than 1 in 100. This procedure is costly to the breeder, and the temptation to retain a ram without an adequate number of test progeny is great. Rams that have enough normal progeny to reduce the probability of being a carrier to less than 5 in 100 have produced spider lambs from the next test breedings needed to complete the progeny test.* Within the purebred industry, breeding stock is classified as “white” (no known spider progeny), “gray” (sire or dam or sibling has produced a spider lamb, but this individual has not), or carrier or “black” (individual has produced a spider lamb). Inaccuracies in sheep pedigrees make prediction of the genetic makeup of any individual risky, and classification without proper testing may be potential grounds for legal action. If parentage of a spider lamb is in question, blood-typing of the sire, dam, and offspring may be helpful.†‡

* Bob Rutherford: Personal communication, 1988.

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38.5 SEPTIC (INFECTIOUS) ARTHRITIS AND OSTEOMYELITIS

JOANNE HARDY

38.5.1 Incidence and Risk Factors

Septic arthritis can result from extension of a periarticular wound infection, traumatic inoculation, iatrogenic inoculation, or hematogenous inoculation. The hematogenous route is the most common avenue of inoculation of organisms in a joint in foals, and bacteremia and septicemia are the most important risk factors for septic arthritis in foals. In one study, septicemia was the most common cause of death (30%) in foals under 7 days of age; septic arthritis was identified as the cause of death in 12.5% of foals age 8 to 31 days.[46] In adults, articular wounds are reported to be the most common cause of joint infection, followed closely by iatrogenic intraarticular injection; postsurgical infection and idiopathic (unidentified cause) are also reported in association with septic arthritis in adult horses.[47,48] Although uncommon, hematogenous spread from a distant focus is possible in adult horses.

Establishment of infection depends on several factors, including size of inoculum, host defense, virulence of the organisms, and local joint factors. In foals, host defense is mainly associated with passively acquired immunity. *Failure of transfer of passive immunity* (FTPI) is the greatest risk factor for development of septicemia in foals.[49] The incidence of disease resulting from FTPI has been reported to be as high as 78%. Organism virulence is related to the ability to establish infection. Attachment factors, ability to resist phagocytosis, and resistance to cell killing all contribute to the establishment of infection. Local joint factors that may predispose to establishment or maintenance of infection include low blood flow, particularly in end-loop capillaries, and poor blood supply, more prominent in bone. In adults, certain intraarticular medications (e.g., corticosteroids, hyaluronate, polysulfated GAGs) have been associated with a higher risk for septic arthritis, potentially by decreasing articular defense.[50,51]

In calves, septic arthritis is associated with FTPI and septicemia and with feeding of mastitic milk *(Mycoplasma)*. In older cattle, direct spread from a perisynovitis is the most common cause, and the distal interphalangeal joint is most often involved.

38.5.2 Pathogenesis

Articular blood supply is provided through a main arteriole that branches to the synovial membrane and epiphysis. Blood supply to the metaphysis is provided by the nutrient artery, but in young foals, transphyseal vessels exists that connect the metaphyseal and epiphyseal blood supply.[52] Experimental intravenous (IV) injection of bacteria results in rapid inoculation of articular and periarticular capillaries. Five types of hematogenous articular infection have been described: *type S* (synovial), where a septic arthritis results from inoculation of the synovial membrane; *type E* (epiphysis), where subchondral bone infection is present (Fig. 38-16); *type P* (physis), where infection of the physis occurs on the metaphyseal side of the growth plate (Fig. 38-17); *type T,* observed in premature foals, with infection of the small tarsal or carpal bones (Fig. 38-18); and *type I,* where joint invasion occurs after a periarticular soft tissue abscess (Fig. 38-19).[53] In young foals, functional transphyseal vessels allow communication of the metaphysis and epiphysis, such that bacteria localize preferentially in the synovial membrane and subchondral bone. Thus, young foals predominantly have infectious arthritis types S and E. Closure of transphyseal vessels occurs after about 7 to 10 days of age, such

that localization of infection to the metaphyseal vessel loops occurs in older foals.[52] Although bone inoculation can occur simultaneously with synovial inoculation in young foals, determination of bone involvement can be delayed until radiographs identify the lesions. In foals the hock, carpus, and stifle are frequently involved in hematogenous joint infection, but it is important to remember that any joints, including those of the vertebral column, can be affected. In young foals, *Actinobacillus equuli, Salmonella* species, *Escherichia coli,* and other Enterobacteriaceae are often involved; in older foals, *Streptococcus* species and *Rhodococcus equi* are common isolates. In foals with type P (physeal) involvement, *Salmonella* and *Rhodococcus* species are typically involved.

Fig. 38-16 Radiograph of a foal with type E septic arthritis showing involvement of the distal femoral epiphysis *(arrow)*.

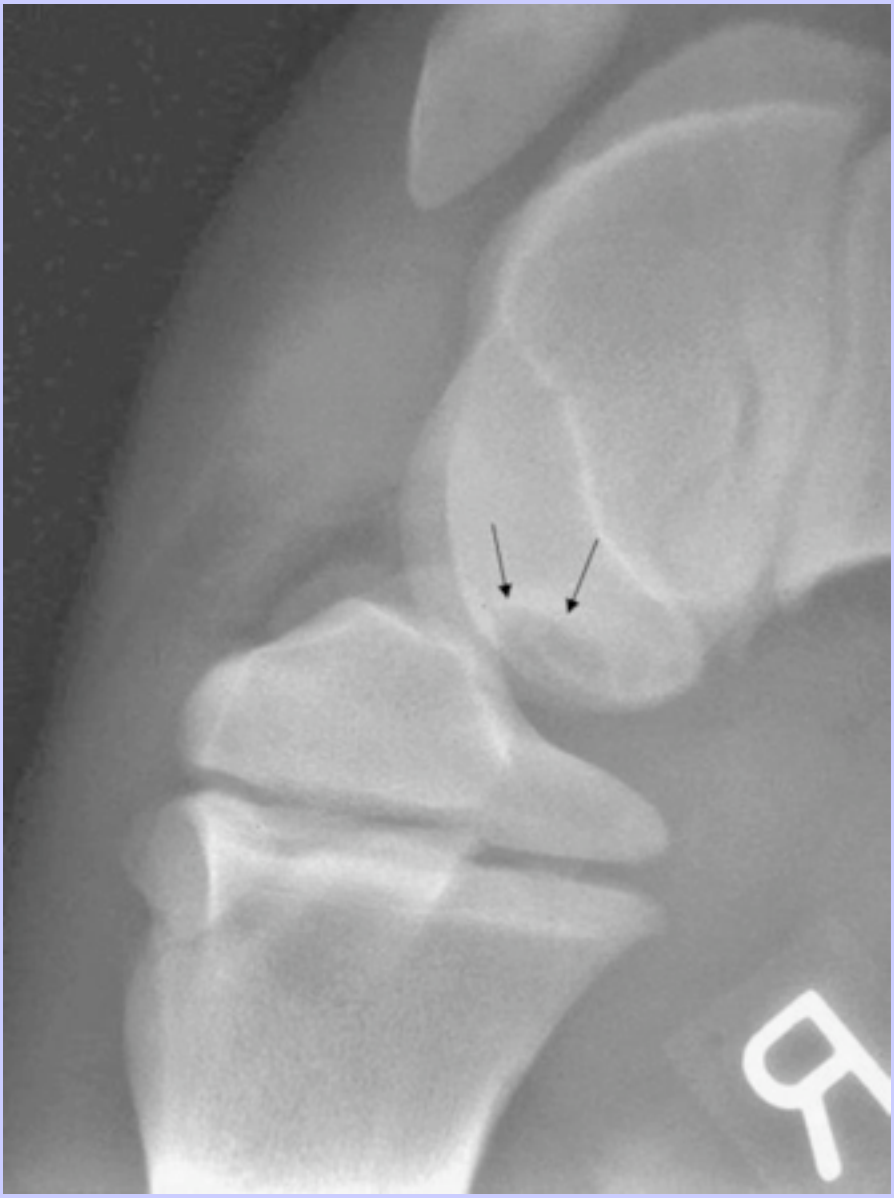
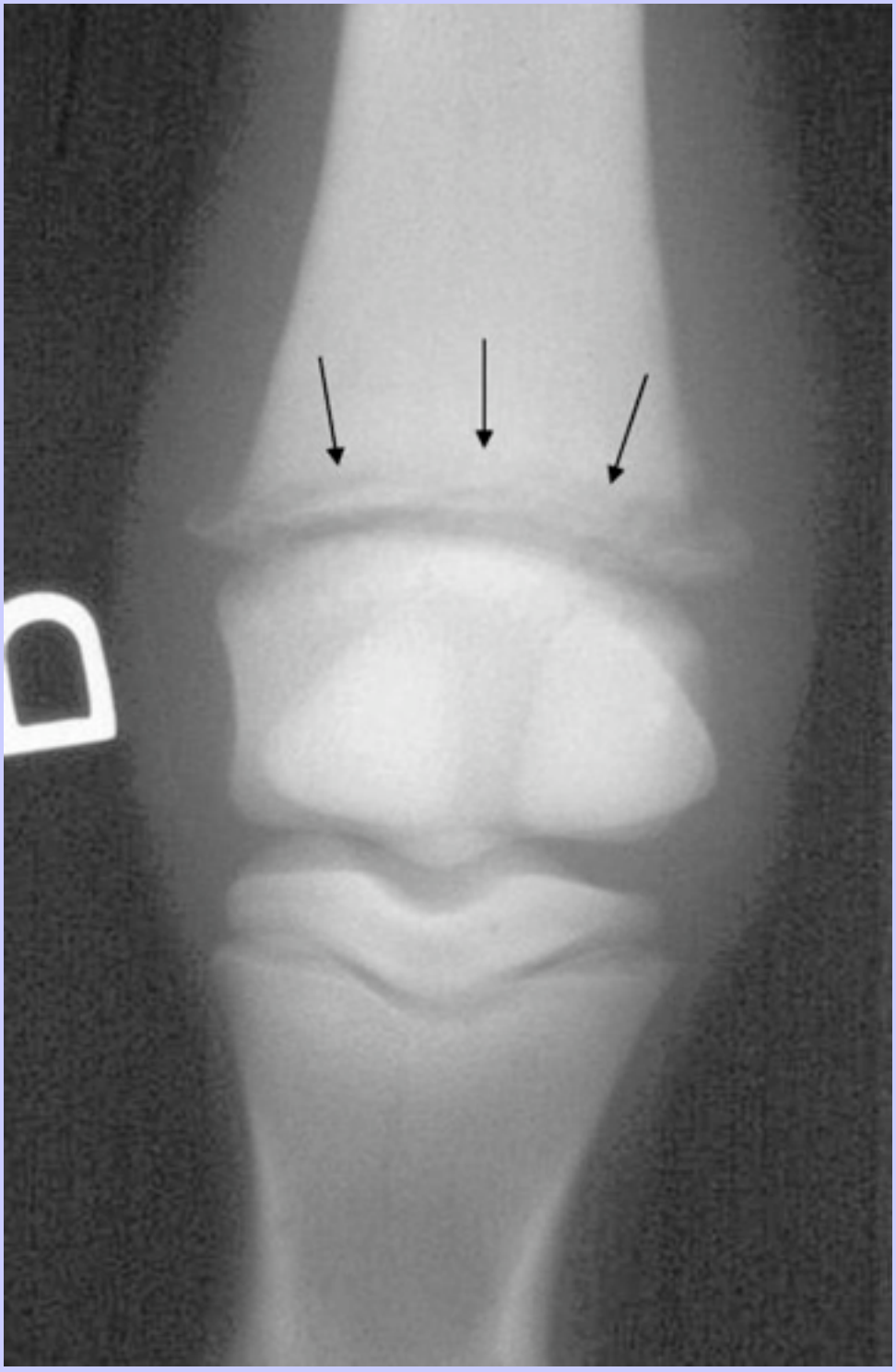


Fig. 38-17 Radiograph of a foal with type P septic arthritis showing involvement of the distal metacarpal physis *(arrows)*.



In adults, inoculation of the joint from an articular wound is the most common cause of joint sepsis. The establishment of infection will depend on size of the inoculum, pathogenicity of the bacteria, and duration before treatment. In one study, 53% of horses examined within 24 hours of an open joint wound developed septic arthritis, versus 92% of horses examined within 2 to 7 days of injury and 100% of horses examined after 7 days.[54] Joints of the lower limb (fetlock, coffin joint) are often involved in open joint injuries because of the poor tissue coverage in those areas.[48,55] Organisms frequently encountered in open joint wounds include Enterobacteriaceae, streptococci, and staphylococci.[48,55] These injuries are also likely to have multiple bacterial infections. Wounds near the hoof are more likely to have anaerobic infection, and *Clostridium* is the most common isolate. Fungal organisms are a rare cause of septic arthritis in horses but should be considered if isolated in pure culture more than once.[56]

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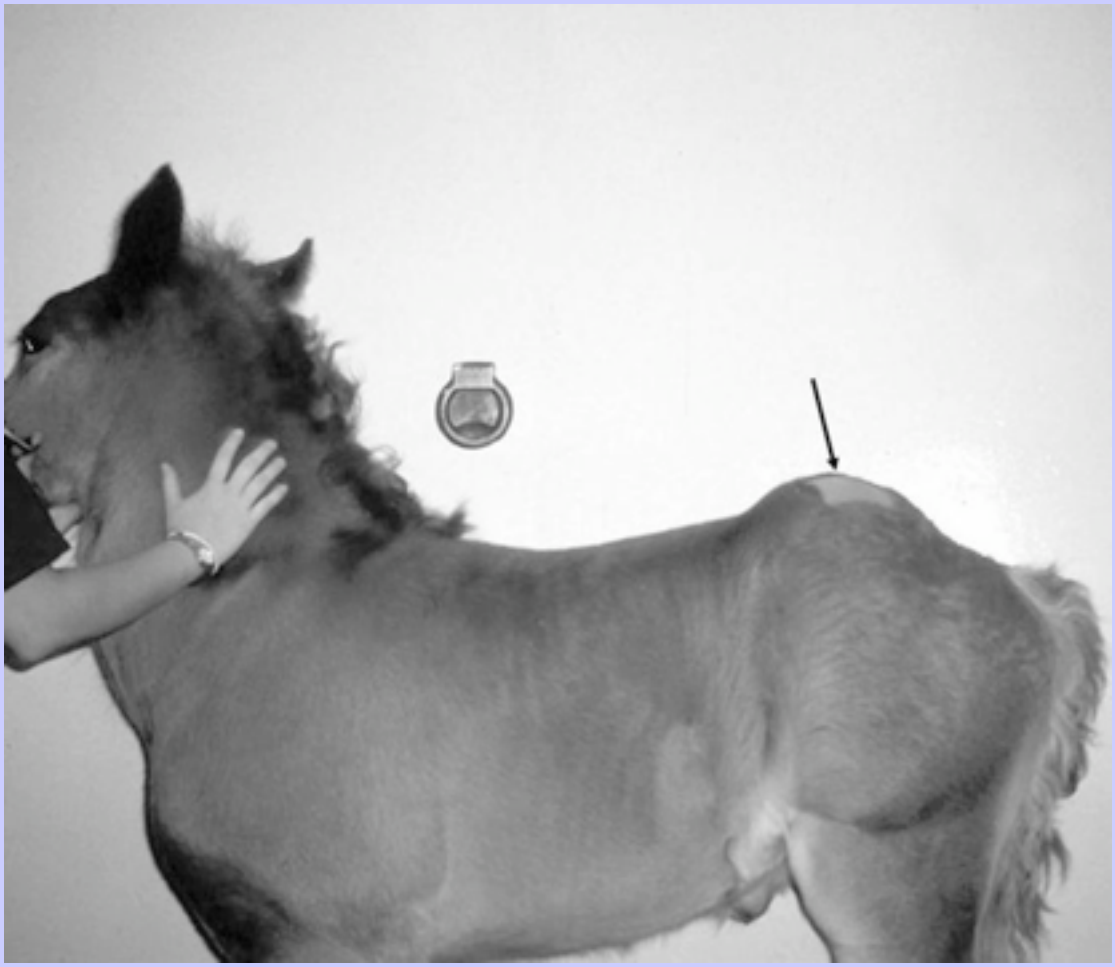
Fig. 38-18 Radiograph of the tarsus of a premature foal with type T septic arthritis showing involvement of the distal tarsal bones *(arrows)*.

Fig. 38-19 Foal with type I septic arthritis where a soft tissue abscess *(arrow)* dissected down into the coxofemoral joint.



Iatrogenic joint injection is the second most common cause of septic arthritis in adults, followed by postoperative infection. The tarsus is the joint most often involved in septic arthritis after joint injection, whereas the carpus is the most common joint involved after surgery.[47,48] Staphylococci, particularly *Staphylococcus aureus,* are the most common organism isolated after iatrogenic joint injections or surgery. When *S. aureus* is isolated from a joint infection, care should be taken to identify further the possibility of methicillin resistance.[57,58] The risk of septic arthritis after arthroscopic surgery is low, 8 of 627 joints (1.3%) in one study.[59] Interestingly in these horses, clinical signs did not develop until several days after discharge.

In adult cattle, common pathogens involved in septic arthritis include *Mycoplasma bovigenitalium, Mycoplasma mycoides, Brucella* species, and *Arcanobacterium (Actinomyces) pyogenes,* which is most often involved.[60] In sheep, goats, and calves, *Chlamydia psittaci* polyarthritis can occur as an endemic or epidemic disease and may be accompanied by keratoconjunctivitis.[61,62] In lambs, *Erysipelothrix rhusiopathiae* is also a

cause of polyarthritis, gaining systemic entrance through the stump of docked tails or castration site. Improving hygiene during these procedures helps prevent the disease.[61]

38.5.3 Diagnosis

Septic arthritis, osteomyelitis, or physitis should be ruled out in any lame foal. Foals with septicemia are at high risk of developing septic arthritis, which generally is noted clinically hours to days after the initial signs of septicemia. Although owners often complain of external trauma, septic arthritis is the most common cause of lameness in foals. In young foals with types S and E arthritis, inoculation of the synovial membrane is the first event, which the astute clinician can identify as periarticular edema. Joint effusion rapidly follows. Involvement of multiple joints is common, and identification of all affected joints is essential for successful management. Because effusion of the shoulder, elbow, or hip joints is more difficult to detect by palpation, arthrocentesis of these joints should be performed in foals with an unidentified lameness. In the stifle, femoropatellar joint involvement results in marked effusion; however, femorotibial joint effusion is usually more difficult to discern. Because of the usual communication between the femoropatellar and the medial femorotibial joint, both are usually involved concurrently. Lateral femorotibial infection is more subtle to identify and can occur separately. Distention of the long extensor pouch is often present in lateral femorotibial infection and suggests involvement of that joint. In foals older than 7 days, physeal infection may be observed. With physeal infection, presence of concurrent synovial effusion depends on the intraarticular or extraarticular localization of the growth plate. For example, distal metacarpal physeal infection results in periphyseal edema, initially without joint effusion. The infection can break through the skin, rather than involving the joint. In foals with septic arthritis, the CBC is consistent with an inflammatory response and includes a neutrophilic leukocytosis and hyperfibrinogenemia.

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Adult horses usually show minimal changes on the CBC and little change in systemic signs; therefore the development or increasing lameness after a wound, joint injection, or surgery indicates the need for further examination. Because of their potent antiinflammatory properties, corticosteroids may delay the onset of clinical signs of septic arthritis after joint injection. In one study of experimentally induced septic arthritis, changes in synovial fluid were present before the onset of clinical signs, and clinical signs of lameness were delayed for 3 days in these horses.[63]

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Table 38-1 Characteristics of Synovial Fluid According to Condition in Large Animal

Characteristic	Normal	Septic	Degenerative Joint Disease	Inflammatory*
Color	Clear	Yellow/green, serosanguineous	Yellow	Yellow to iridescent
Clarity	Transparent	Turbid	Transparent	Translucent
Fluid volume	Low	Increased†	Low	Increased
Viscosity	High	Low	Variable	Low (usually)
WBCs/μL	<500	30,000	<5000	2000-10,000
PMNs (%)	<25	75	25	75
Total protein (g/dL)	<1	2.5	<1	1
Glucose	Equal to blood	<25 mg/dL	Equal to blood	25 to 50 mg/dL lower than blood
Gram or other stain	No bacteria seen	Bacteria may be seen	No bacteria seen	No bacteria seen

WBCs, White blood cells; *PMNs,* polymorphonuclear leukocyte neutrophils.

* May include low-grade sepsis in which bacteria are not found.

† Unless there is an open joint injury, in which fluid may be difficult too obtain.

Arthrocentesis is the mainstay of diagnosis of septic arthritis.[63] Table 38-1 lists the characteristics of synovial fluid according to conditions in large animals. A high protein concentration (>2.5 g/dL) and high white blood cell (WBC, leukocyte) count are observed. Classic counts diagnostic for septic arthritis in foals exceed 30,000 cells/μL, with greater than 90% neutrophils; however, cell counts greater than 10,000/μL may indicate early infection. Neutrophils are not always degenerate. Gram stain is a useful diagnostic tool because it may identify the etiologic agent in up to 25% of cases in which culture results are negative.[64] In foals with a separate physeal infection, where the physis is extraarticular, sympathetic joint inflammation and effusion can occur.[65] This manifests as a moderate increase in WBC count, with less than 90% neutrophils. The presence of such cytologic findings should alert the clinician and practitioner to the presence of physeal sepsis.

In adult horses with a wound localized near a synovial structure, it is crucial to identify as early as possible whether there is synovial involvement. The most convincing evidence is demonstration of synovial communication with a wound by injecting a sterile solution in the synovial structure and observing fluid exiting from the wound. For this purpose, a site remote from the wound and covered with normal skin should be prepared aseptically, and depending on the structure involved, 20 to 200 mL of a sterile solution (e.g., saline, balanced electrolyte) is injected, after collection of synovial fluid samples using aseptic technique.[66] If synovial involvement is detected, therapy is immediately instituted.

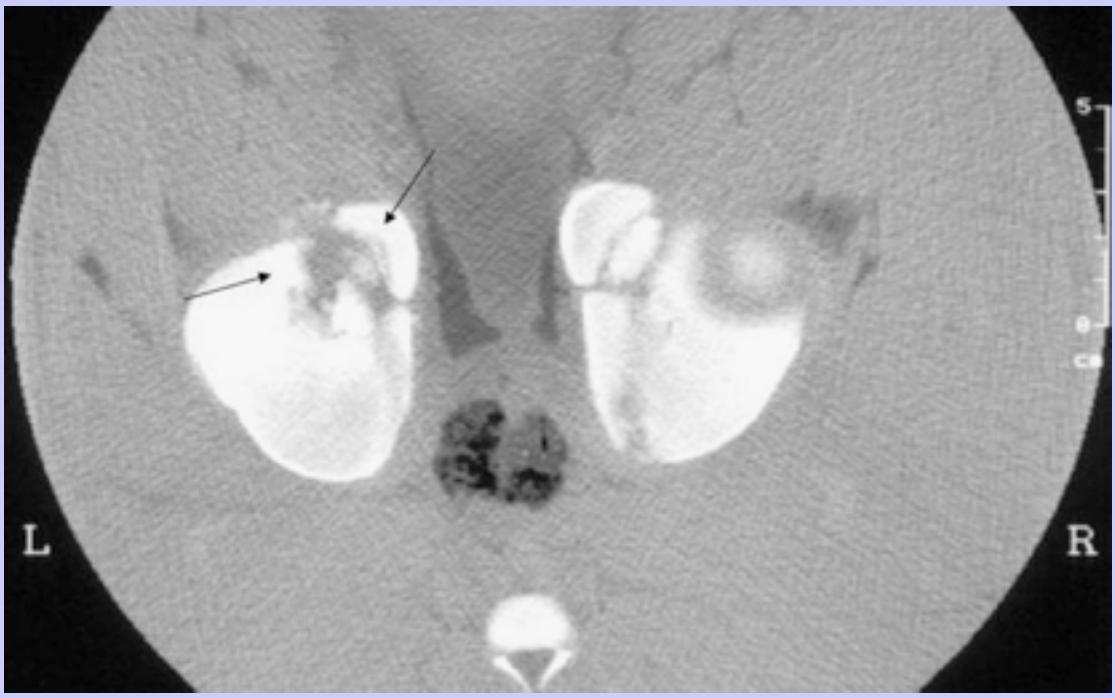
Radiographs of all affected joints are essential. The presence of osteomyelitis may affect prognosis and dictate prolonged antibiotic therapy. Radiographs should be repeated weekly until resolution of clinical signs, or any

time there is deterioration in the clinical condition. Radiographs are also indicated whenever a change in therapy is planned (e.g., from IV to oral antibiotics).

Nuclear scintigraphy has been used to diagnose infectious foci in odd localizations in foals. For example, vertebral and atlantooccipital involvements have been diagnosed using this imaging modality. It must be remembered that local bone infarcts, which are often present in osteomyelitis, will result in areas of decreased rather than increased uptake. Scintigraphy using technetium-99 m ($^{99\,m}$Tc)–labeled WBCs or ciprofloxacin labels has potential uses in foals with multiple-limb involvement and warrants further investigation as an imaging modality for septic arthritis.[67] Newer imaging capabilities (e.g., MRI, CT) may evolve as diagnostic modalities in septic arthritis (Fig. 38-20).

Identification of the organism should be attempted in all cases of septic arthritis. Gram stains, culture of synovial fluid in blood culture bottles, and culture of synovial biopsies have been suggested to increase the likelihood of identification of the organism. In general, the positive culture rate from synovial fluid samples is approximately 50%, and synovial biopsy culture has a low yield to increase this figure.[64] Appropriate culture techniques should be used for organisms such as *Chlamydia* or *Mycoplasma* species, and special stains may be required. In foals, because bacteremia or septicemia precedes the local signs, blood cultures should be obtained. In addition, any other local sites of infection should be cultured. In cases of septic physitis, needle aspiration of the affected site under radiographic or fluoroscopic guidance can be performed. In the future, other techniques for early identification of synovial sepsis may become available.[68]

Fig. 38-20 Computed tomography scan of a foal with septic arthritis of the left coxofemoral joint showing osteomyelitis of the acetabulum *(arrows)* that was not radiographically evident.



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38.5.4 Treatment

Septic arthritis is an emergency. Immediate assessment followed by institution of treatment should be done as soon as possible after problem identification. Treatment of septic arthritis includes systemic broad-spectrum antibiotics, local joint lavage and debridement, and local antibiotics. Systemic antibiotics are best administered intravenously to ensure adequate tissue concentrations. Most often the combination of a β-lactam and an aminoglycoside or fluoroquinolone is used in adults; a β-lactam and aminoglycoside combination is most often used in foals because fluoroquinolones may have detrimental effects on articular cartilage in young animals. In open joint injuries, particularly if an anaerobic organism is suspected, metronidazole may be added to the antibiotic regimen. Gram-positive organisms can be isolated from blood cultures in up to 33% of foals with sepsis, so gram-positive coverage is also important.[69] In foals with physeal involvement, Gram stain and culture of a physeal aspirate are helpful to identify the causative agent. The most common organisms isolated from septic physitis are *Salmonella* species and *Rhodococcus equi*. If *R. equi* is identified, appropriate therapy with erythromycin, azithromycin, or clarithromycin and rifampin should be instituted, keeping in mind that resistance to rifampin and erythromycin has been reported; therefore, obtaining susceptibility patterns may be warranted.[70] In general, the presence of osteomyelitis may warrant an antibiotic combination that reaches effective bone levels; rifampin with another antibiotic is often used. Rifampin should not be used as the sole antimicrobial because resistance is acquired rapidly with this antibiotic. Other antibiotics that reach effective bone concentrations include tetracyclines, chloramphenicol, fluoroquinolones, and cephalosporins. If cephalosporins are chosen, third-generation agents (e.g., ceftiofur, cefotaxime, ceftriaxone, ceftazidime) are preferred because they are more effective against gram-negative bacteria. In foals, fluoroquinolones should be reserved for organisms that are only susceptible to this class of drugs because evidence shows cartilage lesions developing in immature animals with their use.[71,72]

Local lavage of the joint or synovial structure is an important component of therapy; removal of debris, fibrin, and inflammatory mediators helps minimize damage and eliminate the organism. In foals, joint lavage can be performed under heavy sedation or short-term general anesthesia. In adults, sedation and a regional block can be used or short-term general anesthesia. Joint lavage can be performed using through-and-through needle technique; use of a pressure bag or a pump will facilitate efficient lavage of several liters of fluids through the joint. This technique may be sufficient in joints where the diagnosis was made early, where the infection is not severe, and in simple joints (fetlock, carpus). If there is poor response to treatment after one or two sequential joint lavages, arthrotomies should be performed without hesitation. Often, fibrin accumulation in the affected joint precludes effective lavage and allows sequestration of bacteria. Once arthrotomies have been performed, the affected joint will need to be covered with a sterile bandage. During subsequent lavages, a teat cannula inserted in the arthrotomies may be used to lavage the joint. The arthrotomies are left to heal by second intention; the joint will need to remain bandaged until the arthrotomies are closed. Occasionally, delayed closure of the arthrotomies is necessary, particularly in arthrotomies localized over high-motion joints. In joints with multiple compartments (stifle, hock), in severe infection or osteomyelitis, in cases of longer duration, or in animals with poor response to joint lavage, arthroscopic debridement is indicated.[73] Arthroscopy has several advantages over simple needle lavage. It allows thorough debridement, removal of fibrin, and lavage of all compartments, as well as evaluation and debridement of cartilage and underlying bone lesions. In addition, arthroscopy may have prognostic value when radiographic lesions are equivocal. The arthroscopic portals can be left open for drainage and subsequent lavage but must be kept under a sterile bandage.

Intraarticular antibiotics are advocated for the management of septic arthritis. Delivery of local antibiotics to the affected joint can be achieved by intraarticular injection, regional IV or intraosseous (IO) perfusion, continuous

antibiotic delivery, or implantation of antibiotic-impregnated, biocompatible materials. Aminoglycosides (gentamicin, amikacin) and ceftiofur have been shown to maintain levels above the minimum inhibitory concentration (MIC) for 24 hours after a single intraarticular injection.[74,75] Other third-generation cephalosporins are also routinely used in the treatment of joint sepsis, at least until the susceptibility patterns are obtained. Antibiotic-impregnated polymethylmethacrylate (PMMA) beads can also be used, although direct implantation into a joint can result in cartilage damage.[76–78] PMMA implants are fabricated by mixing the desired antibiotic with the powder before adding the polymerizer. Antibiotics evaluated for inclusion in PMMA include gentamicin, metronidazole, vancomycin, ceftiofur, cefazolin, and amikacin.[79–87] Tetracyclines do not elute from PMMA and should not be used. Antibiotic combinations have also been used; metronidazole and gentamicin elute well from PMMA, but the combination of cefazolin and gentamicin is not recommended.[85,86] The implant is then molded into beads and strung on nonabsorbable suture material. The implant is placed into the affected joint or bone, and elution usually persists for approximately 7 days, with peak levels in the first 24 to 48 hours depending on the antibiotic used; the implant is then removed and may be replaced. Antibiotic-impregnated implants, such as gentamicin-impregnated collagen sponges,* have been evaluated experimentally and are commercially available in Europe.[88–90] Garamycin sponges consist of highly purified cattle collagen; the gentamicin molecules are embedded within the pores of the collagen. No stabilizing agents or foreign substances are added. A 50 × 50-mm sponge contains 32.5 mg of gentamicin base and 70 mg of collagen. The main advantage of these implants is that a separate procedure for their removal is not needed.

Regional intravenous perfusion (RIP) or intraosseous perfusion (ROP) are also advocated for the treatment of septic arthritis complicated with osteomyelitis.[91,92] The techniques are performed by first placing a tourniquet around the limb proximal to the location of the joint and/or bone involved. Regional perfusion cannot be performed for joints above the carpal/tarsal region because of the inability to place a tourniquet in those locations. After tourniquet placement, a regional vein is catheterized using a 23-gauge butterfly catheter for RIP; an IO screw is inserted for ROP.† The antibiotic is subsequently injected and the tourniquet left in place for 30 to 45 minutes. Antibiotics, particularly aminoglycosides and enrofloxacin, should be diluted in 20 to 40 mL of saline to avoid phlebitis at the injection site.

Continuous infusion of antibiotics can also be accomplished by placing a small catheter into the joint and attaching it to an infusion system‡ (pump syringe, balloon infuser).[93] In foals it is difficult to maintain these catheters in place, and considering the concentration of antibiotics achieved after intermittent intraarticular injection or regional perfusion, the aggravation of trying to make the system work is probably not warranted.

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With extensive physeal lesions in foals, curettage, autologous bone grafting, and external coaptation may be required.[94,95] The addition of tricalcium phosphate granules or bioresorbable paste may be considered.[96] Angular limb deformities may result from growth disturbances or collapse of the physis on the affected side. In adults with septic arthritis and osteomyelitis, curettage of the bone lesion followed by bone grafting and external coaptation may also be indicated.[97] Adjunctive therapies that may help alleviate inflammation include sodium hyaluronate, polysulfated GAGs, and dimethyl sulfoxide (DMSO). Sodium hyaluronate and polysulfated GAGs can be used systemically or locally, but local use should be reserved for when infection is under control because these agents decrease joint defense mechanisms.[51,98] Although DMSO has significant antiinflammatory properties in joints, it should be used with caution because of its negative effects on cartilage metabolism.[99]

In addition to specific therapies, management of pain, stress, and other metabolic disturbances are indicated. Pain can be managed by judicious use of NSAIDs, using the smallest dose that will keep the animal

comfortable. If a foal continues to show severe pain despite appropriate treatment, it is important to ensure that other joints in the limb are not involved. Other pain management modalities, such as opiates, fentanyl patches, and epidural analgesia, can be attempted. It is important to remember that in foals, continued pain in one limb may result in development of a varus deformity in the contralateral weight-bearing limb, because of the tripod stance that these foals acquire to maintain the weight-bearing limb under the center of gravity. Application of a lateral extension to the contralateral foot may help increase the weight-bearing surface and prevent the development of this complication. Continued pain is a negative prognostic indicator in the affected foal. In adults, continued pain in one limb may result in the development of contralateral limb laminitis.[100] When continued pain in the treated limb is a problem, preventive measures (e.g., hoof support, therapeutic shoeing) should be undertaken.

The use of antiulcer agents is indicated in foals and adult horses that are in pain, stressed, and receiving high doses of NSAIDs. Omeprazole is currently the only medication that has been shown significantly to prevent formation of gastric ulcers and promote healing of existing ulcers in adult horses. Although evidence for its efficacy in preventing and treating NSAID-induced ulcers is lacking, omeprazole is still indicated when NSAIDs are used in stressed animals.

In cattle, facilitated ankylosis is a reasonable alternative when the disease is too advanced, and it is a particularly good option for involvement of the distal interphalangeal joint. Articulations of the distal limb in general are well suited to facilitated ankylosis. In brief, the involved joint is opened and debrided of all debris, all infected tissue is curetted and removed, and a cast is applied and maintained until ankylosis is achieved.[101] Alternatively, the digit may be amputated, although a reduced production life should be expected.[102]

* Garamycin Sponge, Essex Chemie AG, Luzern, Switzerland.

† Self-tapping infusion bone screw, Mercury Orthopedics, Chesterfield, MI.

‡ Elastomeric pump, Syringe pump, Mila International, Florence, KY, http://www.milaint.com

38.5.5 Prognosis

Despite the relatively high prevalence of septic arthritis or osteomyelitis in foals, few studies have examined long-term outcome in affected foals. Furthermore, treatment is often limited by economic considerations, and therefore the true long-term outcome of treatment is not known. Prognosis for septic arthritis should always be guarded. Factors that will influence prognosis are systemic condition of the foal, number of joints involved, localization of joint involvement, severity of the infection, early versus delayed identification and institution of treatment, presence of osteomyelitis, and virulence of the organisms. In one study, 73/93 (78%) of foals survived to discharge, but only a third reached racing performance.[103] Isolation of *Salmonella* species and presence of multisystem diseases were negatively associated with survival and ability to race. In another study, 58/69 (84%) of foals survived to discharge, although signs were present for less than 24 hours in 74% of foals, only five foals had more than one joint involved, and only one foal had osteomyelitis.[104] This population of foals therefore appeared less severely affected. Of the affected foals, only 40.5% started in one race, and of the affected foals that were discharged, only 48.3% raced versus 66.2% in the control (sibling) group. This study concluded that even if foals are successfully discharged from the hospital, they are significantly less likely to start in at least one race than their siblings. Furthermore, these foals took significantly longer to appear on the track than their siblings.

In adults with open joint injuries, the prognosis can be favorable if the joint is contaminated but not yet infected, and if aggressive treatment is immediately started. However, with established infection, the prognosis

should always be guarded. In one study of horses with open joint injury, 53% of those examined within 24 hours developed septic arthritis, and overall survival was 65%. In horses presented within 2 to 7 days of injury, septic arthritis developed in 92%, and survival was 38.5%; in horses examined more then 7 days after injury, septic arthritis developed in all, and survival was 50%.[54] In one study of 101 horses with heel bulb lacerations, those with involvement of synovial structures had worse outcomes then those that did not; 5 of 17 horses with synovial involvement were euthanized.[55] Horses with contaminated or infected synovial structures treated by arthroscopic debridement appeared to have a better long-term outcome, with 106 of 118 (90%) surviving and 96 (81%) returning to previous use.[55] In a study of horses with septic tenosynovitis, 40 of 51 horses (78%) were discharged, and 37 of 40 (73%) survived long term, with 21 (57%) returning to intended use.[105] Surgical technique did not influence outcome in this study. Owners should be informed of the prognosis and high cost of treatment of infected synovial structures.

In cattle the prognosis for septic arthritis is generally better than in horses, probably because of the lack of expectation for athletic use. The prognosis depends on time of presentation, degree of bone involvement, and degree of extracapsular ankylosis. In two studies the success rate was reported as 72% and 85%; cattle with septic tarsi had a worse prognosis.[105a,105b] In another study, arthroscopic lavage and implantation of gentamicin-impregnated collagen sponges resulted in recovery in 12 of 14 cattle.[106] After arthrodesis of the distal interphalangeal joint, 85% success was reported.[102] For carpal arthrodesis, 87% success was reported if no carpal bone was removed, 72% success if one row of carpal bones was removed, and 35% if both carpal rows were removed. Tarsal arthrodesis has a reported success rate of 87% in cattle.[102]

38.6 *MYCOPLASMA MYCOIDES* POLYARTHRITIS OF GOATS

NANCY EAST

38.6.1 Definition and Etiology

Mycoplasma mycoides subspecies (ssp.) *mycoides* is a pathogenic mycoplasma that causes a variety of clinical syndromes in goats. Although the organism was formerly considered exotic to the United States, several large herd outbreaks have been described.[107,108] In most outbreaks the predominant clinical signs are polyarthritis and pneumonia in goat kids, occurring concurrently with mastitis in does. Abortions also may occur in pregnant does. Overwhelming generalized infection can occur in kids or adults, resulting in death.

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38.6.2 Clinical Signs and Differential Diagnoses

Affected kids are from a few days of age to weaning age and have multiple warm swollen joints, elevated body temperatures of 40.8° C to 41.5° C (105.4° F to 106.7° F), pneumonia, and weight loss. They may have conjunctivitis. Many kids are unable to arise or reluctant to move. The acute febrile phase lasts 1 to 3 days, after which polyarthritic kids will be bright and alert and continue to eat. In addition, a few very young kids may exhibit central nervous system (CNS) signs (opisthotonos) or sudden death. Failure to respond to conventional antibiotic treatment or rapid relapse after treatment also characterizes outbreaks. Acute mastitis caused by *M. mycoides* ssp. *mycoides* is characterized initially as an agalactia with a firm, hot gland(s); the milk is brownish and watery with sandy clots. The affected doe is febrile, depressed, and anorexic; has diarrhea; may abort; and may have swollen joints or pneumonia. Some does develop a toxic shock—like syndrome and die rapidly, whereas others make an apparent clinical recovery with variable amounts of udder fibrosis and atrophy

remaining. The milk becomes normal in appearance, but intermittent chronic shedding of *M. mycoides* ssp. *mycoides* may occur.

Differential diagnosis in kids includes septic arthritis caused by bacteria, chlamydial polyarthritis, or white muscle disease, whereas in adult does the mastitis must be differentiated from that caused by *Mycoplasma putrefaciens* and other bacteria. Other *Mycoplasma* species, particularly *M. putrefaciens,* occasionally cause polyarthritis in goat kids.

38.6.3 Clinical Pathology and Laboratory Aids

Most affected kids have an increased WBC count (>13,000 WBCs/mm^3 with neutrophilia >7200 cells/mm^3, monocytosis >530 cells/mm^3) and plasma fibrinogen (>400 mg/dL). Peracutely affected kids and does have a CBC typical of toxic shock, with neutropenia and a degenerative left shift. The joint fluid is increased in volume and contains large fibrin clots with increased numbers of neutrophils and lymphocytes. The organism is usually cultured on mycoplasma media from the most applicable affected site (joint fluid, milk, tracheal wash).

38.6.4 Pathophysiology

M. mycoides ssp. *mycoides* infection leads to mycoplasmemia and multiple organ involvement of varying degrees, with pyrexia, fibrinopurulent polyarthritis, pneumonia, pleuritis, pericarditis, peritonitis, mastitis, abortion, and encephalitis the most common clinical expressions of infection. Recovery is accompanied by the conversion to carrier status in many animals with intermittent shedding of *M. mycoides* ssp. *mycoides* in milk and in ocular and nasal secretions. Pathogenic mycoplasmas are thought to produce toxins, but little is known of the pathogenesis of mycoplasmal diseases.

38.6.5 Epidemiology

M. mycoides ssp. *mycoides* is usually a milk-borne infection that enters herds through inapparent carriers (usually adult milking does). The organism is an obligate intracellular parasite and survives poorly in the environment. It is easily transmitted to other does during normal milking operations and to young stock by ingestion. One milliliter of infected milk contains enough organisms (10^6) to cause polyarthritis in kids.[109] In reported outbreaks the morbidity is high (60% to 90%), and the mortality is 15% to 91%. The morbidity and mortality are highest in young animals. Transmission by contact occurs in conjunction with high-density stocking rates. Environmental and other stressors (transport, kidding, kid processing, changes in herd grouping) induce shedding in chronic carrier animals and may facilitate herd outbreaks. The goat ear mite (genus *Psoroptes*) may play a role in maintaining a reservoir for *M. mycoides* ssp. *mycoides*.[110] Numerous isolations have been made from the external ear canals of clinically normal goats infected with mites.

38.6.6 Necropsy Findings

Gross necropsy findings may include fibrinopurulent polyarthritis, with erosions of articular surfaces, fibrinous pleuritis, fibrinous pericarditis, pneumonia, mastitis, peritonitis, and conjunctivitis. Subcutaneous edema often extends into soft tissues above and below the joint. In addition, meningoencephalitis may be appreciated on gross examination. Histologically, affected tissues exhibit neutrophilic infiltration with perivascular infiltration of plasma cells and lymphocytes.[107,108]

38.6.7 Treatment and Prognosis

There is no effective treatment for *M. mycoides* ssp. *mycoides*. Treatment with antibiotics may result in complete or transient remission followed by relapse. Naturally recovered animals are considered to be carriers, although the number of exposed-recovered kids that remain carriers is not well understood. Treatment with tylosin (10 to 50 mg/kg three times daily) may result in apparent clinical improvement, but the associated risk of producing carrier animals weighs against treatment. Newly developed antibiotics may make successful treatment possible in the future.

38.6.8 Prevention and Control

M. mycoides ssp. *mycoides* can be prevented from entering goat dairies by isolating and performing milk cultures on new herd additions. Milk cultures should be performed at purchase and 2 and 4 weeks later, before the doe is declared free of *M. mycoides* ssp. *mycoides*. If the doe is dry at purchase, isolation should be maintained until she is cultured at kidding and 2 and 4 weeks fresh. Herd outbreaks are controlled by feeding cow colostrum, cows' milk, or milk replacer to kids and by performing milk cultures on individual does. Initially, each doe should have a composite milk sample cultured for mycoplasma.

Does with positive cultures are culled to slaughter or are housed together and milked last until they can be sold to slaughter. At weekly intervals after the milk tank has been emptied, a culture is taken after each string is milked, and the identity of each doe that contributed to the can or tank string sample is recorded. If a positive culture occurs in a string, individual cultures must be performed on that string to identify the doe(s) shedding *M. mycoides* ssp. *mycoides*. After 1 to 2 months of weekly cultures, monthly string cultures are adequate, combined with individual cultures for all does kidding. After 6 to 8 months, monthly bulk tank samples and fresh doe samples are monitored for 1 more year. The majority of infected lactating does are identified in the first 4 weeks of milk culturing. Some does infected with *M. mycoides* spp. *mycoides* may remain undetected for years even with intensive surveillance, thereby leading to sporadic disease. All kids that were being fed milk on the dairy during the outbreak should be sold for meat if they are in satisfactory condition, whereas clinically affected kids should be euthanized because, even with treatment, they may become carriers.

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38.7 CAPRINE ARTHRITIS-ENCEPHALITIS VIRUS

KEVIN E. WASHBURN

38.7.1 Definition and Etiology

Caprine arthritis-encephalitis virus (CAEV) is an RNA-enveloped lentivirus from the Retroviridae family that infects cells of the monocyte-macrophage lineage, with manifestations ranging from subclinical disease to severe encephalitis. Time from infection by the virus to clinical disease may vary from months to years. Infection with CAEV is lifelong, so efforts to eradicate and control its prevalence and incidence are paramount to maintaining successful goat herds. The economic impact of this disease in herds and the goat industry involves loss of productivity, death, and restrictions on the export of diary goats in the United States.

38.7.2 Clinical Signs

Clinically, only approximately 20% of CAEV-infected goats display signs of disease during their lifetime. Recognized forms of disease include a leukoencephalomyelitis, interstitial pneumonia, chronic mastitis, and debilitating polysynovitis-arthritis. *Leukoencephalomyelitis* is observed primarily in kids 2 to 6 months of age, although cases have been reported in adults.[111] This form of CAEV infection is characterized by an ascending paresis leading to paralysis, beginning in the hindlimbs and sometimes involving the forelimbs. These signs may or may not be accompanied by a mild interstitial pneumonia. Goat kids surprisingly may continue to be bright, alert, and appetent. The most severe manifestation of leukoencephalomyelitis is progressive paresis to paralysis to urinary retention and bloating. *Chronic interstitial pneumonia* with progressive weight loss and dyspnea is another recognized form of CAEV infection. Primary ruleouts for this form should include lung worms, pulmonary abscessation, and chronic bronchopneumonia. The mammary gland is a target organ for CAEV, resulting clinically in a firm udder with decreased milk production *(chronic mastitis)*. Although quantity of milk is reduced, grossly, there are no apparent abnormalities.

The most common form of CAEV infection is *polysynovitis-arthritis,* which can be recognized in goats as young as 6 months but more frequently is observed in mature goats. Lameness caused by this form is intermittent and insidious in onset; eventually, however, affected joints become painful and enlarged. Enlargement of the joints is most often caused by hyperplasia of the synovial tissues and their associated sheaths, rather than increased volume of joint fluid. The carpus is most frequently involved, but the stifle, coxofemoral, atlantooccipital, and hock joints are also potential locations. Affected goats have a stiff, stilted gait and progress to walking on their carpus or recumbency. Range of motion is greatly affected, which contributes to chronic contracture of the soft tissue. This polysynovitis-arthritis form of CAEV infection can be accompanied by chronic interstitial pneumonia and weight loss and typically is also associated with some form of mammary involvement.[111]

38.7.3 Diagnosis and Clinical Pathology

On suspicion of the polysynovitis-arthritis form of CAEV infection, arthrocentesis usually yields a brown to red-tinged fluid, with an increased cell count and decreased protein. Joint fluid cell counts in affected joints are dominated by mononuclear cells, which differs from the bacterial synovitis usually observed, consisting predominantly of neutrophils. This predominance of mononuclear cells is also seen in the cerebrospinal fluid (CSF) of goats affected with the leukoencephalomyelitis form. Radiographs may be a useful tool in the diagnosis of CAEV polysynovitis-arthritis in that early cases display soft tissue swelling dorsal to the carpus. Later, as the disease progresses, mineralization can be observed in the periarticular tissue, tendon sheaths, joint capsules, and ligaments. Roughened bone proximal and distal to the joint becomes apparent, along with a periosteal reaction.

The U.S. Department of Agriculture (USDA) recognizes agar gel immunodiffusion (AGID) using ovine progressive pneumonia virus antigen as the official test for CAEV. However, an enzyme-linked immunosorbent assay (ELISA) has been developed for detection of whole-virus, core, or envelope proteins. Both AGID and ELISA are considered reliable enough to be incorporated into prevention and control programs. The AGID test is reportedly more specific, but less sensitive, than the ELISA.[112] Detection of antigen in milk, tissue, and blood can be facilitated through polymerase chain reaction (PCR) techniques. A positive AGID or ELISA in adults is synonymous with lifelong viral infection. Generally, time from infection to seroconversion ranges from 4 to 16 weeks, although some infected goats shed virus for long periods without seroconversion.[113] Goat

kids may be transiently positive for the presence of antibodies during the first 8 to 16 weeks of life after consuming CAEV antibody—containing colostrum; however, because of the nonprotective nature of the maternal antibodies, such kids may seroconvert from true viral infection due to shedding of the virus from the infected dam.

38.7.4 Pathophysiology

The characteristic granulomatous inflammatory pathology produced in affected tissues is thought to be caused by immune complexes generated by the interaction of nonneutralizing antibodies produced by lymphocytes and associated virus-infected macrophages. Localization of such inflammatory lesions occurs where tissue-associated macrophages are found. Tissues of importance in CAEV localization include the synovium, mammary gland, and CNS; therefore the clinical manifestations of the disease are logical.

38.7.5 Epidemiology

Transmission involves the transfer of virus-laden cells from one animal to the next. Transfer of CAEV to neonates through colostrum and later milk is a highly efficient, natural mode of transmission.[114,115] Transmission has also been reported through direct contact; consequently, herds that do not practice segregation of seropositive animals have ongoing difficulty controlling and eradicating the disease.[114–117] Complete separation of kids from the dams immediately after parturition and during the periparturient period is necessary because even kids not allowed to nurse become infected. CAEV proviral DNA has been recently detected in the female caprine genital tract,[118] and experimental infection of goat embryos with CAEV has been reported.[119] Intramammary and in utero transmission also have been described.[117,120] All these means of acquiring CAEV are potential explanations for continued transmission in herds that practice segregation and sound colostrum and milk management.

Maedi-visna virus (MVV), also known as “ovine progressive pneumonia,” is another lentivirus that, together with CAEV, is often referred to as “small ruminant lentivirus” (SLV). Although sheep are most likely to display clinical signs of MVV and goats to have signs of CAEV, studies have shown that these viruses can be transmitted from sheep to goats, and vice versa.[121] Therefore, eradication programs aimed at eliminating SLV from herds and flocks should not allow contact between sheep and goats.

The last study examining the prevalence of antibody to CAEV in the United States found that 31% of all goats tested were seropositive and that 73% of herds had at least one seropositive member. Serum samples in this study were obtained from 28 states. The prevalence was highest in the western Pacific and northern plains regions, on family-owned farms, and increased with age. Prevalence in this study was lowest in the Angora breed.[122] 1206 1207

38.7.6 Necropsy Findings

Grossly, goats affected with the polysynovitis-arthritis form of CAEV have thickened, sometimes folded synovium consistent with synovial hyperplasia resulting from chronic inflammation. Microscopically, synovial hyperplasia is characterized by mononuclear infiltration of lymphocytes, plasma cells, and macrophages. Synovial spaces contain fibrin, whereas synovial villi and collagen are necrotic.[111]

No gross lesions are apparent in the CNS of goats affected with the leukoencephalomyelitis form of CAEV; microscopically, however, perivascular infiltration of lymphocytes, macrophages, and plasma cells are observed. Perivascular infiltration is often accompanied by malacia of the brain and spinal cord in addition to loss of myelin. Occasionally, degenerative lesions are seen in the gray matter.[123]

38.7.7 Treatment and Prognosis

Prognosis for CAEV infection varies because most goats do not show clinical disease; once signs begin, however, rapid deterioration ensues. Arthritis and accompanying weight loss are progressive, and there is no treatment. Kids or mature goats affected with the leukoencephalomyelitis form do not survive and should be euthanized for humane reasons. Reportedly, a genetically determined predisposition for development of the CAEV arthritis exists and can be identified through the use of DNA fingerprinting.[124]

38.7.8 Prevention and Control

Prevention and control are based on colostrum and milk management, although kids should also be prevented from any contact with the dam after parturition. Heat treatment of colostrum by holding it at 45° C (113° F) for 1 hour is effective in inactivating the virus.[117] Kids can then be fed pasteurized milk until weaning. Goats' milk from seronegative dams that is not pasteurized is a risky substitute for heat-treated milk because some seronegative goats shed virus for long periods before seroconversion occurs. Pooling of colostrum increases the prevalence of disease on goat dairies, so this practice should be restricted. Kids should be tested serologically at periodic intervals to detect and remove infected individuals. Seronegative goats should be isolated from seropositive ones by a minimum of 6 feet (1.8 m).[117] Sharing of feed and water troughs should not be allowed, nor should the use of common needles during routine vaccination or administration of medication. During breeding, seronegative does should not be housed with seropositive bucks; however, they can be hand-mated and quickly reisolated. New additions to the herd should be tested and isolated until seronegative status is confirmed before entry into the herd.

Despite diligent prevention and control programs based on elimination of colostrum and milk transmission, isolation of seronegative goats, and serologic monitoring, obstacles to a CAEV-free herd are often encountered. Detection of virus has been reported in properly treated colostrum.[114] Colostrum that is overheated denatures immunoglobulin, thereby preventing effective passive transfer of immunity, and colostrum not heated long enough or at sufficiently high temperature fails to inactivate the virus. Feeding overheated colostrum may also cause diarrhea in the kids.[125] Therefore, attention to times and temperatures during heat treatment of colostrum and pasteurization of milk is crucial for effective colostrum and milk management. Some farms routinely feed cow colostrum; however, neonatal isoerythrolysis has been reported in kids consuming cows' milk, and the lack of goat-specific immunoglobulin transfer is less than ideal.[125] Serologic monitoring can be complicated by shedding of the virus before seroconversion. All goats must therefore be tested at least twice yearly to ensure that new cases are detected and managed accordingly. Unfortunately, no vaccine is currently available for CAEV.

38.8 OSTEOARTHRITIS

MELINDA H. MacDONALD

38.8.1 Definition

The term osteoarthritis (OA) encompasses a large group of joint disorders that are characterized by progressive, permanent deterioration of the articular cartilage.[126–129] Cartilage damage is often accompanied by changes in the adjacent bone and soft tissue structures, including subchondral bone sclerosis, periarticular new bone formation, and synovial inflammation. Unfortunately, some confusion and debate surround the best term to use for this broad group of disorders. Osteoarthritis, degenerative joint disease (DJD), osteoarthrosis, and secondary joint disease have been used almost interchangeably in veterinary medicine.[126,127] However, *osteoarthritis* emphasizes the characteristic synovial inflammation detected in most patients, and this term is used here.

Interestingly, OA is one of the oldest documented orthopedic conditions. In fact, the fossilized remains of early dinosaurs suggest that OA predates the evolutionary development of mammals. Unfortunately, however, questions remain regarding the etiopathogenesis of OA, and this condition is still regularly diagnosed in most large animal species, including horses, cattle, and small ruminants. In goats, OA is frequently associated with CAEV (see previous discussion).[130,131] In pigs, OA is a common debilitating sequela of infectious arthritis or osteochondrosis.[132] Although not routinely diagnosed in sheep, OA has been reported to develop in individuals infected with ovine progressive pneumonia.[130] In contrast, joint disease is a common and expensive problem in the equine industry, and a wide variety of athletic injuries can progress to a common endpoint with stereotypic features of chronic OA.[126–128]

38.8.2 Etiology and Classification

Many factors, including athletic performance, repetitive trauma, and age, are thought to influence cartilage homeostasis and contribute to degenerative changes in the joint. Contrary to the traditional view of articular cartilage as a passive bystander subjected to overexertion and traumatic wear-and-tear damage, it is now recognized that both resident and infiltrating articular cells have a critical role in the development of OA. Cartilage degeneration is an active process ultimately resulting from the inability of resident cells to maintain a normal balance between matrix synthesis and degradation. This occurs when chondrocytes and synovial cells are exposed to various nonphysiologic stimuli, including trauma and inflammation. Once the balance is disrupted, proteoglycans within the hyalin cartilage matrix are depleted and reduced in size, while the collagen meshwork progressively deteriorates. These changes in turn alter the mechanical properties of articular cartilage. A variety of different joint problems can initiate an imbalance between the rates of cartilage degradation and repair and, if left untreated, will ultimately progress to a common endpoint of OA.

Although a number of initiating and predisposing conditions have been identified, it is generally thought that trauma, either a single severe injury or low-grade repetitive damage, is the most important basis for the development of OA in large animal species.[126–128] In many cases the traumatic damage is augmented by abnormal weight bearing, poor-quality cartilage, or congenital joint instability, such as that seen with hip dysplasia in calves. In addition, OA frequently develops in joints that have unresolved or untreated osteochondrosis, subchondral bone collapse, or septic arthritis. In all these cases, the link between the cause and the end result of OA is a series of complex biochemical and metabolic events that are not yet fully understood. Regardless of the inciting etiology, advanced OA is characterized by fibrillated and ulcerated cartilage, eburnation and sclerosis of the subchondral bone, hyperplasia of the synovial membrane, and development of periarticular osteophytes.

Several classification schemes have been proposed to group clinical OA conditions in both human and veterinary medicine. One useful classification developed for equine OA defines three main categories of disease based on predisposing causes and clinical findings.[131] The categories include OA associated with synovitis and capsulitis (type 1), OA secondary to other identified injuries or disorders (type 2), and incidental or nonprogressive articular cartilage erosion (type 3).[127] For example, type 2 OA would include the chronic degenerative changes typically associated with intraarticular fractures, septic arthritis, osteochondrosis, and traumatic cartilage or ligament injuries. All three categories are routinely identified in equine athletes, but this simple scheme can easily be applied to other large animal species as well. For example, cattle most often develop type 2 OA as a consequence of septic arthritis, cruciate rupture, osteochondrosis, or nutritional deficiencies.[132]

A second way of classifying OA is based on the possible deleterious effects of biomechanical forces on normal and abnormal joints.[128] According to this scheme, the first of two major causes of OA is the concentration of abnormal forces on a previously normal joint. For example, OA can develop when there is increased weight bearing on one limb to protect a painful contralateral limb. The second major cause is the concentration of normal forces on an abnormal articulation, such as the joint damage that occurs when normal weight-bearing forces are applied to cartilage previously exposed to infection.

38.8.3 Pathology and Pathogenesis

Despite the many pathways by which OA may develop, the resulting changes in the joint are essentially indistinguishable regardless of the initiating cause. By definition, this condition has a characteristic picture of cartilage damage with variable amounts of hypertrophic cartilage and bone remodeling. Pathologic features include different degrees of cartilage splitting and fragmentation, extending to complete erosion and loss of articular cartilage.[126–128] Typically, the rate of disease progression and severity of OA are related to the nature and severity of the primary insult, the animal's age at the time, the joint location, and the animal's type and level of activity.

The pathogenesis of these changes is only partially understood. Several explanations have been proposed for the failure of resident chondrocytes to maintain the extracellular matrix. Mechanical trauma to the joint surface could initiate matrix damage, and repetitive microtrauma could damage chondrocytes and physically disrupt the joint surface. Leukocytes in an inflamed joint release destructive enzymes, which can degrade the cartilage surface. Recent work has also demonstrated that various polypeptide mediators released in inflamed joints can stimulate chondrocytes to degrade their surrounding matrix. Regardless of the initiating factor, once the balance of chondrocyte-matrix turnover is shifted toward degradation, proteoglycans are rapidly depleted from the extracellular matrix, and collagen fibers are exposed to direct traumatic and enzymatic breakdown. Unfortunately, hyaline cartilage has no effective intrinsic repair mechanism.

Articular cartilage damage is accompanied by changes in the adjacent subchondral bone (e.g., sclerosis), joint capsule (e.g., synovial hyperplasia, thickening of fibrous joint capsule), and joint margin (e.g., osteophyte formation, enthesophyte formation at joint capsule and ligament insertions).[128] Subchondral bone sclerosis may develop from an abnormal distribution of forces under damaged articular cartilage, or it may actually precede the cartilage damage. It is now known that bone remodeling and subchondral bone sclerosis occur in response to repetitive cyclic compression during exercise and, in certain cases, could result in trauma to the overlying articular cartilage and predispose to the development of OA (e.g., third carpal bone disease in horses). Joint

margin changes occur as a result of progressive cartilage deterioration and subchondral remodeling (osteophytes) or joint instability (enthesophytes).

38.8.4 Clinical Signs

History and occupation are important for identifying animals at risk for developing OA. Typically, the first sign that an owner or caretaker recognizes in an affected animal is lameness or stiffness. Whereas the pain and dysfunction may develop insidiously, the owner will often report a sudden onset of clinical signs. Flexion and extension of an involved joint frequently exacerbates the lameness or elicits a pain response. Because articular cartilage is aneural, pain is thought to result from joint inflammation and secondary changes in adjacent tissues. Pain receptors are abundant in joint capsule, articular ligaments, and subchondral bone. Joint stiffness may be associated with guarding of a painful joint. Decreased range of motion with joint capsule inflammation is also common. Osteophytes and enthesophytes may be palpable in chronic cases of bone spavin and ringbone. A postural deformity may be evident if articular degeneration progresses to ankylosis. It is also important to remember that OA may exist in the absence of any clinical signs.

Gait abnormalities compatible with OA include shortened stride length, limb abduction, and dragging the toe. Increased lameness after sustained flexion of a single joint suggests that the joint is involved. Horses with OA often present early in the course of disease with a primary complaint of poor performance. These individuals can warm out of the lameness, or temporarily improve with rest, and are often difficult to diagnose. In contrast, food animals typically present in the advanced stages of OA. Rams and bulls may stand post-legged and appear weak in the rear when the hindlimbs are severely affected. In all species the severity of signs varies with the joint affected, stage of disease, amount of inflammation, cartilage degeneration, and periarticular changes.

38.8.5 Diagnosis

Regional nerve blocks and intraarticular anesthesia can be useful for determining the origin of lameness. Unfortunately, standard synovial fluid analysis typically shows only minimal, nonspecific changes. Although 1208
not useful for determining the severity of cartilage destruction, cytology is often useful for differentiating OA 1209
from other causes of synovial inflammation (e.g., septic arthritis). A variety of synovial fluid markers have been evaluated as possible diagnostic aids for evaluation of equine synovitis and joint disease (e.g., cytokines, eicosanoids, GAG concentrations, immune complexes, collagen type-specific antibodies and propeptides, cartilage wear fragment, free-radical oxidation products, polymerization of hyaluronate, chondroitin sulfate epitopes). Current detection techniques for cytokines and eicosanoids may prove useful diagnostically and prognostically.

After identification of an involved joint, radiographs are used to determine the severity and extent of disease. Articular cartilage is not visualized but may be indirectly assessed by evaluating joint space width. In contrast, the associated subchondral and periarticular bone reaction can be directly evaluated. Radiographic signs of OA develop gradually, affect opposing joint surfaces, and may include destructive as well as productive lesions. Changes typical of advanced OA include marginal osteophyte proliferation, periosteal new bone production at sites of joint capsule and ligamentous attachments (enthesophytes), narrowing or obliteration of the joint space, subchondral bone sclerosis, and occasionally, subchondral lysis. Early in the disease, no bony lesions may be detected, and clinical findings from the entire examination must be considered. Radiographic changes associated with OA must be differentiated from similar bone reactions caused by active infection, fractures, osteochondrosis, and invasive tumors. Infectious arthritis classically causes rapid, widespread osteochondral destruction. Minimally displaced fractures may mimic OA but are usually discrete, isolated lesions. Knowledge

of the characteristic site distribution and site-respective appearances of osteochondroses in each species is useful for differentiation from OA. The presence of OA in joints with osteochondrosis usually worsens the prognosis.

Scintigraphy is particularly valuable in early disease states when conventional diagnostic methods have not revealed bone or soft tissue changes. Increased scan activity is associated with soft tissue inflammation or increased bone remodeling, but alone it is not diagnostic for OA. Arthroscopy is the best method for gross evaluation of articular cartilage and is most useful when lameness has been localized to a specific joint but no bony changes are detected radiographically. This technique provides the added therapeutic benefit of simultaneous joint lavage. Although arthroscopy was initially promoted for diagnostic and therapeutic use in equine patients, these techniques are gaining popularity in food animal practice as well.[133]

38.8.6 Treatment

The choice and efficacy of treatment depend on the inciting cause of OA, stage of cartilage degradation, joint involved, and degree of active inflammation. In general the treatment of OA should be directed at eliminating any primary causes, reducing active joint inflammation, and treating articular cartilage loss or degeneration.[126,127,134] Early treatment of primary problems minimizes the extent of secondary joint damage. For example, fractures and osteochondritis dissecans can often be managed successfully with arthroscopic surgery; however, early intervention is essential to avoid the secondary changes of OA.

Many therapeutic options are designed to treat active soft tissue inflammation and prevent progression of articular cartilage damage. Rest is the simplest but often the most difficult recommendation to enforce, especially when dealing with elite performance horses. There are also valid concerns that complete rest may result in resorption of subchondral bone and predispose the horse to subsequent injury. Other treatments for soft tissue disturbances in the joint include physical therapy and controlled exercise, systemic NSAIDs (e.g., phenylbutazone, flunixin meglumine), joint lavage, and topical application of antiinflammatory products.

Numerous medications have been specifically designed and marketed for treating OA in human and veterinary patients. However, many of these products remain controversial in terms of their safety and efficacy in large animals. The most popular formulations include intraarticular corticosteroids, intraarticular and intramuscular polysulfated glycosaminoglycans (GAG), intraarticular and intravenous hyaluronan, and oral GAG supplements.

Intraarticular steroids are the most potent antiinflammatory agents available; historically, however, they have been associated with progressive cartilage damage.[134,135] Nevertheless, investigations critically evaluating the effects of corticosteroids in equine joints suggest that when administered at physiologic doses, these drugs may have beneficial protective effects.[134,135] Current recommendations emphasize the need for appropriate caution and encourage the use of low doses of steroids in conjunction with other antiinflammatory medications. Hyaluronan (sodium hyaluronate) is currently used both intravenously and intraarticularly to treat synovial inflammation and OA in the horse.[134,136] The intraarticular products vary in molecular weight and cost and include cross-linked hylans, which may prolong intraarticular retention. Clinical reports document the efficacy of hyaluronan for mild to moderate synovitis, and some research supports an inhibition of proteoglycan degradation and inhibition of synoviocyte release of various inflammatory mediators. Other studies failed to demonstrate beneficial effects in joints with significant articular cartilage damage or osteochondral fragmentation.

The intraarticular administration of polysulfated GAG has been reported to reduce progressive degenerative changes in articular cartilage, but is controversial in terms of its ability to augment the chondrocyte repair response.[134,137] Intramuscular use is advocated because intraarticular use has been associated with adverse reactions and potentiates the risk of iatrogenic joint infection.[134,137]

There is still great interest in the use of nutritional supplements to prevent and treat OA, with a proliferation of products promoted as beneficial to joint health and cartilage regeneration.[138] Among the most popular are the oral glucosamine sulfate and chondroitin sulfate preparations. However, oral absorption of chondroitin sulfates has not been documented in the horse, and although clinical reports suggest a beneficial effect from these supplements, additional controlled studies are needed to confirm these effects. Methylsulfonylmethane (MSM), a dietary derivative of DMSO, is also being used as a dietary supplement to control the inflammation associated with OA. Again, minimal documentation exists regarding its value in treating joint disease in large animals. Other compounds to treat OA include *S*-adenosyl-L-methionine and various vitamins known to provide antioxidant protection.

The most challenging aspect of OA management is treatment of existing articular cartilage degeneration and loss. Partial-thickness cartilage defects do not heal, and full-thickness defects heal with inferior fibrocartilaginous tissue. Some surgical techniques (e.g., curettage, subchondral bone drilling, microfracture) facilitate defect repair by enhancing fibrocartilage ingrowth from the underlying subchondral bone; however, fibrocartilage is biomechanically inferior to normal hyaline cartilage. Grafting cartilage defects with periosteum, perichondrium, and sternal cartilage has not been encouraging. More recent work focuses on transplantation resurfacing using chondrocyte grafts and growth factors to stimulate repair.[139]

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38.8.7 Prognosis

Prognosis for animals with OA depends on the initiating factor(s), extent of the secondary disease, joint affected, and intended use of the animal. With early and aggressive treatment, many animals can return to soundness and athletic performance. In other cases, salvage in the form of surgical arthrodesis may provide the most favorable outcome.

38.9 SPRAINS, SUBLUXATIONS, AND LUXATIONS

WILL C. JORDAN

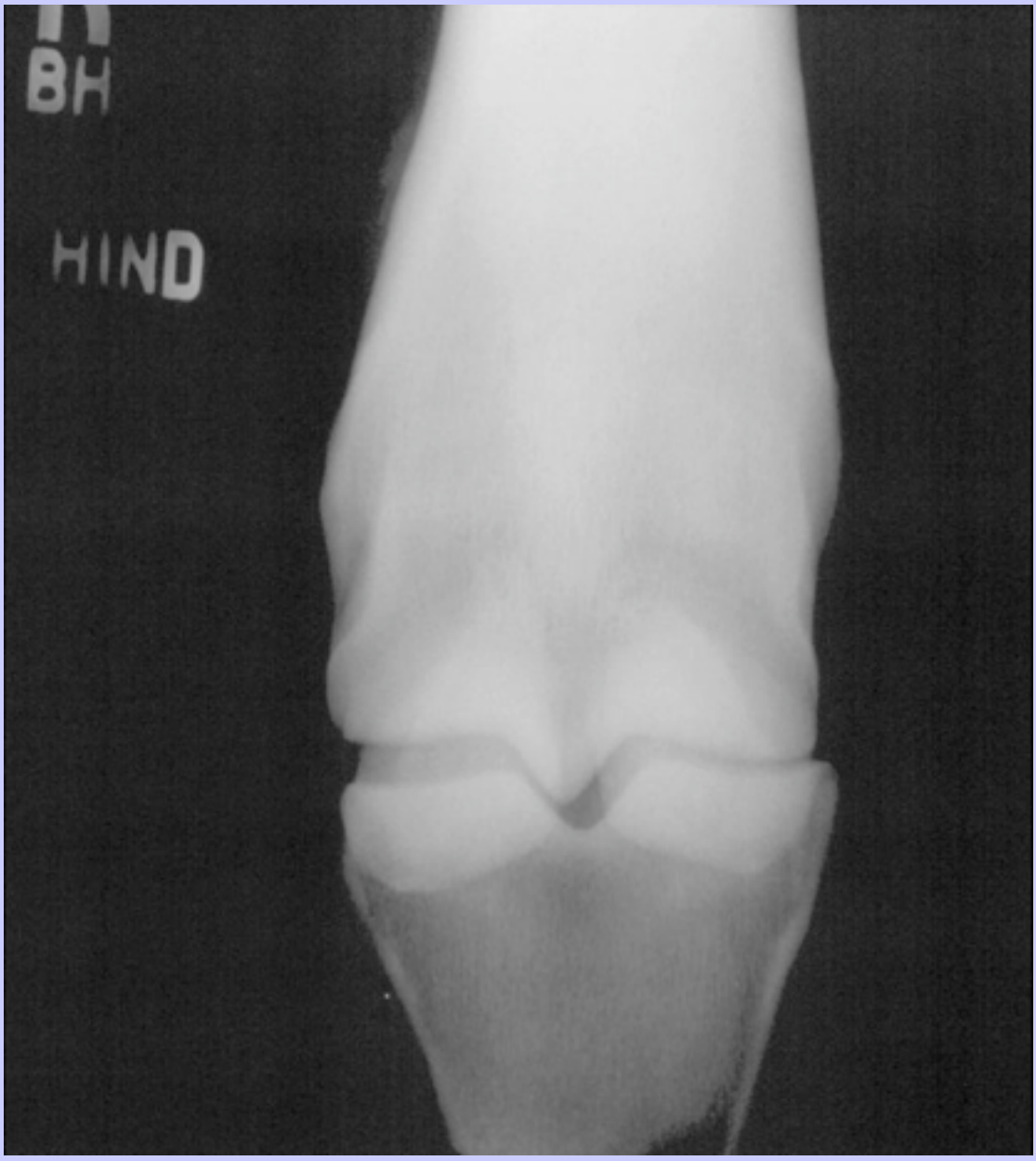
38.9.1 Definitions

Sprains and luxations have been classified as a type 2a traumatic arthritis.[140] These injuries have been categorized in three forms: mild, moderate, and severe. *Mild* sprains constitute injuries that involve the tearing or disruption of minimal number of ligament fibers, with no loss of integrity to the ligament. Hemorrhage and edema typically are present in the ligament. Injuries that involve a portion of the ligament, with loss of integrity, are considered *moderate* sprains. Laxity of the joint is often present with moderate injury; however, complete separation of the ligament from the bone or complete separation of the body of the ligament is not seen. Significant hemorrhage and edema are present in the ligament. Injuries that involve tearing of the ligament, resulting in either complete separation from the bone or widening of the tendon fibers, are considered

severe sprains. These injuries will result in some form of joint instability, especially when the affected joint is manually stressed.

Luxations and subluxtions are usually the result of severe sprains of periarticular or articular ligaments. *Luxations* represent the complete dislocation of the articular surfaces, with *subluxations* having only partial and incomplete disarticulation (Fig. 38-21).

Fig. 38-21 Dorsopalmar radiograph of a subluxated metacarpophalangeal joint after the joint has been manually stressed.



38.9.2 Etiology and Pathophysiology

Sprains can be associated with acute injuries in which there is excessive strain on the ligament fibers, on ligamentous attachments, or secondary to repetitive actions on the ligament. The latter results when there is maximal or near-maximal loads repeatedly applied to the ligaments and associated structures, causing a degenerative type of lesion. Age can also be a contributing factor to these degenerative changes. Furthermore, muscle fatigue can contribute to the weakening of adjacent structures, increasing the stresses applied to the supporting ligaments.

Typically, hemorrhage and edema form within the ligament(s) surrounding the joint capsule, or in severe lesions the hemorrhage can be periligamentous or intraarticular. Inflammation ensues, and the ligamentous or capsular lesion heals through fibrosis, forming a scar, with type III collagen the predominant type produced. Type III collagen contains a smaller fibril diameter and has fewer cross-links then type I collagen, which is the predominant collagen type in normal tendons and ligaments. As the lesion matures, the fibril diameter will increase along with the number of cross-links, in addition to the proportion of type I collagen. This will increase the strength of the injury, which can take weeks to months to heal but will ultimately be weaker than the normal tissue.[141] Often the affected joint capsule and surrounding ligaments become fibrotic as healing occurs, resulting in a decreased range of motion in the affected joint. Secondary calcification of the affected soft tissue structures may occur and adversely affect the joint's mobility.

Luxations of the coxofemoral joint in calves may be associated with calving injuries during a dystocia or in cows being ridden while in estrus, or with a traumatic fall in the immediate postpartum period.[142,143] Shoulder joint luxations are usually the result of trauma.[144]

38.9.3 Clinical Signs and Differential Diagnosis

The clinical signs vary depending on the severity of the sprain and the duration from the initial injury. The animal may have a history of mild lameness or decreased performance, as well as a history of a positive response to NSAIDs or stall rest. Patients with moderate to severe sprains will typically have a more pronounced, acute lameness or may be non—weight bearing on the affected limb. There may also be localized swelling, heat, increased joint effusion, or pain elicited on palpation or manipulation of the affected joint. Other signs may include abnormal limb positioning, decreased range of motion, crepitus, and joint laxity. Injuries may present after an acute or traumatic insult, as a chronic lameness, or a chronic mild injury can present acutely with severe lameness if the ligament completely separates. Chronic injuries are characterized by a thickening of the joint capsule or enthesophyte formation at the origin and insertion of the affected ligament.

Subluxations and luxations result in the loss of joint function and mobility and may present with a varus or valgus deformity. Complete luxations in the horse are most common with the pastern, fetlock, and hock joints.[140] Luxations can occur in the shoulder, carpus, and coxofemoral joint; however, these luxations are less common in horses. Coxofemoral luxations are the second most common type of luxation in cattle.[143]

Differential diagnoses vary depending on the region affected and duration of injury but may include soft tissue contusion, synovitis and capsulitis, osteoarthritis, bursitis, musculotendinous injuries, fractures, physeal fractures, septic arthritis, tenosynovitis, and flexural or angular limb deformities.

38.9.4 Diagnostic Tests

A thorough history and physical examination should be performed at presentation. The exam should include assessment of pain, swelling, heat, effusion, or instability of the joint. Patients able to ambulate with only mild lameness should have a lameness examination that includes perineural anesthesia to localize the affected region or joint. The clinician should take extra caution if there is any evidence of joint laxity or instability or severe lameness.

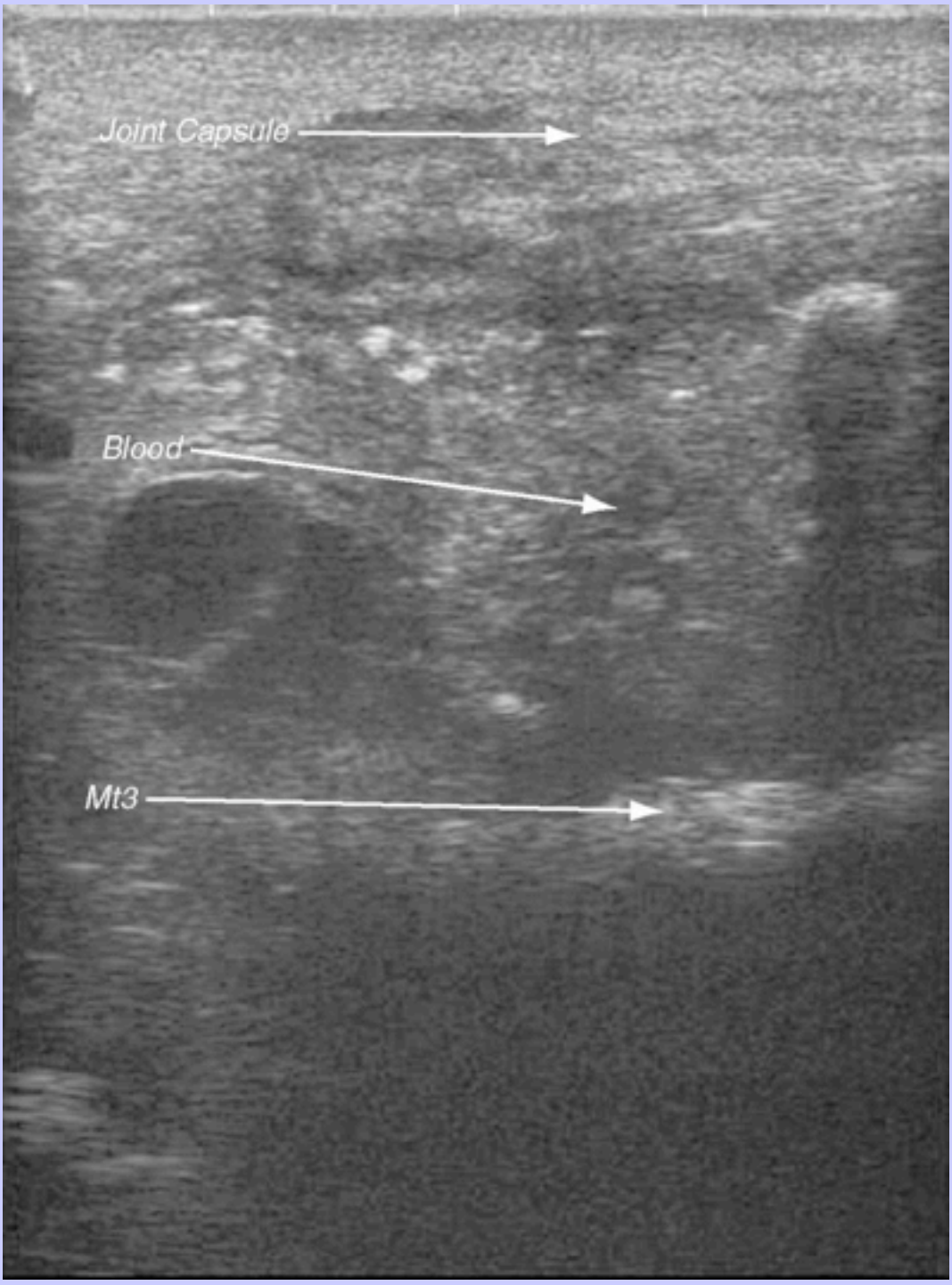
Radiographs should be obtained to assess the bony structures of the joint because concurrent factures are common with traumatic insults resulting in luxation. Stress views can be performed to assess the level of instability of joints (see Fig. 38-21). Fractures of the proximal or middle pastern bones can cause luxation or subluxation of the proximal or distal interpastern joint. Furthermore, radiographs are useful in detecting avulsion fractures or insertional desmopathies and enthesophytes associated with chronic disease. Nuclear scintigraphy can also be used to evaluate insertional desmopathies that may not be radiographically apparent. Arthroscopy may be indicated as a diagnostic aid if disruptions of intraarticular ligaments are suspected or if damage to the articular cartilage is suspected. Ultrasonography is used to locate the ligamentous lesions and characterize the extent of the lesion. Ultrasound should also be used to evaluate the joint because arthritis is a common sequela. Magnetic resonance imaging (MRI) is becoming more readily available in the veterinary field and has been found useful in identifying and characterizing lesions in ligaments. In addition, there may be concurrent damage to adjacent structures of the joint or avulsion fractures that might not be ultrasonographically or radiographically detectable but that can significantly influence the prognosis.[142,145–147]

38.9.5 Treatment

Treatment is largely based on the severity of the lesion and associated structures involved. Mild sprains can be treated conservatively with support bandages, NSAIDs, polysulfated GAGs, and rest for 3 to 4 weeks, followed by a controlled exercise program before returning to normal activity. Adjunctive physiotherapies may also be considered, such as hydrotherapy or shock wave treatment. Moderate sprains involving significant ligament damage may necessitate the use of a cast or splint to provide joint stability during the initial healing process. In acute cases, ultrasound evaluation of the affected joint often shows hemorrhage within the joint capsule (Fig. 38-22). This hemorrhage usually resolves after 7 to 10 days; however, it can also subsequently form a fibrinous clot within the joint capsule, resulting in a chronic mild synovitis that can be treated with intraarticular medications, such as sodium hyaluronic acid, triamcinolone, and amikacin antibiotic. Arthroscopy should be considered to treat joints with persistent fibrin accumulation. Arthroscopy has the advantage of further evaluating damaged cartilage or intraarticular ligaments and serving as a portal for high-volume flush. If arthroscopic surgery is performed, a cast or splint should be applied to the affected limb during recovery from anesthesia to prevent luxation of the affected joint and further injury. Severe sprains may need some form of internal or external coaptation or arthrodesis of the joint, depending on the degree joint instability. Support of the contralateral limb should be considered for non—weight-bearing injuries.

Luxations of the coxofemoral joint in cattle can be repaired by open or closed techniques, and success depends on duration of the luxation, concurrent fractures or soft tissue injury, and age. Open reduction was reported as being more successful than closed reduction, although closed reduction should be attempted immediately after the injury if possible.[143] Shoulder joint luxations can also be reduced by closed and open techniques.[144] Open reduction with internal stabilization seems to result in a better survival outcome for the animal.[144]

Fig. 38-22 Ultrasound image of a metacarpophalangeal joint from a horse with an acute sprain. Note the hemorrhage accumulation within the joint capsule. *Mt3,* Third metatarsal bone of fetlock joint.



38.9.6 Prognosis

Prognosis depends on the severity of damage to the intraarticular cartilage and surrounding soft tissue structures. Horses sustaining mild joint or ligamentous strains have a good prognosis for returning to previous athletic use. Horses sustaining moderate or severe sprains or joint luxations usually develop secondary DJD in the affected joint, which may require intraarticular medications and NSAIDs to return to previous use. The long-term prognosis for returning to athletic performance in these cases is poor. Simple shoulder luxations in large animals generally carry a guarded to poor prognosis. Simple coxofemoral luxations in cattle have a fair to good prognosis, with calves having a better prognosis than adult cows.

38.10 ARTHROGRYPOSIS

K.C. KENT LLOYD

BRADFORD P. SMITH

Arthrogryposis is one of the most frequently encountered congenital diseases affecting calves; foals, goat kids, and lambs are less frequently affected (see also Chapters 51 and 52). The condition is usually characterized by flexural deformity of the interphalangeal, metacarpophalangeal, carpal, and/or metatarsophalangeal joints (Fig. 38-23). Beef breeds are typically affected (e.g., Charolais, Herefords, Simmental), and the incidence is greater in bull calves. The disease is multifactorial in origin and thus often accompanied by other anatomic and neurologic defects, including hydranencephaly, scoliosis, and cleft palate.

1211 1212

Fig. 38-23 Two-day-old heifer calf with bilateral congenital arthrogryposis of the carpus.

Arthrogrypotic diseases can be categorized on the basis of their suspected etiology: infectious (e.g., epizootic bovine and ovine congenital arthrogryposis-hydranencephaly caused by Akabane virus, bluetongue virus, border disease virus, and Cache Valley virus), genetic[148,149](e.g., arthrogryposis and palatoschisis of Charolais calves; arthrogryposis and other abnormalities in Norwegian Fjord horses, Welsh Mountain,[150] merino,[151] and inbred sheep flocks), and toxic[152] (e.g., arthrogryposis in foals associated with Sudan pasture and crooked calf and lamb disease associated with lupine alkaloid). Lambs also may have scoliosis, kyphosis, brachygnathism, and cleft palate.

Cache Valley virus (CVV) is widespread in the western United States and has been isolated in Wisconsin and Michigan; 19% of young sheep from 50 flocks in western states were seropositive. CVV appears capable of causing arthrogryposis-hydranencephaly in fetal lambs.[153] Experimentally infected gnotobiotic lambs developed head tremors and convulsions. Other toxins, as well as lamb manganese deficiency, poisonous plants such as *Solanum dimidiatum,* and sporadic genetic accidents resulting in maldevelopment, also are associated with arthrogryposis and related defects.

Despite numerous causes, the clinical features of arthrogryposis are similar. Varying degrees of irreducible and rigid flexural deformity of both carpi and forelimb fetlock joints are more frequently observed than hyperextension of the tarsus, flexural deformity of the hindlimb fetlocks, or tetramelic arthrogryposis. In contrast, flexural deformities caused by contracted tendons are not associated with improper articular alignment or rotational deformity, and the limb often can be straightened manually. Flexural deformities that could be confused with arthrogryposis may be secondary to septic arthritis or fracture (Box 38-1).

Rigid flexural deformity is a common cause of dystocia in cattle and horses. Failure to straighten a flexed limb manually through the vagina usually indicates the need either for cesarean section or fetotomy if the fetus is dead. Forced extraction is dangerous to the dam, because during the procedure the flexural deformity may cause damage to the uterus, cervix, and vagina. Depending on the etiology, other defects are observed in association with arthrogryposis (Table 38-2). The most frequently observed triad of signs is arthrogryposis, scoliosis, and cleft palate in Charolais calves.[148,154]

38.10.1

Box 38-1 Mechanisms of Joint Immobility and Arthrogryposis

Agenesis of ventral motor horn cells of spinal cord

Fractures involving one or more joints

Severe joint or tendon swelling

Contracture of muscles or tendons

Septic arthritis

Ankylosis

Skeletal neoplasia

Agenesis or dysgenesis of joint structures

Table 38-2 Other Defects Associated with Arthrogryposis Syndromes

Disease	Related Signs
Epizootic bovine congenital arthrogryposis—hydranencephaly (Akabane virus—exotic)	Incoordination, hydranencephaly, blindness, abortion, microencephaly
Arthrogryposis and palatoschisis (genetic in Charolais breed)	Cleft palate, hydrocephalus, kyphosis, scoliosis, hypoplastic patella
Crooked-calf disease (lupine toxicity)	Scoliosis, torticollis, cleft palate
Hereditary arthrogryposis	Kyphosis, torticollis, scoliosis, cleft palate

The pathogenesis of arthrogryposis is speculated to be related to restricted fetal movement in utero as a result of mechanical limitations, agenesis of α-motoneuron cell bodies in the ventral horn of the sixth cervical segment of the spinal cord, and radial nerve dysfunction.[148] Agenesis of some motoneuron cell bodies may result in lack of normal fetal movement, hypoplastic musculature, and frozen joints.[155] The cause for agenesis of motor horn cells in the spinal cord in unknown, but in virus-associated outbreaks it is probably virally induced.

Treatment of mildly rigid flexural deformities may be effective if joint mobility and the ability to stand progressively improve over several days. Passive stretching and flexing of the affected limbs, bandages, splints, and later casts may be beneficial. Vitamin E and selenium supplementation has been suggested, but the only mineral deficiency associated with arthrogryposis is manganese.[154] Surgical techniques also have been described for transection of the flexor retinaculum and flexor tendons and for excision of the carpal bones with arthrodesis of the joint, depending on the location and severity of the deformity. These procedures are intended to salvage the animal for rearing to market weight. Calves with suspected inherited deformities should not be returned to breeding stock.

38.11 ANKYLOSIS

TAMARA M. SWOR

38.11.1 Definition and Etiology

Ankylosis is the abnormal adhesion or fusion of the bones in a joint. This process is naturally occurring, resulting in a consolidation of two or more bones into one structure.[156] Development of ankylosis is often the result of disease or traumatic injury to the region involved. Septic arthritis may be an inciting factor for secondary ankylosis, as can DJD, severe articular or periarticular trauma, and prolonged joint immobilization from bandaging, splinting, or casting.[157,158] *Congenital ankylosis* (absence of an articulation) may occur, but it is rare in horses and cattle and is often associated with other congenital abnormalities.[159]

The process of joint fusion is initiated by biomechanical and biochemical factors, leading to joint instability and degeneration of cartilage and chondrocytes. Joint immobility occurs from periarticular contracture, capsular fibrosis, and chronic muscle spasm, leading to synovitis and cartilage destruction. Ossification of the periarticular soft tissue structures begins to develop, resulting in partial bone bridging of the joint. The final stage of ankylosis is complete bone bridging with trabecular bone and joint obliteration.[160]

Common sites of ankylosis in the horse include the tarsometatarsal joint, distal intertarsal joint, thoracolumbar intervertebral articulations, proximal interphalangeal joint, and distal interphalangeal joint. In high-motion joints, naturally achieving complete bony bridging across the articular surface is rare, and the resulting cartilage degeneration leads to severe lameness.[156] Low-motion joints are more likely to achieve complete ankylosis without intervention. Large animals with vertebral ankylosis may show neurologic deficits caused by bony impingement of the spinal cord or by dynamic compression leading to abnormal motion or spinal ligament hypertrophy.[160] Pathologic fractures may occur near joints that are ankylosed because of abnormal biomechanical forces on the limb, and animals are prone to secondary injuries and osteoarthritis from abnormal stresses imposed on neighboring normal joints.[161]

Facilitated ankylosis refers to a procedure in which the joint is stimulated by a method intended to promote joint fusion. The speed at which ankylosis occurs may be enhanced through the use of chemical destruction of the chondrocytes or surgical obliteration of the joint.[162] A recent study evaluating surgical drilling to achieve ankylosis of the distal intertarsal joint and tarsometatarsal joint reported that 59% of the horses were sound and able to perform at their previous level of athletic performance.[163] A neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has also been used for facilitated ankylosis in the distal tarsal joints.[164] Chemical fusion options include the use of ethyl alcohol or sodium monoiodoacetate (MIA) injected into the intraarticular space.[156,162,165] A study comparing surgical drilling, laser surgery, and injection of MIA into the distal tarsal joints revealed that bone bridging was greater in the MIA and surgically drilled horses at 6 and 12 months after treatment; however, animals receiving laser treatment were more comfortable after surgery and less lame on the treated limb.[156,164] Injection of 70% ethyl alcohol into the tarsometatarsal joint of healthy horses resulted in progression to joint fusion 4 months posttreatment, although complete obliteration of the joint had not occurred by 12 months after treatment.[162]

Arthrodesis involves surgical fixation of a joint using procedures designed to promote joint fusion. An arthrodesis therefore may be considered a type of ankylosis.[156] A typical arthrodesis involves the use of stainless steel screws and dynamic compression plates, after removal of the articular cartilage.[156]

38.11.2 Clinical Signs and Differential Diagnosis

Typical indications of ankylosis include fused joint bones evident on radiography, stiffness of the joint and joint immobility, and decreased range of joint motion. Limited joint mobility is most obvious if high motion or multiple joints are involved. In the early stages, there may be local signs of inflammation with a corresponding lameness. The degree of lameness ranges from mild to severe. Enlarged and thickened periarticular structures, conformational abnormalities, disuse atrophy of muscles, and gait stiffness may also be identified. Once ankylosis is complete and no cartilage remains, the condition is nonpainful and the articulation will be immobile.

In calves and foals, congenital ankylosis may occur between vertebrae (i.e., block vertebrae) or in multiple joints of the limbs, resulting in dystocia related to musculoskeletal inflexibility.[160]

Differential diagnoses should include soft tissue injuries or contracture, intraarticular or periarticular adhesions, luxation of a joint, joint or bone neoplasia, arthrodesis, spondylosis, an intraarticular mass, osteomyelitis, and fracture. Diagnosis of ankylosis should be based on a complete physical examination, lameness evaluation, and radiographs. Multiple radiographic views should be acquired for definitive diagnosis; however, other imaging techniques such as ultrasonographic evaluation, computed tomography (CT), and MRI may be useful and provide more detailed information.

38.11.3 Treatment and Prognosis

Early treatment focuses on making the animal comfortable because ankylosis is a chronic and progressive disease process. Treatment may include antiinflammatory medications, polysulfated polysaccharides (Adequan), hyaluron, oral joint supplements, joint immobilization, and a decrease in the level of athletic performance required. Common antiinflammatory medications include systemic phenylbutazone and intraarticular administration of corticosteroids.[162] A low level of exercise appears to be beneficial in some animals and may increase and stimulate the development of new bone, resulting in a more rapid and complete ankylosis. In unstable joints, immobilization with splints or casts may be necessary to allow the fusion to progress. Although further studies are warranted, the neurolytic properties of intraarticular 70% ethyl alcohol may allow the horse to continue in athletic work during the fusion process.[162] In horses that remain lame, have end-stage joint osteoarthritis, or are not completing ankylosis naturally, facilitated ankylosis and arthrodesis are viable treatment options that may result in a usable animal.

Ankylosis may require 6 to 12 months for completion and in some animals may take longer.[158,165] Prognosis depends on which joint is involved and the intended use of the animal. Low-motion joints (distal tarsal joints in horse) hold a good prognosis for return to soundness and athletic activities after completion of the fusion process. Animals requiring the use of a high-motion joint to sustain their athletic career have a poor prognosis for return to function. Once the bony bridge is complete, ankylosis is not painful, but it is irreversible, and joint mobility is absent.

38.12 OSTEOMYELITIS

PATRICIA A. HOGAN

CLIFFORD M. HONNAS

38.12.1 Definition and Etiology

Osteomyelitis is an infectious inflammatory disease of the substance of bone and its marrow cavity. Most large animal bone infections are of bacterial origin; mycotic infections rarely occur. Osteomyelitis may be acute or chronic and may involve the epiphyseal, metaphyseal, or diaphyseal region of a bone. Osteomyelitis can originate hematogenously, secondary to a contiguous focus of infection, or by direct bacterial inoculation (e.g., trauma, orthopedic surgery).[166,167]

38.12.2 Clinical Signs and Differential Diagnosis

Diagnosis is based on history, physical examination findings, microbiologic culture results, and radiographic findings. Clinical signs vary with the length and severity of infection and the organism involved.

Animals with acute osteomyelitis usually exhibit localized inflammation and soft tissue swelling, may resent palpation of the affected area, and often have an obvious lameness. Fever, anorexia, depression, and general malaise may be observed. Acute bacterial osteomyelitis is seen most often in very young animals and is usually of hematogenous origin.[166,168] In the neonate it is frequently secondary to other foci of infection (e.g., respiratory or gastrointestinal tract) or umbilical remnant.[168] There is often a history of prematurity, failure of passive transfer of colostral immunoglobulins, or peripartum difficulties. Osteomyelitis in foals, calves, kids, and lambs is typically associated with septic arthritis and may or may not involve infection of the epiphyseal, physeal, and metaphyseal regions of the long bones.[168]

The acute form of osteomyelitis is rare in adults and usually is associated with direct bacterial inoculation during trauma or open reduction of a fracture. Clinical signs of fever, localized pain, inappetence, and soft tissue swelling often make differentiation between infection and postoperative inflammation difficult. Persistent elevation in rectal temperature for more than 48 hours may be more indicative of an acute infectious process.

Fever and depression are usually not observed in chronically affected animals. In adults, infection is usually localized and the result of direct trauma to bone. Clinical signs typically observed in chronic osteomyelitis include firm swelling of the affected area, reluctance to bear weight on the limb, mild to moderate lameness, and presence of a draining fistulous tract. Drainage may be constant or intermittent and is usually purulent.

Radiographic signs of acute osteomyelitis are often subtle and can be difficult to interpret. Soft tissue swelling adjacent to the affected area may be the only radiographically visible abnormality during the initial signs of infection. Osteolysis may be observed as early as 3 days; however, serial radiography is often necessary to visualize bony changes, which may lag 7 to 14 days behind the evolution of infection.[168] Destruction of cortical bone initially appears as focal radiolucent holes that subsequently enlarge and coalesce to involve a region of bone (Fig. 38-24). Radiographic changes frequently noted in animals with chronic osteomyelitis include sclerotic bone, cortical resorption and thinning, and periosteal proliferation that may be smooth, expansile, or spiculated.[166] A *sequestrum,* a necrotic portion of cortical bone devoid of an osseous blood supply, is a classic radiographic observation. It appears radiodense and is surrounded by an area of cortical lysis[169] (Fig. 38-25). As the body's defenses attempt to isolate the area of infection, periosteal new bone forms an *involucrum,* or bony sheath, around the sequestrum with a cloaca that allows inflammatory debris an avenue to egress through a fistulous tract to the skin[169] (Fig. 38-26).

Osteomyelitis at a fracture repair site delays healing and fracture instability is often noted clinically. Radiographically, lysis or bone resorption around implants may be observed, and fracture gap widening or nonunion is frequently seen.[166] Implant loosening and fixation collapse may occur with progression of bone lysis.

Fig. 38-24 Osteomyelitis of the distal metaphyseal, physeal, and epiphyseal regions of the third metacarpal bone of a 3-week-old foal that did not receive colostral immunity at birth. Bony destruction is advanced. Note the associated soft tissue swelling.

Fig. 38-25 Cortical sequestration of the dorsal aspect of the third metatarsal bone in a horse 4 weeks after blunt trauma to the region.

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Fig. 38-26 Lateral radiograph of the third metacarpal bone of a cow with chronic osteomyelitis. A sequestrum is visible surrounded by an area of osteolysis. An involucrum formed by medullary sclerosis and periosteal new bone and a cloaca *(arrows)* are evident.

A definitive diagnosis of osteomyelitis is made by culture of the suspected focus of infection. Samples for culture may be obtained from deep needle aspirates, sequestra, and necrotic tissue removed during surgical debridement or metallic implants removed from the affected area. It is not recommended to culture draining tracts because tract organisms are not usually the pathogen(s) responsible for bone infection. Blood cultures are advisable in the neonate. Culture for both aerobic and anaerobic bacterial pathogens is indicated. Clinical characteristics suggestive of, but not limited to, anaerobic infection include a fetid odor, presence of bony sequestra, and purulent discharge. Anaerobic infection should be suspected if bacteria are identified on cytologic analysis but routine aerobic cultures show no bacterial growth.[166] Anaerobes are frequently associated with infection after surgical repair of an open fracture. Culture results will most accurately reflect the causative bacteria if samples have been collected and transported properly.

38.12.3 Clinical Pathology

The WBC count is usually elevated in animals with acute osteomyelitis. A degenerative left shift in the leukogram is often present. In neonates an initial leukopenia may be observed as the result of a primary disorder such as generalized septicemia or enteritis. Plasma fibrinogen also may be elevated in acute infection. The leukogram tends to return to normal with chronicity.

Osteomyelitis is frequently associated with septic arthritis in the neonate.[167,168] Synovial fluid of affected joints has an elevated leukocyte count and total protein concentration. Gram stain of synovial fluid can be helpful initially in determining the type of bacteria present, to aid in the selection of appropriate antimicrobial therapy before culture results are known. Blood cultures also may be helpful for identification of causative organism(s) in the neonate.

38.12.4 Pathophysiology

Sequestration of cortical bone results from mechanical trauma to the periosteum and overlying soft tissues, which compromises the defenses of normal cortical bone and leads to regional vascular injury and venous stasis.[166,167,169] Increased capillary permeability permits inflammatory cells to infiltrate the injured area and engulf bacteria. Lysed neutrophils release proteolytic lysosomal enzymes that induce local tissue and bone necrosis; and an exudate composed of serum, neutrophils, bacteria, and nonviable tissue accumulates.[167] If host defense mechanisms are inadequate to contain the infection, bacterial colonization of adjacent periosteal, cortical, and medullary regions ensues.[167] Antibodies and antibiotics cannot easily penetrate the infected area because of the compromised blood supply. The necrotic cortical bone or sequestrum is enveloped by granulation tissue and new bone, forming an involucrum in an effort to contain the infection.[167] Draining sinus tracts may eventually form as the disease progresses. Acute hematogenous osteomyelitis has historically been attributed to sluggish blood flow in the metaphyseal region of long bones in young, growing animals.[166,167] It was thought that vascular stasis in the capillary loops of the primary spongiosa resulted in localization of blood-borne bacteria in the metaphysis. Recently it has been shown that the endothelial lining of the capillaries pervading the primary spongiosa of neonates is incomplete and allows extravasation of bacteria and erythrocytes.[166] Because leukocytes are absent from this location in the young animal, macrophages provide the sole defense against bacterial colonization in this region.[166] The inability of these macrophages to eliminate bacteria effectively appears to be a critical factor in the development of hematogenous osteomyelitis in young animals.

38.12.5 Treatment

Selected cases of acute osteomyelitis may respond to aggressive antimicrobial treatment in the early stages, but once infection is established in bone, it is difficult to resolve without surgical intervention. Broad-spectrum antimicrobial administration in combination with surgical management constitutes the hallmark of treatment for osteomyelitis.[166,167]

The goal of surgical treatment is to facilitate the penetration of blood-borne antibiotics to the site of infection by eliminating necrotic debris and encouraging vascular access to compromised tissues. The most important precepts are careful and thorough debridement of all nonviable tissue and sequestrated bone fragments, establishment of open drainage, and removal of foreign material implants.[166,167] Certain bacteria (e.g., staphylococci) are capable of producing a viscous substance that enshrouds bacterial colonies and facilitates adhesion of bacteria to necrotic bone and foreign implants.[166] When combined with host-derived matrix proteins and cellular debris, this biofilm protects bacteria from host defenses and may actually alter bacterial susceptibility to certain antibiotics.[166]

The exception to implant removal arises when the implant is required for fracture stabilization. Although healing is delayed, stable fractures can heal in the presence of infection.[166] Therefore it is advisable to maintain implants until they are no longer necessary for fracture stability while treating the infection. However, delayed healing can lead to excessive cycling of the implant and fixation failure.

Initially the choice of appropriate antibiotic is based on known susceptibilities of the organism suspected to be responsible for infection. Antibiotic therapy may require modification after a definitive organism(s) is isolated and in vitro susceptibilities determined. The ideal antibiotic demonstrates the greatest bactericidal activity against the offending organism, with the least toxicity to the patient, and is economically feasible. Duration of antibiotic therapy is empirical and depends on clinical response. Because compromised bone requires 4 to 6 weeks for revascularization, this time frame has generally been accepted for treatment duration in cases of chronic osteomyelitis.[166,170]

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The most common aerobic bacterial groups isolated from musculoskeletal infections in horses include Enterobacteriaceae, streptococci, and staphylococci.[171] *Actinomyces pyogenes* is the most frequent isolate recovered from adult cattle, sheep, and goats. Neonates appear particularly susceptible to infection from *Escherichia coli* and *Salmonella* species.[168] *Bacteroides* species is the most predominant obligate anaerobic genus encountered; however, most infections include a mixture of anaerobes or a combination of aerobes and anaerobes.

Parenteral administration of antibiotics constitutes the mainstay of antimicrobial therapy in the treatment of osteomyelitis.[170] Localized antibiotic therapy, however, is a useful adjunct to systemic antibiotic treatment. Regional limb antibiotic perfusion, local implantation of polymethylmethacrylate (PMMA) antibiotic-impregnated beads, and use of autogenous cancellous bone grafts enhance the resolution of osteomyelitis.[172–174]

Regional limb perfusion delivers a systemic dose of antibiotic to an isolated area of infected tissue,[172,173] subjecting the tissue to antibiotic concentrations in excess of the MIC for the infectious agent. This technique is particularly useful for cases of septic arthritis in which vascular compromise of synovial membrane may

prevent adequate antimicrobial distribution.[172] A tourniquet is placed proximal to the site of infection. A systemic dose of antibiotic is administered through a catheterized vein distal to the site of infection,[172,173] or through a single, 4.5-mm-diameter hole into the medullary cavity and allowed to perfuse the isolated area for 30 minutes. In horses, cattle, and rabbits, synovial antibiotic concentrations are significantly greater than peak serum concentrations associated with systemic administration.[172,173] We have used regional limb perfusion as an adjunct treatment in selected cases of septic tenosynovitis and navicular bursitis and osteomyelitis of the calcaneus, phalanges, and distal sesamoid bone.

Antibiotic-impregnated PMMA beads are an effective drug delivery system for bone and soft tissue infections in human medicine.[166,174] Although this treatment is gaining popularity in large animal orthopedics, there are no published reports of its efficacy in veterinary medicine. Gentamicin is the traditional antibiotic impregnated in beads and elutes over time to yield local concentrations well above the therapeutic concentration range for as long as 80 days postimplantation.[174] Aminoglycoside toxicity does not appear to be a problem, with human serum and urine concentrations below those associated with systemic administration.[174] Gentamicin-impregnated PMMA beads are used routinely in our hospital in the repair of open fractures and in the internal fixation of closed fractures that incurred significant soft tissue trauma.

The use of autogenous cancellous bone graft has been advocated as an ancillary treatment in some cases of septic navicular bursitis and osteomyelitis of the navicular bone in horses.[175] Placement of the graft in a surgically created defect underlying the navicular bone may reduce dead space, provide protection of the deeper tissues from environmental contamination, and afford a temporary scaffold for the ingrowth of capillaries and precursor cells of granulation tissue.[174] We believe this modality has merit for continued clinical application and routinely use it for deep-seated infections of the foot.

38.12.6 Prevention and Control

Early and aggressive medical therapy for neonates suspected to be at risk for developing septicemia is prudent in the prevention of acute hematogenous osteomyelitis. Therapy may include administration of prophylactic antibiotics and hyperimmune plasma in animals with failure of passive transfer of colostral antibodies. Prompt and meticulous debridement of avascular and necrotic tissue in treatment of soft tissue wounds and repair of open fractures cannot be overemphasized. Delayed wound closure may be desirable in select cases of overwhelming contamination or infection.

Many infections associated with fracture repair occur during open reduction and internal fixation of closed fractures.[166] Strict adherence to the principles of aseptic technique is imperative to a successful outcome. Prophylactic antibiotics are often used because the risk of infection increases with metallic implants. The timing of antibiotic administration is crucial for efficacy and should achieve sufficient blood antibiotic levels while the amount of bacteria in the exposed tissues exceeds the host's ability to eliminate the organisms and allow tissue healing to commence.[167] For elective uncomplicated orthopedic procedures, antibiotics should be administered 1 to 2 hours before surgery and continued for no more than 72 hours after surgery.[167] For long-bone fracture repair, the risk of infection is much greater because of increased operative time, the presence of metallic implants, and the soft tissue trauma incurred during the injury and subsequent fixation.[171] In this case, administration of the most effective broad-spectrum antibiotic combination for an extended period is advisable.

38.13 NAVICULAR DISEASE (PALMAR FOOT PAIN)

ROBIN M. DABARIENER

Approximately one third of all forelimb lameness in horses originates from the caudal third of the foot. Lameness originating from this area has generally been associated with pain arising from the navicular bone and its related structures, although other structures in the foot can also cause lameness. Any one or combination of the following structures should be considered as a potential source of injury in horses that exhibit lameness localized to the posterior aspect of the foot:

1. The navicular bone itself.
2. Desmitis of the navicular suspensory apparatus, which includes the sesamoid impar ligament (IL) distally and the collateral suspensory ligament (CSL) proximally.
3. Synovial membrane of the navicular bursa; navicular bursitis or inflamed tissue (adhesions) between the navicular bursa and DDFT.
4. Desmitis of the deep digital flexor tendon (DDFT) at (a) the insertion, (b) palmar to the navicular bone, or (c) proximal to the navicular bone.
5. Laminar tearing in the heel region.
6. Solar bruising in the heel region.
7. Some aspects of the palmar region of the distal phalanx.
8. Synovial structures located in the distal interphalangeal (DIP) joint.
9. Structural damage to the hoof capsule in the heel region (e.g., underrun heels, collapsed foot).
10. Desmitis of the distal annular ligament.

38.13.1 Diagnosis

The diagnosis of heel pain is not difficult when a horse's lameness resolves with a palmar digital nerve block. 1216
However, determining which foot structure is the source of pain and establishing correct treatment are 1217
becoming more difficult. It seems that the more we learn about diagnostic anesthesia, the more clouded the picture becomes. Horses with navicular or heel pain can be a diagnostic and therapeutic challenge to the owner, clinician, and farrier.

Diagnosis is based on historical data, clinical findings, and both routine and advanced imaging techniques to localize the structure causing pain within the hoof capsule. My approach to horses with lameness originating from the heel region is to determine which structure in the foot is causing the pain and then develop a therapeutic plan. Severity and duration of the lameness, the horse's activity, and potential owner compliance, as well as the farrier's experience, should be considered. The horse's hoof wall quality, conformation, environment, and occupation will all affect therapy.

38.13.2 HISTORICAL DATA

Common complaints reported by owners of a horse exhibiting chronic foot pain include intermittent unilateral or bilateral forelimb lameness and increased severity of lameness for several days immediately after shoeing or at the end of the shoeing period (when the toes are long). Occasionally the horse may point the affected forelimb, stumbling, with a short, choppy gait and increased lameness when ridden on hard ground.

Horses sustaining acute injuries to soft tissue structures in the caudal aspect of the foot (e.g., impar or CSL of navicular suspensory apparatus, distal DDFT), laminar tearing, or severe bruising of the heel region may have a history of becoming acutely lame during or immediately after a performance event. Historical data are often overlooked but may suggest which foot structure is damaged.

38.14 Clinical Findings and Diagnostic Evaluation

Signalment can be helpful in the diagnosis of chronic heel pain. Middle-aged quarter horses and thoroughbred and warmblood horses in general are often affected by navicular disease. Arabians, draft horses, ponies, donkeys, and mules are rarely affected with palmar foot pain. A hereditary predisposition may be related to the development of navicular disease. Many quarter horses are heavily muscled and have relatively small hoof size. Poor hoof conformation plagues many thoroughbred and warmblood horses. Since 1978, Dutch warmblood stallions with grade 4 classification on navicular bone radiographs (0 = excellent, grade 4 = poor) have not been certified for breeding. The incidence of grade 3 or 4 navicular radiographs has decreased from 11% in 1997 to 3% in 2002.[176] Although hindfeet can be affected with navicular disease, it is predominantly considered a forelimb problem.

Observation of limb conformation, as well as hoof size and shape and hoof-pair asymmetry, can aid in the diagnosis and treatment of palmar foot pain. A broken back hoof-pastern axis is frequently seen in horses with navicular or heel pain, but a small subset of horses with navicular pain will have a broken forward or normal hoof-pastern alignment. In one report of horses diagnosed with navicular disease, 72% had a broken back hoof-pastern axis and 8% a broken forward axis.[177] Horses having a long-toe, low—heel-hoof conformation or underrun heels (defined as >5 degrees difference between heel and toe angle of foot) was reported in 77% of a group of horses with chronic heel pain.[177] Atrophy of the frog and contracted heels (defined as frog width less than two-thirds its length) can be seen in horses with palmar foot pain and has been attributed to lack of weight bearing in the posterior portion of the foot, which reduces the dynamic movement of the frog.[177] Hoof-pair asymmetry in which one foot is smaller, narrower, and has a higher heel length is also common in horses with navicular area pain. The smaller and more upright foot is usually the lamest limb.

A thorough musculoskeletal examination should include palpation and comparison of the digital pulses in the feet and assessment of the hoof capsule for increased heat. Of 23 horses diagnosed with navicular area pain, 97% had an increased digital pulse in the most severely affected limb.[178] Hoof tester evaluation can be beneficial in determining pain location. Pain involving the navicular area is identified by application of intermittent hoof-tester pressure over the middle third of the frog, which results in persistent, nonfatigable reflex withdrawal of the hoof from the examiner. It is important to assess if the withdrawal reflex is resulting from real pain and not a whimsical reaction by the horse. Both front feet should be tested and results from each foot compared. A positive hoof-tester response over the wall of the foot across the ends of the navicular bone may occur in horses with radiographic evidence of proliferative new bone on the abaxial margins of the navicular bone. Horses sustaining an injury to the impar ligament or insertion of the DDFT seem particularly sore with hoof tester pressure near the junction of the middle and anterior thirds of the frog. Horses with underrun heels, bruised heels, or damaged laminae in the

heel area will often have more pain over the affected heel. It is important, if possible, to differentiate peripheral versus central hoof pain with a thorough hoof tester examination. Many horses with heel pain will land toe first and may bruise the sole in the toe region, resulting in pain from hoof testers in this area. The hoof-tester exam is a useful diagnostic tool, but horses can have navicular area pain and not respond to hoof tester pressure. This will occur more often during periods of dry weather, when the horse's feet are excessively hard, or in horses with thick soles and hard frogs.

38.14.1 LAMENESS EXAMINATION

Horses with bilateral forelimb involvement have a stiff, shuffling, short-strided gait that owners often perceive as shoulder lameness. The horse should be observed at a slow trot in a straight line and circled in both directions. A smooth, hard surface is optimal. In horses with heel pain the lameness will often be exacerbated when trotted on hard versus soft ground. The severity of lameness should be assessed before and immediately after application of hoof-tester pain. Horses with navicular area pain may have increased severity of lameness when trotted after the hoof-tester application in the central frog area. Several tests may exacerbate lameness in horses with navicular pain, such as allowing the horse to stand on a small block of wood centered over the frog for 60 seconds before trotting, or elevating the toe with a block of wood. A 30-second lower-limb “fetlock” flexion test may also exacerbate lameness in horses with navicular area pain.

38.14.2 DIAGNOSTIC ANESTHESIA

Perineural anesthesia of the palmar digital nerves (PDNs) with 1 to 2 mL of mepivacaine placed axial and distal to the proximal limits of the medial and lateral collateral ligaments will desensitize the palmar half of the foot, entire sole, and palmar aspect of the coffin joint. This block is performed just below the proximal limits of the collateral cartilages to avoid desensitizing the dorsal nerve branches. One study demonstrated that lameness secondary to solar pain created by a setscrew-induced pain model was eliminated 10 minutes after anesthesia using 2 mL mepivacaine over each PDN.[179] In the past, coffin joint (DIP) anesthesia was thought to be helpful in diagnosing navicular area pain, but investigators have recently demonstrated a lack of specificity with this block. DIP anesthesia has been shown to eliminate lameness associated with pain in the navicular bone itself, navicular suspensory apparatus, navicular bursa, and sole of the foot, because the sensory nerves to the navicular area are close to the DIP joint, and passive diffusion of the anesthetic occurs to the PDNs. Solar pain in the toe region was eliminated before solar pain in the heel region after DIP anesthesia, and a maximum 6 mL of anesthetic was recommended for analgesia of the DIP joint. This suggests that horses with heel bruises or laminar tearing in the heel region should not improve after DIP analgesia using low-volume anesthetic and evaluating the horse after 10 minutes.

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The navicular bursa is a thin synovial structure located between the navicular bone and distal aspect of the DDFT. Analgesia of the navicular bursa may be more specific for navicular area pain. A positive response to navicular bursa analgesia probably reflects pathology in the navicular bursa, navicular bone, or supporting ligamentous structures. The normal navicular bursa has a 3-mL capacity, which may be reduced in horses with inflamed tissue or adhesions between the navicular bursa and DDFT. Synovial fluid is obtained infrequently when performing navicular bursa analgesia.

Horses that improve but do not have total resolution of the lameness until after a high palmar digital or abaxial nerve block may have pain associated with a desmitis of the DDFT within the hoof capsule or desmitis of the DIP joint collateral ligament. Horses with DDFT desmitis may also improve after DDFT analgesia.

38.14.3 RADIOGRAPHIC EXAMINATION

A minimum of three high-detail radiographic views should be used to evaluate the navicular bone; additional views are needed to evaluate the entire foot. Lateromedial (LM), 60-degree dorsoproximal-palmarodistal oblique with grid (D60Pr-PaDiO), and palmaroproximal-palmarodistal oblique (Pa45Pr-PaDiO) views of the navicular bone are obtained. Some clinicians also include two oblique views of the navicular bone. Abnormal radiographic changes include variation in size and shape of synovial foramina on the D60Pr-PaDiO projection; cystic changes within the navicular bone; enthesophyte formation at the attachment of the CSL ligament on the LM projection; flexor cortex erosions and loss of corticomedullary distinction, best viewed on the Pa45Pr-PaDiO projection; calcification of the flexor surface and distal DDFT; and osseous fragments associated with avulsion of the impar ligament. Previous studies have shown that abnormal synovial fossae are poorly correlated with lameness, rarely progress over time, and are inconclusive for the diagnosis of navicular disease. Radiographic abnormalities more strongly associated with lameness are flexor cortex defects, medullary sclerosis, proximal border remodeling, and loss of medullary trabecular pattern.

Although radiographic evaluation is important in the diagnostic workup of a horse showing palmar foot pain, it is not very sensitive in defining the actual pathologic condition of the navicular bone. Radiographs often underestimate the extent of pathology seen on necropsy in horses with navicular lesions.

38.14.4 NAVICULAR BURSOGRAPHY

Administration of a 3-mL mixture of 1:1 contrast media and anesthetic into the navicular bursa, followed by a Pa45Pr-PaDiO radiographic view, is used to evaluate pathologic changes on the flexor surface of the navicular bone and adhesions or scarring of the DDFT. The advantage of this technique is confirming pathologic changes on the flexor surface of the navicular bone, which may not be apparent on survey radiographs, and injection of the anesthetic into the navicular bursa. Navicular bursography identified pathology in the flexor region of the navicular bone 60% more often than plain radiographs.[179a] The disadvantages are that some horses are not very tolerant of needle penetration of the DDFT and insertion into the navicular bursa, and the procedure carries risks such as trauma to the navicular bone, sepsis, acute synovitis of the bursa, and possibly DDFT damage secondary to needle penetration.

38.14.5 NUCLEAR SCINTIGRAPHY

Radiography has lower sensitivity than, but equal specificity as, scintigraphy for the diagnosis of navicular disease. For detecting abnormal bone activity within the hoof, nuclear scintigraphy is a sensitive but rather nonspecific imaging method. Scintigraphy detects increased ^{99m}Tc uptake in areas of active osteoblastic activity; however, because of the proximity of anatomical structures in the caudal third of the foot, specific structural location of the source of pain in a horse with palmar foot pain is limited with scintigraphy. The reliability of scintigraphy in diagnosis of foot pain has been criticized because of common false-positive and false-negative results. Lateral bone-phase images were found to be less sensitive than palmar images, and views taken 1 hour after radioisotope administration were as diagnostic as those taken 2 to 4 hours after administration.

38.14.6 ULTRASONOGRAPHY

Diagnostic ultrasonographic images can be obtained for some structures in the foot region. Ultrasonographs of the collateral ligaments of the DIP joint are obtained by positioning a 7.5- or 10-MHz transducer on the firm part of the dorsolateral and dorsomedial aspects of the coronary band. The normal DIP joint collateral ligament for a large horse is about 0.66 cm.[177] The distal aspect of the DDFT can be visualized from between the heel bulbs in the palmarodistal aspect of the pastern joint. The frog of the foot can also be used as a window to image the DDFT and impar ligament near the flexor surface of the navicular bone. Before imaging, the frog should be trimmed to pliable tissue and the foot soaked in a water bath overnight. Limitations of ultrasound are that the images are restricted to the axial midline, and off-incidence artifacts can confuse image interpretation. If the frog is excessively hard or has deep sulci, poor contact between the frog and transducer may prevent propagation of the ultrasound beam. Variation in cross-sectional area and width of the DDFT and impar ligament both within and between limbs of normal horses also may make image interpretation difficult.

38.14.7 COMPUTED TOMOGRAPHY

CT is the best modality for detecting and evaluating bone pathologies in the cortex or trabecula and can also provide an accurate three-dimensional assessment of soft tissue structures of the foot. Although less expensive than MRI, CT is less versatile. Special contrast studies are needed to evaluate articular cartilage with CT, but not with MRI. One advantage over MRI is that CT can be used to assess accurate needle or scalpel placement for specific treatment options. One disadvantage for CT in horses is the need for general anesthesia and special equipment design to accommodate the horse.

38.14.8 MAGNETIC RESONANCE IMAGING

MRI offers a superior diagnostic tool to image soft tissue structures in the foot. The recent use of MRI in equine lameness has provided valuable insight into the pathologic problems occurring in horses with palmar foot pain. MRI is particularly useful in the recognition of abnormally high signal (fluid) in structures such as the DDFT, IL, and collateral ligaments. MRI also can detect navicular bone edema as well as articular cartilage damage in the navicular region. MRI can be performed under general anesthesia or in the standing horse, depending on the equipment available. In one study of 199 horses with lameness localized to the foot by clinical signs and perineural anesthesia, MRI was found to be superior to nuclear scintigraphy, ultrasound, or radiology in identifying the specific foot structure causing the pain. The most common injury was DDFT desmitis (59%), followed by desmitis of the DIP collateral ligament (31%); 17% of horses had injuries to multiple structures. Only 28% of horses with DDFT or collateral ligament injuries of the DIP joint returned to previous use.[180]

38.15 Etiology

The exact etiology of navicular pain is unclear, but two theories exist. Initially, vascular occlusion of the navicular arteries was believed to result in ischemic necrosis of the navicular bone; however, this theory lacks experimental support. The biomechanical theory suggests that the degenerative changes in the navicular bone result from abnormal forces exerted on the bone and its supporting ligaments. Compression of the navicular bone by the DDFT is an important aspect of this theory. Peak compressive forces of the DDFT on the navicular bone are about 0.77 times body weight during a slow trot and occur at approximately 70% of the stance-phase duration.[177] In addition, the navicular bone suspensory apparatus (IL and CSL) is under excessive tension and possibly

compression when the horse has dorsopalmar hoof imbalance (broken back hoof-pastern axis or long-toe low—heel-hoof conformation). Faulty conformation and improper hoof balance resulting in abnormal biomechanical forces in the navicular area cause pathologic changes in the navicular bone that appear similar to those seen in clinical cases. Pain presumably results from interosseous pressure in the navicular bone or from strain of the supporting soft tissue structures. The biomechanical force applied to the navicular bone depends on hoof conformation and is negatively correlated ($p < 0.05$) to both the angle between the distal phalanx and the ground and the ratio between heel and toe length. Experimental studies seem to support the biomechanical theory.

38.16 Treatment

There are numerous treatment regimens for horses with palmar foot pain, and no one treatment can be recommended in all cases. Factors to consider in determining a treatment plan include prior treatment, duration of clinical signs, structure injured, severity of disease, use of horse, hoof conformation, and shoeing. Treatment options include variable periods of rest, therapeutic trimming and shoeing, antiinflammatory medications, intraarticular therapy, systemic osteoarthritis-modulating drugs, and surgery.

38.16.1 MEDICAL THERAPIES

38.16.1.1 Rest

Taking the horse out of work and confinement to a small area such as a stall and small run allow the horse freedom of movement without being able to run and buck, which could exacerbate the lameness. Controlled exercise at a walk and trot for 15 minutes daily has been shown to increase blood flow to the feet by 15%. Although the duration of the rest period is variable, 3 to 6 weeks will allow soft tissue inflammation to subside and the horse to adjust to changes in trimming and shoeing. If the lameness has resolved after the rest period, a gradual increase in exercise is recommended before returning to normal use. An exception is the horse with an acute ligamentous injury to the navicular suspensory apparatus or distal DDFT injury. These injuries are usually severe and require 6 to 12 months of rest and confinement.

Although rest may be beneficial as part of the treatment regimen, the owner's situation may not allow for a rest period. Other treatments are then required to minimize the pain while allowing the horse to continue working, as often preferred by many professional horsemen.

38.16.1.2 Farriery

Therapeutic trimming and shoeing to reduce biomechanical forces on the navicular/heel area is the cornerstone of treatment for horses with palmar foot pain. Many horses respond to this without further need for medical or surgical therapy. Other horses improve after corrective shoeing but still require additional treatments. Horses with poor hoof conformation or inappropriate shoeing often respond best to corrective shoeing, whereas horses with good farrier management and good hoof conformation may show minimal or no improvement after therapeutic trimming and shoeing. The goals are to (1) restore hoof balance, (2) improve existing problems such as underrun heels, (3) reduce biomechanical forces on the navicular region, and (4) protect injured areas of the hoof. There is no standard shoeing technique for horses with heel/navicular pain; however, observing abnormalities in the hoof and lower-limb conformation and following basic principles can often accomplish these goals. Proper trimming alone may restore correct hoof balance such that special shoes or pads are not necessary; even with proper trimming, however, many horses still require special shoes or pads to achieve the desired hoof conformation. Although many horses benefit greatly

from therapeutic shoeing, some have permanent structural problems that cannot be corrected. The veterinarian, farrier, and owner must work together and consider the horse's hoof shape and hoof wall quality, environment, conformation, use, and severity of disease.

38.16.1.3

Basic Principles for Proper Hoof Balance

The configuration of the hoof capsule reflects the stresses applied to the foot during the previous months. *Hoof balance* refers to both mediolateral and dorsopalmar balance. Dorsopalmar balance refers to proper hoof-pastern alignment. Ideally, when viewed from the side, a line drawn through the central aspect of the first phalanx should bisect the hoof capsule, and the toe angle and heel angle should be parallel to this line. A broken back hoof-pastern axis is common in horses with long-toe low-heel conformation and results in increased stress on the phalangeal joint capsules, navicular suspensory apparatus, and distal DDFT and increases pressure between the navicular bone and DDFT.

Breakover (break-over point) of the foot is the terminal part of locomotion when the heel looses contact with the ground surface, followed by the toe. Tension of the DDFT over the navicular area and flexion of the coffin joint occur during breakover. A low hoof angle or long toe is associated with prolongation of breakover time. A high heel angle reduces breakover, causing a reduction of forces exerted on the caudal structures of the foot and limb (e.g., navicular suspensory apparatus, DDFT, suspensory ligament). Breakover should be made as easy as possible by decreasing toe length.

Corrective trimming is often more important but can be more difficult than corrective shoeing. The toe is shortened as much as possible, and the heels are trimmed back to the widest aspect of the frog. One of the most common problems I see is allowing the heels to grow forward, thus decreasing heel support and contributing to dorsopalmar hoof imbalance (Fig. 38-27); the heels lose mechanical strength and often collapse. In addition, the bars of the hoof flatten out and lose support. Proper trimming of the heels back to the widest aspect of the frog increases the functional weight-bearing surface of the foot. The ground surface of the properly trimmed foot has a more rounded appearance (Fig. 38-28). Palmar hoof support is essential for horses with navicular/heel pain. Full-fitting shoes provide more support hoof by increasing the weight-bearing surface. Ideally, the shoe should fit about 1/16 inch wider than the hoof behind the last shoe nail to allow heel expansion. The nails should be placed in a line parallel to the ground approximately 1 inch (2.5 cm) proximal to the shoe, and no nails should be placed behind the widest aspect of the hoof.

Using a wedged shoe or pad to elevate the heels by 2 to 3 degrees after the foot is properly trimmed decreases tension in the DDFT, thus reducing pressure applied to the navicular region. The effect of raising the heels is helped by rolling or rockering the toe to quicken the breakover of the foot. The use of an egg-bar shoe is controversial. Although horses with long-toe, low—heel-hoof conformation may gain caudal foot/heel support from the shoe, egg-bar shoes had no effect on reducing forces between the DDFT and navicular area.

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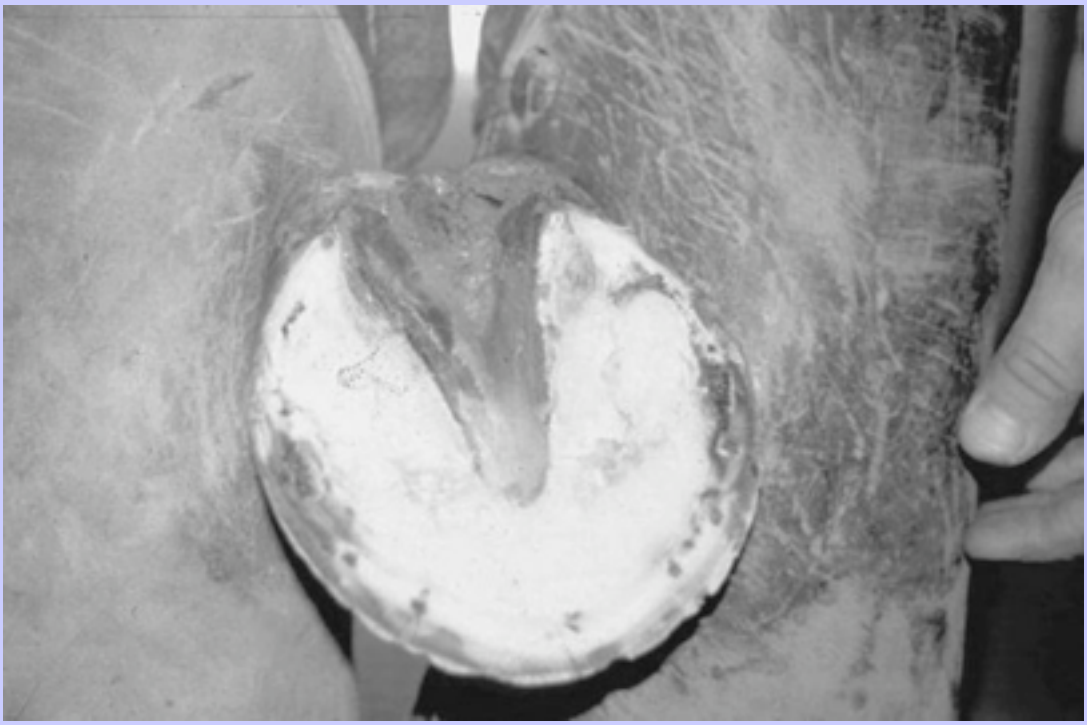
Fig. 38-27 Hoof with the heels allowed to run too far forward. The heels are located at the pointer but should be back at the widest aspect of the frog.

Fig. 38-28 Hoof from Figure 38-27 after trimming the heels back to the widest aspect of the frog. Note the larger, rounded shape to the hoof with increased heel support.



When selecting a particular corrective shoe or shoe/pad combination, the horse's use is an important factor because the desired corrective shoe for the individual hoof conformation may not be suitable for the horse to perform its intended use. A compromise must be made between shoeing for the "ideal" and shoeing for athletic performance, taking into consideration such factors as weight of the shoe, traction, and interference of other limbs. Another important factor is hoof quality. The ideal shoe/pad selected for proper hoof balance may be impossible to apply if the hoof wall is thin or damaged. In these cases, a secondary shoeing regimen is selected that will accomplish similar results until hoof quality improves. Although no standard shoeing technique exists for horses with navicular pain, the following suggestions may be beneficial.

A *rim shoe* or *half-round shoe* has a rounded edge that will enhance breakover. The rim shoe has good traction and is useful in western performance horses, such as roping horses, barrel racers, and cutting horses. The Natural Balance Shoe has a rockered toe and, because of its design, artificially shortens the toe length and enhances breakover. It is made of aluminum or steel; owners of some western performance horses seem to prefer the steel shoe, which is thought to provide better traction than the aluminum shoe.

Acute ligamentous injuries involving the distal aspect of the DDFT or navicular suspensory apparatus require extended periods of rest. During the rest period, application of a 3- to 4-degree wedge pad to the shoeing regimen may decrease tension of these soft tissue structures. Controlled exercise is important in the treatment of these injuries. My group often begins with a 3- to 4-degree pad, depending on the horse's hoof conformation, and gradually decreases the quantity of heel elevation over time.

Different shoeing techniques will accomplish the same goals of easing breakover, supporting the heels, and protecting injured areas of the foot.

38.16.1.4 Nonsteroidal Antiinflammatory Drugs

Phenylbutazone is most common NSAID used in the treatment of navicular/heel pain. It reduces pain by inhibiting the enzyme cyclooxygenase and the subsequent cascade of prostaglandins. It also inhibits platelet aggregation, which may theoretically increase blood flow to the foot. Phenylbutazone can break the pain cycle and allow adjustment to new hoof angles and shoeing changes. The recommended dosage depends on individual horse needs and severity of disease. An initial dosage of 4.4 mg/kg once daily for 5 to 7 days seems appropriate to allow adjustment to shoeing changes. Many horses will require additional treatment during competition. Gastric and right dorsal colon ulceration has been associated with phenylbutazone administration in some horses.

38.16.1.5 Isoxsuprine Hydrochloride

This β-agonist, α-antagonist is a peripheral vasodilator working to increase blood flow to the foot. Its absorption after oral administration in the horse is erratic, and it usefulness is questioned. The recommended dose of isoxsuprine is 0.6 mg/kg twice daily orally for 3 weeks; if no response is seen, the dose is increased to 1.2 mg/kg twice daily for 3 weeks, then once daily for 3 weeks, then every other day for an additional 3 weeks. No adverse drug reactions have been reported. Isoxsuprine's efficacy appears to be horse dependent.

38.16.1.6 Intraarticular Medications

Intraarticular medication of the DIP joint can be beneficial in horses with navicular area pain. Some horses fail to respond adequately to corrective shoeing, rest, and NSAID therapy, or the horse may have responded initially but no longer. If the lameness has been previously localized to the caudal aspect, intraarticular anesthesia of the DIP joint is performed at the recheck examination. If significant improvement is seen in the lameness, the client is offered intraarticular medication as a treatment option. Alternately, if the horse improves after PDN anesthesia in one limb and becomes lame in the opposite limb, anesthesia of the DIP joint is performed. If significant improvement is seen, medication of the DIP joint is offered as an initial treatment option. It is important to remember that DIP joint anesthesia is not specific for navicular area pain, as discussed earlier.

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Selection of intraarticular medication varies with the clinician, severity of disease, and client. I usually inject 20 mg of sodium hyaluronate and 6 to 9 mg of triamcinolone (Vetalog), which often alleviates clinical signs of lameness for 6 to 12 weeks. In severe cases of navicular disease, 20 to 40 mg of methylprednisolone acetate (Depo-Medrol) in combination with the sodium hyaluronate may provide a slightly longer duration of effect. Hyaluronate is used for joint lubrication and to increase the hyaluronan content of synovial fluid. Corticosteroids interact with steroid-specific receptors in the cytoplasm of cells and inhibit inflammatory infiltration into the joint and neutrophil function by impairing lysosomal enzymatic release. Corticosteroids also inhibit phospholipase A_2, preventing both cyclooxygenase and lipoxygenase inflammatory pathways.

The two primary reasons not to use intraarticular corticosteroids in horses with joint disease are risk of sepsis and potential adverse effects on articular cartilage and subchondral bone. Using aseptic technique and combining intraarticular antimicrobials with the injection medication should decrease the risk of synovial

infection. I prefer to use 50 to 100 mg of amikacin sulfate for joint injections. To minimize the negative effects of intraarticular corticosteroids, the lowest clinically effective dose is used. Minimal research has been performed in this area, so clinician experience and empirical information are often consulted. Both systemic and intraarticular corticosteroids have been associated with laminitis in horses. DIP joint medication is injected using a 20-gauge sterile needle placed approximately 1 cm dorsal to the hoof capsule on midline, penetrating the extensor tendon while entering the DIP joint. The angle of needle insertion is about 45 degrees from perpendicular to the ground surface. Synovial fluid is usually obtained.

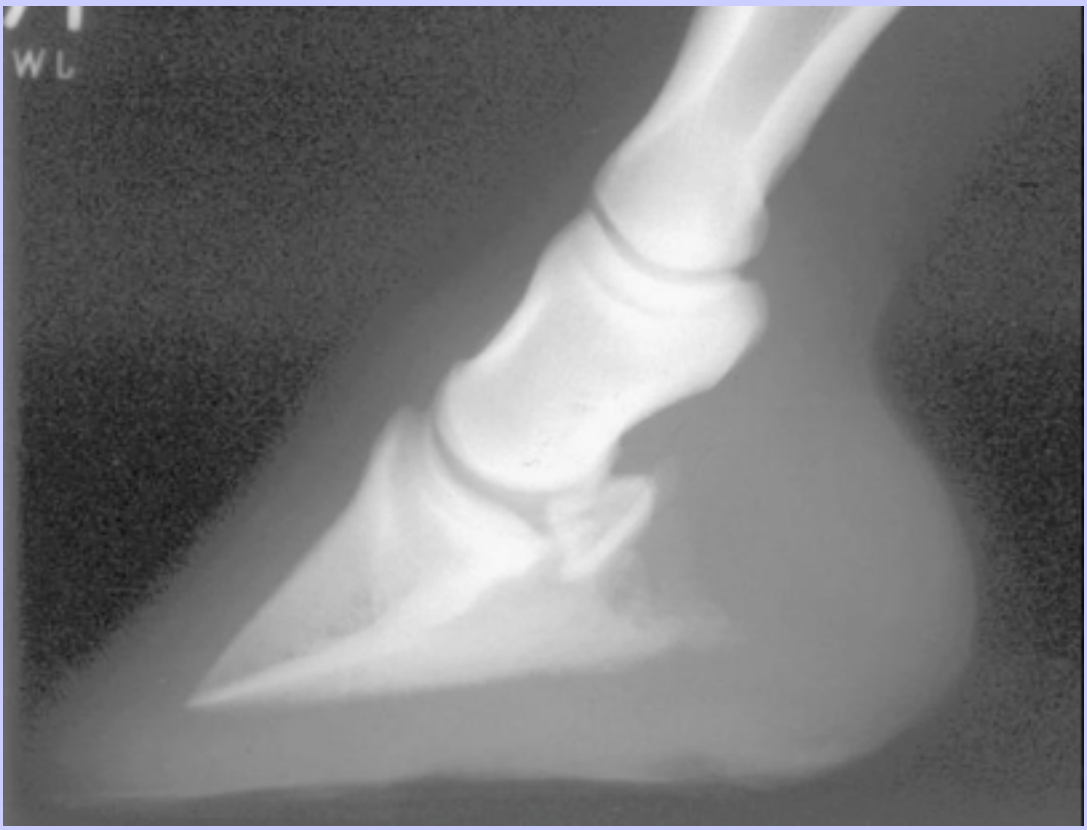
About 30% of horses with pain localized to the navicular area either do not improve or may improve but remain lame after DIP joint anesthesia, which may be associated with different diffusion properties of the local anesthetic versus the intraarticular medication. Drug treatment of the navicular bursa may be beneficial in some of these horses. We recently reported on 25 horses with pain localized to the navicular region that did not respond to corrective shoeing, phenylbutazone, or DIP joint medication.[178] These horses did improve after navicular bursa injection with 40 mg methylprednisolone and remained sound for a mean of 4 months. Most of the 25 horses had moderate to severe radiographic changes involving the navicular bone. Approximately half had an enthesophyte located at the proximal aspect of navicular bone at the attachment of the CSL, possibly indicating chronic CSL desmitis (Fig. 38-29). The technique for navicular bursa injection has been previously described.[178]

38.16.1.7

Systemic Joint-Modulating Drugs

Hyaluronan (HA) is a normal component of synovial fluid and functions as a joint lubricant. It also appears to have some antiinflammatory properties, but the exact mechanism is unknown. Exogenous HA inhibits chemotaxis and phagocytosis of granulocytes and reduces the stimulation of lymphocytes and may decrease the formation of prostaglandin synthesis. The antiinflammatory properties of HA appear to be dose dependent, and HA with a molecular weight greater than 500,000 daltons may be more effective. Systemic HA may be more effective in horses with mild synovitis/capsulitis and less effective on horses with chronic osteoarthritis. The recommended dose is 40 mg HA intravenously once weekly for 3 weeks, then once monthly for maintenance. Some horses with mild navicular pain improve after systemic HA administration, but its use is usually combined with other treatments.

Fig. 38-29 Lateral-to-medial radiograph of foot showing an enthesophyte at the proximal aspect of the navicular bone where the collateral suspensory ligament attaches. Horses with this type of radiographic abnormality usually respond better to medication of the navicular bursa than distal interphalangeal joint medication.



Polysulfated GAGs such as Adequan are referred to as “chondroprotective agents” and are used to prevent, attenuate, or reverse morphologic cartilaginous lesions associated with osteoarthritis. Adequan is made from bovine lung and trachea extracts containing mainly chondroitin sulfate. Previous studies have shown that the antiinflammatory effect of GAGS involves the inhibition of enzymes and cytokines associated with osteoarthritis, such as interleukin interleukin-1 (IL-1, a potent chemotactant agent), metalloproteinases (MMs), and prostaglandin E_2 (PGE_2). Both in vivo and in vitro equine studies have been performed, with conflicting results. More recently, a survey of 1522 equine veterinarians assessing the efficacy of systemic polysulfated GAGS resulted in the subjective conclusion that their use was more effective than HA for treatment of subacute DJD and less effective for acute synovitis. Intramuscular GAG administration was shown to improve lameness in horses diagnosed with navicular syndrome in one double-blind study.[181] The dose was 500 mg IM every 4 days for eight treatments. In our hospital we see many middle-aged western

performance horses with chronic navicular problems. IM Adequan (500 mg) every 1 to 2 weeks subjectively seems to benefit these cases, although no scientific studies support the change in frequency of its use.

The oral chrondromodulatory nutraceutical Cosequin has been evaluated in the treatment of 10 horses with navicular syndrome.[181a] The nutraceutical consisted of 9 g glucosamine, 3 g chondroitin sulfate, and 600 mg manganese ascorbate and was given orally twice daily for 60 days. The clinical impression from the owners was that the horses' lameness showed improvement. Glucosamine has been shown to reduce expression of MMPs and increase the expression of natural inhibitors of MMPs in the joint when studied in vitro. The ability of the horse to absorb these oral nutraceuticals has been questioned, and recent work suggests that doubling the dose currently recommended by the manufacturer improves efficacy of the product, although 4 to 6 weeks of treatment is often needed before a response is seen. I have found that nutraceutical use is variable in horses with navicular area pain, with some showing improvement with daily administration and some showing no effect. Empirically, the benefit of oral nutraceuticals seems inferior to systemic administration of IV hyaluronan or IM Adequan.

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38.16.1.8 Other Medical Treatments

Tiludronate, a biphosphonate, is used in human medicine to reduce bone resorption. It has been used to treat navicular area pain in horses with promising results.[182]

Investigated as a treatment for navicular disease in horses, extracorporeal shock wave therapy (ESWT) directs a pressure wave to a specific area of the body to increase osteogenic activity in bones and induce neovascularization at the tendon-bone junction. Human patients have variable duration of analgesic effect after treatment with ESWT. The equine study reported that a single ESWT treatment had no effect on horses with navicular disease.[183]

38.16.2 SURGICAL OPTIONS

38.16.2.1 Palmar Digital Neurectomy

Neurectomy of the palmar digital nerves is occasionally required to allow horses with chronic heel or navicular pain to remain athletically sound. Despite aggressive medical treatment with corrective shoeing, NSAIDs, and intraarticular/intrabursal injections, many horses fail to respond or only improve temporarily, which leaves palmar digital neurectomy as a final treatment option. Before surgery the horse should improve greater than 90% after palmar digital nerve perineural anesthesia. Palmar digital neurectomy resulted in improvement in lameness for a mean of 2 years in one study evaluating 59 horses with navicular disease. Diligent postoperative care is critical to achieve prolonged soundness.[183a] After surgery, a padded pressure bandage is applied to the limb and changed every 4 to 5 days for 2 weeks. The horse remains in a stall for 30 days, followed by 30 days of light riding and resumption of normal activity 60 days after surgery. The limited activity and diligent bandaging after surgery may reduce the inflammatory response and reduce scar tissue formation around the nerve stumps.

38.16.2.2 Navicular Suspensory Desmotomy

This procedure has been recommended for horses with navicular syndrome in the past and applied to a number of cases, without favorable long-term results. Therefore, we are not currently using this procedure and believe it has fallen out of favor as a treatment for horses with navicular pain.

38.16.3 SUMMARY

No single treatment option is suitable for all horses with heel or navicular area pain. Each horse must be evaluated individually to determine which structure in the palmar aspect of the foot is injured, severity of disease, horse and hoof conformation, and horse use and level of performance expectation before a treatment plan can be developed. Many treatment options are available to help these horses to perform.

38.16.4 SPONDYLITIS

SARAH M. REUSS

38.16.4.1 Definitions

Spondylitis is inflammation or infection of the vertebral body. *Diskospondylitis* is an inflammatory lesion that includes the intervertebral disk and its adjacent vertebrae. It is usually confined to one intervertebral joint. Both spondylitis and diskospondylitis are rare in large animals but life threatening. Also called *vertebral osteomyelitis,* spondylitis is most often seen in swine[184] but is also described in horses, cattle,[185] goats,[186] and sheep. Infection is the most likely cause, but an etiologic agent may be difficult to isolate. Neonates are especially at risk for spondylitis. Diskospondylitis in large animals is most often reported in adult horses and cows in the cervical vertebrae.[194–196] Lesions have been identified less frequently in the thoracic,[190,191] lumbar,[192] and sacral[193] regions. The clinical signs and diagnostic approach are similar for spondylitis and diskospondylitis.[190]

38.16.4.2 Clinical Signs and Differential Diagnosis

The earliest signs of spondylitis may include fever, lethargy, stiffness, and localized spinal pain. Soft tissue swelling may be evident with paravertebral abscessation.[194] Muscle atrophy has also been reported in a quarter horse.[191] Because diskospondylitis most often affects the cervical and thoracic vertebrae in horses, neck pain and reluctance to lower the head to graze are common signs. Animals may develop an abnormal stance with one forelimb forward and the other back in order to graze.[190] Vertebral osteomyelitis may progress to spinal cord compression and variable degrees of ataxia, paresis, sensory and proprioceptive deficits, and recumbency. Neurologic signs depend on the vertebral section affected and the amount of spinal cord compression. Clinical signs are usually progressive.

Early clinical signs in ruminants include abnormal behavior, decreased appetite, and weight loss. Difficulty in extending the head and neck ventrally is often the reason for presentation to a veterinarian.[185] Varying degrees of neurologic deficits are reported, from occasional stumbling[185] to tetraparesis[195] and paraplegia.[186]

Differential diagnoses for spinal pain include spondylosis, vertebral fracture, muscle strain, dorsal spinous process impingement, vertebral subluxation, vertebral infarcts, and aberrant parasite migration.[196] Additional differentials for spinal cord ataxia in horses include cervical stenotic myelopathy, equine protozoal myeloencephalopathy, herpes myeloencephalopathy, and neoplasia.

38.16.4.3 Etiology and Pathogenesis

Both spondylitis and diskospondylitis are thought to be septic conditions, although etiologic isolation usually is not successful. Even in cases where bacteria are not isolated, response to antimicrobials may indicate a bacterial pathogenesis.[190] Bacterial infection is more common than fungal infection, and the hematogenous route of infection is the most common. Spondylitis occurs most frequently in neonates. This age predisposition may be caused in part by failure of passive transfer leading to sepsis.[184] In general, spondylitis is often secondary to a preexisting focus of infection elsewhere in the body.[184] Tail-docking wounds,[197] umbilical infections,[184,195] pneumonia,[193] and lung abscesses[184] are possible sources of infection. Septic thrombi embolize into the metaphyseal arteries of the vertebrae, where flow is sluggish and bacteria can colonize.[197] In adults, direct injury to the intervertebral disk or the vertebral endplate may contribute to the formation of diskospondylitis. The injury disrupts the vasculature, increasing susceptibility to infection. Diskospondylitis is also reported to occur secondary to spread of local infection[188] and traumatic injury.[187] Infection results in destruction and remodeling of affected bone. Inflammation of the disk and vertebrae leads to spinal cord compression and the associated neurologic dysfunction. The intervertebral disk may actually prolapse into the spinal canal.[188] The neurologic signs may also be secondary to the infection eroding into the meninges and causing a suppurative meningitis.

Pathogens that have been cultured from adult horses with vertebral osteomyelitis include *Brucella abortus,*[198] *Aspergillus* species, *Streptococcus zooepidemicus,*[184] *Staphylococcus* species,[189,192] and *Mycobacterium bovis*.[199] Vertebral osteomyelitis isolates in foals include *Rhodococcus equi,*[193,194,200] *Streptococcus* species, *Actinobacillus* species, *Eikenella corrodens,*[201] *Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus* species, and *Corynebacterium pseudotuberculosis*.[196] Isolates from cattle with vertebral osteomyelitis include *Aspergillus fumigatus*, *Bacteroides nodosus*, *Clostridium perfringens*, *Streptococcus* species, *Staphylococcus* species,[185] *E. coli,*[197] *Actinomyces pyogenes*, *Fusobacterium necrophorus*, and *Pseudomonas* species.[202] *Staphylococcus* species and *Arcanobacterium (Actinomyces) pyogenes* were cultured from the intervertebral disk of a goat.[186]

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38.16.4.4 Diagnosis

Diagnosis is based on clinical signs and imaging modalities. Clinicopathologic findings may include anemia, leukocytosis, neutrophilia, and hyperfibrinogenemia.[184] Hyperproteinemia resulting from hyperglobulinemia may also be seen.[190] Cerebrospinal fluid is usually normal, unless the osteomyelitis has progressed to meningitis. Blood and urine cultures should be obtained but often are not diagnostic.

Radiography is the basis of diagnosis. Radiographic signs of spondylitis include bony proliferation, lysis, sclerosis, and localized soft tissue swelling.[184] Radiographic abnormalities in diskospondylitis include osteolysis of adjacent endplates with surrounding sclerosis and collapsed intervertebral disk space.[192]

Contrast radiography may be used to delineate spinal cord compression.[192] However, radiographic changes may lag 2 to 8 weeks behind clinical signs, compromising early diagnosis.[184] With vague clinical signs, the neuroanatomic location within the vertebral column may be difficult to identify, making targeted radiographs impossible. Nuclear scintigraphy may help to localize the lesion to a specific vertebral section that can then be radiographed.[184] Scintigraphy may also allow earlier detection because of the lag time in radiographic changes. Ciprofloxacin and WBC-labeled scintigraphy may also prove useful in the diagnosis of vertebral osteomyelitis.

Ultrasonography is currently being investigated as a useful imaging modality. Abnormalities include irregular endplates or bone surfaces, wide or narrow disk spaces, vertebral step formation, and associated abscessation or muscle involvement.[192] Transrectal ultrasonography of the lumbar vertebrae may be performed, and transcutaneous studies can image the rest of the vertebral column. Advantages are that ultrasound can be done in the field and can be used for needle-guided aspirates of potentially infectious lesions and as a screening tool to localize lesions.[192] MRI and CT may also be considered as they allow visualization of the endplates, vertebral disk, and spinal cord. CT has been used in a goat to diagnosis diskospondylitis; bone lysis, bone proliferation, mineral opacity in the intervertebral disk, and spinal cord displacement were seen.[186]

38.16.4.5 Treatment

Long-term antimicrobial therapy is indicated for animals with vertebral osteomyelitis. Blood, urine, or tissue culture and sensitivity may be used to guide antimicrobial choices. When this is not possible, broad-spectrum bactericidal antimicrobials should be used. Long-term treatment is necessary and may last 3 to 6 months.[193] NSAIDs can also be used for pain control. In nonresponsive cases, curettage of infected bone may be necessary.[189,193] This also provides an opportunity to collect material for bacterial culture.[193] In horses with instability and spinal cord compression, surgical decompression and stabilization may be indicated.

38.16.4.6 Prognosis

The prognosis for horses with diskospondylitis is guarded to poor. If there are no neurologic deficits and thus presumably no spinal cord compression, the prognosis is more favorable. Early diagnosis and long-term treatment are essential.

38.16.5 SPONDYLOSIS

SARAH M. REUSS

38.16.5.1 Definition

Spondylosis is a degenerative condition of the intervertebral joints. In middle-age and older horses and cattle, the thoracic and lumbar vertebrae are susceptible to chronic, progressive development of enthesophytes within the ventral longitudinal ligament or the ventral margins of the anulus fibrosus. Osteophytes extend across the intervertebral space toward osteophytes on the adjacent vertebrae, resulting in partial bridging where a lucent line persists between the two. Complete bridging *(ankylosis)* can occur, however, without significant loss of intervertebral disk width. A variety of terms are used in veterinary medicine to describe

vertebral enthesophyte formation, including *spondylosis deformans, vertebral osteophytosis,* and *ankylosing spondylosis*.[203]

Spondylosis in horses is most common in mature animals and reportedly in a higher proportion of mares.[204] The most common location in horses is from the tenth to fourteenth thoracic vertebrae. When spondylosis occurs in the thoracic region, the osteophytes are usually ventrolateral, whereas in the lumbar region the osteophytes are more lateral.[205]

Middle-age and older bulls have a higher prevalence of vertebral enthesophytes than other cattle. Bulls used for artificial insemination are especially at risk; in one study, more than 49% of those 8 years and older had spondylosis.[206] In another study, middle-age bulls also had significant pathology, with 21 of 21 dairy bulls age 65 to 90 months having some degree of lumbar osteophytes; 13 had complete ankylosis of at least one intervertebral space.[207]

38.16.5.2 Etiology and Pathogenesis

The exact cause of spondylosis is unknown but is apparently related to altered biomechanics and inflammatory mediators. Some believe that spondylosis is a result of excessive dorsiflexion when the back muscles fatigue.[208] Mechanical stress then leads to tearing of the ventrolateral anulus fibrosus. Chemical mediators act on the periarticular ligaments and joint capsule, leading to metaplastic change. Ossification occurs within the anulus fibrosus and ventral longitudinal ligament, resulting in partial bridging. The cycle may continue until ankylosis is complete and a continuous medullary cavity exists.[203] Partial or complete ankylosis at one site puts more stress on adjacent segments, so there is more active bone remodeling elsewhere in the vertebral column.[205] Secondary DJD of the dorsal articular facets may also develop as a result of altered biomechanics.

The enthesophytes and then the ankylosed vertebral bodies are at higher risk for fracture because of their inability to absorb normal forces. Three percent of bulls at artificial insemination centers have vertebral fractures.[209]

Spondylosis in bulls is not related to force of ejaculatory thrust at service,[210] frequency of semen collection, or high-calcium diets.[209] Despite previous thinking, limited dietary calcium does not reduce the prevalence of spondylosis in bulls.[209]

Nerve roots may be compressed as they exit the intervertebral foramen, and spinal cord compression may occur if the bony proliferation extends dorsally into the vertebral canal. This results in neurologic deficits such as progressive ataxia and paralysis.

38.16.5.3 Clinical Signs and Differential Diagnosis

Spondylosis may be an incidental finding in animals with no history or clinical signs of back pain. However, spondylosis can account for acute, recurrent, and chronic back pain in some animals. Pain is caused by inflammation, impingement, and fracture. Palpation of the spine may be poorly tolerated. Horses may "guard" their vertebral column by using muscle contraction to disallow ventroflexion. Resentment of girthing and mounting may be noticed. Riders may report poor performance, vague lameness, or altered gait.[208] Bulls with spondylosis will have a good appetite and are afebrile, but they may have difficulty rising, be reluctant

to move, and have difficulty mounting.[203] Once present, clinical signs are slowly progressive. Lameness becomes more severe, and neurologic deficits may be seen, when there is nerve root impingement or spinal cord compression. Abnormalities include bilateral proprioceptive deficits of the hindlimbs, with hoof dragging, excessive hindlimb flexion, and incoordination. Hindlimb ataxia can progress to paralysis in some animals, especially older dairy bulls.[207]

Differential diagnoses for spinal pain include muscle strain, vertebral fracture, diskospondylitis, dorsal spinous process impingement, vertebral infarct, and aberrant parasite migration. Additional differentials for cattle with hindlimb neurologic deficits include lymphosarcoma, encephalopathy, progressive degenerative myeloencephalopathy, and downer cow syndrome.[203]

38.16.5.4 Diagnosis

Diagnosis is suggested by clinical signs and, in bulls, a history of reluctance to mount or breed. Palpation of the dorsum may elicit signs of pain. Rectal palpation may reveal ventral osteophytes if they are located on the caudal lumbar vertebrae. A thorough neurologic examination is indicated if there are hindlimb deficits. Cerebrospinal fluid is usually normal.

Standing lateral radiographs are the mainstay of diagnosis. Diagnostic radiographs can be difficult to obtain, however, given the depth of the vertebrae in the thoracolumbar region. If spondylosis is suspected, targeting radiographs to areas of predilection is helpful. Spondylosis in horses is most common in the caudal thoracic vertebrae. In bulls the most common locations are C3-C5, T2-T6, and T11-L5. The largest osteophytes occur in older bulls at the thoracolumbar junction.[206,210] Radiographic changes include smooth bone that blends with the vertebral body and bridges apparently normal intervertebral disks. The clinical significance of radiographic change must also be determined based on history and clinical signs, as spondylosis can be an incidental finding. Nuclear scintigraphy can be useful for determining the activity and potential clinical significance of a lesion based on the radiopharmaceutical uptake. Scintigraphy is also helpful in localizing the lesion for targeted radiography and is an excellent imaging option if diagnostic radiographs cannot be obtained because of size constraints.

38.16.5.5 Treatment and Prognosis

Treatment for clinical spondylosis consists of palliative care. Systemic antiinflammatory drugs, cryotherapy (ice packs, cold hosing), and stall rest are recommended during the acute phase. Once complete fusion occurs, clinical signs should improve. However, if vertebral fractures or neurologic deficits are present, the prognosis is poor.

38.17 LAMINITIS (FOUNDER)

ROBERT L. LINFORD

38.17.1 Definition

Laminitis (“inflammation of the laminae”) is a disease that causes degeneration, necrosis, and inflammation of the dermal and epidermal laminae in the hoof wall of horses and ruminants.

38.17.2 Etiology and Pathogenesis

Because the epidermal laminae suspend the distal phalanx and therefore the body weight of a horse, laminar degeneration destroys the suspension mechanism and permits weight-bearing forces to push the distal phalanx ventrally. Failure of the laminar suspending mechanism causes a painful and potentially crippling lameness. Laminitis is often a sequela of digestive disturbances and other disorders that cause endotoxemia and elaboration of inflammatory mediators. Unless preventive measures are taken, laminitis often occurs after colonic torsion, proximal enteritis, colitis, grain overload, pleuropneumonia, and septic metritis (i.e., postparturient retention of the placenta).[211–215]

In horses, laminitis is sometimes seen following changes in feed, excess intake of cold water after strenuous exercise, grazing on lush spring grasses containing highly available carbohydrates, or persistent feeding of a high-concentrate ration.[211,212] Laminitis may also be precipitated in horses by administration of high levels of corticosteroids,[216] which decrease protein synthesis and potentiate digital vasoconstriction and microthrombosis.[217] Excessive weight bearing in the support limb during severe lameness of the contralateral limb can produce laminitis, as can work on hard ground or extreme exhaustion and dehydration.[211,214,215] A water-soluble toxin in black walnut shavings also has been shown to induce laminitis in horses.[218]

In cattle, laminitis is most often seen immediately after calving in fat heifers that have been fed excess concentrates and kept on concrete surfaces.[219]

38.17.3 Pathophysiology

The pathophysiology of laminitis has not been totally elucidated; however, laminitis is often considered a local manifestation of a variety of disorders that cause a generalized metabolic disturbance. Several factors may produce laminar degeneration. The integrity of the laminar suspending mechanism depends on maintenance of proteins in the cytoskeletal networks, intercellular junctions, and basement membrane of the epidermal laminar cells. This process is energy dependent, and disorders that decrease laminar perfusion or decrease protein synthesis have the potential to initiate laminar degeneration. In addition, laminar degeneration may be initiated by disorders that cause the elaboration of factors cytotoxic to the epidermal laminae, by disorders that activate metalloproteinases, or by disorders that increase the tension on the laminae. Because the laminae and their sustaining vasculature are confined within the rigid hoof wall, factors that cause tissue swelling (e.g., inflammation, edema) can theoretically increase the interstitial tissue pressure beyond critical capillary closing pressure, producing a compartment syndrome and functional ischemia of the corium. Opening of arteriovenous shunts within the corium occurs during carbohydrate-overload laminitis, but such shunting has not conclusively been shown to be the major factor producing laminar degeneration.

Laminitis is often a sequela of diseases producing gram-negative sepsis and endotoxemia, but experimental administration of endotoxin has failed to produce laminitis. However, overingestion of grain or other feeds containing large amounts of highly available carbohydrates is thought to produce endotoxemia and is the most common cause of acute laminitis. Carbohydrate overload results in bacterial overgrowth in the colon, lactic acidosis, decreased colonic pH, colonic mucosal slough, and death of colonic bacteria with concomitant liberation of endotoxin. Degeneration of the colonic mucosa is thought to allow endotoxin to gain access to the portal circulation. The mechanistic link between endotoxemia and laminar degeneration is not totally understood; however, endotoxin that crosses a compromised bowel wall into the portal circulation is removed

by reticuloendothelial cells in the liver, where it likely triggers activation of leukocytes and upregulation of proinflammatory cytokines observed during colitis and grain overload. Hyperimmune serum to gram-negative core antigens has a strong protective effect on horses at high risk of developing laminitis as a result of intestinal crises or carbohydrate overload.[220]

Sequential biopsies of the epidermal laminae and corium during the development of grain-overload laminitis indicated that initial laminar degeneration was most compatible with ischemic or cytotoxic injury, and that a major influx of inflammatory cells, edema, and microthrombosis did not precede laminar degeneration but occurred later and was likely to accelerate the degeneration.[221]

Recent evidence indicates that proinflammatory cytokine expression is increased[222] and leukocytes are activated[223] and begin to emigrate into the perivenular interstitium of the laminar dermis[224,225] during the developmental stages of black walnut extract—induced laminitis. Levels of latent metalloproteinase also increase in the plasma and vascular and perivascular tissues of the dermal laminae during the developmental stages of black walnut extract—induced[226] and carbohydrate-overload laminitis.[227] Matrix metalloproteinases (MMPs) in the laminar region are normally located in the laminar epidermis, where they are thought to play a major role in laminar epidermal remodeling to facilitate hoof wall growth and migration.[228] Early histologic lesions during the developmental stages of laminitis are compatible with excess activation of MMPs and disruption of cell-cell and cell—basement membrane linkages.[221,227] Increased expression of proinflammatory cytokines and activation and emigration of leukocytes during the developmental stage of laminitis may alter the balance between normal levels of activation and inhibition of constitutive MMPs in the laminar epidermis, leading to disruption of the laminar suspending mechanism. Continuous 48-hour application of an ice-water bath to the distal limb is thought to decrease MMP enzyme activity and was recently shown to protect the chilled digit while the contralateral nonchilled digit developed laminitis after carbohydrate overload.[229]

Because perfusion of the most dorsal laminae depends on vessels that course through vascular canals in the distal phalanx, distal migration of the distal phalanx caused by laminar degeneration may compromise laminar perfusion and result in a cycle that intensifies the laminar lesion. It is also theorized that the pain associated with laminar degeneration may cause release of catecholamines that potentiate peripheral vasoconstriction and further diminish laminar perfusion.

38.17.4 Clinical Signs

The signs of acute laminitis are lameness, depression, anorexia, and reluctance to move. Early in the disease, affected animals often paddle or shift weight from one foot to the other. Increased pulsations can be palpated and sometimes visualized in the digital arteries. Hoof-tester examinations reveal sensitivity over the sole at the toe, and tapping on the hoof wall at the toe may elicit pain. Severely affected animals may be unwilling to pick up a forefoot or hindfoot because they are reluctant to bear full weight on the contralateral foot (Obel grade III lameness[230]). The forefeet are usually affected more often and more severely than the hindfeet in horses, and the most dorsal laminae are more severely involved than laminae in the heel regions. Therefore, horses with laminitis typically draw the hindlimbs under the body and place the forelimbs forward to shift weight to the hindquarters and load the heels more than the toes. In ruminants the hindlimbs are most often involved, and affected animals characteristically become recumbent. In severe cases, when laminar degeneration circumferentially involves the foot, a noticeable depression can be palpated along the coronary band. In such cases, exudation is sometimes noted in the coronary region, and the skin may separate from the hoof wall. These signs indicate that the distal phalanx has shifted distally with respect to the hoof wall (i.e., severe rotation

or sinking of the distal phalanx) and suggest a poor prognosis. With dislocation of the distal phalanx, the sole loses its normal cupped appearance and is flat or bulges between the toe and apex of the frog. Pulse and respiratory rates are usually increased, and other clinical signs reflect underlying disease processes.

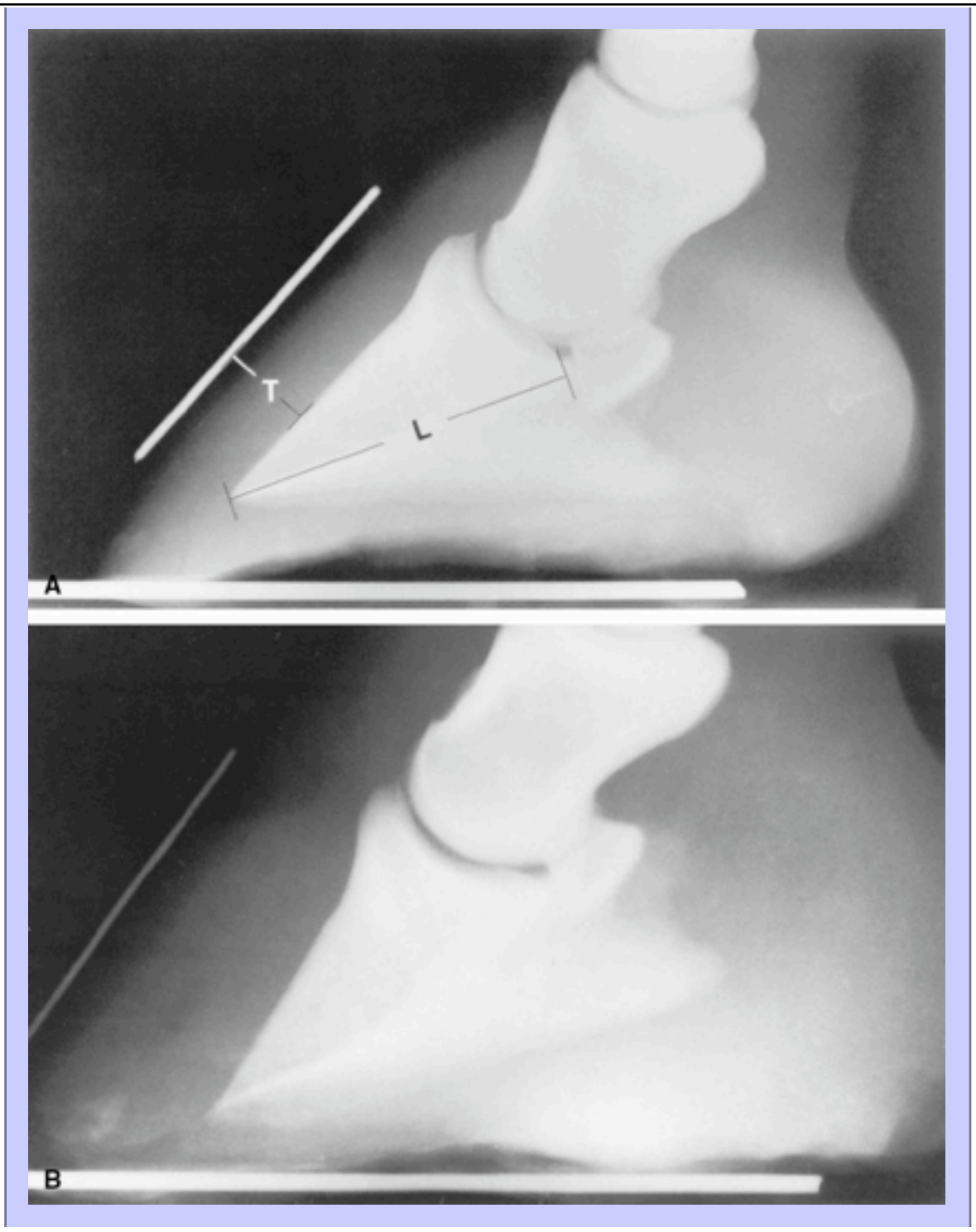
Signs of chronic laminitis are lameness and abnormal conformation of the foot. The sole is flat or dropped, the white line is widened, and the hoof wall shows signs of uneven growth. Irregular rings of horn, closely spaced at the toe and more widely spaced near the heels, encircle the hoof wall. In ruminants the sole softens and assumes a light-yellow discoloration. Hemorrhages can often be identified in the abaxial white line region, and fissures parallel to the coronary band may be seen in the hoof wall. The signs of subsolar abscessation sometimes mimic those of laminitis; however, abscesses most often involve only one foot and rarely cause anorexia, depression, or increased pulse and respiratory rates.

38.17.5 Clinical Pathology and Radiology

Clinical pathologic findings during the development of acute laminitis most frequently represent alterations associated with underlying disease processes, such as enteritis, colitis, or metritis, and are not pathognomonic for laminitis. During the onset of alimentary laminitis, packed cell volume, total plasma protein, heart rate, respiratory rate, rectal temperature, and blood glucose level are often elevated. Arterial blood pressure is usually elevated in horses but depressed in ruminants.[231] Neutropenia often precedes laminitis caused by disorders that produce endotoxemia; neutrophilia and eosinopenia are often seen later. Changes are thought to reflect compartmental fluid shifts and a stress response consistent with release of glucocorticoids and catecholamines. Horses with chronic severe laminitis, in which euthanasia was deemed necessary, had total WBC counts that were significantly elevated (5,000 to 18,000/μL) compared with control horses and horses that recovered from less severe bouts of laminitis.[232] The persistent neutrophilia was presumably a response to infection and was thought to signify an unfavorable prognosis.

Radiographic examinations should be performed on the affected digits of horses suspected to be developing laminitis. The initial examinations should include lateromedial and 65-degree dorsoproximal-palmarodistal projections. These views should be taken to assess the appearance of the distal phalanx, the soft tissues of the hoof wall and corium, and their relationship. Lateromedial examinations are periodically repeated to check the progression of the disease. Radiographic signs of laminitis include ventral displacement of the extensor process with respect to the coronary groove of the hoof wall, increased distance between the dorsal cortex of the distal phalanx and the surface of the hoof wall, and ventral rotation of the tip of the distal phalanx. Linear radiolucencies are noted interior to the hoof wall in cases where the corium has separated from the epidermal laminae. Increasing degrees of rotation of the distal phalanx and increases in the distance between the dorsal surface of the distal phalanx and the hoof wall indicate progression of the disease (Fig. 38-30).

Fig. 38-30 **A,** Lateromedial radiograph of a normal digit. Two radiopaque markers can be seen. One has been placed on the block below the foot to mark the bearing surface of the wall, and the other marker identifies the location of the dorsal surface of the hoof wall. Notice that the dorsal surface of the hoof wall and the dorsal cortex of the distal phalanx are parallel, and that the distance between them, the soft tissue thickness *(T),* is approximately 25% of the distance from the tip of the distal phalanx to the articulation of the distal phalanx and the navicular bone, that is, the length of the distal phalanx *(L)*. **B,** Lateromedial radiograph of a digit from a horse with severe laminitis. The distal phalanx has dropped ventrally without rotating. This phenomenon is seen in some horses with laminitis. The most consistent radiographic manifestation in such cases is an increased distance between the dorsal cortex of the distal phalanx and the dorsal surface of the hoof wall. The soft tissue thickness, as measured between the dorsal cortex and the dorsal surface of the hoof wall, in this case is 45% the length of the distal phalanx. The soft tissue thickness is normally less than 28% of the distal phalanx length for thoroughbred racehorses. **C,** Lateromedial radiograph of a digit from a horse with severe laminitis. Note the linear radiolucency dorsal to the distal phalanx *(arrowhead)*. This lucency indicates a separation between the corium and primary epidermal laminae and marks the inner aspect of the hoof wall *(arrows)*. The dorsal cortex of the distal phalanx is rotated approximately 14 degrees with respect to the inner surface of the hoof wall. Note that the dorsal and inner surfaces of the hoof wall are not parallel. This is the result of rasping along the distal portion of the dorsal surface of the hoof wall. The soft tissue thickness in this case is greatly increased to almost 42% of the distal phalanx length.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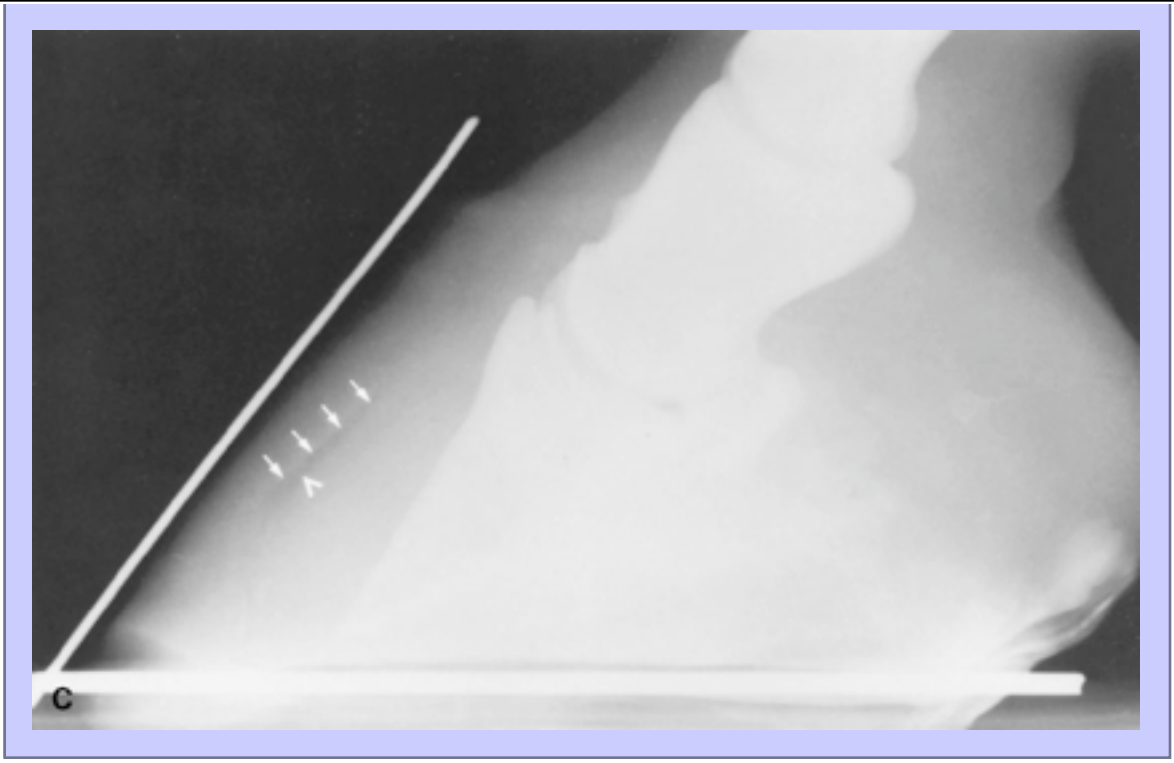


Because variations in technique affect subsequent radiographic distance and angle measurements, it is essential to standardize the radiographic procedure to detect small changes between examinations. For the lateromedial radiograph, the foot is cleaned and placed on a wooden block approximately 3 inches (7.5 cm) thick. A radiopaque marker can be embedded in the dorsal surface of the block and along the dorsal surface of the hoof wall to aid in determining the amount of rotation of the distal phalanx. However, marking the surface of the dorsal hoof wall is generally not necessary when digital radiographs are available. A small section of metal wire or a groove can be placed in the proximodorsal hoof wall as a reference for measuring vertical displacement of the distal phalanx in repeated radiographs, and a thumbtack is often useful in marking the apex of the frog for radiographic and anatomic correlation before therapeutic shoeing.

The radiographic beam should be perpendicular to a sagittal plane through the digit and should be centered midway between the toe and heels, about 1 inch (2 to 3 cm) above the bearing surface of the wall. The radiographic cassette should be parallel to the sagittal plane through the digit and should be placed as close to the foot as possible. Using a consistent technique and performing the examination in a standardized manner permit straight lateral radiographs to be produced and allow accurate quantification of radiographic parameters so that subtle changes may be identified early.

One of the earliest and most reliable radiographic signs of laminar deformity is an increase in distance between the dorsal surface of the hoof wall and the dorsal cortex of the distal phalanx. When the laminar suspending mechanism fails, weight-bearing forces cause the distal phalanx to displace distally or rotate away from the dorsal hoof wall, and the increased distance between the structures can be quantitated radiographically. Increased distance between the dorsal hoof surface and the dorsal cortex of the distal phalanx was significantly associated with increased laminar deformity during laminitis.[221]

A *laminar index* measurement has been developed to reduce the need to account for differences in radiographic magnification when comparing radiographs from different hospitals, from different breeds, or from different sizes of horses. It is useful to calculate the laminar index adjacent to the proximal and distal aspects of the dorsal cortex of the distal phalanx. The *proximal* laminar measurement is taken as the shortest distance between the linear portion of the dorsal cortex of the distal phalanx and the dorsal surface of the hoof wall immediately distal to the extensor process of the distal phalanx; the *distal* laminar measurement is taken in the same way, 5 to 6 mm proximal to the tip of the distal phalanx (see Fig. 38-30). The proximal and distal measurements are used to produce proximal and distal laminar indices by expressing them as a proportion of the length of the palmar cortex of the distal phalanx, as measured from the tip of the distal phalanx to its articulation with the navicular bone. The palmar cortex measurement serves as an index of foot size, and if the proximal or distal measurements spanning the laminae are increased in relation to the length of the palmar cortex, laminar deformity has occurred. Both the proximal and the distal laminar index measurements should be less than 30% of the palmar cortex length. The index measurements ranged between 20% and 28% for nonlame racing thoroughbreds[221,233] and were greater than 30% in horses with laminitis,[234] ranging up to 50% to 55% in those with severe laminar deformity.[221] If the proximal and distal laminar indices are almost equal and both are greater than 30%, the distal phalanx has sunk in relation to the hoof capsule, without rotation (see Fig. 38-30). When both indices are greater than 30% and the distal index is greater than the proximal index, sinking and rotation of the distal phalanx have both occurred. Sinking generally indicates that laminar degeneration involves more than the dorsal wall laminae and carries a worse prognosis than for horses with rotation alone.

38.17.6 Epidemiology

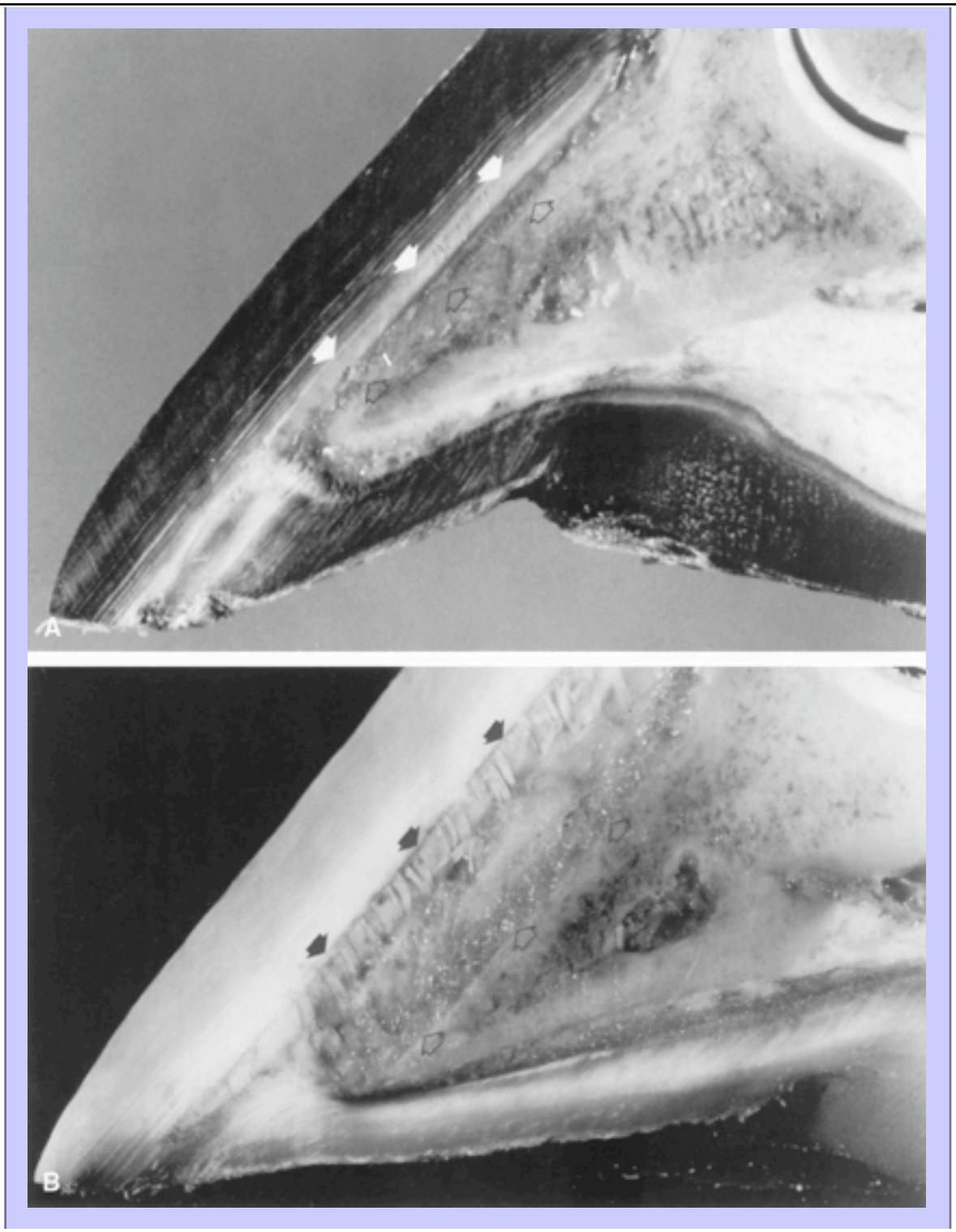
A survey of the risk factors associated with laminitis indicated that intact mares and stallions were at greater risk of developing laminitis than geldings. Ponies also accounted for a significantly greater number of laminitis cases than expected based on their proportion of the caseload. The peak incidence of new cases also corresponded with growth of lush spring grasses, suggesting that ingestion of large quantities of fresh grass is also a significant risk factor for pastured horses.[235]

Other risk factors include diseases that cause excess weight bearing or trauma in the digit and diseases that produce endotoxemia. Persistent feeding of a high-concentrate ration, stabling on concrete surfaces, long van trips, and exposure to or ingestion of black walnut wood products are also thought to be associated with an increased risk of laminitis. In addition, horses that previously had laminitis are at greater risk than other horses.

38.17.7 Necropsy Findings

Peracute cases may have total degeneration of the secondary epidermal laminae, which causes a separation between the primary epidermal laminae of the hoof wall and the collagen fibers of the corium. Abscessation may occur in the necrotic laminae or subsolar tissues. The distal phalanx may sink or may be rotated ventrally with respect to the hoof capsule, and the tip may penetrate the sole (Fig. 38-31). Severe cases are accompanied by fractures of the solar margin, osteomyelitis, or severe resorption of the distal phalanx. The necropsy findings generally demonstrate a variable degree of elongation of the epidermal laminae, which depends on the severity and duration of the problem (Fig. 38-32).

Fig. 38-31 **A,** Midsagittal section from the foot of a horse with a normal digit. Note the distance between the dorsal surface of the dorsal cortex of the distal phalanx *(open arrows)* and the inner surface of the hoof wall *(arrows)*. The dorsal surface of the hoof wall and dorsal cortex of the distal phalanx are parallel. Compare with Figure 38-30, *A*. **B,** Midsagittal section from the foot of a horse with severe laminitis, a "sinker." Note the increased distance between the dorsal surface of the dorsal cortex of the distal phalanx *(open arrows)* and the inner surface of the hoof wall *(arrows)*. Also note that the distal phalanx has not rotated with respect to the hoof wall. Compare with Figure 38-30, *B*. **C,** Midsagittal section from the foot of a horse with severe laminitis. There is approximately an 18-degree rotation of the distal phalanx, and its tip has penetrated the sole *(curved arrow)*. Note the increased distance between the dorsal surface of the dorsal cortex of the distal phalanx *(open arrows)* and the inner surface of the hoof wall *(arrows)*. Compare with Figure 38–30, *C*.


A
B

38.17.8 Treatment

Treatment of animals developing acute laminitis should be considered an emergency. Laminar degeneration is underway by the time clinical signs of lameness appear, and even a few hours of delay in treatment can mean the difference between success and failure. Therapy should be initiated before development of clinical signs when the untreated animal is at high risk of developing laminitis (e.g., animals that recently ingested a large quantity of grain; mares with retention of placenta; horses with enteritis, colitis, or strangulating intestinal lesions).

General principles of therapy are aimed at eliminating the cause, promoting digital circulation, reducing tension on the laminae, reducing platelet activation and coagulation, and administering NSAIDs and free-radical scavenging agents to minimize digital inflammation and necrosis and to relieve pain.

38.17.9 ELIMINATING CAUSE

A laxative or purgative should be administered to animals that have ingested a large quantity of grain. In such cases, 3 to 4 L of mineral oil is usually given through a nasogastric tube. Intravenous administration of balanced electrolyte solution is indicated for horses with laminitis resulting from exhaustion, dehydration, and hypovolemia. Retained placentas should be treated appropriately if the placenta has not been expelled within 3 hours after parturition in mares. Antiendotoxin hyperimmune serum may be indicated for horses at risk of developing endotoxemia as a result of colon torsion, toxic diarrhea, toxic proximal enteritis, septic metritis, grain overload, or other disorders.

38.17.10 ADMINISTERING NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Phenylbutazone is recommended, and at the onset of the syndrome it may be given once at a dose of up to 8.8 mg/kg intravenously (IV), usually followed by 4.4 mg/kg orally (PO) twice daily for several days. The dose should be tapered to 2.2 mg/kg (PO twice daily) as soon as possible. For horses with endotoxemia, flunixin meglumine* (1.1 mg/kg IV twice daily) is often used instead of phenylbutazone. Dimethyl sulfoxide (DMSO) also may be given daily (0.2 to 1.0 g/kg) for 2 or 3 days. To administer it IV in a 450-kg horse, 250 mL of the 90% solution is mixed in 3 L of balanced electrolyte solution and given slowly. DMSO should be diluted to a concentration that is less than 20% to avoid hemolysis when given IV. The use of aspirin (10 mg/kg IV or PO once daily) is sometimes advocated for its antiinflammatory and antiplatelet activities. Corticosteroids and adrenocorticotropic hormone (ACTH) are contraindicated because they decrease protein synthesis and may potentiate peripheral vasoconstriction and microthrombosis.

* Banamine, Schering Plough Animal Health, Union, NJ.

38.17.11 REDUCING TENSION ON LAMINAE

The force related to suspending the weight of the horse by the attachment between the hoof wall and the distal phalanx is likely to be a major factor producing laminar deformity in horses with laminitis. Reduction of laminar tension may be achieved by focusing the forces of weight bearing more on the frog and sole and reducing the amount of weight taken by the hoof wall. This can be accomplished by using frog support bandages or shoes, sole casts, or sand stalls. Elevation of the heel with an 18-degree wedge has been advocated to reduce the pull of the deep flexor tendon and decrease the tension on the laminae.[236] This elevation can be achieved with a plastic-cuff shoe* that is bandaged or glued to the hoof wall and used with a frog support cushion† and an 18-degree heel wedge. An elevated-heel hoof cast has also been advocated and shown to reduce strain on the dorsal hoof wall laminae.[237]

For horses with severe acute laminitis, do not lower the heel in the acute stage, and avoid shoes that require the horse to bear full weight on one foot for a prolonged period while the shoe is being nailed on the other. Avoid using shoes that increase laminar tension by transferring more weight-bearing forces to the hoof wall. A plastic-cuff heel-wedge shoe can be temporarily taped to the hoof with minimal trauma and effort. If it makes the horse more comfortable, the shoe can be glued in place. Frog support shoes continue to put pressure on the frog when the horse is recumbent and may predispose to subsolar necrosis. Frog support bandages or Lilly Pads‡ provide satisfactory support and avoid the complications associated with shoeing. The toe should be dubbed off to decrease the lever arm effect that a long toe has on prying the wall away from the distal phalanx during breakover.

Affected horses should be encouraged to lie down to reduce laminar tension. This goal can usually be accomplished with sedation. The stall should be heavily bedded with straw and pine chip shavings to a depth of 1 to 2 feet (30 to 60 cm) for comfort and to reduce the risk of pressure sores.

* Modified Ultimate, Nanric, Inc., Lawrenceburg, KY.

† Advanced Cushion Support, Nanric.

‡ Therapeutic Equine Products, Indianapolis, IN.

38.17.12 PROMOTING DIGITAL CIRCULATION

Walking with frog supports in soft ground for 5 to 10 minutes every 3 to 4 hours is beneficial for nonlame horses during the developmental stages of laminitis. It may increase the amount of laminar deformity when used in horses with lameness or in nonlame horses that have a depression at the coronary band indicating that laminar degeneration has already begun. Alpha-adrenergic blocking drugs such as acetylpromazine, phenoxybenzamine, and prazosin have also been advocated to decrease peripheral vasoconstriction and promote digital circulation. Acetylpromazine (0.02 to 0.04 mg/kg intramuscularly four times daily) may be given for its theoretic effect on digital circulation and for the sedative effect that encourages the horse to lie down and reduce laminar tension. Before lameness develops, heparin may be administered (40 to 100 units/kg subcutaneously two or three times daily) to provide laminitis prophylaxis by attenuating potential microthrombosis. This therapy significantly reduced the proportion of horses developing laminitis after proximal enteritis when given before onset of lameness.[238]

38.17.13 OTHER TREATMENTS

Antibiotics may be indicated in severe cases to reduce the risk of secondary sepsis in the foot. Methionine (20 to 60 mg/kg PO once daily) and biotin (0.03 to 0.2 mg/kg PO once daily) have been used for their effect on keratinization. Recently, a continuous (48-hour) ice-water bath has been advocated to chill the distal limbs of horses at risk for developing laminitis. Other methods of cooling the distal limbs include using bandages that continuously circulate ice water and simply adding crushed ice to a rectal sleeve and tying it to the pastern to chill the dorsal hoof wall, replacing it several times daily as needed. Rectal sleeves with ice are economical, well tolerated by horses, and simple to use, but are likely to be less effective than continuous ice-water baths or bandages.

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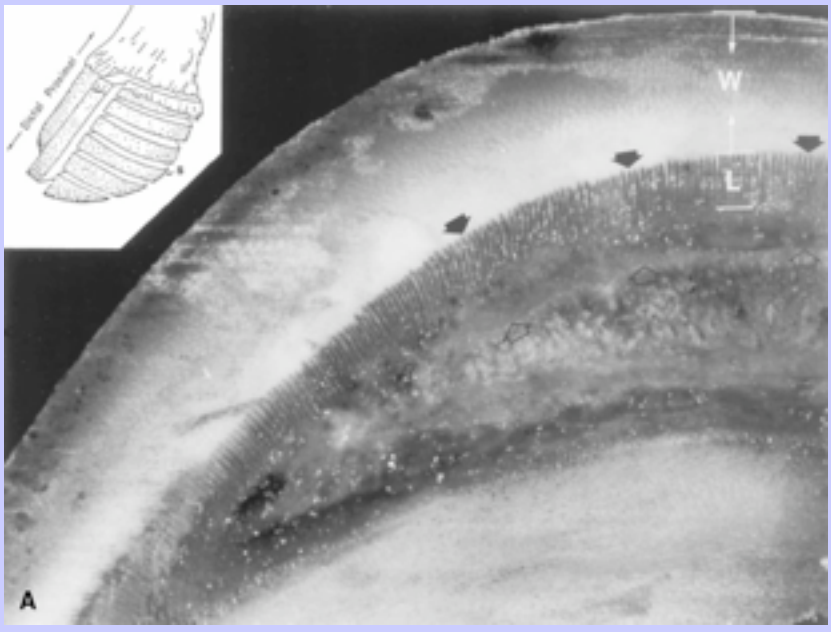
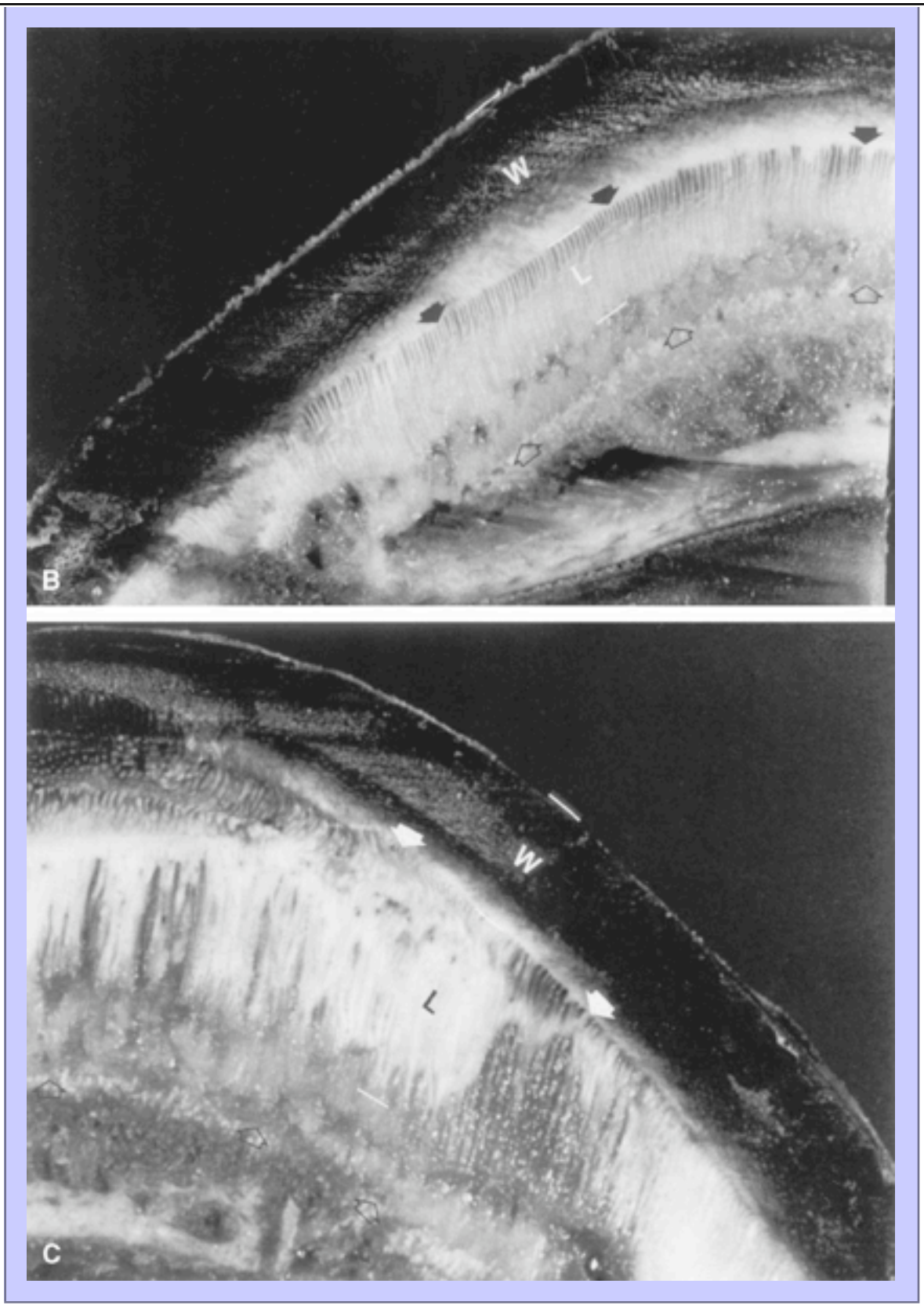
Fig. 38-32 **A,** Section of a healthy foot. The section was cut parallel to the coronary band, midway between the coronary band and the bearing surface of the hoof wall *(inset, S)*. The length of the epidermal laminae *(L)* is approximately 33% of the thickness of the hoof wall *(W)* in normal horses. The distance between the dorsal cortex of the distal phalanx *(open arrows)* and the inner surface of the hoof wall *(arrows)* is normally less than 75% of the thickness of the hoof wall. **B,** Foot section, cut in a manner similar to that of *A,* from a foot of a horse with moderate laminitis. Note the increased length of the epidermal laminae *(L)*. The increase in epidermal laminar length has allowed the distance between the dorsal cortex of the distal phalanx *(open arrows)* and the inner surface of the hoof wall *(arrows)* to become almost as large as the thickness of the hoof wall *(W)*. **C**, Foot section, cut in a manner similar to that of *A,* from a foot of a horse with severe laminitis. Note the marked increase in length of the epidermal lamina *(L)*. The distance between the dorsal cortex of the distal phalanx *(open arrows)* and the inner surface of the hoof wall *(arrows)* is abnormally increased to almost three times the thickness of the hoof wall *(W)*.

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38.17.14 Prognosis

Owners should be advised that it is often difficult to arrive at an accurate prognosis for up to 6 weeks after the original insult. Redden[239] has suggested the following general guidelines regarding prognosis.

Horses that become sound within 24 to 48 hours of the onset of treatment, remain sound, demonstrate no radiographic changes, and have no palpable increased pulsation of the digital arteries after cessation of all medications for 5 days have a good prognosis. They should be given 10 additional days of stall rest, after which they can be vanned or put back to regular work.

Horses that develop 2 to 5 degrees of rotation or a laminar index measurement of 30% to 35% within the first 30 days of the onset but then become sound, remain sound, and show no further radiographic progression after an additional 45 days without treatment have a good prognosis. They may resume light exercise, but they should not be shipped long distances for several months, and they should be considered to have an increased risk of recurrence.

Horses that develop 5 to 10 degrees of rotation in the first 6 weeks but then have no further radiographic progression should receive an additional 90 days of stall rest. If they remain sound without medication, they may resume light exercise with caution after they have been turned to pasture for an additional 12 months. Such horses will not return to their previous level of performance and are not suited for racing or endurance, but they may function as pleasure horses.

Horses that develop 10 to 15 degrees of rotation within the first 4 to 6 weeks have a poor prognosis. The tip of the distal phalanx often penetrates the sole. Necrosis of the dermal and epidermal laminae and subsolar tissues usually occurs. Drainage often is noted at the coronary band or heels and is an indication of subcapsular abscessation. Gas or fluid pockets may develop between the hoof wall and the dorsal surface of the distal phalanx. Such cases require drainage and debridement of the necrotic tissue, which may be accomplished through an anterior hoof wall resection. If the keratinized sole is underrun, it is thinned enough to be elevated off the underrun areas so that necrotic debris can be curetted and the area flushed with antiseptic solution. Daily bandage changes and antiseptic flushing or soaking are required. If all necrotic subsolar tissue can be accessed without removing the keratinized sole, a thin layer of keratinized tissue should be left in place. Horses with a thin layer of keratinized sole are usually more comfortable than those in which the sole has been completely removed. Leaving a thin layer of keratinized tissue reduces the potential for exuberant granulation and seems to increase the rate of reepithelialization across granulating wounds in the sole.

Horses with this degree of laminitis require several months of stall rest and will be chronically crippled, at best. They will require several thousand dollars of care and bandaging just to stabilize the foot. The foot usually remains chronically painful, and, if so, euthanasia is justified on humane grounds. Tenotomy of the deep digital flexor tendon is beneficial in these cases. It seems to permit such severely affected horses to become more comfortable, enhances reepithelialization of defects in the sole, and permits the dorsal hoof wall to grow better.

Horses that have circumferential laminar necrosis in which the distal phalanx drops 2 cm or rotates 15 to 20 degrees with respect to the hoof capsule, or horses that develop a laminar index greater than 50% within the first 4 to 6 weeks of onset, carry a grave prognosis.

38.17.14.1 Prevention and Control

Prevention should be aimed at controlling as many risk factors as possible. Unrestricted grazing on lush spring grasses should be avoided, especially in areas where horses have developed laminitis in preceding years, and especially for horses with a history of laminitis. Horses should not be allowed to have unrestricted access to grain or concentrates, nor should they be fed a ration that primarily consists of concentrates. Factors that cause gastrointestinal upsets should be avoided; for example, changes in the ration should be made slowly, and overheated horses should not be allowed to engorge on cold water. Retained placenta in the mare should be treated within 3 hours after parturition.

Preventive measures should be instituted before clinical signs develop for horses that are at high risk of developing laminitis from conditions such as metritis, torsion of the colon, pleuropneumonia, proximal enteritis, or colitis. Preventive therapy should include frequent walking, frog support bandages and stabling on soft surfaces, cooling the distal limb, and administration of NSAIDs and antiendotoxin hyperimmune serum.

38.17.15 FLUOROSIS

JOHN MAAS

38.17.15.1 Definition and Etiology

Ingestion of excessive fluoride by cattle, sheep, and horses can result in toxicosis. Acute fluoride toxicosis is relatively rare and is the result of accidental massive ingestion of fluoride compounds such as sodium fluoride or sodium fluorosilicate. Signs of acute fluoride toxicosis include restlessness, stiffness, anorexia, agalactia, salivation, vomiting or regurgitation, urinary incontinence, diarrhea, clonic convulsions, hyperemia, weakness, severe depression, and cardiac failure. Necrosis of the gastrointestinal mucosa and high concentrations of fluoride in plasma and urine are present in acute fluoride toxicosis. Chronic fluoride toxicosis is most often referred to as *fluorosis,* a general term that includes osteofluorosis and dental fluorosis. The most common sources of excess fluorides in the diet are (1) water with a naturally high fluoride content, (2) forages contaminated with fluorides from nearby (upwind) industrial plants (e.g., phosphate-processing plants, aluminum plants, smelters), (3) mineral (nondefluorinated rock phosphorus) and feed supplements with excessive fluoride content, (4) forages contaminated by soil or water (particularly sprinkler irrigation water) with a high fluoride content, and (5) volcanic activity, which can deposit fluoride-containing ash on soil, plants, or in water used for agriculture.

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38.17.15.2 Clinical Signs, Differential Diagnosis, and Patho-physiology

Clinical signs of fluorosis are usually first recognized as either dental fluorosis or osteofluorosis. Developing teeth are very sensitive to the ingestion of excess fluorides. The deciduous teeth rarely show signs of dental fluorosis because a partial placental barrier to the accumulation of fluorides appears to be present in the fetus. During tooth development, excess fluorides cause ameloblasts to reduce in size prematurely and the enamel epithelium to form an irregular matrix. This matrix does not calcify normally, producing defects in the mature teeth. Cattle are susceptible to dental fluorosis during enamel matrix formation, from approximately 6 months to 3 years of age. Excess fluoride intake after 3 years of age does not result in the typical fluoride-induced dental lesions. Changes in incisor teeth are observed most frequently and include chalkiness,

mottling (striations or patches in enamel), hypoplasia (defective enamel), and hypocalcification. Clinical lesions can be graded from normal to excessive.[240] Factors that influence dental fluorosis include the amount of fluoride ingested, the animal's age, the duration and consistency (intermittent vs. continuous) of exposure to fluoride, and the source and chemical form of fluoride ingested. Although diagnostically useful, dental lesions should not be used as the sole criterion to determine the degree of fluorosis.

Fluoride accumulation in bone occurs over a prolonged time; *osteofluorosis* can eventually develop if excessive fluoride is ingested. In cattle the first palpable lesions occur on the medial surface of the proximal third of the metatarsal bones. Later, lesions can be palpated on the mandible, metacarpal bones, and ribs. Radiographically, osteofluorotic bones are thickened with a chalky, roughened, and irregular periosteal surface.

The presence of osteoporosis, osteosclerosis, hyperostosis, osteophytosis, or osteomalacia depends on the amount of fluoride ingested and the duration of exposure to fluorides. The articular surfaces are not involved in osteofluorosis and can be used to differentiate osteofluorosis from osteomyelitis, osteoarthritis, and septic arthritis. The osseous lesions eventually cause intermittent lameness and stiffness, which may affect feed intake, body condition, milk production, and reproduction. Severe dental fluorosis causes reduced feed intake and efficiency, and affected animals are sometimes reluctant to drink cold water.

Table 38-3 Fluoride Concentration in Bones of Dairy Cattle Fed Various Levels of Sodium Fluoride

	Fluoride in Bone (ppm; Dry, Fat-Free Basis)		
Fluoride in Feed (ppm, Dry Basis)	**2 years**	**4 years**	**6 years**
0-15 (Normal conditions)	401-714	706-1138	653-1221
15-30 (No adverse effects)	714-1605	1138-2379	1221-2794
30-40 (Borderline fluorosis)	1605-2130	2379-3138	2794-3788
40-60 (Moderate fluorosis)	2130-3027	3138-4504	3788-5622
60-109 (Severe fluorosis)	3027-4206	4504-6620	5622-8676

38.17.15.3 Clinical Pathology and Diagnosis

Diagnosis of fluorosis is difficult and complicated by many factors that affect fluoride intake and deposition. Fluorosis may be suspected by history, clinical signs, and physical examination. Radiographic findings of bone disease without evidence of joint involvement are highly suggestive of fluorosis in the live animal. The fluoride concentration in the urine of cattle may help to approximate recent fluoride exposure. The diagnostic value of urine fluoride analysis increases as the duration of excess fluoride ingestion increases. Normal cattle have a urine fluoride concentration of about 2 to 6 parts per million (ppm). Cattle exhibiting moderate fluorosis have urine fluoride concentrations of about 15 to 20 ppm. Cattle with urine fluoride concentrations

of 40 ppm or greater or a urinary fluoride/creatinine ratio of 0.025:1 or greater could be suspected of ingesting a diet with a fluoride concentration of 60 ppm or greater.[240,241] The concentration of fluoride in bone is quite helpful in the diagnosis of fluorosis (Table 38-3). Fluoride content in cancellous bone (e.g., rib, pelvis) is greater than in cortical bone. In addition, fluoride concentrations may vary in different areas of the same bone.

Fluoride concentration of bone is usually expressed as ppm (mg/kg) of dry, fat-free bone; however, some bone samples are ashed before fluoride determination. Therefore, it is critical to note precisely which bone was sampled, how it was prepared, and what part of the bone was analyzed. The metatarsus and metacarpus are typically analyzed for fluoride content. For all practical purposes, fluoride concentration is equal in either of these bones from the same patient.[170] Using sawdust from a longitudinal section of bovine metatarsus (dividing the bone into lateral and medial halves or dorsal and palmar halves) yields virtually the same fluoride concentration as the whole bone.[242] The fluoride concentration of the fourteenth coccygeal vertebrae (ash basis) is approximately twice that of the metacarpus (dry, fat-free weight basis).[243] This is a practical tool for clinical diagnosis.

Analysis of dietary fluoride is a valuable adjunct to the diagnosis of fluorosis. The upper safe limit of fluoride in water for livestock is 2 mg/L (ppm).[244,245] This safe limit may not protect against fluorosis in all field situations because of the large number of variables involved in the pathogenesis of fluorosis. Table 38-4 lists the long-term dietary tolerances for cattle. Under field conditions, the clinician must consider all possible sources of fluoride ingestion in evaluating total intake. In addition, because fluoride intake may be intermittent, a low dietary intake at one time may not necessarily eliminate a diagnosis of fluorosis.

38.17.15.4 Treatment and Prognosis

No specific treatment is known for ruminants with severe fluorosis, and the prognosis is poor for cattle lame from extensive bony lesions. Animals removed from the offending diet or water may lose 50% of the fluoride from bone within 2 to 5 years;[246] however, severe dental damage is irreversible.

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Table 38-4 Long-Term Tolerances of Dietary Fluoride for Cattle

Animal	Dietary Fluoride (ppm, Dry Basis)
Dairy or beef heifers	30-40
Mature dairy cattle	40
Mature beef cattle	40-50
Fattening cattle	100

38.17.15.5 Prevention and Control

Prevention involves avoiding feeds, water, and supplements with excessive fluoride concentrations. Feeding aluminum sulfate at 0.5% of the total diet reduces bone fluoride storage by 30% to 40%. However, additional phosphorus must be supplied in the diet, or osteoporosis and possibly spontaneous fractures may occur. Aluminum chloride or calcium aluminate also can be fed to cattle to reduce fluoride absorption. Calcium carbonate added to soils high in fluorides aids in reducing fluoride in forages. Cereal grains do not

accumulate fluorides and thus can be helpful in reducing overall fluoride consumption. In circumstances of high fluoride concentrations in water, use of flood irrigation rather than sprinkler irrigation decreases the fluoride content of crops such as alfalfa hay.

38.17.16 HYPERTROPHIC OSTEOPATHY

M. KEITH CHAFFIN

38.17.16.1 Definition and Etiology

Hypertrophic osteopathy (HO), also known as *Marie's disease,* is an uncommon condition in horses and is characterized by symmetric proliferation of connective tissue and subperiosteal bone along the diaphyses and metaphyses of the bones of the distal extremities.[247–249] The skeletal manifestations of HO are usually secondary to a primary underlying disorder elsewhere in the horse's body, often involving a space-occupying mass.[247–250] Most often, intrathoracic disorders are the primary cause;[248] intraabdominal and intracranial lesions have been less frequently associated with HO.[248,250,251] In addition to horses, HO has also been described in humans, dogs, cats, cattle, deer, and fowl. In humans the term *hypertrophic osteoarthropathy* is used because the articular surfaces are usually affected; in animals, however, HO apparently does not frequently affect the articular surfaces.[247–249]

In the horse, HO has been associated with a number of primary intrathoracic disorders, including mycobacterial pneumonia,[248,252] lung abscess,[247,248] suppurative pneumonia,[247,248,253] granulomatous pneumonia, systemic granulomatous disease,[248,249] fibrosing pneumonia,[254] primary and metastatic lung neoplasia,[253,255–258] pulmonary infarction,[259] rib fracture,[260] pleural adhesion,[248] and pericarditis.[261] Reported primary extrathoracic disorders associated with HO include ovarian neoplasia,[262–264] pituitary adenoma,[251] and gastric squamous cell carcinoma.[250] There is one report of HO in a mare that was thought to be associated with pregnancy; signs of HO developed during three different gestational periods and regressed each time after parturition.[253] In occasional cases, HO may develop in the absence of an identifiable underlying disorder.[248]

38.17.16.2 Pathophysiology

The pathophysiology of HO is not completely understood. Initially, blood flow to the distal limbs is increased, followed by proliferation of connective tissue, then bony proliferation along the inner aspect of the periosteum.[247–249] The periosteal proliferation results in the bony enlargements seen clinically. The link between the primary lesion and the skeletal abnormalities is poorly understood. Proposed explanations include hormonal abnormalities, hypoxia, arteriovenous shunting, and neurologic mechanisms.[247–249] No single theory offers a completely satisfactory explanation.

Horses of any age or breed and either gender can be affected with HO. Some evidence suggests that HO may be more common in male horses and large-breed horses.[248] Ponies, donkeys, cattle, and sheep can also be affected.[253,256] The condition appears to be most common in mature horses.[253]

38.17.16.3 Clinical Signs

Common clinical signs of HO include lameness, stiff gait, and reluctance to move or trot.[247–249] Firm bony enlargements are present on the distal extremities. In some cases, there may be soft tissue swelling or edema adjacent to the bony enlargements. In some horses the limb swelling is warm and painful to palpation, whereas in others the swelling is cold and painless.[248] Pain can frequently be elicited by forced flexion of the major joints. Bony enlargements are usually bilateral and symmetric and often affect the cranial, lateral, and medial aspects of the affected bones.[247,248] All four limbs are usually affected.[248] The metacarpal and metatarsal bones are most often affected; other sites that can be affected include the phalanges, carpus, tarsus, radius, and tibia, as well as the maxilla, mandible, and nasal bones.[248]

Affected horses may or may not show signs related to the primary underlying disorder, such as cough, fever, weight loss, ventral edema, tachypnea, or colic.[248] Clinicopathologic features are highly variable and depend on the underlying primary disease process. Generally, there is increased serum activity of alkaline phosphatase, associated with increased osteoblastic activity at the sites of periosteal proliferation.[248,249]

Radiographically, the bony enlargements are characterized by periosteal proliferative, new bone formation of the diaphysis and metaphysis of affected bones.[248] The periosteal reaction often exhibits an irregular, palisade pattern of osteophyte formation.[247,248] The bony reaction may extend to the chondrosynovial junctions; the articular surfaces are usually not affected.[249] In a few cases, nuclear scintigraphy revealed focal areas of intense uptake of radiopharmaceutical at the sites of bony enlargement.[247,261]

38.17.16.4 Treatment and Prognosis

The prognosis for horses with HO is guarded and depends on the underlying disorder. In one study, 71% of horses with HO were euthanized.[248] Gradually progressive limb swelling and pain is the typical clinical course in most affected horses for which an underlying cause is either not identified or effectively managed. Thus, management of HO should be directed at identification and treatment of the underlying primary disorder, if possible. Common methods to aid in identification of the underlying disease include hematology, serum chemistries, fibrinogen, thoracic radiography, thoracic and abdominal ultrasonography, abdominocentesis, thoracocentesis, gastroscopy, and rectal examination. Successful management of the primary underlying disorder has resulted in partial or complete regression of the skeletal disease in a limited number of equine cases.[247,248,262] Regression of HO is characterized by a decrease in limb swelling and lameness, and a return to athletic performance is possible if bony lesions are not advanced.[247] In a few idiopathic cases in which an underlying disorder was not identified, bony reactions decreased with rest and phenylbutazone therapy.[248]

38.17.17 FESCUE FOOT

ERIC W. DAVIS

38.17.17.1

Definition and Etiology

Fescue foot is a toxicosis of cattle grazing pastures that contain tall fescue grass (*Festuca arundinaceae* Schreb). The condition is characterized by lameness, particularly of the rear limbs, progressing to dry gangrene of the feet and lower legs. The end of the tail and the ear tips occasionally may be affected.

Fescue pastures also cause three other syndromes. “Summer slump” is characterized by reduced gain and milk production, dull hair coat, and poor heat tolerance. Abdominal fat necrosis also has been reported in cattle on fescue pasture.[265] Equine reproductive problems, including prolonged gestation and agalactia, as a result of grazing tall fescue late in gestations have also been described.[266]

The earliest description of “fescue foot” appeared in 1949 in Australia. It has been reported in Europe, New Zealand, and the United States, particularly in the Southeast. The etiologic agents in fescue have not been definitely established, although several toxins have been identified.[265,267–271] Chemicals produced by the grass itself (e.g., loline, perloline, several organic acids) could be toxic agents contributing to fescue foot and other syndromes, but mycotoxins produced by endophytic fungi, which infect tall fescue, are generally accepted as being the most important agents. The endophytic fungus of tall fescue, *Acremonium coenophialum* (formerly *Epichloe typhina*), produces ergovaline, ergonine, ergosine, and lysergamide.[265,267,271] All these toxins are capable of producing vasoconstriction similar to that caused by ingestion of the ergot fungus *Claviceps purpurea*. In fact, the symptoms of fescue foot are identical to gangrenous ergotism. Pastures not infected with *Acremonium* do not produce any of the symptoms of fescue toxicosis in animals.[271]

Environmental factors also play a role in the development of fescue foot. Although the disease can occur over a range of seasons, symptoms usually occur during colder months. Another factor is the level of pasture fertilization. High levels of nitrogen in soil, regardless of the form applied, increase pasture toxicity. Certain strains of fescue, particularly Kj-31, seem to be more toxic.[272] Finally, because the endophyte imparts a selective advantage on the infected plant by increasing growth rate and disease resistance, the number of toxic plants in a pasture increases. The infestation rate of the fescue endophyte is high; more than half the forage samples from states in which fescue foot occurs are infected with *A. coenophialum*.[273]

38.17.17.2

Clinical Signs and Differential Diagnosis

Clinical signs of fescue foot usually begin as hindlimb lameness. Affected cattle also are underweight and have a dull, “rough” hair coat. The feet and pasterns become cold to palpation, and the coronary bands become reddened and swollen. Hair may be rubbed from the pastern area with the fingers, and limb edema may be present. As the condition progresses, the classic signs of fescue foot appear, including a sharp line of demarcation at the level of the pastern or fetlock, distal to which the skin becomes dry and gangrenous and eventually sloughs. The tips of the ears and tail also may necrose. Affected animals lose condition initially and eventually are unable to stand or to walk. Susceptibility to the toxin in animals on a given pasture seems to vary considerably. Generally, morbidity is low, although 20% to 30% of the herd may be affected in some circumstances.[274]

The diagnosis is made on the basis of characteristic signs and gross lesions, as well as the presence of tall fescue in the pasture. As mentioned, gangrenous ergotism is identical clinically, except that it occurs in the

presence of the easily recognizable “ergot” fungus *C. purpurea,* which grows on rye grass. Similarly, chronic selenium toxicosis (“alkali disease”) mimics fescue foot, except that this disease does not occur on fescue pastures, and affected animals have elevated tissue selenium concentrations. Both ergot and selenium poisoning affect animals other than cattle, whereas fescue foot has been described only in the bovine.

Early in the course of the disease, mechanical foot injury, foot rot, or laminitis can resemble fescue foot, especially because only a few animals in a herd are affected. Close inspection of the foot, however, reveals lesions that are typical of these diseases. Necrosis as a result of freezing may be difficult to distinguish from fescue toxicosis because both occur at the same time of year.

38.17.17.3 Pathophysiology

Pastures that contain tall fescue infected with *A. coenophialum* produce toxins responsible for vasoconstriction. Peripheral vasoconstriction causes blood stasis, endothelial damage, and thrombosis in peripheral vessels. As a result of impaired circulation, tissues of the distal extremities become ischemic and gangrenous. By decreasing peripheral circulation, cold ambient temperatures exacerbate the condition.

38.17.17.4 Necropsy Findings

At necropsy the principal finding is a characteristic line of demarcation between normal and gangrenous tissues. Generalized loss of condition also is found because of the animal's inability to ambulate and eat. Vascular thrombosis and necrosis of the tissues of the lower limbs are found microscopically.

38.17.17.5 Treatment and Prognosis

When animals with fescue foot are recognized early in the disease course, they should be removed from pasture as soon as possible. Antibiotic treatment to prevent bacterial invasion of injured skin and hooves is valuable; recovery can occur in 2 weeks. Once the extremities have necrosed, however, treatment is unsuccessful and euthanasia is recommended.

38.17.17.6 Control

Unlike *C. purpurea,* which grows only on the seed head of grasses, the toxins causing fescue foot are contained in the leaves and stems. As a result, mowing contaminated pastures is not an effective control measure. Growing strains of tall fescue with low toxicity, mixed with legume forage plants, seems to be the best management technique for controlling fescue foot. In cold weather, feeding hay to cattle when the pasture contains tall fescue decreases the ingestion of toxins.

38.17.18 INTERDIGITAL NECROBACILLOSIS (FOOT ROT) IN CATTLE

JARED J. JANKE

38.17.18.1 Definition and Etiology

Interdigital necrobacillosis is an infectious disease of cattle that is a leading cause of lameness in feedlots and confinement dairies. The condition can affect cattle at any age, although most cases are in mature or weaned

animals. Sporadic cases are encountered with pastured beef and dairy animals. A variety of names have been used to describe this condition, including "foul-in-the-foot," foot rot, and interdigital phlegmon (phlegmona interdigitalis). The condition is characterized by inflammation and tissue necrosis of the soft tissues of the interdigital space.[275] Deep structures (e.g., tendons, ligaments, synovium, bone) may be involved in severe cases. *Fusobacterium necrophorum,* a gram-negative anaerobic rod, has classically been considered the etiologic agent associated with foot rot; however, multiple anaerobic organisms are likely to be synergistically involved. Typical foot rot lesions could be induced 5 days after inoculation of the interdigital cleft with *F. necrophorum* alone.[276] *Prevotella melaninogenicus* and more recently *Porphyromonas levii* (both previously classified in the genus *Bacteroides*) have been reported to play an important role.[275] The presence of *Dichelobacter nodosus*, the agent associated with contagious foot rot in small ruminants and interdigital dermatitis in cattle, may facilitate penetration of the skin with *F. necrophorum*. Wet, unsanitary conditions and rough environmental flooring are important factors in precipitating infection.

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38.17.18.2

Clinical Signs

Early in the course of foot rot, symmetric swelling and heat of the interdigital space are noted, progressing to the coronary band and possibly extending proximally to the level of the fetlock. The claws begin to spread as a result of severe cellulitis, leaving a widened interdigital space. Soft tissue swelling leads to necrosis and fissure formation within a few days,[277] starting at the dorsal interdigital space and spreading toward the heels. The edematous skin margins protrude and roll outward (Fig. 38-33). Exudation and pseudomembrane formation are seen, but significant purulent drainage is not evident. A characteristic foul odor accompanies the necrotic lesion. Acute and progressive lameness in one limb is typical, with the hindlimbs more frequently involved than the forelimbs.[278,279] Septic synovitis, osteomyelitis, or tendon involvement is more likely to result in non-weight-bearing lameness and limb carriage. Mild to moderate elevation of the body temperature (39.4° C to 40° C [103° F to 104° F]) may be recorded. The associated pain leads to reduced ambulation, feed intake, and milk production as well as weight gain. Affected animals may spend a significant amount of time lying down, predisposing them to injury from herdmates. Systemic effects of inflammation and infection can result in reduced fertility in breeding bulls. Differential diagnoses for lameness of the foot include trauma, interdigital dermatitis, verrucose dermatitis, and laminitis.[280]

A severe form of foot rot described more recently is peracute in onset and refractory to conventional treatments.[278,281] Severe interdigital swelling is noted in multiple limbs and most often in the hindlimbs. The condition is rapidly progressive, leading to recumbency and a rapid extension to deeper structures. Euthanasia may be warranted on animal welfare grounds.[282] Penicillin/sulfonamide-resistant *F. necrophorum* has been isolated from several cases.[281] Concurrent infection with bovine viral diarrhea (BVD) virus and the resultant immunosuppression have been suggested as an etiology.[283]

Fig. 38-33 Foot rot in a mature Angus cow. The interdigital skin is cracked and swollen. *Photo courtesy of Dr. Kevin Washburn, Texas A&M University, College of Veterinary Medicine & Biomedical Sciences, Large Animal Clinical Sciences.*

38.17.18.3 Clinical Pathology

Laboratory analysis of blood is not typically done, although a normal or an inflammatory leukogram may be encountered. Collection of samples for microbial culture is seldom done because of the ability to diagnose the condition through typical clinical findings. Lesional swabs or biopsy samples may be submitted for bacterial culture. A mixed population of environmental and fecal contaminants is likely; however, isolation of *F. necrophorum* and other anaerobes suggests true foot rot. Microscopic evaluation of biopsy samples may identify spirochetes, although this is not a consistent finding.

38.17.18.4 Pathogenesis

The mechanisms of interdigital necrobacillosis are complex and incompletely understood. Compromise of the skin barrier is critical for invasion of the offending pathogens. Chronic exposure of feet to wet and dirty conditions leads to softening and maceration of the skin. Exposure to sharp gravel and stones, excessive stubble, irregular concrete, and other forms of mechanical trauma can result in significant abrasions and damage to the interdigital skin, particularly in wet environments. The combination of these two factors can result in penetration of the offending pathogens and resultant infection. Initial microbial flora may reduce

tissue oxygen tension, allowing anaerobes an ideal environment to proliferate.[280,284] Once the organisms colonize the subcutaneous tissues, multiple mechanisms likely promote growth and evasion of the host defense systems.

The two subspecies of *F. necrophorum* currently recognized are biotypes A and B. Biotype A appears to be more virulent and is more frequently isolated.[285,286] Others have described differentiation of virulent strains by colony morphology,[287] and PCR differentiation of strains is available.[288] Although *F. necrophorum* is also a human pathogen, differences apparently exist between human and animal strains.[285] *F. necrophorum* is a normal inhabitant of the gastrointestinal tract of ruminants, although isolation from feces is generally rare.[285,289] Oral administration of some antimicrobials has been shown to increase fecal shedding of *F. necrophorum*.[290] The increased number of organisms in exudate from necrotic lesions may provide an important source of transmission to other animals. Major virulence factors associated with this organism are a high—molecular-weight leukotoxin and lipopolysaccharide (LPS).[291,292] The leukotoxin is cytotoxic to ruminant neutrophils and, when combined with LPS, may protect the organism from phagocytosis.[285]

Recent findings suggest that *P. levii* did not stimulate a significant chemotactic response in bovine macrophages in vitro, and suppression of phagocytosis occurred when the organism was present in low numbers.[275] These properties of *P. levii* may facilitate a local tissue environment that allows other anaerobic organisms, including *F. necrophorum,* to colonize and evade host defense mechanisms.

38.17.18.5 Epidemiology

Interdigital necrobacillosis has been recognized worldwide for centuries.[293] Wet and humid climates predispose to disease, and foot rot has been associated with rainy seasons.[284,294] The risk of disease is higher in management systems that expose animals to traumatizing ground underfoot, such as concrete confinement 1235
with water and excrement accumulation, irrigated pastures, muddy lots, high stocking densities, and stony 1236
walkways. As noted, cattle of any age are susceptible, but mature animals account for most cases. *Bos indicus* breeds appear to have a lower incidence of foot rot than *Bos taurus*, and Jersey cattle may be overrepresented in the dairy breeds.[294]

38.17.18.6 Necropsy Findings

Postmortem examination is rarely performed. Characterization of the lesions reveals subcutaneous and soft tissue necrosis, with suppurative inflammation of the foot. In severe cases, evidence of osteomyelitis, tenosynovitis, and septic arthritis may be identified.

38.17.18.7 Treatment and Prevention

Most animals are responsive to parenteral antimicrobial therapy. Local treatment (e.g., topical preparations, wound care, bandaging) is probably not necessary for minor cases identified early, although local therapy may reduce the number of infectious organisms spread to the environment.[284] The organisms are typically susceptible to a variety of antimicrobials.[278] Procaine G penicillin (22,000 to 44,000 IU/kg intramuscularly [IM] once or twice daily) has been used successfully when infection is detected early.[284] These dosages of penicillin are considered extralabel, and the clinician must take appropriate steps to ensure adequate meat-

and milk-withdrawal periods. Currently, a number of drugs have been approved for the treatment of foot rot in the United States.[278,282] Amoxicillin (6.6 to 11 mg/kg IM or subcutaneously [SC] for 5 days), oxytetracyline (10 mg/kg IM or SC), sulfadimethoxine (55 mg/kg PO or IV loading, then 27.5 mg/kg PO or IV daily for 5 days), erythromycin (2.2 to 4.4 mg/kg IM daily for 3 to 5 days), ceftiofur (1.1 to 2.2 mg/kg SC daily for 3 to 5 days), tylosin (18 mg/kg IM daily for up to 5 days), sulfamethazine (30 g/100 kg PO, repeated in 72 hours), and florfenicol (40 mg/kg SC once).[278,280,282,284]

Early recognition and treatment can produce clinical improvement in 2 to 4 days.[278] The antimicrobial of choice can be tailored to suit the needs of the farm in terms of withdrawal times, number of treatments, route of administration, and familiarity with the product. Investigators found that 5 mg/kg of extralabel tilmicosin SC at the onset of lameness resulted in a 74% cure rate, significantly higher than with placebo.[295] Antiinflammatory therapy, including flunixin meglumine or aspirin, may reduce fever and provide analgesia, resulting in improved appetite and ambulation.[282]

When topical therapy is warranted, cleaning the wound and curettage of the necrotic tissue are beneficial. A variety of topical antimicrobial or astringent preparations can be placed under a foot bandage. The main objectives of bandaging are to keep the wound clean and prevent further contamination from fecal organisms for several days. Moving treated animals to clean, dry areas is recommended.[280] Dressing the foot to prevent further spreading of the digits helps to protect the interdigital space. Foot bandaging may also reduce the amount of exudate from infected feet, which could infect herdmates.[284]

Spontaneous recovery is possible, although the risk of complications is increased, and recovery may take several weeks.[280] Animals with significant deep structure involvement may require prolonged therapy and repeated wound management. Animals with evidence of septic arthritis of the distal joints or other synovial structures may require amputation of the digit to allow drainage. Claw amputation has been described.[282,296]

Metaphylaxis, or the mass treatment of animals, may be warranted in some circumstances. Methods to mass-treat animals involve topical treatment in the form of footbaths or the addition of feed-grade antimicrobials and supplements to diets. It is prudent to inform owners that no feed additives are currently approved for the prevention or treatment of foot rot.[297] Extralabel use of feed additives, as governed by the Animal Medicinal Drug Use Clarification Act, is strictly prohibited.[278,297] The only antimicrobials approved for nonenteric disease as food additives are chlortetracycline and oxytetracycline.[297] Ethylenediamine dihydriodide (EDDI) has been used to reduce the severity and incidence of foot rot,[298] although high doses are toxic in cattle. EDDI use for this purpose is prohibited, based on the present regulation of feed additives.[278,297]

Footbaths are an appealing alternative for many producers, but proper use is important. Contact time and efficacious ingredients are sometimes difficult to ensure. Footbath additives often are rapidly contaminated with organic material, eventually leading to inactivation.[297] Antibacterial agents and astringents have been traditionally used, including 3% formalin, 2% copper sulfate, oxytetracycline, and lincomycin-spectinomycin formulations. Dry footbaths have also been reported and include 10% copper sulfate and slaked lime.[280] Practitioners must check state and local laws, which may prevent the use of some substances that could cause environmental contamination and might be unsafe for handlers.

Vaccination against *F. necrophorum* has been available for some time, but firm evidence of its efficacy in peer-reviewed publications is limited.[278] One study evaluating the incidence and severity of hepatic

abscesses and foot rot suggested a positive response to vaccination of feedlot cattle compared with controls, although the significance was evident only in the free-choice forage program. The same positive result was not evident when the analysis included all cattle, particularly the limit-fed grain program. The benefit of vaccination may not be able to overcome the challenge of diets that promote rumenitis.[299]

38.17.19 INFECTIOUS FOOT ROT IN SHEEP AND GOATS

JARED J. JANKE

38.17.19.1 Definition and Etiology

Infectious foot rot is a highly contagious foot disease of sheep and goats and is the leading cause of infectious lameness in these species.[300,301] The essential pathogen is the anaerobic bacterium *Dichelobacter nodosus*.[301–310] Synergistic activity with other microbes, primarily *Fusobacterium necrophorum,* plays an important role in the pathogenesis.[300,303,304] Equally important are the roles that environmental moisture and climate contribute to the transmission from animal to animal.[300,303–305,309] The infection has been reported in a variety of species, including cattle, horses, pigs, deer, and mouflon, but is generally considered a sheep and goat—specific disease.[307]

38.17.19.2 Epidemiology

Foot rot accounts for significant economic losses in sheep-producing countries[302,304,306,307] and has often resulted in government control programs.[301,305] Reduced body and fleece weight and increased costs of management, treatment, and culling make control of this disease important. Infectious foot rot is found worldwide wherever sheep and goats are reared, although it is primarily a problem in warm and humid climates.[300,303–305,309] Sheep raised on improved pastures in arid regions may also develop the disease.[304] Prolonged periods of moisture are required to facilitate transmission; short periods of heavy rainfall do not lead to significant increases in clinical disease.[300,303,304] Consistent temperatures greater than 10° C (50° F) are considered favorable for transmission.[300] Incidence rates are likely to correspond with the seasons that favor these conditions and may vary between geographic regions. Using pastures with ground cover that promotes trauma to the foot is likely to increase the risk of disease. The natural herding behavior of sheep and goats is likely to propagate the spread of the organism within a flock. Traditionally, routine hoof trimming was thought to reduce the incidence by improving general foot health; however, others have not made this association and have actually proposed trimming as a risk factor.[300,301,304,309]

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Sheep are the primary species of concern, although other ruminants can be infected. An association with increased severity in lambs from aged ewes has been suggested.[304] The merino breed appears to be the most susceptible, whereas British breeds demonstrate less severity.[303,304] Clinical disease is more often diagnosed in adults, although lambs may also be affected. Age and breed have been identified as risk factors, with an increase in incidence with age. Breed genetics and heritability may play important roles in resistance to disease, and reducing matings from chronically infected sheep may be an important step in propagating less susceptible breeding lines.[301,304] Introduction of the organism to a naive flock is almost exclusively by the addition of asymptomatic, chronic carrier animals, which may harbor the organism on their feet for years.[303,304] Animals exposed to pastures or housing facilities immediately contaminated by infected feet are at

risk of contracting the organism. *D. nodosus* is an obligate parasite of hooves and survives only a short time in the environment, but it may remain viable for up to 2 weeks in favorable conditions.[303,304]

38.17.19.3 Pathogenesis and Clinical Signs

The interdigital skin is typically an adequate barrier to infection. In prolonged wet conditions, however, the skin becomes macerated and weakened. Initially, *F. necrophorum* invades the skin and superficial soft tissues, resulting in *ovine interdigital dermatitis* (OID). This organism may produce a local tissue environment that promotes invasion of *D. nodosus*. These two organisms work synergistically to allow *F. necrophorum* to invade into deeper tissues and allow bacterial proteases produced by *D. nodosus* eventually to cause horn separation. Both organisms are essential for true foot rot to occur.[300] The lesion associated with foot rot is characterized as exudative inflammation and necrosis of the epidermal tissues of the foot.[307] A characteristic foul odor is almost always present.[303,304] Both claws of multiple limbs are typically involved. The interdigital skin becomes moist and swollen, and the soft horn is pale, pitted, and may be separated from the skin.[303]

Disease associated with *D. nodosus* infection is highly dependent on the virulence of the organism, resistance of the animal, and environmental conditions. All these factors are extremely variable; relatively low virulent strains in wet conditions may contribute to more severe disease than a highly virulent strain in dry weather. Virulence is associated with the keratinolytic ability of a strain and occurrence of type IV fimbriae.[300,302,304–307] The fimbrial subunit gene, fimA, appears to be essential for virulence.[304] Heat-stable protease production is characteristic of virulent strains.

Infectious foot rot is categorized into two clinical syndromes, benign or virulent, based on clinical severity and the ability to transmit through the flock. Some have included a third, intermediate syndrome for cases that clinically are more involved than the benign form but are not associated with the appreciable production losses that occur with the virulent form.[300] Foot rot accounted for a 10% decrease in body weight and wool production in one report.[307] It may be difficult to define clearly each case early in the disease process; what appears to be benign may be the early onset of the more virulent form. Benign foot rot may progress to separation of the soft horn from the underlying hard horn; however, it does not progress beyond this point. Virulent foot rot is characterized by severe interdigital lesions with separation of the soft and hard horn from the sensitive laminae. The separation begins at the axial surfaces of the heels and progresses in a dorsolateral direction.[303,304] Underrunning of the sole occurs, and in the most severe cases, the entire hoof may be sloughed. When confronting acute, multiple-limb lameness in several animals in a flock, a practitioner should strongly consider virulent foot rot.

The spread from animal to animal is generally rapid, and multiple stages of the infection are present within the flock. Inspection of the flock is indicated to categorize the severity of infection. In some flocks, only a small portion needs to be examined to determine the classification of disease, whereas evaluation of the majority of the flock is required in other cases. If uncertainty exists, 2 weeks is usually adequate to allow lesions to progress to a stage that will accurately allow classification of the clinical syndrome.[300] Affected animals may graze on their knees to relieve the foot pain or may remain recumbent in severe cases. Systemic signs of infection may include fever, anorexia, and weight loss.[303] Complications of the foot wounds include blowfly strike and secondary bacterial infection.[303,304] Although susceptible, the clinical course in goats is

often less severe. Interdigital dermatitis is a more prominent clinical finding than separation of the horn in this species.[303]

Differential diagnoses for foot rot include traumatic injury, laminitis, foot abscess, OID, and *contagious ovine digital dermatitis* (CODD). The presence of interdigital dermatitis increases the risk of the development of foot rot, and the prevalence may be high in the early stages of foot rot infection. It may be impossible to distinguish clinically between interdigital dermatitis and benign foot rot.[300]

Identified in the United Kingdom in the mid-1990s, CODD was initially thought to be a severe form of virulent foot rot. Clinically, the disease shows similarity to infectious foot rot, although initial involvement of the interdigital space is usually absent with CODD. Ulcerative lesions involving haired skin adjacent to the coronet are more common. This condition responds poorly to traditional foot rot treatment strategies. The complete pathogenesis of CODD is unclear, but one report isolated *D. nodosus* in 74% and a spirochete in 70% of affected feet. The spirochete was from the genus *Treponema,* which has been associated with similar lesions in cattle.[310]

38.17.19.4 Clinical Pathology, Diagnostic Tests, and Necropsy Findings

Samples collected by swabs or lesion material can be submitted for anaerobic microbial culture. The mixed bacterial population present and the fastidious growth of *D. nodosus* make isolation difficult and time-consuming.[302,307] Collection of samples in anaerobic transport containers and rapid submission to the laboratory are required. One report found that *D. nodosus* could not be isolated from field samples if they remained longer than 3 hours in transport.[302] Routine growth media found in most laboratories is usually not sufficient to grow this organism, and selective media and techniques are helpful in isolating this microbe.[302] Microscopic examination of *D. nodosus* organisms by Gram stain reveals large, barbell-shaped, gram-negative rods.[303,307] Some investigators have reported colony morphology and correlation with virulence, but others have been unable to make this correlation.[302]

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Biochemical testing for elastase activity and thermal stability of bacterial proteases has been used to differentiate benign from virulent strains. Thermostability of bacterial proteases can be measured by the gelatin gel test,[304,305,307] although false-positive results have been reported.[305] Advanced molecular techniques, including PCR and DNA sequencing, have recently become available for detecting gene sequences that encode for virulence, particularly fimA.[302,305,306] These advanced techniques have expanded the classification and number of strains and serotypes identified[302,305,306] and allow a rapid and sensitive diagnostic tool for use in control programs.[304] Serum antibody detection using an ELISA is available, but its specificity may be lacking.[304] Serology may be helpful in determining flock involvement. Infectious foot rot is usually diagnosed on clinical findings, and postmortem examination is not typically necessary.

38.17.19.5 Treatment and Prevention

Once *D. nodosus* infection is identified in a flock, treatment to control and potentially eradicate the organism should be initiated. Eradication may not be possible in all flocks, and the severity of disease, management practices, strain virulence, and environmental factors undoubtedly play a critical role. Separation of animals confirmed to have lesions is likely to reduce the transmission to uninfected flockmates; however, this may not be possible under some management strategies. When possible, planning pasture rotation to allow 2-week

dormancy periods enables producers to have infection-free zones. Improving pastures to prevent areas of standing water, excrement, and mud will theoretically reduce the potential for transmission. Routine flock foot trimming has been a mainstay in the prevention of foot rot, although supportive clinical data are lacking.[300,301] Regions having consistent problems with foot rot have discontinued this practice because of the lack of evidence and the increase in time and labor.[301] However, judicious foot trimming for the treatment of foot rot is probably beneficial on an individual basis and when topical treatments are employed.[301,303,304] Meticulous paring of the hoof may be necessary if the disease has produced overgrown and misshapen feet that promote hiding places for *D. nodosus*. Disinfection of knives and shears between each animal is important to reduce iatrogenic transmission. Treatment is typically more successful during the dry periods of the year, when transmission is reduced.

Medical treatment methods for foot rot include topical therapy, including footbaths, topical medications, and parenteral antimicrobials. Although bandaging individual feet may increase the contact time of medications and reduce the spread of infectious material, this is not practical and does not allow the foot to dry. Topical 5% oxytetracycline tincture has been used successfully.[304] Chemicals used in footbath solutions include 5% copper sulfate, 3% to 5% formalin, and 10% zinc sulfate.[300,303,304] When used properly, these agents are usually highly effective, but caution must be used with each chemical to prevent adverse effects. All these agents are potentially toxic to varying degrees if ingested, and copper sulfate will stain the fleece. Comparison of formalin and zinc sulfate in footbath preparations yields similar results.[304] Formalin is more resistant to contamination by organic material, but higher concentration and frequent application are extremely irritating to the skin. Additionally, considerable human health concerns and government regulations may prevent the use of formalin in some flocks. Efficacy and improved safety make zinc sulfate an ideal agent for use in footbaths. Improved chemical penetration of the hoof can be achieved when the surfactant sodium lauryl sulfate is combined with the footbath solution, reducing the need for foot trimming before treatment. Use of footbaths requires facilities and construction (6 to 12 m [20 to 40 ft] long) that ensure all feet on each animal are treated. The ideal contact time has not been established in clinical studies, but brief walk-through or soaking for up to 1 hour has been shown to be successful.[300] The frequency of treatment is also not clearly defined and may be dictated by the contact time. Because of its irritating properties, formalin should not be used more than once a week.[304] Although the response is likely multifactorial, cure rates of 50% to 80% have been reported with foot bathing. Separate footbaths for infected and noninfected animals reduce the risk of inadvertent transmission. Washing the feet by walking animals through a plain-water bath and allowing the feet to dry 2 hours before and at least 1 hour after treatment is ideal.[300] Once treated, the groups should be immediately moved to clean, dry pastures or lots that have not held livestock for at least 2 weeks.[300,303,304]

Currently, no antimicrobial drugs in the United States are labeled for use against infectious foot rot in sheep, so use is extralabel. One-time treatment without foot trimming can produce similar results to foot bathing. Parenteral antimicrobials have produced recovery rates of 85% after one dose when sheep were kept on dry floors for 24 hours after treatment.[300] Although *D. nodosus* has been reported to be sensitive to many antimicrobials in vitro, this gives no indication of sensitivity when used clinically.[304] Medications used successfully have included procaine penicillin G (20,000 to 30,000 IU/kg IM twice daily),[303] long-acting oxytetracycline (20 mg/kg SC once, or repeated in 72 hours),[303,304] erythromycin (10 mg/kg once, or 3 to 5 mg/kg IM twice daily),[303,304] florfenicol (20 mg/kg IM, repeated in 48 hours),[303] and lincomycin (5 mg/kg SC once) in combination with spectinomycin (10 mg/kg SC once).[304] Maintaining dry footing for 24 hours,

yielding meat- and milk-withdrawal times, and the potential of reinfection are important considerations when using parenteral antimicrobials.[300]

Vaccination against *D. nodosus* is available, and its use in the treatment and control of foot rot has been reported.[300,301,303,304,308] A reduction in disease severity and quicker response to treatment may be evident when this is used as a treatment modality. Several strategies have been used for classifying *D. nodosus* strains, based on fimbrial types, and at least 10 serogroups with 19 serotypes have been identified.[300,302–304,306,307] Fimbrial gene variation undoubtedly plays an important role in vaccine efficacy.[304] The current commercial vaccine available contains 10 serotypes, and antigenic competition is likely to impede additional serotypes.[300,304] Identifying the most prominent strain or fimbrial type in a geographic region or flock may facilitate vaccine selection and development. Eight strains of *D. nodosus* have been reported to infect one foot.[304] Response to vaccination appears to be strain specific, with poor cross-protection between strains. Successful resolution of clinical signs by the use of an autogenous vaccine, without other treatments, has been reported.[308] The use of adjuvants in killed vaccines are required to produce an adequate antibody response, and the addition of adjuvants, particularly oil based, has led to a high incidence of injection site reactions.[300,303,304] The response to vaccination is likely short-lived, about 8 to 12 weeks,[300] and requires multiple doses. Vaccination of animals during the dry period, several weeks before the optimal transmission period, is likely beneficial in a control program.

Control and eradication can potentially be achieved in regions where the climate allows a break in the transmission period; however, the investment in labor and the cost of medical therapy may be high. A combination of topical treatment, parenteral antimicrobials, and vaccination is likely to be employed. Careful observation for early signs of infection and quarantine of any new animals are critical to controlling or preventing a flock outbreak. Using a weekly zinc sulfate footbath for 2 to 4 weeks, along with vaccination and culling of severe and unresponsive cases, has been suggested.[303] Based on evidence of resistance heritability, careful breeding programs should be explored.[301,304] Complete eradication from a farm can be achieved if the entire flock is removed, the facilities are left dormant for at least 2 weeks, and the flock is repopulated with noninfected animals.[300]

38.17.20 OTHER INFECTIOUS CONDITIONS OF THE FOOT

ROBIN M. DABAREINER

Infections involving the foot of horses and cattle are common and almost always caused by contamination from the environment gaining access to the soft tissue or bony structures of the foot within the hoof capsule. Typically the animal has an acute, progressive lameness such that the animal is almost non—weight bearing on the affected limb or will bear weight on the toe region of the foot but resist putting the heel on the ground. Other clinical signs include increased digital pulse pressure, heat and sensitivity to hoof tester pressure over the affected area. Regional nerve blocks can be used to localize the lameness to the foot but frequently are not necessary. Because the foot is encased in a shell of horny tissue, exudate from an infectious process often accumulates between the soft tissue and horn. The exudate then spreads or dissects along that plane until it reaches a soft tissue surface such as the coronary band, especially near the bulbs of the heels, where rupture and drainage can occur.

38.17.21 PROBLEMS ASSOCIATED WITH HORSESHOE NAILS (“NAIL PRICK”)

38.17.21.1 History and Clinical Signs

Nail prick (“quicking”) refers to penetration of the sensitive hoof structures, usually the sensitive laminae, by a driven horseshoe nail. The horse will usually react as the farrier drives or clinches the nail by jerking the foot from the farrier. In some cases, blood may appear on the nail or leak from the nail hole. It is important to realize that nail pricks occur for many reasons and are not always caused by a misdirected nail. Poorly made shoes, nails that are too large, poorly placed nail holes, and faulty nails can also result in a nail prick. Horses with poor hoof quality, thin hoof walls, or flaring hoof walls can be difficult to nail and thus are at greatest risk. Fractious horses and young horses not previously shod may lean on the farrier or repeatedly pull the foot from the farrier, making nail driving difficult. Damage from an improperly driven nail can vary from minimal to serious infection.

38.17.21.2 Diagnosis

Diagnosis of a misdirected nail warrants great diplomacy from the veterinarian because many owners become unjustifiably upset with the farrier. Some horses will repeatedly stomp the affected foot or paw the ground immediately after shoeing. Others may point the affected limb after shoeing. Lameness may not be apparent immediately after shoeing and may occur days later when the nail hole becomes infected and the trapped pus begins to exert pressure. The horse usually becomes acutely lame and worsens over time unless treated. Some infected nail holes will travel up the lamellae (white line) and create an abscess or soft spot at the hairline of the coronary band. The abscess will be directly aligned with the hoof wall tubules, leading to the infected nail hole, which is an important diagnostic aid. Hoof tester examination, paying particular attention to pressure over the driven nails, is an essential diagnostic tool to locate the offending nail. Using a hammer to strike the outside hoof wall may also elicit a painful response over the nail. Increased digital pulse and heat may be present.

38.17.21.3 Treatment

Pricks from nails can be potentially serious and require immediate treatment. If the nail prick is discovered by the farrier at the time of shoeing, the nail is removed. The nail should be examined for moisture or blood. The nail hole can be irrigated with DMSO, povidone-iodine (Betadine) solution, or hydrogen peroxide. The nail hole is packed with iodine-soaked cotton and the nail hole left open. Often the nail is redirected, and no further treatment is needed. If the horse's immunization status is not current, a tetanus vaccine is given.

If the offending nail cannot be localized or the nail hole is infected, the shoe is removed. Hoof testers are then used to localize the painful nail hole. Frequently the pressure from the hoof testers will cause black, malodorous liquid “pus” to exit from the hole. The basis of treatment is to establish drainage. The infected nail hole often requires enlargement with a loop hoof knife or curette. Ideally a cone-shaped hole is made, with the larger opening at the bottom of the hoof. The hole is irrigated or the entire foot soaked in an Epsom salt—Betadine footbath for 20 to 30 minutes twice daily until the infection is gone. It is important to protect the foot from the environment (e.g., mud, dirt) by keeping the foot bandaged between foot soaks. Additional medications are usually not necessary unless involvement is extensive. Antiinflammatory medications may be beneficial to decrease pain. Once the infection has cleared, the shoe is replaced. The affected nail hole can be packed with iodine-soaked cotton and the horse reshod with a plastic pad covering the sole. Alternately, a

hole can be drilled into the shoe over the affected nail hole and the shoe replaced, leaving access to the infected area for daily irrigation and povidone-iodine packing.

38.17.21.4 Prognosis

Prognosis is usually good provided that minimal damage occurs to vital structures of the foot. Establishing drainage for sepsis is important to avoid potential complications, such as third phalanx osteomyelitis or coffin joint sepsis.

38.17.22 SUBSOLAR ABSCESS

Subsolar abscess is one of the most common causes of lameness in the horse and cow, but it is relatively rare in sheep and goats. In one study in cattle, 88% of cases of lameness were caused by problems in the hoof.[311] Most often, lameness is caused by a hole or crack in the horny sole, which then becomes packed with dirt, and eventually contamination extends to and is trapped within the sensitive soft tissue beneath the sole. Animals that are housed in filthy or muddy conditions and that have inadequate hoof care or overgrown feet are more prone to this problem. Horses taken from a very dry to a very wet environment, and vice versa, also tend to have a higher incidence of sole abscesses, apparently because of the sudden change in the moisture content of the hoof and the resultant cracking of the sole. Cattle with “corkscrew claw” (a hereditary condition) or other growth deformity in the claw are more prone to sole abscess. Puncture wounds or any form of trauma that introduces contamination to the soft tissue of the sole also may result in abscessation.

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38.17.22.1 History and Clinical Signs

Subsolar abscess is a common cause of acute lameness seen in all horses. There is no signalment or breed disposition. “Gravel” is a lay term describing the assumed etiology in which a piece of gravel migrates proximally from the white line to coronary band, leaving an infected tract. Subsolar abscesses may originate from a penetrating wound in the white line, a nail hole, or a deep subsolar bruise. Lameness is usually acute and severe (grade 3 to 4 of 5) and may worsen over time until drainage is established. The horse will often point and may not bear full weight on the affected limb. Distal limb swelling often accompanies a subsolar abscess that has not had drainage established. Systemic signs of infection (fever, lethargy) usually are not associated with subsolar abscesses unless deeper structures are involved. The infected tract may migrate and open at the coronary band. Before breaking open, a soft, painful area can be located by digital palpation of the coronary band.

38.17.22.2 Diagnosis

Digital pulses are usually increased, and the hoof capsule may radiate heat. A focal painful area can usually (but not always) be located with careful hoof tester examination. Careful paring of the sole and frog may be helpful in locating the abscess, but the clinician must be careful not to damage good, healthy tissue looking for the infection site. Foot poultices and hot-water footbaths with Epsom salts will help eventually to localize the affected area. Gray or black malodorous liquid will leak from the infected tract (Fig. 38-34). Radiographs are useful to rule out other causes, such as third phalanx and navicular bone fracture. In some cases a gas or fluid pocket can be identified on radiographs.

38.17.22.3 Treatment

Treatment is aimed at establishing adequate drainage. If an opening in the tract is present at the solar surface, it should be enlarged just enough for good irrigation and drainage. This may or may not require sedation or peripheral anesthesia of the foot. If pink tissue or blood is encountered, debridement is discontinued. Large holes should be avoided to prevent solar corium protrusion, which can be a painful sequela to overzealous hoof paring. If drainage occurs at the level of the coronary band and solar surface, through-and-through lavage is beneficial. Debridement at the coronary band level should be minimal to prevent iatrogenic coffin joint contamination. Once drainage is established, the foot is protected from the environment and from recontamination with a foot bandage. Continued foot soaks in warm-water povidone-iodine and Epsom salt footbaths should be continued until sepsis and inflammation are eliminated. The shoe is replaced when the affected are is dry and cornified. Large areas may require a plastic pad under the shoe for solar protection. Antibiotics and NSAIDs are rarely needed, except in severe cases or if penetration of deeper structures has occurred. The patient's tetanus immunization should be checked and a booster injection administered if needed.

Fig. 38-34 Horse's hoof with a recently opened subsolar abscess demonstrating gray exudate.

38.17.22.4 Prognosis

Prognosis for simple subsolar abscess is excellent but worsens if complications develop in which deeper structures of the foot become involved.

38.17.23 DEEP PENETRATING INJURIES TO THE SOLE

38.17.23.1 History and Clinical Signs

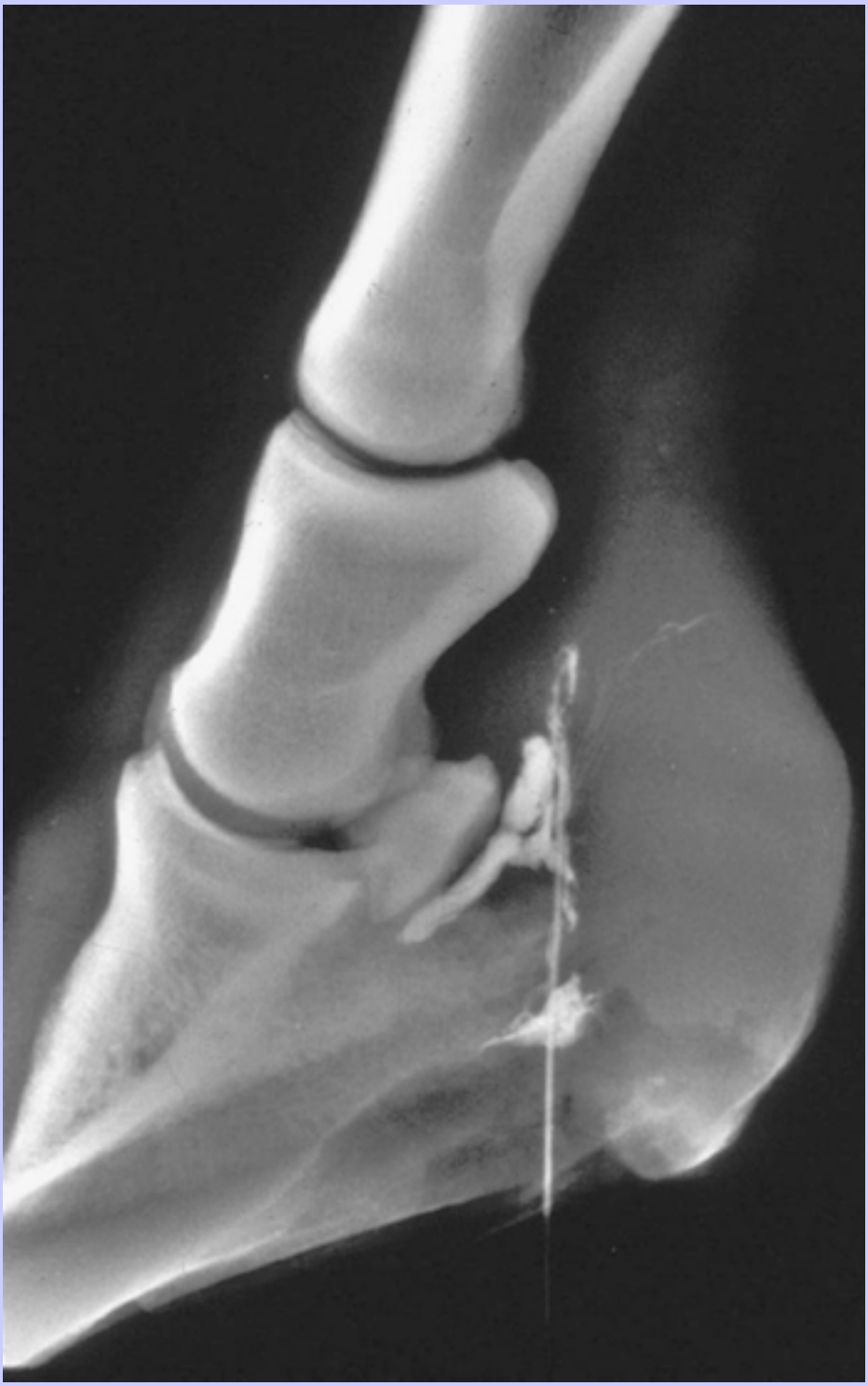
Most animals' environment is filled with sharp objects that can penetrate the sole, causing severe damage to structures deep within the hoof capsule. All puncture wounds should be considered potentially serious, but those involving the solar white line or caudal frog area require special attention because of potential navicular bursa, digital tendon sheath, deep digital flexor (DDF) tendon, or distal phalanx involvement.

The clinical signs of a penetrating wound to the sole vary with the anatomic structure involved and chronicity of the injury. The animal may show minimal lameness initially at the time of injury, but severe lameness once sepsis is established days later. Animals with penetrating wounds to the podotrochlear bursa or DDF tendon attachment to the third phalanx are in considerable pain and are reluctant to bear weight on the heel region.

38.17.23.2 Diagnosis

If owners find a foreign body in the bottom of the animal's foot, they usually should be instructed to leave the object in the foot unless there is danger of further penetration. A radiograph is taken immediately to determine depth of penetration. Digital pulses are increased, and the foot is usually warm to touch. Hoof testers are useful to determine the focal point of pain, but often the entire surface of the foot is reactive. Systemic sedation and peripheral anesthesia using an abaxial sesamoid nerve block may be needed to examine the penetrated foot thoroughly. Light paring of the sole and frog areas with a hoof knife may reveal a black spot indicating the penetration site. Often, however, the entry is not discovered because of the elastic nature of the hoof structures and collapsing of the penetration site. Regional intravenous anesthesia (Bier block) using a tourniquet is the method of choice for producing local anesthesia in cattle. Paring should be performed carefully so that the solar corium is not injured with the hoof knife. Because the corium represents the horn-producing epithelial covering of the foot, injuries to it heal the same way as skin injuries. If an entry wound is discovered, the foot is scrubbed and prepared for further diagnostic testing. A sterile, flexible probe can be gently inserted into the hole and a radiograph taken to determine the depth and direction of the hole. The clinician must be careful so that inadvertent force or horse movement does not cause the probe to penetrate previously unaffected structures. Alternately, a less invasive and preferred method is to catheterize 1240
or place a sterile teat cannula into the hole and inject sterile radiopaque material to determine which 1241
structures are involved (Fig. 38-35).

Fig. 38-35 Radiograph of a foot after injection of contrast dye to determine the path of the penetrating foreign body.



If sepsis of the podotrochlear bursa, distal interphalangeal joint, or digital tendon sheath is suspected, paracentesis and joint fluid cytology and culture and microbial sensitivity should be performed. Synovial fluid with an abnormal color, viscosity, elevated number of degenerative neutrophils, and high total protein concentration should suggest sepsis. If distal limb swelling is present, arthrocentesis should be delayed until the cellulitis subsides.

A series of radiographs should be taken to include a lateromedial, 60-degree dorsopalmar view of both the navicular bone and the third phalanx, and flexor (tangential) view of the navicular bone. Repeat examination 1 to 2 weeks after the original injury may be necessary because bony lysis takes time to develop and may not be apparent at the initial radiographic examination.

38.17.23.3 Treatment

Broad-spectrum systemic antibiotics, antiinflammatory medications, and tetanus prophylaxis are administered if penetration of deep hoof structures is suspected. Depending on the severity of the lameness, the animal may require an NSAID such as phenylbutazone (4 mg/kg twice daily in horses; 10 mg/kg once daily in cattle) to reduce pain and lameness in the initial stages. Antibiotic therapy should be continued for 2 weeks after resolution of clinical signs of infection in most cases. Preferably, antibiotics are initiated after a culture and microbial sample has been obtained. Establishment of drainage, copious lavage with sterile ionic fluid, and debridement of all necrotic tissue are indicated. Involvement of the podotrochlear bursa indicates use of navicular bursoscopy and aggressive medical therapy, consisting of daily lavaging of the bursa under general anesthesia and local treatment using antibiotics instilled within the bursa and regional limb perfusion. Surgical treatment such as the “street nail” procedure is reserved for animals not responding to aggressive medical therapy.

If the DDF tendon is involved (septic tendinitis), debridement and removal of frayed and infected tendon fibers may be performed in the standing, sedated horse using a tourniquet and peripheral anesthesia, or under general anesthesia, depending on horse temperament and owner financial constraints. After debridement, placing the horse in a 4- to 8-degree wedge shoe decreases weight-bearing forces on the DDF tendon and provides some pain relief. The wedge shoe angle is gradually decreased over several months as the DDF tendon begins to heal and strengthen. The bottom of the foot requires protection with a bandage or hospital plate until the surgical site granulates in and cornifies.

Deep penetrating wounds to the sole, especially the solar—white line junction, can result in infectious osteitis of the distal phalanx. The horse usually presents with a chronic, recurrent draining tract at the coronary band or solar surface and varying degrees of lameness. Infection of the distal phalanx often results from undetected soft tissue infection or dissecting subsolar abscesses. Septic pedal osteitis may also be a sequela to laminitis secondary to recurrent abscessation and ischemia at the toe region. As the bone infection progresses, blood supply to the area is compromised, and the area of avascular bone separates from the parent bone, forming a sequestrum. Localized third phalanx septic osteitis and sequestrum formation may not become radiographically evident for weeks after the initial penetration injury. Radiology often reveals a radiolucent area within the margins of the third phalanx, with or without sequestrum formation.

Debridement and curettage of all soft and necrotic bone can usually be performed in the standing, sedated animal if its temperament permits. The foot is desensitized with peripheral anesthesia, cleaned with a hoof knife and steel brush, then prepared for aseptic surgery using standard techniques. Hemostasis is achieved by wrapping a roll of Vetrap firmly around the fetlock joint to compress and occlude the palmar digital arteries.

Access to the infected bone is made by removing sequential layers of sole using either a motorized Dremel tool or a Galt trephine with a retractable pilot bit.[312] The infected bone is usually discolored and soft and should be curetted to healthy bone margins. The infected bone should be cultured and undergo microbial sensitivity testing. A postoperative radiograph should be taken to ensure complete debridement. After surgery the site is packed with sterile gauze sponges soaked in antiseptic or antimicrobial solutions, and then the foot is bandaged. Disposable diapers and duct tape are inexpensive materials for a waterproof foot bandage. The bandage is changed every 1 or 2 days for the initial few weeks. Application of a bar shoe and hospital plate provides solar protection and decreases the labor and cost of daily bandage changes (Fig. 38-36). The bolts and metal plate are removed so that the surgical site can be cleaned and treated, and then the hospital plate is bolted back in place.

After surgery the horse is confined to a small area until the hole granulates in and cornifies, usually 4 to 6 weeks. If granulation tissue becomes excessive at the surgical site, application of 2% tincture of iodine will hasten healing. If severe infection is present, the site can be packed lightly with antibiotic-impregnated beads for continued antibiotic release at the infected site. Regional limb perfusion with antibiotics is also beneficial in severe cases. 1241 1242

Fig. 38-36 Treatment plate for medicating an open wound in the bottom of a horse's foot.

In cattle, simple sole abscesses may heal quite satisfactorily without bandaging. In cows, use of a wooden block on the unaffected claw of the affected foot elevates the affected claw to a non—weight-bearing level and greatly reduces lameness. The block is attached with an epoxy such as Technovit and allowed to wear off over a period of weeks.

38.17.23.4 Prognosis

Prognosis depends on severity of injury, structures involved, and chronicity of the problem before initiating treatment. Horses with acute penetration wounds that receive immediate and aggressive treatment have a good chance of returning to athletic use. Penetration injuries that have an established infection involving the podotrochlear bursa, digital tendon sheath, or distal interphalangeal joint have a poor prognosis. In one study, only 12 of 38 horses with sepsis of the navicular bursa had a satisfactory outcome.[313] Chances of survival increased if treatment was started within a week of the penetration injury. Osteomyelitis of the navicular bone and DDF tendon rupture are common complications of a septic navicular bursa.

Prognosis for infectious osteitis of the distal phalanx is good if sepsis is not caused by laminitis. In one study, up to 24% of the distal phalanx was removed, and the horse returned to athletic soundness.[314]

38.17.24 THRUSH

38.17.24.1 Definition and Etiology

Thrush is a bacterial infection characterized by an accumulation of black, malodorous, necrotic material usually originating within the central or collateral sulci of the frogs of the hoof. This degenerative condition may spread to involve deeper structures of the foot, such as the digital cushion, hoof wall, and heel bulb region of the foot, causing inflammation and breakdown of these structures.[315] Many keratolytic organisms may be present, but *Fusobacterium necrophorum* is often isolated. Thrush is most often caused by poor environmental conditions; animals standing in soiled stalls, deep mud, swampy land, or wet pastures are at risk for developing thrush, especially if the feet are not cleaned daily. Another predisposing factor is poor hoof conformation. Saddlebreds, Tennessee Walkers, and other gaited horses have long feet with naturally deep frog sulci and are at risk of thrush.[316] Horses with sheared heels or acquired frog deformity are also predisposed. Horses shod with full pads may develop thrush secondary to moisture and dirt collection under the pad. Other, well-kept, clean horses can develop thrush for no apparent reason.

38.17.24.2 Clinical Signs and Diagnosis

Lameness may or may not be present, and the severity can vary. Diagnosis is based on the presence of black, malodorous discharge, most often within the frog sulci. The central frog sulcus is often malformed and very deep. A painful response may occur when the affected sulci are cleaned because the degenerative process may extend to sensitive structures of the foot. If structural damage has occurred, the heels may move independently of each other, causing pain on manipulation. Horses with mechanical instability of the heels may show caudal heel pain.

38.17.24.3 Treatment

The basis for treatment is removing the predisposing cause of the thrush. The horse should be moved to a clean, dry environment and have the feet cleaned daily. Any necrotic debris and undermined tissue are carefully debrided and cleaned using a hoof knife. Foot bandages may be necessary if the debridement is extensive. Systemic antibiotics may be necessary in severe cases that involve deep or more proximal tissues. Infection is usually managed by topical medication. Several caustic materials have been recommended, including a combination of phenol, tincture of iodine and 10% formalin, Kopertox solution, or methylene blue. Others have recommended soaking the foot in chlorine bleach (1 oz bleach per gallon water). If poor hoof conformation is the cause, proper farrier management should be pursued to correct existing problems. If heel instability is present, a bar shoe may be necessary to stabilize the caudal aspect of the foot. Exercise is important to strengthen the caudal aspect of the foot and will naturally clean the feet. The best treatment for thrush involves prevention by educating the client on proper hoof hygiene.

38.17.24.4 Prognosis

Prognosis is favorable if the cause of thrush can be identified and eliminated and if the condition is treated before extensive hoof damage has occurred.

38.17.25 WHITE LINE DISEASE (“SEEDY TOE”)

38.17.25.1 History and Clinical Signs

The white line, visible at the sole, is created by the junction of the insensitive laminae of the hoof wall and the horn of the sole. White line disease has historically described the separation of the hoof wall from its laminar attachments. A crack or opening occurs within the white line, allowing a bacterial or fungal infection to invade the stratum medium close to the laminae, causing cavities to develop between the laminae and outer hoof wall. In environmental conditions with too much moisture (continuous wet pastures) or in drought conditions producing excessively dry feet, animals are at risk of developing a crack or opening in the white line. Horses with poor-quality hoof walls that split or crack may develop white line disease. In addition, horses with chronic laminitis having a thickened or stretched white line in the toe region (“seedy toe”) are predisposed (Fig. 38-37). 1242 1243

Fig. 38-37 Stretched white line secondary to chronic laminitis.

The hoof wall separation is usually a chronic condition beginning weeks or months before presentation. Horses with white line disease often show little or no lameness and therefore are not perceived as an immediate concern by many owners. Hard ground may exacerbate any lameness seen.

38.17.25.2 Diagnosis

Visual examination of the white line, assisted by a probing instrument, will reveal a cavity with separation of outer hoof wall from the laminae. Radiographic evaluation will determine the full extent of hoof wall separation. Often the cavity is either dry or filled with necrotic debris, which may involve a bacterial or fungal infection. The cavity is usually not painful to probing.

38.17.25.3 Treatment

Treatment begins with removal of the separated outer hoof wall using a hoof nippers, hoof knife, and motorized tools. It is important to remove any unattached or loose hoof wall to reveal cracks or crevices that could harbor bacteria. The Dremel tool burr is useful to smooth any cracks in the insensitive laminae that are exposed after hoof wall removal. After thorough debridement, large defects usually exist in the hoof wall and require protection (Fig. 38-38). A heart-bar shoe redistributes weight-bearing forces to the frog and caudal region of the foot and away from damaged and weakened areas. The hoof wall defects prevent normal nailing procedures, and shoe clips can help secure the shoe to the hoof. After hoof wall removal, the exposed laminae may still have an “active” infectious component. With the heart-bar shoe in place, the owner is instructed to keep the horse in a clean, dry stall and topically treat the exposed laminae with iodine or methiolate daily for 10 days or until the exposed laminae are dry and “inactive.” At this point, the horse may be a candidate for prosthetic hoof wall repair using a product such as Equilox. The plastic acrylic is trimmed and shaped to the horse's natural hoof wall at the next shoeing. The owner should keep the hoof dry to avoid losing the acrylic patch. The horse may return to normal activity once the prosthetic patch is in place.

Fig. 38-38 Hoof with white line disease after the undermined hoof wall has been removed.

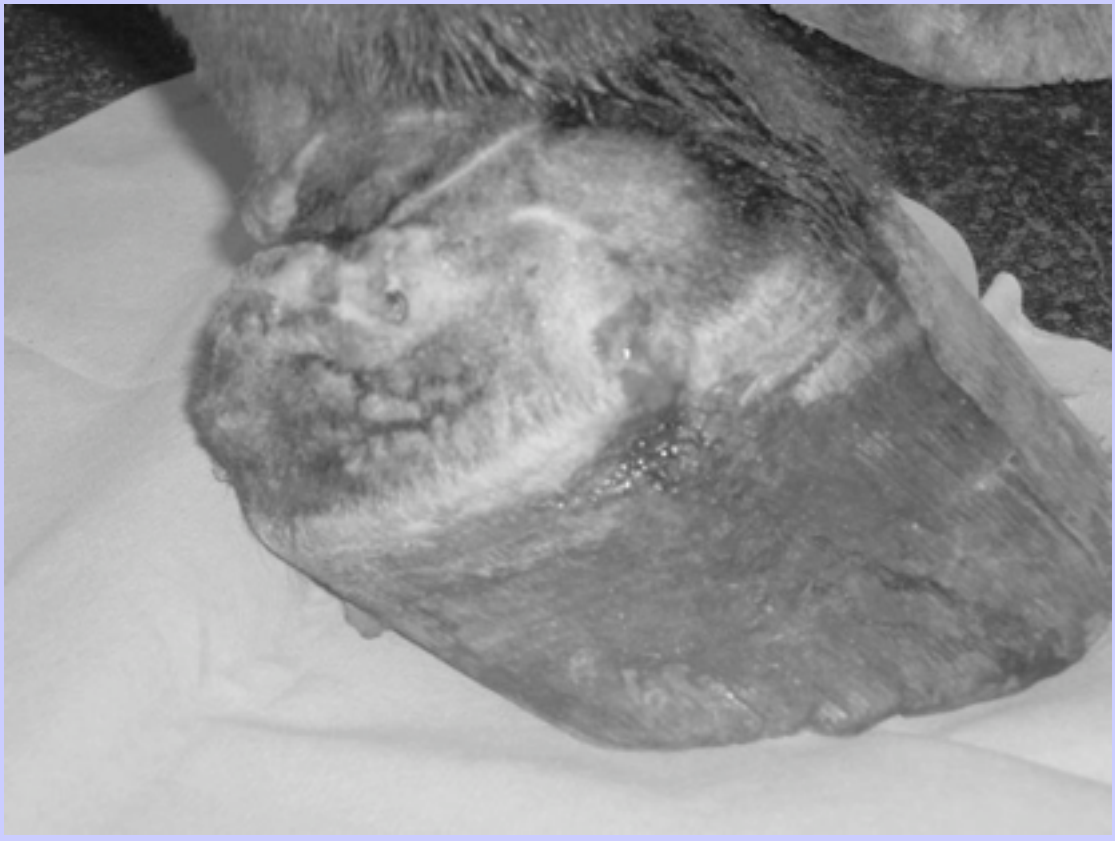
38.17.25.4 Prognosis

Prognosis depends on response to treatment and cause of the original white line problem. Horses with poor hoof quality or seedy toe will often have disease recurrence. If the horse responds to original treatment and environmental conditions improve, prognosis is good.

38.17.26 QUITTOR

Quittor is a term used to describe chronic infection of the medial or lateral collateral cartilage of the distal phalanx in the horse. This condition is characterized by local inflammation and necrosis of the affected cartilage, with subsequent formation of draining tracts proximal to the coronary band. The infection is usually caused by a wound, and the horse often presents with moderate to severe lameness and a history of chronic or recurrent drainage. Obtaining a dorsopalmar radiographic view after injecting contrast dye into the draining tract helps to demonstrate the infected collateral cartilage (Fig. 38-39).

Fig. 38-39 Horse's hoof with an infected collateral cartilage.



Although this condition occasionally responds to medical therapy, the treatment of choice is surgical debridement with the horse under general anesthesia, the foot in full extension, and a tourniquet around the pastern. An elliptical section that includes the draining tract should be incised above the coronary band and

discarded. All underlying infected soft tissue and necrotic cartilage should be excised. If the case has not become chronic and only a small amount of cartilage needs to be removed, the wound may be packed and partially sutured. The pack can be removed in 24 to 48 hours and the wound flushed twice a day until it has healed. If the condition is chronic with extensive cartilage necrosis or multiple draining tracts, the infectious process usually extends below the level of the coronary band. In this case it is best to trephine a hole in the hoof wall at the lowest point of the infection. This procedure provides better drainage, facilitates debridement of the necrotic cartilage, and allows for complete closure of the surgical incision above the coronary band. The wound should be packed through the trephine hole and treated as an open wound until it heals. In cases with extensive cartilage necrosis, care should be taken to avoid accidental opening of the coffin joint. If debridement is complete, the prognosis for the return to soundness is fair to good.[317]

38.17.27 FISTULOUS WITHERS

SARAH M. REUSS

38.17.27.1 Definition

Fistulous withers is a chronic inflammatory condition of the supraspinous bursa and associated tissues in horses and mules. The supraspinous bursa is located dorsal to the dorsal spinous processes of the second through fifth thoracic vertebrae (T2 to T5). The normal bursa may extend laterally to the scapular cartilage and may be asymmetric. Normal bursal volumes range from 30 to 90 mL.[318]

38.17.27.2 Clinical Signs

Affected horses may show nonspecific signs, including lethargy, fever, and generalized muscle stiffness. These may progress to the more specific signs of pain, heat, and swelling of the withers and cervical area. Over days to weeks, these swellings mature and rupture at one or more locations, releasing serous or purulent drainage. The classically described discharge is yellowish brown and mucoid or serous with white, yellow, or red flakes (“rice bodies”).[319] Fistulous tracts may extend to the dorsal spinous processes of the vertebrae, as well as to the scapula, ribs, and occasionally the thoracic cavity. Lesions and drainage may wax and wane.[318]

38.17.27.3 Etiology and Pathophysiology

There are two forms of fistulous withers: idiopathic and traumatic. The more common *idiopathic* form results from the spread of inflammation and infection of the supraspinous bursa to surrounding structures, including the nuchal ligament. Organisms reported to be the primary cause of fistulous withers include *Brucella abortus, Actinomyces bovis,* and *Onchocerca cervicalis. B. abortus* has a predilection for synovial structures and is often associated with septic supraspinous bursitis. In 1937, *B. abortus* was isolated from 80% of fistulous withers cases; 92% of affected horses had contact with cattle, and 65% were from farms with *Brucella*-positive cattle.[319] Currently, the disease has some geographic variability. In New York, where the prevalence of *B. abortus* infection in cattle is low, *B. abortus* is rarely isolated from equine cases of fistulous withers. In 1988 the prevalence of *B. abortus* in horses presented to the New York State College of Veterinary Medicine had apparently decreased, with only 2 of 14 horses (14%) having positive titers.[320] In Texas, however, where seropositive cattle are still prevalent, 9 of 28 horses (37.5%) with fistulous withers were seropositive for *B. abortus,* and these horses were more likely to be pastured with seropositive cattle.[321]

Researchers have also experimentally produced fistulous withers by injecting *B. abortus* and *A. bovis* into the supraspinous bursa.[322] *O. cervicalis* has also been proposed as an etiology for fistulous withers, especially in Australia. This parasite migrates through the nuchal ligament causing inflammation, which may extend to the supraspinous bursa. Fibrous and calcified tracts develop around dead and viable parasites, causing necrosis and degeneration of the nuchal ligament.[323]

The traumatic form of fistulous withers is preceded by an open wound or blunt trauma to the withers and then secondary infection. Infection may result from external contamination or from hematogenous spread to devitalized tissue. Secondary contamination of open wounds with *Streptococcus equi* subsp. *zooepidemicus*[320] or environmental microorganisms is reported.

38.17.27.4 Diagnosis

A careful history must be obtained, including duration and severity of clinical signs and response to previous treatment. Physical examination with careful palpation over the withers may reveal pain, swelling, or draining tracts. Complete blood count may show leukocytosis caused by neutrophilia, as well as hyperfibrinogenemia, indicating chronic inflammation.

If the swelling is encapsulated and not draining, needle aspiration should be performed to obtain a sample for culture and sensitivity. Once tracts are open and draining, culture is of questionable validity because of secondary bacterial contamination. Negative cultures can also be misleading because *B. abortus* is difficult to grown in culture and may be overgrown by other bacteria. Biopsy of inflamed tissue may also be obtained for culture and histology. Blood cultures may also be diagnostic in febrile animals.

All animals with fistulous withers should have serology for *Brucella* performed because of the public health implications. Plate agglutination is the test of choice and is more sensitive and specific than the card test. *Brucella* titers are considered to be negative when they are less than 1:50. Ideally, paired titers should be performed, with any rise in titers 2 weeks apart indicative of current infection.[324] Chronic infections may not show an increase, however, so a single high titer with compatible clinical signs should be considered diagnostic.

Radiographs should also be obtained in suspected cases of fistulous withers. They may show osteomyelitis and periostitis of the dorsal spinous processes of T1 to T9. There may also be swelling or granular opacity of the soft tissue in the withers region.[320] Horses with positive *B. abortus* titers are more likely to have radiographic evidence of osteomyelitis of the dorsal spinous processes than seronegative horses.[321] A positive-contrast fistulogram may help determine the extent of any draining tracts. Ultrasonography may also help delineate draining tracts.

38.17.27.5 Treatment

Medical treatment may be attempted but is often unsuccessful alone. Antimicrobial selection should be guided by culture and sensitivity results. In the absence of a culture, systemic broad-spectrum antimicrobials may be used. This can also be combined with lavage of the draining tracts. Systemic antiinflammatories are also indicated to control pain.

Brucella vaccination with the S19 strain has been reported in *Brucella*-confirmed cases as an effective extralabel treatment. The vaccination regimen varied from single-dose subcutaneous (SC) injection, to a

series of three SC injections 10 days apart, to intravenous (IV) injection. In 1937, Duff[319] reported that 95 of 134 horses that received two or three SC injections recovered after vaccination; 35 of these horses were also treated surgically. SC injection reportedly causes severe local and systemic reaction, including fever and abscessation.[324] The IV route may also be used, but it resulted in death in three of four horses; the other horse fully recovered in 4 weeks.[321] At this time, there are no approved vaccinations for use in horses, and the RB51 vaccine has not been used in equids. Also, the apparent decline in frequency of *Brucella* in fistulous withers would make vaccination of questionable value.

Medical management usually needs to be combined with aggressive surgical debridement for effective treatment. Conservative treatment alone may lead to recovery periods of 4 or more months. Reportedly, 80% of horses with traumatic fistulous withers treated conservatively will have recurrent lesions.[325] Drainage and debridement with the horse standing has been performed, but general anesthesia with aggressive debridement is the preferred treatment.[320] Ostectomy and curettage of the dorsal spinous processes may be necessary. Primary closure is difficult to achieve but will provide a more cosmetic result and quicker healing time. Wounds left open to heal by second intention may take 2 to 4 months to heal.[320]

38.17.27.6 Prevention and Control

Brucella abortus infection, if present, carries great public health implications. Horse owners and veterinary staff must be notified of the possible exposure and take appropriate precautions. Brucellosis in humans may cause acute fever with pneumonia, spondylitis, orchitis, or pyelonephritis. Chronic brucellosis causes a transient fever in people.[318]

Parasite control is an important aspect of prevention of fistulous withers. Horses should also be kept separate from *Brucella*-positive cattle. Proper saddle and harness fit will also decrease the incidence of traumatic fistulous withers.

38.17.28 FLEXURAL LIMB DEFORMITIES

A. BERKLEY CHESEN

38.17.28.1 Definition

Flexural limb deformities are defined as hyperflexion or hyperextention of a limb. Flexural deformities are described by the joint involved, typically the *distal interphalangeal* (DIP) joint, *metacarpophalangeal* (MCP) or *metatarsophalangeal* (MTP) joint, carpus, and rarely the tarsus. Although commonly referred to as "contracted tendons," the tendons themselves are not truly contracted, but rather short relative to the adjacent bone. Flexural limb deformities can be classified as either congenital or acquired. Contractural deformities are very common in horses and cattle. Small ruminants and camelids are much less frequently affected.

38.17.28.2 Pathogenesis

Congenital flexural deformities (deformed at birth) are likely caused by a multitude of factors. Although intrauterine positioning has been suggested, it is probably not a common cause of flexural limb deformities. Exposure of the mare during pregnancy to diseases and teratogenic agents is a more likely cause of congenital deformities. Evidence for a definitive inciting cause is lacking, but the following have been

implicated in contributing to flexural limb deformities: ingestion of locoweed *(Astragalus)* and hybrid Sudan grass, equine goiter, defective cross-linking of collagen, defects in elastin formation, neuromuscular disorders, and viruses.[326–329] It is common for foals with congenital flexural deformities to have other anatomic abnormalities, such as spinal deformities, which may result in dystocia.

Fig. 38-40 Contractural deformity of the distal interphalangeal joint (clubbed foot).

Acquired flexural deformities are seen typically from 4 weeks to 4 months of age, as well as in yearlings to 2-year-olds. These deformities have been implicated as part of the developmental orthopedic disease complex. Two general theories explain how acquired flexural deformities occur. The first theory is that the tendon unit is unable to elongate passively relative to the bone.[330] In the case of the DIP joint, the rigid accessory ligament of the *deep digital flexor* (DDF) tendon causes a palmar rotation of the foot (club-footed) (Fig. 38-40). Flexural deformities in the MCP joint are usually caused by the accessory ligament of the *superficial digital flexor* (SDF) tendon. The second theory is that increased tension within the tendon induces pain, leading to the deformity.[331] Acquired deformities are often noticed with an acute onset, which may add validity to the latter theory.

38.17.28.3 Diagnosis

38.17.28.3.1 CONGENITAL DEFORMITIES

Digital hyperextension deformities occur in neonates because of a lack of tension in the flexor muscles. Typically these deformities correct without intervention after a few weeks. In severe cases the palmar or plantar surfaces of the foal's pastern and fetlock area may become ulcerated as a result of contact with the ground, if not protected.

Contractural deformities may involve one or a combination of the following: SDF tendon, DDF tendon, and suspensory ligament. Congenital flexural deformities are most often seen affecting the carpus, tarsus, MCP joint, and MTP joint[332] (Fig. 38-41). Contracture of the DIP joint also occurs and presents with the foal walking on the toes. Depending on the severity of the deformity, if the MCP joint is affected, the foal may or may not be able to stand. Although not truly a contractural deformity, rupture of the *common digital extensor* (CDE) tendon results in a similar appearance. These foals have a characteristic swelling on the dorsolateral aspect of the carpus. Often these foals bow at the carpus because of the lack of support over the lateral aspect of the carpus.[326,333] More importantly, foals with ruptured CDE tendons should be checked for incomplete ossification of cuboidal bones because these conditions often occur together.[330]

Fig. 38-41 Contractural deformity of the metatarsophalangeal joint.

38.17.28.3.2

ACQUIRED DEFORMITIES

Contractural deformities are typically described by the joint affected. The most common acquired flexural deformity involves the DIP joint. The affected limb will have a steeper hoof wall angle with a shorter toe than the unaffected limb. The heel will elongate on the affected limb, and the MCP joint will concurrently begin to hyperextend. Two stages have been used to describe contractural deformities of the DIP joint: Stage I is defined as an angle of less than 90 degrees between the dorsal hoof wall and the sole; stage II is a dorsal hoof wall that exceeds the vertical angle.[334]

Early detection of contracture of the MCP joint is characterized by a straight fetlock angle, or upright conformation. More severe contracture of this joint is evident by buckling at the fetlock. By placing pressure in a dorsopalmar direction on the fetlock, the flexor tendons are stretched, allowing the practitioner to determine which structure is tightest, which is important for selecting an appropriate treatment.[330]

Carpal contractures tend to occur within the first 6 months of life. These foals tend to be fast-growing, heavier foals (Fig. 38-42).

Although not as common, contractural deformities of the *proximal interphalangeal* (PIP) joint occur and are usually bilateral.[330] The exact mechanism is unknown, but it is thought that as the musculotendinous unit of the DDF complex shortens, the SDF tendon becomes more lax.[335] This can lead to a dorsal subluxation of the joint. Often a clicking sound is appreciated when the foal walks. This contractural deformity is most often seen in weanlings with a high growth rate.[330]

Fig. 38-42 Bilateral, mild carpal contractural deformity.

Flexural deformities also occur after foals or horses are non—weight bearing for a time. These deformities can be permanent if the joint undergoes “contracture” or fibrodesis (fixed without osseous ankylosis).[330]

38.17.28.4 Treatment

38.17.28.4.1 CONGENITAL DEFORMITIES

Hyperextension deformities require exercise to hasten recovery. Excessive exercise is contraindicated because this leads to fatigue and possible injury. Treatments include swimming, corrective shoeing, and light bandaging when indicated. Swimming allows muscle tone to increase without bearing weight on the limbs. If the foal's toe lifts off the ground when weight bearing, glue-on shoes with a heel extension may be indicated. Glue-on shoes must not be left on a growing foal for an extended period because they may prevent the foot from expanding normally. Bandaging is only indicated when the palmar/plantar surface of the pastern or fetlock is in contact with the ground, to prevent ulcerations of the skin. Excessive bandaging and support will only cause more laxity and should be avoided.

Treatment for congenital contractural deformities should include pain management by judicious use of NSAIDs. The use of gastroprotectants is strongly suggested to help avoid the ulcerogenic effects of NSAIDs.

Oxytetracycline at a dose of 44 mg/kg diluted in physiologic saline given slowly IV has been used for many years in foals with contractural deformities.[336] Renal function of the foal should be considered before administration of oxytetracycline. Many mechanisms have been proposed to explain how oxytetracycline achieves a decrease in the angle of the MCP joint. One mechanism is the chelation of calcium resulting in muscle contraction.[336] Oxytetracycline has also been shown to be a neuromuscular blocking agent, although this mechanism does not explain why other muscle groups are unaffected.[336] An in vitro study showed that oxytetracycline also works through matrix metalloproteinase-1 mRNA expression to inhibit tractional organization of collagen fibrils by myofibroblasts; this interaction may cause relaxation of the musculotendinous unit.[337] Regardless of the mechanism of action, foals treated with oxytetracycline should also undergo forced exercise to make the improvement permanent. Without exercise, the angle of the MCP joint tends to return to its previous value within 96 hours.[338]

Toe extensions benefit the foal in two ways: (1) helping to protect the toe from being overworn and (2) lengthening the breakover of the foot, adding strain to the flexor tendons, potentially helping stretch them. Toe extensions may be made using acrylic hoof products or glue-on shoes with built-in extensions. Shoes and extensions should be removed within 2 weeks because they can prevent the hoof from growing and expanding naturally in a young foal. Typically, 2 weeks is sufficient time to achieve correction. For foals with contracture of the DIP joint, frequent rasping of the heels will help stretch the DDF tendon.

Splints and casts have been used to treat flexural deformities by giving support to the limb, thereby allowing the muscle-tendon unit to relax. When using splints, it is vital to use plenty of padding on the limb and to change the padding every time the splint is changed, to ensure pressure sores are not developing. Pressure sores can be very serious and even life threatening. Splints are made from a variety of materials but most often, polyvinyl chloride (PVC) pipe cut to an appropriate length and width; commercially made splints are also available. Splints are applied by placing the splint over the padding on the palmar or plantar surface of the limb. If the contractural deformity involves the DIP joint, the splint

should touch the ground. If the deformity is in the carpal region, the splint should end at the fetlock. Splints should be left in place for a period deemed adequate for the individual patient, ranging from several hours to 2 or 3 days.[330,332] One major advantage over casts is that splints may be removed every few hours if desired. Casts used for the lower limb are typically half-limb casts, incorporating the foot. The exception is the carpal region, where a tube cast is more appropriate, ending at the fetlock. Casts should never be left in place longer than 2 weeks at a time because of the rapid growth rate of foals. Cast sores are a serious complication and a legitimate disadvantage to using casts.

A combination of conservative treatments should be considered when treating foals with contractural deformities. If nonsurgical management does not correct the problem, surgical intervention may be necessary; however, foals with severe congenital contractural deformities have a poor prognosis. Surgery is more often attempted for foals with carpal contracture. Other congenital contractural deformities usually respond to nonsurgical treatments. Surgical correction for contractural deformities in the carpal region involves transection of the tendons of the flexor carpi ulnaris and ulnaris lateralis, as well as transection of the palmar carpal fascia.[330,332] The prognosis for mild to moderate congenital flexural deformities is good for an athletic future if the foal improves over the first 2 weeks and is able to stand and nurse.[332] Contractural deformities that can be manually straightened have a much better prognosis than those that cannot be straightened.

Foals with ruptured CDE tendons are best treated nonsurgically. Affected foals should be confined to stall rest with the application of a splint.[333] As with any splint, it should be well padded to protect the limb. The splint will provide support to the limb and help protect immature cuboidal bones, which often accompany this condition.[330]

38.17.28.5

ACQUIRED DEFORMITIES

Conservative management for acquired contractural deformities is similar to that for congenital deformities. Other conservative therapies include dietary restrictions, including early weaning. Surgical management is selected for animals unresponsive to nonsurgical treatments.

For contractural deformities of the DIP joint, desmotomy of the accessory ligament of the DDF tendon is indicated. This surgery has an excellent prognosis for full athletic potential for stage I horses. For more severe flexural deformities of this joint (stage II), a tenotomy of the DDF tendon may be necessary.[339] This procedure is not performed to promote an athletic career. It is acceptable for pasture soundness, breeding animals, and for some, light riding.

Acquired flexural deformities of the MCP joint are treated nonsurgically with a combination of NSAIDs, corrective shoeing (raising the heel with or without using a vertical bar shoe with rubber dorsal tubing) and splints. Physical therapy has been used to help stretch the tendons by having the horse hop on one leg by holding the other up in a flexed position, moving in a lateral direction toward the down limb.[330] If surgical correction is needed, it is important first to determine which structure is creating the tension. Most often the SDF tendon is involved, although the DDF tendon and even the suspensory ligament may be involved. For treatment of contracture of the SDF tendon, desmotomy of its accessory ligament is performed. If the DDF tendon is the most taut, desmotomy of its accessory ligament is completed. Both accessory ligaments may be cut when indicated. In severe cases the suspensory branches may be transected, but this procedure is done for salvage because it usually leads to subluxation of the PIP joint.[330]

Carpal contractures are treated with splints and controlled exercise. Early weaning should be considered in these foals. If surgery is necessary, a tenotomy of the flexor carpi ulnaris and ulnaris lateralis in addition to splints may yield good results.

Contracture of the PIP joint is not as common but can be a serious threat to the future athletic potential of the horse. Over time the soft tissues around the joint will fibrose, and the PIP joint may undergo degenerative joint disease. At this stage, a pastern arthrodesis may be necessary to achieve a pain-free and potentially sound limb. Desmotomy of the accessory ligament of the DDF tendon may benefit affected horses early in the disease process.[330,335]

38.17.28.6 TENDINITIS

ELIZABETH J. DAVIDSON

38.17.28.6.1 Definition and Etiology

Tendon injuries can have a profound influence on the future athletic careers of horses. The superficial digital flexor (SDF) tendon is the most frequently injured tendinous structure in the performance horse.[340] It occurs more frequently in the thoroughbred and standardbred racehorse, although it is typically seen in all types of performance horses. Deep digital flexor (DDF) tendon injuries in the metacarpal/metatarsal region occur infrequently[340–342] and are identified in older horses (9 to 10 years)[341–344] and in horses that jump.[343] Western performance horses more often have hindlimb deep flexor tendinitis (or tendonitis), probably because of their sudden turns and quick stopping in roping, cutting, or reining competition. Recently, DDF tendinitis has been identified as the major contributor of lameness in horses with foot pain.[343,345] Desmitis of the accessory ligament of the DDF tendon[346] and the accessory ligament of the SDF tendon[347] are unusual injuries in performance horses.

Tendons passively transfer muscle activity to the bone. In the equine distal limb, the palmar tendons act to support the fetlock during normal weight bearing and must withstand high—tensile stress forces during locomotion. To combat these forces, tendons contain a high proportion of type I collagen, and the tendon fibers are aligned longitudinally. When loaded, these fibers deform elastically by stretching. Normally, substantial elongation, up to a 20% increase in length,[348] occurs before failure. In thoroughbred horses, normal SDF tendons have stains reaching up to 16% when galloping.[349] This suggests that tendons in racehorses are close to their physiologic limit and may explain the high incidence of injury. Also, age-related and exercise-related tendon matrix deterioration may contribute to tendon weakness.[350] In addition, landing after a jump increases the SDF load,[351] which may explain the incidence of tendon injury in horses used for Grand Prix jumpers and eventing.

Tendon injury may occur as a single event or a cumulative fatigue failure and involves stretching of the fibers beyond physiologic limits. Response to tendon injury is similar to other tissue healing and includes inflammation, repair, and remodeling. During the acute inflammatory phase, hemorrhage and edema occur, and the degree of the response is determined by severity of the injury. Angiogenesis quickly follows, and recruited fibroblasts produce new type III collagen. A fibrinous scar of weak, haphazardly arranged collagen is formed. At this stage the tendon is prone to reinjury. Finally, the scar tissue remodels over several months, converting type III collagen to type I collagen. Controlled loading of the tendon

promotes this conversation and aligns the collagen fibrils in the direction of force (longitudinally). In severely injured tendons the entire process can take 12 or more months, and tendon reinjury is common.

38.17.28.6.2

Clinical Signs

Clinical signs of acute SDF tendon injury include swelling and heat in the tendon and peritendinous tissues. Thickening or enlargement of the tendon is noted when it is viewed from the lateral aspect, and the classic convex or bowed profile in the metacarpal region is apparent. A painful response to direct digital palpation can be appreciated and is best performed by holding the leg and palpating the tendon between thumb and forefinger. Unless the injury is severe, most horses with tendinitis are not lame.

Horses with DDF tendinitis are moderately lame,[341,342] become more lame after distal limb flexion, and have distention of the distal digital tendon sheath.[341] Injuries are usually unilateral.[341,342] Horses with DDF tendon injuries within the hoof capsule have unilateral or bilateral lameness without any palatable abnormalities.[343,345] Horses with desmitis of the accessory ligament of the DDF tendon have obvious swelling and acutely are moderately to severely lame.[346] Thickening and effusion in the carpal canal may be noted in horses with desmitis of the accessory ligament of the SDF tendon.

38.17.28.6.3

Diagnosis

Diagnosis of SDF tendon injury in the metacarpal region is obvious based on abnormal clinical signs. Diagnostic analgesia may assist the clinician in localization of the tendon injury if clinical signs are subtle or absent. This is particularly true for DDF tendon injury within the hoof capsule. Pain from DDF tendon injury in the distal metacarpal region can improve after intrasynovial analgesia of the distal digital tendon sheath.[341] Antebrachial or proximal metacarpal analgesia alleviates pain from accessory ligament of the SDF tendon.[347]

Ultrasonography is the technique of choice to diagnose tendinitis, and considerable advances in instrumentation and clinical aptitude have occurred in the past decade. The entire palmar/plantar area of the metacarpus/metatarsus should be examined in transverse and longitudinal planes. The variables typically measured include cross-sectional area, echogenicity, and fiber alignment. The severity of the injury is determined by the length of the lesion, cross-sectional area of the tendon, cross-sectional area of the lesion, lesion echogenicity, and fiber alignment of the lesion.[340,352,353] The severity rating score has been correlated with successful outcome. The most common type of SDF tendon injury is a central core lesion that appears as an anechoic lesion.[340,352]

Tendon injuries of the DDF within the hoof capsule have been identified using transcuneal ultrasonography.[344] Clinician expertise and meticulous foot preparation are required. With the advent of MRI, DDF tendon injuries within the foot have been described. Injury types include core lesions, sagittal tears, and fibrillation along the dorsal border, and most lesions occur at or near the navicular bone.[343,345,354]

38.17.28.6.4

Treatment

Proper treatment of tendinitis includes assessment of the injury using ultrasonography, control of the acute inflammatory episode, controlled return to function, and adjunct medical/surgical therapy. In acute injury,

a combination of systemic NSAIDs (e.g., phenylbutazone, flunixin meglumine) and topical therapy (e.g., cold-water hydrotherapy, poultice, distal limb bandage) is recommended. DMSO and antiphlogistically impregnated gauze bandages may also be beneficial. Rest is essential during the acute phases.

A variety of intratendinous and peritendinous injections have been advocated. Intralesional corticosteroids dramatically decrease the swelling and pain but cannot be recommended because of delayed tendon healing and the risk of continued injury and catastrophic injury in horses that remain in training. β-Aminoproprionitrile fumarate (BAPTEN) temporary blocks the cross-linking between collagen fibers and improves tendon healing, resulting in superior fiber alignment;[355] horses with moderately to severely injured tendons were more likely to return to racing after intralesional treatment.[356,357] This treatment has fallen out of favor because of complications associated with the procedure. For DDF tendon injuries, intrathecal injections of sodium hyaluronate into the distal digital tendon sheath are beneficial.[358] Intralesional sodium hyaluronate for SDF tendonitis has been advocated,[359] although other reports failed to document any significant benefit.[357,360] Intramuscular polysulfated glycosaminoglycan (GAG) has a positive effect on tendon healing in a collagenase-induced model.[361] However, no difference in return to racing or recurrence of SDF tendinitis has been demonstrated with intralesional or intramuscular polysulfated GAG.[357] Newer therapies include intralesional injections of urinary bladder matrix powder and stem cells derived from fat or bone marrow. Long-term effects have yet to be determined.

Surgical treatments include tendon splitting,[362] desmotomy of the superior check ligament,[363–366] and desmotomy of the palmar/plantar annular ligament.[367] Tendon splitting is believed to enhance revascularization and has a tendency toward improved tendon repair.[362] It is currently used for in horses with core lesions to decompress areas of hemorrhage. Superior check desmotomy may improve the likelihood that horses return to racing[363] and is clearly beneficial in standardbred racehorses.[363,364] In thoroughbred racehorses, postoperative success was initially promising;[365] however, no difference between horses treated conservatively and horses treated with desmotomy has been reported.[366] In addition, desmotomy may predispose horses to desmitis of the suspensory ligament.[364,366] Annular desmotomy has been successful performed in horses with signs of annular ligament constriction[367,368] and is usually combined with superior check desmotomy.[368] Immediate decompression and improved gliding function are presumed benefits.

Other therapies for SDF tendinitis include therapeutic ultrasound, low-power laser treatment, and extracorporeal shock wave therapy. Counterirritation (internal or external blisters) and pin firing in combination with controlled exercise or turnout in a large pasture are time-honored treatments, but their effects on tendon healing have been questionable.

Controlled exercise in combination with the previous treatments guides the repair process in hopes of producing a functional tendon or tendon substitute. If exercise is excessive, fibrous tissue is produced rather than remodeled. If no stress is applied, the tendon is more adapted to pasture exercise than performance. Therefore, the exercise regimen must be adapted to the individual patient's needs. Depending on the severity of the tendon injury, stall rest with hand walking and gradual introduction of trot is indicated. Horses should be monitored every 2 months using ultrasonography until they have returned to their previous athletic function or have failed to do so. The exercise program is dictated by the amount and type of healing. As the tendon heals, its echogenicity increases and short, linear echoes are detected. With continued healing, there are longer linear echoes and improved fiber alignment. Decrease in the cross-

sectional area is a good indication that the tendon is healing and remodeling. Ideally, complete repair will occur, and the tendon will no longer have a discretely visible area of injury because it has filled in with tissue that is isoechoic with normal tendon, and fiber alignment is parallel to normal.[352] 1248 1249

38.17.28.6.5 Prognosis

Prognosis for horses with SDF tendinitis depends on the severity of the lesion and the type of athletic work performed. Racehorses usually have a poorer prognosis, and 58% return to racing with severe injuries, 66% for moderate injuries, and 64% for mild tendinitis.[369] Most horses treated with superior check desmotomy returned to racing; however, recurrence[363–365] and suspensory desmitis[364,366] may develop. Show horses have a higher likelihood of return to function,[357] and many can continue to compete, although at a lower level. Horses with DDF tendon injuries have a poor prognosis.[341,343,345] Prognosis for horses with desmitis of the accessory ligament of the DDF tendon is good.[346] Prognosis for horses with uncomplicated desmitis of the accessory ligament of the SDF is fair, although horses with concurrent injuries are likely to have recurrent lameness.[347]

38.17.28.7 SUSPENSORY LIGAMENT DESMITIS

ELIZABETH J. DAVIDSON

38.17.28.7.1 Definition and Etiology

Suspensory ligament desmitis is a common injury of performance horses and affects all breeds of horses. Injuries to the ligament occur in both the forelimbs and the hindlimbs, and bilateral desmitis may be seen. The suspensory ligament, also named the third interosseous muscle, can be divided into three regions of interest: the proximal (origin) portion, the body, and the branches. The proximal portion originates from the distal row of carpal or tarsal bones, the proximal palmar/plantar aspect of the third metacarpus/metatarsus, and the palmar carpal or tarsal ligament. The body of the suspensory ligament descends between the second and fourth metacarpal/metatarsal bones and then divides into the medial and lateral branches in the middle metacarpal/metatarsal region. The branches insert on the abaxial surface of their respective sesamoid bones. The main function of the suspensory ligament is to support the hyperextension of the metacarpophalangeal or metatarsophalangeal joint during weight bearing.[370] Injury to the ligament occurs when it is overwhelmed with stress and its structural integrity is compromised. The damage induces a repair process characterized by inflammation (desmitis) and fibroplasia. It is surmised that this process is similar to tendinitis.[370]

Catastrophic traumatic disruption of the suspensory apparatus occurs almost exclusively in the forelimbs of thoroughbred racehorses. It is the most common cause of racetrack breakdown injuries.[371] Fatigue and high speed are components of this career-ending injury.

Degenerative suspensory desmitis is a progressive degeneration primarily affecting the suspensory branches. It is most often reported in Peruvian Pasos,[372] although has been identified in other breeds. The pathogenesis remains unclear, although the disease appears to run in families.[373] This disorder has no gender or age predilection and can occur in the absence of athletic activity. Affected horses have

continuous enlargement of the suspensory ligament because of ineffective collagen fiber repair and generalized interstitial and periligamentous fibrosis.[372]

38.17.28.7.2

Clinical Signs

Clinical signs of acute suspensory ligament desmitis include local heat, swelling, and sensitivity on palpation. In horses with proximal suspensory desmitis, swelling is in a palmar or plantar direction and frequently mild and transient because of the bony borders of the ligament. Most horses are lame, and the degree and duration of lameness depend on location and severity of the lesion. The lameness is usually worse when the horse is trotted in a circle with the affected limb on the outside of the circle. Lameness and local signs may resolve after a short period of rest and antiinflammatory treatment.

Acute, severe traumatic disruption of the suspensory apparatus results in obvious swelling, grade 4 to 5 lameness, and a hyperextended fetlock. Affected horses require first-aid treatment by application of a splint that aligns the metacarpus with the phalanges in a straight column to prevent fetlock bending.

Clinical signs of chronic suspensory desmitis include thickening of the body and branches of the ligament. Lameness is variable and may be bilateral. Chronic desmitis is typically associated with sesamoiditis, periostitis, or fractures of the small metacarpal/metatarsal bones and sesamoid bones. Straight hock conformation and hyperextension of the fetlock joints appear to be predisposing factors in proximal hindlimb suspensory desmitis, and affected horses are chronically lame despite rest.[374] Degenerative suspensory desmitis is characterized by recurrent chronic lameness, marked fetlock swelling, dropped fetlocks, excessive lying down, and reluctance to move. The majority of horses will be affected in all four limbs.[372]

38.17.28.7.3

Diagnosis

If suspensory desmitis is suspected and clinical signs are not obvious, diagnostic analgesia techniques assist in the localization of the lameness to the palmar/plantar metacarpal/metatarsal region. If proximal suspensory desmitis is suspected, perineural analgesia of the lateral palmar nerve[375] or deep branch of the lateral plantar nerve just distal to the tarsus[376] will alleviate the lameness in the forelimb or hindlimb, respectively. Desmitis of the suspensory body and branches can be localized using low palmar/plantar analgesia.

Diagnosis of suspensory desmitis is confirmed by ultrasound examination. The severity of the lesion is assessed by obtaining cross-sectional and longitudinal views of the ligament and cross-sectional area measurements. Ultrasonographic changes include cross-sectional area enlargement, focal or diffuse areas of hypogenicity, core lesions, loss of normal fiber pattern, and periligamentous thickening. Mild injuries to the suspensory ligament may be difficult to identify because of the wide variation in its normal ultrasonographic appearance. This is especially true in the proximal region, where the suspensory ligament origin is more heterogenous than for other tendons and ligaments because of a variable amount of muscle tissue. Comparison of the affected and nonaffected limbs in the same horse is recommended because of large variation among breeds and individuals.[370,377]

Radiographic examination is useful for identification of the bony abnormalities usually noted with suspensory desmitis. Bony abnormalities such as subchondral sclerosis, avulsion fracture, and enthesophyte formation have been identified in horses with proximal suspensory desmitis.[378,379] “Blind

splints" associated with axial exostosis of the second and fourth metacarpal/metatarsal bones or fractures may also contribute to suspensory desmitis. Proximal sesamoiditis and apical sesamoid fractures may be noted in horses with desmitis of the suspensory branches. In acute traumatic disruption of the suspensory apparatus, comminuted fractures of both proximal sesamoid bones are common.

Nuclear scintigraphic findings are normal in the majority of horses with suspensory desmitis.[380] Increased radiopharmaceutical uptake associated with the proximal palmar/plantar metacarpus/metatarsus can be identified in horses with avulsion fractures and other stress-related bone injuries seen in complex suspensory desmitis.[378,379] Recently, MRI evaluation has been used to diagnose proximal suspensory desmitis and fibrous adhesions between the suspensory ligament and the small splint bones.[381]

38.17.28.7.4

Treatment

Treatment of acute suspensory desmitis is aimed at reducing inflammation by the administration of systemic NSAIDs, local cold hydrotherapy, limb bandage, and controlled exercise. Initial clinical signs often dissipate quickly, even though there may be significant fiber disruption of the ligament; therefore it is strongly recommended to assess the initial injury using ultrasonography. In uncomplicated desmitis, a controlled exercise program may be initiated as soon as the acute inflammation has resolved. The duration of rehabilitation will depend on the extent and severity of the desmitis. Fractures of the small metacarpal/metatarsal bones or proximal sesamoid bones should be removed before rehabilitation. Horses are confined to a stall and hand-walked. Ligamentous healing should be monitored every 60 days using ultrasound. Ideally, there should be a progressive reduction in cross-sectional area, improved echogenicity, and fiber alignment. A gradual increase in exercise can be prescribed depending on healing.

Damaged suspensory ligaments have been injected with various corticosteroids, iodine compounds, sodium hyaluronate, and polysulfated glycosaminoglycans in an effort to reduce inflammation and promote a more rapid return to function. Pin firing, blistering, and cryotherapy with liquid nitrogen have also been used. Although these therapies assist with the initial inflammation, they do not restore normal fiber architecture and can put the ligament at increased risk because of overuse of the horse based solely on reduction of clinical signs.

Recurrent or chronic proximal suspensory desmitis has been treated successfully with extracorporeal shock wave therapy.[382] Other treatments, such as plantar metatarsal neurectomy,[383] intralesional injection of autologous stem cells,[384] desmotomy,[385] and fasciotomy,[383–385] have also been beneficial.

For horses with acute traumatic suspensory desmitis, it is crucial to place in the affected limb in a protective splint that aligns the metacarpus with the phalanges in a straight column to prevent fetlock bending. Successful nonsurgical management using splints, casts, and special shoes to support the fetlock has been reported.[386] Surgical management involves fetlock arthrodesis using dorsal plating.

For horses with degenerative suspensory desmitis, treatment is palliative and consists of stall confinement for 6 to 12 months and extended heel or large egg-bar shoes. Humane euthanasia is recommended with continued breakdown despite treatment.

38.17.28.7.5

Prognosis

The prognosis for horses with suspensory desmitis depends on the location and severity of the injury. Uncomplicated cases with minimal disruption of the ligament can recover and resume preinjury athletic function; 90% of horses with acute proximal suspensory desmitis in the forelimb will return to full athletic function.[387] Complicated, chronic, or recurrent desmitis has been associated with a worse prognosis; only 13% of horses with hindlimb proximal suspensory desmitis return to full work.[374] Most horses with traumatic disruption of the suspensory ligament can be salvaged for breeding, although meticulous nursing care in horses treated conservatively and uncomplicated surgical repair are imperative. Prognosis for horses with degenerative suspensory desmitis is extremely poor.

38.17.29

FRACTURES

TAMARA M. SWOR

The ability to treat fractures in large animals depends largely on rapid and correct diagnosis, appropriate first-aid treatment and stabilization of the injured limb, and safe transportation to a referral surgical center. Emergency treatment administered by a veterinarian in the field is crucial to provide the most treatment options and to enhance the prognosis. Accurate knowledge of available treatment options and the prognosis for various fracture types is critical during discussions with clients. The surgeon receiving a patient with a fracture should be contacted early and involved in the decisions regarding limb stabilization, transportation, and owner financial commitments. Treatment options are discussed in this section; specific surgical principles related to fracture repair can be found in surgical textbooks.

38.17.29.1

Definition and Etiology

A fracture is defined as a break or rupture of a bone. In large animals, fractures are usually classified as complete or incomplete, articular or nonarticular, displaced or nondisplaced, open or closed, simple or comminuted, and transverse, oblique, or spiral. Classification by location is also common and includes terms such as physeal, metaphyseal, and diaphyseal.

Fractures in large animals are typically associated with an acute traumatic event, followed by a sudden, severe lameness. Horses may have a history of falling or running into a solid object, receiving a kick from another horse, being hit by a car, or flipping over backward (typically young animals). In another common scenario, the owner hears a loud pop or cracking sound while the horse is being longed or is participating in an athletic activity.

Stress fractures may also occur and often are a result of cyclic loading over time with corresponding fatigue, leading to bone microfracture. Intensive training schedules create a high number of loading cycles with insufficient time to remodel and repair local areas of stressed bone (e.g., racehorse training). Specific locations of stress fractures include the distal end of the scapular spine, caudoproximal humeral head, craniodistomedial aspect of the humerus, medial humeral diaphysis, caudal aspect of the radius, dorsal middiaphyseal and distodorsolateral third metacarpal, caudal border of the ilial wing and adjacent to the pubic symphysis, proximolateral tibia, and caudal diaphysis of the tibia.[388]

Other, less common causes of large animal fractures include nutritional deficiencies, neoplasia, and infectious causes leading to pathologic fractures. Fractures related to difficult parturition events are seen in neonatal foals and calves.

38.17.29.2 Clinical Signs and Differential Diagnosis

An animal with a long-bone fracture will typically present with an acute, non—weight-bearing lameness of the affected limb. Moderate to severe soft tissue swelling and inability to control the limb often accompany other clinical signs of distress, agitation, and pain. Because of the horse's "fight or flight" reaction to traumatic situations, the patient will often continue attempts to place weight on the fractured limb. Fractures in locations with limited soft tissue coverage are often open (e.g., third metacarpal). Severe hemorrhage or laceration of large vessels is uncommon but may occur.

Complete, catastrophic fractures are often easily identified based on limb instability and soft tissue trauma or swelling. Proximal limb fractures may be difficult to palpate but have adjacent severe soft tissue inflammation and edema, crepitus, and difficulties in limb function. Nondisplaced or incomplete fractures may be associated with a wound or may be painful to manual palpation. Focal pain on palpation, a corresponding lameness, and a history of trauma or being kicked by another animal warrant radiographic evaluation in search of an incomplete fracture. An unrecognized incomplete fracture may progress to a complete fracture with time and exercise. Physeal fractures should be considered in young animals.

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Stress fractures often present with a history of an acute, severe lameness followed by a rapid decrease in the degree of lameness. There may also be reports of intermittent lameness that improves with stall rest. Palpation of the limb often reveals a focal area of pain, heat, and swelling. The horse may resist manipulation of the limb.

Differential diagnoses should include hoof and sole abscesses, joint subluxation, joint luxation, nerve damage, soft tissue injury, and septic synovial structures.

38.17.29.3 Clinical Evaluation

A complete physical examination should be performed on initial evaluation. Animals that are not immediately identified as having a fractured limb may be in need of systemic support. Fluid therapy, pain control, antiinflammatory medications, and antimicrobials should be used as necessary.

Definitive diagnosis is made by taking multiple radiographic views; nuclear scintigraphy, ultrasonography, CT, and MRI may also be used. Information from imaging studies will provide fracture configuration details essential for determining prognosis. The bone involved, degree of comminution, articular involvement, physeal involvement, and condition of the bone fragments all affect potential repair attempts and long-term prognosis. Incomplete fractures may not be readily identified at the time of injury, and radiographs should be repeated in 10 to 14 days if a fracture is suspected.

Table 38-5 Emergency Splinting Techniques for Fractures in Large Domestic Animals

Location	Species/Age	Splint
Distal phalanx	Horses, foals Cattle, calves	No splint needed
Middle phalanx	Horses, foals	Bandage with dorsal (forelimb) or plantar (hindlimb) splint to proximal third metacarpal/tarsal and cast material, Kimzey splint*
Proximal phalanx	Horses, foals	Bandage with dorsal (forelimb) or plantar (hindlimb) splint to proximal third metacarpal/tarsal and cast material, Kimzey splint*
	Cattle, calves	No splint needed
Distal sesamoid (navicular)	Horses, foals	No splint needed
Proximal sesamoids	Horses, foals	
		Bandage with dorsal (forelimb) or plantar (hindlimb) splint and cast material, Kimzey splint*
Metacarpal/tarsal 3	Horses, foals	Bandage with dorsal (forelimb) or plantar (hindlimb) splint and cast material, Kimzey splint* if fracture distal
Metacarpal/tarsal 3 & 4	Cattle, calves	Bandage with dorsal (forelimb) or plantar (hindlimb) splint and cast, cast
Metacarpal/tarsal 2 & 4	Horses, foals	No splint needed
Olecranon/ulna	Horses, foals	Robert Jones—type bandage with caudal splint to lock carpus in extension
Radius	Horses, foals Cattle, calves	Robert Jones—type bandage with lateral splint to withers, second caudal splint if needed
Humerus	Horses, foals Cattle, calves	No splint needed
Scapula	Horses, foals Cattle, calves	No splint needed
Tibia	Horses, foals	Robert Jones—type bandage with lateral splint to tuber coxae
Femur	Horses, foals Cattle, calves	No splint needed
Pelvis	Horses, foals Cattle, calves	No splint needed

* Leg-Saver splint, Kimzey Inc, 164 Kentucky Ave, Woodland, CA 95695 (530-662-9331, fax 530-662-9178); http://www.kimzeymetalproducts.com.

Stress fractures also are diagnosed using radiographic evaluation and may be identified as an incomplete cortical fracture, endosteal callus, or periosteal callus.[389] As with incomplete fractures, it may be difficult to identify a stress fracture by conventional radiography in the acute stages. Radiographs should be repeated in 10 to 14 days if a fracture is suspected. Other imaging modalities, especially nuclear scintigraphy or CT, may be useful in stress fracture identification.

38.17.29.4

Emergency Treatment

The goals of emergency treatment include preventing further soft tissue damage, stabilizing the injured limb to decrease the patient's anxiety, minimizing further damage to the fractured bone ends, keeping the fracture closed, and preventing further injury and stretching to the surrounding vessels and nerves.[390] A large animal with a fractured limb should be immediately restrained and calmed. Sedatives and tranquilizers should be used with caution, however, because the desired result may be difficult to achieve if the animal is agitated or in shock. The goal of sedation should be to allow manipulation of the limb and placement of external coaptation. Common sedatives should be used with caution to avoid creating additional ataxia; butorphanol should not be used if the horse has sustained a front limb fracture because it will make the horse lean onto the forehand. If a soft tissue wound is present, the clinician should assume that the fracture is open. The wound should be cleaned, topical antimicrobials used, a bandage placed to prevent further contamination, and the animal started on systemic antimicrobials. Antiinflammatory medications should be used as necessary.

Appropriate external coaptation and stabilization of the fracture for transport can greatly influence the options available for fracture repair and the prognosis for success. Table 38-5 outlines specific emergency splints for different fractures in bones.[390,391] Splinting techniques are designed to be placed on the standing horse and attempt to neutralize forces acting on the fractured limb. Splints should be made of a strong, lightweight material such as polyvinyl chloride (PVC) pipe or wooden boards. Bandages over fractures should be placed tightly over the injured area to decrease soft tissue swelling and minimize slippage. A layer of cotton padding should be followed by a layer of gauze or a self-adhering bandage. Multiple layers can be placed if needed (e.g., Robert Jones—type bandage). The splint should not end at the fracture location. In general, splinting techniques can be divided into categories based on fracture location.

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38.17.29.5

DISTAL LIMB FRACTURES (PHALANGES, DISTAL METACARPUS/METATARSUS)

A light cotton bandage should be placed on the affected limb from the carpus to the ground. A splint is then positioned on the dorsal aspect of a forelimb or the plantar aspect of a hindlimb. The toe is pointed toward the ground to align the dorsal cortices and to minimize stretching of the palmar/plantar vascular and nerve structures. A second splint should be placed on the medial or lateral side of the limb if any instability is present in those directions. The splint should be secured with inelastic tape. For additional stability, several rolls of fiberglass casting tape should be placed around the entire bandage and splint structure, incorporating the hoof into the cast.

38.17.29.6

MIDLIMB FRACTURES (MIDMETACARPUS TO DISTAL RADIUS, MIDMETATARSUS TO PROXIMAL METATARSUS)

A Robert Jones—type bandage should be placed on the limb from the ground to the elbow in a forelimb or the ground to the calcaneal tuber in a hindlimb. The bandage should be less extensive in the hindlimb to

facilitate splint placement. In the forelimb, splints should be placed on the lateral and caudal aspects of the limb from the ground to the elbow. In the hindlimb, splints should be placed on the lateral and caudal aspects of the limb from the ground to the calcaneal tuber. The splints are secured using inelastic tape, followed by several rolls of fiberglass casting tape around the entire structure.

38.17.29.7 UPPER LIMB FRACTURES (MIDDLE AND PROXIMAL RADIUS, TARSUS, TIBIA)

A Robert Jones—type bandage should be placed on the limb from the ground and extending as proximal as possible. In the forelimb, a splint should be placed on the lateral aspect of the limb from the ground to the withers. A second splint may be placed on the caudal or cranial side, from the ground to the proximal forearm, if needed for increased stability. Horses with olecranon fractures that disable the triceps muscle benefit from reestablishment of carpal extension by placement of a caudal splint. In the hindlimb, a splint should be placed on the lateral aspect from the ground to the tuber coxae. Splints placed high in this fashion will assist in minimizing abduction of the limb.

38.17.29.8 HIGH LIMB FRACTURES (PROXIMAL TO ELBOW JOINT, FEMUR)

Fractures in these locations are covered by extensive muscle, and attempts at splinting are usually unsuccessful and not helpful to the animal. If triceps muscle function is disabled, a splint on the caudal aspect of the carpus, locking it into extension, is beneficial.

38.17.29.9 TRANSPORT

Transportation of horses with long-bone fractures can be difficult. It is best to confine the patient in the trailer so that they may lean on dividers for support. The horse should be tied loosely in the trailer to prevent turning around, but allowing the animal to use its head for balance. When possible, horses with forelimb fractures should be transported with the head facing the rear of the trailer, and those with hindlimb fractures should be transported with the head facing the front of the trailer. These positions allow the horse to control its weight most easily with the uninjured limbs during deceleration of the trailer.

38.17.30 Pathophysiology of Bone Healing

Healing of a fracture terminates in the return of the injured bone to its original form.[392] The process of fracture healing involves several biologic steps that overlap and interact with each other. Typically, three phases are recognized: inflammatory, reparative, and remodeling.[392,393] The *inflammatory phase* occurs in the initial 2 to 3 weeks after bone fracture, and chemical mediators cause chemotaxis, migration of leukocytes, and vasodilation to the injured area. These mediators protect the injury from infection and stimulate angiogenic factors. Cytokines from platelets aid in angiogenesis and mesenchymal cell growth.[392] Granulocytes and macrophages destroy invading bacteria and stimulate cell repair through the release of growth and angiogenic factors. If the inflammatory phase is impaired, fracture healing may be compromised.[392]

The *reparative phase* overlaps with the inflammatory phase and may last up to 12 months. This phase attempts to reestablish bone union. Interfragmentary stabilization by periosteal and endosteal callus formation begins if the fractured ends are not immobilized.[393] Bony union develops as a result of endochondral and intramembranous ossification.[392,393] In the reparative phase, interfragmentary motion may greatly influence fracture healing.

The *remodeling phase* takes place both during and after the reparative phase. Osteonal remodeling allows for replacement of the necrotic regions of bone. When the bone is loaded, the negatively charged concave surface will attract osteoblasts to add new bone, and the positively charged convex surface will attract osteoclasts to remove bone.[392,393] The result is the ability of a fractured bone to straighten itself by creating new bone formation on the concave surface and removing bone from the convex surface.

Repair of a fractured bone with the use of rigid internal fixation will inhibit the naturally occurring callus formation and encourage bone to heal through haversian remodeling. *Haversian remodeling* requires that a fracture be rigidly fixed, have adequate reduction, and have an adequate blood supply.[392,393] Haversian remodeling then functions to revascularize necrotic bone at the fragmented ends of the fracture and bridge interfragmentary gaps. This form of remodeling begins 2 to 3 months after injury.

Fractured bones are often described as healing by primary (direct) or secondary (indirect) intention.[389,392,393] Primary bone healing only occurs with complete anatomic reduction and rigid stability. In large animal fracture repair, this is difficult to achieve because of the size of the animal and micromotion at the repair site.[389] Secondary bone healing utilizes endosteal and periosteal callus formation, and new bone formed at the fracture site develops after initial formation of fibrous tissue or fibrocartilage.[392,393]

The rate of bone healing may be decreased if blood supply is inadequate, infection is present, soft tissue damage is extensive, or stability of the bone fragments is inadequate.

38.17.31 Treatment and Prognosis

Treatment options for fractures in large animals include conservative therapy with stall rest and external coaptation (casts, splints) and surgical stabilization with open reduction and internal fixation. It is important to recognize incomplete and stress fractures in order to manage them appropriately with conservative therapy, preventing progression to a catastrophic fracture. The majority of fractures require some form of stabilization for the best chance of a successful outcome. Most horses require surgical stabilization for successful fracture repair. Ruminants are more amenable to successful fracture repair with nonsurgical options.[389] 1252 1253

Conservative therapy with stall rest and external coaptation may be successful in some foals and calves with complete, nondisplaced fractures. Young animals have a greater and faster ability to heal bone in a reasonable amount of time, and their body weight is much less than that of a mature animal. In foals and calves, the fracture configurations tend to be simpler, and the surgical implants available for repair are of a suitable strength compared to the animal's size. Complications in young animals include closure of a physes with fractures in these areas, infection, and angular limb deformities from overuse of the contralateral limb.

In adult animals, it is more common to identify severely comminuted fractures due to the large force needed for bone breakage. Proximal limb fractures in an adult horse are often unable to be successfully treated because severe comminution of the bone occurs, implants are not strong enough to support the bone until it is healed, these horses are less likely to protect the limb, and laminitis formation in the contralateral limb is a common complication. Stall rest with external coaptation alone is rarely associated with a good outcome, and most horses require some form of internal fixation for success. Horses are often required to be athletes, and fracture repair resulting in survival, but not soundness, may be unacceptable. In general, ruminants have a better prognosis for survival than horses because of their less excitable temperament, and complete soundness is often unnecessary for a successful outcome. External fixation may be more successful in ruminants than external

coaptation because it provides increased stability and costs less than internal fixation.[389] Open fractures in horses greatly decreases the prognosis for survival and may delay the ability to perform internal fixation. In ruminants, open fractures are less common but also carry a poorer prognosis.

Table 38-6 Treatment and Prognosis for Large Animal Fractures

Fracture Location	Fracture Type	Treatment	Prognosis
Distal phalanx	Articular	Medical/surgical	Guarded
	Nonarticular	Medical	Good
Middle phalanx	Comminuted	Surgical	Guarded
Proximal phalanx	Comminuted	Surgical	Guarded
	Noncomminuted	Medical/surgical	Good
Distal sesamoid	Fragmented	Medical/surgical	Poor to guarded
Proximal sesamoids	Articular	Medical/surgical	Poor to guarded
	Nonarticular	Medical/surgical	Fair to good
Third metacarpal/tarsal			
Lateral condyle	Nondisplaced	Surgical	Good
	Displaced	Surgical	Guarded
Medial condyle	Articular	Surgical	Guarded
Diaphyseal	Comminuted	Surgical	Guarded
Third and fourth metacarpal/tarsal	Diaphyseal	Medical/surgical	Good to excellent
Second and fourth metacarpal/tarsal	Distal	Medical/surgical	Good to excellent
	Proximal	Surgical	Guarded to good
Olecranon/ulna	Articular	Surgical	Good
	Nonarticular	Medical/surgical	Good
Radius	Complete	Surgical	Poor
	Complete*	Surgical	Guarded to good
	Incomplete	Medical	Good
Humerus	Complete	Medical	Poor
	Complete*	Surgical	Guarded to good
Scapula	Complete	Surgical	Poor to fair
Tibia	Complete	Surgical	Poor
	Complete*	Surgical	Guarded to good
Femur	Complete	Medical	Poor
	Complete*	Surgical	Guarded to good
Pelvis	Articular	Medical	Guarded
	Nonarticular	Medical	Guarded to good

* Foals, calves, and small ruminants.

Implants used for surgical open reduction and internal fixation methods vary based on the specific bone involved, the animal's age, the strength of the bone fragments used in the repair, and the surgeon's preference. Common implants used in large animals include intramedullary (IM) interlocking nails, dynamic compression plates (DCPs), locking compression plates, limited-contact DCPs, screws, wires, pins, and dynamic condylar screw plates. Table 38-6 lists specific treatment options and prognoses.[391]

38.17.32 HUMERUS

The humeral fracture is often in a spiral or long oblique configuration. In ruminant and equine species, both conservative and surgical treatments have been used. In foals, surgical repair may include the use of IM interlocking nails, DCPs, or IM nails. Prognosis for a closed fracture in a foal is fair to good and depends on configuration, age, and weight.[394,395] Humeral fractures in adult horses are not reparable at this time. Conservative treatment may be successful in adult horses with nondisplaced fractures and has been used in small ruminants and foals with acceptable outcomes. Ruminants have a better prognosis in general than equine species.[389]

38.17.33 RADIUS

Survival rates for ruminants with radial fractures repaired by external or internal fixation have been reported as 86%.[396] Radial fractures in foals repaired with internal fixation have a good prognosis; however, in adult horses the success rate is poor.[397] Animals with incomplete fractures that do not progress have a good prognosis for a full recovery.

38.17.34 OLECRANON

There are several different fracture configurations, and the olecranon fracture may be articular or nonarticular. These fractures are common in both young and older horses. Surgical and conservative treatments have been used with success, although internal fixation is the preferred treatment method.[398,399] Typically, the fracture is repaired with a DCP applied as a tension band. The prognosis with surgical repair is good, with 62%, 75%, and 87% of horses returning to athletic use, depending on the fracture type.[398–400] Conservative treatment has been reported to result in a 73% return to soundness.[401]

38.17.35 FEMUR

Diaphyseal fractures are more common in calves, whereas proximal physeal fractures are more common in foals.[389] Femoral fractures in calves may occur during parturition events. In young calves, these fractures have been repaired by internal fixation and femoral head and neck osteotomies with success. In foals, fracture repair with internal fixation gives the best chance of survival, and the use of IM interlocking nails has shown positive results.[402] Femoral fractures in adult horses are not reparable at this time.

38.17.36 TIBIA

Ruminants sustaining tibial fractures have been repaired using splints, external fixators, transfixation pin casts, and DCPs. Fractures repaired with external fixation in adult cattle had a 64% success rate, versus conservative therapy success at 44%.[403] Internal fixation is the repair method of choice in horses. Foals have a fair to good prognosis for survival. Adult horses have a poor prognosis for survival because tibial fractures are often open, have limited blood supply, and are often severely comminuted.

38.17.37 METACARPUS/METATARSUS

In cattle, these fractures are common and have a good prognosis when treated with internal fixation, casts, or transfixation pin casts.[389] Calves may incur distal physeal fractures after forced extraction during a dystocia, and these may be casted with good success. In horses, cannon bone fractures are frequently open because of a lack of soft tissue coverage. Treatment options include internal fixation with DCPs and screws or transfixation pin casts. One study reported a 67% success rate with surgical repair.[404]

38.17.38 PHALANGES

In ruminants, fractures of the proximal or middle phalanx are treated with reasonable success by applying a block to the uninjured claw or by cast application. In horses, proximal and middle phalangeal fractures have been treated by internal fixation with screws and DCPs. Prognosis for survival is good, but return to athletic function depends on the degree of osteoarthritis that develops after fixation. One review of proximal phalangeal fractures in racehorses reported that 61% to 75% were able to race.[405] Prognosis for comminuted middle phalangeal fractures repaired with proximal interphalangeal joint arthrodesis is 50% for forelimbs and 80% for hindlimbs.[389] Severely comminuted fractures may also be treated with transfixation pin casts or the Nunamaker external skeletal fixator. Fractures of the distal phalanx in horses may be successfully treated with surgical fixation, hoof casts, or modification in shoeing, depending on fracture configuration.[406]

38.17.39 SUMMARY

Animals identified with incomplete fractures should be treated conservatively with stall rest and should be tied to prevent them from lying down if the fracture is at risk of becoming complete (e.g., radius). Animals with stress fractures should be treated conservatively with stall rest and a careful rehabilitation program, with ongoing radiographic evaluation.

Many fractures in large animals are able to be repaired and allow survival of the animal. Prognosis in general is better if the animal is young, it weighs 500 pounds (225 kg) or less, the fracture is closed, appropriate emergency stabilization is implemented, and prompt reduction and stabilization are performed.

38.17.40 SPONTANEOUS FRACTURES IN RUMINANTS

JOHN MAAS

38.17.40.1 ## Definition and Etiology

Spontaneous fracture of bone is a syndrome that occurs when underlying bone disease weakens bone(s) to the point where otherwise normally applied stresses result in bone failure. The terms *spontaneous fracture* and *pathologic fracture* are synonymous for clinical usage. Fractured bones typically include (1) long bones of the limbs, (2) vertebrae, (3) ribs, and occasionally (4) the mandible or pelvic bones.

38.17.40.2 ## Clinical Signs and Differential Diagnosis

Clinical signs of postural deformity, swelling, and lameness are observed, with bone fracture resulting from minimal or no apparent stress. Thorough physical examination often reveals additional fractures that are in the process of healing, particularly of the ribs and long bones. A fracture that occurs in normal bone in response to applied stress is the main differential diagnosis.

38.17.40.3 ## Pathophysiology, Epidemiology, and Clinical Pathology

The specific causes of spontaneous fractures in ruminants are varied and include pathologic processes that affect the tensile strength of bone. Although spontaneous fractures are not common, certain disease processes predispose animals to this condition, including (1) tumors affecting individual bones, (2) osteomyelitis, (3) rickets (osteodystrophy) in young ruminants, (4) osteomalacia in adult ruminants, and (5) osteoporosis associated with copper deficiency.

The effect of localized infection or tumor growth is to weaken bone tissue by dissolution of the mineral matrix. More common tumors causing bone weakness and fracture include lymphosarcoma and primary bone tumors in ruminants. Osteomyelitis, as a primary condition or as an extension from septic arthritis, can severely affect the strength of bone over time. Osteomyelitis causing pathologic fractures can be associated with wounds or can occur in diseases such as actinomycosis.

Rickets in young, growing animals occasionally can result in spontaneous fractures of long bones and vertebrae. Osteomalacia in adult ruminants is caused by the same factors that result in rickets in young, growing livestock. As in young ruminants, the cause of osteomalacia is most often a deficiency of phosphorus or vitamin D. Calcium deficiency (primary or secondary), however, can be involved in the pathogenesis. Individual uremic animals may develop osteomalacia and spontaneous fractures from a lack of active vitamin D (1,25-dihydroxycholecalciferol). The pathogenesis of osteomalacia in the adult differs from that of rickets, in that mature and well-mineralized bone is removed and replaced by inadequately mineralized organic matrix. Therefore, radiographic and histologic examination of osteomalacic bone occasionally reveals signs of osteoporosis. Osteomalacia of the metaphysis and epiphysis is less prominent than with rickets. Spontaneous fractures associated with osteomalacia are usually accompanied by pica, skeletal deformities, and hypophosphatemia.

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Copper deficiency can be caused by a lack of adequate dietary copper (primary) or a relative excess of sulfates and molybdenum (secondary), which bind copper and make it unavailable for metabolism, resulting in osteoporosis[407] (see Chapter 37). The biochemical mechanism of bony lesions in copper deficiency is unknown; however, lysyl oxidase, a copper-containing metalloenzyme, may be involved. Copper deficiency can be a significant cause of lameness even without spontaneous fractures.[408,409] Radiographic and histologic findings in affected bones of lame, copper-deficient ruminants are similar to those seen with

rickets.[410] Copper-deficient ruminants can also exhibit signs of anemia, achromotrichia, alopecia, diarrhea, poor growth, decreased feed efficiency, osteoporosis, and sudden death. Diagnosis of copper deficiency can be made when serum or plasma copper concentration is less than 0.5 μg/mL (ppm) or when hepatic copper concentration is less than 35 μg/g on a dry-weight basis. Differentiating primary from secondary copper deficiency requires the analysis of diet and water. In my experience with spontaneous fractures associated with copper deficiency, two additional findings are frequently seen: (1) concurrent selenium deficiency and (2) hypophosphorosis with adequate dietary calcium. Syndromes seen in the field may be more complicated than we currently understand.

There are a number of possible causes of spontaneous fractures in ruminants. Factors that might affect a group of animals include dietary deficiencies of phosphorus, calcium, copper, and trace minerals (Se, Mn, Zn); mineral (Ca, P, Mg) imbalances; indoor housing (vitamin D deficiency); protein deficiency (osteoporosis); rapid growth; lactation; and advanced pregnancy. The differentiation of spontaneous fractures from other causes of bone fractures is made by history, physical examination, and identification of one or more associated conditions mentioned previously.

38.17.40.4 Treatment and Prevention

Treatment of spontaneous fracture is similar to that of common orthopedic problems caused by trauma. In addition, the underlying condition(s) must be corrected. Although the prognosis must be considered guarded or poor, I have examined recovered and ambulatory cattle with multiple healing rib fractures and two healing long-bone fractures. With spontaneous fractures associated with osteomalacia, rickets, and osteoporosis caused by copper deficiency, the animals' ability to heal is remarkable. Prevention of spontaneous fractures depends on identifying and correcting all underlying problems.

38.17.41 BUCKED SHINS AND STRESS FRACTURES OF THE METACARPUS IN THE HORSE

SUSAN M. STOVER

38.17.41.1 Definition and Etiology

Bucked shins and stress fractures are the acute and chronic manifestations of disease of the dorsal cortex of the third metacarpal bone. Bucked shins is a painful condition most often involving the middiaphyseal dorsal cortex of 2-year-old and occasionally 3-year-old horses in their first year of race training.

Stress or fatigue fractures are incomplete fractures located in the mid-diaphyseal dorsal cortex and less often in the distal diaphyseal dorsal or dorsolateral cortex. These fractures are seen most frequently in 3-year-old horses but can also affect 2-year-old horses later in the racing season and, with decreasing numbers, older horses.

Bucked shins and stress fractures are occupational diseases of horses in race training. These conditions are more prevalent in young horses training at fast speeds on dirt surfaces than in older horses or horses training on grass surfaces.

38.17.41.2 Clinical Signs and Differential Diagnosis

A general pattern of clinical signs was observed in one study of 2-year-old thoroughbred horses in race training.[411] Bucked shins usually occurred bilaterally. Both metacarpi usually were affected simultaneously, although occasionally one was affected several days before signs were observed in the contralateral metacarpus. In most horses the first clinical indication of bucked shins was a painful response to palpation of the metacarpus. Subtle pain often was found before the detection of an unwillingness of the horse to work at fast speed. Lameness was not necessarily manifested by affected horses.

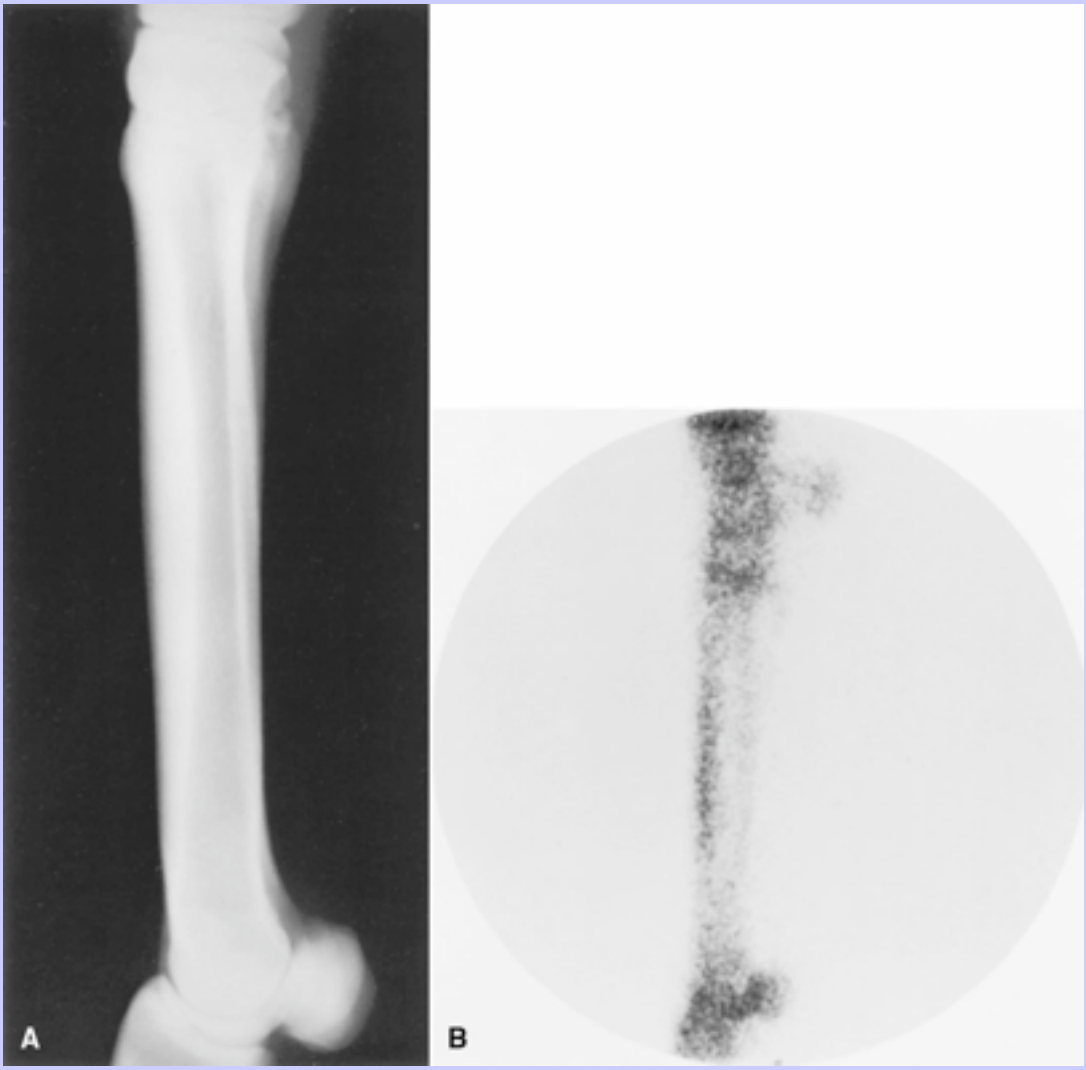
Pain usually was localized to the dorsal aspect of the middiaphysis or near the junction of the proximal and middle thirds of the diaphysis. Initially, pain was mild and elicited from a diffuse area. With continued training, soft tissue thickness became palpable, and diffuse swelling became visible on the dorsum of the metacarpus. Later, soft tissue thickness and swelling became more focal unless hard work was continued. Approximately 2 to 3 weeks after pain first was detectable, discrete hard swellings could be palpated on the dorsum of the metacarpus. Radiographic abnormalities often are absent in horses with acute bucked shins.[412] The dorsal cortex thickens during adaptation to the stresses associated with training,[413] but indistinct periosteal proliferation, subperiosteal demineralization,[412] or subperiosteal radiolucencies support a diagnosis of bucked shins. Even in the absence of radiographic abnormalities, bone scintigraphy demonstrates a diffuse region of intense radiopharmaceutical uptake in the dorsal cortex of affected horses[414] (Fig. 38-43).

Differential diagnoses include cellulitis, periostitis, and osteitis of traumatic or infectious origin, although these conditions are much less common in the racehorse population. Signs of external trauma or infection (e.g., elevated temperature, wound drainage) may be present with these other conditions.

Incomplete cortical fractures occur approximately five times more frequently in the left than in the right metacarpus.[411,415] Left metacarpal fractures occur more often in the mid-diaphysis than in the distal diaphysis; however, in one study a large proportion of right metacarpal fractures occurred in the distal diaphysis.[411] Horses with incomplete cortical fractures are more likely to be examined because of lameness of the affected leg(s) than horses with bucked shins. Lameness, which may be marked after activity, usually subsides within a few days.[415,416] With chronicity a discrete, hard tissue enlargement is visible and palpable overlying the fracture. Focal pain usually can be elicited by digital palpation of the enlargement.

Incomplete cortical fractures may be detected radiographically; however, not all fractures can be visualized. Fracture lines usually extend in a proximopalmar direction from the periosteal surface of the dorsal cortex at a 30- to 45-degree angle to the dorsal cortical surface (Fig. 38-44, *A*). Occasionally, fractures extend in a distopalmar direction from the periosteal surface, and less frequently a saucer-shaped fragment is noted within the dorsal cortex. Fractures rarely appear to course completely to the endosteal surface of the dorsal cortex. In the absence of a radiolucent fracture line, a localized periosteal or endosteal reaction is highly indicative of an incomplete cortical fracture. Alternatively, occult fractures may be identified with bone scintigraphy by intense focal accumulation of radiopharmaceutical[414] (Fig. 38-44, *B*).

Fig. 38-43 **A,** Lateromedial radiograph, and **B,** lateral scintigram, of the third metacarpal bone of a horse with bucked shins. Although dorsal cortical thickening is present, distinct radiographic changes associated with acute metacarpal disease cannot be detected. However, diffuse exaggerated radiopharmaceutical uptake is demonstrated in the dorsal cortex. *Courtesy P.D. Koblik.*



Differential diagnoses for stress fractures include traumatic periostitis or osteitis and osteomyelitis. Radiographic findings and clinical signs of external trauma are helpful diagnostically.

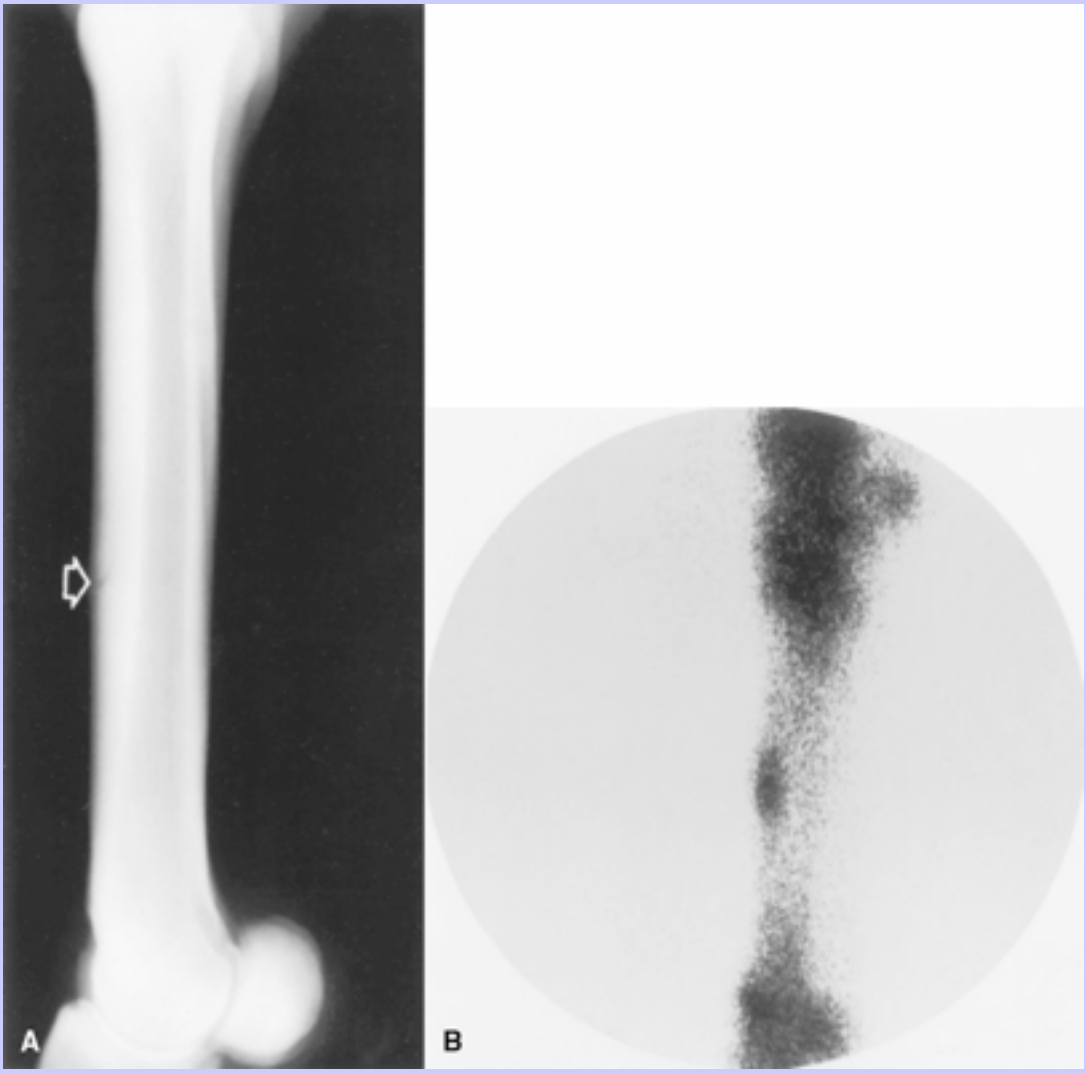
38.17.41.3 Pathophysiology

Bucked shins are believed to result from cumulative microscopic damage within the dorsal cortex of the third metacarpal bone. Microdamage results from excessive strain (i.e., deformation) of young, developing metacarpal bones during training at fast speeds on hard surfaces.

Although third metacarpal bones of 2- to 3-year-old horses have attained adult length, the bone continues to adapt to the increased stresses of race training by enlarging in diameter and replacing intracortical bone through internal remodeling. These processes strengthen the metacarpal bone by increasing its resistance to deformation, decreasing its susceptibility to microdamage with repeated loading, and repairing microdamage. Adaptation usually is completed by 3 to 4 years of age and accounts for the lower incidence of bucked shins and stress fractures in older horses.

If accumulated microdamage with continued training exceeds adaptive and remodeling processes of the metacarpal cortex, bucked shins or chronically incomplete cortical fracture may become clinically and radiographically evident. Because fractures result from accumulation of damage caused by repetitive loading, they are often referred to as “fatigue” fractures. Evidence indicates that the direction of maximum strain on the surface of metacarpal bones changes with a shift from training to racing gaits.[417] Because bone adapts by responding to the magnitude and direction of strain encountered, adaptation during training (i.e., trot and slow gallop) is probably different from that occurring during racing (i.e., racing gallop). Thus, metacarpal bones that have adapted to training may not adapt well to the strains of racing and may incur significant microdamage during initial exercise at racing speeds.[413]

Fig. 38-44 **A,** Lateromedial radiograph, and **B,** lateral scintigram, of the third metacarpal bone of a horse with an incomplete cortical fracture *(arrow)* associated with focal, intense radiopharmaceutical uptake. *Courtesy P.D. Koblik.*



38.17.41.4 Epidemiology

The incidence of bucked shins in 2-year-old thoroughbred racehorses is approximately 70%,[415] occurring most often during the first year of race training. With continued training, horses with cortical microdamage develop stress fractures, which are most common in 3-year-old horses.

The incidence of bucked shins and stress fractures is lower in quarter horse and standardbred racehorses than in thoroughbreds. The high incidence in thoroughbred horses may be associated with running long distances at the racing gallop.[418] Thoroughbred horses are subjected to more high-stress loading cycles than quarter horses running shorter distances or than standardbred horses trotting or pacing. Therefore, thoroughbred horses are more likely to accumulate clinically significant amounts of cortical microdamage.

38.17.41.5 Necropsy Findings

Bucked shins and incomplete cortical fractures may be found incidentally on postmortem examination of racehorses. Callus may be evident on the periosteal surface. Cross sections of the bone may disclose an incomplete cortical fracture or endosteal bony proliferation. Histologic examination usually reveals an indistinct fracture line characterized by marked bone resorption.[419]

38.17.41.6 Treatment and Prognosis

Treatment of bucked shins varies with the degree of pain and the decrease in the performance of affected horses. On palpation, mildly and moderately affected horses exhibit resentfulness and mild soreness, which disappears within 2 to 4 days.[420] Training should be continued, but at a slower pace, to promote continued adaptation of bone to the stress of racing and to prevent the accumulation of additional microdamage. In severely affected horses, pain remains evident after 1 week of rest. These horses may require complete rest for a minimum of 3 months before they can be returned to training. After a horse has recovered from bucked shins, the prognosis is good for return to training, although the condition will recur in severely affected horses that were not rested for long enough before their return to training and in horses whose exercise intensity was accelerated too rapidly on return to training.

Many adjunctive therapies, including pin firing, cold therapy, and electrostimulation, also are frequently used. Their effectiveness, however, is difficult to assess without considering concurrent training or rest therapy. Horses with incomplete cortical fractures must be rested for a minimum of 3 to 6 months. Most rested horses show radiographic evidence of bone healing and can be returned to training. Some chronic fractures are refractory to rest alone. Occasionally, returning these horses to light exercise stimulates fracture healing. Alternatively, interfragmentary drilling has resulted in better healing of fractures with fewer adverse effects than lag screw fixation. After interfragmentary drilling and adequate rest (e.g., 3 to 6 months), the prognosis is good for return to racing. Without an apparent relationship to type of treatment, however, incomplete fracture recurs in some horses.

38.17.41.7 Prevention

Factors in the prevention of bucked shins and stress fractures include training regimen, racetrack surface, and shoeing. In general, a training program should gradually increase the degree of exercise, allowing time for concurrent bone adaptation, and should subject the metacarpus to similar strains encountered during racing.[413] Experimental evidence suggests that the metacarpus would have to encounter the strain associated with racing stress only for short duration a few times per week to stimulate the appropriate adaptive response.[421] The effect of exercise on bone adaptation and remodeling is under active investigation. Hard racetrack surfaces are associated with a higher incidence of bucked shins than softer surfaces.[422] The stresses and

strains incurred by the metacarpus probably can be modified by changing the character of the racing surface or the horseshoe.

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39 Chapter 39 Diseases of the Eye

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39.1 OPHTHALMIC HISTORY AND EXAMINATION

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Before pursuing a detailed ophthalmic history, it is imperative to document the species, breed, age, gender, coat color, and use of the animal(s) to be examined and to obtain a general medical history. Because ophthalmic diseases of large animals may be genetic, an awareness of breed-related ocular abnormalities is also important.

The primary complaints of the owner regarding the animal's eye(s) or vision may generally be categorized into one of the following areas of concern:

- Abnormal appearance of one or both eyes (i.e., asymmetry or color change)
- Presence of ocular discharge
- Presence of ocular pain
- Reduced vision or blindness

Additional reasons for obtaining a thorough ophthalmic history and performing a detailed ocular examination are to follow up on a preexisting or previously treated eye condition or to examine the eyes as part of a prepurchase examination. Examinations for inherited eye diseases in horses may be performed by board-certified veterinary ophthalmologists and registration forms submitted to the Equine Eye Registration Foundation.[1]

39.2 OPHTHALMIC HISTORY

A series of questions should be directed to the owner or responsible person regarding the signs observed, the duration and clinical course of the condition, the animal's ability to function in its normal environment, the existence of previous eye problems, and whether related animals or other animals on the premises have been affected. Potential causes for an ophthalmic or visual problem, including any possible relationship to neurologic or iatrogenic (e.g., drug-induced) disease, toxin exposure, or systemic illness, should be explored. To ensure that the necessary questions are asked in a reasonable sequence, a history form is suggested (Fig. 39-1).

39.3 OPHTHALMIC EXAMINATION PROCEDURES

39.3.1 General Inspection

It is optimal to observe the animal's activities and movements in its normal environment. Before restraining the animal, the examiner should study the animal's unencumbered movements, posture, coordination, and head

carriage. During this initial inspection, the animal's vision and its response to visual stimuli should also be observed.

As the animal is approached, closer inspection reveals whether facial and ocular symmetry and normal eye movements are present. Signs of ocular pain (i.e., blepharospasm, apparent photophobia, or epiphora) are noted, as well as size and position of the globes and the presence of ocular or nasal discharge, opacities, or masses.

39.3.2 Restraint

Adequate restraint is an essential prerequisite to performing a detailed ophthalmic examination in large animals. Manual restraint of small ruminants and neonates is usually adequate. For most cattle, restraint with a chute, head catch, and halter is essential; restraining the horse with a halter in stocks is recommended. However, chemical restraint may be necessary in cattle and is almost always needed for horses before a thorough examination can be performed. This may consist of a combination of injectable sedative (e.g., xylazine or detomidine for horses), with or without an injectable analgesic (e.g., butorphanol for horses), with auriculopalpebral (and occasionally frontal) nerve blocks using a local anesthetic agent such as 2% lidocaine. A neuroophthalmic assessment, including menace responses and palpebral/pupillary light reflexes, should be done before administration of sedatives, analgesics, or local anesthetics.

39.3.3 Neuroophthalmic Assessment

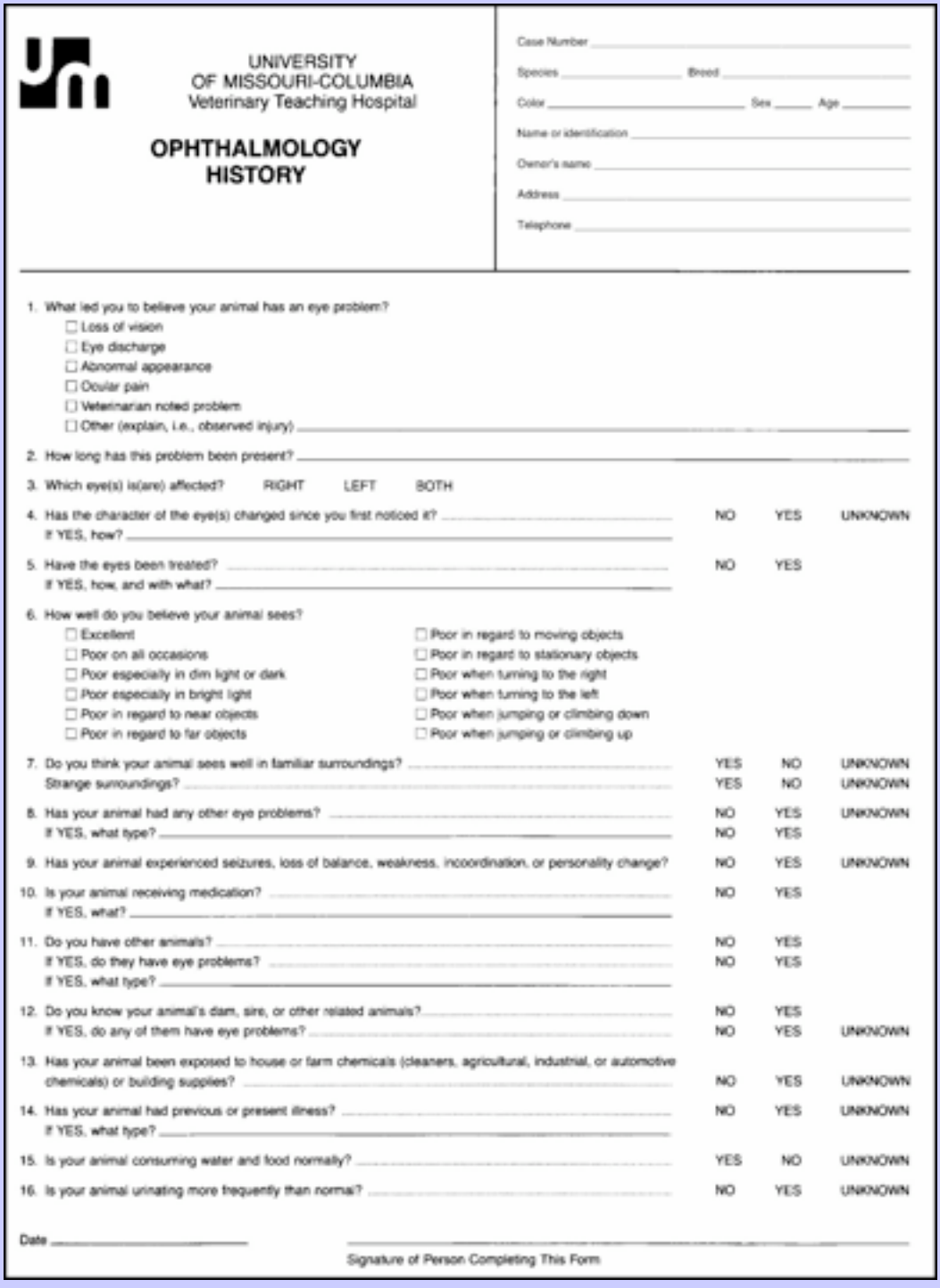
An evaluation of the integrity of cranial nerves associated with normal ocular function is conducted (see Chapter 8). This includes a rapid assessment aimed at determining the animal's ability to do the following:

- Perceive tactile stimuli of the facial and ocular surfaces
- Blink effectively with complete eyelid closure
- Move and position the eyes normally
- Constrict or dilate pupils in response to background and focal illumination
- Respond to visual stimuli such as hand motions or moving objects

39.3.4 Instruments and Materials

After a general inspection, restraint, and neuroophthalmic assessment, a detailed ophthalmic examination is performed. A few basic instruments and materials facilitate an efficient and thorough examination. These include a focused light source (a 3.5-V halogen rechargeable light source with a Finoff transilluminator is preferred), a direct ophthalmoscope, magnifying loupes, and thumb forceps (blunt-tipped forceps with shallow serrations are recommended). Sterile fluorescein dye strips, tear test strips, culture swabs, physiologic saline solution (flushing solution), topical anesthetic (0.5% proparacaine), and mydriatic solution (1% tropicamide) are often also necessary. For irrigating nasolacrimal ducts, polyethylene tubing (5 French) should be available.

Fig. 39-1 Example of an ophthalmologic history form that may be completed by the owner, an animal caretaker, veterinary technician, or clinician.



UNIVERSITY
OF MISSOURI-COLUMBIA
Veterinary Teaching Hospital

OPHTHALMOLOGY HISTORY

Case Number _____

Species _____ Breed _____

Color _____ Sex _____ Age _____

Name or identification _____

Owner's name _____

Address _____

Telephone _____

1. What led you to believe your animal has an eye problem?
   - ☐ Loss of vision
   - ☐ Eye discharge
   - ☐ Abnormal appearance
   - ☐ Ocular pain
   - ☐ Veterinarian noted problem
   - ☐ Other (explain, i.e., observed injury) _____

2. How long has this problem been present? _____

3. Which eye(s) is(are) affected? RIGHT LEFT BOTH

4. Has the character of the eye(s) changed since you first noticed it? NO YES UNKNOWN
   If YES, how? _____

5. Have the eyes been treated? NO YES
   If YES, how, and with what? _____

6. How well do you believe your animal sees?
   - ☐ Excellent
   - ☐ Poor on all occasions
   - ☐ Poor especially in dim light or dark
   - ☐ Poor especially in bright light
   - ☐ Poor in regard to near objects
   - ☐ Poor in regard to far objects
   - ☐ Poor in regard to moving objects
   - ☐ Poor in regard to stationary objects
   - ☐ Poor when turning to the right
   - ☐ Poor when turning to the left
   - ☐ Poor when jumping or climbing down
   - ☐ Poor when jumping or climbing up

7. Do you think your animal sees well in familiar surroundings? YES NO UNKNOWN
   Strange surroundings? YES NO UNKNOWN

8. Has your animal had any other eye problems? NO YES UNKNOWN
   If YES, what type? NO YES

9. Has your animal experienced seizures, loss of balance, weakness, incoordination, or personality change? NO YES UNKNOWN

10. Is your animal receiving medication? NO YES
    If YES, what? _____

11. Do you have other animals? NO YES
    If YES, do they have eye problems? NO YES
    If YES, what type? _____

12. Do you know your animal's dam, sire, or other related animals? NO YES
    If YES, do any of them have eye problems? NO YES UNKNOWN

13. Has your animal been exposed to house or farm chemicals (cleaners, agricultural, industrial, or automotive chemicals) or building supplies? NO YES UNKNOWN

14. Has your animal had previous or present illness? NO YES UNKNOWN
    If YES, what type? _____

15. Is your animal consuming water and food normally? YES NO UNKNOWN

16. Is your animal urinating more frequently than normal? NO YES UNKNOWN

Date _____

_____
Signature of Person Completing This Form

39.3.5 Detailed Examination

For recording results of the ophthalmic examination, use of a standard form is recommended (Fig. 39-2). The detailed examination begins with palpation of the boundaries of orbit for irregularities, asymmetry, masses, or fractures. Next, the globe is retropulsed to assess for increased resistance (indicating a space-occupying mass) and to inspect the anterior aspect of the nictitating membrane ("third eyelid"). Retropulsion should not be done if the cornea is compromised by a deep ulcer or laceration.

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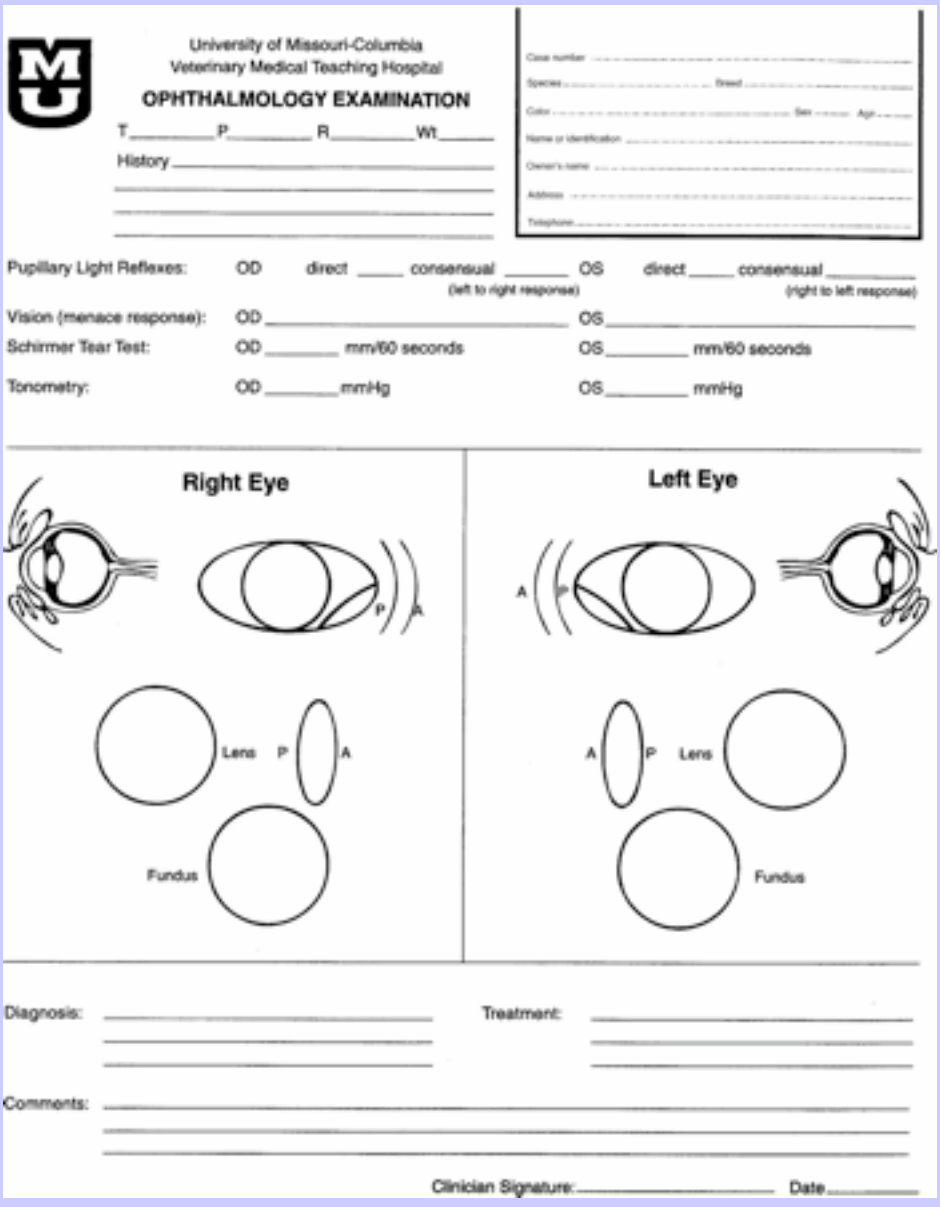
Fig. 39-2 Use of an ophthalmologic examination form allows the clinician to perform a complete, systematic ocular examination.



At this point, the examiner determines if ocular cultures or tear measurements are desired, because these procedures must be completed before further manipulations are performed and before topical pharmacologic agents are instilled.[2] Depending on the clinical signs, severity of ocular disease, and species being examined, viral, bacterial (e.g., *Chlamydia, Mycoplasma*), or fungal cultures may be indicated. Sterile swabs moistened with saline and appropriate enrichment broth or transport media are applied to the tissue to be cultured (usually cornea or conjunctiva). The moistened tip is placed in direct contact with the tissue surface and the swab rotated by spinning the end of the stem with the fingertips.

The rest of the ophthalmic examination is performed in a darkened area, initiated by directing a focused light through each pupil to establish the presence of a fundus reflex (light reflected from back of eye that normally fills pupil space). By evaluating the fundus reflex in each eye, the examiner may compare pupil sizes, characterize pupillary light reflexes, and assess clarity of the ocular media.

Examination of ocular structures should be performed in a set pattern (i.e., anterior to posterior).[3–6] Use of an ophthalmic examination form is helpful in systematically guiding the clinician through the examination and providing a record of examination findings (see Fig. 39-2).

The eyelids are inspected for integrity, position, and movement. Each lid is digitally everted for inspection of the margins, meibomian gland openings, and palpebral conjunctiva. Paresis, malposition (entropion, ectropion), defects, masses, inflammation (swelling, ulceration, exudates), alopecia, foreign bodies, and abnormal lashes are noted.

The nictitating membranes are examined for normal position, integrity of surfaces and margin, degree of pigmentation, and the presence of follicles or masses. To inspect for foreign bodies possibly concealed by the third eyelid, topical anesthetic solution (0.5% proparacaine) is instilled repeatedly onto the ocular surface. Two drops every 20 to 30 seconds for four applications is generally adequate. After topical anesthesia is applied, the nictitating membrane is grasped and manipulated with blunt-tipped, slightly serrated thumb forceps, and both sides are examined for foreign bodies.

Normally the conjunctiva appears moist, glistening, and semitransparent. Signs of conjunctivitis are chemosis (conjunctival edema), hyperemia, and ocular discharge. Color changes of the conjunctiva usually accompany anemia (blanched, pale) or icterus (yellow, amber). Chemosis may indicate severe hypoproteinemia. Conjunctival lesions noted include focal swellings, follicles, adhesions, or masses. The sclera underlying the bulbar conjunctiva is inspected for color, contour, swellings, masses, pigmented areas, or surface irregularities.

The avascular cornea should be smoothly contoured and transparent with a moist, reflective surface. The cornea is examined for irregularities and opacities and for the presence of blood vessels and melanin. Corneal edema appears as a hazy blue corneal opacity and should be characterized as localized or diffuse. With severe corneal edema, the epithelial surface may bulge and bullae (vesicles) may be noted. With corneal suppuration and necrosis, the cornea becomes more densely opaque and acquires a beige, green, or milky appearance. Infectious keratitis is characterized by suppuration and necrosis. Corneal abscesses occur as focal areas of suppuration within the stroma underlying a nonulcerated cornea.

Corneal opacities may also result from focal or diffuse scarring, areas of corneal degeneration or dystrophy, or stretching of Descemet's membrane from previous elevation of intraocular pressure or previous trauma. Inflammatory products clustered on the corneal endothelium (keratic precipitates) appear as multiple beige or brown foci, usually on the ventral aspect of the corneal endothelial surface. This finding indicates the presence of anterior uveitis.

Lacrimal system examination entails evaluation of both secretory and excretory components. Normal secretions result in a moist, glistening ocular surface. Although not typically performed in large animals, tear test strips may be used to quantify the volume of aqueous tear secretion (see Ancillary Diagnostic Procedures). To examine the excretory components, the upper and lower puncta and nasal openings of the nasolacrimal system are identified. Any overflow of tears onto the face (epiphora) is noted. Causes of increased ocular secretions (e.g., frictional irritants, foreign bodies, corneal ulcers, ocular inflammation) must be ruled out. Causes for stimulation of lacrimal secretions must be differentiated from causes of outflow occlusion, such as congenital atresia and acquired obstruction of the nasolacrimal system.

Fluorescein dye instillation determines if corneal ulceration is present and aids in assessment of nasolacrimal system patency. Passage of dye from the nasal opening of the nasolacrimal duct within 5 minutes confirms patency. Retrograde irrigation of the nasolacrimal duct by inserting a length of 5-Fr flexible tubing into the nasal punctum and flushing with physiologic saline solution may be necessary to differentiate insufficient drainage from excessive secretions.

Intraocular examination begins with evaluation of the clarity and depth of the anterior chamber. Opacities within the anterior chamber include inflammatory products (cells and fibrin), proteins (flare), red blood cells (hyphema), or white blood cells (hypopyon). Suspended or clustered inflammatory materials in the anterior chamber indicate intraocular inflammation (anterior uveitis). Besides the presence of exudates, loss of anterior chamber transparency may result from lens luxation, anterior synechia, or intraocular masses (neoplasia or foreign bodies). Loss of normal anterior chamber depth may result from flattening of the cornea, leakage of aqueous humor, staphyloma formation (protrusion of uvea through the cornea), iris bombé (forward bulging of the iris caused by iris-lens adhesions), or forward displacement of the lens. Increased depth of the anterior chamber may be caused by a protruding cornea (keratoconus) or posterior displacement of the iris or lens.

The iris is inspected for altered contour, pigmentation, mobility, neovascularization, pupil size and shape, and the presence of iridal masses (including the normal granula iridica). Transillumination of iris masses allows differentiation of solid iridal masses (e.g., melanoma) from iris cysts. In animals with lightly colored or spotted hair coats, multicolored irides should be recognized as normal variants. Although uncommon, congenital iris thinning (hypoplasia) may be noted as dark, flat, or translucent areas. The lens-iris interface is best evaluated when the pupil is dilated. Iris membranes, adhesions, or strands should be characterized as congenital (persistent pupillary membranes) or acquired (synechiae or remnants of iris atrophy).

Pupillary openings are evaluated for size, shape, symmetry, movements, and opacities. Direct and indirect (consensual) pupillary light reflexes are assessed. The examiner must recall that pupillary light reflexes are not a test of vision (i.e., abnormal responses may be observed in visual animals, and normal reflexes may occur in nonvisual animals). Pupillary abnormalities that should be noted are inequality in size (anisocoria), abnormal movements (hippus), abnormal location (corectopia), or abnormal shape (dyscoria). 1262 1263

Opacities of the pupil usually result from loss of lens transparency or from presence of intraocular exudates. Obscuration of the pupil space may occur with severe miosis (from acute anterior uveitis), condensation of anterior chamber exudates, or synechiae formation (from chronic uveitis). In animals with normal pupillary light reflexes, complete examination of the lens and structures posterior to the lens (i.e., vitreous and fundus) may be achieved only after dilation with a mydriatic agent such as 1% tropicamide, which usually occurs 20 to 30 minutes after instillation.

Using a focused light, the lens is inspected for a smooth, transparent, convex anterior capsule and normal position (no part of the equator should be visible). When evaluating for lens opacities (cataracts), the examiner

should direct the focused light through the axial part of the lens to establish the presence of a fundus reflex. Cataracts may be classified according to the extent to which a fundus reflex occurs; a *partial* reflex indicates an incomplete cataract, whereas an *absent* reflex indicates a complete cataract). Focal cataractous changes are observed as dark areas seen within the area of reflected light.

An ophthalmoscope must be used to examine the vitreous and fundus. Using the monocular direct ophthalmoscope, the vitreous should be in focus with a dioptric setting between +6 to +1, and the fundus is usually in focus between +1 and −2 diopters. The vitreous is examined for congenital remnants (retained hyaloid structures) and opacities, including degenerative materials or exudates.

Examination of the fundus begins with identifying the optic disc (papilla) and studying its size and shape. The shape, location, and vascular pattern of the optic disc and the appearance of the fundus vary considerably among species. In ruminants the optic disc margin typically appears irregular and fluffy, indicating myelination of axons entering the optic disc. However, it tends to be horizontally elliptical or kidney shaped and located in the tapetal portion of the fundus.[4] An optic disc with extensive myelination may be elevated above the surface of the fundus (sometimes called *pseudopapilledema*). In ruminants the major retinal arterioles are large and are accompanied by venules that anastomose on the surface of the optic disc. The dorsal arteriole and venule usually intertwine as they course away from the disc over the midtapetum (Fig. 39-3). By contrast, the equine fundus is characterized by a large, pink or salmon-colored, horizontally elliptical or oval disc located in the nontapetum[5] (Fig. 39-4). In equidae, multiple small retinal blood vessels extend radially from the margin of the disc, and no anastomotic venules are visible over the optic disc.

In both ruminants and horses the fibrous tapetum is penetrated by choroidal capillaries; thus the fundus in these species is typified by dark, stippled foci termed *stars of Winslow*. Coloration of the tapeta of large animals also varies considerably and may range from gold to bluish green. In animals with heterochromia irides, areas of the fundi may characteristically be devoid of pigmentation and may lack a tapetum. These areas may appear orange or red because of direct visualization of the choroidal vasculature.

Abnormalities of the optic disc include hypoplasia (micropapilla), elevation (papilledema), depression (cupping), degeneration (atrophy; Fig. 39-5), and vascular changes (e.g., congestion, attenuation, hemorrhage). The tapetal fundus is evaluated for clarity, coloration, pigmentation (Fig. 39-6), and integrity of the retinal vessels (Fig. 39-7). The nontapetal fundus is evaluated for uniformity of pigmentation. Both tapetal and nontapetal areas are assessed for retinal elevations or separations (Fig. 39-8), hemorrhages, degenerations, disorganization (dysplasia), or scleral defects (colobomas).

Fig. 39-3 Normal ruminant fundus characterized by a large, kidney-shaped, myelinated optic disc. Note that the large retinal arteriole and venule intertwine as they course dorsally.

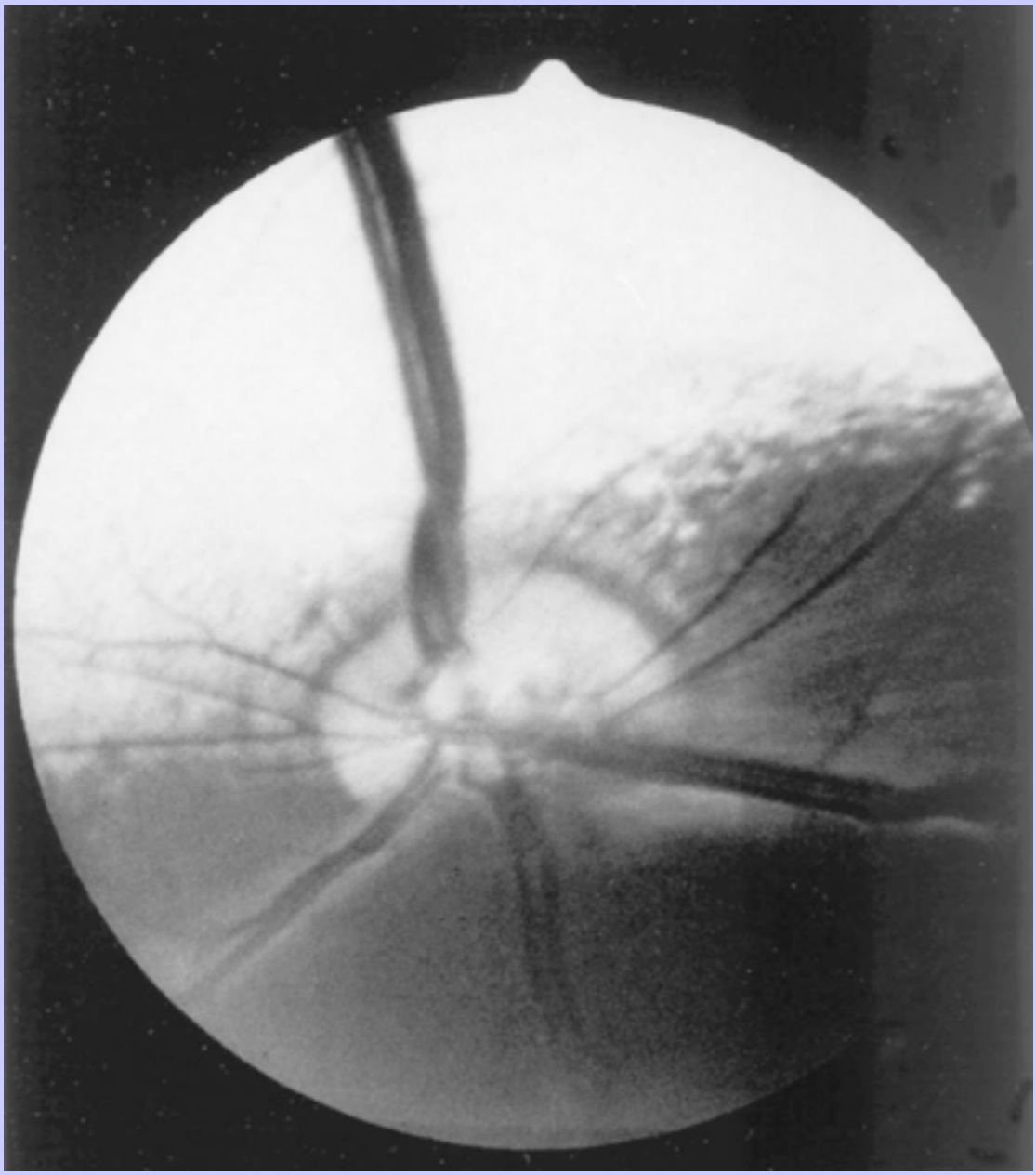
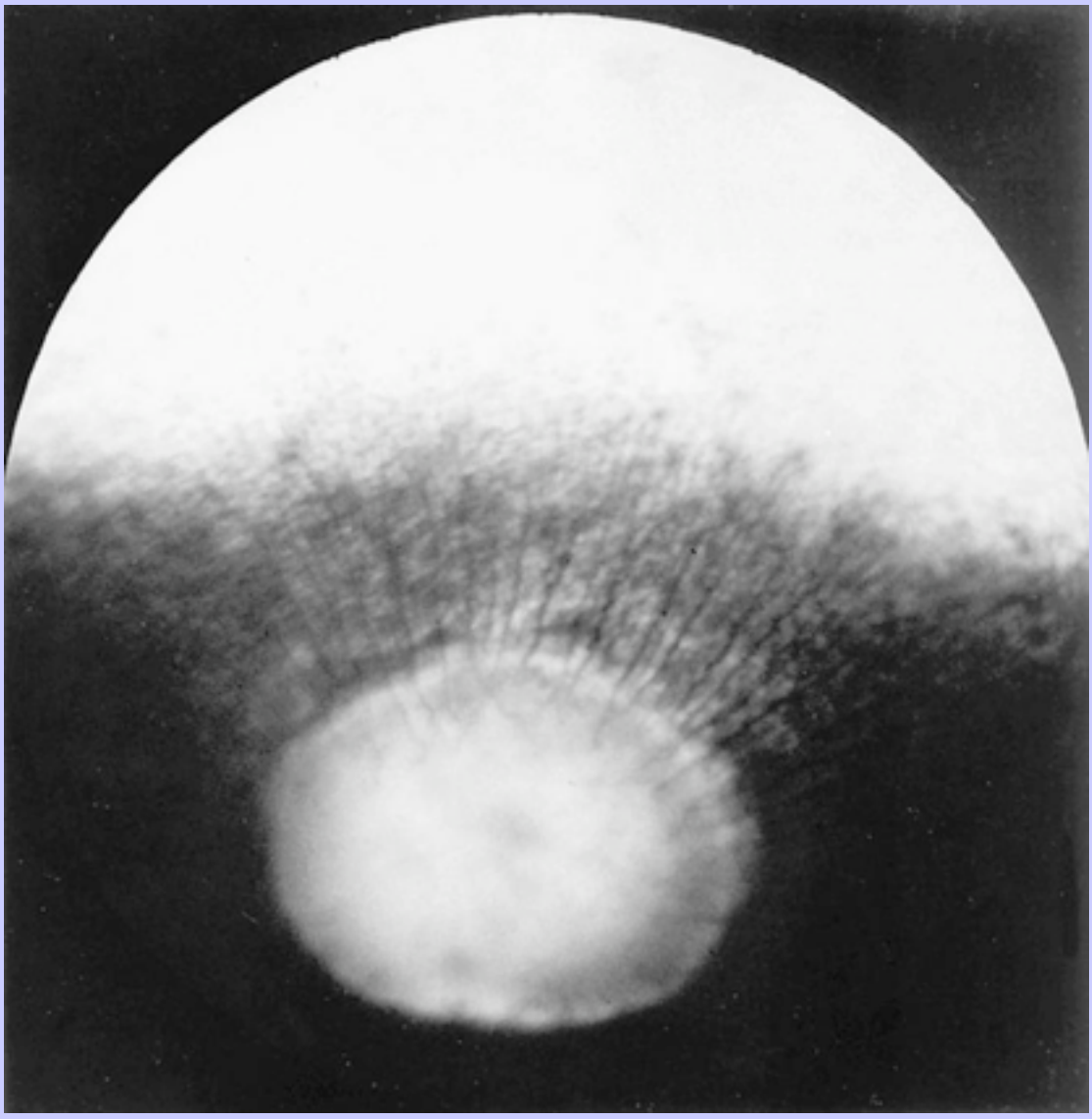


Fig. 39-4 Normal equine fundus characterized by a large horizontally elliptical optic disc with numerous small retinal vessels entering (arterioles) and exiting (venules) the margin of the optic disc. Note that the optic disc lies in the nontapetal portion of the fundus.



39.4 ANCILLARY DIAGNOSTIC PROCEDURES

Several additional procedures may form important supplements to the complete ophthalmic examination. Although some ancillary procedures require specialized equipment and expertise, many may be performed in general practice.

Fig. 39-5 Optic nerve atrophy (equine). The margin of the disc is quite distinct because of myelin loss, which is characteristic of optic nerve atrophy. Note absence of retinal blood vessels.

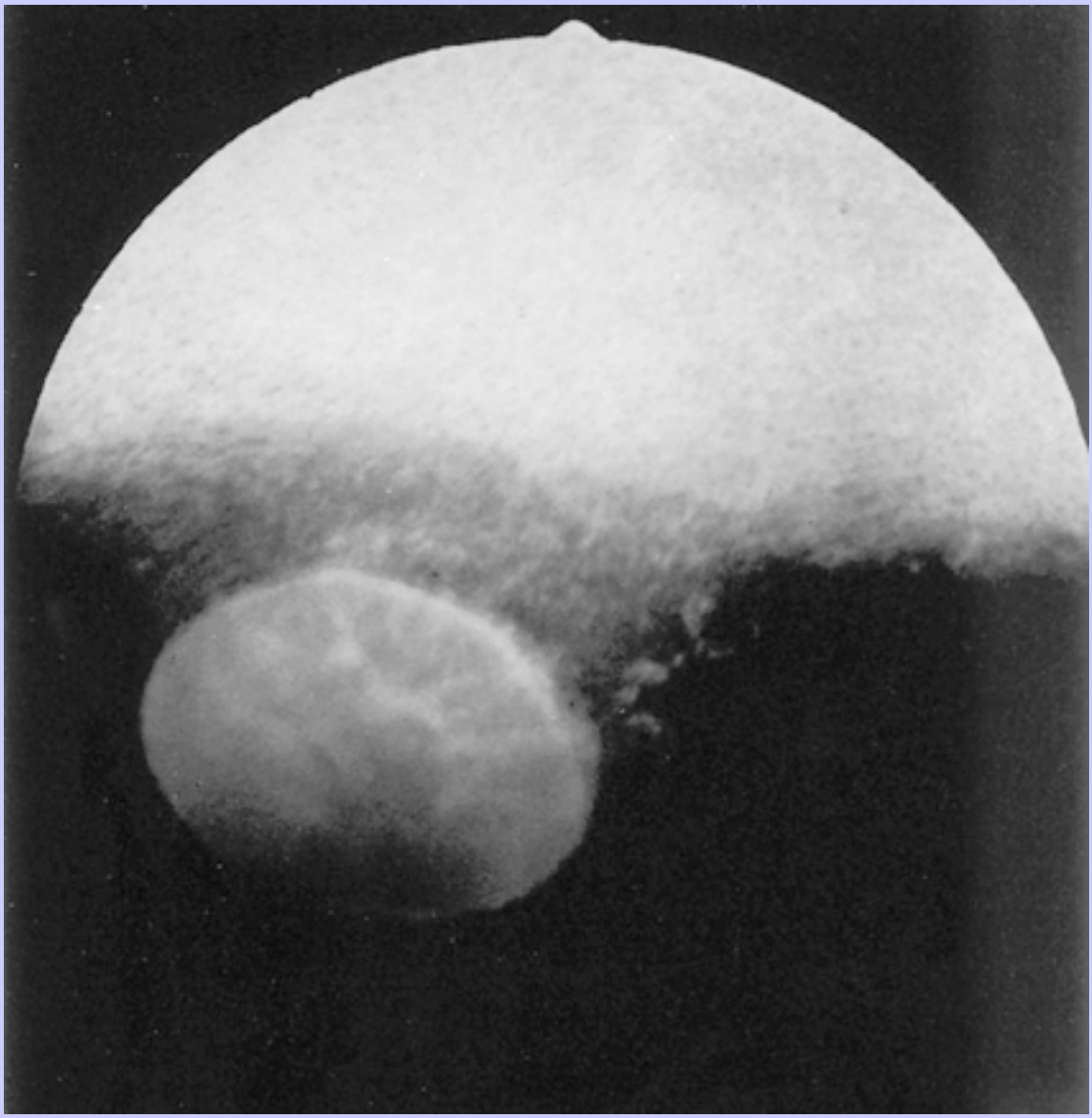


Fig. 39-6 Pigmentary changes after traumatic chorioretinopathy. Irregular linear areas of hypopigmentation and hyperpigmentation are present in the tapetal fundus of a horse after ocular trauma. Pigmentary changes reflect retinal pigment epithelial disturbance from previous hemorrhage and edema. *Courtesy Dr. K.N. Gelatt*.

Fluorescein and rose bengal are ocular surface stains most often used as aids in diagnosing conjunctival and corneal diseases. The tip of a sterile dye-strip is moistened with saline or eye-irrigating solution, and a drop of the stain is instilled onto the eye. Fluorescein is a water-soluble dye used to detect exposed corneal stroma resulting from an epithelial defect (erosion), stromal ulceration, or descemetocele. The pattern of fluorescein staining for a

descemetocele is characterized by a donut-shaped area of positive fluorescence, with the perimeter retaining stain and the center or deepest area (Descemet's membrane) not retaining stain. Fluorescein may also be used to evaluate the patency of nasolacrimal ducts because an open duct allows the transmission of stain, which may be observed exiting the duct system at the nasal orifice. Rose bengal is retained by devitalized surface cells and is 1264
therefore useful in detection of subtle abnormalities such as hyperplastic or desquamating cells associated with 1265
ocular surface drying, herpetic infection, or squamous cell carcinoma.

Fig. 39-7 Retinal degeneration (bovine). Peripheral retinal vessels are greatly attenuated near the tapetal-nontapetal junction. The attenuation is accompanied by hyper-reflectivity of the tapetal region. These changes are consistent with generalized retinal atrophy.

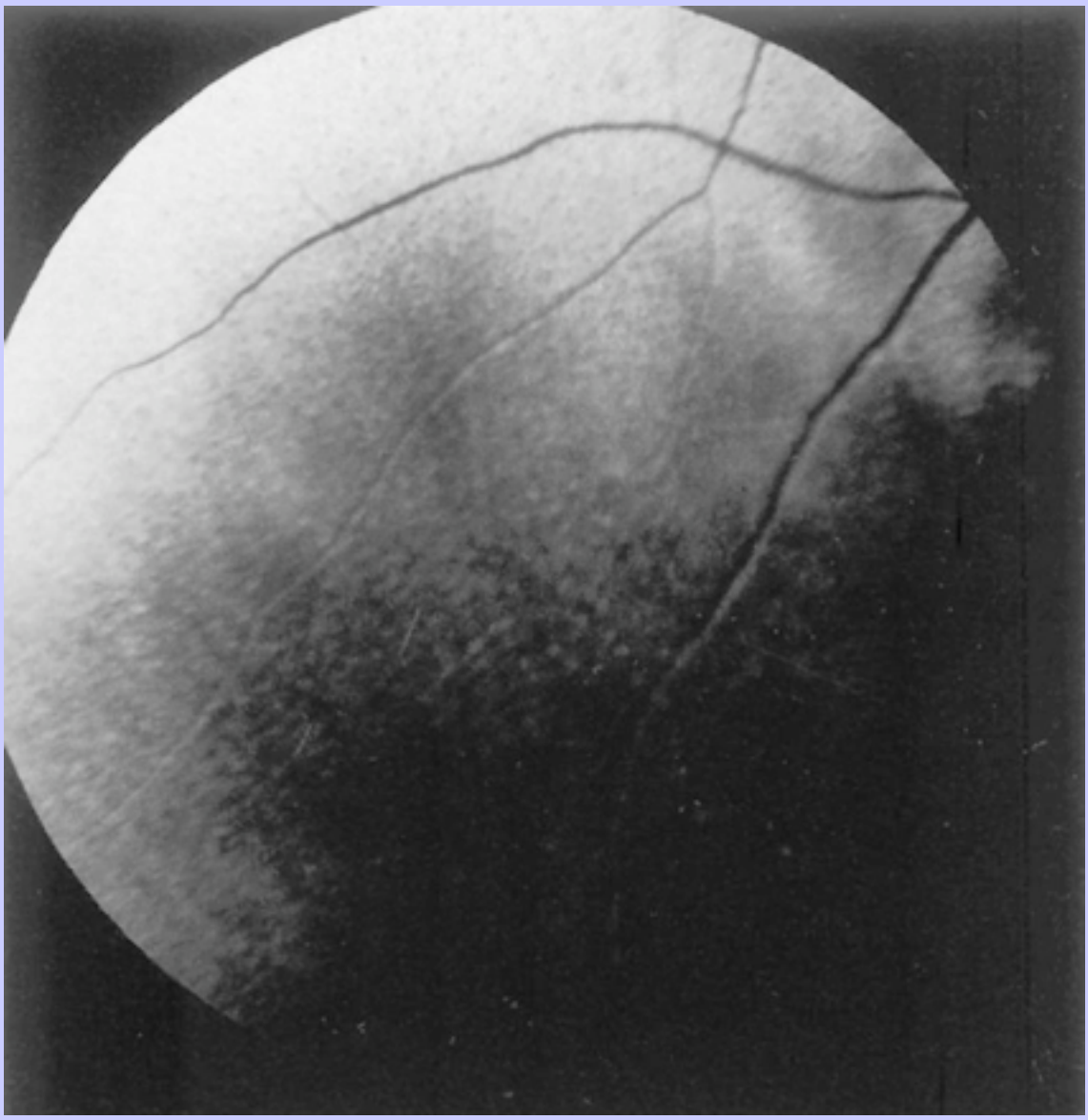
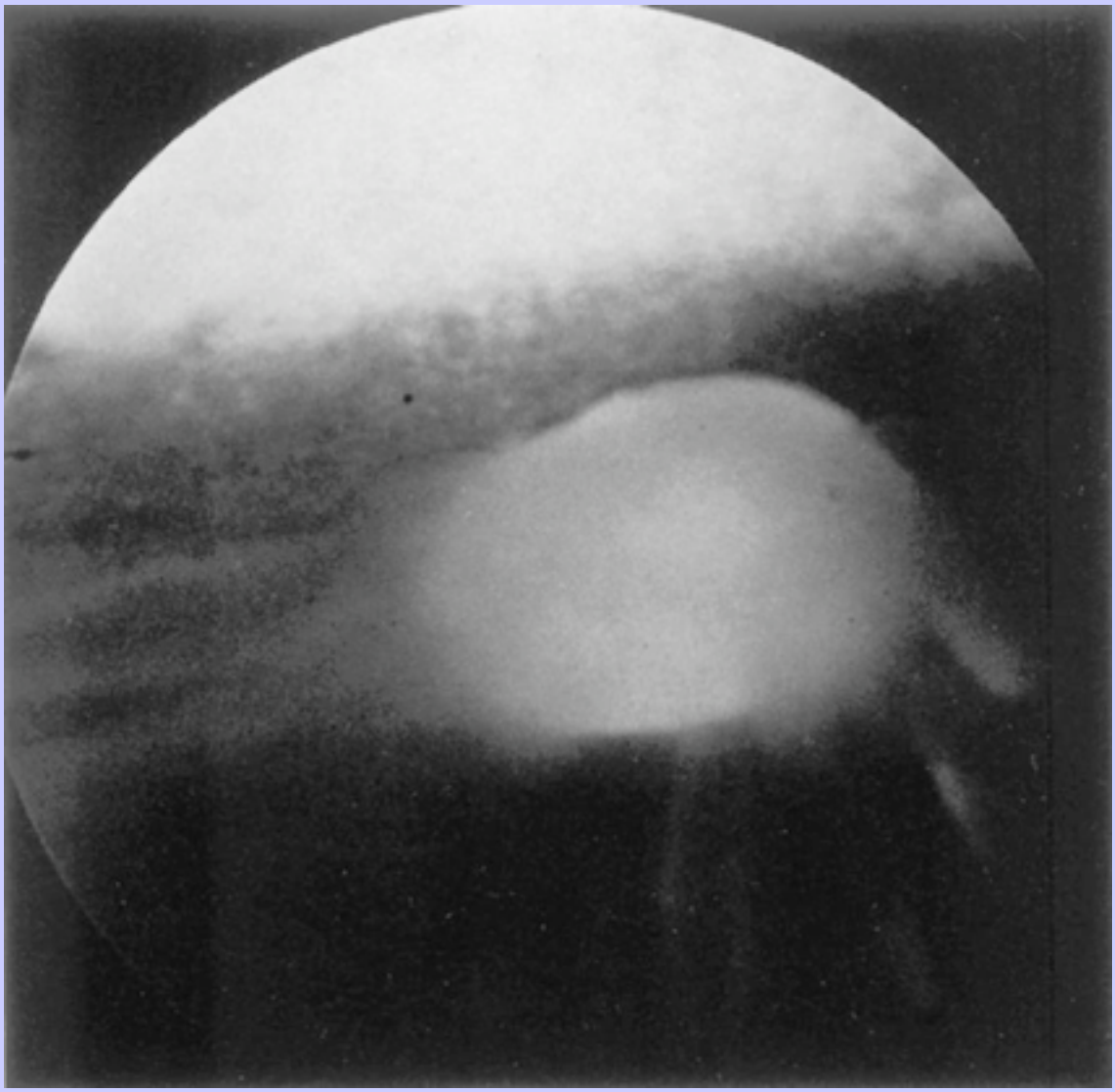


Fig. 39-8 Retinal separation (equine). Gray, linear areas radiate from the optic disc into the nontapetal region of the fundus. Note that the margin of the disc is quite indistinct in the affected area. An absence of retinal vessels indicates concurrent retinal degeneration.



Although tear deficiencies are uncommon in large animals, tear test strips may be beneficial to quantify aqueous tear production in selected cases. A sterile filter paper strip (40 × 5 mm with notched end) is inserted into the lower conjunctival fornix. In large animals it is sufficient to measure the amount of wetting in 30 seconds (≥20 mm is normal).

Cytologic evaluation of ocular surface scrapings or intraocular aspirates may differentiate between inflammatory and neoplastic diseases or in some cases may provide a definitive diagnosis. Orbital aspirates may be diagnostic in

cases of exophthalmos caused by neoplasia (e.g., lymphosarcoma). Immunofluorescent testing of cytologic specimens may confirm viral (e.g., infectious bovine rhinotracheitis) or chlamydial infections.

Bacterial cultures taken from the ocular surface or from ocular aspirates, with subsequent antimicrobial susceptibility testing, may be necessary for definitive diagnosis and appropriate treatment of ocular infections. The diagnostic laboratory performing ocular cultures may offer suggestions on culture procedures, including preferred transport media and handling of samples. It is especially important to consult with the laboratory in advance when anticipating culturing for fungi, *Mycoplasma, Chlamydia,* or viral agents.

Tonometry, a means of measuring the intraocular pressure (IOP), is useful in diagnosing glaucoma (elevated IOP) and uveitis (low IOP) and in assessing response to therapy for these conditions. Digital tonometry (gently indenting the globe through the upper eyelid) provides a general evaluation of IOP, at best characterizing the globe hypotensive, normotensive, or hypertensive. Digital tonometry should not be done if the cornea is compromised by a deep ulcer or laceration. By contrast, applanation tonometry using the Tonopen provides accurate and reproducible IOP readings in large animals and is routinely performed at referral institutions or specialty practices. Schiøtz tonometry is not applicable to large domestic species.

Biomicroscopy, using a portable handheld slit lamp, is useful for identifying the location and nature of anterior ocular opacities. Focal irritants (e.g., ectopic cilia, small foreign bodies) may only be visible with the magnification provided using biomicroscopy. In addition, subtle opacities of the lens and anterior vitreous may only be detected with the use of a slit-lamp biomicroscope.

Funduscopic examination may be performed relatively quickly and easily using the technique of indirect ophthalmoscopy. Monocular indirect ophthalmoscopy is performed using a handheld light source and a separate 20- or 28-diopter focusing lens. Binocular indirect ophthalmoscopy uses a light source mounted on a head band with an incorporated prism and binocular viewing apertures. Binocular indirect ophthalmoscopy provides a stereoscopic, panoramic view of the fundus and is routinely performed by veterinary ophthalmologists. The light sources used for indirect ophthalmoscopy may be adjusted to relatively high intensities and therefore enhance visualization of the fundus through partially opacified or hazy ocular media.

Other ancillary diagnostic procedures include electroretinography, visual-evoked potentials, and imaging procedures (radiography, ultrasonography, computed tomography). Although plain skull radiographs and some contrast studies (e.g., dacryocystorhinography) may be performed in a general practice setting, the remaining procedures require techniques and equipment usually available only at referral centers.

39.5 SIGNS OF OCULAR DISEASE

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The five major signs of eye disease are as follows:

- Ocular or periocular asymmetry
- Ocular color change
- Ocular discharge
- Ocular pain

- Visual deficits or blindness

Although any one of these signs alone may be the most obvious evidence of ocular disease, they frequently occur in various combinations. This section provides a general description of the signs and examples of ocular diseases in which a particular sign predominates. Table 39-1 summarizes common signs of ocular disease in large animals.

39.6 OCULAR OR PERIOCULAR ASYMMETRY

Ocular or periocular asymmetry results from unilateral changes in anatomy of the orbit, orbital contents, globe, eyelids, or pupils. Such changes often involve reduction or increase in volume of a certain tissue. *Reduction* in tissue volume occurs with congenital hypoplasia, cicatricial shrinkage, atrophy, or dehydration. *Increase* in tissue volume may involve the whole globe (buphthalmos) or be characterized by irregular enlargement, as seen with inflammatory or neoplastic lesions involving the globe, orbit, or lids. Asymmetry may also result from neurologic dysfunction. Common examples include reduced palpebral fissure size (secondary to facial nerve paralysis), strabismus, third eyelid protrusion, and anisocoria (see Chapter 8). This section describes a method of approaching the eye examination and of categorizing lesions noted. It is not the intent to describe in detail each of the diseases that may be noted; these are covered in other sections of this chapter.

Forward displacement of the eye (exophthalmos) is often associated with a space-occupying orbital lesion or, less often, a congenitally shallow, underdeveloped orbit. Posterior malposition of the globe (enophthalmos) may result from active globe retraction caused by pain or from loss of supporting retrobulbar soft tissues. Congenital strabismus is a developmental abnormality that results in ocular asymmetry and is typically seen in Jersey, Shorthorn, and Holstein cattle.[7]

Unequal globe size can also account for ocular asymmetry. A congenitally small globe (microphthalmia) occurs as a genetic defect in cattle and horses.[7,8] Microphthalmia is frequently accompanied by multiple ocular anomalies and sometimes is associated with multiple organ involvement. Acquired variations in ocular size usually result from fibrosis and shrinking (phthisis bulbi) secondary to chronic uveitis, or stretching of the globe (megaloglobus, buphthalmos) because of glaucoma.

Asymmetry of the upper or lower lid may occur as a result of entropion, ectropion, blepharitis, conjunctivitis, or facial nerve paralysis (ptosis). Nictitating membrane (third eyelid) protrusion is frequently seen secondary to active retraction of the globe in response to ocular pain, enophthalmos caused by loss of orbital contents (as seen with marked dehydration or malnutrition), presence of third eyelid masses, orbital space-occupying masses, or neurologic disorders (e.g., Horner's syndrome, tetanus). Pupillary asymmetry, or anisocoria, may occur for a variety of reasons, including Horner's syndrome, intraocular diseases (uveitis, glaucoma, unilateral retinal lesions), diseases involving the optic nerve or brainstem, and previous use of pharmacologic agents such as atropine that alter iris smooth muscle function.

Table 39-1 Causes of Important Ocular Signs in Large Animals

Signs/Findings	Cause(s)		
	All Species (Ruminants and Horses)	Ruminants	Horses
RED EYES			
Surface Redness			
Hemorrhage	Trauma Clotting disorders		
Hyperemic mass	Granulation/healing corneal ulcer		*Habronema* granuloma
	Ocular squamous cell carcinoma		
	Hemangiosarcoma		
Diffuse Redness			
Conjunctivitis/keratitis	Entropion Foreign body Chemical irritation	*Moraxella* (IBK) *Mycoplasma* (O, C) *Chlamydia* (O) Herpesvirus (IBR) (B, C) *Branhamella* (B) Bluetongue	Fungal keratitis *Pseudomonas* *Streptococcus* Coliforms
Uveitis	Septicemia Trauma	*Mycoplasma* Malignant catarrhal fever (B)	Immune-mediated uveitis (ERU)
Glaucoma	Trauma	IBK (B)	ERU
Hemorrhage	Trauma		
CLOUDY EYE (OCULAR OPACITIES)			
Cornea	Keratitis Trauma Ulcers Scars (healed ulcers)	Infectious keratoconjunctivitis (see causative agents above for Conjunctivitis/keratitis by genus)	
	Uveitis (see under Red Eyes)	IBK (B)	ERU
	Glaucoma		
Anterior chamber			
Exudates, blood	Trauma Uveitis (see under Red Eyes) Glaucoma	*Mycoplasma* (C) Septicemias (B, C, O)	ERU
Lens luxation (anterior)	Trauma		ERU
Lenses (cataracts)	Trauma Congenital (see Chapters 51 and 52) Genetic Uveitis (see under Red Eyes)		ERU

Vitreous			
Exudates, blood	Trauma (hemorrhage, detached retina) Uveitis (see under Red Eyes)	Congenital hyaloid vascular remnants (B)	ERU
Lens luxation (posterior)	Trauma		ERU
OCULAR DISCHARGE			
Watery (serous)			
Painful eye	Ectopic or misdirected cilia	Conjunctivitis/keratitis (see specific etiologies under Red Eyes)	
	Foreign body (plant awn) Entropion Uveitis (see under Red Eyes) Trauma (ulcer, uveitis)Chemical irritation		
Nonpainful eye	Nasolacrimal atresia Nasolacrimal obstruction (acute blockage)		
Thick (mucoid or mucopurulent)	Foreign body Surface tumors Dacryocystitis Chronic nasolacrimal blockage Foreign body Sinusitis Bacterial infections	Infectious keratoconjunctivitis (see causative agents under Red Eyes for Conjunctivitis/keratitis by genus)	
Hemorrhage	Trauma Foreign bod Ulcerative conjunctivitis Tumor		

IBK, Infectious bovine keratoconjunctivitis; *IBR,* infectious bovine rhinotracheitis; *ERU,* equine recurrent uveitis; *O,* ovine; *C,* caprine; *B,* bovine.

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The presence of an ocular mass may be the primary cause of ocular asymmetry. Ocular surface neoplasms are relatively common in horses and cattle. Ocular squamous cell carcinomas usually arise from nonpigmented tissues of the nictitating membrane, the lateral limbal region, or the eyelid margin. They may appear as irregularly raised surface masses or, less often, as smooth, vascularized lesions that invade the globe. Ulceration, exudation, and mucopurulent ocular discharge are frequent concurrent findings (see Ocular Neoplasia). Periocular sarcoids are also common in horses and appear as firm, raised, nonulcerative lesions.[9] Other ocular tumors, such as adenomas, adenocarcinomas, angiomas, angiosarcomas, mastocytomas, and melanomas, occur in large domestic animals but are relatively uncommon. Dermoids and orbital cysts are congenital masses involving the eye or orbit. Other nonneoplastic ocular masses seen in large animals include firm parasitic and foreign body granulomas and soft, fluctuant subconjunctival swelling characteristic of prolapsed periorbital fat. Ocular and orbital pseudotumors have also been described in the horse.[10]

39.7 OCULAR COLOR CHANGE

Changes in the color of the ocular or periocular tissues or the presence of opacities in the clear ocular media (cornea, aqueous humor, lens, or vitreous) are important features of ocular disease. Such changes must be differentiated from normal congenital differences in ocular pigmentation. Developmental color dilution or absence of ocular pigmentation results in light or multicolored irides (heterochromia iridis). When this occurs unilaterally, the resulting appearance may be striking. Examples of abnormal coloration include hyperemia of conjunctival (superficial) or episcleral (deep) blood vessels associated with ocular inflammation (see Red Eyes, Table 39-1), hemorrhage secondary to trauma or coagulopathies, pallor of the conjunctiva, which reflects severe anemia, and yellowing of the sclera and sometimes iris, indicating icterus.

Opacities of the ocular media may occur either as surface (corneal) or intraocular (anterior chamber, lens, or vitreous) phenomena. Sources of corneal opacification include melanosis ("pigmentation") secondary to chronic exposure, grayish scars from previous episodes of ulcerative keratitis, neovascularization secondary to chronic inflammation, and bluish discoloration caused by corneal edema. These color changes frequently occur in various combinations in more severe keratitis, especially those of infectious origin such as chronic keratoconjunctivitis caused by *Chlamydia* species, *Mycoplasma* species, or *Moraxella bovis*. Cataracts are perhaps the most obvious cause of intraocular opacities in large animals. However, the presence of exudates within the aqueous humor or vitreous, congenital vascular remnants in the vitreous, or retinal detachment may also account for intraocular opacities (see Table 39-1).

39.8 OCULAR DISCHARGE

Ocular discharges are characterized as serous ("epiphora"), mucoid (catarrhal), purulent, or hemorrhagic (sanguineous). The type of discharge may be used to aid in determination of the severity and chronicity of the eye disease. For example, serous discharge generally indicates milder forms of eye disease, whereas mucopurulent or hemorrhagic discharge indicates more serious disorders. A notable exception to this generalization is *equine recurrent uveitis* (ERU), which is a serious and potentially blinding disease but is usually associated with serous discharge (see Immune-Mediated Ocular Diseases). The nature of ocular discharge tends to change as the disease progresses or improves. This is most notable in inflammatory or infectious ocular diseases. Initially, the discharge is predominantly serous; however, it tends to become mucopurulent with chronicity (see Table 39-1).

Epiphora describes facial wetting and results from overflow of tears over the eyelid margin. This may result from excessive secretion of tears or from obstruction of the nasolacrimal system. In large animals, reflex lacrimation with an associated overabundance of tears is the typical response to ocular inflammation (e.g., conjunctivitis, keratitis, uveitis). When epiphora is noted, careful digital and visual examination for foreign bodies within the conjunctival fornix or under the third eyelid is indicated. Epiphora is generally one of the earliest signs of conjunctivitis, ulcerative keratitis, or anterior uveitis. In cattle with keratoconjunctivitis caused by *Moraxella bovis,* epiphora is present several days before visible corneal ulceration occurs[11] (see Infectious Bovine Keratoconjunctivitis).

Developmental defects or malformations of the nasolacrimal duct system (e.g., imperforate puncta) may account for ineffectual outflow of tears in neonates. In these cases the presence of epiphora may be misinterpreted as an overproduction of tears. Previously undiagnosed congenital defects may also be the cause of persistent ocular discharge in adult animals. Acquired obstructions of the nasolacrimal ducts may result from infections, foreign bodies, facial trauma, nasal tumors, or sinusitis that involve the duct system. When nasolacrimal obstruction is present, the nature of the ocular discharge depends on the chronicity of the lesion and the presence or absence of

infection within the nasolacrimal system. Whether congenital or acquired, simple nonseptic obstructions are characterized by epiphora. Occlusions with concurrent sepsis result in mucopurulent discharge from the eye or nostril on the affected side. Excessive mucus production is a feature of follicular conjunctivitis, possibly as a result of the rubbing of elevated lymphoid follicles on apposing conjunctival surfaces. Lymphoid follicles are noted in subacute or chronic forms of chlamydial conjunctivitis in sheep and with *Onchocerca* larval migration in horses. Mucoid ocular discharge may be observed concurrently with epiphora in acute ocular surface infections caused by viral or chlamydial agents. Excessive, tenacious mucus may also result from inadequate secretion of the aqueous component of tears (i.e., keratoconjunctivitis sicca). Although keratoconjunctivitis sicca is not diagnosed as commonly in large animals as it is in dogs, it has been reported in horses, usually as a complication of guttural pouch pathology.[12]

Purulent to mucopurulent material is the characteristic ocular discharge when bacterial organisms, including *Mycoplasma* species, are the primary cause of, or secondary contaminants in, ocular disease. Bacterial conjunctivitis occurs frequently in large domestic species and manifests as red eyes with copious amounts of mucopurulent ocular exudate. Ocular foreign bodies and surface masses (e.g., squamous cell tumors) typically have associated bacterial infections. Mucopurulent discharge in the absence of ocular inflammation suggests infection of the nasolacrimal sac (dacryocystitis) or ducts, with reflux of exudate from the lacrimal puncta.

Sanguineous of hemorrhagic discharge most often occurs after blunt or penetrating trauma to the eye (see Ocular Trauma). Foreign body penetration may damage the eyelid, conjunctiva, or globe, resulting in bleeding onto the ocular surface. Corneal ulcers may rupture and result in uveal prolapse and subsequent hemorrhage on the ocular surface. Ulcerative conjunctivitis from abrasion or infection may result in bleeding into the tear fluids. Similarly, ocular surface tumors may become ulcerative and cause bloody ocular discharge. Whenever blood is noted on the surface of the eye, it is imperative that a thorough ophthalmic examination be performed to determine the cause and to evaluate integrity of the globe.

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39.9 OCULAR PAIN

Blepharospasm, epiphora, apparent photophobia, and periocular hyperesthesia are signs of ocular pain. Animals with severe ocular pain usually resist manipulation of the eyelids or any form of ocular examination by persistently jerking the head away from the examiner and by closing the eyelids tightly. In cases of persistent ocular inflammation, discomfort and pruritus may be manifested by rubbing and self-trauma to ocular or periocular structures.

Ocular pain may result from blunt or penetrating trauma. Corneal ulceration and uveitis are painful sequelae to ocular trauma. Limbal (scleral) ruptures from blunt injury or penetrating lacerations of the fibrous tunic may result in uveal prolapse (staphyloma), which is extremely painful. Periocular trauma may cause eyelid swelling or paresis with exposure and drying of ocular surface tissues, resulting in painful ulcerative keratitis. Inflammatory diseases of nontraumatic origin (e.g., infectious keratoconjunctivitis, ERU) may also cause severe ocular pain in an affected animal. Other causes of ocular pain include frictional irritation, resulting from entropion, trichiasis, distichia, or ectopic cilia, or direct irritation of the ocular surface by foreign material. Foreign bodies causing ocular irritation in large animals are typically plant materials such as seeds, hay stems, straw, twigs, bark, or thorns, although particles of sand or soil can also cause severe ocular irritation. Nonembedded particulate matter is usually entrapped by mucus and washed out of the eye by reflex tearing; therefore it typically results only in transient discomfort. By contrast, embedded foreign material (i.e., between ocular surface layers or within ocular tissues) causes persistent ocular pain.

39.10 BLINDNESS

Visual deficits in large animals manifest in a variety of ways. Obvious signs include bumping into objects in the path of locomotion and being unable to respond to visual stimuli such as light or hand motions. Other signs of blindness are reliance on stationary objects, such as fences, railings, or other animals, to maneuver within the environment. Behavioral changes include reluctance to move or to venture into unfamiliar areas. The nonvisual animal is frequently found standing isolated from the group. Searching nystagmus is also seen in some animals with congenital blindness.

Nonvisual animals attempt to compensate for loss of vision with their other senses, resulting in behaviors that seem peculiar. For example, as an apparent overcompensation for visual deficits, the blind animal may raise its head extremely high with the ears erect at the slightest auditory stimuli. A similarly dramatic response to olfactory stimuli may be noted in affected animals when snorting or intensive sniffing associated with nervousness and maximum neck extension is observed. Frequently, blind animals will show exaggerated elevation of the limbs while walking. This must be differentiated from true hypermetria (see Chapter 8). Partial loss of vision may be difficult to determine, and detection depends on observing more subtle behavioral changes such as slight head cocking or tilting, difficulty maneuvering in dim light, or shying and startling from objects on one side or objects present in some specific part of the visual field. Animals may effectively compensate for congenital blindness or slow diminution of vision, particularly when they remain with other unaffected animals in a familiar environment. Visual disturbance may not be apparent until an affected animal is isolated or moved to an unfamiliar area.

39.10.1 Box 39-1 Lesions and Diseases Causing Visual Deficits or Blindness

39.10.1.1 OBSTRUCTION OF THE OCULAR MEDIA*

39.10.1.1.1 Cornea

Scarring, edema, melanosis (“pigmentation”), inflammatory cell infiltration

39.10.1.1.2 Anterior Chamber

Hyphema, hypopyon, fibrin

39.10.1.1.3 Lens

Cataract

39.10.1.1.4 Vitreous

Vitreal exudation (white blood cells), vitreal hemorrhage

39.10.1.2 RETINOPATHIES

39.10.1.2.1 Degenerative

Glaucoma

Retinal degeneration

39.10.1.2.2 Congenital

Retinal dysplasia

Microphthalmia

Retinal detachment

39.10.1.2.3 Inflammatory

Retinitis/chorioretinitis

Phthisis bulbi

Retinal detachment

39.10.1.3 EXTRAOCULAR AND CENTRAL NERVOUS SYSTEM DISEASE

39.10.1.3.1 Congenital/Inherited

Optic nerve hypoplasia

Storage diseases (e.g., ceroid lipofuscinosis in sheep)

39.10.1.3.2 Inflammatory

Optic neuritis

Meningitis/encephalitis

Trauma

Neoplasia

39.10.1.3.3 Toxic/Nutritional

Toxic optic neuropathy (e.g., Male fern)

Vitamin A deficiency (e.g., optic neuropathy/hydrocephalus)

* See Cloudy Eye (Ocular Opacities) in Table 39-1.

There are numerous causes of blindness in large animals, including those that involve only the visual system and some that involve other nervous system tissues or are multisystemic (Box 39-1). A functional approach to blindness involves anatomically classifying the cause as one of the following:

- Obstruction of the ocular media (light does not reach the retina).
- Failure of the retina to process the light appropriately.
- Failure of the central nervous system (CNS), including the optic nerve, to transmit or assimilate the visual stimuli appropriately.

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Assessment of the pupillary light reflexes (PLRs) aids in the localization of the lesion. Animals with lesions involving the retina, optic nerves, optic chiasm, or optic tracts generally do not have a normal PLR, whereas those with more central ("higher") lesions involving the lateral geniculate bodies, optic radiations, or occipital (visual) cortex are likely to exhibit a normal PLR (see Chapter 8).

39.11 OCULAR TRAUMA

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39.12 CAUSES OF TRAUMA

Because the eye is anatomically prominent in horses and food animals, it is prone to blunt and sharp trauma, which can range in severity from a mild abrasion caused by a conjunctival foreign body to a severe corneal laceration with globe rupture and orbital bone fracture. Ocular injuries may result from a variety of causes, including foreign materials such as soil, sand, or stones, which may be thrown into the eye during running or by the wind; trauma from disciplinary action; scratches by vegetable matter such as hay, weed stems, tree limbs, or thorns; exposure to chemical irritants; and sudden, violent head movements during training, working, or

grooming. Other sources of ocular injury include stanchion, stall or trailer latches, hooks, protruding nails, bucket handles, fencing materials, and other animals, particularly horned ruminants.

Recumbent neonates and animals with CNS disease or severe illnesses that cause depressed mentation often suffer eye injuries from abrasion by debris or bedding materials such as sand, straw, hay, or wood shavings. Such injuries may be prevented by protecting the eye from trauma through the use of a padded hood or soft mats under the head, by keeping the cornea well lubricated in dehydrated animals with reduced blinking frequency, and by administering sedation to prevent thrashing. Following ocular trauma, opportunistic or pathogenic organisms may become established in the wound bed and may cause superficial or deep corneal infections.[13] Ocular flora native to the conjunctiva include potential pathogens that may cause severe infections.[14]

39.13 OCULAR EXAMINATION IN CASES OF HEAD TRAUMA

The goals of examination are to determine the degree of ocular trauma and to offer a prognosis for recovery of vision and preservation of the eye. The history should elicit information as to the cause and duration of the injury, previous ocular and systemic disease or therapy, and a description of any recent sedation, anesthesia, or therapy.

Blunt or sharp facial trauma frequently results in damage to the orbit and globe, including fractures or soft tissue injuries of the orbit, corneal abrasions and edema, hyphema, traumatic uveitis, lens luxation, traumatic cataract, vitreal hemorrhage, retinal tear or detachment, corneal or scleral rupture, or proptosis. Therefore, the orbit and globe and vision should be examined as thoroughly as possible when evaluating a patient with facial trauma.

Ophthalmic examination can be performed only after adequate restraint of the head (see previous discussion). Intravenous (IV) sedation, sensory and motor nerve blocks, topical anesthesia, and the use of a halter, twitch (in horses), or nose tongs (in cattle) often are necessary for adequate examination of the traumatized eye.

39.14 TRAUMA TO THE ORBIT

Orbital injuries in domestic animals frequently include fractures of the orbital rim and zygomatic arch and damage to the supraorbital process of the frontal bone.[15] Fractures of the orbit may be identified by palpation, conventional or digital radiography, computed tomography (CT), or magnetic resonance imaging (MRI). Contusions or lacerations of orbital soft tissues and temporary or permanent neurologic dysfunction also may be present.

Radiographic examination of the bony orbit in large animals is technically difficult and often unrewarding with conventional radiography. Standard lateral and dorsoventral views require powerful radiographic equipment for penetration of bony structures in horses and cattle.[16] Large fractures may be identified, but distinct delineation of the bony orbit is difficult because of overlying sinus and nasal structures. An oblique view of the frontal bone is often the most helpful projection.[16] This view may be taken with a portable machine because only minimal radiographic penetration of skull structures is required. Outlining the orbit and surrounding bony structures allows identification of fractures, osteomyelitis, with or without bony sequestra, and soft tissue abnormalities, including swelling and radiopaque foreign bodies. If a periorbital sinus is involved in the fracture, subcutaneous emphysema may be present. The use of digital radiology may allow enhanced visualization of the bony structures of the orbit, especially when only subtle changes are present.[17] Digital radiography systems used in conjunction with portable equipment may provide adequate detail in standard as well as oblique projections. CT and MRI are available at many referral centers. Detail of the bony and soft tissue structures is greatly enhanced by the cross-sectional views acquired by CT, as are the structures of the calvarium, sinuses, and teeth.[17] MRI is also very beneficial in

delineating soft tissue abnormalities within the orbit and sinuses.[17–19] Immediate evaluation for orbital fractures should include careful examination of the globe. In cases with substantial swelling, ice packs applied to the fracture site may reduce swelling. Systemic antiinflammatory therapy (e.g., flunixin meglumine, ketoprofen, phenylbutazone) may also be given. Systemic antibiotics should be used if sinus involvement is suspected. If the fracture fragments are only minimally displaced, surgical intervention may not be required. Surgical repair should be considered if fragment displacement or entrapment of extraocular muscles has occurred or could occur.[16,20] Trauma sufficient to cause fractures may also result in neurologic dysfunction and immobility of the eyelids.

If eyelid movement is impaired, the globe must be adequately protected and lubricated until neurologic function returns. If the globe is only minimally exposed, a sterile ophthalmic lubricant may be used at least three or four times daily. In more severe cases, a nictitating membrane flap or temporary partial tarsorrhaphy may be required. If neurologic dysfunction is permanent and results in significant exposure conjunctivitis or keratitis, partial or complete permanent tarsorrhaphy should be performed.[16] Enucleation or enucleation with the placement of an orbital prosthesis may be required for severely affected eyes.

Scleral rupture is another potential consequence of blunt trauma to the orbit and globe. A recent study found that the most consistent clinical sign of scleral rupture in horses is eyelid and conjunctival swelling.[21] Other clinical features of this condition are hyphema, subconjunctival hemorrhage, and a collapsed anterior chamber. 1269
Ultrasonographic findings include poorly defined scleral margins and echoic/hyperechoic material in the anterior 1270
and posterior chambers and in the vitreous.[21]

Traumatic puncture wounds of the eyelids and conjunctiva may result in orbital cellulitis and exophthalmos in food animals and horses. The onset of swelling may be sudden. Pyrexia and leukocytosis may be present. If a retrobulbar abscess occurs, temporomandibular movement causes extreme pain; the animal may have the eyes partially closed, be off feed, and stand with the neck extended. The client may observe a relatively sudden onset of exophthalmos, eyelid swelling, severe chemosis, and exposure keratitis.[16,22] Therapy should consist of systemic and topical antibiotics. Ophthalmic ointments and lubricants should be used to provide protection from desiccation of the exposed cornea and conjunctiva. With time, the cellulitis may organize into a discrete abscess that can be located by palpation or ultrasound. The wound or abscess should be debrided or drained to facilitate healing, especially if a well-organized abscess is present.

Although traumatic proptosis is uncommon, it may occur in horses and food animals. The prognosis for return of vision is guarded to poor, depending on the extent of the damage to the optic nerve and retina. If the globe is ruptured or the extraocular muscles are avulsed, the eye should be enucleated. If the extent of the damage cannot be evaluated initially, the globe should be repositioned, a temporary tarsorrhaphy performed, and the globe reevaluated after 7 to 10 days of topical therapy. Treatment should include topical broad-spectrum antibiotics and atropine. With severe fractures or serious ocular damage, consultation or referral to the appropriate specialist is advised.

39.15 TRAUMA TO THE EYELID

Eyelid trauma is frequently accompanied by injuries to other ocular structures. Careful ocular examination should be part of the evaluation of animals with eyelid trauma.[23] Injuries may range from swelling (blepharedema) or orbital cellulitis to extensive lacerations and avulsion. Blepharedema may be accompanied by hemorrhage and usually resolves quickly without therapy; however, recovery may be hastened by the use of ice packs and systemically administered ketoprofen or flunixin meglumine.

Horses are particularly prone to eyelid lacerations because of the prominence of the eye and their tendency toward sudden head movements when startled. Lacerations may be divided into those without eyelid margin involvement, those with eyelid margin involvement, and avulsions of part or all of an eyelid. For all types of eyelid injury, several basic principles should be followed. Lacerations should be treated promptly to avoid distortion from excessive swelling, infection, scarring, and loss of function. Lacerated or displaced tissue should not be excised. It is impossible to replace the mucocutaneous junction of the eyelid margin. If eyelid margin is sacrificed, the risk of scar formation and secondary corneal damage is high. The laceration should be thoroughly and carefully flushed with sterile saline and explored to remove all foreign material. In acute trauma, cold compresses may assist in decreasing swelling. In suturing an eyelid laceration, it is essential to preserve the eyelid margin; therefore, eyelid lacerations should be repaired with minimal debridement. In cases of long-standing or infected lacerations, the wound should be packed with an antibiotic dressing for 24 to 48 hours before surgical repair.[24] In cases of avulsion of part or all of the eyelid, a variety of blepharoplastic procedures may be performed to help restore functional eyelid margin.[23–25]

For a more detailed description of the principles of surgical repair of the eyelids, an ophthalmic surgical text is recommended.[23,24,26]

Postoperative care of all eyelid lacerations should include standard wound hygiene, application of fly repellent and topical ophthalmic antibiotics, and prevention of self-trauma. In contaminated wounds, systemic antibiotic therapy is indicated for 5 to 7 days. Tetanus prophylaxis should be administered.

Improper repair of eyelid lacerations can lead to abnormal function and secondary problems, including chronic epiphora and associated dermatitis, exposure keratitis, ulcerative keratitis, cicatricial entropion or ectropion, conjunctivitis, and pigmentary keratitis.

39.16 TRAUMA TO THE NICTITATING MEMBRANE

Lacerations involving the nictitating membrane (third eyelid) should be repaired to avoid irritation and damage to the cornea. This appears to be more important in horses than in ruminants. The margin should be realigned as precisely as possible, and the lacerated conjunctiva should be repaired with absorbable, small suture material such as 5-0 to 7-0 polyglactin.* Topical ophthalmic antibiotics should be used three to six times daily for 7 to 10 days. The entire nictitating membrane should be excised only if it is irreparably damaged.

* Vicryl, Ethicon, Somerville, NJ.

39.17 TRAUMA TO THE CONJUNCTIVA

Conjunctival lacerations result in swelling (chemosis) and hemorrhage. The cornea and sclera should be examined carefully for evidence of lacerations or perforation. If the globe is excessively soft on digital palpation, the anterior chamber is shallow or flat, or hyphema or subconjunctival hemorrhage is present, a concurrent scleral laceration is probable.[12,21]

Chemosis and hemorrhage frequently resolve without therapy. However, if the chemosis is severe enough to cause exposure and drying of tissues, topical sterile ophthalmic lubricants or antibiotic ointments are indicated to prevent secondary irritation. Conjunctival lacerations rarely require closure unless they are extensive. Subconjunctival hemorrhage sustained during parturition is common in foals and calves and requires no therapy, although topical ocular lubricants or antibiotic ointments are often prescribed.

39.18 TRAUMA TO THE CORNEA

Corneal injuries in horses and food animals include blunt compressive trauma, foreign body penetration, ulcerative keratitis, and lacerations. Corneal perforation often results in iris, or iris and ciliary body, prolapse. Therapy is dictated by the type and extent of corneal injury, the complications encountered, the intended use and economic value of the animal, and other financial considerations.

39.18.1 Blunt Trauma to the Cornea

Blunt trauma to the globe from lead shanks, whips, and other objects can result in corneal endothelial injury and subsequent edema. Signs of traumatic uveitis also may accompany such an injury. The corneal edema that results from blunt trauma to the globe may be focal, linear, or diffuse. Therapy for blunt trauma includes a topical hypertonic (5%) saline solution or ointment two to four times a day to decrease corneal edema.[27] A linear keratopathy, characterized by a nonedematous, deep, striate, refractile opacity in the cornea, may represent a focal thinning or break in Descemet's membrane that has resulted from blunt trauma to the cornea. This type of lesion must be distinguished from Haab's striae, which are linear breaks in Descemet's membrane that result from elevated IOP in glaucoma.

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39.18.2 Corneal Foreign Bodies

Plant matter embedded in the epithelium or superficial stroma is the most frequently encountered corneal foreign body. Foreign bodies usually are easily removed with a moistened, cotton-tipped applicator or ophthalmic forceps. Sedation, motor or sensory nerve blocks, and topical anesthesia facilitate removal. Culture and sensitivity tests and cytologic examination of corneal samples are recommended before therapy is initiated. The cornea is stained with fluorescein dye to evaluate the extent of corneal ulceration. While awaiting laboratory results, medical therapy should include a topical ophthalmic antibiotic (bacitracin-neomycin-polymyxin, gentamicin, or tobramycin three or six times daily) and atropine (as needed). The prognosis is guarded until the cornea heals; the eye should be reevaluated in 24 to 48 hours.

Complications of corneal foreign bodies include bacterial and fungal infection, corneal perforation, and severe corneal scars that may restrict vision. Subpalpebral lavage systems are used in severe injuries when frequent, prolonged therapy is needed or when treating intractable animals (see later under Bacterial Keratitis in Horses).[28]

39.18.3 Corneal Ulcers

Corneal ulcers in horses are usually initiated by trauma and should be considered contaminated by bacteria or fungi until proved otherwise. Trauma may play a lesser role in food animals in which primary infectious etiologies are more common (see Infectious Bovine Keratoconjunctivitis). The conjunctival fornices and eyelids should be carefully examined for foreign material. Diagnosis is based on cytologic examination, culture and sensitivity testing of corneal samples, and fluorescein staining of the cornea. Material for bacterial and fungal culture is collected from the ulcer with sterile rayon-tipped swabs. Cotton swabs are less satisfactory because cotton exhibits some antimicrobial properties. The eyelid margins and skin should be avoided, and better culture results are obtained if the swab is moistened with a sterile solution (sterile water or saline) before specimen collection. The most reliable results are obtained if the swabs are placed in a transport medium at the

time of collection.* The use of a culture tube with saline in an enclosed, breakable ampule is also helpful.[29] The ampule is crushed, and fluid is allowed to moisten the swab before specimen collection. Immediately after collection, the swab is replaced in the tube or inoculated onto standard bacterial and fungal agar plates, or blood agar and thioglycolate broth.

Corneal scrapings for microscopic examination are collected with the use of topical anesthesia. The eyelids are retracted, and the margin of the corneal ulcer is gently rubbed with a small brush, cytology spatula, or the blunt, handle end of a Bard-Parker scalpel blade until a small amount of cellular material is collected. This material is transferred to two to six clean glass slides, spread over a 1-cm (0.4-inch) area and allowed to air-dry. One smear is stained with Diff-Quik; one with Wright-Giemsa, periodic acid—Schiff (PAS), or GMS for fungal hyphae; one with Gram stain; and possibly one with new methylene blue.

Therapy of corneal ulcers is based on the removal of the cause if it is still present, control or prevention of infection with topical antimicrobials, use of topical atropine for relief of painful ciliary body spasm and prevention of synechia, and, in horses, the systemic use of nonsteroidal antiinflammatory drugs (NSAIDs) such as flunixin meglumine, ketoprofen, or phenylbutazone. Some ophthalmologists also like to sterilize the base of the ulcer by application of povidone-iodine solution (Betadine) diluted 50:50 with sterile saline or collyrium. The initial choice of topical antibiotic should be based on the results of cytologic evaluation and later modified, if necessary, according to the results of culture and sensitivity testing. One study showed that oxytetracycline combined with polymyxin B had in vitro efficacy against isolates from infectious keratitis that was comparable to gentamicin and superior to chloramphenicol.[30] If cytology demonstrates fungal hyphae, initial therapy with a topical antifungal agent should be instituted immediately. One study demonstrated that natamycin,* miconazole, itraconazole, and ketoconazole are superior to fluconazole† based on the results of in vitro susceptibility testing.[31] Voriconazole is a newer antifungal drug that may be compounded for use in veterinary ophthalmology. Subpalpebral lavage systems greatly facilitate the delivery of topical medication to the equine eye (see Bovine Keratitis in Horses).[28,32]

Surgical intervention should be considered in cases of deep corneal ulceration and especially when Descemet's membrane is exposed. Surgical procedures most often used for corneal ulceration include conjunctival pedicle flap, keratoplasty, and tarsorrhaphy.[12,33–35] Ophthalmic tissue adhesives and soft contact lenses may also be used as nonsurgical therapy for deep corneal ulcers. Perforating ulcers with iris prolapse and mixed bacterial and fungal keratitis or ulcers present greater than 2 weeks usually have a poor visual outcome.[36]

* Port-A-Cul, Becton Dickinson, Sparks MD.

* Natacyn, Alcon Laboratories, Fort Worth, TX.

† Diflucan, Pfizer, Exton, PA.

39.18.4 Corneal Lacerations

Corneal lacerations may be caused by sharp, protruding objects or projectiles. Corneal lacerations can occur with or without scleral laceration and, if they are nonperforating, may be treated as corneal ulcers. By contrast, perforating corneal lacerations must be repaired surgically. Preoperative preparation includes tetanus prophylaxis (horses and goats), systemic antibiotics, and sample collection for corneal culture and sensitivity. Ocular ultrasonography is very useful in determining the integrity of intraocular structures. However, care must be exercised during ocular examination, ultrasonography, and during surgery and anesthesia (especially induction and recovery) because extrusion of the intraocular contents may occur if excessive pressure is exerted

on the globe or if the eyelids are forced open. In some cases, complete examination of the globe should be delayed until the animal is anesthetized.

General anesthesia, adequate magnification, proper instrumentation, appropriate suture material and needles, and adequate postoperative care are necessary for successful repair of a corneal laceration. Postoperative therapy must include topical antibiotics and mydriatics/cycloplegics, along with systemic antiinflammatory agents.[34,37] The prognosis for recovery of vision and preservation of the globe generally is guarded. Complications that may occur after repair of corneal lacerations include phthisis bulbi, corneal fibrosis, synechia formation, blindness, retinal detachment, cataract formation, uveitis, endophthalmitis, bacterial or mycotic keratitis, and wound dehiscence with subsequent iris prolapse.

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The prognosis after surgical repair of corneal or corneoscleral lacerations is best when the animal is presented immediately with a small wound in which the cornea or sclera is sealed and the anterior chamber has re-formed. Minimal hyphema, clear intraocular media, a clearly visible fundus, and laceration length of less than 15 mm are additional findings that indicate a favorable prognosis.[33,36] In horses the success rate when only the cornea is involved is about 70% for recovery of vision and 90% for a cosmetically acceptable globe.[33] With corneoscleral lacerations the prognosis is much worse. In our experience the success rate in such cases is 20% for recovery of vision and 70% for a cosmetically acceptable globe. Most phthisical globes are not considered cosmetically acceptable. Therefore, enucleation should be considered initially with severe corneoscleral lacerations because the prognosis is poor for return of vision and guarded for preservation of the globe. Several surgical procedures have been described in horses to provide a cosmetic appearance to the globe and orbit, including placement of an intraocular silicone prosthesis.[38–40]

39.19 TRAUMA TO THE UVEAL TRACT

Trauma to the globe can damage the iris, ciliary body, and choroid. The resulting inflammatory response may range from very mild with rapid recovery to loss of vision and chronic discomfort. Signs of inflammation of the iris and ciliary body include blepharospasm, epiphora, miosis, aqueous flare, corneal edema, fibrin in the anterior chamber, hyphema, hypopyon, low IOP, and synechia formation. Concurrent damage to the corneal epithelium may be present and must be evaluated with fluorescein dye. Damage to the choroid may also affect the retina and lead to retinal detachment or degeneration.

Traumatic uveitis is treated in a manner similar to uveitis of other etiologies. Therapy is directed toward dilating the pupil to prevent synechia formation, cycloplegia to prevent painful ciliary spasm, and controlling the intraocular inflammatory response. Topical atropine is instilled to maintain mydriasis and provide cycloplegia. Topical corticosteroids and prostaglandin inhibitors such as 0.1% diclofenac* are used to decrease inflammation of the anterior segment.

The topical corticosteroid of choice is 1% prednisolone acetate or 0.1% dexamethasone.[16,41,42] Subconjunctival injection of corticosteroids may also be quite beneficial in controlling inflammation. However, the use of topical and subconjunctival corticosteroids must be avoided in the presence of corneal ulceration or abrasion. Systemic medication should include flunixin meglumine, ketoprofen, phenylbutazone, or oral corticosteroids. In horses, prednisolone is given by mouth at 0.5 to 2 mg/kg for 7 to 21 days. Care must be taken to avoid secondary complications from systemic corticosteroids.

Trauma-induced hyphema usually has a good prognosis if the blood has clotted and fills less than half the anterior chamber. Stall rest, topical 1% atropine, topical corticosteroids, and systemic antiinflammatory therapy should be

instituted to control the associated uveitis. If a penetrating wound is suspected, topical and systemic antibiotic therapy should be included with periodic fluorescein staining. Surgical intervention to remove large blood clots is rarely indicated because it may result in additional bleeding or may worsen the uveitis. Dilute tissue plasminogen activator* (tPA, 25 to 50 µg) may be injected into the anterior chamber to disrupt or lyse intraocular hemorrhage and fibrin and to aid in resolution of synechiae. For maximum effectiveness, tPA should be used within 24 to 72 hours of clot formation.[43,44] Systemic tPA for use in humans is diluted for intraocular use but is expensive. However, diluting the drug and repackaging it into sterile vials that are stored at −70° C and then thawed for injection has made the cost more reasonable for veterinary use.

Chronic uveitis after ocular trauma may be associated with lens damage or the introduction of infectious or foreign agents into the eye and carries a poor prognosis. If the lens is ruptured, its surgical removal is advocated. Ocular perforation is a frequent cause of panophthalmitis in food animals and horses. Although therapy consists of systemic and topical antibiotics, as well as tetanus prophylaxis in susceptible species, panophthalmitis usually necessitates eventual enucleation.

* Voltaren, Novartis, East Hanover, NJ.

* Activase, Genentech, South San Francisco, CA.

39.20 TRAUMA TO THE LENS

Blunt or sharp trauma to the eye may damage the lens by causing lens opacity (cataract), rupturing the lens capsule, or less often may cause a shift in position (subluxation or luxation). A luxated lens should be removed if it causes obstructive glaucoma or chronic corneal edema from endothelial contact, or if it becomes cataractous and reduces vision.

Release of lens protein into the eye after lens capsule rupture may induce severe granulomatous uveitis. In such cases the eye should be treated vigorously for lens-induced uveitis with topical atropine and topical and systemic antiinflammatory drugs. If the globe has been penetrated, topical and systemic antibiotics are indicated. The prognosis for preservation of vision is poor. Lens removal is often required to control the inflammatory response.

Cataracts (lens opacities) associated with ocular trauma may occur acutely or develop weeks after the initial injury. The opacity may be only focal and not appreciably affect vision, or it may be complete and cause a visual deficit. If the remainder of the eye is normal, surgical removal of the cataractous lens may improve vision.[45] Removal of cataracts secondary to uveitis is not recommended currently; however, with the advent of new surgical techniques, procedures such as combined vitrectomy (possibly to remove the immunologic stimulus in recurrent uveitis) and lensectomy may become more commonplace.[46]

39.21 TRAUMA INVOLVING THE VITREOUS

Trauma to the eye may result in hemorrhage into the vitreous or release of inflammatory products that cause vitreal degeneration. Either circumstance can result in vitreal syneresis (liquefaction), formation of vitreal traction bands, and subsequent retinal detachment. Symptomatic treatment of inflammation is generally adequate; however, vitrectomy may be beneficial in the management of severe vitreal hemorrhage.[16] Foreign material that becomes entrapped in the vitreous may be an inciting factor for endophthalmitis. If infectious endophthalmitis is suspected, diagnostic paracentesis of the vitreous or anterior chamber should be performed to obtain samples for bacterial and fungal culture and for sensitivity and cytologic examination. After the samples are obtained, but before removing the needle from the globe, 200 µg gentamicin and 2.2 mg cefazolin, or 200 µg gentamicin and 1

mg vancomycin, should be injected into the vitreous.[47] Further therapy should be based on culture and sensitivity (C&S) results, as well as cytologic findings. If a foreign body is identified, removal and vitrectomy may be beneficial, but the prognosis for successful treatment is poor.

39.22 TRAUMA TO THE RETINA

Retinal tears, hemorrhage, edema, and detachment may be caused by trauma.[48,49] In cases of opaque ocular media, retinal separation may be diagnosed by ocular ultrasonography (Fig. 39-9). Retinal degeneration may follow ocular trauma. Retinal hemorrhage and edema should be treated with systemic corticosteroids. With current technology, surgical repair of retinal tears, lacerations, or detachments in food animals and horses may be feasible in selected cases.

39.23 TRAUMA TO THE OPTIC NERVE

The pathogenesis of damage to the optic nerve is not well understood. Shearing forces at the optic foramen from displacement of the brain after severe head trauma (Fig. 39-10), direct contusion or avulsion of the optic nerve, or loss of blood supply to the nerve and subarachnoid hemorrhage probably all have roles in optic nerve injury.[50] Early examination may reveal only a dilated pupil that may be partially or completely unresponsive to light. Later, changes may include optic nerve atrophy (Fig. 39-11) and peripapillary retinal pigmentation changes. Therapy with systemic antiinflammatory drugs may be of benefit, but severe damage is usually irreversible.

Traumatic optic nerve atrophy is usually characterized by sudden onset of unilateral or bilateral blindness; dilated, fixed pupils; and a lack of menace response. In horses the traumatic episode is frequently characterized by damage to the poll from rearing over backward and striking the back of the head, from rearing up and hitting a ceiling beam, or from blunt trauma (blows) to the side or front of the face. The animal usually stands without loss of consciousness, and the injury is not considered serious by the owner at the time. Initially, blindness with a normal-appearing ocular fundus is observed.

Fig. 39-9 Ocular ultrasound of a horse eye after blunt trauma to the globe. Note the characteristic V-shaped retinal detachment.

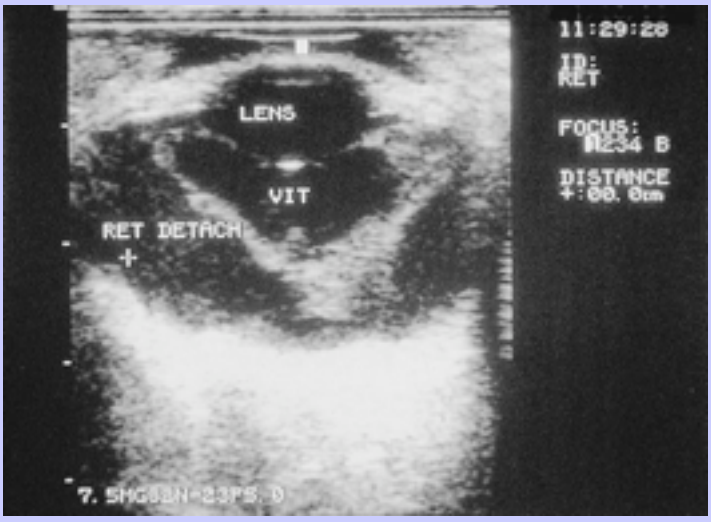
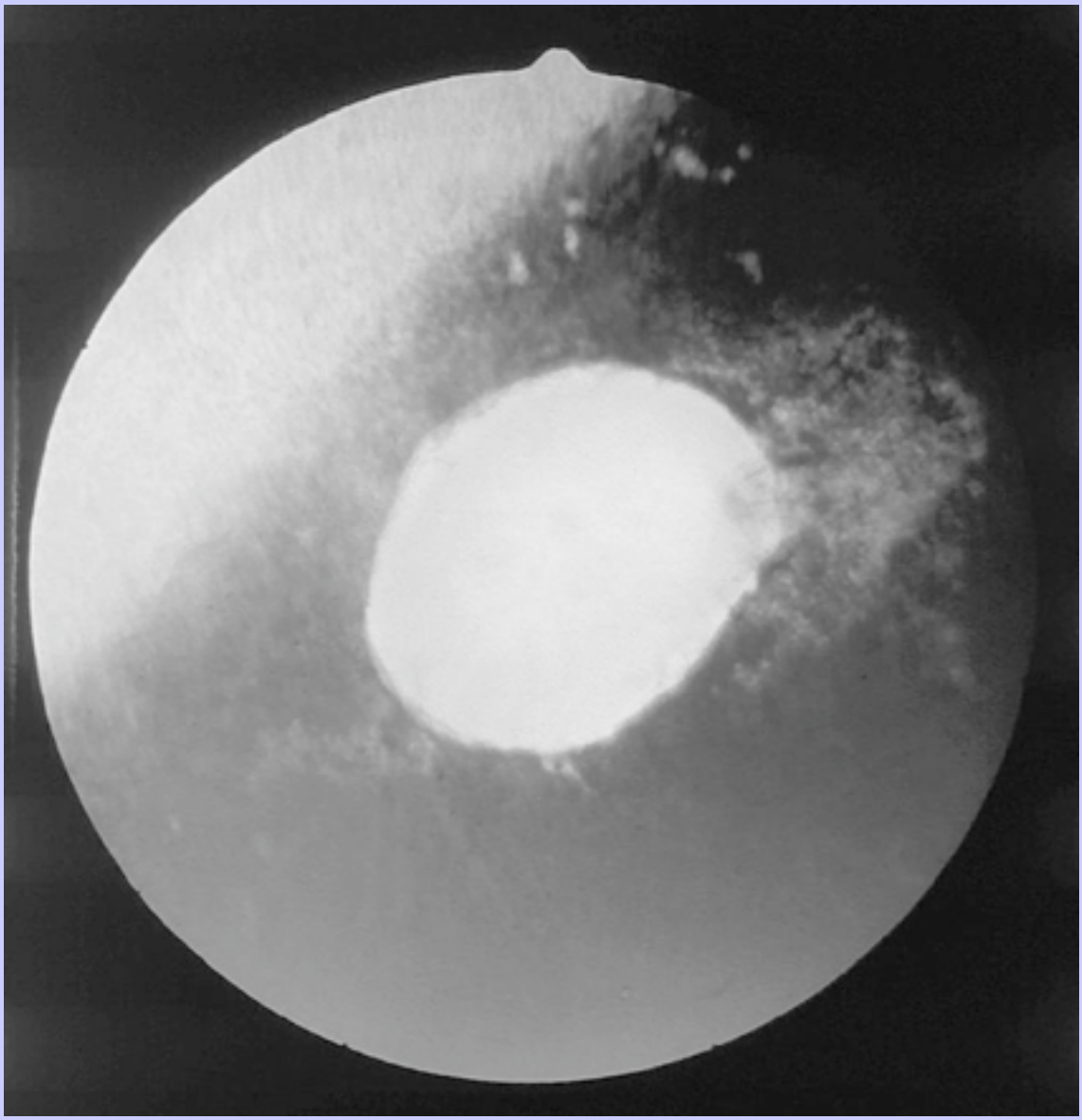


Fig. 39-10 Optic nerves and chiasm of a foal that was blind as a result of head trauma. Note the constrictions of the optic nerves caused by necrosis and degeneration. *Courtesy Dr. C.L. Martin.*

Fig. 39-11 Appearance of the optic nerve 3 months after head trauma in a horse. Note the pale optic disc and peripapillary retinal degeneration. *Courtesy Dr. C.L. Martin.*



Within 3 to 4 weeks after the trauma, examination of the fundus reveals a pale optic disc (see Fig. 39-11). Later, loss of peripapillary retinal vessels is usually evident. The optic disc often appears depressed, with increased prominence of the lamina cribrosa. Confirmation of optic nerve or optic tract lesions causing blindness may be made by the absence of a direct pupillary light reflex with a normal electroretinogram. In some cases the pathologic lesion is a rupture of the nerve axons from stretching forces produced by movement of the brain.[50] Chiasmal hemorrhage and fractures of the basisphenoid bone may be observed at necropsy. Therapy with

systemic corticosteroids (dexamethasone, 1 mg/kg) and IV dimethyl sulfoxide (DMSO) has generally not been successful,[50] although the lack of response to medical therapy appears related to the severity of the injury. 1273

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A segmental optic nerve atrophy involving one to three quadrants of the optic disc occurs in horses. The appearance is characterized by pallor, loss of normal vasculature, and increased prominence of the lamina cribrosa in the affected quadrants. The etiology is unknown; however, traumatic injury is suspected in most cases. Response to medical therapy is poor.

39.24 CHEMICAL INJURY

Ocular irritation caused by insecticides and disinfectants inadvertently applied to the eye is relatively common in the farm or ranch setting. Chemical burns to the cornea and adnexa may have serious consequences and may warrant a poor prognosis for salvage of the eye. Alkali burns are more severe than acid burns. Corneal burns from acids tend to be sharply demarcated and nonprogressive, whereas alkali burns cause progressive coagulation, melting, and sloughing of the corneal stroma.[16] Chemically induced melting of the cornea must be differentiated from bacterial and fungal infections. Treatment for a suspected or known chemical burn should include lavage of the affected area with copious amounts (500 to 2000 mL) of sterile saline solution. Tap water may be used by the owner until veterinary assistance is available. It may be necessary to sedate the animal. No attempt should be made to neutralize the substance because this may cause precipitation within the cornea. The damage should then be evaluated with the aid of local nerve blocks.

Treatment should include appropriate topical antimicrobials, atropine, and a collagenase inhibitor such as autologous serum or possibly acetylcysteine,* which inhibits collagenases and metalloproteinases by binding calcium. The commercially available preparations contain 10% and 20% acetylcysteine and should be diluted to 5% and 10% to avoid epithelial toxicity. Acetylcysteine lasts only about 4 days once opened and should be refrigerated. Hourly application of serum or acetylcysteine may be needed. Systemic antiinflammatory drugs should be used to control secondary uveitis. Therapeutic soft contact lenses have been used to protect the corneal stroma in patients with extensive corneal ulcerations.

* Roxane Laboratories, Columbus, OH.

39.25 THERMAL INJURY

Facial burns secondary to barn or stable fires may damage the eyelids, conjunctiva, and cornea. Thermal injuries also may cause anterior uveitis and exfoliation of the lens capsule. Therapy for minor burns to the eyelids is directed toward keeping the injured area moist with antibiotic dressings and protecting the cornea if eyelid dysfunction occurs. Treatment for injury to the conjunctiva or cornea should include topical antibiotic and systemic antiinflammatory drugs in horses. Full-thickness eyelid burns may require grafting procedures to protect the cornea and to minimize scarring.[24,26] Third eyelid or conjunctival flaps may be required to protect the cornea until eyelid function returns.

39.26 INFECTIOUS OCULAR DISEASES

JOAN DZIEZYC

NICHOLAS J. MILLICHAMP

This section describes the major infectious ophthalmic diseases of large animals (Table 39-2), concluding with a discussion of infectious bovine keratoconjunctivitis (IBK), or "pinkeye," the most common ocular disease of cattle.

39.27 MYCOPLASMAL KERATOCONJUNCTIVITIS IN GOATS AND SHEEP

39.27.1 Definition and Etiology

Mycoplasma conjunctivae has been frequently isolated throughout the world from epidemics of keratoconjunctivitis, respiratory disease, and arthritis in goats and sheep.[51–54] *Mycoplasma mycoides* subsp. *mycoides* has been isolated from an epidemic of mastitis, arthritis, and keratoconjunctivitis in goats.[55] *Acholeplasma oculusi (oculi)* has been isolated from sheep and goats in epidemics of keratoconjunctivitis.[56,57] *Mycoplasma agalactiae* and *Mycoplasma arginini* have also been described as causing keratoconjunctivitis and systemic disease.[58]

39.27.2 Clinical Signs and Differential Diagnoses

Clinical signs of mycoplasmal keratoconjunctivitis include epiphora, conjunctival hyperemia, and occasionally follicular conjunctivitis. In experimental conjunctival inoculation with *M. conjunctivae*, clinical signs began on day 2 and lasted for 5 weeks.[59] Later in the disease, keratitis with corneal neovascularization (Fig. 39-12) and occasionally anterior uveitis can be seen.[51,60] One case of choroiditis and hyalitis has been described.[61] Signs can be seen in individuals, as well as in herd or flock outbreaks. The disease is usually unilateral but can be bilateral. Differential diagnoses include other infectious causes of keratoconjunctivitis, such as *Chlamydia* species (sheep), *Branhamella (Neisseria)* species, aerobic bacteria, parasites, and infectious bovine rhinotracheitis (goats), as well as noninfectious causes such as trauma.

39.27.3 Clinical Pathology

In conjunctival scrapings taken early in the disease, many neutrophils are seen; later, lymphocytes predominate. Plasma cells and necrotic epithelial cells are also seen.[62] Organisms can be seen occasionally in epithelial cell cytoplasm as coccobacillary or varied forms.[61] Pigment granules can be mistaken for organisms.[56,62,63]

Mycoplasmal organisms can be cultured and identified from conjunctival swabs; serum antibody titers can be measured,[64,65] or polymerase chain reaction (PCR) can be used to identify *M. conjunctivae* in conjunctival smears.[66,67] Egwu and Faull[68] describe rising serum and lacrimal antibody titers in sheep topically inoculated with *M. conjunctivae*. However, Trotter et al.[52] report low serum titers to *M. conjunctivae* in normal animals and no rise in titer in animals inoculated with *M. conjunctivae* subconjunctivally that subsequently developed signs of disease.

39.27.4 Epidemiology

Mycoplasmal infections apparently are transmitted directly from animal to animal, as evidenced by herd or flock outbreaks. The presence of carrier animals is postulated, and *M. conjunctivae* can be cultured from

unaffected animals.[69,70] Animals can become reinfected. Keratoconjunctivitis can be induced in sheep with topical inoculation of *M. conjunctivae*.[68,71,72] Clinical signs were identical to natural outbreaks and spread to uninoculated sheep. The organism can be cultured from eyes long after clinical signs abate.[59] See Chapter 38 for more details on *M. mycoides*.

39.27.5 Treatment and Prognosis

In most animals, mycoplasmal keratoconjunctivitis associated with *M. conjunctivae* is transient. Affected animals usually recover spontaneously in 10 days, although some animals seem to have recurring episodes that last for several weeks. In a controlled clinical trial, one dose (20 mg/kg) of long-acting oxytetracycline was given to experimentally inoculated lambs. This treatment seemed to hasten the cessation of clinical signs, although the results were not analyzed statistically.[73] The treatment did not, however, eliminate the *M. conjunctivae* infection. Other drugs recommended for the ocular disease include topical oxytetracycline or oxytetracycline and polymyxin B.[51] Subconjunctival oxytetracycline is not currently recommended because it may cause a severe inflammatory reaction. In vitro antibiotic testing of *M. conjunctivae* shows that tylosin, oxytetracycline, streptomycin, and chlortetracycline are suitable for treatment.[74]

Table 39-2 Major Infectious Ocular Diseases of Large Animals

Agent	Common Name/ Disease	Major Sign(s)	Cattle	Sheep	Goats	Horses
Mycoplasma conjunctivae	Pinkeye	Keratoconjunctivitis		++	++	
Mycoplasma mycoides subsp. *mycoides*	Pinkeye	Keratoconjunctivitis			+	
Acholeplasma oculusi (oculi)	Pinkeye	Keratoconjunctivitis		+	+	
Chlamydia psittaci	Pinkeye	Keratoconjunctivitis		++		
Branhamella (Neisseria)	Pinkeye	Keratoconjunctivitis		+	+	
Mycoplasma agalactiae		Keratoconjunctivitis		+	+	
Mycoplasma arginini		Keratoconjunctivitis		+	+	
Listeria monocytogenes		Keratoconjunctivitis	+	+		
Infectious bovine rhinotracheitis		Keratoconjunctivitis	++		+	
Colesiota (Rickettsia) conjunctivae	Pinkeye	Keratoconjunctivitis		+		
Equine viral arteritis		Keratoconjunctivitis				+
Equine herpesvirus type 2		Keratoconjunctivitis				+
Mycoplasma bovoculi		Conjunctivitis	+			
Ureaplasma species		Conjunctivitis	+			
Equine adenovirus		Conjunctivitis				+
Moraxella species		Conjunctivitis				+
Streptococcus equi	Strangles	Conjunctivitis				+
Moraxella bovis	Pinkeye	Corneal ulcer	++			
Equine herpesvirus type 1	Rhinopneumonitis	Keratitis				+
Malignant catarrhal fever		Uveitis, keratitis	+			

Neonatal septicemia		Uveitis	+	+	+	+
Mycobacterium bovis	Tuberculosis	Uveitis	+			
Salmonella species		Uveitis				+
Borrelia burgdorferi	Lyme disease	Uveitis				+
Leptospira interrogans		Recurrent uveitis				+
Brucella abortus		Recurrent uveitis				+
Scrapie		Retinitis		+		
Histophilus somni (Haemophilus somnus)	Infectious thromboembolic meningoencephalitis	Retinitis	+			
Bovine viral diarrhea		Retinal dysplasia, cataracts	+			
Bluetongue		Chorioretinitis, conjunctivitis	+	+		
Toxoplasma gondii		Chorioretinitis				+
Rhodococcus (Corynebacterium) equi		Panophthalmitis				+
Bovine leukemia virus		Exophthalmos	+			
Cryptococcus neoformans		Exophthalmos				+

39.27.6 Prevention and Control

Introduction of new animals into a herd or flock has been implicated in starting an outbreak of keratoconjunctivitis. Therefore, isolation and, if necessary, treatment of new animals are important before contact with the herd. No other specific recommendations have been made for prevention and control of *M. conjunctivae*. See Chapter 38 for control of *M. mycoides* subsp. *mycoides*.

39.28 CHLAMYDIAL KERATOCONJUNCTIVITIS IN SHEEP

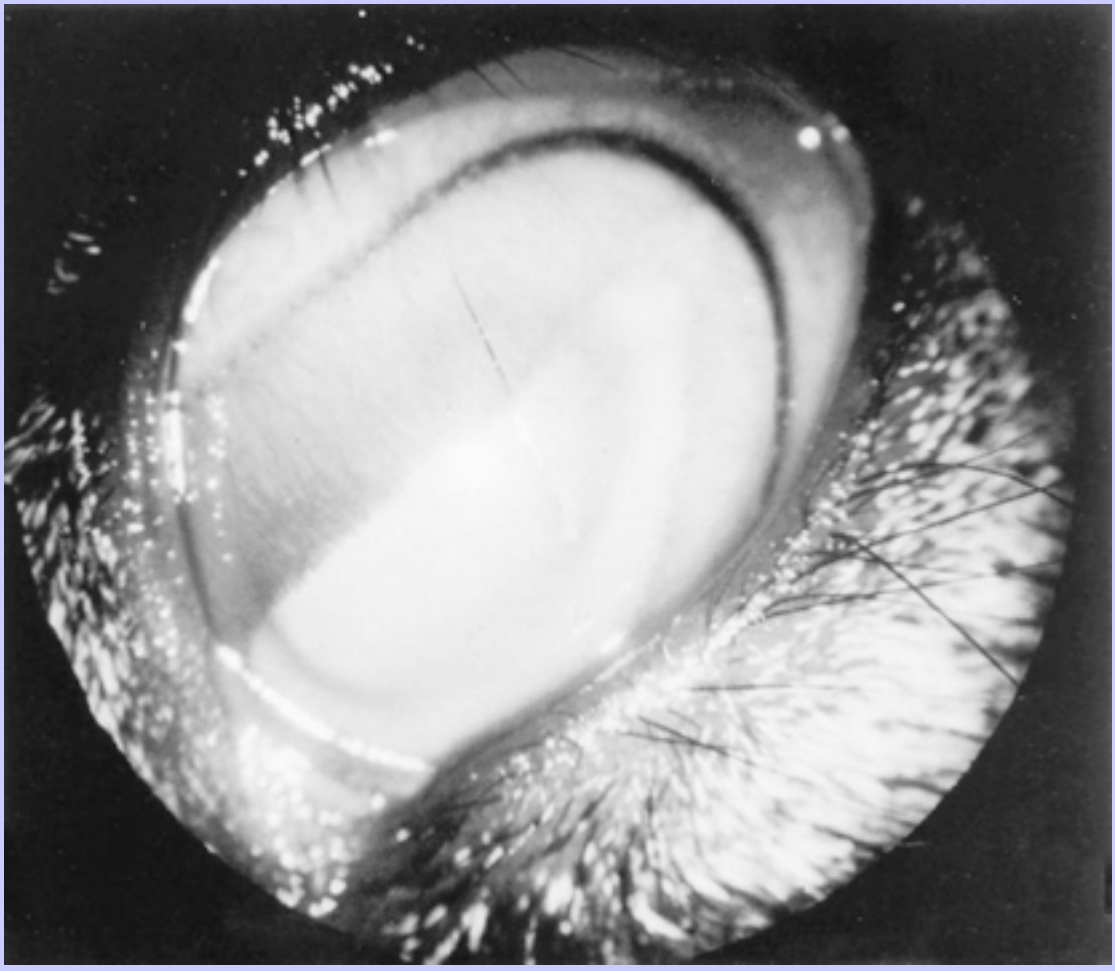
39.28.1 Definition and Etiology

Chlamydial agents have been isolated from outbreaks of keratoconjunctivitis in sheep flocks. The agent was originally described as a strain of *Chlamydia psittaci*. The agent is now called *Chlamydophila pecorum,* which can also cause abortion (see Chapter 43) and polyarthritis (see Chapter 38) in lambs.[75,76]

39.28.2 Clinical Signs and Differential Diagnoses

Early clinical signs consist of epiphora, chemosis, and conjunctival hyperemia. Later in the disease, follicle formation in the conjunctiva becomes prominent. Still later, corneal neovascularization may be seen. Most cases are bilateral and symmetric.[77,78] In some flock outbreaks of keratoconjunctivitis, outbreaks of polyarthritis are also noted. Most lambs that develop chlamydial polyarthritis will also develop conjunctivitis.[77,78] Differentials include other infectious causes of keratoconjunctivitis, such as *Mycoplasma* and *Branhamella (Neisseria)* species, aerobic bacteria, and parasites, as well as noninfectious causes such as trauma. 1275 1276

Fig. 39-12 Left eye of goat with mycoplasmal keratoconjunctivitis. Note diffuse corneal edema and dorsally the marked corneal neovascularization.



39.28.3 Clinical Pathology

Early in the disease, conjunctival smears show numerous neutrophils and some lymphocytes. Later, there are more neutrophils and fewer mononuclear cells. Cytoplasmic chlamydial inclusions are occasionally seen in up to a third of the eyes scraped and can be definitively identified by fluorescent antibody staining.[75] Conjunctival epithelial cells are often necrotic. Chlamydial organisms can be cultured from conjunctival scrapings and from blood taken from sheep with polyarthritis and conjunctivitis.[77–79] In one study, titers to chlamydial antibodies were found at 1:16 or higher in a number of the affected lambs, although titers on normal lambs were not reported.[78] Polymerase chain reaction (PCR) can also be used to identify the organism.

39.28.4 Epidemiology

Chlamydial organisms are apparently transmitted by direct contact, as evidenced by flock outbreaks. Chlamydial organisms caused conjunctivitis in five lambs inoculated topically.[80] An uninoculated lamb housed with the five lambs also developed conjunctivitis. Lambs subsequently developed follicular conjunctivitis.[79] In another study, chlamydial organisms were injected intraarticularly, intravenously, and intramuscularly and caused polyarthritis and conjunctivitis.[79]

39.28.5 Treatment and Prognosis

In uncomplicated cases the disease is self-limiting, and eyes are normal within 2 to 3 weeks.[78] The same treatments indicated for *Mycoplasma mycoides* subsp. *mycoides* (systemic oxytetracycline and, when possible, a topical tetracycline ophthalmic preparation) are also effective in treating chlamydial conjunctivitis/polyarthritis of sheep.

39.29 *BRANHAMELLA (NEISSERIA) OVIS* KERATOCONJUNCTIVITIS IN SHEEP AND GOATS

Branhamella ovis is a gram-negative diplococcus similar to *Moraxella* species. This agent has been cultured from sheep and goats with keratoconjunctivitis;[81,82] however, it can also be cultured from normal eyes.[83] *B. ovis* has also been cultured from cattle with serous conjunctivitis and rarely keratitis.[84] Clinical signs are usually mild and include epiphora and conjunctival hyperemia.

In one outbreak, neutrophils and gram-negative coccobacilli were seen on conjunctival scrapings. *B. ovis* was cultured from the initial outbreak and was then instilled into the conjunctival sac of goats with or without ultraviolet radiation. The experimentally infected goats developed epiphora and conjunctivitis, but no keratitis.[85] In another study, *B. ovis* instilled into the conjunctival sac of lambs induced reddened conjunctiva and follicle formation. *B. ovis* could be cultured from these eyes for up to 20 days after inoculation.[86]

In one outbreak, animals were treated with parenteral tylosin and topical neomycin, polymyxin B, and a corticosteroid, and all 10 recovered.[81] Bankemper et al.[85] used subconjunctival penicillin to treat affected goats.

39.30 SCRAPIE-ASSOCIATED RETINOPATHY IN SHEEP AND GOATS

The scrapie agent causes a degenerative CNS disease in sheep and less often in goats. Barnett and Palmer[87] described two sheep with scrapie that also had multifocal hyperreflective areas in the tapetum, histologically seen as small areas of retina raised by an accumulation of eosinophilic material between photoreceptors and retinal pigment epithelium. The eosinophilic material was characterized as a complex lipid. It was not shown that scrapie had caused the lesions.[87] Subsequently, using a monoclonal antibody, a goat with natural scrapie was found to have the scrapie prion protein in the retina without any microscopic retinal lesions.[88] A sheep experimentally infected with scrapie was also found to have prion proteins in the retina,[89] as was a sheep experimentally infected with the prion responsible for bovine spongiform encephalopathy (BSE).[90] Prion proteins can also be found in the nictitating membrane,[90,91] which may permit the antemortem diagnosis of scrapie. (See Chapter 35 for more information on scrapie.)

39.31 BLUETONGUE-INDUCED RETINAL DYSPLASIA IN SHEEP AND CATTLE

Bluetongue is a disease of ruminants caused by an arbovirus that is transmitted by *Culicoides* gnats. Clinical signs include fever and vasculitis that leads to oral lesions, lameness, swollen face, pulmonary edema, and death (see Chapter 32). In pregnant ewes vaccinated with modified live virus (MLV) on day 40 of gestation, fetuses developed cerebral anomalies.[92] These anomalies have also been described in clinical cases in which ewes had been vaccinated with MLV at about 5 or 6 weeks of gestation. In addition, when the fetus was vaccinated with MLV vaccine between days 50 and 75 of gestation, lesions of retinitis and choroiditis were noted that appeared centered around retinal vessels. In some eyes, inflammatory lesions produced persistent areas of retinal dysplasia.[93]

39.32 LISTERIA MONOCYTOGENES IN SHEEP, CATTLE, AND HORSES

Listeriosis in ruminants is manifested mainly as either an encephalitis or as a septicemia in neonates, or as a reproductive problem manifested as abortions. Ocular signs with the neural form include facial paralysis and ptosis, often unilateral, on the side of the central lesion; medial strabismus, often on the ipsilateral side because of involvement of the abducens nucleus; nystagmus; and amaurosis.[94] Uveitis with hypopyon has been described in chronic cases.[95]

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Listeria monocytogenes has been cultured from conjunctival smears taken from sheep and cattle with keratoconjunctivitis.[96] In most of the sheep, *Branhamella (Neisseria) ovis* was also cultured. Clinical signs included conjunctival hyperemia, epiphora, photophobia, and corneal opacification. Treatment with topical chlortetracycline was curative. Walker and Morgan[97] provide a description of two experimental sheep that developed unilateral anterior uveitis. *L. monocytogenes* was cultured from the conjunctiva of each animal. Both animals recovered after treatment with parenteral ampicillin and topical antibiotics. *L. monocytogenes* has been cultured from the conjunctiva of three cows with keratitis (one with keratitis and uveitis) and from a corneal scraping of one horse with keratitis.[98] In another case report, *L. monocytogenes* was cultured from the cornea of a horse with chronic keratitis.[99] Diagnosis is usually achieved by isolation of *L. monocytogenes* from tissues at necropsy. Early treatment with broad-spectrum antibiotics may be effective in some cases.

39.33 INFECTIOUS BOVINE RHINOTRACHEITIS KERATOCONJUNCTIVITIS IN GOATS

Goats are susceptible to infectious bovine rhinotracheitis (IBR) virus, which in some cases may result in ocular disease. In one goat with ocular signs, conjunctivitis and keratitis with keratoconus were seen 5 days after the onset of severe respiratory illness. IBR virus was isolated from ocular and nasal discharge.[100]

39.34 *COLESIOTA (RICKETTSIA)* KERATOCONJUNCTIVITIS IN SHEEP

Colesiota (or *Rickettsia*) *conjunctivae* has been described as the cause of infectious keratoconjunctivitis in sheep, but documentation is sparse. The organism has not been cultured; only identified on conjunctival scrapings. Clinical signs include epiphora, conjunctival hyperemia, and corneal neovascularization.[101] Several authors have since suspected that this organism is the same as *Chlamydia psittaci* (now known as *Chlamydophila pecorum*).[102,103]

39.35 INFECTIOUS BOVINE RHINOTRACHEITIS CONJUNCTIVITIS

39.35.1 Etiology

IBR is a herpesvirus that may involve the respiratory or reproductive tracts, nervous system, or conjunctiva or may cause widespread systemic disease (see also Chapter 31). Conjunctivitis is the most common ocular manifestation of the disease, and it may occur as an isolated clinical entity or with involvement of other body systems.[104–106]

39.35.2 Clinical Signs and Differential Diagnoses

Although conjunctivitis is frequently bilateral, it can be unilateral. Ocular discharge; initially serous and later becoming mucopurulent, is usually seen without blepharospasm. Chemosis may be severe, especially by 1 week after infection. Both the palpebral and the bulbar conjunctiva are injected, and petechial hemorrhages may occur. Multiple white plaques 0.2 to 0.5 mm in diameter may develop on the palpebral and, to a lesser extent, the bulbar conjunctival surfaces at 1 to 2 weeks after onset of clinical signs. These may coalesce later in the disease (5 to 9 days). Corneal vascularization and perilimbal edema and opacification occur in severe cases. Iridocyclitis (seen as miosis) may occasionally occur in severe cases.

Corneal changes of IBR are differentiated from those of infectious bovine keratoconjunctivitis (IBK) caused by *Moraxella bovis* by their peripheral rather than central distribution and lack of corneal ulceration in IBR, unless IBR and IBK occur concurrently in the same eye (see later IBK section). Corneal vascularization and opacification in malignant catarrhal fever accompany marked signs of anterior uveitis[107] and other signs of generalized vasculitis.

Although ocular disease may occur as an isolated entity, ocular signs may be found in animals with upper respiratory tract signs, including rhinitis and dyspnea. Affected animals may be pyrexic, and a fall in milk yield may occur. Abortion in pregnant animals may occur following ocular manifestations of the disease.

39.35.3 Diagnostic Procedures

IBR can be recovered from infected eyes during the first 7 to 9 days of the disease but infrequently thereafter. Swabs may be taken for viral isolation in cell culture, which is probably the most reliable means of making a definitive diagnosis. Fluorescent antibody techniques may be used on conjunctival scrapings, and serology may be helpful if blood samples can be collected during the acute and convalescent stages of the disease. PCR is also being used. Histopathology to detect intranuclear inclusions is not likely to allow reliable diagnosis of the disease.[107,108]

39.35.4 Pathophysiology

Specific strains of the virus usually cause only one form of the disease (e.g., ocular form) in a herd. Ocular infection results in lymphoid hyperplasia, visible as white plaques. On histology, these are composed of plasma cells and lymphocytes in the conjunctival stroma and subepithelial area. Mild conjunctival epithelial ulceration may occur. During the recovery phase of the disease, diphtheritic membranes secondary to conjunctival necrosis develop on the conjunctival surface.

39.35.5 Treatment and Prognosis

Recovery from the conjunctival form of the disease is spontaneous within 10 to 20 days. In certain situations, palliative treatment may be helpful. This is achieved by cleaning the ocular discharge from the lids and applying a topical broad-spectrum antibiotic to prevent secondary bacterial infection. Treatment of the conjunctival form of the disease with topical antiherpetic agents has not been studied and would rarely be practical or cost-effective.

39.35.6 Prevention and Control

Vaccination of susceptible animals is the most effective means to prevent and control the disease. IBR vaccination programs are discussed in Chapter 48.

39.36 MALIGNANT CATARRHAL FEVER KERATOCONJUNCTIVITIS

Malignant catarrhal fever (MCF) is a sporadic disease characterized by fever, lymphadenopathy, and generalized vasculitis resulting in inflammation of the mucosal membranes of the mouth, nose, and eye; the skin; and the gastrointestinal (GI) and nervous systems, with variable but usually high mortality. The African form is caused by alcelaphine herpesvirus type 1. The North American form is caused by a similar virus, ovine herpesvirus.[109,110]

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Various forms of the disease are described on the basis of clinical signs (see Chapter 32). Ocular involvement is seen in the acute “head and eye” form, which is the most common presentation of the disease. Ocular signs include photophobia, epiphora, episcleral injection and scleritis, severe conjunctivitis, keratitis (corneal opacification caused by edema and vascularization appearing perilimbally), anterior uveitis, and exophthalmia. Less significantly, and difficult to diagnose clinically, retinal vasculitis may develop. Bullous keratopathy may develop as a result of edema in the anterior cornea, with subsequent rupture of bullae to form painful corneal erosions.[111] The absence of central corneal ulceration distinguishes the disease from IBK, and the severity of the ocular lesions is worse than would be expected in IBR, bovine viral diarrhea/mucosal disease (BVD/MD), or

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bluetongue. Differentiating this disease from Rinderpest could be clinically difficult in areas where both are endemic in cattle.

Serology and PCR are being used to confirm the clinical diagnosis.[112,113] The ocular lesions are those of a nonsuppurative uveitis and vasculitis. The lesions involve the conjunctiva, cornea, anterior uvea, and retinal blood vessels; the choroid is rarely involved. Serofibrinous and cellular infiltrates develop in the uvea and retina as a result of vasculitis and thrombosis. Perivascular cuffing and optic neuritis may be detected histologically.[114–116]

Prognosis for the eyes and the animal's recovery is poor.[111] Most importantly, in endemic areas, cattle should be kept away from sheep, which may act as a reservoir for the disease, and affected animals should be isolated.

39.37 BOVINE MYCOPLASMAL CONJUNCTIVITIS

Mycoplasma bovoculi and *Ureaplasma* species have been isolated from cattle with conjunctivitis and IBK. Inoculation of normal calves with *M. bovoculi* or *Ureaplasma* isolates produced conjunctivitis characterized by serous discharge and localized to diffuse conjunctival hyperemia. Experimentally induced conjunctivitis ran a course of over 1 month. Cases can be confirmed by culture or PCR performed on conjunctival swabs.[117] Mycoplasmal infection may predispose the animals to development of IBK from *Moraxella bovis*[118,119] (see later IBK section). Therefore, although treatment of mycoplasmal conjunctivitis per se may not be warranted, it may be advisable in areas where IBK is endemic. Topical oxytetracycline ointment applied three times daily or intramuscular (IM) injection of long-acting oxytetracycline is recommended.

Other mycoplasmal organisms (e.g., *M. arginini*) can be isolated from cows' conjunctiva but are not thought to cause the disease. *M. bovis* was found using PCR performed on normal conjunctival samples,[117] but it was not thought to cause conjunctivitis. *M. bovigenitalium, M. bovirhinis,* and *M. bovoculi* were isolated from members of two cattle herds with conjunctivitis and bronchopneumonia.[120] However, when viral cultures were performed, IBR was isolated in the same individuals. The mycoplasmal organisms may have contributed to the disease in these herds. In another cattle herd with outbreak of respiratory disease, keratoconjunctivitis followed, and *M. bovis, M. bovirhinis,* and *M. bovoculi* were isolated in various combinations from affected calves.[121]

39.38 *HISTOPHILUS SOMNI* CONJUNCTIVITIS AND RETINITIS

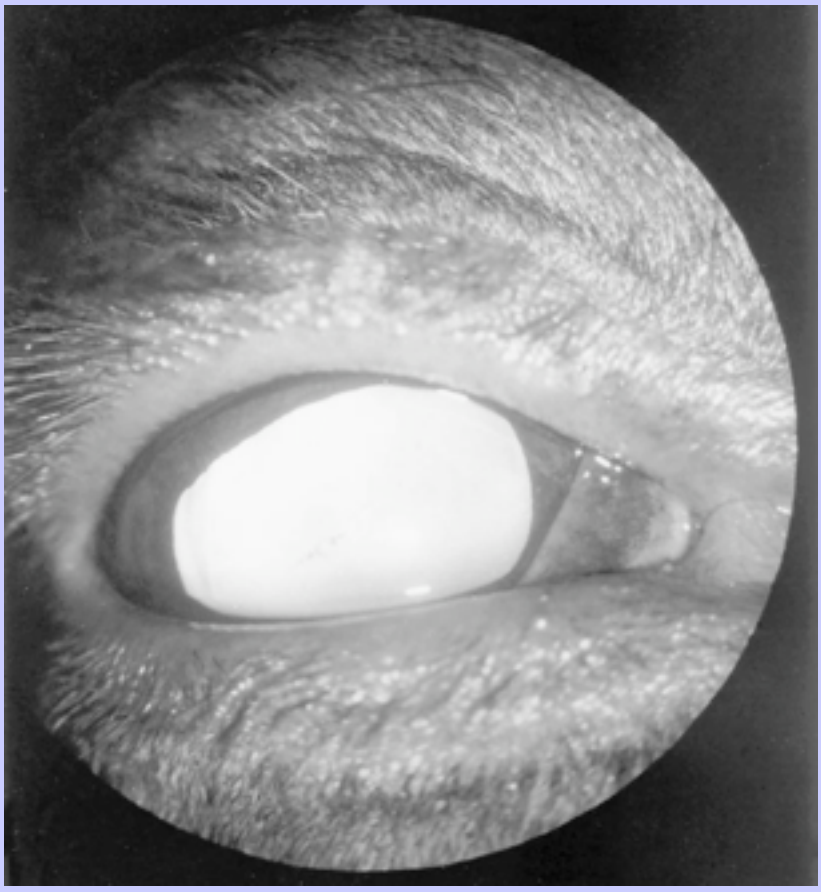
Thromboembolic meningoencephalitis (TEME) is a fatal septicemia caused by infection with *Histophilus somni* (see Chapter 35). Calves and young adult cattle can be affected, but the disease most often occurs in feedlot cattle less than 1 year of age. The organism is capable of damaging vascular endothelial cells and activating blood clotting. Therefore, most of the ocular histologic signs are referable to thrombosis of retinal vessels.

Although conjunctivitis may be seen, the main ocular findings are in the fundus. Retinal hemorrhages and exudates may be focal or diffuse. Retinal infiltrates may elevate the retina and involve the vitreous. Retinal edema, hemorrhage and necrosis, vascular thrombosis, and infiltration of the retina and vitreous with neutrophils are seen histologically. Eosinophilic cytoid bodies (swollen axons) are seen in the nerve fiber layer of the retina. Retinal detachments may result from retina edema. Later in the disease, areas of chorioretinitis result in chorioretinal scars. The anterior segment is less involved in this disease than in MCF, in which keratitis and anterior uveitis are usual.[122,123]

39.39 BOVINE VIRAL DIARRHEA—INDUCED RETINAL DYSPLASIA, CATARACTS, MICROPHTHALMIA, OPTIC NEURITIS, AND LEUKOCORIA

The causative agent of bovine viral diarrhea (BVD) is a pestivirus (part of the togavirus group; genus *Pestivirus,* family Togaviridae) that, in congenitally affected animals, causes retinal inflammation and necrosis. Cattle infected between days 75 and 150 of gestation may produce calves with cerebellar hypoplasia or ocular lesions. Calves with ocular signs may be blind, and nystagmus may be present. Pupillary light reflexes may or may not be absent. Other abnormalities may include microphthalmia, cataract, leukocoria (either as a result of cataract or dense white inflammatory infiltrate in the anterior vitreous; Fig. 39-13), retinal hemorrhages, chorioretinitis, retinal dysplasia or folds, retinal detachment, or optic neuritis or atrophy.[124–127] The optic disc may appear atrophic, and areas of tapetal color change and hyperreflectivity may be seen, with retinal vascular attenuation. In some cases, inflammatory debris may persist in the vitreous after birth, precluding adequate fundic examination. Congenital cataracts also occur in this disease, and although the pathophysiology is unknown, they probably develop secondary to the intraocular inflammation and necrosis. Cataracts mainly involve the lens cortex. 1278 1279

Fig. 39-13 Leukocoria (white pupil) in a Simmental calf caused by inflammatory debris in the vitreous and on the posterior capsule of the lens after intrauterine infection with bovine viral diarrhea.



Transplacental infection may occur when the dam is infected during pregnancy. The severity of the disease is related to fetal age at the time of intrauterine infection. Severe fetal disease and often fetal death occur in cattle infected between 100 and 200 days of gestation. Infected fetuses can also survive and become persistently infected with the virus. In these cattle, viral antigens can be found in neurons of the retina and CNS in the absence of clinical signs.[128] Ocular discharges have been reported in cases of acute or chronic cases of BVD, although the significance of these observations is uncertain.[127,129]

Serum samples collected from affected calves before ingestion of colostrum can be submitted for serologic assessment using the serum-virus neutralization test, or virus isolation can be attempted from buffy coat cells of a whole-blood sample collected into EDTA. (See Chapter 32.)

39.40 BLUETONGUE CONJUNCTIVITIS

Conjunctivitis and mucopurulent ocular discharge may be seen in cattle chronically infected with bluetongue virus. Although topical antibiotics could be applied to reduce secondary bacterial infection and reduce the ocular discharge, this would rarely be necessary.[130]

39.41 BOVINE LEUKOSIS AS A CAUSE OF EXOPHTHALMOS

Lymphosarcoma in adult cattle is usually caused by bovine leukemia virus, although noninfectious sporadic cases are reported in young animals. Lymphosarcoma may result in unilateral or bilateral progressive exophthalmos.[131,132] This is the most common orbital neoplasm in cattle. If undiagnosed, exposure keratitis and chemosis develop. Intraocular involvement can occur, although it is less common than orbital neoplasia. Generalized lymphadenopathy or other signs of generalized lymphosarcoma usually accompany the orbital form. Specific serologic tests will confirm the diagnosis. Enucleation or exenteration is rarely indicated because of the poor prognosis for affected animals. Differential considerations for progressive exophthalmos include frontal or maxillary sinusitis or nasal neoplasia, actinomycosis, and actinobacillosis.

39.42 OCULAR MANIFESTATIONS OF TUBERCULOSIS

Tuberculosis caused by *Mycobacterium bovis* may cause granulomatous lesions in the eye of affected cattle. The uveal tract (iris, ciliary body, or choroid) is initially affected, with later expansion of granulomas into other ocular structures. Uveitis, keratitis, and chorioretinitis with retinal detachment are seen clinically.[133]

39.43 OCULAR MANIFESTATIONS OF NEONATAL SEPTICEMIA

Neonatal septicemia in calves, foals, lambs, and kids may occur in the first few weeks after birth and may arise from umbilical infection or oral intake of bacteria (see Chapter 18). Septicemia is especially common in colostrum-deprived neonates. Secondary meningitis, polyarthritis, uveitis, and chorioretinitis may develop. Ocular signs include miosis, aqueous flare with fibrin deposition in the anterior chamber, hypopyon or hyphema, and in severe cases, panophthalmitis. Bacteria involved include *Escherichia coli, Streptococcus* species, *Pasteurella* species, *Salmonella* species, *Rhodococcus equi, Corynebacterium pyogenes,* and *Klebsiella* species. The incidence of infection with different bacteria varies among the domestic species. Therapy should include systemic antibacterial agents (based, when possible, on sensitivity testing) and treatment for uveitis. Prognosis for cases treated early is still guarded.[134–137]

39.44 BACTERIAL KERATITIS IN HORSES

39.44.1 Definition and Etiology

Bacterial keratitis occurs when a traumatic corneal ulcer becomes infected with opportunistic bacteria; no bacteria are known to *initiate* ulcers in horses. The most devastating clinical manifestations are associated with *Pseudomonas aeruginosa* and *Streptococcus equi* subsp. *zooepidemicus*. Additional bacteria isolated from infected corneas include nutritionally variant streptococci,[138] *Staphylococcus* species, *E. coli, Acinetobacter* species, *Clostridium* species,[139] *Corynebacterium* species, and others.[140,141]

39.44.2 Clinical Signs and Differential Diagnoses

Whether infected or not, corneal ulcers cause signs of pain (blepharospasm, epiphora, apparent photophobia). The conjunctiva is hyperemic, and the ulcerated area of the cornea retains fluorescein stain. A deep ulcer (resembling a crater in the corneal stroma) should be assumed to be infected. Superficial ulcers, on the other hand, are usually not infected, and the cornea maintains its normal curvature in the ulcerated area. Other signs of an infected ulcer are rapid progression and white or yellowish opacity of the cornea (signifying corneal stromal influx of neutrophils and bacterial colonization). An ulcer that is rapidly becoming wider or deeper or a "melting" ulcer, in which corneal stroma liquefies (Fig. 39-14), is highly suggestive of a bacterial infection. Fungal keratitis can appear similar but usually has a more insidious, or at least a slower, course. However, a cornea with fungal keratitis can become secondarily infected with bacteria. Bacterial keratitis can also present as a stromal abscess.[142] In these cases a cellular infiltrate is seen in the corneal stroma over which the initially damaged epithelium has healed. Therefore, such lesions do not stain with fluorescein, and many topical antibiotics cannot reach the site of infection.

Fig. 39-14 Right eye of horse with a melting corneal ulcer caused by *Pseudomonas* infection. Corneal stroma has liquefied and is overlying the lower lid.

39.44.3 Clinical Pathology

A diagnosis of a bacterial keratitis is made using Gram-stained corneal scrapings. Stained scrapings usually show many bacteria (some intracellular) and many neutrophils (some degenerate). Bacterial organisms are definitively identified after culture of the ulcerated cornea.

39.44.4 Pathophysiology

Bacterial keratitis is the result of pathogenic or opportunistic organisms colonizing a damaged cornea. The cornea is most likely to be damaged by mechanical trauma, but chemical damage is seen occasionally. Many different types of bacteria can be cultured from a normal eye, including *Corynebacterium, Streptococcus*, *Staphylococcus, Bacillus,* and rarely *Pseudomonas* species or other gram-negative bacteria.[143,144] Damage to the epithelium enables bacteria to adhere to the exposed corneal stroma and begin replicating.[145] Some bacteria

such as *Pseudomonas* elaborate collagenases and other proteoglycanolytic enzymes,[146] which results in corneal melting. Proteases and collagenases liberated by white blood cells and possibly corneal epithelial and stromal cells also contribute to the melting process. In this way, what begins as a small wound to the cornea can progress to a corneal perforation within 24 to 48 hours.

39.44.5 Treatment and Prognosis

Prognosis is guarded for any corneal ulcer that is rapidly progressing or melting. These ulcers can easily progress to corneal perforation and loss of the eye despite timely, appropriate treatment. On the other hand, with vigorous therapy some eyes with infected ulcers can be saved, leading to a visual eye, although usually a permanently scarred cornea.

In any ulcer in which a bacterial component is suspected, C&S of the ulcer and a corneal scraping for Gram staining and cytology should be taken. The horse is restrained or sedated, a palpebral block performed, topical anesthetic applied to the cornea, and a culture of the ulcer taken with a moistened swab. The ulcer margins are then scraped with a Kimura spatula or the blunt, handle end of a scalpel blade.

In cases of equine bacterial keratitis, including stromal abscesses, the therapeutic goals are to eliminate the bacteria, prevent or slow melting if present, and treat the concurrent uveitis. Because this requires very frequent applications of numerous medications to a horse with a painful and often fragile eye, a subpalpebral lavage system is usually required.

39.44.5.1 PLACEMENT OF SUBPALPEBRAL LAVAGE SYSTEM

The following equipment is necessary:

- Subpalpebral lavage kit (Fig. 39-15)
- White tape
- Applicator stick
- Lidocaine
- Topical ophthalmic anesthetic (proparacaine)
- Monofilament nonabsorbable suture on a cutting needle
- Tetanus toxoid

The horse should be tranquilized and/or twitched. The auriculopalpebral nerve is blocked over the zygomatic arch to paralyze the orbicularis oculi muscle and reduce spontaneous eyelid movement. The supraorbital (frontal) nerve is blocked at its exit from the supraorbital process to anesthetize the upper eyelid (Fig. 39-16). Topical anesthetic (proparacaine) is then applied to the eye by directing a gentle stream into the upper conjunctival fornix with a small syringe with a broken-off 25-gauge needle.

The blunt end of the 12-gauge needle is used to probe the lateral conjunctival fornix to establish the placement of the needle. The needle then is reversed and pushed through the eyelid in a lateral direction using a pair of needle holders as resistance (Fig. 39-17). The tip of the needle enters the dorsalmost aspect of

the fornix and exits near the orbital rim (Fig. 39-18). After the needle is pushed through the skin (Fig. 39-19), the Silastic Mila tubing is pushed through the needle, starting at the blunt end. When the tubing appears at the sharp end of the needle, the needle and tubing are pulled through the eyelid (Fig 39-20). The tube is then pulled up until the footplate fits snugly up into the dorsal conjunctival fornix (Fig. 39-21). During the manipulations, care must be taken to ensure that the needle or the hands of the operator do not push against the cornea.

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Fig. 39-15 Subpalpebral lavage kit (Mila International Inc.)

Fig. 39-16 Frontal (supraorbital) nerve block in horse. A 25-gauge needle is inserted into the supraorbital foramen, and 5.0 mL of lidocaine is injected alongside the nerve.

Fig. 39-17 The 12-gauge needle is pushed through the eyelid with open needle holders used as resistance and to keep the eyelid skin from tenting.

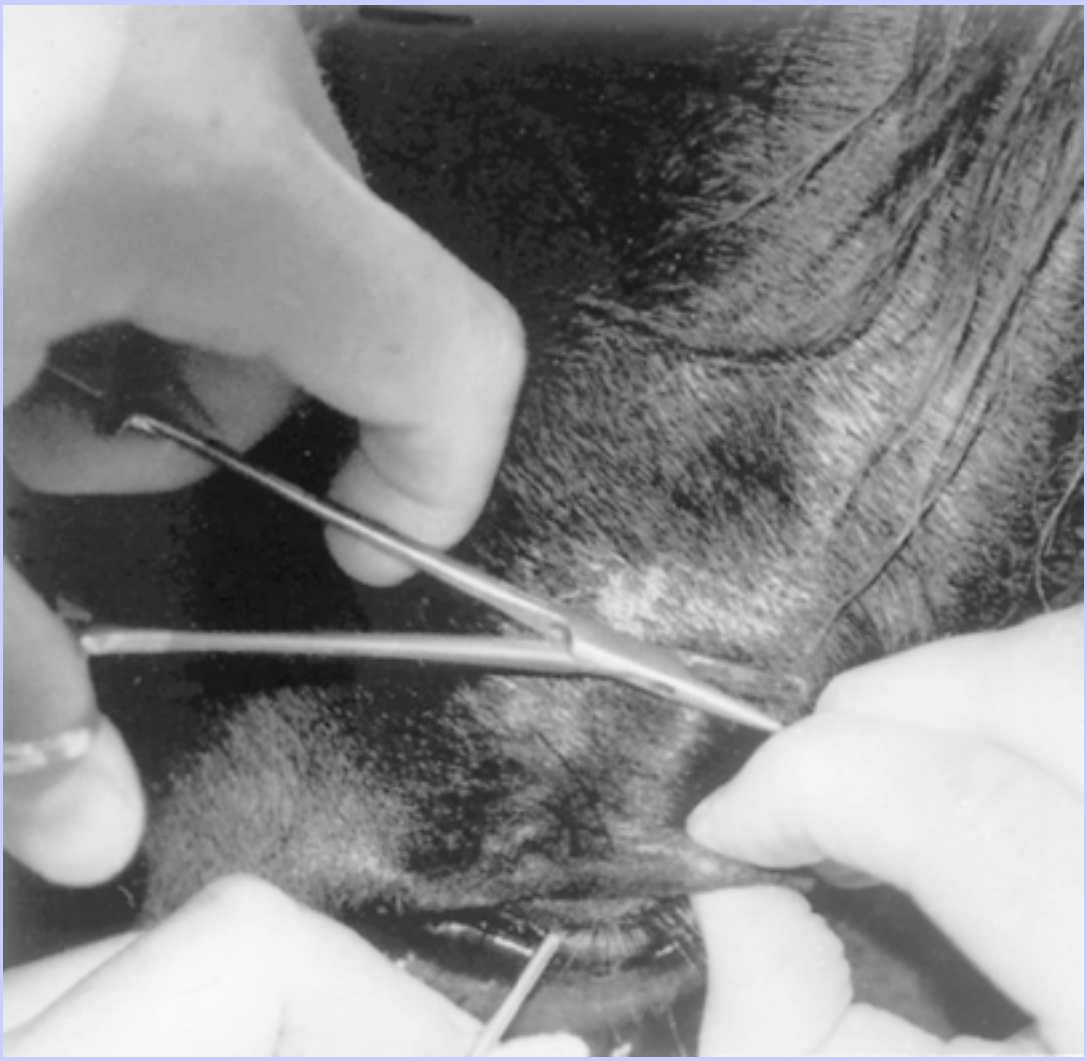

Fig. 39-18 Preparing to push the 12-gauge needle with a gauze sponge before placing a palpebral lavage system.

Tape is used to secure the tubing to the upper eyelid, and sutures secure the tape to the skin (Fig. 39-22). Alternatively, the green-plastic securing device in the pack can be sutured near the exit hole, securing the tubing without putting tape on the tubing. Additional tape and skin sutures can be placed several centimeters from the first tape, or tubing can be braided through the forelock. The Silastic tubing is then run down the neck through several braids to keep it secure. A catheter is run into this distal end of the tubing, an injection port is fixed to the end of the catheter, and the catheter and tubing are taped to an applicator stick to prevent kinking. The stick is then taped to a braid of the mane.

Fig. 39-19 Correct orientation of the 12-gauge needle as it is advanced through the upper lid from deep in the dorsal conjunctival fornix to exit near the orbital rim. Needle pushed through the eyelid laterally. Note that the needle was inserted 45 degrees to the eyelid margin. The lavage system is now threaded through the needle and the needle removed.

Fig. 39-20 The 12-gauge needle is withdrawn dorsally from the upper eyelid and the lavage tubing pulled through until the footplate is snug in the dorsal fornix.

Poorly placed lavage tubes or tubes that slip ventrally can rapidly produce a corneal ulcer. A displaced tube footplate can also cause topical medications to leak into the subcutaneous tissues, rapidly leading to a swollen and inflamed eyelid. Therefore the tube position should be checked at least once daily by gentle dorsal traction on the exposed tubing to ensure it has not slipped into the conjunctival cul-de-sac. Excess traction will pull the footplate through the conjunctiva and into the eyelid itself. Most horses tolerate this system well, and we have kept the tubing in place for up to 6 weeks. Occasionally, horses try to rub their heads and can damage the tubing; neck cradles or protective eye cups can be used in such horses. 1281 1282

Fig. 39-21 Footplate of the subpalpebral lavage kit.

Fig. 39-22 Subpalpebral lavage system secured in final position with tape "wings" sutured to the skin.

39.44.5.2

MEDICAL/SURGICAL APPROACHES AND GOALS

In a cornea with rapidly developing keratitis or melting ulcer, the clinician should always suspect the presence of *Pseudomonas* organisms, although other organisms such as *Streptococcus* have also been described. Treatment should be started with an appropriate antibiotic used every 1 to 2 hours. Fluoroquinolones such as ciprofloxacin (Ciloxan, Alcon) and ofloxacin (Ocuflox, Allergan)[147] are good choices for treatment of *infected* ulcers. They are not necessary for bacterial prophylaxis in *uninfected* ulcers. If gram-positive organisms are seen on the corneal scraping, ticarcillin, cefazolin (Ancef), penicillin, or ampicillin can be used.[148,149] Cefazolin is mixed to a concentration of 55 mg/mL,[150] ampicillin to 10 mg/mL,[148] and penicillin G to 100,000 U/mL. If the ulcer continues to worsen, antibiotics should be changed on the basis of the initial sensitivity results, and corneas should always be recultured in these cases because organisms can become resistant to the first antibiotic used. For resistant organisms, sensitivity testing that gives minimum inhibitory concentration (MIC) may be very useful because higher drug concentrations are more readily and safely attainable in the cornea than in the systemic circulation.

Melting of the cornea can be treated with collagenase and protease inhibitors. Experimentally, these drugs were not always effective in reducing melting.[151] However, some ophthalmologists believe that these drugs are efficacious. Certainly the main goal of therapy should be to kill the microorganism that is elaborating the enzymes. Autologous serum, EDTA, or acetylcysteine can be used topically, as can systemic doxycycline (10 mg/kg orally twice daily),[137] for their antiprotease and anticollagenase activity.

Surgical therapy can also be used and may improve prognosis. Conjunctival pedicle grafts can be used to bring a blood supply and subconjunctival fibroblasts to deep corneal ulcers and possibly slow progression and aid stromal reconstruction[149] while still allowing medication to reach the site of the ulcer. A conjunctival graft allows observation of the cornea so that treatment can be changed as corneal health improves or if the cornea continues to deteriorate. A nictitating membrane “flap” should *not* be used in rapidly progressing or deep ulcers because it does not allow topical medication or observation of the cornea. In the presence of a third eyelid flap, topically applied medications fail to reach the cornea, worsening of the ulcer goes unnoticed, reculturing cannot be performed, and appropriate changes in therapy cannot be instituted.

A corneoconjunctival transposition using autologous tissue or a corneal graft (penetrating keratoplasty) using donor cornea is an excellent treatment to repair very deep ulcers, descemetoceles, and perforations if melting has ceased and the ulcers are sterile.[140,151,152] Other substances that can be substituted for cornea are porcine small intestinal submucosa,[153] equine amniotic membrane,[154] or bovine pericardium (Dura Guard, Synovis). Placement of any graft requires microsurgical instruments, techniques, training, and experience. Highly specialized techniques, such as keratectomy with a conjunctival graft, penetrating keratoplasty, posterior lamellar keratoplasty, or deep lamellar endothelial keratoplasty, are necessary to treat stromal abscesses.[155–158]

The initial desired response to appropriate therapy of a malacic ulcer is simply cessation of worsening of the ulcer. That is, the ulcer does not appear to be healing or shrinking but also is not becoming larger or deeper. This suggests that bacteria have been killed and tissue destruction has halted. Epithelium will then begin to grow down the sides of the ulcer, covering the stroma or Descemet's membrane, and blood vessels will slowly begin growing into the cornea from the limbus. Once reepithelialization is complete, new infection with microorganisms is unlikely. If surgery has not been performed, however, the area that had been

ulcerated will be (sometimes markedly) thinner than the surrounding stroma. Thickening of this area will occur by very slow reconstruction of stromal collagen by corneal fibroblasts ("keratocytes") or when corneal blood vessels fill the old ulcer bed. This can take weeks to months, and until this happens, the cornea is susceptible to traumatic rupture.

Another goal of therapy for an infected ulcer is inhibition of "reflex uveitis" associated with any corneal irritation and mediated by the trigeminal nerve. Topical atropine is used for this purpose because it decreases pain associated with ciliary body spasm and maintains pupil dilation, which reduces the chance of posterior synechia formation. Atropine should be applied to effect (i.e., until reduced pain or pupil dilation noted). This may be as frequently as every 1 or 2 hours initially but may soon be limited to once daily or once every other day. Because topical atropine is absorbed into the systemic circulation and is associated with altered GI motility, borborygmi and signs of colic should be assessed frequently. Topical or systemic NSAIDs also can be used to decrease corneal and uveal inflammation. However, these drugs do slow corneal neovascularization to some extent, and topical NSAIDs (as with corticosteroids) are contraindicated in infected ulcers.[159,160] Topical corticosteroids are sometimes recommended to reduce corneal vascularization and minimize scar formation once epithelialization is complete. However, corneal vascularization is a critical means by which corneal stroma (and strength) is re-formed, and topical corticosteroids hasten regression of granulation tissue, suggesting that this approach may not be wise. In fact, no evidence indicates that steroid administration decreases the final size of the scar, and steroids may compromise healing and predispose to corneal rupture.

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39.44.5.3 FUNGAL KERATITIS IN HORSES

39.44.5.3.1 DEFINITION AND ETIOLOGY

Fungal keratitis (or keratomycosis) occurs when an ulcerated cornea becomes infected with a mycotic organism. As with bacteria, no fungi are known to *initiate* corneal ulcers. The most common genera isolated in cases of equine fungal keratitis are *Aspergillus* and *Fusarium* species, but *Cylindrocarpon destructans* and *Phycomycetes, Penicillium, Paecilomyces, Candida, Mucor, Alternaria,* and species of other genera have been cultured.[161–165] Horses seem to be unusually susceptible to fungal keratitis compared with the other domestic species.

39.44.5.3.1.1 Clinical Signs and Differential Diagnoses

Fungal keratitis has various manifestations.[166] A common presentation is a corneal ulcer, often with a history of chronicity. Typical history is a nonhealing or worsening ulcer despite antibiotic and antiinflammatory therapy. The eye is painful; the conjunctiva is hyperemic; and blepharospasm, epiphora, and apparent photophobia are also present. Corneal edema and cellular infiltrates surround the ulcer. Sometimes the cellular infiltrates can be very dense and appear as a white or yellow area throughout the corneal ulcer. The cellular infiltrate can be deep in the cornea and in some cases on the endothelial surface of the cornea, or even protruding into the anterior chamber, because fungus has a predilection for Descemet's membrane in the horse cornea. Corneal neovascularization is usually seen (Fig. 39-23). Signs of secondary uveitis can be severe. If ulcerated, fluorescein will stain the cornea. In some cases of fungal keratitis, however, the epithelium heals over the fungal infection, forming a stromal abscess, and the cornea will not stain with fluorescein.

Fig. 39-23 Right eye of horse with fungal keratitis. Note corneal neovascularization and dense cellular infiltrates in the cornea.

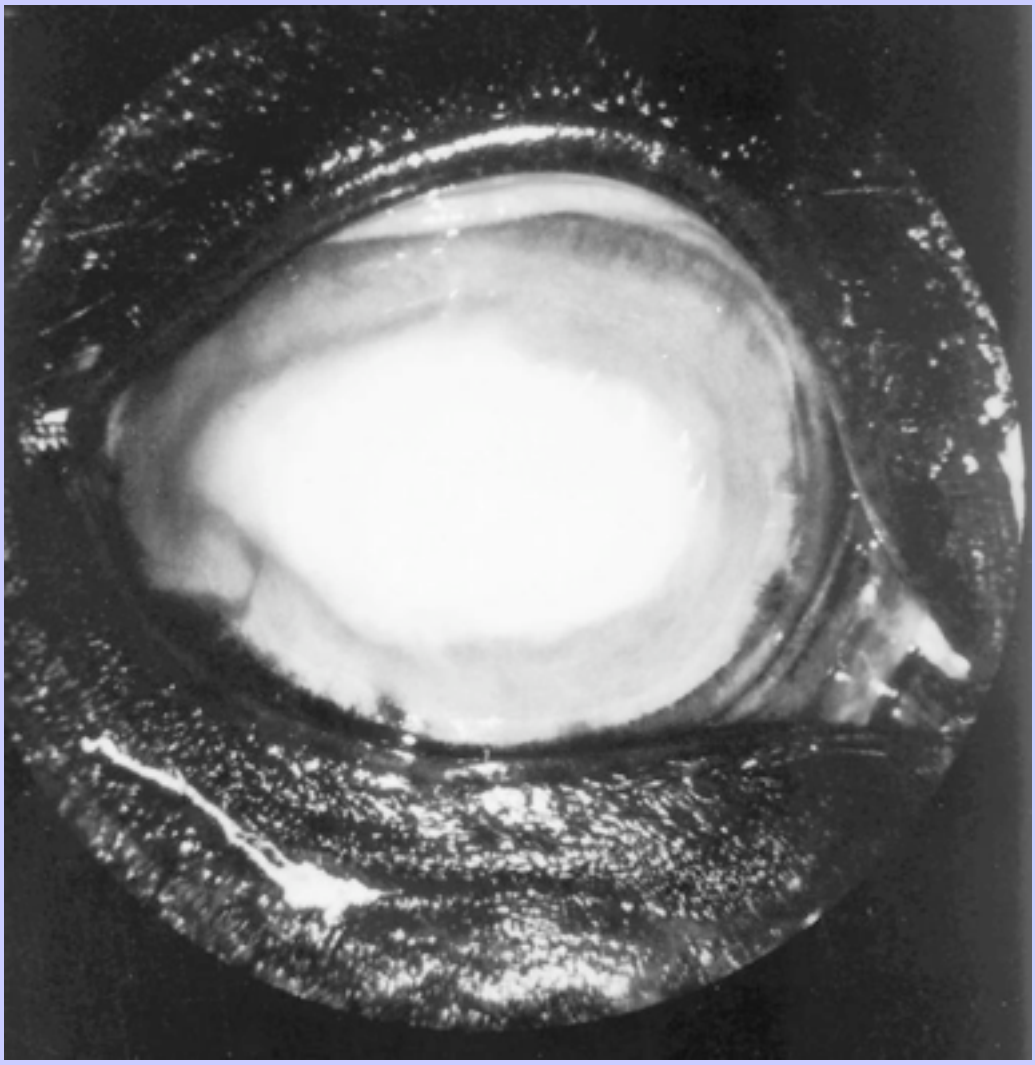
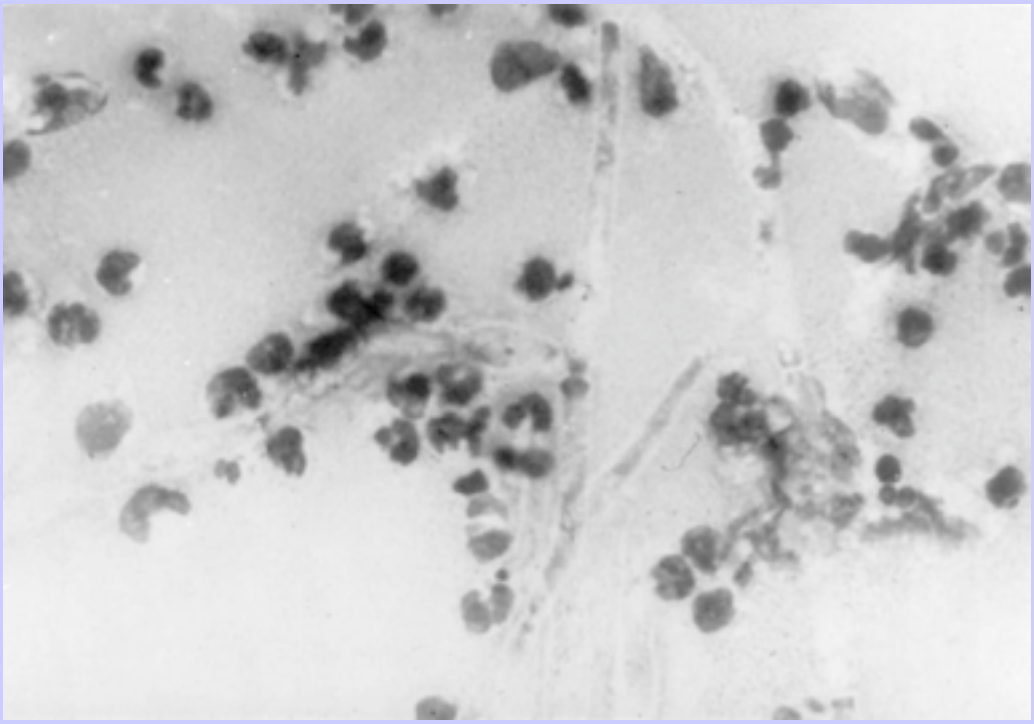


Fig. 39-24 Corneal scraping from horse with fungal keratitis. Note septate hyphae and surrounding inflammatory cells.



Fungal keratitis can also present as chronic, mild corneal disease. Small, multifocal, superficial opacities can be seen. In some cases there are small focal areas of fluorescein stain retention; sometimes there is no uptake of stain. Horses usually appear mildly painful with some epiphora; usually there is neither corneal neovascularization nor uveitis.

In all cases of fungal keratitis, differential diagnoses include other causes of corneal ulceration, such as bacteria (which may be coincident).

39.44.5.3.2

Clinical Pathology

A diagnosis of superficial fungal keratitis is made when fungal hyphae or yeast are seen on cytology or cultured from corneal scrapings (Fig. 39-24). Because fungi have a predilection for the deeper stroma and Descemet's membrane, a diagnosis of deep keratitis may require a full-thickness corneal biopsy from which the fungus is identified using culture or histopathology. Unfortunately, this predilection means some diagnoses of fungal keratitis are made only after enucleation.[167] If culture of an ulcer is positive when scrapings or biopsy do not show hyphae, the possibility of a commensal organism or incidental surface contaminant must be considered; especially if only one or two colony-forming units are cultured. Because treatment is prolonged and expensive, a definitive diagnosis of fungal colonization ideally should be made before treatment is initiated. The diagnostic utility of PCR for fungal keratitis is currently under investigation.

39.44.5.3.3

Pathophysiology

Fungal hyphae do not colonize intact cornea. Damage to epithelium is necessary for pathogenic or opportunistic fungi to begin growth in the corneal stroma. This usually results from a traumatic incident that may or may not be noticed by the owner. The use of antibiotics and corticosteroids alters normal flora and decreases the normal immune response, which may encourage fungal growth. Fungi implicated in keratomycoses are usually present in the horse's environment and can be cultured from more than 90% of normal horse eyes, with *Aspergillus* species being the most common isolate.[161] There is one report in the literature of keratomycosis caused by *Candida albicans* secondary to disseminated candidiasis.[168]

39.44.5.3.4

Epidemiology

This disease is sporadic, with varying seasonal distribution.[162,165]

39.44.5.3.5

Treatment and Prognosis

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Treatment consists of eliminating the fungus from the cornea and controlling secondary bacterial invasion and melting, along with reflex uveitis (if present), as for bacterial keratitis. Antifungal agents are required, and the course of treatment usually lasts for a number of weeks. Subpalpebral lavage systems are usually essential for delivering these drugs. Healing is usually not complete until corneal neovascularization has reached the infected area, except when the fungus has reached Descemet's membrane, and in these cases blood vessel growth does not always stop fungal growth. Medical therapy is most effective for treating superficial disease. For deep disease, surgical therapy can also be used with the medical therapy. Deep lamellar and penetrating keratoplasties probably carry the best prognosis,[150,155,167,169] although superficial keratectomies with a conjunctival graft can also be used for more superficial lesions.

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A number of antifungal agents are available. Miconazole, used as the undiluted IV preparation, was once the drug of choice for many ophthalmologists. Unfortunately, it is no longer available commercially in this formulation, although it can be compounded. Natamycin (Natacyn) is manufactured as an ophthalmic suspension and is the drug of choice for treating fungal keratitis in humans. However, natamycin does not penetrate intact epithelium well, and some *Fusarium* species may be resistant to this drug.[170] Fluconazole (Diflucan) is now often recommended as a replacement for miconazole. However, one study reported that fluconazole had lower in vitro activity than a number of other antifungal drugs.[171] The IV preparation is a 2 mg/mL solution, which is used undiluted as a topical preparation. Miconazole and fluconazole do penetrate intact corneal epithelium when given topically, but drug concentrations in the stroma are higher if epithelium is absent.[172] Fluconazole can also be used subconjunctivally, intracamerally, or intravitreally. Ophthalmologists are also beginning to use fluconazole systemically to treat deep corneal fungal disease because this drug does reach adequate concentrations in the aqueous humor, which may be appropriate for deep stromal or endothelial infections.[173] No toxicity studies have been performed on the horse, but anecdotal evidence does not suggest toxicities, and fluconazole has been associated with resolution of deep disease.

Compounded formulations of itraconazole/DMSO ointment have also been used for equine keratomycosis. High concentrations of itraconazole can be achieved in the corneal stroma with this preparation, even

when the overlying epithelium is intact, and it has been used successfully in clinical cases.[174] In contrast to fluconazole, systemically administered itraconazole does not penetrate normal equine eyes.[175]

Other drugs have been suggested as treatment for fungal keratitis. Voriconazole administered either topically or systemically does penetrate normal equine eyes and reaches concentrations that could be therapeutic.[176] Miconazole dermatologic or vaginal creams seem to work for mild, superficial disease; however, no clinical trials describing their efficacy and safety for ocular use have been reported. Amphotericin B has good antifungal properties but can be very irritating and is probably not the drug of choice. In vitro research shows that silver sulfadiazine is fungicidal against isolates from equine patients with keratomycosis.[170] Unfortunately, in vitro results do not necessarily correlate with clinical results in patients with keratomycosis. Corneal penetration of the drug, the horse's immune system, and the site and severity of the fungal infection all play important roles in choice of drug.[170]

In addition to the antifungal agent selected, topical mydriatic/cycloplegic agents such as atropine should be used to combat the accompanying uveitis, and topical antibiotics are indicated to prevent superinfection with bacteria. Systemic NSAIDs should be used for the secondary uveitis, especially at the beginning of treatment, when fungal death can exacerbate the uveitis. However, NSAIDs probably slow neovascularization of the cornea, and treatment with these drugs should be decreased as the uveitis is controlled.[177]

Prognosis is guarded to poor in many cases of fungal keratitis. Usually the best possible outcome is a visual eye with some degree of residual corneal scarring and possibly synechiae. Because no evidence suggests that corticosteroids decrease the eventual size of the scar, and because they will promote the presence of residual hyphae, the use of corticosteroids is not recommended in a healing fungal ulcer. Complications of fungal keratitis include perforation of the ulcer with loss of the eye, superinfection with bacteria, and phthisis bulbi.

39.44.5.4 UVEITIS ASSOCIATED WITH LEPTOSPIROSIS IN HORSES AND COWS

Leptospirosis is caused by a filamentous bacterium known as a spirochete. Disease is seen in most domestic animals as well as humans. Various serovars of *Leptospira interrogans sensu stricto*, *L. kirschneri*, and *L. santarosai* have been shown to affect various organs, such as kidneys, liver, spleen, muscles, CNS, and eyes and have been associated with abortions.[178] These organisms primarily cause a vasculitis and endotheliitis in these organs.[179]

Because leptospiral organisms cause vasculitis, it is reasonable to assume that uveitis might be present in an acute infection, and this has been reported in horses during the acute phase of leptospirosis.[180] Uveitis has also been seen experimentally in a calf during acute disease.[181] However, the role of leptospires in uveitis seen weeks to months after the acute disease remains much more controversial. Evidence for such a role is most complete in the horse, in which leptospiral uveitis and its role in equine recurrent uveitis (ERU) or “periodic ophthalmia” have been described.[180,182,183] Uveitis in these horses was bilateral or unilateral and frequently was recurrent, leading to loss of or decrease in vision.[182] Uveitis was not seen until 18 to 24 months after the acute outbreak of leptospirosis. Treatment with systemic antibiotics did not seem to affect the uveitis. In this study, serum titers to *L. interrogans* serovar *pomona* often remained high for at least 6 years.[182] In another study, uveitis was seen in 22 eyes of 18 ponies experimentally infected with serovar

pomona. The earliest sign of uveitis was seen at 1 year after inoculation. Anterior uveitis with cataract formation and posterior synechiae were also seen; as were recurrences.[183]

Recently, leptospiral organisms have been identified using PCR[184] or by culture[184–186] in the eyes of horses with ERU. A study in California using a PCR assay for *Leptospira* showed that 30 of 55 eyes (21 of 30 horses) with ERU had detectable *Leptospira* DNA in their aqueous humor.[184] Interestingly, in other studies, treatment with systemic antibiotics did not decrease the inflammation.[187–189] In Western Europe a total of 618 vitreous and/or aqueous samples were taken from the eyes of 501 horses with either active ERU or a history of ERU. Leptospires were isolated from 199 (32.2%) of the samples. Most belonged to serogroup *grippotyphosa,* with the rest in serogroup *australis, sejroe, pomona,* or *javanica*.[185] In contrast, 36 samples of vitreous from 21 normal horses did not grow leptospires.[186] Although leptospires are involved in ERU in many horses with this syndrome, controlling or treating this disease remains a problem. The best means of symptomatic control of ERU at this time appears to be the use of ocular bioerodible cyclosporin A implants.[190] These are placed intravitreally or, more recently, suprachoroidally and were investigated for this drugs ability to control immune-mediated inflammation elsewhere in the body and within the eye. More recently, however, cyclosporine has been shown to be toxic to *L. interrogans* in vitro at the same concentration that is achieved in uveal tissue with a suprachoroidal implant.[190] In one study a leptospiral vaccine in horses with ERU was not recommended.[191] (See also Equine Recurrent Uveitis.)

1284 1285

39.44.5.5 OCULAR MANIFESTATIONS OF EQUINE ADENOVIRUS

Equine adenovirus is a DNA virus that causes bronchopneumonia in foals, especially if they are immunodeficient. Mucopurulent nasal and ocular discharge accompanies the respiratory system disease. Histologically, swelling and necrosis of conjunctival cells with intranuclear inclusions are seen, with accumulation of neutrophils in the lumina and adventitia of uveal blood vessels.[192]

39.44.5.6 OCULAR MANIFESTATIONS OF SALMONELLOSIS IN HORSES

Salmonella species cause one of the more common and serious bacterial enteritides in foals and adult horses. It is often accompanied by septicemia in foals. Anterior uveitis and hypopyon have been seen in animals with salmonellosis, and *Salmonella* species can sometimes be cultured from these eyes.[193]

39.44.5.7 *MORAXELLA* CONJUNCTIVITIS IN HORSES

Two reports have described a *Moraxella* species recovered from several horses in herd outbreaks of conjunctivitis, ocular discharge, and erosions of eyelid epithelium at the canthi.[194,195] The organism was similar but not identical to *M. bovis,* and the disease was reproduced experimentally in horses by instillation of the organism into the conjunctival sac. Huntington et al.[195] described successful treatment of the lesions with chloramphenicol ointment, whereas Hughes and Pugh[194] described the lesions as healing spontaneously.

39.44.5.8

OCULAR MANIFESTATIONS OF EQUINE VIRAL ARTERITIS

Equine viral arteritis is a rare disease caused by an RNA virus classified as Arteriviдae. Most animals are subclinically infected, but ocular and nasal discharges; palpebral, periorbital, limb, or ventral edema; skin rash; pyrexia; rhinitis; leukopenia; abortions; and neonatal death are seen.[196,197] Corneal opacity and apparent photophobia have also been described.[198] The virus characteristically causes a panvasculitis.

39.44.5.9

OCULAR MANIFESTATIONS OF *RHODOCOCCUS (CORYNEBACTERIUM) EQUI* IN HORSES

Rhodococcus equi is a gram-positive coccobacillus that causes bronchopneumonia in young foals. One report of *R. equi* from the eye of a foal with bilateral panophthalmitis and pneumonia can be found.[199] Clinically, the foal had bilateral miosis and hypopyon.

39.44.5.10

OCULAR MANIFESTATIONS OF BORRELIOSIS IN HORSES

Borrelia burgdorferi, the agent of Lyme disease, has been most often described as causing polyarthritis in horses, cows, and dogs. However, one case of apparent ocular disease has been reported in a pony infected with *B. burgdorferi*.[200] Unilateral anterior and posterior uveitis was noted, and spirochetes were found in the anterior chamber. Other clinical signs included arthritis and synovitis of both carpal joints.

39.44.5.11

OCULAR MANIFESTATIONS OF CRYPTOCOCCOSIS AND HISTOPLASMOSIS IN HORSES

Exophthalmia and blindness caused by *Cryptococcus neoformans* have been described in a horse.[201] The frontal sinus and retrobulbar area were involved with a fungal granuloma, but the eye itself was normal. The chorioretinitis seen in other species associated with *C. neoformans* has not been described in the horse. *Cryptococcus albidus* has been cultured from the cornea of a horse with chronic keratitis.[202] Organisms consistent with *Histoplasma* spp. were seen on cytology of a corneal scraping taken from a horse with chronic keratitis.[203] The horse was successfully treated with topical fluconazole.

39.44.5.12

OCULAR MANIFESTATIONS OF EQUINE HERPESVIRUS TYPE 2 (EHV-2)

Equine herpesvirus serotype 2 (EHV-2) has been isolated from eyes in herd outbreaks of keratoconjunctivitis in horses.[204,205] Clinical signs in one outbreak included apparent photophobia, epiphora, corneal neovascularization, corneal color change, and pinpoint ulcerations; eyes healed within 2 weeks.[204] In the other outbreak, conjunctivitis, and multifocal superficial corneal opacities were seen; eyes healed within 2 weeks on topical idoxuridine.[205] Experimental inoculation of EHV-2 intranasally in two ponies pretreated with dexamethasone caused conjunctivitis, as well as lymphadenopathy and coughing.[206] Conjunctiva from both ponies was positive for virus by PCR 6 months after inoculation. EHV-2 can also be isolated from the blood of normal horses,[207] and positive PCR results can be obtained from normal eyes as well as eyes with keratoconjunctivitis, making diagnosis difficult.

Miller et al.[208] confirmed EHV-2 by fluorescent antibody staining after isolating virus from the cornea of a thoroughbred mare with multiple superficial punctate corneal lesions. The keratitis was successfully treated with topical 1% trifluridine ophthalmic solution.*

* Viroptic, Burroughs-Wellcome, Research Triangle Park, NC.

39.44.5.13

OCULAR MANIFESTATIONS OF STRANGLES (*STREPTOCOCCUS EQUI* SUBSP. *EQUI*)

Strangles is a respiratory infection caused by *Streptococcus equi* subsp. *equi* that can have an accompanying ocular discharge.[209] Chorioretinal depigmentation was noted in the nontapetal fundus of several horses in one group clinically diagnosed with strangles. Because these lesions repigmented with time, it was suggested that they were caused by embolism to the choroid during bacteremia.[210] One case of panophthalmitis caused by *S. equi* in a horse has been described.[211] Ten days after a bout of strangles, this horse developed anterior uveitis, which progressed to corneal stromal abscesses and panophthalmitis. *S. equi* was cultured from the eye at enucleation.

39.44.5.14

OCULAR MANIFESTATIONS OF EQUINE HERPESVIRUS TYPE 1

Equine herpesvirus serotype 1 (EHV-1) is a cause of rhinopneumonitis in horses. It has been cultured from cases of superficial punctate keratitis in the horse; the significance of these isolations is unknown.[212]

Six foals were experimentally inoculated intranasally with EHV-1.[213] All developed typical mild signs of upper respiratory infection. One foal developed vision problems 1 month after inoculation. Bilateral chorioretinitis was diagnosed. On necropsy, chorioretinal degeneration with mononuclear cell infiltration in some areas was seen, as well as demyelination of the optic nerve and mononuclear cell infiltrate in parts of the CNS.[213] These findings are not surprising in that EHV-1 causes vasculitis and CNS disease in horses.[214]

39.44.5.15

OCULAR MANIFESTATIONS OF BRUCELLOSIS IN HORSES

Brucella abortus has been suggested as a cause for ERU,[215] although serum agglutination titers for *B. abortus* in normal horses and horses with ERU are similar.[216]

39.44.5.16

OCULAR MANIFESTATIONS OF *MYCOBACTERIUM AVIUM* IN HORSES

A case of anterior uveitis and bilateral chorioretinitis with retinal detachments has been described in a horse from Denmark. Acid-fast organisms were seen in both eyes as well as in numerous other organs. *Mycobacterium avium* was cultured from these organs.[217]

39.44.5.17

INFECTIOUS BOVINE KERATOCONJUNCTIVITIS

JOHN ANGELOS

Infectious bovine keratoconjunctivitis (IBK), or "pinkeye," is the most common ocular disease of cattle and has been identified in cattle populations worldwide. The clinical signs of IBK include corneal ulceration, corneal edema, photophobia, blepharospasm, and lacrimation. In less severely affected animals, recovery with or without permanent corneal scarring occurs. In the most severely affected animals, corneal rupture and lens/iris prolapse may occur, causing permanent blindness. IBK is most common in calves, typically affecting one eye, although both eyes may be affected. Estimates of annual incidence of IBK are 5% of all beef cattle, with more than 50% of herds affected.[218] Epizootics occur, with case-attack rates approaching 90% to 100% of yearling cattle.[219,220] Cattle of all breeds may be affected; however, a higher incidence is reported in Herefords[221] and a lower incidence in Brahmans and cattle with more pigmentation at the ocular margins.[222,223]

39.44.5.17.1

Economic Impact

Cattle with IBK have reduced weight gain that results in economic losses to producers. Postweaning 205-day weights of bulls and heifers with IBK showed losses of 36 and 40 pounds (16 and 18 kg), respectively, over unaffected herdmates.[224] In 1169 pasture-raised calves over a 4-year period, the average weight reduction was 11 pounds (5 kg) for calves with IBK in one eye and 35 pounds (15.75 kg) for calves with IBK in both eyes.[225] A recent study of more than 45,000 health records of weaned calves demonstrated almost 20-pound (9-kg) lighter weaning weights in calves diagnosed with IBK versus healthy calves.[221] The economic losses from reduced weight gains along with treatment-associated expenses account for annual losses in the United States estimated at $150 million in 1976.[226] It is likely that current losses greatly exceed this estimate.

39.44.5.17.2

Etiology and Epidemiology

Moraxella bovis is the only organism for which Koch's postulates have been fulfilled with respect to IBK.[227] However, other viruses and bacteria have also been associated with IBK. Infectious bovine rhinotracheitis (IBR) virus[228,229] and *Mycoplasma* species[230] are probably the most important and likely act as risk factors for IBK by enhancing opportunities for corneal injury[231–233] and increasing ocular and nasal discharge, which may facilitate transmission of *M. bovis*.

Other potentially pathogenic bacteria have been isolated from the eyes of cattle with IBK. In 1966, hemolytic gram-negative cocci were isolated from calves with severe keratitis and corneal ulceration.[234] In Australia, *Neisseria* species were isolated in 24 of 25 outbreaks of IBK; *M. bovis* was identified in only two of these outbreaks.[235] *Neisseria* (*Branhamella*) *catarrhalis* was reported in almost 45% of IBK cases, whereas *M. bovis* was isolated from only 28% of IBK cases.[236] *M. bovis* and *Neisseria* species were also cultured from normal eyes of cattle.[237,238] *M. ovis* and *Neisseria ovis* were reported from cattle in Israel with IBK.[239,240] During summer 2002 in northern California, the majority of bacterial isolates from IBK-affected calves were hemolytic gram-negative cocci.[241] *N. ovis* experimentally inoculated into the eyes of calves did not cause lesions typical of IBK, despite previous corneal irradiation.[242] *M. bovis* has been reported in mule deer with keratoconjunctivitis, although experimental inoculation of *M. bovis* isolates into eyes of mule deer fawns did not result in disease.[243] Recently, hemolytic and cytolytic activity from

culture filtrates of *M. ovis* isolated from cattle with IBK has been described, suggesting a possible role for bacteria other than *M. bovis* in IBK pathogenesis.[244]

In addition to bacterial infection, other risk factors for IBK include flies, solar irradiation, and mechanical trauma from plant awns. *M. bovis* survives up to 3 days on the external surface[245] and 2 days in the gut[246] of face flies *(Musca autumnalis)*. IBK was experimentally induced in cattle that were exposed to face flies that had fed on *M. bovis* cultures.[247] Insecticide-impregnated ear tags or back/face rubbers to reduce fly populations have proved effective in reducing IBK in cattle populations.[248] An association between solar irradiation and IBK is also documented.[249–251] Corneas of calves exposed to ultraviolet (UV) irradiation incur corneal epithelial cell degeneration [252] that predisposes eyes to establishment of *M. bovis* and IBK. An experimental model for IBK has been developed in which calves are exposed once daily for 2 or 3 days to UV irradiation using sunlamps held 24 inches (60 cm) from the corneal surface; after the last exposure, animals are infected by instillation of *M. bovis* into the eye.[253–255] Plant awns, by causing mechanical corneal damage, can predispose eyes to infection with *M. bovis* and IBK.

Hemolytic strains of *M. bovis* are considered pathogenic, whereas nonhemolytic, nonpathogenic *M. bovis* can be isolated from normal cattle,[219,256–258] from cattle exhibiting conjunctivitis,[259] and simultaneously with hemolytic *M. bovis* from cattle with IBK.[258] Outbreaks of IBK typically occur annually during summer months, and such outbreaks may be caused in part by cattle harboring *M. bovis* subclinically.[258,260] Shifting between hemolytic and nonhemolytic phenotypes of *M. bovis* has also been described.[261]

39.44.5.17.3

Pathophysiology of Moraxella bovis

M. bovis produces many hydrolytic enzymes, including C4 esterase, C8 esterase-lipase, C14 lipase, phosphoamidase, phosphatase, leucine and valine aminopeptidases, and gelatinase.[262] Of these, however, only two proteins have been linked to pathogenicity: pili and cytotoxin. Pilin proteins of *M. bovis* are of the *N*-methylphenylalanine type (type 4 pili[263–265]) and enable bacteria to adhere to the corneal epithelium and colonize the surface of the cornea.[266–268]

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The *M. bovis* cytotoxin (cytolysin/hemolysin) is a pore-forming protein that is also considered necessary for pathogenesis. Broth supernatants of hemolytic, but not nonhemolytic, strains of *M. bovis* will cause lysis of bovine erythrocytes, neutrophils, lymphoma cells, and corneal epithelial cells in vitro.[269–272] The lytic activity of *M. bovis* cytotoxin occurs through calcium-dependent formation of transmembrane pores in target cell membranes.[273] Ocular lesions induced by a purified hemolytic and cytolytic fraction of *M. bovis* are identical to the ocular lesions observed in naturally occurring IBK; extracts from nonhemolytic *M. bovis* do not result in corneal lesions.[274]

An association between the *M. bovis* cytotoxin and the RTX (***r***epeats in the structural ***t***o***x***in) family of bacterial exoproteins followed the discovery that *M. bovis* cytotoxin induces the formation of pores in target cell membranes.[273] It was subsequently shown that an approximately 110-kilodalton protein in concentrated culture supernatants from cytolytic *M. bovis* cultures could be recognized by a monoclonal antibody to HlyA, an RTX toxin of uropathogenic *Escherichia coli*.[275] The presence of RTX toxins has been reported in a numerous animal pathogens, including *Mannheimia (Pasteurella) haemolytica,* the agent of shipping fever pleuropneumonia in cattle;[276] *Actinobacillus pleuropneumoniae,* an agent of swine

pleuropneumonia;[277] *Pasteurella aerogenes*, an abortifacient in swine and other mammals;[278] and *Actinobacillus equuli,* associated with foal septicemia.[279] Enterohemorrhagic *E. coli* O157:H7 also harbors a plasmid-encoded RTX toxin.[280]

The best-characterized RTX toxin is HlyA of uropathogenic *E. coli*. The gene encoding this toxin is assigned the abbreviation *hlyA* and is contained within a four-gene operon organized 5′-C-A-B-D-3′. The product of the RTX A gene is a structural toxin that must be activated by the RTX C gene product to become hemolytic.[281–283] The activation occurs through fatty acylation of conserved lysine residues.[284,285] After activation the toxin is secreted by membrane transport proteins encoded by the B and D genes and a third protein, TolC.[286,287] The regulation of transcription through the RTX operon in *E. coli* is a complex process and involves the protein RfaH and JUMPStart DNA sequences.[288] As with *E. coli* hemolysin, the *M. bovis* cytotoxin gene *(mbxA)* is contained within an operon that encodes activation and export proteins; this operon is called the *mbx* operon of *M. bovis* and is absent in nonhemolytic *M. bovis*.[289] The *mbx* operon defines a pathogenicity island, and acquisition/loss of *mbx* genes may explain the ability of *M. bovis* to change from the hemolytic to nonhemolytic phenotype.[290]

39.44.5.17.4

Immunity to Moraxella bovis

Secretory IgA is the major immunoglobulin found in normal bovine lacrimal secretions.[291] During experimentally induced IBK, tear IgG1 and IgG2 concentrations increase.[292] Early studies suggested that calves with more severe IBK had higher lacrimal IgA titers to crude *M. bovis* antigen preparations than calves with less severe IBK.[293] A subsequent study identified a predominant tear IgG response to a crude, whole-cell *M. bovis* antigen in calves with naturally occurring IBK and concluded that *M. bovis*—specific antibodies in lacrimal secretions did not prevent IBK in calves.[294] Enzyme-linked immunosorbent assay (ELISA) has been used to quantify nonspecific *M. bovis* antigens in tears and has revealed that IgA titers are higher than IgG titers.[295] A study on a small number of calves then suggested that both lacrimal (secretory IgA) and humoral (IgG) antibodies against *M. bovis* whole-cell antigen conferred resistance against IBK, versus a humoral IgG antibody response alone.[296] It was concluded that serum antibodies against *M. bovis* may account for a reduction in the length and severity of clinical signs associated with IBK. Unfortunately, none of these studies adequately controlled for total antibody isotypes present in serum or ocular secretions. In addition, crude *M. bovis* antigen preparations were used in these assays.

In other diseases associated with RTX toxin—producing pathogens, the protective role of immunity against RTX toxins is not well understood. In one study a *Mannheimia (Pasteurella) haemolytica* leukotoxin subunit vaccine was not protective;[297] however, calves infected with a mutant strain of *M. haemolytica* that secreted inactive leukotoxin had reduced lung lesion scores but similar clinical severity scores as calves receiving wild-type *M. haemolytica*.[298] The introduction of genes encoding the hemolysin (HlyA) into other *E. coli* strains increased virulence,[299] although an HlyA-deficient mutant was still pathogenic.[300] Pigs infected with nonhemolytic *Actinobacillus pleuropneumoniae* developed lung lesions that were similar to lesions in pigs infected with a virulent strain, and it was concluded that the hemolysin of *A. pleuropneumoniae* serotype 2 was not essential for disease.[301] However, another study found that pigs vaccinated with *A. pleuropneumoniae* serotype 1 hemolysin were protected after challenge.[302,303] These studies underscore the fact that immunity to diseases caused by RTX toxin—producing bacteria is complex and may not depend on an antibody response to an RTX toxin alone.

39.44.5.17.5

Experimental Vaccination

Early studies that reported reduced *M. bovis* infection rates and decreased occurrence of IBK after reexposure to *M. bovis* indicated that vaccination against IBK might prevent disease.[250] Subsequent work showed that calves vaccinated intramuscularly with live *M. bovis* had less severe IBK after challenge.[304] Formalin-killed *M. bovis* was also reported to be as effective as live cultures in preventing experimentally induced IBK[305]; under field conditions, however, a formalin-killed autogenous bacterin was not efficacious.[306]

In an effort to identify other candidate *M. bovis* vaccine antigens, researchers began to examine the use of component or subunit vaccines to prevent IBK. In early studies, *M. bovis* pilin antigens were found to protect calves from homologous challenge.[307] Purified *M. bovis* ribosomes were not protective.[308] Bacterin-containing pili plus corneal-degrading enzymes were protective in field trials, and protection was correlated with the corneal-degrading enzyme level in the vaccine.[309] In that study, however, the exact composition of corneal-degrading enzymes was not reported. In a later study, two commercial *M. bovis* pilus-based vaccines were not protective for calves in a heterologous challenge model.[310] Although pilin is immunogenic, there is marked antigenic diversity between different pilin types because of the presence of two structural pilin genes and variability in the amino acid composition of the pilin molecule caused by inversions within pilin genes.[267,268,311,312] Limited antigenic cross-reactivity was reported between heterologous pili,[313,314] and emergence of novel pilus types can precipitate IBK outbreaks.[315] Such antigenic variability is believed to reduce the overall efficacy of pilin-based vaccines. Nevertheless, more recent work has demonstrated conserved epitopes across different pilin types,[316,317] suggesting a possible future role for conserved pilin antigens in vaccines against IBK.

Unlike pili, the *M. bovis* cytotoxin seems to be more conserved across different *M. bovis* strains. IBK-affected cattle were shown to develop systemic immune responses to cytotoxin[318–321] and antihemolysin antibodies to one *M. bovis* strain, neutralized hemolysin from 33 different strains of *M. bovis*.[321] A partly purified cytotoxin vaccine also protected calves against IBK after challenge with heterologous *M. bovis*.[318] These reports suggest a role for a cytotoxin-based vaccine to prevent IBK from multiple *M. bovis* strains, which could therefore be superior to traditional pilus-based vaccines.

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Methods to purify partly the *M. bovis* cytotoxin have now been published,[322] and its efficacy in a vaccine to prevent IBK has been demonstrated.[323] The labor-intensive process of preparing native cytotoxin has also led to the investigation of recombinant *M. bovis* cytotoxin vaccines to prevent IBK. In one field trial, calves vaccinated with the recombinant carboxy terminus of *M. bovis* cytotoxin had a lower cumulative proportion of ulcerated eyes compared with saline and adjuvant control calves.[324]

Parenteral routes of vaccination have been tested most often, although aerosol vaccination also has been found to be effective against IBK.[325]

39.44.5.17.6

Treatment and Prevention

IBK prevention hinges on minimizing risk factors for disease, reducing infection of the ocular surface with *M. bovis* through antimicrobial use, and vaccination. To reduce fly populations, insecticide-impregnated

ear tags and topical insecticides with back and face rubbers are employed. Clipping mature grasses before cattle are turned out may also help minimize risks associated with direct mechanical corneal injury from plant awns.

Moraxella bovis is susceptible to numerous approved antimicrobials. These include penicillin administered subconjunctivally,[326] oxytetracycline parenterally or orally (20 mg/kg once or twice followed by 2 g/calf/day for 10 days),[327–329] florfenicol intramuscularly (two 20-mg/kg injections 48 hours apart) or subcutaneously (40 mg/kg once),[330,331] ceftiofur crystalline-free acid subcutaneously (6.6 mg ceftiofur equivalents/kg once) in the posterior aspect of the pinna,[241] and tulathromycin (2.5 mg/kg) subcutaneously.[332]

For vaccination against IBK, most producers use commercially available bacterins. Many different vaccines are available but are not universally effective, as previously discussed. Anecdotal evidence suggests that autogenous vaccines against non—*M. bovis* isolates of gram-negative cocci from IBK-affected eyes may provide an alternative prevention strategy to conventional commercial *M. bovis* vaccines when such vaccines are ineffective.

39.44.5.18 IMMUNE-MEDIATED OCULAR DISEASES

MARY Belle GLAZE

Except for the conjunctiva, the eye has no lymphatic drainage. Access of antigens to potentially reactive lymphoid tissue is also restricted by the avascularity of the cornea and the presence of selective blood-ocular barriers. As unlikely as immunologically mediated abnormalities might seem under these circumstances, immune-related inflammation remains a leading cause of blindness in the horse. Reports of immune-mediated ocular disease in ruminants are rare.

39.44.5.19 Ocular Immunology

The conjunctiva represents an extension of the mucosal immune system. A variety of immune cells can be found in conjunctival tissue, including intraepithelial $CD8^+$ lymphocytes and mast cells, as well as aggregates of $CD4^+$ T-helper (Th) and B lymphocytes, $CD1^+$ dendritic cells and macrophages, and within the substantia propria.[333] The conjunctiva processes ocular surface antigens with the help of regional lymph nodes. Antigen presentation is likely preceded by local tissue damage and release of inflammatory mediators that recruit inflammatory cells to the site. Under the influence of cytokines such as interferon alpha (IFN-α), tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-12 released by local and recruited cells, tissue dendritic cells process and carry host and pathogen molecules to regional lymph nodes to activate $CD4^+$ Th cells. Stimulated lymphocytes migrate back to the conjunctiva (T cells) and lacrimal gland (B cells), where they participate in cell-mediated reactions and local production of IgA and to a lesser degree IgG, respectively.[333–335]

Because the globe itself is without lymphatic drainage, intraocular antigens must be processed at a distant site. These antigens pass into the systemic circulation, preferentially stimulating the spleen as well as the bone marrow and other distant lymphoid organs. After 5 to 7 days, sensitized lymphocytes migrate back to the eye and localize within the uvea and limbal conjunctiva. As with those on the ocular surface, these immunologically competent cells are capable of antibody production and can participate in cell-mediated

reactions. Further exposure to the same antigen can provoke an anamnestic response, endowing the uveal and limbal tissues with behavior comparable to that of a regional lymph node.[336]

The intraocular immune response varies from that of a classic immune reaction, presumably to limit excessive inflammation within the eye. Anterior chamber—associated immune deviation (ACAID) is characterized by preferential stimulation of T suppressor cells that inhibit development of both $CD4^+$ and B cells necessary in delayed-type hypersensitivity reactions and production of complement-fixing isotypes of antibody, respectively.[333,337] Cells in the uvea and corneal endothelium also express Fas ligand (FasL), which limits inflammation through apoptosis of activated leukocytes entering the eye.[333]

Each of the four major types of immunologic reactions occurs within the eye.[338] Type I (immediate) hypersensitivity is usually manifest as conjunctivitis, an acute local inflammatory reaction that follows IgE-mediated release of histamine, proinflammatory cytokines and chemotactic mediators from tissue mast cells, and synthesis of cytokines, leukotrienes, prostaglandins, thromboxane, platelet-activating factor (PAF), and kinins.[339] These mediators of the IgE/mast cell inflammatory pathway increase vascular permeability, constrict smooth muscle, dilate blood vessels, and activate leukocyte chemotaxis and the complement cascade. Allergic reactions of the lids and conjunctiva undoubtedly occur in all domestic species.

Type II (cytotoxic/cytolytic) hypersensitivity is an antibody-mediated cytolytic reaction in which the antigen is a cell surface or basement membrane component. Three basic effector pathways lead to cell destruction: (1) opsonization, with increased efficiency of phagocytic destruction; (2) antibody-dependent cellular cytotoxicity, inducing the release of enzymes capable of destroying cells and digesting basement membranes; and (3) lysis of immunoglobulin-bearing cells.[340] Conjunctival damage resulting from autoantibodies directed against epithelial basement membranes is described in equine ocular pemphigoid.

Type III (immune complex) hypersensitivity may share similar effector mechanisms with those described for cytolytic reactions, but antigen locale accounts for dissimilar disease manifestations in these two pathways. 1288 1289
[339] This immune complex reaction may explain the clinical signs of pemphigus foliaceus[341] and the intraocular inflammation observed in horses after influenza vaccination or contact with infected animals.[342] Antibody-mediated cell destruction has also been implicated in uveitis.[338]

Type IV (cell-mediated/delayed) hypersensitivity is an important factor in contact allergy of the lids and conjunctiva and may also play a role in ocular toxoplasmosis. The tissue destruction associated with herpetic keratoconjunctivitis in the horse has been attributed to a cell-mediated response.[338] Increasing evidence implicates delayed hypersensitivity in the pathogenesis of equine recurrent uveitis.[343,344] The reaction requires an initial antigen exposure that results in sensitization of antigen-specific T lymphocytes. Reintroduction of antigen induces interleukin production, with subsequent T-cell activation, proliferation, and cytokine production. Once activated by cytokines, recruited leukocytes display increased activity to many antigens.[345]

39.44.5.20

ALLERGIC BLEPHAROCONJUNCTIVITIS

In humans, several forms of allergic conjunctivitis are mediated by immunoglobulin E (IgE), and histamine (H_2) receptors have been discovered on the human ocular surface.[346] The ubiquitous presence of H_2

receptors in domestic animals implies a similar distribution[334] and the potential for immediate hypersensitivity reactions of the eyelids and conjunctiva.

Affected animals demonstrate acute swelling of the eyelids and conjunctiva, accompanied by serous ocular discharge, mild conjunctival hyperemia, and pruritus. If the stimulus persists, multiple subconjunctival aggregates of lymphocytes appear as tiny, semitransparent follicles within the conjunctival cul-de-sac. In contrast to bacterial conjunctivitis, crusting and purulent discharge are not typical of allergic conjunctivitis.

Diagnosis of allergic blepharoconjunctivitis is often presumptive, based only on careful and thorough elimination of all other causes of lid and conjunctival swelling. Trauma, orbital inflammation, neoplasia, mechanical irritants, conjunctival parasites, and other infectious agents (both ocular and systemic) should be considered. In support of an allergic etiology, conjunctival cytology may reveal eosinophils in response to mast cell degranulation.

The offending allergen may be difficult to identify. Insect stings and toxic plants (e.g., nettle) are possible causes, as are molds and pollens. Allergic conjunctivitis was described in 17 of 187 cows pastured adjacent to a field of blossoming cotton.[347] A group of Angus-Holstein cattle demonstrated excessive lacrimation and ocular pruritus associated with familial allergic rhinitis. Several inhaled allergens have been incriminated, including capeweed, clover, dock, lucerne, pepper tree, paspalum, wattle, ryegrass, sorrel, and fungal extracts.[348] New feeds and certain drugs (e.g., oxytetracycline, penicillin, sulfas) may produce generalized urticaria, with accompanying eyelid and conjunctival edema.[349] Similar findings have been reported in cattle with milk allergy. Agents directly inducing mast cell degranulation through osmotic or charge interactions include hypertonic saline, nonsteroidal antiinflammatory drugs (NSAIDs), thiopental, opiates, neuromuscular blocking agents, mannitol, radiocontrast agents, polymyxin B, and vancomycin.[350] Occasionally, allergic conjunctivitis may be associated with a topical medication such as neomycin. Clinical signs exacerbate with continued application and diminish when the medication is discontinued.

Ocular signs subside with removal of the offending allergen, but this is often impractical. Individual animals may be treated with a topical ophthalmic corticosteroid preparation such as 0.05% dexamethasone ointment* to hasten resolution of swelling and redness. An agent with antiprostaglandin activity such as oral or parenteral flunixin meglumine† (0.5 mg/kg every 12 hours) may be of benefit in the horse. Signs associated with urticaria respond to a decreasing regimen of oral prednisone or prednisolone, initiated at a dosage of 1 mg/kg once daily in the nonpregnant animal.[351] Single parenteral doses of short-acting corticosteroids, epinephrine, or antihistamines have also been used with reported success in food animals.[348]

* Bausch & Lomb, Tampa, FL.

† Banamine, Schering-Plough, Kenilworth, NJ.

39.44.5.21

OCULAR MANIFESTATIONS OF IMMUNE-MEDIATED DERMATOSES

Pemphigus refers to a group of chronic blistering diseases that affect healthy skin and mucous membrane. Although these disorders are of presumed autoimmune origin, their exact pathogenesis is unknown. Direct immunofluorescence reveals intercellular deposition of immunoglobulin G (IgG) and complement within the epidermis. Circulating autoantibodies can be demonstrated in humans.[352] Pemphigus foliaceus and bullous pemphigoid have been described in the horse.[353–356]

Ocular manifestations may include ulceration or crusting of the periocular skin and erosions of the conjunctiva. Chemosis and hyperemia are likely; secondary corneal disease may follow that of the mucous membranes. Diagnosis is based on clinical findings, cytology, histopathology, and positive immunofluorescence of affected skin. See the discussion of immune-mediated dermatologic disorders for therapeutic recommendations and prognosis.

Other immune-mediated diseases, such as systemic lupus erythematosus (SLE), occur infrequently in the horse but can affect the eyelids. In addition to skin lesions, vasculitis may be manifest by hemorrhages in mucous membranes, including the conjunctiva.[353,357]

39.44.5.22 EOSINOPHILIC KERATOCONJUNCTIVITIS

Eosinophilic keratoconjunctivitis is an uncommon disorder of horses characterized clinically by corneal ulceration and plaque formation in one or both eyes.[358–361] Its name is derived from the predominance of eosinophils found in cytologic samples. The specific cause of this disorder is still unknown.

39.44.5.22.1 Clinical Signs

Clinical signs may be unilateral or bilateral and include nonspecific signs of blepharospasm, ocular discharge, and conjunctival hyperemia. Perilimbal corneal ulcers appear as raised, white corneal plaques because of adherent caseous exudates, often accompanied by corneal edema and superficial vascularization.

39.44.5.22.2 Diagnosis

Differential diagnoses include mycotic keratitis, onchocercal keratoconjunctivitis, neoplasia, foreign body granuloma, traumatic keratitis, and calcific degeneration. Definitive diagnosis is based on clinical signs and cytologic findings. Eosinophils and segmented neutrophils predominate in corneal scrapings, with fewer mast cells, plasma cells, and lymphocytes. Light microscopy of corneal tissue reveals coalescing foci of degenerated collagen fibers in the corneal plaques.

39.44.5.22.3 Pathophysiology

The exact cause of the disorder is unknown. The finding of eosinophils in equine ocular surface disease is usually attributed to parasitic infection by *Onchocerca* or *Habronema* species,[362] although neither has been identified in the reported cases to date. One proposed mechanism for eosinophilic keratoconjunctivitis is an allergic or inflammatory response to long-term use of ivermectin as an anthelmintic, triggering the complement cascade and cellular chemotaxis in patients with ocular onchocerciasis.[359] Similarities to vernal keratoconjunctivitis in humans suggest that eosinophil-granule major basic protein may play a significant role in the equine disease, inhibiting corneal epithelial migration and protein synthesis and promoting collagen degeneration.[363] Eosinophil-derived collagenase also has been reported to degrade type I collagen, the predominant collagen in cornea.[358]

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39.44.5.22.4 Treatment and Prognosis

Treatment consists of topically applied 0.05% dexamethasone and prophylactic topical antibacterial ointments every 6 hours until clinical signs resolve. Lesions remodel with minimal corneal scarring, but mean duration of treatment in one series of patients was 64 days (range, 45 to 105 days).[359] Use of ophthalmic NSAID preparations may increase the severity of clinical signs of eosinophilic keratoconjunctivitis in horses because of potentiation of leukotrienes, the primary promoter of eosinophilic inflammation.[358] Excision of the corneal plaques by superficial keratectomy appears to enhance healing, attributable to removal of the eosinophil-granule major basic protein.[358,359]

39.44.5.23 IMMUNE-MEDIATED KERATITIS

39.44.5.23.1 Nonulcerative Keratouveitis

Nonulcerative keratouveitis is an uncommon corneal disease in the horse characterized by a pink, vascularized and somewhat localized stromal infiltrate of predominantly lymphocytes near the limbus.[364,365] The overlying epithelium is intact, so fluorescein dye is not retained by the cornea. Accompanying anterior uveitis is typically severe and unremitting, with blepharospasm, epiphora, conjunctival hyperemia, corneal edema, miosis, aqueous flare, and hypopyon. The primary differential diagnosis is a corneal stromal abscess; other considerations include fungal keratitis, eosinophilic keratoconjunctivitis, onchocerciasis, and neoplasia.

The pathogenesis is presumably immune mediated, based on histopathology and response to therapy.[364] Systemic leptospirosis was incriminated etiologically in a 2-year-old thoroughbred filly with a unilateral corneal infiltrate of lymphocytes and macrophages and a choroidal infiltrate of lymphocytes, eosinophils, and basophils that was also positive to IgG and C3.[366] Brooks et al.[364] speculated that autoimmunity against corneal antigens may play a role.

Before beginning therapy, it is essential to rule out stromal abscessation and fungal keratitis, in which the prescribed antiinflammatory regimen would be contraindicated. Treatment consists of a potentially lifelong regimen of a potent topical corticosteroid that will penetrate through intact corneal epithelium (1% prednisolone acetate or 0.1% dexamethasone) every 4 to 6 hours, 1% cyclosporine every 12 hours, and/or an NSAID such as flurbiprofen every 8 hours.[364,367,368] Topical 1% atropine is administered to effect to minimize ciliary spasm and limit synechiae. A systemic NSAID such as flunixin meglumine is administered every 12 to 24 hours. Clinical signs typically recur if medication is discontinued. Prognosis is poor, without expectation of cure. Chronic inflammation may result in phthisis bulbi or unremitting pain that necessitates enucleation.[369]

39.44.5.23.2 Nonulcerative keratitis

Chronic, nonulcerative corneal opacities without signs of overt discomfort or intraocular inflammation have been described.[370,371] In a report of 19 horses age 5 to 11 years diagnosed with nonulcerative keratitis, 11 horses had clinical signs for more than 12 months before referral.[370] The disorder comprises three distinct clinical entities, classified as superficial, midstromal, or endothelial, based on the location of

the corneal pathology. *Superficial* keratitis is characterized by a superficial, white to yellow infiltrate with diffuse, mild to moderate vascularization. *Midstromal* lesions are typically more diffuse, with denser cellular and vascular components. A deep cellular infiltrate with mild corneal vascularization and variable degrees of diffuse corneal edema are typical of *endothelial* keratitis. Intraocular inflammation is not a feature of the disorder, regardless of lesion location. Differential diagnoses include stromal abscess, eosinophilic keratoconjunctivitis, bullous keratopathy, and nonulcerative keratouveitis.

An immune-mediated pathogenesis is theorized, based on histopathologic characteristics and response to therapy. Regardless of lesion depth, histopathology reveals a predominantly lymphocytic-plasmacytic infiltrate, with stromal fibrosis and vascularization. Three of five horses were seropositive for *Leptospira* in one study.[370] Presumably the immune system is reacting to a self-antigen or antigens of a foreign protein or infectious agent within the cornea. Even though infectious agents have not been documented in this particular disorder, immunologic cross-reaction with self-antigens (i.e. molecular mimicry) may occur, as described with leptospiral organisms or their DNA in the equine cornea.[372,373]

Lesions of superficial stromal keratitis can be controlled with long-term topical dexamethasone and/or cyclosporine applied every 12 to 24 hours.[370,371] Lesions in 4 of 11 horses treated by superficial keratectomy and conjunctival grafting resolved without the need for ongoing medication, suggesting that surgical removal of the inciting antigen will stop the inflammatory process. A similar chronic therapeutic regimen is used in midstromal keratitis; Matthews[371] states that topical corticosteroids are less effective than cyclosporine in the deeper stromal disorder. Keratectomy followed by a conjunctival graft was curative in one horse.[370] Response to antiinflammatory agents varies in patients with endothelial keratitis, resulting from differences in pathogenesis. Only two of four horses were controlled with constant topical dexamethasone and cyclosporine in Gilger et al.'s report.[370] In contrast, Matthews[371] described complete resolution of endothelial keratitis with topical 1% dexamethasone applied every 6 hours for 3 to 7 days. Although retention of vision is likely in most cases of nonulcerative keratitis, long-term or even lifelong therapy is required to control the corneal disease.

39.44.5.24 EQUINE RECURRENT UVEITIS (PERIODIC OPHTHALMIA, “MOON BLINDNESS”)

39.44.5.24.1 Definition and Etiology

Equine recurrent uveitis (ERU) is distinguished by a pattern of intraocular inflammation in which recurring episodes of acute uveitis are separated by periods of clinical quiescence. Inflammation of the iris and ciliary body (anterior uveitis or iridocyclitis) predominates in the early stages; repeated episodes damage the cornea, lens, vitreous, retina, and optic nerve. A more insidious form of ERU characterized by persistent, low-grade inflammation occurs in the Appaloosa and draft breeds of horse.

Equine recurrent uveitis is a leading cause of blindness in the horse and mule. Although the exact prevalence is unknown, estimates as high as 10% to 25% have been reported .[374,375] The financial impact on the equine industry is estimated at 100 to 250 million U.S. dollars annually as a result of the effects on performance and the costs of veterinary care.[376] 1290 1291

Despite extensive clinical research, the specific cause of ERU is still unknown. The pathogenesis is immune mediated, and characterization of T-lymphocyte populations in affected horses documents a delayed hypersensitivity reaction as the basic immunologic mechanism underlying the recurrent

inflammatory episodes.[344] Identification of the triggering antigen has proved more elusive, suggesting the disease does not result from the persistence of or repeated exposure to a single antigen, but rather to a variety of circulating antigens or native ocular antigens. *Leptospira interrogans* serovar *pomona* is the most frequently incriminated infectious pathogen,[375] but diversification of T-cell responses to a particular antigen or group of antigens over time may result in evolution of the immune response to encompass endogenous ocular self-antigens.[341,377]

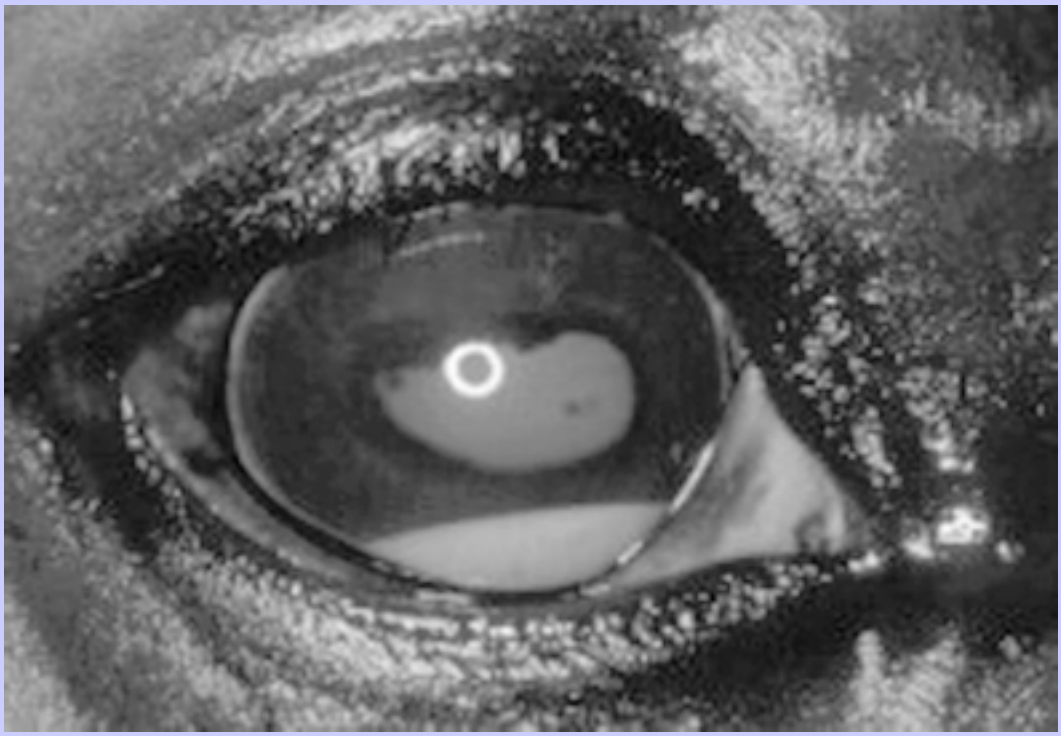
39.44.5.24.2

Clinical Signs

The ocular lesions observed in ERU vary, depending on the severity and duration of the disease.[369,374,376,378,379] ERU can occur at any age, but the initial uveitis episode frequently occurs in horses 4 to 8 years of age. Acute episodes are painful, characterized by blepharospasm and excessive tearing. Affected eyes are often described by owners as “red and/or cloudy” because of changes in the conjunctiva, cornea, anterior chamber, or vitreous. Dilation of subconjunctival vessels near the limbus, termed “ciliary flush,” may intensify the generalized conjunctival hyperemia. As corneal endothelial function decreases, diffuse corneal edema gives the eye a bluish white appearance. The cornea may also exhibit peripheral, circumferential vascularization, cellular precipitates on its inner (endothelial) surface, and linear stromal opacities.

Increased uveal vessel permeability causes the aqueous humor to appear cloudy after influx of plasma proteins (flare), inflammatory cells (hypopyon), erythrocytes (hyphema), or fibrin into the anterior chamber (Fig. 39-25). The iris often appears edematous and lackluster or “muddy.” A change in iris color may be noted in breeds with lightly colored eyes, changing from blue to green in response to uveal edema, vascular congestion, and cellular infiltration. Prostaglandins and other inflammatory mediators cause pupillary constriction, favoring the formation of adhesions between the iris and lens (posterior synechiae) that distort the pupillary shape. Even without adhesions, the inflamed iris responds poorly to mydriatic agents. Intraocular pressure (IOP) is usually decreased because of diminished aqueous production by the inflamed ciliary body, but intermittent IOP elevations can occur.[380] The ciliary body can also deposit cellular exudates within the anterior vitreous, creating an opacity within the pupillary space that may be mistaken for cataract.

Fig. 39-25 Active uveitis characterized by hypopyon, pupillary irregularities secondary to posterior synechiae, melanin adherent to the anterior lens capsule, and a dull tapetal reflection.



Active chorioretinitis causes dullness and loss of detail in affected tissues. Retinal detachment may follow choroidal exudation. Multifocal depigmented or hyperpigmented foci on either side of the optic disc are the inactive sequelae of chorioretinitis ("chorioretinal scars"), commonly referred to as peripapillary "butterfly" lesions (Fig. 39-26).

Intraocular damage increases each time inflammation recurs. Permanent corneal opacity caused by edema results if the corneal endothelium is severely compromised. Chronic recurrent uveitis is characterized by widespread posterior synechiae, iris depigmentation or hyperpigmentation, and iris atrophy. The anterior chamber may appear shallow if aqueous trapped in the posterior chamber by extensive iris-to-lens adhesions causes the iris to balloon forward (iris bombé). Most lens changes occur weeks or months after uveitis begins. Abnormalities may range from pigment flecks on the anterior lens capsule (Fig. 39-27) to dense cataracts. Lens luxation often follows degeneration of the lens zonules and vitreous. Retinal detachment may also follow vitreous liquefaction or may result from traction by fibrous tissue bands within the vitreous. If retinal degeneration is substantial, the optic disc atrophies (Fig. 39-28). Permanent hypotony is followed by shrinkage of the globe (phthisis bulbi). Conversely, chronic uveitis may result in secondary glaucoma. The combination of these acute and chronic ocular lesions determines the degree of vision loss in the affected animal.

Equine recurrent uveitis may be accompanied by transient and variable inflammation of the pineal gland.[381–384] Similar pineal inflammation has been reported in experimentally induced recurrent uveitis in laboratory animals.

Fig. 39-26 Fundus adjacent to optic disc takes on mottled appearance as a result of pigment migration after previous chorioretinal inflammation in recurrent uveitis. Because of their shape, such lesions are sometimes referred to as “butterfly lesions.”

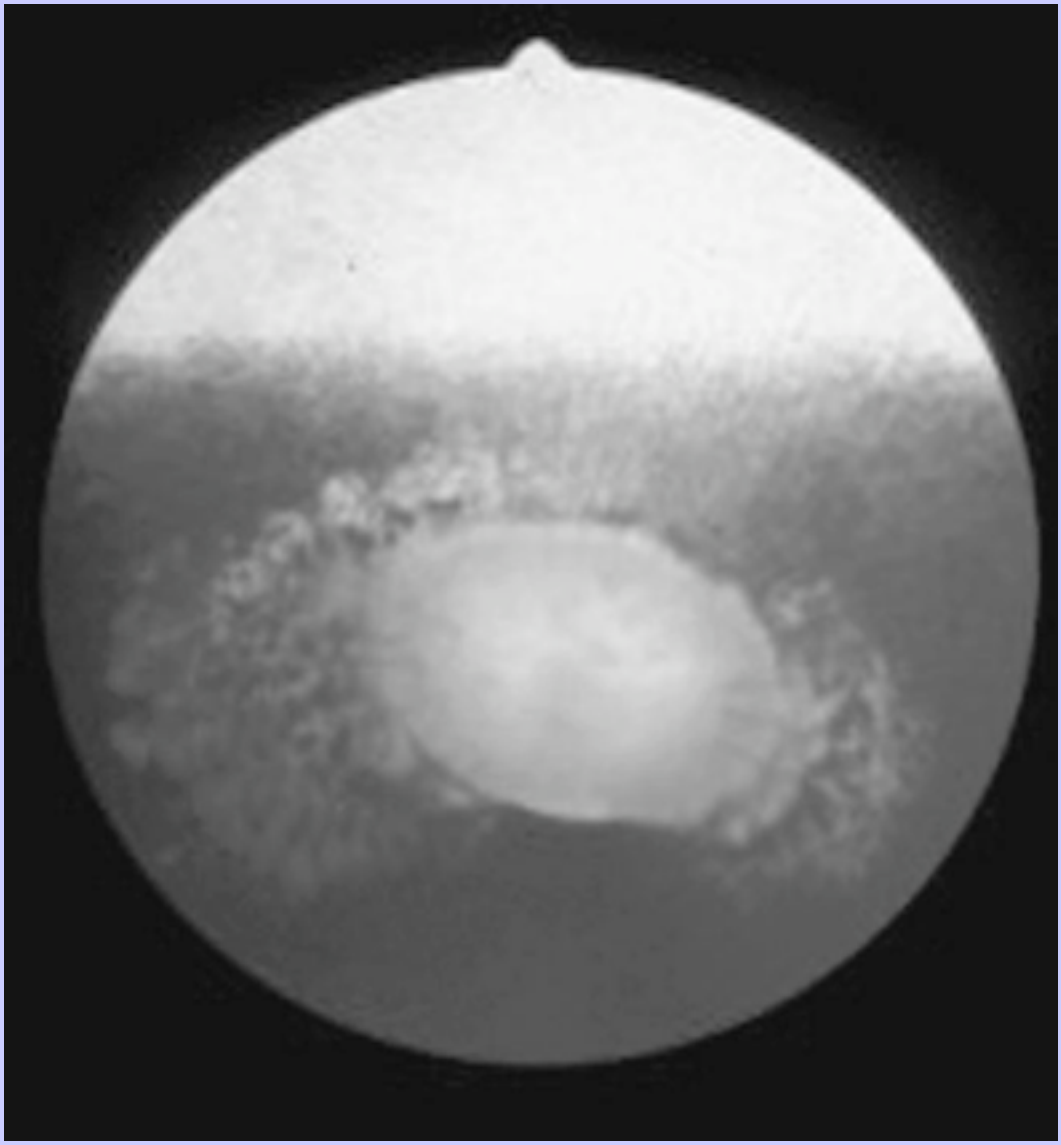


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Fig. 39-27 Prior episodes of anterior uveitis are indicated by pigmented remnants on the anterior lens capsule following adhesions of iris to lens (posterior synechiae). The pupil is pharmacologically dilated.

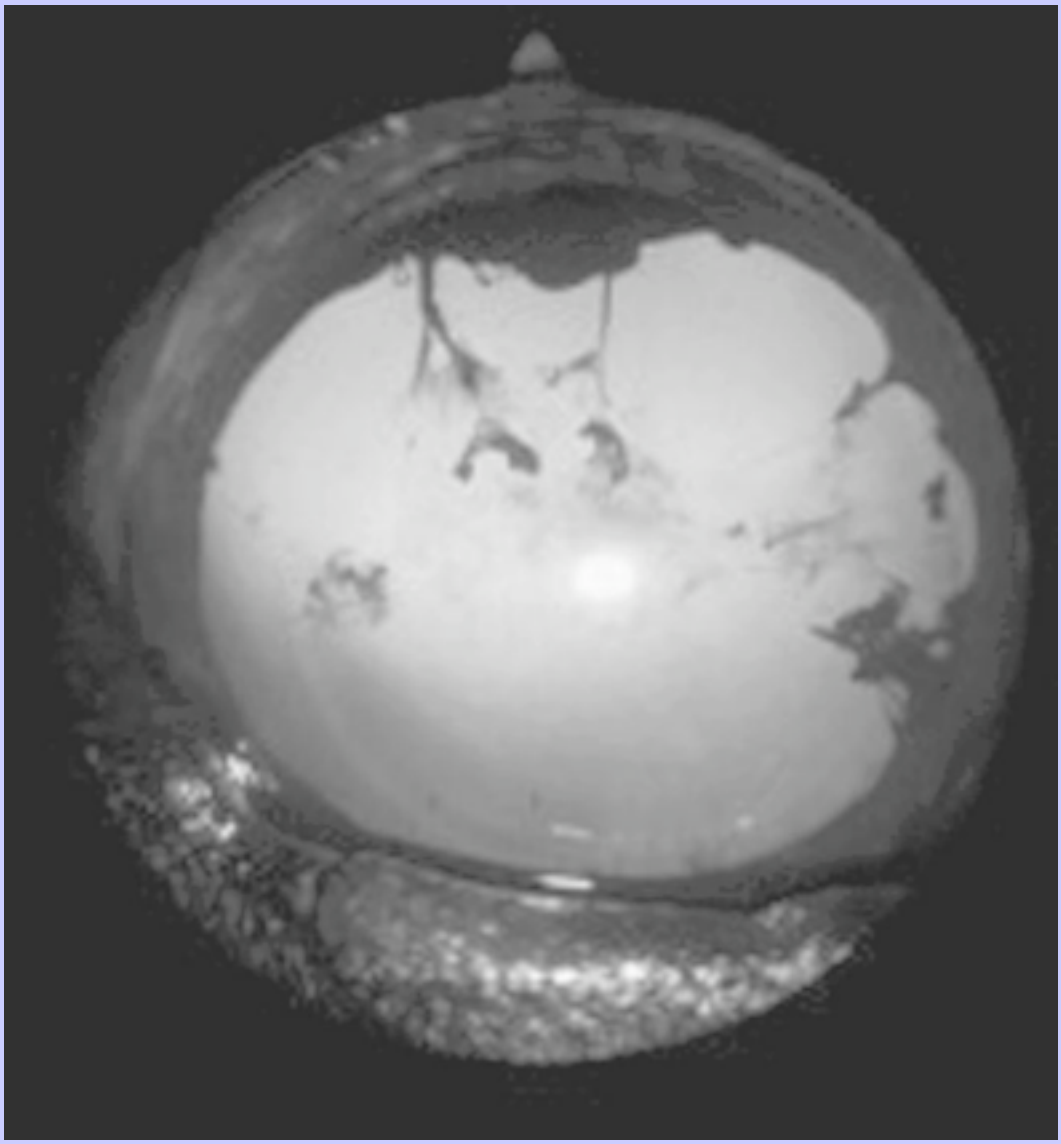
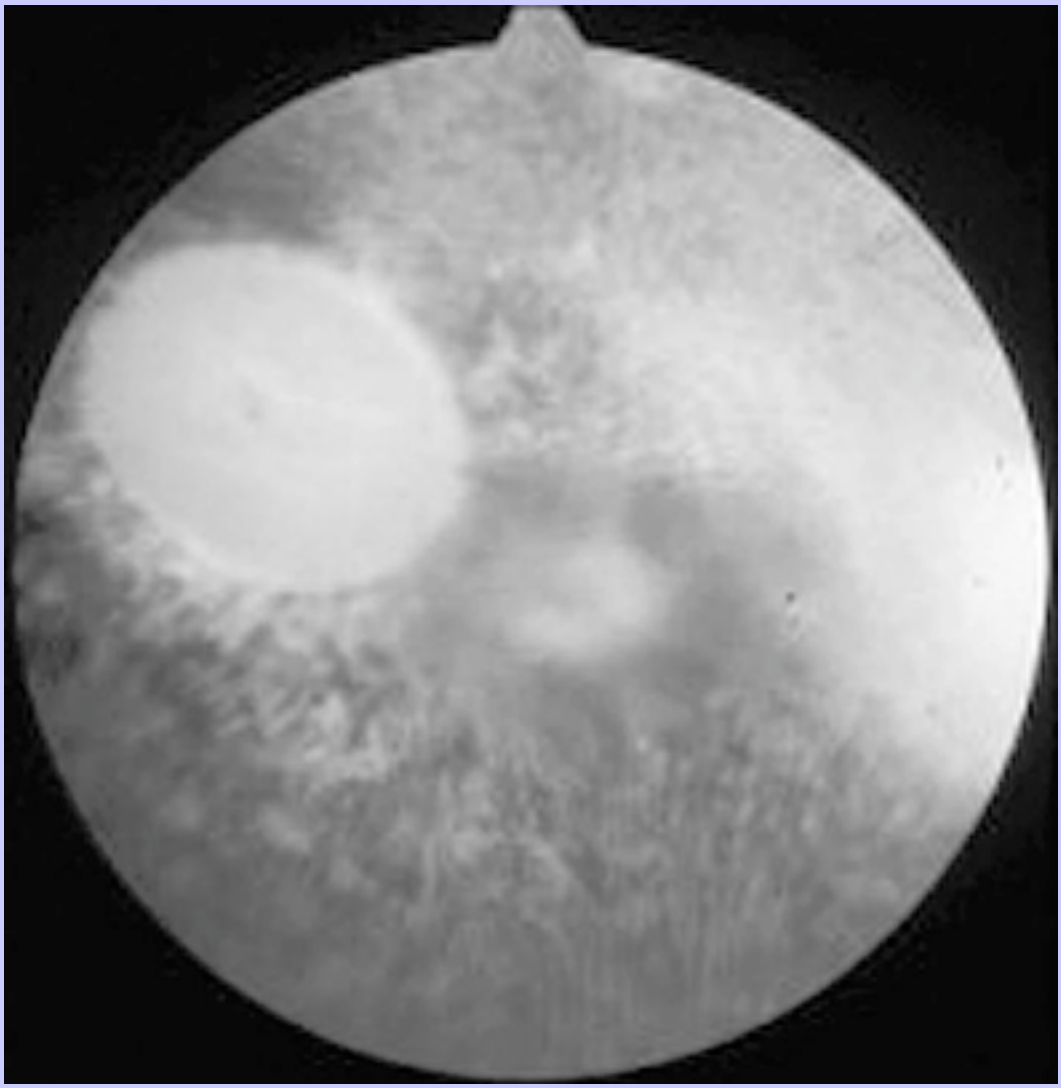


Fig. 39-28 Disc pallor and nontapetal depigmentation accompany a dark-gray pre-retinal exudate in a patient with chronic active recurrent uveitis. This patient had poor vision.



39.44.5.24.3

Diagnosis

Not every case of uveitis in the horse qualifies as ERU. Diagnosis is based on a chronic, recurrent history of intraocular inflammation and the presence of characteristic ocular lesions. In cases in which the history is unknown but recurrent disease is suspected, at least three of the following indicators of previous inflammation should be observed before a presumptive diagnosis of ERU is made: corneal edema or vascularization, synechiae, iris atrophy or color change, lens capsular pigmentation, cataract, lens luxation/subluxation, vitreous opacities or traction bands, retinal detachment, or peripapillary scarring.[374] Other

causes of a red and painful eye that can mimic acute ERU include conjunctivitis, corneal ulceration, corneal stromal abscessation, keratouveitis, and glaucoma.

Serologic testing of paired serum samples for *Leptospira* species or other infectious agents incriminated as causes of equine uveitis (see Table 39-2) may contribute to a diagnosis of ERU, but negative titers neither exclude the diagnosis nor eliminate leptospirosis as a contributing factor to the disease.[385,386] Acute leptospiral infections are characterized by high-titer seroreactivity to at least one serovar by the eighth day;[387] the titer usually falls with time, but seroreactivity may persist for many years. Some authors suggest that a leptospiral titer of 1:400 or higher is of clinical importance, particularly for *Leptospira interrogans* serovar *pomona*.[374] A higher titer in the aqueous than in the serum is indicative of intraocular antibody production and further supports a leptospiral cause for the uveitis.[388] *Onchocerca* microfilariae may be identified in conjunctival biopsies, although detection of live microfilariae does not necessarily indicate a causal relationship.[389,390] Equine leukocyte antigen (ELA) typing may help determine susceptibility to ERU.[391]

Histopathologic lesions of the ciliary body considered pathognomonic for ERU include the presence of a thick, noncellular hyaline membrane adherent to the nonpigmented epithelium (NPE) and the presence of eosinophilic linear cytoplasmic inclusion bodies within the NPE.[392,393] Clusters of lymphocytes and plasma cells also accumulate in the posterior iris, ciliary body, near the ora ciliaris retinae, within the choroid, and near the optic nerve head.[376,394] Dense bundles of fibrils coupled with necrotic cells and mononuclear inflammatory cell infiltrates characterize the changes within the vitreous.[395]

39.44.5.24.4

Pathophysiology

Breed has been established as a risk factor for ERU. In a 1988 retrospective study of more than 16,000 equine patients at Cornell University, researchers determined that the Appaloosa had a significantly higher risk of developing uveitis than did thoroughbreds.[396] A subsequent New York field study substantiated the breed predilection, concluding that the Appaloosa was 8.3 times more likely to develop uveitis than all other breeds combined.[375] Within the Appaloosa breed, those with overall light hair coats and focal dark spots are more likely to develop ERU than horses with a dark, basic coat pattern and a light “blanket” over the rump.[376] Trotters and warmbloods were overrepresented in a report of 130 ERU-affected horses in Germany.[397] Of 669 mares included in a serologic study of leptospirosis, significantly fewer positive titers were found in thoroughbreds and standardbreds.[398]

In humans, an immunogenetic predisposition to certain types of uveitis has been linked to the major histocompatibility complex (MHC), a closely aligned cluster of genes designated the HLA region (for human leukocyte antigen), located on a single chromosome.[399] Similar genetic loci occur in the horse, and the gene products are referred to as *equine leukocyte antigens* (ELAs). Products of these genes are glycoproteins found either on most nucleated cells (class I antigens) or restricted to accessory cells such as monocytes or macrophages (class II antigens). The immunoregulatory role of the MHC is especially important in discriminating self-peptides from those of nonself origin. Recent studies have shown an increased risk of uveitis linked with the MHC class I haplotype ELA-A9 in a group of German warmblood horses.[391] As proposed in studies of human HLA-associated uveitis, cross-reactivity between self-antigens and ELA cell surface peptides could explain an inadvertent immunologic attack on normal cells.[400,401]

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Experimental findings in ERU patients indicate that a T-cell—mediated autoimmune mechanism underlies the recurrent episodes of inflammation. T lymphocytes are the predominant cell type to infiltrate the anterior uvea,[343,394] choroid,[402] and vitreous[403] of horses with ERU, and affected horses demonstrate cell-mediated immunity to retinal autoantigens and peptides.[403–405] B lymphocytes have been reported primarily in retinas from horses seroreactive for *L. interrogans* serovar *pomona*, suggesting that *leptospira*-associated ocular inflammation may be a distinct subset of equine uveitis.[406] Equine ciliary body epithelium may play a role in recruitment and activation of leukocytes through expression of a chemotactic cytokine (chemokine),[407] although in the normal ocular microenvironment, ciliary body pigment epithelium suppresses T-cell activation by direct cell contact and the action of unidentified molecular mediators.[408] Analysis of mRNA collected from horses with uveitis demonstrates elevated levels of IL-2 and IFN-γ, indicating a Th1 response in the disease process.[409] In the absence of bacteria or viruses, this Th1 response by $CD4^+$ uveal T-lymphocytes suggests a delayed-type hypersensitivity (DTH) reaction to self-antigens or sequestered antigens in the uveal tract.[344,410] In contrast to the ocular T-lymphocyte population, systemic lymphocytes of ERU-affected horses do not exhibit a Th1 response.[344] The expression of a deviant MHC class II antigen on resident ocular cells (e.g., Müller, retinal pigment epithelial) suggests that aberrant immune regulation may also play a role in ERU.[343,411]

Aqueous and vitreous immunoglobulin levels have been used to characterize immunologic responses within ERU-affected eyes. Using radioimmunoassay, an early study found that aqueous levels of IgG, IgM, and IgA were 50% to 120% greater in diseased eyes than in normal controls, but that the IgG/albumin ratio suggested leakage of protein through an impaired blood-aqueous barrier rather than intraocular antibody synthesis.[412] Subsequent reports support local ocular antibody production but disagree on the dominant immunoglobulin in ERU-affected eyes. Wagner et al.[413] found selectively increased IgA levels in the vitreous of affected horses; Eule et al.[414] reported substantial IgM titers in 79.6% of ERU samples. In contrast to the intraocular immunoglobulins, there are no significant differences in serum immunoglobulin concentrations between healthy and ERU-affected horses.[413,414]

Both exogenous and endogenous antigens have been proposed as stimuli for these basic immunologic responses. One theory suggests that an infectious agent such as *L. interrogans* (or another, perhaps noninfectious, exogenous antigen) causes the initial iridocyclitis. Sensitized immunocompetent cells enter the uvea during this first inflammatory episode, imparting immunologic memory that is specific for the inciting antigen. Subsequent challenge of these cells by the immunogen causes recurrence of the inflammatory reaction.[338,415] However, the premise of an infectious agent that exclusively induces and maintains ERU through a classic anamnestic response does not fully account for the disorder's clinical course and response to therapy.

The role of leptospiral infection in ERU has been studied extensively in recent years. All major serogroups of *L. interrogans* have been identified in the horse and implicated as initiating factors in ERU.[375,386,416–419] In a report of 130 ERU cases in Germany, 58.8% demonstrated positive titers to leptospirosis, an incidence 7 to 10 times higher than the control population.[397] Anti-*Leptospira* antibodies have been found in the serum, tears, aqueous humor, and vitreous of infected horses.[386,417,420–422] Wollanke et al.[422] reported positive serum antibody titers to *Leptospira* serovars in 25% (24/97) of normal-eyed horses and 22% (50/227) of ERU-affected horses, but only the ERU-affected animals had positive antibody titers in the vitreous.[422] Leptospiral organisms have been cultured from the aqueous and vitreous of ERU-affected

horses.[385,386,419,423,424] Horses seropositive to *L. interrogans* serovar *pomona* are reportedly 13.2 times more likely to have signs of uveitis than seronegative horses.[375] Ocular signs during the acute infection are subtle or absent, but overt ocular inflammation develops months to years later.[425–428] Risk factors for equine leptospirosis include rodent and wildlife exposure, proximity to ponds and rivers, a dense equine population on site, and increasing age.[398,429,430]

Although direct *Leptospira*-mediated injury to the eye cannot be ruled out in the pathogenesis of ERU, a growing body of evidence instead links leptospiral infection with autoimmune responses to ocular tissue components. Complement-binding anti-*Leptospira* antibodies capable of cross-reacting with equine corneal tissue and lens have been found in the tear film and aqueous humor of horses with leptospirosis.[420,421,431] These antibodies bind corneal epithelial cells, activating complement and initiating tissue damage, a mechanism replicated in tissue culture.[432] A leptospiral protein epitope that shares antigenic determinants with the equine cornea and lens has been found in bacterial homogenates,[372] and a DNA fragment of several serovars of *L. interrogans* was determined to encode a 90-kilodalton protein that cross-reacts with equine corneal proteins.[373,433] Novel leptospiral lipoproteins, identified as LruA and LruB, stimulate local intraocular IgA and IgG production and also cross-react with equine ciliary body, lens, and retina.[434] Immunohistopathologic examination has also demonstrated leptospiral cross-reactivity with iris pigment epithelium and retina from horses with ERU.[406,435] This antigenic relationship between *Leptospira* species and equine ocular tissues supports the concept of molecular mimicry as a contributing factor in ERU; exposure to exogenous antigens that share molecular structural sequences with equine self-antigens initiates an autoimmune response.[342]

Toxoplasmosis, brucellosis, salmonellosis, streptococcal hypersensitivity, *Escherichia coli, Rhodococcus equi,* borreliosis,[436,437] intestinal strongyles, and onchocerciasis have also been implicated as causes of ERU, with no consistency in culture or serology results in affected horses.[369,375] Viruses suspected of a role in ERU include equine influenza virus, equine herpesvirus (EHV-1, EHV-4),[438] equine arteritis virus, and possibly equine infectious anemia.[369,374,376] More recent studies on vitreous and serum samples from affected horses question the role of *Borrelia burgdorferi,* Borna disease virus, and *Toxoplasma* in ERU.[439,440]

Both humoral and cell-mediated hypersensitivities have been implicated in the lesions of ocular onchocerciasis. Immunoelectrophoretic studies have demonstrated an influx of IgG and complement (C3) into the tears of affected horses in response to larval death.[441] The resulting chemotaxis of mast cells, eosinophils, and lymphocytes perpetuates the inflammatory response and facilitates destruction of the parasite. Human patients with ocular onchocerciasis demonstrate conjunctival infiltration by $CD3^+$ T lymphocytes and increased expression of class II MHC antigens in conjunctiva and iris,[442] as well as deficiencies in suppressor T-cell function that may interfere with the normal regulation of antibody function.[443]

In addition to the role of infectious agents in the pathogenesis of ERU, autoimmunity may occur when a normally sequestered component is exposed to lymphoid cells or when the antigenicity of a component increases as a result of a structural alteration.[444] Several endogenous ocular proteins, including retinal soluble antigen (S-antigen, or S-Ag), interphotoreceptor retinoid-binding protein (IRBP), and uveal melanin-associated proteins are known to induce uveitis in various animal models.[445–448] Clinical studies

also implicate these potent autoantigens in the pathogenesis of some forms of human uveitis.[449–451] An autoimmune phenomenon in response to damaged uveal tissue has been proposed in the pathogenesis of ERU.[452] The isolation of S-antigen in the horse and the subsequent finding of anti-S antibodies in the aqueous humor and vitreous of horses with uveitis support the theory that this species is similarly capable of local production of antibodies to normally sequestered autoantigens.[403–405,453] Experimental uveitis with features similar to spontaneous ERU has also been induced in horses after injection of IRBP in complete Freund's adjuvant.[402] Autoantibodies to S-Ag and IRBP were found in 72% of vitreous specimens from horses with uveitis.[403] A more recent equine study concluded retinal S-Ag is a weaker autoantigen than IRBP; T and B cells were activated after immunization with S-Ag, but only one of five horses developed uveitis or demonstrated inflammatory cell infiltration of the uveal tract.[454] Because the retina and NPE of the ciliary body originate from neuroectoderm, it is even possible that ciliary body damage may release an S-like antigen or another uveitogenic substance.[455] Evidence suggests that response to S antigen is predominantly T-cell dependent.[456]

Verma et al.[434] proposed a link between leptospiral cross-reactivity and the release of other ocular autoantigens, based on strong IgG and IgA responses to LruA and LruB lipoproteins in uveitic eyes but not in companion sera. The early phase of ERU may involve production of non-complement-fixing antibody and non-DTH T lymphocytes specific for LruA and LruB. The antibodies and cells react with the leptospiral lipoproteins, initiating a process that ultimately liberates IRBP and other ocular autoantigens.

The concept of “epitope spreading” has been offered as an explanation for the relapsing character of ERU.[457] The theory proposes that after destruction of an initial target, the immune response spreads from the first autoantigenic determinant to others not previously recognized by the immune system.[458,459] Active uveitis subsides as regulatory cells suppress the inflammation, recurring as the immune response shifts to an epitope of the same autoantigen (intramolecular spreading) or a completely different autoantigen (intermolecular spreading). A recent 22-month study of peripheral T-cell reactions in eight horses with spontaneous ERU demonstrated intramolecular shifts to different S-Ag—derived (6/8) or IRBP-derived (5/8) epitopes and intermolecular shifts in all horses, spreading from IRBP-derived to S-Ag—derived peptides (5/8), or vice versa (3/8).[457] A shift of the immune reaction could be correlated to new uveitic episodes in 10 of 14 relapses that occurred during the observation period. The confounding factor in this theory is the shifts in immune response observed during quiescent stages, perhaps to minor uveitogenic epitopes that fail to result in overt inflammation, or as part of an unknown regulatory or protective function of these T-cell clones.

Regardless of etiology, the ocular inflammatory process may attract other reactive lymphocytes to the eye. During primary uveitis, only 10% of the ocular immunoglobulin-secreting cells are specific for the inciting antigen. The remaining cells produce antibodies against immunogens that may not have entered the eye, but with which the host had previous contact. As a consequence, the eye may develop recurrent inflammation after systemic exposure to any one of multiple antigens. It is therefore conceivable that subsequent episodes of uveitis may differ etiologically, creating a perplexing clinical picture.[460]

39.44.5.24.5 Treatment

39.44.5.24.5.1 ACTIVE INFLAMMATION

Reduction of intraocular inflammation is the primary therapeutic objective in acute uveitis. Preservation of vision depends on successful management at this stage, when sight-threatening sequelae are minimal. If a specific cause for the uveitis is identified, it is also targeted pharmacologically. In most cases, symptomatic therapy combines corticosteroids, NSAIDs, and mydriatic/cycloplegic agents. Nonspecific suppression of T-lymphocyte activation with cyclosporine implants[461] and surgical removal of T cells and potentially organisms from the eye by core vitrectomy[462] are recent innovations aimed at preventing recurrence of disease.

No therapy is indicated in nonpainful eyes with lesions of chronic end-stage uveitis. Those eyes that remain painful or do not respond to therapy are candidates for enucleation or evisceration, followed by silicone prosthesis implantation in the orbit or sclera, respectively.

39.44.5.24.5.2 Corticosteroids

The severity of the uveitis dictates the routes and frequency of corticosteroid administration. Although topical therapy is most often used, efficacy is limited by the agents' relatively short contact time with the eye. Therefore, topical corticosteroids must be applied three or four times daily, even in eyes with mild clinical signs. In more severe uveitis, topical preparations should be applied every 2 to 4 hours or combined with other routes of therapy. A subpalpebral lavage system should be considered when such frequent application is indicated (see under Bacterial Keratitis in Horses).

Either ophthalmic solution or ophthalmic ointment is acceptable for topical use in the horse. Prednisolone acetate* has excellent intraocular penetration and is considered the drug of choice. Potent dexamethasone preparations (Maxidex)† are also effective. In general, therapy should be continued for at least 2 weeks after clinical signs have resolved. Ideally, that assessment includes an objective IOP measurement to ensure resolution of ciliary body inflammation and dysfunction.

The subconjunctival injection of a repository corticosteroid preparation is an alternative or supplement to frequent topical therapy. Triamcinolone acetonide‡ is effective for 1 to 3 weeks when injected in a 0.5- to 1.0-mL volume (20 to 40 mg) beneath the superior bulbar conjunctiva. Subconjunctival methylprednisolone acetate§ has comparable antiinflammatory effect but is more likely to cause granuloma formation at the injection site. Duration of effect of either drug depends on the severity of the uveitis. Nonocular use of either drug has been linked to equine laminitis.

Evaluation of inflamed eyes should always include topical application of fluorescein dye to rule out ulcerative keratitis. This precaution is especially critical when considering the use of subconjunctival corticosteroids that deliver prolonged and irreversible effects. Topical and subconjunctival corticosteroids are contraindicated in the presence of corneal ulcers because they delay healing, potentiate the destructive effects of endogenous and microbial enzymes, and predispose the cornea to secondary infection.

* 1% suspension, Falcon Ophthalmics, Fort Worth, TX.

† 0.1% solution/0.05% ointment, Alcon Laboratories, Fort Worth, TX.

‡ Kenalog, Westwood-Squibb Pharmaceuticals, Buffalo, NY.

§ Depo-Medrol, Upjohn, Kalamazoo, MI.

39.44.5.24.5.3

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Parenteral corticosteroids may be used when topical and subconjunctival agents are ineffective in controlling inflammation, but NSAIDs are usually preferred in such cases. Use of these antiprostaglandin agents counteracts an important mediator of intraocular inflammation, minimizing the role of parenteral steroids in uveitis therapy and the attendant risk of laminitis. Flunixin meglumine (Banamine) is the NSAID of choice for the eye, administered at a dose of 0.5mg/kg intravenously or intramuscularly twice daily for 5 days, then 0.25 to 0.5mg/kg orally once or twice daily. Oral phenylbutazone* at 4.4 mg/kg twice daily can be used in cases of mild uveitis or in animals requiring chronic low-dose oral prophylaxis for recurrent disease. Dosage requirements for aspirin make it less practical in acute cases, but prolonged oral administration of 15 mg/kg twice daily has been used to avert relapses. Frequency of NSAID administration should be reduced as clinical response occurs, because antiprostaglandins have been linked to gastrointestinal ulceration and renal dysfunction with high doses or chronic use.

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Topical ophthalmic NSAIDs are generally more costly than and not as potent as corticosteroids if used alone. However, an additive antiinflammatory effect can be seen when topical NSAIDs are used in conjunction with topical corticosteroids in horses with acute or resistant uveitis. Although generally considered a safe alternative to topical corticosteroids in the presence of corneal ulceration, topical NSAIDs have been implicated in the development of melting corneal ulcers in humans. Available generic solutions include 0.03% flurbiprofen sodium† and 0.1% diclofenac sodium.‡ Dosage frequency is empirical, with intervals ranging from 6 to 12 hours.

* Butazolidin, Cooper's Animal Health, Kansas City, MO.

† Bausch & Lomb Pharmaceuticals, Tampa, FL.

‡ Falcon Ophthalmics, Fort Worth, TX.

39.44.5.24.5.4

MYDRIATIC/CYCLOPLEGIC AGENTS

A parasympatholytic mydriatic/cycloplegic agent must be used if equine uveitis is to be managed successfully. By dilating the pupil and decreasing iris-to-lens contact, the chance of posterior synechia formation—and secondary glaucoma—is reduced. An adequately dilated pupil may also promote vision during the acute episode. Ciliary spasm is relieved, making the horse more comfortable, and the iridociliary vessels return to a more normal state of permeability, with normalization of aqueous humor constituents.

Topical application of 1% atropine solution or ointment is indicated two to four times daily until the pupil dilates. The ultimate goal is to maintain mydriasis with the least frequent application possible, keeping in mind the resistance of the inflamed iris and ciliary body to the effects of atropine. Horses on an intensive parasympatholytic regimen should be strictly monitored for signs of reduced gut motility and colic because systemic effects occur with frequent topical atropine administration.[463] Pupillary dilation may persist for 4 weeks or more after cessation of therapy.

If mydriasis is slow or incomplete, 10% phenylephrine hydrochloride solution may be used topically in conjunction with atropine.[464] Although a study in the horse suggests that phenylephrine is ineffective when combined with a parasympatholytic agent, investigators did not rule out a possible benefit if dosage or duration of therapy was increased.[465] However, frequently applied phenylephrine has been associated with the development of corneal ulcers, corneal endothelial toxicity with secondary corneal edema, and increased uveal exudation, so response to the drug should be carefully monitored.

39.44.5.24.5.5

ANTIBIOTICS

Because current evidence suggests an immune rather than an infectious basis for recurrent uveitis, antibiotics have assumed a secondary role in ERU management. Topical antibiotic preparations may discourage opportunistic bacteria during intensive corticosteroid therapy; however, few will cross the intact cornea and reach therapeutic levels in the anterior chamber or uveal tract. In horses with positive leptospiral titers in serum or ocular fluids, systemic antibacterial therapy with oral doxycycline (10 to 20 mg/kg twice daily for 4 weeks) may minimize recurrences of uveitis.[466]

39.44.5.24.5.6

OTHER THERAPIES

If leptospiral infection has been well documented in a group of horses with uveitis, periodic vaccination against the disease may be considered. However, although vaccination significantly increased the interval to recurrence (median, 126 days) compared with nonvaccinated controls (median, 86 days), the practice failed to slow the progression of disease in a group of 41 ERU-affected horses.[467] Currently, no commercial bacterin is approved for use in the horse.

An intracameral injection (25 µg/0.1 mL) of tissue plaminogen activator (tPA) can be used to accelerate fibrinolysis and clear hypopyon in the anterior chamber of horses with severe uveitis. However, tPA should be avoided in eyes with evidence of hemorrhage in the previous 48 hours.

The precise role of *Onchocerca* species in the pathogenesis of ERU is not yet determined, and considerable controversy exists regarding the necessity or benefit of microfilaricidal therapy in cases of ocular onchocerciasis (see later under Ocular Parasites).

Acupuncture and homeopathic remedies such as poultices of chamomile and oral methylsulfonylmethane (MSM) have been used in the treatment of ERU, but efficacy of these unconventional modalities is unknown.

39.44.5.24.6

Prevention of Disease Recurrence

39.44.5.24.6.1

CYCLOSPORINE

Cyclosporin A (CsA) is a noncytotoxic, immunosuppressive drug that blocks the transcription of IL-2 and decreases T-cell responsiveness during the initiation of inflammation.[468,469] These properties could block the nonspecific activation of T cells in recurrent episodes of ERU. With its poor inherent antiinflammatory properties, cyclosporine is likely to be more effective in preventing recurrences than treating active inflammation. Unfortunately, topical application of cyclosporine fails to achieve effective

intraocular levels in horses and other species.[470] However, reports of sustained intraocular levels of CsA in ocular tissues[471,472] and resolution of clinical signs in experimental uveitis after implantation of a CsA-impregnated device into the vitreous of rabbit eyes[473] set the stage for implantation of a similar device into the anterior vitreous of horses with experimental uveitis. The CsA-containing implant significantly decreased the duration and severity of inflammation, cellular infiltration, tissue destruction, protein concentrations, and the level of transcription of proinflammatory cytokines in the experimental group.[461] The intravitreal device also prevented recurrences in 81% of horses with spontaneous ERU, but overall success was limited by complications from intraocular hemorrhage, cataract progression, and retinal detachment.[474] Because of significant risk of postoperative complications in the face of concurrent inflammation, a horse with active uveitis is not a suitable candidate for cyclosporine implantation until the inflammation is adequately controlled by conventional means.[376] Intravitreal delivery devices containing other immunosuppressive agents such as tacrolimus are also effective in suppressing inflammation after intravitreal implantation in rabbits with experimental uveitis.[475]

To minimize ocular morbidity related to implantation, ongoing studies of cyclosporine have focused on development and evaluation of a deep scleral delivery device.[476] Superficial episcleral implantation failed to achieve substantial intraocular levels of CsA or control inflammatory episodes in ERU-affected horses. Therefore, effects of a bioerodible implant infused with CsA and inserted into the suprachoroidal space beneath a partial-thickness scleral flap 1 cm posterior to the dorsolateral limbus were studied. Initial reports of the suprachoroidal device are encouraging. High concentrations of CsA were achieved in the equine ciliary body, choroid, retina, and optic nerve. In horses with severe ERU, only 15% of eyes were blind a mean of 14.2 months after implantation. In contrast, 90% of patients with severe ERU treated conventionally are blind within 1 year.[376] In vitro studies of CsA also documented a direct inhibitory effect on *Leptospira* growth at concentrations achievable within the uveal tissues after deep scleral implantation. Duration of CsA delivery with current devices is approximately 24 months.

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39.44.5.24.6.2

CORE VITRECTOMY

Pars plana vitrectomy has been used to remove fibrin, inflammatory cells, and debris trapped in the vitreous; improve vision; and delay progression of clinical signs in affected horses.[462,477,478] Proponents theorize that removal of T cells or infectious organisms such as *Leptospira* may reduce adverse interactions between the vitreous and the uveal tract, thereby reducing the recurrence of ERU. The technique appears more beneficial in European warmbloods with ERU than in Appaloosas with ERU in the United States. In one German study, recurrence of ERU was prevented in 85% (29/34) of treated eyes followed for 5 months to 5 years, but 45% of horses developed significant cataract formation.[462] A study of vitrectomy performed in the United States was also complicated by postoperative cataract formation and progressive loss of vision, despite some decrease in recurrence of uveitis.[479] More recent reports of vitrectomy performed on more than 1200 eyes at the University of Munich described no further recurrences of ERU in 98% of patients.[480] Cataract formation and retinal detachment were reportedly rare in this group of animals. Investigators explained their success on the basis of improved patient selection and surgical expertise.

39.44.5.24.7 Prognosis

The long-term prognosis for vision in horses with recurrent uveitis is poor, although statistics of actual rates of vision loss are limited. Dwyer's 11-year study of ERU-affected horses reported that 56% of the 160 study animals experienced blindness in one or both eyes.[376] Appaloosas and *Leptospira*-seropositive horses were at increased risk for blindness over the course of the study. All seropositive Appaloosas (100%) lost vision in at least one eye; 50% were completely blind. Of seronegative Appaloosas, 72% lost vision in one or both eyes; 29% were totally blind. Seropositive horses of other breeds lost vision in one or both eyes 51% of the time, with total blindness in only 17%. Seronegative, non-Appaloosas had the best prognosis, with 34% losing vision in one or both eyes and total blindness in only 6%.

39.44.5.25 BOVINE-SPECIFIC OPHTHALMIA

A recurrent uveitis of cattle has been described and compared to that of the horse.[481,482] As with ERU, its definitive etiology is unknown, although a viral infection was originally suggested. Clinical signs include conjunctival hyperemia, corneal edema and vascularization, inflammatory cells and hemorrhage within the anterior chamber and uveal tract, and retinal and choroidal edema and hemorrhage. The disorder is uncommon and does not share the notoriety of its equine counterpart. Therapy is directed at reducing inflammation, as described for the horse.

39.44.5.26 OCULAR PARASITES

ROBERT ENGLISH

MARK NASISSE

Parasites are an often overlooked cause of ocular disease in large animals. Many ocular parasitic diseases can threaten vision and can reduce the economic value of the animal through decreased function, decreased production, or both. The mechanisms by which parasites damage ocular tissues are extremely varied and range from direct tissue effects of aberrant parasite migration to complex immunopathologic responses to parasitic antigens. This section reviews the major ocular parasites of large animals, with reference to the ocular tissue of primary importance. Parasitic eyelid diseases are discussed in Chapter 40.

39.44.5.27 CORNEAL AND CONJUNCTIVAL PARASITISM

39.44.5.27.1 Ocular Onchocerciasis

Ocular disease caused by *Onchocerca cervicalis* is the result of aberrant migration of noninfective microfilariae into the palpebral, conjunctival, and corneal tissues.[483] The larvae do not appear to have a predilection for ocular tissues; rather, the eye is involved merely as part of a generalized subcutaneous migration. Approximately 50% of horses with cutaneous onchocerciasis will have ocular involvement.[484]

The pathogenesis of ocular onchocerciasis remains unclear. In humans, keratoconjunctivitis and uveitis associated with local presence of *Onchocerca volvulus* microfilariae occur only after the microfilariae die. Because *Onchocerca* microfilariae are typically found in equine ocular tissues without evidence of

inflammation, a similar mechanism is probably involved. Therefore, some change in the parasite and/or in the host's immune response likely occurs to incite an inflammatory response.

Ocular onchocerciasis occurs mostly in adult horses. The older the host, the greater is the exposure to the vector and the parasite, and presumably the greater the potential for ocular migration of microfilariae. Furthermore, increased immune sensitivity may occur with increased exposure to dead microfilariae.

39.44.5.27.2

Clinical Signs

Conjunctivitis and keratoconjunctivitis concentrated at the temporal limbus are the most common manifestations of ocular onchocerciasis. Acutely, chemosis and hyperemia of the conjunctiva occur, accompanied by increased lacrimation and blepharospasm. Small, raised, white nodules (0.5 to 2 mm in diameter) in the limbal conjunctiva and similar-sized punctate, subepithelial corneal opacities are often present. Corneal lesions are often wedged shaped, with the base of the triangle at the limbus, and are characterized by varying degrees of superficial and deep neovascularization and cellular stromal infiltrates. Untreated, the lesions progressively enlarge, although the rate of progression and the severity of the disease vary. With chronicity, patches of depigmentation (vitiligo) occur in the perilimbal bulbar conjunctiva. Recurrent episodes of keratoconjunctivitis are common.

Migration and subsequent death of microfilariae in the uveal tract result in uveal inflammation. Both the anterior and the posterior uveal tract may be involved. The clinical signs of *Onchocerca* uveitis include apparent photophobia, epiphora, miosis, aqueous flare, inflammatory cells in the anterior chamber, and globe hypotonicity. However, these signs are not specific for onchocerciasis, and other etiologies must be considered (see Table 39-2).

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Chorioretinitis reportedly is a common manifestation of posterior segment involvement. Active lesions are recognized ophthalmoscopically by hyporeflective areas, representing chorioretinal edema and inflammatory exudates, usually observed around the optic papilla in a “butterfly-shaped” pattern.[485] However, aqueous and vitreous opacification often precludes accurate assessment of the fundus.

39.44.5.27.3

Diagnosis

Characteristic clinical signs are highly suggestive of *Onchocerca* keratoconjunctivitis, but definitive diagnosis requires corneal or conjunctival biopsy. Conjunctival biopsy may be collected after topical anesthesia, whereas general anesthesia is necessary for partial-thickness lamellar keratectomies to obtain corneal biopsies. A single, 3- to 5-mm biopsy is divided into two samples. One sample is placed on a slide with physiologic saline, minced, and warmed to 37° C (98.6° F) to stimulate larvae movement and therefore enhance their detection. Slides are examined repeatedly over the next hour for migrating microfilariae. The organisms are 200 to 240 mm long and 4 to 5 mm in diameter, with a short, unsheathed tail. The other half of the biopsy specimen is placed in 10% buffered neutral formalin for histopathologic examination.

The presence of microfilariae in ocular tissue does not substantiate a diagnosis of *Onchocerca* keratoconjunctivitis unless evidence of a host inflammatory response exists. The cytologic response is usually pleomorphic, with neutrophils, lymphocytes, plasma cells, and eosinophils present. Varying degrees of neovascularization, pigmentation, lamellar disorganization, collagen degeneration, and calcification are present in the cornea. The overlying epithelium becomes thickened and keratinized. The presence of eosinophils in corneal and conjunctival scrapings is suggestive of a parasite etiology; however,

Onchocerca microfilariae are rarely found. Definitive diagnosis of *Onchocerca* as the cause of uveitis is rarely possible.

The differential diagnosis for equine keratoconjunctivitis also includes squamous cell carcinoma, habronemiasis, and mycotic infections. Because horses with ocular *Onchocerca* have a generalized larval migration, they may also have dermatitis, especially of the ventral thorax.

39.44.5.27.4

Treatment

In humans chronically infected with *O. volvulus,* systemic ivermectin therapy decreases ocular microfilaria burden and improves associated ocular disease. In horses, however, microfilaricide therapy has been associated with increased ocular inflammation. Therefore, treatment is directed at first controlling the inflammatory reaction and then eliminating the parasite.[486,487] Corticosteroids are the mainstay of this initial antiinflammatory treatment and may be given topically, subconjunctivally, or systemically, depending on the severity of the inflammation, the extent of ocular and dermal involvement, and the temperament of the horse.

Because of superior solubility, prednisolone acetate[*] and dexamethasone alcohols[†] are the preferred topical corticosteroid preparations. Mild lesions without concurrent uveitis are treated four to six times daily. When keratoconjunctivitis is severe or when uveitis is present, hourly application may be indicated. Subconjunctival corticosteroids are also beneficial but must be used with caution if corneal ulceration exists or is possible. Therapy is tapered as the inflammation is controlled.

Systemic corticosteroids are indicated for severe uveitis, with concurrent *Onchocerca* dermatitis, and before larvicidal therapy. Prednisolone, at an initial dose of 0.5 to 1 mg/kg daily for 5 to 7 days, is tapered as the inflammation decreases. Refractory cases have been treated for extended periods with 0.25 mg/kg prednisone every other day.[488] The antiprostaglandin activity of NSAIDs such as phenylbutazone and flunixin meglumine is also beneficial, especially when corneal ulceration prohibits the topical use of corticosteroids.

Elimination of the microfilariae is recommended once inflammation is controlled (see Chapter 40). The use of topical antibiotics is also recommended to prevent bacterial infection when corneal or conjunctival epithelial ulceration is present. With uveal involvement, topical mydriatic/cycloplegic agents such as atropine are indicated to relieve ciliary spasm and reduce the risk of posterior synechia formation.

* Pred-Forte, Allergan Pharmaceuticals, Irvine, CA.

† Maxitrol, Alcon Laboratories, Fort Worth, TX.

39.44.5.27.5

Ocular Habronemiasis

Equine ocular habronemiasis occurs when larvae from *Habronema muscae, Habronema microstoma,* or *Draschia megastoma* are deposited on ocular tissues. Flies serving as intermediate hosts for *Habronema* are attracted to moist areas of the body, including the conjunctiva, for feeding; ocular discharge and periocular wounds provide additional sites. As the flies feed, *Habronema* larvae are deposited on the surface of ocular tissues, migrate into the tissues, and produce a local granulomatous inflammatory reaction. Equine habronemiasis occurs worldwide.

39.44.5.27.6

Clinical Signs

Ocular lesions typically consist of raised, proliferative, nonhealing wounds present at the medial canthus. The lesions are friable and pruritic and bleed easily. Lesions often contain small (1 to 2 mm), yellow, caseated nodules ("sulfur granules"). Fistulous tracts and subdermal nodules may develop below the medial canthus. Corneal neovascularization, edema, and ulceration can occur as a result of altered lid function and irritation to the cornea from contact with the rough, irregular surface of the lesion. Corneal involvement increases the degree of ocular pain and blepharospasm.

Habronemiasis lesions are typically seasonal, occurring in the warm summer months when the fly population increases. Certain horses appear to be predisposed to developing cutaneous and ocular habronemiasis, and recurrence may be seen in these animals each summer.

39.44.5.27.7

Diagnosis

Demonstration of the larvae in the granulomatous lesions or fistulous tracts is diagnostic. Biopsies of the affected tissue are directly examined for *Habronema* larvae and may also be submitted for histopathologic examination. Cytologic examination of conjunctival scrapings reveals a mixed inflammatory response, with neutrophils, eosinophils, and macrophages predominating; however, *Habronema* larvae are usually not seen. The differential considerations for these lesions include neoplasia (especially squamous cell carcinoma), sarcoids, phycomycosis, onchocerciasis, foreign body reaction, and exuberant granulation tissue.

39.44.5.27.8

Treatment

Until recently, routine treatment was topical, with systemic therapy reserved for severe or refractory cases. However, oral ivermectin (0.2 mg/kg) has become the treatment of choice. Lesions begin to regress in 7 days and are usually healed by 4 to 6 weeks after treatment. Other effective larvicides include trichlorfon, ronnel, and diethylcarbamazine (DEC).

Topical, intralesional, and systemic corticosteroids may be used to decrease the inflammatory response to the larvae, but with ivermectin larvicidal treatment, they may not be needed. Topical antibiotics are indicated and topical corticosteroids avoided if corneal ulceration is present. Debridement and drainage of granulomatous areas and fistulous tracts may increase topical drug penetration and prevent abscess formation. Fly control and prompt treatment of disorders causing ocular discharge or exposure of fresh tissue are important in prevention of habronemiasis.

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39.44.5.27.9

Ocular Thelaziasis

Thelazia nematodes in the conjunctival sac of large animals are considered commensal but can cause clinical ocular disease. *Thelazia* species have a worldwide distribution, with *Thelazia lacrymalis* found more often in horses and *Thelazia gulosa, Thelazia rhodesii,* and *Thelazia skrjabini* found more frequently in cattle. The infection rate for cattle and horses in the United States is estimated at 15% to 38%, with horses less than 3 years of age affected more often than adult horses. The complete life cycle of the parasite is unknown, but *Muscae autumnalis* (face fly) and other *Muscae* species serve as the intermediate hosts.

39.44.5.27.10 Clinical Signs

Most horses and ruminants infested with *Thelazia* show no clinical signs. However, chronic conjunctivitis, conjunctival cysts, and superficial keratitis can occur, especially in the summer months when flies are active. The disease is often mild but can progress to cause corneal neovascularization, edema, and ulceration. Dacryocystitis from parasite migration in the nasolacrimal system occurs and is more common in cattle than horses. Migration into the lacrimal gland and its ducts is seen and theoretically may lead to keratoconjunctivitis sicca.[489]

39.44.5.27.11 Diagnosis

Direct visualization of the adult *Thelazia* worms in the conjunctival sac or nasolacrimal flushings is diagnostic. The parasites are motile unless topical anesthetic is used. Adult *Thelazia* are 8 to 18 mm long and milky white, and their cuticle contains prominent transverse striations.

39.44.5.27.12 Treatment

In cattle, both ivermectin and doramectin given systemically at 200 mg/kg are effective in eliminating *Thelazia*.[490,491] It is unclear if ivermectin therapy is effective in eliminating *Thelazia* in horses.[491] Alternatively, the parasites may be removed manually with saline flushes or forceps after topical anesthetic is administered, followed by topical ophthalmic organophosphate therapy.[492]

39.44.5.27.13 Ocular Elaeophoriasis

Elaeophoriasis, or “sore head,” is a disease of sheep that is caused by the nematode *Elaeophora schneideri*. Adult *Elaeophora* organisms are found in the common carotid and internal maxillary arteries of deer, where microfilariae are produced and migrate into the capillaries of the face and head. Biting flies of the genera *Hybomitra* and *Tabanus* transmit the microfilariae to new hosts. The disease is most prevalent in the fall and winter in western parts of the United States where sheep are grazed at high altitudes. *Elaeophora* infections in deer are usually not associated with clinical signs. In small domestic ruminants and elk, however, the migrating microfilariae can cause a hypersensitivity reaction in facial and ocular capillaries.

39.44.5.27.14 Clinical Signs

Migration of *Elaeophora* microfilariae in ocular capillaries leads to local inflammation. Although the uveal tract is affected more often, sheep with elaeophoriasis may develop chronic keratoconjunctivitis evidenced by epiphora, blepharospasm, conjunctival hyperemia, chemosis, and corneal opacities. Clinical signs of anterior uveitis caused by *Elaeophora* are nonspecific and include epiphora, blepharospasm, miosis, clouding of the anterior chamber, and cataract formation. Funduscopic changes indicative of chorioretinitis and optic neuritis are common and include retinal edema, pigment changes in the tapetal and nontapetal fundus, optic disc edema, and optic disc atrophy.[493]

39.44.5.27.15 Diagnosis and Treatment

Diagnosis depends on demonstrating the microfilariae in skin or conjunctival biopsies. Treatment of heavily parasitized animals may cause death by occlusion of the carotid arteries with *Elaeophora* adults. Drugs used in treatment include piperazine (50 mg/kg orally), DEC (100 mg/kg), and stibophen (35 mL intravenously). The efficacy of ivermectin to treat *Elaeophora* is unknown, but it is poor against other filarides. Symptomatic treatment of keratitis and uveitis is indicated.

39.44.5.27.16 Ocular Manifestations of Nasal Bots

Larvae of the arthropod *Oestrus ovis,* the sheep botfly, can aberrantly migrate up the nasolacrimal duct and enter the conjunctival sac, causing local inflammation. Conjunctival migration is accompanied by epiphora, conjunctival hyperemia, and chemosis. Finding the larvae within the conjunctival sac is diagnostic. Treatment consists of mechanical removal and topical or systemic organophosphates. The nasal botfly *Gedoelstia hassleri* is reported to cause ocular lesions in horses in South Africa.

39.44.5.27.17 Ocular Manifestations of Trypanosomiasis and Piroplasmosis

Many species of the protozoal blood parasite *Trypanosoma* can infect horses and ruminants, causing edema, hyperemia, and petechiation of the conjunctiva. Sheep infected with *Trypanosoma brucei* can develop keratoconjunctivitis and panuveitis, including chorioretinitis and optic neuritis. Demonstration of the organism in blood smears is diagnostic.

Other blood protozoans, including *Babesia* and *Theileria,* can also cause conjunctival edema, petechiation, icterus, swollen eyelids, and blood-stained tears.

39.44.5.28 Uveal and Retinal Parasitism

39.44.5.28.1 Onchocerciasis, Elaeophoriasis, and Trypanosomiasis

Onchocerca cervicalis causes equine parasitic uveitis and chorioretinitis, and *Elaeophora* and *Trypanosoma* cause uveitis in sheep. Ocular manifestations of these diseases are discussed under Corneal and Conjunctival Parasitism.

39.44.5.28.2 Toxoplasma Iridocyclitis and Retinitis

The intracellular protozoan parasite *Toxoplasma gondii* can cause ocular disease in large animals. Invasion and replication in the retina and uveal tract lead to retinitis, chorioretinitis, and anterior uveitis. The acquired form of toxoplasmosis in ruminants, however, is often not associated with clinical signs, and ocular lesions are uncommon. Toxoplasmosis is rare in horses.

39.44.5.28.3 Clinical Signs

The most common ocular findings with ocular toxoplasmosis are iridocyclitis and retinitis.[494] Retinitis is the primary posterior segment lesion, with secondary involvement of the chorioid. Retinal degeneration,

clumping of pigment in the retinal pigment epithelium and chorioid, and optic disc avascularity are seen ophthalmoscopically; however, these lesions are not pathognomonic for toxoplasmosis. Orbital pain and swelling may result from parasitic invasion of extraocular muscles and orbital fat.

39.44.5.28.4 Diagnosis and Treatment

39.44.5.28.4.1 MISCELLANEOUS INTRAOCULAR PARASITES

The most common intraocular parasite in horses is *Setaria,* with *Setaria digitata* found more frequently within the eyes of horses than *Setaria equina.* Ocular infestation is presumed to result from aberrant migration of the larval stage. Although *Setaria* causes minimal inflammation in the peritoneal cavity, it can cause serious intraocular inflammation. Diagnosis is by visualizing the parasite in the aqueous humor. Treatment involves symptomatic antiinflammatory therapy and surgical removal.

Other filarides found free within the anterior chamber of horses' eyes include *Dirofilaria immitis* and *Onchocerca cervicalis*. Diagnosis and treatment are the same as for *Setaria*. Severe endophthalmitis resulting from intraocular infection with the free-living nematode *Halicephalobus* has been reported in a horse.[495] The ocular disease was accompanied by a fatal encephalopathy. Diagnosis was based on finding the parasite during microscopic examination of intraocular tissues.

The canine cestodes, *Echinococcus granulosa* and *Echinococcus multilocularis,* may form intraocular hydatid cysts in horses and ruminants, thereby producing extensive inflammation and retinal detachment. There is no medical treatment, and surgical removal is often impossible. Diagnosis is made on histopathologic examination of affected tissues.

Coenurus cerebralis, the intermediate form of *Taenia multiceps* and *Taenia serialis,* can develop in the CNS of sheep, causing a disease known as "sturdy" or "gid." Besides having abnormal gait, affected animals are often centrally blind. No treatment exists.

39.44.5.28.4.2 OCULAR NEOPLASIA

STEVEN M. ROBERTS

A wide variety of tumor types may involve the ocular or periocular tissues of food animals. Except for the most common neoplasms, limited information is available regarding treatment modalities, drug dosages, overall prognosis, and prevention or control. The tendency has been to adapt information and methods used in other areas of medicine for use in large animals. Table 39-3 lists potential presenting signs and corresponding ocular neoplastic conditions or related differential diagnoses for horses, cattle, sheep, and goats. Table 39-4 categorizes ocular neoplasms that have been reported in the literature for each of these species. The greatest amount of information pertains to the horse.

Despite the variety of primary and secondary neoplasms affecting the ocular and periocular tissues, most tumors produce similar effects on the eye, with tissue distortion and loss of function being the initial concerns. Strategic therapy and management goals may vary from curative or palliative (e.g., eliminating discomfort by enucleation) for individuals to elimination of the problem (e.g., culling from the herd) for a population. Specific tumor treatment options are often similar for neoplasms involving a particular ocular region or location; when designing a management plan, however, the specific

histologic tumor type is important in determining prognosis. Classification of a tumor as "benign" versus "malignant" or "localized" (e.g., equine sarcoid) versus "systemic" (e.g., lymphosarcoma) greatly influences treatment options and management approaches. The following discussion addresses the major tumors of concern in large animals and briefly surveys miscellaneous tumors that have been associated with ocular signs.

Table 39-3 Ocular Neoplasia and Differential Diagnoses by Species Based on Presenting Clinical Signs

Clinical Sign	Equine	Bovine	Caprine	Ovine
Ocular pain	*Habronema* blepharoconjunctivitis* Brainstem neoplasia Ocular dermoid Ocular trauma Squamous cell carcinoma* Sarcoid	Brainstem neoplasia Ocular dermoid Orbital lymphosarcoma* Sporadic bovine leukosis Squamous cell carcinoma*	Brainstem neoplasia Ocular dermoid Squamous cell carcinoma	Brainstem neoplasia Ocular dermoid Squamous cell carcinoma
Exophthalmos	Optic nerve neuroepithelial tumor Lymphosarcoma Retrobulbar neoplasia	Enzootic adult lymphosarcoma* Nasal and paranasal sinus neoplasia Nonprogressive bilateral exophthalmos Oral, maxillary, and mandibular neoplasia Retrobulbar neoplasia Sporadic bovine leukosis Squamous cell carcinoma*	Nasal and paranasal sinus neoplasia Oral, maxillary, and mandibular neophasia Squamous cell carcinoma	Adenocarcinoma of nasal cavity Nasal and paranasal sinus neoplasia Squamous cell carcinoma
Intraocular mass	Exudative optic neuritis Mastocytoma Medulloepithelioma Ocular melanoma Optic disc astrocytoma Optic nerve neuroepithelial tumor Squamous cell carcinoma Proliferative optic neuropathy Uveal or iris cyst	Ectopic lacrimal gland Ocular melanoma Squamous cell carcinoma	Ocular trauma Squamous cell carcinoma	Ocular trauma Squamous cell carcinoma
Nictitating membrane protrusion	Horner's syndrome Ocular trauma Orbital neoplasia Nasal and paranasal sinus neoplasia	Horner's syndrome Lymphosarcoma Ocular trauma Nasal and paranasal sinus neoplasia	Ocular trauma Nasal and paranasal sinus neoplasia	Ocular trauma Nasal and paranasal sinus neoplasia
Nasolacrimal duct obstruction	Cutaneous squamous cell carcinoma* *Habronema* blepharoconjunctivitis Nasal and paranasal sinus neoplasia	Nasolacrimal duct occlusion Nasal and paranasal sinus neoplasia	Nasolacrimal duct occlusion Nasal and paranasal sinus neoplasia	Nasolacrimal duct occlusion Nasal and paranasal sinus neoplasia

Ocular discharge	Conjunctivitis Ocular trauma Lymphosarcoma Nasal and paranasal sinus neoplasia Retrobulbar neoplasia	Conjunctivitis Ocular trauma Lymphosarcoma Nasal and paranasal sinus neoplasia Retrobulbar neoplasia	Conjunctivitis Lymphosarcoma Nasal and paranasal sinus neoplasia	Conjunctivitis Lymphosarcoma Nasal and paranasal sinus neoplasia
Periorbital or eyeball mass	Adenocarcinoma Angiosarcoma Hemangioma Hemangiosarcoma Lipoma Lymphosarcoma Mastocytoma Melanoma Nasal and paranasal sinus neoplasia Ocular dermoid Reticulum cell sarcoma Retrobulbar neoplasia Sarcoid* Squamous cell carcinoma* Warts	Ectopic lacrimal gland Fibroma Fibrosarcoma Ocular dermoid Ocular melanoma Retrobulbar neoplasia Squamous cell carcinoma*	Fibroma Fibrosarcoma Melanoma Nasal and paranasal sinus neoplasia Ocular dermoid Papillomatosis Squamous cell carcinoma	Fibroma Fibrosarcoma Melanoma Nasal and paranasal sinus neoplasia Ocular dermoid Papillomatosis Squamous cell carcinoma
Buphthalmia	Glaucoma Ocular melanoma Ocular trauma Medulloepithelioma Infectious bovine keratoconjunctivitis* Ocular melanoma Ocular trauma	Ocular trauma Ocular melanoma Ocular trauma		
Corneal mass	Angiosarcoma Hemangioma Hemangiosarcoma Keratomycosis Ocular dermoid Squamous cell carcinoma*	Enzootic adult lymphosarcoma Infectious bovine keratoconjunctivitis* Interstitial keratitis Ocular dermoid Squamous cell carcinoma*	Keratomycosis Ocular dermoid Squamous cell carcinoma Fibroma	Keratomycosis Ocular dermoid Squamous cell carcinoma

Facial mass	Angiosarcoma Cutaneous habronemiasis Hemangioma Hemangiosarcoma Lymphosarcoma Mastocytoma Nasal and paranasal sinus neoplasia Ocular dermoid Ocular melanoma Oral, mandibular, and maxillary neoplasia Retrobulbar neoplasia Salivary gland neoplasia Sarcoid* Schwannoma of eyelids Sialoadenitis	Enzootic adult lymphosarcoma Fibroma Melanoma Nasal and paranasal sinus neoplasia Ocular dermoid Ocular melanoma Papillomatosis Retrobulbar neoplasia Sebaceous cyst Sporadic bovine leukosis Squamous cell carcinoma*	Fibrosarcoma Histiocytoma Melanoma Nasal and paranasal sinus neoplasia Papillomatosis Squamous cell carcinoma Fibroma Fibrosarcoma Lymphosarcoma Nasal and paranasal sinus neoplasia Ocular melanoma Papillomatosis Squamous cell carcinoma

* Denotes the most prevalent and important differential diagnostic considerations.

Table 39-4 Ocular Neoplasms Reported in Large Animal Species

Neoplasm	Equine	Bovine	Caprine	Ovine
Adenocarcinoma	+			+
Angiosarcoma	+			
Basal cell tumor	+			
Chondroma rodens	+			
Equine sarcoid	+			
Hemangioma	+			
Lymphangioma	+			
Lymphosarcoma	+	+	+	+
Mastocytoma	+	+	+	+
Medulloepithelioma	+			
Nasal/paranasal sinus neoplasia	+			+
Ocular melanoma	+			
Optic nerve astrocytoma	+			
Optic nerve neuroepithelioma	+	+		
Papilloma	+			
Retrobulbar neoplasia	+			
Reticulum cell sarcoma	+	+	+	+
Schwannoma	+			
Squamous cell carcinoma	+	+	+	+

39.44.6 OCULAR SQUAMOUS CELL CARCINOMA

39.44.6.1 Definition and Etiology

Bovine ocular squamous cell carcinoma (OSCC), also commonly called “cancer eye,” represents the most economically important neoplasm of large animals. It is the most common tumor affecting cattle in North America, and according to estimates from federally inspected abattoirs in the United States, 12.5% of all bovine carcass condemnations were caused by OSCC.[496] The economic impact includes carcass condemnations, production losses, treatment expenditures, and management costs.

Ocular SCC arises from the epithelial surfaces of the conjunctiva (corneoscleral junction, nictitating membrane, and palpebra) or cornea. The etiology is probably multifactorial, with genetic, environmental, and viral factors being proved or suspected.[496–498] In particular, increasing levels of solar irradiation and decreasing amounts of circumocular pigmentation are linked to an increased prevalence of OSCC.[499,500]

Equine OSCC is the most prevalent equine ocular neoplasm (followed by equine sarcoid) and typically occurs in horses with unpigmented eyelids.[498,501] The amount of perilimbal and nictitating membrane pigmentation represents another important causal factor in cattle and horses that has received little attention but should be considered on prepurchase and health examinations (see Chapters 1 and 2).

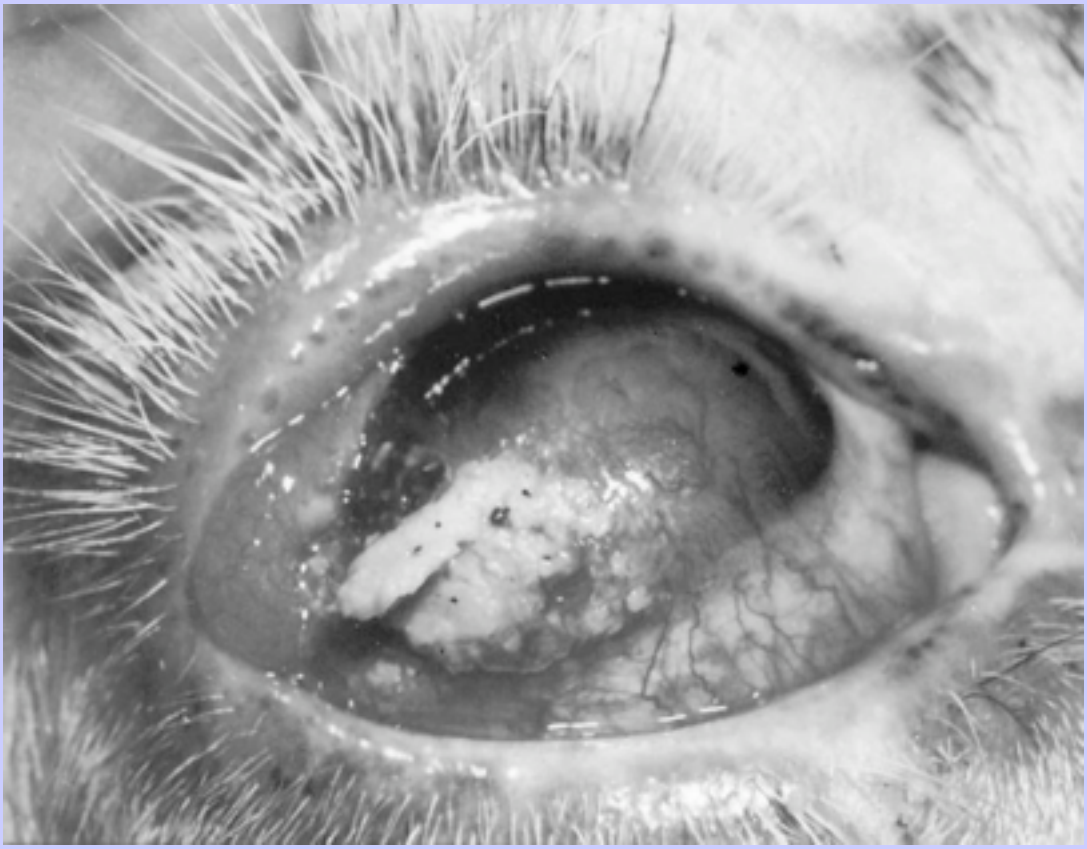
39.44.6.2

Clinical Signs and Differential Diagnoses

The gross appearance depends not only on the anatomic tumor site (because this determines the overall interaction between epithelium and underlying connective tissue elements) but also the stage of malignancy. In general, premalignant squamous cell tumors are small, white, elevated, hyperplastic plaques or papilloma-like structures with verrucous surfaces (Fig. 39-29). In contrast, malignant tumors are more irregular, nodular, pink, erosive, and necrotic in nature (Fig. 39-30). Necrotic tumors often have a characteristic foul odor. Squamous cell carcinomas that invade the orbit may become massive and eventually aggressively invade bone. Often the gross appearance allows a diagnosis to be established, but at times, cytology or histology is necessary to differentiate among benign tumors, carcinoma in situ, and invasive SCC. Bovine OSCC typically involves (in decreasing order of frequency) the lateral limbus, eyelid margins (especially the lower), nictitating membrane, and medial canthal regions.[496,497] Similar tissues are involved in horses, although some reports suggest that the nictitating membrane is more frequently involved than the corneoscleral junction.[498,502] Clinical signs resulting from metastatic lesions are not common, although lymphatic tissues may become infiltrated with neoplastic cells.

Fig. 39-29 Bovine ocular squamous cell carcinoma (OSCC). Note the small, premalignant, hyperplastic plaque involving the medial limbus and the large, malignant, nodular mass on the lower eyelid. The large mass is becoming ulcerated and necrotic.

Fig. 39-30 Bovine OSCC involving the cornea and conjunctiva. Note the irregular and invasive growth into the cornea. The surface is rough and necrotic.



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Despite the characteristic appearance of lesions, differential considerations (especially in the horse) include adenocarcinoma, adenoma, angiosarcoma, basal cell tumor, conjunctival follicular hyperplasia, dermoid, fibroma, fibrosarcoma, granulation tissue, habronemic blepharoconjunctivitis, lymphosarcoma, mastocytoma, plasma cell tumors, sarcoid, and schwannoma (see Tables 39-3 and 39-4).

39.44.6.3

Pathophysiology

The tumor in all species develops through a series of premalignant stages (i.e., hyperplastic plaques or epidermal plaques and papillomas) to progress over months and years to a carcinoma in situ and finally an invasive squamous cell carcinoma. Neoplastic lesions may arise without notable precursor stages. It is unlikely that tumors arise in the cornea unless previous vascularization has occurred.[503] Spontaneous regression of 30% to 50% of bovine precancerous lesions may occur,[496] and in rare cases, early OSCC may regress spontaneously. Tumors arising at the limbus are confounded by the dense and poorly vascularized sclera and cornea, thus hindering metastasis to extraocular sites. Nictitating membrane tumors extend to the base of the membrane and cartilage more rapidly, with spread into the orbit and surrounding bones occurring

much sooner than with tumors involving the globe. Although metastasis will eventually occur, extensive extraocular spread is limited in cattle by the practice of sending most affected animals to slaughter. Horses demonstrate multiple tumor locations and local invasion in up to 50% of cases.[502,503] Metastasis beyond extraocular sites is rare in horses.

39.44.6.4

Epidemiology

Although OSCC has been reported in a wide variety of cattle breeds, the Hereford breed (either purebred or crossbred) is most often diagnosed with this tumor as a result of the common use of this breed as a range animal and the strong genetic trait for a white face. Thus, selective breeding for partially to fully pigmented periocular skin greatly reduces the occurrence of this tumor.[496] The tumor is more common in older cattle, with the peak age prevalence being 7 to 8 years. Exposure to increasing levels of actinic radiation raises the prevalence of bovine OSCC.[499] The prevalence of ocular squamous cell tumors, including nonmalignant tumors, involving Hereford herds in regions with abundant sunlight can range from 20% to 40%. Research performed in cattle herds suggests that a high plane of nutrition or a lower-than-normal body weight in cows for the first 2 years acts to increase the prevalence.[496] The intriguing possibility that bovine OSCC may be induced by viruses (e.g., papillomavirus) warrants further research.

Equine OSCC in North America demonstrates an increased prevalence with increasing longitude (°W), altitude, and mean solar irradiation.[501] Breeds with a greater risk of developing OSCC include draft breeds, especially the Belgian (odds ratio [OR] = 21.7), Appaloosa (OR = 7.9), paint and pinto (OR = 4.5), and grade horses (OR = 3.1). Coat colors showing an increased risk include white (OR = 26.7), creamello/palomino (OR = 13.7), gray (OR = 6.7), red/white and strawberry/white (OR = 4.7), buckskin (OR = 4.4), and chestnut/sorrel (OR = 3.8).[501]

39.44.6.5

Necropsy Findings

Depending on the extent of involvement, gross changes are noted that involve the globe, conjunctiva and nictitating membrane, orbit, bones of the orbit, and regional cervical lymph nodes. In rare instances, metastasis to thoracic and abdominal organs can occur.

39.44.6.6

Treatment and Prognosis

Numerous modalities are available, and applications depend on availability of instrumentation, location and extent of the tumor, and value and intended function of the animal. Choices include radiofrequency hyperthermia,[*] cryonecrosis, intralesional injection of biologic response modifiers (BRMs; e.g., allogeneic OSCC extract, mycobacterial cell wall fraction,[†] *Propionibacterium acnes*[‡]), intralesional chemotherapy with cisplatin[§] (with or without initial debulking),[504,505] radiotherapy (cesium-137, cobalt-60, gold-198, iridium, strontium-90), and surgical removal (local excision, enucleation, and exenteration with or without salivary gland and lymph node resection). Intralesional use of cisplatin (1 mg/cm^3 of tumor volume) is highly effective, but multiple injections are necessary (four times at 2- to 3-week intervals). Handling of the drug and animal after treatment must adhere to U.S. Occupational Safety and Health Administration (OSHA) guidelines,[506] and animals must not be used for food consumption. Appropriate precaution should be followed with extralabel use of cytotoxic drugs. Surgical debulking with adjunctive cryonecrosis or radiofrequency hyperthermia is an effective and affordable treatment modality. Cryonecrosis is achieved with

liquid nitrogen, using a probe or spray delivery system to freeze the tissues to −30° C (−22° F) twice, with complete thawing between freeze cycles. Radiofrequency hyperthermia is performed with piercing or surface probes to heat the tissues to 50° C (122° F) for 30 seconds. Multiple treatment sites are necessary for lesions larger than 0.5 cm in diameter.

Because recurrence rates range between 30.4% and 42.4%,[498,502] the willingness of the owner to return the animal for follow-up treatment is a significant determinant in overall survival. Financial constraints were the most common reason for cessation of treatment. Many horses that die as a consequence of OSCC are euthanized at the owner's request. The overall prognosis is determined by the degree of neoplastic involvement of normal tissue, but a guarded prognosis is warranted. If treatment is to be undertaken, intervention should begin at the earliest stages of tumor development. In animals destined for slaughter, the guidelines for condemnation of bovine carcasses affected with OSCC shown in part A of Box 39-2 should be considered.

* RDM Hypertherm, RDM International, Phoenix, AZ.

† Normagen, Fort Dodge Laboratories, Fort Dodge, IA.

‡ ImmunoRegulin, ImmunoVet, Tampa, FL.

§ Platinol, Bristol-Meyers, Wallingford, CT.

39.44.6.7

Prevention and Control

In cattle, factors such as genetics, UV light, and environmental factors (e.g., wind, dust) are known to be involved in OSCC. Ocular viral infection may also be contributory. If possible, affected animals should be culled as soon as possible because most production situations preclude environmental factor modification. Specific preventive measures have not been systematically evaluated in horses, but recommendations include reducing UV light exposure, using protective fly masks in horses (to decrease solar irradiation and environmental irritants), tattooing lightly pigmented periocular skin, and avoiding breeds thought to have an increased risk of tumor development.

39.44.7

OCULAR MANIFESTATIONS OF LYMPHOSARCOMA

39.44.7.1

Definition and Etiology

Lymphosarcoma is a fatal systemic neoplastic disease of the lymphoreticular tissue. The adult or enzootic form of bovine lymphosarcoma is likely the most devastating and common neoplasm of dairy cattle. This is a systemic disease with ocular manifestations rather than a pure ophthalmic problem. (See Chapter 37 for specific information regarding bovine lymphosarcoma and the bovine leukemia virus.) Lymphosarcoma represents the most common cause of orbital neoplasia in cattle,[507] excluding OSCC that involves the orbit by local extension. Lymphosarcoma may affect horses[508] and goats. The etiology in horses and goats is unknown.

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39.44.7.1.1

Box 39-2 Guidelines for Inspection (Antemortem and Carcass) and Disposal of Animals, Carcasses, and Parts Affected with Neoplasia

A Epithelioma of the eye

1 Any animal found on antemortem inspection to be affected and the eye has been destroyed or obscured by neoplastic tissue and which shows extensive infection, suppuration, and necrosis, usually accompanied by foul odor, or any affected animal with cachexia, regardless of extent, shall be condemned.

2 Carcasses of animals with the eye or orbital region affected will be condemned if the affection has:

a Involved the osseous structures of the head with extensive infection, suppuration, and necrosis;

b Metastasized from the eye or orbital region to any lymph node (including the parotid lymph node), internal organs, muscles, skeleton, or other structure, regardless of the extent of the primary tumor; *or*

c Regardless of extent is associated with cachexia or evidence of absorption or secondary changes.

3 Carcasses of animals affected to a lesser degree than above may be passed for human food after removal and condemnation of the head, including the tongue, provided the carcass is otherwise normal.

B Neoplasms

1 An individual organ or other part of a carcass affected with a neoplasm shall be condemned. If there is evidence of metastasis or that the general condition of the animal has been adversely affected by the size, position, or nature of the neoplasm, the entire carcass shall be condemned.

2 Carcasses affected with malignant lymphoma shall be condemned.

From *Code of Federal Regulations,* Title 9, Chapter 3, Parts 309.6, 311.11, and 311.12 (1-1-87 edition).

39.44.7.2

Clinical Signs and Differential Diagnoses

Clinical signs are usually associated with exophthalmos caused by orbital disease. Neoplastic lymphoid cell infiltration behind the globe results in exophthalmos, subsequent exposure keratitis, and eventual proptosis[507] (Fig. 39-31). One report has documented intraocular lymphosarcoma in a Holstein cow as the presenting sign of generalized lymphosarcoma.[509] Subtle exophthalmos is often overlooked because of the natural exophthalmic state of some dairy breeds. Typically, these animals present with a history that suggests an acute onset of exophthalmos, when actually orbital involvement has been present for a time. Clinical signs associated with the exophthalmos and exposure keratitis include corneal edema, vascularization, ulceration, epidermalization, conjunctival hemorrhage, chemosis, and ocular discharge. These signs may develop, progress, and change quickly once corneal protection is compromised. Other physical examination findings are discussed in Chapter 37. Differential considerations for exophthalmos include orbital cellu-litis, trauma, retrobulbar hemorrhage, retrobulbar soft tissue masses, chronic sinusitis, and sinus neoplasia (see Tables 39-3 and 39-4).

Fig. 39-31 Orbital lymphosarcoma. Diffuse orbital involvement causing exophthalmos and secondary exposure keratitis of the right eye.

39.44.7.3

Clinical Pathology

Definitive diagnosis is achieved by cytologic samples obtained with a spatula after topical anesthesia[496] or specimens excised for biopsy and fixed in formalin. Benign lesions typically contain superficial, anucleated, keratinized squamous cells and deeper epithelial cells with enlarged nuclei and coarse chromatin clumping. Biopsies of these lesions show that the basal layer or basement membrane has not been invaded. Malignant OSCC lesions are composed of pleomorphic cells with bizarre shapes, large hyperchromatic nuclei containing large clumps of chromatin, and prominent nucleoli. On biopsy examination, invasion across the basement membrane is noted, and keratin-pearl formation or marked anaplasia is usually present.[503] In the event of regional lymphatic involvement, fine-needle aspiration or preferably a biopsy may demonstrate neoplastic infiltration.

Equine lymphosarcoma involving the eye also represents a systemic disease with ocular manifestations. Other systemic manifestations are discussed in Chapter 37. Ocular lesions include uveitis, nictitating membrane masses, chemosis and conjunctivitis, and neoplastic infiltration of the eyelids and orbit.[509] Differential considerations should include any chronic inflammatory disease, equine infectious anemia, equine piroplasmosis, and infectious causes of uveitis (see Table 39-2).

39.44.7.4 Necropsy Findings

As with the clinical signs, necropsy findings are variable. In cattle, orbital involvement is common, with lymphoid tumors being firmly attached to the periorbita and walls of the orbit. Extraocular muscles are frequently infiltrated with tumor cells. The globe itself is typically not involved.[503] Ocular lesions occur less often in horses than in cattle. In the horse the globe (uveal tract) can be involved, in addition to extraocular tissues. As with other systemic neoplastic diseases, multiple organ involvement is expected with lymphosarcoma.

39.44.7.5 Treatment and Prognosis

This systemic disease may be treated palliatively or systemically in an attempt to achieve remission for a time. Enucleation provides palliative treatment, and chemotherapy with corticosteroids, vincristine, and L-asparaginase may induce remission. Extralabel use of these cytotoxic drugs must be approached with extreme caution, and treated animals must not be used for food consumption. Most cattle with orbital lymphosarcoma either die or are euthanized in terminal stages of disease within 6 months of the original diagnosis.[507] Horses can have a much more protracted disease course, with many presenting because of chronic illness of up to 12 months' duration.[508] The overall prognosis is unfavorable, regardless of the species involved.

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39.44.7.6 Prevention and Control

Control of bovine lymphosarcoma depends on efforts to eradicate bovine leukemia virus, a monumental task in most cases. In other large animal species, prevention and control recommendations for lymphosarcoma are not possible until the etiology can be identified. If animals are destined for slaughter, the guidelines for condemnation of bovine carcasses affected with lymphosarcoma as shown in part B of Box 39-2 should be followed.

39.44.8 OCULAR MANIFESTATIONS OF EQUINE SARCOID

39.44.8.1 Definition and Etiology

Equine sarcoid is a locally aggressive, nonmalignant, fibroblastic tumor of the equine skin (see Chapter 40). It appears to be the most common equine neoplasm, with 14.7% of ocular and adnexal tumors in the horse being sarcoids (all involved the eyelids).[510] This neoplasm develops more frequently in sites predisposed to trauma and areas that come into contact with existing sarcoids, and it does not metastasize to internal organs.

39.44.8.2 Clinical Signs and Differential Diagnoses

Sarcoids involving the eyelids are classified according to the scheme used for cutaneous lesions: verrucous, fibroblastic, mixed, or occult. Tumors of the eyelids may appear smooth and nodular, crusted and nodular, ulcerated, or pedunculated (Figs. 39-32 and 39-33). Regardless of their appearance, the tumors are nonregressing. Periocular sarcoids are subject to trauma; thus the verrucous type frequently transforms into the fibroblastic type with surface ulceration. It is difficult to differentiate sarcoid from fibroma, fibrosarcoma,

neurofibroma, neurofibrosarcoma, schwannoma, or nonneoplastic granulation tissue (see Tables 39-3 and 39-4).

39.44.8.3 Treatment and Prognosis

Problematic lesions can be treated by a variety of modalities, none of which is uniformly successful. Often, multiple treatment sessions are required for tumor control. Treatment modalities include surgical excision (50% success rate), cryonecrosis (30% success rate), radiofrequency hyperthermia (RDM Hypertherm), intralesional injection of BRMs (bacille Calmette-Guérin),[510] chemotherapy with intralesional cisplatin (Platinol; with or without initial debulking),[503,504] radiation therapy (cesium-137, cobalt-60, gold-198, iridium, strontium-90), and chemotherapy (5-fluorouracil) combined with surgical excision. BRM therapy has not proved as successful for sarcoids located at other body sites. An available commercial *Mycobacterium* product (Normagen) can be used, but it does not demonstrate the clinical efficacy seen with previously used research preparations. If the sarcoid is static, flat, and hairless, it may be best left alone because any trauma, surgical or otherwise, could increase the growth rate and invasiveness of the lesion. Response to therapy varies on the basis of tumor location, duration, severity, and previous therapeutic measures.

Fig. 39-33 Equine sarcoid involving the medial aspect of eyelid. At examination or during treatment, sarcoids may become ulcerated. This tumor became ulcerated after one injection of a *Mycobacterium* cell wall preparation but subsequently resolved.

Fig. 39-32 Equine sarcoid. The upper eyelid exhibits a smooth, nodular mass typical of many periocular sarcoids.

Treatment of periocular sarcoid with BRMs shows particular promise but has the disadvantage of requiring a potentially long course of treatment, involving a series of intralesional injections. Intratumoral use of cisplatin is highly effective (see Chapter 40). Successful treatment measures exist for equine sarcoid, and if a complete treatment protocol is followed, the prognosis is favorable. As with any neoplastic disease, at the first evidence of recurrence, the animal should be reevaluated.

39.44.9 MISCELLANEOUS TUMORS WITH OCULAR INVOLVEMENT

The tumors previously discussed represent the most significant ocular or periocular neoplasms of large animals. However, to the individual animal or owner, any tumor type represents a significant problem. Thus, clinicians must remember that numerous primary and secondary neoplastic processes can involve the eye and surrounding tissues. Secondary tumors may be either metastatic masses or locally invasive masses extending from sites near the eye. The greatest variety of ocular neoplastic disease has been reported in the horse (see Table 39-4).

Adnexal tumors that have been reported include adenoma, adenocarcinoma, basal cell carcinoma, fibroma, fibrosarcoma, hemangioma,[511] hemangiosarcoma,[512] lymphosarcoma, melanocytoma, melanoma, papilloma, plasma cell tumors, and schwannoma. Few reports address treatment of these tumors thoroughly. 1304 1305

Surgical excision of small lesions, cryosurgery, radiation therapy, intralesional cisplatin,[504,505] and medical treatment with cimetidine[513,514] have been used successfully on select tumors. Oral cimetidine (2.5 mg/kg three times daily for an initial 3-month period) is useful as a means of melanoma control. If lesions are progressively enlarging, cimetidine has been particularly successful in arresting or resolving tumor lesions. This treatment is also a useful adjunct to cryonecrosis, surgical excision, or chemotherapy. The prognosis is poor for malignant masses because metastatic disease or local recurrence usually results. This is especially true with angiosarcomas[502] that involve primarily the conjunctiva but may also involve the corneoscleral junction. Limited success with angiosarcoma treatment has been achieved in a case of equine orbital lymphangiosarcoma through enucleation and chemotherapy with intravenous vincristine (four doses of 1.3, 1.3, 1.2, and 1 mg/m^2 of body surface area on days 0, 7, 14, and 51, respectively) and prednisone. Seven years after treatment, the horse showed no signs of recurrence. An additional case of conjunctival and nictitating membrane malignant hemangiosarcoma was treated by local excision and perioperative intratumoral cisplatin. Follow-up demonstrated tumor lysis and no recurrence after 6 months.

Any tumor involving the nasal and paranasal cavities has the potential to involve the ocular structures as the result of orbital spread. Enzootic adenocarcinoma in sheep is an example of this type of process. Although infrequently noted, exophthalmos secondary to orbital invasion of this tumor has been reported.[515] Primary orbital neoplasia in the form of a multilobular osteoma (chondroma rodens) has been reported in the horse[516] and reminds one that a space-occupying mass (neoplasia) can affect the eye by causing progressive exophthalmos.

Neoplasia involving the CNS, diencephalon, or occipital cortex can result in a central blindness, abolished pupillary light responses, and mydriasis. Other forms of intracranial neoplasia can secondarily involve the eye as a result of cranial nerve dysfunction. For example, an intracranial schwannoma caused exposure ulcerative keratitis in a cow that presented with left facial paresis.[517]

Reports of neoplasia involving the globe, all in horses, describe the clinical, histologic, and treatment aspects of epibulbar melanocytoma,[518] intraocular melanoma,[519,520] and medulloepithelioma.[521] Optic nerve tumors have included neuroepithelial tumors and meningiomas. In the intraocular cases the globe was rendered nonfunctional by the neoplastic process, and the involved eye was subsequently enucleated. An optic nerve neuroepithelial tumor displayed metastatic spread as a result of extension into the brain through the optic foramen, causing brain compression.[522] Although documented cases of these miscellaneous ocular neoplasms are not widespread, they must be taken into consideration as possible causes of large animal ocular neoplasia.

Other than vascular tumors, most ocular tumors do not display a severe metastatic threat. Although enucleation may be curative, histologic evaluation of excised tissues and long-term patient follow-up are necessary if accurate epidemiologic and prognostic data are to be available. Once an accurate diagnosis has been made, the clinician and owner must determine, in light of all available medical information and the proposed use of the animal, whether treatment should be curative or palliative or whether elimination of the problem from the herd should be of greater concern than care of the individual animal.

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40 Chapter 40 Diseases of the Skin

Consulting Editors

Stephen D. White

40.1 IMMUNE-MEDIATED SKIN DISORDERS

STEPHEN D. WHITE

40.2 PEMPHIGUS FOLIACEUS

40.2.1 Definition and Etiology

The term *pemphigus* is derived from the Greek word for "blister" and is used to describe a group of autoimmune vesiculobullous disorders characterized histologically by intraepidermal acantholysis and immunologically by intercellular deposition of immunoglobulin. Pemphigus foliaceus is the most common of this group of autoimmune diseases; in large animals it has been reported in horses,[1,2] goats,[3,4] and a donkey.[5] In small animals, pemphigus foliaceus has been putatively associated with drugs,[6] but this has not been identified in large animals. The factors precipitating the development of pemphigus foliaceus in large animals are unknown. The clinical lesions recognized in horses and goats are primarily scaling and crusting.

40.2.2 Pathophysiology

Pemphigus foliaceus is characterized by the production of autoantibodies. In humans and dogs, these are directed against transmembrane proteins (desmoglein 1 in humans and a minority of dogs). The pemphigus autoantibody binds to the transmembrane protein, resulting in the release or activation of one or more proteolytic enzymes. These enzymes destroy the attachments between adjoining epidermal cells. The result is *acantholysis;* the epidermal cells assume a rounded shape and separate from one another, leading to the formation of intraepidermal clefts and vesicles.[7]

40.2.3 Clinical Signs

Pemphigus foliaceus is characterized clinically as a generalized exfoliative dermatitis (Fig. 40-1). Ventral or peripheral limb edema and crusts are the most common clinical signs.[1] In one recent study, no age, breed, or gender predilection was noted, although (80%) of affected horses first exhibited signs between September and February.[1] In the horse, lesions are usually first noted on the head, limbs, or ventrum. Initial lesions also may be associated with fever, depression, or rarely urticaria. The disease usually progresses to involve the entire body over days to weeks. The primary lesion is a pustule, but these are fragile and transient lesions. Pustules rupture soon after formation, resulting in erosions, epidermal collarettes (rings of exfoliating superficial epidermis), scale, and crust. The lesions may or may not be associated with pruritus or pain.[1,2*]

In the goat, pemphigus foliaceus also presents as a generalized exfoliative dermatitis. In the limited number of cases described, lesions were initially noted on the limbs, perineal region, and ventrum. The lesions consisted of

crusting and scaling resulting from rupture of vesicles and bullae. Pruritus and malaise appear to be variable findings.[3]

* Portions of this chapter are adapted from previous editions, which were written by Anne G. Evans, DVM.

40.2.4 Diagnosis

Diagnosis of pemphigus foliaceus in large animals is typically based on biopsy of lesions submitted for routine histopathology. Characteristic histologic findings include intragranular to subcorneal cleft and vesicle formation associated with acantholysis. Both follicular and surface epithelia are frequently involved. Neutrophils tend to predominate in the inflammatory infiltrate, although eosinophils may also be present.[1–3] Because certain strains of *Trichophyton* species of dermatophytes may also cause acantholysis, any histology suggestive of pemphigus foliaceus must be stained for fungi.[8] Direct immunofluorescence or immunohistochemistry as an aid in the diagnosis of pemphigus foliaceus in horses and goats has also been reported but is somewhat limited to research and academic institutions.[3,7,9] Indirect immunofluorescence testing (for pemphigus antibodies in serum) is reported to be unreliable for the diagnosis of pemphigus foliaceus in horses.[7,10]

40.2.5 Therapy

Treatment is corticosteroids at immunosuppressive doses, such as prednisolone at 1 mg/kg every 24 hours (q12h) or dexamethasone at 0.08 to 0.1 mg/kg q24h, then tapering. Oral prednisolone is preferred to prednisone because some horses are unable to metabolize prednisone into the active metabolite of prednisolone.[11] Injectable gold (Solganal, Schering) was also used successfully, but this product is no longer available. There are anecdotal reports of benefits using another gold salt, aurothiomalate (Myochrysine, Rhône-Poulenc Rorer), 1 mg/kg intramuscularly (IM) every 7 days. Gold salts take 1 to 3 months to reach effectiveness, when dosage frequency can be tapered to every 14 to 30 days. Adverse reactions of gold salts, although rare in the horse, include thrombocytopenia and glomerulonephropathy.

There are also reports of azathioprine (1 to 3 mg/kg q24-48h) being used for various autoimmune skin diseases in horses.[12,13] A potential side effect is thrombocytopenia because horses have low levels of the enzyme thiopurine methyltransferase (TPMT),[14] which is responsible for the metabolization of azathioprine in other species, including humans. However, I have administered azathioprine (1 to 3 mg/kg for 1month, then q48h) to eight healthy horses with no deleterious effects.[15] Azathioprine is used as a steroid-sparing drug with corticosteroids, eventually to decrease the steroid needed. Approximate cost in a 500-kg horse for daily azathioprine is $300/month.

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Fig. 40-1 Pemphigus foliaceus in a horse; note generalized crusts.

Goats have also been treated successfully with corticosteroids (dexamethasone, prednisolone) and aurothioglucose.[3,4,9] Dosages approximate those for the horse.

40.2.6 Prognosis

The response to treatment in equine pemphigus foliaceus varies from patient to patient. Many horses require lifelong administration of medication to control the clinical signs; others may be gradually weaned from medication without further relapse. In one study in which follow-up information was available for 13 horses, four were euthanized because of complications from the disease or its treatment. The reported cases of caprine pemphigus foliaceus are insufficient in number to establish a prognosis reliably.

40.3 BULLOUS PEMPHIGOID

Bullous pemphigoid is an autoimmune, vesiculobullous, and ulcerative disorder that affects the cutaneous basement membrane zone (BMZ). It has been rarely noted in horses.[7,16] Initiating triggers for the disease in the horse are unknown.

The pathophysiology of bullous pemphigoid in horses is assumed to be similar to that described in other mammals. Complement-activating anti-BMZ antibodies bind to a glycoprotein antigen in the lamina lucida of the BMZ. In horses, this has been shown to be bullous pemphigoid antigen II (also called collagen XVII). Complement activation results in degranulation of mast cells and chemotaxis of neutrophils and eosinophils. Eosinophils release tissue-destructive enzymes with resultant injury to the BMZ, loss of dermoepidermal adherence, and subsequent blister formation.[7]

Equine bullous pemphigoid is characterized clinically by painful, crusted, or ulcerative lesions of the skin (face and axillae), mucous membranes, and mucocutaneous junctions. Bullae are rare.[7,16] Ulceration may involve the gastrointestinal (GI) tract. The diagnosis is based on histopathologic and, when available, immunofluorescent findings. Treatment is the same as for pemphigus foliaceus; the few cases reported have not had favorable outcomes, but I have seen a case that initially responded well to corticosteroids.

40.4 HYPERSENSITIVITY DISORDERS

STEPHEN D. WHITE

40.5 ATOPIC DERMATITIS

40.5.1 Definition and Etiology

Atopic dermatitis may be defined as an abnormal immunologic response to environmental allergens, such as pollens, barn dust, and molds. It is increasingly being recognized as a cause of pruritus in horses. The disease may be seasonal or nonseasonal, depending on the allergen(s) involved. Age, breed, and gender predilections have not been extensively reported. A familial predisposition may be present.[17]

The presumed etiology is a type I (immediate) hypersensitivity response, mediated by immunoglobulin E (IgE). Although evidence indicates that atopic horses do produce allergen-specific IgE,[18] etiology is largely extrapolated from other species. The IgE is presumed to be directed against specific allergens. When that allergen is bound to two or more IgE antibodies on the surface of a mast cell, the mast cell releases granules containing various substances that cause erythema, vascular leaking, and pruritus.

40.5.2 Clinical Signs

Pruritus, often affecting the face, distal legs, or trunk, is the most common clinical sign. Alopecia, erythema, urticaria, and papules may all be present. Urticarial lesions may be severe but nonpruritic. Horses may have a secondary pyoderma, typified by excess scaling, small epidermal collarettes, or encrusted papules (“miliary dermatitis”). Diagnosis of atopic dermatitis is based on clinical signs and the exclusion of other diagnoses, especially parasite *(Culicoides)* allergy.

40.5.3 Diagnosis

Diagnosis is based on clinical signs and exclusion of other pruritic skin disease. Confirmation to formulate allergen-specific immunotherapy (ASIT, “hyposensitization”) is based on either intradermal testing (IDT) or serum allergy tests. The IDT involves a series of intradermal injections of aqueous allergen extracts along with a positive (histamine) and negative (saline) control. The injections are usually performed over the lateral cervical or thoracic region. The injection sites are then observed for 30 minutes to 24 to 48 hours for evidence of wheal formation associated with the injection site. A positive reaction does not necessarily mean that the horse's clinical signs are caused by the reacting allergen, but rather that the horse has antibodies to the allergen that, on intradermal exposure, trigger those clinical signs. False-negative IDT reactions may occur, the most important cause of which is the use of corticosteroids, antihistamines, or phenothiazine tranquilizers before testing.

Thus, although horses with atopic dermatitis generally have a higher incidence of positive reactions than healthy horses, the diagnosis (as in other species) cannot be solely made on the basis of the IDT or serologic test alone; rather, these tests should be interpreted in light of the history of the disease; for example, a horse with seasonal signs is more likely to have an allergic response to seasonal allergens (pollens in summer, barn dust in winter). This interpretation thus will help the clinician determine which allergens might be relevant in hyposensitization, should the owners choose that treatment.[18–21]

There is continuing controversy in the horse (and other domestic species) in regard to IDT versus the serologic tests available. These tests look for the allergen-specific IgE in the animal's blood.[22] I have used serologic tests as the basis for determining the allergens to be used for hyposensitization when the owner did not want the horse shaved for the IDT or the horse was receiving antihistamines. Preferentially, IDT and/or serologic testing is performed on horses with atopic dermatitis and with owners who are interested in pursuing hyposensitization. It should be remembered that in regard to food allergy, neither serologic testing nor IDT likely has any relation to reality. Clinical research is ongoing to determine the most important allergens, their testing dilutions, and effective control substances.[23,24]

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40.5.4 Therapy

Corticosteroid treatment is usually effective in the control of pruritus or urticaria resulting from atopic dermatitis. The usual oral medication used is prednisolone (1 mg/kg q24h), although dexamethasone (0.05 mg/kg q 24h) may also be used. The injectable dexamethasone solution may be used orally, although the clinician should remember that the bioavailability is 60% to 70% of the injectable route.

Corticosteroids in horses may cause various adverse effects, including steroid hepatopathy, laminitis, and iatrogenic hyperadrenocorticism. Therefore, other modalities of treatment may be used, such as the antihistamines hydroxyzine pamoate (200 to 400 mg/500 kg q12h), or cetirizine (0.2 mg/kg q12h), doxepin (a tricyclic antidepressant with antihistaminic effects; 300 to 600 mg/500 kg q12h), or diethylcarbamazine syrup (6 to 12 mg/kg q24h). Hydroxyzine, cetirizine, and doxepin may cause either drowsiness or nervousness, although these adverse effects are uncommon. Some clinicians have noted improvement when an essential fatty acid (EFA) product is added to the feed; Platinum Performance has been used successfully in some atopic horses as an adjunctive treatment.*

In general, hyposensitization injections for any manifestation of atopic dermatitis in the horse should be evaluated for efficacy for at least 12 months. The veterinarian should maintain consistent communication with the client to monitor the progress of treatment and encourage the owner to continue with the injections for the full year. If hyposensitization is successful, it is thought that, as in other domestic species, most horses will need to be maintained on the injections for life, although sometimes at a reduced frequency (one to three times monthly). Approximately 70% of the owners of atopic horses at the Veterinary Teaching Hospital, School of Veterinary Medicine, University of California, Davis (UCD), that have had IDT or serologic testing have elected to try hyposensitization. In general, I find that approximately 60% to 70% of atopic horses improve with hyposensitization[25]; other researchers have reported even better results, but in a noncontrolled study.[26]

40.5.4.1

Box 40-1 Possible Causes of Urticaria in Horses and Ruminants

40.5.4.1.1

ALLERGIC URTICARIA

40.5.4.1.1.1

Inhalants

Pollens, animal danders, mold spores, feather down, aerosols, smoke, dust, and volatile chemicals

40.5.4.1.2

Injectants

Drugs, diagnostic agents, vaccines, insect stings, serums, and blood

40.5.4.1.3

Ingestants

Drugs, various food items, beverages, and occult additive materials found in foods

40.5.4.1.4

Infections

Foci of bacteria, fungal, viral, and parasitic infections

40.5.4.1.5

Contactants

Animal products, plant materials, cosmetics, plastic, and other chemicals

40.5.4.1.6

Drugs

Penicillin, aspirin, quinine, sulfonamides, insulin, and many others

40.5.4.1.7 Milk Proteins

Milk retention (cattle)

40.5.4.1.8 URTICARIA CAUSED BY URTICARIOGENIC MATERIALS

40.5.4.1.8.1 Drugs

Cocaine, morphine, codeine, atropine, quinine, thiamin, pilocarpine, polymyxin B, D-tubocurarine, dextran, dehydrocholate sodium (Decholin), and other drugs

40.5.4.1.8.2 Foods

Certain citrus fruits, strawberries, and certain fish

40.5.4.1.8.3 Toxins

Cobra venoms, jellyfish toxin, and certain plant and insect toxins

40.5.4.1.9 PHYSICAL URTICARIA

Dermographic (induced by blunt-scratch injury)

Heat

Cold

Light

Erythema multiforme

Pemphigus foliaceus

40.5.4.1.10 SECONDARY URTICARIA

Infections

Collagen vascular disease

	Neoplasia
	Psychogenic

* Platinum Performance, Inc; Buellton, Calif; Dr. W. Rosenkrantz, personal communication, 2004.

40.6 URTICARIA

40.6.1 Definition and Etiology

Urticaria is characterized by transient focal swellings in the skin or mucous membranes called *wheals,* which represent localized areas of dermal edema. Angioedema is essentially identical but involves the subcutaneous tissues. The swelling of angioedema is diffuse, often involving the entire face and neck of the animal.

Urticaria is more frequently recognized in the horse than in ruminants. *Allergic* urticaria is usually caused by atopic dermatitis (environmental allergens such as pollens),[17,20,21,27] drug eruptions (especially antibiotics and nonsteroidal antiinflammatory drugs), contact allergies, and food allergies (rarely).[7]

Physical urticarias are less common and involve a nonimmunologic pathogenesis. The three most important categories include mechanically induced, such as dermatographism, essentially a "pressure" urticaria; cold urticaria; and exercise-induced urticaria. Miscellaneous diseases that can cause urticaria include dermatophytosis (initial lesions),[28] pemphigus foliaceus, "stress" (sometimes seen in racehorses immediately before a race), and vasculitis (Box 40-1). Urticaria is a recognized manifestation of milk allergy in cattle.[29]

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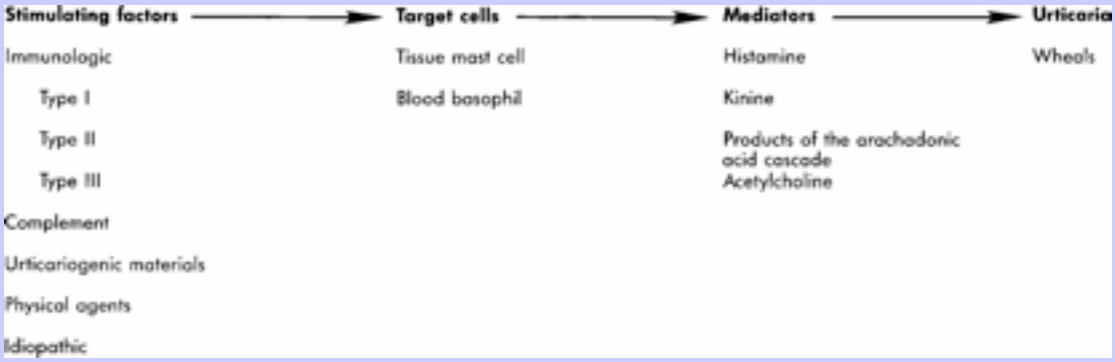
Fig. 40-2 Flow of pathophysiologic events in the development of urticaria.



40.6.2 Pathophysiology

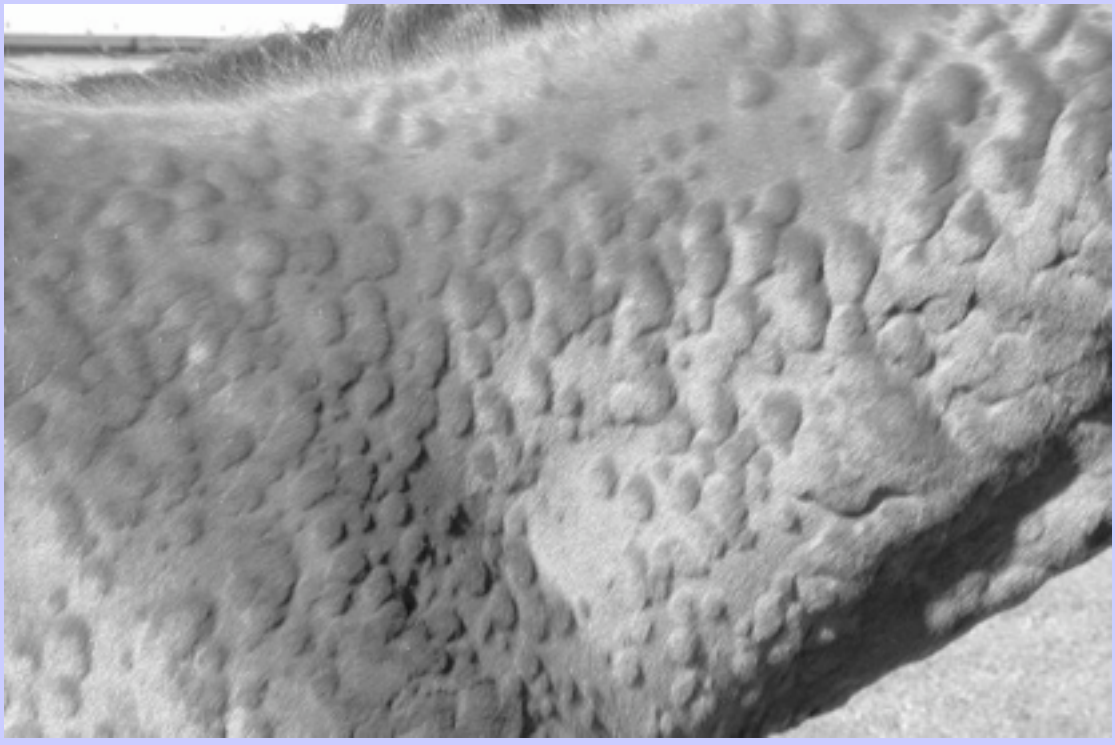
The wheals result from vasodilation and transudation of fluid from capillaries and small blood vessels. Both immunologic and nonimmunologic factors can trigger the release of mediators from mast cells and blood basophils that will ultimately produce the characteristic wheals (Fig. 40-2). The most frequently cited immunologic mechanism of urticaria is a type I hypersensitivity (IgE). Non-IgE-dependent, immune-mediated urticaria may be induced by either type II (cytotoxic, involving antibody and complement) or type III (immune

complex) hypersensitivity reactions. Complement-activated urticaria may involve either immunologic or nonimmunologic mechanisms and may occur through either the classic or the alternative pathway. Urticariogenic materials can induce wheal formation without involving immunologic mechanisms by being ingested, injected, or contacting the animal. Physical agents, including mechanical injury, thermal changes, and solar radiation, may induce urticaria. An example of mechanically induced urticaria is *dermatographism* (whealing after blunt scratch injury to the skin). Local or generalized exposure to heat or cold may induce urticarial lesions in certain individuals.

40.6.3 Clinical Signs and Differential Diagnosis

Wheals range from 1 to 10 cm (0.4 to 4 inches) in diameter and tend to involve the cervical and craniolateral thorax (Fig. 40-3). The animal may or may not be pruritic. Alopecia is not usually a feature of urticaria. The most important factor in distinguishing urticaria from other nodular diseases is that the individual lesions pit with pressure. This is easily demonstrated in the early stages of wheal formation, when the lesions consist primarily of dermal edema. In the later stages, when there is cellular infiltration into the dermis, the pitting is less apparent.

Fig. 40-3 Acute urticaria in a horse caused by an adverse drug reaction.



40.6.4 Diagnosis

Urticaria is usually a clinical diagnosis; the diagnostic dilemma is to determine the *cause* of the urticarial eruption. A skin biopsy not only will lend support to the clinical diagnosis of urticaria, but also may show

evidence of pemphigus foliaceus, dermatophytosis, or vasculitis, Initiation of ectoparasite control, IDT or serologic tests for atopic dermatitis, and feed trials may all be used to determine the underlying disease.[27]

40.6.5 Therapy

Avoiding the allergen/initiating factor or treating the underlying disease is the best therapy. When this is not possible or when the allergens cannot be identified, medical therapy should be used, as described under Atopic Dermatitis.

40.7 MILK ALLERGY

The principal cutaneous manifestation of milk allergy is urticaria and is usually seen in cows during the drying-off period. Increased intramammary pressure presumably causes milk proteins to gain access to the circulation, where they induce a type I hypersensitivity reaction.[30] The disorder is believed to be hereditary and familial, with cattle of the Channel Island breeds demonstrating increased susceptibility.

The urticarial reaction can be localized or generalized. Other clinical signs that may be noted include muscle tremors, respiratory distress, restlessness, ataxia, dullness, and even maniacal behavior. Diagnosis is made by observing an edematous swelling at the site of an intradermal injection of the cow's milk or the milk protein casein diluted 1:1000, in combination with the appropriate clinical signs.[30,31]

Treatment involves the use of antihistamines early in the course of the disease. Prevention requires avoiding milk retention. An affected cow is likely to suffer recurrences of milk allergy, so culling is usually recommended.

40.8 ERYTHEMA MULTIFORME

Erythema multiforme (EM) has been recognized clinically in the horse and in one bull (Fig. 40-4). This is an immunologic reaction in the skin, and programmed keratinocyte cell death (apoptosis) is the prominent change seen on biopsy. The keratinocytes may be killed specifically by killer lymphocytes. The many possible etiologic factors include infectious diseases, drugs, systemic disease, and neoplasia. In the horse, drugs are probably the most frequent inducers of EM, although in many cases an underlying disease is undiagnosed.[32,33] In one bull the EM may have been caused by a pyelonephritis found on necropsy.[34] Clinical lesions are characterized by macules, papules, urticarial lesions, or vesicular bullous lesions. Individual lesions may expand peripherally, leading to the formation of target-like lesions. Scaling and crusting are usually not a feature of equine EM, unless the disease is characterized by erosions or ulcers. Individual lesions can persist for several days, unlike urticarial lesions. Pruritus and pain are variable but usually are not seen. Lesions may occur in association with or after an infection or drug administration. The late Dr. A.A. Stannard of UCD had theorized that reticulated and hyperesthetic leukotrichia may also represent a type of EM in the horse.[33] Interestingly, a similar disease, toxic epidermal necrolysis, has rarely been reported in cattle.[34a]

Fig. 40-4 Erythema multiforme in a horse.

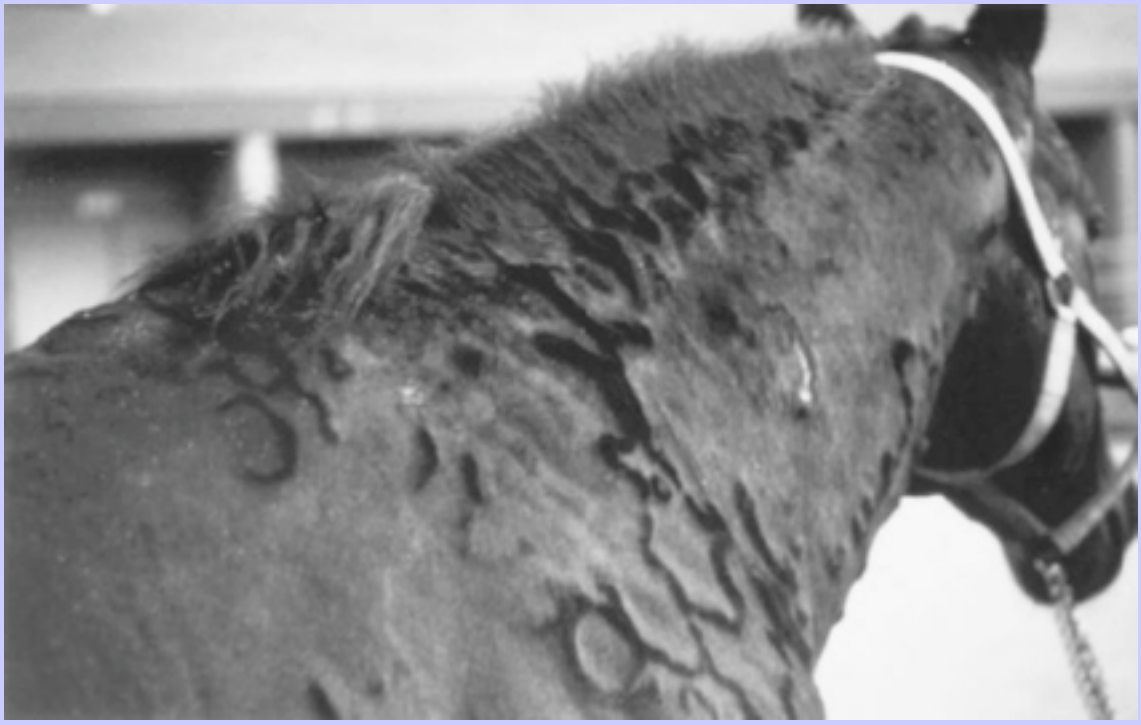


Fig. 40-5 Cutaneous vasculitis in a horse. **A,** Vasculitis involving the forelimbs. **B,** Vasculitis involving the mucous membranes of the inner lip.

Differential diagnoses include urticaria, amyloidosis, and other nodular papular diseases. The diagnosis is made on history, physical examination, and skin biopsies. The histologic changes are distinctive and often include a lichenoid pattern with keratinocyte apoptosis. Vesicular lesions may be present and can include more confluent areas of keratinocyte destruction, with massive spongiosis and subepidermal and intraepidermal edema.

Treatment should be directed toward the underlying cause, if one can be found. A drug eruption should be high on the list, and searching the history for recent drug administration is important. Although some cases of EM are self-limiting and may resolve within 1 to 3 months,[32] corticosteroid treatment as for pemphigus foliaceus may be tried. In my experience, reticulated leukotrichia does *not* resolve spontaneously and does not respond to corticosteroids.

40.9 VASCULITIS

Vasculitis is a histopathologic term that implies the presence of inflammatory changes in the walls of blood vessels, and it is associated with a broad spectrum of disorders. *Cutaneous vasculitis* is recognized in horses and is most often seen as a feature of drug reactions, urticaria, photoactivated/leukocytoclastic vascultitis, or purpura hemorrhagica. Affected vessels may be limited to the skin or may involve other organs, resulting in systemic disease. The cutaneous lesions are characterized by purpura, necrosis, and ulceration, most often affecting the head and extremities (Fig. 40-5).

Pastern leukocytoclastic vasculitis (photoaggravated vasculitis) seems to be more common (if poorly understood) in California and the western United States as a clinical entity. It generally affects mature horses and produces lesions confined to the lower extremities that lack pigment. Lesions are multiple and well demarcated, with the medial and lateral aspects of the pastern the most common sites. Initially, erythema, oozing, crusting, erosions, and ulcerations develop, followed by edema of the affected limb(s). Chronic cases may develop a rough or "warty" surface. The pathogenesis is uncertain; an immune complex etiology has been suggested, and lesions being restricted to nonpigmented areas suggests a role for ultraviolet (UV) radiation. Drug reactions may be a potential cause.[33] A recent report also implicated *Staphylococcus intermedius*.[35]

The differential diagnosis is photosensitization, particularly that caused by contact. The diagnosis is confirmed by skin biopsy, which demonstrates leukocytoclastic vasculitis with vessel wall necrosis and thrombosis involving the small vessels in the superficial dermis. These changes may be difficult to demonstrate.

Treatment involves corticosteroids at relatively high doses (prednisolone at 1 mg/kg q12h or dexamethasone at 0.08 to 0.2 mg/kg q24h) for 2 weeks, then tapered over the next 4 to 6 weeks. Reducing UV light exposure is helpful, either by bandaging affected legs or stabling inside during daylight hours, or both. In some cases, topical corticosteroids (e.g., betamethasone valerate cream 0.1% or triamcinolone spray 0.015%) may enable the horse to be weaned off systemic corticosteroids. I have also used pentoxifylline (8 to 10 mg/kg q12h) as an adjunct treatment in one case, to good effect. Another alternative (but more expensive) is 0.1% tacrolimus ointment q24h (Protopic, Astellas Pharma US). This disease does not usually recur, which downplays sunlight's role in its initiation. These horses are prone to secondary bacterial infections, and a month of antibiotic treatment (usually trimethoprim-sulfa) is often indicated if the horse has fever or if the legs are extensively swollen.

Cutaneous vasculitis seemingly is rare in ruminants; one report in calves describes lesions on the forelegs and ear tips occurring within a month on one farm. Histology showed a fibrinous-necrotic or leukocytoclastic vasculitis. Glucocorticoid (prednisolone) therapy was effective.[36]

Vasculitis and purpura hemorrhagica are discussed in more detail in Chapter 37.

40.10 DRUG ERUPTION

A drug eruption is a cutaneous reaction to any agent that enters the circulation by ingestion, injection, inhalation, or percutaneous absorption. Drug eruptions may or may not be associated with systemic signs. Many drug eruptions are thought to be immunologically mediated hypersensitivity reactions, although on occasion they may occur with the initial administration of a drug and therefore without any prior sensitizing exposure characteristic of an immunologic reaction. Drug eruptions may also occur after years of repeated asymptomatic exposure to a drug, although this is probably less common than formerly supposed. Any medication can cause a drug eruption, but the compounds most frequently incriminated include antibacterial agents (especially semisynthetic penicillins and the sulfas), phenothiazine tranquilizers, nonsteroidal antiinflammatory drugs (NSAIDs) and antipyretics (especially phenylbutazone), local anesthetics, and anticonvulsants. In general, the more recent a drug has been given, the more likely it may be the cause of a skin disease; the clinician should try to determine a temporal association between administration of the drug and the skin disease.

Fig. 40-6 Drug eruption in a horse; note pruritus.

Because drug eruptions can result in a wide variety of cutaneous manifestations, they must be considered in the differential diagnosis of all skin disorders. Certain clinical symptoms are more often associated with drug eruptions. Urticaria and angioedema, diffuse erythema, papular rashes, intense pruritus that is poorly responsive to

corticosteroids (Fig. 40-6), sharply demarcated ulcers secondary to vasculitides, vesicular and bullous eruptions, and photosensitization should arouse clinical suspicion of a drug eruption. Typically, cutaneous lesions are noted 24 to 48 hours after drug administration, although there may be a longer lag interval. The eruption usually subsides within 24 to 48 hours after exposure ceases, although lesions may persist up to 6 months after the offending agent is eliminated.[33]

A diagnosis of drug eruption is based on clinical suspicion associated with an incriminating history of drug administration and by ruling out other possible causes. In a suspected case, all medications should be discontinued. If lifesaving medications are being administered, a chemically unrelated compound with similar pharmacologic effects should be substituted. Administration of corticosteroids may provide some relief, but drug eruptions are variably responsive to corticosteroids. Although development of a cutaneous reaction after readministration of the suspected agent would support a diagnosis of drug eruption, readministration is not advisable because it can be fatal. Future exposure to any implicated compounds and chemically related substances should be avoided.

40.11 CONTACT DERMATITIS

40.11.1 Definition and Etiology

Contact dermatitis is recognized in both horses and ruminants and can be subdivided into irritant and allergic contact dermatitis. *Irritant* contact dermatitis occurs more often and is defined as a cutaneous reaction to an irritating concentration of an offending agent. The substance chemically damages the skin without immunologic mediation. The reaction may occur after a single contact with a strong irritant or after repeated contacts with a milder irritant. *Allergic* contact dermatitis represents a cutaneous reaction in a sensitized animal to a nonirritating concentration of the offending agent. Tissue damage is immunologically mediated by delayed-type hypersensitivity (type IV); thus prior exposure is required to sensitize the skin to the material eliciting the dermatitis.[7,29] It may be difficult to differentiate between the two types of contact dermatitis, and it may not be clinically important. In my experience the vast majority of contact dermatitis cases are iatrogenic, caused by topical products placed on the skin by veterinarians or owners.

40.11.2 Clinical Signs

The clinical lesions associated with allergic and irritant contact dermatitis are very similar. Predisposed areas include the muzzle, the extremities, and the areas contacted by tack. Early lesions include erythema, edema, and vesiculation, which progress to erosions, ulcerations, and crusting and ultimately to lichenification and hyperpigmentation. A gravity-induced drip pattern may be evident when the irritant is a liquid.[37]

40.11.3 Diagnosis

Patch testing is possible but usually impractical. Provocative exposure is the most useful test for diagnosis of contact dermatitis, although it does not reliably distinguish between allergic and irritant contact dermatitis. Provocative exposure requires avoiding contact with all suspected agents for 7 to 10 days to permit clearing of the skin lesions. The patient is then reexposed to these agents on an individual basis at 7- to 10-day intervals while being observed for recurrence of the dermatitis. When a positive reaction is observed, challenge with the suspected agent should be repeated to confirm the diagnosis. The process is time-consuming, requiring patience and cooperation from the owner.

40.11.4 Therapy

An animal with a suspected or confirmed diagnosis of acute or irritant contact dermatitis should be placed in an environment where there is negligible chance of exposure to agents that might have produced the dermatitis. Symptomatic treatment pending spontaneous resolution includes gently washing the affected regions with water. Pentoxifylline at the dose noted earlier for vasculitis may be helpful in horses.

40.12 BACTERIAL DISEASES

STEPHEN D. WHITE

40.13 DERMATOPHILOSIS (STREPTOTHRICOSIS, RAIN SCALD, LUMPY WOOL, STRAWBERRY FOOT ROT)

40.13.1 Definition and Etiology

Dermatophilosis is caused by an actinomycete bacterium, *Dermatophilus congolensis*. The organism is a gram-positive, non-acid-fast, branching, filamentous, aerobic bacteria that divides longitudinally and then transversely to form parallel rows of coccoid zoospores. Dermatophilosis affects horses, cattle, sheep, and goats, as well as a wide host range of other mammals.[38–41]

Three conditions must be present for *Dermatophilus* to manifest itself: a carrier animal, moisture, and skin abrasions. Chronically affected animals are the primary source of infection; however, they become a serious source of infection only when their lesions are moistened, which results in the release of zoospores, the infective stage of the organism. Mechanical transmission of the disease occurs by both biting and nonbiting flies, ticks, and possibly fomites. Because normal healthy skin is quite impervious to infection with *D. congolensis*, some predisposing factor that results in decreased resistance of the skin is necessary for infection to occur, especially prolonged wetting of the skin by rain. The organism has only recently been isolated from the environment of affected animals. Although the distribution is worldwide, the frequency of occurrence of dermatophilosis varies with geographic location. There is no apparent age, breed, or gender predilection.

Fig. 40-7 Dermatophilosis *(Dermatophilus congolensis)*. **A,** Horse with suppurative crusts and matted hair on the back. **B,** Scaling and crusting over withers and neck of a bovine.

40.13.2 Clinical Signs

Dermatophilosis is usually seen during the fall and winter months, with the dorsal surface of the animal most often affected (Fig. 40-7). In horses, this association with the wetter months of the year has led to the term “rain scald.” Occasionally the lesions involve the lower extremities when animals are kept in wet pastures (“dew poisoning”) or if horses are left in the stall while the stall is cleaned with high-pressure water hoses. In the early stages of disease the lesions can be felt easier than they can be seen. Thick crusts can be palpated under the hair coat. Removing the crusts and attached hair exposes a pink, moist skin surface, with both the removed hair and the exposed skin assuming a paintbrush shape. The undersurface of the crusts are usually concave, with the roots of the hairs protruding. In cattle and goats the older term “cutaneous streptothricosis” is sometimes used. In sheep the condition is referred to as “lumpy wool” or “mycotic dermatitis” when wooled areas are affected and “strawberry foot rot” when the distal extremities are involved.

Body areas predisposed to infection include those that are most susceptible to maceration and trauma. The distal extremities, muzzle, and entire length of the dorsum are frequently the initial sites of infection. Nonpigmented skin is also reported to be more susceptible to infection. Horses develop lesions in areas rubbed by tack, and cattle often have involvement of the udder and scrotum. Goat kids reportedly have a tendency to develop lesions on the pinnae and under the surface of the tail. Sheep may develop a form of dermatophilosis that begins as an encrusted, proliferative dermatitis at the coronet region; removal of the external crusts reveals a pink-red granulation bed that resembles the surface of a strawberry. Lesions can extend from the hoof to the hock, and with loss of the crusts, ulceration occurs. Under appropriate conditions, dermatophilosis can become generalized.

40.13.3 Diagnosis

Diagnosis is made by demonstrating the “railroad track” cocci on impression smears. A portion of one of the crusts should be minced and mixed with a few drops of sterile water on a glass slide, Gram stained, and examined microscopically. Alternatively, bacterial culture or histopathology may be used for diagnosis, particularly in chronic cases. A thick crust composed of alternating layers of parakeratotic stratum corneum, dried serum, and degenerating neutrophils is the most characteristic change. A superficial folliculitis may be a prominent feature of the disease.[38] In Gram-stained sections the branching, filamentous organisms can be observed in the crusts and in the follicles.

40.13.4 Therapy

The animal should be removed from the wet environment, if possible. Careful removal of possibly painful crusts, washing with iodophors or lime sulfur, and administration of antibiotics (for horses, 22,000 mg/kg procaine penicillin G intramuscularly twice daily, or 30 mg/kg trimethoprim-sulfa orally twice daily) for 7 to 10 days.[41] Long-acting oxytetracycline given as a single 20-mg/kg intramuscular dose has been reported to be effective for bovine and ovine dermatophilosis. The crusts are important in contagion, so these should be disposed of rather than brushed to the ground.

40.14 FOLLICULITIS/FURUNCULOSIS AND IMPETIGO

40.14.1 Definition and Etiology

Bacterial *folliculitis* (superficial pyoderma) is defined as inflammation of the hair follicles secondary to a bacterial infection. *Furunculosis* is the term used to describe a follicular infection that breaks through the follicular wall ("boil"). Bacterial infection that causes subcorneal pustules but does not involve the hair follicles is called *impetigo*. Folliculitis and furunculosis are often seen in horses[28,38,41] and goats[40] but are an uncommon problem in cattle and sheep. Impetigo is relatively common in cattle and goats.

Bacterial folliculitis is usually caused by a coagulase-positive *Staphylococcus* species. Both *S. aureus* and *S. intermedius* have been isolated.[28,42] In one study in horses, *S. aureus* accounted for twice as many isolates as *S. intermedius;* the same study isolated some strains of *S. hyicus* as well.[43] Many isolates are resistant to penicillin G.[43] Occurrence of pyoderma has been linked to poor nutrition and husbandry in some cases.[44]

40.14.2 Clinical Signs

Clinical signs of staphylococcal pyoderma are most often crusts, usually in a circular pattern suggestive of dermatophytosis (this may be the reason that equine pyoderma is underdiagnosed), epidermal collarettes (circular skin lesions with an exfoliative border as seen in dogs with superficial pyoderma), or encrusted papules similar to the miliary dermatitis reaction pattern in cats.[28] These infections tend to vary in intensity of pruritus. Histology often shows folliculitis and furunculosis, but bacterial colonies are not always seen. A truncal form of bacterial folliculitis (contagious acne, contagious pustular dermatitis, Canadian horsepox) is often associated with poor grooming and trauma from tack and saddle, warm wet weather, and heavy work. It is painful and interferes with working and riding. It is usually caused by a coagulase-positive *Staphylococcus* species but may also result from *Corynebacterium pseudotuberculosis*[45] (more often a cause of deep pyoderma, as discussed later). In horses, folliculitis often develops in the saddle and lumbar region, particularly in the summer. The affected area initially may be swollen and sensitive, followed by formation of follicular papules and pustules. These may become confluent or may rupture, forming plaques and crusts. Deep pyoderma followed by ulceration may develop over large areas of the body, especially the neck, sides of the thorax, inner surface of the thighs, and prepuce.

A pastern bacterial infection (pastern folliculitis) is often seen. Again, the causative agent is usually a coagulase-positive *Staphylococcus* species. As with most "primary pyodermas," the mechanism by which the organism gains its foothold is unknown; it is not contagion or poor sanitary conditions. The lesions are usually limited to the posterior aspect of the pastern and fetlock regions; one or more limbs may be involved. The initial lesions consist of papules and pustules. If left untreated, the lesions coalesce and may produce large areas of ulceration and suppuration, which may be quite painful. The disease is usually not associated with systemic signs, and the general health of the horse is not affected.

A relatively uncommon nodular disease termed *botryomycosis* mimics actinomycosis or a deep fungal infection but is most often caused by *Staphylococcus* species in the horse. These may require surgical excision as well as long-term antibiotics.

40.14.3 Public Health Considerations

In a 2000 study, methicillin-resistant, coagulase-negative staphylococcal species were cultured from healthy horses in Japan; the authors concluded, "These organisms must be considered a potential threat to horses and veterinarians who care for them."[46] In a 2006 study from the Netherlands, methicillin-resistant coagulase-negative staphylococci were found frequently.[47] The organism was usually *Staphylococcus sciuri*, as opposed to *S. epidermidis,* which was found in the humans in close contact with these horses. No methicillin-resistant *Staphylococcus aureus* (MRSA) was found in healthy horses.

In contrast, a single strain of MRSA was isolated from *both* humans (13%) and horses (4.7%) on horse farms in Canada and New York state.[48] In looking at horses admitted to a university teaching hospital (Ontario Veterinary College), MRSA was isolated from 120 (5.3%) of 2283 horses. Of these 120 horses, 50.8% were positive at admission, and clinical infections attributable to MRSA were present or developed in 14 animals. Horses colonized at admission were more likely to develop clinical MRSA infection. Administration of ceftiofur or aminoglycosides during hospitalization was the only risk factor associated with nosocomial MRSA colonization. Another strain of MRSA was isolated from a small number of horses at the Veterinary University, Vienna, Austria.[49]

Of most concern is the finding of humans reporting skin lesions after contact with a community MRSA-positive affected foal, despite short-term contact with standard protective barriers. The isolates from the foal were indistinguishable from those affecting humans.[50]

40.14.4 Therapy

The antibiotic usually used for bacterial skin infections in the horse is trimethoprim-sulfamethoxazole (TMS) orally (PO, 30 mg/kg q12h for 2 to 6 weeks, longer for deep infections).[7,28] Interestingly, dosing intervals for intravenous (IV) administration of TMS in horses may not be appropriate for use in donkeys or mules. Donkeys eliminate the drugs rapidly compared with horses.[51] In cases of staphylococcal resistance to TMS, enrofloxacin or doxycycline may be used. Doxycycline is less expensive, but is associated with a higher incidence of colic. Dosage is usually 10mg/kg q12h. Off-label use of oral enrofloxacin formulations for poultry, ruminants, or swine has been suggested; a dose for the poultry formulation has been suggested as 7.5 mg/kg PO once daily. The formulation for poultry may be used; the dose is 7.5 mg/kg PO once daily. Use of enrofloxacin in young horses (<2 years old) should be avoided because of concerns about damage to the articular cartilage.[52] A recent report of the usage of an oral gel formulation of enrofloxacin (100 mg/mL of gel) showed good clinical efficacy for infections in several organs; however, almost one-third of the horses had some diarrhea, and 10% had oral lesions.[53] The authors believed that this latter side effect could be overcome with a tap water rinse of the oral cavity after administration. Interestingly, enrofloxacin binds to melanin in equine hair, although the clinical implication is unknown.[54] Ceftiofur sodium 2.2 mg/kg, q12-24h, IM or IV, may also be used for pyoderma in horses, although its usefulness over a long period is limited by its parenteral route. In one report of 15 horses, vancomycin was used, alone or in combination with an aminoglycoside, to treat MRSA and enterococcal infections. The average vancomycin dosage was 7.5 mg/kg q8h IV over 30 minutes. The antibiotic, alone or in combination with an aminoglycoside, was safe and effective. Because of the problems with emerging resistance, the authors recommended vancomycin use in horses be limited to cases in which culture and susceptibility indicate effectiveness and no reasonable alternative treatment exists.[55]

For localized lesions, mupirocin ointment 2% or silver sulfadiazine cream (Silvadene) may be effective. As shampoos, ethyl lactate (Etiderm, VIRBAC, Fort Worth, Texas) or chlorhexidine (2% to 4%) are helpful.

Pyoderma in ruminants has not been studied as much as in horses. In goats, lesions (often pustules that progress to crusts) usually begin on the udder and spread to the abdomen, thigh, perineum, and face. Pruritus is variable. Stress from parturition is also an important predisposing factor in goats. In sheep a generalized, staphylococcal, scalded skin—like disease has been reported in lambs.[56] In addition, staphylococcal infections in association with *Psoroptes ovis* infestation have been noted.[57,58]

In cattle, furunculosis caused by *C. pseudotuberculosis* manifests as a locally extensive, raised, raw lesion that is frequently hemorrhagic. The lesions are almost constantly covered with a serosanguineous exudate, and palpation of the lesions usually elicits a pain response. Treatment is similar to treatment of dermatophilosis, taking into consideration culture and susceptibility results, as well as withdrawal times for food animals.

40.15 EQUINE STAPHYLOCOCCAL CELLULITIS

Cellulitis is a severe, deep, suppurative process in which a poorly defined area of infection tends to dissect through tissue planes. Although many organisms are capable of producing cellulitis, staphylococcal cellulitis has been recognized as a specific disease entity in thoroughbred racehorses.[59] Coagulase-positive staphylococci have been isolated from all reported cases, and when speciated, the isolates were classified as *Staphylococcus aureus*.[60] Other studies of pathogenic *Staphylococcus* species from horses have suggested that *S. aureus* and *S. intermedius* are the major cutaneous pathogens,[60,61] with no significant difference in their susceptibility patterns.[60] In a recent retrospective study of limb cellulitis in 44 horses, coagulase-positive *Staphylococcus* spp were cultured from 33 of 36 horses from which specimens were obtained. Horses that were febrile at admission or that developed laminitis were significantly less likely to survive.[61a]

The cause of staphylococcal cellulitis is uncertain. Management practices may be associated with the condition because bathing, grooming devices, and handlers can be a source of the organism.[61]

The initial symptom is acute swelling and lameness that involves one or more limbs. Lesions progress rapidly by dissection along tissue planes. The overlying skin becomes devitalized and frequently sloughs. Accompanying systemic signs include increased rectal temperature and heart rate. Laminitis of either the affected or the contralateral limbs, osteomyelitis, and bacteremia are possible sequelae.[59] Diagnosis is based on the results of bacterial culture and biopsies for routine histopathology.

Treatment must be aggressive and initiated early in the course of the disease. Pending the results of bacterial culture and sensitivity, treatment should include broad-spectrum antibiotics such as potassium penicillin G and gentamicin sulfate or TMS. To decrease edema, promote weight bearing, and reduce the chance of laminitis, therapy should include NSAIDs, hydrotherapy, and support wraps.[59] The prognosis for complete recovery is guarded.

40.16 EQUINE *CORYNEBACTERIUM PSEUDOTUBERCULOSIS* CELLULITIS

Unlike equine staphylococcal cellulitis, solitary or multiple abscesses or nodules with many draining tracts that progress to diffuse cellulitis are often caused by *Corynebacterium pseudotuberculosis*; when it affects the pectoral region, it is termed “pigeon fever” in the United States. This type of deep *Corynebacterium* infection may occur

where caseous lymphadenitis is common in sheep, although proximity to sheep is not a requirement, and it also may be seen seasonally when insect population and activity are maximal. Insect vectors seem probable, especially stable, horn, and house flies.[62] The draining nodules or abscesses are especially common in the pectoral region and occasionally affect the face, neck, axilla, groin, and limbs; they begin deep and enlarge, often with much edema, and rupture in 1 to 4 weeks, discharging viscid, creamy pus, a major source of contamination. Abscesses most often rupture externally.

Diagnosis is by clinical signs, with the infection readily identified by bacterial culture of aspirate samples from abscesses. The synergistic hemolysis inhibition test is useful for diagnosis of internal abscesses but is unreliable for external abscesses.[63]

Treatment depends on location. For example, if the abscess is in the axilla and thus is painful on movement or prevents locomotion, establishment of drainage is important, and antibiotics are indicated. The antibiotics most often used are procaine penicillin (20,000 to 50,000 IU/kg/day) with rifampin (3 to 5 mg/kg PO); alternatively, TMS (30 mg/kg q12h) may be used.[64] Treatment with TMS and rifampin concurrently may lead to a greater incidence of colitis and should be avoided. If the decision is made to use antibiotics but drainage cannot be easily established (e.g., axillary abscess, with owner unwilling to allow veterinarian to use trocar and drain), the antibiotics *must* be used for a minimum of 1 month. If the abscess is solitary and not causing pain or fever, antibiotics are usually not necessary, but bringing the abscess to a head with hot packs or heat-inducing agents (ichthymol) is important. Once an abscess has drained, gentle cleaning with tamed iodines or chlorhexidine is indicated.

40.17 PAPILLOMATOUS DIGITAL DERMATITIS (DIGITAL DERMATITIS, FOOT WARTS, HEEL WARTS, HAIRY FOOT WARTS, MORTELLARO's DISEASE, STRAWBERRY HEEL WARTS)

STEVEN L. BERRY

Papillomatous digital dermatitis (PDD) of cattle is an infectious, contagious dermatitis of the digital skin of cattle. It is primarily a disease of housed dairy cattle. PDD was first described in Italy in 1974 and in New York in 1980. During the early 1990s the reported first observations of PDD increased dramatically in the United States, and this disease is a major cause of lameness in dairy cattle in many countries.[65,66] Financial losses are from reduced milk production, reduced reproductive efficiency, costs of treatment, and premature culling. European and U.S. studies estimate the cost per case to be approximately $130. Prevalence in endemically infected herds is typically 10% to 60%.

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40.17.1 Clinical Signs

About 80% of PDD lesions occur on the plantar aspect of the hindfoot, immediately proximal to the heel bulbs and adjacent to or extending into the interdigital space.[65] Less common sites for lesions are the plantar aspect of a forefoot and the dorsal aspect of any foot. Multiple lesions may exist on a single animal, even on a single foot, but lesions are confined to the digital skin and have not been reported to occur above the level of the dewclaws.[65]

The gross appearance of the lesions and the predilection for hindlimbs and skin-horn junctions, especially those bordering the heel bulbs and interdigital space, distinguish this disease from other bovine dermatitides. Lesions

are most often 2 to 6 cm (0.8 to 2.4 inches) across at their greatest dimension, are circular or oval, and have clearly demarcated, raised borders.[65,67] Lesion borders are often surrounded by hairs that are two to three times normal length. Lesion surfaces may have filiform papillae varying in length from 1 mm to 3 cm (1.2 inches) and 0.5 to 1 mm in diameter, thus the name "hairy foot warts." Lesions lacking the filiform papillae ("hairs") may have a granular surface. Lesions vary in color and appearance. Washed surfaces are generally very painful and either red and granular or composites of white, yellow, gray, brown, or black papillary areas with red, granular areas interspersed.[65] The lesions bleed easily if traumatized. When PDD lesions develop in the interdigital space, they frequently occur on a preexisting fibroma.

The lesions slowly enlarge and become raised (papillomatous) masses 2 to 6 cm in diameter that are red, gray, or black and oval, spherical, or U shaped. Proliferative or papillomatous lesions are seen less often in Europe than in the United States and are less common on dairies with a consistent treatment and control program.

A foul odor may be present and appears to be caused by secondary bacterial growth in the exudate covering the PDD lesion. Swelling of the pastern and fetlock regions is not present in uncomplicated cases. Lameness is a herd characteristic on dairies where PDD has a high prevalence but is an inconsistent finding on individual infected cattle and is not consistently related to lesion size or maturity.[68] If PDD lesions remain untreated, the claws of feet with plantar or palmar lesions may develop a clubbed appearance because the cow prefers to bear weight on (and wear down) the toes.[65]

40.17.2 Differential Diagnoses

Differential diagnoses for an individual case of PDD include interdigital necrobacillosis (foot rot, "foul in the foot," or interdigital phlegmon), interdigital hyperplasia (corns or interdigital fibroma), interdigital dermatitis, and traumatic injury with granulation tissue. For herd problems of lameness localized to the digit, differential diagnoses should include PDD, interdigital necrobacillosis, interdigital dermatitis, laminitis, excessive sole wear from caustic or abrasive flooring, and improper claw trimming. If signs of polysystemic disease exist, coronitis from viral diseases (e.g., bovine viral diarrhea) should also be considered.

40.17.3 Epidemiology

Once introduced into a herd, PDD spreads rapidly within adult cows, often affecting the majority of adults within the first year of infection.[65] When established in a herd, lameness is most often seen in first- and second-lactation cows.[65,67] Lesions are typically present in a proportion of older cows, but lameness is less apparent than in the younger cows. Bulls and yearling heifers may also be affected but usually comprise a small fraction of clinical cases. In California the disease appears to be most severe during the spring and summer months,[65] whereas in Europe it is most severe in the winter months. Free-stall herds are more often affected than stanchion (tie-stall) herds, probably because of better foot hygiene in the stanchions. Cattle confined to pasture are rarely affected,[69] but the disease is emerging in some South American countries with wet pastures during part of the year. PDD is almost exclusively seen in dairy cattle, with Holsteins more likely to be affected than Jersey or dual-purpose breeds.[69,70] Eradication of PDD from an endemically infected herd is unlikely.

Retrospective epidemiologic studies indicated that two risk factors are significant in high-prevalence herds: muddy or wet conditions and purchasing replacement cattle from off premises.[69,71,72] Other risk factors identified were the use of outside hoof trimmers and not washing hoof-trimming equipment between cows.[72]

Attempts to transmit the disease experimentally were successful when scrapings from active lesions were applied to the feet of calves subjected to constant moisture and low oxygen tension. Constant moisture and low oxygen tension are present on confinement dairies if manure management and hygiene are not adequate. Poor free-stall or bedding area management will exacerbate the problem by forcing cows to stand in manure slurry for longer periods and will not allow the feet of cattle to dry out periodically.

40.17.4 Pathogenesis

Numerous obligate anaerobic organisms have been associated with PDD.[73] Spirochetes from the genus *Treponema* have been identified most consistently.[74–78] During experimental transmission studies, *Treponema* species are the first organisms to appear, comprise the bulk of the colonizing bacterial mat found on active lesions, and are the organisms that invade the epidermis and dermis.[76] These spirochetes also produce a humoral response in cows with active lesions.[65,78] PDD lesions show gross and histologic similarities to viral papillomas; however, bovine papillomavirus has not been found.[65]

Current evidence indicates that PDD is multifactorial, involving environmental, microbial, host, and management factors. Factors such as rough flooring; poor drainage; accumulation of feces and urine on floors; dirty, wet, or uncomfortable bedding areas; and overcrowding have an adverse effect on digital skin health and could increase the risk of PDD. The mode of transmission between cows and between herds is currently unclear, although one study found concurrent spirochetal infection of feet and colon in cattle.[79] Clinically and subclinically affected cows and fomites such as foot-trimming instruments, livestock trailers, and farm equipment may be sources of infection for naive herds.

A California study found that antibodies against two antigenically distinct spirochetes were increased on dairies with PDD compared with PDD-free dairies.[78] Also, cattle with PDD on a high-prevalence dairy were much more likely to have antibodies to the spirochetes than were cattle without lesions on the same dairy.[78] There was no cross-reactivity between the two spirochetes or to other spirochetal diseases of cattle.[78] The concentration of clinical disease in the younger animals of an endemically infected herd suggests that some degree of immunity may develop in older cows. Nonetheless, chronic and recurrent cases in otherwise healthy adult cattle have been reported, and immunity to PDD, if it does develop, may be incomplete or temporary. One study found high recurrence or new lesions 7 to 12 weeks after successful treatment.[65] Spontaneous regression of lesions and resolution of lameness have also been observed but appear to be rare.

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40.17.5 Pathologic Findings

Histopathologic criteria to establish a diagnosis of PDD are as follows[65]:

- Circumscribed plaque of eroded acanthotic epidermis attended by parakeratotic papillomatous proliferation profusely colonized by spirochete-dominant bacterial flora.
- Loss of stratum granulosum.
- Invasion of stratum spinosum by spirochetes.
- Infiltration of neutrophils, plasma cells, lymphocytes, and eosinophils in the dermis.

If performed, biopsies should be full-thickness 6-mm punch biopsies, washed off with sterile saline, and placed in buffered formalin. Histopathology is helpful to confirm a diagnosis of PDD but is not necessary because lesions have such a characteristic appearance and location.

Preliminary results of a biopsy study on treatment and recurrence of PDD indicate that the gross visual and histopathologic diagnoses were in agreement for active lesions before treatment. Histopathology on day 28 after treatment with lincomycin or oxytetracycline, however, found a high percentage (55%) of lesions that visually appeared to be healed but still had microscopic evidence of infection.[80] It could not be determined if lesions were incompletely healed or recurrent infections.

40.17.6 Treatment and Prevention

The most common treatments for PDD involve the use of topical antibiotics.[68,81] There are limited reports of nonantibiotic products being efficacious, although research and development continue. Currently, no antibiotics are labeled for treatment of PDD in the United States; therefore, adherence to extralabel drug use regulations is imperative.

The most common treatment for PDD in the United States is topical oxytetracycline or lincomycin used as a spray or applied with a bandage. For topical spray treatments, oxytetracycline or lincomycin are mixed with deionized or distilled water in a 2- to 4-L agricultural sprayer (25 g/L oxytetracycline, 8 g/L lincomycin) and applied directly to the heels of PDD-affected cattle once daily for 5 to 10 days. Recurrence is sufficiently common that topical treatments need to be repeated every 45 to 60 days on affected cattle to control the disease. No antibiotic residue violations have been reported resulting from topical application of antibiotics.[82] Efficacy from parenteral antibiotics has been inconsistent.

Footbaths are often used on dairies to control PDD and other infectious causes of lameness, although most footbath products have not been rigorously evaluated.[68] Products used include antibiotics, copper or zinc sulfate (5%), formalin (5%), and various proprietary products. On large dairies, footbaths may be more effective at controlling PDD when the disease is at a low prevalence (<10%). When the disease has a high prevalence, individual topical treatment is probably more efficacious at reducing the prevalence. The efficacy of footbaths is reduced if feces and debris are allowed to accumulate in the treatment solution. This problem can be limited by placing two footbaths in tandem, with the first containing water or a mild detergent solution for cleaning the feet and the second containing the antiseptic solution. The footbath solution should be changed every 150 to 300 cow passages, depending on soiling. Footbaths should be a minimum of 8 feet long and 2 to 3 feet wide, with a depth of 5 to 6 inches so that cows have to place all four feet in the solution as they walk through. The baths should be covered to limit dilution by rain and should be located in an exit alley off of the milking parlor to avoid splash contamination of the teat ends before milking. Additional footbaths can be placed in other locations to treat bulls, dry cows, and heifers. Treatments should occur every 2 to 7 days depending on response on the individual dairy. Laws regarding the use and disposal of certain chemicals, as well as *where* on the dairy such medications can be used, often vary among locales. Consultation with local regulatory agencies is prudent before initiation of a control program on a dairy.

The efficacious use of footbaths on dairies signals major husbandry problems on dairies because the environmental and hygiene problems are often not addressed.[83] Improvement of stall, corral, and alley hygiene; provision of dry and comfortable bedding; reduction of stocking rate; and improved ventilation to allow drying of stalls and alleys may result in reduction of the incidence or severity of clinical cases. Claw-trimming

equipment, mobile tilt tables, and livestock trailers should be thoroughly cleaned and disinfected to prevent potential transmission of the agent(s) of PDD between dairies.

A *Treponema* bacterin was developed, tested, and licensed for use in the United States. A blind field study where half the lactating cows were vaccinated and half received a placebo vaccine (no *Treponema*) did not find a prophylactic or therapeutic effect of the vaccine.[84]

40.18 INTERDIGITAL DERMATITIS

Interdigital dermatitis (ID) is acute or chronic inflammation of the interdigital skin that usually does not cause lameness. Inflammation is confined to the epidermis. Diffuse epidermal erosion in the interdigital cleft may be seen in early cases. More chronic cases show hyperkeratosis, which creates a roughened appearance to the interdigital skin and dorsal and palmar commissural skin folds. A malodorous, gray, serous exudate may be present, and there is mild sensitivity to pressure. This condition is frequently accompanied by cracks in the heel *(heel horn erosion)*, with potential underrunning of the heel horn, and some researchers consider ID and heel horn erosion to be the same disease (IDHE). When severe, IDHE will cause lameness.

Dichelobacter nodosus and *Fusobacterium necrophorum* may be primary or contributory pathogens for ID. Several investigators have speculated that ID and PDD are forms of the same disease complex. Both share several histologic characteristics, including spirochetal involvement, and both can be successfully treated and prevented with the same topical antibiotics or footbaths. However, ID can persist on dairies that practice regular foot bathing because the causative organisms may survive within deep heel cracks that are not permeated by footbath solutions. During claw trimming, heel cracks must be trimmed away to allow for exposure.

Interdigital dermatitis differs from interdigital necrobacillosis (foot rot), in which infection extends into the dermis, leading to fissure formation, infection of deeper structures, and cellulitis of the pastern and fetlock regions.

40.19 VIRAL DISEASES

STEPHEN D. WHITE

40.20 PAPILLOMAS (WARTS, FIBROPAPILLOMAS)

40.20.1 Definition and Etiology

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Cutaneous papillomas or warts occur (in decreasing order of frequency) in cattle, horses, goats, and sheep.[85–88] The growths usually occur in young animals,[88] as well as on teats of mature cattle and goats, and are white, tan, or gray, firm protruding masses with a dry, horny surface. They vary in size from 1 to 500 mm and may be single or multiple. Species-specific papillomaviruses (subgroup of papovavirus) are responsible for causing warts. It is now accepted that parts of the bovine papillomavirus (BPV) genome are found in naturally occurring equine sarcoids.[89] There are at least 10 BPV strains, designated BPV-1 through BPV-10 (Table 40-1),[90] and there are probably more. Only one strain of virus is currently recognized in horses, goats, and sheep, but little research on papillomas has been done in these species, and two horse and two goat strains are likely.

Table 40-1 Distribution and Appearance of Bovine Warts by Type of Virus

Virus Strain	Usual Site	Appearance	Comments
BPV-1	Nose, teats, glans penis	Filamentous or frondlike	Can prevent breeding when on penis
BPV-2	Head, neck, brisket, occasionally alimentary tract	Pedunculated or broad-based mass	Most common typical warts
BPV-3	Atypical warts, head, neck, possibly interdigital*	Nonpedunculated protruding growths, delicate fronds with hair between	Persist for years
BPV-4	Alimentary tract, urinary bladder	Pedunculated mass	See Chapters 32 and Chapter 34
BPV-5	Teat	Smooth, white	Persist for years; other types may also occur on teats
BPV-6	Teat	Round and either flat or frondlike	Similar in appearance to BPV-1 when frondlike

Modified from Hunt E: *Vet Clin North Am Large Anim Pract* 6:163, 1984.

BPV, Bovine papillomavirus.

* Suspected, but BPV-3 not yet isolated from interdigital warts. Some authors speculate that interdigital warts may be caused by yet another new BPV strain.

40.20.2 Clinical Signs

Warts are usually small, benign growths that appear on young animals under 2 years of age, persist for 3 to 12 months, and then spontaneously regress without causing clinical signs (other than a blemish). In cattle, warts on the teats, penis, or interdigital skin[91] or in the alimentary tract may produce clinical signs of pain or occlusion. Warts usually develop in the ears of young cattle after tagging or tattooing, especially if instruments are not disinfected between individuals; these are not age related. Teat warts also predispose to environmental mastitis. Occasionally, individuals with (presumed) defective cellular immunity may develop multiple, extremely large warts that may result in weight loss.

In horses, warts on the face are rather common but rarely cause a significant problem (Fig. 40-8). The previously reported congenital wart in young horses has now been more properly termed a hamartomatous lesion (epidermal nevus) and has been shown not to be virus induced.[92]

Fig. 40-8 Typical warts (papillomas) on the nose of a yearling horse.

Warts are relatively rare in goats. They occur mainly on teats and may spread throughout the herd. A 1936 report described a herd outbreak involving the head, neck, shoulders, and forelegs in milking goats.[93] Does without adequate pigmentation on the udder develop persistent mammary gland warts that may undergo transformation to become squamous cell carcinomas.[94] There are probably at least two different strains of goat papilloma virus (head/neck and mammary).

Warts are rare in sheep but may occur on the face or legs. Differential diagnosis in sheep and goats includes contagious ecthyma (orf), ulcerative dermatosis, dermatophilosis, and sheeppox and goatpox.

40.20.3 Treatment and Control

Small warts can be crushed, pinched off, or surgically removed. Cryosurgery can be used on larger warts. Many regress spontaneously within a few months, even without treatment.

When show animals are involved or when animals have multiple large papillomas, tissue can be removed and made into crude autogenous vaccine (2 mL intradermally three times weekly) by homogenizing, grinding, freeze-thawing twice, filtering, and killing virus with 0.5% formalin. Autogenous wart vaccines are variable in their efficacy, as are commercial vaccines.[95–97] The latter rarely seem to result in effective regression of existing warts, but may prevent the development of new lesions if the same BPV strain is involved. Autogenous

vaccines are capable of preventing new lesions caused by the same BPV strain in a herd. There is no indication that cattle vaccines have any efficacy in other species. No wart vaccines for horses, sheep, or goats are currently marketed.

Because the viruses can be directly or fomite transmitted, prevention involves isolation, preventing animals from rubbing on each other, and not sharing halters, brushes, and other equipment. Dipping of dehorning, tagging, and tattooing instruments in a viricidal solution between animals will also slow spread of the virus.

40.21 AURAL PLAQUES

Aural plaques may be a form of viral papilloma that often affects the inner pinna (Fig. 40-9). Nonpruritic, these plaques may also occur on the genitalia and mammary glands. The color varies from pink to grayish-white. 1317
Plaques do not resolve spontaneously, as do the "classic" papillomas seen in young horses. Biopsy or "shaving 1318
off" aural papillomas may stimulate reduction or resolution of the masses, although in some horses, this may only be temporary (6 to 12 months). This has been theorized to be due to the release of "papilloma antigens" into the blood stream during the surgical procedure, prompting an immune response against the tumor. Imiquimod (Aldara, 3M, Minneapolis), a nonsteroidal local immune response—modifier cream, has been helpful in some cases, used three times weekly, every other week, for 2 to 4 months. Owners should wear gloves and should be forewarned that there is frequently an impressive inflammatory reaction to the cream in the initial weeks of treatment.

Fig. 40-9 Aural plaques on the inner surface of the pinna of the ear in a horse.

A papillomavirus has been demonstrated in aural plaques on electron microscopy and with immunohistochemical techniques.[98]

40.22 PSEUDOCOWPOX

Pseudocowpox is a common parapoxvirus of cattle related to the viruses of contagious ecthyma (soremouth) of sheep and goats and bovine papular stomatitis (see Chapter 32 for these diseases). All three parapoxviruses may cause nodular lesions on humans. The lesions of pseudocowpox are usually confined to the teats of cattle, and the disease is common worldwide. Cyclic waves of reinfection occur in a herd, where it causes minor teat lesions characterized initially by a small papule 2 to 3 mm in diameter, followed by crusting and circular spread of the lesion. Approximately 10 days later, the 15- to 20-mm lesion appears as a ring or horseshoe-shaped scab.[99] Lesions occasionally involve the udder, medial thighs, or scrotum. Deep ulceration is rare. There are no systemic signs of illness.[29] The major problem associated with the teat lesions is an increased incidence of mastitis. The most important and common differential diagnoses are bovine herpes mammillitis and viral papillomas. Rare viruses involving the teat include vaccinia and cowpox.[99] Cowpox is a rare disease of cattle in Europe that causes ulcers and may also produce lesions in humans. Vesiculation is rare in pseudocowpox, in contrast to bovine herpes mammillitis, vaccinia, and cowpox.[29]

40.23 BOVINE HERPES MAMMILLITIS (BOVINE HERPESVIRUS, BOVINE ULCERATIVE MAMMILLITIS)

Bovine mammillitis teat lesions are caused by bovine herpesvirus type 2 (BHV-2), which is widely disseminated in most cattle populations.[100,101] The disease may be epidemic or endemic. The virus may also cause oral lesions, udder lesions, or generalized skin disease in cattle. The teat lesions start as swollen, tender, edematous teats. Vesicles may appear in some lesions, whereas others ulcerate almost immediately. The teats become painful, and ulcers require 3 to 10 weeks to heal.[100,101] Mastitis is increased because the scabs on the teats are laden with bacteria. Diagnosis may be confirmed by isolation of the virus, the BHV-2 serum neutralization tester, or histologic demonstration of herpesvirus particles.[100,101] Therapy consists of segregation of affected animals from the rest of the herd, and affected cows should be milked last. Milkers should wash hands between cows. In severe cases, secondary infection may be controlled by topical antibiotic creams or parenteral antibiotics, with proper residue avoidance precautions in place.

40.24 SHEEPPOX AND GOATPOX

Sheeppox and goatpox are caused by capripoxviruses.[102] Both occur in Africa, Asia, and the Middle East; goatpox also occurs in parts of Europe and the United States. The two diseases are clinically similar, although sheeppox has the most severe systemic signs of the animal pox diseases. However, recent studies have showed that the viruses are phylogenetically distinct and can be differentiated by molecular tools.[103] The diseases affect all ages, causing pyrexia, anorexia, conjunctivitis, rhinitis, and skin lesions. Prophylaxis using attenuated vaccines is the preferred control measure because the immunity is long-lasting.[102,103] Morbidity is high. Mortality may reach 80% with sheeppox but usually is low with goatpox. Humans may develop skin lesions from goatpox.

40.25 FUNGAL DISEASES

STEPHEN D. WHITE

40.26 DERMATOPHYTOSIS (RINGWORM)

Dermatophytosis refers to infections of the keratinized tissues of the skin (stratum corneum layer of epidermis, hair, claws, hoof, and horns) by *Microsporum* and *Trichophyton* species. Dermatophytosis is relatively common in the horse and in cattle, less so in goats, and rare in sheep.

40.26.1 Etiology and Pathogenesis

The most common equine dermatophyte species isolated from horses are *Trichophyton equinum, Microsporum equinum, Trichophyton mentagrophytes,* and *Trichophyton verrucosum*.[7,28,104] *T. verrucosum* infections in humans caused by transmission from horses have been reported.[105] In ruminants the majority of dermatophytosis lesions are caused by *T. verrucosum* and to a lesser extent by *T. mentagrophytes*. The transmission of the disease is usually from animal by direct contact or indirectly through fomites such as grooming instruments, tack, housing, fencing, or feed bunks. The incubation period may range from 1 to 6 weeks.

Several factors may influence the susceptibility of an animal to dermatophyte infection. Age is probably most important, with younger animals more susceptible to infection. The susceptibility of young animals is most likely related to lack of prior exposure/infection and thus no immunity, as well as crowding of young animals and conditions that decrease resistance to infection (e.g., poor nutrition). Environmental factors such as warmth and humidity also may play a role. Calves kept indoors or exposed to foggy weather with little or no sunlight have an increased incidence.

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Under normal circumstances, dermatophytes only invade fully keratinized, nonliving tissues.[7] This results in weakened hair shafts, leading to alopecia.

In many cases, dermatophytosis is theorized to be a self-limiting disease, with the duration of infection ranging from 1 to 4 months. The spontaneous regression is at least partly related to the development of immunity, of which cell-mediated immunity is the more important. The immunity that develops is probably not complete, and its duration is unknown.

40.26.2 Clinical Signs

The lesions are often circular and usually appear first on the face or in the axillary/girth area and may spread over the trunk, rump, neck, head, and limbs (Fig. 40-10). Occasionally in the horse, dermatophytoses may be limited to the pastern region. Rarely, dermatophytes may be a cause of coronary band disease in horses. The mane and tail are rarely involved. Cattle and goats are frequently affected around the eyes and face (Fig. 40-11).

Lesions may be superficial or deep. Superficial infections are much more common and manifest with the development of thick crusts or more generally a diffuse moth-eaten appearance with desquamation and alopecia, sometimes in a ring pattern. A small crust may form over the follicle, and the hair is lost. Occasionally the initial lesions may be urticarial, progressing to multifocal, sharply demarcated areas of alopecia and scaling.

The degree of pruritus varies but is usually mild or absent. Erythema is usually absent or obscured by pigmented skin. The lesions in cattle are usually characterized by excessive crusting, taking on an almost wartlike appearance.

Fig. 40-10 Ringworm lesion in flank area of a horse (*Trichophyton* species).

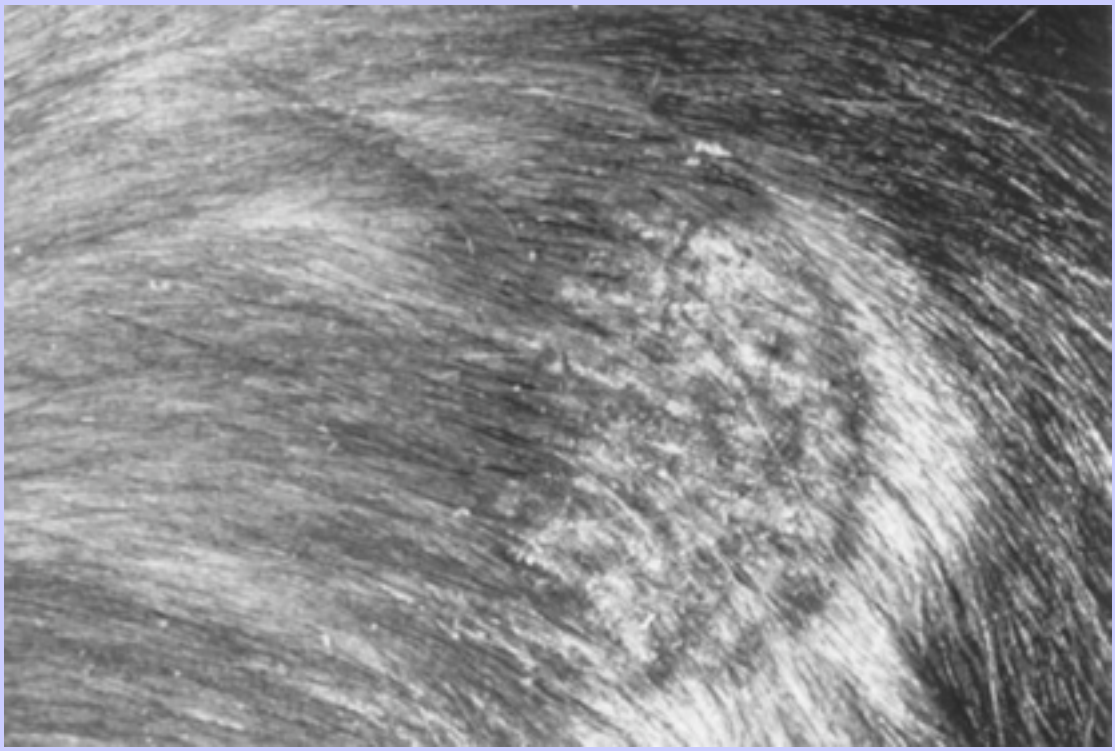
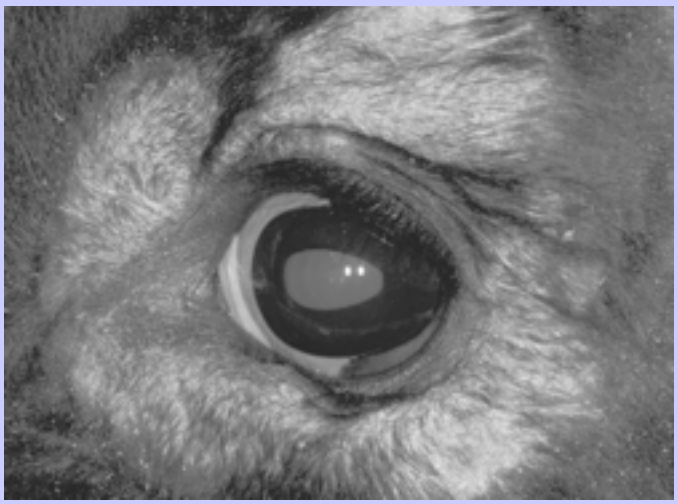


Fig. 40-11 Ringworm lesions around the eye of a calf, caused by *Trichophyton verrucosum*.



Dermatophytosis must be considered in the differential diagnosis of any dermatoses characterized by multifocal alopecia or scaling and crusting. For a solitary lesion in horses, the occult sarcoid is the primary differential diagnosis. The two most important differential diagnoses of more extensive lesions are dermatophilosis and pemphigus foliaceus.

40.26.3 Diagnosis

Direct microscopic examination of infected hairs is of value, but in general the most common and reliable method of diagnosing dermatophytosis is fungal culture (see Chapter 11). Broken hairs at the periphery of lesions are most satisfactory for this purpose. Large crusts and areas of separation should be avoided. The use of specialized indicator media is preferred. On occasion, dermatophytosis is diagnosed histopathologically. Interestingly, *Trichophyton* species occasionally may cause acantholysis, mimicking pemphigus foliaceus on histopathology.[106]

40.26.4 Therapy

Although 50% captan (2 tablespoons powder in 1 gallon water) has been recommended in the past and is certainly safe for tack, its effectiveness has been questioned. Lime Sulfur (LymDyp, IVX Animal Health, St. Joseph, MO), 1 cup to 1 gallon of water, and bleach 1:10 with water are both effective, but messy, odiferous, and staining. Miconazole shampoos are becoming more widely used and may be as effective. In Europe and Canada an enilconazole rinse (Imaveral, Jaansen), approved for horses and cattle, is highly effective.

Systemic treatment is occasionally needed. The efficacy and proper dose of griseofulvin in horses has not been thoroughly researched. However, a dosage of 100 mg/kg daily for 7 to 10 days has been advocated and has been used with good success on a small number of horses by the author. Griseofulvin is a teratogen and should not be used in pregnant mares. Alternatively, 20% sodium iodine (NaI) may be given IV (250 mL/500-kg horse once or twice every 7 days) but also is contraindicated in pregnant mares because it may cause abortion.[28]

Vaccinating cattle against *T. verrucosum* has long been successful in Eastern Europe and Scandinavia. Effective control of ringworm in cattle has been achieved in regions implementing systematic vaccination.[107] Vaccination against *T. equinum* in horses may reduce the incidence of new infections and protect a high percentage (>80%) of vaccinates from infection. These data are based on results with an inactivated vaccine containing both conidia and mycelial elements.[108] In cattle, newer vaccines consisting of recombinant protein and deoxyribonucleic acid (DNA) derived from heat-shock protein 60 of *T. mentagrophytes* have shown success experimentally.[109] Such vaccines are not yet available in the United States.

40.27 SPOROTRICHOSIS

Sporotrichosis is caused by the yeast *Sporothrix schenckii*, which is most common in vegetation. The yeast becomes pathogenic in animals as a result of its dimorphic ability to convert from a yeastlike form at (tissue) temperatures between 35° C and 37° C (95° F and 98.6° F) to a mycelial phase (with branching, septate hyphae) at environmental or laboratory temperatures of 25° to 30° C (77° to 86° F).[110] The disease has been reported in many species of domestic animals.

The initial lesions are nodules, which frequently ulcerate, and the disease may progress to a lymphatic-cording disease. Rarely, the fungus will eventually spread to the lungs. Diagnosis is made by demonstrating the organism on histopathology, immunofluorescent antibody testing on affected tissues, impression smears, and culture.[111] This is a zoonosis, so care should be taken in handling suspected samples.

Successful therapy with a number of different systemic iodine preparations (NaI, KI) has been reported. The organic iodides have proved to be superior in efficacy to the inorganic iodides in the treatment of equine sporotrichosis, with ethylenediaminedihydroiodide* being the drug of choice. This product is in the form of a feed additive and can be mixed with a small amount of grain and administered at 1 to 2 mg/kg of the active ingredient once to twice daily for the first week, then 0.5 to 1.0 mg/kg once daily for the remainder of the treatment. In general, lesions will begin to regress during the first month of treatment, and therapy should be continued for *at least 1 month* beyond the complete resolution of all cutaneous nodules and the healing of any ulcerated lesions. Discontinuing therapy prematurely will invariably result in an unnecessary relapse of the disease. During treatment the horse should be closely observed for any evidence of iodide toxicity (iodism), which includes excess scaling and alopecia, a serous ocular or nasal discharge, excess salivation, anorexia, depression, coughing, nervousness, or cardiovascular abnormalities. Should any of these signs develop, the treatment should be discontinued for 1 week, then resumed at three-quarters the dosage at which the iodism was noted. In most cases the treatment is subsequently well tolerated.[112] Although both itraconazole and terbinafine have been shown to be effective in vitro against the organism isolated from a horse, I am unaware of any clinical reports in this species.[113]

* Organic iodide powder, Neogen Corp, Lexington, KY, or EDDI 20 Gr. Dextrose base, Vedco, 5503 Corporate Dr, St. Joseph, MO.

40.28 PHAEOHYPHOMYCOSIS

Phaeohyphomycosis is actually caused by a number of ubiquitous fungi that are either saprophytes or plant pathogens. These include *Alternaria, Dreschlera, Cladophialophora, Cladosporium, Phialophora,* and *Stemphylium* species. The correct terminology currently depends on the histologic appearance of the organism, as follows[114]:

- *Chromomycosis:* Any pigmented fungi.
- *Chromoblastomycosis:* Pigmented fungi, primarily yeast.
- *Phaeohyphomycosis:* Pigmented fungi, both hyphal elements and yeast.
- *Hyalohyphomycosis:* Nonpigmented fungi, mainly hyphal elements.

Cutaneous lesions arise from either trauma to the skin or disseminated disease. Animals with disseminated disease probably have a deficient immune system. Similar to the other deep mycoses, these lesions present as expanding nodules and draining tracts. Diagnosis is by biopsy or occasionally cytology. Histopathology shows foamy or epithelioid macrophages, and special stains will show the organisms. Veterinarians and their staff should be careful in handling material from infected animals, because the inadvertent inoculation of these organisms can cause human infections.

Treatment has generally included surgical excision or amputation if practical. Potassium iodide (PI), as for sporotrichosis, and (if the owners can afford it) fluconazole at 5 mg/kg may be effective.

40.29 ZYGOMYCOSIS

Similar to phaeohyphomycosis, zygomycosis is caused by a number of related fungal species that are ubiquitous saprophytes. Gastrointestinal and respiratory tract involvement is possible. Cutaneous lesions are thought to be caused by wound penetration. The disease typically occurs in tropical and subtropical areas. The two orders of Zygomycetes that cause disease are Mucorales, including the genera *Rhizopus* and *Mucor,* and Entomophthorales, including the genera *Conidiobolus* and *Basidiobolus*. Most cutaneous reports are in horses, although ruminants may have other organ systems affected.

The skin disease is ulcerative, nodular, and generally found on the trunk and neck. Generally, only one large nodule is present. Diagnosis is by histopathology and culture; a serum agar immunoprecipitation test has been useful in diagnosing conidiobolomycosis. Surgical removal, if possible, is preferred for treatment. Medical options include the iodides (not effective against the order Mucorales) and possibly the azoles or amphotericin B.[7]

40.30 PYTHIOSIS

Not a true yeast, but rather a protista, *Pythium insidiosum* is considered to be the causative agent of "swamp cancer," also known as "Florida horse leech," bursattee, and kunker. This organism is found in tropical and subtropical areas worldwide. The pythiosis lesion occurs most often on the limbs, abdomen, neck, and lips and consists of dense granulation tissue containing masses of yellow-gray necrotic tissue, which sometimes are calcified and often are present as cores in fistulae and are removable intact. Such masses are known as "leeches" or "kunkers." The granuloma ulcerates and extends peripherally and may reach a very large size in a short time; the overlying and adjacent skin is destroyed by both the inflammatory reaction and the self-mutilation by the horse. Important differential diagnoses are systemic fungal infections, habronemiasis ("summer sore"), and neoplasia. Although most reports in large animals are in horses, cattle and sheep may also be affected.[115,116]

Histopathologic examination of affected tissue reveals pyogranulomatous inflammation directly surrounding the organism. Isolation of organisms from the lesions is necessary for further identification and study, but histologic demonstration of the protozoa within tissues that are reacting to its presence is critical in establishing the causal relationship in an individual lesion. In obtaining culture, the kunkers are preferred to the actual tissue. For samples that cannot be processed immediately, acceptable handling techniques include storage at room temperature for up to 3 days, refrigeration for up to 5 days, shipping on cold packs, and storage in antibiotic solution, each combined with subsequent inoculation on selective media.[117] Recent advances in ELISA or molecular techniques offer better potential for organism detection and identification.[118] Wide surgical excision combined with immunotherapy has the best chance of success.[118,119]

40.31 PARASITIC SKIN DISEASES

STEPHEN D. WHITE

40.32 PEDICULOSIS

Lice are obligatory ectoparasites that are generally host specific. Adults and nymphs are seldom able to live more than a few days away from their host. Large domestic animals suffer from infestation with several species of lice that belong to the orders Mallophaga, the biting lice, and Anoplura, the sucking lice (Table 40-2).[120]

Table 40-2 Lice Associated with Large Domestic Animals

Host	Mallophaga (Biting)	Anoplura (Sucking)
Horse	*Bovicola (Damalinia) equiWerneckiella equi equi*	*Haematopinus asini*
Cattle	*Bovicola (Damalinia) bovis*	*Haematopinus eurysternus*
		Haematopinus quadripertusus
		Haematopinus tuberculatus
		Linognathus vituli
		Solenopotes capillatus
Goats	*Bovicola (Damalinia) caprae*	*Linognathus stenopsis*
	Bovicola (Damalinia) limbatus	*Linognathus africanus*
	Bovicola (Damalinia) crassipes	*Linognathus vituli*
Sheep	*Bovicola (Damalinia) ovis*	*Linognathus pedalis*
	Bovicola (Damalinia) capre	*Linognathus ovillusLinognathus africanus*

Clinical infestations are most apparent during the winter months and reflect efficient louse reproduction during the late fall and that summertime temperatures on body areas exposed to sunlight are too high for lice. Apparent "carrier" animals within a herd maintain populations during the "off" season and serve as a source for reinfestation of the herd during the fall.[120] The hallmark of infestation is pruritus, and many clinical changes result from self-trauma. The neck and tail are typically affected first,[121] but infestation and clinical signs may become generalized. The coat becomes dry and scaly. Patchy alopecia and crusted ulcerations result from excoriation. A heavily infested animal may become anemic. Significant hide damage occurs as a result of excoriation, and hairballs may accumulate in the gastrointestinal (GI) tract from self-grooming. Reduced productivity and weight loss result from decreased feed intake associated with restlessness. Diagnosis is usually by examination; a hand lens is useful (e.g., otoscope without cone). Interestingly, when a horse is exercised and becomes warm and sweaty, the lice will climb out toward the tip of the hair and are easier to find.[122]

Several treatment approaches exist. Ivermectin at 200 µg/kg every 14 days for two applications is effective for sucking lice but not biting lice. Application of an appropriate topical insecticide to infested animals and to all contact animals at 2-week intervals for two or three treatments is usually curative for both types of lice. Repetition of treatment is necessary to break the louse life cycle because eggs are not killed by insecticides and will hatch despite therapy. Effective topical agents include pyrethroids, permethrins, selenium sulfide, imidacloprid, phoxim, and fipronil.[122] Appropriate attention should be paid to withdrawal times in food animals. Cleaning of fomites such as blankets, brushes, and rope halters is probably indicated, although lice do not live long off the host.

40.33 TROMBICULIDIASIS

Trombiculidiasis is caused by the larval stages of mites commonly known as "harvest mites" or "chiggers." The most common species affecting large animals are *Eutrombicula alfreddugesi* and *Neotrombicula autumnalis*. The

adults and nymphs are free living. The larvae feed on mammalian hosts, secreting substances in their saliva that hydrolyze the epidermis and allow extraction of tissue fluids. The individual larval stage is short, but the infestation may be ongoing with the acquisition of new larvae from the environment. In the Northern Hemisphere, *E. alfreddugesi* is active from late spring through early fall, whereas *N. autumnalis* is more common in the late summer to midfall. The mites may be found in wooded areas, grass, and hay.[122,123]

The clinical signs of trombiculidiasis are crusts and papules, especially on the face, neck, and extremities. Pruritus is variable.[123] Diagnosis may be made early in the course of infestation by careful inspection (e.g., hand lens) and finding the minute, red-orange larvae in the center of a papule. The six-legged larvae have round bodies and may be identified specifically on skin scrapings or acetate tape preparations.[122] Although the larvae only remain on the animal host for several days, clinical signs may persist longer. Thus, trombiculidiasis should be suspected even in the absence of mites in an animal with appropriate signs in the summer and fall.

The disorder is in theory self-limiting because of the short time of attachment of the parasite. However, if the pruritus is severe, corticosteroid administration is indicated.[122] Various products have been used on the horse to eliminate the larvae; 5% lime sulfur, fipronil, and permethrin are generally the safer parasiticides to use.

40.34 MANGE

40.34.1 Psoroptic Mange

Psoroptic mange has been recognized in horses, cattle, sheep, and goats (and rabbits). The host specificity of *Psoroptes equi, P. ovis, P. natalensis,* and *P. cuniculi* is controversial; two recent reports state that the mites are all genetically homogenous with little or no host specificity,[122,124] whereas another report documents an inability to transfer *Psoroptes ovis* to goats.[125] The mites do not affect people. Psoroptic mange is common in cattle but has been eradicated from horses and sheep in the United States; it is still a concern for sheep production in the United Kingdom and elsewhere in the world. The mites have a 2-week life cycle on their host but can live away from the host for up to 3 weeks. *Psoroptes* mites live on the surface of the epidermis and do not burrow. Symptomatic infestation tends to be more prevalent during the cooler months.

The hallmark of infestation in all species is pruritus. In cattle, crusted papular lesions are typically first apparent on the withers but then generalize, resulting in weight loss, secondary infections, and decreased production.[126] Horses develop papules, crusts, and alopecia most often at the base of the mane, tail, ears, and intermandibular area, with subsequent spreading to the trunk.[122] An otitis externa may be present, seemingly with *Psoroptes cuniculi*.[122] In sheep, typical lesions include papules and crusts in wooled areas, and secondary infection with *Staphylococcus aureus* may occur.[127] The intense pruritus can be debilitating. Certain sheep breeds (e.g., merino) are more susceptible to infestation than others.[125] The immune response in sheep has been extensively studied, with early innate and longer-term adaptive cutaneous immunoinflammatory responses as well as mite antigen—directed IgE being reported.[126] Goats usually have lesions restricted to the ears, although infestation and symptoms may spread to the neck and body.[29]

Diagnosis is based on demonstrating mites in skin scrapings and ear swabs from affected animals. Psoroptic mites are recognized by their round bodies and long, segmented pedicles.[29]

A number of topical insecticides have been recommended for treatment and should be applied to all affected and contact animals according to the manufacturer's guidelines. These include deltamethrin, coumaphos, diazinon, malathion, toxaphene, and lime sulfur.[29,123,128] The contaminated environment should also be treated. Ivermectin, doramectin, and moxidectin have been used for *Psoroptes* species in large animals at 0.2 mg/kg subcutaneously (SC),[123,129,130] but treatment does not eliminate live mites from all animals. It has been recommended that *P. ovis*–infested cattle be isolated for a minimum of 14 days after treatment to prevent transmission to susceptible contact cattle.[130] *Psoroptes*-infested ears in horses should not be treated topically because of the resulting discomfort; reliance is on systemic treatment. Psoroptic mange is a reportable disease in the United States.

40.34.2 Chorioptic Mange

Chorioptic mange, also known as leg mange, is common in cattle and sheep, uncommon in goats, and seen with variable frequency in horses depending on geographic area. Draft horses may be more susceptible than other breeds. *Chorioptes* species are relatively host specific and include *C. bovis*, *C. texanus*, *C. ovis*, *C. equi,* and *C. capre*.[29,123,131] The mites do not penetrate the epidermis[123] and do not affect humans.[130] They have a life cycle that spans 2 to 3 weeks and can live off the host for only a few days.[29]

This disease is variably pruritic, more so in ruminants than horses, and less so than infestations with *Psoroptes* or *Sarcoptes* mites. Lesions consisting of papules, erythema, scaling, crusting, ulceration, and alopecia result from self-trauma. In cattle the lower aspects of the hindlimbs, the perineum (particularly the perianal fossa), tail, and scrotum are usually affected. Sheep typically demonstrate involvement of the lower limbs and scrotum. Goats have involvement of the lower limbs. Horses typically have lesions on the pasterns, although the ventral abdomen may become involved in severe cases. In all species, infestation can become generalized.[122,123,130]

Mites are often numerous and readily demonstrated with skin scrapings. Cattle may be asymptomatic.[130] Chorioptic mange will respond to treatments described for psoroptic mange, although ivermectin and related compounds are more effective in ruminants than horses; in horses, lime sulfur or fipronil applied once weekly for at least 1 month is recommended.[122,132,133] A recent study in horses showed efficacy using a single dose of moxidectin 2% oral gel (Equest, Fort Dodge, IA) at the manufacturer's recommended therapeutic dose of 0.4 mg/kg body weight.[133a] Chorioptic mange is a reportable disease in the United States.

40.34.3 Sarcoptic Mange

Sarcoptic mange is an uncommon, contagious disease of horses, cattle, sheep, and goats. The etiologic agent is *Sarcoptes scabiei;* several subspecies are relatively host specific but can be transmitted to humans. The mite burrows into the epidermis, where the egg is deposited, and its life cycle is complete in 10 to 17 days. Transmission is usually by direct contact, but the mite has a variable survival time off the host; therefore, environmental and fomite transmission is possible.[122,123]

The clinical signs are all referable to the severe pruritus caused by the mite. Lesions include papules, scaling, crusting, ulceration, and alopecia. The head (especially the ears) and neck are usually the initial areas of involvement, although lesions become generalized.[29,122,123] Horses in areas frequented by infected wild foxes may have lesions affecting the legs and the ventral abdomen.[122] Dairy cattle may have an associated udder cleft

dermatitis.[134] Sheep tend to have initial involvement of the nonwool areas. The ears should always be scraped for mites; the mite is identified by its rounded body, terminal anus, short legs, and long unsegmented pedicles.[29,122,123]

Because mites may be present only in small numbers, negative skin scrapings do not rule out the disease. Diagnosis should be based on clinical suspicion and response to therapy.[7,29,122,123]

Topical acaricides have been recommended for treatment and are applied to all affected and contact animals at 10- to 14-day intervals for four to six treatments. These include lindane, coumaphos, diazinon, malathion, toxaphene, and lime sulfur.[29,122,123] Ivermectin, 0.2 mg/kg at 2-week intervals for two to four injections (ruminants) or orally (horses), has been shown to be effective, as has injectable moxidectin and topical doramectin. The contaminated environment should also be treated. It is recommended that the state regulatory agency for livestock disease control be consulted for methods of treatment and products to use because sarcoptic mange is a reportable disease.

40.34.4 Demodectic Mange

Demodectic mange is a rare disorder, although it has been recognized in all the large domestic species. The mites live in the hair follicles and in the sebaceous and sweat glands and are host specific. They are not contagious between members of the same species, but *Demodex* species are presumably transmitted from mother to offspring during the first few days of life by direct contact with the dam. Little else is known regarding the life cycle of the mite.[122,123] Two species of *Demodex* are recognized in the horse.[7,122] *Demodex caballi* is a normal inhabitant of the pilosebaceous apparatus of the eyelids and muzzle and may be found in skin scrapings of these areas on horses in the absence of skin lesions. *Demodex equi* inhabits the pilosebaceous apparatus of the remainder of the body and is the species found on horses that has been associated with disease. The species found on cattle, sheep, and goats are *Demodex bovis, D. ovis,* and *D. caprae,* respectively.[29,122,123,130]

Clinical signs are variable, depending on the species affected. The disease is quite rare in horses, which may develop alopecia of the head and trunk; I have seen one case of concurrent demodicosis and chorioptic mange on the legs of a draft horse. Underlying pituitary dysfunction of the pars intermedia has been seen in some horses.[122] Pruritus and secondary pyoderma are variable. Goats and cattle usually develop nodular lesions that involve the face, shoulder, and neck.[135,136] In goats the nodular contents are white and caseous; microscopic examination for mites differentiates the lesions from *Corynebacterium pseudotuberculosis*.[136] Sheep tend to develop periocular nodular lesions.

Diagnosis is based on recognizing mites with microscopic examination of skin scrapings or exudates obtained from nodular lesions. The mites are elongated and have short, stubby legs.[29,122,123]

No treatment has proved to be consistently effective in large animals, although relatively few case reports exist in the literature. Amitraz has not been successful in the treatment of caprine demodicosis.[136] Horses sprayed with 0.025% amitraz developed somnolence, depression, ataxia, muscular weakness, and progressive large intestinal impaction, suggesting that amitraz is contraindicated in equids.[137] Daily ivermectin has been suggested as a successful treatment for equine demodicosis, but dosages have not been codified. Oral ivermectin (0.67 mg/kg once weekly for 12 weeks) and pour-on eprinomectin (0.5 mg/kg) each successfully treated one goat with generalized demodicosis.[138]

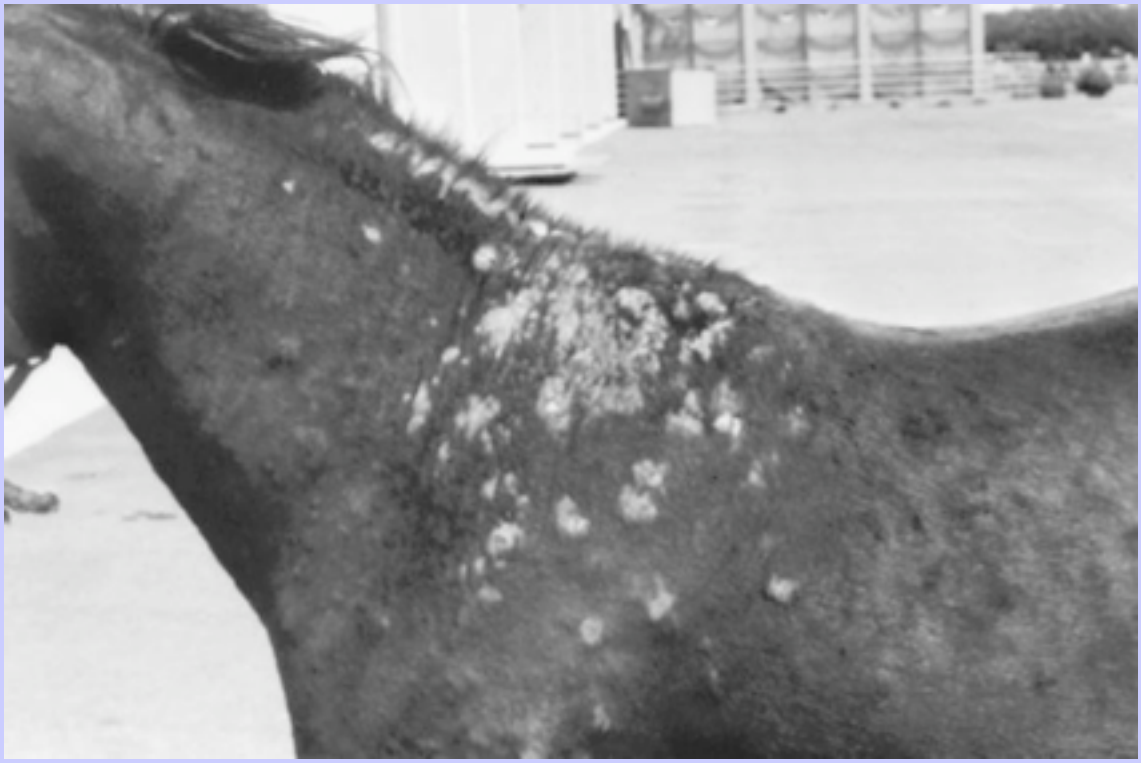
40.35 *CULICOIDES* HYPERSENSITIVITY

The females of various *Culicoides* fly species ("no-see-ums," "punkies") may feed either on the dorsal or the ventral surface of the horse, affecting the mane, saddle, and rump or causing a ventral midline dermatitis in a diffuse pattern. Alopecia, papules, crusts, and erythema may all be present (Fig. 40-12). The insects induce a hypersensitivity response through salivary antigens; this condition is termed *Culicoides* hypersensitivity (Queensland itch, sweet itch) and is recognized in various areas of the world. Evidence indicates a hereditary predisposition to develop the hypersensitivity. Histopathology of lesions frequently reflects a hypersensitivity response.[139] Although many species of *Culicoides* exist, the two most commonly suspected of causing the allergic response are *C. variipennis* and *C. nubeculosus*.

Recent studies have attempted to define the nature of the hypersensitivity response. One study found serum antibodies to *Culicoides* salivary glands in both healthy horses exposed to *Culicoides* bites and in horses with insect "dermal" hypersensitivity.[140] In contrast, no antibodies were detected in serum from native Icelandic horses which had not been exposed to *Culicoides*. Anti—salivary gland immunoglobulin G (IgG) antibodies were detected in both groups of horses, whereas IgE antibodies were only detected in clinically affected horses.[140] A more recent study compared two groups of affected Icelandic horses: those born in Iceland (no previous exposure to *Culicoides*) and transported to Europe, where they were then exposed to the flies, and those born in mainland Europe. The former had IgE and IgG antibodies to a greater number of the insects' salivary proteins.[141] Another study found significantly more IgE-bearing cells in the dermis and epidermis of acute and chronic lesions than in skin biopsies from healthy horses.[142] Further evidence for a hypersensitivity response was demonstrated in a study in which intradermal injection of a *Culicoides* antigen extract induced T lymphocyte and eosinophil accumulation in the skin of affected horses.[143] Other studies have supported the immunologic nature of this disease.[144–148]

The hallmark of disease is pruritus. Although no gender predisposition has been noted, Icelandic horses may have a higher incidence of allergic reactions to the *Culicoides* insects than other breeds. The disease is uncommon in horses under 1 year of age, with an onset usually between 2 and 4 years. *Culicoides* hypersensitivity may be seasonal, at least during the first few years of life, in temperate climates. Diagnosis is primarily by clinical signs. *Culicoides* antigens (commercially available in the United States by Greer, Lenoir, NC) seem useful in both diagnosis and treatment,[149,150] but this needs to be documented in large case studies.

Fig. 40-12 Severe *Culicoides* hypersensitivity in a horse, showing typical distribution of withers, shoulders, and head (not visible).



Therapy is aimed at insect control, especially the following:

1 Stabling horses at sunrise and sunset, peak *Culicoides* feeding hours.

2 Ultrafine setting or screens placed in windows (60 squares to the square inch).

3 Fly control, especially keeping horses away from standing water and using permethrin repellents, usually 2% permethrin sprays. Frequently, sprays must be applied more often than the label recommends (i.e., daily, at least at first). I have had some success using a nonpesticide "herbal" spray or roll-on (MedZone Vet Shield & Sheen, Sun City, AZ).

4 Overhead or stall fans (drafts interfere with insects' flight).

5 "Dresses" that physically obstruct the insects from reaching the skin.

6 Hyposensitization is controversial; success may vary with the presence of an adjuvant, or the actual antigen used.

7 Oral prednisolone to manage the pruritus.

40.36 VENTRAL MIDLINE DERMATITIS OF HORSES

This is a reaction pattern in horses to ectoparasites, and not necessarily specific for any one arthropod. *Culicoides* hypersensitivity, *Onchocerca cervicalis* infestation, and black flies (Simuliidae) may cause generalized ventral midline dermatitis (VMD), whereas horn flies *(Haematobia irritans)* cause a focal dermatitis. Severe chorioptic mange may also involve the ventral midline. In all cases, the lesions have variable alopecia, pruritus, and crusts. Treatment is based on eliminating or repelling the causative organism.

40.37 OTHER FLYING INSECTS

Stable flies *(Stomoxys calcitrans),* black flies (Simuliidae), horn flies *(Haematobia irritans),* horse flies (*Tabanus* and *Hybomitra* species), deer flies (*Chrysops* species), house flies *(Musca domestica),* face flies *(Musca autumnalis),* and mosquitos are commonly associated with irritant and allergic skin disease, as well as being vectors of many parasites. They must be controlled by limiting breeding areas and by repellents; 2% permethrins are often used. It is important to remember the relationship of these various flies to the environments they favor or require for breeding and when they feed, as follows:

Horse flies, deer flies	Vegetation and water	Daytime feeders
Horn flies	Cattle	Daytime feeders
Stable flies	Manure/decaying bedding	Daytime feeders
Black flies	Running water	Morning and evening
Culicoides	Standing water, manure/decaying vegetation	Twilight to dawn
Mosquitoes	Water	Dusk to 2 hours after sunset

40.38 SCREWWORM INFESTATION

Screwworm flies cause primary myiasis; the species of importance in the Americas is *Cochliomyia hominivorax (Callitroga americana)*. The fly was formerly found throughout the American tropics and subtropics from the southern United States to northern Chile.[151,152] It is no longer found in the United States or Mexico as a result of state, federal, and international eradication efforts.[153]

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The adult fly is about three times the size of a house fly, with a metallic bluish or blue-green color.[151,153] Females are attracted to fresh wounds (castration, dehorning, branding and shearing sites), abraded body orifices, areas soiled by discharges or excretions, and navels of newborns. They lay batches of 150 to 500 white eggs on the margin of damaged tissue in rows that overlap like shingles. Eggs hatch within 24 hours, and the larvae begin to feed in a head-downward position. Larvae are obligate parasites that require living tissue as feedstuff. They cannot develop in carrion. Larval development continues for 4 to 10 days, and at the time of their maturation, they may have created a cavity 10 to 12 cm (4 to 5 inches) in diameter.[152] Mature larvae are about 2 cm in length, pink in color, pointed anteriorly, and blunt posteriorly. The larvae then drop to the soil and pupate. The life cycle averages about 21 days and is favored by hot, humid weather.

Screwworms do not have a dormant stage in their life cycle and cannot overwinter in cold climates.[151] Thus the susceptible stage of development is the pupae, which will not survive soil temperatures below 15° C (59° F). The feeding larvae burrow deeply, creating a cavernous lesion characterized by liquefaction necrosis, profuse brownish exudate, and an objectionable odor. The syndrome is self-perpetuating in that wounds infested by screwworm larvae become increasingly attractive to gravid females. The end result is often death of the host as a result of secondary bacterial infection, toxemia, and fluid loss.[152]

Treatment of wounds requires clipping and cleansing, as well as destroying all larvae. Dressings containing larvicides and antiseptics should be applied. Preparations containing lindane or organophosphates have been used in an ointment or gel base. The treatment is repeated twice weekly. When large numbers of animals are affected, a 0.25% solution of coumaphos, chlorfenvinphos, or fenchlorphos may be applied to herds with a power sprayer. Calves may become ill from the spray; thus applications should be restricted to the ventral abdomen.[152] More recently, the curative efficacy of fipronil 1% against *C. hominivorax* larvae infestation in castration wounds was 100%.[154] Even more impressive, doramectin as a prophylactic treatment was 100% effective in prevention of *C. hominivorax* infestations.[155]

Control of screwworm flies in the United States has been achieved largely through the release of sterile males, because of the single mating tendency of the female fly. The eradication program has proceeded through Mexico south to the twenty-first-degree parallel.[151] Screwworm myiasis is a reportable disease in the United States, and suspect larvae should be preserved in 70% alcohol for positive identification.[156]

40.39 BLOW FLY STRIKE (FLEECEWORMS, WOOLMAGGOTS, SECONDARY SCREWWORMS)

Blow flies are found throughout the Western Hemisphere. The species of importance include *Cochliomyia macellaria* (secondary screwworm), *Phaenicia sericata* (green bottle fly), and *Phormia regina* (black blow fly). The flies tend to be most common in the warmer regions, with the exception of *P. regina,* which is widespread throughout the cooler parts of North America and Europe.[151] Blow flies cause serious loss of sheep and wool in many countries.[153] Female flies are attracted to decaying animal matter, such as wounds infested by primary screwworms, infected sores, carcasses, and fleeces that are dampened with feces, urine, or bloody fluids.[151] They lay eggs in batches of up to 300, which hatch within hours. The larvae feed on necrotic tissue but may invade healthy tissue. Larvae develop for 3 to 5 days and, when fully mature, are white and 6 to 12 mm in length. The larvae then drop to the ground for pupation. As soil temperatures fall, larvae fail to pupate and may overwinter until the following spring. The entire life cycle is generally complete in 2 to 4 weeks under ideal conditions of warm temperatures and high humidity.[152]

Unlike primary screwworms that feed in pocket-like aggregations, secondary screwworms tend to be dispersed throughout the infested tissue. In wool infestation the larvae may remain on the skin surface, feeding on the decomposing wool, or may penetrate the skin through small abrasions. The most common site of involvement is the breech. Infested tissue attracts more ovipositing females, and thus the syndrome is perpetuated.[151] Affected sheep are restless and do not feed. They move with their heads close to the ground, bite or kick at their wounds, and continually wriggle their tails. Affected wool is moist and brown with an obvious odor. Animals may become systemically ill and die.[156]

Treatment of individual wounds is as described for screwworms. Control involves management practices that decrease the incidence of wounds or skin irritations. Sheep are often clipped below the tail and between the hindlimbs ("crutched"), where wool is likely to become saturated with urine or feces. Castration, shearing, docking, and lambing are avoided during the summer season.[151]

40.40 CUTANEOUS ONCHOCERCIASIS

40.40.1 Definition and Etiology

Cutaneous onchocerciasis in horses is a common filarial dermatitis with a worldwide distribution. Its incidence in the United States has decreased dramatically since the introduction of ivermectin for routine deworming. In a recent report from South America, *Onchocerca cervicalis* microfilariae were detected in midventral skin biopsy samples in 215 (17.9%) of 1200 horses examined, and the adult worms were recovered from 200 (16.6%) ligamentum nuchae from the same animals.[157]

The disease is caused by the microfilaria of *O. cervicalis* and is seen primarily in adult horses.[158,159] Adults typically are found coiled in the funicular part of the ligamentum nuchae, where they produce calcified nodules. Viviparous females may live for up to 5 years and produce large numbers of microfilariae that migrate through connective tissues to the superficial layers of the dermis. Preferential areas of microfilarial localization include the ventral midline, lower eyelid, and lateral limbus of the eye.[158] The infection is transmitted by *Culicoides,* which act as an intermediate host. The larvae are ingested by the vector and undergo development into the third-stage larvae (L_3) in approximately 2 weeks. The L_3 larvae enter the animal host through lesions created by the feeding vector.[33] Many horses are infected with the parasite without demonstrating clinical disease.[33,158]

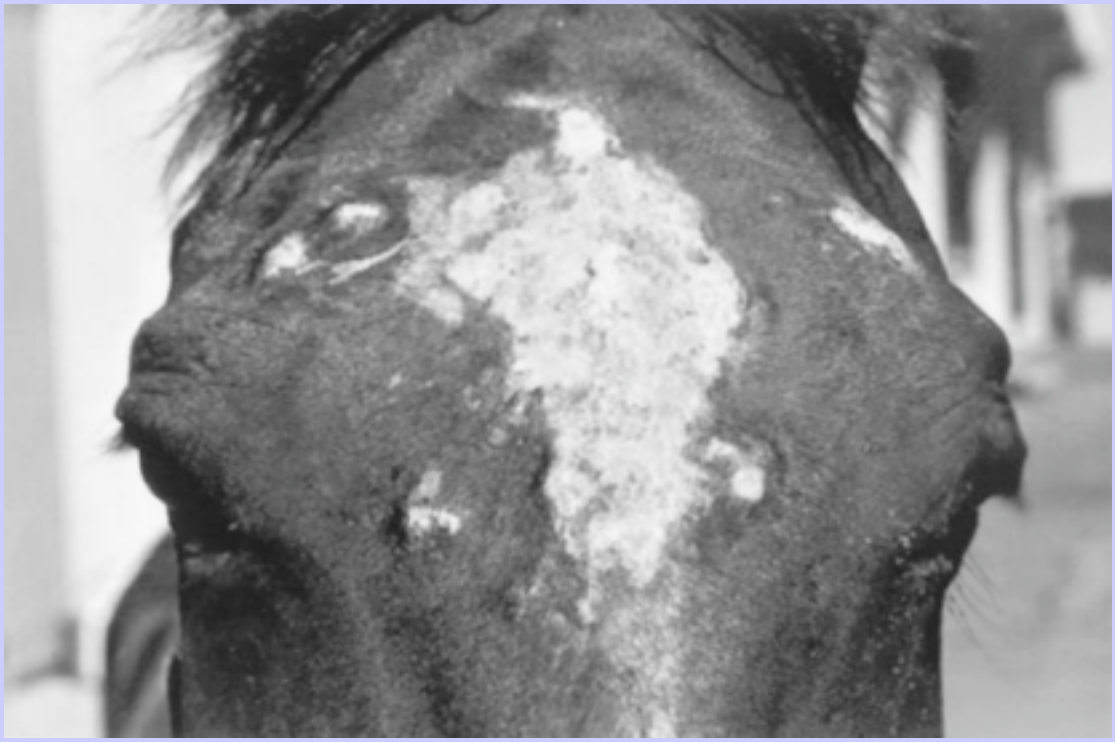
40.40.2 Pathophysiology

Pathogenesis is believed to involve a hypersensitivity reaction to antigens released by dying microfilariae.[33,158] This theory has support because not all infected horses demonstrate disease, neither the presence nor the severity of the dermatitis is correlated with the number of organisms present, and treatment with filaricides often causes a temporary exacerbation of clinical signs.

40.40.3 Clinical Signs

Clinical signs occur most often in older horses and can include both ocular and cutaneous lesions.[33,158] Ocular lesions include uveitis, conjunctivitis, keratitis, and depigmentation of the lateral limbus.[160] Cutaneous lesions include diffuse or patchy alopecia, erythema, and scaling. Focal cutaneous depigmentation is common. Lesions tend to occur in regions where microfilariae are typically present in highest concentrations, such as the ventral midline, face (Fig. 40-13), base of the mane, anteromedial proximal forelimbs, and anterior pectoral region. An inflammatory, alopecic, or hyperpigmented area in the center of the forehead is highly suggestive of the disorder.[33] The dermatitis is generally reported as being nonseasonal and nonpruritic.[33,161]

Fig. 40-13 Cutaneous onchocerciasis in a horse.



40.40.4 Diagnosis and Histopathology

Because many normal horses have microfilariae without disease, the finding of microfilariae does not prove that they are the cause of the cutaneous lesions. In addition, because microfilariae tend to "nest" in the dermis, there is a tremendous difference in the number of microfilariae recovered from adjacent skin samples.[158,162] Thus, although the absence of microfilariae makes cutaneous onchocerciasis unlikely, it does not definitively exclude it as a diagnosis. Differential diagnoses should include ventral midline dermatitis caused by the horn fly *Haematobia irritans,* hypersensitivity reaction to *Culicoides,* dermatophytosis, and infestation with mange mites.

Ultimately, diagnosis should be based on history, supportive clinical findings, exclusion of other differential diagnoses, and most importantly, response to treatment.

A positive *Onchocerca* microfilarial saline preparation demonstrates slender, delicate microfilariae that are approximately 8 × 220 µm. Typical histopathologic changes include an eosinophilic and lymphocytic perivascular dermatitis, a finding that is nonspecific and common to many other equine parasitic dermatoses (see Chapter 11). Aggregations of microfilariae may be found in the superficial dermis or perifollicular region.[33,158,162]

40.40.5 Therapy

Ivermectin or moxidectin are the treatments of choice and are administered at 0.2 mg/kg PO.[163,164] Most horses improve within 2 to 3 weeks. Minor adverse reactions, including fever and swelling of the periorbital, facial, and ventral midline regions, may occur in up to 25% of infected horses treated with ivermectin; moxidectin did not cause posttreatment dermal reactions in one study.[164] Severe reactions may benefit from treatment with corticosteroids, but most reactions resolve within 24 to 72 hours. Because there is no effective adulticide, recurrence may be noted as soon as 2 months after therapy. Most animals remain free of clinical signs for 6 to 12 months.[161,163] Re-treatment is recommended at 4-month intervals.

In cattle, onchocerciasis has been caused by the microfilariae of *Onchocerca gutturosa* and *Onchocerca lienalis* and in Africa, *Onchocerca ochengi*.[165,166] Flies of Simuliidae are the vectors. The disease causes nodules and crust on the skin, including the teats; adult worms surrounded by neutrophils were detected free in the teat canal.[166] Ivermectin and moxidectin are effective treatments.[165]

40.41 STEPHANOFILARIASIS

Cutaneous stephanofilariasis is a filarial dermatitis of cattle. The disease is caused by organisms of the genus *Stephanofilaria* and has been observed in cattle in many countries.[167,168] Within the United States the disease is most prevalent in the western and southwestern regions, where it is caused by *Stephanofilaria stilesi*.[156,159,169] Adults and microfilariae inhabit the epidermis. The parasite is transmitted by the female horn fly *(Haematobia irritans)* when it feeds on lesions on the ventral midline.[159] The microfilariae are ingested and develop to infective L_3 larvae in 2 to 3 weeks. The L_3 stage is introduced into the animal host on subsequent feedings.[169]

Clinical signs of cutaneous stephanofilariasis include a ventral midline dermatitis initially associated with a papular eruption. The scrotum may also be affected.[170] The lesions progress to nodules, alopecia, and crusted ulcers. There may be mild pruritus.[152] Diagnosis is based on history and appropriate clinical signs, excluding differential diagnosis and demonstration of the nematode. Biopsies may be taken as described for equine onchocerciasis, or the crust can be removed from an acute lesion and deep skin scrapings performed to recover the parasite. The tissues should be minced in isotonic saline and then examined microscopically. Multiple skin scrapings may be required to demonstrate the parasite. Either adults or microfilariae may be found. The adult male is about 3 mm in length and the adult female 6 mm in length.[167] Microfilariae are 50 μm in length.[167] Characteristic histopathologic findings include a perivascular dermatitis associated with an eosinophilia. Microfilariae may be noted in the dermis, and adults in epithelial-lined cysts at the base of the hair follicles, although both may be difficult to find.[167]

There is no approved treatment for stephanofilariasis, although approved topical organophosphates have been suggested.[159] Some authors have not recommended treatment because clinical signs are relatively mild in many animals.[169] Cattle with zebu ancestry may be more resistant.[168]

40.42 HYPODERMA (WARBLES)

40.42.1 Definition and Etiology

Infestation with the larvae of *Hypoderma* species is a common and serious economic problem in cattle and is recognized sporadically in horses that are pastured near cattle. Occurrences have also been reported in sheep, goats, and humans.[171] Warble flies are present in the Northern Hemisphere between 25 and 60 degrees latitude in more than 50 countries of North America, Europe, Africa, and Asia. *Hypoderma* species are not established south of the equator.[152,171] The U.S. cattle industry loses millions of dollars annually because of cattle grubs.

Two species of *Hypoderma* parasitize cattle: *H. bovis* and *H. lineatum*. The latter prefers warmer climates and is the only *Hypoderma* species present in the southern United States. Each of the species occurs in the northern United States and in Canada.[152] *H. lineatum* and *H. bovis* have very similar life cycles, but the stages of *H. lineatum* tend to occur 3 to 8 weeks earlier than those of *H. bovis*. Timing of the life cycle also varies with local geographic and climatic factors.[152,171]

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The adult flies are beelike in appearance, covered with dense chin bristles (hair), 12 to 188 mm in length, and have nonfunctional mouthparts.[172] They have a short lifespan, only 1 week. Adult flies are active in the spring to early summer, with *H. lineatum* appearing 3 to 4 weeks before *H. bovis*. Female *H. lineatum* flies deposit eggs on the hairs of the legs or lower body, whereas *H. bovis* tends to deposit eggs on the rump or upper parts of the hindlimbs. Total egg production by a single female has been estimated to range from 500 to 800.[172] The eggs hatch in 3 to 7 days, after which the larvae penetrate the skin and begin their migration through the connective tissues. *H. lineatum* larvae migrate to the subcutaneous connective tissues of the esophageal wall, whereas *H. bovis* larvae migrate toward the spinal canal. The first-stage (L_1) larvae remain in this location for 2 to 4 months, during autumn and early winter. Between January and February the larvae begin a final migration through the connective tissues to the subdermal tissue of the back of the host, where they form a breathing hole through the skin. Cysts (warbles) develop around L_1 larvae. Within the cyst the larvae undergo two molts over a 4- to 6-week period. The L_3 larvae (grub) emerge from the breathing pore, fall to the ground, and pupate. Adult flies emerge from the pupae in 1 to 3 months, and emergent adults are ready to mate almost immediately.[172,156] The life cycle is complete in 1 year. Most larvae fail to reach normal size and complete their life cycle in the horse.[171,172]

40.42.2 Clinical signs

40.42.2.1 CATTLE

During the spring and summer when adult flies are active, “fly worry” may be a serious problem. Cattle exhibit a stampeding behavior called “gadding” when chased by ovipositing females, even though the flies do not bite or sting. This fear reaction results in self-injury and decreased feeding and milk production.[172] Diagnosis of warble flies in goats by ELISA has been reported, but it is not known whether this is applicable to cattle.[173]

Clinical lesions are not usually observed in association with migration of L_1 larvae unless the larvae die along the migratory path.[171] Lesions that have been associated with infestation of L_1 larvae of *H. bovis* include fat necrosis and inflammation of the connective tissues surrounding the spinal canal. Secondary periostitis, osteomyelitis, and rarely paralysis or other nervous disorders may occur. Similarly, infestation with L_1 larvae of *H. lineatum* in the submucosa of the esophagus may cause inflammation and edema in the surrounding tissues. Swallowing and eructation may be hindered, resulting in bloat and subsequent respiratory failure.[171]

Lesions most often observed with *Hypoderma* infestation are attributed to L_3 larvae. Warbles occur along the back from the shoulders to the tailhead and from the dorsal midline to a point about one-third the distance down the sides. The lesions may be firm to fluctuant, raised, and painful to the touch. They measure approximately 3 cm in diameter and contain a breathing pore that usually exudes a yellowish serum. Excisional biopsy of a nodular lesion reveals the larvae within a cystlike structure that contains yellow fluid. The surrounding tissue is necrotic. Secondary infection of the cysts can result in large, suppurating abscesses. The number of warbles in an infested animal may range from 1 to 300. Infestations are most serious in younger animals and become progressively less severe with age. Emergence of the grub results in healing, although carcasses retain evidence of infestation and are devalued at slaughter.[152,171]

40.42.2.2 HORSES

Most horses have only one or two grubs, but heavy infestation is present in rare cases. Lesions associated with L_3 larvae include small, nodular swellings that develop dorsally and frequently in the region of the withers. Most lesions have a breathing pore.[156] Differential diagnosis is most often nodular collagenolytic granuloma (nodular necrobiosis), but mastocytoma, sterile nodular panniculitis, and amyloidosis should also be considered. Posterior paralysis associated with involvement of the spinal cord has been reported in both horses and cattle.[171]

The season, location of the lesion(s), and presence of a breathing pore are usually diagnostic. Larvae can be recovered by enlarging the breathing pore with a scalpel and extracting the grub.

40.42.3 Therapy

When small numbers of cattle are affected with just a few grubs, manual removal of the grubs is possible by simply enlarging the breathing pore. This is usually the preferred treatment in horses as well, if only one or two lesions are present. Care must be taken to remove the larvae in their entirety because breaking the larvae and rupturing the cyst during removal can result in a severe systemic reaction.[152,171]

Systemic insecticides are the only means of eliminating the migrating larvae. Organophosphates or the macrocyclic lactones (doramectin, eprinomectin, ivermectin, moxidectin) have been used for this purpose and are applied on the midline of the back.[171,174] Administration of insecticides should be timed to provide treatment in early autumn after all eggs have hatched and larvae are in the early stages of their connective tissue migration. Third-stage larvae are less susceptible to insecticides, and destruction of larvae in later stages of migration increases the risk of serious secondary illness. It is advisable not to administer systemic insecticides later than 8 to 12 weeks before the anticipated first appearance of grubs along the back.[152,171] In the northern United States and Canada, treatment of cattle with systemic insecticides is not recommended from October 1 to

March 1 because this is when *H. bovis* larvae are located in the epidural space and *H. lineatum* larvae reside in the esophagus.[152]

40.43 SHEEP KEDS

The sheep ked, *Melophagus ovinus,* is a wingless fly approximately 6 to 7 mm in diameter with a ticklike appearance. Sheep keds have a worldwide distribution. They primarily parasitize sheep and occasionally goats that are kept under poor management conditions.[152,175]

The entire life cycle is spent on the host. Females live 4 to 5 months, laying 10 to 15 larvae individually that are cemented to the wool or hair. The larvae pupate in 12 hours, and the adult emerges 3 weeks later. Adults feed on blood and do not survive longer than a few days off the host. Transmission is by direct contact, and infestation is more common in the winter months.[152,153,175]

Clinical signs of infestation include pruritus with subsequent self-trauma, wool stains from the flies' fecal material, and in severely parasitized animals, anemia. Multiple firm nodules (cockles) develop as a result of repeated puncture of the skin as the keds feed.[152,153] Infestation results in economic loss from a reduction in dressed carcass weights of lambs, reduced clean dry weight of fleece, wool staining, and reduced value of sheep skins because of nodular defects.[152,175,176] Diagnosis is based on demonstration of the parasite.

Therapy involves shearing all sheep in the affected flock, followed by two topical applications of malathion, diazinon, or coumaphos at 14- to 21-day intervals to kill emerging adults.[152] Because the larvae are attached to the wool or hair some distance above the skin surface, many larvae and pupae are removed by shearing.[153,176] Recently, imidacloprid was found to be effective in killing the parasite.[177] All new animals should be isolated and treated before introduction to prevent reinfestation. A control program includes annual treatment of the entire flock.

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40.44 CUTANEOUS HABRONEMIASIS (EQUINE SUMMER SORE)

Habronemiasis ("summer sore") is a granulomatous disease caused by the deposition of *Habronema microstoma*, *Habronema muscae,* or *Draschia megastoma* larvae by flies at the site of wounds or natural body moisture (sheath, eyes).[178,179] The adult parasites normally reside in the stomach, where they cause little tissue reaction, with the exception of *D. megastoma,* which produces gastric nodules of varying sizes near the margo plicatus. Females are viviparous, and larvae are passed in the feces, where they are then ingested by the larvae of flies acting as intermediate hosts. *H. muscae* and *D. megastoma* develop in the house fly, *Musca domestica,* and *H. microstoma* develops in the stable fly, *Stomoxys calcitrans*.[159] The L_3 larvae are then deposited around the horse's mouth and swallowed to pass to the stomach, where they mature to adults. Cutaneous lesions occur when the larvae are deposited in damaged skin or areas of natural body moisture. The larvae cannot penetrate normal healthy skin.[33] In these aberrant locations, they are unable to mature to adults, and the resulting proliferative lesions are thought to represent a hypersensitivity reaction to the dead or dying larvae. In temperate parts of the world, habronemiasis is a seasonal disease, occurring in warm, wet weather.

Arabians, gray horses, and horses with a dilute hair coat seemingly have a predilection for this disease. The medial canthus of the eye, male genitalia, nictitating membrane ("third eyelid"), and distal extremities are the most common parts of the body affected.[178] Lesions consist of ulcers and nodules. Diagnosis is based on clinical

signs, history, and the presence of calcified concretions (sulfur granules) and is confirmed by biopsy. The nodular lesions may take on the gross appearance of neoplasia. Alternatively, the larvae may infest a preexisting tumor, especially squamous cell carcinoma of the male genitalia, and a biopsy is crucial for accurate diagnosis. Characteristic histopathologic findings include granulation tissue with a diffuse infiltration of eosinophils and an ulcerative epithelial surface. The granulation tissue usually contains focal areas of coagulation necrosis surrounded by a dense eosinophilic infiltrate. Cross sections of larvae can often be identified within some of the necrotic foci.[178] Rarely, larvae are found in scrapings from the lesions.[159] Larvae are not always found in the biopsy sections[178]; in these cases, if neoplasia has been ruled out, presumptive treatment for habronemiasis should be performed. Recently, a PCR assay for diagnosing habronemiasis has been developed; this may hold promise in the future for those cases wherein the larvae are not found on biopsy.[179a]

Treatment in the past has been either corticosteroids or organophosphates, topical or systemic. Ivermectin (0.3 mg/kg PO) has been shown to be effective and is considered the treatment of choice by many clinicians. Moxidectin (0.4 mg/kg PO) may also be used. Systemic corticosteroids (e.g., prednisolone, 1 mg/kg once daily for 10 to 14 days, then tapered over 2 weeks) or intralesional or topical corticosteroids often are used because of the hypersensitivity-reaction nature of the disease process. In severe cases, surgical removal or debulking of the lesion should be considered.[179]

Habronemiasis has been seen in horses routinely given ivermectin as part of their deworming program.[179] Prompt removal and disposal of manure and soiled bedding are important to eliminate vector breeding habitats. Insect repellents should be applied to affected horses. Face guards (fly masks) will also prevent infection. In general, the prognosis for resolution of individual lesions is good if the therapeutic goals are achieved.

40.45 TUMORS AND CYSTS

40.45.1 SQUAMOUS CELL CARCINOMA

STEPHEN D. WHITE

40.45.1.1 Definition

Squamous cell carcinomas (SCCs) are tumors composed of squamous epithelial cells. They occur in all domestic species and are the most common bovine ocular tumor (see Chapter 39) and the second most common tumor recognized in the horse.[180] Although their gross appearance may vary, these tumors are usually slightly raised, broad based, and white to pink and have a cobbled or cauliflower-like surface. SCCs frequently occur on the penis and sheath of aged stallions and geldings (see Chapter 43). They also occur on the lips, nose, eyelids, eyes, and ears of horses. SCC often accompanies cutaneous papillomas of the udder and teats in Saanen milk goats, as well as in female Angora goats in South Africa. The ears, base of the horns, and prepuce may also be affected.[181] SCC is reported as being the most common cancer of the ear of sheep; an outbreak primarily affecting the eyelids in 15% to 18 % of a sheep population has been reported.[182] Diagnosis is by biopsy.

The treatment of choice is wide surgical excision.[183,184] Solar elastosis (aggregates of thick, wavy, interwoven elastic fibers, mixed with areas of degenerated collagen), when seen histologically with SCC, may lend a more favorable prognosis after complete surgical removal of lesions.[185] Other treatment

modalities reported as successful include cryosurgery, radiofrequency hyperthermia, and radiation therapy.[186] More recently, topical application of 5-fluorouracil (5-FU) and intralesional cisplatin were shown to be effective in horses with SCC.[187–190] Piroxicam was successful in the long-term control of SCC with metastases in one horse.[191]

40.46 EQUINE SARCOID

ALAIN P. THÉON

40.46.1 Epidemiology and Pathogenesis

The equine sarcoid was first reported in 1936 by Jackson.[192] It is the most common tumor in Equidae (horses, mules, and donkeys) worldwide and accounts for more than 50% of cutaneous tumors.

Sarcoids are locally aggressive, nonregressing, fibroblastic tumors of the dermis and subcutis with a variable proliferative epithelial component. This dual epidermal-dermal involvement is the hallmark of the sarcoid and explains its multiple and evolving clinical appearance. The epidermal component of sarcoid shares features with benign papilloma, and the fibroblastic component is consistent with low-grade fibrosarcoma.[193] These characteristics can lead to an incorrect histologic diagnosis of fibrosarcoma or nerve sheath tumors when the skin is not included in the tissue analyzed.[194]

Despite numerous clinical reports on sarcoids, the clinical and epidemiologic data are still puzzling. The inconsistent and sometimes conflicting data do not support a gender, breed, age, or genetic predisposition or any anatomic predilection.[195] These data reflect in part the frequent lack of histologic confirmation of the disease in reported studies and may represent regional or national variations in the clinical characteristics of sarcoids.

Epidemiologic evidence of a causative agent comes from the fact that age is not a risk factor. Unlike spontaneous tumors, affected horses are likely to have synchronous or metachronous lesions,[195] and sarcoid outbreaks have been reported.[196] It is widely accepted that bovine papillomavirus (BPV) types 1 and 2 are associated with the pathogenesis of sarcoid disease. The presence of viral genetic material is apparently necessary because it is always found in sarcoids, although it is not sufficient to produce the disease. The lesions and surrounding normal cutaneous margins contain detectable sequences of the viral genome, including E5, E6, and occasionally E2.[197,198] Both the epithelial and the fibroblastic component of the tumor contains viral genetic sequences.[199] However, the infecting viral genome sequences are nonproductive for infectious virions, and viral particles have never been detected. Transmission studies of sarcoids have been unsuccessful. Inoculation of sarcoid cell—free extract does not induce warts in cows or sarcoids in unaffected horses.[194] Experimental infection with BPV induces fibropapillomas clinically similar to sarcoids that regress spontaneously with production of antibodies to the virus.[200]

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The mode of transmission of sarcoid disease is unknown. It does not occur by casual contact with contaminated fomites or affected horses[201] or by BPV-infected insect bites.[202] The mechanisms of cellular oncogenesis are similar to those of other transforming papillomaviruses. Oncogenesis is associated with genomic integration and expression of the two transforming genes E6 and E7, which respectively bind to cell cycle control gene products, the Rb and p53 proteins.[203]

40.46.2 Biologic Behavior

Clinically, many sarcoids behave initially as benign lesions because they are slow growing, giving the false impression that the lesion is inactive. In addition, sarcoids are frequently classified as biologically "benign" tumors because they do not metastasize to distant organs, and regional metastasis is rare and usually associated with unsuccessful treatments.[204] However, the equine sarcoid is not a benign tumor because it is a progressive disease that invades and destroys surrounding normal tissue, does not regress spontaneously, and recurs predictably after surgical removal.[194,203,205] Early lesions are restricted to the dermis and epidermis, but advanced lesions typically invade the subcutis and may extend through fascia into deeper muscular structures. Considering sarcoids as benign tumors leads to inappropriate management early in the course of the disease and thus to multiple recurrences, resulting in unsatisfactory cosmetic and functional outcomes as well as unnecessary expenses to control the disease.

40.46.3 Clinical Findings and Diagnosis

Sarcoids are recognized as having different clinical manifestations, including occult, verrucous, and nodular clinical types[194] (Fig. 40-14). In addition, approximately one third of affected horses have multiple sarcoids at different clinical stages on diagnosis.[195] The different types represent stages of tumor progression and reflect the relative predominance of the dermal or epidermal component. Lesions with a predominant epidermal component include occult and verrucous sarcoids. *Occult* sarcoids appear as an almost-circular area of alopecia with a gray, scaly surface. *Verrucous* sarcoids may be sessile (flat variety) or pedunculated (warty variety); the skin is thickened with a dry rough surface, with partial or total alopecia. *Nodular* sarcoids, also called *fibroblastic* sarcoids, range in appearance from a dermal or subcutaneous nodule to a large, exophytic mass with a skin surface that eventually ulcerates. The nodular type is locally invasive, destroying adjacent tissues, and may ultimately infiltrate lymphatic vessels and nerve sheaths and disseminate to form regional metastases.[204] Mixed forms represent a transition from one type to another. Other classifications have been proposed, including up to six clinical types with four subtypes.[206] The multiplicity of recognized clinical forms confirms the equivocal and progressive nature of sarcoid disease. A classification, however, must be simple and reflect the biology of the disease to be clinically relevant and have prognostic value. As a result, tumors should be categorized as *indolent* sarcoids, including occult and verrucous types, or *invasive* nodular sarcoids. Invasive sarcoids may result from a sarcomatous progression of an indolent form or may appear de novo.

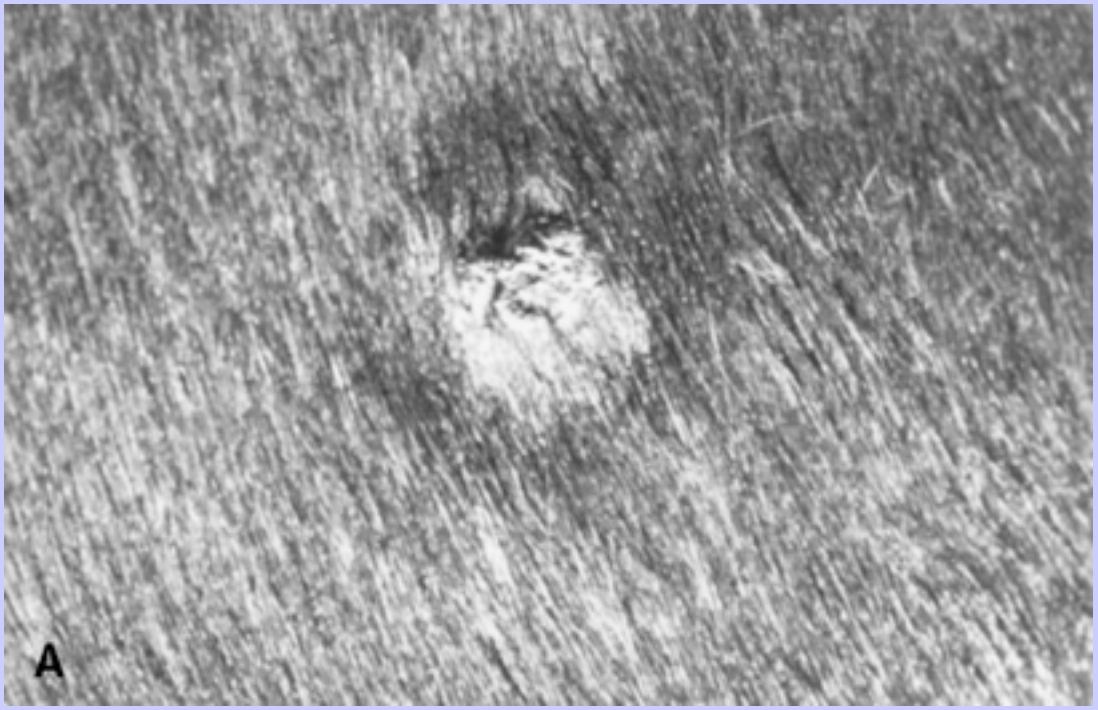
The polymorphic appearance of sarcoids, the lack of consensus on clinical classification and anatomic distribution, and the long list of differential diagnoses make the clinical diagnosis of sarcoids unreliable. The diagnosis and treatment of sarcoids require a biopsy because they are often overdiagnosed clinically. In a review of 681 horses referred to the Oncology Clinic at the Veterinary Medical Teaching Hospital of the UCD School of Veterinary Medicine for evaluation and treatment of sarcoids from January 1995 to June 2004, 345 cases were presented with a clinical diagnosis of sarcoid without a biopsy, and 31% of these were found to have nonneoplastic dermatologic conditions.[207] After ruling out a nonneoplastic skin condition, any clinically suspicious lesion should be biopsied.[208] As with any tumor, early recognition and treatment of a small lesion are always associated with a better prognosis. It is important to keep in mind that any large and invasive sarcoid associated with a poor prognosis was, earlier in its evolution, an apparently inactive small lesion that was not recognized or was deliberately neglected. There is no contraindication for biopsy of a suspicious skin lesion as long as definitive treatment is instituted immediately after the diagnosis is made. Clinicians should not be concerned about performing a biopsy of a suspected sarcoid because effective treatments are available. As with

any trauma, however, a biopsy can increase proliferation of a previously slow-growing tumor and may accelerate tumor progression. As a result, a biopsy should not be recommended if the owner is not willing to pursue treatment, if needed, because the process of biopsy without subsequent treatment has the same effect on overall prognosis as an unsuccessful attempt at treatment.

40.46.4 Therapy

Because tumor size and previous unsuccessful treatment attempts are the most important prognostic factors,[205,207] early and complete surgical resection is the mainstay of treatment of sarcoids.[208] Failure to eliminate the disease results in regrowth of a tumor that is histologically and biologically more aggressive and requires wider excision than the primary lesion. After surgery, it is critical to submit the resected specimen for histopathologic examination to determine the status of the surgical margins. As a rule, grossly or histologically incomplete resection (i.e., positive or close pathologic margins, <5 mm) must be followed by a re-resection, if possible, or by effective adjuvant treatment. For noninvasive sarcoids resected with pathologic margins greater than 5 mm and invasive sarcoids with margins greater than 1 cm, the risk of recurrence is low, and no further treatment except observation at regular intervals for at least 1 year is recommended. For invasive sarcoids resected with surgical margins between 5 and 10 mm, the risk of recurrence is high, and adjuvant treatment may be recommended, particularly when tumor recurrence may be difficult to manage because of unfavorable anatomic location. Access to molecular techniques (PCR and TaqMan PCR) designed to detect BPV E5 or E6 in pathologic margins will help assess the risk of recurrence and determine the need for adjuvant treatment.[209]

Fig. 40-14 Equine sarcoids. **A,** Small occult sarcoid. **B,** Multiple verrucous sarcoids. **C,** Fibroblastic sarcoid.



C

Among the nonsurgical treatments, interstitial radiation therapy and intralesional chemotherapy with cisplatin have well-documented efficacy against biopsy-confirmed sarcoids of all clinical types in any location.[210,211] Compared with radiation therapy, intratumoral chemotherapy with cisplatin is as effective, but without long-term side effects, and it does not require a special license. Although several antineoplastic drugs[212–215] and drug formulations[205,207,213,214,216] for intralesional chemotherapy have been evaluated, a crystal suspension of cisplatin in a sesame seed oil and Sorbitan monooleate (Span 80) emulsion has been shown most effective. (Native protein [i.e., the patient's own serum] preparations are proscribed because of their strong binding to cisplatin.[217]) When all stages and clinical types were combined, the cure rate after treatment with intratumoral cisplatin therapy used alone or as an adjuvant to surgery has been reported to be as high as 96%.[207] Treatment includes a series of four intralesional doses of cisplatin (~1 mg/cm^3 tissue) given at 2-week intervals. Generic cisplatin is widely available and inexpensive. Treatments are done on an outpatient basis, and the methods of administration and safety precautions have been described.[214]

Nonspecific immunotherapy using bacille Calmette-Guérin (BCG) cell wall derivatives* administered intralesionally[211] has been shown to be effective only for periocular sarcoids.[205,218,219] The number of treatments depends on the rate of tumor regression, and the treatment schedule is dependent on normal tissue toxicity; most sarcoids require 2 to 9 treatments over several weeks.[205]

Encouraging results have been reported with imiquimod, a biologic response modifier, used topically.† The ointment is recommended for the treatment of viral warts and basal cell carcinomas in people. It is applied as a thin layer to the tumor surface three times a week on nonconsecutive days, up to 32 weeks until resolution.[220] The reported 60% response rate suggests that topical imiquimod may be a therapeutic option for specific equine sarcoids. However, the data must be confirmed in a larger series of horses with sarcoids and after adequate long-term follow-up.

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Topical applications of escharotics with zinc chloride—based caustic ointments* or 5-FU cream† are used empirically for treatment of sarcoids. Unfortunately, no scientific data have been published documenting treatment efficacy against actual equine sarcoids. As a result, no information on treatment protocol, efficacy, prognosis, or toxicity is available.

* Nomagen, Fort Dodge Laboratories, Fort Dodge, Iowa.

† Imiquimod 5% cream; Aldara, 3M Pharmaceuticals, Minneapolis, MN.

* Indian Mud, Original Cream Company, Magnolia, AR; XXTERRA, Larson Laboratories, Fort Collins, Colo; Animex, NIES, Las Vegas.

† Efudex (5% fluorouracil), Hoffmann La Roche, Nutley, NJ.

40.47 MASTOCYTOSIS

STEPHEN D. WHITE

In horses, mastocytosis (mast cell tumors, mastocytomas) occur in animals 1 to 18 years old (average, 9 years), with no breed predilection. A predilection for males has been proposed but is not always sustained.[221,222] In addition, multiple mast cell tumors resembling urticaria pigmentosa of humans may occur in newborn foals; these spontaneously appear and regress.[222,223]

Equine mastocytosis is usually solitary and occurs most often on the head and trunk. Lesions are 0.5 to 20 cm in diameter, well to poorly circumscribed, firm to fluctuant, dermal or subcutaneous, and may or may not be alopecic, ulcerated, and hyperpigmented. Lesions on the legs tend to be very firm and immovable.

Histology may vary from sheets of mast cells with few eosinophils (presumably early lesions) to sections showing both sheets of mast cells with numerous eosinophils and collagen degranulation. Ultrastructural features are similar to those noted in mastocytomas of other species.[224]

Clinically, most mast cell tumors in horses do not recur after being excised (22 of 25 in one study).[224] In one anecdotal case of metastasis from a tumor on the muzzle to regional lymph nodes, the tumor and the nodes were removed, and the horse was clinically sound 3 years later. There is some debate as to whether equine mastocytomas are benign neoplasias or focal dysplasias of mast cells.

Mastocytomas are uncommon in cattle but typically occur in young calves.[225,226] One report describes a cutaneous mast cell tumor in a kid goat.[227] Although equine mastocytomas are almost always benign, mastocytosis in cattle may be malignant or benign and therefore carry a more guarded prognosis.

40.48 MELANOMA

STEPHEN D. WHITE

40.48.1 Equine Melanomas

Melanomas occur in all domestic animals, but of the large domesticated species, they are most important in the horse. Excessive exposure to sunlight has not been definitively proven to predispose horses to the development of melanoma. A disturbance in melanin metabolism associated with graying has been hypothesized to stimulate formation of new melanoblasts or to stimulate their activity, resulting in focal areas of overproduction in the dermis and epidermis, with subsequent tumor formation.[228] A higher incidence is observed in the Arabian, Lipizzaner, and Percheron breeds, probably because gray coat color occurs more often in these breeds. There is no gender predilection.

Melanocytic skin tumors of horses traditionally have been described in aging gray horses, in *typical* locations: the ventral tail, perineum, external genitalia, lip, udder, and periocular and parotid gland regions. These tumors have been the subject of several classification schemes in attempting to correlate histopathologic appearance with clinical behavior (i.e., benign or malignant). One study distinguished three basic types of melanocytic skin tumors, as discussed next.[229]

Melanocytic nevi (melanocytoma) occur in the superficial dermis or at the epidermal-dermal junction and frequently have epithelial involvement, with nests of relatively large, mildly to moderately pleomorphic cells showing variable cytoplasmic pigmentation and occasional mitoses. More than 70% of these occur in horses less than 6 years of age and may occur in horses of any color (not just gray). Most of these tumors occurred in *atypical* locations. Of 28 melanocytic nevi, only one became invasive; the rest exhibited benign behavior.

Dermal melanomas are found in the deep dermis and are composed of small, homogenous, indistinct tumor cells, either round or dendritic, with no mitoses. (If there are multiple, confluent dermal melanomas, this is referred to as *dermal melanomatosis*). About 80% of these tumors are in horses older than 6 years[229] or

between 5 and 15 years[230] and are much more common in gray horses. Most of these tumors occurred in *typical* locations. Of 14 cases available for follow-up in one study,[229] eight had malignant behavior, as demonstrated by metastases.

In another study, clinicopathologic characteristics of cutaneous melanomas occurring in 83 Camargue-type gray-skinned horses showed that the tumors occurred most frequently underneath the tail (93.9%) and at high rates in the perianal region (43.0%), the lips (33.0%), and the eyelids (24.0%), but rarely in the vulva (3.8%).[231] Microscopic examination indicated that these tumors were composed mostly of melanocytes and numerous melanophages, and that these cells manifested a remarkable cellular atypia. Early stages of the tumors occurred in close association with apocrine sweat glands, but not at the dermal-epidermal junction.

A clinical study was conducted on 296 gray horses of the Lipizzaner breed.[232] Of the 296 horses, dermal melanomas were present in 148 horses (50%), 68 of which were older than 15 years; 51 of these were melanoma bearing. In 75.6% of cases, melanotic tumors were detected underneath the tail. None of the affected individuals had any severe clinical effect or was handicapped in performance. The authors concluded that in contrast to melanomas in solid-colored horses characterized by early metastases, melanomas in gray horses showed less malignancy. Affected individuals often had encapsulated nodules or structures similar to human blue nevi. This finding at least partially reflects confusion in terminology between true malignant melanomas and dermal melanomas.

Anaplastic malignant melanomas are composed of sheets of extremely pleomorphic epithelioid cells with poor pigmentation and many mitoses. These are usually seen in horses older than 20 years of age and occur in horses of any color. Metastasis usually occurs first to the regional lymph nodes, then to the lungs, spleen, and liver. Hematogenous spread may also occur. Metastatic growths may be larger than the primary lesions and softer in consistency.

In regard to treatment, one study reported good success with excising dermal melanomatosis from the perineal, perianal, perirectal, or ventral tail regions.[233] In a study of three horses, cimetidine (2.5 mg/kg PO q8h) was shown to decrease the number and size of melanoma growth.[234] However, a more recent study of 10 horses found that cimetidine had no consistent effects on either the number of tumors or the tumor surface area over the 16 weeks of treatment at 5 mg/kg PO q12h.[235] Another recent article noted a cure rate of 81% for melanomas treated with intratumoral injections of cisplatin.[207]

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40.48.2 Bovine Melanomas

Melanomas represented a large proportion of the cutaneous neoplasms of cattle in an older study.[236] The majority are benign, well-differentiated tumors, subcutaneous in location, and without site predilection. Dark-haired cattle are predisposed, particularly the Aberdeen Angus breed. There is no gender predilection.[236] Melanomas usually occur in young cattle and are occasionally recognized as congenital lesions.[237]

40.48.3 Caprine and Ovine Melanomas

Melanomas have been observed only rarely in sheep and goats.[236–239] A survey of 800,000 slaughtered goats revealed only five melanomas.[237] The most common site for melanomas in the goat is the perineal region,[29]

although there is a case report of a malignant melanoma occurring in the coronary band region.[238] Melanomas in Angora goats histologically resemble the corresponding tumors in humans.[239]

40.49 CUTANEOUS LYMPHOSARCOMA

STEPHEN D. WHITE

40.49.1 Equine Lymphoma

Cutaneous lymphoma has occasionally been reported in horses.[240–247] Both T-cell and B-cell forms have been reported. Lesions present as nodules, either cutaneous or subcutaneous. Diagnosis is made by biopsy and, ideally, immunohistochemistry to determine cell type.[246,247] In one horse, progesterone receptors were demonstrated on the lymphoma (B) cells, and the lesions regressed after removal of an estrogen-secreting ovarian tumor.[243] This horse also had a history of partial regression of its tumor after administration of a synthetic progestin, altrenogest (0.044 mg/kg PO once daily for 10 days). Another horse demonstrated reduction in tumor size after administration of another synthetic progestagen, megestrol acetate (0.2 mg/kg PO once daily for 8 days) as well as a local injection of 20 mg betamethasone into a mass.[244] Clearly, treatment is far from standardized, but the progesterone drugs may offer a reasonable treatment modality.

Lymphosarcoma is discussed in Chapter 37.

40.49.2 Bovine Lymphoma

Cattle occasionally are affected by cutaneous lymphoma. The presentation is multifocal intracutaneous nodules, often accompanied by alopecia. Lymphadenopathy, leukocytosis, and lymphocytosis are often present, and internal organs may be affected.[248]

40.49.3 Ovine Lymphoma

There are rare reports of cutaneous lymphoma in sheep.[249,250]

40.50 CYSTS

STEPHEN D. WHITE

Cutaneous cysts are benign lesions characterized by an epithelial wall with keratinous contents. Cutaneous cysts are subdivided into several types on the basis of their histopathologic features.

40.50.1 Epidermal Cysts

Among large animals, epidermal cysts have been reported in horses,[251] cattle,[252] and sheep.[253] These cysts may be more properly called *follicular cysts* because the epithelial lining is probably most often derived from the follicular epithelium rather than the epidermis. The cysts can be found anywhere on the body, single or multiple, congenital or acquired, and generally range in size from 0.2 to 3 cm in diameter. The cysts are covered by intact epithelium and generally do not attach to the overlying epidermis. Microscopically, epidermal cysts

consist of a wall of stratified squamous epithelium surrounding a keratin-filled lumen. Epidermal appendages are not associated with the cyst wall, a feature that distinguishes epidermal from dermoid cysts.

Epidermal cysts are thought to originate from occlusion of a hair follicle or by traumatic implantation of the epidermis. A tentative diagnosis may be made by performing fine-needle aspiration of a lesion and obtaining a fluid that is clear to brownish in color. Aspiration of the contents may temporarily decrease the size of the cyst, but it typically refills. Definitive diagnosis is made by excisional biopsy, which is curative. Epidermal cysts are benign lesions, although painful inflammatory responses and ulceration may result if the cyst is ruptured, with extrusion of contents into the adjacent dermis and subcutis.

40.50.2 Dermoid Cysts

Dermoid cysts are very similar clinically to epidermal cysts but are much less common. Among large animals, they have been identified in horses,[251] goats,[254] and cattle.[255] In cattle, dermoid cysts may be congenital, have been reported to be as large as 10 cm (4 inches) in diameter, and are said to develop most frequently over the cranial area of the thorax[255] and in the pharyngeal region. In horses, dermoid cysts may be single or multiple and are observed most frequently along the dorsal midline between the withers and the croup. Dermoid cysts are believed to result from displacement of embryonic cells into the subcutaneous tissue. They can be distinguished histologically from epidermal cysts by the presence of epidermal appendages within the wall of the cyst and by a lumen that often contains hair and secretions from sebaceous and sweat glands in addition to keratin. As with epidermal cysts, surgical excision is diagnostic and curative.

40.50.3 Dentigerous Cysts

Dentigerous cysts are a congenital defect recognized in horses and are believed to be the result of an abnormality of the first branchial cleft.[256] Clinically, a unilateral saclike swelling that contains embryonic teeth is seen at the base of the ear. The lesion may be firmly attached to the concheal cartilage or temporal bone. Dentigerous cysts tend to fistulate. Treatment consists of surgical excision.[256] Dentigerous cysts have also been reported in sheep and are suspected of being related to a nutritional deficiency of copper.[257]

40.50.4 Wattle Cysts

Wattle cysts are found in goats and usually are present at the base of the wattle. Nubians and Nubian crossbreeds may be predisposed to developing these cysts. The cysts are congenital, but they may not be apparent until the animal is several months old. Tentative diagnosis is based on aspiration of clear fluid, which will temporarily decrease the size of the cyst. Surgical excision is diagnostic and curative. Histologic examination reveals a cyst wall composed of one or two layers of cuboidal to columnar epithelial cells. The cyst cavity contains homogenous, amorphous basophilic substances.[257]

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40.51 FROSTBITE

STEPHEN D. WHITE

Frostbite is an uncommon injury among healthy, well-nourished animals, with all species being susceptible. It is caused by prolonged exposure to subfreezing temperatures. The length of time needed to cause frostbite depends

on the ambient temperature, area of the body exposed, and health status. The areas most often affected by cold injury include the ears, tail, teats, scrotum, and distal legs.

Frozen tissue must be handled gently and thawed rapidly in warm water 38° C to 44° C (100.2° F to 111.1° F) as soon as possible after it is known that refreezing can be prevented. Tissue damage is greatly increased if thawing and subsequent refreezing occur (freeze-thaw-freeze-thaw syndrome). Tissue thawing is painful, and analgesics should be administered. Slow thawing is less painful than rapid thawing but results in much greater tissue damage. Frozen tissue should not be massaged during warming. Damaged areas are best left exposed during the healing process rather than covered with occlusive dressings, and premature debridement should be avoided because more tissue may be viable than first apparent. The animal should be given good supportive care and may need to be restrained to prevent self-mutilation. Management practices should be changed to prevent recurrence. Tissues previously damaged by freezing are more susceptible to cold injury when reexposed to subnormal temperatures. [7,258]

40.52 SKIN DISORDERS OF UNKNOWN OR GENETIC ORIGIN

STEPHEN D. WHITE

40.53 EQUINE SEBORRHEA

Several possibly related equine skin diseases characterized by scaling and crust formation are referred to as "seborrhea." Contrary to claims in the older literature, there is little evidence that seborrhea is related to excess sebum production by the sebaceous glands. Most types of seborrhea are probably diseases of abnormal cornification (development of the stratum corneum). Further, most cases reported as "generalized seborrhea" in the horse were probably pemphigus foliaceus, equine sarcoidosis (chronic granulomatous disease), or some other immune-mediated or autoimmune disease. Mane and tail seborrhea is typified by moderate to heavy scaling, with minimal or no pruritus. Some horses have considerable alopecia of the tail.

Cannon keratosis is a common equine skin condition. It involves the cranial surface of the rear cannon bone region and rarely the forelimbs. The lesions consist of areas of scaling and crusting with varying degrees of alopecia. There is no pruritus or other signs of inflammation. Cannon keratosis occurs in both males and mares, so there is no basis for the theory that the condition is caused by urine splatter ("stud crud").[33]

40.54 LINEAR KERATOSIS AND LINEAR ALOPECIA

Linear keratosis and linear alopecia are rare equine dermatoses of unknown cause. There is one report in a cow.[259] The lesions do not follow blood or lymphatic vessels, nerves, or dermatomes. Because both conditions coexist in some horses, it has been suggested that they are variations of the same abnormality, although this is difficult to justify histopathologically. Both conditions have been seen in a wide variety of breeds, but quarter horses appear to be predisposed. Most horses develop lesions between 6 months and 5 years of age.

Linear alopecia is characterized by the gradual development of annular areas of alopecia, usually in a linear, vertically oriented configuration. One or more linear areas may be present. The lesions are usually 2 to 10 mm wide by a few centimeters to over 1 m in length and occur on the neck, shoulder, and lateral thorax. Mild surface scale and crust may be present. The lesions are neither painful nor pruritic. Affected horses are typically otherwise healthy.

Linear keratosis is characterized by the gradual, asymptomatic occurrence of one or more unilateral, linear, vertically oriented bands of hyperkeratotic papules that progress to marked hyperkeratosis and alopecia. The lesions vary from 0.25 to 3.5 cm in width by 5 to 70 cm in length and occur most often over the neck, shoulder, and lateral thorax. Lesions have also been reported to involve the legs, hip, and pectoral region. Again, affected horses are typically otherwise healthy.

These disorders are visually distinctive. Histopathologic findings in linear alopecia include early lymphocytic, infiltrative, mural folliculitis and later granulomatous, infiltrative, mural folliculitis. The mural infiltrate is often directed at the middle area (isthmus) of the follicle. Sebaceous glands may be involved in some cases, and complete follicular destruction and permanent alopecia are seen in severe chronic lesions. Histopathologic findings in linear keratosis include irregular to papillated epidermal hyperplasia and marked compact orthokeratotic hyperkeratosis.[260] I have seen one horse that had lesions grossly diagnosed as linear keratosis, whereas the histopathology had features of both conditions.

Neither condition is known to undergo spontaneous resolution. Owners should be advised of the potential hereditary nature of these disorders. Linear alopecia has been anecdotally reported to respond to topical or systemic glucocorticoids, but recurrence is likely. Response to therapy is more likely to be seen in early lesions, when complete destruction of hair follicles has not occurred. Linear keratosis responds poorly to treatment. Topical keratolytic and keratoplastic agents, such as sulfur/salicylic acid—containing shampoos or 50% propylene glycol, can reduce the hyperkeratosis but must be continued for life. I have had some success using tacrolimus (Protopic, Astellas Pharma US, 0.1% ointment), a drug similar to cyclosporine but better absorbed through the skin, once or twice daily. Because neither condition is symptomatic, observation without treatment may be an acceptable approach.

Interestingly, a report exists of a familial incidence of linear epidermal nevi in Belgian horses.[261]

40.55 ALBINISM

Complete and partial albinism occurs in cattle, sheep, and horses. It is a genetic defect (probably autosomal recessive) in melanin synthesis, resulting in white skin, white hair, pink eyes, and photophobia. In horses, albinism must be distinguished from *lethal white syndrome,* which is primarily a problem in Paint horses (especially, but not exclusively, in overo breedings). The defective gene has also been found in American miniature horses, half-Arabians, thoroughbreds, and cropout quarter horses (foals born to registered quarter horses that have too much white to register as with the AQHA).[262] The Veterinary Genetics Laboratory at UCD offers a diagnostic test to determine carrier status.[*]

The lethality of albinism in horses comes from the association with intestinal aganglionosis. The foals die shortly after birth. Because some white foals are not affected, euthanasia should be performed only after signs of intestinal malfunction occur. This disease is similar to Hirschsprung disease in humans and is linked to a mutation in the endothelin-B receptor gene.[263]

* www.vgl.ucdavis.edu/service/horse/index.html.

40.56 JUVENILE ARABIAN LEUKODERMA (ARABIAN FADING SYNDROME, PINKY SYNDROME, HEREDITARY VITILIGO)

Loss of melanin in the skin (depigmentation) occurs in young Arabian horses 6 months to 2 years of age (Fig. 40-15,*A*). The areas most frequently affected are periocular tissues, muzzle, genitalia, anus, perineum, inguinal region, and undersurface of the base of the tail. Depigmentation may persist, repigment, or wax and wane. The condition is probably hereditary.[33]

40.57 VITILIGO

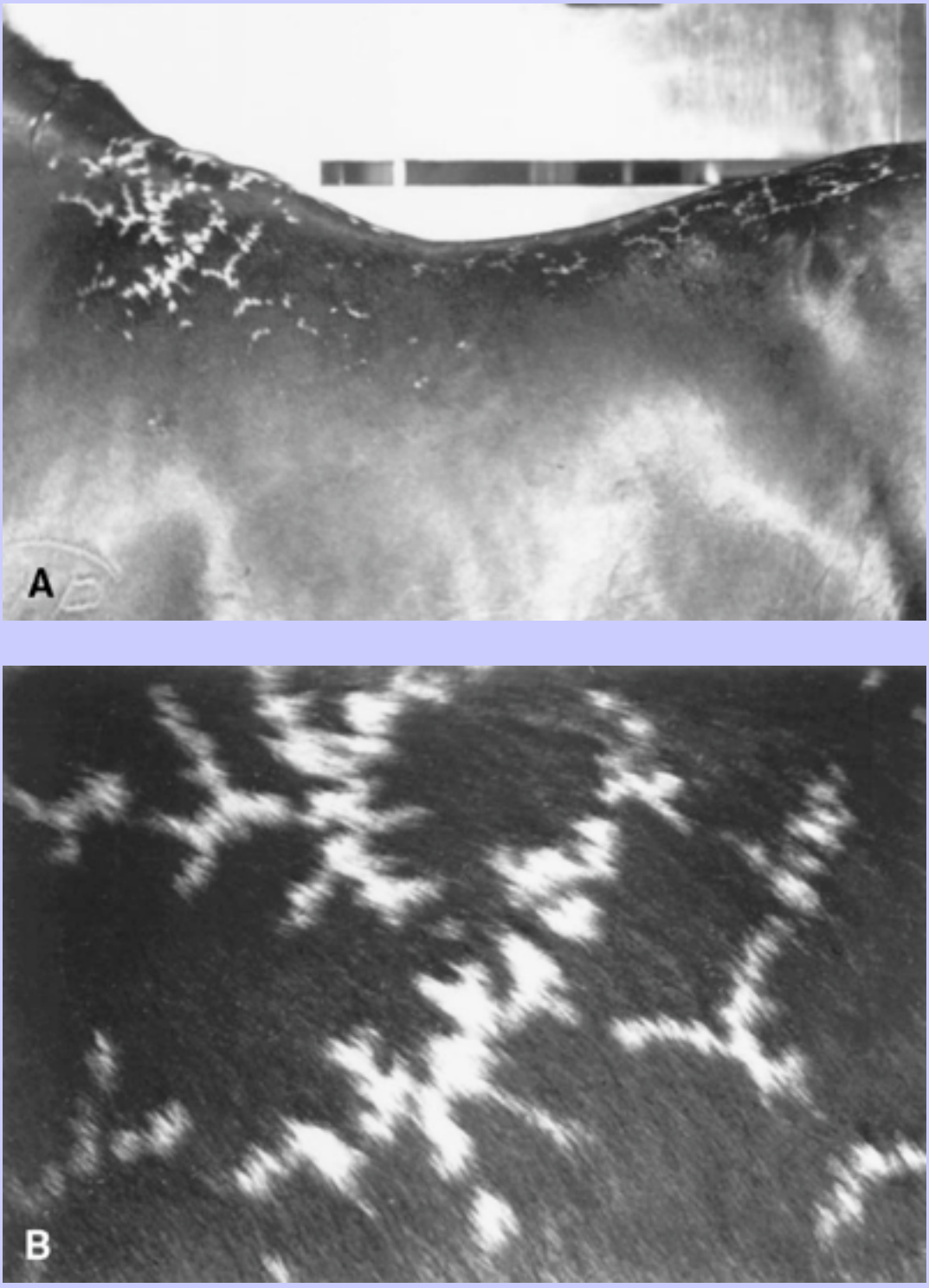
This condition is best defined as "idiopathic depigmentation." Typically, no trauma has occurred to produce the loss of pigment, and other skin structures are not affected (i.e., no scarring or alopecia) (Fig. 40-15,*B*). There is no known treatment for vitiligo.

40.58 RETICULATED AND HYPERESTHETIC LEUKOTRICHIA

Reticulated leukotrichia occurs mainly in quarter horses, usually as yearlings, and occasionally in other breeds. The lesions occur on the dorsal midline and consist initially of linear crusts arranged in a characteristic cross-hatch pattern (Fig. 40-16). The crusts shed, alopecia occurs, and white hair grows in permanently. There is leukotrichia without leukoderma (depigmented skin). Histologically, these lesions resemble an epidermal form of erythema multiforme, resulting in individual keratinocyte necrosis. *Hyperesthetic leukotrichia* is a similar disease both clinically and histologically, except the crusts are extremely painful to the touch. Within a few weeks, white hairs appear in the affected areas. The crusts resolve, and the pain subsides in 1 to 3 months, but the leukotrichia persists. Several cases have been linked to recent rhinopneumonitis vaccination. These diseases may rarely recur, and there is no known effective treatment.[33]

Fig. 40-15 **A,** Juvenile Arabian leukoderma. **B,** Vitiligo in a horse. (Courtesy Dr. Anthony Stannard.)

Fig. 40-16 Reticulated leukotrichia in a yearling quarter horse. (Courtesy Dr. Anthony Stannard.)



40.59 HEREDITARY EQUINE REGIONAL DERMAL ASTHENIA (HYPERELASTOSIS CUTIS)

Hereditary equine regional dermal asthenia (HERDA) occurs early in life in horses. Most affected horses are quarter horses, but registered Paint horses and Appaloosas with quarter horse lineage have developed this disease.[264,265] Many of the quarter horses are from high-quality cutting lines. The disease (or similar condition) has also been reported in a crossbred Arabian mare, a thoroughbred gelding, a Hanoverian foal, and a Hafflinger horse.[7,266–268] Rarely, a similar disease has been noted in cattle, termed *dermatosporaxis;* this is caused by mutations in the procollagen I N-proteinase gene.[268,269]

The working hypothesis for HERDA in horses is a defect in the structure or healing process of the collagen fibers in the middle to deep dermis. Typically, these areas are over the back and sides of the neck (Fig. 40-17). The skin in these areas may be easily torn or stretched and often develops seromas and hematomas ("blisters" filled with either serum or blood). Healing is usually adequate but often leaves rather unsightly scars. Diagnosis is often based on the clinical signs alone; histologic findings are sometimes subtle, but "clumped" or poorly organized collagen fibers below the level of the hair follicles may be seen. A zone of middermal to deep dermal separation has been reported in two horses and is present in some biopsy samples.[265,270] "Poorly oriented" collagen fibers are sometimes seen on electron microscopy.

Fig. 40-17 Hereditary equine regional dermal asthenia (HERDA, hyperelastosis cutis) in a horse showing hyperextensible skin. (Courtesy Dr. Anthony Stannard.)

This condition is almost certainly present at birth, but HERDA is often not noticed until about 2 years of age

This condition is almost certainly present at birth, but HERDA is often not noticed until about 2 years of age, when horses start being trained with tack and saddle, and the resulting friction and trauma induce the typical lesions. As with many genetic diseases, no effective treatment or cure exists; some of these horses have been maintained as "pasture pets."

This disease follows an autosomal recessive mode of inheritance, so in order for the foal to be affected, both the sire and the dam must carry the gene, and if they were bred again, there would be approximately a 25% chance that the next foal would also be affected.[271] Recently, a genetic marker was determined for this disease.[271a] The Veterinary Genetics Laboratory at the University of California, Davis offers a diagnostic test to determine carrier or affected status (http://www.vgl.ucdavis.edu/service/horse/index.html). Both carriers and clinically affected horses with HERDA should be removed from breeding programs.

40.60 EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa (EB) includes a number of diseases typified in humans by the common finding of blister formation after minor trauma. Most forms are congenital and apparent soon after birth. In animals and humans, subsets of EB are classified by the histologic location of the blister or cleft. These subtypes (and respective cleft location) are termed EB *simplex* (basal cell layer of epidermis), *junctional* EB (intralamina lucida or basal cell layer), and *dystrophic* EB (sublamina densa).

Junctional EB has been reported in Belgian foals of both genders, in other breeds, and in a donkey.[272–275] Lesions are usually noted within 3 days of birth and include multiple asymmetric skin erosions and ulcers, often encrusted. Lesions may be especially prominent around the coronary bands (causing the hoof to crack and slough) and on the oral, anal, and genital mucosa. Histology and ultrastructural findings indicate a cleft in the intralamina lucida of the basement membrane zone. This is presumably caused by a defect in the anchoring filaments that connect the basement membrane to filaments in the superficial dermis.[273] A laminin-5 defect has been demonstrated in Belgians and in two French draft breeds, Trait Breton and Trait Comtois; the mutation is a cytosine insertion in exon 10 of the LAMC2 gene.[276–278] Because of this knowledge, the Veterinary Genetics Laboratory at UCD offers a diagnostic test to determine carrier status in Belgian draft horses and related breeds.*

Clinical presentation and the age of the foal are highly suggestive of EB diagnosis. Histology and ideally electron microscopy are required to confirm the diagnosis. There is no known treatment, and affected horses, as well as the sires and dams of affected horses, should not be bred; the mode of inheritance is autosomal recessive.

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This disease differs from epitheliogenesis imperfecta (see following discussion) in that large areas of the skin are *not* at first devoid of epidermis, but rather lose their skin because of the fibril defect.

* www.vgl.ucdavis.edu/service/horse/index.html.

40.61 EPITHELIOGENESIS IMPERFECTA (APLASIA CUTIS)

Epitheliogenesis imperfecta is a rare inherited congenital discontinuity of squamous epithelium. It is thought to be an autosomal recessive trait and has been reported in several breeds. Lesions are most common on the limbs, head, and tongue. Hooves may slough in severe cases. Clinical presentation is usually diagnostic.[279] In moderately to severely affected animals, the disease is fatal within a few days; the foals die of septicemia or other developmental abnormalities. Mildly affected areas may heal by scar formation. More recent reports suggest that some of these horses (saddlebreds) may have a condition similar to the junctional epidermolysis bullosa in [280–282]

Belgian foals previously noted.[280–282]

40.62 EOSINOPHILIC GRANULOMA (NODULAR NECROBIOSIS, COLLAGENOLYTIC GRANULOMA)

Eosinophilic granuloma is the most common nontumor nodular disease in the author's practice. In most cases the etiology is unknown, although a hypersensitivity reaction to insect bites has been suggested. There is no apparent age, breed, or gender predilection. The disease often begins in warmer months. Lesions up to 5 cm (2 inches) in diameter may be single or multiple and most often affect the neck, withers, and back (Fig 40-18). Skin biopsy reveals multifocal areas of abnormal-staining collagen surrounded by granulomatous inflammation containing eosinophils, lymphocytes, and histiocytes.[33] This is not thought to be caused by "degeneration," but rather by degranulation of eosinophils and the coating of normal collagen fibers with the degranulated material.[283]

Development of equine eosinophilic granuloma has been noted in areas of previous injections using standard silicone-coated, stainless steel hypodermic needles.[284] The reaction may occur at sites of intravenous as well as intramuscular injections. The lesions consist of nonpainful, cool, raised papules or nodules 0.25 to 1 cm in diameter at sites of previous injection. The nodule appears 24 to 48 hours after the injection, and the subsequent eosinophilic granuloma can persist for months to years. Affected horses do not develop a lesion at the site of injection if nondisposable, noncoated needles are used. The use of the noncoated needles is recommended for any horse that develops injection-site collagenolytic granulomas.

Fig. 40-18 Eosinophilic granuloma (nodular necrobiosis), with dermal nodules on the withers of a horse. (Courtesy Dr. Anthony Stannard.)

Horses with solitary or a few lesions may be treated by surgical excision (not in the saddle area) or glucocorticoid

Horses with solitary or a few lesions may be treated by surgical excision (not in the saddle area) or glucocorticoid injections under the lesions. Triamcinolone acetonide (3 to 5 mg per lesion) is effective. It has been recommended that no more than 20 mg triamcinolone acetonide be administered at once to any horse because any more of this drug may cause laminitis.[33] Horses with multiple lesions may be treated with oral prednisolone at 1 mg/kg once daily for 2 to 3 weeks. Multiple, small (<1 cm) lesions may be indicative of insect bite hypersensitivity.

40.63 CUTANEOUS AMYLOIDOSIS

Cutaneous amyloidosis is an uncommon nodular dermatosis of unknown etiology. There is no age, breed, or gender predilection. The condition appears to be a primary form of amyloidosis, in that concurrent inflammatory processes are not present, and amyloid (a fibrillar protein substance derived from immunoglobulins) deposition is usually restricted to the skin and occasionally the regional lymphatics, regional lymph nodes, and upper respiratory mucosa.[7,33] One case was documented as being caused by lambda—light chain deposition from an extramedullary plasmacytoma.[285] Another horse showed amyloidosis concurrent with lymphoma.[286]

Papules, nodules, and plaques on the head, neck, shoulders, thorax, or inguinal areas are firm, 0.5 to 10 cm in diameter, nonpainful, and nonpruritic. The overlying skin is normal, although it may scale or crust in severe cases (Fig. 40-19). The course of cutaneous amyloidosis is progressive and prolonged. Megestrol acetate may be an effective treatment (0.2 mg/kg PO q24h until lesions resolve). Because certain forms of primary amyloidosis in humans have a genetic basis, it may not be advisable to use affected horses for breeding until more is learned about the genetics of the equine disorder.

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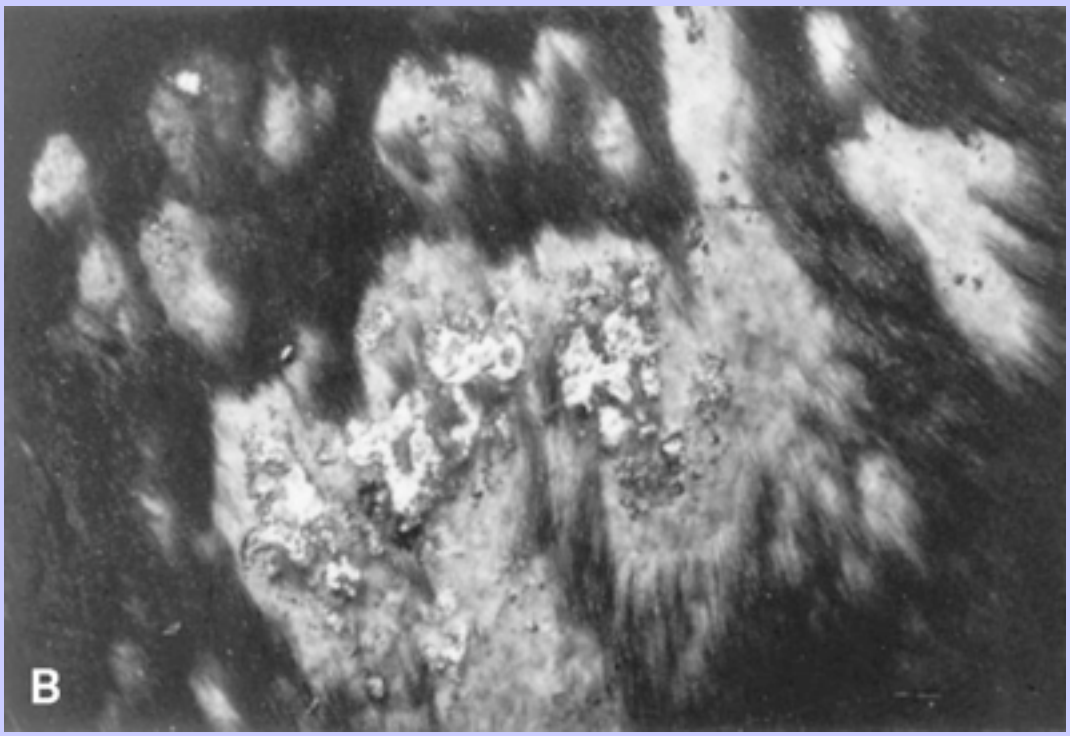
Fig. 40-19 **A** and **B,** Cutaneous amyloidosis in a horse. (Courtesy Dr. Anthony Stannard.)



40.64 EQUINE SARCOIDOSIS (GENERALIZED GRANULOMATOUS DISEASE)

EQUINE SARCOIDOSIS (GENERALIZED GRANULOMATOUS DISEASE)

Equine sarcoidosis is characterized by skin lesions and usually concurrent systemic involvement. It is *not* a neoplastic disease and should *not* be confused with equine sarcoids.

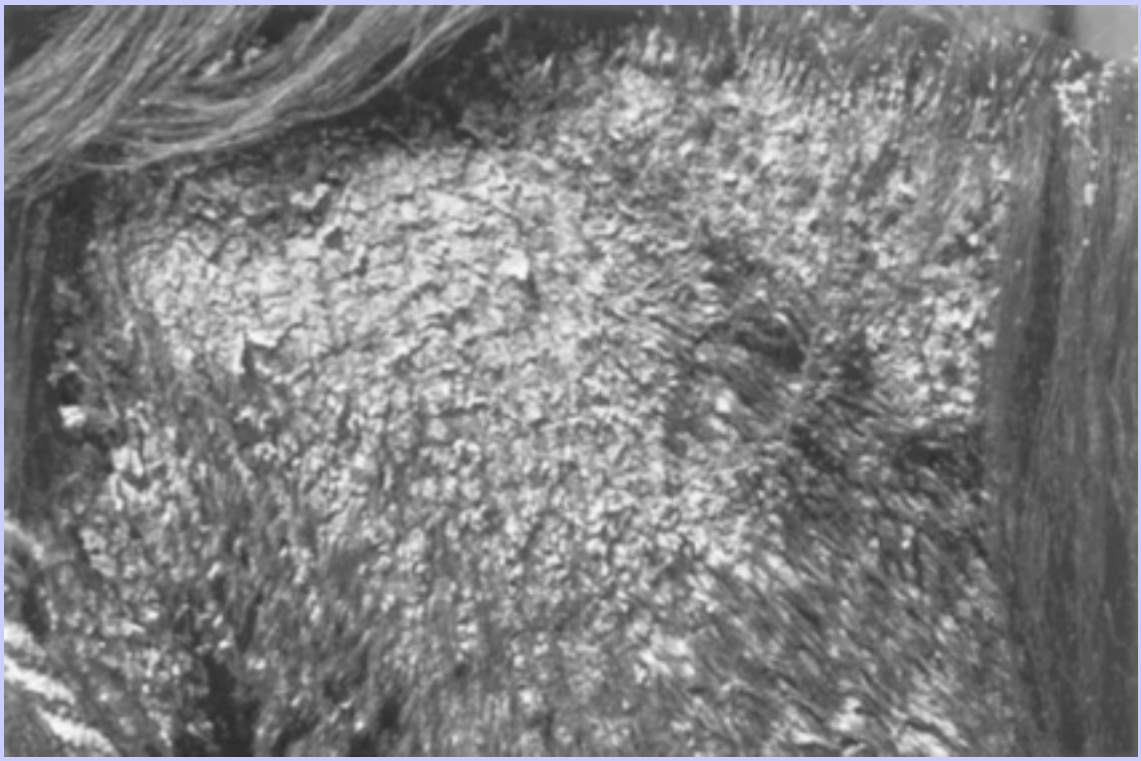
The disease is infrequently encountered, and there is no known breed predilection. Geldings may be at increased risk.[287] The skin lesions typically are generalized scaling and crusting associated with varying degrees of alopecia (Fig. 40-20). Occasionally, the disease is focal or multifocal in distribution. Rarely, the skin lesions consist of nodules or large, tumor-like masses. The different types of skin lesions may coexist. In addition to skin lesions, the most frequent presenting complaints are weight loss, decreased appetite, and a persistent low-grade fever. Lung involvement is manifested by exercise intolerance, increased resting respiratory rate, and mild dyspnea.[288–290] Although one report showed positive titers to *Borrelia burgdorferi* in three of four horses with equine sarcoidosis,[291] a more recent report was unable to demonstrate the presence, using PCR and histologic stains, of any causative organism.[287]

Diagnosis is by histopathology and ruling out infectious etiologies. The major histologic change is the presence of noncaseating granulomas consisting of aggregates of epithelioid cells and multinucleated giant cells. Neutrophils, lymphocytes, and plasma cells are present in small numbers. In the skin the granulomas tend to be located in the superficial portion of the dermis. Because of the small number of horses studied and the variability of clinical signs, response to therapy has not been well documented. A recent abstract reported that five of six horses did well and lived longer than 1 year with prednisolone treatment.[292] Another extensive review showed that some horses did well on corticosteroid therapy (usually at doses approximating those used to treat pemphigus and other autoimmune skin diseases); gastrointestinal involvement was a sign of poorer prognosis.[287]

40.65 PHOTOSENSITIZATION

Photosensitivity is an abnormal reaction of the skin when exposed to light. Photosensitivity in the horse is usually caused by a photodynamic agent in or on the skin that absorbs or transfers energy from light and transfers it to body cells. The activating light is generally in the ultraviolet A (UVA) range (320 to 400 nm). Melanin in the skin screens UV light, thereby limiting photosensitivity reactions to the white and light-colored areas of the body.[293]

Fig. 40-20 Equine sarcoidosis (generalized granulomatous disease) in a horse. In addition to the scaling and crusting skin lesions, the horse has systemic involvement. (Courtesy Dr. Anthony Stannard.)



Photodynamic agents may be drugs, topical medications, foodstuffs, contactants, or excessive phylloerythrin from liver disease. Examples of plants containing photodynamic agents follow:

Common Name	Scientific Name	Agent
St. John's wort	*Hypericum perforatum*	Hypericin
Buckwheat	*Polygonum fagopyrum*	Fagopyrin
Perennial ryegrass	*Lolium perenne*	Perloline
Whiteheads	*Spheosciadium capitellatum*	Unknown

In addition, I have sometimes seen alfalfa or clover induce a photosensitivity reaction; these plants have been suspected to contain either an ingested or contact photodynamic agent. Recent reports describe photosensitivities apparently induced by the ingestion of gluten in horses, and of cocoa shells in calves.[294,294a]

As horses ingest plants containing chlorophyll, this molecule is degraded by bacteria in the intestine into the porphyrin, phylloerythrin. Some phylloerythrin is normally absorbed into the portal circulation, removed by the liver, and excreted by the bile. In liver disease the hepatic excretion of phylloerythrin is decreased, leading to excessive levels in the peripheral circulation and eventually in the skin, causing photosensitivity in approximately 25% of horses with liver dysfunction.[295–297] One of the more common reasons for liver disease in the United

States is ingestion of the following plants containing pyrrolizidine alkaloids:

Common Name	Scientific Name
Common groundsel	*Senecio vulgaris*
Ragwort, stinking Willie	*Senecio jacobea*
Tarweed	*Amsinckia intermedia*
Rattleweed	*Crotalaria* species
Salvation Jane	*Echium lycopsis*

In addition, consumption of alsike clover *(Trifolium hybridum)* may induce hepatic dysfunction (with histologic lesions distinct from those caused by pyrrolizidine alkaloids), leading to photosensitization signs (alsike clover poisoning, dew poisoning). Cases seem to be correlated to years with heavy rainfall and the ingestion of the plant blossoms.[298]

Ingested plants and feed should be noted and collected for future analysis. Environmental considerations include the type of pasture (or other material) with which the animal is in contact, the amount of time the animal is exposed to sunlight, any seasonality of the condition, and any other horses involved. A seasonal incidence would tend to negate liver disease; multihorse involvement should arouse suspicion of an ingested or contact photosensitizer. A thorough history of recent drug therapy should be obtained.

Physical examination usually reveals lesions limited to the hairless, white, or lightly pigmented areas of the skin. The involved skin is erythematous, swollen, and painful. The lesions may progress to serum exudation, thickening, fissuring, and in severe cases, necrosis and sloughing (Fig. 40-21).

Therapy is related to etiology. Chronic liver disease carries a guarded prognosis. Removal of feedstuffs containing photodynamic agents, or removal of the horse from a pasture with plants containing these agents, will usually result in full recovery if the horse is also kept out of the sun for 1 to 2 weeks. Corticosteroids are helpful in controlling inflammation and pruritus. Oral prednisolone at 1 mg/kg daily for 1 week, then halving the daily dosage for a second week, is an effective regimen.

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Fig. 40-21 Photosensitization. **A,** White blaze of a horse is selectively affected. **B,** White stocking of a horse is selectively affected. **C,** Area around eye where hair is less dense is most severely affected.

40.66 CHRONIC PROGRESSIVE LYMPHEDEMA

Chronic progressive lymphedema is the term for a condition seen in Shires, Clydesdales, and Belgians. It is characterized by progressive swelling, hyperkeratosis (thickening), and fibrosis (hardening) of the skin on the lower legs. This chronic progressive disease starts at an early age, progresses throughout the life of the horse, and

often ends in disfigurement and disability of the limbs. Inevitably, this condition leads to the horse's premature death. In the Belgian draft horse, it has reduced the average life expectancy of a stallion from 20 to only 6 years.

The pathologic changes and clinical signs closely resemble a condition known in humans as chronic lymphedema, or elephantiasis nostras verrucosa. The lower leg swelling is caused by abnormal functioning of the lymphatic system in the skin, which results in chronic lymphedema (swelling), fibrosis, a compromised immune system, and subsequent secondary infections of the skin. Based on preliminary research, it appears that a similar pathogenic mechanism is involved in the disease that affects these specific draft horse breeds.

The clinical signs of this disease are highly variable. The earliest lesions are characterized by skin thickening and crusting; both are often visible only after clipping the long feathering. Secondary infections develop very easily in these horses' legs and usually consist of either chorioptic mange or bacterial infections. Both dark skin and white skin on the lower legs are equally affected. These lesions are consistent with pastern dermatitis, certainly seen in other breeds. In Shires, Clydesdales, and Belgians, however, these lesions do not respond well to therapy.

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As the disease progresses, one or two thick skin folds and sometimes multiple small, well-demarcated ulcerations develop, predominantly in the rear of the pastern region. The ulcerations are covered with adherent crusts. Manual removal of the crusts or even movement during exercise results in bleeding. These small sores may seem to respond initially to various topical medications, but often reverse course, only to progress in severity and multiply in number. Small lesions tend to coalesce into larger and more intractable (resistant to cure) areas of skin ulceration. Over time, the lesions extend up the leg, often affecting the skin as high as the knees or hocks. These lesions are, at the very least, irritating to the horses and at times can be quite painful. Severely affected individuals often exhibit generalized swelling in all four legs.

This condition therefore is primarily a lymph system disease, and the pastern dermatitis in these draft horses is secondary to the body's inability to supply fluids properly and oxygenate the skin of the lower leg. The lymphatics break down over time, and the protein-rich fluid leaks into the tissues of the lower leg, which results in fibrosis of the tissues under the skin and thickening of the skin itself. The tissue fibrosis leads to even more blockage of fluid within the legs, inhibiting circulatory flow. This results in neovascularization, a process by which the body develops new blood vessels in a futile attempt to provide oxygen to its tissues.

Researchers suspect that a deficiency or abnormality in the connective tissue component known as *elastin* is the underlying factor and perhaps the cause of the lymphatic degeneration in these horses.[299,300] In affected animals the lymph vessels and deep tissues of the skin do not have sufficient amounts or the proper configuration of elastin. The lack of this critical tissue element apparently instigates the progression of disease and the chronic progression of clinical signs. A recent report documents high levels of antielastin antibodies in affected horses.[301]

As the condition becomes more chronic, the lower leg enlargement becomes permanent, and the swelling is firm on palpation. More of the thick skin folds and large, poorly defined, firm nodules develop. The nodules may become quite large and often are described as golf ball or even baseball in size. Both skin folds and nodules first develop in the back of the pastern area. With progression, they may extend and encircle the entire lower leg. The nodules become a mechanical problem because they interfere with free movement and frequently are injured during exercise. This disease often progresses to include massive secondary infections that produce copious amounts of foul-smelling exudates, generalized illness, debilitation, and even death.[300,301]

In a recent report of possibly the same condition in several draft breeds, the authors found a perivascular dermatitis dominated by T lymphocytes with an increase in major histocompatibility complex (MHC) class II–positive, dendritic-like cells. Immunohistochemical labeling for cytokeratins CK5/6(4), CK10, and CK14

indicated a change in their expression pattern. This correlated with the degree of epidermal hyperplasia, indicating abnormal differentiation of keratinocytes. There was a statistically significant correlation between the severity of skin lesions and several other factors, including increasing age, increasing cannon circumference, prominence of anatomic structures (e.g., fetlock tufts of hairs, ergots, chestnuts), and bulges in the fetlock region.[302]

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41 Chapter 41 Endocrine and Metabolic Diseases

Consulting Editors

Dianne McFarlane

41.1 EQUINE ENDOCRINE AND METABOLIC DISEASES

41.1.1 PITUITARY AND HYPOTHALAMUS

DIANNE McFARLANE

The pituitary gland is composed of two embryologically distinct portions: the adenohypophysis, derived from invagination of the pharyngeal epithelium known as *Rathke's pouch,* and the neurohypophysis, derived from neural tissue of the hypothalamus. The adenohypophysis can be further divided into the pars distalis, pars tuberalis, and pars intermedia. The pars distalis contains five different endocrine cell types, each of which is responsible for the release of a unique hormone or set of hormones in response to hypothalamic releasing factors delivered from the median eminence via the hypothalamic-hypophyseal portal system. The pars tuberalis is a highly vascular band of cells surrounding the pituitary stalk. The function of the pars tuberalis is unclear and has yet to be directly investigated in the horse. The neurohypophysis or pars nervosa is a collection of nerve axons and terminals that originate in the paraventricular and supraoptic nuclei of the hypothalamus. Oxytocin and arginine vasopressin (antidiuretic hormone) produced in the cell bodies of these nuclei are transported into the pars nervosa for storage and eventual release into the systemic circulation.

The pars intermedia of the horse incorporates tissue derived from both the adenohypophysis and the neurohypophysis. It is composed of a single endocrine cell type, the melanotrope. Melanotropes are directly innervated by nerve terminals of the hypothalamic periventricular dopaminergic neurons. These originate in the periventricular nucleus of the hypothalamus adjacent to the third ventricle, project through the infundibulum, and terminate in the pars intermedia (Fig. 41-1).[1] These neurons release the neurotransmitter dopamine, which acts to tonically inhibit the release of hormones from adjacent melanotropes. Dopamine released from the nerve terminals interacts at dopamine (D_2) receptors on the melanotropes to inhibit cell proliferation, transcription of proopiomelanocortin (POMC), and release of POMC-derived peptides.[1] Additional regulatory signals to the pars intermedia may be delivered by direct systemic arterial supply and from the hypothalamic-hypophyseal portal veins.[2] In addition to being under tonic inhibition, melanotropes may also be positively regulated by interaction with a melanotrope-releasing factor. Studies have shown that exogenous thyrotropin-releasing hormone (TRH) can directly stimulate hormone release from melanotropes.[3] However, the physiologic significance of TRH regulation of the pars intermedia has not yet been determined.

The primary product of the melanotrope is the hormone precursor protein POMC. POMC is also expressed by the corticotropes of the pars distalis. However, owing to differential posttranslational processing by proteases called *prohormone convertases,* each cell type secretes a different complement of POMC-derived peptides (Fig. 41-2). Because of the action of prohormone convertase I, POMC in corticotropes is primarily processed into adrenocorticotropin (ACTH). ACTH circulates to the adrenal cortex, where it stimulates secretion of cortisol. Melanotropes contain active prohormone convertase I and II, and therefore POMC in the pars intermedia is cleaved into the secretory peptides α-melanocyte—stimulating hormone (α-MSH), β-endorphin (β-END), and corticotrophin-like intermediate lobe peptide (CLIP). A small amount of ACTH may also be produced. Further

processing of the peptides, including cleavage of C-terminal amino acids and *N*-acetylation, serves to control the activity of the final product. For example, the most abundant form of β-END produced in the normal horse's pars intermedia is Ac-β-endorphin-(1–27), which lacks opioid activity. The most abundant β-END in horses with PPID is β-endorphin-(1–31), which is an opioid agonist.[4]

The physiologic role of the pars intermedia POMC derived-peptides α-MSH, β-END, and CLIP has not been extensively studied in the horse. In other species α-MSH has several diverse actions that are mediated through interaction with one of five distinct G-protein—coupled melanocortin receptors. α-MSH is so named because of its ability to induce skin pigmentation in amphibians. Its role in pigmentation is through interaction with melanocortin receptor 1 (MC1R), which is predominantly expressed in skin. In horses, mutation of the *MC1R* gene is associated with the chestnut coat color.[5] In white Camarque horses the degree of coat pigmentation is directly correlated to the plasma concentration of α-MSH.[6] α-MSH is also an integral mediator in control of energy homeostasis. MC3R and MC4R are both expressed in the central nervous system (CNS), particularly in the hypothalamus, where they function in the leptin-melanocortin pathway, regulating appetite-satiety balance and fat metabolism.[7] Animals and humans lacking functional MC3R or MC4R are obese, and melanocortin receptor defects are a common monogenetic cause of obesity in humans.[8] Plasma α-MSH concentration in obese men has been reported to be higher than in lean men.[9] It has been suggested high plasma concentration in obese individuals may be an attempt to maintain homeostasis in individuals with a defect in MC4R. Plasma α-MSH concentration was also found to be positively correlated to obesity in horses.[10] Another function of α-MSH is as a potent antiinflammatory agent.[11] α-MSH has been demonstrated to have multiple immune-modulating effects. Its most profound effect is in regulation of cytokine response. α-MSH inhibits activation of nuclear factor (NF)-κB by lipopolysaccharide (LPS) and interferon-γ (IFN-γ). Recent data in mice have suggested that α-MSH may suppress LPS-mediated inflammation by facilitating the interaction of interleukin receptor-associated kinase (IRAK) and IRAK-M. IRAK is a kinase that functions in activation of NF-κB after TLR-4 (the receptor for bacterial LPS) stimulation.[12] IRAK-M is a negative regulator of IRAK. As a result, NF-κB activation and proinflammatory cytokine release of tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 are all decreased after α-MSH administration. Fever and other clinical evidence of inflammation are also reduced.

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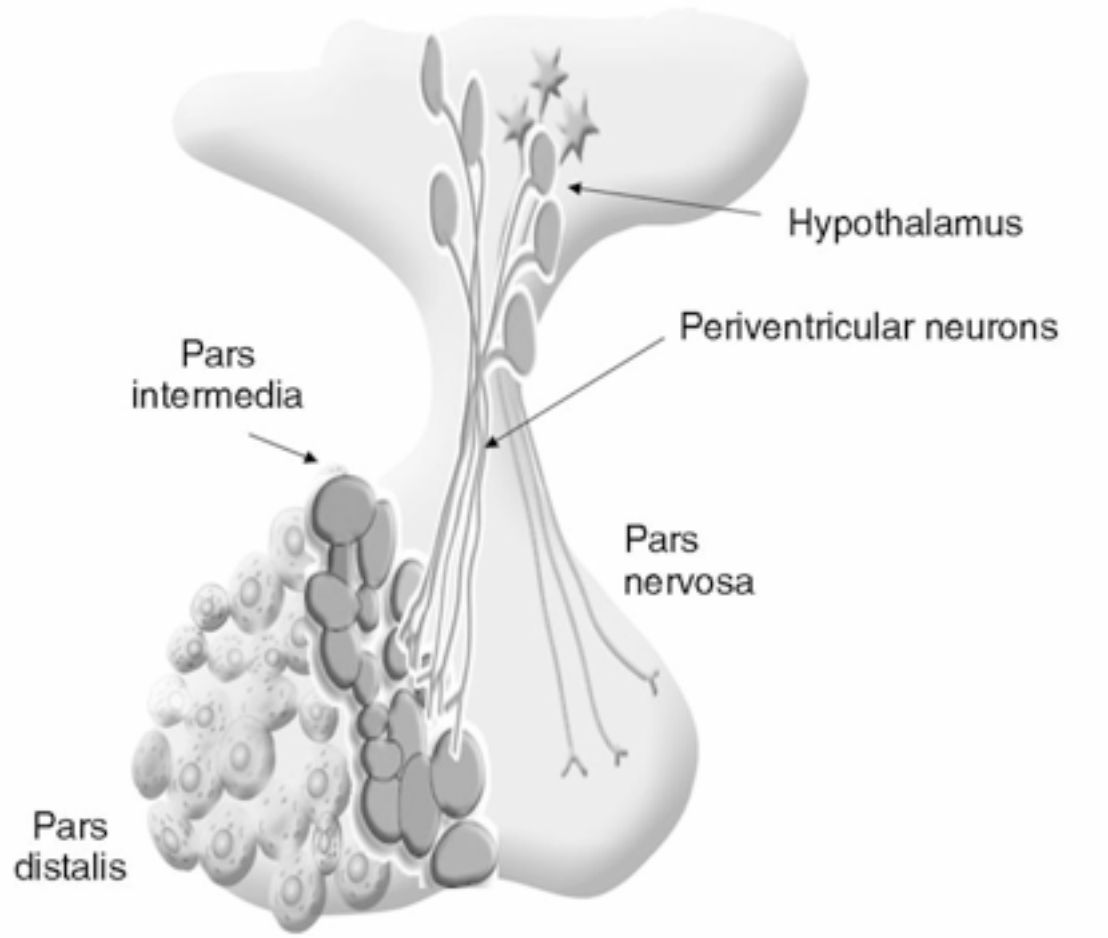
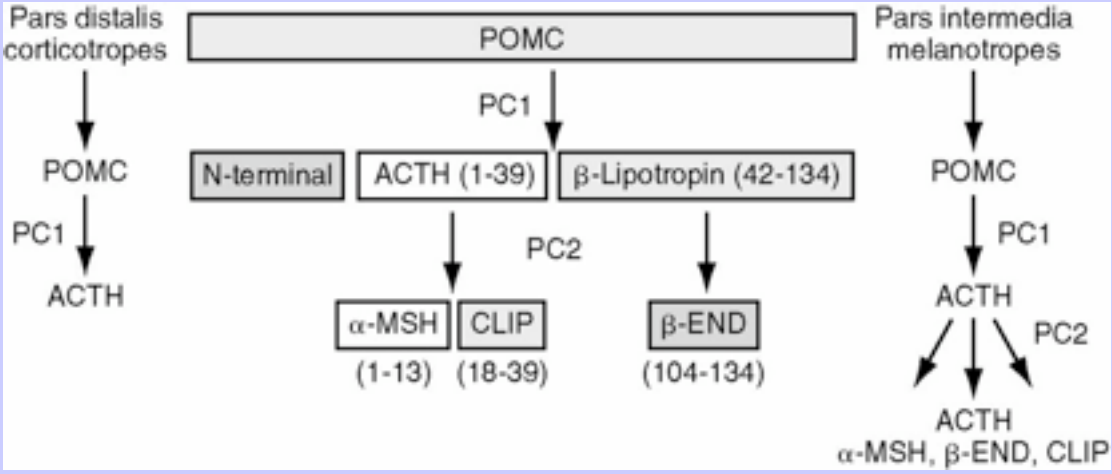
Fig. 41-1 Physiology of the equine pituitary pars intermedia. The melanotropes of the pars intermedia produce the hormone precursor protein, proopiomelanocortin (POMC), which in the pars intermedia is cleaved into the hormones α-melanocyte—stimulating hormone (α-MSH), β-endorphin (β-END), and corticotrophin-like intermediate lobe peptide (CLIP). Production of POMC in the pars intermedia is under inhibitory control by dopamine released from the nerve terminals of the periventricular neurons. The cell bodies of the periventricular neurons are in the hypothalamus, adjacent to the third ventricle.



β-END is a known endogenous opioid. Secretion of β-END provides analgesia and behavioral modification. It also suppresses immune responsiveness and has effects on vascular tone.[13–14] CLIP (ACTH 18–39) has not been extensively studied in any species. In pancreatic islet cells in culture, CLIP was shown to be a pancreatic

beta cell secretagogue, stimulating the release of insulin.[15] However, when administered to rats by either intraperitoneal or intraventricular injection, ACTH but not CLIP resulted in release of insulin and decrease in blood glucose.[16]

Fig. 41-2 Proopiomelanocortin (POMC) processing. POMC is cleaved by prohormone convertase I into ACTH in the pars distalis and into α-melanocyte stimulating hormone, β-endorphin, and corticotrophin-like intermediate lobe peptide by prohormone convertase I and II in the pars intermedia. Only a small amount of ACTH is produced by the normal pars intermedia.



Recent data have demonstrated a distinct seasonal effect on the activity of the pars intermedia of horses and ponies residing in the northeastern United States and Canada.[17] Plasma α-MSH concentration was considerably higher in horses and ponies in September compared with samples collected in the winter, spring, and early summer. An effect of season on α-MSH concentration has been described for humans, hamsters, and sheep.[18–20] The functional importance of the seasonal cycle is unknown, but several physiologic events occur in parallel with the α-MSH cycle. In sheep, body weight, voluntary food intake, and condition all peak simultaneously with α-MSH, with seasonal maximums occurring in September. Soay sheep with surgically created hypothalamic-pituitary disconnection have an increase in circulating concentration of α-MSH and chronic increase in body weight.[19] These findings suggest that α-MSH or other POMC-derived peptides may play a role in metabolic preparation for winter in sheep. It is possible that horses and ponies have a seasonal increase in POMC-derived peptides to metabolically prepare them for a decrease in accessible food observed in the wild in winter. If so, dysregulation of this pathway might be associated with abnormalities in body weight and fat storage. Weight loss and abnormal fat distribution are two clinical signs associated with equine pituitary pars intermedia dysfunction (PPID). Development of a winter coat also begins as length of day decreases in the fall. The development of hirsutism in horses with PPID leads one to speculate that the naturally occurring seasonal increase in POMC-derived peptides contributes to development of winter coat growth. This has not been critically assessed in equids.

41.1.1.1

Equine Pituitary Pars Intermedia Dysfunction

PPID is one of the most common diseases of horses and ponies 15 years of age and older.[21] PPID was originally termed “equine Cushing's disease” because of features similar to human Cushing's disease. However, in contrast to human Cushing's disease, PPID affects the pituitary pars intermedia rather than the pars distalis and is typically not a neoplastic condition, and the adrenocortical contribution to the clinical syndrome is of much less importance.[22] To avoid confusion, equine Cushing's disease is now more correctly referred to as *pituitary pars intermedia dysfunction*.

In the past two decades the population of aged horses has increased dramatically. This, in conjunction with the vast amount of information available to the horse-owning public, has lead to a heightened client awareness of age-associated equine health issues and a desire to promote healthy aging in their horses. As a result, diagnostic testing and treatment of horses for PPID has increased. Yet despite increased clinical recognition of this disease, much about PPID remains poorly understood.

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41.1.1.1.1

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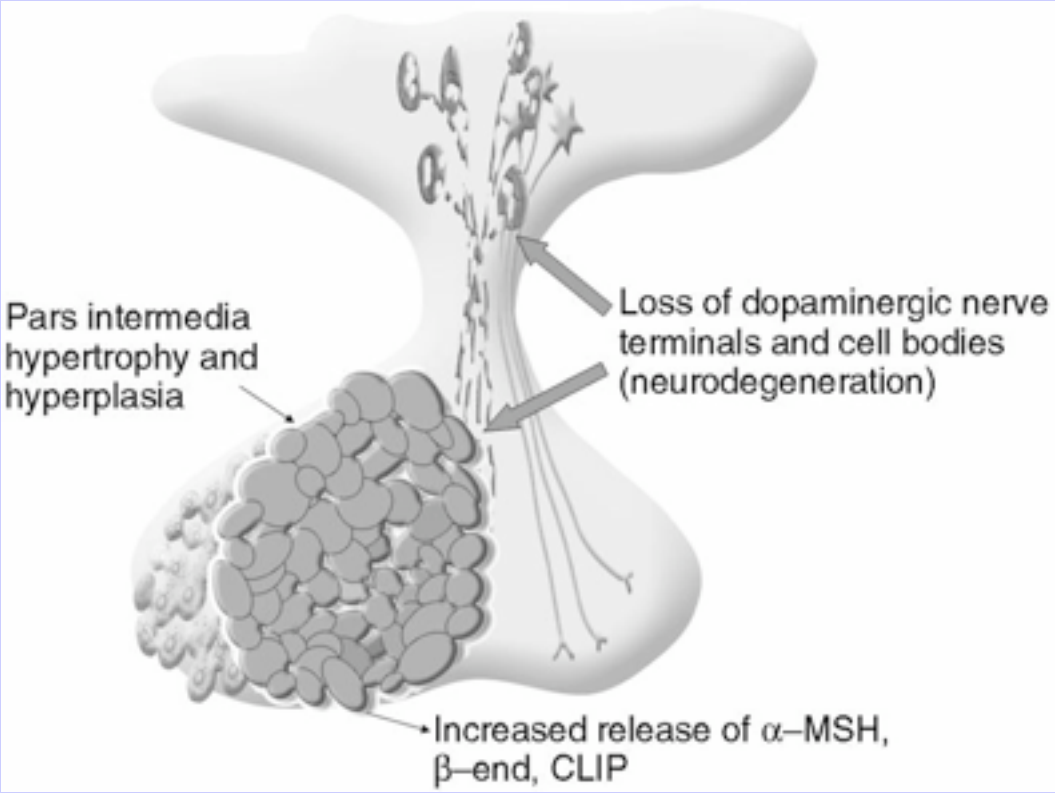
Pathophysiology

The pathologic hallmarks of PPID are hypertrophy, hyperplasia, and microadenoma or macroadenoma formation in the pituitary pars intermedia that results in an increased secretion of POMC peptides. Horses with PPID develop enlarged pituitaries that may reach five times normal weight. As the pars intermedia expands, it compresses the adjacent pituitary lobes and hypothalamus, often resulting in a loss of function of these tissues. In contrast, the pars intermedia remains active in horses with PPID, secreting relatively large quantities of POMC-derived peptides into the peripheral circulation. Horses with disease may have as much as a 40-fold increase in plasma concentration of pars intermedia POMC-derived peptides.[23] Clinical signs of disease likely result from a combination of increased circulating POMC peptides and loss of neuroendocrine function of adjacent tissues.

Evidence indicates loss of dopaminergic inhibition is critical in the pathology of PPID. Dopamine and dopamine metabolite concentrations in the pars intermedia of PPID horses are decreased eightfold compared with age-matched controls.[6] Systemic supplementation of dopamine or a dopamine agonist to horses with PPID results in a decrease in plasma concentration of POMC peptides.[23] Several investigators have reported that horses treated with the dopamine agonist pergolide show improvement in both clinical signs and biochemical abnormalities associated with disease.[24–26] Immunohistochemistry of formalin-fixed tissue showed a fivefold decrease in pituitary dopaminergic nerve terminals ($P < .001$) and a 50% reduction in the number of dopaminergic periventricular cell bodies ($P < .01$) in the hypothalamus of PPID animals.[27] This evidence suggests that a loss of functional periventricular dopaminergic neurons or “dopaminergic neurodegeneration” occurs in horses with PPID (Fig. 41-3). Loss of periventricular dopaminergic inhibition of the pars intermedia in other species results in pathologic changes similar to those of PPID. Surgical disruption of the periventricular hypophyseal dopaminergic tracts in rats results in increased expression of pars intermedia melanotropes.[28] In addition, D_2 dopamine receptor knockout mice develop pars intermedia lesions similar to PPID.[29] These data suggest PPID is primarily a disease of hypothalamic origin rather than the consequence of a spontaneously forming pituitary adenoma.

Fig. 41-3 Pathophysiology of equine pituitary pars intermedia dysfunction. Loss of functional dopaminergic periventricular neurons leads to a decrease in dopamine at the pars intermedia. This in turns results in disinhibition of the melanotropes of the pars intermedia. The outcome is hypertrophy and hyperplasia of the pars intermedia and increased systemic release of the pars intermedia POMC-derived peptides, α-melanocyte—stimulating hormone (α-MSH), β-endorphin (β-END) and corticotrophin-like intermediate lobe peptide (CLIP).



One potential cause for dopaminergic neurodegeneration is oxidative stress. Oxidative stress is modification of cellular components including proteins, DNA, and cell membrane lipids because of excessive exposure to exogenous or endogenous sources of free radicals. This cellular damage ultimately leads to cell death or, in the case of neurons, neurodegeneration. Chronic exposure to oxidants in excess of an animal's antioxidant capacity results in accumulation of functionally impaired cellular components. Dopaminergic neurons are particularly vulnerable to oxidative damage, because dopamine metabolism itself produces free radicals. Horses with PPID have evidence of oxidative damage, including

accumulation of pars intermedia 3-nitrotyrosine[27] and decreased plasma thiol.[30] This oxidative damage does not appear to be the result of impaired antioxidant capacity, as the systemic and pituitary antioxidant capacity of horses appears unchanged.[31]

41.1.1.1.2

Clinical Signs

Equine PPID affects many aged equids, resulting in a variety of clinical signs including hirsutism, laminitis, muscle atrophy, fat accumulation, polydipsia, polyuria, secondary infections, lethargy, infertility, persistent lactation, hyperhidrosis, and metabolic abnormalities including hyperglycemia (Fig. 41-4).[32] The most unique clinical manifestation of PPID is an abnormally long, curly hair coat that fails to shed, referred to as *equine hirsutism*. Often horse owners may report the horse shedding its winter coat slowly or incompletely in the year(s) prior to development of full hirsutism. Hair may be initially retained along the legs or under the mandible. The mechanism responsible for development of hirsutism in horses with PPID has not been investigated. The onset of hirsutism in an aged horse or pony is considered essentially pathognomonic for PPID.

Laminitis secondary to PPID is reported to occur in 24% to 82% of diagnosed cases and frequently necessitates euthanasia in affected animals.[32–35] When adult horses with laminitis of unknown origin were examined, 70% had increased ACTH, suggesting that laminitis in these animals may have been the result of undiagnosed PPID.[36] This study suggests PPID may be underdiagnosed, especially when laminitis is the presenting complaint and hirsutism is absent. The pathogenesis of laminitis in PPID is not currently understood but is the subject of ongoing investigation. It has been suggested that laminitis secondary to PPID is the consequence of high circulating cortisol concentration. However, the inability to induce experimental laminitis in normal horses using corticosteroids indicates the pathogenesis is more complex. Recent data have shown that glucose deprivation in the laminar tissue of the hoof, as would occur with insulin resistance (IR) secondary to endocrinopathy or exogenous glucocorticoid administration, may result in failure of the energy-dependent reactions required to maintain the laminar attachments known as *hemidesmosomes*.[37] Inflammatory cytokine and matrix metalloproteinase activation has been suggested to have a role in acute laminitis associated with endotoxemia or grain overload and may similarly contribute to laminitis in horses with endocrine dysfunction.[38,39]

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Fig. 41-4 Typical horse with pituitary pars intermedia dysfunction (PPID). This 22-year-old Morgan mare shows obvious hirsutism. Other clinical signs of PPID included laminitis and weight loss despite an excellent appetite.

In the author's experience, weight loss caused by muscle mass atrophy is the most common and possibly earliest clinical sign of PPID (Fig. 41-5). Despite weight loss, PPID horses often have a potbellied appearance, and as a consequence owners may fail to notice the lost weight. Weight loss and muscle atrophy may result from several factors including poor dentition, poor nutrition, heavy parasite burden, minimal exercise, and protein catabolism induced by increased cortisol activity. Histologic evidence of type 2 myofiber atrophy has recently been documented in muscle biopsies from horses with PPID, consistent with corticosteroid-associated muscle atrophy in other species.[40] Response to treatment with the dopamine agonist pergolide was assessed in three horses. Pergolide treatment was associated with an improvement in myofiber type composition, although myofiber ratio and cross-sectional area were no different. Improvements in management of PPID horses often result in significant weight gain, even in the absence of pharmacologic treatment.

Despite weight loss and muscle mass atrophy, horses with PPID often have abnormal accumulations of fat, most notably in the crest of the neck, tailbase, sheath, and superorbital fossa. This fat accumulation typically predates the weight loss and has a similar pattern as that observed in horses with equine

metabolic syndrome (EMS). The similarity of these two diseases, in both the breeds that are predisposed and clinical signs, has resulted in misdiagnosis of PPID in animals with EMS. There has also been speculation that animals with EMS or sustained obesity with IR may be at greater risk for developing PPID as they age. Although epidemiologic data are currently lacking to support this association, client-provided anecdotal data suggest this may warrant more critical assessment.

Fig. 41-5 Horse with pituitary pars intermedia dysfunction (PPID). The major clinical sign of disease in this horse with PPID was weight loss. Muscle mass atrophy along the dorsum, with a potbelly appearance, is characteristic of PPID.

Polyuria and polydipsia (PU/PD) have been estimated to occur in 17% to 76% of cases and are typically mild in severity.[32–34,41,42] The mechanism responsible for PU/PD may include (1) compression of the pars nervosa resulting in decreased arginine vasopressin (AVP; antidiuretic hormone) production; (2) osmotic diuresis secondary to hyperglycemia and glucosuria; or (3) factors that are cortisol induced. Cortisol is thought to cause PU/PD in other species by interfering with the secretion and/or action of arginine vasopression.[43] Evidence suggests that ACTH and cortisol may inhibit the renin-angiotensin-aldosterone axis, as well. The mechanism of PU/PD in horses with PPID has not been extensively examined. Glucosuria is not a common finding in horses with PPID. In one study, two PPID horses with marked hyperglycemia were found to have water consumption similar to that of normal horses.[35] These findings suggest it is unlikely that osmotic diuresis is a major mechanism of PU/PD in the PPID horse.

Horses with PPID have been reported to be more susceptible to infection, including endoparasitism, bacterial sinusitis, skin infections, foot abscesses, and respiratory infections.[32] The morbidity and mortality of secondary infection in equine PPID has been reported to range from 27% to 48%.[33–34,41,42] In the absence of parasite control, a heavy parasite burden is common. Routine, quantitative fecal egg counts are recommended to ensure an adequate anthelmintic program. Vigilance on the part of the owner and veterinarian is important in both prevention and early recognition of infections, as they may be clinically insidious. Bronchopneumonia was found at necropsy in 7 of 19 horses with PPID.[36] Bronchopneumonia should be considered in the PPID horse with fever or tachypnea and ruled out in horses with intermittent hyperhidrosis.

41.1.1.1.3

Diagnosis

Equine PPID is both common and life-threatening; therefore early and accurate diagnosis and intervention are imperative. Antemortem diagnosis of PPID currently relies on testing hypothalamic-pituitary-adrenal axis responsiveness or measurement of endogenous plasma concentrations of POMC-derived peptides, such as ACTH. These tests have been the subject of recent evaluation, and the search for new testing strategies is ongoing.

The overnight dexamethasone suppression test (DST) has been considered the gold standard for antemortem PPID diagnosis. In the unaffected horse, intramuscular administration of dexamethasone decreases release of ACTH from the pars distalis, resulting in a serum cortisol concentration of less than 1 μg/dL (27.59 nmol/L) 19 hours after dexamethasone administration (Fig. 41-6).[22] Horses with PPID fail to suppress serum cortisol concentration as a result of ACTH production from the pars intermedia. Originally this test was reported to have a sensitivity and a specificity of 100%.[22] However, a recent report suggests the reliability of the test has been overestimated.[44] When the DST was performed three times at 30-day intervals in seven horses with clinical signs of PPID, only one of the seven horses tested positive for disease on all 3 days. After an initial positive result, five of the seven horses suppressed normally on each subsequent test date, indicating either false-positive results at the initial test period or false-negative results at subsequent testing. These findings are consistent with the observations of the author. Horses with a normal dexamethasone suppression response have been found to have an increased plasma concentration of ACTH or α-MSH and postmortem histologic evidence of pars intermedia adenomatous hyperplasia. Although it has not been critically assessed, a loss of feedback inhibition by glucocorticoid may be a late event in the disease progression, and the high sensitivity originally reported may reflect a case selection bias toward horses with advanced disease. Despite these limitations, the overnight DST remains the test of choice for diagnosis of PPID in the animal when the risk of laminitis is minimal and more intensive testing (DST and TRH) is not practical. In horses in which clinical examination suggests early PPID and diagnostic test results are normal, repeat testing is recommended 6 months later or sooner if clinical signs progress.

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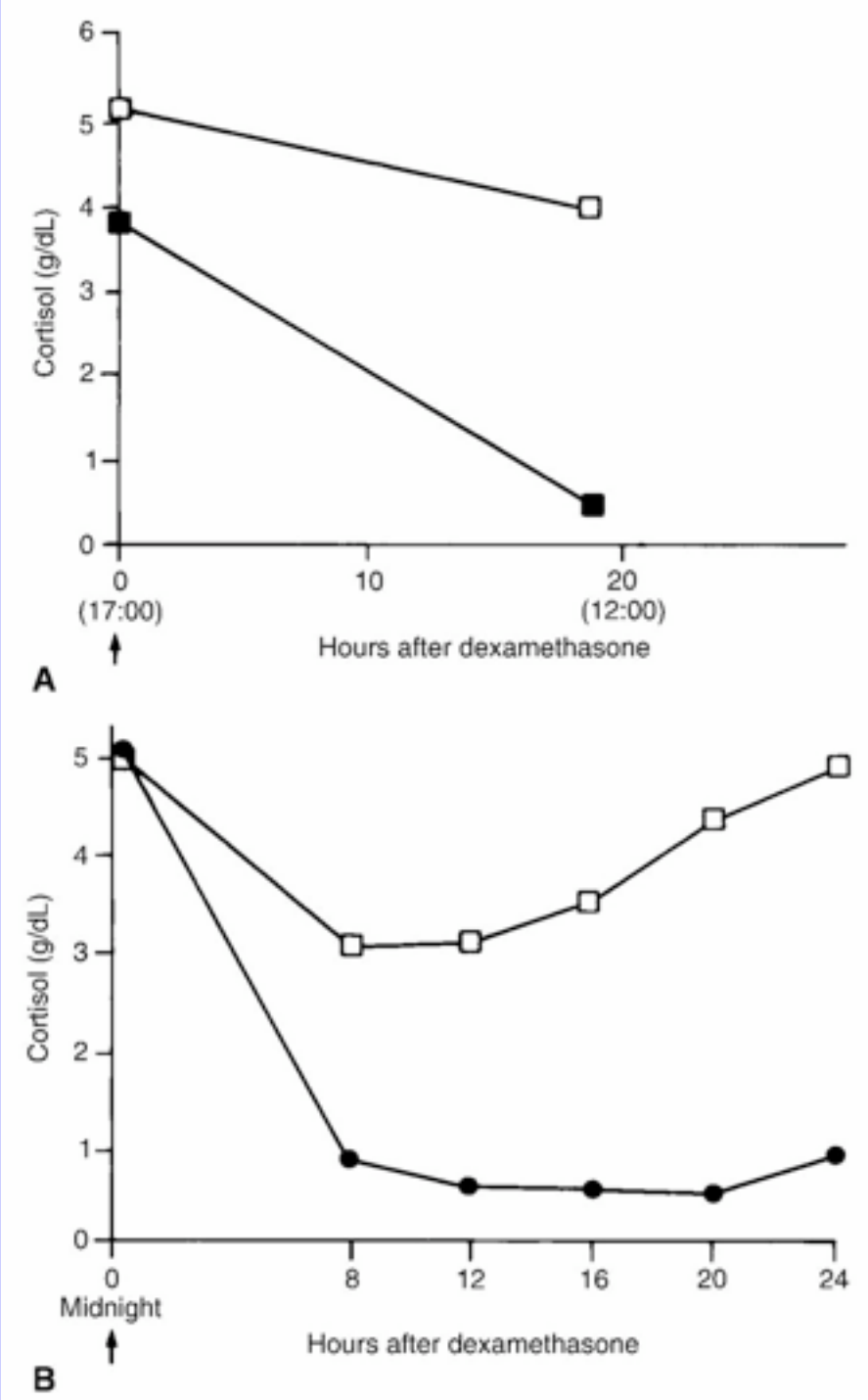
Fig. 41-6 Dexamethasone suppression test. □, Cushing's; ▪, control; ↑, 40 mcg of dexamethasone intramuscularly. **A,** Overnight. **B,** Standard.



Seasonal variation in DST results has been recently documented.[45] Clinically healthy horses and semiferal ponies residing in Pennsylvania had a normal DST in January, but when the same animals were tested in September, 40% of the horses and 21% of the ponies failed to suppress. Other diagnostic tests have also been shown to be affected by season. Plasma ACTH concentration measured in September was significantly higher than in January or May.[45] In plasma samples collected in September, 85% of horses and 97% of semiferal ponies had ACTH concentrations greater than reference range. These animals would have been falsely diagnosed with PPID. In contrast, 100% of the horses and 98% of the ponies had ACTH concentrations within reference range when measured in January or May. Similarly, plasma α-MSH was increased twofold in horses residing in Prince Edward Island, Canada and elevenfold in semiferal ponies in Pennsylvania when measured in the fall compared with spring, summer, or winter concentrations.[17] The effect of season on diagnostic testing needs to be more extensively explored using a larger number of animals in diverse geographic locations.

The TRH stimulation test is also used for diagnosis of PPID, particularly in horses with a history of laminitis. Horses with PPID show an increase in serum cortisol concentration 30 to 90 minutes after TRH administration, whereas normal horses do not.[46] TRH is believed to be a physiologic releasing factor of the equine pars intermedia.[3] In healthy horses, α-MSH (a pars intermedia product) increased over 600% after TRH administration. The exaggerated cortisol release after TRH administration in horses with PPID may be the result of failure of the enzyme prohormone convertase 2 to keep up with the POMC production in the hypertrophic pars intermedia melanotropes, resulting in preferential accumulation and secretion of ACTH. Evaluation of the predictive value of the TRH stimulation test has not been critically assessed in a large number of horses. In one study, 5 of 15 horses without clinical or histologic evidence of PPID had a greater than 50% increase in cortisol 30 minutes after TRH administration.[3] These horses would have been falsely identified as having PPID. Historically, TRH stimulation test was limited by the lack of availability of TRH approved for use in the horse and the high price of human-approved products. The current availability of compounded TRH and its apparent lack of adverse effects have resulted in this test being employed more frequently in field practice.

A diagnostic test that may have better performance than either the DST or the TRH stimulation test is the combined dexamethasone suppression and TRH stimulation test. Sensitivity of the combined dexamethasone suppression and TRH stimulation test has recently been critically evaluated in 42 horses, using histology for diagnosis.[47] Disease was defined as the presence of a discrete mass in the pars intermedia. Horses were included into the study based on availability (horses donated during the time span of the project). This differs from previous studies in which inclusion was based on presence or absence of clinical signs of disease. The method of selection used in the current study is more random and therefore more appropriate for determining sensitivity and specificity of a diagnostic test. Based on histology, prevalence of PPID was 40% in horses of all ages (2 to 33 years) and significantly correlated with age. Sensitivity of the combined test was reported as 88% and specificity as 76%. This test has the disadvantage of requiring multiple sampling over 2 days and an increased cost compared with other methods.

Endogenous concentrations of POMC-derived peptides are also useful in diagnosis of PPID. Increased plasma concentrations of ACTH, α-MSH, and β-END have all been shown to have a sensitivity and specificity of approximately 80% to 90%.[34,48] However, because the DST was used as a gold standard, it is likely these studies overestimate the validity of measurement of POMC-derived peptide concentration in the diagnosis of PPID. Measurement of ACTH is perhaps the most commonly used method for diagnosis

of PPID in ambulatory practice because it requires collection of only a single plasma sample and poses no risk to the patient.

Imaging of the pituitary using computed tomography (CT) has also been examined in a limited number of cases as a method for documenting pituitary enlargement.[49,50] Accuracy of CT at estimating width, height, and length of the equine pituitary gland in disarticulated heads from 25 normal horses was determined to be 81% to 93%, 58% to 71%, and 88% to 99% respectively.[51] Accuracy for volume was calculated to range from 43% to 53% in the same study.[51] Although magnetic resonance imaging is the preferred diagnostic imaging modality for pituitary masses in humans, there are no reports of its use in diagnosis of PPID in the horse.

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41.1.1.1.4

Necropsy Findings

Postmortem examination of the horse with PPID reveals a grossly enlarged pituitary resulting from hypertrophy and hyperplasia of the pars intermedia. The normal horse's pituitary typically weighs 1 to 3 g; the affected horse's pituitary may be two to five times this weight. Enlargement may be the result of an adenoma (>1 cm), which often contains areas of hemorrhage and necrosis. Alternatively, microadenomatous (≤1 cm) hyperplasia may be present. Melanotropic tumor cells are pleomorphic (polyhedral or spindle shaped) with eosinophilic, granular cytoplasm.[52,53] Cells are organized into nodules, rosettes, bundles, or follicular structures separated by fine septal tissue. Pigment deposition is common in the pars nervosa, and hemosiderin may be observed when hemorrhage is present. Other lesions include compression of the pars distalis, pars nervosa, or, in the case of large tumors that outgrow the sella turcica, compression of the optic chiasm or hypothalamus. Other gross lesions may include those related to disease complications such as laminitis, intestinal parasitism, pneumonia, or sinusitis.

41.1.1.1.5

Treatment and Prognosis

Treatment of PPID is aimed at improving general health and reducing the risk of disease complications such as laminitis and immunosuppression. Management practices should be optimized for care of an aged horse. Diet and feeding practices, dental and hoof care, and deworming schedule should be assessed. Feeding of a pelleted diet designed for senior horses and frequent deworming and correction of dental abnormalities are useful in maintaining the animal's weight and improving overall general health. Body clipping the horse with hirsutism during the warm weather is critical to limit hyperhidrosis and avoid hyperthermia. Vigilant observation for evidence of infection or laminitis followed by early intervention is important in avoiding protracted illness.

Pharmaceutical therapies for PPID function by decreasing the concentration of circulating POMC peptides and/or cortisol, which theoretically should reduce the risk of disease complications beyond what can be achieved by management alone. Ideally, treatment should also reverse or retard the hyperplastic growth of the pars intermedia, thereby limiting compression of adjacent tissues. However, minimal data are available evaluating the long-term efficacy of medical therapy for PPID.

The current preferred drug for the treatment of PPID is pergolide, a dopamine agonist. Several reports have indicated that pergolide improves clinical signs and diagnostic test results in treated animals.[24–26] An initial dose of 0.002 mg/kg orally every 24 hours has been recommended.[32] If no response is observed in 4–12 weeks, the dose is increased in 0.002-mg/kg increments monthly until clinical signs and biochemical

abnormalities normalize. A total dose of 0.01 mg/kg should not be exceeded.[32] Complications associated with pergolide use in the horse include anorexia, colic, and diarrhea. These are typically dose dependent and resolve spontaneously after a reduction in dose. Once an effective dose is established, endocrine testing should be repeated every 6 to 12 months to ensure hormonal control is maintained.

Cyproheptadine, a drug with antiserotoninergic, antihistaminergic, and anticholinergic activity, was one of the original drugs used to treat horses with PPID. However, several studies using measurable outcomes failed to show consistent efficacy of the drug.[24,26] In addition, although historically inexpensive, cyproheptadine has increased significantly in cost, making pergolide the more rational treatment choice. Cyproheptadine may be useful as an adjunct therapy in horses resistant to pergolide monotherapy. Cyproheptadine may be added at 0.3 to 0.5 mg/kg orally once daily to horses that show minimal response to 0.004 to 0.006 mg/kg of pergolide.[32]

A newer treatment available in Europe is trilostane, a competitive inhibitor of 3β-hydroxysteroid dehydrogenase (HSD). Trilostane blocks cortisol production by the adrenal gland. In a report of 20 clinical cases diagnosed using the combined DST suppression and TRH stimulation test, trilostane at a dose of 0.4 to 1 mg/kg once daily resulted in improvement of clinical signs and normalization of cortisol after TRH administration 30 days after starting therapy, although baseline cortisol remained unchanged.[54] Adverse effects of trilostane were not reported in this study. The effectiveness of trilostane as a monotherapy or in combination with pergolide remains to be evaluated in a large number of horses. One potential limitation of trilostane as a monotherapy in the treatment of PPID is the lack of downregulation of the pars intermedia melanotropes. Therefore a continued elevation in plasma POMC peptide concentration and enlargement of the pars intermedia would be an expected outcome.

The prognosis of horses with PPID is not well documented. Many horses live for years after diagnosis, particularly if receiving optimized management. Anecdotal reports of PPID horses that have responded to pergolide for more than 4 years suggest treatment may remain effective long term. As with all diseases, early recognition, appropriate intervention, and avoidance of complications are the keys to a positive outcome.

41.1.1.2

DIABETES INSIPIDUS

NOEL O. DYBDAL

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Neurogenic diabetes insipidus results from decreased release of AVP from the posterior pituitary. As already noted, the most common cause of decreased AVP release in the horse is posterior pituitary destruction secondary to pars intermedia enlargement; however, in rare cases, idiopathic neurogenic diabetes insipidus has been reported in the horse.[55] The clinical presentation of PU/PD in an otherwise normal animal must include as differential diagnoses primary renal disease, nephrogenic diabetes insipidus (insensitivity of the kidneys to AVP), psychogenic PD syndrome, PPID, and diabetes insipidus caused by posterior pituitary dysfunction unrelated to PPID. In the horse with idiopathic diabetes insipidus, urine specific gravity is less than 1.01. The affected animals fail to concentrate urine on a water deprivation test. In one reported case the horse responded to exogenous AVP (40 U of pitressin tannate in oil intramuscularly [IM]) with a decrease in water consumption and concentration of the urine, which lasted approximately 24 hours.[55] Blood AVP concentrations were low compared with controls and did not change in response to water deprivation.

Although relatively uncommon, psychogenic PD syndrome occurs in horses. When subjected to a deprivation test, horses with psychogenic PD will moderately concentrate urine (up to 1.025). AVP levels in this disorder have not been reported. With renal disease, specific gravity rarely falls below 1.010, and other laboratory findings (e.g., elevated blood urea nitrogen, creatinine) are consistent with the diagnosis. The same is true of PPID. Because the PU and PD of PPID are not entirely related to decreased AVP levels, affected animals frequently respond normally to water deprivation.

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41.1.2

ADRENAL GLANDS

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The paired adrenal glands in the horse lay craniomedial to the kidneys. The adrenal glands weigh 15 to 17 g each and are 9 to 10 cm in length, 3 to 4 cm wide, and 1.5 cm thick. The right adrenal is medially adherent to the vena cava and cranially lies in the impression in the liver formed by the right kidney. The left adrenal is associated with the cranial mesenteric artery on its medial border, the aorta and renal artery on its dorsal border, and the left aspect of the pancreas on its ventral border.[56] The glands are well vascularized. The adrenal cortex is composed of the outermost zona glomerulosa, which produces mineralocorticoids, primarily in response to angiotensin II and falling serum sodium levels; the zona fasciculata, which produces glucocorticoids in response to stimulation by ACTH; and the zona reticularis, responsible for adrenal androgen production. The centrally located adrenal medulla produces catecholamines. In the horse the primary adrenal medullary catecholamine appears to be epinephrine; however, norepinephrine and dopamine are also produced and secreted to some extent.[57] The adrenal glands are a shock organ in the horse, and adrenal hemorrhage and necrosis are common sequelae to conditions such as severe bouts of endotoxemia and colic.

41.1.2.1

ADRENAL EXHAUSTION

Adrenal exhaustion or “let down” syndrome are much discussed, poorly documented syndromes ascribed to adrenal insufficiency in the horse. Low cortisol levels have not been found in racehorses that turn in poor performances blamed on adrenal exhaustion.[58] Abnormal response to ACTH challenge has not been noted in endurance horses after 22.4-km (36-mile) rides.[59] Low circulating cortisol levels have been noted after 160-km (100-mile) rides; however, adrenal function was not assessed by any provocative tests in this study.[60] At necropsy it is more common to find enlarged adrenal glands in racehorses than it is to find atrophic glands. This hypertrophy may be the result of repeated administration of exogenous ACTH, which in turn could lead to “let down” when injections are discontinued, or it may be caused by chronic stress. Because the adrenals are a shock organ in the horse, they can be damaged (e.g., by hemorrhage and necrosis, which can lead to subsequent scarring) during bouts of endotoxemia, severe colic, or anaphylaxis. Chronic administration of corticosteroids can also lead to adrenocortical insufficiency.

Adrenal insufficiency should be considered in the differential diagnoses of horses with depression, anorexia, weight loss, hyponatremia, hypochloremia, hyperkalemia, or hypoglycemia, particularly if the horse has recently come off the track or some other form of intensive training or corticosteroids have been administered. An ACTH stimulation test can be used to confirm the diagnosis; cortisol should increase twofold to threefold 2 to 4 hours after stimulation.

41.1.2.2

PHEOCHROMOCYTOMA

Although adrenal medullary tumors are generally nonfunctional tumors noted incidentally at necropsy, there are a few case reports in the literature of functional adrenal medullary tumors in horses.[61,62] Clinical signs are attributable to increased circulating catecholamine and include excessive sweating (hyperhidrosis), apprehension, recurrent colic, tachycardia, dilated pupils, hyperglycemia, and hypertension. Pheochromocytomas are predisposed to hemorrhage, and severe hemorrhage secondary to ruptured pheochromocytoma has been reported in horses.[62] Although most cases are diagnosed at necropsy, determination of urinary catecholamine levels can aid in antemortem diagnosis.

41.1.2.3

ANHIDROSIS

Babetta A. Breuhaus

41.1.2.3.1

Description of Disease

Anhidrosis is characterized as an inability to sweat in response to appropriate stimuli. It occurs in geographic areas that experience hot, humid weather for prolonged periods of time. Clinical signs are especially likely to occur when nighttime temperatures do not fall below 70° F. Classically, anhidrosis affects horses that are not accustomed to these environmental conditions and are moved to a hot, humid area. However, partial or complete anhidrosis is also diagnosed in horses that have grown up in the same areas. It appears that horses that are worked or exercised in hot, humid conditions are more likely to develop the condition than horses that are not worked. Stress may also contribute to onset of the problem. Epidemiologic studies performed in the mid 1980s concluded that there was no sex or breed predisposition to the condition.[63,64] However, it is the author's subjective impression that thoroughbreds (and Appendix registered quarter horses) and warmbloods are more likely to be affected.

41.1.2.3.2

Etiology and Pathophysiology

The cause of anhidrosis is unknown. Presumably there is an abnormality in stimulation or production of sweat. Equine sweat glands produce sweat as an ultrafiltrate from plasma; water and electrolytes are secreted into sweat gland ducts, and this fluid is transported to the skin surface as sweat. Physiologic stimulation of sweating in horses is achieved by activation of β_2-adrenergic receptors, both by direct neural stimulation and from circulating catecholamines.[65–67] Sweat glands from anhidrotic horses do not respond normally to direct stimulation, and there is histologic evidence of sweat gland atrophy.[68,69] However, it is unknown whether the observed sweat gland atrophy is the primary cause of anhidrosis or merely secondary to disuse. Histologic examination of skin from anhidrotic horses also showed no evidence of neural disruption to the sweat glands,[69] and circulating concentrations of epinephrine are actually higher in anhidrotic horses than in horses that sweat normally,[70] suggesting that the problem is more likely caused by decreased ability of sweat glands to respond to stimulation, rather than failure of the thermoregulatory system to perceive the need to sweat or failure of stimulation to sweat. Most theories of pathogenesis of anhidrosis suggest downregulation or desensitization of the β_2-adrenoreceptors, but to date no studies have demonstrated either one of these or an alternative mechanism.

In addition to a neural mechanism, there may also be an endocrine component to this disease. Pregnant mares were found to be somewhat less at risk of developing anhidrosis than nonpregnant mares.[64] An association of anhidrosis with hypothyroidism most likely stems from the observation that thyroid supplementation helped anhidrotic horses racing in Hong Kong in the 1950s.[71] However, the author has not observed any improvement in anhidrotic pleasure horses supplemented with thyroid hormones, and measurement of thyroid hormones at rest and in response to TRH showed no difference between normal horses and horses with anhidrosis.[72]

There is evidence in some humans that acquired idiopathic anhidrosis may have an immunologic pathogenesis. Serum IgE concentration was increased in one reported case.[73] Sweat gland atrophy with infiltration by lymphocytes and mast cells and IgG and C3 deposition in the basement membrane has been described.[73,74] Steroid therapy improved the ability of one of these patients to sweat. An immune-mediated basis for anhidrosis has not been studied in the horse. Basement membrane was noted to be thickened in skin biopsies from 10 anhidrotic horses.[69] However, inflammation (i.e., infiltration with white blood cells) was noted in only one of six anhidrotic horses housed at ambient conditions.[69]

1345 1346

Results of a recent study showed that expression of the water channel aquaporin-5 was decreased in sweat glands from anhidrotic horses compared with sweat glands from horses that sweated normally.[75] Although these results may help explain why hypohidrotic or anhidrotic horses cannot produce as much sweat as normal horses, it is not clear whether loss of these water channels is a cause or a consequence of decreased sweat gland secretory capacity.

41.1.2.3.3

Clinical Signs and Differential Diagnoses

Early clinical signs of hypohidrosis include exercise intolerance, particularly in warm humid weather, and tachypnea, initially during or after exercise and then at rest as the severity of disease increases. Owners may call the veterinarian thinking the horse has a respiratory problem. As hypohidrosis worsens or the horse becomes anhidrotic, owners realize the horse is not sweating as much as they would expect for the level of work it is performing, or it is taking longer than normal to cool out after exercise. Areas of residual sweat production often include under the mane, in the axilla or inguinal areas, and under the saddle. Body temperature can increase to dangerous levels if signs are not recognized, and affected horses continue to work in hot weather. The hair coat often becomes dry and thin in chronically affected horses, particularly over the face (Fig. 41-7) and cannon bones.

41.1.2.3.4

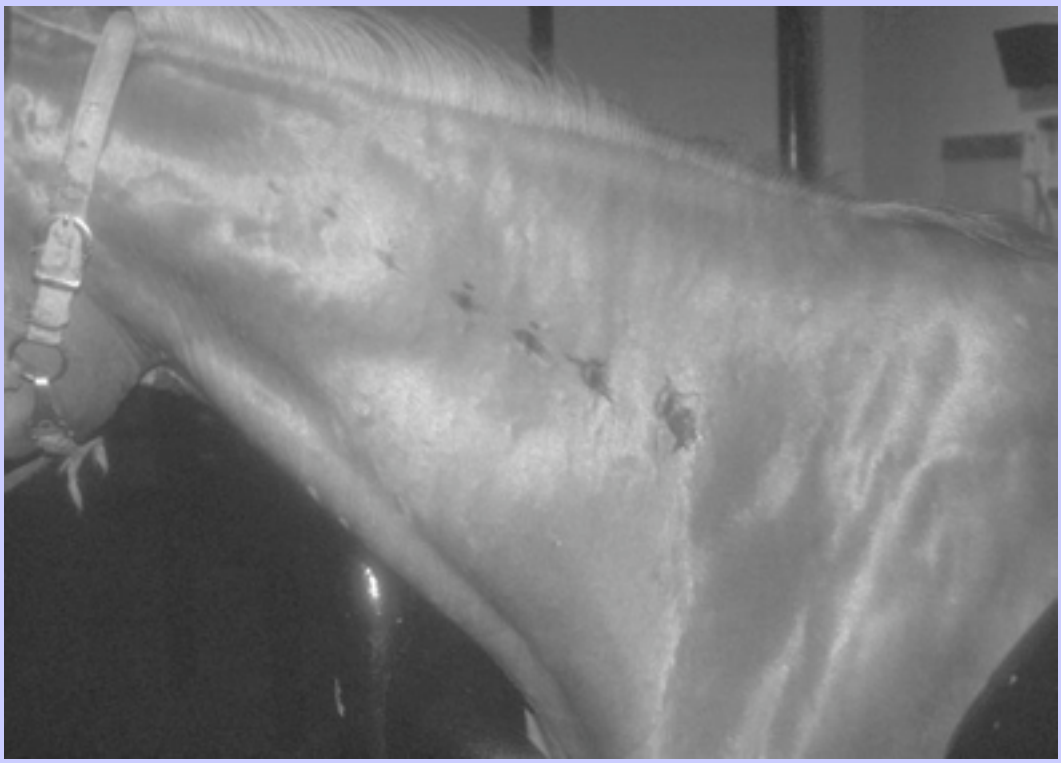
Clinical Pathology and Diagnostic Tests

Hypohidrosis or anhidrosis can be included in a differential diagnosis of exercise intolerance based on history and clinical signs. The diagnosis can be confirmed by performing an intradermal sweat test.[68,76–78] Six serial tenfold dilutions of a β_2-adrenergic agonist such as terbutaline (10^{-3} w/v to 10^{-8} w/v) are prepared. Each dilution (0.1 mL) is injected intradermally along the neck or in the pectoral region. In normal horses a localized area of sweat will appear at the site of injection at all concentrations, except perhaps the most dilute concentration (i.e., 10^{-8}). The amount of sweat produced at each site is proportional to the concentration of terbutaline injected (Fig. 41-8). Sweating will first be noted in normal horses within 5 minutes of injection at the higher concentrations. Onset of sweat production may be

delayed and amount of sweat reduced in hypohidrotic horses, or hypohidrotic horses may sweat only at the higher concentrations of terbutaline. Anhidrotic horses do not sweat, even at the highest concentration.

Fig. 41-7 Chronic anhidrosis often causes facial hair loss or thinning.

Fig. 41-8 Terbutaline intradermal sweat test. Six serial tenfold dilutions of terbutaline are injected intradermally along the neck. Normal horses, such as the one shown here, will sweat at the injection site of all concentrations, except perhaps the most dilute (10^{-8} w/v). In the normal horse, sweating will typically begin within 5 minutes of injection. Reduction in the amount or delay in onset of sweating is diagnostic for hypohidrosis. A complete failure to sweat in response to all terbutaline injections is diagnostic for anhidrosis.



Although failure to sweat in response to intradermal terbutaline injection confirms a diagnosis of anhidrosis, horses that are hypohidrotic may continue to produce sweat, even at the lower concentrations. For these horses, a lunge test will help confirm the diagnosis. Body temperature, heart rate, and respiratory rate are recorded. The horse is then lunged at a trot for 30 minutes on a hot day. During this time, the horse is observed for evidence of sweat production. Body temperature, heart rate, and respiratory rate measurements are made immediately at the end of lunging and every 10 minutes thereafter for the next 30 minutes. Although the heart rate response reflects the degree of fitness, the body temperature and respiratory rate responses correlate better to the horse's ability to cool itself. If the horse's respiratory rate is not back to what is was before the onset of lunging by 30 minutes after the end of the exercise, it is

highly likely that the horse is having a problem cooling. Rarely, horses unable to secrete fluid sweat are observed to secrete salt crystals after a lunge test (Fig. 41-9).

The most likely differential diagnoses for hypohidrosis include various respiratory diseases. In my experience, some hypohidrotic or anhidrotic horses also have mild airway inflammation, documented most often by increased mast cells or eosinophils in bronchoalveolar lavage fluid. It is unknown whether the two problems coexist coincidentally or if there is a mechanistic link. Either way, it is likely that airway inflammation would decrease the ability of a horse to use its respiratory system to help cool itself, and this is likely to be more critical in a horse that cannot sweat.

41.1.2.3.5

Treatment, Prevention, and Prognosis

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The only consistently successful treatment is movement of the horse to a cooler environment, although this is not always practical or feasible. Other environmental or dietary alterations may or may not be helpful. 1347 For hypohidrotic horses or horses that are having their first episode of anhidrosis, it is important to stop any workload and decrease the stress level. Concurrent disease conditions such as airway inflammation should be appropriately treated. Shade, fans, misting fans, and window air conditioners can be used to try to decrease the temperature in the horse's local environment. Applying water by hose or sponging the horse with water during the hot part of the day can take the place of sweat. Electrolyte supplementation (especially KCl) has been advocated,[78] and various products are available commercially that appear to help some but not all horses. One such supplement contains L-tyrosine, ascorbic acid, niacin, and cobalt and claims to improve sweat production by supplying precursors to dopamine synthesis (One AC, MPCO, Phoenix, Ariz.). The theory is that dopamine improves skin vasodilation, resulting in increased blood flow to sweat glands during exercise. To the author's knowledge no studies at present support or refute this claim. Other treatments that have been used with mixed success include acupuncture and Chinese herbs.[78]

Fig. 41-9 Salt crystals secreted in response to exercise (lunge test) in an anhidrotic horse. After a lunge test, this horse excreted salt crystals *(shown here)* without a fluid component to the sweat. The author has observed this in two horses diagnosed with anhidrosis.

Medical therapy of anhidrosis has primarily been unrewarding. Anecdotally, the β_2-adrenergic agonist clenbuterol increases sweat production in hypohidrotic horses and may be beneficial if used sparingly, only when weather conditions are particularly bad (i.e., extremely high heat and humidity). However, traditional recommendations are to avoid use of β_2-adrenergic agonists in hypohidrotic horses because their use may precipitate complete anhidrosis.[79] There is increasing evidence in human medicine that combination treatment of chronic airway disease with both β_2-adrenergic agonists and corticosteroids results in a synergistic effect, with corticosteroids helping to prevent desensitization and tolerance to β_2-adrenergic agonists, and β_2-adrenergic agonists potentiating the antiinflammatory effects of the corticosteroids.[80,81] Thus, combination therapy may be useful in hypohidrotic horses, but to date no controlled studies have been performed. Corticosteroid therapy may also be useful if there is an immune component to the pathogenesis of anhidrosis.

Once a horse has had an episode of anhidrosis, there are certain measures that can be taken to try to prevent recurrence of the problem in subsequent years. Before the hot part of the year begins, start the horse on any supplements that have been helpful previously and make certain the horse is cardiovascularly fit. Also, make sure that any respiratory problems are under control before the onset of hot weather. As the hot season approaches, try to avoid procedures (e.g., dental procedures) that might require administration of heavy doses of α_2 sedatives that stimulate the horse to sweat. Plan to do these procedures during the cooler parts of the year. During hot periods, work the horse only during the cool parts of the day. Use external water sources to decrease the need for the horse to sweat.

The prognosis for hypohidrotic horses is guarded for future athletic performance in a hot environment. It is the author's opinion that the longer an anhidrotic horse has been left untreated or unmanaged, the less likely the horse will be to sweat again despite any of the treatments described earlier. However, if an underlying disease or problem can be identified and treated successfully in a horse that is just becoming hypohidrotic, the likelihood that the horse will sweat better the following season is improved.

41.1.3 THYROID GLANDS

BABETTA A. BREUHAUS

Thyroid gland physiology and control of thyroid hormone secretion in horses is similar to that in other species. Thyroid hormones are important for growth, maturation of organ systems, and regulation of metabolism. They stimulate protein synthesis and catabolism, increase body heat production, and stimulate basal metabolic rate. The thyroid gland concentrates iodides from the blood and synthesizes and secretes both thyroxine (T_4) and triiodothyronine (T_3). Once secreted, thyroid hormones circulate both bound to proteins and unbound (“free”), with the free fractions being the active fractions. T_3 is more metabolically active than T_4, and although some T_3 is secreted by the thyroid gland along with T_4, the main source of T_3 in the body is from conversion of T_4 to T_3 in peripheral tissues.

Thyroid hormone secretion is regulated by the hypothalamus and pituitary. TRH from the median eminence of the hypothalamus stimulates release of thyroid-stimulating hormone (TSH) from the anterior pituitary; TSH travels in the blood to the thyroid gland to stimulate release of thyroid hormones. Circulating thyroid hormones exert negative feedback on the hypothalamus and pituitary to limit further release of TRH and TSH. Neurotransmitters that play a role in thyroid hormone regulation include α-adrenergic agonists (stimulatory)

and somatostatin and dopamine (inhibitory). Glucocorticoids and the cytokines TNF and IL-1β also inhibit TSH secretion.

Alterations in thyroid hormone status that have been described in horses include thyroid gland neoplasia, hyperthyroidism, and hypothyroidism. Certain drugs, diets, and physiologic or pathophysiologic states can also influence circulating thyroid hormone concentrations. Although equine thyroid dysfunction has been reviewed fairly recently,[82,83] a number of studies of equine thyroid function and dysfunction have been performed since that time or are in progress.

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41.1.3.1

THYROID GLAND NEOPLASIA

Thyroid gland neoplasias are not uncommon, and it is not unusual to find them as incidental findings during necropsy of older horses.[84,85] Thyroid adenomas are most common, but other reported thyroid neoplasias include carcinomas, adenocarcinomas, and C-cell tumors. Although there are also scattered case reports in the literature of horses that were found to be hypothyroid or hyperthyroid because of a thyroid tumor, most thyroid gland tumors are benign and nonfunctional. The glands enlarge physically, but there is no metastasis, and circulating thyroid hormone concentrations remain within normal limits. Therefore treatment of most thyroid gland neoplasias is unnecessary until or unless the glands become big enough to start to interfere with swallowing or breathing. Once a thyroid gland tumor becomes enlarged enough for the owner to notice it, a reasonable approach would be to measure circulating thyroid hormones (both total and free concentrations of T_4 and T_3). Provided that the horse is comfortable, the tumor is not big enough to interfere with alimentary or respiratory function, and the circulating thyroid hormone concentrations are normal, surgical removal is not mandatory. The size of the gland should be monitored. If the gland starts to enlarge rapidly or if circulating thyroid hormone concentrations increase, it is best to surgically remove the gland sooner, not later. Once the thyroid glands have been removed, the horse should be treated with thyroid hormone supplementation as needed to maintain circulating concentrations of thyroid hormones within the normal reference range.

41.1.3.2

HYPERTHYROIDISM IN ADULT HORSES

Hyperthyroidism is extremely rare in horses. There are two documented case reports in the literature, and both of these were associated with thyroid gland neoplasia.[86,87] Circulating thyroid hormone concentrations are also sometimes temporarily increased in horses exposed to excess iodine, such as in a topical blister. Clinical signs of hyperthyroidism in horses include weight loss, tachycardia, tachypnea, hyperactive behavior, ravenous appetite, and cachexia. Diagnosis is confirmed by measurement of increased circulating concentrations of free fractions of thyroid hormones. Treatment of a hyperactive thyroid tumor is thyroidectomy. If only one half of the thyroid gland is removed, thyroid hormone supplementation may not be necessary.

41.1.3.3

HYPOTHYROIDISM IN ADULT HORSES

Hypothyroidism in the horse is poorly understood, and its existence is controversial. Although autoimmune thyroid disease is somewhat common in people and dogs, it has not been described in the horse. The prevalence of true hypothyroidism in adult horses is unknown but is almost certainly overestimated. Hypothyroidism has been thought to contribute to a variety of problems in the horse, including obesity, laminitis, anhidrosis, recurrent rhabdomyolysis, and poor fertility. However, proper documentation of hypothyroidism in such cases for the most part does not exist. Anecdotal reports of beneficial effects of

thyroid hormone supplementation in these horses are also largely unsubstantiated. Despite this, many horses with these conditions receive unnecessary thyroid hormone medication over extended periods of time. Besides the obvious waste of money, potential health risks associated with inappropriate thyroid hormone supplementation are only beginning to be explored in horses. In humans, thyrotoxicosis or oversupplementation with levothyroxine can result in decreased bone density, increased risk of atrial fibrillation, and perhaps increased risk of myocardial infarction or congestive heart failure.[88]

Clinical signs of hypothyroidism in adult horses appear to be subtle. Traditionally, horses that gained weight easily, had cresty necks, and tended to have recurrent bouts of laminitis were thought to be hypothyroid. However, in the author's experience results of thyroid function tests in horses that fit this description are usually normal, and it is more likely that these horses have either EMS or PPID. In a few published case reports of horses that were documented to be hypothyroid, clinical signs were primarily lethargy, exercise intolerance, and poor hair coat.[89,91] In experiments in which horses were made hypothyroid either by surgical removal of the thyroid glands or by administration of antithyroid drugs,[92–96] obesity and laminitis were not reported. Although resting heart rate, cardiac output, respiratory rate, and rectal temperature decreased in horses after thyroidectomy,[93] and serum concentrations of triglycerides, cholesterol, and very—low-density lipoproteins (VLDLs) increased,[94] the changes were mild, and absolute values remained within the normal reference range for adult horses. For this reason, measurement of these values would not help identify a hypothyroid horse in the general population.

41.1.3.3.1

Other Alterations of Thyroid Function

Certain drugs, diets, physiologic, or pathologic states can alter thyroid hormone synthesis, metabolism, or binding, resulting in altered serum concentrations of thyroid hormones. For example, fasting lowers circulating concentrations of thyroid hormones in many species studied, including the horse.[97] Phenylbutazone or dexamethasone administration, strenuous exercise, and diets high in energy, protein, zinc, and copper have also been shown to alter circulating concentrations of thyroid hormones in horses.[98–105]

41.1.3.3.2

Nonthyroidal Illness Syndrome

Nonthyroidal illness syndrome has been described in humans, dogs, and cats with systemic illnesses but has not been studied extensively in horses. A preliminary report by the author suggests nonthyroidal illness syndrome is similar in horses compared with other species.[106] In humans, milder forms of illness result in decreases in serum concentrations of T_3, with T_4 remaining within the normal range or slightly decreased. As nonthyroidal illness becomes more severe, total T_4 decreases, and eventually free T_4 also begins to decrease. The magnitude of thyroid hormone suppression has been correlated to severity of disease and mortality.[107–109] Mechanisms by which thyroid hormones decrease during illness include decreased peripheral conversion of T_4 to T_3 by 5'-deiodinase, altered binding to serum carrier proteins, and hypothalamic-pituitary dysregulation or suppression.[109–113]

41.1.3.3.3

Fescue Ingestion

Tall fescue *(Festuca arundinaceae)* is a perennial grass that is grown commonly in the Southeast because it is relatively easy to establish, has a long growing season, and has good disease and drought resistance,

which allows it to survive hot, humid summers. Various reproductive problems have been described in mares consuming fescue that have been shown to be caused by alkaloids produced by an endophytic fungus *(Neotyphodium coenophialum)* that lives symbiotically on the fescue plant. These alkaloids act as a dopamine agonist (for a recent review, see Evans).[114] Because TSH release from the pituitary is inhibited by dopamine,[115] it has been suggested that fescue consumption could lead to secondary hypothyroidism. Fescue ingestion was proposed as the cause of lower serum TSH concentrations in mares and foals consuming endophyte-infected fescue on a central Kentucky farm, compared with neighboring mares and foals grazing mainly endophyte-free fescue pastures.[116] However, when adult, nonpregnant horses were fed endophyte-infected fescue seed for 2 months there was no differences in baseline concentrations of thyroid hormones, TSH, or responses to administration of TRH.[117] It appears that dopamine acts more as an acute modulator of TSH secretion, rather than as the primary control. In humans, although acute dopamine blockade results in increased TSH secretion and increased circulating thyroid hormones, chronic administration does not cause long-term alterations in thyroid hormone status.[115] Therefore it is likely that compensatory mechanisms override any dopaminergic effect of chronic fescue ingestion in the horse.

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41.1.3.3.4 Syndromes Historically Associated with Hypothyroidism

41.1.3.3.4.1 OBESITY

As mentioned earlier, horses that gain weight easily and have a tendency to deposit fat in the crest of the neck, over the rump and tailhead, or in the sheath have long been regarded as hypothyroid. It is now known that these horses are likely to have normal thyroid function and to be insulin resistant. Anecdotally, thyroid hormone administration to these horses usually does not result in weight loss. This is especially true if feed consumption is not restricted and if the amount of thyroid hormone supplementation is titrated to maintain serum thyroid hormone concentrations in the normal reference range. However, because thyroid hormone supplementation decreases blood lipid concentrations and improves insulin sensitivity and disposal in normal horses,[118] it is possible that thyroid hormone supplementation may be useful to help obese horses with metabolic syndrome lose weight. If thyroid hormones are given for this purpose, it is important to understand that they are being used as a pharmacologic tool for a short period of time, and lifelong administration is not indicated. When thyroid hormones are used to help obese horses lose weight, it is likely that the amount of hormone given needs to be enough to make the horse mildly hyperthyroid. Feed intake must also be controlled at 1.5% to 2% of desired body weight per day of grass hay or other feed that is low in soluble carbohydrates.

41.1.3.3.4.2 LAMINITIS

A role for decreased thyroid function in the pathogenesis of laminitis is poorly documented and remains a controversial topic. Although low serum thyroid hormone concentrations have been associated with acute laminitis in some horses, it is unlikely that decreased thyroid function alone causes laminitis. In five studies in which hypothyroidism was induced either by surgical removal of the thyroid glands or by administration of propylthiouracil, laminitis did not occur.[92–96] Therefore any alterations in serum thyroid hormone concentrations in horses experiencing laminitis may be caused by factors associated with the episode of laminitis, rather than being the cause of the laminitis itself. Such factors could include drugs used to treat laminitis (e.g., phenylbutazone), development of nonthyroidal illness syndrome, or a direct effect of proinflammatory mediators that may contribute to the onset of laminitis.

In the author's experience, TRH stimulation tests performed in a horse that has had an episode of laminitis or that has had bouts of recurrent laminitis show normal thyroid hormone responses when these tests are performed after the horse is stabilized and has been off all medications for 4 weeks.

Despite evidence of normal thyroid function in horses with laminitis, some veterinary clinicians still believe that treatment of horses with iodinated casein during an acute episode of laminitis results in improvement. These horses often are treated without prior measurement of thyroid hormones. Some are treated even when measurement shows serum thyroid hormone concentrations to be within the normal range. These horses are then often kept on thyroid hormone supplementation indefinitely. To date, no controlled studies have been performed to determine whether or not administration of thyroid hormones during acute episodes of laminitis is beneficial. However, because the action of α-adrenergic agonists on vasculature is usually vasodilatory, it is possible that thyroid hormone administration increases circulation to the foot by its ability to potentiate α-adrenergic receptor numbers and sensitivity.[119–121] It is also possible that thyroid hormone supplementation alters carbohydrate and fat metabolism in a way that increases insulin sensitivity.[118] Thus, any beneficial effect of thyroid hormone administration in horses with laminitis may be pharmacologic rather than physiologic.

41.1.3.3.4.3

ANHIDROSIS

Anhidrosis is a condition of adult horses characterized by a decreased ability or inability to sweat in response to appropriate stimuli. The cause is unknown. Hypothyroidism has long been associated with anhidrosis, perhaps because treatment with iodinated casein was reported to help increase sweat production in anhidrotic horses in the 1950s.[122] However, the author found that baseline concentrations of thyroid hormones and TSH were normal in horses with anhidrosis.[123] Thyroid hormone responses to TRH were also normal, but TSH responses to TRH were significantly greater in anhidrotic horses than they were in horses with normal sweat production. The clinical significance of this exaggerated TSH response in anhidrotic horses is unknown. It is possible that any observed benefit of thyroid hormone supplementation is pharmacologic, rather than physiologic as was suggested for laminitis. Because equine sweat glands are stimulated to secrete by activation of β_2-adrenergic receptors and because thyroid hormones modulate adrenergic receptor function, perhaps making horses mildly hyperthyroid iatrogenically restores β-adrenergic receptor numbers or sensitivity or potentiates sweat responses to whatever neural stimulation remains.

41.1.3.3.4.4

RHABDOMYOLYSIS

A link between hypothyroidism and rhabdomyolysis was suggested by a report of muscle stiffness, poor performance, and rhabdomyolysis in four thoroughbred and two standardbred racehorses that had low baseline T_4 concentrations.[124] The horses improved after administration of iodinated casein. However, T_4 response to TSH was normal in these horses. A subsequent study showed normal resting concentrations of T_4 but decreased T_4 response to TRH in five horses that had previous episodes of rhabdomyolysis.[125] In a study of 18 quarter horses with polysaccharide storage myopathy and 18 thoroughbreds with recurrent exertional rhabdomyolysis, circulating concentrations of T_4 and T_3 were within normal range. Stimulation tests were not performed.[126] Therefore a role for hypothyroidism in the pathophysiology of equine rhabdomyolysis is unclear. Because it is now known that the clinical syndrome of rhabdomyolysis can be caused by more than one underlying pathophysiologic entity, it is

possible that hypothyroidism may contribute to some but not all cases of equine rhabdomyolysis. If hypothyroidism is suspected, thyroid function should be ideally assessed by measuring both resting concentrations of free thyroid hormones and response to TRH or TSH. If resting concentrations of free thyroid hormones are found to be low, nonthyroidal factors should be ruled out before thyroid hormone supplementation is prescribed.

41.1.3.3.4.5

INFERTILITY IN MARES

1349

Thyroid hormone administration to broodmares has been a fairly common practice, despite lack of evidence that the mares were actually hypothyroid in the first place or that thyroid hormone supplementation improves fertility of horses. This practice presumably is an extrapolation from human medicine, where hypothyroidism in women adversely affects fertility. However, Lowe and colleagues reported that two of three fillies that had undergone thyroidectomy became pregnant without thyroid hormone supplementation,[92] and two recent publications showed no association between thyroid hormone status and conception rates.[127,128] The first study was performed in 329 clinically normal broodmares.[127] Resting serum T_4 concentrations were below normal in 12% of the mares, normal in 86%, and increased in 6%. There was no association between serum T_4 concentration and whether or not the mare was pregnant 15 to 16 days after ovulation. There also was no association between whether or not the mare was receiving thyroid hormone supplementation (60 were, 269 were not) and pregnancy status. In the second study, resting serum concentrations of total T_4 and T_3, as well as their responses to TRH, were measured in 79 thoroughbred and standardbred broodmares.[128] Resting and stimulated thyroid hormone concentrations were not different between mares that became pregnant and mares that did not.

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Although these studies suggest there is no association between thyroid status and fertility or infertility in the mare, it is still possible that hypothyroidism contributes to infertility in a small subset of mares and that this effect is being lost among all the other potential causes of failure to conceive. However, given that true hypothyroidism appears to very rare in the horse, this would have to be a very small number of mares—certainly not as many mares as are currently being routinely supplemented. Is there any basis, then, to the clinical impression held by some that thyroid hormone supplementation helps some mares get pregnant? If there is, perhaps it is more related to obesity, IR, and EMS than to hypothyroidism. Women with IR and metabolic syndrome are subfertile, and there is evidence that thyroid hormone administration to normal-weight mares increases insulin sensitivity.[118] Therefore it is possible that insulin-resistant, overweight mares are subfertile, and thyroid hormone supplementation is beneficial not because the mares were hypothyroid but because it improves their insulin sensitivity. At the time of this writing, no studies have been performed to examine this hypothesis.

41.1.3.3.5

Assessment of Thyroid Function in Adult Horses

Because certain drugs and pathophysiologic states can lower serum concentrations of thyroid hormones in otherwise euthyroid horses, it is important that thyroid function tests not be performed while horses are ill, receiving certain drugs, or on thyroid hormone supplementation. The author recommends that thyroid hormone testing be performed in horses that have not received any medications for at least 2 and preferably 4 weeks before testing. If a horse has been receiving thyroid hormone supplementation without prior documentation of hypothyroidism, the author recommends weaning the horse off supplementation and then testing thyroid function once the horse has not received any supplementation for at least 4 weeks.

Tests that are currently available for assessment of thyroid function in the horse include measurement of total and free fractions of T_4 and T_3 and response of these hormones to administration of either TRH or TSH.[98–100,125,129–132] Although results of TRH or TSH stimulation tests are thought to provide a better indication of thyroid status than single-point-in-time measurements of thyroid hormone concentrations, these tests are not routinely performed by ambulatory clinicians because of the impracticality of having to take multiple blood samples over time. In addition, TRH and TSH either are not readily available commercially for sterile, single-dose application or are prohibitively expensive.

For performance of a stimulation test, a control blood sample is obtained, TRH (1 mg to the average 450- to 500-kg horse) or TSH (5 IU) is given intravenously (IV), and subsequent blood samples are obtained. Most references say that T_3 should double at 2 hours and T_4 should double at 4 hours. The author routinely performs TRH stimulation tests and prefer to measure both T_3 and T_4 before and 1, 2, and 4 hours after TRH administration, in order to make sure the peaks are not missed. In 36 normal horses that participated in various studies the author conducted, the mean increase in total T_4 was 2.2 times at 4 hours. However, the range was 1.3 to 3.8 times. Increases in free T_4 and free T_4 by dialysis (mean and range) were 1.7 (1.1 to 2.1) times and 1.8 (1.1 to 2.8) times at 4 hours, respectively. Increases in total and free T_3 (mean and range) were 3 (1.1 to 10.3) times and 4.2 (1 to 53) times at 2 hours, respectively. These seemingly lower thyroid hormone responses to TRH injection are in agreement with findings in a recent report of levothyroxine administration to normal horses.[133] Closer examination of the data from the author's horses revealed that in general the few individuals with small increases in T_4 or T_3 either started with higher resting values or had peaks that occurred later (T_4) or earlier (T_3) than 4 or 2 hours. Individuals with lower T_4 responses in general were not the same individuals with lower T_3 responses. Therefore one must be careful when interpreting results of a TRH stimulation test. Failure of T_3 to double by 2 hours or T_4 to double by 4 hours after TRH injection does not necessarily mean that the horse is hypothyroid. Individuals with high responses tended to be individuals with very low resting thyroid hormone concentrations.

If single-point-in-time measurement of thyroid hormones is the only option available for evaluation of thyroid status, measurement of free fractions of thyroid hormones (alone or in conjunction with measurement of total amounts of hormone) provides more useful information than measurement of total amounts of thyroid hormones alone. Measurement of serum TSH concentration in single samples will likely aid diagnosis of thyroid status once a TSH assay for the horse becomes commercially available.

During illness in humans, measurement of serum free T_4 by direct methods often underestimates values when compared with measurements of free T_4 after dialysis or ultrafiltration.[134–138] This also appears to be the case in dogs[139] and horses.[106] Therefore serum concentrations of free T_4 measured by equilibrium dialysis are more likely to reflect true thyroid status in ill horses, compared with other methods of free T_4 measurement. Measurement of fT_4D instead of fT_4 may help prevent equine clinicians from misdiagnosing ill horses as being hypothyroid.

41.1.3.3.6

Treatment of Hypothyroidism in Adult Horses

Management of horses that have been properly diagnosed as being hypothyroid or horses that have undergone thyroidectomy theoretically should be fairly straightforward. Serum thyroid hormone concentrations should be monitored and dosages of thyroid hormone supplementation adjusted to maintain

serum thyroid hormones in the normal range. This is not necessarily as simple as it sounds. T_4 is the most common form of thyroid hormone supplementation. T_4 administration increases serum concentrations of T_4; however, serum concentrations of T_3 may not change or may actually decrease if T_3 is not also given or if the horse is not truly hypothyroid. In addition, T_4 dosage recommendations have been made based on thyroid hormone concentrations obtained after thyroid administration to normal horses with intact thyroid glands.[140] Thyroid hormone pharmacokinetics may be different in truly hypothyroid horses; pharmacokinetic studies in horses made hypothyroid by thyroidectomy or by administration of antithyroid drugs would be useful. Until such studies are performed, the following recommendations can be made. T_4 is available in several forms. Iodinated casein contains approximately 1% T_4 and is given at 5 to 15 g/horse/day by mouth [PO].[92] The recommended starting dose of levothyroxine was 20 g/kg/day PO,[82,140] but a more recent study suggested that doses as high as 50 to 100 g/kg/day are well tolerated and may be necessary.[133] If a sensitive TSH assay becomes commercially available, dosages should be adjusted to normalize TSH.

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41.1.3.4 THYROID FUNCTION IN NORMAL NEONATAL FOALS

Fetal concentrations of T_3 and cortisol are low.[141] In many species fetal serum thyroid hormones increase just before birth and probably play a role in the rapid growth and organ system development that occur in late gestation. Normal neonatal foals have serum concentrations of thyroid hormones that are approximately 10 times adult concentrations.[142–144] Thyroid hormones remain very high during the first week of life, then slowly decline, reaching normal adult concentrations by approximately 1 month of age. These high concentrations of thyroid hormones are thought to be important in maintaining thermogenesis, regulation of cell differentiation, and maturation of many body systems, especially the respiratory, nervous, and musculoskeletal systems. Thyroid hormones increase thermogenesis by increasing metabolic rate and, of particular relevance to the neonate, increasing heat production from brown fat.[145] Thyroid hormones also stimulate lung development and surfactant production, and these effects are potentiated by concurrent administration of glucocorticoids.[146] Skeletal growth and maturation are stimulated synergistically by thyroid hormones and growth hormone (GH).[147] The mechanisms by which thyroid hormones are increased in the peripartum period are unknown. One might expect the increase to be centrally driven. However, in a study the author recently completed,[144] serum TSH concentrations were not increased in equine neonates compared with adults, nor did they change over the first month of life while serum thyroid hormone concentrations were declining.

41.1.3.4.1 Thyroid Function in Premature Foals

Premature human infants experience transient hypothyroxinemia, with serum T_4 concentrations correlated to gestational age.[148–151] In a study recently conducted by the author, serum concentrations of thyroid hormones and TSH at rest and in response to TRH were measured in foals to determine the possible contributions of an immature hypothalamic-pituitary axis and nonthyroidal illness to thyroid function. Three groups of foals were examined: (1) normal, healthy neonatal foals that were full term and not receiving any medications (normal foals); (2) premature neonatal foals (premature foals); and (3) full-term neonatal foals that were hospitalized for conditions similar to those encountered in premature foals (sick foals).[144] Both sick and premature foals received medications routinely used to treat their conditions, which included (but were not limited to) failure of passive transfer, sepsis, and perinatal asphyxia

syndrome. Blood samples were collected for measurement of baseline concentrations of total and free thyroid hormones and TSH at predetermined ages. TRH stimulation tests were performed in foals at less than 3 days of age. Premature foals had significantly lower serum concentrations of total and free fractions of thyroid hormones than normal foals. Baseline serum concentrations of TSH were not different, but TSH responses to TRH were exaggerated in premature foals compared with normal foals. Serum concentrations of T_3 and TSH were similar in sick full-term foals and premature foals, but serum concentrations of T_4 in sick full-term foals were intermediate between those of premature and normal foals. These results suggest that sick foals experience nonthyroidal illness syndrome, primarily a low T_3 state. The effects of drugs commonly used to treat ill foals on serum thyroid hormone concentrations in the premature and sick foals in this study were not examined. More profound alterations in thyroid function in premature foals compared with sick full-term foals may be caused by an immature hypothalamic-pituitary-thyroid axis. It remains to be seen whether early thyroid hormone supplementation in premature foals might improve short-term survivability and preserve long-term athletic function. Traditional thought has been that administration of thyroid hormones to patients with nonthyroidal illness syndrome is not beneficial and might even be detrimental. However, these beliefs have recently been challenged,[109,110] and the issue remains controversial. Although results are variable, treatment of premature human infants with T_4 has resulted in improved IQ and neurologic development at 2 years of age,[148,149] and T_3 administration to human neonates with severe respiratory distress syndrome has been shown to improve survival.[152]

41.1.3.4.2

Congenital Hypothyroidism in Foals

Two syndromes of congenital hypothyroidism have been described in foals. Hypothyroid foals with visible goiters have been produced by mares ingesting either too much or too little iodine and by mares ingesting goitrogenic plants.[153–155] These foals are born weak, with poor sucking and righting reflexes, hypothermia, and developmental abnormalities of the musculoskeletal system, including tendon contracture or rupture and delayed bone development, particularly of the small cuboidal bones of the carpus and tarsus. Thyroid hormone supplementation to more severely affected foals may improve survivability, but dosage recommendations are scarce. Irvine recommends basing the dose on secretion rate.[147] For oral administration of T_4, this would equal 10 × 0.22 × kilograms of body weight × 0.08 × plasma T_4 (g/L). This calculates to approximately 2.5 mg/day PO for a 1- to 3-day-old 50-kg foal. Because there is a time delay for T_4 to act and because T_3 is more active than T_4, T_3 supplementation at one third the calculated T_4 dose may provide more benefit initially.

A second syndrome of congenital hypothyroidism has been described in foals, primarily in the western parts of the United States and Canada.[156–160] This syndrome is characterized by thyroid gland hyperplasia, increased gestational length, and musculoskeletal abnormalities, including mandibular prognathia, flexural limb deformities of the front legs, ruptured digital extensor tendons, and incomplete ossification of the carpal and tarsal bones. Despite the prolonged gestation, other indicators of prematurity may be present, such as a silky hair coat. At the time of birth, baseline serum concentrations of T_4 and T_3 are usually within the normal neonatal ranges, but the response to TSH administration is decreased.[161] The cause is unknown but suspected to be a dietary deficiency or toxicity of the mare during gestation. Likely candidates include nitrate, low iodine, low selenium, or goitrogenic plant ingestion by the mare.[159,161] Because thyroid hormone concentrations are normal at the time of birth, thyroid hormone supplementation is usually not administered. Supportive care to try to prevent collapse of the carpal and tarsal bones is recommended.

41.1.4 EQUINE METABOLIC SYNDROME

NICHOLAS FRANK

41.1.4.1 Definitions

Equine metabolic syndrome (EMS) is characterized by obesity or regional adiposity, IR, and subclinical or clinical laminitis. Regional adiposity occurs in the form of adipose tissue accumulation in the neck or tailhead region, and subclinical laminitis is detected by the presence of abnormal growth rings (also called *founder lines*) on the hooves. The term *equine metabolic syndrome* has been adopted because IR and regional adiposity are components of metabolic syndrome in humans. However, EMS is unique to this species because other components of metabolic syndrome, including abdominal adiposity, hypertension, and microalbuminemia, have not been detected in horses.[162,163] The term *prelaminitic metabolic syndrome* (PLMS) has also been introduced to describe ponies at risk for developing pasture-associated laminitis because of IR.[164] This is sometimes referred to as *endocrinopathic laminitis* because of its association with IR in horses and ponies.

Obesity is defined as an increase in body weight because of excessive fat accumulation within the body. When the body condition score (BCS) system developed by Henneke and colleagues[165] is applied, obesity is defined by a BCS ≥7 on a 1 (poor) to 9 (extremely fat) scale. Obesity and IR are associated in horses and ponies.[166,167] *Insulin resistance* refers to the failure of insulin-sensitive tissues to respond to insulin. Skeletal muscle, adipose, and liver tissues are primarily affected because they are the primary sites for insulin-mediated glucose disposal. Hyperinsulinemia is a feature of compensated IR, whereas uncompensated IR occurs when beta-cell insufficiency (pancreatic failure) develops. Compensated IR is more common in horses and ponies, but uncompensated IR sometimes accompanies advanced PPID. Type 2 diabetes mellitus occurs when hyperglycemia develops as a result of uncompensated IR. *Diabetes* actually refers to excessive production of urine (polyuria), which is caused by glucosuria in the case of diabetes mellitus. There has been a recent report of diabetes mellitus in a Spanish Mustang,[168] but this condition is rare in horses.

41.1.4.2 Etiology

Genetic predisposition plays an important role in the development of obesity and IR in horses. Ponies tend to be more insulin resistant than horses,[167] and certain breeds of horse including Morgan horses, Arabians, and Norwegian Fjords appear to more predisposed to obesity and IR.[162,166] Horses with this predisposition are sometimes referred to as “easy keepers” because they require fewer calories to maintain body weight. Environmental factors including diet and exercise are also likely to play important roles in the development of obesity and IR in horses. Feeding concentrates to a susceptible animal is often enough to induce obesity and the grass consumed on pasture can be a significant source of calories. Carbohydrate intake on pasture is influenced by grazing time, the area grazed, and the water-soluble carbohydrate (WSC) and starch content of pasture grasses. Amounts of these carbohydrates vary considerably by geographic location, climate, soil quality, and season.[169] Exercise increases insulin sensitivity in humans and horses, so more sedentary horses may be more susceptible to obesity.[170,171] EMS affects adult horses, and most affected animals are over 5 years of age. There is no identifiable sex predilection.

41.1.4.3

Clinical Signs and Differential Diagnoses

Obesity is detected on physical examination of the horse and application of a BCS system. A mare with EMS is shown in Fig. 41-10. Regional adiposity is commonly detected in horses with IR, and mean neck circumference has been negatively correlated with insulin sensitivity in obese horses with IR.[166] The technique for measuring mean neck circumference is presented in Fig. 41-11. Expansion of adipose tissues within the neck is commonly referred to as a "cresty neck," and with the exception of stallions this finding is suggestive of IR in horses. Enlarged fat deposits may also be found close to the tailhead, within the sheath, or randomly distributed as subcutaneous swellings. Abnormal fat deposits may also develop in older horses with PPID but are usually accompanied by hirsutism, loss of skeletal muscle mass, polyuria, or polydipsia.[172] Horses with EMS commonly have laminitis, which is detected by observing the horse's gait or applying hoof testers to the feet. Some horses do not show signs of laminitis on physical examination but have a history of previous disease. Others have abnormal growth rings (founder lines) or radiographic evidence of third-phalanx rotation or sinking. IR predisposes ponies to pasture-associated laminitis,[164] and there is anecdotal evidence to suggest that the same association exists in horses.

41.1.4.4

Clinical Pathology

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Complete blood count and serum biochemical analysis results are usually unremarkable, except blood glucose concentrations are sometimes toward the upper end of the reference range. Hyperglycemia is more commonly detected in ponies. It occasionally occurs in horses with PPID and may be accompanied by mature neutrophilia with lymphopenia. Elevated serum triglyceride concentrations may be detected in ponies[164] or horses[166] with obesity and IR, but this finding is inconsistent in our experience. Plasma concentrations of VLDL and high-density lipoprotein cholesterol (HDL-C) are significantly higher in obese horses with IR, but these measurements are not readily available.[166]

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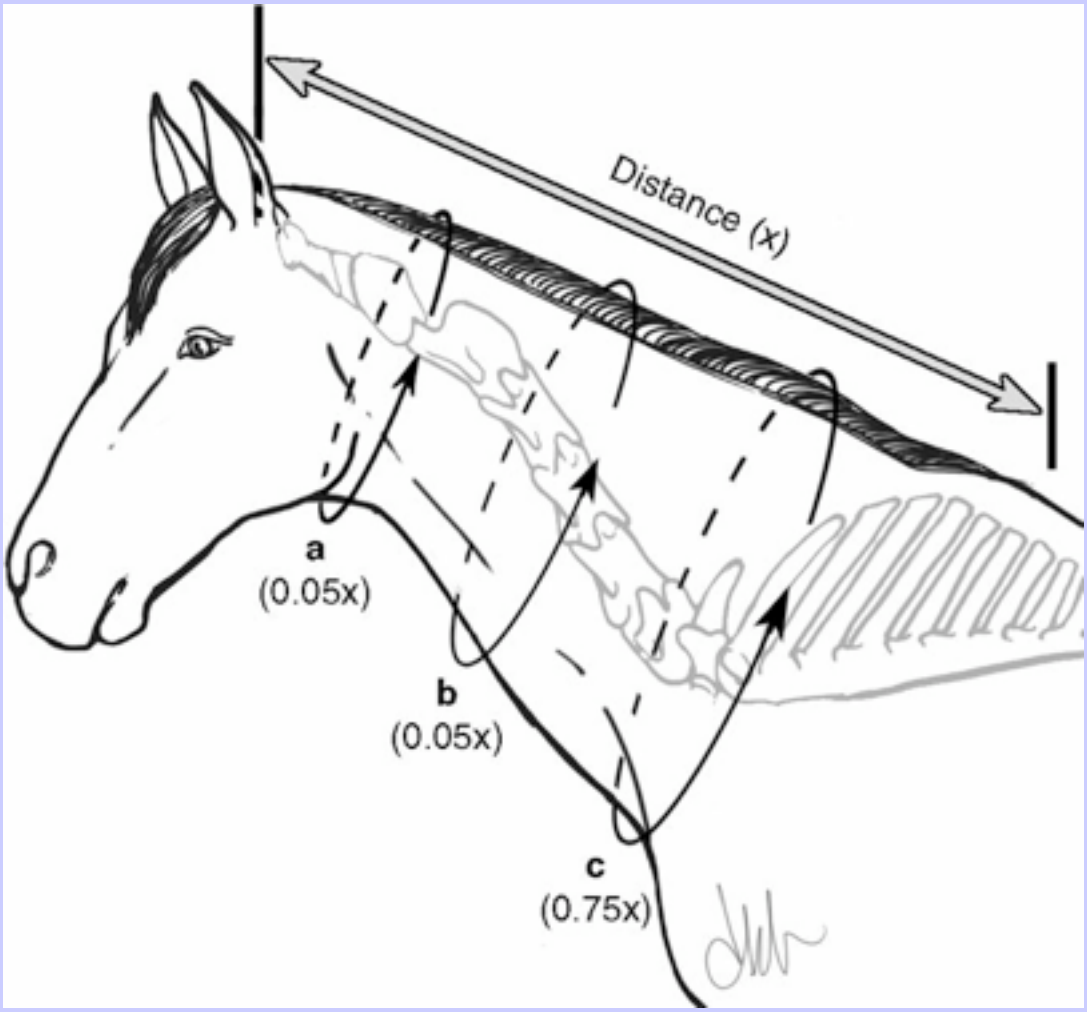
Fig. 41-10 A 7-year-old Morgan horse cross-bred mare with equine metabolic syndrome.

Fig. 41-11 A procedure used to measure mean neck circumference in horses. *a* = 0.25 of the distance from poll to withers; *b* = 0.50 of the distance from poll to withers; *c* = 0.75 of the distance from poll to withers. Reprinted with permission from the *Journal of the American Veterinary Medical Association* 228:1383, 2006.



Low resting total triiodothyronine (tT_3) or total thyroxine (tT_4) concentrations are sometimes detected in obese horses with IR, but the significance of this finding has been overstated in the past. It is a common misconception that obese horses have hypothyroidism because obesity is associated with hypothyroidism in dogs and humans. However, advanced testing rarely supports a diagnosis of hypothyroidism in horses with EMS. Serum thyroid hormone concentrations rise appropriately when TRH is injected intravenously, indicating that the hypothalamic—pituitary gland—thyroid gland axis is functioning normally. It is therefore likely that serum thyroid concentrations reflect responses to extrathyroidal changes in metabolism. Breuhaus and co-workers[173] recently detected markedly lower serum tT_4 and free T_4 concentrations in horses with

systemic illness, and these values were below the reference ranges used by most laboratories. Results of that study illustrate that extrathyroidal factors lower serum thyroid hormone concentrations, which may lead to the incorrect diagnosis of primary hypothyroidism. Phenylbutazone also significantly lowers serum tT_4 concentrations in horses, and this drug is commonly used to treat laminitis in horses with EMS.[174]

41.1.4.5

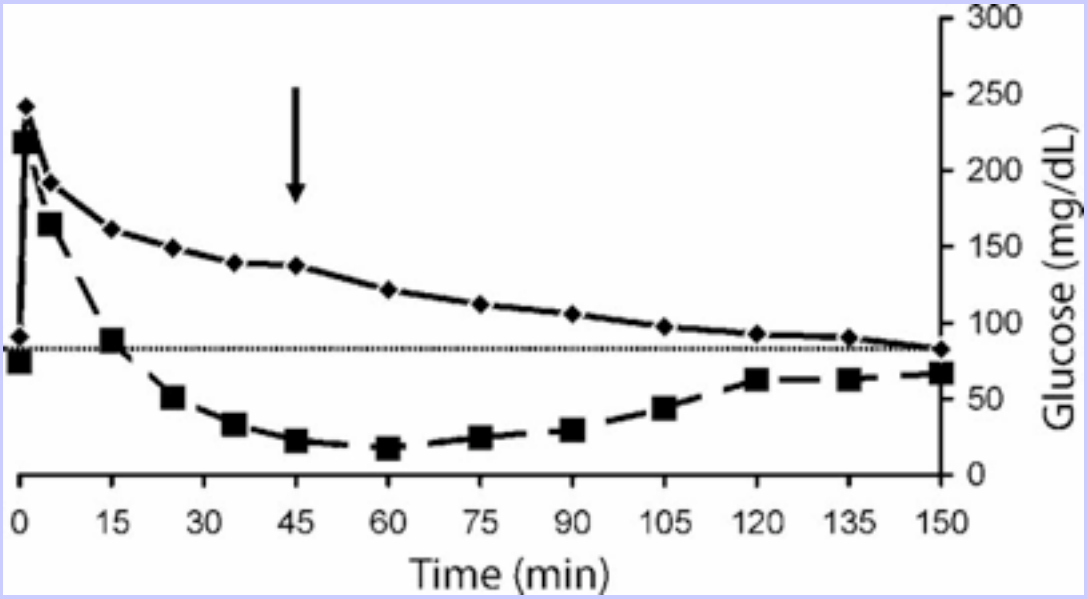
Diagnostic Testing

Horses can be screened for IR by measuring resting serum insulin concentrations. Results should be interpreted using the reference range provided by the laboratory. In our laboratory a resting serum insulin concentration above 20 μU/mL is suggestive of IR, and a concentration above 30 μU/mL defines hyperinsulinemia. Resting serum insulin concentrations can be measured to screen horses for IR and assess responses to diet or exercise, but it should be recognized that this diagnostic test does not detect uncompensated IR. Grass consumed on pasture and concentrates can potentially elevate serum insulin concentrations, so it is important to remove horses from pasture and feed only grass hay for a minimum of 24 hours (and ideally 72 hours) before collecting blood samples.

Two proxies have recently been established to provide measures of insulin sensitivity and pancreatic beta-cell function in horses and ponies.[175] The reciprocal of the square root of insulin (RISQI) measurement uses the resting serum insulin concentration and provides a measure of insulin sensitivity, whereas serum concentrations of both glucose and insulin are used to calculate the modified insulin-to-glucose ratio (MIRG), which represents the pancreatic beta-cell response. Horses with compensated IR have a low RISQI and high MIRG, whereas both the RISQI and MIRG are low in horses with uncompensated IR.

The combined glucose-insulin test (CGIT) is a useful field test for detecting IR in horses.[166] This test involves collection of a baseline blood sample followed by intravenous infusion of 150 mg of 50% dextrose solution per kilogram of body weight, then immediately by 0.10 unit of regular insulin per kilogram of body weight.[176] Blood samples are collected at 1, 5, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135, and 150 minutes postinfusion. When the CGIT is used, IR is defined as maintenance of blood glucose concentrations (measured with a hand-held glucose meter) above the baseline (preinjection) value for 45 minutes or longer (Fig. 41-12). The test can be abbreviated to 60 minutes when used in the field, but it is advisable to complete the measurements so that the time taken for the blood concentration to return to baseline can be recorded for future reference. This allows responses to diet, exercise, or medications to be assessed. There is a small risk of inducing hypoglycemia when this test is performed, so two 60-mL syringes containing 50% dextrose should be kept on hand and administered if muscle fasciculations or profound weakness are observed or if the blood glucose concentration drops below 40 mg/dL. Note that stress is an important cause of transient IR that can significantly affect CGIT results. In one study, IR was detected in healthy nonobese horses when CGIT procedures were performed immediately after endoscopic examinations.[176] Horses must therefore remain calm before and during the procedure to avoid false-positive results. An intravenous catheter should ideally be placed the night before testing to minimize stress. Because pain affects results, horses with acute laminitis must be given time to recover before testing is performed. Feed deprivation also causes stress, so horses are permitted to eat grass hay during the testing procedure.

Fig. 41-12 Blood glucose concentrations during the combined glucose-insulin test (CGIT) in a healthy nonobese mixed-breed horse *(dashed line)* and an obese insulin-resistant Morgan horse mare *(solid line)*. The horizontal line represents the approximate baseline plasma glucose concentration, and the arrow indicates the time point (45 minutes postinjection) selected to define insulin resistance when the CGIT is used. Blood concentrations remain above the baseline value for 45 minutes or longer if the horse is insulin resistant.



41.1.4.6

Pathophysiology

Relationships among obesity, IR, and laminitis in horses are complex. It is likely that certain horses are genetically predisposed to obesity and IR and these animals are recognized by their owners as easy keepers. Adipose tissues expand as obesity develops, through an increase in adipocyte size (hypertrophy) or number (hyperplasia). This appears as generalized obesity and/or regional adiposity, and either may be accompanied by IR. In horses, regional adiposity increases the size of adipose tissues within the nuchal crest, and neck circumference has been negatively correlated with insulin sensitivity in obese insulin-resistant horses.[166] Fat thickness over the rump has also been used as a measure of body fat mass in horses,[177] and some affected animals develop pronounced fat pads in this area. It has been suggested that visceral adipose tissues play an important role in the development of IR because expansion of visceral fat depots is a feature of metabolic syndrome in humans. This syndrome is caused by increased 11β-HSD activity and excessive local cortisol production within visceral adipose tissues.[162] However, insulin sensitivity has not been correlated with visceral fat mass in horses, and no evidence presented to date has supported an association between IR and

altered 11β-HSD activity in this species. Regional adiposity may simply reflect an altered metabolic state in IR horses. 1354

Horses that are evolutionarily adapted to sparse forages and harsher conditions may be predisposed to obesity because lipid accumulates more readily when excessive calories are provided in the diet. A state of overnutrition may be induced when genetically predisposed horses are turned out on lush pastures. The natural equine diet contains little fat, but excess glucose can be converted into fat via de novo lipogenesis. Fats are used for energy or stored as triglyceride within cells. When the storage capacity of adipose tissues is exceeded, fats are directed toward nonadipose tissues (repartitioning). Skeletal muscle, liver, and pancreatic tissues attempt to use fats by increasing beta oxidation, but lipid can accumulate within these tissues and alter normal cellular functions. This pathophysiologic condition is sometimes referred to as *lipotoxicity*.[178] Reactive oxygen species are also generated as oxidative pathways are upregulated. Oxidant damage contributes to lipotoxicity and lipid-induced programmed cell death (lipoapoptosis). Inflammation accompanies these events, resulting in the release of TNF-α and IL-6 from adipose tissues. Adipocytes can also release proinflammatory cytokines referred to as *adipokines* that act locally or enter the blood. IR develops when these events affect insulin-sensitive adipose, liver, and skeletal muscle tissues. Insulin receptors or their downstream signaling pathways are disrupted, which lowers insulin sensitivity. More insulin is released from the pancreatic beta cells to compensate for the reduction in insulin sensitivity, which results in compensatory hyperinsulinemia.

Associations between laminitis and insulin sensitivity require further study, but results of in vitro studies suggest that equine hoof keratinocytes have a high requirement for glucose and dermoepidermal attachments are weakened when the availability of glucose is reduced.[179,180] IR is also likely to affect vascular dynamics within the foot because insulin serves as a slow vasodilator and recruits capillaries to the local circulation.[181] Insulin stimulates the release of the vasodilator nitric oxide from vascular endothelial cells, and this process is inhibited when IR develops.[181] It is therefore conceivable that dietary exacerbation of IR, including intracellular lipid accumulation and the generation of inflammatory mediators, causes parallel impairment of metabolic and vascular responses, which significantly reduces nutrient delivery to hoof tissues.

41.1.4.7

Management

The principal components of management are exercise and diet. Horses that are free of overt laminitis should be ridden or exercised on a lunge line each day. Although laminitic horses should not be exercised during the acute phase of the disease, hand walking may be beneficial once the condition stabilizes.

Weight loss should be induced in obese horses by restricting the total number of calories consumed. In horses that are being overfed, removal of all concentrates from the diet is often sufficient to achieve the ideal body weight. Total caloric intake should initially be met by feeding grass hay exclusively in amounts equivalent to 1.5% to 2% of current body weight (e.g., 18 to 24 lb of grass hay per day for a 1200-lb horse). If the horse does not lose weight, the amount fed should be lowered over several weeks to 1.5% of ideal body weight (e.g., 15 lb of grass hay for an ideal weight of 1000 lb). These strategies are effective for horses kept in stalls or dirt paddocks, but weight loss is more difficult to achieve when horses are grazing on pasture. Strategies for limiting grass consumption on pasture include shortened turnout time, confinement to a small paddock, round pen, or area enclosed with electric fence, or use of a grazing muzzle.

When managing horses with EMS, close attention must be paid to the amount of sugar consumed in the diet. Concentrates such as sweet feed should be eliminated altogether because they tend to be rich in readily

available sugar. However, forages can also be a concern if they contain large amounts of hydrolyzable carbohydrate in the form of starch or fermentable carbohydrate such as fructans, which are polymers of fructose.[182] Hay samples should be submitted to a forage laboratory for analysis. Laboratories provide values for WSC (simple sugars and fructans) and starch or collectively report these components as nonstructural carbohydrate (NSC). Structural carbohydrates include cellulose and lignin, which are measured as neutral detergent fiber (NDF).[182] Insulin-resistant horses should ideally be fed grass hay containing less than 12% NSC, and clients should be encouraged to analyze each batch of hay before purchasing. If hay with a higher NSC content must be fed, soaking in water for 30 minutes will leach out some soluble sugars.[183] Pasture grass also provides large quantities of NSC that can exacerbate IR and increase the likelihood of laminitis.[164] Grass growing on pasture varies in NSC content according to location, soil type, rainfall, season, and time of day.[169] It is therefore advisable to restrict or eliminate access to pasture when managing horses with EMS. If grazing is permitted, pasture grass samples should ideally be collected from different pastures at various times of the year to determine the best location and safest time for grazing affected horses.

Insulin-resistant horses that exhibit regional adiposity but have a thinner overall body condition are more difficult to manage because additional calories must be provided without exacerbating IR. Some of these horses are affected by PPID, and others have lost weight through regular exercise but remain insulin resistant. Diets rich in fat and fiber increase insulin sensitivity in horses, whereas feeds rich in starch and sugar have the opposite effect.[184] It is therefore advisable to select low-sugar feeds such as molasses-free beet pulp and add vegetable oil to provide additional calories. Commercial feeds containing more fat and fiber are also available, and these feeds may be appropriate for thinner horses with IR. However, these feeds are not recommended for obese horses; these animals require only grass hay and an appropriate vitamin and mineral supplement.

Some horses with EMS that have repeated episodes of laminitis must be removed from pasture altogether. These horses should be kept in dirt paddocks and fed only grass hay and a vitamin and mineral supplement. After weight loss has been achieved, reintroduction to pasture can be attempted. However, some horses are so sensitive to alterations in pasture nutrient content that they must be held off pasture permanently in order to avoid pasture-associated laminitis. Grazing in the early morning is likely to be safer for horses with IR, except after a hard frost, when grasses rapidly accumulate sugars.[185]

Levothyroxine sodium can be administered to accelerate weight loss when treating an obese horse that cannot be exercised, when obesity persists despite dietary interventions, or if the horse has repeated episodes of laminitis. It has previously been demonstrated that levothyroxine sodium (Thyro-L, Lloyd, Inc., Shenandoah, Iowa) lowers body weight and improves insulin sensitivity in horses.[186] Levothyroxine can be administered orally or in the feed at a dose of 4 tsp (48 mg) per day until the ideal body weight is achieved or for up to 6 months. When treatment is discontinued, the dosage should be lowered to 2 tsp (24 mg)/day for 2 weeks and then 1 tsp (12 mg)/day for 2 weeks. Health problems have not been associated with the administration of levothyroxine to horses for 12 months, but the 4 tsp (48 mg)/day dose should not be exceeded, and treatment at this higher dose should not extend beyond 6 months. In the past, levothyroxine has been inappropriately prescribed to horses for extended or lifelong treatment of hypothyroidism. As described here, levothyroxine is used for a defined period of time to induce weight loss presumably by increasing basal metabolic rate.

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Numerous other treatments have been proposed for the management of IR in horses including magnesium supplementation, chromium,[187] clenbuterol,[188] and cinnamon. Each of these therapies may be of benefit, but further studies are required to establish their efficacy in the management of EMS.

41.1.5 PARATHYROID GLAND AND CALCIUM DYSREGULATION

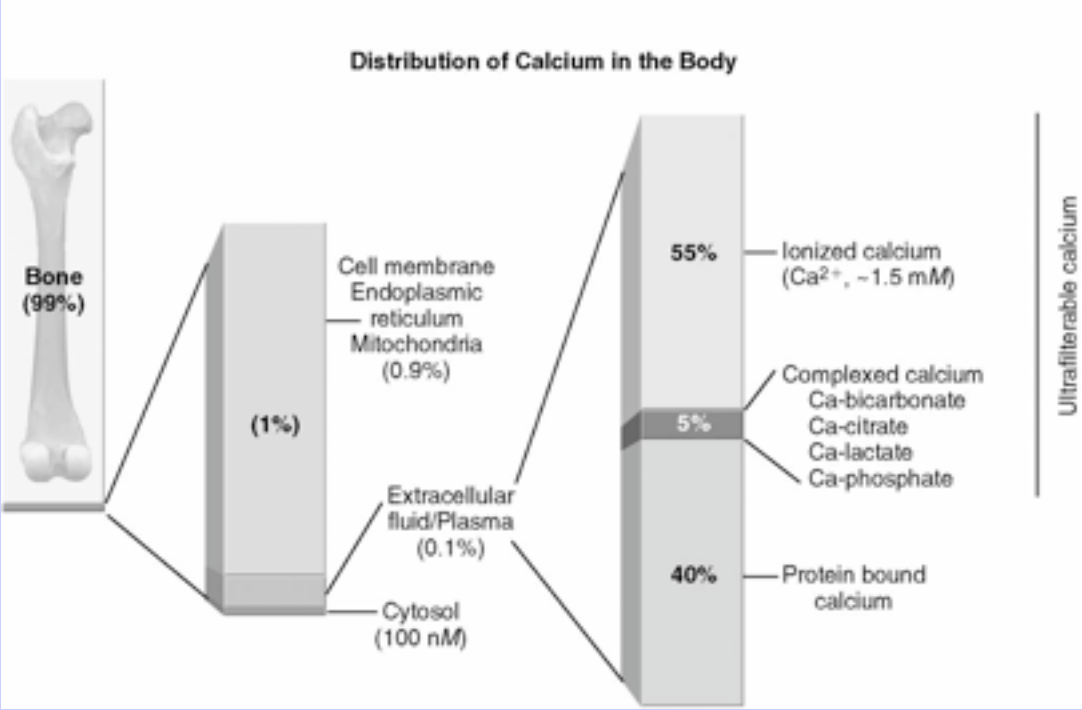
Ramiro E. Toribio

41.1.5.1 CALCIUM

Calcium is the fifth most abundant element in the body, representing approximately 1.5% of the body weight. Physiologic functions such as muscle contraction, hormone secretion, enzyme activation, cell division, cell membrane stability, neuromuscular excitability, and blood coagulation are calcium-dependent.[189] Processes that result in cell injury and death such as free radical production, cytokine release, protease activation, vasoconstriction, and apoptosis also depend on calcium.

Calcium has structural and nonstructural functions, and it is found in three main compartments: the skeleton, soft tissues, and extracellular fluid. The skeleton contains approximately 99% of the total body calcium (and 80% of phosphorus) as hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) in a calcium:phosphorus ratio of 2:1. As part of the skeleton, calcium provides support against gravity, protects vital internal organs, and houses blood-forming elements. The skeleton also acts as a reservoir for calcium. The nonstructural functions are related to calcium as a regulatory ion. The remaining calcium is present in the cell membrane, mitochondria, endoplasmic reticulum, and extracellular fluid.[189] In blood, most calcium is in plasma in a free or ionized form (approximately 55%), bound to proteins (approximately 40%), and complexed to anions such as citrate, bicarbonate, phosphate, and lactate (approximately 5%) (Fig. 41-13).[189–191] In horses, serum ionized calcium represent 50% to 55% of the total serum calcium.[191–193] Free, unbound, or ionized calcium (Ca^{2+}) is the biologically active form of calcium. Of the protein-bound calcium, approximately 80% is associated with albumin and 20% with globulins. Calcium binds to negatively charged or anionic proteins. This affinity is pH dependent. During acidosis, increased H^+ concentrations decrease Ca^{2+} binding to anions, resulting in increased plasma Ca^{2+} concentrations. Alkalosis lowers Ca^{2+} concentrations. Hypoalbuminemia results in total hypocalcemia (pseudohypocalcemia), with Ca^{2+} concentrations remaining within the normal range.

Fig. 41-13 Calcium distribution in the body.[190] Approximately 99% of the total body calcium is in the skeleton. The remaining calcium is present in the cell membrane, mitochondria, endoplasmic reticulum, and extracellular fluid. In blood, calcium exists in a free or ionized form (Ca^{2+}), bound to proteins, and complexed to anions such as citrate, bicarbonate, phosphate, and lactate. In horses, serum Ca^{2+} represents 50% to 55% of the total serum calcium concentration.



Calcium and phosphorus requirements in horses depend on age, physiologic status, and amount of work or exercise performed (Table 41-1). Serum Ca^{2+} concentrations are not a reliable indicator of dietary calcium intake. An acceptable diet for horses must have 0.15% to 1.5% of calcium and 0.15% to 0.6% of phosphorus in feed dry matter (Box 41-1). A calcium:phosphorus ratio less than 1:1 can have negative effects on calcium absorption and skeletal development; however, a calcium:phosphorus ratio as high as 6:1 for growing horses may not be detrimental if phosphorus intake is adequate.[194] Adult horses should receive approximately 40 mg of calcium/kg/day (see Table 41-1). Average horses must absorb 20 to 25 mg of calcium and 10 to 12 mg of phosphorus/kg/day to meet their needs and balance losses. Calcium and phosphate content in some mineral supplements and equine feeds are presented in Tables 41-2 and 41-3.

Horses have distinctive features with regard to calcium metabolism. These include high serum total and ionized calcium concentrations,[193] poorly regulated intestinal Ca^{2+} absorption,[195] high urinary fractional

excretion of calcium,[193] low serum concentrations of vitamin D metabolites,[196] and decreased parathyroid gland sensitivity to Ca^{2+}.[197,198]

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Most calcium absorption occurs in the small intestine.[195,199] Compared with other species, horses absorb a larger proportion of dietary calcium. Horses can absorb 50% to 75% of the calcium and less than half the phosphorus in their diet, with little effect of age.[195] Calcium absorption is inversely related to dietary calcium content. High content of phosphate (or phytate, oxalate) inhibits calcium absorption; however, high dietary calcium content has minimal effect on phosphorus absorption. Oxalates reduce calcium absorption. Some plants containing harmful amounts of oxalate are listed in Table 41-4. The dietary cation-anion balance (DCAB) affects Ca^{2+} absorption in horses; a low DCAB increases intestinal Ca^{2+} absorption, whereas a high DCAB has the opposite effect.[200] Glucocorticoids decrease intestinal absorption of calcium, decrease bone resorption, and increase urinary excretion of Ca^{2+} in horses.

Table 41-1 Calcium and Phosphorus Requirements in Horses[249]

	Percent in the Diet		Daily Intake (grams)	
	Ca	P	Ca	P
Foals (<6 months)	0.80	0.55	33	20
Weanlings	0.60	0.45	34	25
Yearlings	0.50	0.35	31	22
2-year-olds	0.40	0.30	25	17
Mare, late pregnancy	0.45	0.30	34	23
Mare, lactation	0.45	0.30	50	34
Mature horses	0.30	0.20	23	14

Adapted from Schryver HF, Hintz HF: Minerals. In Robinson NE, ed: *Current therapy in equine medicine,* ed 2, Philadelphia, 1987, Saunders, p 393.

41.1.5.1.1

Box 41-1 Acceptable Ranges of Minerals and Vitamins in Feed of Horses[250]

Ca (%)	0.25–1.5
P (%)	0.15–0.6
Mg (%)	0.08–0.16
Vitamin D (IU/kg)	300–800

Table 41-2 Calcium and Phosphorus Content of Some MineralSupplements

	Calcium (%)	Phosphorus (%)
Calcium carbonate	34	0
Dicalcium phosphate	27	21
Monocalcium phosphate	17	21
Bone meal	30	14
Monosodium phosphate	0	22
Defluorinated phosphate	32	15
Calcium gluconate 23%	2.14	0

Adapted from Toribio RE: Disorders of the endocrine system. In Reed SM, Bayly WM, Sellon DC, eds: Equine internal medicine, St Louis, 2004, Saunders, p 1295.[190]

Calcium is eliminated through the kidneys, milk, sweat, feces, and fetus. In the kidney approximately 60% of calcium is reabsorbed in the proximal tubules by passive mechanisms, and 35% is reabsorbed in the thick ascending loop of Henle and distal tubules by active mechanisms. The rest (approximately 5%) represents the urinary fractional excretion of calcium. Endogenous losses of calcium in horses have been estimated to be 20 to 25 mg/kg of body weight per day. Assuming a 50% calcium digestibility, a 500-kg horse would require 20 g of calcium to replace losses, or 40 mg/kg/day; growing and lactating horses can double these requirements. 1356 1357 Interpretation of the urinary excretion of calcium can be difficult because horses eliminate large amounts of calcium (primarily calcium carbonate) in urine.[190]

Table 41-3 Mineral Composition of Some Equine Feeds on a Dry Matter Basis[250]

Source	Ca (%)	P (%)	Mg (%)
Alfalfa	1.71	0.30	0.36
Alfalfa hay	1.41	0.21	0.34
Timothy	0.40	0.26	0.16
Timothy hay	0.51	0.29	0.13
Bluegrass	0.50	0.4	0.18
Oat hay	0.32	0.25	0.29
Orchard grass	0.25	0.39	0.31
Barley	0.05	0.37	0.15
Corn	0.05	0.60	0.03
Oats	0.09	0.38	0.16
Wheat	0.05	0.42	0.14
Cottonseed meal	0.18	1.22	0.59
Linseed	0.43	0.90	0.67
Skim milk	1.36	1.09	0.13
Soybean meal	0.40	0.71	0.31
Molasses, cane	1.10	0.15	0.47
Wheat bran	0.14	1.27	0.63

Adapted from the National Academy of Sciences: *Nutrient requirements of horses,* ed 5, Washington, DC, 1989, National Research Council.

Table 41-4 Plants That Contain Oxalates*

Common Name	Scientific Name
Bermuda grass	*Cynodon dactylon*
Buffel grass	*Cenchrus cilaris*
Dallis grass	*Paspalum* species
Elephant grass	*Panicum* species
Foxtail grass	*Setaria* species
Greasewood	*Sarcobatus vermiculatus*
Halogeton	*Halogeton glomeratus*
Kikuyu	*Pennisetum clandestinum*
Kochia, summer cypress	*Kochia scoparia*
Lamb's-quarters	*Chenopodium* species
Napier, mission grass	*Pennisetum* species
Pangola	*Digitaria decumbens*
Panic	*Panicum* species
Para grass	*Brachiaria* species
Pokeberry	*Phytolacca americana*
Purple pigeon grass	*Setaria incrassate*
Purslane	*Portulaca oleraceae*
Red-rooted pigweed	*Amaranthus* species
Rhubarb	*Rheum rhaponticum*
Russian thistle, tumbleweed	*Salsola* species
Setaria	*Setaria sphacelata*
Sorrel	*Rumex* species
Soursob, shamrock	*Oxalis* species
Sugar beet	*Beta vulgaris*

* These plants have an oxalate content higher than 0.5% of dry matter, or a calcium:oxalate ratio of <0.5.

Calcium deficiency can be acute or chronic. Horses with acute calcium deficiency have clinical signs associated with neuromuscular excitability. Chronic calcium deficiency in general is manifested as abnormal cartilage and bone development (developmental orthopedic disease [DOD]) and lameness. When calcium deficiency is suspected, feed analysis is recommended to determine if dietary calcium and phosphorus are adequate.

41.1.5.2

PHOSPHORUS

In blood, phosphorus exists as organic (intracellular) and inorganic (extracellular) phosphates. Organic phosphate consists of phosphate esters (phospholipids) bound to proteins and blood cells and represents most of the phosphorus in circulation; however, only inorganic phosphate (PO_4) is measured. PO_4 is found as ionized phosphate (approximately 50%), complexed with cations (Na^+, Ca^{2+}, Mg^{2+}; approximately 35%), and bound to proteins (approximately 15%). At pH 7.4, PO_4 exists as divalent (HPO_4^{2-}) and monovalent ($H_2PO_4^-$) anions in a 4:1 ratio. In acidosis this ratio is 1:1, and it can be as high as 9:1 during alkalosis.[201] In soft tissues, most of the phosphate is organic, intracellular, and incorporated into nucleic acids, phospholipids, and energy compounds such as adenosine triphosphate (ATP) and creatine phosphate. Phosphate is important for muscle contraction; neurologic functions; enzyme activity; electrolyte transport; oxygen transport (2,3-diphosphoglycerate [DPG]); intermediary metabolism of proteins, carbohydrates, and fats, gene transcription, and cell proliferation and differentiation. Approximately 80% of the PO_4 is in the skeleton bound to calcium as hydroxyapatite. PO_4 regulation is closely associated with Ca^{2+} homeostasis.

Phosphorus requirements depend on age, physiologic status, and amount of work or exercise performed (see Table 41-1). In horses, phosphorus absorption ranges from 30% to 55% and occurs in the small and large intestines.[195,202] High aluminum in the diet reduces phosphorus absorption. In the kidneys, most of the PO_4 is reabsorbed in the proximal tubules by an Na^+-dependent mechanism, and the urinary fractional excretion of PO_4 in horses is low (<0.5%).

Chronic excess of phosphorus results in clinical signs consistent with calcium deficiency including lameness, abnormal cartilage and bone development, fractures, and osteodystrophia fibrosa (nutritional secondary hyperparathyroidism). Acute renal failure and hypoparathyroidism are associated with hyperphosphatemia. Conditions that result in cell lysis such as hemolysis, rhabdomyolysis, and tumor necrosis may cause acute hyperphosphatemia.

Hypophosphatemia occurs from inadequate intake, decreased intestinal absorption, renal waste, hyperparathyroidism, sepsis, and intracellular shift. Intracellular PO_4 shift is a common cause of hypophosphatemia in critically ill humans and small animals and occasionally occurs in horses with starvation or refeeding syndrome or receiving parenteral nutrition (hyperglycemia, hyperinsulinemia). Acute hypophosphatemia is associated with cell membrane fragility and lysis (hemolysis, rhabdomyolysis). Chronic phosphate deficiency can be manifested as weight loss, weakness, pica (depraved appetite), lameness, and DOD. Rickets, as described in other species with PO_4 or vitamin D deficiency, is not a recognized condition in foals. Serum PO_4 concentration is more indicative of dietary phosphorus intake and status than serum Ca^{2+} because PO_4 homeostasis is not as precise as that of Ca^{2+}. Normal PO_4 concentrations are presented in Table 41-5.

Table 41-5 Normal Serum Concentrations in Healthy Horses

Variable	Concentration
Total calcium (mg/dL)	11.1–13
Ionized calcium (mg/dL)	6–7
Phosphorus (mg/dL)	1.2–4.8
Total magnesium (mmol/L)	0.53–0.91
Ionized magnesium (mmol/L)	0.46–0.66
PTH (pmol/L)	<4; (<40 pg/mL)
Calcitonin (pg/mL)	<40
PTHrP (pmol/L)*	<3 2–8 0.0–0.5
25-Vitamin D_3	1.90 ± 0.23 ng/mL—winter[251] 2.43 ± 0.09 ng/mL—summer[251] 4.2 ± 0.34 µg/L—winter[252] 6.2 ± 0.36 µg/L—summer[252]
1,25-Vitamin D_3	18.6 ± 7.3 ng/L—winter[252] 18.7 ± 8 ng/L—summer[252] 55.0 ± 24 pmol/L[8]
Data from the College of Veterinary Medicine, Ohio State University	

* Measured in ethylenediaminetetraacetic acid (EDTA) plasma. FE_{Ca}, Urinary fractional excretion of calcium; FE_P, urinary fraction excretion of phosphorus; *PTH*, parathyroid hormone; *PTHrP*, PTH-related protein.

41.1.5.3

CALCIUM AND PHOSPHORUS HOMEOSTASIS

Extracellular ionized calcium (Ca^{2+}) concentrations are regulated by a homeostatic system that includes three hormones (parathyroid hormone [PTH], calcitonin, and 1,25-dihydroxyvitamin D_3[$1,25(OH)_2D_3$]; calcitriol); three body systems (kidney, intestine, and bone); and a calcium-sensing receptor (CaR).[190,193,203] PTH increases during hypocalcemia and hyperphosphatemia, whereas calcitonin increases during hypercalcemia (Fig. 41-14). Under physiologic conditions PTH-related protein (PTHrP), which also activates the PTH-1 receptor, has little effect on Ca^{2+} homeostasis.[204] PO_4 is closely associated with Ca^{2+} homeostasis. The role of phosphatonins, which inhibit renal PO_4 reabsorption and $1,25(OH)_2D_3$ synthesis, is unknown in the horse.[205]

PTH is secreted by the chief cells of the parathyroid gland in response to hypocalcemia and hyperphosphatemia. Parathyroid chief cells detect changes in Ca^{2+} concentrations by a CaR.[197,206] Through the PTH receptor, PTH increases renal Ca^{2+} reabsorption (distal nephron), decreases renal PO_4 reabsorption (proximal tubules), stimulates renal calcitriol synthesis (proximal tubules), and stimulates osteoclastic bone resorption (see Fig. 41-14). Calcitriol then increases intestinal absorption and renal reabsorption of Ca^{2+} and

PO_4 and inhibits PTH synthesis and secretion.[190] PTH secretion is under the influence of Ca^{2+}, PO_4, and vitamin D. Biologically active intact PTH is measured with immunometric assays.

Vitamin D plays an important role in Ca^{2+} and PO_4 homeostasis and to lesser extent in magnesium metabolism. Vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are secosterols derived from photolytic cleavage of the B rings of ergosterol (plants and yeasts) and 7-dehydrocholesterol (animals), respectively. Vitamin D_3 is hydroxylated in the liver to produce 25-hydroxyvitamin D_3 [$25(OH)D_3$; calcidiol], which is transported to the kidney to produce the active metabolite 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$; calcitriol] by 1α-hydroxylase. In mammalians, 25(OH)D is the major circulating form of vitamin D. Hypocalcemia, hypophosphatemia, and PTH stimulate $1,25(OH)_2D$ synthesis by inducing renal 1α-hydroxylase activity, whereas hypercalcemia, hyperphosphatemia, and increased $1,25(OH)_2D$ concentrations inhibit 1α-hydroxylase.

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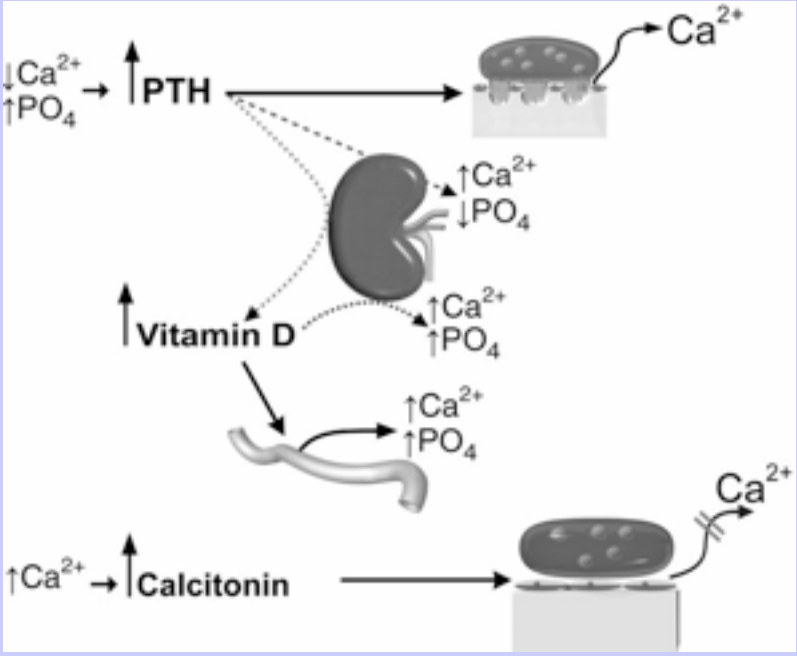
Fig. 41-14 Calcium and phosphate homeostasis. A decrease in serum Ca^{2+} or increase in serum PO_4 concentrations increases PTH secretion. PTH increases renal Ca^{2+} reabsorption and vitamin D synthesis, decreases renal PO_4 reabsorption, and increases osteoclastic bone resorption. In turn, vitamin D increases intestinal absorption and renal reabsorption of Ca^{2+} and PO_4. On the contrary, hypercalcemia decreases PTH secretion and stimulates calcitonin secretion to inhibit osteoclastic bone resorption.



Vitamin D stimulates intestinal absorption and renal reabsorption of Ca^{2+} and PO_4. $1,25(OH)_2D$ increases the expression and activity of proteins important for transcellular Ca^{2+} transport, including epithelial Ca^{2+} channels, Ca^{2+} binding proteins (calbindin D_{9k}, calbindin D_{28k}), Na^+/Ca^{2+} exchangers, and Ca^{2+} -ATPases. The effects of $1,25(OH)_2D$ on intestinal absorption and renal reabsorption of PO_4 are mediated by Na^+ -PO_4 cotransporters. In addition, $1,25(OH)_2D$ increases Mg^{2+} renal reabsorption.[207] In bone, $1,25(OH)_2D$ increases bone matrix synthesis and mineralization and stimulates osteoclastic activity and bone resorption. In the parathyroid gland, $1,25(OH)_2D$ inhibits PTH synthesis and secretion.[208] Vitamin D deficiency results in rickets in young animals and osteomalacia in adults; however, the existence of rickets in the horse is not clearly documented.

Calcitonin is a 32—amino acid peptide secreted by the parafollicular cells (C cells) of the thyroid gland in response to hypercalcemia. Calcitonin inhibits osteoclast function and bone resorption and decreases renal reabsorption of Ca^{2+} and PO_4 in most species. There is limited information on calcitonin in the horse.[209]

PTHrP is produced by almost every tissue in the body and has a broad range of functions that have little to do with Ca^{2+} homeostasis.[204] Under physiologic conditions, PTHrP functions (morphogenesis, cell differentiation) are considered to be paracrine, autocrine, and intracrine. For the most part, the endocrine functions are considered pathologic (humoral hypercalcemia of malignancy [HHM]). HHM is a paraneoplastic syndrome that results from excessive secretion of PTHrP by some tumors. By interacting with PTH receptors, PTHrP promotes bone resorption and inhibits renal Ca^{2+} excretion, causing hypercalcemia in humans and domestic animals, including the horse.[210–215]

Organs involved in Ca^{2+} homeostasis (parathyroid gland, thyroid gland, and kidney), known as the *calcium-sensing system,* express a CaR, which is a G protein—coupled seven transmembrane domain receptor that is activated by extracellular Ca^{2+} and to lesser affinity by Mg^{2+}.[206] CaR activation inhibits PTH secretion and stimulates calcitonin secretion in various species, including the horse.[197,198] In the kidney, CaR regulates Ca^{2+} and Mg^{2+} reabsorption independently of PTH. Renal CaR activation inhibits the furosemide-sensitive $Na^+/K^+/2Cl^-$ cotransporter in the distal nephron, resulting in diuresis and urinary waste of Ca^{2+} and Mg^{2+}.[206]

41.1.5.4

CALCIUM DISORDERS IN THE HORSE

Calcium dysregulation in the horse is associated with hypocalcemic and hypercalcemic disorders. Equine pathologic conditions characterized by abnormal calcium homeostasis include hypoparathyroidism,[216,217] primary hyperparathyroidism,[218] nutritional secondary hyperparathyroidism,[219] renal failure,[220] HHM,[211,212,214] vitamin D toxicity,[221] exercise-induced hypocalcemia,[222] idiopathic hypocalcemia of foals,[223] cantharidiasis,[224] and sepsis.[193,225,226] Normal calcium concentrations for horses are presented in Table 41-5.

41.1.5.4.1

Hypocalcemic Disorders

Conditions associated with hypocalcemia in the horse are presented in Box 41-2. Most clinical signs of hypocalcemia are the result of increased neuromuscular excitability and decreased smooth muscle cell contractility (Box 41-3). A decrease in extracellular Ca^{2+} concentrations increases cell membrane Na^{+} permeability, decreasing the resting membrane potential, thus making muscle cells and nerve fibers more excitable. This results in spontaneous and continuous discharges, muscle fasciculations, tremors, tetany, and seizures. Tachycardia and cardiac arrhythmias may be present, although bradycardia may develop during severe hypocalcemia. Decreased serum ionized magnesium (Mg^{2+}) concentration occurs frequently in horses with hypocalcemia and further increases neuromuscular excitability.

Synchronous diaphragmatic flutter (SDF) or "thumps" may occur in horses with hypocalcemia associated with gastrointestinal disease,[193] endurance exercise,[227] hypoparathyroidism,[217,228] idiopathic hypocalcemia,[223] tetany (lactation, transport),[229] sepsis,[193] blister beetle toxicosis,[230] and alkalosis.[190] SDF develops when depolarization of the right atrium stimulates action potentials in the phrenic nerve as it crosses over the heart. Clinically, affected animals have a rhythmic movement on the flank from diaphragmatic contractions that are synchronous with the heartbeat.

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41.1.5.4.1.1

Box 41-2 Equine Clinical Conditions in Which Hypocalcemia Has Been Reported

Acute renal failure

Bicarbonate administration

Cantharidin toxicosis

Chronic renal failure

Colic

During lactation (lactation tetany)

During transport (transit tetany)

Dystocia

Endotoxemia

Endurance exercise

Enterocolitis

Furosemide administration

Heat stroke

Hypomagnesemia

Late pregnancy

Liver disease

Magnesium toxicosis

Malignant hyperthermia

Oxalate ingestion

Pancreatitis

Pleuropneumonia

Postoperative myopathy

Primary hypoparathyroidism

Retained placenta

Rhabdomyolysis

Sepsis

41.1.5.4.1.2

Box 41-3 Clinical Signs Reported in Horses with Hypocalcemia

Anxiety

Asphyxia

Ataxia

Bruxism

Cardiac arrhythmias

Colic

Convulsions

Death

Depression

Dysphagia

Dyspnea

Excitation

Hyperhidrosis

Hypersalivation

Hyperthermia

Ileus

Laryngeal spasm

Muscle fasciculation

Seizures

Stiff gait

Synchronous diaphragmatic flutter

Tachycardia

Tachypnea

Tetany

Tremors

Trismus

During alkalosis there is increased Ca^{2+} binding to albumin, resulting in ionized hypocalcemia. Exercising horses may develop alkalosis from hyperventilation (respiratory alkalosis) and chloride losses in the sweat (metabolic hypochloremic alkalosis). Hypomagnesemia is common in horses with SDF and hypocalcemia.

Hypocalcemic tetany is the development of sustained skeletal muscular contractions in horses with hypocalcemia. Although hypocalcemic tetany can occur in any horse with hypocalcemia, lactating mares and horses transported for long distances are at greatest risk. Lactation tetany may occur anytime in mares immediately before foaling up to the end of the lactation period. In particular, mares producing large amounts of milk and eating diets low in calcium, grazing lush pastures, or performing physical work (draft mares) are at risk. Clinical signs may include anxiety, depression, ataxia, muscle fasciculations and tremors, stiff gait, tachypnea, dyspnea, dysphagia, hypersalivation, and hyperhidrosis (see Box 41-3).[190]

Hypocalcemic seizures, seen in foals and adult horses, are caused by decreased CNS extracellular Ca^{2+} concentrations leading to increased neuronal excitability. Clinical signs usually improve with calcium treatment, although some animals may require repeated treatments. In general, horses and foals with refractory hypocalcemic seizures have a poor prognosis for recovery.

Ileus and retained placenta in mares are both believed to result from decreased smooth muscle tone and contractility secondary to hypocalcemia. Whereas in skeletal muscle most of the Ca^{2+} required for contraction comes from the sarcoplasmic reticulum, in smooth muscle Ca^{2+} comes from the extracellular space. For this reason, any condition that results in hypocalcemia can decrease smooth muscle contractility. Retained placenta in mares has been reported to occur in up to 10% of foalings.[231]

Hypoparathyroidism in horses is characterized by hypocalcemia, hyperphosphatemia, hypomagnesemia, and decreased serum PTH concentrations. Primary hypoparathyroidism results from decreased secretion of PTH, whereas secondary hypoparathyroidism results from magnesium depletion and sepsis. There are few documented cases of primary hypothyroidism in horses.[217,228] Hypoparathyroidism should be suspected in any horse or foal with refractory hypocalcemia. Clinical signs include ataxia, seizures, hyperexcitability,

SDF, tachycardia, tachypnea, muscle fasciculations, bruxism, stiff gait, recumbency, ileus, and colic.[190,217,228] Laboratory findings include hypocalcemia, hyperphosphatemia, and low or normal serum intact PTH concentrations. Hypomagnesemia may be present in some horses and foals.[217,228] Secondary (functional or acquired) hypoparathyroidism per se has not been reported in the horse; however, some critically ill foals and horses with hypocalcemia have impaired parathyroid gland function, which we believe represents hypoparathyroidism secondary to sepsis and/or hypomagnesemia.

Critically ill foals may develop a form of hypocalcemia that is refractory to calcium treatment.[223] These foals have low or normal PTH concentrations despite hypocalcemia, suggesting hypoparathyroidism. This condition has been called *neonatal idiopathic hypocalcemia*.[223] It is believed that abnormal parathyroid gland function may result from increased inflammatory cytokines. IL-1 and IL-6 have been shown to increase CaR activation and decrease PTH secretion by equine parathyroid cells.[197] Prognosis for survival in foals with refractory hypocalcemia is poor.

Sepsis and endotoxemia are the most common cause of hypocalcemia in equine patients admitted to veterinary hospitals. Clinical observations also indicate that hypocalcemia is common in horses with severe gastrointestinal disease.[193] Hypocalcemia in septic patients often results from parathyroid gland dysfunction (insufficient PTH secretion) as well as intracellular calcium sequestration.[190,193] Inflammatory mediators known to be increased in horses and foals with sepsis and endotoxemia such as TNF-α, IL-1, and IL-6 decrease equine parathyroid cell sensitivity to Ca^{2+} and PTH secretion.[197]

Horses under intense exercise develop electrolyte and acid-base abnormalities. Unlike humans, who may develop either hypocalcemia or hypercalcemia, hypocalcemia is a more consistent finding throughout exercise in the horse. Exercise-induced hypocalcemia may result from Ca^{2+} losses in the sweat, intracellular movement of Ca^{2+}, increased Ca^{2+} binding to albumin, lactate, phosphate, and bicarbonate during alkalosis, and parathyroid gland dysfunction.[222]

Oxalate toxicity causes hypocalcemia by interfering with calcium absorption; a diet consisting of 1% oxalate or higher can reduce most intestinal calcium absorption.[232] It is important that the equine diet contain less than 0.5% oxalate or a calcium:oxalate ratio over 1.0. Clinical signs associated with oxalate excess are those of phosphate excess, calcium deficiency, and nutritional hyperparathyroidism. Oxalates are present in several grasses and toxic plants (see Table 41-4).

Equine cantharidiasis (blister beetle toxicosis) is a condition reported in the southwestern and midwestern United States and results from the ingestion of alfalfa contaminated with beetles (*Epicauta* species) that produce cantharidin (cantharidic acid). Clinical signs develop from the irritant effects of cantharidin on mucosal surfaces (gastrointestinal and urinary tracts). Cantharidin often causes acute hypocalcemia and hypomagnesemia. Therefore clinical signs of severe hypocalcemia (muscle fasciculations, SDF, ataxia, dyspnea, laryngeal spasm, and cardiac arrhythmias) may be present. It is unclear why these horses develop hypocalcemia; however, it may be a combination of severe gastrointestinal disease associated with acute renal failure and parathyroid gland dysfunction.

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Hypocalcemia and hypomagnesemia are common findings in horses with acute renal failure. Reabsorption of Ca^{2+} and Mg^{2+} in the kidney is highly dependent on functional epithelial cells, and these cells are very susceptible to various insults (hypoxia, ischemia, toxins). The loss of epithelial cells and their absorptive capacity results in decreased reabsorption of Ca^{2+} and Mg^{2+}.

The pathogenesis of hypocalcemia in exertional rhabdomyolysis is unknown. It is speculated that damage to muscle fibers during intense exercise results in Ca^{2+} influx and sequestration in the sarcoplasmic reticulum.

41.1.5.4.1.3

TREATMENT OF HYPOCALCEMIA

Calcium deficit, maintenance, losses, and sequestration should be considered when treating hypocalcemia. If parathyroid gland function is normal, minimal to no calcium supplementation may be required. Most horses with hypocalcemia do not show overt signs of hypocalcemia. Lack of therapy, however, can result in development of additional complications, in particular ileus. Horses with functional kidneys can rapidly eliminate large amounts of calcium, and hypercalcemia from excessive calcium administration is rare, particularly if the horse is receiving fluid therapy. When possible, calculate the calcium deficit based on Ca^{2+} concentrations (mg/dL = mmol/L × 4). From a practical standpoint, the use of standard formulas for electrolyte deficit can be used (multiplied by 10, as calcium is expressed as mg/dL). Total calcium can be used to estimate calcium deficit, keeping in mind that total calcium has more variability than Ca^{2+} concentration, as it is dependent on plasma protein concentration. A horse can have total hypocalcemia, but serum Ca^{2+} concentrations may be within the normal range (pseudohypocalcemia), and calcium administration may not be necessary. It is also important to remember that 9.3% of calcium gluconate is elemental calcium, which means that a 23% solution of calcium gluconate contains 2.14% of elemental calcium or 21.4 mg/mL. Avoid the use of calcium chloride, as it can cause subcutaneous irritation.

Frequent monitoring of Ca^{2+} concentration and adjustment of dosage are important. Rapid administration of calcium may result in cardiovascular complications, especially in horses with sepsis, which may be more vulnerable to the toxic effects of calcium. In our experience, horses can handle high calcium doses. For an average size horse with mild hypocalcemia (5 mg/dL), we administer 50 mL of 23% calcium gluconate per 5 L of crystalloid fluids at a fluid rate twice maintenance. Oral treatment with calcium salts is feasible in some horses with non—life-threatening, refractory hypocalcemia. Dicalcium phosphate and calcium carbonate (limestone, 200 to 300 g/day) can be used safely (see Table 41-2).

41.1.5.4.2

Hypercalcemic Disorders

Hypercalcemic disorders in horses are divided into two groups: (1) parathyroid gland—dependent hypercalcemia (develops because of parathyroid gland hyperfunction), and (2) parathyroid gland—independent hypercalcemia (develops despite parathyroid gland suppression). This distinction is clinically relevant in the differential diagnosis and in the interpretation of specific diagnostic tests, including intact PTH, PTHrP, Ca^{2+}, PO_4, and vitamin D concentrations. Parathyroid gland—dependent hypercalcemia in the horse is limited to primary hyperparathyroidism, whereas parathyroid-independent hypercalcemia results from various conditions (secondary hyperparathyroidism, chronic renal failure [CRF], hypercalcemia of malignancy, and hypervitaminosis D).

Primary hyperparathyroidism results from an excessive and autonomous synthesis and secretion of PTH by the parathyroid gland that is not responsive to the negative feedback of Ca^{2+}. Primary hyperparathyroidism has been reported in ponies and horses[218,233–236] and results from parathyroid

adenomas or parathyroid hyperplasia. The elevated PTH concentrations increase renal Ca^{2+} reabsorption, decrease PO_4 reabsorption, increase $1,25(OH)_2D_3$ synthesis, and increase bone resorption (osteodystrophia fibrosa). Laboratory findings include hypercalcemia, hypophosphatemia, hypocalciuria, and hyperphosphaturia. PTHrP concentrations are within normal limits (low or undetectable). Clinical findings include facial bone enlargement, lameness, and a poor body condition. Radiographic findings include decreased long and facial bone density, fibrous proliferation of the maxilla and mandible, and loss of the lamina dura surrounding the molars.[218] Endoscopic examination may reveal narrowing of the nasal passages.

Postmortem findings include enlargement of the maxilla and mandible, stenosis of the nasal passages, and loosening of premolars and molars. Histologic evaluation of the parathyroid gland is important to confirm the diagnosis of primary hyperparathyroidism; however, finding the parathyroid glands in the horse is a challenge because of their small size and variable location.[190] Although not documented in horses, treatment consists of surgical removal of the affected parathyroid gland.

Secondary hyperparathyroidism is characterized by excessive secretion of PTH in response to hyperphosphatemia and hypovitaminosis D from chronic renal failure (renal secondary hyperparathyroidism) or hyperphosphatemia and/or hypocalcemia from nutritional imbalances (nutritional secondary hyperparathyroidism). Renal secondary hyperparathyroidism is not a well recognized disease in the horse. Unlike humans and small animals, in which CRF results in hyperphosphatemia, horses with CRF often have hypophosphatemia. Moreover, the hypercalcemia in horses with CRF is the result of renal Ca^{2+} retention rather than increased PTH concentrations. The increased Ca^{2+} concentrations in turn decrease PTH secretion; therefore PTH concentrations in horses with CRF frequently are below or within the normal range.[216,237] In contrast, nutritional secondary hyperparathyroidism is a well documented pathologic condition of the horse.

41.1.5.5

NUTRITIONAL SECONDARY HYPERPARATHYROIDISM

41.1.5.5.1

Definition and Etiology

Horses fed diets low in calcium, high in phosphorus, or with a phosphorus:calcium ratio of ≥3:1 may develop nutritional secondary hyperparathyroidism, also known as *bran disease, Miller's disease, big head, osteodystrophia fibrosa, osteitis fibrosa,* and *equine osteoporosis*.[234] Pastures and toxic plants with high content of oxalates (see Table 41-4) predispose to secondary hyperparathyroidism.

41.1.5.5.2

Pathogenesis

Excessive dietary PO_4 reduces intestinal calcium absorption and results in hyperphosphatemia. Dietary oxalates form insoluble calcium oxalate ($Ca[COO]_2$), reducing calcium absorption. Both high-phosphorus and low-calcium diets induce parathyroid cell hyperplasia and stimulate PTH secretion in the horse.[234] Hyperphosphatemia directly stimulates PTH secretion and inhibits renal $1,25(OH)_2D$ synthesis. Because $1,25(OH)_2D$ inhibits parathyroid cell proliferation, low $1,25(OH)_2D$ concentrations contribute to parathyroid cell hyperplasia and PTH secretion. Hyperphosphatemia also results in the formation of calcium phosphate precipitates, reducing blood Ca^{2+}, and inducing additional PTH secretion. PTH increases osteoclastic activity, bone resorption, and bone loss (Fig. 41-15).[238] There is facial bone loss

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with excessive accumulation of subperiosteal unmineralized connective tissue (osteodystrophia fibrosa) resulting in facial enlargement (big head) (Fig. 41-16). Because this is a condition of slow progression, the homeostatic mechanisms that regulate extracellular Ca^{2+} concentrations (PTH, vitamin D, calcitonin) in general are effective in maintaining Ca^{2+} within the normal range. Affected horses preserve normocalcemia at the expense of the skeletal reserves and do not develop clinical signs of acute hypocalcemia.

41.1.5.5.3

Clinical Signs

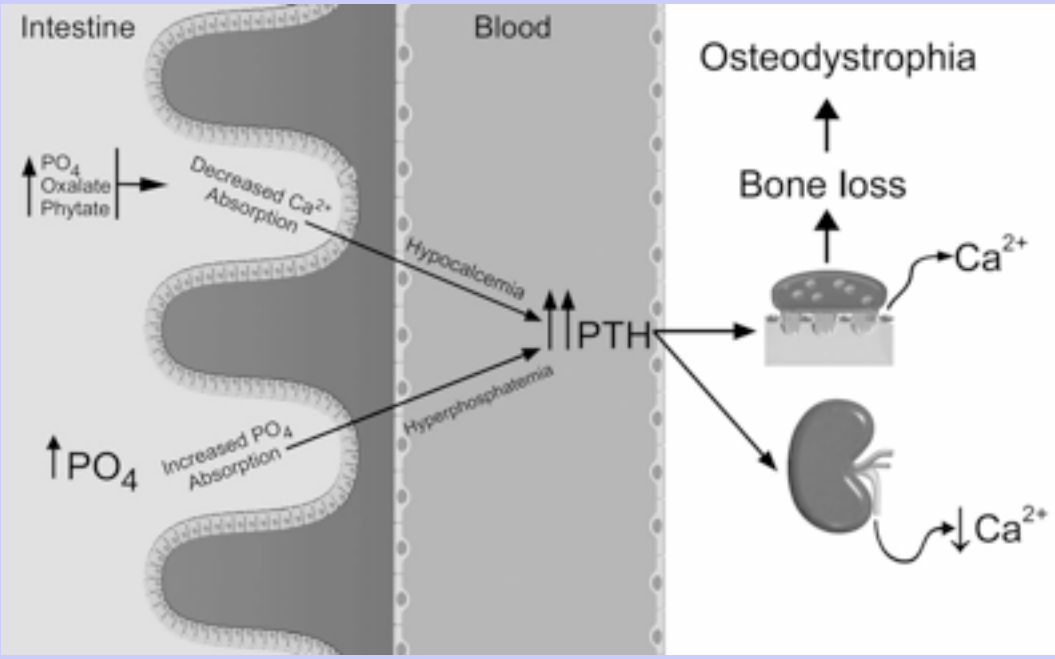
Clinical signs result from increased bone resorption and include unthriftiness, intermittent, shifting lameness, and a stiff gait. Younger animals may develop physitis and limb deformities. There is a typical and symmetric swelling of the facial bones; however, facial bone enlargement may not be evident in old horses (see Fig. 41-16). The facial changes and the increased bone resorption around molars and premolars may result in masticatory problems. These horses are physically weak and may be in poor body condition from the pain associated with lameness and mastication. In severe cases, teeth may become loosened and spontaneous fractures of long bones may occur. Upper airways obstruction, dyspnea, and epiphora may be present.[239,240]

41.1.5.5.4

Laboratory Findings

Typical laboratory changes in horses with nutritional secondary hyperparathyroidism include hyperphosphatemia, hypocalcemia or normocalcemia (hypercalcemia is unusual), and increased intact PTH concentrations, especially if the animal is eating a low-calcium or high-phosphorus diet at the time of evaluation. The urinary fractional excretion of calcium is low (hypocalciuria), whereas the excretion of phosphorus is increased (hyperphosphaturia). Serum alkaline phosphatase activity and collagen degradation products may be increased. Laboratory findings may be within normal limits if the animal is eating a balanced diet.

Fig. 41-15 Pathogenesis of nutritional secondary hyperparathyroidism in horses. Excessive dietary phosphorus reduces intestinal absorption of calcium and induces hyperphosphatemia. In addition, phosphate, oxalate, and phytate bind dietary calcium to reduce absorption. Both high-phosphorus and low-calcium diets induce parathyroid cell hyperplasia and stimulate PTH secretion. PTH increases osteoclastic activity and bone resorption, resulting in bone loss (osteodystrophia fibrosa).



41.1.5.5.5

Radiologic Findings

Decreased bone density is frequent; however, bone density must be decreased by 30% before it can be detected radiographically.[241] Decreased facial bone density along with fibrous proliferation is a consistent finding. Resorption of alveolar sockets and loss of the dental lamina dura may be present before other radiographic changes are present, and long bones are affected only in advanced cases.

41.1.5.5.6

Necropsy

There is increased bone resorption, bone fragility, accumulation of fibrous tissue around facial bones, obstruction of nasal passages, and parathyroid gland hyperplasia (see Fig. 41-16). Soft-tissue mineralization has been reported in affected foals.[241a]

41.1.5.5.7

Treatment

Diet evaluation is indicated. Eliminate or reduce any grain-based diet and avoid high-containing oxalate feeds. The addition of alfalfa to the diet may be helpful. Supplementation with calcium carbonate (limestone; $CaCO_3$) or dicalcium phosphate may result in improvement.[219] Ground limestone, which contains no phosphorus, is recommended as a good source of calcium (35%). An affected animal may require a total of 100 to 300 g/day. The diet should have a Ca:P ratio of 3:1 or 4:1. Limestone may decrease feed palatability, and adding molasses should be considered. Supplementation with vitamin D has been proposed. Horses may require 9 to 12 months for complete recovery, although some bone changes may not regress. Confinement of severely affected horses is advised. The use of NSAIDs may be indicated in some animals.

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Fig. 41-16 Big head. Two-year-old Belgium horse presented to the Ohio State University Veterinary Teaching Hospital with clinical signs consistent with nutritional secondary hyperparathyroidism, including facial bone enlargement and upper respiratory noise. The horse was fed excessive amounts of grain. There was narrowing of the nasal passages, loss of bone mass, and excessive accumulation of unmineralized bone matrix (osteodystrophia fibrosa) in maxillary and mandibular bones.

41.1.5.6 # HYPERVITAMINOSIS D

41.1.5.6.1 ## Definition and Etiology

The ingestion or administration of ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) results in disturbances of calcium and phosphorus metabolism in horses.[221,242–244] Ingestion of plants containing 1,25$(OH)_2$D-like compounds results in typical clinical signs of vitamin intoxication.[243,245] The ingestion of *Solanum glaucophyllum (Solanum malacoxylon)* results in a condition known as "enteque seco" in Argentina and "espichamento" in Brazil.[242,245] In Hawaii, *Solanum sodomaeum,* and in the southern United States, jessamine *(Cestrum diurnum)* may cause hypervitaminosis D.[243] In Europe the ingestion of golden oat *(Trisetum flavescens)* results in enzootic calcinosis.

41.1.5.6.2 ## Pathogenesis

Hypervitaminosis D increases the intestinal absorption and renal reabsorption of calcium and phosphorus. Hyperphosphatemia is the most consistent and early laboratory finding in horses with vitamin D intoxication.[246] Serum calcium concentrations may be increased or within the normal range.[221,243,244] Hypervitaminosis D results in parathyroid cell atrophy and decreased PTH secretion. In addition, hypercalcemia contributes to decreased PTH secretion, lowering bone turnover. Azotemia and hyposthenuria may be present.[221]

41.1.5.6.3 ## Clinical Signs

Most clinical findings in horses with hypervitaminosis D are the result of hyperphosphatemia. Affected horses often have weight loss, poor appetite, lameness, and painful stiffness and are reluctant to move. Acute death from severe cardiovascular mineralization has been reported.[221] Polyuria and polydipsia are frequent findings. In cases with hypercalcemia, mineral deposition in the kidneys may precede mineralization elsewhere, resulting in renal failure. Lameness is probably caused by calcification of ligaments and tendons.

41.1.5.6.4 ## Radiologic Findings

These horses often have increased bone density, decreased size of the medullary cavity, and increased calcification of soft tissues.

41.1.5.6.5 ## Treatment

Reducing dietary calcium intake and using calcium-binding agents such as sodium phytate have been proposed.[244] Glucocorticoids are used in humans with hypervitaminosis D, as they may inhibit the vitamin D—mediated intestinal calcium absorption. In equids, glucocorticoids decrease intestinal absorption of calcium, increase urinary excretion of calcium, and decrease bone resorption.[190] Dexamethasone has been administered to horses with hypervitaminosis D with variable results. The prognosis for horses with hypervitaminosis D is poor.

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41.1.5.6.6

Necropsy Findings

Postmortem examination may reveal mineralization of soft tissues. Mineralization of the endothelium of the aorta and pulmonary vessels and of the endocardium is frequent. Mineralization may be found in the kidney, liver, lymph nodes, lungs, ligaments, and tendons. Osteopetrosis of epiphyses and metaphyses may be present. Atrophy of the parathyroid gland can be severe.[247]

41.1.5.7

HYPERCALCEMIA OF MALIGNANCY

HHM (pseudohyperparathyroidism) is a paraneoplastic condition in which humans and animals develop hypercalcemia associated with various types of tumors. These malignancies secrete PTHrP, which interacts with PTH receptors to increase renal reabsorption of Ca^{2+} and bone resorption.[248] In horses, HHM has been associated with squamous cell carcinoma, adrenocortical carcinoma, lymphosarcoma, multiple myeloma, and ameloblastoma.[190] Laboratory findings include hypercalcemia, hypocalciuria, hypophosphatemia, hyperphosphaturia, normal or low PTH concentrations, and increased PTHrP concentrations. HHM should be suspected in any horse with hypercalcemia, no evidence of renal disease, and normal PTH concentrations.

Table 41-6 Normal Equine Reference Values and SI Conversion Factors

Variable	Normal Range	Conversion
Total calcium	11.1–13 mg/dL*	mmol/L = mg/dL × 0.25
Ionized calcium	6–7 mg/dL*	mmol/L = mg/dL × 0.25
Phosphorus	1.2–4.8 mg/dL*	mmol/L = mg/dL × 0.323
Total magnesium	0.53–0.91 mmol/L*	mg/dL = mmol/L × 2.43
Ionized magnesium	0.46–0.66 mmol/L*	mg/dL = mmol/L × 2.43
PTH	1–4 pmol/L*	pg/mL = pmol/L × 9.5
Calcitonin	<40 pg/mL*	pmol/L = pg/mL × 0.29
PTHrP	<1 pmol/L*	pg/mL = pmol/L × 10
25-Vitamin D_3	See text	nmol/L = ng/mL × 2.5
1,25-Vitamin D_3	See text	pmol/L = pg/mL × 2.4
Glucose	89–112 mg/dL†	mmol/L = mg/dL × 0.05551
Insulin	<300 pmol/L† <30 μIU/mL‡	μIU/mL = pmol/L × 0.1296
Cortisol	85–180 nmol/L†	μg/dL = nmol/L × 0.03625
ACTH	2–10 pmol/L†	pg/mL = pmol/L × 4.5
α-MSH	<31 pmol/L§ <20 pmol/L¶	pg/mL = pmol/L × 1.67
tT_4	7–27 nmol/L†	nmol/L = mg/dL × 12.87
tT_3	0.7–2.5 nmol/L†	nmol/L = ng/dL × 0.01536
fT_4	6–24 pmol/L†	nmol/L = mg/dL × 12.87
fT_3	1.7–5.2 pmol/L†	nmol/L = ng/dL × 0.01536

ACTH, Adrenocorticotropin; *fT_3,* free triiodothyronine; *fT_4,* free thyroxine; *α-MSH,*α-melanocyte—stimulating hormone; *PTH,* parathyroid hormone; *PTHrP,* PTH-related protein; *tT_3,* total triiodothyronine; *tT_4,* total thyroxine.

* College of Veterinary Medicine, Ohio State University.

† Michigan State University Diagnostic Center, Endocrinology Section.

‡ College of Veterinary Medicine, University of Tennessee.

§ Atlantic Veterinary College, 94 clinically normal horses collected in spring, summer, or winter.

¶ Laboratory of Comparative Aging Research (McFarlane), Oklahoma State University. 25 clinically normal Oklahoma horses collected in spring, summer, or winter. (Reference range = mean ± 2 SD).

41.1.5.8 NEONATAL HYPERCALCEMIA AND ASPHYXIA

Clinical observation indicates that a number of critically ill newborn foals develop hypercalcemia associated with peripartum asphyxia. The mechanisms underlying this problem are unknown, although it is speculated to be associated with placental insufficiency.

41.1.5.9 TREATMENT OF HYPERCALCEMIA

Hypercalcemia as an equine emergency is rarely presented; however, the differential diagnosis of hypercalcemia is important for its treatment. Few disorders in the horse are associated with hypercalcemia (hyperparathyroidism, CRF, HHM, hypervitaminosis D). Mild to moderate hypercalcemia in general is not life-threatening, and treatment should be directed to the primary cause. Although unreported, parathyroidectomy is the treatment of choice for primary hyperparathyroidism. Surgical removal of epithelial tumors can be a successful treatment for HHM. Some horses with lymphosarcoma may show improvement with chemotherapy. In severe cases of hypercalcemia that may require medical treatment, initial therapy should include the administration of a 0.9% saline solution and loop diuretics. Furosemide is the diuretic of choice because it inhibits the $Na^+/K^+/2Cl^-$ contransporter in the distal tubules, increasing the urinary excretion of calcium. Thiazide diuretics are contraindicated because they stimulate calcium reabsorption. Glucocorticoid administration should be considered, in particular for horses with hypervitaminosis D.

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41.1.6 BOVINE METABOLIC DISORDERS

41.1.6.1 KETOSIS OF RUMINANTS (ACETONEMIA)

SHERRILL A. FLEMING

41.1.6.1.1 Definition

Ketosis is a condition characterized by abnormally elevated concentrations of ketone bodies in the body tissues and fluids.[253] The ketone bodies are acetone (Ac), acetoacetic acid (AcAc), and β-hydroxybutyric acid (BHB), which is technically not a ketone body but is formed from AcAc. Ketosis has been categorized as type I or type II based on blood glucose and blood insulin.[254] Type I ketosis is the classic primary or spontaneous ketosis, causing a reduction of glucose in the blood and liver (decreased glycogen) and an increased fat mobilization culminating in elevated ketone body accumulations from a negative energy balance during early lactation.[254,255] Type II ketosis involves high blood insulin and transient hyperglycemia secondary to overconditioning and fatty infiltration of the liver (also see Chapter 33 for discussions of fatty liver and pregnancy toxemia). Baird and co-workers[256] stated that "a certain degree of ketosis is a natural state in the ruminant, and the ketotic animal may only represent the extreme of a normal metabolic range." Ketosis becomes a disease condition only when the absorption and production of ketone bodies exceed their use by the ruminant as an energy source, resulting in elevated blood ketones, free fatty acids (FFAs), or nonesterified fatty acids (NEFAs) and decreased blood glucose. The clinical signs of ketosis tend to be vague and nonspecific. Therefore ketosis is classified as clinical or subclinical on the basis of levels of ketone bodies in the blood, urine, and milk and the presence or absence of clinical

signs. Any disease process occurring in early lactation that reduces feed intake may cause secondary ketosis.

41.1.6.1.2

Etiology

Ketosis is a production disease of modern agriculture. Dairy cattle have been genetically selected for high milk yield, which has resulted in elevated milk production during early lactation. This milk production exceeds the capacity of the animal to ingest sufficient feed to meet requirements for energy.[257] The input into the animal must equal or exceed the output to prevent a negative energy balance (Table 41-7).

The milk production of dairy cattle peaks by approximately 4 weeks after parturition, but the dietary intake on a dry matter basis does not peak until 7 to 8 weeks.[258] High-producing dairy cows will be in a negative energy balance for as long as 8 weeks, despite the provision of a high-quality, palatable diet. To offset the negative energy balance, the individual cow must mobilize body fat and protein stores in the form of triglycerides and amino acids for gluconeogenesis. Ketone bodies are normally produced by the liver and ruminal wall, although ruminal wall ketone production is insignificant during clinical ketosis.[259] The mammary gland indirectly contributes to ketone body production by using glucose for lactose production.[260] The liver, however, is the major source of overall ketone production during ketosis. All tissues in the normal cow can adapt to the use of ketone bodies as an alternate energy source except the liver. It must be stressed that normal, high-producing dairy cows will have some level of ketosis during the rising curve of their lactation until their energy intake balances milk production, despite the provision of good-quality feed. During this period cows lose 30 to 100 kg (65 to 220 lb).[261–263] The difficulty is in identifying and preventing the factors that move a cow from the normal level of ketone body formation into the subclinical and clinical categories.

Table 41-7 Summation of Components of Energy Balance in the Bovine

Inputs	Throughputs	Outputs
Food	Digestion	Defecation
Water	Hepatic metabolism	Urination
Respiration and O_2	Fat metabolism	CO_2
Endocrine influences	Mammary gland metabolism	Lactation
Environment and stress		Muscular activity
	Tissue metabolism (fetus)	Heat loss Reproduction

Any disease condition that decreases dietary intake may cause secondary ketosis as a result of increased fat mobilization and ketone production. During the immediate postpartum period cows are susceptible to many diseases that are likely to reduce their normal feed intake. Ketosis may also be secondary to the ingestion of preformed ketones in the diet (silage high in lactic or butyric acid).[258] Biogenic amines such as putrescine, tryptamine, cadaverine, and histamine contained in ketogenic silage may play a role, possibly by decreasing intake.[264,265] Cobalt deficiency has been implicated as a potential cause of ketosis.[266] There is also a high incidence of ketosis in herds affected by fluorosis.[267] Contamination of concentrates with low levels of lincomycin have been reported to cause herd outbreaks of clinical ketosis.

[268] The onset of bovine somatotropin (BST) use in dairies was speculated to increase the incidence of ketosis, but this has not been demonstrated.[269,270]

41.1.6.1.3

Clinical Signs and Differential Diagnoses

Clinical ketosis is most commonly seen as a gradual loss of appetite and decrease in milk production over several days. Loss of appetite is usually sequential, with refusal of grain, then silage, and lastly forages. As feed intake decreases, weight is lost rapidly, and milk production drops. During early lactation, reduction in milk production lags behind the reduction in energy intake. The incidence of type I ketosis tends to occur 3 to 6 weeks postpartum as milk production peaks, in contrast to type II, which is seen immediately after calving.[254] Physical findings include normal vital signs; firm, dry feces; moderate depression; and sometimes reluctance to move. Ruminal motility may be decreased if the animal has been anorectic for several days. Occasionally pica is seen. Often the odor of ketones can be detected on the breath and in the milk. Clinical signs may spontaneously disappear without treatment when an equilibrium between milk yield and dietary intake is reached. Transient nervous signs such as staggering and blindness may occur for short periods of time. Displaced abomasum (particularly left displacement or LDA), metritis, mastitis, and peritonitis (particularly traumatic reticuloperitonitis) are common primary disease entities leading to secondary ketosis. Although LDA has traditionally been thought to result in ketosis, recent work has demonstrated that elevated blood NEFAs and ketones precede LDA by 2 days and increase the risk of the condition by as much as eightfold.[271] Ketosis decreases immunoresponsiveness, leaving affected cows more vulnerable to concurrent infections. This is attributed to the hypoglycemia and suppressive effects of NEFAs.[271] Less common causes of secondary ketosis are subclinical hypocalcemia, mild ruminal overload and laminitis, lameness caused by sole abscesses and ulcers, pyelonephritis, and musculoskeletal injuries after calving.

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In the nervous form of ketosis, there is an acute onset of bizarre neurologic signs, including circling, proprioceptive deficits, head pressing, apparent blindness, wandering, excessive grooming behavior, pica, and excessive salivation. These animals may show hyperesthesia, bellowing, moderate tremors, and tetany.[272] They may behave aggressively toward people or inanimate objects and appear ataxic when ambulating. Episodes of nervous signs last 1 to 2 hours and recur at 8- to 10-hour intervals.[260] Diseases such as listeriosis, rabies, lactation tetany, acute lead poisoning, and *Claviceps paspali* poisoning should be considered as possible differential diagnoses.

A very thorough physical examination must be performed to differentiate primary from secondary ketosis. A mild fever and increased heart rate are often associated with primary diseases that are inflammatory in nature. Moderate to severe ketonuria may be seen. During the first 2 weeks after calving, cows may require treatment for concurrent diseases. If appetite does not return after standard therapy for the primary disease entity, further therapy for ketosis may be necessary. The tendency for ketosis to recur necessitates careful reassessment by repeating the physical examination to detect primary diseases causing secondary ketosis.

41.1.6.1.4

Clinical Pathology and Laboratory Aids

Ketone bodies may be detected in urine, plasma, and milk (Table 41-8).[260,273–280] The literature is reported in the International System of Units (SI units) (mmol/L) and conventional units (mg/dL), which makes interpretation difficult. The vagueness of clinical signs has made it difficult to determine precise

definitions of ketone bodies in clinical ketosis. As a general guideline, animals with clinical ketosis will have blood glucose concentrations of 20 to 40 mg/dL, total blood ketones >30 mg/dL, total urine ketones >84 mg/dL, and total milk ketones >10 mg/dL. Individuals with subclinical ketosis are those that have no clinical signs of ketosis but have low-normal blood glucose, total blood ketones of 10 to 30 mg/dL, and total milk ketones of 2 mg/dL. Recent studies have statistically determined BHB to give the best correlation for subclinical ketosis with a threshold of 1400 µmol/L (14.4 mg/dL).[281] Secondary ketosis tends to fall between the ranges for clinical and subclinical ketosis, depending on the duration of the primary disease process.[259]

Table 41-8 Blood, Urine, and Milk Analysis in Ketosis

	Normal		Subclinical		Clinical	
	(mg/dL)	(mmol/L)	(mg/dL)	(mmol/L)	(mg/dL)	(mmol/L)
Blood glucose	52	(2.86)			28	1.54
FFA	3				33	
Ac	0				15.1	0.26
AcAc	0	<0.35		0.36–1.05	4.4	1.05, 0.5
BHB	10.7	(1.08)	10	0–1.5	23.5	1.5
TOTAL	3; 6.1		10–30		30; 41; 48	5
Urine Ac	1	(0.17)			22	3.78
AcAc	3.4	(0.35)			37.3	3.80
BHB	11.7	(1.18)			25.1	2.54
TOTAL	9.54; 16.1				89; 305.77	
Milk Ac	0			0.17–0.25; 0.4	16.2	1–2
AcAc	0				1.6	0.16
BHB	4.9	(0.49)			7.9	0.80
TOTAL	4.9		2		27.5; 37.35	

Ac, Acetone; *AcAc,* acetoacetic acid; *BHB,* β-hydroxybutyric acid; *FFA,* free fatty acid.

Commercially available tests have changed substantially in the past few years, with greatly improved diagnostic capability. Urine ketones may give a positive result in otherwise normal cows, because ketones are concentrated to 2 to 20 times the blood ketone level. Ketone bodies in the milk more closely reflect ketone blood levels, making milk ketones a better indicator of ketosis (approximately 50% of blood concentration).[279,280] Of the ketone bodies, AcAc tends to be the most unstable and difficult to detect in samples. Various products that detect the Ac, AcAc, and/or BHB are available. A recent review of available tests found that two products, one detecting AcAc in urine at the “small” reading (Ketostix, Bayer, Elkhart, Ind.) and the other detecting BHB in milk (KetoTest, Sanwa Kagaku Kenkyusho, Nagoya, Japan), had acceptable sensitivity and specificity for screening herds for subclinical ketosis.[282] In a second

study, Pink test liquid (www.profs-products.com, Germany) and Ketolac (Hoescht, Germany) were also found to be satisfactory for diagnosis of subclinical ketosis.[283] Blood levels of volatile fatty acids (VFAs), FFAs, and NEFAs are increased in ketosis. New test kits have been developed that are capable of assessing NEFAs on site (VDx Diagnostic Analyzer, Newburg, Wis.). NEFA levels of >0.5 mEq/L were satisfactory in detecting herd problems with subclinical ketosis.[284,285] Problems exist with diurnal variation in blood levels of VFAs, FFAs, and NEFAs, making timing of blood sampling difficult.[280,286,287] These tests can be used to monitor dairy herds for negative energy balance and the risk of subclinical and clinical ketosis and associated disease problems.[285]

The central role of the liver in energy metabolism of ruminants associates the onset of clinical ketosis with elevations of liver enzymes and abnormal liver function test results. Serum aspartate aminotransferase (AST) and sorbitol dehydrogenase (SDH) may be increased in severe cases. The degree of liver dysfunction is mild compared with that of cows with fatty liver syndrome. The sulfobromophthalein (BSP) clearance test was the classical evaluation of liver function particularly in overconditioned cows at risk for fatty liver syndrome development (see Chapter 33) but is currently unavailable. Serum bile acid levels have had variable results and may not be useful in differentiating mild, moderate, and severe fatty infiltration of the liver, but they do correlate with severe hepatic damage.[288,289] The BSP clearance test also did not differentiate between mild and moderate fatty infiltration of the liver. Liver biopsy and determination of triglyceride or triacylglycerol (TAG) are the gold standards for accurately assessing the degree of hepatic lipidosis and are relatively simple to perform in cattle.[290]

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White cell counts vary and may reflect stress or the primary disease process that the animal is experiencing. Studies vary in the reported effect of elevated ketone bodies and decreased blood glucose on lymphocyte proliferation and immunoglobulin production.[271] Serum calcium and magnesium levels may be slightly decreased in animals that are anorectic. Cortisol levels are usually within the normal range, and plasma insulin is elevated initially but depressed as the feed intake is decreased.[254]

41.1.6.1.5

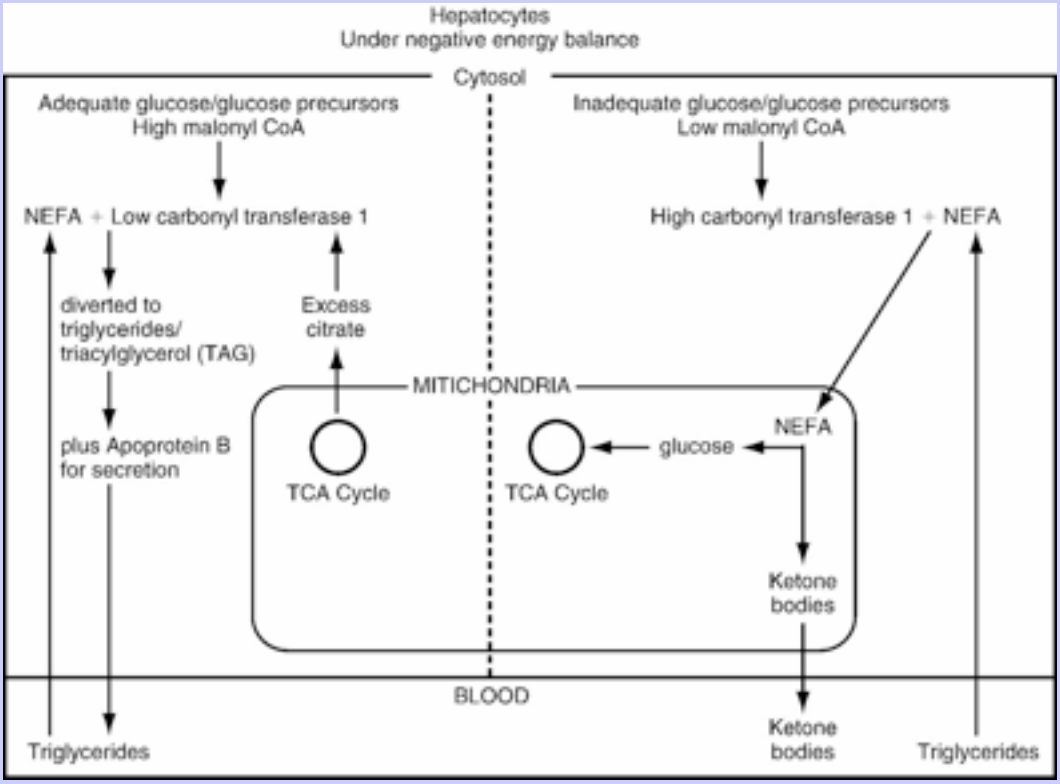
Pathophysiology

Ruminants are exquisitely programmed to use forages in the production of energy for growth, maintenance, pregnancy, and lactation. The control of energy in the ruminant is under the hormonal control of mainly insulin and glucagon. Corticosteroids, GH, catecholamines, and leptins have also been shown to have important roles in the fine-tuning required at the critical times of transition between late pregnancy and early lactation. It is important to keep in mind that ketone bodies are an integral part of normal energy metabolism in ruminants, and it is only when the negative energy balance overwhelms the ability of the cow to use the available ketone bodies that a disease condition occurs.

Control of blood glucose in ruminants is mainly under the control of insulin, which favors cellular uptake of glucose, lipogenesis, and glycogen synthesis while decreasing lipolysis and hepatic gluconeogenesis.[290,291] Ruminants are considered to be relatively insulin resistant, but during early lactation low insulin concentrations are accompanied by high tissue insulin sensitivity.[292] Glucagon counteracts insulin by increasing lipolysis and hepatic gluconeogenesis and decreasing lipogenesis. Catecholamines modulate energy metabolism by favoring lipolysis and decreasing lipogenesis. GH levels are normally high in early lactation and inhibit lipogenesis in adipose while increasing gluconeogenesis in the liver. Adipocytes have been of increasing interest in all species, as they have been shown to produce a variety of endocrine factors (leptin, resistin, IL-6, TNF-α, and adiponectin).[293,294] Leptin has potential for influencing feed intake and

resistance to insulin and increasing energy expenditure and has been documented to be increased in obesity. The extent and importance of these interactions have not been completely investigated in ruminants.

Fig. 41-17 Hepatocyte cellular metabolism under negative energy balance in the presence *(left side)* or absence *(right side)* of adequate glucose or glucose precursors.



In the normal lactating cow, energy is presented to the liver in the form of VFAs, bacterial protein, and a small amount of glucose and protein that escapes degradation in the rumen (Fig. 41-17).[255,260,261] The principal VFAs are acetate, propionate, and butyrate, which are produced in an approximate 70:20:10 ratio, respectively, in the rumen. Acetate is mainly used in fat synthesis, although there is some evidence to suggest that it may be a minor glucose source by entering at the acetyl coenzyme A (CoA) level. Butyrate is condensed into acetoacetyl CoA, which can be partially oxidized to ketone bodies or transformed into acetyl CoA that can enter the tricarboxylic acid (TCA) cycle (no net gain of glucose). Propionate enters the TCA cycle directly at the level of succinyl CoA (equivalent to 30% to 50% of glucose production in the ruminant).[295] Therefore acetate and butyrate are ketogenic, and propionate is glycogenic. The normal ratio of production in the rumen is four ketogenic to one glycogenic VFA. Significant production of ketone bodies occurs in the ruminal epithelium and mammary gland, as well as in the major production site, the liver.[259,295] Ketone bodies are normally used by the TCA cycle in the heart, kidney, skeletal muscles, and mammary gland through the acetyl CoA pathway.

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Efficient oxidation of acetyl CoA depends on an adequate supply of oxaloacetate, which is generated from gluconeogenic precursors, mainly propionate (from the rumen) and lactate and pyruvate (from anaerobic metabolism of glucose).[255] Skeletal muscle mass also provides amino acids for gluconeogenesis. Lactating cows preempt a large quantity of propionate and lactate for milk production in the form of lactose.[291] Supplies of oxaloacetate are reduced, slowing down the TCA cycle and the use of acetyl CoA. The backlog of acetyl CoA is diverted into the formation of ketone bodies.

Adipose tissue stores energy in the form of triglycerides, which can be mobilized to provide NEFAs that either enter the TCA cycle through acetyl CoA, adding to the formation of ketone bodies, or are reesterified into triglycerides or TAG (see Fig. 41-17). The ruminant liver is inefficient in partitioning the increased NEFAs into triglycerides and secreting them into the circulation as lipoproteins. Apoprotein B is required to form VLDLs. Deficiency of apoprotein B will result in accumulations of TAG or fatty infiltration of the liver and abnormally elevated ketone bodies. The negative energy balance that occurs in postpartum dairy cows further reduces available carbohydrate and accelerates fat mobilization and ketone body formation. The ketone bodies in clinical ketosis are mainly produced from NEFAs in the liver, which shift in response to low carbohydrate supplies from the pathways of esterification and complete oxidation of acetyl CoA to CO_2 to partial oxidation of acetoacetyl CoA to ketone bodies.[259,291,295] The net results are ketonemia, ketonuria, ketolactia, hypoglycemia, and low levels of hepatic glycogen.

Clinical ketosis in ruminants occurs when the demand for glucose by the mammary gland or fetus exceeds the energy resources available from the diet and fat mobilization, resulting in hypoglycemia. The daily glucose requirements of a dairy cow increase above normal maintenance by 30% in late gestation and by 75% with the onset of lactation.[291] The average energy requirements of a 1000-lb lactating cow have been estimated to be 50 g of glucose per hour.[296] Only 10% of the glucose requirement is available in the form of glucose.

In late pregnancy and early lactation it is common for a negative energy balance to occur, which results in subclinical ketosis. Any additional nutritional, metabolic, or other disorder resulting in decreased feed intake will make the subclinical ketosis clinical.

41.1.6.1.6

Epidemiology

The morbidity of clinical ketosis is extremely variable and difficult to measure. Management and nutrition are influential factors that vary widely from farm to farm and area to area. Prevalence rates (number of cases at a point in time) have been reported to be 13.1% (range 3% to 22%, depending on lactation) for clinical ketosis and 33.8% (range 31% to 41%) for subclinical ketosis.[297,298] Incidence rates (number of cases that occur in 1 year) have been reported to range from 1.87% to 13% for clinical ketosis and 7.3% to 12.1% for subclinical ketosis.[297–301] Studies using newer tests for ketone bodies have reported subclinical ketosis incidence rates of 59% and 43% using cutoff points of 1400 and 1200 μmol/L, respectively.[302] Most cases occur in the first 6 weeks after calving, with the peak incidence at 3 to 4 weeks after calving.[298,303,304] Breed differences have been found, as well as genetic tendencies within bull-daughter families.[299,300] The incidence of clinical ketosis increased with parity, peaking at the fifth to sixth lactation.[298,299] Cows that were diagnosed with clinical ketosis once had increased risk of ketosis at subsequent calvings.[301,303] Recurrence of ketosis in individuals may reflect digestive capacity and metabolic efficiency, as well as milk production, which are likely to have a multifactorial mode of inheritance.

Generally, clinical and subclinical cows are high producers and are overconditioned at calving.[304,305] Fat cows have been shown to have a 25% reduction in dry matter intake (DMI) and higher turnover rates of fatty acids because of more fat mobilization.[306] Environmental factors that affect the incidence of clinical ketosis include season (increased during midwinter), climate, stabling (increased in stabled vs. loose housing), and feeding regimen (increased with number of feedstuffs used and fewer numbers of feedings per day).[301,304,307] Diets that are less than 8% protein on a dry matter basis before calving or that have high protein levels (greater than 20% DM) after calving have been associated with high incidences of herd ketosis.[308] One study reported an association of increased incidence with a high standard of management and decreased incidence if the wife, versus other family members or paid workers, assisted with chores.[307]

Thirty percent to 40% of cases are complicated by concurrent diseases such as metritis, traumatic reticuloperitonitis, and abomasal displacements.[308] These cows are classified as having secondary ketosis. A diagnosis of parturient paresis, alone or in combination with retained placenta, increased the risk of clinical ketosis.[301,304] Cows with metritis are more likely to be diagnosed as having subclinical ketosis.[297] Displaced abomasum and lameness in a previous lactation were associated with clinical ketosis.[304] One study reported that cows with elevated NEFA concentrations prepartum and elevated BHB postpartum had an increased risk of developing an LDA and ketosis.[270] Cystic ovaries, increased calving to first service interval, and increased calving to last service interval have been associated with subclinical ketosis.[297,304,305] Others reported no association between ketosis and the calving interval and number of inseminations.[309] Most genetic studies are based on the lactation previous to the diagnosis of ketosis and have found either no difference or a tendency toward higher production in cows with ketosis.[299,309–312] One study demonstrated a genetic correlation between milk production and ketosis using only first lactation records.[313] Subclinical ketosis was found to be associated with losses of 1 to 1.4 kg of milk per day or 4.4% to 6% of the mean daily production.[297] Other authors[312] found an association between diagnosis and treatment of clinical ketosis, with an increase of 2.5% in production over the entire lactation. A negative correlation of ketosis with culling rate indicated that high-producing cows with ketosis were less likely to be culled than low-producing cows.[301,314]

41.1.6.1.7

Necropsy Findings

The mortality rate from primary ketosis is extremely low. In animals that die with clinical ketosis, a fatty liver is likely to be the only pathologic finding. In secondary ketosis lesions are associated with the primary disease condition.

41.1.6.1.8

Treatment and Prognosis

Treatment of secondary ketosis requires correction of the primary condition while ensuring the provision of an adequate diet. In ketosis secondary to the butyrate content of silage, the diet can be manipulated to eliminate or dilute the silage.[258]

Many treatments have been used for primary clinical ketosis. The goal of treatment is to limit the mobilization of fat by increasing the availability of glucose or glucose precursors and promoting uptake of glucose by cells.[315] The pathophysiologic reasoning for specific treatments of ketosis has been reviewed.

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[316] Clinical response to traditional treatment with intravenous glucose, oral propylene glycol, corticosteroids, and insulin has been well documented. In addition, many nontraditional treatments and feed supplements have shown variable success in treating and preventing ketosis.

Traditional therapy with intravenous injections of 100 to 500 mL of 50% glucose (dextrose) gives marked clinical improvement. A transient hyperglycemia is produced; return to preinjection levels occurs in 2 hours. Blood ketones drop immediately, clinical signs disappear, and milk production increases by 5 to l0 lb for at least one milking.[317] Nervous signs may reappear in l2 to 24 hours, and milk production drops again over 2 to 3 days. There are fewer relapses if the glucose injections are repeated frequently. Solutions containing a mixture of 25% dextrose and 25% fructose have been used in an attempt to prolong the hyperglycemic action. Ideally a continuous intravenous glucose infusion at 0.5 g/min should be administered until milk ketone test results are negative.[296,317] In my opinion a slow infusion of 20 L of 2.5% glucose (with half normal saline) over 24 hours improves the clinical response. This solution allows fast enough drip rates for ease of catheter maintenance without the danger of causing osmotic diuresis and excessive water loading. Urine is monitored by dipsticks for negative glucose and decreasing levels of ketone bodies several times daily. Daily monitoring of the blood glucose (once or twice daily) measures the adequacy of dextrose administration. Careful monitoring for hypoglycemia is required when intravenous glucose is discontinued. This may be impractical for field situations but is worthwhile in clinical settings with valuable individuals.

Glucose precursors may be given orally in the feed or as a drench and provide a source for gluconeogenesis. These include a propylene glycol drench at 225 g (8 oz) bid for 2 days, followed by 110 g (4 oz) once daily for 2 days or glycerol at 500 g bid for up to 10 days.[318] Overuse of propylene glycol may have a deleterious effect on ruminal flora, decrease ruminal motility, and cause diarrhea, necessitating its discontinuation and the institution of ruminal transfaunations. In one study, adding propylene glycol to the diet of postpartum cows decreased NEFA and BHB levels but did not significantly change milk production, health, or fertility and therefore was not economically beneficial.[319] Glycerol drenches at 1 to 2 L orally per cow alleviated symptoms of ketosis, but including glycerol in the transition feed did not.[320,321] Sodium propionate (125 to 250 g bid orally), ammonium lactate (120 g bid orally), and sodium lactate (360 g bid orally) have also been used as feed additives to provide alternate glucose sources. All of these tend to lower the butterfat test result and may cause digestive disturbances if prolonged treatment is used.[317]

Glucocorticoids are often used to prolong the hyperglycemic effect by decreasing tissue uptake of glucose and reducing milk production for up to 3 days. Dexamethasone (0.04 mg/kg) and betamethasone are most commonly used. In one study a single treatment of dexamethasone (0.04 mg/kg) significantly increased blood glucose for 6 to 9 days and decreased milk production for 1 to 7 days.[322] Caution must be used, because overdosing may reduce feed intake and exacerbate the condition of cows with fatty liver syndrome.[323] Anabolic steroids such as trienbolone acetate have resulted in decreases in blood levels of ketone bodies without depression of milk production but are prohibited in the United States.[324]

Low doses of long-acting insulin (200 IU of protamine zinc insulin subcutaneously [SC] once every 48 hours) have been used as an adjunct to intravenous glucose and glucocorticoid therapy. Use of the newer slow-release insulin (Humilin, Ultralente human insulin rDNA, Eli Lilly, Indianapolis, Ind.) at a dose of 0.14/IU/kg of body weight IM provided an insulin peak by 12 hours postinjection, with return to preinjection levels by 24 hours.[325] Blood glucose lowered by 21% at 6 to 12 hours and returned to

preinjection levels within 24 hours. Pancreatic secretion of insulin is reduced in ketotic cows in response to intravenous infusions of glucose.[326] Insulin assists in suppressing fatty acid mobilization and increasing tissue uptake of glucose while stimulating hepatic glycolysis. Intravenous glucose combined with insulin when administered over several days has been shown to decrease NEFAs and liver triglycerides and increase hepatic glycogen.[327]

There has been interest in using glucagon injections to stimulate gluconeogenesis and limiting lipolysis, which decreases triglyceride accumulation in the liver during early lactation. Recent studies reported glucagon had no adverse effects but had only minor effects on the lipid transport in early lactation.[328] Glucagon is not commercially available.

Lipotrophic agents such as choline (25 to 50 g daily PO), cysteamine (750 mg IV every 2 to 3 days), and L-methionine have been suggested as feed additives or treatments that increase mobilization of fat in the liver.[329–331] Choline (25 g daily) may also be given subcutaneously but should *not* be given intravenously because it acts as a neuromuscular blocker. Therapy with lipotrophic agents has not been proven effective in controlled trials and may even be harmful in cases of severe liver damage.[330]

Cobalt deficiency and therefore vitamin B_{12} deficiency have been implicated as a cause of ketosis.[263] Vitamin B_{12} is an essential cofactor in the metabolism of propionate as it enters into the TCA cycle.[262] Blood and liver levels of vitamin B_{12} are reduced in the postparturient cow.[266] Although vitamin B_{12} and cobalt may be added to the diet, the effectiveness of vitamin B_{12} has not been proven.[332]

Supplementation of prepartum and early lactation diets with chromium decreased serum NEFAs but had no effect on milk production or milk components.[333] Decreased NEFA was greatest at 1 week postpartum. Chromium may potentiate the action of insulin and has a role in the activation of thyroid hormone.

Nicotinic acid (niacin) and nicotinamide have been used with variable effects.[262] Nicotinamide coenzymes in mammary tissue were reduced in ketotic cows compared with normal cows.[334] The suggested dose of nicotinic acid is 6 g orally once daily for up to 10 weeks after calving. Milk production was slightly increased, and blood levels of ketone bodies and FFAs were lower in niacin-treated cows.[335] Niacin decreases blood ketones and FFAs and increases blood glucose. Niacin has also been used in combination with propylene glycol or monensin, but no significant differences were found between treatment and control groups.[336,337] Biotin is a coenzyme in the process of gluconeogenesis and has been studied in the peripartum period.[338] Although NEFAs and hepatic TAG were lower, biotin did not decrease BHB.

Ionophores increase the ratio of propionate formation in the rumen and have been documented to decrease the incidence of clinical ketosis.[281] As of October 2004 monensin (Rumensin, Elanco, Greenfield, Ind.) was cleared for inclusion in feed for dry and lactating dairy cattle in the United States and is valuable as a tool for preventing clinical and subclinical ketosis.

Chloral hydrate is a traditional treatment that increases the breakdown of starch in the rumen and influences the ruminal production of propionate. The initial oral dose is 30 g, followed by 7 g bid for several days.[317] Chloral hydrate may be particularly helpful for its sedative effects in treating cows with recurring nervous ketosis.

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As in all metabolic diseases, nursing care is important. Supportive therapy may include ruminal transfaunations, provision of a variety of palatable feeds, and exercise.

41.1.6.1.9

Prevention and Control

Because the underlying mechanism of clinical and subclinical ketosis is one of negative energy balance during the first 8 weeks of lactation, prevention and control can be addressed in three steps. The feeding and management of cows during late lactation and the dry period should promote good body condition at calving (see Chapter 9 for BCS system). Optimum intake of lactating rations at the commencement of lactation must be encouraged by introducing the ration in a stepwise fashion. The ideal ration during early lactation is highly palatable and of an appropriate energy density.[263,285]

A moderate amount of body fat should be available for mobilization and milk production at parturition. The body fat that is lost in early lactation must be stored in the previous late lactation by feeding to National Research Council (NRC) recommendations.[263] Body condition of the dry cow must be maintained, and fetal growth provided for. It is essential that cows do not become too fat before parturition.[261,305,306] There is evidence that fatty infiltration of the liver begins before parturition, particularly in individuals with fat cow syndrome.[288]

The introduction of the lactating ration should be made as smoothly as possible to encourage maximum intake and minimize digestive upsets. Feeding of the lactation ration in limited amounts may begin as early as 4 to 5 weeks before parturition so that typically 8 to 9 lb of concentrates are being fed at parturition. After calving, incremental increases of a few pounds per day are made until ad lib levels are reached (at approximately 2 to 4 weeks).[260] Ensuring adequate bunk space and minimizing pen changes at the time of parturition will have a critical, positive effect on DMI immediately.[285]

The ideal early lactation ration is highly palatable and meets NRC recommendations. It is beyond the scope of this text to outline detailed ration balancing. The key aspects are maintaining high energy density and optimum levels of fiber and protein without compromising the DMI. Calculations of the energy requirements of a lactating cow are expressed as total net energy of lactation and are obtained from NRC charts.[263] Recommendations for fiber content of the diet are based on the acid detergent fiber (ADF) and NDF. NDF is a good estimate of the bulk of a diet, and the DMI of a ration depends on the NDF (1.2% of body weight). Not all forage analysis laboratories report the NDF, but it can be approximated by dividing the total digestible nutrients by 100. Protein should be provided as both rumen degradable (soluble and nonprotein nitrogen) and rumen undegradable (bypass). Excess protein and fat should be avoided.[285] Specific instructions for formulating these ingredients into a ration are provided by multiple ration-balancing programs.[263]

The diet must also be balanced in its minerals. Cobalt may be added if there is an indication of inadequate levels. Nicotinic acid is recommended as a feed additive at 6 to 12 g/head/day in early lactation rations.[335] Inclusion of chromium in peripartum diets may also be beneficial.[333]

Problems that arise from silage with high butyrate concentrations may require substitution or dilution of the affected silage with other feeds for the cows in early lactation. High-butyrate diets are often tolerated because they encourage a higher milk butterfat content.[258,317] The addition of protected fats in the form of

the calcium salts of long-chain fatty acids or a high proportion of saturated long-chain fatty acids (palmitic and stearic acids) increases the energy density of the ration without reducing the fiber content.[339] These compounds are not degraded in the rumen but are digested in the abomasum and small intestine. Feeding protected fats results in increased milk production, slightly decreased DMI, and increased FFAs, as well as stabilized blood ketones and weight loss through a glucose-sparing effect. However, there is some evidence that added fat does not help in the periparturient period and may interfere with other treatments.[340] Glucogenic precursors such as propylene glycol and sodium propionate have been incorporated into early lactation rations for many years. Both of these compounds are not palatable to dairy cattle and are better reserved for treatment of individual cases of ketosis.

Subclinical and clinical ketosis should be detected and treated as early as possible to prevent deleterious effects on health and production. This may be accomplished by encouraging clients to use ketone tests routinely on milk or urine during the first 50 to 60 days after parturition. Several companies are developing commercial automated sampling systems that can routinely test milk for ketone bodies.[341–343] Cattle with positive test results should have a thorough physical examination. Institution of supportive therapy for subclinical ketosis should include administration of oral propylene glycol. A high prevalence rate of clinical and/or subclinical ketosis would necessitate investigation of the feeding program.

41.1.7 CALCIUM, MAGNESIUM, AND PHOSPHORUS

JESSE P. GOFF

Adequate blood calcium (Ca), magnesium (Mg), and phosphorus (P) concentrations are vital to normal function of animals. Mechanisms for maintaining blood Ca, Mg, and P concentrations within normal limits perform efficiently most of the time. Occasionally, these homeostatic mechanisms fail, and metabolic diseases, such as milk fever, occur. Inadequate blood Ca, P, Mg, or potassium (K) concentrations (discussed later in chapter) can cause a cow to lose the ability to rise to her feet, as these minerals are necessary for nerve and muscle function. Less severe disturbances in blood concentrations of these minerals can cause reduced feed intake, poor ruminal and intestine motility, poor productivity, and increased susceptibility to other metabolic and infectious disease.

41.1.7.1 CALCIUM

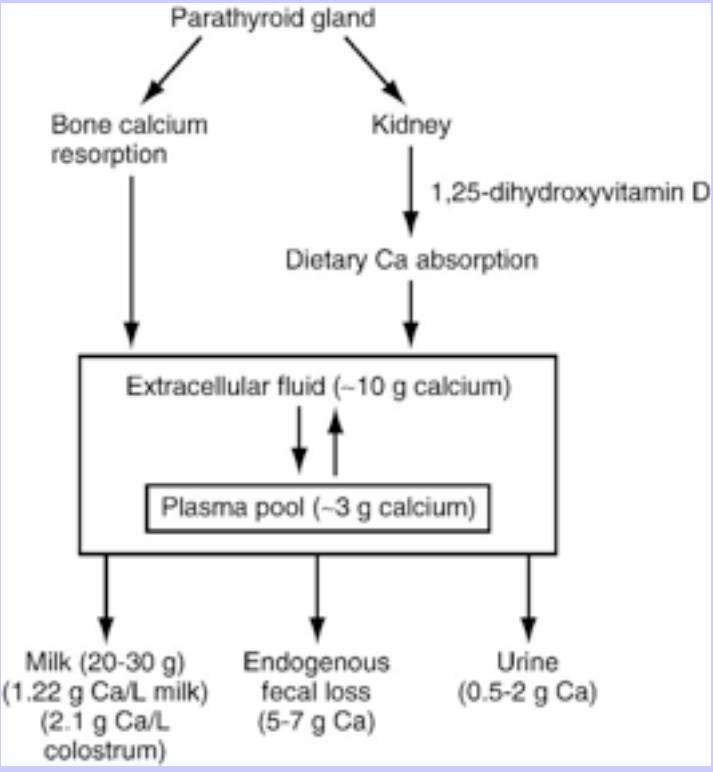
Ca is the major mineral of bone. The skeleton of a 600-kg cow contains approximately 8.5 kg of Ca. Extracellular Ca is also essential to ensure transmission of nervous tissue impulses, excitation of skeletal and cardiac muscle contraction, and blood clotting and as a component of milk. Intracellular Ca, although 1/10,000 the concentration of extracellular Ca, is involved in the activity of a wide array of enzymes and serves as an important second messenger conveying information from the surface of the cell to the interior of the cell. Low extracellular Ca concentration causes hyperexcitability of the nervous system, causing muscle fasciculations or even tetany. At the neuromuscular junction, the amount of acetylcholine released during an endplate action potential is directly related to the amount of Ca that enters the terminal end of the motor neuron, which is in turn dependent on extracellular Ca concentration. Thus, hypocalcemia reduces the strength of muscle contraction, resulting in paresis. In many species (dog, cat, human, horse) the prevailing effects of hypocalcemia result in tetany. In the cow and sheep, hypocalcemia manifests as paresis, though it is important to point out that both effects of hypocalcemia are occurring at the same time and careful evaluation of a hypocalcemic animal will reveal both signs.

41.1.7.1.1

Calcium Homeostasis

Blood Ca concentration in the adult cow or sheep is maintained at 8.5 to 10 mg/dL and is slightly higher in young animals (Fig. 41-18). There are approximately 3 g of Ca in the plasma pool of a 600-kg cow and 8 to 9 g in the extracellular pool. The Ca concentration in the blood is tightly regulated, primarily by the parathyroid gland, which responds to even a small decrease in Ca concentration by secreting PTH into the blood. PTH first will act on the kidney to increase renal tubular reabsorption of Ca from the glomerular filtrate. However, because only small amounts of Ca are lost in urine (<1 to 2 g/day in the cow), this action of PTH is sufficient to restore normal blood Ca concentration only if the total deficit is small. Larger Ca deficits cause prolonged secretion of PTH (hours to days), which stimulates osteoclastic resorption of bone Ca and stimulates renal production of 1,25-dihydroxyvitamin D. The 1,25-dihydroxyvitamin D stimulates the intestinal epithelial cells to produce Ca binding proteins and Ca pumps so that Ca within the lumen of the gut is efficiently transported across the intestinal epithelial cells into the blood. Should an animal be fed a Ca- or vitamin D—deficient diet, it will generally maintain normal blood Ca concentrations for weeks to months by resorbing bone Ca. However, this ultimately will cause bone disease such as osteoporosis and osteomalacia. An increase in blood Ca concentration above normal shuts off PTH and stimulates release of calcitonin from the thyroid gland C cells. This hormone increases renal clearance of Ca and decreases osteoclast activity so more Ca is retained in bone.

Fig. 41-18 Calcium (Ca) homeostatic response of the 600-kg cow in early lactation to a decline in blood calcium concentration at the onset of lactation.



41.1.7.2

ACUTE HYPOCALCEMIA (MILK FEVER) IN DAIRY COWS

Nearly half of all dairy cows will experience subclinical hypocalcemia (<7.5 mg/dL) within 24 hours of calving. Although this reduces ruminal and abomasal contractility and reduces feed intake, clinically these animals appear normal. Hypocalcemia also contributes to metritis, mastitis, and retained placenta by negatively affecting uterine and teat sphincter contractility and the immunity of the cow. With further reduction in blood Ca concentration the animals can appear ataxic, and some will be slightly bloated as eructation is reduced. Finally, in as many as 5% of U.S. cows, blood Ca will fall below 5 mg/dL, and in a few Ca will be as low as 2 mg/dL. These cows are recumbent and unable to rise and have a condition commonly referred to as *milk fever* or *parturient paresis*. They often lay with the neck out in an S-shaped curve, and close examination of muscles in the legs and neck will reveal fasciculation of some muscle groups. The heart muscle does not contract strongly, so on auscultation the heartbeat is muffled. The heart rate is generally increased to try to compensate for the low ventricular ejection volumes. The cow loses the ability to thermoregulate and takes on the ambient temperature of its surroundings. In most cases this causes the skin, especially skin of the ears, to be cold. However, in hot climates or when the cow is recumbent in the hot sun the body temperature may be elevated well above normal. Milk fever typically occurs within a day or two of calving—usually after but occasionally just before calving.

Acute hypocalcemia also occurs with many infectious conditions, such as mastitis or metritis, especially if endotoxins are elaborated. As a rule the blood Ca concentration is 6 to 8 mg/dL. This form of hypocalcemia is a result of redistribution of Ca within organs and will not be discussed further other than to note that not all hypocalcemic cows have the syndrome known as milk fever (Box 41-4).

Treatment of milk fever and hypocalcemia should be done as early as possible, especially if recumbency is present. The pressure exerted by the massive weight of the cow can cause a “crush syndrome” effect on the down side appendages in as little as 4 hours. This causes ischemia of the muscles and nerves and is followed by necrosis of these tissues, resulting in the “downer syndrome” cow.[344] The fastest way to restore normal plasma Ca concentration is to administer an intravenous injection of Ca salts (commonly Ca borogluconate). In general, commercial preparations for intravenous use supply from 8.5 to 11.5 g of Ca per 500 mL. They may also contain sources of Mg, P (often as ineffective phosphite), and glucose. The most effective intravenous Ca dose is approximately 2 g of Ca per 100 kg of body weight. A good rule of thumb is to administer the Ca at a rate of 1 g/min. If Ca is administered too rapidly, fatal arrhythmia of the heart and cessation during systole can occur. Intravenous Ca treatments increase blood Ca above normal for approximately 4 hours. Ca salts can also be injected subcutaneously, but absorption is variable because blood flow to the periphery is often compromised. The amount of Ca that can be injected into a single subcutaneous site should be limited to 1 to 1.5 g of Ca (50 to 75 mL of most commercial preparations). Ca preparations designed for intramuscular administration are also available (Ca levulinate or Ca lactate). Most of these preparations must be limited to 0.5 to 1 g of Ca per injection site to avoid tissue necrosis. To get an effective dose of Ca into the clinically hypocalcemic animal might therefore require 6 to 10 injections into widely separated spots. Oral Ca treatments are not recommended as treatments for clinical milk fever cases, although they can be effective aids in prevention of milk fever.

41.1.7.2.1

Box 41-4 Primary Causes of Recumbency Initiating the?"Downer Cow Syndrome"

Mineral imbalances

- Hypocalcemia—plasma Ca <5 mg/dL
- Hypomagnesemia—plasma Mg <1.2 mg/dL
- Hypophosphatemia—plasma P <1.5 mg/dL

Severe toxemia—moderate reduction in plasma Ca, Mg, and P

Dystocia

Pregnancy toxemia syndrome—low plasma Ca, Mg, P, and glucose

Fractures

Coxofemoral luxation

Rupture of gastrocnemius muscle

Lymphosarcoma of spinal cord

41.1.7.3

HYPOCALCEMIA IN LATE-GESTATION BEEF COWS AND EWES

For beef cows and ewes, especially those carrying twins, meeting the sudden increase in fetal skeletal demand (8 to 10 g/fetal calf/day) for Ca often presents a greater challenge to Ca homeostasis than does lactation. Estrogen, which increases dramatically in late gestation, decreases osteoclast activity. This reduces the ability to use bone Ca reabsorption to meet fetal skeletal Ca demands. As a result, most primary hypocalcemic disorders of the beef cow and ewe occur in late gestation. They are usually prevented by increasing Ca and/or Mg in the gestation diet; provided the animal is eating. Often the syndrome in beef cows and ewes is complicated by inadequate energy intake and a state of inappetence associated with the pregnancy toxemia syndrome.

41.1.7.3.1

Etiology of Milk Fever

Dairy cows producing colostrum (containing 1.7 to 2.3 g of Ca per kilogram) or milk (containing 1.2 g of Ca per kilogram) typically secrete 20 to 30 g of Ca each day in early lactation. Put simply, hypocalcemia and milk fever occur when cattle do not obtain enough Ca from their bones and diet to replace Ca lost to milk. The long-accepted reason this occurs was that high dietary Ca fed to the cow before calving placed

the cow in such a state of positive Ca balance that the parathyroid gland atrophied, rendering it too sluggish to adequately respond when onset of lactation placed the cow into negative Ca balance. However, in recent years it has been discovered that high dietary Ca does not have this effect, and in most cases PTH secretion is quite adequate in these animals.

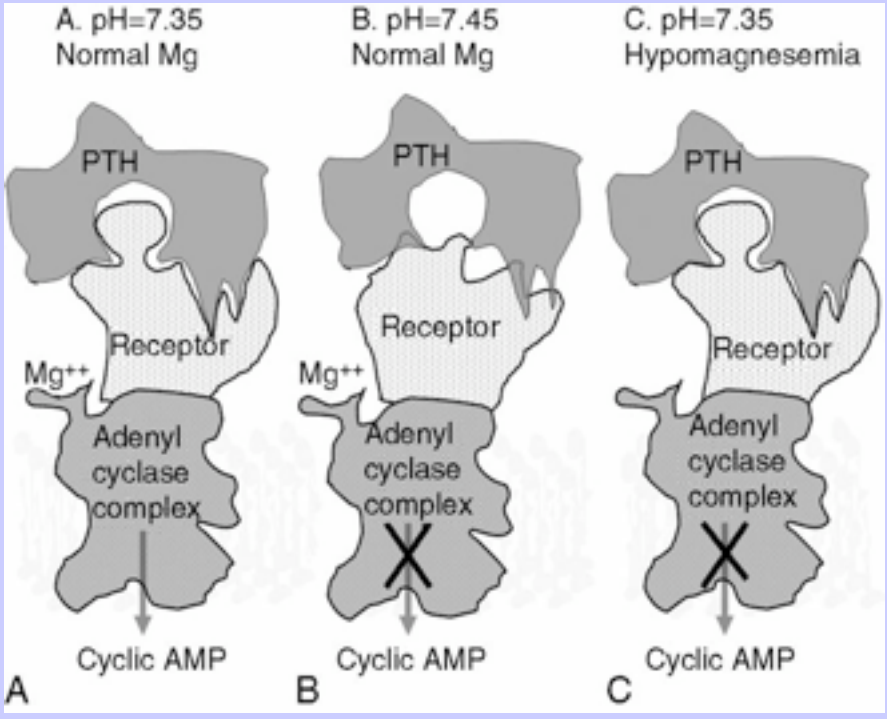
41.1.7.3.2

Role of Metabolic Alkalosis

Metabolic alkalosis predisposes cows to milk fever and subclinical hypocalcemia by altering the conformation of the PTH receptor, rendering the tissues less sensitive to PTH (Fig. 41-19).[345–347] Lack of PTH responsiveness by bone tissue prevents effective use of bone canaliculi fluid Ca (sometimes referred to as *osteocytic osteolysis*) and prevents activation of osteoclastic bone resorption. Failure of the kidneys to respond to PTH reduces renal reabsorption of Ca from the glomerular filtrate. More important, the kidneys fail to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Therefore enhanced intestinal absorption of dietary Ca, which normally would help restore blood Ca to normal, fails to be instituted.

Metabolic alkalosis of dairy cows is caused by high-potassium diets. This is best explained by Stewart's[348] strong ion difference theory of acid-base physiology, which states that the number of moles of positively charged particles (cations) in any given solution (including body fluids) must equal the number of moles of negatively charged particles (anions) in the solution. Put into extremely simplified terms, if positively charged particles are added to a solution, such as the plasma, the number of H^+ cations will decrease and the number of OH^- anions will increase to maintain the electroneutrality of the solution (the solution becomes more alkaline). Conversely, adding anions to a solution causes an increase in H^+ and a decline in OH^- to maintain electroneutrality, and the pH decreases (the solution becomes more acidic).

Fig. 41-19 Parathyroid hormone (PTH) effects at the surface of target bone and kidney cells. **A,** Under normal conditions, PTH released in response to hypocalcemia interacts with its receptor, located on the surface of bone and kidney cells, in a lock-and-key fashion. This stimulates G-proteins and adenylate cyclase (adenylate cyclase complex), resulting in production of cyclic adenosine monophosphate (AMP), which acts as a second messenger within the cytosol of target cells. This initiates mechanisms such as bone calcium (Ca) reabsorption and renal production of 1,25-dihydroxyvitamin D to restore blood Ca concentration to normal levels. **B,** Alkalotic conditions induced by high-potassium diets induce a change in the shape of the PTH receptor protein so that it is less able to recognize and bind PTH, resulting in failure to activate the cell by producing cyclic AMP. **C,** Magnesium is required for function of the adenylate cyclase complex. Hypomagnesemia reduces the ability of PTH-stimulated cells to produce cyclic AMP, resulting in failure to activate the cell.



Cations and anions enter the blood from the digestive tract, making the cation-anion difference of the diet the ultimate determinant of blood pH. The major cations present in feeds and the charges they carry are sodium (+1), potassium (+1), Ca (+2), and Mg (+2). The major anions and their charges found in feeds are chloride (−1), sulfate (−2), and phosphate (assumed to be −3). Cations or anions present in the diet will alter the pH of the blood only if they are absorbed into the blood. The difference between the number of cation and anion particles absorbed from the diet determines the pH of the blood.

When formulating dairy cow late-gestation diets, the cation-anion difference of a diet is described in terms of mEq/kg or mEq/100 g of diet, using various equations involving Na, K, Ca, Mg, Cl, sulfur, and P, with and without adjustments for absorbability of each mineral in the diet:

$$\text{Dietary Caution - Anion Difference (DCAD)}$$
$$= (Na^{+} + K^{+}) - (Cl^{-} + S^{--})$$
$$= (Na^{+} + K^{+}) - (Cl^{-} + 0.6S^{--})$$
$$= (0.2Ca^{++} + 0.16Mg^{++} + Na^{+} + K^{+}) - (Cl^{-} + 0.6S^{--} + 0.64P^{---})$$

The equations largely become an academic pursuit, as several of the variables in the formulas shown are somewhat fixed constants. A strategy I use is to set dietary Ca at 0.85% to 1% and dietary P and Mg at 0.4%. Dietary sulfur needs to be above 0.22% to ensure adequate substrate for ruminal microbial amino acid synthesis but below 0.4% to avoid possible neurologic problems associated with sulfur toxicity. The key to milk fever prevention is to keep sodium and potassium as close to the requirement of the cow as possible (0.1% for Na and 1% for potassium). The key to reduction of subclinical hypocalcemia is to then add chloride to the ration to counteract the effects of low levels of potassium on blood alkalinity. As a rule of thumb, the amount of dietary chloride needed to acidify the cow's blood (and urine) is approximately 0.5% less than the concentration of K in the diet. For example, if dietary K can be reduced to only 2% of the diet, Cl would need to be roughly 1.5% to acidify the cow. This level of Cl in the diet is likely to cause a decrease in DMI. Chloride sources differ in their palatability, and because achieving low dietary K can be difficult, it is prudent to use a palatable source of Cl when formulating the diet. Ammonium chloride (or ammonium sulfate) can be particularly unpalatable when included in rations with a high pH. At the higher pH the ammonium cation is converted to ammonia, which is highly irritating when smelled by the cow. Prilling the Cl (and SO_4) salts can reduce the unpleasant taste of the salts. In our experience, hydrochloric acid has proved the most palatable source of anions. Hydrochloric acid can be extremely dangerous to handle when it is procured as a liquid concentrate. Several companies now manufacture hydrochloric acid —based anion supplements that are safe to handle.

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These are simply guidelines for anion supplementation that I use and are based on inclusion of Ca, Na, S, Mg, and P at the levels outlined previously. Urine pH of the cows provides a cheap and relatively accurate assessment of blood pH and can be a good gauge of the appropriate level of anion supplementation.[349] Urine pH on high-cation diets is generally above 8.2. Limiting dietary cations will reduce urine pH only a small amount (pH 7.5 to 7.8). For optimal control of subclinical hypocalcemia the average pH of the urine of Holstein cows should be between 6.2 and 6.8, which essentially requires addition of anions to the ration. In Jersey cows the average urine pH of the close-up cows has to be reduced to between 5.8 and 6.3 for effective control of hypocalcemia. If the average urine pH is between 5.0 and 5.5, excessive anions have

induced an uncompensated metabolic acidosis, and the cows will experience a decline in DMI. Urine pH can be checked 48 or more hours after a ration change. Urine samples should be free of feces and made on midstream collections to avoid alkalinity from vaginal secretions. Anion-supplemented diets are generally fed for the last 2 to 3 weeks before calving.

41.1.7.3.3

High Dietary Phosphorus

High blood P concentrations inhibit the activity of the renal 25-hydroxyvitamin D 1α-hydroxylase enzyme.[350–351] As summarized by Jorgensen,[352] the incidence of milk fever increases when dietary P exceeds 90 g/day and little negative effect of dietary P is seen when dietary P is less than 50 g/day. Cows need approximately 35 to 40 g of P each day.[353]

41.1.7.3.4

Use of Low-Calcium Prepartal Diets to Prevent Milk Fever

By feeding late-gestation cows a diet that supplies less Ca than they require, the cows can be placed into negative Ca balance. This causes a minor decline in blood Ca concentration, which stimulates PTH secretion, which in turn stimulates osteoclastic bone resorption and renal production of 1,25-dihydroxyvitamin D. This increases bone Ca release and prepares the intestine to absorb Ca efficiently, should it become available. At parturition, the lactational drain of Ca is more easily replaced because the cow's bone osteoclasts are already active and in high numbers and the previous stimulation of enterocytes by 1,25-dihydroxyvitamin D allows efficient use of dietary Ca. Unfortunately, a truly low-Ca diet should supply considerably less than 20 g of absorbed Ca per day. This is difficult to actually achieve on most dairy farms, although increasing use of straw in prepartal diets and the use of Ca binders, such as zeolite or vegetable oils, may make this approach more practical.[354]

41.1.7.3.5

Physiologic Milk Fever Risk Factors

The incidence of milk fever rises as a cow ages, especially as she enters her third or greater lactation. As animals age the number of active bone cells is reduced. Heifers, which are still growing, rarely have problems with hypocalcemia. Lower numbers of active osteoblasts mean fewer cells to respond to PTH and mobilize bone Ca. In addition, as animals age the number of receptors for 1,25-dihydroxyvitamin D on target tissues declines.

The incidence of milk fever is higher in Jersey cows compared with Holstein cows. Although Jersey cow colostrum and milk Ca concentration tend to be higher than in Holsteins, this does not appear to be the only factor. Preliminary data from our laboratory suggest that the intestine of Jersey cows possesses approximately 15% fewer receptors for 1,25-dihydroxyvitamin D than does intestine of Holstein cows.

41.1.7.3.6

Preventing Milk Fever with Vitamin D

Earlier literature often recommended feeding or injecting massive doses (up to 10 million units) of vitamin D 10 to 14 days before calving to prevent milk fever. This will pharmacologically increase intestinal Ca absorption and can help prevent milk fever. Unfortunately, the dose of vitamin D that effectively prevents milk fever is very close to the level that causes irreversible metastatic calcification of soft tissues, and therefore this strategy cannot be recommended. Lower doses may actually induce milk fever because the

high levels of 25(OH)D and 1,25-dihydroxyvitamin D induced by the treatment suppress PTH secretion and directly suppress renal synthesis of endogenous 1,25-dihydroxyvitamin D.[355]

Treatment with 1,25-dihydroxyvitamin D and its analogues can be much more effective, but problems with timing of administration, withdrawal from treatment, expense, and availability have made these treatments not practical.[356,357]

41.1.7.3.7

Hypomagnesemia as a Cause of Hypocalcemia

Hypomagnesemia affects Ca metabolism in two ways. Moderate hypomagnesemia (<1.6 mg/dL) interferes with PTH action on tissues. When PTH binds its receptor on bone or kidney tissues, it normally initiates activation of adenylate cyclase and phospholipase C, resulting in production of the second messengers, cyclic adenosine monophosphate (AMP) and inositol 1,4,5-triphosphate. Both adenylate cyclase and phospholipase C have an Mg^{++} binding site that must be occupied by an Mg ion for full activity.[358] Hypomagnesemia, from inadequate absorption of dietary Mg, is the second most common cause of milk fever in cows around the time of calving and is the most common cause of midlactation milk fever in dairy cows. More severe hypomagnesemia (<1.2 mg/dL) can inhibit PTH secretion in response to hypocalcemia. 1372
This appears to be a factor in the development of some hypomagnesemic tetany syndromes of grazing beef 1373
and dairy cattle. In these syndromes blood Mg concentration falls slowly over time until such point that PTH function is impaired. It is at this point that blood Ca concentration declines precipitously and clinical symptoms, such as tetany, become apparent.[359]

41.1.7.3.8

Agronomic Considerations for Producing Low—Dietary Cation-Anion Difference Forages

Reducing K in the ration of the late-gestation cow can present a problem. By restricting K application to the soil, it is possible to avoid luxury consumption of K by legumes and cool season grasses. Producers should also be aware that forages take up Cl from the soil, and it is possible to find hays that are low in K and high (1% to 1.2%) in Cl. Producers should use the lowest DCAD forage possible, not simply the lowest K forage. Forages intended for the close-up dry cow should routinely be analyzed for both K and Cl by a wet chemistry method. Near infrared determinations of forage mineral content are not currently useful.

41.1.7.3.9

Oral Calcium Treatments at Calving

Ca is absorbed across the intestinal mucosa by two methods. The first method is by the active transport of Ca across intestinal cells—a process mediated by the hormone 1,25-dihydroxyvitamin D. The second method is by passive diffusion across the tight junctions that hold adjacent mucosal cells together. The concept behind oral Ca supplementation is that the cow's ability to use active transport of Ca *across* intestinal cells is inadequate to help her maintain normal blood Ca concentrations. By giving the animal large amounts of very soluble Ca, it is possible to force Ca across the intestinal tract by means of passive diffusion *between* intestinal epithelial cells. Best results are obtained with doses of Ca between 50 and 125 g. For best control of hypocalcemia, a dose is given at calving and again 24 hours later. Administering 50 g of Ca from CaCl as a drench in 250 mL of water is roughly equivalent to administering 4 g of Ca intravenously.[360] Unfortunately, hypocalcemic cows have poor swallowing and gag reflexes, making them vulnerable to aspiration pneumonia. Aspiration of Ca solutions leads to a severe pneumonia. Ca chloride

has been used in oral Ca preparations but can be very caustic. Ca propionate is less injurious to tissues and has the added benefit of supplying propionate, a gluconeogenic precursor. Toxic doses of Ca can be delivered orally; approximately 250 g of Ca in a soluble form will kill some cows.

41.1.7.4 CHRONIC CALCIUM DEFICIENCIES

41.1.7.4.1 Nutritional Secondary Hyperparathyroidism

A deficiency of dietary Ca or vitamin D can reduce the amount of Ca that can be absorbed across the intestine into the extracellular fluids. Diets severely deficient in Ca will not supply adequate Ca to replenish Ca lost from extracellular pools. As a result, blood Ca concentration decreases and PTH secretion increases. PTH can act on the kidney to reduce urinary Ca loss and increase synthesis of 1,25-dihydroxyvitamin D to enhance intestinal Ca absorption efficiency. But if dietary Ca is very low, increasing the efficiency of intestinal Ca absorption cannot substantially increase the amount of Ca entering the extracellular pool of Ca. The only action of PTH that can improve blood Ca concentration in this situation is to enhance bone Ca resorption. The continued removal of bone without replacement results in fibrous osteodystrophy. The clinical signs of nutritional secondary hyperparathyroidism include hypertrophy of the parathyroid glands (although they rarely can be palpated) and cessation of growth in young animals. The lack of Ca available for mineralization of bone matrix causes the growth plates to be soft, weak, and swollen. The cortices of the long bones are thin, and minor or major fractures are common.

Vitamin D deficiency prevents the kidneys from being able to synthesize 1,25-dihydroxyvitamin D. Therefore unless dietary Ca is greatly elevated, the reduced efficiency of dietary Ca absorption will prevent adequate Ca from entering the extracellular fluids, and, again, PTH will activate bone resorption mechanisms to attempt to maintain normocalcemia.

41.1.7.4.2 Renal Secondary Hyperparathyroidism

Renal secondary hyperparathyroidism is a syndrome caused by renal failure and is occasionally observed in older animals. In cows, pyelonephritis can develop in late gestation through early lactation owing to poor urine flow and retrograde urine flow resulting in destruction of renal tissue. A major function of the kidneys in most species is to remove excess phosphate from the circulation. As renal function is lost, phosphate is retained and hyperphosphatemia develops. This occurs when the remaining amount of functional renal tissue is less than 25% of normal.

Hyperphosphatemia has two effects. The first effect is to reduce the ionized Ca content of the blood. This is because Ca and phosphate ions normally exist in blood at concentrations that are slightly below the levels that would cause saturation of the fluids resulting in precipitation of Ca phosphate salt from the solution. However the greatly elevated phosphate level in the blood of renal failure patients can exceed the equilibrium of Ca and phosphate in solution, causing precipitation of Ca from the blood. More important, as phosphate builds up in the blood it has a second effect on the remaining renal tissue. It blocks the activation of the 1α-hydroxylase that catalyzes conversion of 25-dyhydroxyvitamin D to 1,25-dyhydroxyvitamin D within the kidney. Therefore even though PTH should stimulate the remaining functional renal tissue to produce 1,25-dyhydroxyvitamin D, this action of PTH is blocked by hyperphosphatemia.

As renal function is lost, the amount of renal tissue available for production of 1,25-dyhydroxyvitamin D decreases, and blood concentrations of 1,25-dyhydroxyvitamin D decline. This reduces dietary Ca absorption and further depresses blood Ca concentration. This in turn stimulates increased PTH secretion, and reabsorbing bone Ca reserves again becomes a major means of maintaining normocalcemia. Fibrous osteodystrophy follows the prolonged secretion of PTH.

As bone Ca is reabsorbed, more P is also reabsorbed. However, the loss of renal function prevents PTH from having its usual phosphaturic effect, exacerbating the hyperphosphatemia. A vicious cycle of increasing blood P, increasing PTH, and increased bone resorption ensues. The loss of renal function can rarely be reversed.

41.1.7.4.3

Osteoporosis

Three forms of osteoporosis commonly occur. Of these, only lactational osteoporosis is a common syndrome of concern in animals. During lactation in virtually all species there is an obligatory loss of bone mass from the skeleton. In this case the osteoclasts within a bone resorption unit reabsorb bone to a 50-micron depth if dietary Ca is adequate, or to greater depths if the animal is in severe negative Ca balance. 1373 1374 However, osteoblast movement into the resorption cavity is transiently inhibited, and no new bone is deposited. This occurs to some extent in all females shortly after parturition, even when they are in positive Ca balance. However, the degree and duration can be magnified greatly by negative Ca balance. Once the animal has undergone the obligatory period of lactational osteoporotic bone loss (4 to 5 weeks in the cow), if the animal is in positive Ca balance the osteoblasts migrate to the resorption cavity and replace the lost bone. Lactational osteoporosis can help the female meet the Ca demands of lactation by uncoupling bone formation from bone resorption. In high-producing dairy cows, dietary Ca intake is inadequate to meet lactational Ca demands for the first 4 to 6 weeks of lactation. These animals can lose as much as 13% of their skeletal mass during this period, which is replaced in later lactation when dietary Ca intake allows the cow to enter a period of positive Ca balance.

41.1.7.5

MAGNESIUM

Mg is a major intracellular cation serving as a cofactor for enzymatic reactions vital to every major metabolic pathway. Extracellular Mg is vital to normal nerve conduction, muscle function, and bone mineral formation. In a 600-kg cow there is approximately 0.84 g of Mg in the blood, 3 g of Mg in the extracellular fluids, 84 g of Mg inside cells, and 210 g of Mg within bone mineral. Bone is not a significant source of Mg that can be used in times of Mg deficit, as bone reabsorption occurs in response to Ca homeostasis, not Mg status. Maintenance of normal plasma Mg concentration is nearly totally dependent on continuous dietary Mg absorption.

41.1.7.5.1

Hypomagnesemia

Hypomagnesemia generally leads to hyperexcitability, tetany, convulsion, and, too often, sudden death. Hypomagnesemia is often accompanied by and complicated by hypocalcemia. Hypomagnesemia is a common problem in ruminants.

Normal plasma Mg concentration is 1.8 to 2.4 mg/dL in cows and 2.2 to 2.8 mg/dL in sheep. The kidneys play a key role in maintaining Mg homeostasis under conditions of hypermagnesemia when they fail to reabsorb Mg from glomerular filtrate, increasing renal Mg excretion to lower blood Mg concentration. The

renal threshold for Mg (plasma concentration at which all Mg filtered across the glomerulus is reabsorbed) is 1.8 mg/dL in the cow and 2.2 mg/dL in sheep. Plasma Mg concentrations below these levels indicate that dietary Mg absorption is not sufficient and little or no Mg will be detected in urine.

Moderate hypomagnesemia (1.1 to 1.8 mg/dL) is associated with reduced feed intake, nervousness, and reduced milk fat and total milk production. This can be a chronic problem in some dairy herds that often goes unnoticed. It can also predispose these animals to milk fever as described earlier.

41.1.7.5.2

Role of the Rumen in Hypomagnesemia

Mg is well absorbed from the small intestine of young calves and lambs. As the rumen and reticulum develop, these sites become the main, and perhaps the only, sites for net Mg absorption.[361] In adult ruminants the small intestine is a site of net secretion of Mg. Mg absorption from the rumen is dependent on the concentration of Mg in solution in the ruminal fluid and the integrity of the Mg transport mechanism, which is an Na-linked active transport process.[362]

The soluble concentration of Mg in ruminal fluid can be low for several reasons. Chief among these are low Mg content of forages and inadequate dietary supplementation. Mg solubility also declines sharply as ruminal pH rises above 6.5. Grazing animals tend to have higher ruminal pH because of the stimulation of salivary buffer secretion. When high-grain rations are fed, ruminal fluid pH is often below pH 6.5, increasing Mg solubility and thus availability. Forages can also contain organic compounds, such as unsaturated fatty acids, which are converted to tricarballylate, which can form insoluble Mg salts in the rumen.

High dietary K can reduce the rumen's ability to absorb Mg. High K concentration in the ruminal fluid depolarizes the apical membrane of the ruminal epithelium, reducing the electromotive potential needed to drive Mg across the ruminal wall.[362] Feeding ionophores (monensin, lasalocid) can improve activity of the Na-linked Mg transport system in the rumen, increasing Mg absorption efficiency approximately 10%.[363] Lush high-moisture pastures increase the rate of passage of material, including Mg, from the rumen so that Mg may leave the rumen before it can be absorbed.

41.1.7.5.3

Occurrence of Hypomagnesemic Tetany

Hypomagnesemic tetany occurs most often in beef cows, dairy cows, and ewes in early lactation grazing lush pastures high in potassium and nitrogen and low in Mg and Na. This is often referred to as *grass tetany, spring tetany, grass staggers,* or *lactation tetany*. Mg deficiency occurs most often in spring or fall when pastures are growing at maximal rates and is most common in grazing lactating ruminants, as milk production removes 0.15 g of Mg from the blood for each liter of milk produced. Cool weather seems to play a factor as well, probably through its effects on plant Mg uptake, although there is some indication that the physiologic response of the cow to cool weather affects Mg status directly.

When plasma Mg levels fall below 1.1 mg/dL, twitching is sometimes seen in the muscles of the face, shoulder, and flank. As hypomagnesemia progresses, tetanic spasms of the muscles become more common, eventually causing the cow or ewe to stagger and fall. Clonic convulsions quickly follow, with chomping of the jaws and frothy salivation. Affected animals lay with the head arched back and the legs paddling. The heart rate can approach 150 beats/min, and the heartbeat is often audible without a stethoscope. Respiratory rate approaches 60 breaths/min, and rectal temperature can approach 40.5° C

(105° F) as a result of the excessive muscular activity. The eyelids flutter, and there is usually marked nystagmus. Animals may get up after several minutes and repeat these convulsive episodes several times before they finally die. Hypomagnesemic tetany in calves is clinically similar to that in adults and is often accompanied by moderate hypocalcemia.

Ewes are generally hypocalcemic and hypomagnesemic. Affected ewes are usually in the second to fourth week of lactation and are usually suckling more than one lamb. Affected ewes are generally depressed, stand with their heads down, and are reluctant to move. As hypomagnesemia and hypocalcemia progress, the animals develop tetany and clonic convulsions just as in cattle. The clinical signs in goats are similar to those observed in cattle.

Cerebrospinal fluid (CSF) Mg concentrations below 1 mg/dL are responsible for the clonic convulsions seen in animals with hypomagnesemic tetany. Blood samples obtained during or shortly after an episode of tetany may have near-normal levels of Mg as a result of muscle damage and leakage of Mg from intracellular pools. CSF Mg concentration will remain low during tetany and also can be a reliable indicator of Mg status for up to 12 hours after death. Vitreous humor Mg concentrations below 1 mg/dL are also found in animals with tetany and can be a reliable indicator for 24 to 48 hours after death, provided that environmental temperatures have not exceeded 23° C.[364] Aqueous humor has not proved a reliable sample.

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41.1.7.5.4

Treatment of Hypomagnesemia

Animals exhibiting hypomagnesemic tetany need immediate treatment. This will require administering 1.5 to 2.25 g of Mg intravenously in the adult cow. Most of the commercially available intravenous solutions used to treat milk fever supply 1.5 to 4 g of Mg, usually as the chloride, borogluconate, or hypophosphite salts of Mg. Response to therapy can be disappointing, and success is related to the interval between onset of tetany and treatment. Cows should not be stimulated to rise for at least 30 minutes after treatment, to avoid initiating tetany and convulsions. Cattle that recover do so approximately an hour after treatment, which is the time it takes CSF Mg concentration to return to normal. Many of these cows will relapse and require further treatment within 12 hours.

The rate of relapse can be reduced using orally administered Mg salts once the animal has regained good swallowing reflexes (to avoid aspiration pneumonia). Administering a slurry of 100 g of Mg oxide in water intraruminally or by drenching can be effective. This provides approximately 50 g of Mg to the animal. Adding 50 g of Ca carbonate, 100 g of dicalcium phosphate, and 50 g of sodium chloride may enhance the effectiveness of the slurry, especially if hypocalcemia and hypophosphatemia accompany the hypomagnesemia. Alternatively, 200 to 400 mL of a 50% Mg sulfate solution can be administered by drench. Mg sulfate is more available for absorption than Mg oxide. If hypomagnesemic tetany has occurred in one cow or ewe in a herd or flock, steps should be taken immediately to increase Mg intake in other members of the herd to prevent further losses. Administering an additional 10 to 15 g of Mg per pregnant cow, 20 g of Mg per lactating beef cow, and 30 g of Mg per lactating dairy cow daily, usually in a grain mix, will often prevent further hypomagnesemic tetany cases. Ewes and does can be treated with ⅛ of these formulas. The problem with prevention is ensuring the extra Mg gets into the animal, especially when working with animals at pasture.

41.1.7.5.5 Prevention

41.1.7.5.5.1 USING OTHER TRANSPORT MECHANISMS TO ABSORB DIETARY MAGNESIUM

The active transport mechanism for Mg absorption across the ruminal wall is critical to the survival of the animal when dietary Mg concentration is less than 0.25%. Unfortunately there are several known factors, such as dietary K, and several unknown factors that prevent this pathway from functioning well. A second pathway for absorption of Mg exists and operates only at high ruminal fluid Mg concentrations. At high ruminal Mg concentration the Mg will flow down its concentration gradient into the extracellular fluids of the cow. This passive transport mechanism is not subject to inhibition by K and is subject only to the concentration of Mg in solution in the rumen.[362]

The concentration of Mg in ruminal fluid required to use concentration gradient—driven absorption of Mg is at least 4 mMol/L. The minimum level of Mg required in the diet to use this pathway in order to prevent negative Mg balance in the face of high K levels in ruminants is approximately 0.35%.[365] Mg content of the close-up dry cow ration and the early lactation ration should be between 0.35% and 0.4% as insurance against the possibility that the active transport processes for Mg absorption are impaired.

41.1.7.5.5.2 ASSESSING MAGNESIUM STATUS AT PARTURITION

PTH causes increased renal tubular reabsorption of Mg. The kidneys excrete less Mg, increasing blood Mg in the typical milk fever cow. However, if dietary Mg is insufficient or ruminal absorption of Mg is impaired, the blood Mg concentration will be below the normal renal threshold for Mg (1.85 mg/dL in cattle) and almost no Mg will appear in the urine. The animal should be considered abnormal for Mg. Sampling the blood of several cows within 12 hours of calving is a simple, effective index of Mg status of the periparturient cows. If serum Mg concentration is not at least 2 mg/dL in 9 of 10 cows sampled, it suggests inadequate dietary Mg absorption from either lack of dietary Mg or interferences with absorption. This same test can be used in the first weeks of lactation to see if the lactating cow diet is providing adequate Mg to the animal. This can be important, as hypomagnesemia may limit productivity of lactating cows as well as contributing to hypocalcemia in the herd.

41.1.7.6 PHOSPHORUS

Traditionally, *phosphorus* in clinical medicine is abbreviated as P, although it should be understood by the reader that the biologically relevant form of phosphorus is actually inorganic phosphate, not elemental phosphorus. P is a component of phospholipids, phosphoproteins, nucleic acids, and energy-transferring molecules such as ATP. P is an essential component of the acid-base buffer system. It is second only to Ca as a major component of bone mineral, with the skeleton of a 600-kg cow containing approximately 3.9 kg of P.

41.1.7.6.1 Phosphorus Homeostasis

Plasma P concentration is normally 4 to 8 mg/dL. Approximately 1 to 2 g of P are present in the plasma inorganic P pool, and 4 to 7 g of P in the extracellular P pool, of a 500-kg cow. Intracellular P concentration is approximately 78 mg/dL, and total body intracellular P content is approximately 155 g,

with 5 to 6 g located within erythrocytes. Maintaining the extracellular P pool involves replacing P removed for bone and muscle growth, endogenous fecal loss, urinary P loss, and milk production with P absorbed from the diet or reabsorbed from bone. During late gestation, fetal skeletal development can withdraw up to 10 g of P per day from the maternal P pools. Approximately 0.3 g of P is incorporated into each kilogram of body tissue (muscle) gained during growth of the animal. Production of milk removes from the extracellular pool approximately 0.9 g of P per kilogram of milk produced. Salivary secretions remove between 30 and 90 g of P from the extracellular P pool each day.[353] Factors affecting salivary phosphate secretion include the time spent ruminating (chewing activity) and the PTH status of the animal. PTH stimulates parotid salivary P secretion and can increase salivary phosphate concentrations twofold to threefold.[366] Salivary phosphate secretions help buffer the rumen and supply ruminal microbes with a readily available source of P necessary for cellulose digestion. Most of the salivary phosphate secreted is recovered by intestinal absorption. However, even on low-P diets, a minimum of 5 g of secreted P per day is not recovered and is lost to feces. Urinary P loss is usually between 2 and 12 g/day. Bones of a 600-kg cow contain approximately 4 kg of P, some of which can be withdrawn and returned to the blood during osteoclastic resorption of bone.

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Ruminal microbes are able to digest phytic acid, so most of the phytate-bound P, the form of up to 70% of P in plants, is available for absorption in ruminants. P is primarily absorbed in the small intestine via an active transport process that is responsive to 1,25-dihydroxyvitamin D. Intestinal P absorption efficiency can, in theory, be upregulated during periods of P deficiency, as renal production of 1,25-dihydroxyvitamin D can be directly stimulated by very low plasma P. However, the plasma P level must reach very low levels (<1 to 2 mg/dL) to stimulate increased renal production of 1,25-dihydroxyvitamin D. Plasma P concentrations are generally well correlated with dietary P absorption. P absorbed in excess of needs is excreted in urine and saliva.

PTH, secreted during periods of Ca stress, increases renal and salivary excretion of P, which can be detrimental to maintenance of normal blood P concentrations. This is one reason that hypocalcemic animals tend to become hypophosphatemic. PTH could conceivably increase blood P concentration because it stimulates bone mineral resorption. Also, because PTH stimulates the kidney to produce 1,25-dihydroxyvitamin D, it can increase the efficiency of intestinal phosphate absorption. However, it must be remembered that PTH is secreted primarily in response to hypocalcemia, not hypophosphatemia.

41.1.7.6.2

Hypophosphatemia, Pregnancy Toxemia, and Downer Cows

Beef cows and ewes fed a diet marginal in P will have a chronic hypophosphatemia of 2 to 3.5 mg/dL. In late gestation, plasma P can decline precipitously as the growth of the fetus accelerates and removes substantial amounts of P from the maternal circulation. These animals often become recumbent and are unable to rise, though they appear fairly alert and will often eat feed placed in front of them. Cows and ewes carrying twins are most often affected. Plasma P concentration in these recumbent animals is often less than 1 mg/dL. The disease is often referred to as *pregnancy toxemia* and is usually complicated by concurrent hypocalcemia, hypomagnesemia, and in some cases hypoglycemia. Diets that are marginal in P are generally indicative of diets that are marginal in energy, because grains are usually very good sources of P.

At the onset of lactation in the dairy cow, the production of colostrum and milk draws large amounts of P out of the extracellular P pools. This alone often causes an acute decline in plasma P levels. In addition, if the animal is also developing hypocalcemia, PTH will be secreted in large amounts, increasing urinary and salivary loss of P. In dairy cows, plasma P concentrations routinely fall below the normal range at

parturition, and in cows with milk fever plasma P concentrations are often 1 to 2 mg/dL. Plasma P concentrations usually increase rapidly after treatment of the hypocalcemic cow with intravenous Ca solutions. This rapid recovery is caused by reduction in PTH secretion, which reduces urinary and salivary loss of P. Administration of Ca generally causes resumption of gastrointestinal motility, which allows absorption of dietary P and reabsorption of salivary P secretions that were sequestered within the rumen.

Some dairy cows that develop acute hypophosphatemia do not spontaneously recover normal plasma P concentration. This is sometimes the case in cows that are classified as downer cows. This syndrome often begins as milk fever, but unlike the typical milk fever cow, in these cows the plasma P remains low (<1 mg/dL) despite successful treatment of the hypocalcemia. Protracted hypophosphatemia in these cows appears to be an important factor in the inability of these animals to rise to their feet, but why plasma P remains low is unclear. In some cases the inability to absorb the salivary phosphate is secondary to poor ruminal motility, but not in all cases. Excessive cortisol secretion could also drive blood P concentration down, probably by forcing extracellular P inside cells. Treatment of cows with phosphate-containing solutions can effect a recovery in some animals. For oral treatment, the dose is 50 g of P supplied in a 200-g monosodium phosphate drench. Intravenous treatment consists of 6 g of P supplied by 23 g of monosodium phosphate dissolved in 1 L of saline. Oral treatment restores normal blood Pa a little more slowly than intravenous treatment, but the effect lasts much longer.[367] If depletion of intracellular P stores is also involved in the downer syndrome, it seems likely that intravenous treatment alone simply does not supply enough P to replenish intracellular stores of P.

The hypophosphatemic downer cow syndrome does not appear to be caused by low P diets, as affected cows are often receiving diets containing 0.4% dietary P. The best preventative measure seems to be to avoid development of hypocalcemia.

41.1.7.6.3

Chronic Phosphorus Deficiency

P deficiency is fairly common in grazing ruminants. Plant growth in arid climates or on tropical soils is often limited by poor soil P content or availability. Although P content of the immature plant may be suitable (0.3% P on a DM basis) the mature dry plants often contain less than 0.15% P, which can lead to P deficiency in ruminants forced to subsist on these forages. With the exception of rickets and postparturient hemoglobinuria, the clinical problems associated with P deficiency are general and nonspecific. They can include an unthrifty appearance, reduced feed intake, pica, reduced rate of gain, and reduced milk production.

41.1.7.6.3.1

OCCURRENCE

The most common of the P deficiency syndromes is the unthrifty cow that grows slowly, milks poorly, and is infertile. In arid areas of the world with inferior soil quality, infertility and poor growth resulting from inadequate P intake affects nearly all animals. Beef animals grown in these areas may routinely require 3 or more years to reach market weight. Brood cows often calve only every other year. In more temperate areas, P deficiency can develop in animals grazing overly mature forages or crop residues, such as corn stalks. Cows subsisting on forages that are low in digestibility are at risk for developing P deficiency unless supplemented. Increasing awareness of the environmental problems associated with P content of animal wastes and increasing expense of P supplements may encourage producers to feed diets marginally sufficient in P.

Sheep can, in some instances, be successfully raised on pasture that has been associated with P deficiency in cattle, suggesting that sheep are slightly more resistant to P deficiency syndromes than are cattle. This may simply reflect the higher intake per kilogram of body weight of sheep and their habit of selecting the less mature plants, which are generally higher in P.

41.1.7.6.4

Rickets and Osteomalacia

Rickets is a disease of young, growing animals in which the cartilaginous matrix at the growth plate and the osteoid matrix formed during bone remodeling fail to mineralize. In adults (no active growth plates), the term *osteomalacia* is used to describe the failure of osteoid matrix to mineralize. Ca and phosphate ions come together in a ratio of 10 Ca ions to 6 phosphate ions at the point of mineralization of the bone cartilage or osteoid matrix. Bone ash content varies somewhat with the bone examined but is generally 57% to 62% of bone dry weight, with 36% Ca and 17% P in adult animals. Failure to supply P in the diet will result in low plasma P concentrations that will not support the mineralization process, and the bone matrices will fail to mineralize. Bone ash, as well as total P and Ca content, will be below normal.

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Low plasma Ca concentrations (arising from vitamin D deficiency or severe Ca deficiency) can also result in failure to mineralize bone matrices. Bone ash is reduced, and the bones of young animals become "rubbery," bending without breaking. Joint surfaces are often eroded, contributing to lameness in affected animals.

In principle, Ca deficiency differs from P deficiency in that normal osteoid is formed but fails to mineralize in P deficiency, whereas in Ca deficiency the normal osteoid is either not formed at all (osteoporosis) or replaced by fibrous tissue. In vitamin D deficiency it is common to see mixed lesions (osteomalacia, osteoporosis, and fibrous osteodystrophy) all in the same bone. Vitamin D deficiency also seems to reduce secretion of type X collagen by the chondrocytes within the growth plate and somehow prevents the programmed cell death of chondrocytes within the zone of provisional calcification, a requirement for bone formation.

41.1.7.6.5

Chronic Moderate Hypophosphatemia

Animals fed diets containing less P than necessary to meet physiologic needs will develop hypophosphatemia and all the physiologic consequences of failure to grow, inappetence, and unthriftiness. Milk production, but not P content, will decline. Impaired reproduction has often been attributed to "P deficiency." However, in most cases in which cows develop P deficiency the situation is complicated by concurrent energy deficiency, likely the direct cause of the reproductive failure.

Unfortunately the belief that "marginal" dietary P contributes to reproductive inefficiency has been used as justification for feeding diets that are much higher in P than is required. Wu and Satter[368] present convincing evidence that high-producing cows perform well in terms of milk production and fertility when fed diets containing 0.37% to 0.40% P.

41.1.7.6.6

Postparturient Hemoglobinuria

Intravascular hemolysis, anemia, and hemoglobinuria are occasionally reported during the first 6 weeks of lactation. Cows that have been treated for ketosis seem at greater risk for developing postparturient hemoglobinuria. Many, but not all, cows that develop this syndrome are hypophosphatemic. Severe

hypophosphatemia is postulated to depress the ability of erythrocytes to produce ATP> Glyceraldehyde-3-phosphate dehydrogenase, a key enzyme in glycolysis, requires inorganic phosphate as a cofactor. Without sufficient ATP to power sodium pumps, the intracellular sodium concentration rises, the cells become more rigid, and as a result they rupture as they pass through the capillary beds. However, hypophosphatemia alone is rarely sufficient for increased red blood cell fragility. Often these cows are on diets that are also deficient in selenium, copper, and energy. In light of these observations, it is likely naive to suggest that the cause of postparturient hemolysis is hypophosphatemia alone (Table 41-9).

Table 41-9 Diagnosing Acute and Chronic Macromineral Insufficiency or Imbalance in Ruminants*

Mineral	Tissues to Use	Normal	Subclinical Deficiency	Clinical Deficiency
Calcium (acute)	Serum, plasma (mg/dL)	8–10.5	5.5–7.5	<5.0
Calcium (chronic)	Serum, plasma (mg/dL)	8.0–10.0	8.0–10.0	6–10
	Rib bone ash (% Ca)	37–39	35–37	<35
	Urine (mg/dL)	2	0.5–1.5	<0.1
Phosphorus (acute)	Serum, plasma (mg/dL)	4–6	2–4	<1.2
Phosphorus (chronic)	Serum, Plasma (mg/dL)	4–6	3–4	<3.0
	Rib bone ash (% P)	17–20	15–17	<12
Magnesium (acute)	Serum, plasma (mg/dL)	2.0–2.3		<1.1
	Vitreous humor (mg/dL)	1.9–2.5	1.5–1.85	<1.5
	Urine (mg/dL)	10–25	2–5	<0
	Cerebrospinal fluid (mg/dL)	2–2.5		<0.5
Magnesium (chronic)	Serum, plasma	2.0–2.3	1.6–1.9	<1.5

* The tissue needed to ascertain acute problems is intended to guide diagnosis of the initial cause of recumbency in downer cows.

41.1.7.7

HYPOKALEMIA SYNDROME IN CATTLE

NICOLAS SATTLER

Based on reports available in the literature, hypokalemia syndrome in cattle can be defined as presence of flaccid paralysis, recumbency, abnormal neck position, and serum potassium concentration below 2.5 mmol/L.

41.1.7.7.1

Occurrence

Hypokalemia is a frequent biochemical finding in cows presented with anorexia and gastrointestinal stasis.[369] It is often mild (>3 mmol/L) and not associated with obvious clinical signs in ruminants. Hypokalemia syndrome is a rare clinical condition reported in a total of 25 animals in three studies.[370–372] Lactating dairy cows appear to be at a higher risk, but the syndrome has also been described in calves and heifers.

41.1.7.7.2

History

Lactating dairy cows less than 60 days in milk (DIM) constitute the majority of cases in the literature. Any disease causing significant anorexia for 1 week or more, particularly infectious disease, is a risk factor.[371] Repeated administration of isoflupredone acetate is reported in most cases, for treatment of either acetonemia in lactating cows[370] or infectious respiratory disease in calves and heifers.[371] In one case, repeated off-label intramammary administration of isoflupredone acetate preceded hypokalemia syndrome. Multiple doses of dextrose and insulin are also reported to be risk factors.[370] Intravenous fluid administration for 2 days or longer without serum biochemistry followup has been documented in two cases of calves with severe neonatal diarrhea.

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In most cases recumbency caused by hypokalemia syndrome was not the initial event but rather occurred during the evolution of another disease such as acetonemia or infectious disease. Moreover, recumbency was not always the presenting complaint.[371] Some animals first manifested anorexia, reduced fecal output, kyphosis, and reluctance to move. However, evolution to severe paresis and decubitus occurred rapidly in all these cases.

41.1.7.7.3

Clinical Signs

In the early stages of the syndrome, absence of feces, paretic gait, kyphosis, inability to stand for a long time, and tachycardia are observed. Sometimes an abnormal neck posture is evident before recumbency. The typical case presentation of hypokalemia syndrome includes decubitus, S-shaped neck, abnormal feces and ruminal motility, abnormal appetite, and tachycardia with or without arrhythmia. Decubitus is a result of flaccid paralysis: the tail has little to no tonus and is held in an abnormal position, resistance to all manipulations is weak, and the cow is unable to raise her head. It is not rare to observe that the animal eats and drinks willingly if food and water are provided near the mouth. Abnormal appetite therefore may be partly caused by an inability to move the head to reach food and water. The neck is carried in an S-shaped and twisted fashion that differs from that of the hypocalcemic cow. The neck is never fixed in this abnormal position. When moved there is no resistance, and if the head is placed in an anatomically correct position there is an odd feeling of luxation. As soon as the head is not held, the neck resumes the abnormal S-shaped position, deviating to either direction. This neck posture may precede decubitus and persist after decubitus has resolved. Cardiac arrhythmias (Fig. 41-20) also accompany hypokalemia syndrome and may be ventricular (ventricular tachycardia, accelerated escape ventricular rhythm) or supraventricular (atrial fibrillation) in origin.

Fig. 41-20 Electrocardiograms. *Panel 1,* Electrocardiograms of a cow with hypokalemia syndrome before treatment (base-apex, 25 mm/sec, 1 cm = 1 mV). Potassium serum concentration was 2 mmol/L. **A,** Note the ventricular escape rhythm: normal heartbeat and more than five ventricular QRS complexes. **B,** Note the flattened T waves and increased intervals. *Panel 2,* Electrocardiogram of a cow with hypokalemia syndrome after treatment (base-apex, 25 mm/sec, 1 cm = 1 mV). Potassium serum concentration was 4 mmol/L. Note the normal T waves and intervals.

Hypokalemia syndrome is most often the consequence of a concomitant disease or treatments administered. Fever and acetonemia are the most frequently associated problems. The identification of the concomitant disease(s) is essential for accurate prognosis and treatment.

41.1.7.7.4

Etiology

Hypokalemia may result from an imbalance of the internal or external potassium balance or both (Fig. 41-21).[369,370,373–376] Internal potassium balance is determined by exchanges between extracellular and intracellular compartments, whereas external balance is a result of systemic intake and losses. Currently, except for cases with documented repeated isoflupredone acetate administrations, the exact determinants causing hypokalemia syndrome in cows are not known.

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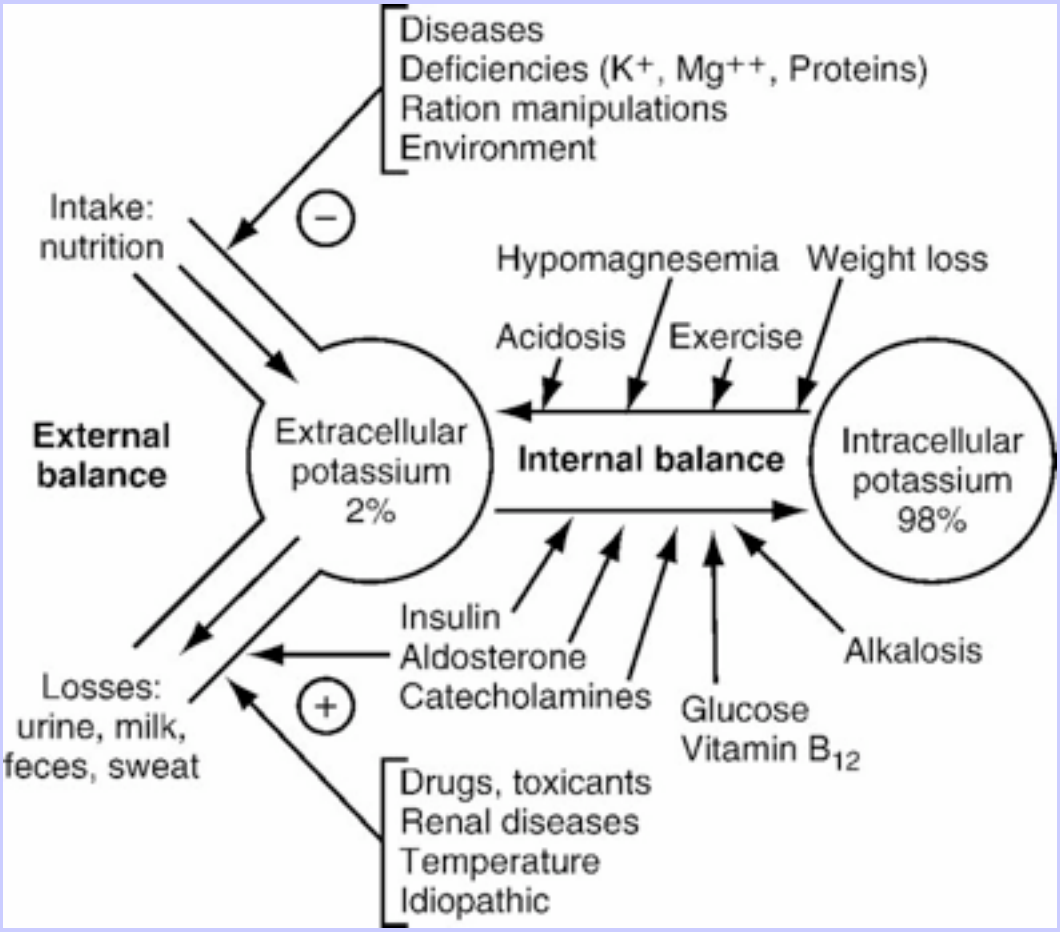
Fig. 41-21 Potassium balances and major determinants in cattle. Adapted from Brobst D: *J Am Vet Med Assoc* 188:1019, 1986.



At present, because of the limited data available, it is not possible to determine if hypokalemia syndrome cases are mainly a result of potassium depletion, internal imbalance, or both. The prolonged inappetence observed before hypokalemia, along with the amount and duration of potassium needed for treatment, suggests potassium depletion is significant. Serum potassium concentration is a poor indicator of the potassium status of the organism because 98% of whole body potassium is located in the intracellular compartment.[374,377] Determination of intracellular potassium concentration in erythrocytes or muscle cells

could be a more accurate way to assess potassium depletion.[377,378] At present these data are not available for hypokalemia syndrome cases.

As a result of the potent mineralocorticoid activity of isoflupredone acetate, cases associated with its administration show both internal and external potassium balance abnormalities (see Fig. 41-21).[376] Repeated doses can reduce blood potassium concentration by 70%.[379] In a small experimental study (N = 9), we were able to reproduce the syndrome by combining food restriction and multiple doses of isoflupredone acetate in lactating dairy cows.[380] The use of this steroid could also complicate the treatment of the hypokalemia syndrome by increasing the renal losses of potassium. Based on current knowledge, use of isoflupredone acetate in the anorectic, acetonemic cow that has received dextrose, with or without insulin, should be restricted to one administration at the labeled dosage. Hypokalemia syndrome has also been reported with dexamethasone administration, although it is a less potent mineralocorticoid.[372]

In noniatrogenic cases the relationship between protracted disease and severe hypokalemia may be explained by a decrease in potassium intake (anorexia) with increased release of catecholamines caused by stress (see Fig. 41-21). Alternatively, renal potassium adaptation[381] may be responsible for the potassium loss. Animals chronically fed a high-potassium diet are able to survive the high potassium load due to increased renal losses. These increased losses persist when potassium intake is suddenly reduced. Renal adaptation (reduction of urinary potassium excretion) takes 24 to 48 hours to occur, thus creating a potassium depletion.[381] Because of a forage-based diet, lactating dairy cows may eat more than 10 times their daily potassium requirement, causing high urinary potassium excretion.[371] Therefore these cows appear to be at risk for potassium depletion because of delayed renal adaptation when potassium intake is abruptly reduced. This model cannot explain why some cows develop the syndrome when exposed to these conditions but others do not.

Other factors known to promote significant hypokalemia have not been documented in cows with hypokalemia syndrome, such as anomaly of the aldosterone system, diuretic (particularly furosemide) abuse, nephropathy (proximal or distal tubular renal acidosis), or severe diarrhea. Diarrhea with protracted reduced potassium intake, increased losses, and internal potassium imbalance resulting from acidosis has been associated with hypokalemia syndrome in calves.[371] Error in fluid administration causing increased urinary losses of potassium along with return to a normal internal potassium balance can further exacerbate hypokalemia in diarrheic calves.

41.1.7.7.5

Pathophysiology

Potassium is the most important intracellular cation.[382] The gradient between the potassium concentrations of the intracellular and extracellular compartments is the determinant of the resting cellular membrane potential and plays a role in the formation and transmission of action potentials.[383] Therefore, clinical signs reported in cattle and other species with severe hypokalemia are multisystemic. Moreover, structural consequences in the myocardium[373] and the muscle cells have been reported in cattle.[370,371]

Dysrhythmia and electrocardiographic changes were present in 50% of cases in one study.[371] The arrhythmogenic electrical activity changes implicated in hypokalemia include the following: hyperpolarization of the cardiac cell resulting in spontaneous automatic activity, slow conduction caused by increased difference between resting membrane potential and threshold potential, increased action

potential duration as a result of slow repolarization, depressed fast responses because of higher membrane potential when a slow repolarizing cell is stimulated, slow responses in fibers normally exhibiting fast responses, and conduction block.[384] These electrical events alone or in combination with structural changes such as necrosis can induce the atrial and ventricular arrhythmia observed.

Pathophysiology of cardiac and muscle necrosis caused by potassium depletion includes (1) ischemia caused by lack of vasodilatation during muscle cell contraction, resulting from absence of potassium release into the extracellular space, and (2) glycogen deficiency resulting from impaired glycogen synthesis.[376,385] Muscle lesions compatible with hypokalemic myopathy have not been consistently documented.[370–372] It is presently not known if the presence of hypokalemic myopathy is necessary to the occurrence of the clinical signs observed in the bovine syndrome or if it is a prognostic determinant.[370,371]

41.1.7.7.6

Diagnosis and Ancillary Test Results

Initial presentation of hypokalemia syndrome (intestinal ileus, abnormal gait) could mimic an intestinal syndrome. History may allow distinction between these conditions. Hypokalemic syndrome often follows or is concomitant with a long disease, in contrast with the usual acute evolution of an intestinal syndrome. According to the results of a small experimental study,[380] potassium fractional urinary excretion (FE_K) could be a useful tool in the medical management of a cow suspected to be developing bovine hypokalemia syndrome. In this study, FE_K was abnormally high in the presence of severe hypokalemia 12 to 24 hours before manifestation of clinical signs.

According to our experience the clinical signs of a twisted, S-shaped neck associated with flaccid paralysis as described earlier are almost pathognomonic. Other conditions that could be included in the differential diagnosis are hypocalcemia, botulism, tick paralysis, and myelopathy (cervical spinal trauma, cervical osteomyelitis). Conditions like listeriosis, vertebral malformations, luxations, fractures, and torticollis can be associated with abnormal neck position but not flaccid paralysis and absence of pain during manipulations. Hypokalemia syndrome, even if rare, should be included in the differential diagnosis of hypocalcemia, particularly when response to calcium administration is not normal.

Confirmation of the clinical diagnosis requires serum biochemical analysis. To date, all published cases of bovine hypokalemia syndrome have been associated with serum K^+ concentrations less than 2.5 mmol/L. Aside from hypokalemia, moderately elevated AST and creatine kinase (CK) activity (median value of 171 and 1564 IU/L respectively[371]), severe metabolic hypochloremic alkalosis (median value [TCO_2] = 41.5 mmol/L, [Cl^-] = 86.9 mmol/L[371]), and mild hyperglycemia (median [glucose] = 6.05 mmol/L[371]) are observed in the majority of published cases.

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Lumbar muscle biopsy (between L2 and L5) is a way to differentiate primary hypokalemic myopathy from secondary myopathy caused by decubitus. Determination of the serum creatine kinase MB isoenzyme (CK-MB) activity could help to detect myocardium damages. Detection of myopathy in epaxial muscles and/or myocardium at necropsy is not diagnostic if potassium depletion or hypokalemia is not documented.

Some authors have suggested that electrocardiographic changes could be used to detect a potassium-depleted status, irrespective of the serum potassium concentration.[386] A method of determining both the internal and external potassium balances simultaneously in dairy cows has been presented.[378] In this study,

ingested potassium, milk potassium concentration (LK), and FE_K defined the potassium external balance. Serum potassium concentration (SK) and red blood cell potassium concentration (CIEK) defined the potassium internal balance. Significant variations were detected throughout the day for CIEK, LK, and FE_K.[378] Therefore, in order to monitor potassium balances over time, samples should be collected at the same time each day.

41.1.7.7.7

Treatment

Nursing care is of primary importance to prevent complications such as mastitis or myopathy caused by prolonged decubitus; to maintain alimentation by providing food and water near the mouth; and to provide favorable conditions for the cow to get up. The animal should be kept on clean and atraumatic bedding such as pasture, sand, or accumulated litter. It must be regularly milked and turned from one side to the other at least every 8 hours. Use of a flotation tank (Aquacow Rise System) is of great value once the serum potassium concentration has returned to normal range.

All other identified problems must be addressed, including dehydration, acetonemia, and infectious disease. Treatments for arrhythmias, other than potassium, were not given in the reported cases.

Specific treatment is mainly per os potassium chloride supplementation. Based on the published data and our experience, we recommend a total (per os and intravenous) KCl dose per day of 50 g/100 kg of body weight of cow. Intravenous administration should be reserved for dehydrated cows, as overhydration may worsen hypokalemia by increasing potassium renal losses. When potassium chloride is given IV, the rate should not exceed 0.5 mEq of K^+/kg/hour, to avoid high risk of cardiac toxicity. Serum potassium should be monitored twice daily to allow adjustment of the treatment regimen. Potassium supplementation is needed for an average of 5 days.[371]

The abnormal neck position can be the first and last clinical sign in the evolution of the hypokalemia syndrome. Other clinical signs usually disappear on average in 3 days, the same day potassium concentration typically returns to normal. Some degree of paresis may persist for 2 to 3 days after return to normokalemia. We recommend continued potassium supplementation for 1 or 2 days after the return to normal clinical state and appetite. Increased renal potassium losses are promoted by the high quantity of potassium given during the treatment. In our experience it is important to decrease potassium supplementation slowly to avoid potassium depletion caused by delayed renal adaptation to the lower potassium diet. For example, 25 g of KCl per 100 kg of cow may be given the day after return to normokalemia, then 12.5 g of KCl per 100 kg of cow for 2 more days.

Because potassium depletion is a primary cause of myopathy, it is important *not* to try to raise the cow before hypokalemia has resolved. This emphasizes the importance of good nursing care and regular decubitus side changes. Once serum potassium concentration reaches the normal range, a water flotation tank is the best system to manage the recumbency.

41.1.7.7.8

Prognosis

The survival rate was very different in the two series of cases reported: 2 of 8[370] versus 11 of 14.[371] The prognosis may be affected by the age, concomitant disease, initial potassium depletion degree, presence and severity of hypokalemic myopathy, or treatments received.[369] The quality of the supportive care is probably a major determinant of the outcome, as for any downer cow. In the field, because of time and

energy needed from the owner, our experience warrants a guarded prognosis. The availability of a flotation tank appears a significant positive prognostic factor.[371,372]

41.1.8 BOVINE SOMATOTROPIN

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AURORA VILLARROEL

Somatotropin, also known as *growth hormone* (GH), is a peptide hormone produced in the anterior pituitary gland of all animals and is an important endocrine factor for normal growth of all tissues[387] and lactation in mammals. It is released under the influence of GH-releasing factor and inhibited by somatostatin. High-producing dairy cattle have naturally elevated circulating levels of endogenous somatotropin.[388,389] The lactogenic effect of somatotropin was first discovered in 1928 after rabbits were injected with crude extracts of anterior pituitary glands,[390] and its effect in lactating dairy cows was first reported in 1937.[391] Since the 1980s, recombinant DNA manipulations allowed large-scale production of purified somatotropin.[392,393] Because the use of several synonyms of somatotropin throughout the literature can be confusing, this chapter will use *GH* to refer to natural somatotropin and *rBST* to refer to recombinant BST. It has been shown that rBST has biologic activity similar to that of bovine GH.[394] Four variants of bovine GH have been reported, according to whether it has 190 or 191 amino acids (additional phenylalanine in *N*-terminal) and either valine or leucine in position 127.[395,396] The genetic determination of the amino acid present in position 127 seems to be breed-specific. Homozygosity for leucine is more frequent in larger breeds such as Holstein and Brown Swiss (85% and 100%, respectively) compared with smaller breeds such as Jersey and Ayrshire (31% and 59%, respectively).[396] This variation may account for differences in milk production.

Four recombinant analogues have been developed[397,398] and differ in 0 to 9 amino acids from GH. Methionyl-rBST (leucine variant with 190 amino acids)[399] was approved for use in lactating dairy cows in the United States in November 1993[400] and is available for commercial use in more than 20 countries, including Mexico, Brazil, South Africa, South Korea, and Russia. The release of rBST for commercial use provides new opportunities and challenges for the dairy herd manager, veterinarian, and nutritionist.

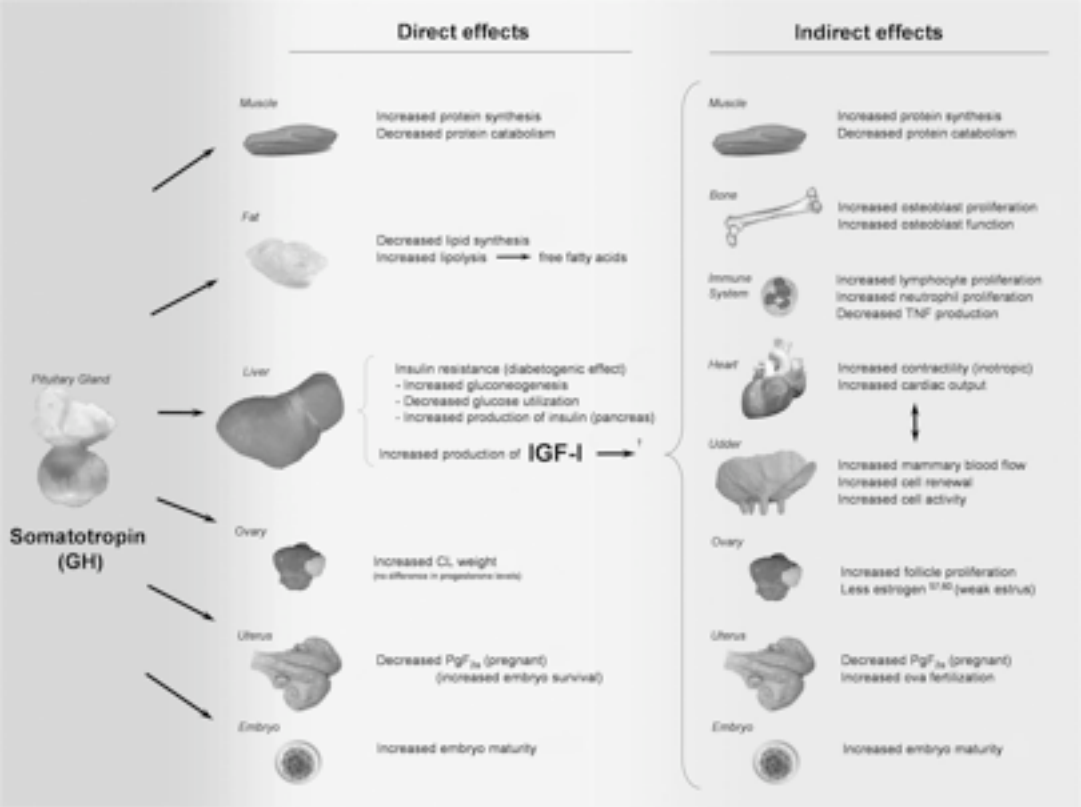
41.1.8.1 PHYSIOLOGY OF GROWTH HORMONE

Physiologic concentrations of GH in blood are secreted in a pulsatile pattern and vary throughout the day, being lowest after midnight and highest during the day (diurnal variation) both in humans and in dairy cattle. [387,401] Baseline levels and frequency and intensity of the secretory pulses of GH are highest during the first week of age and then decrease with age.[389,402,403] Apparently, GH levels in neonates are not influenced by colostrum intake, as evidenced by a study in which calves that received their first colostrum 24 hours after birth did not differ in serum GH levels from calves that received their first colostrum feeding at 2 hours, 6 hours, or 12 hours after birth.[404] Physiologic GH levels are heavily influenced by gonadotropin hormones; intact bulls had higher baseline levels and higher frequency and intensity of pulses of GH as compared with steers, which in turn had higher levels and pulses than heifers (intact or ovariectomized).[405] In lactating cows, GH levels are highest during the postpartum period and gradually decrease as the lactation advances

and milk production decreases.[388,406–408] Blood concentrations of GH are naturally higher in high-production cows as compared with low-production cows,[389,408,409] even during the dry period.[388,406]

GH must bind to GH receptors located in specific tissues to exert its direct effects, one of which is the local secretion of somatomedins throughout many organs.[387,402,410] Of the four somatomedins identified to date, the type I insulin-like growth factor (IGF-I) is the most important.[387] IGF-I is found in serum attached to IGF binding proteins. It exerts its action when bound to IGF receptors on target tissues. The complete somatotropic axis consists of GH, GH receptors, IGF-I, IGF-I receptors, and IGF-I binding proteins. Fig. 41-22 depicts the target organs for GH action via direct effects of GH and indirect effects of IGF-I.

Fig. 41-22 Summary of direct and indirect effects of somatotropin in cattle.†IGF-I is produced in the liver and locally in many tissues throughout the body.



Overall, GH promotes increased cell size and mitosis in almost all tissues of the body that are capable of growing (directly or indirectly through the action IGF-I) and a shift in metabolism to use fat for energy in preference to carbohydrate and proteins, which are spared.[387,402] The immediate result of the increased use of fat as energy source for the body is a measurable rise in NEFA concentrations in blood.[387,402,410] Another direct effect of GH on the liver is to increase glucose synthesis.[387,402] GH stimulates the pancreas to secrete increased amounts of insulin, although a simultaneous IR is induced that results in a diabetogenic effect.[387] It

has been shown in humans and rats that an increase in serum FFAs impairs the action of insulin on tissue glucose use.[411,412] The effects of GH on liver, pancreas, and adipose tissue are direct because of the presence of multiple GH receptors in these tissues.

Muscle is affected directly by GH and indirectly by IGF-I. Both GH and IGF-I act on muscle cells to increase protein synthesis and decrease protein catabolism.[387,402] The net effects of the changes in muscle and fat metabolism are to increase lean body mass.[387,402] When rBST is administered to growing cattle, it has an anabolic effect [402,413–415] similar to that of steroid hormones[415] that seems to be a result of increased feed intake rather than an increased efficiency of feed conversion.[403] GH also has an effect on bone growth through the action of IGF-I, which increases osteoblast proliferation and function.[387,402] IGF-I also mediates an enhanced response to induced infection and endotoxemia through lymphocyte blastogenesis,[416] neutrophil proliferation,[417,418] and decreased levels of TNF.[419,420]

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The most obvious outward manifestation of rBST administration in the lactating cow is an increase in milk production.[391,421,423] Other manifestations include changes in body composition, both positive and negative effects on reproduction, and proliferation of immune cells. These changes are achieved through an "orchestrated control" of the metabolic functions (homeorrhesis) to support the new physiologic state of higher milk production. Table 41-10 shows the short-term and long-term effects (after homeorrhesis) of rBST administration in lactating dairy cows. The use of rBST in lactating cows increases milk production through its effect on nutrient partitioning,[410] increased rate of cell renewal in the mammary gland,[424] and support of mammary cell function.[425] Although receptors for GH in the mammary gland were recently discovered,[426,427] bovine GH does not appear to have a direct galactopoietic effect on mammary tissue.[428,429] The galactopoietic effect of rBST has been reported to be indirect, through the action of IGF-I.[430,431] IGF-I is associated with increased mammary blood flow and enhanced mammary extraction of substrates.[430,432] The heart plays a major role in nutrient partitioning by increasing contractility and output, which increases blood flow to the mammary gland.[430,433,434] These actions are responsible for a higher persistency of milk production in rBST-treated cows (Fig. 41-23). The ultimate effect is the increased use of fat as an energy source to spare glucose and acetate for mammary gland lactogenesis.[430] This avoids excessive weight gain during late lactation as measured by BCS[422,435] but can also can result in weight loss when dietary energy is restricted.[436–438] The use of rBST does not cause significant changes in blood mineral levels.[431,439]

Table 41-10 Short-Term and Long-Term Effects of the Use of Subcutaneous Injections of 500 mg of rBST Every 14 Days in Lactating Dairy Cows

Target	Short-Term Effects	Long-Term Effects
Milk production	Increased, with peak on day 7–11 with a gradual decrease to baseline levels around day 14	Increased, following a typical downward trend in production as DIM increase, although with higher persistency than in untreated cows; no effect on production during the next lactation
Feed intake	No change	Increased, starting 4–10 weeks after the initial treatment to provide energy for the increased milk production
Energy balance	Decreased because of increased milk production and unchanged feed intake	Normal, as feed intake accommodates to higher milk production
Milk composition	Initial increase in fat % and decrease in protein, reflecting initial negative energy balance	Normal or slightly increased protein percentage
Reproduction	Positive influence because of increase in IGF-I levels in blood.	Negative influence of higher milk production and higher clearance rate of steroid hormones because of higher liver blood flow
Metabolism	Changes that reflect the state of initial negative energy balance: increased plasma levels of NEFA, insulin and glucose	After feed intake increases to adapt to the increased milk production, metabolic indices return to normal; lower NEFA and BHB plasma levels in the next lactation
Body condition	Decrease in fat content and therefore in body weight, especially if the negative energy balance is severe	Maintenance of healthier body condition (leaner body) during late lactation than in untreated cows
Health		
Mastitis	Improved response to infection due to a proliferation of immune cells	Tendency to increase the crude incidence of lameness, although it can be attributed to the higher risk normal for higher production; incidence by pounds of milk produced is decreased
Lameness	No change	Tendency to increase the crude incidence of mastitis, although it can be attributed to the higher risk normal for higher production
Ketosis	No change	Decreased incidence of ketosis in the postpartum period that follows the lactation in which cows were treated; attributed to a leaner body composition

BHB, β-hydroxybutyric acid; *DIM,*days in milk; *IGF-I,* insulin-like growth factor; *NEFA,* nonesterified fatty acid.

Other effects of rBST in cows include direct and indirect effects on reproductive organs. GH receptors (direct effect) are found mostly in the ovary, primarily on the corpus luteum (CL), with nearly undetectable levels on follicles.[440,441] Cows treated with rBST had heavier CLs [442] but no difference in blood progesterone levels.[442–444] Other tissues with high expression of GH receptors, although not as abundant as in the CL, included (in decreasing order) myometrium, endometrium, and oviduct.[440] In vitro exposure of endometrial cells to rBST attenuated the production of phorbol ester—induced prostaglandin (PG) $F_{2\alpha}$; on the other hand, IGF-I increased its production.[445] Receptors for IGF-I in the reproductive organs were expressed primarily in the myometrium and less in the endometrium, ovary, and oviduct.[440] Although follicles did not show high expression of GH or IGF-I receptors, treatment with rBST increased follicle proliferation and recruitment.[443,444] The dominant follicles were larger but contained lower levels of estrogen.[443,446] Pregnant cows had higher expression of IGF-I receptors throughout the reproductive tract compared with nonpregnant cows, especially in the myometrium.[440] The embryo has receptors for both GH and IGF-I, and both peptides increase the rate of embryo maturation.[447–449] GH is additive to IFN-tau (produced by the embryo) in its effect of attenuating uterine production of $PGF_{2\alpha}$.[445] Therefore somatotropin may be an important factor for maternal recognition of pregnancy.

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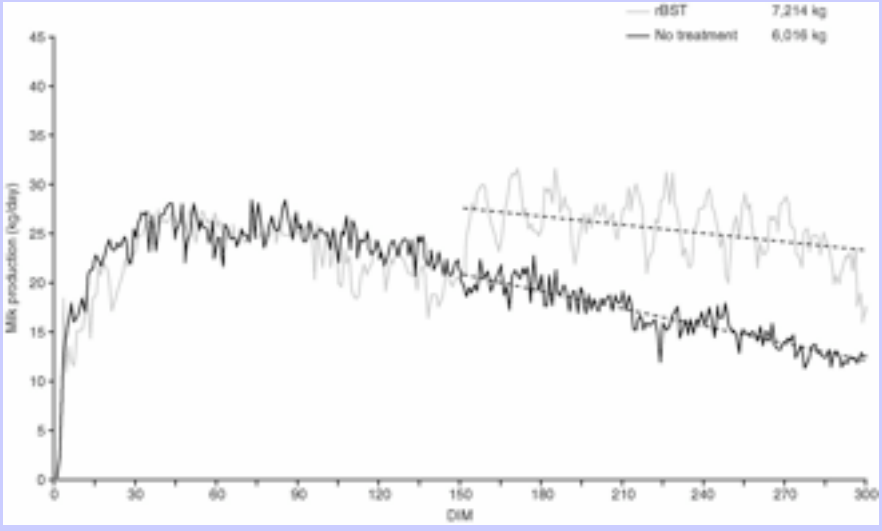
Fig. 41-23 Comparison of lactation curves of two first-lactation cows, one treated with rBST and one untreated, showing the cyclic response to rBST injection every 14 days and the improved persistency of milk production. The dips in the treated cow correspond to the administration of a new injection of rBST (every 14 days). Dashed lines represent average daily milk production. Note the variable response to different injections. From Lane VM, Villarroel A, unpublished data.



Half-life for important lactopoietic hormones is as follows[387]:

- Somatostatin: 3 minutes
- Insulin: 6 minutes
- GH: 20 minutes
- IGF-I: 20 hours

41.1.8.2

IMPACT OF SOMATOTROPIN ON MILK PRODUCTION

Many studies have reported a consistent effect of increased milk production after short- and long-term administration of rBST. Most trials are not directly comparable to one another because of the use of different somatotropin analogues, dosages, lengths of study, and intervals between doses used in the studies. These experimental trials have been conducted under differing feed conditions and show similar responses in milk production to treatment with rBST in pasture-based dairy cows,[450,451] stalled cows,[452,453] and cows fed a total mixed ration (TMR).[392,454] Studies show a wide range of increase in milk production (8% to 61%) over the baseline production before rBST administration. This range reflects individual cow variation in the response to rBST, and it has been recognized since the first trial in 1937 (pituitary extract) that some cows do not respond at all.[391,455] In general, larger responses were observed at higher doses of rBST,[436,437,456] although the dose response could be characterized as a negative exponential relationship: milk response per milligram of rBST is diminished at higher doses. Larger responses have been observed when rBST was administered daily (up to 61%)[453,457–459] as compared with administration at 14-day intervals (up to 31%)[422,453,460,461] or 28-day intervals (up to 18%).[392,454] Most of these studies with large responses reported the short-term effects of rBST supplementation, whereas long-term trials reported milk increases ranging from 11% to 29%.[422,435,451,462] Consistently higher responses (both in kilograms and percentages) occur in adult cows as compared with first-lactation heifers.[421,422,463] Furthermore, the effect of rBST use on milk production varies according to production level before rBST administration and stage of lactation, in that lower-producing cows seem to respond better than higher-producing cows,[463–465] and late-lactation cows respond better than early-lactation cows,[422,463] both in kilograms and percentages. Although Holstein cows have a higher response to rBST treatment than Jersey cows[437,465] the effective response (return on rBST investment) may be higher in Jerseys because of their higher milk solids.

In February 1994 the rBST named *sometribove* (zinc-methionyl BST, Monsanto) was first commercialized in the United States for use at a dose of 500 mg to be given every 14 days beginning at 57 to 70 days in milk (DIM) and continuing until the end of lactation.[400] Since then, multiple studies have been reported that are now comparable because of the uniformity of product and application. Production responses were reported in 176 control herds and 164 herds using sometribove in the Northeast United States for a period of 4 years before approval and 4 years after approval.[423] In this study, cows from herds using rBST produced an average of 894 kg more milk, 27 kg more fat, and 31 kg more protein during a 305-day lactation compared with control herds. A metaanalysis of data from 28 studies using various analogs of rBST reported a production improvement of 11.3% in primiparous cows and 15.6% in multiparous cows, equivalent to 3.03 and 4.36 kg/day, respectively, over control cows.[421] In another study[422] the reported average response to sometribove in 15 U.S. herds was 4.9 kg/cow/day with a wide range among herds (2.9 to 7.6 kg/cow/day),

corresponding to production increases that ranged from 11% to 31%.[423,450,453,460,461] Some trials conducted over multiple lactations have reported a lower response of cows treated in a second lactation[436,466–469]; however, all these trials used daily administration of rBST. Studies conducted using the approved 14-day interval application showed that previous treatment with rBST did not diminish milk production in subsequent lactations,[423,470] even in a study conducted over four lactations.[471]

Lactation graphs of cows responding to rBST administered at 14-day intervals show a cyclic response to treatment,[422,460,472] in which milk production started increasing on day 1 after injection, peaked on day 7 to 11, and then decreased until the next dose (see Fig. 41-23). The use of rBST does not practically alter milk components,[460,470,472] although minor changes in milk fat and protein have been observed in association with shifts in energy balance.[422,471,472] Cows with higher somatic cell counts (SCCs) before treatment can be expected to have a diminished response to rBST compared with cows with lower SCCs.[422]

41.1.8.2.1

Factors Limiting Response to Recombinant Bovine Somatotropin

Nutrition is the most important factor that can limit milk production response to rBST. Although short-term treatment with rBST increases milk production without increasing dry matter intake (DMI),[457,462] long-term treatment (4 to 10 weeks) results in increased DMI to compensate for the increased production.[437,458,462] Current nutritional standards for high-producing cows[473] meet requirements for rBST-treated cows, assuming emphasis is given to consistency of the ration and feed-bunk management. If ration inconsistency leads to indigestion and “off-feed” conditions, or if feed is periodically unavailable to the cow, DMI and therefore milk production will be reduced. These off-feed conditions may affect the response to rBST. McGuire and colleagues[474] found that after restriction of feed intake to lactating cows, plasma concentrations of IGF-I were markedly decreased, indicating that the stimulatory effects of rBST on lactation would not be observed in underfed cows. In this study, underfeeding of cows resulted in a marked decrease in milk production despite rBST treatment. Radcliff and co-workers[475] have shown that DMI partially controls expression of GH receptor mRNA and that cows on feed restriction had lower receptor activity for at least 1 week after ad libitum feed was restored.

Heat stress is another important factor affecting the response of milk production to rBST. Trials conducted under hot humid conditions[450,476,477] suggest that milk production response to rBST may be more variable than that obtained under temperate conditions and that responses to higher doses may be reduced. In one trial the use of rBST was associated with reduced DMI in cows exposed to heat stress[478]; this effect was not observed in other trials.[458,479] Collier and co-workers[480] reported that acclimation to heat stress is a two-step homeorrhetic process that occurs in an acute stage of changes in secretion rate of hormones and a chronic stage of receptor population adjustments in target tissues. The time frame of acclimation is weeks rather than days. Cows treated with rBST adapt to heat stress by increasing water intake, respired vapor, and skin vapor.[476–478] These adaptations require energy and divert cardiac output away from the udder. Several studies have shown that the milk response to rBST administration is lower (up to 55%) in cows exposed to high temperatures provided with shade as opposed to shade and an evaporative cooling system.[450,479] Several studies have shown that higher rectal temperatures may be experienced in rBST-treated cows under heat stress conditions.[450,458,465,477] Although milk production was increased, the response may likely have been depressed because of energy expense toward homeostatic thermoregulation. The lower responses to rBST observed in herds in hot climate conditions may be explained in part by the effect

of decreased DMI on IGF-I in plasma.[474] Dietary rations for heat stressed cows may need reformulation for higher nutrient density to offset the reduced DMI. No negative effects have been observed during rBST use under cold conditions.[481,482]

41.1.8.3

IMPACT OF SOMATOTROPIN ON REPRODUCTION

The aspect of rBST use most likely to result in involvement of the veterinarian is its effects on fertility. The positive effects of rBST on milk production can be accompanied by both positive and negative effects on reproduction. Although a study by De la Sota and colleagues[443] found that lactational status (lactating vs. nonlactating) had a greater effect on reproduction than the use of rBST, the following discussion is limited to the reproduction of lactating cows.

In general the negative effects of rBST on reproduction in lactating cows have been reported to be an increase in twinning rate and days open.[472,483,484] The increased twinning rate is likely due to better embryo survival, because ovulation rate does not appear to be increased in rBST-treated cows.[448,485] There is, however, reason to suspect an increased ovulation rate based on recent studies that reported that increased feed intake results in higher rates of steroid metabolism in the liver.[486,487] More rapid metabolism of estradiol can result in decreased negative feedback on follicle-stimulating hormone (FSH), allowing additional follicles to undergo changes necessary to proceed to ovulation.[487] The increase in days open could be attributable to a prolonged negative energy balance associated with the increased milk production. The magnitude of the increase in days open was estimated to be 5 days in a metaanalysis performed on data from 18 studies.[484] The relative risk of nonpregnancy in rBST-treated cows during the same period as control cows was 1.38 in a metaanalysis of nine studies.[484] One explanation for nonpregnancy can be that cows treated with rBST do not show outward signs of estrus with the same intensity as untreated cows,[444,488] and therefore accurate heat detection is hindered. Estrous detection rate decreased linearly with increasing dose of rBST[488] despite the finding that rBST treatment had no effect on incidence of cystic ovaries.[452,484,485,489]

A confounding factor in any evaluation of the effect of rBST on reproduction is the fact that rBST-treated cows maintain profitable milk production longer and therefore these cows can be rebred, if open, at longer DIM than untreated cows. The resultant pregnancies from these breedings late in lactation will increase the average days open for the herd. On the other hand, any additional pregnancies under rBST use as a result of longer breeding windows could be considered a positive effect of the use of rBST, because they would not be obtainable under the same management in untreated cows. The evidence that these two effects offset each other comes from a study that evaluated the effect of rBST use on culling in 32 herds, which showed no difference between culling rates (overall and culling because of reproductive factors) in herds that used rBST and control herds.[490] The potential negative effects of rBST on estrous behavior may favor the decision to use timed artificial insemination (TAI) programs, because TAI does not rely on estrous detection to breed the cow.

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Positive effects of rBST on reproduction have been elucidated in recent studies that showed first-service pregnancy rate is increased in rBST-treated cows.[491–493] This effect is not independent of the timing of the last rBST injection.[444,491] The first-service pregnancy rate was increased in cows receiving rBST between 1 and 3 days before the first gonadotropin-releasing hormone (GnRH) injection of the Ovsynch program. In another study, pregnancy rates were increased in lactating, multiparous cows when a single dose of rBST was administered at time of insemination.[493] Some studies have found increased conception rates in cows treated

with lower doses of rBST as compared with cows treated with higher doses.[488,494] Furthermore, rBST has shown a positive effect on embryo transfer (ET) programs, both in the donor and the recipient animals.[448,495] When rBST was given at the initiation of the superovulation regimen in donor animals, two more transferable embryos were obtained—a net increase of 28% to 37%. The increased recovery of transferable embryos can be attributed to a direct effect of rBST on the superovulated ovary and an indirect effect of IGF-I. The effect on recipient animals when the donor cow was not treated was to increase pregnancy rates by 68%,[448] explained by better embryo survival, because GH and IFN-tau have added effects in inhibiting uterine $PGF_{2\alpha}$ production.[445] The effect of rBST on the fetus has shown some inconsistencies. In one study, calves born to rBST-treated cows had a gestation length 2 days shorter and weighed 2 kg less compared with contemporary controls,[454] whereas in another study they weighted 3 kg more than controls.[472] The effect could be dependent on energy balance (similar to the effects on milk production). In summary, rBST initially has positive effects on reproduction, but within weeks the metabolic consequence of increased milk production has a negative impact on reproduction. In herds not using rBST for increased milk production, the use of low doses of rBST could be beneficial for individual cow conception rates.

41.1.8.4 IMPACT OF SOMATOTROPIN ON HEALTH

41.1.8.4.1 Mastitis

Several studies have reported that rBST use was associated with an increase in clinical cases of mastitis.[422,484,489,496,497] In these studies no attempt was made to differentiate between contagious and environmental mastitis cases or the effect that increased milk production has on mastitis incidence. Studies on well managed farms where contagious mastitis was being controlled reported no effect of rBST on clinical mastitis.[498,499] SCC levels in milk from rBST-treated cows are not significantly different from those in untreated cows.[422,423,460,484] If rBST supplementation is used in cows with high SCC levels, the response in milk production is lower than if rBST is used in cows with lower SCC levels.[422] The incidence of clinical mastitis in rBST-treated cows has been reported to be similar to the mastitis incidence consistent with the genetic improvement of milk yield per cow.[497,500] White and colleagues[497] suggested that mastitis should be evaluated as incidence per unit of milk produced. Cows of a given production stratum reportedly had similar mastitis incidence whether they were treated with rBST or not.[497] A metaanalysis of 11 studies found an increase in clinical mastitis cases of approximately 19.4% in the rBST-treated cows, without controlling for the increase in milk production (11% to 15.6%).[484] To further complicate interpretation of the effect of rBST, the incidence of mastitis in mid and late lactation (31 to 150 DIM and 151 to 365 DIM) depends on the incidence early in lactation (0 to 30 DIM).[501] Therefore if mastitis incidence is not measured before treatment with rBST (according to label after 57 to 70 DIM), mastitis incidence during the treatment period should be interpreted with caution. No differences in culling rates as a result of mastitis were observed in a comparison of herds that used rBST and control herds (total of 64 herds in three studies).[489–490,498] Several trials were designed to assess the effect of rBST on experimentally induced mastitis with environmental bacteria (*Streptococcus uberis*[418,502] and *Escherichia coli*[503]). Clinical signs of mastitis, milk composition changes, and bacteria counts in milk were all reduced in rBST-treated cows. Therefore overall production losses during induced mastitis episodes were lower in rBST-treated cows than in control cows, indicating a positive effect of rBST on the immune response.[416–418]

41.1.8.4.2

Lameness

Preapproval trials for rBST were designed as either dose titration studies or clinical trials of the effect on milk production; the trials did not capture in-depth health information. A metaanalysis[484] of 18 preapproval studies that collected data on disease incidence reported negative effects of rBST on lameness and culling of adult cows (second or greater lactation). This study reported a risk ratio (RR) of 1.55 for clinical lameness and 1.36 for culling of older cows treated with rBST compared with control cows. Ruegg and colleagues,[490] however, showed no differences in culling rates (overall or because of lameness) between herds that used rBST and control herds. Another study showed that the higher risk of lameness occurred in the lactation after treatment with rBST but not during treatment.[452] In this study, however, the higher risk of lameness was attributed to management (tie-stall housing), because no changes could be found on histopathology preparations.

41.1.8.4.3

Metabolic Diseases

The effect of rBST on fat mobilization is a decrease in body condition score,[436,437,469] which in turn results in lower NEFA and BHB plasma levels and a lower incidence of postparturient metabolic diseases such as ketosis and milk fever (hypocalcemia) in the subsequent lactation.[452,469] One study within the previously reported metaanalysis[484] showed a fourfold reduction in the incidence of metabolic diseases (RR = 0.25) owing to the carryover effect in the lactation after rBST treatment. Data on the incidence of other diseases commonly reported in dairy cattle were either insufficient or not collected in a consistent manner to allow objective evaluation.

41.1.8.4.4

Toxicity

Studies on the potential toxicity of high doses of rBST in dairy cattle,[457,470,504] even when administered for long periods (six times the approved dose over two consecutive lactations),[470] have shown no negative effects. The highest tested dose was 60 times the approved dose of rBST administered weekly for 4 weeks.[504] Apparent negative health effects were also not observed in the many experimental studies of rBST use.* Although cows treated with rBST tend to have lower hematocrit (packed cell volume) and hemoglobin values,[457,504,506] both remain within the normal range for dairy cattle. 1385

* References 436, 460, 472, 489, 504, 505. 1386

41.1.8.5

HUMAN AND FOOD SAFETY

The safety of milk and meat products from rBST-treated cows is based on three tiers of biologic protection:

1 Bovine GH has no activity in humans, even if injected.

2 GH and IGF-I have no oral activity and are inactivated in the gastrointestinal tract.

3 GH and IGF-I concentration in milk and meat are essentially unchanged with rBST use.

Bovine GH has been studied in depth as a potential source for therapeutic GH for hypophysectomized human patients.[507] Bovine and human GH differ in 69 of 191 amino acids in their sequences (approximately 36%).[395] The difference in their structure and the much lower binding affinity of bovine GH for human GH receptors (up to 3000 times)[508–510] renders bovine GH inactive in humans. Therefore contact with rBST should have no effect on people, even if injected.

The safety of consuming animal products (meat and milk) from cows treated with rBST has been extensively studied. Milk naturally contains GH and IGF-I; concentrations of both are highest during the first days of lactation[407,511–513] when milk cannot be marketed for human consumption (colostrum),[514] and decrease as lactation progresses. GH levels in milk were similar in cows treated with rBST and untreated cows and decreased by 85% to 90% when milk was heat-treated.[515] IGF-I concentration in cow milk has been reported in colostrum to be 233.8 ± 26.9 ng/mL, decreasing to 8.8 ± 1.5 ng/mL at 2 weeks postpartum.[516] Physiologic concentrations of IGF-I in cow milk vary widely according to parity and stage of lactation, ranging between 1.27 and 8.10 ng/mL in bulk tank samples.[398,511] Although treatment with rBST slightly elevates IGF-I concentration in milk,[398,519] levels remain within physiologic range. Therefore, it is not possible to determine whether cows have been treated with rBST based on measurement of IGF-I and GH in milk.[519,520] The only reliable method to determine whether cows have been treated with rBST is the measurement of GH levels in blood several times over the 14-day injection interval.[519,520]

Levels of IGF-I in milk tended to be higher after pasteurization than in raw milk (8.2 ± 0.35 ng/mL vs. 5.6 ± 0.56 ng/mL),[511] presumably because IGF-I is released from its binding proteins. Infant formulas, which require higher pasteurization temperatures, had almost undetectable levels of IGF-I (0.7 ng/mL).[511] Muscle of cows treated with rBST had levels of GH and IGF-I similar to those of untreated cows.[521] Like most ingested proteins, rBST and IGF-I are degraded by the digestive enzymes of the gastrointestinal tract, rendering them biologically inactive.[398,515,521,522] Therefore rBST has been shown to be safe and has been approved to be used with zero days withholding of meat and milk for human consumption.[400]

Table 41-11 Relative Magnitude of Increased Milk Production Obtained by the Use of Different Technologies in Dairy Cows*

Technology and Reference Category	Cost	Effect on Milk Production: Cow	Effect on Milk Production: Offspring	Effect on Milk Production: kg/year	Reference
AI vs. natural service	$ Semen · S/C · % female calves · (1 – mortality)†	—	✓	367–441 730	523524
ET vs. AI	$ Embryo · PR · % females · (1 – mortality)†	—	✓	‡372	525
3× milking vs. 2× milking	Labor + energy + milking hygiene products§	✓	✓	1,417 1,573	526527
Cooling in hot weather vs. not cooling	Installation + maintenance + increased feed intake	✓	✓	769	526
rBST vs. none	$ rBST + labor + increased feed intake + facilities (if not in place) + cost of TAI program (if not in place)	✓	✓	1,298 1,301	526527

AI, Artificial insemination; *ET,* embryo transfer; *PR,* pregnancy rate; *rBST,* recombinant bovine somatotropin; *S/C,* services/conception; *TAI,* timed artificial insemination.

* The reference category for each technology is provided. When comparing offspring, the reference category was the offspring of cows not exposed to the technology. Note that the effect on the cows is immediate, whereas the effect on the offspring will start approximately 3 years later (9 months of pregnancy plus 2 years until calving). The effect on offspring is restricted to female offspring that survive to freshening: less than 50% of all offspring.

† Mortality of female calves from birth until they calve (2 years of age).

‡ Estimated genetic gain.

§ Teat dips, towels, backflush products, and so on.

41.1.8.6

RECOMMENDATIONS FOR USE OF RECOMBINANT BOVINE SOMATOTROPIN

As described previously, there is overwhelming evidence that rBST has a strong galactopoietic effect and will increase average herd production when used according to label directions. When compared with other technologies developed over time to increase milk production in the dairy industry, the use of rBST and 3× milking are the two methods that can make an immediate and significant impact on herd milk production (Table 41-11). Genetic methods[523–525] of improving milk production do not affect the cow on which they are applied. They will improve milk production in the female offspring, once they are mature (less than 50% of all offspring). In contrast, methods such as cooling cows during hot weather,[526] milking cows 3 times per

day (3×) as opposed to twice per day (2×),[526,527] and using rBST improve milk production directly in the cows and their mature offspring. In fact, use of rBST can further increase milk production in herds that are already benefiting from higher production resulting from 3× milking.[526,527]

Responses to rBST are highly variable among herds; therefore individual dairymen need to determine whether the rBST response justifies the cost. Basic costs that need to be taken into account include the cost of the product plus additional labor and feed costs. Another expense to consider is the cost of implementing a TAI program (labor and drugs) to offset the negative effect of rBST on estrous expression and pregnancy rate, although TAI may have benefits independent of rBST use. Not all studies have found rBST to be significantly profitable.[528,529] The use of rBST has minimum facilities and management requirements such as a reliable restraint method (automatic headlocks, stanchions, or tie-stalls), visual identification of all cows (eartags or freeze brands), herd management computer software, and the ability to deliver a consistent, high-quality ration, preferably a TMR.

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The labeled use of rBST in the United States is 500 mg administered SC every 14 days starting at 57 to 70 DIM. Individual cow identification, restraint, and computerized records are important to ensure that cows are treated with rBST every 14 days. Because all cows will not show a significant improvement in milk production, individual responses may be monitored so that treatment can be limited to responsive cows. Herds that intend to profit from rBST must provide the husbandry needed to maximize DMI in the cows. Feed quality, palatability, and availability are major determinants of DMI, along with water availability, cow comfort, and heat abatement, and thus will influence success of rBST usage. Feed consistency can best be guaranteed by a large high-quality forage base so that minimal ration adjustments are necessary. When cows treated with rBST become sick, they should remain on rBST because of the enhanced response to infection and endotoxemia.[416–420] The sick cow diet should not significantly drop in energy, or the effect of rBST (through IGF-I) on milk production and immune function will likely be reduced. Because the response to rBST in cows is greater in late lactation than in early lactation, both in kilograms and in percentage improvement, delaying the start of rBST use until later in lactation could further benefit the cows, allowing additional pregnancies to occur without a large reduction in overall response in milk production.

Potential uses of rBST, other than blanket herd use for improved milk production, include treating repeat breeder cows for improved fertility, improving fertility in embryo transfer programs (in both donor and recipient cows),[448,495] helping fat cows achieve target BCS,[422,435] preventing ketosis in the subsequent postpartum period,[452,469] and reducing or delaying culling in cows that abort and in “do not breed” cows. Potential uses of rBST in the future (if approved) may include production enhancement of cows after lactation induction,[530] integration into programs with no dry periods,[407,531,532] and use on young stock to induce more rapid growth of lean body mass[475,533] and in nutrient management programs to reduce manure, urine, and methane production per pound of milk produced.[534]

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42 Chapter 42 Diseases of Muscles

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42.1 EXAMINATION OF THE MUSCULAR SYSTEM

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Clinical evaluation of the muscular system requires a systematic and routine method of examination. Often a veterinarian is asked to examine an animal with a history of a relatively nonspecific disease process that may be the result of muscular dysfunction. Animals with electrolyte imbalances, pleuritis, colic, chronic wasting diseases, poor performance, and a number of lameness problems may initially have signs similar to those seen with some forms of muscular dysfunction.

A thorough history of the animal or animals involved is an integral part of characterizing the muscle disorder, particularly because many disorders are intermittent in nature and triggered by certain environmental stimuli. A careful description of the animal's muscle tone, muscle mass, gait, degree of pain, exercise intolerance, and weakness while experiencing clinical signs should be obtained. In addition, the duration of illness, intermittency of clinical signs, factors precipitating clinical signs, exercise schedule, diet, current medications, vaccination history, and number of other animals affected and their familial relationships should all be recorded before the muscular system is examined.

42.2 PHYSICAL EXAMINATION

Initially the animal can be observed from all aspects at a distance while the horse is standing with forelimbs and hindlimbs exactly square. The examiner should observe the size, shape, and symmetry of all muscle groups and look for muscle fasciculations. This observation helps provide impressions about tropic changes, alterations in symmetry of particular muscle groups, and spontaneous muscle activity.

The animal can then be walked, trotted, or driven and evaluated for gait abnormalities. The symmetry of the gait and evidence of lameness, weakness, stiffness, and pain associated with movement can be noted. Gait abnormalities may result from pain, muscle weakness, muscle cramping, spasticity, decreased range of joint motion, dysfunction of motor neurons, and ataxia. A number of muscular diseases may result in one or many of these clinical manifestations. For example, horses with exertional rhabdomyolysis (ER) may be lame or stiff and demonstrate significant pain when encouraged to move. In contrast, horses with fibrotic myopathy may demonstrate a characteristic exaggerated gait abnormality with little evidence of pain.

After initial visual evaluation, muscles should be palpated. It is suggested that as many muscle groups as possible be palpated to obtain an overall impression of muscle tone, consistency, sensitivity, swelling, atrophy, and heat. Firm, deep palpation of the lumbar, gluteal, and semimembranosus and semitendinosus muscles may reveal pain, cramps, or fibrosis. Comparisons between muscle groups and areas of the animal can then be made to identify atrophy or swelling. Some animals are tense and demonstrate apparent evidence of myalgia when palpation is first performed. However, given time and patience, many of these animals relax, and muscles or muscle groups that at first examination appeared to be very sensitive or hypertonic may in reality be normal. By this stage it can often be determined whether individual muscles, muscle groups, a limb or limbs, or the whole body musculature is

involved. The symmetry or absence of symmetry of affected muscles or muscle groups is also important for potential evaluation of muscle disorders. Horses should stand perfectly square when bilateral muscle groups are compared.

Fine muscle tremors can be palpated and auscultated with a stethoscope. Concurrent signs of anxiety or pain should be noted and the animal reevaluated in calm surroundings if necessary. In animals with spontaneous muscle activity, muscle groups should also be percussed with a percussion hammer. The triceps, pectoral, gluteal, and semitendinosus muscles are often easily accessed for percussion. A positive percussion sign occurs when the soft tissue overlying the muscle becomes dimpled for several seconds (percussion myotonia) (Fig. 42-1). This occurs as the result of abnormal mechanical irritability and sustained contraction of the percussed fibers. Running a blunt instrument such as artery forceps, a needle cap, or a pen over the lumbar and gluteal muscles should elicit extension (swayback) followed by flexion (hogback) in healthy animals. Guarding against movement may reflect abnormalities in the pelvic or thoracolumbar muscles or pain associated with the thoracolumbar spine or sacroiliac joints.

If there is evidence of weakness, differentiation between myasthenia of muscular and neurologic origin is ideal. This requires a detailed neurologic examination. However, this can often be extremely difficult because a close junctional relationship exists between the nervous and muscular systems. In general, muscular weakness is not associated with ataxia unless it is extremely severe. Weakness is often manifested by muscle fasciculations, knuckling at the walk, frequent recumbency with difficulty rising, and shifting of weight because of an inability to fix the stifles.

If the primary abnormality identified is related to exertion, a lameness evaluation including flexion tests is often indicated as part of evaluation of the muscular system. Muscle pain may be secondary to changes in movement caused by lower limb lameness. The horse should be observed at a walk or trot for any gait abnormalities and in some cases longed for 15 minutes or ridden until clinical signs are elicited.

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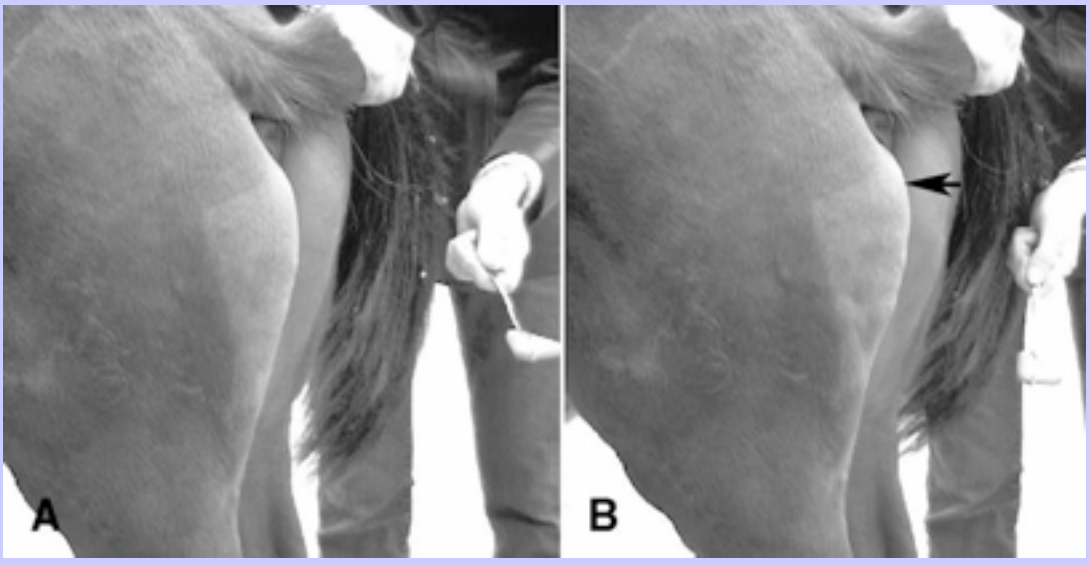
Fig. 42-1 Percussion of the semitendinosus muscle showing the muscle at rest **(A)** and an abnormal persistent firm contracture after the muscle has been tapped with a percussion hammer **(B)** in a horse with myotonia.



42.3 CLINICAL PATHOLOGY

42.3.1 Serum Enzyme Activities and Myoglobin Concentrations

Serum enzyme activities can be extremely useful in determining whether muscle cell necrosis is a predominant feature of a suspected muscle disease. Under normal conditions the serum activities of the enzymes used to assess muscle damage are low. However, leakage of the enzymes from myocytes into the bloodstream may occur if the cell membrane is disrupted through muscle cell necrosis or if the permeability of the cell membrane is increased. A number of other factors may influence the activities of enzymes within the circulation. These include rate of enzyme production, alternative sources of the enzyme, rate of enzyme excretion and degradation, and alterations to the pathways involved in enzyme removal or inactivation.[1]

Three enzymes are used routinely in the assessment of muscular diseases in large animals: creatine kinase (CK), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH). Carbonic anhydrase III and serum myoglobin have also been suggested as markers of equine muscle necrosis.[2,3]

Serum CK offers remarkable sensitivity as an indicator of myonecrosis. This enzyme is found predominantly in skeletal and heart muscle. It is intimately involved in energy production within the cell, is highly concentrated within the cytoplasm, and is readily liberated into the extracellular fluid when the muscle cell membrane is disrupted.[1,4]

Changes in CK can be used as an indicator of muscle dysfunction in relation to a variety of insults. Serum activity of this enzyme increases within hours in response to a muscle insult. Limited elevations in CK may accompany training, transport, and strenuous exercise. Elevations of CK to 400 or 500 IU/L may occur when training commences or in response to moderate exercise.[5] Extremely fatiguing exercise (e.g., endurance rides or the cross-country phase of a 3-day event) may result in CK levels being increased to more than 1000 IU/L but usually less than 8000 IU/L. These elevations usually are not reflective of an extensive myopathy, and serum levels of CK rapidly return to baseline (i.e., less than 250 IU/L in 24 to 48 hours). Recumbent animals also may have slightly elevated CK levels that are usually less than 3000 IU/L. In contrast, more substantial elevations (from several thousand to hundreds of thousands of international units per liter) in the activity of this enzyme may occur with rhabdomyolysis.[1,4]

Several different isoforms of CK exist. Electrophoretic migration in a field of direct current results in the separation of three bands: MM, MB, and BB. Skeletal muscle is rich in the MM isoform, cardiac muscle is rich in the MB isoform, and neural tissue contains the BB isoform. Rhabdomyolysis results in a proportionately greater increase in the MM isoform than the MB isoform.[6]

Serum AST, previously known as *serum glutamic-oxaloacetic transaminase* (SGOT), also has been used as an aid to diagnose muscular necrosis in large animals.[1,4] The enzyme has high activity in skeletal and cardiac muscle and also in liver, red blood cells (RBCs), and other tissues. Elevations in AST are not specific for myonecrosis, and increases can be the result of hemolysis or muscle, liver, or other organ damage. Alterations in AST activity are an integral component of many serum biochemical “profiles.”

AST activity rises more slowly in response to myonecrosis than does CK, often peaking 24 hours after the insult, and the half-life of AST is much longer than that of CK.[7] By comparing serial activities of CK and AST

in animals with suspected myopathy, information concerning the progression of myonecrosis may be derived. Elevations in CK and AST reflect relatively recent or active myonecrosis; if CK remains persistently elevated, myonecrosis is likely ongoing; and elevated AST activities accompanied by decreasing or normal CK activities indicate that myonecrosis is not continuing.[1,4]

Elevations in serum LDH activity occur because of damage to various organs within the body. LDH is composed of muscle (M) and heart (H) subunits. The enzyme is a tetramer made up of combinations of the M and H subunits, with five isoenzyme forms. Although the distribution of isoforms is genetically determined, electrophoretic separation suggests that the M_4 (LDH_5) and M_3H (LDH_4) isoforms are found predominantly in skeletal muscle. Elevations in LDH may be detected in horses with rhabdomyolysis, myocardial necrosis, and/or hepatic necrosis. Therefore in the presence of elevations of total LDH activity, electrophoretic separation of LDH into its isoenzyme forms may be necessary if definitive evidence of skeletal myonecrosis is to be obtained.[1]

Whenever possible, consideration should be given to providing optimum conditions for collection, handling, and storing of serum or plasma samples for subsequent determination of enzyme activities. CK is labile when stored at room temperature. Activity of CK in serum samples stored for 24 hours at room temperature falls to approximately 25% of activity at the time of collection. When kept at between 0° C and 4° C (32° F and 39° F), only 32% to 65% of the activity remains after 24 hours. In contrast, freezing of samples allows maintenance of CK activities for several days. However, after 8 days of frozen storage, activity falls to approximately 25% of the original value. Despite this apparent rapid decline in the serum activity of CK, CK determination from samples stored under less than ideal conditions may still reveal useful information.[1] This is particularly true in cases in which large elevations in CK activity occur in response to myonecrosis. In these animals, CK activity may rise to a peak value of hundreds of thousands of international units per liter. Even if CK activity does fall significantly in storage, it remains elevated within the sample for several days, potentially providing evidence of myonecrosis. The enzymes AST and LDH are much more stable under a variety of storage conditions, with less than 25% of the activities of both enzymes being lost over an 8-day period in samples stored at room temperature, 0° C to 4° C (32° F to 39° F), or frozen. Freezing samples for LDH isoenzyme determination alters the configuration of the isoforms, making interpretation of the results unreliable. However, total LDH activity remains unaffected.[1]

Therefore under ideal conditions samples for subsequent determination of CK, AST, and/or LDH should be collected into a glass (serum) or heparinized tube. The serum or plasma should be harvested as soon as possible, because anoxia and lysis of RBCs allows the liberation of AST and LDH. If possible, serum and plasma samples should be transported rapidly to the laboratory. Otherwise they should be kept chilled (4° C [39° F]) if analysis is to occur within 24 hours. When determination of CK activity is required and a delay of more than 12 hours is anticipated, freezing of the samples is desirable.[1]

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Elevations in plasma and serum myoglobin concentrations provide an indication of recent muscle damage. Myoglobin is a small protein that leaks into plasma immediately after muscle damage and is rapidly cleared in the urine by the kidney. It is particularly useful for determining exercise-associated muscle damage, because peak concentrations are reached shortly after exercise compared with 4 to 6 hours later for CK.[8,9] Unfortunately, few laboratories can routinely measure myoglobin. Normal concentrations in resting horses have been determined by nephelometry (range 0 to 9 µg/L),[3] with measured concentrations with rhabdomyolysis ranging from 10,000 to 800,000 µg/L.[10]

42.3.2 Urinalysis

Urine can be obtained free catch from horses placed in stalls with fresh bedding or via catheterization. The most accurate reflection of fractional excretion (FE) of electrolytes is obtained from samples obtained without tranquilization. Urinalysis is particularly important in horses with myoglobinuria, elevations in creatinine, or suspected electrolyte imbalances. Urine specific gravity, protein content, white blood cell (WBC) count, RBC count, and evaluation of cast formation should be performed to assess the potential for concurrent renal disease. A positive Hemastix test (orthotoluidine) result in the absence of hemolysis or RBCs in urine is highly suggestive of myoglobinuria. Further differentiation of myoglobin from hemoglobin is sometimes warranted, and where available electrophoresis, nephelometry, or spectroscopy may be used. Spectroscopy does not always reliably distinguish between myoglobin and hemoglobin.

Determination of electrolyte, mineral, and creatinine concentrations in urine and blood has been used to determine electrolyte balance in horses with muscle cramping or ER.[11] Problems often encountered however, are the large fluctuations in daily electrolyte excretion that occur in the same horse and among horses, the interference of high urinary potassium concentrations with measures of sodium concentrations when an ion-specific electrode is used, and the presence of calcium crystals in equine urine, which artifactually decrease the calcium and magnesium measured if urine samples are not acidified.[12] Renal fractional excretion (FE) can be calculated using the following formula:

$$FE_X = \frac{S_{Cr} \times U_X \times 100}{U_{Cr} \times S_X}$$

where *U* is urine, *S* is serum, *x* is measured electrolyte, and *Cr* is creatinine.

If urine calcium is to be determined, acidification of urine to dissolve all calcium oxalate crystals is recommended to provide exact calcium excretion. Determination of potassium, chloride, magnesium, and phosphorus concentrations can be performed using ion-specific electrodes or inductively coupled plasma atomic absorption.

Normal values for FE of electrolytes depend on a horse's diet. Normal values (%) for horses consuming grass, hay, and a sweet feed mix with available salt are FE_{Na} 0.04 to 0.08, FE_K 35 to 80, FE_{Cl} 0.4 to 1.2, FE_{Ca} 5.3 to 14.5, FE_P 0.05 to 4.1, and FE_{Mg} 14.2 to 21.4.[12,13]

42.3.3 Exercise Testing

Evaluation of muscle disorders that are precipitated by exercise may require an exercise challenge test. An exercise test should not be used in horses with overt signs of rhabdomyolysis but rather to determine if horses not currently showing clinical signs are prone to ER. The goal is to induce subclinical elevations in serum CK activity. Abnormal increases in CK are more likely to occur if slow trotting is performed rather than strenuous exercise.[9] Often 15 minutes of exercise at a walk and trot in unfit horses or at a constant slow trot in fit horses will elucidate subclinical elevations on CK. If signs of stiffness develop before this, exercise should be concluded. CK activities in blood samples taken immediately after exercise do not reflect the amount of exercise-induced muscle damage. For best results, blood samples for CK activity should be taken before and 4 to 6 hours after exercise. In healthy horses, 15 to 30 minutes of light exercise rarely causes more than a threefold increase in CK activity.[14,15] Elevations greater than fivefold are indicative of ER. Standardized

treadmill exercise testing can also be used to evaluate muscle responses and measure metabolic responses to exercise.

42.3.4 Electromyography

Electrodiagnostic studies detect spontaneous or evoked potentials of neurogenic or myogenic origin using electrodes positioned in the muscle. Electromyography (EMG) is particularly useful to evaluate large animals with altered muscle tone. EMG of normal skeletal muscle shows a brief burst of electrical activity when the needle is inserted (insertional activity) in muscle and then quiescence, unless motor units are recruited (motor unit action potentials) or the needle is very close to a motor end plate (miniature end plate potentials). Normal muscle shows little spontaneous electrical activity unless the muscles contract or the horse moves. Horses with abnormalities in the electrical conduction system of muscle, or denervation of motor units, show abnormal spontaneous electrical activity in the form of fibrillation potentials, positive sharp waves, myotonic discharges, or complex repetitive discharges.[16–19] Fibrillation potentials and positive sharp waves represent spontaneous firing of muscle fibers. Myotonic discharges are bursts of complex high-frequency potentials, whereas complex repetitive discharges are similar but have fixed amplitude and frequency. They both represent simultaneous firing of groups of muscle fibers. Motor unit action potentials can be evaluated to assess their amplitude, duration, phase, and number of phases. Myopathic changes include a decrease in duration and amplitude of motor unit action potentials.[17,19] More information about the motor unit could be provided by nerve conduction velocities (NCVs); however, the inaccessibility of motor nerves makes measurement difficult in large animals. Both EMG and NCVs are used to classify the primary disease as neuropathic or myopathic, to determine the distribution of the disease, and to provide insight into the pathophysiologic mechanisms of the disease.[16,20] Equipment costs are relatively high, and expertise is required in operation and interpretation of results. Readers are advised to consult Chapter 35 before considering the use of EMG.

42.3.5 Nuclear Scintigraphy

Nuclear scintigraphy is useful for identification of some forms of muscle damage, particularly an area of deep muscle damage that was not suspected based on clinical examination.[21] Technetium-99 m methylene diphosphonate (MDP) is taken up in some damaged muscle in the horse and is best seen in bone phase images (e.g., 3 hours after injection). Scintigraphy has been used in horses with a history of poor performance, with or without stiffness after exercise, to confirm a diagnosis of equine rhabdomyolysis.[22] The mechanism of MDP binding is unknown, but the release of large amounts of calcium from damaged muscle or the exposure of calcium binding sites on protein macromolecules in the damaged muscle may be responsible. Scintigraphy may be helpful in some cases involving focal damage to either proximal forelimb or hindlimb muscles.[21]

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42.3.6 Ultrasonography

Diagnostic ultrasonography is potentially very useful for identification of muscle trauma, crepitus, fibrosis, and atrophy. Muscles have a rather typical striated echogenic pattern, but this varies according to the muscle group, and careful comparisons must be made between similar sites in contralateral limbs, in both transverse and longitudinal images.[21] The appearance of muscle is also sensitive to the way the animal is standing and whether the muscle is under tension, so it is important that the animal be standing squarely and bearing weight evenly. Muscle fascia appears as well-defined relatively echodense bands.[21] Care must be taken in identifying large vessels and artifacts created by them.

In an acute injury, muscle fiber disruption is seen as relatively hypoechoic areas within muscle, with loss of the normal muscle fiber striation. The jagged edge of the margin of the torn muscle may be increased in echogenicity.[21] Tears in the muscle fascia may be identified. The defect in muscle may be filled by loculated hematoma that is hypoechoic. As the muscle repairs, it becomes progressively more echogenic. Relatively hyperechoic regions may be a result of increased connective tissue or loss of muscle cell mass. Hyperechoic shadowing artifacts usually represent mineralization or gas pockets.[21]

42.3.7 Muscle Biopsy

Examination of muscle fibers, neuromuscular junctions, nerve branches, connective tissue, and blood vessels within a biopsy sample can provide additional information necessary to fully characterize a neuromuscular disorder.[23–25] Routine light and electron microscopic examinations, combined with histochemical evaluations, may provide insights into the particular manifestations of neuromuscular diseases and their rate of progression. A number of basic pathologic responses of muscle can be identified in paraffin-fixed sections. These include inflammatory infiltrates, muscle fiber necrosis, muscle fiber regeneration, increased number of central nuclei, variations in muscle fiber sizes and fiber shapes, vacuolar change, and proliferation of connective tissue. However, many pathologic alterations cannot be detected in formalin-fixed tissue but can readily be seen in histochemical stains of fresh-frozen biopsy samples.[23–25] These include muscle fiber types and their pattern of distribution, differentiation of neurogenic atrophy from disuse atrophy or a primary myopathy, characterization of vacuolar storage material, characterization of inclusion bodies, assessment of mitochondrial density, and additional clues that may allow identification of a specific disorder or category of muscle disorders. Furthermore, formalin fixation results in artifactual cracking, fiber shrinkage, and leakage of substrates such as glycogen, which can affect proper interpretation of muscle pathology.

When collection of muscle biopsies is under consideration, some general guidelines apply. Preferably samples should be collected from what is considered abnormal or diseased muscle. A 6-mm outer diameter* percutaneous needle biopsy technique can be used to obtain small muscle samples through a ¼-inch skin incision using a local anesthetic subcutaneously. If this technique is used, enough muscle should be obtained to form a ½-inch square sample at a minimum. These samples do not, however, tolerate shipment to an outside laboratory. The optimum biopsy sample for shipment of histopathology tissues to a laboratory is collected using surgical or open techniques, performed under local anesthesia. Care must be exercised to infiltrate only the subcutaneous tissues, not the muscle, with the anesthetic agent. The objective is to obtain approximately a ½-inch cube of tissue; hence a suitably long skin incision is required. Two parallel incisions ½ inch apart should be made longitudinal to the muscle fibers with a scalpel. The muscle should be handled only in one corner, using forceps, and crushing should be avoided. The muscle sample is then excised by cross-secting incisions ½ inch apart, and the tissue is fixed appropriately. Routine histopathology samples can be placed in formalin; fresh samples can be placed in a watertight hard container after being wrapped in gauze moistened with saline, and shipped chilled to laboratories for freezing. On arrival at specialized laboratories, fresh samples for histochemical analysis are fixed in isopentane (methylbutane) chilled in liquid nitrogen to ensure rapid freezing and minimization of freeze artifact. Samples that potentially may be used for biochemical analysis should be immediately frozen in liquid nitrogen. Other routine histopathologic techniques may also be of diagnostic value. A special fixative may be required if such practices are to be undertaken. Samples for electron microscopy (EM) require appropriate fixation in glutaraldehyde preparations. Ideally, thin sections of muscle for EM should be clamped in vivo to maintain fibers at a resting length before they are excised. However, if pathology other than the alignment of thick and thin myofilaments is to be investigated, small muscle pieces can be excised and placed directly in appropriate EM fixative.

Responses of strips of fresh muscle to stimuli such as caffeine, halothane, and a variety of other agents can also be ascertained by specialized laboratories, but these are not routine diagnostic procedures.[26–28]

* Jørgen Kruuse, Marslev, Denmark.

42.4 CLASSIFICATION OF MUSCLE DISORDERS

STEPHANIE J. VALBERG

A muscle disorder is usually suspected in large animals because of (1) increased, decreased, or abnormal muscle contractions, (2) focal or generalized muscle necrosis (rhabdomyolysis), (3) muscle atrophy, or (4) exercise intolerance not associated with respiratory, cardiovascular, or skeletal causes.

42.4.1 ALTERED MUSCLE TONE

Increased muscle tone may be neural in origin. For example, tetanus and strychnine poisoning increase muscle tone as a result of suppressed inhibition of upper motor neurons by interneurons. Increased motor neuron firing also occurs during seizures, with electrolyte imbalances, and with equine ear tick infestation. Visual, tactile, or auditory stimuli often precipitate painful sustained motor unit activity. Other probable neural disorders that intermittently increase muscle tone include periodic spasticity and spastic paresis in cattle, stiff horse syndrome, and shivers in draft and warmblood horses.

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Increased muscle tone can also result from myopathic disorders. Persistently enhanced muscle tone may occur because of muscle contractures, which are characterized by fixation of myofilaments in a persistently shortened position without neural input.[29] Contractures are usually extremely painful and associated with rhabdomyolysis. Contractures occur with malignant hyperthermia (MH) and some forms of exertional myopathy. Intermittent, abnormal muscle contractions without rhabdomyolysis occur when sarcolemmal ion channels within the muscle cell membrane are dysfunctional.[30,31] Caprine myotonia congenita and equine hyperkalemic periodic paralysis (HYPP) are examples of diseases caused by sarcolemmal ion channel dysfunction.

Moderate weakness in horses may be caused by central spinal cord disorders. More profound weakness may arise from neuropathies affecting motor neurons (equine motor neuron disease, hypocalcemia), decreased neural input at motor end plates (botulism), marked muscle atrophy or rhabdomyolysis of postural muscles, or severe electrolyte imbalances (hypokalemia). The few operative motor units fatigue easily, resulting in muscle fasciculations, shifting of weight, low head posture, difficulty prehending grain, long periods of recumbency, and difficulty rising.

42.4.2 MUSCLE ATROPHY

Atrophy is defined as a reduction in muscle size, specifically a reduction in muscle fiber diameter or cross-sectional area. Atrophy may occur in response to a variety of stimuli. Denervation removes the normal low-level tonic neural stimulus that is necessary to maintain muscle fiber mass. Complete denervation of a muscle results in more than a 50% loss of muscle mass within a 2- to 3-week period.[23,32] A good example of this is “sweeney” in horses, in which the suprascapular nerve is damaged and muscles over the scapula atrophy. Other denervating conditions such as equine motor neuron disease show a slower progression of gross muscle atrophy. Electromyographic abnormalities after denervation are apparent within 5 days, and it may take 3

weeks for maximal changes to develop. Increased insertional activity, positive sharp waves, and bizarre high-frequency discharges and fibrillation potentials are seen in denervated muscle.[19] Pyknotic nuclear clumps and small angular slow-twitch type 1 and fast-twitch type 2 fibers with concave sides are characteristic of neurogenic atrophy in muscle biopsies. In some cases hypertrophy of remaining motor units may occur in neurogenic atrophy, and renervation is indicated by target fibers and fiber type grouping.

Muscle atrophy also may be caused by disuse, malnutrition, cachexia, corticosteroid excess, and immune-mediated myositis. Skeletal muscle is a plastic tissue, with approximately 1% to 5% of the contractile mass undergoing remodeling on a daily basis. If a negative nitrogen balance occurs, net protein withdrawal from the skeletal muscle mass begins within 48 to 72 hours. This type of atrophy is distinguished from neurogenic atrophy by a slower progression of atrophy, normal electromyographic findings, and muscle biopsies that are characterized by exclusive atrophy of type 2 muscle fibers. The overall response of skeletal muscle is to maintain essential postural muscle groups, whereas less essential groups undergo significant reduction in muscle mass. With malnutrition, 30% to 50% of the muscle mass may be lost in the first 1 to 2 months.[32] Rapid atrophy is characteristic of immune-mediated myopathies in quarter horse—related breeds, which can result in the loss of 30% of muscle mass within 48 hours because of necrosis and atrophy of myofibers.[33]

42.4.3 MUSCLE NECROSIS

Muscle necrosis (rhabdomyolysis), as evidenced by elevations in serum CK, LDH, and AST, can be focal or generalized. Many infectious, toxic, nutritional, ischemic, and idiopathic factors result in muscle fiber necrosis. When attempting to identify a cause, it is helpful to characterize rhabdomyolysis in horses as associated with exercise or not exercise-associated. Specific causes of exertional and nonexertional rhabdomyolysis are listed in Box 42-1

Necrosis represents injury to organelles within a muscle fiber or within a segment of that fiber. Many myopathies associated with generalized rhabdomyolysis interrupt normal muscle metabolism, and cell death results from an inability to maintain homeostasis within the myofiber. Although various external or internal insults may cause rhabdomyolysis, they often share a final common pathway leading to cell death.[34] Under normal conditions, considerable energy is expended by muscle cells to pump the calcium that accumulates in the sarcoplasm during contraction into the sarcoplasmic reticulum. If cell membrane function is disrupted or if the energy pathways that generate adenosine triphosphate for the calcium pump are impaired, excessive calcium may accumulate in the sarcoplasm. Although some calcium can be sequestered by the mitochondria, eventually mitochondria become overloaded and oxidative metabolism ceases; oxygen free radicals are generated; phospholipases are activated, inducing the arachidonic cascade; calcium-dependent proteases are stimulated, and complement is activated. The contractile proteins within a necrotic segment are destroyed and appear homogenized with no evidence of cross-striations, and mitochondrial and sarcolemmal membranes appear disrupted. When necrosis occurs as a result of internal disruption of muscle homeostasis, the basement membrane of the cell is left intact. Macrophage infiltration and phagocytosis of necrotic debris usually occur within 16 to 48 hours of the muscle injury. Satellite cells migrate along the remaining basement membrane and form regenerative myotubes within 3 to 4 days of injury, with mature muscle fibers developing within a month of the original damage.[23]

42.4.3.1 Box 42-1 Causes of Rhabdomyolysis in the Horse

42.4.3.1.1 MYOPATHIES NOT ASSOCIATED WITH EXERCISE

42.4.3.1.1.1 Inflammatory Myositis

Clostridial species

Equine influenza virus A2 and equine herpesvirus 1

Sarcocystis fayeri

Acute rhabdomyolysis with *Streptococcus equi* infections

Infarctive hemorrhagic purpura

Immune-mediated myopathy with atrophy

42.4.3.1.1.2 Nutritional Myodegeneration

Vitamin E or selenium

42.4.3.1.1.3 Toxic Myopathy

White snake root or rayless goldenrod

Pasture myopathy, atypical myopathy

Ionophores

Chemical toxins

42.4.3.1.1.4 Traumatic Myopathy

Compartment syndrome and capture myopathy

42.4.3.1.1.5 Anesthetic-Related Myopathy

Malignant hyperthermia

Focal myoneuropathy

42.4.3.1.2 EXERTIONAL RHABDOMYOLYSIS

42.4.3.1.2.1 Sporadic Causes

42.4.3.1.2.1.1 Dietary

Excess carbohydrate diet

Low-sodium diet

Low-potassium diet

High-calcium, low-phosphorus diet

Low vitamin E or selenium status

42.4.3.1.2.2 Infectious

Equine herpesvirus 1

42.4.3.1.2.3 Overexertion

Excessive exercise relative to training status

Postendurance ride (hyperthermia, electrolyte imbalances)

42.4.3.1.2.4 Chronic Causes

Polysaccharide storage myopathy

Recurrent exertional rhabdomyolysis

Chronic exertional rhabdomyolysis (unknown causes)

Muscle ischemia occurs commonly with acute trauma, the compartment syndrome in recumbent animals, downer syndrome, and vascular occlusion. Compartment syndrome often involves the triceps muscle or extensors of the hindlimb, because they are often compressed in down animals or during anesthesia. Hypotension during surgery contributes to the development of this syndrome. Acute muscle infarction may occur with purpura hemorrhagica or disseminated intravascular coagulation, and on postmortem examination characteristic well-demarcated areas of hemorrhagic necrosis are evident. Clinically, acute infarctions are an extremely painful condition that may resemble colic. Chronic occlusive diseases, such as iliac thrombosis, often allow collateral circulation to develop, thereby avoiding acute signs of ischemia at rest. Although muscle has an impressive ability to regenerate, if a disease process is severe enough to disrupt the basement membrane, muscle may be replaced by connective tissue and fat. This occurs most frequently after trauma such as tearing of the semimembranosus or tendinosus in horses (fibrotic myopathy).

42.5 DISORDERS OF MUSCLE TONE

42.5.1 MYOTONIC DISORDERS

STEPHANIE J. VALBERG

Myotonic muscle disorders represent a heterogeneous group of diseases that share the feature of delayed relaxation of muscle after mechanical stimulation or voluntary contraction. Abnormal muscle membrane excitability appears to be the shared abnormality among myotonic disorders. The nondystrophic myotonias in large animals include myotonia congenita in horses and goats and equine HYPP.[35] Sarcolemmal ion channel dysfunction causes these nondystrophic myotonias. Dystrophic myotonia, a progressive disease that may also be associated with abnormalities in other body systems, has been reported in horses.[36,37] In addition, it has been noted that some horses with ear tick infestations develop percussion myotonia and painful muscle cramps.[38]

A condition that demonstrates myotonic-like signs in cattle is spastic paresis[39,40] or “Elso heel.” Commonly calves 2 to 7 months of age are affected and have an extremely straight angle to the hock and stifle. Signs reflect a decreased ability or inability to flex the hock because of continuous tension on the gastrocnemius muscle when standing. Involvement may be unilateral or bilateral. The Holstein-Friesian breed is most commonly affected, although other breeds have been found to have the disorder.[39–42] Spastic paresis may have a distinct familial pattern, but environmental exposure to toxins in utero has also been implicated as a cause.[39–41,43]

Clinical signs similar to those of spastic paresis are seen in horses with “shivers.” Shivers is most commonly seen in draft horse breeds, warmbloods, and warmblood crosses >1 year of age, although it may occur in light horse breeds.[44] Suggested causes include genetic, traumatic, infectious, and neurologic diseases, although its exact basis is unknown. The disease primarily affects the hindlimbs and is characterized by periodic, involuntary spasms of the muscles in the pelvic region, pelvic limbs, and tail that are exacerbated by backing or picking up the hindlimbs. The affected limb is elevated and abducted and may actually shake and shiver, and the tail head is usually elevated concurrently and trembles (Fig. 42-2). In more severely affected animals, on backing up the hindlimb is suddenly raised, semiflexed, and abducted with the hoof held in the air for several seconds or minutes; the tail is elevated simultaneously and trembles. After a variable period of time, the spasms

subside, the limb is extended, and the foot is brought slowly to the ground. There are no distinct myotonic discharges on EMG with shivers, indicating it is not a true myotonic condition.

42.5.1.1 Myotonia

42.5.1.1.1 Clinical Signs

Myotonia congenita in humans, horses, and goats is usually detected in the first year of life.[45–48] Affected animals commonly have conspicuously well-developed musculature and display mild pelvic limb stiffness. Gait abnormalities are usually most pronounced when exercise begins and frequently diminish as exercise continues. Bilateral bulging (dimpling) of the thigh and rump muscles is often obvious and gives the impression that the animal is very well developed (Fig. 42-3). Stimulation of affected muscles, especially percussion, exacerbates the muscle dimpling below a large area of tight contraction (Fig. 42-4). Affected muscles may remain contracted for up to a minute or more, with subsequent slow relaxation.[37,48,49]

In goats, myotonia congenita appears to an autosomal dominant mutation in the skeletal muscle chloride channel that has incomplete penetrance.[31,47,50] Affected goats are commonly referred to as “fainting goats.” Signs are usually recognizable by 6 weeks of age and vary from stiffness after rest to marked general rigidity after visual, tactile, or auditory stimulation. Clinical signs remain throughout the animal's life but are not progressive.[51]

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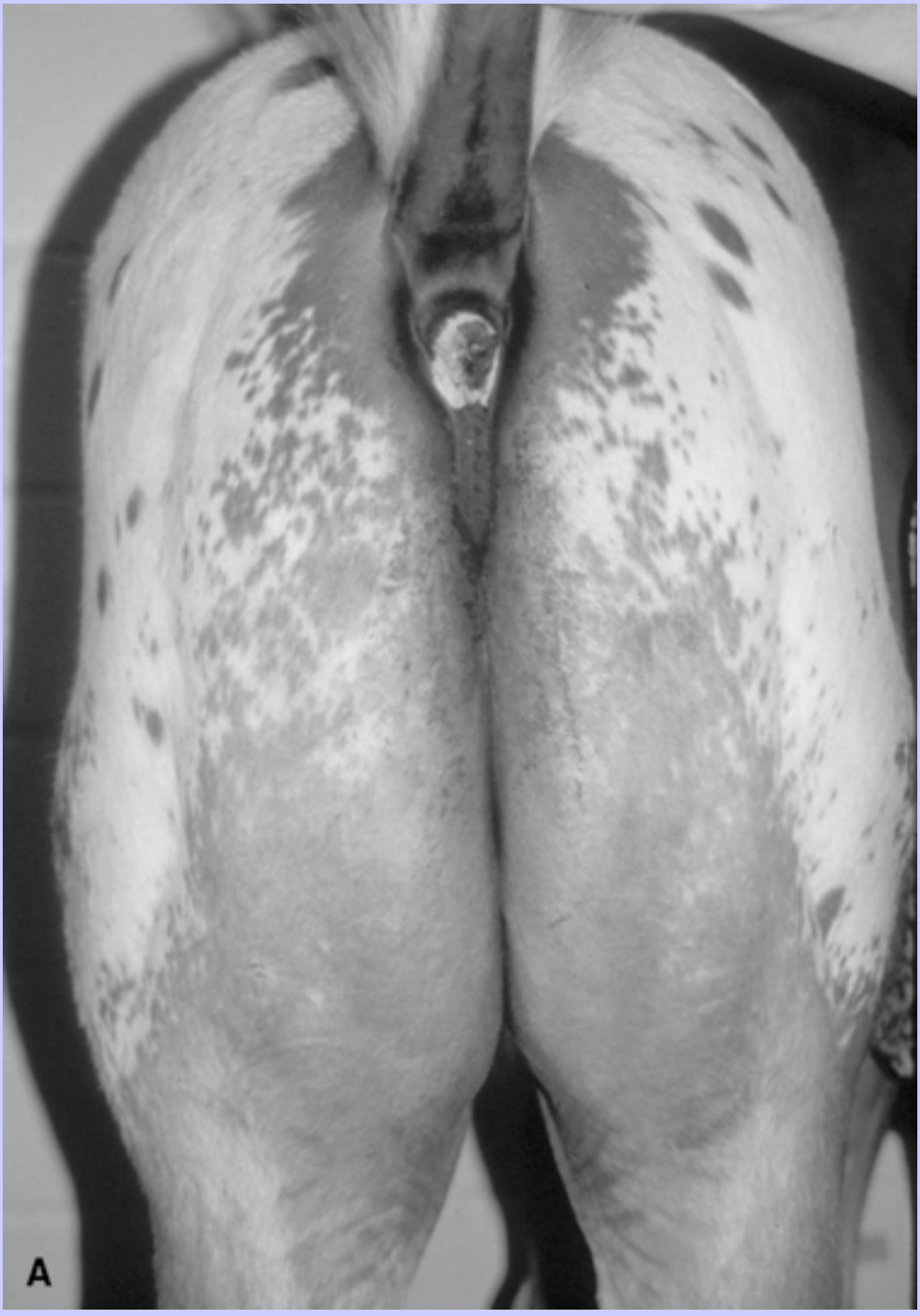
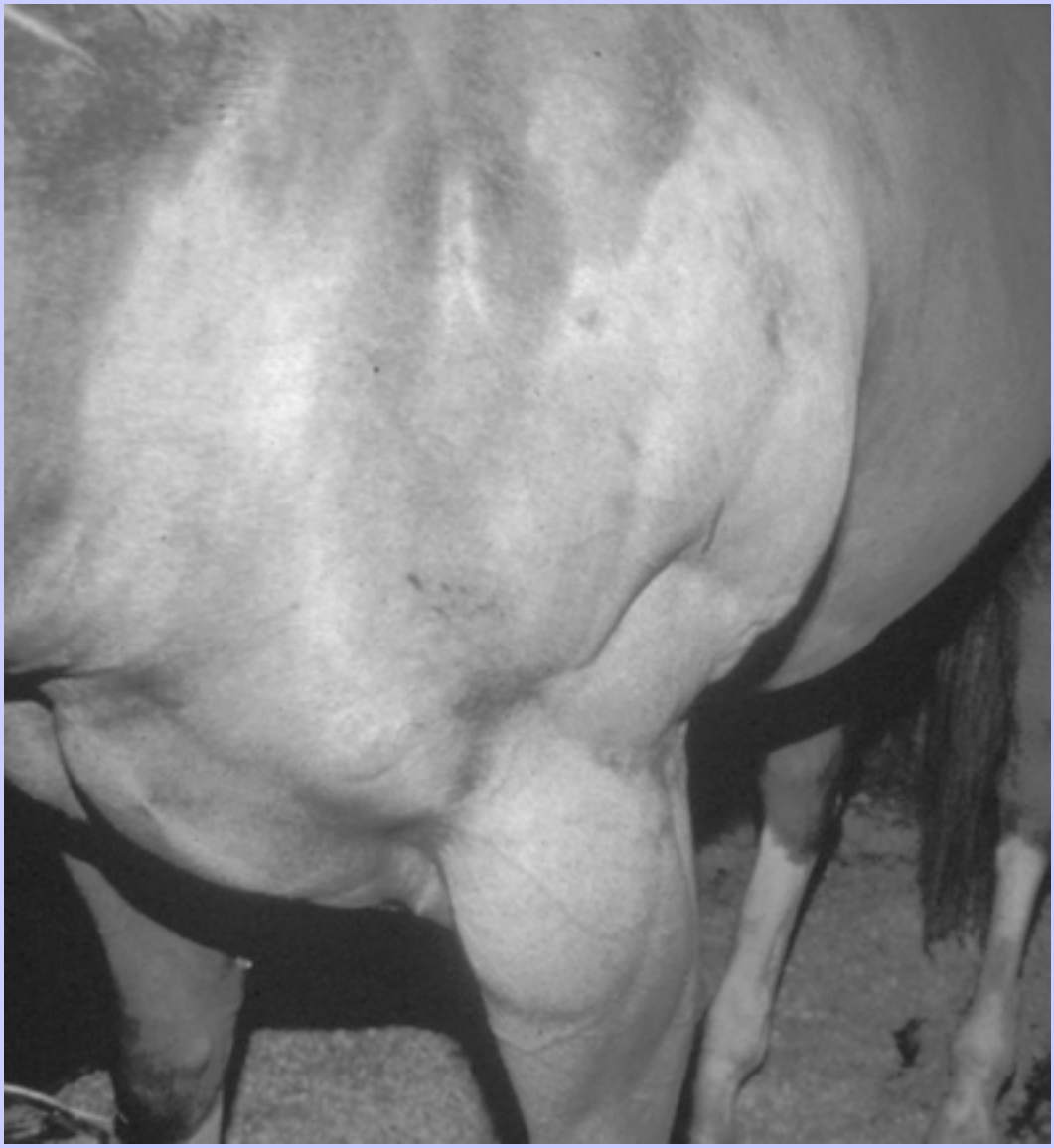
Fig. 42-2 Classic stance of a horse with shivers, in which the left hindlimb is held in an abducted flexed position and the tail is elevated and trembling.

Fig. 42-3 Normal muscle mass in an Appaloosa foal **(A)** and spontaneous myotonic dimpling of semimembranosus muscles in a foal with myotonic dystrophy **(B).**



B

Fig. 42-4 Myotonic dimpling of the triceps in a horse with hyperkalemic periodic paralysis.



Myotonia congenita does not usually show progression of clinical signs beyond 6 to 12 months of age in horses.[37] To date no abnormalities in sarcolemmal chloride conductance have been demonstrated in horses, and an inherited basis has not been established in horses.

Myotonia dystrophica appears to be a separate form of myotonia in horses.[36,37,52] Severe clinical signs of myotonia that progress to marked muscle atrophy and possibly involve a variety of organ systems have been observed in quarter horse, Appaloosa, and Italian-bred foals. Retinal dysplasia, lenticular opacities, and gonadal hypoplasia have been reported in one such quarter horse foal.[36] This condition resembles

myotonia dystrophica in humans, which is caused by genetic mutations involving either the *DMPK* gene or the *ZNF9* gene.[53,54] In both cases a short segment of DNA is abnormally repeated many times, forming an unstable region in the gene, which alters mRNA processing. The genetic basis of myotonic dystrophy in horses is not yet known.

42.5.1.1.2

Diagnosis

A tentative diagnosis frequently can be made on the basis of age, clinical signs (stiff gait, particularly at the onset of exercise), muscle bulging, and prolonged contractions after muscle stimulation.

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Definitive diagnosis of myotonia is usually based on electromyographic examination. Affected muscle manifests pathognomonic, crescendo-decrescendo, high-frequency repetitive bursts with a characteristic "dive bomber" sound.[36,52,55] This sound is produced by the repetitive firing (after contractions) of affected muscle fibers. After a contraction diminishes, the excitability of muscle fibers is decreased, and the action potentials recorded by EMG reflect the diminution of electrical activity.[56]

Muscle biopsy samples from foals with myotonia congenita may be normal or may demonstrate extremely variable muscle fiber dimensions up to twice those of normal age-matched controls.[48] Type I fiber hypertrophy may be seen with accompanying signs of fiber splitting. The major changes noted with myotonic dystrophy are ringed fibers, alterations in the shape and position of myonuclei, sarcoplasmic masses, and an increase in endomysial and perimysial connective tissue.[36,37,52,57] Fiber type grouping and atrophy of both type I and type II muscle fibers may be present.

42.5.1.1.3

Treatment

Considering that the pathophysiologic basis of myotonia in horses has not been clearly identified, recommendations for specific, effective therapy are almost impossible. In affected humans and dogs some relief of signs has been provided by drugs such as quinine, procainamide, and phenytoin. However, responses vary among patients. Phenytoin has been reported to be efficacious in two quarter horses with HYPP and myotonic dystrophy.[55]

42.5.1.1.4

Prognosis

Prognosis appears to be variable and dependent on the severity of clinical signs. Mildly affected animals may undergo some amelioration of clinical signs with increasing age. In animals that exhibit mild clinical signs, manifestations of the disorder may abate over a period of months to years. The reason(s) for this regression of signs is unknown. Other more severely affected horses may have progression of signs, including atrophy and fibrosis or pseudohypertrophy to the point at which the animal is no longer able to move without great pain and difficulty (Fig. 42-5). Euthanasia of such animals is often warranted.

Although conclusive evidence regarding the genetic basis of this disorder in horses is still not available, owners of affected horses should be cautioned about the possibility that this disease is heritable.

Fig. 42-5 Marked progressive atrophy of the epaxial and gluteal muscles of a horse with myotonic dystrophy.

42.5.1.2

Hyperkalemic Periodic Paralysis

SHARON J. SPIER

Equine HYPP is caused by an inherited defect in the skeletal muscle sodium channel.[35,58–61] This myopathy manifests as abnormal skeletal muscle membrane excitability leading to episodes of myotonia, or sustained muscle contraction, and paralysis. In humans, numerous muscle membrane channel defects (so-called "channelopathies") have been characterized, and the molecular basis for disease is well described.[46] Other reported disorders with suspected membrane defects in horses include myotonic dystrophy and congenital myotonia.[36,48] HYPP was the first equine disease attributed to a specific genetic mutation and detectable through DNA technology.[60]

HYPP is an autosomal dominant trait affecting quarter horses, American Paint horses, Appaloosas, and quarter horse cross-bred animals worldwide. A "syndrome" in related horses was first recognized in the 1980s by breeders and veterinarians and was first reported to be similar to HYPP in humans by Cox at the American Association of Equine Practitioners (AAEP) convention in 1985.[61] In December 2002, this genetic disease was publicly linked to a popular quarter horse sire named Impressive. This prolific sire, born in 1969, has 355,000 offspring registered with the American Quarter Horse Association (AQHA),[*] and these

offspring dominate the halter horse industry. Current estimates indicate that 4% of the quarter horse breed may be affected.[62] Unfortunately, the gene frequency has not decreased in the past 14 years since genetic testing has been available to breeders, and controversy continues among horse breeders whose stock carry this gene.[†] Affected horses appear to have been preferentially selected as breeding stock because of their pronounced muscle development, and there is evidence of selection of HYPP-affected horses as superior halter horses by show judges.[63] In 1996 AQHA officially recognized HYPP as a genetic defect or undesirable trait. To increase public awareness of this genetic defect, mandatory testing for HYPP with results designated on the registration certificate began for foals descending from Impressive born after January 1, 1998. In response to requests from the membership, in 2004 the AQHA Stud Book and Registration Committee ruled that foals born in 2007 and later testing homozygous affected for HYPP (H/H) will not be eligible for registration. Breeders opposed to restrictions argue that the disease can be controlled through diet and medication and that these horses are highly successful in the show ring.[64]

* Griffith G, AQHA Registrar. Personal communication, 2005.

† Statistics from UCD Veterinary Genetics Laboratory HYPP Testing, 2006.

42.5.1.3

Clinical Signs

Clinical signs among horses carrying the same mutation range from none (horses are asymptomatic) to daily muscle fasciculations and weakness. In the majority of horses, intermittent clinical signs begin by 2 to 3 years of age with no apparent abnormalities between episodes.[35,59] Ingestion of diets high in potassium (>1.1%), such as those containing alfalfa hay, molasses, electrolyte supplements, and kelp-based supplements or sudden dietary changes commonly trigger episodes.[65] Fasting, anesthesia or heavy sedation, trailer rides, and stress may also precipitate clinical signs; however, the onset of signs is often unpredictable and without a definable cause. Other possible precipitating factors that have been noted in humans and horses are exposure to cold, fasting, pregnancy, and concurrent disease and rest after exercise. Exercise per se does not appear to stimulate clinical signs, and serum CK shows no change or only modest increases during episodic fasciculations and weakness.

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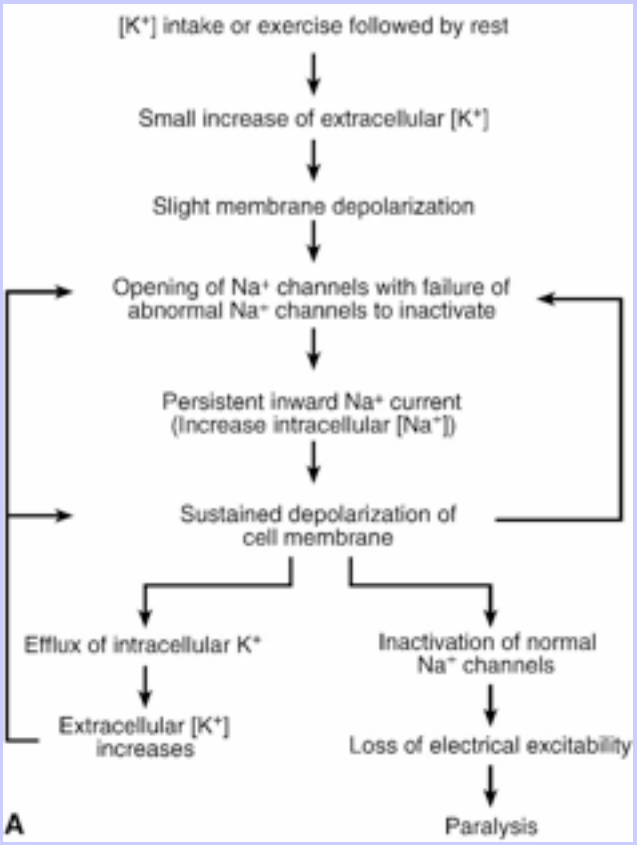
In most cases clinical episodes begin with a brief period of myotonia, with some horses showing prolapse of the third eyelid. Sweating and muscular fasciculations are observed commonly in the flanks, neck, and shoulders. The muscle fasciculations become more generalized as additional muscle groups are involved. Stimulation and attempts to move may exacerbate muscular tremors. Some horses may develop severe muscle cramping. Muscular weakness during episodes is a common characteristic of HYPP. Horses remain standing during mild attacks. In more severe attacks, clinical signs may progress to apparent weakness with swaying, staggering, dog sitting, or recumbency within a few minutes. Heart and respiratory rates may be elevated, and horses may show manifestations of stress (anxious appearance) yet remain relatively bright and alert during episodes. Affected horses usually respond to noise and painful stimuli during clinical manifestations of the disorder. Episodes last for variable periods, usually from 15 to 60 minutes. Several horses have died during acute episodes.[1] Respiratory distress occurs in some animals as a result of paralysis of upper respiratory muscles, and a tracheostomy may be necessary. In addition, young horses that are homozygous for the HYPP trait have been observed to manifest respiratory stridor and periodically may develop obstruction of the upper respiratory tract. Horses homozygous for HYPP may have dysphagia or respiratory distress, and endoscopic findings include pharyngeal collapse and edema, laryngopalatal dislocation, and laryngeal paralysis.[66] After the episode subsides, horses regain their feet and appear normal with no apparent or minimal gait abnormalities. Although horses with HYPP appear normal between attacks,

electromyographic examination of affected horses reveals abnormal fibrillation potentials, complex repetitive discharges with occasional myotonic potentials, and trains of doublets between episodes.[35,67]

Fig. 42-6 A, Explanation for paralytic attacks in horses with hyperkalemic periodic paralysis (HYPP). B, A horse suffering from an episode of HYPP-associated collapse after exposure to a cool rain shower.



42.5.1.4 Etiology

HYPP results from a point mutation that results in a phenylalanine-leucine substitution in a key part of the voltage-dependent skeletal muscle sodium channel alpha subunit.[60] In horses with HYPP, the resting membrane potential is closer to firing than in normal horses.[68] Sodium channels are normally briefly activated during the initial phase of the muscle action potential. The HYPP mutation results in a failure of a subpopulation of sodium channels to inactivate when serum potassium concentrations are increased. As a result, an excessive inward flux of sodium and outward flux of potassium ensues, resulting in persistent depolarization of muscle cells and temporary weakness (Fig. 42-6).

42.5.1.5

Diagnosis

Descent from the stallion Impressive on the sire's or dam's side in a horse with episodic muscle tremors, weakness, or collapse is strongly suggestive of HYPP. Quarter horse foals born after 1998 that are offspring of an affected parent have a statement recommending DNA testing for HYPP on the Certificate of Registration. In most cases hyperkalemia (6 to 9 mEq/L), hemoconcentration, and mild hyponatremia occur during clinical manifestations of the disease, with normal acid-base balance.[35] Serum potassium concentration returns to normal after the abatement of clinical signs. Some affected horses may have normal serum potassium concentrations during minor episodes of muscle fasciculations.[59] Differential diagnoses for hyperkalemia include delay before sample centrifugation, hemolysis, acidosis, renal failure, severe rhabdomyolysis, and high-intensity exercise.

Because veterinarians may not be present during acute episodes, the definitive test for identifying HYPP is the demonstration of the base-pair sequence substitution in the abnormal segment of the DNA encoding for the alpha subunit of the sodium channel.[60] Submission of mane or tail hair with hair root should be made to a licensed laboratory such as the Veterinary Genetics Laboratory at the University of California, Davis (www.vgl.ucdavis.edu). 1396 1397

42.5.1.6

Treatment

Mild exercise can sometimes abort an episode in mild cases or if horses are just beginning to exhibit clinical signs. Feeding grain or corn syrup to stimulate insulin-mediated movement of potassium across cell membranes may also be helpful. Other treatment options that may abort an episode include intramuscular administration of epinephrine (3 mL of 1:1000 per 500 kg) and administration of acetazolamide (3 mg/kg orally [PO] every 8 to 12 hours). Many horses experience spontaneous recovery from episodes of paralysis and appear normal by the time a veterinarian arrives.

In severe cases, administration of calcium gluconate (0.2 to 0.4 mL of a 23% solution per kilogram, diluted in 1 L of 5% dextrose) will often provide immediate improvement. An increase in extracellular calcium concentration raises the muscle membrane threshold potential, which decreases membrane hyperexcitability. To reduce serum potassium, intravenous dextrose (6 mL of a 5% solution per kilogram) alone or combined with sodium bicarbonate (1 to 2 mEq/kg) can be used to enhance intracellular movement of potassium. With severe respiratory obstruction, a tracheostomy may be necessary.

42.5.1.7

Control

Decreasing dietary potassium and increasing renal losses of potassium are the primary steps taken to prevent HYPP episodes. Feedstuffs to avoid include high-potassium feeds such as alfalfa hay, orchard grass hay, brome hay, soybean meal, sugar molasses, and beet molasses. Optimally, later cuts of timothy or Bermuda grass hay and grains such as oats, corn, wheat, and barley, and beet pulp should be fed in small meals several times a day (Table 42-1). Regular exercise and/or frequent access to a large paddock or yard are also beneficial. Pasture works well for horses with HYPP because the high water content of pasture grass makes it unlikely that horses will consume large amounts of potassium in a short period of time. Ideally, horses with recurrent episodes of HYPP should be fed a balanced diet containing between 0.6% and 1.1% to 1.5% total potassium concentration and meals containing less than 33 g of potassium.[65,69,70] Horses will adapt to diets higher in potassium over a period of 2 weeks and will experience fewer fluctuations in potassium in blood with subsequent decreased frequency of clinical signs.[69] Because there is wide variation in potassium concentration of forages depending on maturity and soils, it is advisable to have feeds analyzed for potassium concentrations and other nutrients.[70] The table below contains examples of feeds containing varying concentrations of potassium. Supplement with vitamin E, selenium, salt, and balanced minerals where indicated to meet nutritional requirements. Commercially available complete feeds with a guaranteed K^+ content may be more convenient for some HYPP horses, especially for owners with few horses.

Table 42-1 Examples of Feed Containing High, Medium, or Low Concentrations of Potassium (K^+)

	K^+ (%)	g K^+/lb of feed
High-Potassium Feed		
Electrolyte supplements	30	136
Molasses	6	27
Kelp supplements	4	18
Alfalfa hay (90% DM)	1.4-2.4	6.4-10.9
Canary grass hay	2.6	2.6
Orchard grass hay	2.4-2.6	10.9-11.8
Soybean meal	2	9.1
Medium-Potassium Feed		
Fescue hay	1.7-2.1	7.7-9.5
Rice bran	1.8	8.1
Timothy hay	1.4-2.1	6.4-9.5
Coastal Bermuda hay	1.2-1.9	5.5-8.2
Kentucky bluegrass hay	1.4	6.4
Oat hay	1.4	6.4
Low-Potassium Feed		
Pure fats and oils	0	0
Beet pulp	0.2-0.3	0.9-1.4
Corn, oats, or barley	0.3-0.5	1.4-2.3
Pasture grass (23% DM)	0.3-0.8	1.4-3.6
Wheat	0.4	1.8
Wheat bran	1.2	5.45
Soybean hulls	1.2	5.45

DM, Dry matter.

To decrease the frequency of episodes, avoid high-potassium feed; select feed that contains medium to low K^+. Feeding a balanced ration containing less than 1.5% K^+ and meals <33 g K^+ decreases fluctuations of blood K^+, lowering the frequency of hyperkalemic periodic paralysis symptoms.[12,15,16]

For horses with recurrent episodes of muscle fasciculations even with dietary alterations, acetazolamide (2 to 3 mg/kg PO every 8 to 12 hours) or hydrochlorothiazide (0.5 to 1 mg/kg PO every 12 hours) may be helpful. These agents exert their effects through different mechanisms; however, both cause increased renal potassium excretion. In addition, acetazolamide stabilizes blood glucose and potassium by stimulating insulin secretion. Breed registries and other associations may have restrictions on the use of these drugs during competitions, as diuretics may mask prohibited substances.

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42.5.1.8 Prognosis

In most cases HYPP is a manageable disorder, although recurrent bouts may occur and severe episodes can be fatal. Owners of affected horses should be strongly discouraged from breeding these animals for the long-term health of the quarter horse and other breeds. As this is a dominant trait, breeding an affected horse to a normal horse results in a 50% chance of producing a foal with HYPP. All affected horses share the same mutation, regardless of whether or not owners have witnessed signs in their horses.[71] Affected horses are not suitable for young or inexperienced riders. Owners of affected horses should advise veterinarians of HYPP status before anesthesia or procedures requiring heavy sedation, as these circumstances could precipitate an episode of paralysis.

42.6 MUSCLE CRAMPING

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GARY CARLSON

Muscle cramps are a painful condition that arises from hyperactivity of motor units caused by repetitive firing of the peripheral and/or central nervous system. The origin of the cramp in most cases is believed to be the intramuscular portion of the motor nerve terminals.[29,72] Most muscle cramps are also accompanied by fasciculations in the same muscle. Muscle cramps can be induced by forceful contraction of a shortened muscle, by changes in the electrolyte composition of extracellular fluid, and by ear tick infestations in horses.[29,38] In contrast, muscle contractures are painful muscle spasms that represent a state of muscle contracture unaccompanied by depolarization of the muscle membrane.[72] Muscle contractures occur with MH and some forms of exertional myopathies and are invariably accompanied by markedly increased serum CK activity.

42.6.1 Dietary Electrolytes

Some horses develop muscle stiffness and occasional elevations in serum CK when fed a diet deficient in sodium or potassium. These chronic deficiencies are rarely reflected in serum electrolyte concentration but may be detected by performing renal FE of electrolytes.[11] Sodium deficiency is particularly common because forage and grain diets are low in sodium and chloride and high in potassium. Supplementation of the equine diet with salt is a necessity. Salt blocks may not be adequate in this regard, and loose salt (1 to 2 oz) added directly to the grain is often the best mechanism of supplementing horses with salt. Some horses may require higher dietary salt supplementation to maintain an adequate sodium balance. Balancing dietary electrolytes has been reported to decrease muscle cramping and serum CK activity in those horses with dietary deficiencies.[11]

42.6.2 Exhaustion in Endurance Horses

Muscle cramping in endurance horses occurs commonly during prolonged exercise in hot weather, particularly when the humidity is high.[73,74] Under such circumstances rectal temperatures reach as high as 41° C and horses may lose up to 15 L/hr of fluids in the form of sweat that is rich in sodium, potassium, and chloride.[75,76]

42.6.2.1 Clinical Signs

Affected horses demonstrate stiffness and cramping in the muscles of locomotion. Pain is a characteristic of the disorder, and affected muscle groups often undergo periodic spasms. In addition, exhausted horses are often dull, depressed, and clinically dehydrated with elevated heart and respiratory rates and persistently elevated body temperature. Common electrolyte abnormalities include hypochloremic metabolic alkalosis with hypokalemia, hypomagnesemia, and low serum ionized calcium concentrations.[73,74,77] Synchronous diaphragmatic flutter (SDF) may be seen in association with cramping.[73]

Although many of the signs of muscular dysfunction are similar to those of ER, affected horses do not generally develop myoglobinuria.[73]

42.6.2.2 Etiology

Factors contributing to cramping are dehydration, electrolyte abnormalities, and disturbances in thermoregulatory and local circulatory function. Whether this disorder is similar to heat cramps seen in human athletes is not known.

42.6.2.3 Diagnosis

A variety of electrolyte abnormalities occur in affected animals.[73,77] Mild cases are distinguished by the presence of muscle cramps that subside with rest or light exercise in heat-stressed horses. In more severe cases clinical signs of dehydration and shock are often present. Horses with muscle cramping will not have marked elevations in serum CK or AST, nor will they exhibit myoglobinuria. Exhausted horses, however, may progress to develop rhabdomyolysis with marked electrolyte derangements. These horses require immediate treatment.

42.6.2.4 Treatment

Under most circumstances the mild form of muscle cramping is self-limiting, and the signs abate with rest or light exercise. However, if evidence of other metabolic derangements exists, treatment for these disorders (e.g., plasma volume expansion with oral or intravenous isotonic polyionic fluids, cooling using water and fans) is frequently beneficial to the horse.[78] Because most horses with this condition are alkalotic, administration of solutions containing sodium bicarbonate is contraindicated. Dietary analysis should be performed to determine the extent of salt and electrolyte supplementation necessary in affected horses. Daily direct addition of 2 oz of sodium chloride and 1 oz of potassium chloride to the feed is recommended for horses with recurrent cramping in addition to electrolyte supplementation before and after endurance rides.

42.6.3 Synchronous Diaphragmatic Flutter

SDF, also known as “thumps,” usually occurs in horses with derangements in fluid and electrolyte balance. Inciting causes include endurance exercise, hypocalcemia, hypoparathyroidism, digestive disturbances, and possibly the administration of medications. A characteristic clinical manifestation of the disease occurs when the diaphragm contracts in synchrony with atrial depolarization.[79–81]

42.6.3.1 Clinical Signs

The classic sign of SDF is a contraction or twitch in the flank region (unilateral or bilateral) as the diaphragm contracts synchronously with the heart. In severe cases this twitch may produce an audible thumping sound.

The metabolic derangements leading to SDF also may be clinically apparent in some cases. These may include signs of dehydration and volume depletion. Endurance horses with SDF in association with the exhausted horse syndrome may demonstrate dehydration, inappropriate sweating responses, persistently elevated body temperature, depression, anorexia, and aperistalsis.[73,74] In some horses, SDF may be a chronic, recurring problem.[79]

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42.6.3.2 Etiology

A variety of stimuli may result in SDF. These include prolonged exercise, particularly during hot weather; hypocalcemia resulting from lactation, transit, or stress; digestive tract dysfunction; furosemide therapy; trauma; and primary hypoparathyroidism.[79,81] The most consistent metabolic derangement reported in horses with SDF is low serum ionized calcium concentrations, usually associated with hypochloremic metabolic alkalosis.[79,80] Metabolic alkalosis may alter the ratio of free to bound calcium (increasing calcium binding to protein and decreasing ionized calcium), which possibly induces SDF.

SDF occurs in association with atrial depolarization in horses. It has been postulated that fluid, electrolyte, and acid-base derangements may disrupt the normal membrane potential of the phrenic nerve, which passes directly over the atrium, resulting in nerve discharges in response to atrial depolarization.[79,80,82]

42.6.3.3 Treatment

In most cases SDF is a transient event, usually abating when the underlying cause resolves, either spontaneously or in response to treatment.[79] Most horses undergo rapid remission of signs when given calcium solutions intravenously (IV) as described in the section on hypocalcemia in horses. Although hypomagnesemia is often present with SDF, horses do not respond to magnesium supplementation unless calcium is administered concurrently. Response to therapy is also reflected by improved mental status, return of appetite, and gut motility.[79]

42.6.3.4 Control

Electrolyte supplementation and some dietary manipulations may help reduce the incidence of SDF in some endurance horses that experience recurrent bouts. Provision of chloride, potassium, and sodium during prolonged exercise may help reduce fluid losses and the metabolic alkalosis that commonly accompanies this form of exercise and frequently occurs in association with SDF. Metabolic alkalosis decreases the amount of free calcium available. Supplementation of calcium and magnesium during endurance rides has been suggested to be helpful in horses prone to SDF.

suggested to be helpful in horses prone to SDF.

Alternative approaches involve reduction of dietary calcium in horses prone to SDF for a few days before an endurance ride. It is postulated that this reduction in dietary calcium stimulates the endocrine homeostatic mechanisms and increases osteoclastic activity. In the short term the horse depends less on dietary calcium and is able to mobilize substantial amounts of calcium in response to the demands imposed by the exercise; calcium losses in sweat are overcome by the release of calcium from endogenous storage pools (bone).[79] Furthermore, horses routinely fed alfalfa hay, which has a relatively high calcium concentration, may be more prone to development of SDF. Limitation of this feedstuff may be indicated in chronically affected horses.

42.6.4 Hypocalcemia in Horses

Hypocalcemia is a relatively rare disorder in horses that has also been referred to as *lactation tetany, transport tetany, idiopathic hypocalcemia,* and *eclampsia*.

42.6.4.1 Clinical Signs

Clinical signs are variable and include increased muscle tone; a stiff, stilted gait; rear limb ataxia; muscle fasciculations (especially temporal, masseter, and triceps muscles); trismus; dysphagia; salivation; anxiety; profuse sweating; tachycardia; elevated body temperature; cardiac dysrhythmias; SDF; convulsions; coma; and death.[83,84] Clinical signs may be remarkably similar to some of those seen with tetanus. This disorder may be progressive (in lactating mares in particular) over a 24- to 48-hour period, and some animals die. Clinical signs are related to the magnitude of the serum calcium concentration. Increased excitability is usually the only sign when values are below normal but above 8 mg/dL. Values of 5 to 8 mg/dL usually produce tetanic spasms and incoordination. Concentrations below 5 mg/dL usually result in recumbency and stupor.

42.6.4.2 Etiology

Loss of calcium in milk, especially in mares that produce large amounts of milk, seems to predispose to this disorder.[83,84] Other factors such as heavily lactating mares grazing lush pastures, hard work, prolonged transport, and ingestion of blister beetles (cantharidin toxicosis) may precipitate attacks.

42.6.4.3 Diagnosis

Clinical signs often are highly suggestive of hypocalcemia in affected horses. Historic aspects such as lactation, previous prolonged exercise, or transport also may direct the clinician to the suspected diagnosis.[83]

Definitive diagnosis depends on laboratory demonstration of hypocalcemia, with total calcium concentrations as low as 4 to 6 mg/dL in some cases. In addition, metabolic alkalosis, hypomagnesemia or hypermagnesemia, and hyperphosphatemia or hypophosphatemia have all been found in association with hypocalcemia in horses.[83] These alterations may need correction before a return to normal function is seen in some affected animals.

42.6.4.4

42.6.4.4 Treatment

Although many animals with mild cases recover without specific treatment, in others this disorder may be life-threatening. Therefore therapy is to be encouraged in most cases. Treatment involves the intravenous administration of calcium solutions such as 20% calcium borogluconate or those recommended for the treatment of parturient paresis in cattle.[83] Administration of these solutions at the rate of 250 to 500 mL/500 kg diluted 1:4 with saline or dextrose often results in full recovery, although in some cases it may take several days.[83] Relapses do occur. These preparations should be administered slowly in conjunction with close monitoring of the cardiovascular response. Dilution in saline or dextrose before infusion decreases the chance of cardiotoxicity. Normally there is a positive inotropic effect in response to calcium administration.[85] However, alterations in rate or rhythm provide evidence to suspend the infusion. If no response to an initial infusion occurs, a second dose may be given 15 to 30 minutes later. Most cases respond to this form of therapy, although in some cases in which signs persist, repeated treatments may be necessary.

42.6.5 Ear Tick—Associated Muscle Cramping

Intermittent painful muscle cramps have been described in a small number of horses with severe *Otobius megnini* infestations.[38] Muscle cramping is not associated with exercise. These horses show intermittent signs of severe muscle cramping of pectoral, triceps, abdominal, or semitendinosus or semimembranosus muscles lasting from minutes to a few hours, with severe pain that often resembles colic. Horses may fall over when stimulated. Between muscle cramps horses appear to be normal. Percussion of triceps, pectoral, or semitendinosus muscles results in a typical myotonic cramp. Horses have elevated serum CK levels ranging from 4000 to 170,000 IU/L. Numerous ear ticks, *O. megnini,* can be identified in the external ear canal of affected horses. Without treatment for ear ticks, the spasms continue; however, local treatment of the ear ticks using pyrethrins and piperonyl butoxide results in recovery within 12 to 36 hours. Acepromazine may be helpful to relieve painful cramping.

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42.7 NONEXERTIONAL RHABDOMYOLYSIS

42.7.1 INFLAMMATORY MYOPATHIES

42.7.1.1 Clostridial Myonecrosis

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Various species of clostridial organisms cause acute myonecrosis in many farm animal species. Infections are characterized by a rapid clinical course, fever, systemic toxemia, and high mortality.[86–88] Clostridial diseases are infectious but not contagious. Specific bacteria associated with clostridial myonecrosis include *Clostridium chauvoei (Clostridium welchii), Clostridium septicum, Clostridium sordelli,* and occasionally *Clostridium novyi* type B, *Clostridium perfringens* type A, and *Clostridium carnis*. Mixed infections involving several agents are common.[89] Synonyms for clostridial diseases include *blackleg, malignant edema, false blackleg, gas gangrene,* and *gangrene*. Although there may at times be distinct differences among the specific disease syndromes associated with the different clostridial agents, the pathophysiology of

these diseases is similar enough to be covered under the general topic of clostridial myonecrosis.

42.7.1.1.1

Clinical Signs

Commonly, clostridial myonecrosis is rapidly progressive with the development of tremors, ataxia, dyspnea, recumbency, coma, and death within 12 to 24 hours. Therefore many affected animals may be found prostrate or dead.[86,87] Mortality may approach 100%. Affected animals that are still alive are usually severely depressed, febrile (40° C to 41° C [104° F to 106° F]), tachypneic, anorectic, and lame. These signs are associated with a rapidly developing muscle infection and toxemia. There is usually only one primary site of infection in an affected animal. Any skeletal muscle group in the body can be involved, but most infections affect the limb or trunk muscles. Occasionally muscles such as those around the vulva, tongue, and diaphragm can be involved, or the udder in a cow may be the primary site of sepsis. Areas around recent injections are common sites of myonecrosis in the horse.[88,90] Initially the skin over the area may be swollen, hot, and discolored; however, as the disease progresses the skin over the area may become cool and insensitive with progressive sloughing. Crepitus may be detectable, indicating subcutaneous gas production. If a wound is present, malodorous, serosanguineous fluid may discharge (Fig. 42-7). Aspiration of the swelling often reveals fluid with similar qualities.

Clostridial myonecrosis generally has characteristic pathologic lesions that are absent in most other conditions, making diagnosis relatively straightforward. Differential diagnoses may include other fulminant disease processes in which there is rapid debilitation or death of the animal.

42.7.1.1.2

Clinical Pathology

Clinicopathologic data alone are seldom specific enough to confirm the presence of clostridial myonecrosis. Hematology and serum biochemical analyses usually reflect a generalized state of debilitation and toxemia (e.g., hemoconcentration and a stress or toxic leukogram may be present). Elevations in the activities of serum CK and serum AST usually occur; however, they often do not reflect the toxicity of clostridial myonecrosis.

Fig. 42-7 Clostridial myositis in the right gluteal muscle after an injection of flunixin meglumine which has progressed to involve the

biceps femoris muscle. Fenestrations were created for debridement.

Aspirates from the affected tissues can yield diagnostic information. It is preferable to obtain tissue specimens for direct smear examination and fluorescent antibody testing, and for anaerobic bacterial culture from affected tissues.

culture from affected tissues.

42.7.1.1.3

Pathophysiology

Clostridial agents are ubiquitous in the environment and can frequently be cultured from the feces, intestinal tract, and other internal organs of a variety of species.[86] Spore-forming characteristics allow these organisms to remain in the environment for long periods, but the exact mechanisms involved in the pathogenesis of clostridial myonecrosis are not fully known. Development of clostridial myonecrosis after an intramuscular injection or penetrating wound may be the result of direct spore deposition into the tissue in association with penetration. If suitable conditions prevail within the muscle, the spores undergo a conversion into the vegetative, toxin-producing form of the organism. In contrast, the pathogenesis of the disease is more difficult to explain when a wound does not exist. It is postulated that clostridial agents gain access to the body through the alimentary tract and are present in liver and muscle in the dormant spore form.[91] Subsequently, when local tissue is devitalized and conditions become appropriate for the spores to germinate, the rapid vegetative process ensues. Muscle trauma associated with injection, transporting, herding, and handling has often been incriminated as creating a suitable environment for the development of clostridial myonecrosis. The proliferation of clostridial agents in devitalized tissues is associated with the release of powerful exotoxins responsible for the local necrotizing myositis and systemic toxemia. Toxins are released by multiplying clostridia; the toxins vary, depending on the clostridial species involved. Necrotizing (lecithinase) and hemolyzing (hemolysin) toxins as well as neuraminidase appear to be of greatest importance. The toxins act locally and systemically to create widespread organ dysfunction. The toxins of *C. sordelli* are the most potent of all the clostridial species, and myonecrosis caused by this organism is fatal.

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42.7.1.1.4

Epidemiology

Clostridial agents are common in the environment, and susceptible animals are constantly exposed to them. Areas where previous death losses from clostridial disease have occurred may have a higher incidence or risk of disease because of increased environmental contamination. In cattle clostridial myonecrosis is generally a disease of animals between 4 and 24 months of age. However, *C. sordelli* is a more common problem in older feedlot cattle, in which excessive muscle bruising may occur. Younger animals are probably protected by colostral immunity and older animals by some degree of acquired immunity. Animals on high planes of nutrition and in excellent body condition are more likely to develop the disease. Infections with *C. chauvoei* occur most commonly during the warmer seasons, with the highest incidence varying from the spring to fall, depending on when calves reach the most susceptible age group. *C. septicum, C. novyi,* and *C. perfringens* type A infections can occur at any time and are usually associated with skin wounds such as injection sites, punctures, and castration wounds. The umbilicus may be a site of invasion. Infections in the genital area can occur, usually in association with a recent dystocia.

In sheep and goats, clostridial myonecrosis is most frequently associated with wounds such as those occurring after shearing, docking, and unsanitary surgical procedures. Sheep dipped for parasites after shearing may have an increased risk if the dip becomes contaminated with clostridial spores.

Most reports of clostridial myonecrosis in horses suggest an association with puncture wounds and intramuscular injection sites.[88,90] Intramuscular administration of irritating drugs (including antihistamines, anthelmintics, and phenylbutazone) may enhance the susceptibility to clostridial

antihistamines, antihelmintics, and phenylbutazone) may enhance the susceptibility to clostridial myonecrosis. Horses often are presented with or have a history of another complaint such as colic, exertional myopathy, or laminitis for which they have received injections of drugs in the preceding 48 hours.[92] Previously administered drugs (e.g., phenylbutazone) may mask the fever associated with clostridial myonecrosis, potentially confusing the diagnosis.

42.7.1.1.5

Necropsy Findings

Swelling and autolysis are rapid in animals that have died from clostridial myonecrosis. Bloodstained fluid is often observed discharging from body orifices. Extreme swelling and crepitus may be noted over the affected body area. When acting alone, each of the clostridial agents associated with clostridial myonecrosis produces somewhat different postmortem lesions. However, it is unwise to assume that in clostridial myonecrosis only a single clostridial agent was involved, because mixed infections frequently occur.

C. chauvoei infection is characterized by engorgement of the subcutis and adjacent tissues with bloodstained fluids and gas bubbles. Cut tissue from the affected area reveals moist, dark-colored muscle in the periphery of the lesion, with lighter-colored, drier muscle with gas bubbles separating the separate bundles of muscle toward the center. Other changes include severe degeneration of parenchymatous tissues caused by the systemic toxemia. The carcass usually has a foul odor similar to that of rancid butter. This odor is a characteristic of most cases of clostridial myonecrosis. The lungs are often congested with edema, and hemorrhage and a fibrinohemorrhagic pleuritis are common. The heart may be friable and show evidence of endocardial hemorrhages, particularly on the right side. The spleen may be normal or enlarged and friable. The liver is usually pale and friable and may be autolytic and porous. Lesions are similar in sheep and cattle, except that there is usually less gas and the muscles are not as dry in affected sheep.

Similar necropsy findings are found with myonecrosis caused by *C. septicum* and *C. novyi* type B. *C. septicum* and *C. perfringens* generally occur as part of mixed wound infections in which abundant malodorous, serosanguineous fluid is found at the wound site. *C. perfringens* is common in horses.

Myonecrosis resulting from *C. sordelli* is most often associated with lesions of the neck or brisket area of cattle. Death is frequently so rapid that subcutaneous gas accumulation is rare. In addition to local myonecrosis, these animals often have massive subendocardial hemorrhages in the left ventricle of the heart and hemorrhage in the trachea, bronchi, and thymus. Extensive perirenal edema and hemorrhagic renal calyces and severe congestion of the lungs are common findings.

42.7.1.1.6

Treatment

Although clostridial myonecrosis is often fatal, aggressive specific therapy combined with supportive care may be successful in individual cases. A presumptive diagnosis of clostridial disease on the basis of history and clinical signs is usually made before obtaining the results of culture and laboratory determinations such as fluorescent antibody tests. In horses, clostridial myonecrosis resulting from infections with *C. perfringens* seems to be most amenable to treatment and has the best prognosis for survival, although extensive skin sloughing over the affected area is common.[88]

Antibiotic therapy, aggressive surgical debridement including fasciotomy, and supportive care are the

Antibiotic therapy, aggressive surgical debridement including fasciotomy, and supportive care are the hallmarks of successful treatment.[88] With most clostridial infections penicillin is the drug of choice. In horses, penicillin is used at a dosage of 44,000 U/kg IV every 2 to 4 hours until the animal is stable (1 to 5 days). The intravenous dose is then reduced to four times a day or is replaced by oral metronidazole (15 mg/kg three or four times daily). In ruminants, similar intravenous or intramuscular drug therapy is indicated. In all cases, prolonged antimicrobial therapy may be necessary.

Surgical intervention at the affected site by means of debridement or fenestration in an attempt to reduce tissue swelling, aerate the tissues, and remove necrotic tissue is considered imperative for survival in horses (see Fig. 42-7). Incisions are made through the skin and into the affected muscle to establish adequate drainage and, it is hoped, alter the anaerobic conditions. Sufficient fenestrations should be made to establish drainage and aeration over the entire affected area.

Use of specific antitoxins is recommended when possible. However, these are often not available or not used for immediate therapy because the exact species of *Clostridium* causing the myonecrosis is not known. Cost considerations may also preclude their use.

Supportive fluid therapy and use of analgesics and antiinflammatory agents for control of pain and swelling are recommended. Short-acting corticosteroids such as dexamethasone, prednisolone, or hydrocortisone may be used for initial therapy of systemic and toxic shock, but continued use is contraindicated in the face of overwhelming sepsis.

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If required, specific therapy should also be directed toward any other underlying problems.

42.7.1.1.7

Prognosis

The prognosis for life in all cases of clostridial myonecrosis is guarded to poor. The disease process is often rapidly fulminant, making treatment unrewarding. However, some animals have survived because of early diagnosis, aggressive therapy, and long-term supportive care. This is particularly true in cases involving *C. perfringens* in horses. The owner should be aware from the start of treatment that extensive skin sloughing may involve most of a limb and may force euthanasia to become a consideration at a later stage.

42.7.1.1.8

Prevention

Protection against clostridial myonecrosis is based on immunization procedures. Although clostridial agents are ubiquitous in the environment and frequently appear in the body of susceptible animals, rarely does adequate natural protection occur, although some colostral and acquired immunity may at times occur. Infection in unprotected animals usually follows a rapid, degenerative clinical course and terminates before the animal is able to generate an appropriate protective immune response. At present, only ruminants are commonly vaccinated against the agents responsible for clostridial myonecrosis. Vaccines used include multivalent bacterin toxoids containing antigens against two or more clostridial species, including *C. chauvoei, C. septicum, C. novyi, C. sordelli,* and *C. perfringens*. A rational program for protection usually involves vaccinating at an early age to establish immunity. Vaccination age is partly determined by other management factors, including when calves are handled for branding and castration, but 4 to 6 months of age is the usual time of initial vaccination. In areas of heavy exposure it may be necessary to vaccinate at 3 months and again at 4 months. In all clostridial species except *C. chauvoei,* two doses of vaccine are necessary to establish good protection. The duration of immunity is not long, and booster vaccinations should be administered every 6 to 8 months if protection is to be maintained. In many

booster vaccinations should be administered every 6 to 8 months if protection is to be maintained. In many herds it is necessary to vaccinate only animals under 3 years of age (i.e., those animals that are at greatest risk), but in some high-risk herds it is necessary to maintain a vaccination program for the life of the animal.

Animals that die of clostridial diseases should be disposed of by deep burial, burning, or removal from the premises to avoid further contamination of the environment.

42.7.2 RHABDOMYOLYSIS ASSOCIATED WITH *STREPTOCOCCUS EQUI*

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42.7.2.1 Acute Rhabdomyolysis

Severe acute generalized rhabdomyolysis has been reported to occur in quarter horses less than 7 years of age.[93,94] Affected horses have evidence of submandibular lymphadenopathy and/or guttural pouch empyema caused by *S. equi*. Horses develop a stiff gait that progresses rapidly to markedly firm, swollen, painful epaxial and gluteal muscles. In the majority of reported cases, animals became recumbent and unable to rise, and develop unrelenting pain necessitating euthanasia within 24 to 48 hours of hospitalization (Fig. 42-8). Hematologic abnormalities include mature neutrophilia, hyperfibrinogenemia, and marked elevations in CK (115,000 to 587,000 U/L), and AST levels (600 to 14,500 U/L). Titers to the M protein of *S. equi* are low in affected horses, unless horses are recently vaccinated for strangles. Titers to another protein called *myosin binding protein* were found to be high in a small number of horses that were tested.[93]

Fig. 42-8 A horse in severe pain and unable to rise because of acute rhabdomyolysis concurrent with guttural pouch empyema from *Streptococcus equi*.

At postmortem examination large, pale areas of necrotic muscle are evident in hindlimb and lumbar muscles. The histopathologic lesions are characterized by severe acute myonecrosis with a degree of macrophage infiltration. Sublumbar muscles often show the most severe and chronic necrosis, as indicated by greater

infiltration. Substantial muscles often show the most severe and chronic necrosis, as indicated by greater macrophage infiltration of myofibers.

Two causes have been proposed. The first possibility is a toxic shock—like reaction arising from profound nonspecific T cell stimulation by streptococcal superantigens with the release of high levels of inflammatory cytokines. An alternative explanation for rhabdomyolysis may be a bacteremia with local multiplication and production of exotoxins or proteases within skeletal muscle. *S. equi* virulence factors that may account for muscle necrosis include an unidentified cytotoxic protein, several proteases, streptokinase, and streptolysin S.[95] Although, *S. equi* has not been cultured in skeletal muscle from horses with rhabdomyolysis, *S. equi* bacteria have been identified in affected muscle using immunofluorescent stains for both Lancefield group C carbohydrate and *S. equi* M protein.[93] There is currently no evidence that the *S. equi* involved is an atypical genetic strain of *S. equi*.[96]

A high mortality rate has been reported in horses receiving intravenous penicillin therapy once clinical signs of strangles and myopathy were well established. It is possible that early recognition of the signs of muscle stiffness in horses with *S. equi* infections and prompt aggressive treatment may be required for a successful outcome. Although streptococcal species are exquisitely susceptible to β-lactam antibiotics, a mortality rate of 85% has been reported in human group A streptococcal myositis despite penicillin treatment.[97] An antimicrobial that inhibits protein synthesis, such as rifampin, combined with intravenous penicillin might enhance survival rates in horses with *S. equi* rhabdomyolysis. In addition, flushing infected guttural pouches and draining abscessed lymph nodes will diminish the bacterial load. Nonsteroidal antiinflammatory drugs (NSAIDs) and possibly high doses of short-acting corticosteroids may assist in diminishing the inflammatory response. Control of unrelenting pain is a major challenge in horses with severe rhabdomyolysis. Constant rate infusion of lidocaine, detomidine, or ketamine may provide better anxiety and pain relief than periodic injections of tranquilizers. Horses should be placed in a deeply bedded stall and moved from side to side every 4 hours if they are unable to rise. Some horses may benefit from a sling if they will bear weight on their hindlimbs when assisted to stand.

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42.7.2.2

Infarctive Purpura Hemorrhagica

STEPHANIE J. VALBERG

Infarctive purpura hemorrhagica (IPH) is a severe form of purpura with a high fatality rate. In one study, prevalence of IPH was 3 of 53 cases of purpura.[98] Exposure to *S. equi* within 3 weeks of presentation, vaccination for *S. equi,* and a concurrent *Salmonella infantum* infection are reported inciting causes. Titers for serum enzyme-linked immunosorbent assay (ELISA) M protein may be markedly elevated.[99] The primary presenting complaint is often painful lameness with limb swelling, muscle stiffness, and/or colic. Careful physical examination reveals classic signs of purpura hemorrhagica such as petechia, oral infarctions resembling ulcers, and moderate well-demarcated limb edema; however, in addition, horses with IPH have focal firm intramuscular swellings (Fig. 42-9). Horses with evidence of colic may have markedly decreased borborygmi and hemorrhagic gastric reflux.

Hematologic abnormalities include a leukocytosis characterized by a neutrophilia with a left shift and toxic change, hyperproteinemia, hypoalbuminemia, and marked elevations in CK (47,000 to 280,000 U/L) and AST (960 to 7000 U/L) levels.[94,99] Peritoneal fluid obtained by abdominocentesis may be normal or may have an increased total protein, nucleated cell count, and RBC count if gastrointestinal infarction is present. Ultrasonographic examination of swollen muscle reveals focal hypoechoic lesions within muscle tissue.

Biopsies of abnormal muscle show diffuse acute coagulative necrosis, whereas samples from palpably normal muscle tissue show no pathologic abnormalities.

Fig. 42-9 Marked swelling of the left adductor muscles of the thigh caused by infarctive purpura hemorrhagica.

Fig. 42-10 Numerous infarctions of skeletal muscle caused by infarctive purpura hemorrhagica. (Photo courtesy of Dr. Beth Davis.)

Postmortem findings of horses with IPH include infarction of the skeletal musculature (Fig. 42-10), skin, gastrointestinal tract, pancreas, and lungs and *S. equi* abscessation of a lymph node. Definitive histopathologic findings include leukocytoclastic vasculitis and acute coagulative necrosis resembling infarction in numerous tissues.[99] IPH resembles Henoch-Schönlein purpura in humans, which is characterized by infarctive vasculitis of the skin, kidneys, and gastrointestinal tract resulting from IgA immune complex deposition. Immune complexes are present in the sera of horses with PH that appear to primarily be composed of IgM or IgA and streptococcal M protein.[100] Deposition of complement near immune complexes in vessel walls may result in cell membrane destruction, cell death, and vascular occlusion. The distinctive feature of IPH in horses is the extensive infarction of skeletal muscle and consequently marked elevation in serum CK and AST activity.

Early recognition of signs and aggressive antibiotic and corticosteroid treatment are essential to combat the high fatality rate with IHP. Treatment of Henoch-Schönlein purpura in humans, including cases with intestinal infarctions, involves high-dose intravenous pulse therapy with methylprednisolone followed by oral

corticosteroids plus immunosuppressive agents such as cyclophosphamide and azathioprine. One horse with IPH was successfully treated with penicillin, NSAIDs, and 3 weeks of dexamethasone (0.1 to 0.07 mg/kg) followed by a 10-week tapering course of oral prednisolone (2 mg/kg initially).[99]

42.7.2.3 Immune-Mediated Polymyositis

STEPHANIE J. VALBERG

Immune-mediated polymyositis (IMM) has recently been reported in horses.[33,101,102] The majority of horses are of quarter horse bloodlines and are either ≤8 years of age or ≥16 years of age. In approximately one third of horses with IMM, a triggering factor appears to have been exposure to *S. equi* or a respiratory disease. The most prominent clinical sign of IMM in quarter horses is rapid onset of muscle atrophy, particularly affecting the back and croup muscles (Fig. 42-11), accompanied by stiffness and malaise. Atrophy may progress to involve 50% of the horses' muscle mass within a week and may lead to generalized weakness. Focal symmetric atrophy of cervical muscles has been reported in a pony with IMM.

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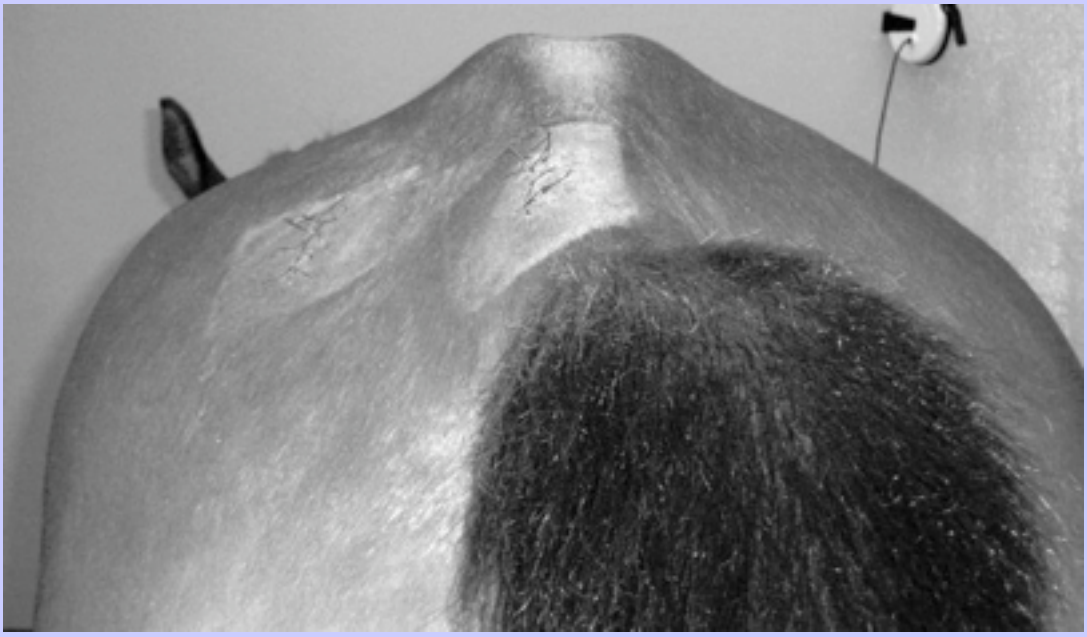
Fig. 42-11 Symmetric atrophy of the gluteal muscles with immune-mediated myositis. (Photo courtesy of Dr. Beth Davis.)



Hematologic abnormalities are relatively minor in affected horses and are usually restricted to mild to moderate elevations in serum CK and AST activity. However, in some cases serum muscle enzyme activities are normal. Muscle biopsy of epaxial and gluteal muscles shows lymphocyte vasculitis, anguloid atrophy, lymphocyte myofiber infiltration, fiber necrosis with macrophage infiltration and regeneration. Biopsies of semitendinosus or membranous muscles may show some evidence of atrophy and vasculitis, but significant inflammatory infiltrates may be absent in these tissues. The extent of the inflammatory infiltrates in epaxial muscles is such that a diagnosis can often be established from several formalin-fixed Tru-Cut samples.

The lymphocytic infiltrate seen in muscle samples from horses with IMM contains a high CD4:CD8 ratio with no evidence of immunoglobulin G (IgG) binding to myofibers.[33] The reason why specific muscle groups are affected in horses with IMM is unclear.

Horses with concurrent evidence of streptococcal infection should be treated with antibiotics. It is likely prudent to avoid intramuscular injections. Administration of corticosteroids appears to immediately improve signs of malaise and inappetence and prevented further progression of muscle atrophy. Recommended dosages are dexamethasone 0.05 mg/kg for 3 days, followed by prednisolone 1 mg/kg for 7 to 10 days tapered by 100 mg/week over 1 month. Serum CK activity often normalizes after 7 to 10 days. Muscle mass usually gradually recovers over 2 to 3 months. Horses that are not treated with corticosteroids may develop extensive muscle atrophy, but in many cases muscle mass will gradually recover. Recurrence of atrophy in susceptible horses is common and may require reintroduction of corticosteroid therapy. Some horses develop focal residual muscle atrophy.

42.7.3 VIRUS-ASSOCIATED MYOPATHY

STEVEN M. PARISH

Necrosis of skeletal and cardiac muscle occurs frequently in association with some viral diseases. In most situations, viral-induced muscle damage represents a component of systemic multiple organ system involvement. For example, myocarditis occurs in association with foot-and-mouth disease, equine influenza, and equine infectious anemia. Other diseases that cause myocarditis or skeletal muscle manifestations include bovine ephemeral fever, malignant catarrhal fever, bovine virus diarrhea, and bluetongue. Equine influenza A2 and equine herpesvirus 1 have been reported to induce primary muscle stiffness and clinical signs resembling those seen in horses with rhabdomyolysis.[103,104] Details concerning specific clinical manifestations can be found in other sections of this text.

42.7.4 SARCOCYSTOSIS

STEVEN M. PARISH

STEPHANIE J. VALBERG

Cysts of the sporozoan parasite *Sarcocystis* are commonly seen in routine histologic sections of the heart, esophageal, and skeletal muscle of cattle, sheep, goats, and horses.[105–108] More than 90% of horses over 8 years of age have sarcocysts in their esophageal muscles. Cysts may pose no problem, but with heavy infestations multisystemic dysfunction occurs.[105,109–111] Experimentally induced acute disease is characterized by fever, mild anemia, chronic myositis, and muscle wasting.

42.7.4.1 Epidemiology

The life cycle of the parasite involves two hosts: carnivores as the definitive host and cattle or horses as the intermediate host. Three species of sarcocysts, *Sarcocystis cruzi, Sarcocystis hirsuta,* and *Sarcocystis hominis,* are known to infect cattle; canids, felids, and primates are the definitive hosts for these species. Three sarcocyst species have been described in horse muscle: *Sarcocystis bertrami, Sarcocystis equicanis,* and *Sarcocystis fayeri*. Dogs have been identified as the definitive host for these equine sarcocyst species. In sheep and goats, *Sarcocystis ovicanis* and *Sarcocystis arieticanis* have been described, with canids as the

sheep and goats, *Sarcocystis ovicanis* and *Sarcocystis capracanis* have been described, with canids as the definitive host.

The most common mechanism for natural infection in cattle is by ingestion of feeds contaminated with infected carnivore feces. Feedlot workers using feed bunks as toilets may be a source of exposure for feedlot cattle.

42.7.4.1.1

Clinical Signs

Although low-level natural infection is common in cattle, when administered experimentally a dose of 200,000 sporocysts of *S. cruzi* is necessary to cause severe clinical disease.[105] Within 4 weeks the animal develops fever (39.4° C [103° F]), anorexia, salivation, weight loss, weakness, muscle fasciculations, severe depression, and sometimes death. Fever is the earliest sign and is biphasic relative to two periods of parasitemia, one occurring at 15 to 19 days and another at 25 to 42 days after inoculation. During the second febrile episode, affected calves frequently develop other clinical signs, particularly anemia. Extravascular hemolysis occurs, and hemorrhage into many tissues is common. The mechanisms involved in the hemolytic and hemorrhagic phases are likely to involve immune mechanisms. Mortality is greatest during this phase of the disease. Laboratory analysis may reveal elevations in serum urea nitrogen and bilirubin concentrations, sorbitol dehydrogenase, LDH, CK, and AST activity. If animals survive, these laboratory values usually return to normal in approximately 2 weeks. Animals surviving this phase commonly continue to be inappetent and have decreased weight gains; muscle atrophy; and hair loss on the neck, rump, and tail. These changes are mediated by alterations in a variety of pathways, the net result being a partitioning away of nutrients that are used for growth.[112] The anemia is ameliorated by a regenerative process, with normal hematologic values obtained in 1 to 2 months after clinical recovery. Similar clinical findings are seen in sheep and goats. Abortion is common. A syndrome similar to that described in cattle has been reported in two horses with malaise, fever, and muscle atrophy.[108,113]

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Diagnosis of sarcocystosis requires history, clinical signs, laboratory and serologic evaluation, and the demonstration of immature cysts in muscle biopsies. It is important to differentiate between the muscle cysts caused by *Sarcocystis* and those produced by toxoplasmosis because toxoplasmosis does not cause clinical disease in cattle.

42.7.4.1.2

Treatment

Specific treatment is effective only in the early stages of sarcocystosis in food animals. Experimental therapy with amprolium or the ionophore antibiotics before the second stage of parasitemia frequently prevents development of clinical sarcocystosis in cattle.[114] Successful treatment of one horse with sarcocystosis using phenylbutazone, trimethoprim-sulfa, and pyrimethamine is reported.[113]

Control involves preventing gross contamination of cattle and equine feeds with carnivore feces. The common use of ionophore antibiotics (e.g., growth promotants and coccidiostats) in cattle is also likely to help reduce the incidence of sarcocystosis.

42.7.4.2

NUTRITIONAL AND TOXIC RHABDOMYOLYSIS

42.7.4.2.1

Nutritional Myodegeneration

JOHN MAAS

STEPHANIE J. VALBERG

42.7.4.2.1.1

Definition and Etiology

Nutritional myodegeneration (NMD; white muscle disease, stiff lamb disease, nutritional muscular dystrophy) is a peracute to subacute myodegenerative disease of cardiac and skeletal muscle caused by a dietary deficiency of selenium or vitamin E.[115–118] This syndrome occurs in most farm animal species but is most commonly found in young, rapidly growing calves, lambs, kids, and foals, particularly those born to dams that consumed selenium-deficient diets during gestation. The disease has also been reported in yearling and adult cattle and has been suspected in adult horses.

Selenium and vitamin E appear to be synergistic in preventing NMD. However, on the basis of prophylaxis and response to treatment, selenium deficiency appears to be more important.

42.7.4.2.1.2

Clinical Signs

There are two distinct syndromes of NMD: a cardiac form and a skeletal form. The cardiac form is associated with signs of peracute to acute myocardial decompensation, but the skeletal form is associated with skeletal myasthenia and difficulty in ambulation. In both forms the most rapidly growing animals in the herd or flock are affected commonly.

Most cases of NMD are diagnosed during the first year of life. Evidence also suggests that an in utero form of NMD may occur, with affected animals born with myodegeneration or developing myodegeneration soon after birth.

The cardiac form of NMD usually has a sudden onset; it is usually diagnosed in the animal that is either in a state of severe debilitation or dead. The cardiac form often manifests with lesions in the heart, diaphragm, and intercostal muscles. In dead animals there may be evidence of sudden agonal death. In living animals there is usually a rapid onset of depression and respiratory distress. A foamy nasal discharge, possibly bloodstained, is seen often, resulting from pulmonary edema and dyspnea. Profound weakness, recumbency, and a rapid, often irregular heartbeat may be detected. Cardiac murmurs are heard occasionally on auscultation. Rectal temperature is normal usually or may be elevated because of increased muscular work associated with respiratory efforts. Most calves are depressed, with dyspnea, tachypnea, and increased rectal temperature. These cases must be differentiated from pneumonia. The clinical course is frequently short, with death occurring commonly in less than 24 hours despite medical therapy. Occasionally an animal responds to therapy, but such animals often fail to thrive because of residual myocardial damage. Animals with predominantly cardiac signs may also manifest mild skeletal muscle problems associated with NMD.

The skeletal form of NMD frequently has a slower onset characterized by muscular weakness or stiffness. Animals may be recumbent and unable to stand. Those that are able to rise on their own or with assistance show muscle weakness, trembling of limb muscles, or stiffness. Stiffness is more

with assistance show muscle weakness, trembling of limb muscles, or stiffness. Stiffness is more pronounced as fibrosis occurs after an acute attack. Most affected animals are able to remain standing only for short periods. Supporting muscle groups of the frontlimbs and hindlimbs may appear swollen and may be hard and painful on palpation. Commonly affected muscle groups may include the gastrocnemius, semitendinosus, semimembranosus, and biceps femoris and muscles of the lumbar, gluteal, and neck regions. If the diaphragm and intercostal muscles are affected, the animal may show respiratory distress and evidence of increased abdominal effort when breathing. Cardiomyopathy occurs often, along with changes in the diaphragm and intercostal muscles. The muscles of the tongue may be involved, resulting in dysphagia. Dysphagia may be the only sign in some affected animals; foals and lambs are presented in this condition more often than calves. The rectal temperature is normal or moderately elevated, resulting from pain and the release of myoglobin associated with myodegeneration. Some animals exhibit what appears to be abdominal pain with violent thrashing. Heart sounds are normal usually, although the heart rate may be increased; however, myocardial damage and signs consistent with cardiac dysfunction may be present in cases of skeletal NMD. Animals with skeletal NMD often respond favorably to treatment and rest. Improvement is evident after a few days, and within 3 to 5 days animals can often stand and walk.

Differentiation of NMD from other diseases causing sudden death or recumbency is important. Infectious diseases resulting in septicemia, pneumonia, and toxemia may have similar presenting signs. Acute heart failure resulting from cardiac anomalies, cardiotoxic agents such as those found in plants (oleander, cassia, yew, white snakeroot, and gossypol toxicity from cottonseed), and the ionophore antibiotics should also be considered. Other diseases that cause stiffness of gait, weakness, and recumbency with no change in mental status must be differentiated from NMD. Spinal cord compression, cerebellar disease, suppurative and nonsuppurative meningitis or myelitis, polyarthritis, neurotoxins such as organophosphates, tetanus, pelvic fractures, and parasitic myositis all can cause recumbency. Clostridial myositis and traumatic injuries to muscles, long bones, and joints should be considered. Diseases characterized by abdominal pain may resemble NMD, because they may also cause stiffness of gait, weakness, and recumbency.

42.7.4.2.1.3

Clinical Pathology

Significantly elevated CK, AST, and LDH activities occur during the acute phase of myodegeneration. In clinical cases CK levels are in the thousands of international units per liter. In animals recumbent because of a disease other than NMD, CK is elevated only into hundreds of or perhaps a few thousand international units per liter in heavy animals. Progressively decreasing activities of CK can be used as a prognostic indicator of a reduction in the myodegenerative process.

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In foals, other reported abnormal laboratory findings include variable hyperkalemia, hyperphosphatemia, hyponatremia, and hypochloremia.[118] Myoglobinuria is found often in foals and yearling cattle with NMD. Myoglobinuria is less common in younger calves. Evidence of dehydration, reflected by elevated serum protein concentrations and hemoconcentration, is common in nonambulatory animals unable to nurse or drink water.

The selenium status of an animal or members of a group can be determined by laboratory analysis of tissue biopsies and whole blood (Table 42-2). Vitamin E status can be determined on serum or plasma samples. In the clinical setting, blood samples are more frequently used. Blood or plasma samples provide information about the circulating levels of selenium and vitamin E, respectively, and are satisfactory for assessing intermediate to long-term nutritional status; however, short-term supplementation or injections can confuse interpretation of circulating levels of selenium or vitamin E

supplementation or injections can confuse interpretation of circulating levels of selenium or vitamin E. Tissue biopsies and tissue specimens obtained at slaughter and necropsy provide an indication of storage and can also be used to assess herd status and success of supplementation. Whole blood selenium analysis is preferred over plasma and serum.[119] Whole blood selenium concentrations ranging from 0.07 to greater than 0.1 ppm (µg/g) are considered normal in large animals. Normal liver concentrations of selenium are 0.9 to 1.75 µg/g of dry matter (DM), 0.9 to 3.5 µg/g DM, and 1.05 to 3.5 µg/g DM for cattle, sheep, and horses, respectively.[120] Selenium-dependent glutathione peroxidase (GSH-Px) formed in the red cells during erythropoiesis also provides an index of body selenium status. Cross-reacting enzymes, such as glutathione reductase, are not found in erythrocytes. Adequate GSH-Px activities are greater than 30 U/mg of hemoglobin per minute in cattle, 60 to 180 U/mg of hemoglobin per minute in sheep, and 20 to 50 U/mg of hemoglobin per minute in horses. However, GSH-Px reference values are specific only to the laboratory where the analysis is performed and must be validated by comparison with blood selenium concentration. The activity of GSH-Px in RBCs of domestic species remains constant for 4 to 6 days when maintained at 39° F (4° C); after this time significant decreases occur. The critical concentration of vitamin E (α-tocopherol) in plasma is 1.1 to 2 ppm (µg/g) in large animals. Vitamin E deteriorates rapidly in plasma samples. Therefore plasma samples for α-tocopherol analysis need to be put on ice immediately, protected from the light by wrapping in tin foil, and stored (–21° F [–70° C]) if analysis is to be delayed.

Table 42-2 Deficient, Marginal, and Normal Concentrations of Whole Blood Selenium and Glutathione Peroxidase Activities in Sheep and Cattle [67,71]

Whole Blood Selenium (ppm)*	GSH-Px (U/mg Hb/min)	Category	Interpretation
0.01-0.04	0-15	Deficient	Selenium supplementation is always beneficial.
0.05-0.06	15-25	Marginal	Selenium supplementation is often beneficial.
0.07	25-500	Normal	Selenium supplementation is never beneficial.
GSH-Px assays are performed by different procedures in individual laboratories, and quantitative relationships between blood selenium concentrations and blood GSH-Px activities can vary. These numeric relationships are site-specific, and interpretation must account for these differences.			

* *GSH-Px,* Glutathione peroxidase; *PPM,* parts per million.

42.7.4.2.1.4

Pathophysiology

The effects of selenium and vitamin E deficiency have been postulated to result, at least in part, from the destruction of cell membranes and proteins leading to a loss of cellular integrity.[115,121] Selenium, which has been shown to be an essential component of at least five selenoproteins[122] (three glutathione peroxidase enzymes, a deiodinase in liver and kidney that converts T_4 to T_3, and selenoprotein-P, a plasma protein of unknown function), and vitamin E (α-tocopherol) serve as biologic antioxidants. During normal cellular metabolism highly reactive forms of oxygen (free radicals) are produced. These include hydrogen peroxide, hydroperoxides, lipoperoxides, superoxide, various hydroxy radicals, and singlet oxygen. Vitamin E is active within the cell membrane as a lipid-soluble antioxidant that scavenges free radicals that otherwise might react with unsaturated fatty acids to form lipid hydroperoxides. In contrast, GSH-Px destroys hydrogen peroxide and lipoperoxides that have already been formed and converts them to H_2O or relatively harmless alcohols. Other enzymes such as catalase and superoxide dismutase are also involved in this protective process.

Apparently important interrelationships exist among the selenium and vitamin E status of the animal, the level of polyunsaturated fatty acids (PUFAs) in the diet,[115,121] and NMD, particularly in ruminants.[115] PUFAs of dietary origin can undergo peroxidation to hydroperoxides, forming toxic free radicals. During active growing periods pasture grasses and plants contain high concentrations of linolenic acid, a PUFA. Under normal conditions the rumen is thought to be important in saturating dietary unsaturated fatty acids. However, concentrations of PUFAs in the plasma often increase in calves recently turned out to pasture, possibly enhancing the chance of free radical formation and tissue damage. This indicates that the capacity of the various protective mechanisms can be overwhelmed by dietary factors such as high levels of PUFAs. It is not surprising that selenium- or vitamin E—deficient animals may be at a greatly increased risk of tissue oxidative damage when exposed to such diets. However, the potential for induction of NMD by this process should not be overemphasized, because calves on a milk diet may be severely affected.

The precise interrelationships among selenium, vitamin E, other metabolic factors, and triggering mechanisms in NMD are not fully understood because many animals deficient in selenium or vitamin E have no evidence of muscle disease. In certain situations deficiencies of both selenium and vitamin E are necessary for disease to occur. In other animals NMD can occur when a deficiency of only one of the agents is present and levels of the other are normal in blood and tissues.

42.7.4.2.1.5

Epidemiology

NMD occurs in all farm animals and is seen most commonly in young, rapidly growing calves, lambs, kids, and foals. The occurrence of NMD in very young animals usually reflects a deficiency in their dams during a substantial portion, if not all, of the gestation period. The selenium and GSH-Px values of neonatal calves tend to be similar to those of their dams.[123,124]

Marginally to severely selenium-deficient areas occur throughout a large portion of the United States and other countries of the world.[115,125] Forages and grains produced in the northeastern and eastern seaboards and northwestern regions of the United States are particularly deficient because of low soil levels of selenium. Acid soils and those originating from igneous (volcanic) rock are often selenium deficient, as are those having high sulfur content or soils treated with sulfur-containing fertilizers. Sulfur inhibits selenium uptake by plants and absorption by animals. Different forages in a specific area will also vary in their selenium content. Legumes take up less selenium than do grasses. Also, forage selenium concentrations are lowest during periods of rapid growth such as in the spring and during

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selenium concentrations are lowest during periods of rapid growth such as in the spring and during times of highest rainfall.

Vitamin E deficiency occurs most commonly when animals are fed poor-quality hay, straw, or root crops. Grain treated with propionic acid and having high moisture content is commonly vitamin E deficient. Storage of grain crops for extended periods results in marked decreases in their vitamin E content. Calves fed milk replacers that contain fish oil, linseed oil, soybean oil, or corn oil, all of which increase the dietary levels of unsaturated fatty acids, require increased dietary supplementation of vitamin E to avoid deficiency. In contrast, cereal grains, green growing pastures, and properly prepared hay usually have adequate vitamin E.

In young ruminants the majority of cases of NMD occur in calves 2 to 4 months of age during the spring and summer months in association with exercise when at pasture, although congenital and perinatal cases do occur. Histologic lesions consistent with NMD have also been seen in late-term aborted fetuses.[120] These findings are suggestive of an in utero form of NMD in large animals. Yearling cattle housed during the winter, fed diets high in grain with high moisture content, and then turned out in the spring may also be affected. Lambs born in confinement and turned out to pasture at 1 to 3 weeks of age frequently develop signs of NMD. Stresses such as transport, herding, and driving may also precipitate signs of NMD. In horses, NMD generally occurs during the first year of life, with most cases observed from birth to weaning.[116,126]

42.7.4.2.1.6

Necropsy Findings

Bilaterally symmetric myodegeneration is a consistent finding in NMD. Skeletal muscle degeneration is characterized by pale discoloration and a dry appearance of affected muscle, white streaks in muscle bundles, calcification, and intramuscular edema (Fig. 42-12). The white streaks seen in muscle bundles represent bands of coagulation necrosis or, in chronic cases in which insults may have occurred weeks before, may represent fibrosis and calcification. Affected muscle bundles are often adjacent to apparently normal or minimally affected muscle. The color of normal muscle in young calves is pale because of reduced myoglobin concentrations; therefore close inspection and histologic examination are necessary in cases of suspected NMD. Cardiac muscle undergoes changes similar to those of skeletal muscle. In calves the left ventricle and septum are most frequently involved (Fig. 42-13), but in lambs both ventricles are usually involved. Myocardial degeneration usually extends through the full thickness of the ventricular wall.

Histologically, affected muscle fibers may be hypercontracted and fragmented with some mineralization of muscle fibers and others undergoing macrophage infiltration. In yearling cattle, type I muscle cells are more frequently affected.

42.7.4.2.1.7

Treatment and Prognosis

In the cardiac form of NMD myocardial damage is often extensive and incompatible with life. Only rarely is treatment successful. In contrast, the skeletal form of NMD is more generally amenable to treatment, although the prognosis for clinical recovery from the skeletal form of NMD is guarded and often depends on whether secondary complications such as respiratory disease develop. In all cases of NMD, therapy should involve specific supplementation with selenium and vitamin E and general supportive care.

Fig. 42-12 White streaks within diffusely pale skeletal muscle caused by nutritional myodegeneration.

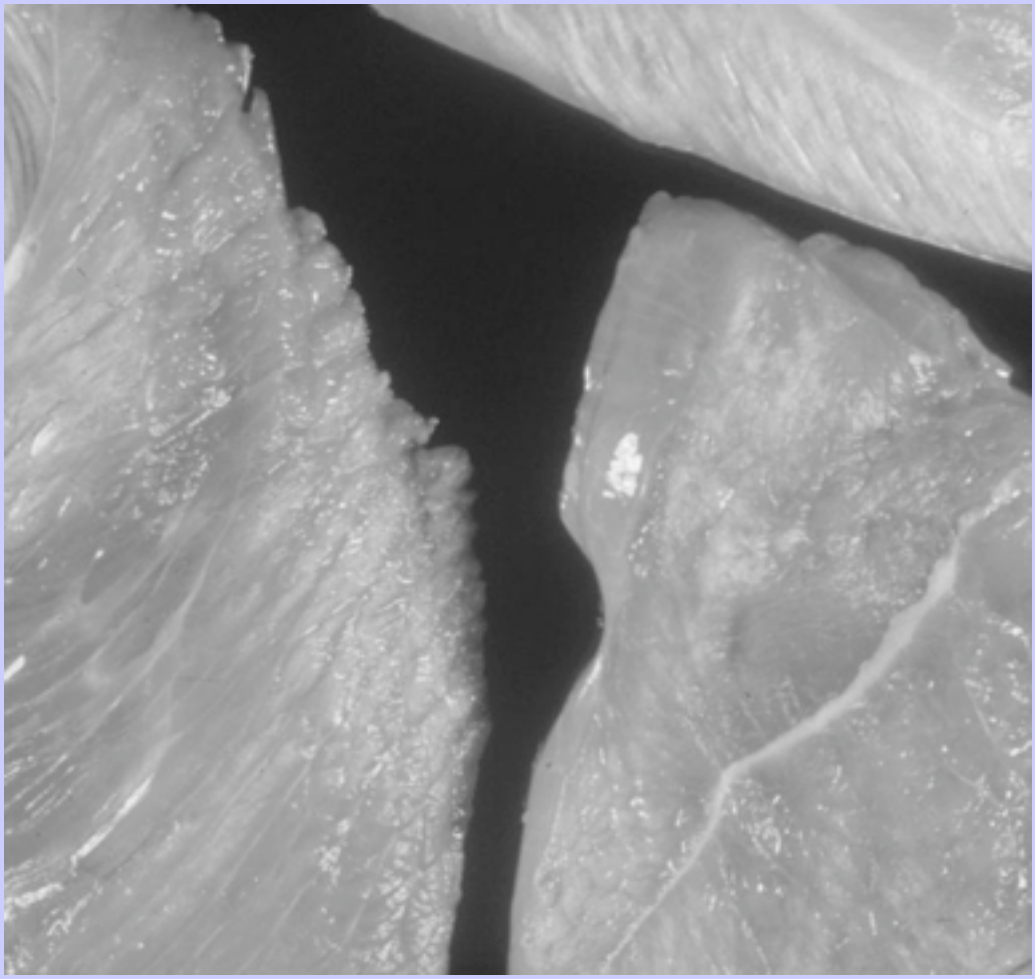
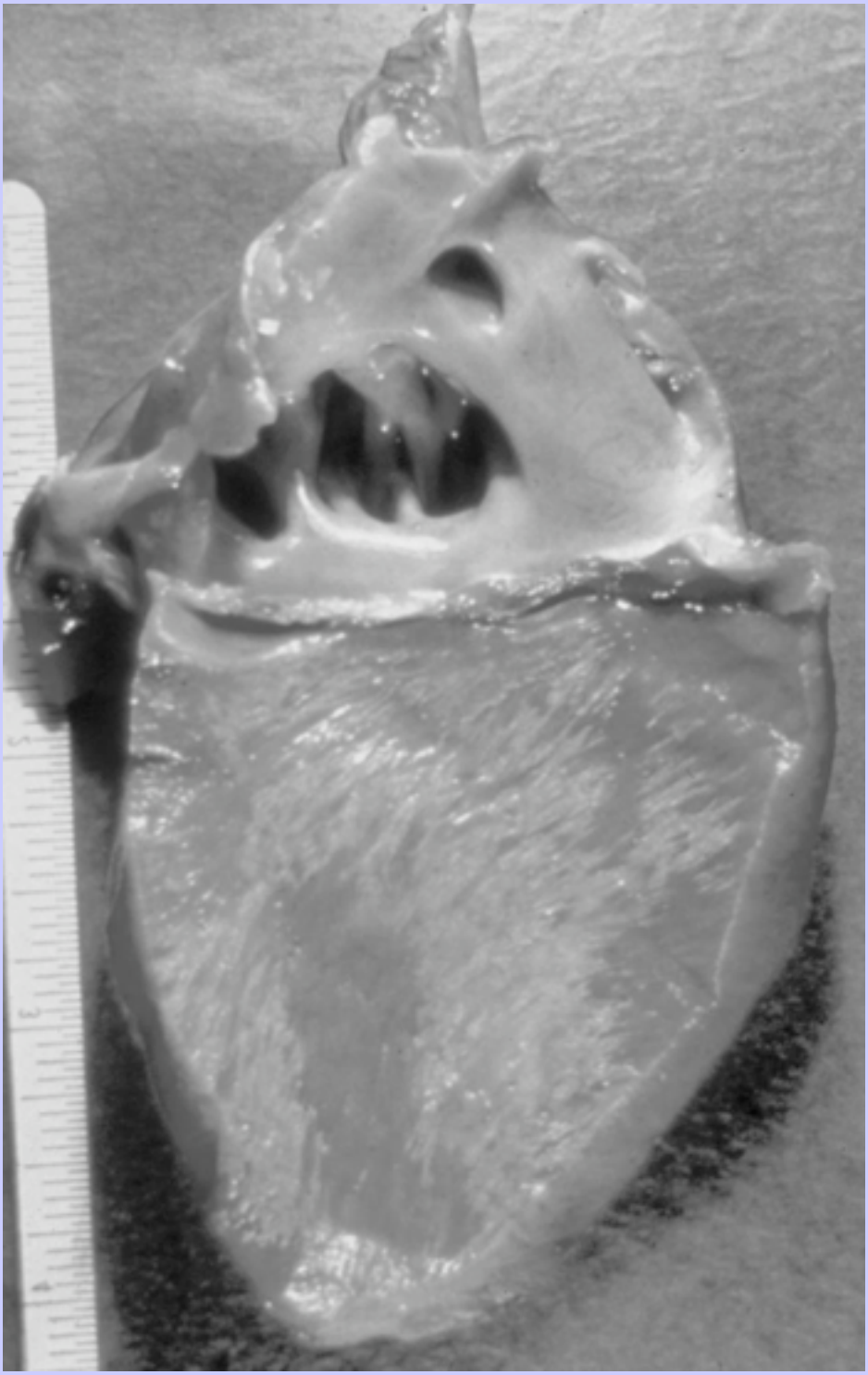


Fig. 42-13 Pale areas of muscle necrosis in the myocardium of a calf with nutritional myodegeneration.



Alleviation of selenium-responsive NMD requires the use of injectable selenium products. These are available with selenium concentrations varying from 1 mg of selenium per milliliter to 5 mg/mL, with all products containing 50 mg/mL (68 IU) of vitamin E as DL-α-tocopheryl acetate. The label dose for

all products containing 50 mg/mL (50 IU) of vitamin E as DL-α-tocopheryl acetate. The label dose for selenium is 0.055 to 0.067 mg/kg (2.5 to 3 mg/45 kg) of body weight given intramuscularly or subcutaneously. Dosage of these injectable products should not be greatly increased above the label dosage to prevent an inadvertent selenium toxicosis. However, when using the vitamin E and selenium combinations, the amount of vitamin E in these combination products is present as a preservative for the solution and is therefore insufficient for vitamin E supplementation. Injectable vitamin E products are now available that contain 300 IU of vitamin E per milliliter as D-α-tocopherol* and 500 IU of vitamin E per milliliter as D-α-tocopherol.† Administration of these products increases the tissue and/or plasma level of vitamin E activity for approximately 3 weeks in farm animals. The bioavailability of vitamin E from injectable products is dependent on the form of vitamin E (the alcohol form, D-α-tocopherol, being the most active) and the amount and quality of the solution emulsifier used. Bioavailability data on injectable vitamin E products should receive careful clinical consideration. Oral supplementation is the general approach to provide additional dietary levels of vitamin E. Recommended levels of supplementation for calves range from 15 to 60 mg of DL-α-tocopheryl acetate per kilogram of dry feed.[125] For horses a daily supplement of 600 to 1800 mg of DL-α-tocopheryl acetate has been recommended.[126] Oral α-tocopherol is now available for all species and contains 500 IU of vitamin E per milliliter.‡ The recommended dose of this product is 1 to 3 IU/lb of body weight. Studies with injectable selenium show that absorption and distribution occur rapidly.[127] It is thought that incorporation of selenium into heart, skeletal muscle, and other tissues may be very rapid and could account for the rapid improvement in clinical signs seen in reversible cases. The discovery of four new selenoproteins may help explain these clinical observations.[122] This improvement can occur even though blood GSH-Px activity rises slowly because of the delay caused by erythropoiesis and release of red cells from the bone marrow.[127] However, platelet GSH-Px activity rises within hours and may be a more accurate reflection of changes in muscle and other tissues.

Supportive therapy may include administration of antibiotics to help combat secondary pneumonia and infected decubital lesions that are common in recumbent patients. Provision of adequate energy intake and attention to the fluid and electrolyte balance are of critical importance if recovery is to be successful.

* Vital E, Schering-Plough Animal Health, Kenilworth, NJ.

† Emject E-500, Stuart Products, Bedford, TX.

‡ Emcelle Tocopherol, Stuart Products, Bedford, TX.

42.7.4.2.1.8

Prevention and Control

The prevention and control of NMD are achieved through supplementation of selenium and vitamin E. Although selenium deficiency is implicated more commonly in most NMD syndromes, attempts to ensure adequate provision of selenium and vitamin E should be undertaken. Under current U.S. federal regulations, selenium can be incorporated into the total ration of ruminants and other species to a level of 0.3 parts per million (ppm). In salt and mineral mixtures formulated for free-choice feeding, selenium can be incorporated at 90 ppm for sheep and 120 ppm for cattle. In certain areas or in herds, levels as high as 200 ppm selenium in salt and mineral mixtures may be necessary to maintain adequate selenium levels in the animals. Federal regulations limit the intake of supplemental selenium by sheep to 0.7 mg/head/day and by cattle to 3 mg/head/day. The use in ruminants of ruminoreticular boluses, which release a precise amount of selenium daily, has been commonplace in many countries of the world; however, under current U.S. Food and Drug Administration (FDA) guidelines these products are not available in the United States. These slow-release boluses can replace supplementation by salt mixtures or by

the United States. These slow-release boluses can replace supplementation by salt mixtures or by injections and are extremely valuable in extensive grazing systems. Alternatively, individual animals can be supplemented by periodic (30- to 60-day intervals) injections of selenium and vitamin E preparations to help maintain body concentrations and assist in transplacental transfer of selenium to the fetus.

Oral supplementation for horses at 1 mg of selenium per day increases blood selenium concentrations above levels known to be associated with NMD.[128] Supplementation of pregnant mares is advised in areas known to be selenium deficient; however, only limited selenium may cross the placenta.[117] Supplementation during lactation increases the levels of selenium in milk and thus provides a potential means of selenium supplementation in foals; however, evidence in cattle indicates that this increased level of selenium in milk may not meet nutrient requirements.[123–125]

Regardless of the method of supplementation, periodic blood (or tissue) sampling of animals at risk is recommended to ensure desired levels of selenium. In high-risk areas, samples should be taken every 60 to 90 days to determine selenium status in susceptible animals and every 6 to 12 months to monitor supplementation. On the basis of these assessments, adjustments to the rate or extent of selenium supplementation may be made.

Feeding animals properly prepared and stored hay and grain or allowing them access to high-quality green forage should ensure adequate vitamin E intake.

42.7.4.2.2

Toxic Causes of Rhabdomyolysis

MICHAEL MURPHY

STEPHANIE J. VALBERG

Ingestion of toxic substances in feed or forage is a common cause of toxic rhabdomyolysis.

42.7.4.2.2.1

Toxic Plants

Gossypol is of greatest significance in swine. Monogastrics, including young calves, should not ingest feed containing more than 200 ppm of gossypol. Mature ruminants may tolerate 20 g of gossypol per day. This normally amounts to 5 to 6 lb of whole cottonseed per head per day.[129] Two common forage toxins that cause myonecrosis are *Cassia* species and tremetone-containing plants. *Cassia obtusifolia* (sicklepod) is prevalent in the southeastern United States, and ingestion of seeds by swine, ruminants, or horses may cause a degenerative myopathy and cardiomyopathy with evidence of myofiber atrophy, segmental necrosis, and mitochondrial disruption.[130] White snakeroot *(Eupatorium rugosum)* grows in shaded areas of the eastern and central United States,[131] and rayless goldenrod *(Isocoma wrightii)* is common in the Southwest on open pastures. These tremetone-containing plants can cause a fatal cardiomyopathy and severe skeletal muscle degeneration in horses when ingested at 0.5% to 2% of body weight.[132,133] Other grazing livestock are likely to be affected by ingestion of these plants at 2% of body weight. Tremetone remains active in hay and in the stalks of the dead plants on pasture, so both the fresh and the dried form of the plants should be kept from livestock.[134] Microsomal activation of the toxin in the liver may be necessary for toxic effects.[132]

42.7.4.2.2.2

Atypical Myopathy

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A highly fatal myopathy that occurs in large numbers of horses on pasture during cold wet conditions occurs in the fall in Europe and the midwestern United States.[135–139] Terms such as *atypical myopathy, atypical myoglobinuria,* and *pasture myopathy* have been used to describe this syndrome. Affected horses are usually kept on pasture for more than 12 hours per day without snow cover when minimum daily temperatures range from 29° F to 56° F and weather is often inclement. Clinical signs develop acutely and include muscular weakness, sweating, fasciculations, stiffness, tachycardia, tachypnea, recumbency, and, when urine is observed, myoglobinuria. The most notable change in serum biochemistry is a marked increase in serum CK and AST activity. Serum troponin I concentrations may be high, indicating cardiomyopathy. Postmortem findings include extensive necrosis in postural and respiratory muscles and, in 50% or more of cases, myocardium (Fig. 42-14). Serum vitamin and selenium as well as urine tremetone concentrations are normal. Frozen sections of myocardium, intercostal, diaphragm, or deep postural muscles show marked intracellular lipid accumulation in oxidative fibers (oil red O stain). A few horses have survived with aggressive fluid therapy, antioxidant, and antiinflammatory treatment including dimethyl sulfoxide (DMSO), vitamin E, vitamin C, and NSAIDs.[135] The cause of pasture myopathy is suspected to be an ingested or enterically produced toxin (e.g., bacterial toxin, mycotoxin, or phytotoxin that disrupts lipid metabolism).[138] Soil-borne ionophores or clostridial toxins have been suggested as possible causes.[139]

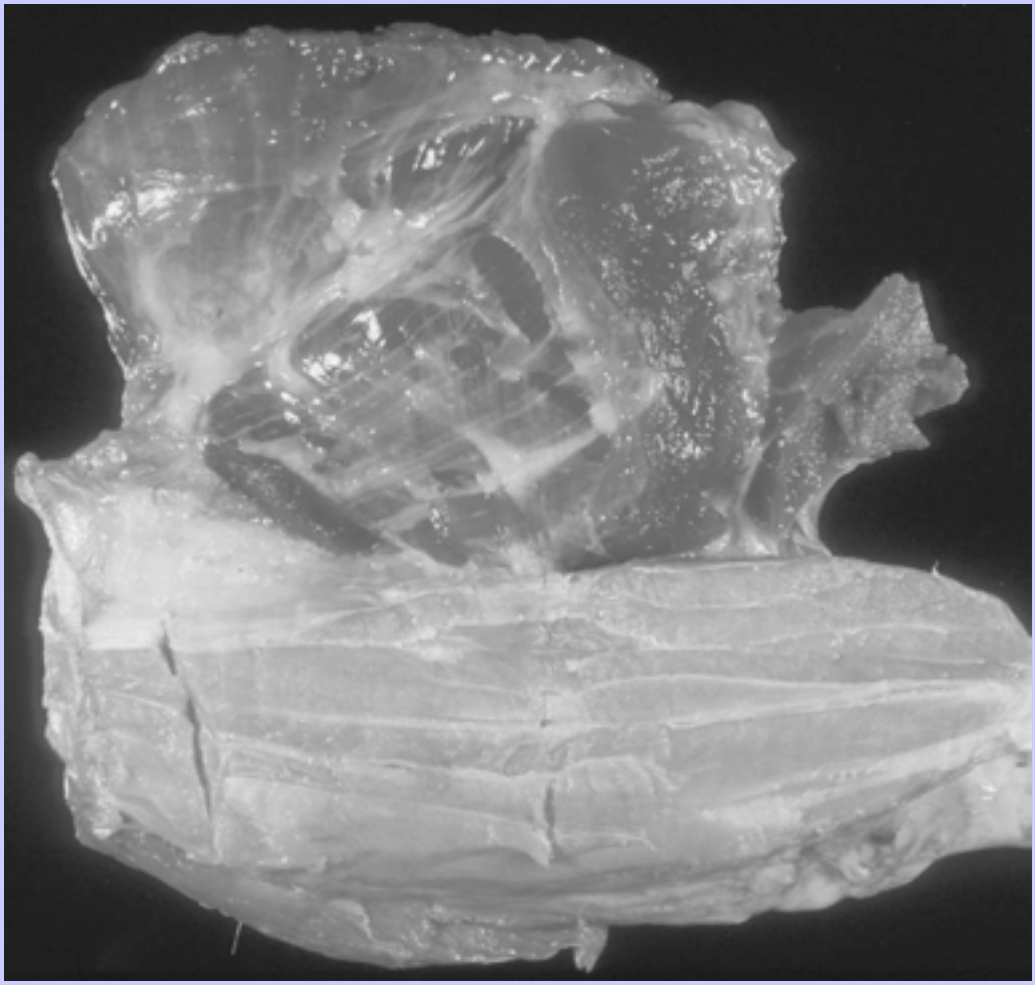
42.7.4.2.2.3

IONOPHORES

Ionophores are commonly added to feeds for their growth promotion and coccidiostat properties. Species differences in sensitivity to ionophores and the variety of ionophores on the market have led to several cases of ionophore-induced toxicosis. Rhabdomyolysis and cardiomyopathies are common sequelae to ionophore toxicosis. Experimental studies have indicated that LD_{50} values for monensin are 2 to 3, 12, 17, 26, and 21 to 36, for horses, sheep, pigs, goats, and cattle, respectively. Feed concentrations of 100 g/ton and 400 g/ton have been fatal to sheep and cattle, respectively.[129,140] Newborn calves given 100 mg of lasalocid three times daily for treatment of cryptosporidiosis experience muscle necrosis.[141] Other ionophores include naracin, salinomycin, and laidlomycin. Ionophores are quickly eliminated from the body after exposure.

Fig. 42-14 The lower muscle group shows severe compartmental muscle necrosis resulting in total pallor and friable muscle

tissue. In comparison the upper muscle group is normal in color and grossly unaffected.



42.7.4.2.2.4

CHEMICAL TOXINS

Several chemical agents have been associated with muscle necrosis on rare occasions. Parenteral products, insecticides, and feed contaminants have been implicated. Muscle necrosis has been reported in cattle and pigs that received injections of lidocaine, diazepam, digoxin, levamisole, nitroclofene, pentazocine, thiazinamium, chloramphenicol, and oxytetracycline and in horses after injectable ivermectin administration. One of 70 horses poisoned with blister beetles developed muscle necrosis.[87,142] Animals with organophosphate toxicosis, particularly from parathion, may develop muscle necrosis.[143–145] Several miniature horses being fed a complete feed containing tetrachlorvinphos, a feed-through fly control agent, were reported to develop chronic myonecrosis involving masseter, tongue, neck, respiratory muscles, and postural muscles and occasionally cardiac muscle.[146] Affected horses showed signs of lethargy, dysphagia, fasciculations, tachypnea, and tachycardia. Muscle tissue showed evidence of chronic myonecrosis as well as lipid accumulation. Myonecrosis was attributed to

acetylcholine accumulation at muscarinic and nicotinic sites, producing oxidant stress. Low selenium concentrations may contribute to the toxicosis.

42.7.4.3 TRAUMATIC RHABDOMYOLYSIS

42.7.4.3.1 Compartment, Downer, and Muscle Crush Syndrome of Cattle

DAVID R. HODGSON

STEPHANIE J. VALBERG

Muscle damage commonly accompanies the downer syndrome in large animals. The downer syndrome is discussed in greater detail in Chapter 41. Animals weakened by disorders such as hypocalcemia are more prone to tearing adductor or semitendinosus and membranosus muscles in attempts to rise.[32,147] Initial traumatic laceration of muscle leads to edema and inflammation, both of which may exacerbate local tissue degenerative changes. In addition, the weight of a recumbent animal on dependent muscle groups creates significant increases in intramuscular pressure, resulting in decreased perfusion and ischemia of muscle and nerve. Signs of weakness and peroneal or tibial nerve paralysis most commonly accompany this type of injury. Mild elevations in serum CK can be expected in cows that are recumbent, but elevations greater than 5000 U/L usually indicate traumatic muscle damage. Treatment requires correcting the underlying cause of recumbency, fluid therapy if renal damage is evident, NSAIDs, good nursing care, adequate footing and bedding, and lifting or rolling the animal several times a day. Aquatherapy using float tanks for cattle also appears to be beneficial in relieving the pressure on muscle groups.

42.7.4.3.2 Postanesthetic Myoneuropathy

Postanesthetic myoneuropathy is a condition that has become much more prevalent since the advent of inhalation general anesthesia. The disorder can be categorized as occurring in two forms: (1) localized myopathy-neuropathy, and (2) generalized myopathy somewhat similar to MH.

42.7.4.3.3 Localized Myopathy-Neuropathy

42.7.4.3.3.1 Clinical Signs

Localized myopathy usually occurs in muscles that are in contact with a hard surface during anesthesia or those in which arterial blood supply is compromised through positional occlusion. Commonly affected muscles include triceps, deltoid, masseter, hindlimb extensors, or, if the horse has been in dorsal recumbency, the hindlimb adductor and gluteal muscles.[148–150] Injury also may occur to nerves in these areas, resulting in temporary radial, peroneal, or femoral nerve paralysis (Fig. 42-15). Clinical signs may be apparent on recovery or may be delayed for periods of up to 30 to 60 minutes after the horse has recovered from anesthesia. Affected muscles may be swollen, hot, and painful on deep palpation; and the horse is often reluctant to bear weight on the affected limb. Myasthenia (weakness) of affected muscles is common, particularly with peripheral nerve involvement. In some horses this condition may limit the animal's ability to stand for some time after anesthesia. The loss of muscle strength, particularly when involving adductor muscles, can contribute to orthopedic injury during repeated attempts to rise. Many horses with mild to moderate muscle injury recover over a period of [148]

hours to days even if untreated.[148]

Fig. 42-15 Postanesthetic myoneuropathy showing paralysis of the right femoral and peroneal nerves.

42.7.4.3.3.2

Etiology

A variety of factors acting alone or in combination have been suggested to contribute to this disorder. The most important factors include ischemia and hypoperfusion as a result of prolonged immobility, muscle compression, systemic hypotension, and hypoxia.[148–152] There is increased lactate efflux from dependent muscles during anesthesia in horses that develop a myopathy, supporting the contention that these muscles experience compromised perfusion.[151,152] Halothane anesthesia has a greater propensity than isoflurane to compromise tissue oxygen delivery even in nondependent muscles.[150] If mean arterial pressure is allowed to fall below 55 to 65 mm Hg for several hours during inhalation anesthesia, particularly if mechanical ventilation is not used, the incidence of postanesthetic myopathy increases substantially.[152]

42.7.4.3.3.3

Diagnosis

Diagnosis is based on a history of anesthesia or prolonged recumbency, clinical signs, and possibly clinical pathology examinations. Laboratory findings include elevations in serum CK and subsequently serum AST and serum LDH activities. Elevations in CK levels of thousands to tens of thousands of international units per liter are commonly demonstrated in horses with moderate forms of the myopathy.

42.7.4.3.3.4

Treatment

Horses demonstrating only minor localized manifestations of the myopathy usually have an uncomplicated recovery with little or no treatment.[148] Supportive care, including the use of antiinflammatory drugs, DMSO, and dantrolene sodium 2 to 4 mg/kg PO, often is sufficient in mild to moderate cases.[153] Significant muscle atrophy may develop over the ensuing 3 to 4 weeks but usually will resolve within 2 to 3 months. Treatment of more severe cases is outlined under generalized reactions.

42.7.4.3.3.5

Control

Correct positioning and judicious use of padding and water- or air-filled mattresses can reduce dependent muscle pressure up to 50%, thereby aiding in the reduction of this disorder. In addition, through elevation of the upper limb during anesthesia, the pressure on the lower limbs is significantly reduced. Pulling the lower forelimb forward also markedly reduces pressure in the dependent triceps muscle. When the horse is in dorsal recumbency, padding under the shoulders and hips is absolutely imperative.

Maintaining anesthesia at the lightest plane possible for a specific surgical procedure is beneficial in prophylaxis. Similarly, if possible, maintaining systemic mean arterial blood pressure above 80 to 85 mm Hg during anesthesia is advisable. The use of inotropic agents such as dobutamine during anesthesia has been useful in reducing the occurrence of anesthetic myopathies. Administration of dantrolene sodium (2 to 4 mg/kg PO) 1 hour before induction of anesthesia may result in a reduction in the incidence of this myopathy in some susceptible horses.

42.7.4.3.4

Generalized Anesthetic Reactions

42.7.4.3.4.1

Clinical Signs

Postanesthetic reactions involving multiple muscle groups can result in clinical signs of anxiety, tachycardia, tachypnea, profuse sweating, and myoglobinuria.[149,150] Horses may not be able to rise and may struggle violently, resulting in prolonged, traumatic recoveries. In some cases a progressive increase in body temperature and muscular contractures may develop under anesthesia, and a fulminant metabolic and respiratory acidosis may be noted.[27,154,155] These animals can die within a matter of hours. In some cases, shock and pigmenturia may lead to renal failure.

42.7.4.3.4.2

Pathogenesis

The generalized form of myopathy cannot be explained by the compartmental syndrome alone. Halothane and succinylcholine have been the most frequently implicated inciting agents for generalized anesthetic-induced myonecrosis in all susceptible species, including the horse.[26,154,155] There appear to be several possible explanations for generalized anesthetic reactions. In some cases, systemic hypotension and hypoxemia may create local ischemic lesions, with the pathologic changes becoming more generalized as a result of the stress of anesthesia and the sensitivity of muscle cells to anesthetic agents or muscle relaxants.[148,152] In other cases, MH[26,154–156] may be responsible for clinical signs of

muscle contracture, heat production, and systemic acidosis resulting from excessive calcium release by the sarcoplasmic reticulum. In swine, MH is caused by a genetic mutation in the ryanodine receptor 1 gene,[157,158] and recently a mutation in the same gene was identified in two quarter horses that developed fatal MH after direct mask induction with halothane.[159,160] A further possible cause of generalized anesthetic myopathies is the triggering of severe myonecrosis in horses with an underlying exertional myopathy. Horses with recurrent ER may be at risk for excessive release of calcium from the sarcoplasmic reticulum during halothane anesthesia, and horses with polysaccharide storage myopathy (PSSM) may develop rhabdomyolysis because of metabolic changes with anesthesia.[26,27,161,162]

42.7.4.3.4.3

Diagnosis

Diagnosis is based on clinical signs, particularly in horses undergoing inhalation anesthesia. Routine monitoring of body temperature during anesthesia may aid in the early detection of MH. Some animals may also demonstrate metabolic and respiratory acidosis and hyperkalemia.[159] Genetic screening for MH or PSSM may be warranted before elective procedures. In humans, individuals suspected of being susceptible to MH may be identified using a halothane-caffeine contracture test. Several horses showing signs of MH have had a positive response to this test.[26,27] However, the test is rather complex to perform and is neither readily available nor feasible for detection of MH-susceptible horses.

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42.7.4.3.4.4

Treatment

Severely affected animals provide a significant therapeutic challenge. Aims of therapy should include (1) relief of pain, (2) correction of fluid and electrolyte abnormalities, (3) attempts to prevent ongoing necrosis, and (4) high-quality nursing care.

Many of the same principles described for treatment of ER can be used for treatment of postanesthetic myoneuropathy (see p. 1413). In severely affected recumbent horses, pain relief and sedation may help prevent struggling and progression of the myopathy.[148,149] Detomidine combined with butorphanol is effective in reducing struggling. Violent struggling only exhausts the horse and increases the potential for further injury and muscle damage. Constant rate infusions of butorphanol, opioids, or detomidine may aid in pain control where practical. Similarly, administration of NSAIDs may help reduce ongoing degenerative changes in muscle. Dantrolene sodium 2 to 4 mg/kg PO every 6 to 8 hours decreases release of calcium from the sarcoplasmic reticulum, helping to break the cycle of muscle damage. Volume expansion and diuresis may prevent renal toxicity.[148]

The most common metabolic derangement with anesthetic-related myopathies is a metabolic and/or respiratory acidosis. If specific therapy for metabolic acidosis is necessary, intravenous administration of sodium bicarbonate can be used. For optimum results, doses are calculated on the basis of the results of acid-base analysis. If facilities for acid-base analysis are not available and the horse appears severely compromised, intravenous administration of sodium bicarbonate at a dose of 1 to 2 mEq/kg slowly is recommended. If hyperthermia and contracture develop during anesthesia, discontinuation of anesthesia is advisable. Additional attempts to cool the animal with alcohol or cold-water baths may also be indicated. Administration of a large amount of soluble, lyophilized dantrolene sodium for intravenous administration may alleviate clinical signs in these horses. However, availability and expense of the agent in this form restrict its use. A dosage rate of 1 mg/kg IV may be appropriate, although more controlled studies are required.[148]

Good nursing care is important in severely affected horses. This involves providing well-padded areas on which horses can lie. Prevention or minimization of trauma around the eyes and appropriate care of decubital sores are important. Recumbent animals may require frequent turning to allow reperfusion of compressed muscle masses. Continued fluid therapy with polyionic fluids and possibly caloric supplementation may be indicated. The use of slings and pools to assist recumbent animals to rise also has been tried.[148] Recovery from the myopathy may occur with no apparent residual lesions. In contrast, recovery from some severe forms of the disorder may be accompanied by muscle atrophy, fibrosis, and scarring.[148]

42.7.4.3.4.5 Prevention

The principles described for localized myoneuropathies apply to the prevention of generalized anesthetic-related myopathies. In addition, dantrolene sodium has been shown to reduce the incidence of MH in susceptible humans and pigs. Similar effects might be anticipated in horses. Because of limited controlled studies, the dosage rate for prevention of MH in the horse is not clearly defined. Administration at a rate of 4 mg/kg PO 1 to 2 hours before anesthesia may be beneficial in reducing the incidence of MH.[153,163]

42.7.5 EXERTIONAL MYOPATHIES IN HORSES

42.7.5.1 LOCAL MUSCLE STRAIN

STEPHANIE J. VALBERG

42.7.5.1.1 Lumbar and Gluteal Muscles

Strain of lumbar and gluteal muscles is common in jumpers, dressage, and harness horses. Several factors may predispose horses to muscle strains, such as an inadequate warmup, preexisting lameness, exercise to the point of fatigue, and insufficient training. Lameness is often mild, and horses usually are reluctant to engage their hindquarters during exercise. Deep palpation of epaxial and gluteal muscles results in pain and dorsiflexion of the spine. Horses that show pain but resist dorsiflexion, ventriflexion, and lateral bending on manipulation may have a myopathy secondary to an underlying disorder of the spine or sacroiliac joint.

42.7.5.1.2 Adductor Muscles

The gracilis muscle can be torn in horses and cause severe pain and occasionally recumbency.[164,165] A careful physical examination reveals swelling of the medial thigh and pain on palpation. Ultrasonography identifies the extent of disrupted muscle fibers.

42.7.5.1.2.1 Treatment

Adequate rest and NSAIDs form the basis for treatment. Hand walking once the initial stiffness has dissipated may be beneficial. In addition, massage and the intermittent application of heat may aid the healing process. Exercise should be resumed gradually, preceded by an appropriate warmup period in a long and low frame. Adequate conditioning should be ensured before strenuous exercise is started. Saddles should be checked for proper fit.

42.7.5.1.3

Semitendinosus and Semimembranosus Muscles

ANDREW J. DART

Semitendinosus and semimembranosus muscles are frequently damaged in working quarter horses and in chronic cases result in a fibrotic myopathy.[166–169] Tearing of the semitendinosus and sometimes the semimembranosus, biceps femoris, and gracilis muscles at the point of a tendinous insertion is usually associated with work that requires abrupt turns and sliding stops. Horses caught in ropes or fences may struggle violently enough to induce sufficient trauma, allowing subsequent development of the myopathy. In one report, 5 of 18 horses developed this condition secondary to intramuscular injections.[168] A congenital form of fibrotic myopathy has been described.[170] Affected animals are usually less than 12 months old when clinical signs characteristic of fibrotic myopathy are first evident. Horses affected with this form of the disorder frequently have no palpable thickening of affected muscles or tendons and no history or evidence of trauma.

Affected muscles in acute cases are painful on deep palpation and may appear warm. Chronically, hardened areas within the muscle may represent fibrosis and ossification. The lameness in chronic cases is usually most apparent at the walk and is characterized by an abrupt cessation of the anterior phase of the stride of the affected limb, causing the leg to jerk suddenly to the ground rather than continue its forward motion. Pain is not a feature in chronic fibrotic myopathy, and manipulative tests have little, if any, effect on the degree of dysfunction. The stride has a short anterior phase with a characteristic hoof-slapping gait. The gait reflects a mechanical hindlimb lameness that restricts normal function. Radiographs may indicate ossification of affected muscles.[168,170]

1411 1412

42.7.5.1.4

Diagnosis

Serum activities of CK and AST are usually only mildly elevated. In addition to palpation, diagnosis can be confirmed by ultrasonography, thermography, or scintigraphy. Light microscopic evaluation of muscle biopsies is frequently normal in acute cases. Chronically fibrous replacement of muscle fibers is apparent.

42.7.5.1.5

Treatment

Several surgical procedures for correction of fibrotic myopathy have been described. These involve either excision[168] or transection[167] of the fibrotic part of the muscle or tenotomy of the tibial insertion of the semimembranosus tendon.[170] Excision of the fibrotic part of the muscle and tenotomy of the tibial insertion of the semimembranosus tendon are performed with the animal under general anesthesia. Excision or transection appears to produce more postoperative complications than tenotomy. However, according to reports, tenotomy has been reported in only a limited number of horses, and complete resolution of the gait abnormality may not occur.[169] In a modification of the procedure described by Irwin and Howell,[167] transection of the fibrotic mass in the standing horse under local anesthesia using a

bistoury knife may be effective. A Penrose drain is inserted through a second incision ventral to the first, and light exercise is resumed the day after surgery. Healing is allowed to occur by second intention.

42.7.6 EXERTIONAL RHABDOMYOLYSIS

STEPHANIE J. VALBERG

ER is probably the most common muscle disorder in horses. It is a frequent cause of poor performance in a variety of breeds, including standardbreds, thoroughbreds, warmbloods, Arabians, Morgans, quarter horses, Appaloosas, and American Paint horses. ER is a complex syndrome that likely has numerous causes. Numerous terms such as *tying up, chronic intermittent rhabdomyolysis, azoturia, Monday morning disease, paralytic myoglobinuria,* and *exercise-associated myositis* have been used for this syndrome.

42.7.6.1 Clinical Signs

Classically, horses develop a stiff, stilted gait, with excessive sweating and a high respiratory rate during or after exercise (Fig. 42-16). Most commonly, signs are seen after only 15 to 30 minutes of light exercise. After exercise, horses may stretch out as if to urinate, become extremely reluctant to move their hindquarters, and in severe cases show signs of colic or become recumbent.[15,171] Attempts to move more severely affected animals may result in extreme pain, obvious anxiety, and possible exacerbation of the condition. Firm painful muscles may be palpated over the back and hindlimbs. Scintigraphic evaluation of horses with rhabdomyolysis after exercise shows symmetric damage to the gluteal, semitendinosus, and semimembranosus muscles.[22] Myoglobinuria is a classic feature of more severely affected horses.[171,172] Endurance horses often show other signs of exhaustion including a rapid heart rate, dehydration, hyperthermia, SDF, and collapse.[73]

Fig. 42-16 Exertional rhabdomyolysis in a horse showing signs of pain, stiffness, sweating, and elevated respiratory rate.

42.7.6.2 Etiology

Several factors appear to precipitate episodes of ER. Some successful athletic horses may experience one or two isolated episodes of rhabdomyolysis during their lifetime, suggesting that environmental influences play an important role in sporadic cases.[173–177] Other horses may have chronic episodes of rhabdomyolysis that compromise their ability to compete. An inherent muscle dysfunction precipitated by certain triggering factors likely contributes to rhabdomyolysis in these horses.[14,178,179] ER is a syndrome that has many causes. To identify the cause in individual horses it may be helpful to initially subdivide cases into those with no intrinsic muscle abnormality (extrinsic or sporadic form) and those with a suspected intrinsic abnormality of muscle function (intrinsic or chronic form). Causes for sporadic and chronic exercise-induced muscle damage are listed in Box 42-1.

42.7.6.3

Sporadic Exertional Rhabdomyolysis

Most cases of ER can be diagnosed on the basis of the animal's history and clinical signs. Confirmation of rhabdomyolysis requires determination of abnormally elevated serum CK, serum AST, or serum LDH. Serum CK is often in the tens to hundreds of thousands of international units per liter, and AST in the thousands to tens of thousands.[9,171] The degree of elevation in enzymes reflects the time lapse between rhabdomyolysis and obtaining a blood sample, as well as the extent of myonecrosis. Myoglobinuria is a common finding in severely affected horses.

42.7.6.3.1

OVEREXERTION

The most common cause of sporadic ER is exercise that exceeds the horse's underlying state of training.[180] This includes both high-intensity exercise and endurance riding. Tears in the junctions between intracellular myofilaments (Z lines) are a common cause of postexercise muscle soreness.[9,181] ER that occurs at the end of endurance rides is covered in the section of this chapter that discusses exhaustion in endurance horses.

42.7.6.3.2

CONCURRENT ILLNESS

The incidence of muscle stiffness and ER has been observed to increase during an outbreak of respiratory disease.[103] Both equine herpesvirus 1 and equine influenza virus have been implicated as causative agents.[104] Mild muscle stiffness with concurrent viral infections is likely the result of the release of endogenous pyrogens.

42.7.6.3.3

ELECTROLYTE IMBALANCES

Electrolyte depletion in horses can occur as a result of dietary deficiency and losses in sweat with strenuous exercise.[11,182] Sodium, potassium, magnesium, and calcium play key roles in muscle fiber contractility. With severe electrolyte depletion after exercise, serum electrolytes may be below normal ranges.[183] These problems are common in endurance horses and are covered in the section on exhaustion in endurance horses. With chronic dietary depletion, however, serum concentrations may not reflect total body electrolyte imbalances. Work by Harris[11] established renal FE as a technique to evaluate electrolyte concentrations in horses with chronic ER. Normal values are dependant on diet and can vary from day to day and horse to horse.[12] In the United Kingdom, horses with chronic ER were shown to have low FEs of

sodium, and daily dietary supplementation of 2 oz of NaCl resulted in abatement of clinical signs.[11] Other horses had high phosphorus excretion, suggesting dietary calcium:phosphorus imbalance, and decreasing bran while providing a daily calcium supplement (2 oz of $CaCO_3$) was helpful in reducing clinical signs of ER. Hypokalemia has also been suggested to play a role in chronic ER. Hypokalemia was determined through low RBC potassium concentrations, which may not reflect total body potassium or low muscle potassium concentrations.[184,185] Supplementation with good-quality forage or 1 oz of KCl per day (Lite salt) is recommended for horses with low renal FE of potassium. Most horses fed on pasture or with high-quality hay do not appear to be potassium depleted.

42.7.6.3.4

VITAMIN E AND SELENIUM DEFICIENCY

The increased oxidative metabolism associated with exercise results in the generation of free radicals. Selenium, acting via the enzyme glutathione peroxidase, and vitamin E, acting within the lipid component of cell membranes, scavenge free radicals and prevent lipid peroxidation of cell membranes. Primary selenium deficiency is common in young animals living in areas with selenium-deficient soil; however, it has rarely been demonstrated as a cause of ER. Many horses with chronic ER have higher concentrations of selenium because of zealous dietary supplementation by owners.[186] Vitamin E deficiency occurs in horses that have limited access to pasture and consume poor-quality hay. It is not known whether horses that experience repeated episodes of ER may generate more free radicals than normal horses. A higher generation of free radicals in horses with chronic ER may explain the perceived benefit of repeated administration of selenium and vitamin E in thoroughbred horses with recurrent ER. Adequate values for blood selenium are greater than 0.07 mcg/mL and for serum vitamin E greater than 1.1 mcg/mL.

42.7.6.3.5

SOLUBLE CARBOHYDRATES

Horses consuming a high-grain diet appear to be more likely to develop ER than horses fed a low-grain fat-supplemented diet. The reason for this is unclear and may differ among forms of chronic ER. For example, in horses with PSSM, high—soluble-carbohydrate diets may enhance glucose uptake and glycogen storage.[187] In horses with recurrent ER, however, glycogen storage does not increase substantially even though serum CK activities are highest on high-grain diets.[188–190] Dietary effects in recurrent ER may in part be related to the psychogenic effects of grain on excitability.

42.7.6.3.6

HORMONAL IMBALANCES

A contribution of reproductive hormones to triggering ER has been postulated because the incidence of some forms of chronic ER appears to be highest in mares. Many owners report that episodes of rhabdomyolysis occur most commonly during estrus, but in one study of racehorses no direct correlation was shown between progesterone fluctuations and serum CK activity.[191] It is likely that the estrous cycle is one of many factors that combine to trigger ER in susceptible horses. In some mares in which episodes of ER coincide with estrus, suppression of estrus using progesterone implants or injections may be helpful. This should be done in conjunction with dietary and training alterations. Hypothyroidism has also been suggested as a cause of ER, but this has never truly been substantiated.

42.7.6.3.7

LACTIC ACIDOSIS

Although lactic acidosis has been postulated as a cause of ER, a significant lactic acidosis never has been documented.[188,192,193] Horses are most prone to development of ER during submaximal exercise. Blood lactate and muscle lactate concentrations in standardbreds, thoroughbreds, and quarter horses that develop rhabdomyolysis are substantially lower than those seen in healthy horses after racing. The most common metabolic derangement in horses with severe rhabdomyolysis is a hypochloremic metabolic alkalosis.[118,194] Therefore there seems to be little scientific evidence to support this theory.

42.7.6.4

Treatment

Treatment of ER is directed at relieving anxiety and muscle pain and replacing fluid and electrolyte losses. Tranquilizers such as acepromazine (0.04 to 0.07 mg/kg), xylazine (0.4 to 1 mg/kg), or detomidine (0.02 to 0.04 mcg/kg) combined with butorphanol (0.01 to 0.04 mg/kg) provide excellent sedation and analgesia. For horses with extreme pain and distress, a constant rate infusion of detomidine, lidocaine, or butorphanol may provide additional pain relief. NSAIDs such as ketoprofen (2.2 mg/kg), phenylbutazone (2.2 to 4.4 mg/kg) or flunixin meglumine (1.1 mg/kg) are frequently used to relieve pain but should be used with caution in dehydrated animals. Intravenous or intragastric DMSO (as a <20% solution) is used as an antioxidant, antiinflammatory, and osmotic diuretic for severely affected horses. Methylprednisolone succinate (2 to 4 mg/kg IV) has been advocated in the acute stage by some veterinarians if horses are recumbent. Muscle relaxants such as methocarbamol (5 to 22 mg/kg IV, slowly) seem to produce variable results, possibly depending on the dose used. The administration of Dantrium (dantrolene sodium) (2 to 4 mg/kg PO) in severely affected horses may decrease muscle contractures and possibly prevent further muscle necrosis. The dose can be repeated every 4 to 6 hours if necessary. Overdosing produces muscle weakness.

Severe rhabdomyolysis can lead to renal compromise owing to the ischemic and the combined nephrotoxic effects of myoglobinuria, dehydration, and NSAIDs. In mildly dehydrated horses, provision of free-choice electrolytes and water or administration of fluids via a nasogastric tube may be adequate. Horses with moderate to severe dehydration require intravenous administration of balanced polyionic electrolyte solutions. Hyperkalemia can occur with severe rhabdomyolysis, necessitating the use of isotonic sodium chloride. If hypocalcaemia is present, then supplementing intravenous fluids with 100 to 200 mL of 24% calcium borogluconate is recommended, but serum calcium should not exceed a low-normal range. Affected animals are usually alkalotic, making bicarbonate therapy inappropriate. In severely affected animals, regular monitoring of serum creatinine is advised to assess the extent of renal damage.

Horses with rhabdomyolysis should be stall rested on a hay diet for a few days. Small paddock turnout in a quiet area for a few hours twice a day is then helpful. Horses may be hand walked at this time, but more than 5 to 10 minutes at a time may induce another episode of rhabdomyolysis. For horses with sporadic forms of tying-up, rest with regular access to a paddock should continue until serum muscle enzyme concentrations are normal. For chronic cases of tying-up, this much rest may not be appropriate. Training should be resumed gradually, and a regular exercise schedule that matches the degree of exertion to the horse's underlying state of training should be established. Endurance horses should be supplemented with electrolytes and water during an endurance ride and monitored particularly closely during hot, humid conditions.

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42.7.6.5

Prevention

Because the inciting cause is usually temporary in sporadic cases, most horses respond to a few weeks of rest, dietary adjustments, and a gradual increase in training. The diet should be adjusted to include high-quality grass hay (or less than 50% alfalfa hay) and the minimum amount of soluble carbohydrate necessary (grains, sweet feed, molasses). A ration balancer containing protein, vitamins, and minerals should be added if necessary. If more than 3 to 5 kg of grain per day is necessary to maintain body weight, the addition of a fat source such as vegetable oil, rice bran, or a complete high-fat, low-starch feed should be considered. The horse should receive on a daily basis an electrolyte supplement that contains at least 1 oz of sodium chloride. A vitamin E and selenium supplement may be necessary in areas with low soil selenium. In addition, myriad treatments are commercially available that are guaranteed to cure tying-up in horses. Many of these have yet to be scientifically tested for efficacy. Skeletal muscle shows remarkable ability to regenerate after injury. After ER complete repair of muscle tissue is possible within 4 to 8 weeks.

42.7.6.6 Chronic Exertional Rhabdomyolysis

Many horses have repeated episodes of rhabdomyolysis with minimal exercise, even when the dietary and training recommendations for sporadic ER are followed. Forms of chronic ER are seen in many breeds of horses including quarter horses, American Paint horses, Appaloosas, thoroughbreds, Arabians, standardbreds, Morgans, draft breeds, and warmbloods. Current research suggests that many of these horses are susceptible to rhabdomyolysis because of an inherent disorder in muscle function.[179,195] Rhabdomyolysis in such horses occurs as a result of specific environmental circumstances that trigger muscle necrosis in genetically susceptible animals. Two heritable causes of chronic ER have recently been identified, but there may be several others that are yet unidentified. These include a glycogen storage disorder called *polysaccharide storage myopathy* and a disorder of muscle contractility called *recurrent exertional rhabdomyolysis*.[14,26,196] Distinguishing among the various forms of chronic ER requires a thorough history, dietary evaluation, physical examination, determination of serum and urine electrolyte concentrations, assessment of serum vitamin E and whole blood selenium concentrations, and histologic evaluation of muscle biopsies using special stains.

42.7.6.7 Polysaccharide Storage Myopathy

A subset of horses with chronic ER includes horses found to have a glycogen storage disorder characterized by the accumulation of glycogen and an abnormal polysaccharide in their muscle.[196] To date, quarter horses, Paint horses, Appaloosas, Morgans, draft horses, draft cross-breds, warmbloods, and a few thoroughbred and Arabian horses have been identified as having PSSM.[197–201]

42.7.6.8 Diagnosis

A definitive diagnosis of PSSM can be made only by evaluation of a muscle biopsy sample.[196] Supportive evidence of PSSM in quarter horses includes clinical signs of ER, persistent elevations in serum CK and AST activities, and a minimum threefold elevation in CK activity 4 hours after an exercise test consisting of a maximum of 15 minutes of lunging at a walk and trot.[193] Supportive evidence in draft and warmblood breeds includes exercise intolerance, muscle atrophy, weakness, and some gait abnormalities without necessarily finding elevations in muscle enzymes.[161,201,202]

A muscle biopsy of any locomotor muscle that provides a 2-cm × 1-cm block of tissue for evaluation is often

A muscle biopsy of any locomotor muscle that provides a 2-cm × 1-cm block of tissue for evaluation is often sufficient for analysis. The site most easily sampled in the field using an open surgical approach is the semimembranosus or semitendinosus muscle. Clinics that can rapidly process muscle for frozen sections often use a modified Bergstrom biopsy instrument inserted into the gluteal muscle through a 1-cm incision. A diagnosis can be made irrespective of diet and proximity of sampling to recent episodes of rhabdomyolysis. The characteristic features in histologic sections include the presence of subsarcolemmal vacuoles, increased staining for amylase-sensitive glycogen in periodic acid—Schiff (PAS) stain, and the presence of amylase-resistant PAS-positive abnormal polysaccharide inclusions in skeletal muscle fibers (Fig. 42-17).[25,196] Laboratories that use the acronym EPSM process formalin-fixed muscle tissue; the diagnostic criteria used in such laboratories may be those described previously, but in addition these laboratories allow the sole criteria for diagnosis to be increased staining for amylase-sensitive glycogen or the presence of PAS-positive sarcoplasmic masses.[198] A much wider spectrum of breeds is diagnosed with PSSM using these criteria, and the specificity for diagnosis is decreased.

42.7.6.8.1

POLYSACCHARIDE STORAGE MYOPATHY IN QUARTER HORSE—RELATED BREEDS

A survey of 164 quarter horses used mainly for breeding or ranch work found that 6% of these horses had PSSM based on identifying amylase-resistant abnormal polysaccharide in skeletal muscle biopsies.[203] These horses were kept on pasture, fed very little grain, and showed no clinical signs of a myopathy. In contrast, 50% of muscle biopsy samples from quarter horse—related breeds submitted to the Neuromuscular Diagnostic Laboratory at the University of Minnesota because of signs of a neuromuscular disorder are diagnosed with PSSM.[197] PSSM appears to be a common cause of neuromuscular disease in quarter horse—related breeds, however, under certain environmental conditions clinical signs may be inapparent.

42.7.6.8.1.1

Genetics

Although in general the prevalence of PSSM is 6% of quarter horses, on some breeding farms the prevalence can be as high as 42%.[203] This suggests that PSSM may be inherited within particular bloodlines. A familial basis for PSSM has been suggested from pedigree analysis and by limited breeding trials at the University of Minnesota.[195,204] Although pedigree analysis initially supported an autosomal recessive pattern of inheritance, identification of PSSM in quarter horse crosses indicates that a dominant mode of inheritance is more likely.

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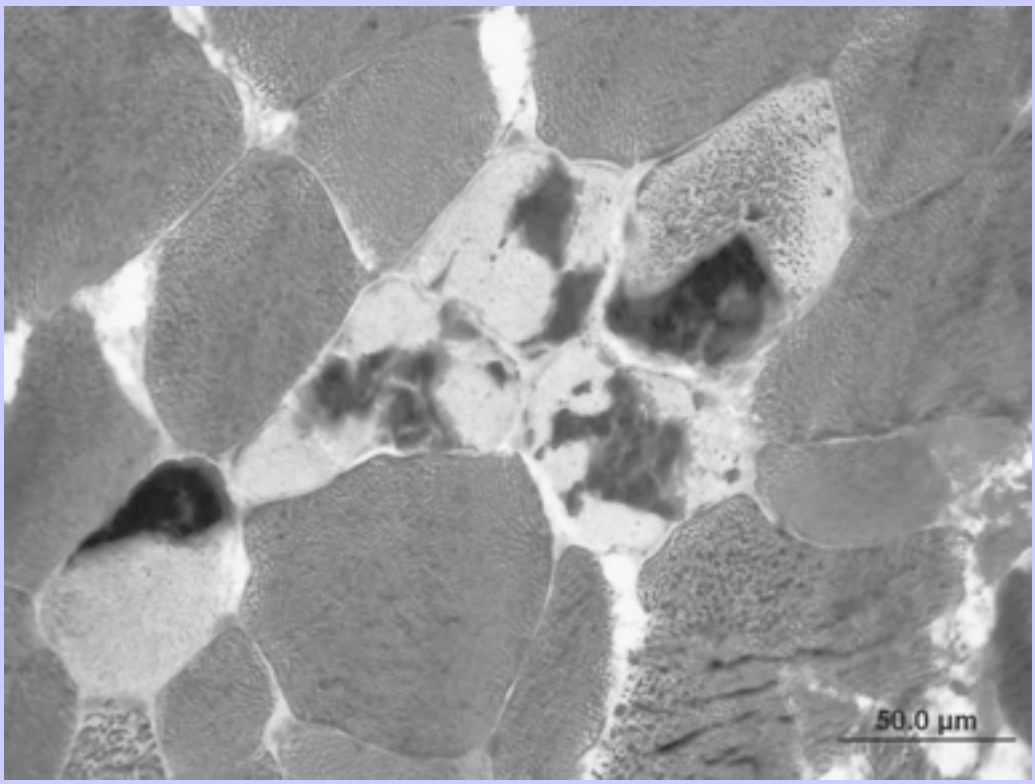
Fig. 42-17 Periodic acid—Schiff stain for glycogen in a gluteal biopsy from a horse with polysaccharide storage myopathy showing

aggregates of intensely staining abnormal polysaccharide in some fibers.



42.7.6.8.1.2

Clinical Signs

The average age of onset of clinical signs of PSSM is 5 years in quarter horses, and ranges from 1 to 14 years of age.[178] There is no significant temperament, body type, or gender predilection for PSSM. Approximately 40% of owners believe there is a seasonal incidence to the development of clinical signs. The most common trigger for clinical signs of PSSM is less than 20 minutes of exercise at a walk and trot, particularly if the horse has been rested for several days before exercise. Signs of ER include firm painful muscles, stiffness, fasciculations, sweating, weakness, and reluctance to move. The hindquarters are frequently most affected, but back muscles, abdomen, and forelimb muscles may also be involved. During exercise, horses may stop and posture as if to urinate, perhaps as a means to alleviate muscle cramping (Fig. 42-18). Signs of pain can be particularly severe, with 30% of horses exhibiting muscle pain for more than 2 hours and approximately 10% of cases becoming recumbent. Less common signs of PSSM in quarter horses include gait abnormalities, mild colic, and muscle wasting.

Quarter horses frequently exhibit elevations of serum CK and AST in association with clinical signs. The median CK and AST levels for all PSSM quarter horses with muscle biopsy samples submitted to the Neuromuscular Diagnostic Laboratory at the University of Minnesota were 2809 and 1792 U/L, respectively. Persistent elevation in CK activity, despite an extended period of rest, is a common observation in PSSM quarter horses.[15]

42.7.6.8.2

POLYSACCHARIDE STORAGE MYOPATHY IN DRAFT BREEDS

The prevalence of PSSM among draft breeds with biopsy samples submitted to the NDL at the University of Minnesota is 54%.[197] The breeds most commonly diagnosed with PSSM at the NDL in Minnesota are Belgians, Percherons, and crosses of these breeds with light horses. A prospective by Firshman and co-workers found a prevalence of PSSM of 36% in Belgian draft horses.[202]

42.7.6.8.2.1

Genetics

Several full- and half-sibling Belgian horses have been identified with PSSM, and many Belgian—light breed crosses have been identified with PSSM, indicating a potential genetic basis.

42.7.6.8.2.2

Clinical Signs

The average age of draft horses diagnosed with PSSM is approximately 8 years.[197,202] No particular gender predilection has been identified for PSSM in draft horses. It is notable that clinical signs are not consistently present with PSSM, as many of the Belgian draft horses that were positive for PSSM in the study by Firshman and colleagues had no clinical signs.[202] PSSM in draft horses likely is the same disorder described as “Monday morning disease” in work horses in the early twentieth century.[172] ER is a manifestation of PSSM in draft horses as well as draft crosses and can be so severe that it leads to recumbency and death.[201,205] In addition, postanesthetic myopathy may also be a complication of PSSM in draft breeds.[161] A number of draft horses with PSSM show signs of progressive weakness and muscle loss resulting in difficulty rising. In these cases serum CK activity is frequently normal. Gait abnormalities, such as excessive limb flexion, fasciculations, and trembling are commonly seen with PSSM in draft horses. Although the condition “shivers” was previously attributed to PSSM,[206] a recent study found no causal association between these two conditions.[202] The very high prevalence of PSSM in draft horses in essence means that there is a 36% chance that any clinical sign could be falsely associated with the disease PSSM. Therefore clinical judgment is required to determine whether the muscle biopsy results could reasonably be associated with a myopathic process or if other possible causes of muscle weakness or gait changes should also be investigated.

Fig. 42-18 Typical stance of a horse with PSSM after 10 minutes of walking and trotting. Note the tucked-up abdomen and

camped-out stance, which were concurrent with firm muscles, fasciculations in the flank, and elevated serum creatine kinase activity.

Serum muscle enzyme activities are often normal in draft horses with PSSM. The median serum CK and AST levels in draft horses from which biopsies were sent to the NDL at the University of Minnesota were 459 and 537 U/L.[197] Mean CK and AST activities in the Belgian horse study by Firshman were 326 ± 380 U/L and 355 ± 193 U/L, respectively. Serum vitamin E and whole blood selenium concentrations are normal in draft horses with PSSM.[202]

42.7.6.8.3

POLYSACCHARIDE STORAGE MYOPATHY IN WARMBLOODS

The true prevalence of PSSM in other horse breeds remains to be established. Based on the number of horses diagnosed with PSSM from muscle biopsy samples submitted to the NDL, PSSM appears to be a common neuromuscular disorder in warmblood horses, with approximately 50% of warmblood biopsy samples being diagnosed with PSSM.[197] This included a wide variety of warmblood breeds, such as Dutch warmblood, Hanoverian, Westfalian, Canadian warmblood, Irish sport horse, Gerdlander, Hussien, and Rheinlander. No reports on the potential inheritance of PSSM in warmbloods have been published.

42.7.6.8.3.1

Clinical Signs

The mean age of onset of clinical signs in warmbloods is reported to be 8 to 11 years of age.[197,207] A gender predilection for PSSM has not been identified. The most common clinical signs reported in warmbloods with PSSM are painful firm back and hindquarter muscles, reluctance to collect and engage the hindquarters, poor rounding over fences, gait abnormalities, and atrophy. Overt signs of ER, such as stiffness, shortness of stride, and reluctance to move after exercise were reported in less than 15% of warmbloods with PSSM.[197] The median CK and AST levels in warmbloods diagnosed with PSSM at the NDL in Minnesota are 323 and 331 U/L, respectively.

42.7.6.8.4

POLYSACCHARIDE STORAGE MYOPATHY IN OTHER BREEDS

A few horses of other breeds have been reported to have PSSM. The prevalence of PSSM within these breeds appears to be quite low. For example, although more than 50% of biopsies of quarter horses, draft horses, and warmbloods resulted in diagnosis of PSSM, fewer than 10% of muscle biopsies from 178 thoroughbreds, 40 Arabians, and 32 standardbreds with neuromuscular disease resulted in diagnosis of PSSM. A slightly higher prevalence was found for Morgans and Tennessee Walking Horses.[197] Previous published reports of PSSM based on amylase-resistant polysaccharide include small numbers of horses of warmblood cross-breeds, Anglo-Arabs, Andalusians, Morgans, Arabians, Welsh cross-breeds, and standardbred breeds.[198] Some of the controversy regarding the number of breeds affected with PSSM may be a result of inclusion of cases with sarcoplasmic masses and increased PAS staining for glycogen as positive criteria for PSSM by some laboratories.

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42.7.6.9

Pathophysiology

Muscle glycogen concentrations in PSSM horses are often one and a half to four times normal, and glucose-6-P concentrations are up to 10 times normal.[115] Glycogen accumulation in PSSM horses is not the result of an inability to metabolize glycogen but rather of increased synthesis of glycogen. There appear to be at least two linked biochemical abnormalities associated with PSSM. The first abnormality is expressed as enhanced sensitivity to insulin in quarter horses with PSSM horses as determined by intravenous or oral glucose tolerance tests as well as euglycemic hyperinsulinemic clamping.[208,209] In association with high dietary starch intake, this enhanced insulin sensitivity may increase uptake of glucose into skeletal muscle and the subsequent formation of glycogen. Draft horses have not been found to have heightened insulin sensitivity. The second biochemical abnormality in horses with PSSM is associated with abnormal regulation of glycogen synthase, resulting in persistent glycogen synthesis. Abnormal polysaccharide formed in PSSM skeletal muscle is less highly branched than normal glycogen and may reflect an imbalance in the heightened activity of glycogen synthase relative to the less tightly regulated glycogen branching enzyme. Abnormal polysaccharide is also occasionally found in the heart of PSSM horses but has not been identified in the liver.

The development of rhabdomyolysis in PSSM horses is not directly associated with heightened insulin sensitivity.[210] If PSSM horses are treated with dexamethasone, their insulin sensitivity can be reduced to well within the normal range; however, they still develop rhabdomyolysis. Rather, muscle necrosis with exercise appears to be associated with a separate but potentially linked biochemical abnormality in energy metabolism. During submaximal exercise, muscle fibers in PSSM horses do not generate adequate energy for muscle contraction, as evidenced by the degradation of adenine nucleotides in individual muscle fibers.[211] It is likely that PSSM is caused by a defect in a pathway that controls both the flux of substrates such as glucose into the cell, as well as the flux of substrates such as glycogen and free fatty acids through metabolic pathways during aerobic exercise.

42.7.6.10 ## Treatment and Prevention

Horses diagnosed with PSSM will always have an underlying predilection for muscle soreness. The best that can be done is to manage horses to minimize clinical signs. With adherence to diet and exercise recommendations, at least 80% of horses show notable improvement in clinical signs, and many return to acceptable levels of performance.[178,212] There is, however, a wide range in the severity of clinical signs shown by horses with PSSM; horses with severe or recurrent clinical signs will require more stringent adherence to diet and exercise recommendations in order to regain muscle function.

Treatment of horses with acute rhabdomyolysis is similar to that described for sporadic ER except that PSSM horses should not be confined to a stall for more than 48 hours. They should be provided turnout in paddocks of gradually increasing size once stiffness has subsided. Hand walking horses recovering from an episode of PSSM for more than 5 to 10 minutes at time may trigger another episode of rhabdomyolysis.

42.7.6.10.1 ### EXERCISE REGIMES

Horses with PSSM should be given 2 weeks to adapt to a new diet before commencing exercise. Less than 10 minutes of a relaxed trot on a longe line without collection is initially recommended, with a very gradual and consistent increase in exercise every day if possible.[15,178] Advancing the horse too quickly often results in an episode of rhabdomyolysis and repeated frustration for the owner. Work can usually begin under saddle after 3 weeks of groundwork and can gradually be increased. It is very common to have subclinical elevations in CK activity when exercise is reintroduced, and a return to normal levels often requires 4 to 6 weeks of gradual exercise.[187] Keeping horses with PSSM fit is important for prevention of further episodes of rhabdomyolysis.

42.7.6.10.2 ### DIETARY MANAGEMENT OF POLYSACCHARIDE STORAGE MYOPATHY

The dietary modifications for PSSM horses are designed to reduce the glucose load and provide fat as an alternate energy source. Anecdotally, owners report that this type of diet improves clinical signs of muscle pain, stiffness, and exercise tolerance in draft horses, warmbloods, quarter horses, and other breeds.[178,212] Dietary change appears to have less of an impact on alleviating gait changes such as shivers.[44] The value of low-starch, high-fat diets in reducing exercise-induced muscle damage has been demonstrated only under controlled experimental conditions in quarter horses.[187] In PSSM quarter horses with increased sensitivity to insulin, dropping dietary starch to less than 10% of daily digestible energy and increasing dietary fat to 13% of daily digestible energy resulted in normal serum CK activity 4 hours postexercise during a 6-week trial. Provision of similar fat content and higher starch content resulted in increased serum CK activity in the most severely clinically affected horses. The beneficial effect of the low-starch, high-fat diet in this study (Re-Leve) appears to result from decreased glucose uptake into muscle cells and provision of more plasma free fatty acids in muscle fibers for use during aerobic exercise.[187] Quarter horses naturally have very little lipid stored within muscle fibers, and provision of free fatty acids may overcome the disruption in energy metabolism that appears to occur in PSSM quarter horses during aerobic exercise.[187,211] Studies clearly show, however, that these dietary changes alone are not beneficial, and an exercise program must be instituted for PSSM horses to show clinical improvement.[178] Further controlled experimental studies of the physiologic effect of low-starch, high-fat diets are necessary in other

breeds of horses with PSSM to determine how and if they truly have a beneficial effect. Anecdotally, some horses appear to have an increased incidence of rhabdomyolysis when on lush pasture. Therefore it seems reasonable to limit exposure to lush pastures. Hay that has a moderate to low content of soluble sugars and nonfermentable starch and fewer gluconeogenic amino acids would seem the best choice for PSSM horses. This includes second cutting of grass hay, brome hay, or oat hay.

The caloric needs of the horse should first be assessed in order to determine the amount of hay as well as low-starch, high-fat concentrates the horse requires. Provision of excessive calories in the form of fat to overweight horses is detrimental. For overweight horses, restricting hay to 1% to 1.5% of body weight and limiting access to pasture grass while increasing daily exercise are recommended. In addition, selection of a low-starch, fat-supplemented feed that is particularly high in dietary fiber may be the best means of providing dietary fat without causing excessive weight gain. Many low-starch high-fat diets are available for horses. The most important dietary principle appears to be that of the total daily calories required (digestible energy [DE]), less than 10% should be supplied by starch and at least 13% supplied by fat. Some authors recommend that 20% of daily caloric intake be supplied by fat (0.5 kg of fat) based on clinical experiences,[212] whereas others report improvement in clinical signs when 10% to 15% of DE is supplied as fat.[178,187,213] There is a great deal of variation in individual tolerance to dietary starch, however; horses with more severe clinical signs of PSSM appear to require the greatest restriction in starch intake.

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42.7.6.11

Recurrent Exertional Rhabdomyolysis

Recurrent episodes of muscle stiffness, sweating, muscle contractures, and reluctance to move occur commonly in racing thoroughbreds, standardbreds, and Arabian horses. Many of these horses likely have tying-up as a result of a defect in the regulation of muscle contraction termed *recurrent exertional rhabdomyolysis* (RER).

42.7.6.12

Epidemiology and Genetics

Most studies show that approximately 5% of thoroughbred horses develop signs of muscle pain and cramping during a racing or polo season.[173,176,177,214] Approximately 75% of thoroughbred racehorses with RER have at least four episodes of rhabdomyolysis and 25% have more than 10 episodes in a 4-month racing season.[214] One predisposing factor for RER appears to be inheritance of susceptibility to developing exercise-induced episodes of rhabdomyolysis.[179,215] Analysis of pedigrees of thoroughbred horses from across the United States suggests that RER is an autosomal dominant trait. Furthermore, subsequent breeding trials confirm that the abnormal contracture test is inherited in an autosomal dominant fashion.[179]

Predisposing environmental factors that trigger rhabdomyolysis in susceptible horses include gender, temperament, diet, exercise duration and intensity, excitement, and lameness.[176,214] Females are most commonly affected by RER (67% female; 33% male), particularly those that are 2 years old and in race training.[214] Nervous horses are five times more likely to develop RER, and horses with lameness are four times more likely to tie up. Susceptible horses receiving more than 5 kg of sweet feed are more likely to develop rhabdomyolysis than those receiving 2.5 kg of sweet feed per day.[189,190]

42.7.6.13

42.7.6.13

Diagnosis

RER affects a specific subset of thoroughbred and likely standardbred and Arabian horses with intermittent episodes of exercise-induced rhabdomyolysis. These horses have increased numbers of centrally located nuclei in muscle biopsy samples and normal muscle glycogen staining (see Fig. 42-8).[14] In addition, RER is characterized by abnormal sensitivity of intact muscle bundles to contractures induced by caffeine or halothane in the muscle bath.[26,28,216] Although studies of muscle contraction indicate similarities to MH in swine, biochemical studies of isolated muscle cell membranes have not identified a similar defect in the function of the calcium-release channel in horses with RER.[156] Many thoroughbreds with RER have developed rhabdomyolysis under halothane anesthesia.[162,217]

42.7.6.14

Clinical Signs

Episodes often occur in horses once they become fit and are frequently associated with excitement at the time of exercise. In thoroughbreds, rhabdomyolysis occurs most frequently during training when horses are held to a slow gallop.[214] In standardbreds, rhabdomyolysis often occurs 15 to 30 minutes into slow jogging.[9] A history of poor performance and elevated serum AST and CK may be the only presenting complaints in some horses. Older thoroughbreds used as riding horses may have very intermittent episodes of rhabdomyolysis associated with lay-ups of fit horses or with the steeplechase in 3-day events. Muscle stiffness and reluctance to collect may be present on a continual basis between episodes in some of these older horses. Arabian horses often develop clinical signs with little exertion, frequently in association with excitement.

42.7.6.15

Prevention

RER appears to be an inherited disorder that is expressed when horses are subjected to the stress and rigors of training, particularly at a young age. Prevention of further episodes of RER in susceptible horses includes adhering to standardized daily routines and providing an environment that minimizes stress. This should include desensitizing horses to stressful situations, moving the stall to a quiet area of the barn, performing regular turnout, and so on. Daily exercise is essential, whether in the form of turnout, longing, or riding.

In the past, horses have been box-stall rested for several weeks after an episode of RER. It is my opinion that this is counterproductive and increases the likelihood that the horse will develop RER when put back into training. The initial muscle pain usually subsides within 24 hours of acute RER, and daily turnout in a small paddock can be provided at this time. Subsequently a gradual return to performance is recommended once serum CK is close to normal range.

The diet should be adjusted to include a balanced vitamin and mineral supplement, high-quality hay, and a minimum of carbohydrates (<2.5 kg) such as grain and sweet feed. Additional dietary fat supplements are helpful to maintain weight in nervous horses without providing excessive carbohydrates. In hard keepers or horses in heavy work, corn oil and rice bran added to the diet may not be adequate to maintain weight. In such cases new commercial feeds that are low in starch and high in fiber, designed for horses with RER, are helpful to maintain weight but avoid rhabdomyolysis.[190] The use of low doses of acepromazine tranquilizers (e.g., a dosage rate of approximately 0.005 to 0.01 mg/kg) 30 minutes before exercise in excitable horses is believed to help some horses.

Dantrolene 2 to 4 mg/kg PO given 1 hour before exercise in fasted horses is effective in preventing RER

Dantrolene 2 to 4 mg/kg PO given 1 hour before exercise in fasted horses is effective in preventing RER.[153,218] Dantrolene decreases the release of calcium from the sarcoplasmic reticulum during contraction. Phenytoin has also been advocated as a treatment for horses with RER. Doses are adjusted in horses to maintain serum levels of 8 to 10 μ/mL. Initial dosages begin at 6 to 8 mg/kg PO for 3 to 5 days. Doses can be increased by 1-mg/kg increments every 3 days until rhabdomyolysis is prevented but should be cut back if horses appear drowsy.[216] If possible, serum phenytoin concentrations should be assessed regularly at the initiation of treatment. Phenytoin acts on a number of ion channels within muscle and nerves including sodium and calcium channels. Unfortunately, long-term treatment with dantrolene or phenytoin is expensive, and efficacy has not been established.

42.7.7 HEREDITARY AND CONGENITAL MYOPATHIES

STEPHANIE J. VALBERG

42.7.8 MITOCHONDRIAL MYOPATHY

A deficiency of complex 1, the first step in the mitochondrial respiratory chain, has been identified in a young Arabian filly that was presented for veterinary attention with clinical signs similar to those of ER.[219] In contrast to cases of ER, however, this horse showed no changes in serum CK after exercise. A marked lactic acidosis developed even with light exercise, and maximum oxygen consumption was drastically reduced, resulting in marked exercise intolerance. Histopathologic evaluation of muscle biopsy samples showed an abnormal increase in mitochondrial density, and biochemical analyses revealed a complex 1 deficiency. The horse has shown slowly progressive signs of muscle atrophy but has otherwise remained healthy at rest.

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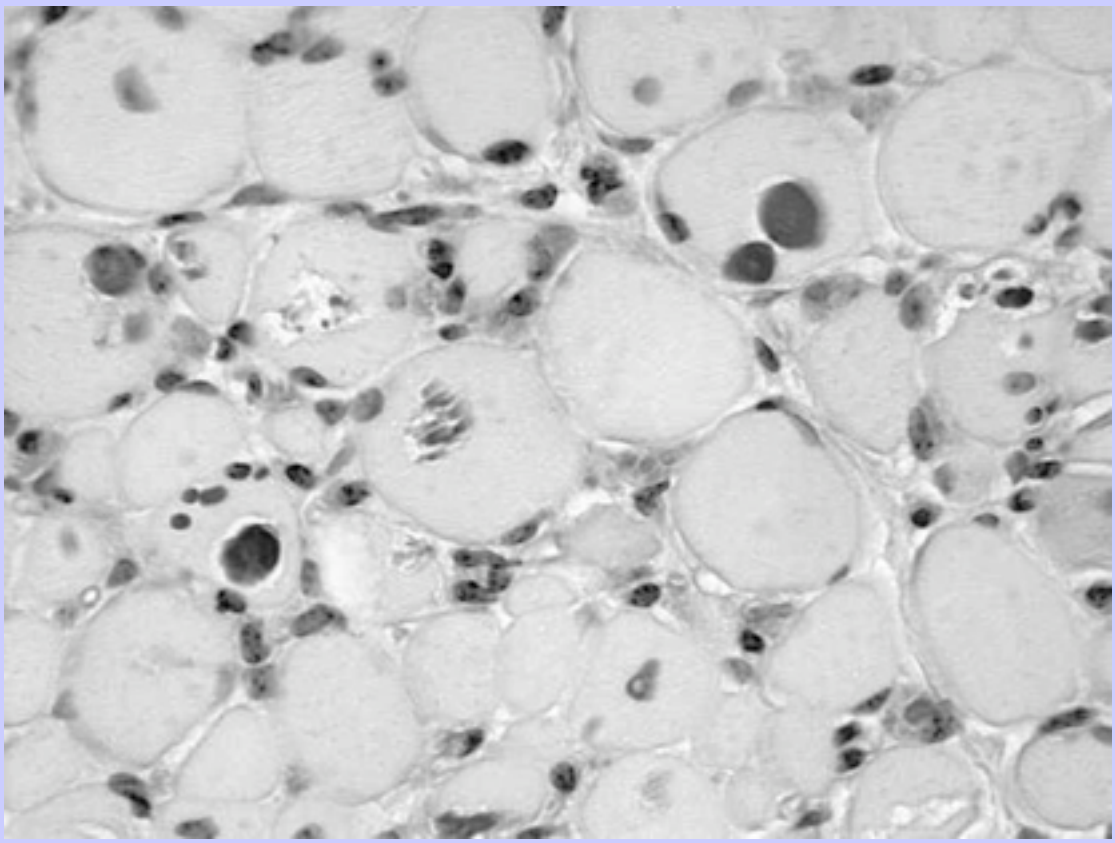
42.7.9 GLYCOGEN BRANCHING ENZYME DEFICIENCY

Glycogen branching enzyme deficiency (GBED) is a glycogen storage disorder causing abortion, seizures, and muscle weakness in quarter horse—related breeds.[220–222] It is a glycogen storage disorder separate from PSSM. GBED is caused by a nonsense mutation in exon 1 of the *GBE1* gene at codon 102 that introduces a premature stop codon.[222] Nine percent of the breed are carriers of this autosomal recessive mutation, and 3% of abortions are attributed to this disease in quarter horses.[220] Most foals diagnosed with GBED are presented with hypothermia, weakness, and flexural deformities of all limbs at 1 day of age. Ventilatory failure may also be a presenting sign, in addition to recurrent hypoglycemia and collapse. All foals have died either from euthanasia because of muscle weakness or suddenly because of apparent cardiac arrhythmia. Persistent leukopenia, intermittent hypoglycemia, and high serum CK (1000 to 15,000 U/L), AST, and γ-glutamyltransferase (GGT) activities are features of affected foals. Gross postmortem changes are not evident, and routine hematoxylin and eosin stains of tissues may be normal or show basophilic inclusions in skeletal muscle and cardiac tissues. Frozen sections of muscle, heart, and liver show a notable lack of normal PAS staining for glycogen as well as abnormal PAS-positive globular or crystalline intracellular inclusions (Fig. 42-19). Branching enzyme activity is minimal in skeletal and cardiac muscle as well as liver. A diagnosis is best obtained by confirming the presence of the genetic mutation in tissue samples or by identifying typical PAS-positive inclusions in muscle or cardiac samples.[220–222]

Fig. 42-19 Periodic acid—Schiff (PAS) stain of skeletal muscle from a foal with glycogen branching enzyme deficiency. Note the lack of

normal diffuse magenta staining for glycogen and the presence of globular and crystalline PAS-positive inclusions.



42.7.10 PHOSPHORYLASE DEFICIENCY IN CHAROLAIS CATTLE

A deficiency of the enzyme phosphorylase (McArdle's disease) has been identified in Charolais cattle in the United States and New Zealand.[223–226] Affected animals had exercise intolerance and often collapsed when forced to exercise. Serum CK was elevated in all affected animals, and one calf had severe rhabdomyolysis clinically resembling white muscle disease. Screening for myophosphorylase can be performed by histochemical staining for phosphorylase activity in frozen sections of muscle biopsies. Confirmation of the autosomal recessive disease is obtained by biochemical analyses or identification of the C-to-T substitution, which changes an encoded arginine (CGG) to tryptophan (TGG). This disease should be considered as a differential diagnosis for white muscle disease in Charolais cattle that are found to have normal vitamin E and selenium status.

42.7.11 MYOFIBER HYPERPLASIA

Myofiber hyperplasia is an inherited condition occurring in certain breeds of cattle and rarely in sheep, characterized by a disproportionate increase in skeletal muscle mass. Synonyms for the disorder include *double muscling, doppellender,* and *culard*.[227–229] The condition is well recognized in cattle and is most commonly seen in the Belgian Blue, Piedmont, and South Devon breeds. The term *double muscling* is misleading because there is no increase in the number of muscle groups. The increase in muscle mass is the result of hyperplastic type 2B myocytes, with a reduction in the number of types 1 and 2A myocytes. The degree of myofiber hyperplasia varies among affected animals. Increases in muscle size are most evident in hindlimbs, forelimbs, lumbar area, and neck; well-defined grooving often separates muscle groups (similar to the muscle definition seen in human bodybuilders). Muscle/bone ratio is increased; decreased amounts of body fat yield a leaner carcass at slaughter. Affected animals show increased weight gains over similarly treated unaffected herdmates. The skin of affected animals is thinner than that of normal herdmates.

Myofiber hyperplasia appears to be inherited as a single major autosomal locus with several modifiers of phenotypic expression resulting in incomplete penetrance. In Belgian Blue and Piedmont cattle an 11 nucleotide deletion and a missense mutation, respectively, have been identified in the myostatin gene. Myostatin is a transforming growth factor that is a negative regulator of skeletal muscle mass during development. Heterozygotes for the gene often show some degree of muscle hyperplasia. Clinical problems encountered as a result of this disorder include dystocia in dams producing affected calves and oral anomalies such as hypertrophy of the tongue, brachygnathism, and prognathism; there is also a very high incidence of inherited spastic paresis (Elso heel) in affected cattle.

A genetic disorder that results in myofiber hyperplasia has also been identified in sheep.[230]

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43 Chapter 43 Diseases of the Reproductive System

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43.1 FEMALE REPRODUCTIVE DISORDERS

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43.1.1 NONPATHOGENIC INFERTILITY

43.1.1.1 THE BREEDING SEASON

43.1.1.1.1 Mares

The mare is a seasonally polyestrous animal, breeding during seasons of long day length. Annual breeding and nonbreeding seasons are divided by fall and spring transitional periods, which are characterized by erratic reproductive behavior and irregular estrous cycles.

43.1.1.1.2 Clinical Signs

During the breeding season, mares ovulate every 21 days (range 19 to 22 days).[1] Estrus (5 to 7 days, but variable) is characterized by the presence of an ovarian follicle, serum progesterone level of less than 1 ng/mL, and sexual receptivity. During estrus the cervix is palpably relaxed and the uterus is edematous. One or two follicular waves occur per cycle, and preovulatory follicles are 45 to 60 mm in diameter, often with a cone-shaped appearance on ultrasonography.[2] Ovulation occurs 24 to 48 hours before the end of estrus and may be accompanied by ovarian sensitivity.[1] The ruptured follicle is replaced by a corpus luteum (CL). Diestrus (luteal phase) is predictable in length because regression of the CL, caused by release of endometrial prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), occurs 14 to 15 days after ovulation.[3] During diestrus and early pregnancy the cervix is tight and the uterus is firm and tubular. Diestrous ovulations occur and may be fertile.[4] First postpartum estrus (“foal heat”) begins in the week after foaling, and ovulation occurs in most mares 7 to 15 days postpartum.

43.1.1.2

Ruminants

43.1.1.2.1

COWS

Cows are polyestrous, but seasonal differences in fertility may be caused by climate. The estrous cycle averages 21 days (range 17 to 25 days), and the duration of estrus averages 12 to 16 hours (range 6 to 24 hours). Cows are unique among domestic animals in that they ovulate spontaneously after the end of estrus, 24 to 30 hours after the beginning of estrus.[5]

In the absence of a bull, estrus can be detected in cows by their homosexual (bisexual) activity. Cows that stand to be mounted by another cow are in estrus (standing heat). Secondary signs that may be helpful in detecting estrus include restlessness and increased activity, vulvar hyperemia and edema, and a clear mucous discharge. Errors in heat detection are a common cause of infertility on large dairy farms.[6] The optimum time for insemination of cows is between 16 and 24 hours after the onset of estrus. Insemination of cows on the basis of standing to be mounted results in a higher pregnancy rate than if it is based on secondary signs of estrus.[7] Well-managed dairy cows with uncomplicated periparturient experiences may ovulate approximately 20 to 25 days after calving, whereas beef cows with nursing calves usually do not ovulate until 40 or more days after calving. The presence of the calf appears to be responsible for the difference in return to cyclicity.[8]

43.1.1.2.2

SHEEP

Coarse-wooled breeds of ewes are seasonally polyestrous during the autumn and winter (short photoperiod) in temperate climates. Ovulation can be induced in seasonally anestrous ewes by artificial simulation of day length and temperatures characteristic of autumn (reduced photoperiod and reduced ambient temperature), but the long latency period required for response to manipulation of light and temperature makes the procedure impractical. Ewes of fine-wooled breeds may be polyestrous throughout the year if adequately nourished. The estrous cycle of ewes averages 17 days (range 14 to 19 days), and the duration of estrus averages 36 hours. Ovulation occurs spontaneously 24 hours after the onset of estrus. Ewes display few, if any, signs of estrus unless a male is present. The primary signs of estrus include seeking the ram and standing for mating. Secondary signs include restlessness and rapid tail switching; vulvar edema and discharge of clear cervical mucus may be observed occasionally. Lambing ordinarily occurs during the anestrous season; therefore ewes do not return to estrus until the next breeding season.[5]

43.1.1.2.3

GOATS

Does in temperate climates are seasonally polyestrous from late summer until early spring (short photoperiod). Onset of the breeding season in yearling does can be advanced by exposing them to 19 hours of artificial light per day for 70 days beginning in mid to late winter. Termination of artificial light results in a relative decrease in day length and stimulation of estrus and ovulation.[5] Alternatively, the breeding season may be hastened by exposing does to 14 to 18 hours of light per day for 3 months, followed by a reduction to 6 hours of light per day.[7] The estrous cycle averages 21 days, and estrus lasts 18 to 36 hours. 1419
Ovulation occurs spontaneously 24 hours after the onset of estrus. An intact male or male pheromone is 1420
usually necessary for estrous detection. The primary signs of estrus are seeking the buck and standing for

service. Secondary signs of estrus in does include rapid tail switching, restlessness, increased frequency of urination and vocalization, transient decrease in appetite and milk production, and edema and hyperemia of the vulva. As in sheep, parturition takes place during the anestrous season, and return to cyclicity in does is delayed until the next breeding season.[5]

43.1.1.2.4 CAMELIDS

South American camelids bred in North America are nonseasonal. In keeping with management decisions, they are often bred in a seasonal manner to avoid having newborn crias during the hottest or coldest months of the year. Some consider the South American camelids to be polyestrous, whereas others argue that they do not have a true estrous cycle.[9] These discrepancies arise from the fact that camelids are induced ovulators. Cyclic ovarian activity (e.g., transition from estrus to diestrus) is caused by coital activity. Unbred female camelids essentially exhibit estrous behavior continually, with perhaps short, occasional, unpredictive intervals of 1 to 2 days of decreased receptivity. Follicular waves in alpacas and llamas last around 17 days. Small follicles (≤3 mm) are always present on the surface of the ovaries. After recruitment, follicles grow to approximately 5 mm in size. Dominance is established when one of the follicles reaches the size of 6 mm, and the female will show signs of receptivity to the male as long as a dominant follicle is present. The sizes of preovulatory follicles are 9 to 13 mm and 8 to 12 mm in the llama and alpaca, respectively. Females maintain fertile, dominant follicles for an average of 8 days before undergoing regression. Usually the next follicular wave has already produced the next dominant follicle before the previous preovulatory follicle begins to regress. For this reason, the female camelid usually maintains estrous behavior continually until she is mated.[9]

43.2 CYSTIC FOLLICULAR DEGENERATION

43.2.1 Cows

Ovarian cysts are follicle-like ovarian structures that arise because of failure of ovulation.[5] They are usually larger than 25 mm in diameter and persist in the absence of a CL for 10 days or more. Follicular cysts have thin walls and may be single, multiple, or multilocular structures on one or both ovaries. Partially luteinized cysts tend to be single, unilateral structures with thicker walls because of the presence of luteal tissue.

The mechanism by which ovulation fails and cysts develop is not known. Failure of ovulation may result from inadequate release of gonadotropins or ovarian dysfunction. Increased stress of conditions such as retained placenta, metritis, and hypocalcemia around the time of calving and postpartum ketosis have been associated with an increased prevalence of cystic follicular degeneration (CFD), as has a hereditary predisposition.[10]

43.2.1.1 Clinical Signs and Diagnosis

Approximately 70% to 80% of cows affected by CFD are anestrus, whereas 20% to 30% display frequent or intense estrus (nymphomania). Cystic ovarian disease affects 10% to 30% of dairy cows. The condition is rare in commercial beef cows because of rigid culling for reproductive failure.

The physical appearance of cows with CFD depends on the duration of the condition. No changes are apparent after a short time, but in long-standing cases relaxation of the pelvic ligaments may result in prominence of the tailhead and masculine characteristics such as a crested neck.

The diagnosis of CFD is based on an accurate history and clinical examination. A history of constant or frequent estrus, short interestrous intervals, or anestrus may suggest CFD. Examination of the ovaries by palpation per rectum reveals the presence of enlarged fluid-filled structures raised above the surface of the ovary that greatly increase total ovarian size. Ovarian cysts are larger (>25 mm) than preovulatory follicles (15 to 25 mm). Differentiation between a single large cyst and several smaller cysts on the same ovary may not be possible, nor may be recognition of the presence of partially luteinized cysts (based on peripheral progesterone concentrations) unless ultrasonography is used. Ovarian cysts appear to be dynamic structures; those that develop early in the postpartum period may regress without treatment, and a normal estrous cycle may follow, or another cystic structure may develop.

During palpation of the ovaries, several normal structures may complicate the diagnosis of CFD. Normal preovulatory follicles may approach 25 mm in diameter and have palpable characteristics similar to those of small cysts. During the follicular phase of the estrous cycle, however, the uterus responds to palpation by becoming more turgid, whereas the uterus of a cow with CFD is typically flaccid and unresponsive. In neglected cases of CFD, mucometra may develop and must be differentiated from pregnancy. During the first 5 to 7 days of the estrous cycle, the developing CL may be smooth and soft and is commonly mistaken for an ovarian cyst. More mature CLs are solid and liver-like in consistency, often feature a palpable ovulatory papilla at the apex, and are more easily differentiated from ovarian cysts. However, 10% to 20% of mature CLs may lack an ovulatory papilla, making them more easily confused with ovarian cysts. Ultrasonography is generally more accurate in identifying subtle structural differences than transrectal palpation. Salpingitis, hydrosalpinx, oophoritis, ovarian abscesses, ovarian neoplasms, and cysts of the fimbria are other causes of enlargement of the ovary and surrounding structures that must be differentiated from ovarian cysts.[11]

Histories that may erroneously suggest CFD include apparently short interestrous intervals because of inaccurate detection of estrus.[12] Oxytocin administered to stimulate milk letdown may result in short interestrous intervals and suggest CFD. The estrous cycle may be shortened by administering 100 IU of oxytocin per day on days 2 through 6[13] or on days 3 through 7 or 8.[14] Heifers treated with 100 IU of oxytocin per day returned to estrus in an average of 12.9 days versus 20.3 days in untreated controls.

43.2.1.2

Clinical Pathology

Plasma progesterone concentrations are low in cows with follicular cysts. Partial luteinization may occur, and progesterone concentrations may increase over time but remain lower than those of cows with normal CLs. Estrogen concentrations in the plasma of cows with CFD are variable.

43.2.1.3

Treatment and Prognosis

The goal in treating CFD is to induce luteinization of the cyst and reestablish normal estrous cycles. Several methods have been recommended.

43.2.1.3.1

SPONTANEOUS RECOVERY

Spontaneous recovery from CFD occurs in up to 60% of cows that develop CFD before the first ovulation after calving but in only approximately 20% of cases that develop after the first postpartum ovulation. Evaluation of therapeutic agents for CFD may be confounded by spontaneous recovery.

43.2.1.3.2

LUTEINIZING HORMONE

Recommended doses of human chorionic gonadotropin (hCG) range from 5000 IU either intravenously (IV) or intramuscularly (IM) to 10,000 IU IM. Of cows treated with a single dose of hCG, 65% to 80% establish a normal estrous cycle within 3 to 4 weeks; a second or third dose may be required in cows that do not respond after 3 to 4 weeks or in cases in which nymphomania persists. Anaphylaxis after repeated treatments with a larger protein hormone such as hCG can occur. Antibodies to hCG may reduce the effectiveness of sequential treatments. Therapeutic response, both endocrinologically and clinically, is essentially equivalent between hCG and gonadotropin-releasing hormone (GnRH). The practical disadvantage of hCG is its higher price.

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43.2.1.3.3

GONADOTROPIN-RELEASING HORMONE

Currently the most common treatment for ovarian cysts, especially follicular cysts, is an injection of GnRH (100 mcg IM). Cows responding to this treatment have an average interval to estrus of one estrous cycle or 18 to 24 days. The treatment to breeding interval can be shortened by administering GnRH at the time of diagnosis, followed by a luteolytic dose of prostaglandin 10 days to 2 weeks later. With this regimen it is not critical whether the cyst is follicular or luteal or even whether it is a misdiagnosed large, smooth CL with or without a fluid-filled central cavity. Most veterinarians agree that accurate differential diagnosis by rectal palpation among follicular cysts, luteal cysts, and some CLs can be a problem.

43.2.1.3.4

PROSTAGLANDIN $F_{2\alpha}$

Luteal-type cysts can be treated with the luteolytic activity of PGF. The advantage is the quicker return to estrus for those cows able to respond and the lower cost of PGF. Cysts that luteinize in response to GnRH regress at a time similar to that of normal CLs. Treatment with PGF may be used to reduce the interval from treatment with GnRH to estrus from 18 to 24 days to an average of 12 to 14 days by administering PGF 9 days after GnRH. Most clinicians are only approximately 50% accurate in determining the degree of luteinization of cysts by palpation per rectum; therefore measurement of concentrations of progesterone in milk or of plasma from affected cows allows the selection of GnRH or hCG for treatment of follicular cysts and PGF for the treatment of luteinized cysts. Ultrasonography can also be used to make an accurate diagnosis.[15]

43.2.1.3.5

MANUAL RUPTURE

Thin-walled follicular cysts may be inadvertently ruptured during examination of the ovaries, and some practitioners may intentionally attempt cyst rupture. Recovery rates after manual rupture have rarely been studied in well-designed controlled experiments but are generally within the range reported for spontaneous recovery. Deliberate manual rupture of ovarian cysts is considered an obsolete form of treatment by some veterinary clinicians, but others routinely use the procedure—especially as an initial treatment for cysts found during the voluntary waiting period. Manual rupture of cysts may be followed by hemorrhage and adhesions between the ovary and surrounding structures. These complications appear to be much more common with use of digital pressure to enucleate CLs than with manual rupture of ovarian cysts.

43.2.2 Ewes and Does

Cystic ovaries appear to be more common in goats than in sheep. In one study 12% of goats had cystic ovaries when examined at a slaughterhouse.[16] The condition is often overdiagnosed by owners observing nymphomania. Treatment typically consists of administering exogenous ovulation-hastening drugs (hCG and GnRH).[17] LH surge is noted usually within 2 hours of GnRH administration. PGF may be administered 10 days later to bring the doe into heat (55 hours after PGF).

43.2.3 Camelids

Hemorrhagic follicles are observed in nonbred llamas and usually regress within 22 days.[18] Follicles larger than 12 mm are considered by some authors as pathologic cysts. These structures may, however, be anovulatory follicles. They may have a negative influence on the emergence of other follicular waves, but this influence seems to last for only approximately 8 days.[9,19]

43.3 POOR NUTRITION

As with other species, poor body condition, depressed energy intake, and decreased vitamin and mineral intake suppress reproductive activity in ewes and does. Lowered energy balance results in poor or weak signs of estrus, depressed ovulation, abnormal cycle, and delayed puberty. Deficiencies in energy, protein, vitamins A and E, phosphorus, and many trace minerals (iodine, copper) are commonly seen. These deficiencies are most commonly associated with irregular estrous cycles.

43.4 PLANT TOXICITY

43.4.1 Ergot Alkaloids

The consumption of fescue infected with *Neotyphodium coenophialum*, is associated with decreased reproductive efficiency. The ergot alkaloids have been shown to affect prolactin production in ewes and to increase the interval from introduction of the ram to conception.

43.4.2 Estrogen-Producing Plants

Sheep appear to be sensitive to the effects of phytoestrogens. Clinical observations include infertility, irregular and prolonged heat cycles, lowered conception rates, and early embryonic death.

43.5 HEAT STRESS

Fertility in lactating cows is decreased during the hot seasons of the year. Heat stress may cause decreased estrous detection, impair follicular development, disrupt function of the reproductive tract, affect oocyte competence, and lead to early embryonic death. Embryos develop resistance to heat shock as they age. Bovine morulae to blastocyst stages are unaffected by heat shock.[19a]

43.6 ANESTRUS

Anestrus, may be defined as ovarian inactivity. The causes of anestrus are multiple and include diseases of the reproductive and other systems. In addition, the problem is complicated by management factors that cause estrus to pass undetected, even though the animal's estrous cycles and estrous behavior are normal. Common causes of anestrus in mares are summarized in Table 43-1.

43.7 MARES

43.7.1 PUBERTY

The mare likely undergoes puberty between the ages of 12 and 24 months. Because the horse is not an agricultural production animal, there has been little interest in studying the onset of puberty as in other species, where hastening puberty increases production. Most mares are not bred until they are at least 3 years old, thus making prepubertal status an unlikely differential diagnosis for infertility.

43.8 SEASONAL ANESTRUS

43.8.1 Clinical Signs and Diagnosis

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The mare is a seasonally polyestrous animal, showing anestrus during the shorter days of the year and cycling regularly during the longer days. Length of anestrus varies from one to several months, although some mares, particularly in the tropics, may cycle year round.[20] In California, Australia, and South Africa 18% to 25% of mares cycle year round.[1,21–23] Anestrous mares may be indifferent to teasing and do not show regular estrous behavior. Ovaries are small and firm on palpation, and the uterus is flaccid with a thin endometrium. The cervix has mild tone and may be indistinct. On speculum examination of the vagina, the vaginal mucosa is pale and dry, and the cervix usually appears closed but is occasionally open or may be easily opened. Mares that experience seasonal anestrus will go through a transition period in late winter and early spring, characterized by the development of waves of antral follicles that regress without ovulation because the ovulatory surge of luteinizing hormone (LH) is absent.[23] Transitional mares exhibit signs of estrus, including clitoral “winking,” tail flagging, and urinating in the presence of the stallion. Eventually, increasing LH concentration coincides with a large follicle, resulting in ovulation. After the first ovulation of the season, the mare will continue to ovulate on successive estrous cycles. A transition period is also observed during the fall as the mare changes from a polyestrous condition to the winter anestrus. Differential diagnoses for seasonal anestrus and transitional mares are listed in Table 43-1.

Table 43-1 Differential Diagnosis of Anestrus in Mares

Cause	Uterus	Cervix	Ovaries	Peripheral Progesterone	Season	Other Laboratory Tests	Treatment
Pregnancy	Increased tone during early pregnancy; enlarged; positive signs of pregnancy by palpation or ultrasound	Tightly closed	Normal size during early pregnancy; out of reach of examiner in late stages	Elevated throughout pregnancy until just before term	Any season; may be more common in spring and summer	Equine chorionic gonadotropin; Cuboni test	Usually none required; therapeutic abortion if mismated
Prolonged diestrus	Normal size, increased tone and tubularity; may be similar to early pregnancy	Tightly closed	Normal size; prolonged corpus luteum is embedded within ovary	Elevated throughout prolonged lifespan (30 to 90 days)	Any season; may be more common in summer		PGF
Seasonal anestrus	Normal size; flaccid; difficult to palpate	Varies from tightly closed to open	Both are small and firm, may or may not have small follicles	Low until first corpus luteum develops	Late autumn, winter, early spring		Artificial lights; wait for normal breeding season
Unobserved estrus	Normal size	Characteristic cyclic changes; relaxed and open during estrus	Development of one (or more) follicles; ovulation	Elevated for ~14 days; low for ~7 days	Spring, summer, autumn		Improve management; tease with another stallion; sequential examinations; PGF
Pyometra	Variable enlargement	May be open, closed, or stenotic; purulent discharge may be present	Normal size, follicular development may be present	Erratic profiles; some are elevated for prolonged periods, others may have luteal regression	Any season	Endometrial cytology; bacterial culture; antibiotic sensitivity	Drain; systemic antibiotics; PGF
Undernutrition	Normal size	Varies from tightly closed to open; no cyclic changes	Bilaterally small and firm	Low	Any season	Hematology; clinical chemistry as indicated; fecal flotation	Improve nutritional status; parasite control; treat concurrent diseases

Granulosa-theca cell tumor	Normal size	Varies	One enlarged, multicystic; other small and atrophic	Low	Any season	Peripheral inhibin concentrations are elevated in ~90% and testosterone in ~50% of mares with granulosa-theca cell tumor	Surgical removal of neoplastic ovary
Gonadal dysgenesis	Small	Varies	Small, firm, atrophic	Low	Any season	Karyotype	None

PGF, Prostaglandin F.

43.8.2 Treatment and Prognosis

As day length increases, most mares ovulate and begin regular cyclicity without treatment. Methods to advance the onset of regular ovulatory periods are discussed in the following sections.

43.8.2.1 ARTIFICIAL LIGHTING

The vernal transition can be moved but not shortened beyond its physiologic length of 6 to 8 weeks by exposure of mares to artificial light. A common artificial lighting regimen is to expose the mares to 16 hours of light and 8 hours of dark by extending the photoperiod in the evening starting in late November to initiate ovulation by February (in the Northern Hemisphere). Light should be added to the end of the day, or split between the beginning and end of the day, as opposed to adding light only at the beginning of the day.[6] An alternative regimen is to expose mares to 1 hour of artificial light 9.5 to 10.5 hours after the onset of darkness.[24] Use of one 200-watt incandescent bulb or two 40-watt fluorescent tubes at a height of 7 to 8 feet in a 12- by 12-ft box stall has been recommended.[25] Paddock lighting has been described.[5]

43.8.2.2 GONADOTROPIN-RELEASING HORMONE

Treatment with GnRH or a GnRH analogue for mares in anestrus or spring transition has been shown to induce ovulation.[26–30] Twice-daily injections of a GnRH agonist induced ovulation in a majority of mares within 2 to 3 weeks.[30] Mares that are in deep anestrus (January and February, Northern Hemisphere) can be expected to return to anestrus after treatment.

43.8.2.3 DOPAMINE ANTAGONISTS

Domperidone and sulpiride have been reported to stimulate follicular activity and advance the first ovulation of the year in seasonally anestrous mares.[31,32] However, the efficacy of dopamine antagonists in advancing follicular growth and ovulation in anestrous mares has recently been questioned, and it has been suggested that adjustments in light and climactic conditions may influence the efficacy of the treatment.[33,34]

43.8.2.4 STEROIDS

Exogenous progestins suppress the release of LH from the anterior pituitary and may be used for estrous regulation during the vernal transition. After treatment of mares for 10 to 14 days, withdrawal of progestin may result in LH release from the pituitary and estrus beginning in 4 to 5 days, with ovulation within 10 days after cessation of treatment. Mares should be in mid to late transition and have a follicle at least 25 mm in size to respond to treatment. Progestins will not induce estrus or ovulation in anestrous mares.[35] The recommended dose of progesterone in oil is 150 to 300 mg daily by intramuscular injection. The synthetic progestin, altrenogest, is administered orally (PO) at 0.044 mg/kg daily. Progestins may be used in combination with extended photoperiod and gonadotropins. Products that are ineffective or unavailable include repositol progesterone, melengestrol acetate, chlormadinone acetate, proligestone, medroxyprogesterone acetate, hydroxyprogesterone acetate, and norgestomet implants.

Synchronization of the first ovulation (or any ovulation during the cyclic season) can be accomplished by the administration of a combination of progesterone in oil (150 mg/day IM) and estradiol-17β (10 mg/day IM) once daily for 10 days.[36] Treatment is most effective if given after mares have been under lights for 45 to 60 days. $PGF_{2\alpha}$ should be given on the last day of steroid treatment. Treated mares will ovulate within 8 to 10 days after the last treatment.

43.8.2.5 GONADOTROPINS

At a dose of 2500 to 3000 IU, hCG may induce ovulation within 48 hours when administered to a mare with a follicle larger than 35 mm in diameter[37] and may reduce time to first ovulaton in transitional mares, particularly when used in combination with lights and/or progesterone treatment. Ovulation response here is less predictable than that induced with hCG during the breeding season.

43.8.2.6 FOLLICULAR ASPIRATION

Ultrasound-guided transvaginal follicular aspiration of follicles <35 mm has been shown to hasten the onset of cyclicity in transitional mares.[38] Follicular aspiration resulted in the formation of an active CL, and subsequent treatment with $PGF_{2\alpha}$ resulted in estrous behavior and ovulation of a dominant follicle.

43.9 PROLONGED LUTEAL PHASE AND PSEUDOPREGNANCY

Mares that experience embryonic loss in the presence of endometrial cups (days 35 to 150 of gestation) are said to be *pseudopregnant*, (*pseudopregnancy*, may also refer to that condition in which a conceptus was lost after maternal recognition of pregnancy and before the development of endometrial cups, resulting in prolonged luteal life). In spite of the loss of the fetus and placental tissue, endometrial cups remain in place and continue to secrete equine chorionic gonadotropin (eCG) for a similar period to that in a pregnant mare, to 100 to 150 days of gestation.[39] The primary and secondary CLs occasionally regress after embryonic loss[40] but usually remain during eCG secretion, maintaining high levels of peripheral progesterone.

43.9.1 Treatment and Prognosis

In untreated mares, cyclic activity is reestablished after the cessation of eCG secretion. Repeated daily injections of PGF products have been reported to cause luteal regression in pseudopregnant mares,[41] but only CLs older than 5 days respond to the treatment, which may prevent mares returning to estrus. Pregnancies have occurred in the face of high eCG,[42] but fertility of treated mares is usually low.

43.10 LACK OF BEHAVIORAL ESTRUS (SILENT ESTRUS)

Behavioral estrus may not be detected in otherwise normal mares as a result of inadequate estrous detection or a failure on the part of the mare to show obvious signs of estrus. The latter may occur in up to 15% of mares on well-managed farms.[43] Inadequate estrous detection may be a result of human apathy or ignorance or a result of using a low-libido or inexperienced stallion. Teasing mares as a group may make detection of estrus more difficult, especially for nervous mares, mares with foals, and mares of low social rank. Use of anabolic steroids may suppress behavioral estrus.

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43.10.1 Clinical Signs and Diagnosis

The mare fails to show estrus on adequate teasing with a stallion. Differential diagnoses are listed in Table 43-2.

Table 43-2 Irregularities of the Equine Estrous Cycle: DifferentialDiagnosis

Etiology	Distinguishing Features
FAILURE TO CYCLE WITH LOW PROGESTERONE	
Winter anestrus	Season; inactive ovaries
Gonadal dysgenesis	Small, hard, inactive ovaries; karyotype; underdeveloped tubular tract; small body
Pituitary adenoma	Systemic signs; inactive ovaries
Granulosa-theca cell tumor	See prolonged or irregular behavioral estrus
Behavioral	Intimidated by stallion; recently foaled; low social rank
FAILURE TO CYCLE WITH HIGH PROGESTERONE	
Pregnancy	Presence of embryonic vesicle or fetus
Persistent CL	CL fails to regress; responds to PGF
Diestrous ovulation	CL immature at time of endogenous PGF; responds to exogenous PGF
Pseudopregnancy	Conceptus loss after maternal recognition of pregnancy; responds to exogenous PGF
Iatrogenic	History of exogenous progestin or nonsteroidal antiinflammatory drug administration
Pyometra	Uterus palpably enlarged
SHORT LUTEAL PHASE	
Uterine infection	Pyometra or endometritis causing premature endogenous PGF secretion
Systemic endotoxemia	Systemic signs; endotoxin-mediated release of endogenous PGF
Iatrogenic	History of uterine manipulation, infusion, invasive procedure, or exogenous PGF
PROLONGED OR IRREGULAR BEHAVIORAL ESTRUS	
Transitional period	Season, variable ovarian activity
Granulosa-theca cell tumor	Affected ovary large and multicystic, contralateral ovary small; elevated inhibin and/or testosterone; anestrus, nymphomaniac or stallion-like behavior
Gonadal dysgenesis	Occasionally irregular cyclicity; as above
Behavioral nymphomania	Otherwise normal mare
Normal mare	Mares in winter anestrus and pregnancy may show estrous signs

CL, Corpus luteum; *PGF*, prostaglandin $F_{2\alpha}$.

43.10.2 Treatment and Prognosis

Management should be examined to ensure a competent teasing routine. When approached by a stallion, mares in estrus stand still with ears held forward; they may elevate the tail, rhythmically evert the clitoris ("winking"), assume a squatting posture, urinate, and lean against the teasing chute toward the stallion. Mares that are not in estrus move about and hold their ears back; they may strike, kick, squeal, swish their tails, and forcefully void small amounts of urine. Experienced personnel should handle both stallion and mare. The teaser stallion should have adequate libido without being aggressive. Transrectal palpation and ultrasonography should supplement teasing. Some mares are indifferent to teasing, and records of sequential palpation must be relied on for breeding. Prostaglandins can be used to control estrus. Progesterone concentrations of less than 1 ng/mL are consistent with estrus but may also occur in anestrous mares. Mares that fail to show behavioral estrus should be bred by artificial insemination (AI) (if allowed by the breed register) or appropriate restraint used for natural cover.

43.11 BEHAVIORAL NYMPHOMANIA

Abnormal estrous behavior and aggression may be demonstrated by otherwise normal mares at any stage of the estrous cycle. Cause is unknown, although exaggerated response to ovarian steroids has been proposed.[44]

43.11.1 Clinical Signs and Diagnosis

Exaggerated signs of estrus occur, initially during estrus and then throughout the cycle. Mares may develop behavioral anomalies and become aggressive. Differential diagnoses are listed in Table 43-2. It is important to differentiate abnormal estrous behavior from unrelated behavioral problems.

43.11.2 Treatment and Prognosis

Exogenous progestins have been used to limited effect. Short-term dexamethasone treatment (5 to 10 mg) may alleviate signs for 3 to 4 days.[44] Bilateral ovariectomy may be successful in some cases.

43.12 RUMINANTS

Common causes of anestrus in cows are summarized in Table 43-3.

43.12.1 UNOBSERVED OR SILENT ESTRUS

43.12.1.1 Cow

Failure of a cow to display, or a manager to observe, the signs of estrus contributes significantly to reproductive inefficiency. When the presenting history suggests anestrus (failure to have a normal estrous cycle), the clinician must determine if the cause is failure of the manager to detect estrus in normal cows or failure of the cow to cycle because of some abnormal process. In dairy herds approximately 90% of cows presented for examination because of a history of anestrus have evidence of normal cyclic ovarian changes,

whereas only approximately 10% are affected by an abnormality that suspends the estrous cycle (i.e., only approximately 10% are in true anestrus).

Nearly 90% of well-managed dairy cows have initiated normal-length estrous cycles by 60 days after calving, but only approximately 60% are detected correctly to be in estrus by that time.[45] Rates of estrous detection by twice-daily observation range from 50% to 73% depending on the skill of the observer.

Table 43-3 Differential Diagnosis of Anestrus in Cows

Cause	Uterus	Ovaries	Peripheral Progesterone	Treatment
Pregnancy	Enlarged; positive signs of pregnancy	Corpus luteum in ovary ipsilateral to pregnant uterine horn	Elevated throughout	Usually none required; PGF or PGF + dexamethasone if unwanted pregnancy
Unobserved estrus	Normal; characteristic tone during estrus; postovulatory edema	Development and regression of corpora lutea and follicular waves diagnosed by sequential examinations	Elevated during diestrus and low for ~3 days before ovulation and ~4 days after ovulation	Improve estrous detection; estrous detection aids; synchronize estrus with PGF; teaser animals
Cystic follicular degeneration	Normal in acute cases; later flaccid mucometra may develop in chronic cases	Fluid-filled cyst(s) greater than 25 mm in diameter; no corpora lutea; unilateral or bilateral; single or multiple cysts	Variable; low in cases of follicular cysts; slight elevation in cases of partially luteinized cysts	Spontaneous recovery; GnRH or hCG to induce luteinization of follicular cysts; PGF for partially luteinized cysts; manual rupture
Pyometra	Variable enlargement; fluid movable from horn to horn, normal-to-thick uterine wall; no positive signs of pregnancy	Corpus luteum in one ovary, frequently contralateral to larger uterine horn	Elevated throughout	PGF
Mummified fetus	Leather-like fetus within involuted uterus; no positive signs of pregnancy	Corpus luteum in ipsilateral ovary	Elevated throughout	PGF; usually slaughter, advisable for economic reasons
Undernutrition	Normal	Small; static; no cyclic changes detected on sequential examinations	Low until corpus luteum forms	Improve quality and quantity of ration
Granulosa-theca cell tumor	Normal	One ovary enlarged; other low atrophic	Low	Surgical removal of neoplastic ovary
Freemartinism	Small to nonexistent	Small to nonexistent	Low	No possible treatment

Ovarian hypoplasia	Very small to near normal	Very small to near normal; unilateral or bilateral; partial or complete	Variable; depends on degree of hypoplasia	No possible treatment

GnRH, Gonadotropin-releasing hormone; *hCG*, human chorionic gonadotropin; *PGF*, prostaglandin $F_{2\alpha}$.

Mounting activity and estrous behavior are reduced by hot and cold ambient temperatures and during the times of milking and feeding. More mounts are observed when cows are kept on dirt than on concrete. Estrous behavior varies with the time of day and may be an inverse reflection of extraneous activity interfering with cow behavior. In one study, 43% of cows showed heat between midnight and 6 AM; 22% between 6 AM and noon; 10% between noon and 6 PM; and 25% between 6 PM and midnight.[46]

Estrus in dairy cows averages 7 to 16 hours in length but ranges from 0.5 to 36 hours. Sixty-five percent of cows are in estrus for less than 16 hours, and 25% are in estrus for less than 8 hours.[47] The number of mounts per hour ranges from 2 to 8, and the total number of mounts during estrus ranges from 11 to 56. Total number of mounts per estrus increases with the number of cows simultaneously in estrus.

43.12.1.2 Clinical Signs and Diagnosis

Dairy herds in which infertility is caused by inaccurate estrous detection are usually characterized by prolonged intervals from calving to first breeding and between services; insemination intervals of 10 to 15 days and 30 to 35 days; records of examinations that confirm cyclic ovarian changes, but in which observation of estrus is not recorded; and finding more than 15% of cows presented for pregnancy examination to be nonpregnant. Insemination during the luteal phase of the estrous cycle may occur in 10% to 20% of cows and is not likely to result in conception; insemination of pregnant cows may be followed by abortion.

The diagnosis of unobserved estrus requires sequential examination of affected cows and accurate records. Other causes of anestrus are eliminated. Conditions such as CFD, pyometra, mummified fetuses, granulosa-theca cell tumors, and segmental aplasia that cause anestrus affect individual animals. Anestrus caused by undernutrition is characterized by depressed milk production and low body condition score.

43.12.1.3 Treatment and Prognosis

PGF is widely used in clinical management of unobserved estrus. Mature CLs (approximately day 6 through day 18 of the estrous cycle) are responsive to PGF-induced luteolysis. Estrus occurs an average of 3 days (range 2 to 5 days) after administration of PGF, depending on the follicular status of the ovaries at the time of injection. The endocrine events surrounding the controlled estrus are indistinguishable from those surrounding spontaneous estrus and ovulation. Treatment with PGF shortens the intervals from treatment to first breeding and from treatment to conception but has no effect on fertility. The benefits of PGF treatment are limited by inaccurate palpation of the temporary ovarian structures, injection during the wrong phase of the cycle, and failure of the manager to observe estrus in treated cows (timed AI can be used to overcome this problem). 1425 1426

Measurement of progesterone concentrations in milk samples taken on the day of breeding is useful in herds with a history of reduced fertility to confirm that cows being inseminated are not in the luteal phase of the estrous cycle. If more than an occasional cow presented for insemination has an elevated concentration of

progesterone, the methods of estrous detection should be reviewed. Enzyme immunoassay kits for measuring concentrations of progesterone in milk and plasma of cows and other female animals have been described and are commercially available.

Various heat detection aids have been developed. Several use devices mounted on the tailhead to record that a cow has stood to be ridden. Pressure-sensitive devices that are glued to the tailhead and change color after sustained pressure by the weight of a mounting cow are commonly used. Similarly, pressure-sensitive devices glued to the tailhead can send a record of riding events directly to a computer. Chalk, cattle crayon marker, or paint applied to the tailhead are inexpensive aids that are rubbed off when the animal is mounted when she is in heat. These methods require daily maintenance and twice daily evaluation to function effectively. Detection aids that measure changes in activity (pedometers), mucous conductivity, or body temperature can be used successfully. Accuracy is enhanced when measurements are related to previous estrous activity and progesterone concentrations.[48]

43.12.1.4 Prevention and Control

Because unobserved estrus is primarily a problem of management, efforts to reduce time lost from delayed breeding are directed at improving efficiency of heat detection. Accurate records are required to identify cows that have not been observed in estrus by 40 days after calving. Cows not observed in estrus by 40 days after calving should be examined, and abnormalities of the reproductive organs that cause anestrus treated as indicated. The time of estrus can be predicted by palpation of the temporary ovarian structures, or estrus can be controlled with PGF. The most significant benefit of a planned herd health program is stimulation of improvements in management that decrease the interval from calving to conception as a result of improved estrous detection.

Anestrus after insemination is frequently interpreted as a clinical sign of pregnancy. However, unobserved estrus in cows that have failed to conceive or have experienced early embryonic death (postservice anestrus) contributes significantly to increased calving intervals. Clinical management of postservice anestrus depends on diligent observation of cows 18 to 24 days after breeding and identification of nonpregnant cows as early as possible after the infertile service so they may be reinseminated with minimum delay. Nonpregnant cows may be accurately identified by ovarian palpation or ultrasonography for absence of a mature CL, by low milk or plasma progesterone at the time of the first expected postservice estrus (approximately 21 days after breeding), or by palpation of the uterus per rectum before the second expected postservice estrus (30 to 42 days after breeding).

43.13 Ewe

The breeding season of most breeds of sheep maintained at temperate latitudes is restricted to late summer, autumn, and early winter, although some breeds cycle all year long. There is almost no homosexual interaction among ewes; therefore a male must be present to stimulate display of estrus.[5]

Introduction of a ram (either intact or vasectomized) into a flock of ewes advances the breeding season. Most ewes ovulate by 3 to 6 days after introduction of rams. The induced ovulation is seldom accompanied by estrus, but the subsequent estrus approximately 17 days later is ovulatory and fertile. The “ram effect” is lost when rams are allowed to associate with ewes throughout the year.

Return to estrus after mating may be detected in a flock of ewes by fitting the ram with a brisket device that marks serviced ewes. Return of an excessive number of ewes to service after breeding alerts the owner to the possibility of infertility.

AI of ewes is rare in the United States but more popular in other countries. Detection of estrus for AI depends on use of teaser rams mingled with the ewes or led through the flock several times daily.

43.14 Doe

The breeding season of does is similar to that of ewes (i.e., it surrounds the autumnal equinox). During periods of short daylight, the normal estrous cycle of does is 20 to 21 days. Homosexual interaction among estrous does rarely occurs; so signs of estrus must be elicited by teasing. Signs of estrus may also be evoked by exposure to male pheromones by way of a “buck jar” prepared by rubbing a cloth over the scent glands caudomedial to the horns of a mature buck during the breeding season and storing the cloth in a tightly closed container. If estrus is not observed in does exposed to a mature buck or to a buck jar during the physiologic breeding season, pregnancy or pseudopregnancy might be considered as possible causes of anestrus. Severely parasitized or inadequately nourished does do not have normal estrous cycles. Deficiencies of phosphorus, iodine, and manganese have been suggested as causes of anestrus in does.

Introduction of bucks into a flock of does early in the breeding season results in initiation of estrous cycles and some degree of synchrony of estrus approximately 10 days after introduction of the bucks.[5] In contrast to ewes, however, the first ovulation after exposure to males is accompanied by estrus and fertile mating.

43.15 Camelids

Most female South American camelids, although showing signs of ovarian cyclicity as early as 5 months of age, have decreased fertility until approximately 15 months of age. A female camelid should be at least 60% of her expected adult weight before she is bred. Male camelids have a preputial attachment of the penis that is not separated until 2 to 3 years of age. Some males may actually detach as early as 15 months of age. Before this time they will show mounting behavior but will not be capable of intromission.[9]

43.16 INFERTILITY CAUSED BY ABNORMALITIES OF THE FEMALE GENITAL ORGANS

43.16.1 ABNORMALITIES CAUSED BY PROBLEMS WITH SEXUAL DIFFERENTIATION

Sexual differentiation occurs in three stages, each stage dependant on the previous one:

1 Chromosomal (genotypic or genetic) sex is determined at fertilization in mammals by the type of sex chromosome contributed by the sperm (X or Y). In mammals, females are XX and males are XY.

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2 Gonadal sex is regulated by the *Sry*, (sex-determining region of the Y chromosome) gene, which produces a protein termed the *HY antigen*, as well as other sex-linked and autosomal genes downstream of *Sry*, activation to induce testis formation, or is regulated by the X-linked *Dax1*, to suppress testis formation.

3 Phenotypic sex is regulated by substances produced in the male testes to cause regression of the female tract and formation of the male tract, or, in the absence of a testis, formation of the female tract.

Chromosomal sex is determined at fertilization. All normal mammalian oocytes contribute an X chromosome in addition to one of each representative autosomal maternal chromosome. Sperm cells contribute either an X or a Y sex chromosome in addition to one of each representative autosomal paternal chromosome. Abnormalities in chromosomal sex occur because of nondisjunctional errors during either mitosis or meiosis. Fig. 43-1 shows some examples of chromosomal sex anomalies.

43.16.1.1

Monosomy X (XO)

Monosomy X is also known as *Turner's syndrome*., Owing to the lack of a Y chromosome and the consequent *Sry*, gene, but the presence of the *Dax1*, gene on the present X chromosome, the phenotype is female. Monosomy X is the most commonly reported chromosomal abnormality in mares.[49] Animals with this syndrome often have a history of poor performance and lack of or sporadic reproductive cyclicity. Ovaries are typically inactive, small, smooth, and firm. The uterus and cervix are usually hypoplastic. Externally the mare's genitalia may appear normal or underdeveloped.

43.16.1.2

XXY Syndrome

The genotype for XXY syndrome is part of Klinefelter's syndrome. Because of the presence of a Y chromosome and the consequent *Sry*, gene, affected individuals are phenotypically male; but probably owing to the presence of two copies of the *Dax1*, gene on the two X chromosomes, they generally have hypoplastic genitalia and reproductive organs. It is thought that some factor (*Dax1*, or some other) on the X chromosome must escape the inactivation process, which happens very early in development (around day 7 or 8 in the horse). Testicular development and spermatogenesis are inhibited, resulting in small, flaccid testes and azoospermia. The testes may be retained or descended, but they are often small and soft. The penis may be normal or smaller than usual. Affected males often show normal libido and sexual behavior. Low testosterone concentrations may be noted. Infertility always accompanies this syndrome. Reports have been made in numerous species, including the horse.[50,51]

Fig. 43-1 Examples of chromosomal sex abnormalities.

			Sperm					
			Normal		Abnormal			
			X	Y	XY	XX	YY	O
Eggs	Normal	X	XX	XY	XXY	XXX	XYY	XO
	Abnormal	XX	XXX	XXY	XXXY	XXXX	XXYY	XX
		O	XO	YO	XY	XX	YY	O

43.16.1.3 XXX

More is not better. A report of an infertile mare with the 65,XXX genotype confirms this.[52] The mare had bilaterally small, inactive ovaries, and a hypoplastic uterus and cervix.

43.16.1.4 Mosaics

Mosaics are individuals that have at least two cell lines with different karyotypes arising from the same zygote (Fig. 43-2).

Phenotypes vary in accordance with the degree of mosaicism. Varying degrees of hermaphroditism and pseudohermaphroditism have been reported in many domestic species. Mosaics often have mixed gonadal dysgenesis, with an ovary and a testis, or ovotestes, owing to sex chromosome mosaic cell lines.[53,54] These are true hermaphrodites.

43.16.1.5 Chimeras

Chimeras are individuals having cell lines from two different embryonic sources. This can occur experimentally or from the natural fusion of blastocysts in utero. The possibility has been reported from a suspected double ovulation and fertilization followed by blastomere fusion in the horse (64,XX/64,XY and 63,XO/64,XY genotypes reported). Freemartinism is a common occurrence in ruminants resulting in chimeric twins.

43.16.1.6 Freemartins

Freemartinism is a phenomenon in ruminants in which an infertile female is twin to a male. The dizygotic occurrence happens when the blastodermic vesicles of the two zygotes fuse early in development (day 18 to 20 in cattle) and share embryonic tissue. The placentas fuse (day 30 to 50 in bovines), and they share blood throughout gestation. This occurs before gonadal differentiation at day 40 to 50. Both individuals are XX/XY chimeras. The *Sry*, gene of the male twin causes the freemartin gonads to develop at least partially toward the male testis. The degree of differentiation varies with each freemartin, and many freemartin gonads remain undifferentiated. The shared circulation allows testosterone and antimüllerian hormone (AMH; discussed later) from the male twin, and possibly from the chimeric freemartin, to affect the freemartin genitalia, and so she lacks a cervix, uterus, uterine tubules, and cranial vagina. The vulva is fairly normal. The yearling freemartin fails to exhibit estrus, the udder and teats remain small, and the freemartin externally resembles a steer (only with a vulva). Diagnosis can be made by establishing a blind end to the vagina (no cranial vagina, no cervix). Of heifers born co-twin to a male, 92% will be freemartins.[55]

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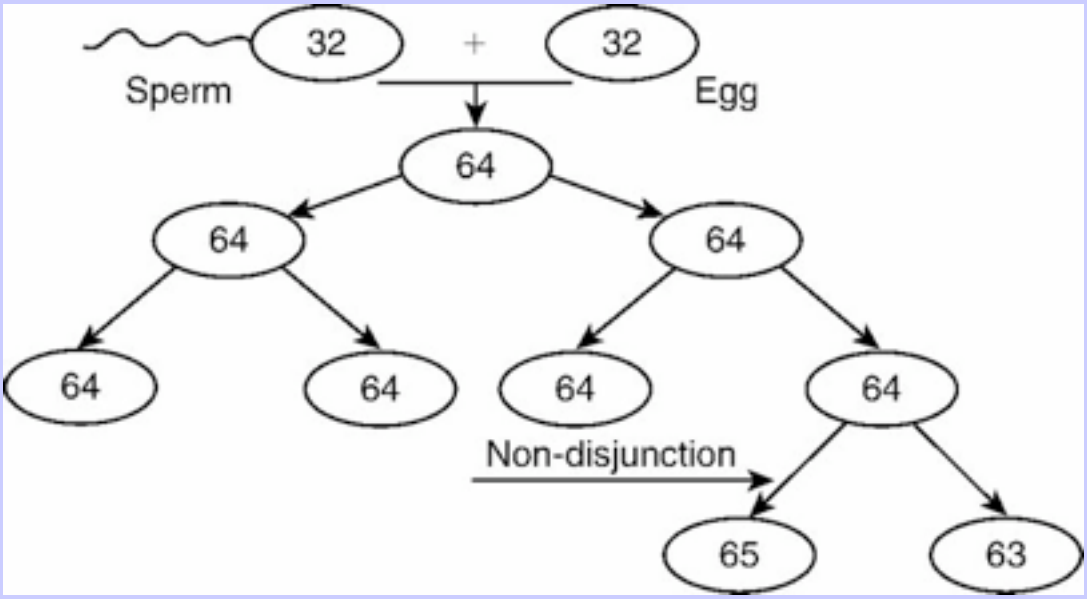
Fig. 43-2 Process of how a mosaic may occur. The haploid sperm and egg form a diploid zygote. Through the process of mitosis, diploid cells are replicated to always produce the same number of chromosomes. If, however, a chromosome pair does not separate during anaphase, called a *nondisjunction event*, cell lines that do not reflect a correct representation of the genome will be created and potentially propagated. If this happens with the sex chromosomes in the germ cell line, fertility of the individual or its offspring may be affected.



The male twin may develop into a fertile adult, but these individuals show a higher incidence of infertility than bulls with a 60,XY genotype. Most male twins to freemartins become steers.

Freemartinism is less common in sheep than in cattle, but it does occur. It has also been reported in goats and pigs. With increased fecundity in modern animals, we observe the phenomenon more often than was reported in the past. This is because ovine freemartinism is rare with twins or triplets but much more common with quadruplets or quintuplets. A notable difference between ovine and bovine freemartinism is the marked masculinity of the ovine freemartin. Gonads within the inguinal canal resemble normal prepubertal testes, and those within the abdomen resemble cryptorchid testes from rams of normal XY gonadal sex. Many ovine freemartins also have epididymides, vasa deferentia, vesicular glands, and even cremaster muscles.

43.17 GONADAL SEX

Chromosomal sex determines gonadal sex. The Y chromosome has very few genes, and all of the ones studied play a role in sex differentiation. The gene located at the sex-determining region on the Y chromosome (*Sry*) has a

DNA binding domain high mobility group (HMG) box. It produces a protein called the HY antigen, and its action appears to be regulated by the transcription of other genes. Their actions initiate differentiation of bipotential embryonic gonadal tissue into testicular tissue. Other genes act downstream of *Sry*, to support gonadal differentiation, including *Sox9, Gata4*, and *Wt1*, and *Sf1*, which act synergistically to promote testicular differentiation. *Sox9*, is a powerful promoter of testicular tissue differentiation. It is hypothesized that *Sry*, upregulates *Sox9*, but there is currently no direct evidence to support this. In the absence of the *Sry*, gene, the dual copies of the *Dax1*, gene on the X chromosomes suppress the formation of testicular tissue by antagonizing the *Sry*, gene and the synergy between *Sf1*, and *Wt1*., Another gene, *Wnt4*, has been shown to support female development, and the absence of this gene in female mice results in masculinization.[56] This evidence refutes the notion that female development is strictly a default process caused by the absence of *Sry*., Further research may elucidate other factors that actively promote the formation of ovarian tissue. Factors affecting *Sry*, or any of the other genes downstream of *Sry*, or any factors governing female development will affect phenotypic sex.

43.17.1 Abnormalities of Gonadal Sex: Sex Reversals

Sex reversals occur when the chromosomal sex and gonadal sex do not agree with each other. XX sex-reversed males and XY sex-reversed females are reported in many domestic species. These individuals are either XX males (testicular tissue), XY females (ovarian tissue), or true hermaphrodites (both ovarian and testicular tissue on separate gonads or the same gonad [ovotestes]). Sex reversals are relatively common in the horse, and all three of the types discussed in the following sections are reported. Sex reversal is considered to occur in horses both sporadically and with familial inheritance.

43.17.2 XY Sex-Reversed Females (Gonadal Dysgenesis)

Reported XY sex-reversed females have been reported to arise because of an absent or mutated (and nonfunctional) *Sry*, gene. It is believed that the Sry chromosome is missing because of an abnormal meiotic exchange with the X chromosome. It is thought that in the sire two crossing-over events occurred between X and Y chromosomes during spermatogenesis. These animals are infertile and have a normal female appearance to their external genitalia. The ovaries and uterus tend to be hypoplastic. The gonads may, in fact, be completely undifferentiated (“streak gonads”). These animals may be true hermaphrodites (ovotestes) or XY females (only ovarian tissue).

43.17.3 *Sry*,-positive XX Sex-Reversed Males

Many XX sex-reversed males conversely arise from a translocation of the *Sry*, gene onto the X chromosome. These animals may be true hermaphrodites or XX males (only testicular tissue).

43.17.4 *Sry*,-negative XX Sex-Reversed Males

There are reports in horses of *Sry*,-negative XX sex-reversed males.[57,58] The exact mechanism of masculinization is still uncertain. Possibilities include Y-specific sequences other than *Sry*, (which would require an XY individual with an inactivated or absent *Sry*, gene), XX/XY chimerism within the testicular tissue, and a mutation in an autosomal or X-linked gene farther down the cascade of genes responsible for sex determination. XX sex-reversed males may have ambiguous sexual characteristics and may be true hermaphrodites or XX males (only testicular tissue).

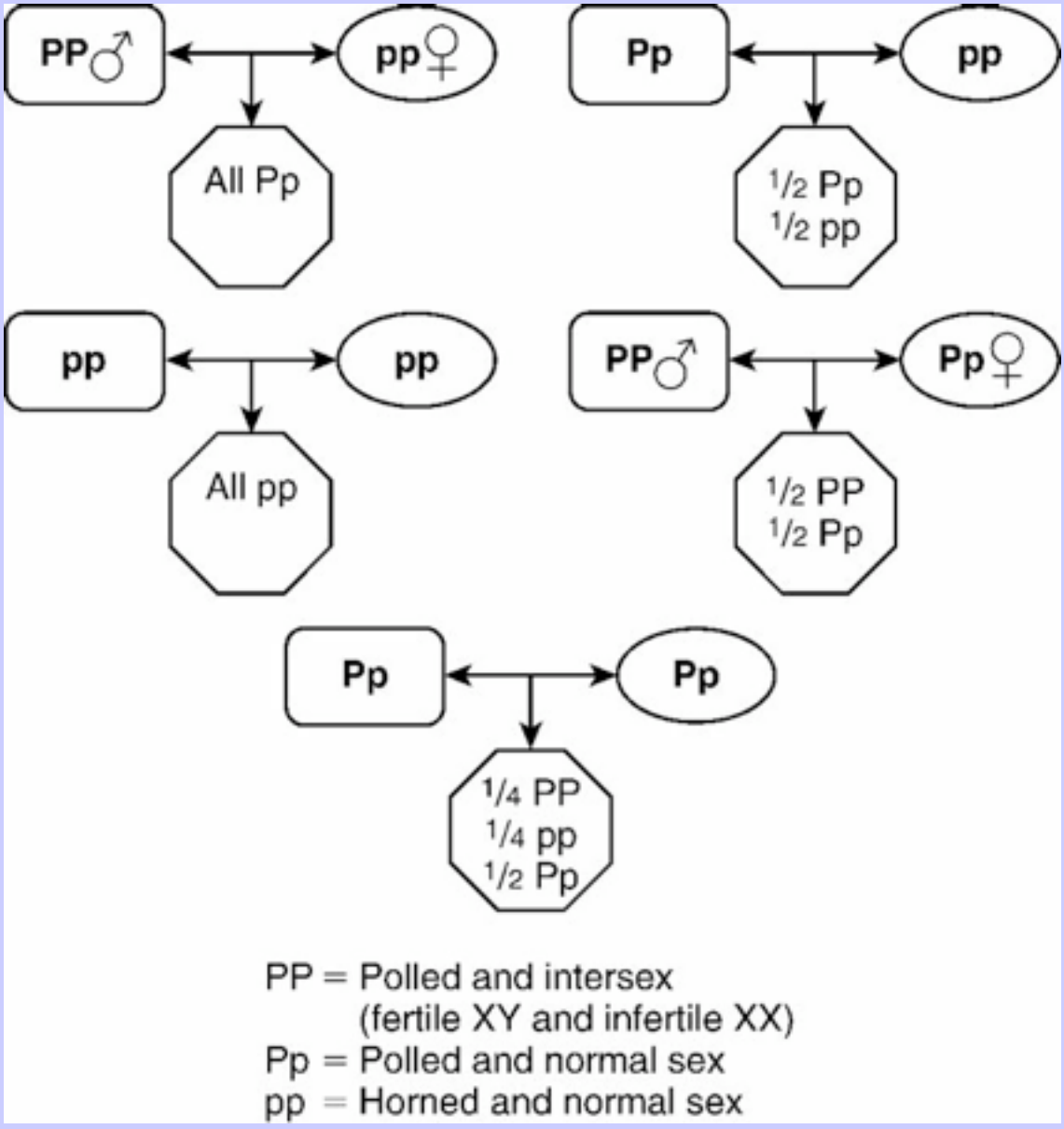
Goats (especially Alpine, Saanen, and Toggenburg) present another classic, common example of *Sry*,-negative XX sex-reversed males. The “polled” (hornless) gene is either very closely linked to an intersex locus, or the polled gene itself is pleomorphic and controls both the hornless and intersex traits. This close linkage or pleomorphism is called the *polled/intersex syndrome*, (PIS). A partial reason for the sex reversal is the deletion that affects a noncoding RNA (Pisrt1) and a transcription factor (FoxL2). The mechanism of testis induction has not been discovered yet. Elucidating this mechanism may be a big step in describing autosomal sex-determining factors in other species, including humans. The intersex gene is currently thought to work by mimicking the *Sry*, gene and codes for the HY antigen.

The polled gene shows a dominant autosomal inheritance pattern, whereas the intersex trait shows a recessive autosomal inheritance pattern. A single dose of the P polled gene is enough to cause the polled trait, but a double dose is required to cause intersexuality in XX individuals. Therefore PP animals are hornless and infertile (if XX, fertile if XY); Pp individuals are hornless (although sometimes have horny bosses) and fertile; and pp individuals are horned and fertile. Intersex individuals are always sterile and have a shortened vagina, large clitoris, bucklike head and neck, buck odor, and buck behavior. The gonads are testes or ovotestes and may be scrotal, inguinal, or abdominal. Even very masculinized intersexes with scrotal testes are azoospermic. A PP polled goat that has an XY genotype is usually initially fertile but often develops sperm granulomas later in life. The only way to avoid the intersex condition is to always breed a polled individual to a horned individual (Fig. 43-3).

43.18 PHENOTYPIC SEX

Gonadal sex determines phenotypic sex. Initially each embryo has both müllerian (paramesonephric) ducts and wolffian (mesonephric) ducts. Within testicular tissue, Sox9 triggers Sertoli cells to secrete müllerian inhibiting substance (MIS; also known as *antimüllerian hormone*, [AMH]), which initiates the irreversible regression of the paramesonephric ducts. The action of MIS or AMH is further regulated by other genes and their proteins (Sf-1, Gata factors, Wt-1, Dax-1, and FSH). Wt-1 and Sf-1 synergistically enhance AMH transcriptional activity. Gata-4 enhances AMH promoter activity by directly binding to DNA and by synergistically interacting with Sf-1. 1428 1429

Fig. 43-3 Assuming classical mendelian genetics, the graph illustrates expected genotypes of progeny from different breedings of polled and wild type goats.



Leydig cells secrete testosterone that is converted by 5α-reductase to dihydrotestosterone. These two steroids promote the differentiation of male genitalia. Testosterone influences the differentiation of the wolffian ducts into the internal male genitalia (vasa deferentia and epididymides), whereas dihydrotestosterone stimulates the formation of the seminal vesicles and male urethra from the urogenital sinus, and the penis from the genital

tubercle. In the absence of these testicular hormones, the wolffian ducts regress and the müllerian ducts become the female internal genitalia.

In the presence of two X chromosomes, the double dose of Dax-1 has an inhibitory effect on the synergistic relationships between Sf-1 and Wt-1 and Gata-4, preventing their support of AMH production.[59] The primitive sex cords (gonadal cords) degenerate in the medulla and remain in the cortex (opposite in the horse). Subsequently there is no communication between the gonad and the mesonephros. In the absence of AMH, the müllerian ducts persist as the oviducts and fuse to form the uterus and cranial vagina. In the absence of testosterone, the wolffian ducts regress. Vestigial traces of these are located in the mesentery of the ovary, the epoophoron, the paroophoron, and Gartner's ducts. The tissues that form the round ligament of the uterus are analogous to the male gubernaculum.

43.18.1 Abnormalities of Phenotypic Sex

Abnormalities of phenotypic sex occur when the chromosomal and gonadal sex agree (XX with ovaries or XY with testes) but the external and/or internal genitalia do not correlate or are ambiguous. Affected animals are the male and female pseudohermaphrodites. The condition can occur because of insensitivity of androgen receptors or because of any abnormality along the pathway that may affect the intervening hormones, such as the conversion of 5α-reductase to dihydrotestosterone.

43.18.1.1 TESTICULAR FEMINIZATION

Testicular feminization is reported in domestic species, including the horse.[60] Patients have external genitalia that are either female or ambiguous in appearance. The vagina may be blind-ending, or the uterus hypoplastic. The gonads are testicles, although they are usually abdominal or inguinal. Male behavior may be reported in horses. The problem lies in the gene for the androgen receptor, located on the X chromosome received from the dam. This X-linked recessive inheritance has been demonstrated in both humans and horses. Affected individuals are male pseudohermaphrodites; the condition has been diagnosed in multiple horse breeds. Serum testosterone is often elevated as a baseline because of loss of negative feedback, or at least in response to an hCG test.

43.19 ABNORMALITIES OF THE OVARIES

43.19.1 MARES

43.19.1.1 ABNORMALLY SMALL OVARIES

The most common causes of bilaterally small ovaries in the mare are (1) seasonal anestrus, (2) immaturity, (3) advanced age, (4) use of anabolic steroids, (5) gonadal dysgenesis, (6) hypothalamopituitary dysfunction, and (7) severe malnutrition. Clinical signs and treatment of malnutrition, hypothalamopituitary dysfunction, and seasonal anestrus are discussed elsewhere in this chapter. The average age at which fillies reach puberty is 18 months, with a wide range of 10 to 24 months. Many older mares (>20 years of age) are still reproductively active, but some mares reach ovarian senescence when they grow older.[61,62] In addition, infertility in aged mares may be a result of defects inherent in ovulated oocytes that result in embryos of lowered viability.[63] Anabolic steroids are derivatives from androgens that have been altered to provide high

anabolic activity with minimal androgenic side effects. A suppression of gonadotropin secretion has been documented when mares have been treated with these drugs.[64] Aberrations of meiosis involving the X and Y chromosomes may lead to genotype abnormalities accompanied by gonadal dysgenesis. Abnormal genotype is most commonly 63X0; but 63X/64XX, 63X/64XY, 65XXX, and 64XY sex reversed have been reported.[65]

43.19.1.1.1 Clinical Signs and Diagnosis

43.19.1.1.1.1 IMMATURITY

Fillies younger than 2 years of age with inactive ovaries and a flaccid and relaxed reproductive tract may be too young to cycle and should be reexamined at a later time. The condition should be differentiated from gonadal dysgenesis. Karyotyping may be indicated if puberty is delayed beyond 24 months.

43.19.1.1.1.2 ADVANCED AGE

Older mares (≥20 years) frequently begin cycling later in the season than younger mares.[61] Older mares that cycle often have a longer follicular phase, and subsequently, a longer interovulatory interval.[61,66] Some aged mares develop large, anovulatory follicles. In one study, significantly more mares aged 16 to 20 years developed anovulatory follicles than mares aged 6 to 10 years.[67] Alternatively, older mares may have fewer follicles on their ovaries and elevated serum gonadotropins. It is postulated that mares with these reproductive characteristics frequently become reproductively senescent.[68] Aged, senescent mares typically have small, inactive ovaries (follicles ≤5 mm) and a flaccid uterus and cervix. Although senescent mares may still show behavioral signs of estrus, similar to anestrous or ovariectomized mares, ovarian function is completely absent.

Oocytes collected from aged donor mares, cultured, and transferred to young recipient mares were less likely to result in pregnancy than oocytes from young donor mares.[63] Furthermore, oocytes obtained from old mares and examined using transmission electron microscopy had more morphologic abnormalities than oocytes from young mares.[69] Results from these studies suggest that oocyte quality declines as mares age, and this factor will contribute to poor fertility in older mares.

1429 1430

43.19.1.2 EXOGENOUS HORMONE TREATMENT

Anabolic steroid administration may affect both estrous behavior and ovarian function. The treatment of mares with low doses of anabolic steroids can cause aggressive or stallion-like behavior, whereas high doses can inhibit ovarian activity and result in failure of follicular development and ovulation.[64] Prolonged treatment of prepubertal mares with anabolic steroids results in hypertrophy of the clitoris.[70]

Progestins are commonly given to cycling mares for the suppression of estrus or synchronization of ovulation. Mares may continue to ovulate during progestin administration, especially if treatment is started late in the luteal phase. A high incidence of persistent CL formation has been observed in mares that ovulate during progestin treatment.[71] Administration of the potent GnRH agonist deslorelin acetate (Ovuplant, Ft. Dodge) to induce ovulation has been associated with delayed follicular development and a prolonged interovulatory interval.[72,73] Deslorelin acetate is very effective in inducing ovulation, but treatment appears

to cause a temporary downregulation of follicle stimulating hormone (FSH) secretion. The low FSH concentrations have been associated with a prolonged period of decreased follicular growth. Administration of $PGF_{2\alpha}$7 to 8 days after ovulation appears to increase the risk of delayed follicular development. It has been suggested that $PGF_{2\alpha}$administration "resets" the timing of the estrous cycle during a period when limited follicular activity is present.

43.19.1.3 GONADAL DYSGENESIS

Chromosomal abnormalities occur in all breeds of horses. Mares are usually small and phenotypically female. The ovaries are small, firm, smooth, and inactive. The tubular tract is thin and flaccid. Endometrial hypoplasia is a common finding. Diagnosis is confirmed by physical findings and karyotype.

43.19.1.4 EQUINE CUSHING'S DISEASE

Mares with hypertrophy, hyperplasia, or adenoma formation in the pars intermedia of the pituitary (equine Cushing's disease [ECD]) have been reported to have abnormal estrous cycles, infertility, or both.[74,75] The mechanisms by which ECD causes reproductive abnormalities have not been determined. Potential cause(s) may be destruction of the gonadotrophs of the anterior pituitary owing to compression by the enlarged pars intermedia[76] or suppression of gonadotropin secretion owing to elevated levels of glucocorticoids or androgens produced by the adrenal cortex.[76] In support of the glucocorticoid hypothesis, administration of dexamethasone to intact mares results in reduced estrous behavior, LH concentrations, follicular growth, and incidence of ovulation.[77] In addition, administration of dexamethasone to ovariectomized mares results in suppression of pituitary LH and FSH secretion,[78] and treatment of pony mares with dexamethasone during the winter eliminates estrous behavior.[79] A majority of horses diagnosed with ECD are older, with the average age being approximately 20 years. Consequently the decrease in reproductive efficiency in mares with ECD may be partly a result of advanced age.

Clinical signs of ECD include hirsutism and abnormal hair-coat shedding patterns, polyuria, polydipsia, and hyperhidrosis.[80] Diagnostic tests for ECD include measurements of serum glucose, insulin, adrenocorticotropic hormone (ACTH) cortisol levels, dexamethasone suppression, ACTH stimulation, and thyrotropin-releasing hormone response tests.[81] The measurement of single samples for basal cortisol or ACTH concentrations is of limited value in the diagnosis of ECD.

43.19.2 Treatment and Prognosis

43.19.2.1 IMMATURITY AND ADVANCED AGE

No treatment is available for age-related ovarian inactivity. Because aged mares often experience a delayed seasonal onset of ovarian activity, they benefit from an artificial light regimen starting 60 to 90 days before the breeding season. GnRH has been used to stimulate follicular growth in mares with poor follicular development attributable to anestrus or transition. Several studies (reviewed by Ginther[23]) have examined the effects of GnRH administered at different doses and intervals to stimulate follicular development in mares. In general, the number of mares responding to GnRH therapy increased as the size of follicle or time of year at the onset of therapy increased.

43.19.2.2 EXOGENOUS HORMONE TREATMENT

Ovarian inactivity in mares treated with anabolic steroids is reversible, and pituitary and ovarian function eventually return to normal in most mares after withdrawal of the treatment. Mares intended for breeding should not be treated with anabolic steroids.

Removal of the deslorelin implant after ovulation has been detected will decrease the incidence of prolonged interovulatory intervals.[82]

43.19.2.3 GONADAL DYSGENESIS

Mares diagnosed with gonadal dysgenesis are sterile, and there is no treatment.

43.19.2.4 EQUINE CUSHING'S DISEASE

The medical management of ECD includes the administration of pergolide mesylate, a dopamine receptor agonist, at a dose of 0.5 to 2 mg every 24 hours in an adult horse. The serotonin antagonist cyproheptadine has also been used, but it may not be as efficacious as pergolide. The dose of cyproheptadine is 0.25 mg/kg every 24 hours, given once in the morning.

43.20 ABNORMALLY ENLARGED OVARIES

The most common causes of enlarged ovaries in the mare are (1) tumors, (2) anovulatory follicles, (3) ovarian hematomas, and (4) pregnancy.

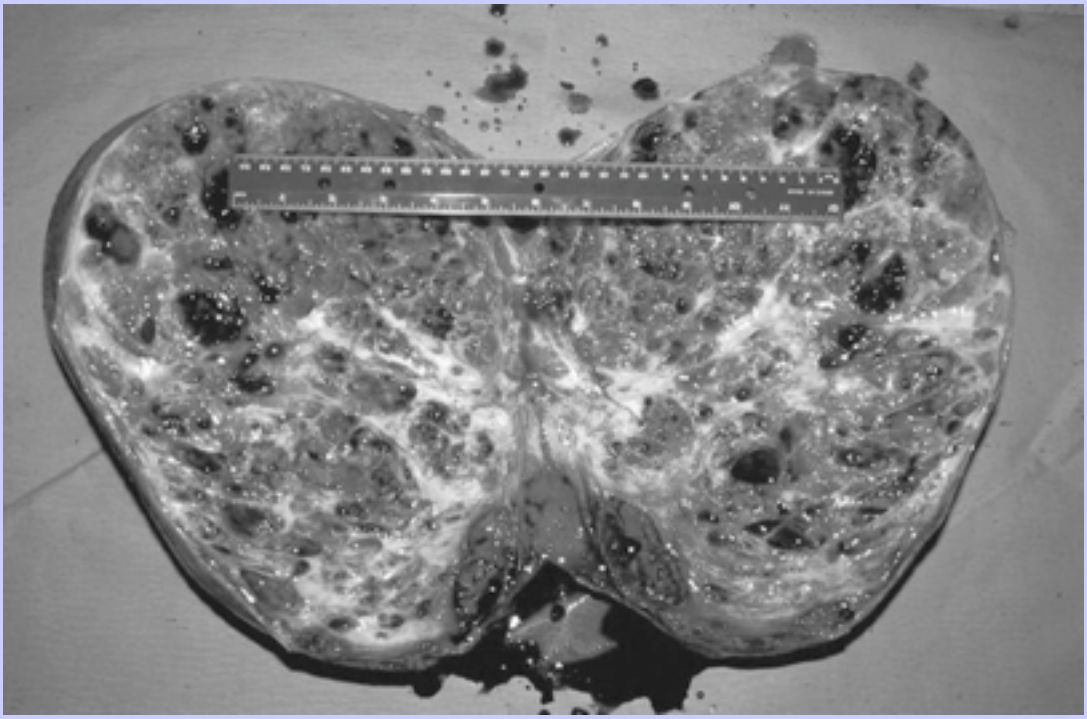
43.20.1 Ovarian Tumors

The majority of equine ovarian tumors can be categorized as sex cord-stromal tumors (granulosa-theca cell tumors), epithelial tumors (cystadenomas), or germ cell tumors (dysgerminomas and teratomas).

43.20.1.1 GRANULOSA-THECA CELL TUMORS

The granulosa-theca cell (GCT) tumor is the most common ovarian tumor in the mare (Fig. 43-4). It is usually slow growing, unilateral, and benign. It occurs in mares of all ages and is occasionally found in pregnant mares. The tumor arises from the steroidogenic cells of the follicle, resulting in abnormal secretion of inhibin and testosterone.

Fig. 43-4 Granulosa cell tumor removed from a mare.



43.20.2 Clinical Signs and Diagnosis

Transrectal sonographic examination of the affected ovary often reveals a multicystic or honeycombed structure, but the tumor may also occur as a solid mass or as a single large cyst. The contralateral ovary is usually small and inactive, although mares with a GCT on one ovary and a functional contralateral ovary have been reported.[83] Granulosa cell tumors are hormonally active, and clinical diagnostic assays for the detection of a GCT include the measurement of inhibin, testosterone, and progesterone.[84–87] α-Inhibin is elevated in approximately 90% of the mares with a GCT.[85,87] It has been hypothesized that inhibin produced by the GCT is responsible for inactivity of the contralateral ovary through the suppression of pituitary FSH release. However, recent reports on a poor correlation between dimeric inhibin and the presence of GCT raise questions about the mechanism by which the contralateral ovary is suppressed in affected mares.[87,88] Serum testosterone in a single blood sample can be expected to be elevated (100 to 200 pg/mL) in approximately 50% to 60% of affected mares. Daily fluctuations in testosterone concentrations have been reported, and repeated samples may have to be obtained on different days in order to detect elevated testosterone.[87] Progesterone concentrations in mares with a GCT are almost always below 1 ng/mL because normal follicular development, ovulation, and CL formation do not occur. As a result of hormone secretion from the tumor, mares may show anestrus, constant estrus, irregular estrus, or stallion-like behavior. They are infertile in the presence of the tumor. Final diagnosis is histologic.

Differential diagnoses for abnormal cyclicity are listed in Table 43-2 and for ovarian enlargement in Table 43-4.

43.20.3 Treatment and Prognosis

The affected ovary should be surgically removed. Surgical approaches for tumor removal include colpotomy, flank and ventral midline laparotomy, and laparoscopy. The prognoses for both life and reproductive use are good. Return to cyclicity varies, but most mares cycle in the year after ovariectomy.

43.21 CYSTADENOMAS

The most common tumor of the surface epithelium of the equine ovary is the cystadenoma. They are rare, benign, hormonally inactive tumors from the surface epithelium of the ovulation fossa. The tumor is unilateral, and the contralateral ovary is normal.

43.21.1 Clinical Signs and Diagnosis

Mares with cystadenomas cycle normally from the opposite ovary and may even become pregnant. Rectal palpation and ultrasonography reveal the presence of one enlarged multicystic ovary, which may appear similar to a granulosa-theca cell tumor, and one normal ovary. Differential diagnoses for ovarian enlargement appear in Table 43-4. Final diagnosis is histologic.

Table 43-4 Unilaterally Large Ovary: Differential Diagnosis

Etiology	Distinguishing Features
Granulosa-theca cell tumor	Sonographically multilocular, high inhibin and/or testosterone; small contralateral ovary
Other ovarian tumor	See text
Ovarian hematoma	Ovulation fossa still palpable, cycles normally
Ovarian abscess	Large, hard ovary; sonographically echogenic
Ovarian follicle	Normal cycling mare, ovulates
Anovulatory hemorrhagic follicle	Free-floating echogenic spots

43.21.2 Treatment and Prognosis

Although cystadenomas are benign tumors and do not affect the reproductive performance of the mare, they are usually surgically removed if diagnosed. The prognoses for both life and reproductive performance are excellent.

43.22 GERM CELL TUMORS

Dysgerminomas and teratomas are rare ovarian tumors of germ cell origin. Both tumors are unilateral and hormonally inactive. Teratomas are considered to be benign, whereas dysgerminomas are potentially malignant.

43.22.1 Clinical Signs and Diagnosis

Both tumors make the affected ovary unilaterally enlarged and multicystic. Dysgerminomas are malignant and often metastasize to the peritoneal and thoracic cavities. Teratomas may arise from all three germinal layers, and the neoplastic ovary may contain bone, cartilage, teeth, hair, muscle, and nerves. Teratomas do not cause clinical signs, interrupt the estrous cycle, or alter the behavior of the mare. Dysgerminomas and teratomas are often detected in association with a routine reproductive examination. Differential diagnoses for ovarian enlargement are listed in Table 43-4. Final diagnosis for germ cell tumors is histologic.

43.22.2 Treatment and Prognosis

Surgical removal is recommended for both dysgerminomas and teratomas. The prognosis for teratomas is usually good, but poor for mares diagnosed with dysgerminomas.

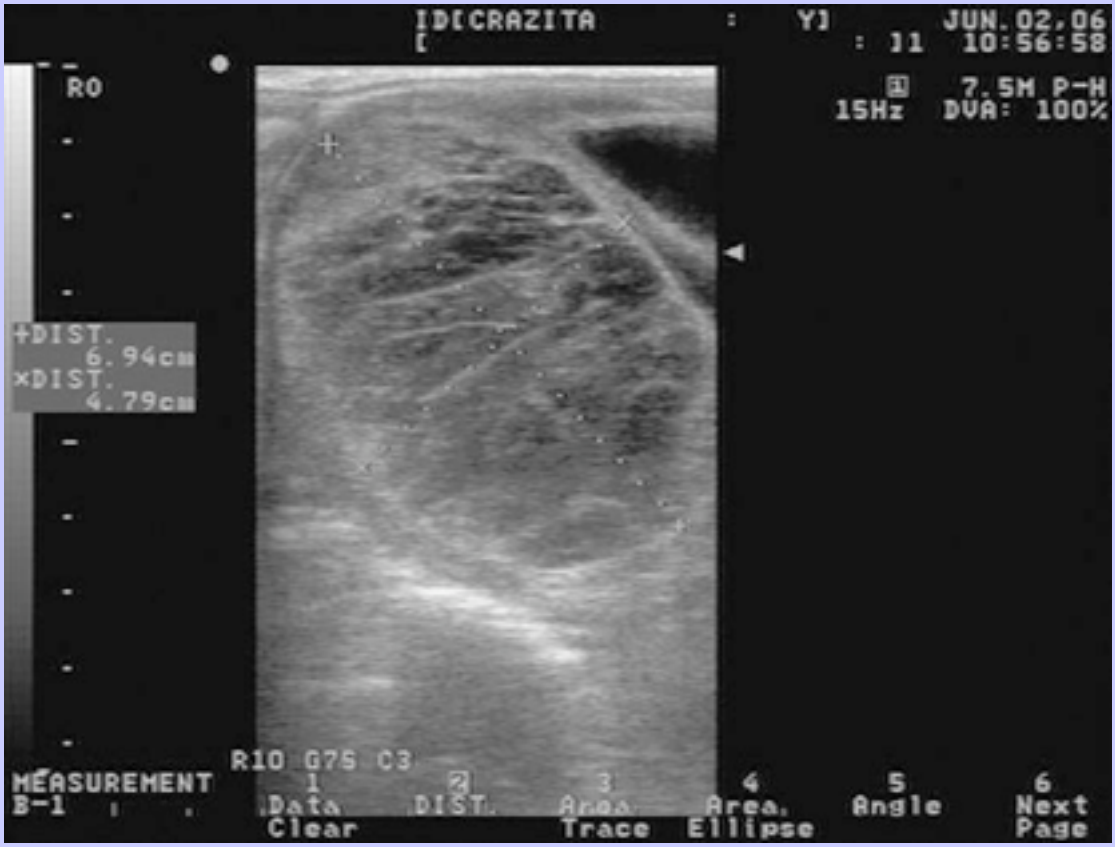
43.23 Anovulatory Follicles

43.23.1 Clinical Signs and Diagnosis

Ovulation failure is a normal physiologic event for the mare during the spring and fall transition periods, but it may also occur occasionally during the physiologic breeding season. Persistent anovulatory follicles (PAFs) may be quite large (5 to 15 cm in diameter), persist for up to 2 months, and result in abnormal estrous behavior and prolonged interovulatory intervals.[89] The cause of ovulation failure has been suggested to be endocrine in nature. Absence of sufficient pituitary gonadotropin stimulation to induce ovulation, or insufficient estrogen production from the follicle, has been proposed as a possible mechanism. PAFs were reported in a recent study to occur in approximately 8.2% of estrous cycles.[67] The formation of an anovulatory follicle was preceded by development of normal endometrial folds or edema in 78.3% of these cases. Initial growth patterns of follicles destined to become anovulatory were usually normal, and the first indication of a problem was the detection of echogenic particles within the follicular fluid. The incidence of PAFs was also found to increase with age.

PAFs may contain blood and have been termed *hemorrhagic anovulatory follicles*., The hemorrhage can be detected ultrasonically as scattered free-floating echogenic spots within the follicular fluid. The follicular fluid may form a gelatinous, hemorrhagic mass within the follicular lumen. Ultrasonographically these structures may contain echogenic fibrous bands traversing the follicular lumen (Fig. 43-5). A thickening of the follicular wall may be observed in anovulatory follicles. This thickening is often associated with luteinization of the follicular wall, and 85.7% of PAFs were found to be luteal structures based on elevations in plasma progesterone concentrations.[67]

Fig. 43-5 Transrectal ultrasonographic image of a persistent anovulatory follicle in a mare.



43.23.2 Treatment and Prognosis

The administration of prostaglandins may result in the destruction of the luteal cells in mares with luteinized PAFs. A majority of nonluteinized PAFs spontaneously regress in 1 to 4 weeks. Treatment with hCG (2500 IU IV) or a GnRH agonist (Ovuplant 2.1 mg subcutaneously [SC]) to induce ovulation or luteinization of the anovulatory follicle is generally not effective. Pregnancy does not usually occur if a persistent follicle eventually spontaneously ovulates or is induced to ovulate. This is likely a result of degeneration of the oocyte over time. Pregnancy obviously will not occur if the follicle becomes hemorrhagic or luteinized without ovulation.

43.24 Ovarian Hematoma

Hemorrhage into the follicular cavity is a normal occurrence at ovulation. Occasionally hemorrhage is severe, resulting in the formation of an ovarian hematoma that may be 10 cm in diameter or larger.

43.24.1 Clinical Signs and Diagnosis

Affected mares continue to cycle normally. Transrectal palpation and ultrasonography reveal an enlarged ovary that is initially irregularly hypoechoic and then echogenic with organization of the hematoma. The ovulation fossa usually remains distinguishable on the affected ovary, and the contralateral ovary remains active.

43.24.2 Treatment and Prognosis

Ovarian hematomas regress spontaneously over a period of weeks or months. The functional lifespan of the luteal tissue in a hematoma is normal, and ovarian activity is unaffected.[90] Because the affected ovary is not permanently damaged and the contralateral ovary is unaffected, the prognosis for fertility is undiminished.

43.24.3 Pregnancy

Multiple secondary CLs form in pregnant mares at 40 to 180 days of gestation, resulting in bilaterally enlarged ovaries that may be mistaken for ovarian pathology.

43.24.3.1 Clinical Signs and Diagnosis

Ovarian enlargement is commonly bilateral. Pregnant mares may show stallion-like behavior associated with increased testosterone production from the fetus during midgestation. Pregnancy should always be considered in a mare with stallion-like behavior, elevated serum testosterone concentrations, and enlarged ovaries. Pregnancy is diagnosed by rectal palpation and ultrasonographic examination.

43.25 PERSISTENT CORPUS LUTEUM

The CL usually regresses 14 to 15 days after ovulation.[3] Although luteal cells appear to be sensitive to $PGF_{2\alpha}$ almost immediately after ovulation, complete luteolysis and return to estrus in response to endogenous or exogenous $PGF_{2\alpha}$ will not occur until 5 days after ovulation. Because the functional CL is lysed by $PGF_{2\alpha}$ from the endometrium, the CL will continue to function in the following situations.

1. In the pregnant mare the equine conceptus produces a PGF inhibitor factor, which is secreted as early as day 11 to 13 after ovulation.[23] The factor prevents PGF from being synthesized and secreted from the endometrium. This results in a prolonged luteal phase of the primary CL until the development of endometrial cups and secretion of eCG ensure the presence of functional luteal tissue in the pregnant mare.
2. Embryonic loss after the time of maternal recognition of pregnancy can result in a persistent CL for a variable period of 35 to 90 days.[91]
3. Destruction of the endometrium in infectious and inflammatory conditions such as pyometra may cause insufficient synthesis of PGF and prolonged luteal life.[92]
4. Late diestrous ovulation will result in a CL that is insufficiently mature to respond to endogenous PGF release.[1]

5 Nonsteroidal antiinflammatory drugs may inhibit endometrial PGF synthesis, resulting in a prolonged luteal phase.

6 Spontaneous CL persistence has been proposed as a clinical entity[76] but has not been adequately documented and is an area of controversy.[93]

43.25.1 Clinical Signs and Diagnosis

This syndrome may be suspected clinically in mares that are not expressing normal estrous behavior during the physiologic breeding season, and it must be differentiated from mares with silent heat. Diagnosis of a persistent CL is made by transrectal sonographic examination of the ovaries. The CL appears as a well-defined hyperechoic structure on the ovary. Mares with a persistent CL will have good cervical and uterine tone on palpation, and the cervix will appear tight and dry on vaginal speculum examination because of the influence of progesterone. The diagnosis may be confirmed by analysis of plasma progesterone concentrations or a clinical response to prostaglandin administration. Progesterone concentrations >1 ng/mL[1] are indicative of the presence of active luteal tissue. Differential diagnoses are listed in Table 43-2.

43.25.2 Treatment and Prognosis

After pregnancy has been ruled out with sonographic examination, luteolysis can be achieved with administration of 10 mg of the PGF product dinoprost tromethamine or similar PGF analog. The mare must be at least 5 days postovulation to respond reliably to treatment. If the mare is treated with PGF in the presence of a mature diestrous follicle (≥35 mm), she may ovulate the follicle without signs of estrus in response to declining progesterone concentrations that allow LH to be secreted from the anterior pituitary. An ultrasonographic or rectal examination of ovarian follicular activity should therefore always be performed before PGF is administered to induce estrus.

43.26 SHORTENED LUTEAL PHASE (PREMATURE LUTEOLYSIS)

Premature (<15 days) luteolysis is associated with an early onset of estrus and a decrease in the interovulatory interval. The most common cause of premature luteolysis in the mare is endometritis. Inflammation of the endometrium results in an acute activation of inflammatory mediators. One of these mediators is $PGF_{2\alpha}$, which in addition to its inflammatory effect also may cause luteolysis and return to estrus. Consequently a mare that exhibits a shortened diestrus should be examined for endometritis. A culture, biopsy, and cytologic examination of the uterus may be indicated.

43.27 LUTEAL INSUFFICIENCY

Primary luteal insufficiency implies a deficiency in progesterone production. Luteal insufficiency has been suggested to be a cause of subfertility in mares.[94] Maintenance of pregnancy in some habitually aborting mares after administration of exogenous progestogens offers circumstantial evidence that progesterone insufficiency may be responsible for some cases of pregnancy loss.

Data are limited and not supported by scientific evidence from controlled studies.

Luteal insufficiency secondary to $PGF_{2\alpha}$ release in mares with endotoxemia has been reported[95] and should be considered in pregnant mares with gram-negative infection and/or endotoxemia-associated colic. Reports on the effect of exogenous administration of $PGF_{2\alpha}$ during the periovulatory period suggest that $PGF_{2\alpha}$ can delay the formation of a functional CL. Suboptimal concentrations of progesterone were found in mares after treatment with $PGF_{2\alpha}$ during the first 2 days after ovulation.[96–100] Although the CL eventually became functional and progesterone concentrations had returned to normal levels at day 14, pregnancy rates were significantly lower in treated mares.[97,98]

43.27.1 Clinical Signs and Diagnosis

The minimum concentration of progesterone required to maintain pregnancy in the mare has been suggested to be 2 ng/mL.[95] Repeated samples are necessary to diagnose luteal insufficiency because progesterone is released episodically.

43.27.2 Treatment and Prognosis

The most common treatment for luteal insufficiency is supplementation with the synthetic progestogen altrenogest (Regumate) at a dose of 0.044 mg/kg PO once daily. Options for duration of altrenogest supplementation include treatment until day 80 to 120 of pregnancy or greater and measurement of endogenous progesterone level of >2 ng/mL (progesterone and altrenogest do not cross-react on radio immunoassay [RIA]), or treatment until the end of gestation. It is important to emphasize the need to monitor fetal well-being when mares are kept on progestin supplementation to maintain pregnancy. A case of fetal mummification of a 5-month-old fetus in a pregnant mare at term has been reported.[101] The mare had been maintained on altrenogest throughout gestation.

43.28 RUMINANTS

43.28.1 PROLONGED LUTEAL FUNCTION

43.28.1.1 Cow

Spontaneous prolongation of luteal function in the presence of a normal, nongravid uterus does not occur in cows. But several conditions affecting the uterus do suspend the luteolytic mechanism, resulting in prolonged luteal function, persistently elevated progesterone concentrations, and anestrus. Common causes of prolonged luteal function in cows include pregnancy, pyometra, mummified fetus, and segmental aplasia, including uterus unicornis.

43.28.1.1.1 Clinical Signs and Diagnosis

Pregnancy resulting from an unobserved or unrecorded breeding must always be considered as a possible cause of anestrus. Examination of the uterus by transrectal palpation or ultrasonography for one of the positive signs of pregnancy (fetal membrane slip, amnionic vesicle, placentomes, or fetus) must precede administration of PGF.

Pyometra is characterized by accumulation of variable amounts of mucopurulent exudate within the uterine lumen, failure of luteolysis, and subsequent anestrus. An enlarged uterus as a result of fluid accumulation and a thickened uterine wall in the absence of any positive signs of pregnancy can be used to differentiate uterine enlargement caused by pregnancy from that caused by pyometra. Fluid associated with pyometra is more viscous than fetal fluid and can be manipulated from horn to horn. Because the cervix is nearly always closed, there is generally no vaginal discharge.

Fetal mummification is occasionally encountered in dairy and beef cows and is characterized by fetal death, failure of expulsion, absorption of fetal fluids, and persistence of the CL. Cows with fetal mummification are usually presented when they do not deliver a calf at the expected time. The condition can be differentiated from pregnancy by palpation per rectum of a dried, leather-like fetus within the involuted uterus. Fetal membranes cannot be slipped, and fetal fluids and placentomes are absent.

43.28.1.1.2

Clinical Pathology

No remarkable changes in hematology and clinical chemistry are associated with pregnancy, mummified fetus, or pyometra in cows. In all three conditions, peripheral concentrations of progesterone remain elevated above 1 ng/mL of plasma until spontaneous luteolysis occurs or the condition is treated.

43.28.1.1.3

Treatment and Prognosis

Unwanted pregnancy is seldom encountered in dairy cows, but when cows or heifers are mated by accident or to an undesired sire, abortion may be reliably induced with PGF products (25 mg of dinoprost tromethamine,* or 500 mcg of cloprostenol;† two injections 8 to 12 hours apart) after 7 days and before 150 days of gestation or with a combination of PGF and dexamethasone (20 mg) beyond 150 days of gestation. The PGF products are also the treatment of choice for pyometra in cows. Mummified fetuses are usually expelled 3 to 5 days after treatment with PGF. The mummy may pass through the cervix, but the vagina is likely to be dry and may not dilate sufficiently, so the mummified fetus may be retained. If the mummified fetus is not expelled by 5 days after treatment, a vaginal examination should be performed, and the mummy delivered by gentle traction if necessary. The prognosis for fertility after delivery of a mummified fetus is good.

* Lutalyse, Pfizer Animal Health.

† Estrumate, Mobay Corporation, Animal Health Division, Shawnee, KS.

43.28.2

OVARIAN HYPOPLASIA

Ovarian hypoplasia occurs sporadically as an autosomal recessive trait in the cow. The condition has incomplete penetrance; therefore it may be partial or complete and unilateral or bilateral. The affected gonad varies in size from a cordlike thickening in the cranial edge of the mesovarium to a bean-sized structure. The tubular genital organs remain infantile in animals with complete bilateral hypoplasia or may develop to near-normal size in heifers with unilateral or partial hypoplasia. Individuals affected with complete bilateral ovarian hypoplasia are sterile, whereas those affected by partial or unilateral hypoplasia may be subfertile. With partial hypoplasia the uterine pole of the ovary is typically affected. On direct observation by laparotomy or laparoscopy or on slaughter, the uterine pole is flat and triangular and shows converging striations. The affected part is devoid of follicles. Animals with partial ovarian hypoplasia can be expected to have a reduced

superovulatory response to gonadotropin treatment. Heifers with abnormal karyotypes are also affected by ovarian hypoplasia. The condition should be differentiated from nonfunctional ovaries and anestrus associated with malnutrition or debilitating diseases. Treatment of ovarian hypoplasia is not successful.[102]

43.28.3 FREEMARTINISM

43.28.3.1 Cow

A freemartin is a phenotypic female, born co-twin to a male, that is sterile because of arrested development of the reproductive tract. The term “freemartin” is said to have originated in England, where it referred to a heifer that was not pregnant after the summer breeding season and therefore “free” for fattening and slaughter at Martinmas, a fall festival in honor of St. Martin.[11] Freemartinism arises as a result of anastomoses between the placental circulations of twin fetuses of opposite sexes. Sexual differentiation of the male embryo occurs earlier than that of the female; therefore the male twin may sterilize the female by transfer of HY antigen, which inhibits development of the female gonad. The ovaries of a freemartin are underdeveloped and contain seminiferous tubules. Abnormalities of the tubular genital organs vary in severity, and the structures range from cordlike bands to near-normal uterine horns. In most freemartins there is no cervix; therefore no communication exists between the uterus and vagina. The latter is a short blind pouch. Frequently, seminal vesicular glands of varying size are present.

As many as 92% of phenotypic females born co-twins to males are freemartins[55]; the history suggests a diagnosis in most cases. Singleton freemartins are possible if male and female twins are conceived and the male is lost after 30 days of gestation. Palpation per rectum of breeding age freemartins reveals aplasia or hypoplasia of the tubular genital organs and hypoplastic ovaries. If animals too small for palpation per rectum are presented, examination of the vagina with a small glass speculum (or test tube) reveals that the vagina of a freemartin is short (6 to 7 cm in freemartins versus nearly double that length in normal heifers). A definitive diagnosis may be made by karyotyping the suspected individual; varying percentages of male cells are found in freemartins.[102] More details on freemartinism are discussed elsewhere in this chapter.

43.28.3.2 Ewe

Although freemartinism is possible in sheep, the condition is rare, despite the high incidence of multiple births. The condition can be confirmed by determination of blood cell chimerism.

43.28.3.3 Doe

Twinning is also common in goats, but vascular anastomosis is either uncommon or occurs after the critical period for sexual differentiation. Caprine freemartins comprise approximately 6% of intersexes.[5]

43.28.4 INTERSEX

43.28.4.1 Doe

Intersexes are common among Saanen, Toggenburg, and Alpine goats. The fetal testes appear to be unable to fully masculinize the duct system or external genitalia. Parts of both the mesonephric and paramesonephric

ducts persist; therefore the phenotype of affected individuals may approach that of either sex. Intersexes are most frequent among polled goats, and the condition is thought to be caused by a recessive gene linked to that for polledness; however, intersexuality may rarely be seen in horned goats. Diagnosis is based on a history of abnormal sexual behavior, and identification of abnormal genital development is by physical examination. There is no satisfactory treatment, but the prevalence of the condition may be reduced by preventing mating between two polled animals.[5] More detailed information can be found elsewhere in this chapter.

43.28.5 OVARIAN TUMORS

43.28.5.1 Granulosa Cell Tumor

43.28.5.1.1 COW

Although rare, various ovarian neoplasms have been described in cows; granulosa cell tumors appear to be most common.[11]

43.28.5.1.1.1 Clinical Signs and Diagnosis

Granulosa-theca cell tumors are characterized by unilateral ovarian enlargement, with the affected ovary being greater than 10 cm in diameter. The surface may be smooth or coarsely lobulated. Function of the contralateral ovary may be suppressed. The behavior of affected cows ranges from anestrus to nymphomania to bull-like behavior. Udder development and lactation may occur in affected heifers. Very few bovine granulosa cell tumors are malignant, and they rarely metastasize. Among the other ovarian neoplasms that have been reported in cattle are dysgerminomas, interstitial cell tumors,[11] and teratomas. Causes of ovarian enlargement that must be differentiated from ovarian neoplasia include ovarian cysts, oophoritis, ovarian abscesses, and parovarian cysts.

43.28.5.1.1.2 Treatment and Prognosis

The treatment for ovarian neoplasia in cattle is surgical removal of the affected ovary; however, cows may not be as fertile as mares after removal of the tumor.

43.28.5.1.2 EWE

Granulosa-theca cell tumors have been reported, but tumors of the genital organs of ewes appear to be rare.[11] Animals with ovarian tumors may exhibit all types of behavioral and physiologic abnormalities (nymphomania, inappropriate lactation). Diagnosis is based on ultrasonographic evaluation of ovaries per rectum or transabdominally. Treatment is ovariectomy.

43.28.5.1.3 DOE

Ovarian neoplasia appears to be rare in does as well. Granulosa-theca cell tumors and dysgerminomas have been reported.

43.28.6 OVARIAN HEMORRHAGE

43.28.6.1 Cow

Ovulation tags develop after ovulation, resulting from blood loss associated with rupture of the follicle.[11] Fine adhesions may develop between the ovarian surface and surrounding structures. Most ovulation tags resolve spontaneously and have no effect on fertility. Severe ovarian hemorrhage may follow attempts to manually enucleate the CL. Adhesions between the ovary and its bursa interfere with their normal function. Enucleation of CLs for treatment of anestrus and pyometra has been superseded by treatment with PGF products.

43.28.7 OOPHORITIS

43.28.7.1 Cow

Inflammation of the ovary may follow traumatic manipulations, such as enucleation of CLs and attempts to drain fluid from ovarian cysts, and ascending infections from the uterus. Oophoritis may also accompany brucellosis, mycoplasmosis, and tuberculosis.

43.29 INFERTILITY CAUSED BY ABNORMALITIES OF THE FEMALE TUBULAR GENITALIA

43.29.1 SALPINGITIS

Inflammation of the oviducts is characterized by macroscopic enlargement. Lesions are frequently bilateral and consist of infiltration by lymphocytes, plasma cells, and neutrophils, and desquamation of epithelial cells.[11]

Most cases of salpingitis follow infections of the uterus. Necrotizing and granulomatous salpingitis may follow infection by *Arcanobacterium pyogenes, Mycobacterium tuberculosis*, and *Brucella abortus*., Mild inflammation of the uterine tubes that does not usually result in permanent damage accompanies uterine infection caused by *Campylobacter fetus*, subsp. *venerealis*, and *Tritrichomonas foetus*., Salpingitis may be a sequela to manipulations of the ovaries and uterine tubes by palpation per rectum, transvaginal ovum pickup, aggressive irrigation of an infected uterus, and inappropriate treatment with estrogenic hormones. Migrating larvae of *Strongylus edentatus*, have been proposed as a possible cause of nonobstructive infundibulitis in mares, but their role is speculative.[11]

Pyosalpinx is characterized by segmental accumulation of pus within the lumen of the oviduct after mechanical blockage of either end. Pyosalpinx frequently follows severe cases of uterine infection and may be complicated by perimetritis and localized peritonitis.

Hydrosalpinx is characterized by accumulation of thin mucus within the lumen of the oviduct. Hydrosalpinx and adhesions to perisalpingial tissues are common sequelae to chronic salpingitis.

43.29.1.1

Clinical Signs and Diagnosis

The usual history associated with diseases of the uterine tubes is one of infertility. Additional history may include uterine infection or traumatic therapy such as uterine irrigation, enucleation of CLs, or administration of exogenous estrogen during CL function. Salpingitis is an uncommon clinical finding in the mare. However in one study, up to 88% of mares were found to have macroscopic lesions in the oviduct, including adhesions, fibrous bands, and parovarian cysts, which may or may not have affected fertility.[103] Accumulations of cells and debris may form intraluminal masses; however, their role in infertility has not been adequately tested.[104] The pathology of the oviduct has been reviewed.[105] Similarly, moderate lesions of uterine tube disease may escape diagnosis by physical examination in cows, but the results of abattoir studies suggest that lesions of the oviducts are not uncommon.[11] In cows, lesions involving adhesions among the ovary, ovarian bursa, oviduct, and surrounding tissues may be identified per rectum by inserting two or three fingers into the ovarian bursa and rolling the oviduct between the fingers and thumb. Easy identification of the oviduct by palpation per rectum is sometimes considered indicative of abnormalities. Diagnosis of diseases of the oviducts in ewes and does is impossible by physical examination. Although a history of infertility after one of the predisposing causes might suggest oviductal lesions, diagnosis is made by exploratory laparotomy, peritoneoscopy, or necropsy.

Lesions of the oviductal or perisalpingial tissues must be differentiated from other causes of abnormal enlargements such as ovarian neoplasia, parovarian cysts, cystic ovarian disease, and ovarian hematomas. Neoplasia of the oviducts in domestic animals is extremely rare.

43.29.1.2

Clinical Pathology

Several tests that determine oviductal patency of mares[106] and cows[107] have been described, but neither the starch test nor the phenolsulfonphthalein dye test is very reliable or consistently diagnostic. For suspected unilateral blockage,[108] each uterine horn may be catheterized individually with a Foley catheter placed at the base of the horn on different days.

43.29.1.3

Embryo Recovery

Embryo recovery after either a single ovulation or superovulation is objective evidence that one or both uterine tubes are patent and functional. Improved reproductive performance of cows may follow uterine lavage; therefore embryo recovery as a diagnostic test may have therapeutic benefits as well.[109]

43.29.1.4

Treatment and Prognosis

Treatment of diseases of the oviducts is not likely to be successful. Appropriate treatment for concurrent uterine infections should be instituted. A period of sexual rest may be beneficial and is indicated in valuable animals. The prognosis for reproduction in cases of bilateral obstruction of the oviducts is poor. In vitro fertilization of ova harvested from affected females is a therapeutic option. Affected females can also serve as embryo recipients.

43.29.1.5 Prevention and Control

Traumatic manipulation of the ovaries, irrigation of the endometrial cavity with large volumes of fluid (over 100 mL in heifers or 150 mL in cows) or irritating chemicals, and administration of estrogenic hormones to luteal phase females should be avoided.[102] Because abnormalities of the oviducts are frequently associated with uterine infections, reduction of the prevalence of uterine infections results in fewer tubal infections as well.

43.29.2 UTERINE ABNORMALITIES

43.29.2.1 Retained Fetal Membranes

43.29.2.1.1 MARES

Retention of the fetal membranes beyond a period of 3 hours is an abnormal occurrence in the mare. The mare has an epitheliochorial placenta characterized by diffuse microvilli that interdigitate with endometrial crypts. After delivery, blood flow through the placental vessels is reduced, and placental microvilli shrink and disengage from endometrial crypts. The condition is more common after abortion, dystocia, cesarean section, and fetotomy. The pathophysiology of the disease is poorly understood but may involve disturbances of normal prepartum endocrine events or myometrial contractility. Partial placental retention may be localized to well-defined areas of continued placental attachment. The most common site of partial retention is the previously nongravid horn.

Equine placentas should be spread on a flat surface after expulsion and examined to ensure that the complete membrane is present. Areas of placental necrosis are common near the tips of the uterine horns, and the fragile area may be incarcerated by the rapidly contracting uterus.

43.29.2.1.1.1 Clinical Signs and Diagnosis

Retained fetal membranes (RFMs) are usually visible at the vulva. However, small tags of placental tissue may remain attached to the uterus without being apparent and may be a nidus for infection, resulting in severe metritis, endotoxemia, and laminitis hours to days postpartum.

43.29.2.1.1.2 Treatment and Prognosis

The severity of sequelae makes early intervention essential. Treatment should begin if fetal membranes are not passed within 3 hours of foaling. Most instances respond to vigorous early pharmacologic treatment. Occasional cases require several days of persistent treatment.

43.29.2.1.1.2.1 MANUAL REMOVAL

Manual removal is contraindicated because trauma induces placental tearing, leaving microvilli in endometrial crypts.

43.29.2.1.1.2.2

OXYTOCIN

Oxytocin induces myometrial contractions, which may aid placental expulsion. Oxytocin may be administered by intravenous injection (5 to 20 IU every 15 to 30 minutes) or intramuscular injection (20 to 40 IU every 30 to 60 minutes), or it may be infused slowly (30 to 80 IU in 500 mL of warm saline over 30 to 60 minutes). Care should be taken to avoid overdosage, which may result in signs of abdominal pain and which will cause tetanic rather than orchestrated uterine contraction.

43.29.2.1.1.2.3

ALLANTOCHORIONIC INFUSION

If the chorioallantois is intact, the chorioallantoic cavity may be filled to distention with 3 to 4 gallons of warm saline or water through the cervical star.[111] The opening in the placenta is held closed until the mare exerts abdominal pressure. Oxytocin may be used in conjunction with this treatment.

43.29.2.1.1.2.4

UTERINE LAVAGE

If the chorioallantois is not intact, uterine lavage with an isotonic saline solution will clear debris, encourage myometrial contractions, and may help to free the retained fragment of the fetal membrane. The isotonic saline solution may be infused into the uterus through an equine nasogastric tube (dedicated to reproductive use) manually held in place. Approximately 5 L may be placed in the uterus of a full-grown, postpartum mare at one time, but care should be taken to observe the mare for signs of discomfort and to gauge the amount of fluid felt within the uterus. During fluid infusion the operator may carefully explore the uterus manually, searching for retained fetal membrane remnants. Once the uterus is relatively full of fluid, the fluid is siphoned out. Care must be taken to protect the fragile endometrium from damage incurred by the strong suction force of the siphon. The operator's hand should guard the end of the tube from direct contact with the endometrium. This process should be repeated until the effluent is clear. Uterine lavage should be performed at least once daily until 12 to 24 hours after the RFM remnants are retrieved.

43.29.2.1.1.2.5

ADJUNCT THERAPY

Concurrent therapy directed at controlling or minimizing common sequelae to retained placenta is often indicated.

1 *Antibacterials*., Bacterial infections are commonly associated with prolonged (>6 to 8 hours) retention of the fetal membranes. The bacterial population is frequently mixed and likely to include beta-hemolytic streptococci and coliforms. In prolonged cases bacterial culture and sensitivity should be performed. Broad-spectrum antibiotics known to be effective against commonly isolated organisms are indicated. Drugs that have been recommended for systemic administration include ampicillin, gentamicin, kanamycin, penicillin, ticarcillin (with gentamicin for *Pseudomonas*, infection), and trimethoprim-sulfamethoxazole. Intrauterine administration of antibiotics and antiseptics depresses phagocytic activity of uterine neutrophils, and many chemicals irritate the endometrium, but drugs that have been suggested include those recommended for systemic administration, as well as amikacin and polymyxin B.

2 *Antiinflammatory drugs*., Laminitis may be a sequela to metritis and is commonly associated with RFMs. Treatment with administration of antiinflammatory drugs such as phenylbutazone or flunixin meglumine is indicated to reduce the likelihood and severity of laminitis. Polymyxin B may also be indicated in cases in which preliminary signs of laminitis are noted, because of its antiinflammatory and antiendotoxic effects. Additional therapy for laminitis should be administered as indicated.

3 *Other treatments*., Caslick's surgery may be indicated in some cases of RFMs to control aspiration of air. Tetanus may complicate RFMs, and prophylaxis with tetanus antitoxin in unvaccinated animals or tetanus toxoid in previously vaccinated animals is indicated.

Some cases of RFMs are refractory to treatment, and membranes may remain firmly attached to the endometrium for several days. Aggressive attempts at manual removal should be eschewed, because severe endometrial damage may follow. Persistent treatment with antibiotics, antiinflammatory drugs, and oxytocin is indicated until the placenta is expelled and bacterial infection of the uterus is controlled.

The prognosis for RFMs is generally good but is reduced if treatment is delayed or if retention is accompanied by infection with virulent pathogens. Sequelae to RFMs include metritis, endometrial fibrosis, invagination of a uterine horn, uterine prolapse, and laminitis.

43.29.2.1.2

RUMINANTS

43.29.2.1.2.1

Cow

The cotyledonary placenta of cows is usually expelled within 3 to 8 hours after calving and is considered retained if not expelled by 12 hours. RFMs are more commonly seen in dairy than in beef breeds. In dairy cattle the reported prevalence ranges from 8% to 12% after spontaneous delivery of single calves. RFMs are more likely after deliveries of male calves or twins and deliveries complicated by dystocia. Parturition after a shorter- or longer-than-normal gestation length is accompanied by an increase in the incidence of RFMs.[112]

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1437

The cause of RFMs in cattle is failure of fetal cotyledons to separate from crypts of maternal caruncles; the process of separation normally begins during the last months of pregnancy. Villi shrink after blood flow is interrupted by rupture of the umbilical vessels. Strong myometrial contractions continue during the third stage of labor, and changes in the size and shape of maternal caruncles contribute to separation of the placenta from the endometrium. A number of factors have been associated with separation failure, but the precise reasons for separation failure are unknown.[5] Deficiencies of selenium, vitamin E, and vitamin A are associated with an increased prevalence of RFMs.[5]

43.29.2.1.2.2

Clinical Signs and Diagnosis

The majority of affected cows show no serious clinical signs other than a transient decrease in appetite and milk production. However, 20% to 25% of cows affected by RFMs develop moderate to severe metritis. The most objectionable clinical signs are the malodorous discharge and objectionable tissue hanging from the genital tract. RFMs are usually expelled by 4 to 10 days after calving when the

caruncular tissue has become necrotic and is sloughed. Some affected cows show signs of endotoxemia, including depression, fever, ruminal stasis, and inappetence, as a result of RFMs.

43.29.2.1.2.3

Treatment and Prognosis

A variety of treatments have been suggested for RFMs in cows, including aggressive attempts at manual removal, myometrial stimulants, intrauterine and systemic antibiotics (alone or in combination with other approaches), and no therapy whatsoever. Because the processes that culminate in RFMs begin during late gestation, it is not unreasonable that treatment initiated at calving has little effect on the loosening process. Most treatments for RFMs are directed toward controlling the intrauterine bacterial population.

43.29.2.1.2.3.1

MANUAL REMOVAL

Manual removal of the placenta is indicated only when gentle traction is sufficient to withdraw the membranes in a short time. Attempts at manual removal are contraindicated if the patient shows clinical signs of septicemia. Trauma caused by manual removal inhibits phagocytosis by uterine neutrophils and predisposes to severe sequelae, including septic metritis and peritonitis.

43.29.2.1.2.3.2

MYOMETRIAL STIMULANTS

Administration of a single dose of oxytocin does not reduce the prevalence of RFMs in cows that calve spontaneously or in cows that require assistance at delivery.[113,114] Cows with RFMs have an elevated plasma concentration of estrogen during the period of retention; therefore administration of additional estrogen for treatment of RFMs may be of questionable value.[115] Intravenous calcium solutions are indicated in cases of RFMs secondary to hypocalcemia.

43.29.2.1.2.3.3

PROSTAGLANDIN

In one trial, treatment with fenprostalene resulted in a shorter period of retention in treated cows, reduced the number of treatments subsequently required for metritis, and slightly reduced the intervals to first service and conception.[116] However, other researchers found that fenprostalene produced no changes in myometrial activity between days 1 and 4 after calving and concluded that uterotonic agents are unlikely to hasten placental expulsion because uterine effort is already increased in animals that have RFMs.[117] An imbalance between synthesis of PGF_2 and PGI_2 between 30 and 60 minutes after parturition has been demonstrated in cows affected by RFMs.[118] Prostaglandin at the time of calving does not reduce the incidence of RFMs or improve reproductive performance.[119]

43.29.2.1.2.3.4

ANTIBIOTICS

Intrauterine tetracycline may reduce fertility,[120] or the reproductive performance of treated cows may be as good as that of untreated herdmates.[7] Intrauterine treatment with 4 to 6 g of oxytetracycline per day until the placenta is expelled may reduce the prevalence of metritis associated with RFMs, but pyometra may develop in treated cows.[121] Bacterial putrefaction and the disagreeable odor of RFMs

may be reduced by intrauterine antibiotics, but the placenta is released only after necrosis of the caruncles. Systemic and intrauterine antibiotics are indicated in cases of RFMs in which the cow has a fever, is off feed, or has a drop in milk production.

Cows that retain their membranes for more than 12 hours after calving are more likely to develop metritis than are cows that promptly expel the membranes. However, reproductive performance of cows that rapidly return to normal after RFMs is similar to that of their unaffected herdmates, indicating that in the absence of a secondary reproductive abnormality, RFMs have a minimum effect on future fertility.

43.29.2.1.2.3.5

COLLAGENASE

An alternative approach to the treatment of RFMs is the injection of collagenase into the umbilical arteries of the retained membranes.[122] This treatment is aimed directly at the lack of cotyledonary proteolysis. Intrauterine infusion of collagenase is not effective. Bacterial collagenase from *Clostridium histolyticum*, is used and is commercially available (Type XI, Sigma Chemical, St. Louis, Mo.). However, collagenase is not currently approved for use in food-producing animals in the United States.

43.29.2.1.3

Ewe and Doe

Fetal membranes are considered retained in ewes and does if not expelled within 12 hours after delivery of the last fetus. The prevalence in does is approximately 6% after spontaneous delivery but may be higher when delivery is complicated by dystocia or abortion. Selenium deficiency has been suggested as a cause.

The clinical signs of RFMs in ewes and does are usually obvious.[5] Does may ingest their placentas, complicating identification of cases of partial retention. RFMs may accompany retention of a fetus within the uterus, and does and ewes should be carefully examined.

Other tissues that may be exposed from the vulva in association with parturition are a prolapsed uterus, a prolapsed or everted urinary bladder, prolapse of some portion of the digestive tract through a uterine rupture, prolapsed rectum, prolapsed vagina, or a twin fetus.

43.29.2.1.4

Treatment and Prognosis

Manual separation of cotyledons from caruncles is impossible in ewes and does; therefore manipulative attempts to remove the placenta are limited to gentle traction on exposed membranes at daily intervals. Treatments with intrauterine and systemic antibiotics, oxytocin (10 to 20 IU) at 12-hour intervals until the placenta is expelled, and antiinflammatory drugs have been suggested. Prophylaxis against tetanus is indicated.

43.29.2.2

Camelids

The placenta is usually passed within 1 to 2 hours of parturition. Camelid placentas resemble equine placentas (diffuse, microcotyledonary, epitheliochorial), with the exception that the left horn is almost always the pregnant horn. RFMs in camelids are most commonly seen as sequelae to dystocia or other disorders of parturition.[9] Treatment is similar to that described for the mare.

43.30 UTERINE INFECTIONS

43.30.1 MARE

43.30.1.1 Endometritis

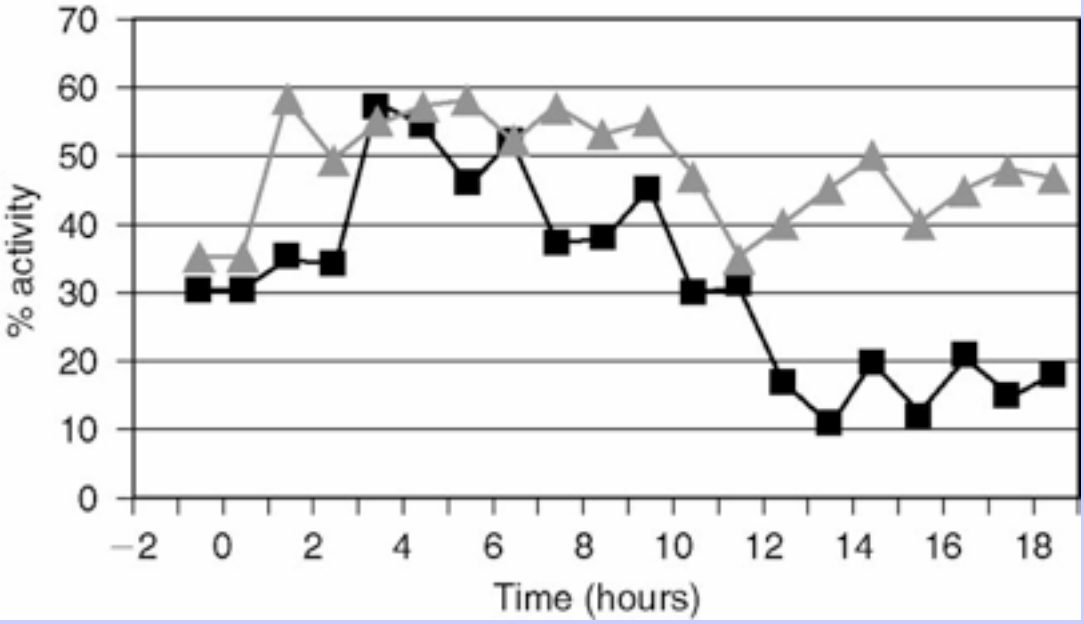
A failure of the uterine defense mechanisms to effectively eliminate an antigen (bacteria or spermatozoa) and inflammatory products from the uterus results in persistent endometritis, which is a major cause of reduced fertility in broodmares.[123] In the normal mare the uterus is well protected from external contamination by physical barriers consisting of the vulva, the vestibule, the vagina, and the cervix, and any compromise of these barriers may predispose the mare to a chronic uterine infection.[124] Breeding is another source of uterine contamination. Intrauterine deposition of semen causes an inflammatory reaction resulting from bacterial contamination of the ejaculate or from spermatozoa.[125] Approximately 15% of a normal population of thoroughbred broodmares developed persistent endometritis after breeding.[126] Natural resistance to experimentally induced bacterial contamination has been demonstrated in young mares, whereas a population of multiparous and barren mares developed persistent endometritis after bacterial contamination of the uterus.[127,128] Based on these studies, mares have been classified as either susceptible or resistant to persistent uterine infection.[127] Endometritis has severe effects on the fertility of affected mares. A persistent inflammation may interfere directly with the survival of an embryo or may cause premature luteolysis and embryonic loss because of increased PGF concentrations.[129]

Several classes of immunoglobulins have been isolated from the equine uterus. Although antibody-mediated uterine defense may be important for effective elimination of bacterial contaminants from the uterus in susceptible mares, concentrations of immunoglobulins in uterine secretion are similar or even elevated compared with those of resistant mares.[130–134] Polymorphonuclear neutrophils (PMNs) are the first inflammatory cells to enter an inflamed site.[135] Chemoattractive properties of uterine fluid have been described in vitro in horses, and the uterus responds quickly to an antigen with release of PMN-chemotactic mediators, which results in a rapid migration of PMNs into the uterine lumen.[136] Complement products and leukotriene B_4 (LTB_4), PGE, and PGF may all serve as chemoattractants for PMNs in the uterus.[136–140] Studies on the role of local uterine factors in PMN function suggested that an impaired phagocytosis by uterine PMNs in susceptible mares is the result of insufficient opsonization in uterine secretion rather than a primary dysfunction of the PMNs.[141]

Mechanical aspects of the uterine defense system are currently believed to be a major contributor in uterine clearance of bacteria and inflammatory products.[142–144] Through use of intrauterine inoculations of a combination of radioactive-labeled microspheres and bacteria, impaired uterine clearance was demonstrated in susceptible but not in resistant mares.[142] Studies using scintigraphic measurements of intrauterine clearance of radioactive colloids further defined a delayed physical clearance in susceptible mares.[143] Through use of electromyography (EMG) to register myometrial activity, it was observed that the impaired uterine clearance in susceptible mares was caused by reduced myometrial activity in response to the inflammation (Fig. 43-6).[144] The dependent position of the mare's uterus may also interfere with effective clearance.

Based on pathogenesis, persistent endometritis can be divided into (1) sexually transmitted diseases (STDs), (2) persistent uterine infection, (3) persistent breeding-induced endometritis, and (4) chronic degenerative endometritis (endometrosis).

Fig. 43-6 Myoelectrical activity before and after uterine inoculation of *Streptococcus zooepidemicus*, in mares susceptible (▪) and resistant (▲) to persistent endometritis. Time 0 indicate time of inoculation. Susceptible mares had impaired myoelectrical activity after inoculation. Modified from Troedsson MH, Liu IK, Ing M, et al: Multiple site electromyography recordings of uterine activity following an intrauterine bacterial challenge in mares susceptible and resistant to chronic uterine infection, *J Reprod Fertil*, 99:307, 1993.



43.30.1.2

SEXUALLY TRANSMITTED DISEASES

Few true STDs are known in the horse. Contagious equine metritis (CEM) is an example of a true STD.[145,146] The disease is caused by *Taylorella equigenitalis*, a highly contagious and pathogenic microorganism. Although the present status of a mare's uterine defense mechanism is important for the manifestation of the disease, this bacterium is highly resistant and capable of overcoming the mare's normal disease barriers.

43.30.1.3 PERSISTENT UTERINE INFECTION

Bacteria most commonly isolated from the uterus of the mare are beta-hemolytic streptococci (*Streptococcus zooepidemicus*, and *Streptococcus equisimilis*), *Escherichia coli, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*., Other aerobic bacteria isolated from reproductive tracts of mares include alpha-hemolytic streptococci, *Corynebacterium*, species, *Staphylococcus*, species, *Enterobacter*, species, *Actinobacter*, species, *Proteus*, species. *Citrobacter*, species, *Candida*, species, and *Aspergillus*, species are the organisms most commonly associated with yeast or fungal endometritis. The role of viruses, mycoplasmas, ureaplasma, and anaerobic bacteria in endometritis is poorly understood. *P. aeruginosa, K. pneumoniae*, and possibly *S. zooepidemicus*, and *E. coli*, can be sexually transmitted in horses, but the consequences of exposure to these microorganisms are determined by the particular strain involved and active participation of all facets of the mare's uterine defense mechanisms. In contrast to a true STD, persistent infectious endometritis is often the result of contamination of the uterus by the mare's fecal and genital flora in combination with compromised uterine defense.[147,148]

43.30.1.4 PERSISTENT BREEDING-INDUCED ENDOMETRITIS

43.30.1.4.1 Bluegrass

Intrauterine deposition of semen causes an inflammatory reaction resulting from spermatozoa.[149,150] The mechanism of the induced inflammation is similar to endometritis caused by bacteria, involving activation of the complement cascade.[150] The role of spermatozoa in breeding-induced endometritis implies that a transient uterine inflammation is a physiologic reaction to semen, and it appears to be a normal process by which excess sperm and bacterial contamination are eliminated from the mare's reproductive tract.[148,151] Transport of spermatozoa from the uterus to the oviduct is completed within 4 hours after breeding, and only a small portion of the ejaculated or inseminated semen reaches the oviduct.[152,153] The rapid transport of spermatozoa to the oviduct coincides with increased uterine activity.[151] Increased myometrial contraction in response to breeding is also responsible for rapid sperm elimination from the uterus through the cervix.[154] However, not all excess spermatozoa are removed from the uterus through this mechanism. The remaining spermatozoa have to be eliminated by means of other uterine clearance mechanisms, such as PMN-phagocytosis of spermatozoa.[148] However, the condition may develop into a persistent inflammation in mares with impaired uterine clearance.[142,143] If sperm elimination and all physical and chemical reactions that are involved in the induced inflammation persist beyond the time when the embryo enters the uterus at 5 days after ovulation, embryonic loss will occur because of an incompatible inflammatory uterine environment. The incidence of persistent breeding-induced endometritis has been reported to be approximately 15% of a normal population of thoroughbred broodmares, and the incidence may be higher for mares bred by artifical insemination with thawed frozen semen.[126]

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In contrast to spermatozoa, seminal plasma has a suppressive effect on complement activation, PMN-chemotaxis, and phagocytosis.[155] A function of seminal plasma may be to act as an inflammatory inhibitor or modulator in the uterus, which may be of importance with regard to the transient nature of breeding-induced endometritis. The duration of breeding-induced uterine inflammation was shown in a study to be shorter when seminal plasma was included in an insemination dose, compared with when all seminal

plasma was removed and replaced by a commercial semen extender.[156] Although the peak numbers of PMNs were the same for both groups, significantly fewer PMNs were recovered from the uterus at 24 hours compared with 6 and 12 hours after insemination when seminal plasma was included. In contrast, there was no significant difference in the number of uterine PMNs at 6, 12, and 24 hours of insemination in the absence of seminal plasma. Another function of seminal plasma in breeding-induced endometritis may be to protect spermatozoa from being phagocytosed and destroyed in an inflammatory environment. PMNs are present in the uterine lumen by 0.5 hours after breeding, but sperm transport is not completed until 3 to 4 hours later.[152,157] In addition, when mares are inseminated twice within a 24-hour period, semen from the second insemination is introduced into an inflammatory environment. This environment is detrimental to sperm motion characteristics, and motile sperm cells appear to bind to PMNs, forming large clusters of PMN and spermatozoa. Addition of seminal plasma has been shown to reduce the binding between spermatozoa and inflammatory cells in vitro.[158] Recent data suggest that equine seminal plasma selectively protects viable but not dead spermatozoa from PMN-binding and phagocytosis.[159,160] Selective protection of viable spermatozoa from PMN-binding and phagocytosis increases their survival in a hostile uterine environment and ensures that a sufficient number of spermatozoa reach the oviduct for fertilization, while effective sperm elimination of nonviable spermatozoa can be maintained.

43.30.1.5

CHRONIC DEGENERATIVE ENDOMETRITIS (ENDOMETRIOSIS)

Degenerative changes of the endometrium such as periglandular fibrosis and glandular dilation are often seen in older multiparous mares. The condition is associated with susceptibility to persistent endometritis[161] and may result from repeated uterine inflammation. However, the condition has also been observed in older mares without any known history of endometritis, suggesting that degenerative fibrosis of the endometrium can be a process of aging rather than inflammation.[162] Based on the possibility of a noninfectious cause of the disease, it was suggested that the condition should be called *endometrosis*, rather than *degenerative endometritis*.,[162] It is not clear why mares with fibrotic degenerative changes to the endometrium have an impaired physical uterine clearance mechanism. Sclerotic changes in the uterine vascular bed impair blood flow to both the endometrium and the myometrium.[163]

43.30.1.5.1

Diagnostic Approach

History compatible with endometritis includes infertility after breeding to a fertile stallion. Mares with severe endometritis may have shortened interestrous intervals and may show vaginal discharge. Physical and speculum examination may show anatomic defects of the vulva or cervix. Excessively easy passage of a vaginal speculum may indicate loss of integrity of the vestibulovaginal sphincter. Discharge from the cervix and vaginal inflammation may be apparent. Transrectal palpation and ultrasonography may reveal accumulations of luminal fluid (Fig. 43-7). Diagnostically, it may be difficult to identify susceptibility to breeding-induced endometritis before breeding. Some mares have free fluid present in the uterine lumen before breeding, but most mares are not diagnosed until after they have been bred. If susceptibility to persistent breeding-induced endometritis is suspected, the mare should be monitored closely by ultrasonography per rectum at 6 to 12 hours after breeding, if possible, and at a minimum within 24 hours after breeding. If free fluid is present in the uterine lumen, the mare should be considered to have persistent mating-induced endometritis. Clearance of charcoal particles from the uterus within 48 hours of inoculation and the use of scintigraphy to measure uterine clearance have been suggested to be useful in

identification of mares that are susceptible to persistent breeding-induced endometritis.[143,164] However, these methods may not be practical under field conditions.

43.30.1.6

MICROBIOLOGY

Quantitative aerobic bacterial culture of the uterine lumen is necessary to identify potential pathogens and for antibiotic sensitivity testing. Samples should be taken during estrus, and the swab plated immediately on a solid medium or transported in a nonnutritive medium to the laboratory. Inadvertent contamination of cultures with bacteria from the lower reproductive tract is common, so the culture instrument should be guarded until it is within the uterus.[165] A false-positive bacterial sample result may be obtained as the result of contamination (even when double-guarded swabs are used), and culture results should always be interpreted together with results from endometrial cytology. Culture alone is not diagnostic. False-negative swab sample results are frequently obtained even under optimal circumstances, and laboratory results should always be interpreted in light of clinical findings. Use of culture and histologic interpretation of an endometrial biopsy appears to be the most accurate method to diagnose persistent infectious endometritis.[166] Cultures may also be performed on endometrial biopsy samples. Culture samples for *T. equigenitalis*, should be taken from the endometrium, cervix, clitoral fossa, and sinuses. Samples should be placed in Amies medium with charcoal or Steward's medium and be kept refrigerated until delivered to the laboratory.

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Fig. 43-7 Transrectal ultrasonographic image of uterine intraluminal fluid accumulation in a mare with endometritis.

Table 43-5 Endometrial Biopsy Grade and Fertility Prognosis (Kenney and Doig)

Biopsy Category	Degree of Change	Predicted Foaling Rate (%)
I	None	80–90
IIA	Mild	50–80
IB	Moderate	10–50
III	Severe	<10

43.30.1.7

ENDOMETRIAL CYTOLOGY

PMNs migrate into the uterine lumen in response to inflammation, so endometritis is rapidly and accurately diagnosed by examination of exfoliated endometrial cells. A sample may be taken with a guarded swab, a cytology brush, or by infusion and aspiration of a small amount of fluid. Air-dried smears are stained with new methylene blue or modified Wright-Giemsa stain. Epithelial cells may be shed singly or in rafts. Arbitrary definitions of endometritis have been established on the basis of relative numbers of PMNs. Using these criteria, more than one PMN per 10 epithelial cells is consistent with endometritis. Endometrial cytology from normal mares may contain PMNs and spermatozoa for several days after breeding. It has been suggested that eosinophils are associated with fungal endometritis and pneumovagina. Urine crystals indicate urovagina.

43.30.1.8

ENDOMETRIAL BIOPSY

Endometrial biopsy is an accurate diagnostic and prognostic tool for endometritis. The biopsy sample should be taken during the breeding season, should be of adequate size, and should be fixed in Bouin's solution for 24 hours and then transferred to 10% formalin. Chronic endometritis is characterized by infiltration of the endometrium with mononuclear cells and deposition of layers of fibrosis around endometrial glands. Fibrosis of the endometrium is a degenerative change and is permanent. The severity of endometrial changes is inversely related to reproductive performance. A system to classify histologic changes has been described and is widely used[5] (Table 43-5). Special stains such as periodic acid—Schiff and Gomori's methenamine silver may be used to identify the presence of fungi in endometrial biopsies.

43.30.1.9

TRANSRECTAL ULTRASONOGRAPHY

The presence of free intraluminal fluid before breeding strongly suggests susceptibility to persistent endometritis.[167] Ultrasonographic examination of the uterus is helpful to assess both the quantity and quality of accumulated fluid in the uterine lumen. Normal mares may retain fluid up to 6 to 12 hours after mating. If fluid is present at 12 hours or more after breeding, the mare should be considered to have a persistent mating-induced endometritis.[168] Increased echogenicity of the fluid is associated with the presence of inflammatory cells and debris.

43.30.1.9.1

Hysteroscopy

Examination of the uterine lumen with an endoscope provides information about degree of inflammation in addition to evidence of foreign bodies, transluminal adhesions, intraluminal masses, and endometrial cysts.

43.30.1.10

Treatment and Prognosis

43.30.1.10.1

SEXUALLY TRANSMITTED DISEASES

Mares with CEM should be treated with intrauterine infusions of antibiotics based on sensitivity tests, in combination with local treatments of the clitoral fossa and sinuses. Best results can be expected when treatment is initiated when the mare is in estrus and is combined with uterine lavage if inflammatory debris or intraluminal fluid is present. Cleansing of the vulva and the clitoris daily for 5 days with a 4% chlorhexidine or nitrofurazone ointment has been recommended.[169] Sinusectomy can also be performed.[170] Import regulations in countries free from CEM serve to prevent outbreaks of the disease. The spread of CEM on farms in endemic countries is best prevented by implementation of strict hygiene, screening of breeding stallions before the breeding season, and the use of AI, if allowed by the breed registry.

43.30.1.10.2

PERSISTENT UTERINE INFECTION

Treatment of mares with persistent uterine infections needs to be directed toward the underlying breakdown of the uterine defense and against the microbial agent. The first therapeutic concern should be to remove predisposing causes, such as a breakdown of external genital barriers. Persistent uterine infection frequently follows degenerative or traumatic anatomic changes and loss of integrity of the barriers of ascending infection. Therefore Caslick's surgery, repair of cervical damage and perineal lacerations, and correction of urovagina should precede specific endometrial treatment. All potential sources of contamination including intrauterine passage of diagnostic and treatment implements should be minimized. In some mares, recovery follows with sexual rest and no further treatment. Mares that are susceptible to persistent uterine infections should be bred using minimal contamination techniques to avoid bacterial contamination of the uterus.[171] Antibiotics may be administered by either local or systemic routes. Intraluminal fluid and inflammatory debris should be removed by uterine lavage before local treatment. Drugs and doses are summarized in Table 43-6. Treatment should be based on sensitivity. Mares should be treated during estrus when natural defense is maximal, and strict aseptic technique should be used. The volume of fluid used for antibiotic therapy is dependent on the size of the uterus. A total volume of 30 to 60 mL is usually sufficient. Treatment should continue daily for 4 to 6 days during the duration of estrus. Bacterial resistance may follow inadequate dosage, and follow-up cultures should be performed. Repeated contamination may indicate an unsuccessfully resolved predisposing cause. Removal of the primary microorganism may result in overgrowth of a second bacteria or fungus (superinfection). Critical studies of the efficacy of systemic antibiotics are limited, although effective levels are produced in the endometrium after systemic administration.[172] Parenteral administration may be easier, and the opportunity to introduce uterine contamination or cause uterine irritation with treatment is eliminated. Treatment of fungal infections is generally more challenging than treatment of bacterial infections. Culture and sensitivity will determine the choice of antifungal drugs (Table 43-6). Fungal endometritis may require daily intrauterine infusions for 7 to 10 days to effectively resolve the infection. In order to avoid

intrauterine infusions in the presence of high circulating concentrations of progesterone, treatment can be initiated 1 or 2 days after an injection of $PGF_{2\alpha}$ in diestrual mares and continues until 1 or 2 days after ovulation. A single dose of a benzyoylphenyl urea (lufenuron) has recently been suggested to effectively treat mares with fungal endometritis.[173] Initial data from four mares were encouraging and need to be confirmed by controlled studies using larger groups of mares.

Treatment with immunostimulatory agents *(Propionibacterium acnes)*, has been reported to improve pregnancy rates in mares with persistent endometritis, but the mechanism is not fully understood.[174]

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Table 43-6 Antibacterial Drugs Used for Intrauterine Administration for Treatment of Uterine Infections in Mares

Drug	Dose (Intrauterine Administration)	Comments
Amikacin sulfate	2 g	Gram-negative spectrum; buffer with equal volume of 7.5% bicarbonate
Ampicillin	3 g	Gram-negative spectrum; may irritate the endometrium
Carbenicillin	2–6 g	Gram-negative spectrum; may irritate the endometrium; buffer with equal volume of 7.5% bicarbonate
Gentamicin sulfate	1–3 g	Gram-negative spectrum; buffer with equal volume of 7.5% bicarbonate
Kanamycin sulfate	1–3 g	*Escherichia coli*, spermatocidal
Neomycin sulfate	3–4 g	Useful against sensitive *E. coli*,
Potassium penicillin G	5 million U	*Streptococcus zooepidemicus*,
Polymyxin B	1 million U	*Pseudomonas*,
Ticarcillin	6 g	Broad spectrum
Ticarcillin/clavulanic acid	6 g/200 mg	Broad spectrum
Ceftiofur	1 g	Broad spectrum *(S. zooepidemicus)*,
Antimycotics		
Nystatin	500,000 U	Dissolve in 30 mL 0.9% saline solution; daily for 7 to 10 days
Clotrimazole	500 mg	Suspension or cream; daily for 1 wk
Miconazole	500 mg	Effective against yeast
Amphotericin B	200–250 mg	Daily for 1 wk
Vinegar	2%	20 mL wine vinegar to 1 L 0.9% saline solution; used as uterine lavage
Lufenuron	540 mg (single dose)	Suspend in 60 mL sterile water

43.30.1.10.3

PERSISTENT BREEDING-INDUCED ENDOMETRITIS

Management of mares susceptible to persistent breeding-induced endometritis should include limiting uterine exposure to semen and bacteria and assisting the uterus to physically clear contaminants and inflammatory products after breeding.[136,173,175] Preexisting uterine infections should be resolved before the mare is bred. Exposure to semen should be limited to a single breeding per cycle, if possible. This can be accomplished by closely monitoring follicular development and hormonal treatment to induce ovulation of mature follicles. Physical clearance can be assisted by the use of uterotonic drugs. Oxytocin or $PGF_{2\alpha}$ treatment 4 to 8 hours after breeding has been shown to aid in uterine clearance, resulting in improved pregnancy rates in susceptible mares.[136,167,173,176] Care must be taken with regard to the timing of $PGF_{2\alpha}$ treatment. Recent reports have demonstrated that $PGF_{2\alpha}$ can cause a delay in the formation of a functional CL when administered within 2 days after ovulation.[96–100] This was associated with pregnancy failure in two of the reports.[97,98] Large-volume uterine lavage 6 to 24 hours after breeding will also effectively assist the uterus in clearing fluid and inflammatory products.[175] Because sperm transport to the oviduct is completed within 4 hours after breeding, uterine lavage 6 to 24 hours after breeding will not have a negative effect on fertility.[152] Manual dilation of the cervix in mares with poor cervical dilation may help these mares to more effectively clear the uterus of fluid.

The use of corticosteroids in mares with excessive inflammation in response to breeding has been suggested.[177] The authors administered acetate 9α-prednisolone (0.1 mg/kg) twice daily during estrus, starting when a follicle >35 mm was detected and ending when ovulation was confirmed. Preliminary results are encouraging, and further research is needed to clarify the mechanism of action for this treatment alternative.

Electroacupuncture has been used clinically to increase uterine contractility in mares with delayed uterine clearance. Anecdotal reports are encouraging, and research is needed to confirm the efficacy of this treatment alternative.

It is important for the clinician to keep in mind that a transient inflammatory response to semen is normal and required for normal fertility. Postbreeding treatments of these mares will most likely not improve fertility but may cause even further contamination and interfere with pregnancy. Only 10% to 15% of all broodmares develop a pathologic persistent form of breeding-induced endometritis.[126] Attention should be given to identify and manage these mares appropriately in order to optimize reproductive efficiency.

43.30.1.10.4

CHRONIC DEGENERATIVE ENDOMETRITIS (ENDOMETROSIS)

Several treatments have been suggested for degenerative fibrosis of the endometrium, but consistent results have not been reported. Mechanical or chemical irritation of the endometrium has been used, but concerns that trauma to the endometrium may produce more scar tissue than repair have limited the popularity of such methods. Infusion of dimethyl sulfoxide (DMSO) into the uterine lumen has been shown to improve fibrosis in mares with chronic degenerative endometritis[178]; however, other researchers were not able to repeat these results.[179]

Prognosis for fertility after endometritis varies with the severity of inflammation and fibrosis and the inciting cause. Prognosis should take into account the age of the mare and the level of reproductive management, in addition to the cause and likely response to treatment.

43.30.2 Metritis

Metritis is classically defined as inflammation of all layers of the uterine wall. Metritis occurs in the first 2 weeks after foaling and commonly follows abortion, dystocia, and RFMs. In mares, metritis is often accompanied by endotoxemia and laminitis. Transluminal adhesions between endometrial folds may follow severe metritis.

43.30.2.1 Clinical Signs and Diagnosis

Metritis is characterized by uterine accumulation of postpartum secretions, bacteria, and the products of inflammation, with discharge from the cervix and possibly the vulva. Discharge is usually fluid and red-brown and may be fetid. Systemic signs of depression accompanied by neutropenia and leukopenia are apparent with development of endotoxemia. Differential diagnoses include normal lochia and causes of profound depression in the postpartum period as a result of uterine tears and abdominal catastrophes. 1441 1442

43.30.2.2 Treatment and Prognosis

Treatment is directed toward removing contamination and microorganisms from the uterus while providing systemic treatment for endotoxemia. Broad-spectrum systemic antibiotics, antiinflammatory drugs, and fluid therapy are indicated. Uterine contamination may be removed by gentle intraluminal infusion of warm water or saline and siphoning off of uterine contents. Vigorous lavage should be avoided, particularly during acute systemic disease. Prognosis depends on severity of clinical signs. If metritis is diagnosed quickly and treatment is instituted, prognosis for fertility and systemic health is good. Prognosis is guarded once endotoxemia and laminitis develop.

43.30.3 Pyometra

Pyometra in mares is an accumulation of purulent exudate in the lumen of the uterus. Impedance to mechanical uterine outflow, such as cervical fibrosis and adhesions of cranial parts of the tract ventrally into the abdomen, may contribute to the development of pyometra. If endometrial irritation causes release of endogenous endometrial PGF, diestrus will be shortened. In some mares, endometrial destruction is so severe that PGF release is inadequate and luteal life is prolonged.[92] A variety of bacteria may be involved, including *E. coli, Pseudomonas*, species, and *Streptococcus*, species. Cultures may be negative.

43.30.4 Clinical Signs and Diagnosis

A purulent vaginal or cervical discharge may be seen. The mare may demonstrate a short diestrus, a normal interestrous interval, or a prolonged diestrus. Occasional mares with pyometra have mild leukopenia and normocytic-normochromic anemia, secondary to mild suppression of erythropoiesis.[92] Transrectal palpation and ultrasonography reveal a fluid-filled uterus. The uterine wall may be thin and flaccid or thick.

43.30.5 Treatment and Prognosis

Treatment should involve correction of predisposing causes, fluid evacuation, and local antibiotic treatment. Evacuation of large amounts of fluid from the uterus may result in redistribution of fluid and circulatory shock. The mare should be monitored for signs of circulatory shock, and intravenous fluid may be administered during evacuation of large amounts of fluid from the uterus. The prognosis for life is excellent; however, the prognosis for return to normal fertility is guarded to poor because the conditions that predispose to development of pyometra in mares (cervical stenosis and adhesions) are difficult to treat and because severe endometrial destruction may develop. Endometrial biopsy should precede vigorous treatment. Hysterectomy should be considered if treatment is unsuccessful and if discharge is unacceptable or if adhesions impair athletic ability.

43.31 RUMINANTS

43.31.1 Parturition

Deliveries complicated by dystocia or RFMs may be followed by severe bacterial infections of the uterus. The most sanitary environment possible should be provided for calving. The use of a clean pasture may be most appropriate on some farms, whereas the use of roomy, well-bedded, indoor maternity pens that are cleaned after each delivery may be appropriate on others.

Cows with abnormalities around the time of calving such as hypocalcemia, dystocia, and RFMs are more likely to develop uterine infections than are cows that calve normally. Routine treatment of cows with antibacterial drugs and chemicals has not been shown to be beneficial and in some cases has reduced fertility. Postpartum uterine infections may be prevented, or the number of such infections reduced, by strict attention to sanitation in the calving environment and during assistance with delivery, along with proper management during the dry period.[180]

43.31.2 Bovine Uterine Infection

Bovine uteri are normally contaminated by a wide variety of microorganisms during the puerperium. Most of the organisms are transient residents of the reproductive tract and are soon eliminated from the involuting uteri of normal cows. *Arcanobacter (Actinomyces) pyogenes*, can persist in the uteri of cows and act with *Fusobacterium necrophorum*, and *Bacteroides*, species to cause uterine infections. Coliforms, *P. aeruginosa*, hemolytic streptococci, and gram-positive and gram-negative anaerobic bacteria are also frequently isolated from animals with postpartum uterine disease. *A. pyogenes*, and *Clostridium*, species occasionally colonize the postpartum uterus synergistically, causing severe gangrenous metritis. Other organisms that appear to have little effect on fertility may colonize the uterus and produce penicillinase, thus influencing the selection and route of administration of drugs used to treat uterine infections.[121]

43.31.2.1 Clinical Signs and Diagnosis

Lochia is normally expelled during the first 2 weeks after calving and may range from dark red or brown to white to clear. If uterine involution is delayed, discharge of lochia may continue until 30 days after calving. Discharge of lochia is not abnormal unless the fluid is fetid or the cow develops other abnormal clinical signs. Abnormalities of uterine involution cannot be diagnosed by palpation per rectum during the first

several days after calving when both normal and abnormal uteri are out of reach and cannot be safely retracted. By 10 to 15 days after calving the entire uterus can be palpated if involution is normal. Fluid should not be palpable within the uterine lumen by 14 to 18 days after calving. Gross reduction in size and histologic repair of the endometrium are complete in dairy cows by 40 to 50 days after calving.

Postpartum metritis in cows is characterized by the presence of variable amounts of lochia within the uterine lumen that may be discerned by palpation per rectum. A vaginal discharge is usually present, but it may become obvious during palpation. Septic metritis is characterized by clinical signs of toxemia that may include fever, depression, partial or complete anorexia, and laminitis. Milk yield is depressed, and cows may be unwilling or unable to rise. Some cases may be complicated by tenesmus. Vaginitis and cervicitis may accompany metritis. Discharges associated with septic metritis vary from scanty white mucus to copious amounts of red to red-black, watery, malodorous fluid. In some cases inflammation may spread through the uterine wall and cause perimetritis and peritonitis.[181] Septic metritis in ewes and does is characterized by fever, depression, anorexia, and tenesmus.

Endometritis in cattle is usually observed between 2 and 8 weeks after calving. Discharge can range from white pus to estrual mucus. Purulent exudate may be observed only with palpation or may be found in the cranial vagina and cervical canal on examination with a speculum. The history may indicate that the cow has failed to conceive after several services but the patient is otherwise healthy. 1442 1443

Culture of endometrial fluid is not usually done in individual cases of bovine uterine infection but may be indicated to determine the antibiotic susceptibility of microorganisms on a particular farm or as a part of the diagnostic plan when the incidence of postpartum metritis or endometritis increases suddenly.

Endometrial biopsies are rarely used in cows but have been recommended when complete evaluation is required of the reproductive tract of cows that do not conceive or that conceive but do not complete their pregnancies.[5]

43.31.2.2 Treatment and Prognosis

To be useful in treating uterine infections in cows, an antibiotic must be active against the primary uterine pathogens (*A. pyogenes*, and gram-negative anaerobes), in the presence of organic debris, and in the anaerobic environment of the postpartum bovine uterus.[182] Organisms infecting the uteri of cows are usually susceptible to penicillin, but during the first month after calving, contaminating microorganisms may produce penicillinase. Therefore penicillin is not likely to be effective if given locally during the early postpartum period. By 30 days after calving, organisms that produce penicillinase are usually eliminated from the uterus, and intrauterine treatment with penicillin may be beneficial. The daily intrauterine dose of penicillin required to reach the minimum inhibitory concentration of common bacteria such as *A. pyogenes*, is 1×10^6 IU.[182] Oxytetracycline is active against many of the microorganisms that infect the bovine uterus, and its activity is only slightly reduced by organic debris and absence of oxygen. Intrauterine treatment with administration of 4 to 6 g of oxytetracycline per day has been recommended. Some preparations of oxytetracycline irritate the endometrium, cervix, and vagina. Intrauterine antibiotic treatment of dairy cows results in residues in their milk.[183] For example, oxytetracycline has been found in milk from 44[184] to 96[185] hours after intrauterine administration.

Penicillin by systemic administration is effective for treatment of some uterine infections in cows. Daily doses of penicillin required to reach the minimum inhibitory concentration of *A. pyogenes*, are 10,000 to

20,000 IU/kg/day. Minimum inhibitory concentration of oxytetracycline for *A. pyogenes*, in the uterus is usually higher than the concentration that can be achieved by systemic administration of the drug.

Treatment of septic metritis should be directed toward controlling septicemia. Large doses of broad-spectrum systemic antibiotics are indicated, along with fluids and other supportive therapy. Attempts to remove RFMs or irrigate the uterus are contraindicated during the acute phase of the disease. After the patient has recovered from acute septicemia, intrauterine therapy may be considered.

43.31.2.2.1

ANTISEPTIC CHEMICALS

A variety of antiseptic chemicals have been infused into the uterine lumen of cows in attempts to treat metritis and endometritis, but few controlled trial evaluations are available. These are attractive as a way to avoid antibiotic residues in the milk intrauterine infusion.[186] Dilute solutions of povidone-iodine (one part povidone-iodine stock solution to 10 to 20 parts saline) have been suggested as being useful in treating fungal endometritis.[44] Povidone-iodine is generally available as a 10% solution with 1% free iodine (10,000 ppm of free iodine), so that a dilution of 20:1 saline:povidone-iodine yields a flush with 500 ppm of free iodine, which should be bactericidal.

43.31.2.2.2

UTERINE LAVAGE

Lavage of the uterine lumen with large volumes of warm saline (40° to 45° C [104° to 118° F]) removes accumulated fluid and debris. Uterine lavage has been used as an adjunct to antibiotic, antiseptic, and plasma treatment. Catheters designed for nonsurgical embryo recovery are suitable for uterine lavage. Saline is infused into the endometrial cavity in 0.5- to 1-L increments, allowed to reflux through the catheter, and collected for inspection. A milk hose and larger fluid volumes may be used in cattle with larger postpartum uteri, but care must be taken not to enter far into the uterus because it is friable and easily perforated. Massage or partial retraction of the uterus by palpation per rectum may be necessary to increase fluid recovery. The uterine lumen is lavaged repeatedly until the fluid returning through the catheter is no longer turbid.

43.31.2.2.3

PROSTAGLANDINS

In cows, repeated administration of PGF results in shortened estrous cycles and may mimic the shortened luteal phase of patients with acute endometritis. PGF therapy may be sufficient in mild cases of endometritis or may be used in combination with intrauterine or systemic therapy. In cases of chronic bovine endometritis, treatment with PGF one or two times at 10- to 14-day intervals decreased the number of days open.[187]

The prognosis in cows for recovery from endometritis is usually good if the condition does not progress to a more severe form of uterine disease. Septic metritis after dystocia or RFMs may result in permanent impairment of reproductive function, laminitis, or death of the patient in spite of aggressive therapy.

43.31.3

Pyometra

In dairy cows, pyometra is likely to develop in cows that ovulate before microorganisms that infect the uterus during the postpartum period are eliminated. The CL that develops after the first postpartum ovulation at

approximately 15 to 18 days after calving persists, possibly because the abnormal uterine contents suspend release of PGF from the endometrium or sequester it within the uterine lumen. The uterus is brought under the influence of progesterone, which depresses phagocytic activity of uterine neutrophils and closes the cervix, allowing the bacterial infection to persist.[188] Pyometra rarely endangers the general health or life of affected cows. Postcoital pyometra may be caused by *T. foetus*.,[189]

PGF is the treatment of choice for bovine pyometra. Treatment with PGF is followed in 3 to 6 days by uterine evacuation in 85% to 90% of treated cows. Response to PGF treatment may be raised with a second injection of PGF in 6 to 12 hours. After endometrial lesions are allowed to heal for 30 days, fertility is restored in most patients.

Treatment of cows with GnRH 2 weeks after calving improves fertility in some but not all situations. In herds with a high prevalence of postpartum uterine infections, treatment with GnRH may decrease fertility by inducing ovulation and CL development; thus the uterus is brought under the influence of progesterone before contaminating bacteria are removed, leading to pyometra.

43.31.4 Perimetritis

Perimetritis may occur in all species as a sequela to severe uterine infections, uterine rupture, penetration of the vagina during mating, traumatic insemination or obstetric procedures, and cesarean section.[102,190] Perimetritis is characterized by inflammation of the peritoneal surface of the uterus and may be accompanied by localized or diffuse peritonitis. Adhesions then develop between the uterus and other pelvic and abdominal organs.

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43.31.4.1 Clinical Signs and Diagnosis

The clinical signs of perimetritis are those of peritonitis and may include fever, depression, partial or complete anorexia, stasis of the gastrointestinal tract, and evidence of abdominal pain. Abdominal pain is typified by colic in mares and by grinding the teeth (odontoprisis) in cows. In cows the condition should be differentiated from traumatic reticuloperitonitis, displacements of parts of the digestive tract, abomasal ulcers, postpartum metritis, and abdominal fat necrosis. Perimetritis in mares must be differentiated from other causes of severe abdominal pain. Antemortem diagnosis of perimetritis is difficult in sheep and goats that are presented mainly with fever, depression, anorexia, and odontoprisis.

43.31.4.2 Clinical Pathology

Cases of acute perimetritis are accompanied by leukopenia, neutropenia, and a degenerative left shift. Further evidence of peritonitis is obtained when peritoneal fluid is obtained by paracentesis and examined for its cellular and microbiologic content.

43.31.4.3 Treatment and Prognosis

The cause of perimetritis should be treated if possible. Cases of severe metritis should be treated appropriately and uterine ruptures sutured if possible. Repair of uterine ruptures inaccessible by flank incisions may be facilitated by intentional prolapse of the uterus after administration of epinephrine, provided the tear is not too close to the cervix (see next section). Treatment with broad-spectrum systemic antibiotics is indicated. Lavage to remove peritoneal exudate has been recommended but is difficult to accomplish,

especially in cows in which the rumen, abomasum, and greater omentum make ventral drainage almost impossible and in which fibrinous peritonitis with loculation of infection occurs rapidly. Other supportive treatments such as intravenous fluids and antiinflammatory drugs should be administered as indicated.

The prognosis depends on the severity of lesions. Fatalities can occur in spite of prompt treatment, and surviving animals may be infertile because of mechanical interference with gamete transport caused by adhesions between the genital organs and other pelvic and abdominal tissues. In general, the prognosis for fertility in affected animals is fair at best.

43.31.4.4 Prevention and Control

Perimetritis occurs sporadically in individual animals; therefore prevention depends on avoiding the causes. Immature females, especially heifers and fillies, should not be allowed at pasture with adult males, to prevent undesired mating complicated by penetration of the vagina. Traumatic obstetric, insemination, and uterine lavage procedures must be avoided. Uterine tears that occur at parturition must be sutured immediately. Postpartum metritis must be treated promptly and appropriately before it progresses to perimetritis.

43.32 SMALL RUMINANTS

Uterine infections may follow dystocia and RFMs in sheep and goats but are not frequently a cause of infertility because lambing and kidding are followed by a period of up to 6 months of sexual rest before the next breeding season. RFMs and metritis follow abortion in ewes caused by *Listeria monocytogenes, C. fetus*, subsp. *fetus*, and *Chlamydia psittaci*.,

Ewes and does affected with metritis are usually treated with systemic antibiotics such as penicillin or sulfamethazine. Early and aggressive treatment is indicated.[190]

43.33 CAMELIDS

43.33.1 Metritis and Endometritis

Camelids are induced ovulators, and females are usually receptive to males unless they are pregnant. Females do not, however, always have a preovulatory follicle present. Therefore it is frequently the case that females are bred at a time when they do not have a fertile follicle present. When camelids breed, the penis is inserted through the cervix and deep into the uterine horns. Unnecessary matings, or overbreeding, is the most important factor causing damage and contamination to the uterus.[191] Other major contributing factors include RFMs, rectal vaginal tears, and unsanitary obstetric manipulations.[191]

Chronic endometritis will often not cause evident clinical signs, whereas acute, postpartum endometritis may cause fever, depression, and signs of toxic shock.[191] A thick, mucoid lochial discharge is normal in the postpartum female for up to a week postpartum. Thin, watery, fetid discharge is a sign of endometritis.[191]

Transrectal ultrasonography and vaginoscopy are helpful in diagnosing endometritis and metritis. Inflamed, thickened uterine walls and hyperechoic, intraluminal fluid may be present on ultrasound examination. Vaginoscopy may reveal cervical discharge. Transrectal ultrasonography may usually be performed in llamas as

in horses or cattle. In alpacas, because of smaller size, an extension probe will be necessary to facilitate transrectal ultrasonographic evaluation.

Uterine culture and cytology samples from the llama may be obtained in methods similar to those in the mare and cow. A double-guarded swab prevents environmental contamination. In the alpaca the swab should be passed through the cervix via visualization using a vaginoscope. These diagnostics should be performed during the peak follicular phase to ensure ease of passage through the open cervix and more reliable test results.[191] The most common bacteria isolated from the uteri of camelids with endometritis are *E. coli, S. zooepidemicus*, β-hemolytic streptococci, *Enterococcus*, coagulase-negative *Staphylococcus, Proteus*, species, *Enterobacter aerogenes, K. pneumoniae*, and *A. pyogenes*,.[191]

Uterine biopsy can be a very useful diagnostic tool for evaluation of metritis and endometritis in camelids. Endometrial biopsy samples in llamas may be obtained as in the mare. The left horn is perhaps better to target unless a particular pathology is suspected in the right horn, because camelid pregnancies almost always occur in the left horn.[191] Pathologic changes, evaluation, and prognosis are all assumed to be similar to those in the mare.[191]

Treatment for endometritis and metritis is also similar to that described for the mare. Uterine lavage with a warm, isotonic saline solution and oxytocin injection (5 to 10 IU) are the major components of treatment. Intrauterine antibiotic infusion is done after uterine lavage. The most common antibiotics used are penicillin K (1.5×10^6 U), gentamicin sulfate (200 to 300 mg), and ceftiofur sodium (250 to 500 mg).[191] Antibiotics should be diluted in sterile water or saline (saline should not be used with ceftiofur) and given once daily for 5 to 7 days. Females should be evaluated after cessation of treatment and completion of 2 weeks of sexual rest.

Prevention of endometritis often requires a "minimum contamination breeding technique."[191] This entails monitoring follicular growth via transrectal ultrasound until the follicle is of preovulatory size, breeding only once, following breeding with an injection of hCG (750 IU) or GnRH, and administering an intrauterine infusion of antibiotics 24 hours after breeding. Females should be evaluated for pregnancy 12 to 14 days after breeding. 1444 1445

Further preventative measures include performing prebreeding examinations on all maiden animals to avoid breeding animals that are too young or do not have follicular activity; breeding only females exhibiting strong receptive behavior (as opposed to mere submissive behavior); performing complete gynecologic examinations of all females with a history of infertility, obstetric problems, or postpartum complications; and observing strict rules of hygiene during breeding and obstetric manipulations.[191]

43.33.2 Pyometra

Pyometra caused by delayed uterine involution may be observed shortly after parturition. Chronic pyometra is often associated with vaginal or cervical adhesions that may be the sequelae to trauma after dystocia or aggressive obstetric manipulation.[191]

43.34 ANATOMIC DEFECTS AS A CAUSE OF UTERINE INFECTION

The most common anatomic defect associated with genital infections is pneumovagina. Other defects include urovagina and perineal lacerations. These defects should be corrected to prevent contamination with environmental and fecal organisms.

43.35 ENDOMETRIAL CYSTS AND LACUNAE

43.35.1 MARES

Endometrial cysts and lymphatic lacunae are common degenerative changes of the endometrium that are more prevalent in mares older than 11 years of age than in younger mares.[192] Endometrial cysts can originate from endometrial glands or obstructed lymphatics. Glandular cysts are small (<10 mm) and are believed to be the result of periglandular fibrosis. Lymphatic cysts can reach several centimeters in diameter. The cause of lymphatic cysts is not fully understood, but lacunae are thought to arise after interference with normal lymph drainage from the genital tract.[5]

43.35.1.1 Clinical Signs and Diagnosis

Endometrial cysts can be visualized by ultrasonography or by hysteroscopy. Cysts may mimic pregnancy when mares are examined per rectum by palpation or ultrasonography.[193] Sequential examination reveals that size of endometrial cysts remains static, whereas amniotic vesicles enlarge. Large, discrete, fluid-filled cysts may be identified by palpation of the uterus per rectum. Smaller cysts and lacunae may be observed in endometrial biopsy sections. Uteri affected by lymphatic lacunae are enlarged and have a thicker wall than normal.

43.35.1.2 Treatment and Prognosis

Endometrial cysts do not require treatment unless they are suspected to interfere with pregnancy. Endometrial cysts have been suggested to cause embryonic death and abortion if large or numerous. However, one study failed to find an association between the presence or number of cysts and fertility.[192] Obliteration of endometrial cysts using endoscopic guided laser surgery removes the cysts permanently, but the long-term effect on fertility has not been critically evaluated. Needle aspiration, mechanical rupture of the cyst, uterine curettage, or intrauterine infusion of hypertonic saline solution have all been suggested to effectively remove endometrial cysts. However, the cysts often recur after treatment.

43.36 UTERINE PROLAPSE

Uterine prolapse occurs when the previously gravid uterine horn becomes invaginated after delivery of the fetus(es) and protrudes from the vulva.

43.36.1 MARES

Uterine prolapse is an uncommon sequela to normal foaling, dystocia, or RFMs in the mare. The tip of the previously gravid horn invaginates to form uterine eversion. Eversion is accompanied by pain and abdominal straining. The myometrium may contract around the ring of invaginated tissue. Transrectal palpation confirms the diagnosis, and the everted tissue may be replaced manually. Eversion may progress to complete uterine prolapse, accompanied by rapid onset of systemic signs.

43.36.1.1 Treatment and Prognosis

The prolapsed uterus should be washed with clean saline and replaced manually in the standing mare as rapidly as possible. Replacement is aided by sedating the mare and administering epidural anesthesia. The uterus should be supported on a clean sheet held at the level of the pelvis. The uterus should be replaced, beginning with the uterine body and working gradually, replacing the tip of the horns last. Correct positioning of the uterus is important to prevent the prolapse from recurring. Replacement should be followed by treatment with broad-spectrum antibiotics, antiinflammatory drugs, and intravenous isotonic fluids. Treatment with oxytocin (10 to 20 IU IM) facilitates uterine involution. Prognosis is related to development of sequelae such as uterine tears, metritis, and endometrial damage.[194]

43.36.2 RUMINANTS

In cows most cases of uterine prolapse occur within a few hours after calving. The condition is invariably associated with hypocalcemia, which results in lack of uterine tone and delayed cervical involution. In addition, dystocia frequently precedes uterine prolapse.

Elective uterine prolapse can be induced within 6 to 12 hours after calving by administration of epinephrine to relax the uterus for the repair of uterine tears. A 10-mL amount of epinephrine (1:1000) is diluted to 250 mL in sterile saline and administered slowly IV. After 100 mL of the solution has been given, the operator reaches through the cervix, grasps the uterine wall and caruncles, and everts the uterine horn toward the cervix. When sufficient uterine tissue has entered the cervical canal, the patient responds by straining, which assists in completion of the prolapse. Epidural anesthesia is administered to abolish further straining *after*, the prolapse is complete.

Uterine prolapse in does has been associated with dystocia, hypocalcemia, and lack of exercise.[5] The predisposing factors are probably similar for ewes.

43.36.2.1 Clinical Signs and Diagnosis

Clinical signs of uterine prolapse are obvious. The membranes may remain attached. Immediately after prolapse occurs the tissues are nearly normal, but within a few hours they become enlarged and edematous. The endometrium is usually contaminated with feces and bedding material. In some cases the prolapsed tissue may be lacerated or severely traumatized and may contain loops of intestines.

Clinical signs that may accompany uterine prolapse include straining, abdominal pain, restlessness, anorexia, and increased pulse and respiratory rates.[102] Parturient paresis is common in affected dairy cows. In most patients these signs are transitory, but shock may complicate some cases.

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43.36.2.2 Clinical Pathology

Uterine prolapse in cows is frequently accompanied by hypocalcemia and a significant increase in the packed cell volume.[195]

43.36.2.3

Treatment and Prognosis

The prolapsed tissue should be protected from further damage by wrapping it in wet towels or covering it with a plastic bag. Beef cows should be restrained where they are found, to prevent trauma to the uterus or rupture of the large uterine vessels should an animal try to escape on arrival of the clinician. Treatment of hypocalcemia is usually indicated before replacement of the uterus if the cow is recumbent and semicomatose; otherwise calcium gluconate is administered after replacement. Epidural anesthesia is frequently (but not always) required.

The prolapsed tissue is washed with a mild presurgical scrub. The membranes are removed if they can be easily separated from the endometrium but are left in place if removal is difficult. Some clinicians recommend that cows stand during replacement, whereas others have found that the organ can be replaced in recumbent cows if the patient is placed on her sternum with the hind legs drawn straight out behind. The prolapse is placed between the extended limbs.[196] In fresh cases, replacement is relatively easy and is begun at the cervical pole of the organ; the dorsal and ventral parts are massaged alternately back into their normal position. After the ovarian pole has been replaced, the previously prolapsed horn must be straightened, and eversion of the uterus corrected. Administration of clenbuterol is reported to relax the uterus, facilitate replacement, and reduce the need for epidural anesthesia, but its use is illegal in the United States.[197] If the patient has been neglected, accumulated fluid must be reduced by lubricating the tissue with an emollient ointment then carefully but vigorously massaging the tissue from the ovarian pole toward the cervical pole. The hygroscopic action of sugar when applied liberally to prolapsed uteri is of limited value and vastly overrated.

Oxytocin is frequently administered to stimulate myometrial contractions after the uterus has been replaced. Metritis is a frequent sequela, and appropriate antibiotic treatment is indicated in most cases. Temporary closure of the vulva with heavy sutures after replacement is not necessary[102] but is practiced by many clinicians.[5] If replacement of the prolapsed uterus is impossible or the tissue is severely traumatized, amputation may be indicated; in this case it is important that the uterine arteries be double ligated.[198]

The prognosis varies but is generally favorable if there has been no serious damage to the uterus.[5,196] Fatalities can occur in cases complicated by shock or by rupture of large uterine vessels. The culling rate from infertility of cows with uterine prolapse is higher than that of their herdmates, and the calving interval is prolonged in affected cows. Barring hypocalcemia, the risk of uterine prolapse at a subsequent calving is no greater than for other cows in the herd.

43.36.2.4

Prevention and Control

Because the condition is associated with hypocalcemia in cows, provision of a properly balanced ration before calving is indicated. Although uterine prolapse can occur after an apparently normal delivery, it is more commonly associated with dystocia and forced extraction; therefore prolapse should be anticipated, and the dam observed so affected patients may receive prompt treatment.

43.36.3 CAMELIDS

Uterine prolapse in camelids usually is a consequence of dystocia, RFMs, or excessive obstetric manipulation. Treatment is the same as described for other species and includes gentle, clean manipulation of the prolapsed uterus, replacing the organ starting at the cervix. Replacement is easier with early cases. Difficulty increases and prognosis decreases greatly with chronicity.[9]

43.37 UTERINE TUMORS

Neoplasia uncommonly affects the uterus of domestic animals. Tumors may arise from within uterine tissues or metastasize from other organs.[11] Leiomyomas are usually benign and arise from the outer smooth muscle of the uterus without need for a preparatory event. The multicentric form of lymphosarcoma may affect the uterus of cattle. Lymphosarcoma also affects does, but a predilection for the uterus is not apparent. Carcinomas, chorionepitheliomas, fibromas, fibrosarcomas, rhabdomyosarcomas, and adenosarcomas are rarely reported.

Small tumors may escape detection, whereas larger ones may be palpable per rectum in mares and cows. Leiomyomas are not necessarily associated with reproductive failure, and tumors and fetuses can coexist. Uterine walls affected by lymphosarcoma may contain discrete neoplastic nodules or be diffusely infiltrated. Tumor masses must be differentiated from normal fetuses, mummified or macerated fetuses, placentomes, abscesses, and fat necrosis.

Solitary leiomyomas thought to interfere with fertility may be removed. Other forms of uterine neoplasia are usually not treated. The prognosis is generally poor.

43.38 SEGMENTAL DEFECTS

Segmental aplasia (white heifer disease) occurs sporadically in all breeds of cattle. In most cases the cranial parts of the genital tract (ovaries, uterine tubes, and cranial part of the uterine horns) are normal, and endometrial secretions from the parts of the uterine horns accumulate because normal drainage through the cervix is impeded. Various defects may be found in affected animals, ranging from nearly complete absence of tubular genital organs to an imperforate hymen that blocks secretion drainage from a normal genital tract.

43.38.1 Clinical Signs and Diagnosis

Segmental aplasia may be associated with a history of anestrus if fluid accumulation within the uterine horns interferes with release of PGF and luteolysis. Other presenting history may involve infertility or difficulty in AI. On palpation per rectum, various degrees of aplasia may be recognized. Fluid-filled parts of the uterine horns may suggest pregnancy, from which they must be differentiated. An imperforate hymen may bulge from the vulvar cleft and may be confused with vaginal prolapse, prolapse or eversion of the urinary bladder, cystic vestibular glands, or neoplasia of the vulva or vagina.

43.38.2 Treatment and Prognosis

The only form of segmental aplasia amenable to treatment is that in which an imperforate hymen occludes an otherwise normal tract. Incision of the hymen is followed by drainage of accumulated secretions and may allow the tract to function normally.

43.39 PARAMESONEPHRIC DUCT APLASIA

Aplasia of one paramesonephric duct leads to development of one uterine horn (uterus unicornis). The condition is relatively rare but does occur in cattle. Subfertility is the result of prolonged periods of anestrus caused by a persistent CL on the ovary ipsilateral to the missing uterine horn (no local luteolytic signal). The condition can be managed with exogenous PGF in the hope that ovulation will occur on the intact side. Alternatively, the unaccompanied ovary can be surgically removed. 1446 1447

43.40 UTERUS UNICORNIS AND UTERUS DIDELPHIS

The caudal parts of the paramesonephric ducts may not fuse properly in cattle, causing duplication of various parts of the caudal tubular tract. Abnormalities of fusion are most common in and around the cervix. The entire cervix may be duplicated; or the cervix and vagina may be normal, with the exception of the presence of a band of tissue extending dorsal to ventral across the external os of the cervix. Partial failure of fusion may involve a part of the cervix, and the affected animal may possess a single uterine body and internal cervical os, duplication of a part of the cervical canal, and a doubled external cervical os. Uterus didelphis results when the cervix and uterine body are completely duplicated. Affected cows may conceive after natural service or if artificially inseminated through the cervix and uterine horn ipsilateral to the ovary about to ovulate. Affected animals may be unable to carry a pregnancy to term because of lack of placental attachment in the nongravid horn.

43.41 HYDROMETRA (PSEUDOPREGNANCY IN GOATS)

Hydrometra occurs sporadically in goats and is characterized by accumulation of several liters of clear fluid within the uterus, abdominal distention, persistence of a CL, and subsequent anestrus.[5] It is most common in pet and dairy goats that are housed separately from males and therefore experience estrous cycles without the opportunity to conceive. Previous breeding is not necessary, but the condition may develop after mating, and does are frequently assumed to be pregnant. It also can occur after early embryonic loss in goats or sheep. The cause of hydrometra is unknown, but a deficiency in production or release of PGF from the endometrium has been postulated, as has exposure to phytoestrogens. The clinical signs of hydrometra mimic those of pregnancy. The diagnosis is suspected if the goat fails to show estrus when it cannot possibly have been bred but is in a herd where heat detection is good. Serum progesterone concentrations are elevated, and abdominal enlargement suggestive of pregnancy may occur. Results of the urinary estrone sulfate test for pregnancy are negative. Amplitude-depth ultrasound for pregnancy is positive because of fluid in the uterus. Rectal Doppler may indicate increased blood flow to the uterus, but no fetal heart sounds are heard. Real-time ultrasound reveals fluid but no fetus or caruncles in the uterus. The animal should be rechecked if fewer than 40 days have elapsed since the last possible breeding. In advanced hydrometra, large fluid-filled compartments are seen separated by undulating tissue walls, which represent the uterus coiled back on itself. The fluid is cloudy and flocculent if aspirated through the abdominal wall. Spontaneous correction is common and varies from red discharge suggestive of early abortion to expulsion of accumulated fluid approximately 150 days after an infertile mating, so-called

"cloudburst." No fetus or placenta is passed. Treatment of false pregnancy is with prostaglandin. The clinician needs to keep in mind that this will abort the goat if it has a true pregnancy. An initial dose of 5 to 10 mg of dinoprost (Lutalyse) or 125 to 250 mcg of cloprostenol (Estrumate) is given and repeated in 12 days. Estrus and emptying of the uterus occur in 1.5 to 4 days. Oxytocin (50 IU bid for 4 days) will cause CL regression, but treatment with oxytocin is normally reserved for goats that still retain fluid in the uterus after prostaglandin therapy. The doe frequently becomes pregnant within a few days to weeks after termination of a false pregnancy if a buck is available. Sometimes hydrometra recurs. Suggestions for prevention have included selenium supplementation and breeding on the first heat of the season. The prevalence is probably increased in herds where breeding is delayed in order to obtain winter milk and in does manipulated hormonally to breed out of season. Routine pregnancy diagnosis of goats with real-time ultrasound should be advised to permit rebreeding during the same season.

43.42 CERVICAL ABNORMALITY

43.42.1 Cervicitis

Inflammation of the cervix usually accompanies endometritis and vaginitis and is frequently secondary to trauma associated with dystocia and obstetric operations. The mucus-secreting epithelium of the cervix is more resistant to bacterial infection than is the epithelium of the uterus and vagina.

43.42.1.1 MARES

The equine cervix is a straight tube made up of layered circular and longitudinal muscle. During estrus it relaxes, and the external os lies on the floor of the anterior vagina. During diestrus or pregnancy, under the influence of progesterone, the cervix is closed and the external os is elevated off the vaginal floor. Cervicitis or inflammation of the cervix may be iatrogenic or may occur secondary to trauma associated with parturition or dystocia or as an extension of vaginitis or endometritis. Endometritis and infertility follow if the cervix lacks anatomic integrity.

43.42.1.1.1 Clinical Signs and Diagnosis

Infertility and history of an inciting cause such as urine pooling or dystocia may be the only signs of cervicitis in the mare. Cervical hyperemia and edema may be apparent on speculum examination in acute cervicitis. In more chronic injuries, direct digital examination of the cervix of the mare in diestrus may reveal transluminal adhesions or anatomic defects.

For treatment and prognosis in mares, see discussion under Ruminants later in this section.

43.42.1.2 RUMINANTS

Similarly, in cows cervicitis is secondary to uterine infections and follows trauma associated with parturition and obstetric manipulations. Infection is usually caused by microorganisms normally present in the cranial vagina such as *E. coli*, streptococci, staphylococci, and *A. pyogenes*., Occasionally infection with anaerobic bacteria complicates cervicitis and results in severe toxemia.[102,199]

Cervicitis in does and ewes is uncommon but may occur secondary to vaginal and uterine infections and obstetric trauma.

43.42.1.2.1 Clinical Signs and Diagnosis

Examination of cows with a vaginal speculum reveals swelling and edema of the external cervical os. The mucous membrane is hyperemic and inflamed. Mucopurulent exudate may be present in the cervical canal or in the cranial vagina. Hypertrophy of the cervix is common in *Bos indicus*, breeds and their crosses and may be a normal finding; therefore cervical size as detected by palpation per rectum may or may not indicate inflammation. Inflammation of the cervix without contemporary endometritis may not affect fertility. Cervicitis may occur in pregnant cows.

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The clinical signs of cervicitis in does and ewes are similar to those in cattle and must be observed with a small vaginal speculum.

43.42.1.2.2 Treatment and Prognosis

Most cases of cervicitis resolve spontaneously when coexisting endometritis and vaginitis improve. Exudate can be flushed from the cervical canal and cranial vagina with warm saline lavages, and a nonirritating antibiotic ointment applied to the affected tissue. Caustic chemicals should not be placed in contact with the cervical mucosa. Aggressive treatment with systemic antibiotics is indicated in cases complicated by infection with anaerobic bacteria.

The prognosis for most cases of simple cervicitis is fair to good. However, inflammation of the cervix in mares may progress to more severe cervical abnormalities. Cervical damage is a serious threat to future reproductive performance in mares. Anaerobic infections of the cervix may be fatal.

43.42.1.2.3 Prevention and Control

Obstetric manipulations and operations must be temperate. When the cervix does not properly dilate during parturition, a cesarean section is preferred over forced extraction.

43.43 CERVICAL LACERATIONS

43.43.1 MARES

Cervical lacerations are most often seen after dystocia. Cervical lacerations may result in adhesions and a nonpatent cervix or in a failure to seal the uterus during diestrus or pregnancy. Cervical adhesions in combination with endometritis are a common cause of pyometra in the mare.

43.43.1.1 Clinical Signs and Diagnosis

Cervical lacerations can be diagnosed by vaginoscopy and digital examination of the cervix. A digital examination of the cervix is often necessary to evaluate the degree and severity of the laceration. Evaluation of the ability of the cervix to close adequately is best performed during diestrus.

43.43.1.2 Treatment and Prognosis

If cervical lacerations are diagnosed shortly after parturition, antimicrobial ointment should be applied frequently to the lesion. Early signs of adhesions should be broken down until the tissue is healed. If the laceration results in an incompetent cervix, it should be corrected surgically. Although surgical repair of cervical lacerations has resulted in restored fertility in many mares, the condition is likely to recur at the time of the next parturition. Embryo transfer should be considered if allowed by the breed registry.

43.44 VAGINAL ABNORMALITIES

43.44.1 Pneumovagina

43.44.1.1 MARES

Pneumovagina is characterized by aspiration of air containing feces and microorganisms into the vagina. Pneumovagina is secondary to changes in perineal conformation, which include cranioventral displacement of the reproductive tract, loss of integrity of the vestibulovaginal sphincter, and loss of integrity of the vulvar labia. These changes occur more commonly in older, multiparous mares and those that have had perineal lacerations. Pneumovagina is a common antecedent to infertility.

43.44.1.1.1 Clinical Signs and Diagnosis

In the normal mare the anus is positioned directly dorsal to the vulva; the perineal body between the dorsal vulva and the anus is thick, muscular, and well formed; the vestibulovaginal sphincter is well formed; the vulva has a vertical alignment; 80% of the vulval labia lies below the floor of the pelvis; and the vulvar labia form a seal. Mares in which the vulva tilts horizontally at its dorsal aspect, the perineal body is thin, and the vulval labia do not form a seal are prone to pneumovagina in cases in which the anus lies rostral to the vulva. A scoring system has been developed to evaluate the perineal conformation in mares.[124] The system uses Caslick's index, which equals the distance (cm) between the dorsal commissure and the pelvic floor multiplied by the degrees of declination of the vulvar lips. Mares with Caslick's index above 150 were found to have subnormal pregnancy rates. Affected mares aspirate air on exercise or when the vulval labia are parted. Aspirated air may be noted on transrectal palpation or vaginal speculum examination. Signs of secondary changes such as vaginitis, cervicitis, or endometritis may be apparent.

43.44.1.1.2 Treatment and Prognosis

Treatment of pneumovagina should be directed toward correcting defective perineal conformation. Cranioventral displacement of the reproductive tract in aged mares may be irreversible. Perineal confirmation in thin mares is often improved by increasing the mare's body condition. Pneumovagina is often successfully corrected by surgical closure of the dorsal vagina via Caslick's operation. Secondary changes should be treated as described elsewhere. Prognosis for correction of pneumovagina is excellent; however, prognosis for fertility depends on the extent of secondary changes.

43.44.2 Urovagina

43.44.2.1 MARES

In normal, young mares the vagina slopes craniodorsally and is largely contained within the pelvis. With aging and repeated pregnancy, the cranial vagina may slope cranioventrally and fall below the level of the pelvic floor. Under these conditions urine collects in the anterior vagina, where it is spermicidal and may predispose to cervicitis and endometritis.

43.44.2.1.1 Clinical Signs and Diagnosis

In mild cases a history of infertility may be the only indicator of urovagina. In more severe cases, urine dribbles from the vulva at rest or during exercise and may accumulate inside the hind limbs. Speculum examination reveals a cranioventral slope of the vagina, variable inflammation of the cranial vagina and cervix, and a pool of urine in the ventral vaginal fornix. Urovagina may occur intermittently or only during estrus.

43.44.2.1.2 Treatment and Prognosis

Surgical procedures to prevent the anterior flow of urine include urethral extension[200] and vaginoplasty.[201] Prognosis depends on the severity of secondary endometritis and the success of surgery.

43.44.2.2 Vaginitis

Vaginitis may occur as a result of ascending infection or exposure to irritants, or secondary to pneumovagina, urovagina, perineal laceration, rectovaginal fistulas, breeding, endometritis, abortion, parturition, or dystocia. Occasionally, traumatic wounds may be infected with clostridial or anaerobic organisms; however, most infection is nonspecific.

43.44.2.2.1 Clinical Signs and Diagnosis

Signs may vary from hyperemia evident on speculum examination to mucopurulent exudation from the vulva. Severe trauma and infection may be followed by necrotic vaginitis with tenesmus, fetid discharge, elevated tail, swollen vulva, and systemic signs. Rapid formation of adhesions follows necrotic vaginitis. Metritis, RFMs, and uterine tears also may show systemic signs and vaginal discharge.

43.44.2.2.2 Treatment and Prognosis

The inciting cause should be treated. Animals with mild vaginitis may recover spontaneously, whereas moderate cases require local lavage with dilute antiseptic or antibiotic solutions. Fertility is unaffected in mild vaginitis without extension, and prognosis is good. Severe, necrotic vaginitis is treated with systemic antibiotics, analgesics, and antiinflammatory agents. Caslick's surgery may be necessary to prevent aspiration of air. Local application of antibiotic and steroid-impregnated ointments may help prevent adhesions. Prognosis for severe vaginitis is guarded. Vaginal stenosis and adhesions may follow vaginitis.

43.44.2.2.3 Prevention and Control

Nonspecific vaginitis may be prevented by preventing or reducing trauma to the vagina. Clinicians should elect appropriate methods for relief of dystocia and apply extractive force to fetuses judiciously.

43.44.2.3 Infectious Pustular Vulvovaginitis

43.44.2.3.1 COWS

Infectious pustular vulvovaginitis (IPV) affects cattle and is caused by bovine herpesvirus 1, also the cause of infectious bovine rhinotracheitis (IBR),[202] although the two strains are genetically distinct.[203] Therefore the respiratory and genital forms of the disease rarely occur concurrently, and abortions usually do not follow an outbreak of the genital form of the disease. IPV is spread by coitus and mechanical means and may affect unbred heifers. The incubation period of IPV is short (1 to 3 days), and the infection spreads rapidly through the herd, affecting 60% to 90% of the animals. IPV is not common.

43.44.2.3.1.1 Clinical Signs and Diagnosis

Early in the course of the disease IPV is characterized by a mucopurulent vaginal discharge, inflammation of the vaginal and vulvar mucosa, and painful urination. Pustules develop over lymphoid follicles and progress from small (<3 mm) ulcers to coalescing erosions. The virus causes inflammation of the penis and prepuce (balanoposthitis) leading to considerable pain. Therefore animals of both sexes with IPV are reluctant to mate. The clinical signs subside in 10 to 30 days, leaving the recovered animals with transient immunity. Early in the course of IPV, lesions may be similar to those of granular vulvitis (see later section), but the lesions of IPV rapidly become more severe. Vulvovaginitis caused by *Haemophilus somnus*, should be a differential diagnosis.

43.44.2.3.1.2 Treatment and Prognosis

Treatment of IPV is usually not required, although lavage of the vagina with dilute antiseptic solutions and emollients has been recommended. Mating among infected animals should be suspended until the disease subsides. The prognosis for recovery is excellent.

43.44.2.3.1.3 Prevention and Control

Vaccination against IBR is not likely to be beneficial in the face of an outbreak, but cattle may be protected if they are vaccinated before exposure. The IPV virus may survive in cryopreserved semen used for AI; therefore semen donors and semen should be free of the virus. Genital carriers may be responsible for sporadic outbreaks of IPV.

43.44.2.4 Vaginal Varicose Veins

43.44.2.4.1 MARES

Vaginal varicose veins are common in older mares. In most cases the condition is not associated with clinical signs, but affected mares may exhibit vaginal hemorrhage. A thorough examination of the reproductive tract is necessary to determine the origin of the bleeding.

43.44.2.4.1.1 Clinical Signs and Diagnosis

Clinical signs of varicose veins vary from no signs to persistent and profuse vaginal hemorrhage. Vaginoscopy or fiber endoscopy of the vagina reveals varicose veins in the vagina or the vestibulovaginal transverse fold. Vaginal hemorrhage from varicose veins should be differentiated from vaginal trauma and premature separation of the placenta in periparturient mares.

43.44.2.4.1.2 Treatment and Prognosis

Most mares with vaginal varicose veins do not require treatment. Surgical ligation, treatment with phenylephrine HCl cream,[204] or laser surgery of the veins may be necessary in cases of severe bleeding. The short-term prognosis after surgery is good, but the condition often recurs.

43.44.3 VESTIBULAR AND VULVAR ABNORMALITIES

43.44.3.1 Coital Exanthema

43.44.3.1.1 MARES

Coital exanthema is caused by equine herpesvirus 3 (EHV-3) and is a venereally transmitted dermatitis of the genital region of mares and stallions.[205,206]

43.44.3.1.1.1 Clinical Signs and Diagnosis

The disease is recurrent, is usually mild and transient, and affects the vulva and perineum of mares and the penis and prepuce of stallions. Lesions are initially small papules that rapidly progress to pustules and then ulcers. Lesions may rarely appear on the conjunctiva, lips, nares, and mucosa of the upper respiratory tract. Rare secondary bacterial infection and systemic signs occur. Intranuclear inclusion bodies are apparent in epithelial cells on histologic sections taken from the active edge of ulcers. Coital exanthema does not affect fertility in mares, but libido may be decreased in affected stallions because of pain during coitus.

43.44.3.1.1.2 Treatment and Prognosis

Lesions usually heal spontaneously within 14 days, leaving depigmented spots. Treatment is unnecessary unless secondary bacterial infection occurs. There is no available vaccine for EHV-3. Sexual rest until the lesions are healed is recommended to prevent further spread of the disease. Prognosis is excellent.

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43.44.3.2 Granular Vulvitis

43.44.3.2.1 COWS

Granular vulvitis may occur in females of all domestic species but is most significant in cattle.[11] The disease is characterized by development of granules or papules in the vulvar mucosa accompanied by genital discharge. Infertility may or may not be a feature of the syndrome. Vulvitis may be secondary to nonspecific vaginitis.[102] *H. somnus*,[207] and *Mycoplasma bovigenitalium*,[5] have been isolated from cattle with vulvitis, but their role in infertility is not well defined, and there may be differences in pathogenicity among strains of the organisms. *Ureaplasma diversum*, has been isolated from cases of granular vulvitis in cows and ewes and may be associated with infertility when the organism is transferred into the uterus during AI.[5]

43.44.3.2.1.1 Clinical Signs and Diagnosis

Granular vulvitis is characterized by the formation of raised granules or papules in the vulvar mucosa and around the clitoris with variable amounts of mucopurulent exudate. In the mild form of granular vulvitis associated with *U. diversum*, only a few granules develop, and the infection has minimal effect on fertility. However, acute severe cases are characterized by hyperemia of the vulva, a profuse mucopurulent discharge, and depressed fertility. Purulent discharge during the acute phase persists for 3 to 10 days, after which the disease becomes chronic. In chronic cases the lesions are reduced in severity, and there is little or no purulent discharge. The chronic form may persist for several months, and the disease may become enzootic in some herds. The clinical signs of granular vulvitis may be similar to early signs of IPV.

43.44.3.2.1.2 Clinical Pathology

Samples for microbiologic culture should be obtained from the vulva, cervicovaginal mucus, and uterus. Use of a transport medium for submission of samples to a laboratory is mandatory. The organisms may be eliminated before the samples are obtained, yielding false-negative results. Conversely, microorganisms incriminated as causing granular vulvitis may be isolated from the genital tracts of normal animals.

43.44.3.2.1.3 Treatment and Prognosis

Most cases of nonspecific vulvitis resolve spontaneously. Infertility associated with *U. diversum*, infections is treated by preventing transfer of organisms to the uterus by using double-sheathed AI

instruments. Natural breeding should be suspended. In addition, infusion of 1 g of tetracycline or spectinomycin in a nonirritating vehicle into the uterus 24 hours after breeding has been recommended to reduce the population of organisms that may have been transferred to the uterus. Local treatment of vulvar lesions with tetracycline or spectinomycin has also been suggested.

43.44.3.2.1.4 Prevention and Control

In chronically infected herds, fertility rates may approach normal if double-sheathed AI instruments are used and affected cows are treated with appropriate antibiotics.

43.44.3.3 Ulcerative Dermatosis Genital Lesions

43.44.3.3.1 SMALL RUMINANTS

Ulcerative dermatosis is a venereal disease of sheep caused by a parapoxvirus similar to but distinct from the virus that causes contagious ecthyma.[7,102] The disease is characterized by ulceration of the skin and mucous membranes of the vulva of ewes and penis and prepuce of rams. Lesions also occur on the lips, nares, feet, and legs. The lesions are painful, and affected animals avoid coitus. The disease subsides in 7 to 10 days.

Because of its viral cause, no specific treatment is available for ulcerative dermatosis.[7] Symptomatic treatment with local astringent and antiseptic ointments has been suggested. Morbidity of 15% to 20% is expected, although up to 60% of a flock may be affected. Mortality is low if the animals are otherwise healthy.

No vaccine is available. Males with the disease should not be used for breeding.

43.44.3.4 Abnormal Labial Approximation

43.44.3.4.1 MARES AND COWS

The most common anatomic defect of the vulva of mares and cows is abnormal labial approximation, which leads to pneumovagina and subsequently to infertility.[44] The defect may be the result of imperfect conformation or traumatic insult to the vulva. Abnormal labial approximation is treated with Caslick's surgery or one of its modifications.

43.44.3.5 Persistent Hymen

In the developing embryo, failure of cannulation of the urogenital sinus by the mesonephric duct system results in absolute or partial occlusion of the vestibulovaginal junction. Total occlusion causes accumulation of endometrial and cervical secretions cranial to the obstruction, and occasionally the membrane may appear at the vulva. Partial occlusion may be noted only as an obstruction to breeding or during speculum examination. The membrane may be manually ruptured or incised. Prognosis is excellent.

43.44.3.6 Clitoral Hypertrophy

Clitoral hypertrophy may be a feature of intersex conditions, may occur in filly foals whose dams received progestins during pregnancy, or may follow administration of anabolic steroids.[64] Hypertrophy may persist after cessation of steroid treatment. In cows it may be associated with freemartinism.

Vulvar wattles in cattle may superficially appear similar, but the elongated epithelial structure does not involve the clitoris.

43.44.3.7 Neoplasia

Melanomas and squamous cell carcinomas (SCCs) are the most common neoplasms affecting the perineum, anus, and vulva of gray- and light-skinned horses, respectively.[208] Lesions are usually proliferative and may have surface ulceration, hemorrhage, and infection. Lesions should be differentiated from habronemiasis, granulation tissue, and sarcoids. Treatment is surgical removal. Sarcomas and melanomas may metastasize. Viral fibropapillomas are the most common tumors affecting the vulva of cattle.[11] SCCs may be seen in all species and may be more common in white-skinned animals exposed to long periods of solar radiation.[209]

Vulvar neoplasia is characterized by variable degrees of tissue proliferation. The surface of SCCs and fibropapillomas may be ulcerated, necrotic, and fly-blown. In cows squamous metaplasia of the nonpigmented skin of the vulva is frequently a precursor of squamous cell carcinoma of the vulva. Vulvar neoplasia must be differentiated from other causes of tissue proliferation, habronemiasis in mares, and ectopic mammary tissue in does.[5] Neoplasia of the vulva and vestibule is diagnosed by biopsy of the tumor.

Surgical excision is the treatment for most neoplasms of the vulva.[208] Viral fibropapillomas regress spontaneously after a period of several months. Recurrence and metastasis may occur.

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43.44.3.8 Ectopic Mammary Tissue

Ectopic mammary tissue has been described in does and is characterized by swelling of the vulvar lips.[5] The abnormal enlargement begins before each parturition and persists for approximately 2 months. The condition is benign unless the tissue enlarges sufficiently to interfere with evacuation of feces or urine. Milk may be aspirated from the mammary tissue, and the condition may be confirmed by biopsy.

43.45 ABORTION

43.45.1 MARES

Information on the major causes of abortion in horses is summarized in Table 43-7.

43.45.1.1 NON-NONINFECTIOUS CAUSES

43.45.1.1.1 Twin Pregnancy

The incidence of abortion caused by twin pregnancy has decreased greatly because of widespread use of ultrasound in diagnosing early pregnancy in mares. Twin pregnancies are routinely detected as early as 12 to 14 days, at which time the twins can be manually reduced to a singleton pregnancy (discussed later). However, despite the overall decrease in the number of twin-related abortions, twinning still remains an important noninfectious cause of abortion in the mare.[210] The mare is unable to successfully support two fetuses to term and only in very rare cases (<2%) is able to carry both fetuses to term and deliver without dystocia.[211] It is much more common for the mare to have a natural reduction to a singleton pregnancy during the embryonic stage or to abort the pregnancy after the fetal stage.[212,213] Some breeds more commonly than others are diagnosed with twins during the embryonic stage (e.g., thoroughbreds have 20% to 30% double ovulations and 10% to 15% diagnosed twin pregnancies).

43.45.1.1.1.1 Clinical Signs and Diagnosis

Mares should be evaluated with transrectal ultrasound 12 to 14 days after documented ovulation during a breeding cycle. The uterus should be carefully scanned from the tip of one horn to the other and along the uterine body to the cervix. Equine embryos at this stage are highly mobile within the uterus and may be located anywhere within the uterus. Increased uterine edema and fluid within the uterine lumen are often negative signs of pregnancy, but pregnancy should not be ruled out until the entire uterine tract has been scanned for the presence of embryos. After one embryo is found, the remainder of the uterus still must be visualized to ensure the absence of a twin. The embryo proper per se is not visible at this stage of pregnancy, but the embryonic vesicle is easily visualized. Care must be taken not to confuse endometrial cysts with embryos, which sometimes can look deceptively similar. It is very helpful to have scanned the mare's uterus with ultrasound before breeding to document the size and location of endometrial cysts.

Table 43-7 Major Causes of Infectious Equine Abortion

Cause and Common Names	Usual Stage of Gestation	Major Fetal Lesions	Diagnostic Tests
Equine herpesvirus 1 (EHV-1)	Seventh month to term	Pulmonary edema, multifocal hepatic and pulmonary necrosis, intranuclear inclusions	Histopathology, virus isolation, fluorescent antibody test, fetal serology
Equine viral arteritis (pestivirus)	5–10 months	Myocardial arteritis	Histopathology, virus isolation, PCR, serology
Nocardioform actinomycete	Mid to late gestation	Characteristic placentitis located ventrally in the uterine body and at the base of the uterine horns	Culture
Streptococcus zooepidemicus,	Any stage	Placentitis with or without inflammation in fetal tissues	Histopathology, culture
Mycotic abortion, *Aspergillus*, and other species	Latter half (often near term)	Placentitis, fetal bronchopneumonia	Histopathology, fungal culture
Leptospirosis	Seventh month to term	Icterus and autolysis	Culture, immunofluorescence, serology

PCR, Polymerase chain reaction.

43.45.1.1.1.2

Treatment and Prognosis

If twins are confirmed before 16 days of pregnancy, the best way to treat the mare is to manually crush one of the vesicles. This is done by visualization of the twins using transrectal ultrasound and spatially separating them from each other within the uterus. One twin is moved away from the other to the tip of a uterine horn where it is crushed manually. The remaining embryo should be evaluated 1 to 2 days later to determine its status. Survival of the remaining embryo is greater than 90% when twin reduction is performed in this manner before day 20.[214]

It is the established practice of some veterinarians to treat mares with a nonsteroidal antiinflammatory agent (e.g., flunixin) and/or altrenogest after a twin-crush procedure. The reasoning behind this practice is that manual stimulation of the uterus may cause a release of oxytocin, signaling a prostaglandin cascade that will result in luteolysis and complete pregnancy loss. There have been no studies performed to support this theory; to the contrary, other studies have shown that the release of prostaglandin after the routine twin-crush procedure does not cause a drop in progesterone and that supplementation with antiinflammatory drugs or progesterone makes no difference in the outcome.[214,215]

Other techniques described for reduction of twins to a single embryo include transvaginal, ultrasound-guided fetal aspiration[216]; transcutaneous, ultrasound-guided fetal intracardiac injection of procaine penicillin or potassium chloride[217]; and craniocervical dislocation.[218] The success of these techniques is lower than that of manual crush, and they are performed later in gestation, after the window for manual crushing has been missed. These are all specialty techniques and are beyond the scope of this chapter. 1451 1452

43.45.1.1.2

Other Noninfectious Causes of Equine Abortion

In a survey of causes of equine abortion in the United Kingdom from 1988 to 1997, nearly 39% were caused by umbilical cord pathology.[219] Most of the cases (35%) resulted from torsion of the umbilical cord. Twisting of the umbilical cord is common in equine fetuses and often is not pathologic. A diagnosis of abortion caused by umbilical torsion should be made only if localized swelling and discoloration accompany the twisting. Congenital abnormalities may cause abortion. The most common congenital abnormality in equine fetuses is contracted tendons, accounting for 5% of abortions in a study from the United States.[210] Fetuses that implant in the uterine body instead of the base of one of the horns develop placental villous atrophy and usually abort, accounting for 2% of abortions in the same study.

43.45.1.2

INFECTIOUS CAUSES

43.45.1.2.1

Placentitis

Placentitis is the leading cause of equine late-term pregnancy loss in the United States.[210] Bacterial organisms most commonly cultured from aborted fetuses include *Streptococcus*, species, *E. coli, Pseudomonas*, species, *Klebsiella*, species, *Staphylococcus*, species, and *Leptospira*, species. Nocardioform actinomycetes are an important cause of placentitis in central Kentucky and have recently been reported in Florida.[220] The route of infection and the pathophysiology of *Nocardia*, abortions are poorly understood. *Aspergillus fumigatus*, and *Mucor*, species are the most commonly diagnosed causes of mycotic abortion in mares. Fungi cause 5% to 30% of infectious equine abortions.[5]

The route of placental infection is most commonly ascending via the cervix, which results in loss of chorionic villi around the cervical star. In addition to loss of chorionic villi, additional allantochorionic lesions may include nodular cystic allantoic masses, edema, necrotic areas of chorion, and necrotic mucoid exudate coating the chorion. Hematogenous placentitis shows a more generalized, diffuse loss of villi.[210] The distribution of the avillous chorionic lesion classically noted in mares with ascending or hematogenous placentitis does not fit the pattern noted with nocardioform placentitis. Mares with nocardioform placentitis classically show a loss of chorionic microvilli in a focal area around the base of the uterine horns. It has been postulated that the pathogen is present or introduced in the mare at the time of breeding and settles in the ventral aspect of the uterus, where it causes the infection. This hypothesis is not proven, though it is very likely that the nocardioform organisms are from the environment. Various nocardioform organisms have been reported in the soil in countries across the globe, although the pathogenicity of most of these organisms is not determined. The pathogenesis of nocardioform placentitis is still unresolved. Nocardioform organisms isolated from equine placentas include *Amycolatopsis*, species and *Crossiella equi*.,[220–223] Nocardioform placentitis often results in abortion or premature delivery.[210]

43.45.1.2.1.1

Clinical Signs and Diagnosis

Mares that abort because of placentitis often show clinical signs of pending abortion before the actual pregnancy termination. Premature udder development and vaginal discharge are common signs of pending abortion caused by placentitis. Transrectal ultrasonography of the allantochorion in an area close to the cervix is useful to detect early signs of placentitis and impending abortion (Fig. 43-8).[224] Ultrasound evaluations may reveal hyperechoic fetal fluids, placental separation, increased or decreased fetal heart rates (normal range 75 ± 7 bpm[225]), and thickening of the combined thickness of the uterus and placenta (CTUP). Consistently low or high fetal heart rates are associated with fetal stress. Foals experiencing fetal distress often become bradycardic initially and then become tachycardic in the terminal phase of life.[226,227] Serial examinations should be performed to verify fetal well-being or distress. Mares considered "at risk" for pregnancy loss are often examined on a daily basis. Fetuses experiencing distress are often evaluated several times a day. Normal measurements of CTUP have been established (Fig. 43-9).[228,229] Mares with placentitis may show increased CTUP, edema of the allantochorion, and separation from the endometrium. A 5-MHz linear transducer should be used for transrectal ultrasonography. The transducer should be positioned 1 to 2 inches cranial to the cervical-placental junction and then moved laterally until a major uterine vessel (possibly the middle branch of the uterine artery) is visible at the ventral aspect of the uterine body.[228] The CTUP should then be measured between the vessel and the allantoic fluid (see Fig. 43-5). It is important to obtain all CTUP measurements from the ventral aspect of the uterine body, because physiologic edema of the dorsal aspect of the allantochorion has been noted in normal pregnant mares during the last month of gestation. 1452 [228] In addition, care should be exercised to be certain that the amniotic membrane is not adjacent to the 1453 allantochorion, because this may result in a falsely increased CTUP. To examine the placenta from a transabdominal approach, a 3.5-MHz sector transducer is used most frequently. A 5-MHz linear transducer can be used for transabdominal evaluation; however, depth penetration can limit evaluation of the areas such as the placenta. All four quadrants of the placenta should be examined; right cranial, right caudal, left cranial, and left caudal. Measurements of the CTUP can be made with this technique if the fetus is not in close apposition with the uterine wall. Mares with normal pregnancies should have a minimum combined thickness of the uterus and the placenta (CTUP) of 7.1 ± 1.6 mm, and a maximal CTUP of 11.5 ± 2.4 mm.[230] Pregnancies with an increased CTUP have been associated with the delivery of abnormal foals.[230]

Fig. 43-8 Transrectal imaging of the combined thickness of the uterus and the placenta (CTUP). Measurements of the CTUP (distance between + and +) were recorded from the ventral part of the uterine body, close to the cervix. *a*, Placenta adjacent to the cervix; *b*, allantoic fluid; *c*, amniotic fluid; *d*, the amnion. Modified from Renaudin CD, Troedsson MH, Gillis CL, et al: Ultrasonographic evaluation of the equine placenta by transrectal and transabdominal approach in the normal pregnant mare, *Theriogenology*, 47:559, 1997.

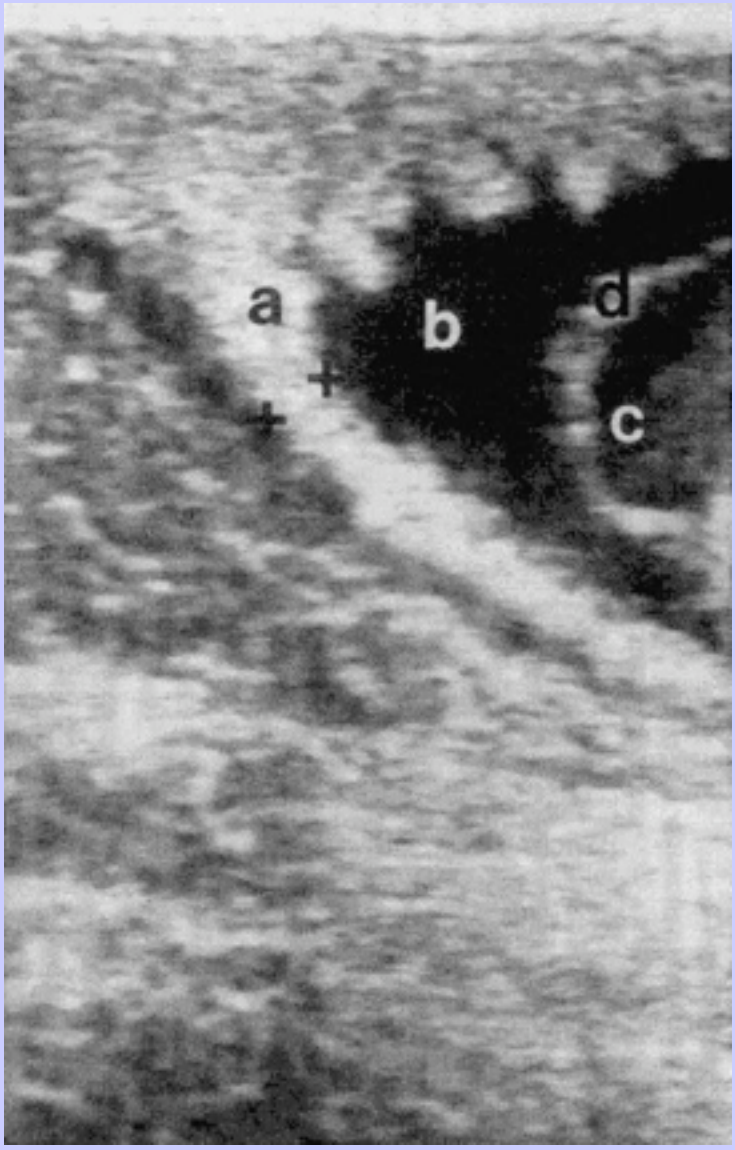
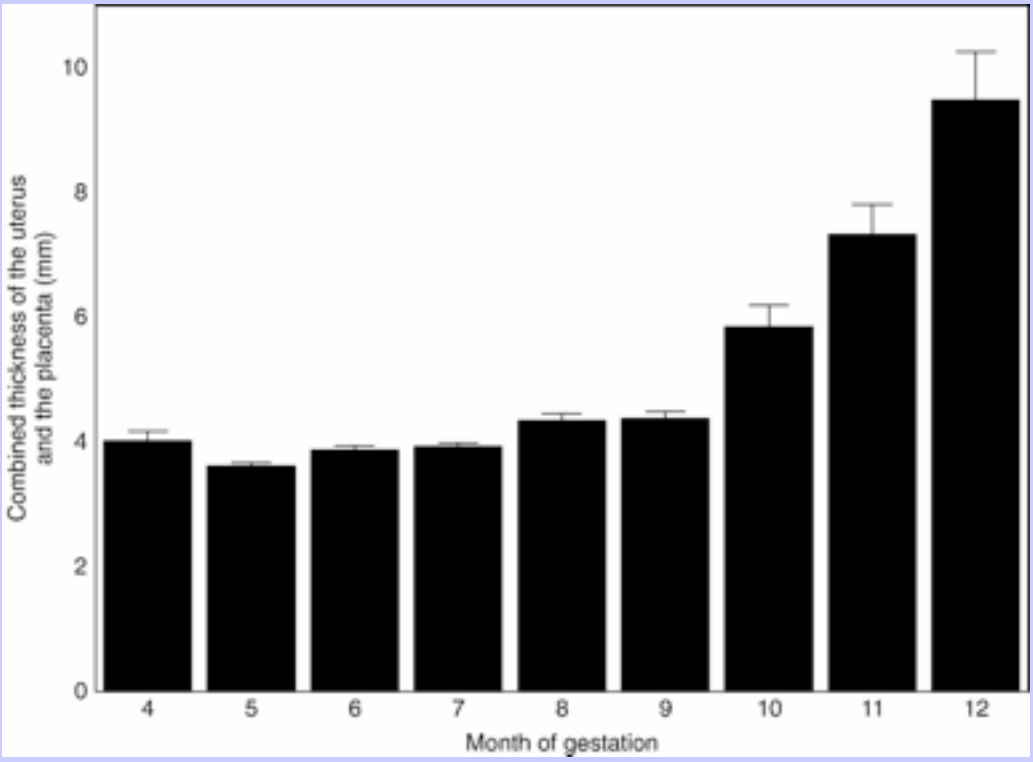


Fig. 43-9 Monthly recordings of transrectal ultrasonographic measurements of the combined thickness of the uterus and the placenta (CTUP) in normal mares from 4 months of gestation and throughout the pregnancy. Month 4 is 91 to 120 days; month 5 is 121 to 150 days; month 6 is 151 to 180 days; month 7 is 181 to 210 days; month 8 is 211 to 240 days; month 9 is 241 to 270 days; month 10 is 271 to 300 days; month 11 is 301 to 330 days; month 12 is 331 to 360 days. Modified from Renaudin CD, Troedsson MH, Gillis CL, et al: Ultrasonographic evaluation of the equine placenta by transrectal and transabdominal approach in the normal pregnant mare, *Theriogenology*, 47:559, 1997.

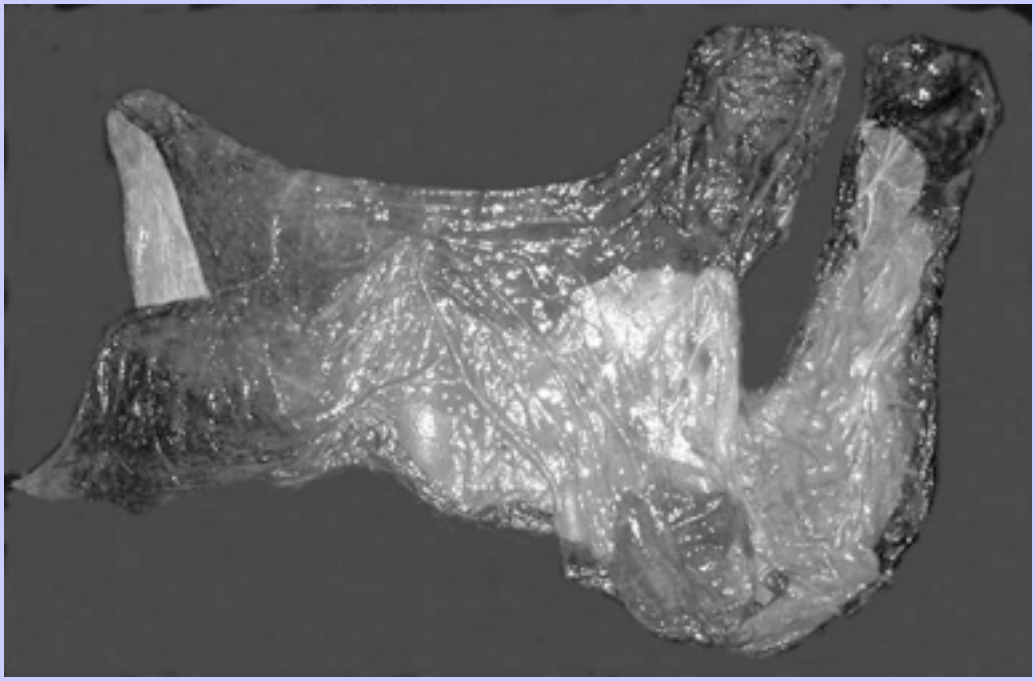


The gross lesions of the fetus are not specific. An increased amount of fluid in the thoracic and abdominal cavities and an enlarged liver are frequently observed in aborted fetuses. Placental lesions are most severe on the chorionic surface at an area from opposite the cervix ("cervical star") to the body of the placenta. The affected area is edematous, thickened, and discolored or brown with a mucoid or fibronecrotic exudate on the surface. The placenta is characteristically thickened and leathery in cases of

mycotic placentitis, with lesions well demarcated from the rest of the chorionic surface. Microorganisms can be isolated from the placenta and several fetal organs, most consistently from the stomach.

Animals with nocardioform placentitis may have premature mammary development but will not have vulvar discharge, owing to the location of the infection. Placental lesions in mares infected with nocardioform actinomycetes are located ventrally in the uterine body and at the base of the uterine horns (Fig. 43-10). Affected areas are avillous, thickened, and covered by thick brown or reddish exudate. Because of the location of the lesions away from the cervical star, transabdominal ultrasonography is needed to diagnose the condition in pregnant mares. Differential diagnoses for this clinical presentation include twins and *Cellulosimicrobium cellulans*, placentitis.[221]

Fig. 43-10 Placenta from a mare with nocardioform placentitis. The characteristic lesions are located ventrally in the uterine body and base of the uterine horns.



Prevalence of fungal abortions varies greatly with region. The most common route of fungal infection is ascending via the cervix, and fungal infections may be seen with a mixed bacterial infection. Abortions are observed from mid to late gestation. Usually no clinical signs in the mare precede the abortion. The chorion generally shows marked evidence of placentitis with edema, thick plaques, and a thick, mucoid exudate. In rare cases, amniotic thickening may be noted. The aborted fetus is often small and emaciated owing to chronic placental insufficiency. Culture of the chorion may be diagnostic but takes time. Culture of the fetus is rarely rewarding. Impression smears of the chorion, and sometimes the fetal stomach, may reveal hyphae.

The equine placenta is part of an endocrine fetal-placental interaction that synthesizes and metabolizes progestagens.[231] This endocrine function of the placenta is important for maintenance of pregnancy

after the endometrial cups and the secondary corpora lutea disappear at approximately day 120 to 150 of gestation. Fetal-placental progesterone is rapidly metabolized to 5α-pregnanes. Mares with placental pathology may have increased plasma concentrations of progestagens as a result of stress to the fetal placental unit.[232,233] Unfortunately, 5α-pregnanes are not readily assayed in a commercial setting, so diagnosis of placental disease using 5α-pregnane concentrations is not possible. There is cross-reactivity between 5α-pregnanes and progesterone using some commercial radioimmunoassays for progesterone. In recent studies[233,234] using an experimental model to induce placentitis, it was found that mares that develop a chronic form of placentitis responded with increased plasma progesterone concentrations. Conversely, mares that developed acute placentitis and abortion soon after infection experienced a rapid drop in plasma progesterone concentrations. It was suggested that measurement of repeated samples of plasma progestin concentrations in mares with placentitis might be a useful method to identify mares that may abort or deliver prematurely.[233] Furthermore, sensitivity of progesterone assays can be improved when they are combined with evidence of placental thickening as detected using transrectal ultrasonography.[234]

43.45.1.2.1.1.1

RELAXIN

Relaxin is produced by the equine placenta and can be detected in peripheral blood plasma from day 80 of gestation and throughout the pregnancy. The role of relaxin during pregnancy is not fully understood, but there is some evidence that placental relaxin production is compromised in mares at risk of aborting their fetuses.[235] There is currently not a commercial test available for equine relaxin.

43.45.1.2.1.2

Treatment and Prognosis

Treatment efforts should be directed at combating infection, reducing inflammation, and controlling myometrial activity. Pregnant mares with clinical signs of placentitis should be treated with systemic broad-spectrum antimicrobials and antiinflammatories. Recent studies have demonstrated that commonly used antibiotics such as penicillin G (22,000 IU/kg q6h), gentamicin (6.6 mg/kg q24h), and trimethoprim-sulfadiazine (30 mg/kg bid) cross the placenta and reach therapeutic concentrations in both placental tissues and the allantoic fluid.[236] Flunixin meglumine (1 mg/kg q12h) and pentoxifylline (8.5 mg/kg bid) have been used to control proinflammatory cytokines associated with placentitis. Treatment with progestins has long been advocated to promote uterine quiescence in mares with uterine pathology. Presumably the antiprostaglandin effect of progestins contributes to reduced myometrial activity by interfering with upregulation of prostaglandin and oxytocin receptors.[237] Without receptor formation, gap junction formation would be inhibited and uterine contractility prevented. Altrenogest at twice the recommended dose (0.088 mg/kg PO q24h) is commonly used.

Work from a large scale clinical trial examined the efficacy of multipronged, long-term therapy for equine placentitis.[238] Investigators examined records of 477 mares over 6 years. Fifteen mares were diagnosed with placentitis. Criteria for treatment included increased thickness of the uteroplacental unit using transrectal ultrasound, placental separation, and/or vulvar discharge and udder development. The average gestational age at diagnosis was 8.6 months. Mares were treated with a combination of systemic antibiotics (trimethoprim-sulfa, ceftiofur, or penicillin and gentimicin), pentoxifylline, altrenogest, and nonsteroidal antiinflammatory agents. Mares were treated until abortion or delivery of a foal. Twelve of 15 treated mares (80%) carried their foals to term, and 11 of 15 (73%) delivered live foals. Birthweights of surviving foals from mares treated for placentitis were similar to those of foals from nonaffected

mares. The benefit of this treatment strategy is supported by recent data from a controlled study on experimentally induced placentitis.[238] Data from these studies suggest that long-term antibiotic, antiinflammatory, and progestin treatment may positively affect pregnancy outcome in mares with placentitis.

Although most mares are capable of conceiving and successfully carrying a foal to term in subsequent breedings, reproductive performance may be negatively affected after ascending and hematogenous placentitis. Treatments for endometritis, such as uterine lavage and intrauterine infusions of appropriate antibiotics, should also be implemented after abortion. Most mares affected by nocardioform placentitis do not require subsequent treatment and show no signs of infertility the following breeding season.

43.45.1.2.2

Equine Herpesvirus 1 Abortion

The most prevalent viral cause of equine pregnancy loss is EHV-1, which causes abortion, paresis, and neonatal foal death. EHV-4 causes abortion in rare cases. The primary route of transmission of EHV-I is via the respiratory tract. The virus invades the respiratory epithelium and establishes a leukocyte-associated viremia. EHV-1 establishes a chronic, possibly lifelong, latent infection. During the initial infection, placental endothelial cells are infected by the virus and transiently present targets to the immune system as the cells present viral particles. The virus eventually inactivates the major histocompatibility complex 1 (MHC-1) ability of the cells to present viral particles, thus evading the immune system.[239] After respiratory infection, EHV-1 causes an episode of viremia and infects the fetus via transplacental migration of virus-bearing leukocytes. Respiratory clinical signs in infected mares may be subclinical. The time between infection and abortion varies greatly from less than 2 weeks to several months.[240] Abortion occurs as a result of a rapid separation of the placenta, causing suffocation of the fetus.[241] Near-term fetuses may be born alive but will die within days. Aborting mares clear the virus quickly from the reproductive tract, and subsequent fertility is often not affected by the disease. Clinical signs and fetal lesions of abortion caused by EHV-1 and those caused by EHV-4 are indistinguishable from each other.[240]

As with all herpesviruses, EHV-1 establishes a latent infection that may recrudesce after stressful events, such as weaning, translocation, introduction of a new animal, or other illnesses. It is unclear whether or not a reactivation event will cause an abortion, but this is considered likely.[242] Recrudescent infections are certainly transmissible. Aborted, infected fetal materials are also highly contagious. Both of these sources may be responsible for abortion epizootics. Although epidemic abortions occur, losses may be confined to only a few mares in a herd.

43.45.1.2.2.1

Clinical Signs and Diagnosis

The primary lesion of EHV-1 is necrotizing vasculitis and thrombosis resulting from lytic infection of the capillary endothelium. The fetus may become infected or remain uninfected, depending on whether or not the virus crosses the uteroplacental barrier. If transplacental fetal infection occurs late in gestation, a live, infected foal may be born but will not usually survive. Stage of pregnancy during which abortions may occur varies, but the vasculitis is most pronounced from the fifth to ninth months of gestation, and 95% of abortions occur in the last trimester of pregnancy.[243]

Abortions occur suddenly without maternal clinical signs. The aborted fetus is fresh with minimal signs of autolysis. Increased fluid in the thoracic and abdominal cavities; congestion and edema of the lungs;

an enlarged liver with small (approximately 1 mm) necrotic, yellow-white lesions; subcutaneous edema; and icterus are commonly found gross lesions in the fetus. Samples for histopathologic diagnosis should be submitted in Bouin's solution. Histologically, the most characteristic lesion consists of areas of necrosis in lymphoid tissue, liver, adrenal cortex, and the lung, with large intranuclear eosinophilic inclusion bodies. In addition, a hyperplastic necrotizing bronchiolitis is often found. Lymphoid tissues are most commonly affected (nodes, thymus, spleen, and Peyer's patches). Other histopathologic lesions may include mild, multifocal, necrotizing lesions in the liver and adrenal cortex and a hyperplastic, necrotizing bronchiolitis. The placenta may be grossly normal or edematous with no specific microscopic lesions.

Available diagnostic methods include serologic tests, virus isolation, and polymerase chain reaction (PCR). Serologic tests are not considered reliable in EHV-1 diagnosis, and virus isolation remains valuable as a method that allows classification and comparative evaluations. Laboratory diagnostics include fluorescent antibody (FA) staining of fetal tissue, virus isolation from aborted fetuses, virus isolation from maternal whole blood, presence of viral inclusion bodies in liver, lung, and thymus, and fetal serology. Equine fetuses have been found to be capable of producing antibodies to EHV-1 at 200 days of gestation. Maternal serology is of limited diagnostic value because mares may abort several weeks after infection. The rise in serologic titer may have disappeared by the time of the abortion.

43.45.1.2.2.2

Treatment and Prognosis

Studies offer conflicting results as to the efficacy of vaccinations in reducing viremia and abortions. Many studies do suggest a beneficial effect of vaccination, and the current recommendation is to vaccinate during the fifth, seventh, and ninth months of gestation.[239,243] Both killed and modified live vaccines are available. The vaccines are not fully protective, and abortion may occur in vaccinated mares. However, consistent vaccination of pregnant mares should be expected to decrease the incidence of abortion storms and sporadic abortions in a herd.

For the effectiveness of a vaccination program to be maximized, it needs to be combined with a management strategy that minimizes exposure of mares to the virus and prevents activation of a latent viral infection. All horses, young, adult, nonpregnant, and pregnant, should be vaccinated to restrict shedding of the virus. Unnecessary stress such as transportation and overcrowding should be avoided. Pregnant mares should be kept separate from other horses on the farm. Newly arrived horses should be isolated from the resident population for 3 weeks, during which time they should be monitored daily for signs of respiratory disease.

After abortion, the fetus and fetal membranes should be transported away from the area without contaminating the surrounding environment. The stall in which the mare aborted should be disinfected with a phenolic or iodinophoric compound, and the bedding should be prevented from contaminating other areas on the farm. All pregnant mares on an infected farm should remain on the farm until they have foaled. No horse should leave the farm until 3 to 4 weeks after the last abortion.

43.45.1.2.3

Equine Viral Arteritis

Equine viral arteritis (EVA) is caused by equine arteritis virus (EAV). The primary target of EAV is the vasculature. Shortly after infection EAV can be found in the macrophages and later in the lymph nodes. The virus infects circulating monocytes and becomes systemic in distribution by 3 days after the primary infection, resulting in a carrier state (important in stallions). In about a week's time after the primary

infection EAV infects the blood vessel endothelium and causes enough damage by 10 days after the primary infection to cause abortion. Abortion is likely due to the effects of myometritis and vasculitis. Serum progesterone concentrations (produced exclusively by the placenta in the last half of equine pregnancy) fall to baseline levels before the abortion, because of placental hypoxia. The virus is also present in the renal tubular epithelium and is shed in the urine.[244]

EVA is caused by a pestivirus. Infection is often inapparent, and abortion is an occasional occurrence in infected animals.[245] Although the pathophysiology is not well established, fetal death may occur by fetal anoxia secondary to compression of myometrial vessels by edema and decreased progesterone production by the placenta.[246]

43.45.1.2.3.1

History and Clinical Signs

Clinical signs may be absent or highly variable and may include pyrexia, depression, anorexia, leukopenia, limb edema, stiffness of gait, rhinorrhea and epiphora, conjunctivitis, rhinitis, urticarial rash, localized or diffuse edema, and abortion. Abortion typically occurs at 5 to 10 months of gestation and follows the onset of clinical signs by several days but up to 2 months. Less frequently, severe respiratory distress, ataxia, mucosal papular eruptions, submaxillary lymphadenopathy, and intermandibular and shoulder edema may be observed.[244] Infection is rarely fatal in adults but is more frequently fatal in neonates. The virus may be transmitted in the semen, and infected stallions may serve as long-term carriers. Clinical pathologic findings are variable, inconsistent, and nonspecific and include hypoxia, hypercapnia, respiratory or metabolic acidosis, lymphocytosis or lymphopenia, neutrophilia or neutropenia, thrombocytopenia, and hyperfibrinogenemia. Gross and histologic lesions differ in severity with the virulence of the particular viral strain. Edema, congestion, and hemorrhage of the subcutaneous and lymphoid tissues and viscera are the most common gross lesions. Histologic lesions may be found in the vasculature, lymphoid tissues, lungs, intestines, adrenal glands, kidneys, and skin.[244] Abortion may occur without any clinical signs in the mare, and the fetus may be fresh or autolyzed. Fetal lesions are uncommon.

43.45.1.2.3.2

Laboratory Diagnosis

Diagnosis is by serologic testing in conjunction with complement-dependent virus neutralization. There are no characteristic features of EVA infection in the fetus, although autolysis and myocardial arteritis have been reported. EAV is readily isolated or detected by PCR techniques in fetal tissues and the placenta.

43.45.1.2.3.3

Epidemiology and Control

Transmission may occur venereally from infected stallions to mares. Reproductive performance of venereally infected mares is not affected, but contact transmission from venereally infected mares to late gestational mares may cause abortion. Outbreaks were reported in 1953, 1984, and 2006 in the United States. With the exception of these incidents, occasional outbreaks have occurred, with abortion occurring at low incidence.[245] Mares may be isolated after infection but usually do not become carriers. A proportion of naturally infected stallions become persistently infected with EAV and shed the virus constantly in semen. Incidence of seropositive animals is higher in standardbreds than in thoroughbreds, and regulatory guidelines may govern the use of seropositive thoroughbred stallions. Carrier stallions

1455 1456

may be the reservoir for the disease between outbreaks and should be isolated and bred only to immune mares. Mares bred in this way should be isolated for 3 weeks. A modified live vaccine is available for mares and stallions. Control involves vaccination of seronegative stallions under the guidance of regulatory authorities. There is some evidence that prepubertal infection of colts does not result in permanent carrier status.

43.45.1.2.4

Equine Infectious Anemia Abortion

Equine infectious anemia (EIA) is a retroviral infection transmitted by horseflies.[247] After systemic infection with EIA, mares abort during the febrile stage of infection and may abort at any stage of gestation. Foals from infected but asymptomatic mares and stallions are seronegative (precolostral) and clinically normal at birth. Mechanism of abortion is unknown but may be secondary to systemic illness because EIA virus is not found in amniotic fluid.[247] Coggins' test will confirm seropositive status but is not a definitive diagnosis for abortion.

43.45.1.2.5

Leptospirosis Abortion

Leptospirosis causes a number of bacterial abortions in some areas and was reported to be responsible for 2.2% of abortions in a Kentucky study.[210] The serovar responsible shows regional variability. Serovar *Leptospira*, Pomona has most commonly been associated with leptospirosis abortion in mares, but *Leptospira*, Grippotyphosa, *Leptospira*, Hardjo, *Leptospira*, Bratislava, and *Leptospira*, Icterohemorrhagiae have also been isolated from sporadic abortions.[248] Infected animals shed the spirochete in their urine, which contaminates groundwater and serves as a source for further infections. Many horses are seropositive for leptospires but are subclinical.

43.45.1.2.5.1

Clinical Signs and Diagnosis

Clinical signs may include pyrexia, hemoglobinuria, jaundice, and abortion. Aborted chorioallantoic lesions are similar to those of other bacterial placentitis cases (nodular cystic allantoic masses, edema, necrotic areas of chorion, and necrotic mucoid exudate coating the chorion) but may show a diffuse pattern of distribution, indicating a hematogenous source of placental infection. Funisitis has been reported in leptospira cases of abortion, and examination, both gross and histologic, of the umbilical cord should always be a part of every abortion investigation.[249] Serologic antibody conversion lasts for years, and so serologic diagnoses are not very helpful. Gross lesions are nonspecific. Diagnosis is best done by FA tests or Warthin-Starry silver stain (WS) staining of the allantochorion and umbilical cord. Demonstration of leptospirosis could aid in rapid diagnosis and have important clinical and therapeutic indications in the case of live-born, weak foals.[249]

43.45.1.2.5.2

Treatment and Control

Horses may shed spirochetes in urine for up to 90 days; therefore affected animals should be isolated and treated with antibiotics. Aborting mares should be isolated, and the stalls should be disinfected. Infected mares may be treated with streptomycin (10 mg/kg twice daily), penicillin (10 to 15,000 IU/kg twice daily), or oxytetracycline (5 to 10 mg/kg) for a period of 1 week. Because *Leptospira*, Pomona is

the most common isolate in the United States, mares should be separated from other leptospiral hosts such as ruminants and pigs. Vaccines for cattle are not effective in horses.

43.45.1.2.6

Protozoal Abortion

Pregnant mares with equine monocytic ehrlichiosis (Potomac horse fever), caused by the protozoa *Neorickettsia risticii*, may abort. Abortions caused by *N. risticii*, have been documented in both natural and experimental cases.[250,251] Mares were infected at 90 to 180 days of gestation and aborted at around 217 days of gestation.

43.45.1.2.6.1

Clinical Signs and Diagnosis

Abortions have been observed 2 to 3 months after clinical signs of ehrlichiosis.[252] Abortions were associated with placentitis and RFMs. Fetal histologic lesions include enterocolitis, periportal hepatitis, myocarditis, and lymphoid hyperplasia with necrosis of the mesenteric lymph nodes and spleen. Recovery of the protozoan may be from fetal bone marrow, spleen, lymph node, colon, or liver.[250,251] The diagnosis can be confirmed by identifying a small number of rickettsiae by PCR assay.

43.45.1.2.6.2

Treatment and Prevention

Treatment with oxytetracycline (6.6 mg/kg IV once daily) for 5 days in pregnant mares with clinical signs of ehrlichial colitis may prevent or reduce the incidence of abortion. Commercial vaccines against equine ehrlichiosis are available, but the protective effect of vaccines against abortion is unknown.

Neospora caninum, is a known protozoal abortifacient in cattle. This protozoan has not been definitively shown to cause abortion in the mare, but its presence has been documented in aborted foals, suggesting the need for further investigation.[253]

43.45.1.2.7

Insect-Related Abortion

In the equine breeding season of 2001, central Kentucky horses experienced pregnancy losses estimated to have affected more than 3000 mares (>60% of mares on some farms[254]) and to have resulted in over $330 million in losses.[255] The syndrome was named *mare reproductive loss syndrome*, (MRLS). On a much smaller scale, MRLS was documented in mare abortions in north central Florida during the 2006 breeding season. Epidemiologic studies noted abnormal weather patterns (sudden freezing in mid April followed by unusually warm springtime temperatures) and positive correlations with the presence of black cherry trees *(Prunus serotina)*, and abnormally large numbers of the eastern tent caterpillar *(Malacosoma americanum)*.,[256] Pregnancy loss was later linked to ingestion of the caterpillars themselves, with the toxic agent related to the larval exoskeleton.

43.45.1.2.7.1

Clinical Signs and Diagnosis

Clinical signs preceding abortion and failure to maintain pregnancy are typically not observed. Both early (40 to 150 days' gestation) and late (near term) pregnancies are affected. Hyperechoic amniotic and allantoic fluids can be noted on ultrasonographic examination, along with a dead or dying fetus

(slow heart rate, <75 beats/min), which would then be expelled within several days.[257,258] Characteristic histologic lesions are noted in the placenta and umbilical cord. In many cases, endometrial cultures are positive for non—beta-hemolytic streptococci and actinobacilli. *Actinobacillus*, species identified in cases of MRLS are identical to commensal organisms found in the oral cavities and alimentary tracts of healthy horses.[259] Larval hairs (cetae) are hypothesized to migrate through gastrointestinal system and translocate commensal organisms from the oral cavity and intestines to other sites.[256]

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43.45.1.2.7.2

Treatment and Prevention

Because clinical signs are absent in the mare before fetal death, treatment is not possible. Prevention is aimed at limiting exposure to *M. americanum*, larvae. Applying insecticides, physically removing caterpillar nests from trees, removing black cherry trees, muzzling mares in pasture, and supplementing hay feeding in pastures to minimize grazing have all been used.

43.45.1.2.8

Salmonella, Abortion

Salmonella, Abortus equi *(Salmonella abortivoequina*, or "contagious abortion") was a common cause of abortion in the early 1900s but is now rare. Non—host-specific species, including *Salmonella*, Typhimurium, now cause most equine salmonella abortions. Abortion caused by *Salmonella*, is discussed under abortions in ruminants.

43.45.1.2.9

Trypanosomiasis (Dourine)

The protozoan parasite *Trypanosoma equiperdum*, causes a venereally transmitted genital infection that may be followed by fatal systemic dissemination in horses. Systemic illness may cause abortion. It occurs in tropical and subtropical regions and has been eradicated from North America.[11] Dourine is diagnosed by isolation of trypanosomes in uterine discharge. Exposed animals can be detected by serology (complement fixation). Control strategies require identification and treatment or slaughter of infected animals.

43.45.1.2.10

Abortion Caused by Endotoxemia

Gram-negative septicemia and endotoxemia associated with intestinal disorders that alter the integrity of the mucosal barrier (e.g., intestinal obstructions, acute enteritis, colitis, grain overload) result in the release of vasoactive metabolites including PGF. Endogenous release of PGF during an episode of experimental endotoxemia has been shown to cause luteolysis and abortion during the first 2 months of pregnancy in mares.[260] The equine pregnancy is dependent on ovarian sources of progesterone for the first 80 days of gestation. After this time the fetoplacental unit takes over progesterone production, which is necessary for maintenance of the pregnancy.

43.45.1.2.10.1

Clinical Signs and Diagnosis

Abortions follow a recent episode of stress induced by endotoxemic shock or gram-negative endotoxemia. Pregnancy loss at early stages of gestation may go undetected unless fetal membranes or

parts are found in the stall. Abortions during later stages of the pregnancy may be observed as vaginal discharge or the detection of an expelled fetus.

43.45.1.2.10.2 Treatment and Prevention

Daily administration of a progestagen (Altrenogest 0.044 mg/kg PO) has been shown to effectively prevent experimental endotoxin-induced abortion.[260] If the animal is treated while the pregnancy is still CL dependent (approximately <day 80), analysis of serum progesterone concentrations after the acute episode of the disease helps in deciding if the supplementation needs to continue. Serum progesterone concentrations of less than 1 ng/mL indicate the loss of an active CL, and supplemental progestagen treatment should continue until the fetoplacental unit is known to be capable of maintaining the pregnancy. For practical reasons supplementation until day 100 is commonly recommended. Serum progesterone concentrations greater than 1 ng/mL are compatible with a functional CL, and the progestagen treatment can gradually be discontinued. Treatments with flunixin meglumine or other prostaglandin inhibitors have not been proven to effectively prevent endotoxin-induced fetal losses unless the agents are administered before clinical signs appear.

43.45.2 RUMINANTS

Information on the major causes of abortion in cows, sheep, and goats is summarized in Tables 43-8 and 43-9.

In large commercial operations a low percentage of intermittently occurring abortions is considered acceptable; such abortions are seen as “background abortions.” In beef and dairy operations 2% to 3% and 10% are considered acceptable, respectively. Abortion levels beyond these are considered abnormal and are usually investigated. Only rarely is a cause established. When investigating bovine abortions, it is important to determine commonalities among abortion events including stage of pregnancy affected, sire used, heifers versus cows affected, dates of new arrivals to the herd, season of year, vaccination protocols, presence of dogs, and management practices among different groups. Cows and heifers on the farm presumed to be pregnant should be evaluated to detect unobserved pregnancy losses. These examinations should document apparently normal, open animals who had previously been documented as pregnant, those with mummified fetuses, and those with pyometra. If possible an entire fetus (or more than one) should be submitted for culture, serology, and histopathology. If the placenta is available, this should be submitted as well. If it is not practical to submit the entire animal and placenta, tissues including lung, stomach and contents, liver, spleen, and placenta should be collected and appropriately submitted for culture (chilled), viral isolation (frozen), and histopathology (formalin fixed).

43.45.2.1 NONINFECTIOUS CAUSES

Noninfectious causes of abortion in ruminants include the following:

- Heat stress
- Other stress
- Nitrate toxicity
- Malnutrition (rare)

- Pine needle toxicity
- Drug induced (corticosteroids)
- Physical

43.45.2.2 INFECTIOUS CAUSES

43.45.2.2.1 Bovine Herpesvirus 1

Bovine herpesvirus 1 causes IPV and IBR. The latter disease is the major cause of bovine viral abortion. IBR manifests as upper respiratory disease and abortion. The virus causes clinical signs in both dam and fetus. Immune dams exposed to the virus do not experience abortions. In naive animals the virus is carried in leukocytes and can become localized in placental tissues. Fetuses exposed to the virus usually die within 24 hours of placental infiltration. Although other stages of pregnancy may be affected, 5 to 6 months' gestation is the most susceptible stage. Fetal lesions include renal hemorrhagic edema; acute general necrosis in the liver, spleen, kidneys, lungs, and adrenal glands; widespread hemorrhage; petechia; epithelial destruction; and hepatic necrosis with intranuclear inclusion bodies. The amnion may be thickened without obvious signs of inflammation.

Diagnosis of IBR is by virus isolation from the placenta, identification of intranuclear inclusion bodies in fetal tissues, or serum neutralization testing. If the latter is to be used, at least two samples must be taken days apart. The first must be negative and the second positive, or the first must be positive and the second titer must show a fourfold increase. Serum testing may not be helpful because the dam may have been infected months before the abortion and the titer after the abortion may actually be falling.

Table 43-8 Major Causes of Bovine Abortion

Cause and Common Names	Usual Stage of Gestation	Major Fetal Lesions	Diagnostic Tests
Bovid herpesvirus 1, IBR	Fifth to ninth months	Multifocal necrosis with intranuclear inclusions (liver, lung, spleen, kidney)	Histopathology, virus isolation, FA test of frozen fetal kidney
Bluetongue (orbivirus)	Any stage	Anomalies of skeletal and nervous systems	Pathology, virus isolation, fetal serology
BVD virus, pestivirus	Any stage	Anomalies of skeletal, nervous, cardiovascular, respiratory, or other systems	Pathology, FA test on fetal tissues, fetal serology (virus neutralization, ELISA), serologic survey in herd
EBA, foothill abortion, spirochete?	Third trimester	Lymphadenopathy, splenomegaly, hepatopathy	Pathology
Brucella abortus, brucellosis, Bang's disease	Third trimester	Placentitis, fibrinous serositis, bronchopneumonia	Culture, maternal serology (card test, plate, or tube agglutination)
Campylobacter fetus, subsp. *venerealis*, campylobacteriosis, vibriosis	Usually early embryonic death	Placentitis, fibrinous serositis, bronchopneumonia, hepatitis	Pathology, darkfield examination, culture
Haemophilus somnus,	Any stage	Placentitis	Histopathology, culture
Leptospira interrogans, leptospirosis	Fifth to ninth months	Icterus, edema, renal degeneration and inflammation	Fetal and maternal serology
Leptospira interrogans, listeriosis	Eighth or ninth month	Placentitis	Histopathology, culture
Salmonella, Dublin, *Salmonella*, Typhimurium	Third trimester	Placentitis	Culture
Aspergillus fumigatus, and all fungal species, mycotic abortion	Third trimester	Placentitis, bronchopneumonia, dermatitis	Histopathology, fungal culture
Sarcocystis cruzi,	Third trimester	Protozoa in caruncles	Histopathology or FA of caruncles
Tritrichomonas foetus, trichomoniasis	First half	Placentitis, bronchopneumonia	Microscopic demonstration of organism, culture

Bovine neosporosis	Mid gestation	Similar to those found in toxoplasma-aborted sheep fetuses	Histopathology, seroepidemiology

BVD, Bovine virus diarrhea; *EBA*, epizootic bovine abortion; *ELISA*, enzyme-linked immunosorbent assay; *FA*, fluorescent antibody; *IBR*, infectious bovine rhinotracheitis.

Table 43-9 Major Causes of Abortion in Sheep and Goats

Cause and Common Names	Usual Stage of Gestation	Major Fetal Lesions	Diagnostic Tests
Bluetongue, orbivirus	Any stage	Anomalies of skeletal or nervous systems	Pathology, IFA, serology
Border disease, pestivirus, hairy shaker disease	Any stage	Dysplasia of skeleton, CNS, and fleece	Pathology, virus isolation, serology (cross-reacts with BVD)
Coxiella burnetii, Q fever	Near term	Necrotizing placentitis	Histopathology, microscopic demonstration of rickettsiae, complement fixation, ELISA
Chlamydia psittaci, EAE	Fourth or fifth month	Necrotizing placentitis	Histopathology, microscopic demonstration of organism, fluorescent antibody on fetal tissues or cultures, paired sera
Campylobacter fetus, subsp. *fetus*, vibriosis	Last 6 weeks	Placentitis, serositis, multifocal hepatic necrosis	Pathology, microscopic demonstration of organism, culture
Toxoplasma gondii, toxoplasmosis	Any stage	Necrosis and calcification in cotyledons	Pathology, demonstration of organism, serology (e.g., agglutination, ELISA)

BVD, Bovine virus diarrhea; *CNS*, central nervous system; *EAE*, enzootic abortion of ewes; *ELISA*, enzyme-linked immunosorbent assay; *IFA*, immunofluorescent antibody.

Prevention of disease is by vaccination (though infection and latency may occur despite vaccination). It is recommended to vaccinate heifers at 6 months and administer a booster 3 to 4 weeks before breeding. A modified live virus is commonly used but is unsafe in pregnant cows from the third to eighth months of gestation. A killed viral vaccine is available for pregnant cow use; a modified live virus vaccine labeled for intranasal administration is also available.[261]

43.45.2.2.2

Bovine Virus Diarrhea Virus

Bovine virus diarrhea virus (BVDV) is a pestivirus that can produce early embryonic death, fetal anomalies, or abortion (see Chapter 32 for complete discussion). Isolates from bovine aborted fetuses are usually noncytopathic.[262]

43.45.2.2.2.1

History and Clinical Signs

Although fetal death is most common during the first trimester, abortion can occur at any stage of gestation.[263,264] Pathogenicity of the disease depends on gestational time of infection, the viral strain, viral biotype (cytopathic or noncytopathic), and fetal immunocompetence.[265] Often there is a history of repeat breeding and a recent episode of febrile disease in the herd before the onset of abortions.[266]

43.45.2.2.2.2

Laboratory Diagnosis

Fetal loss generally occurs 10 to 27 days postexposure, with expulsion of the fetus up to 50 days later.[265] As a result the fetus is most often autolyzed, although in some cases it may be mummified or fresh. The aborted fetus may have a variety of dysplastic lesions, including cerebellar hypoplasia, cerebral malformations (hydrencephaly, porencephaly, microencephaly) and cataracts, brachygnathia, arthrogryposis, alopecia, thymic hypoplasia, and intrauterine growth restriction.[5,263,266,267] Microscopic lesions include a mild nonsuppurative placentitis. Nonsuppurative vasculitis may be observed in the placenta, liver, or lymph nodes.[266]

Virus isolation from fetal tissue is seldom successful, likely because of the protracted time before fetal expulsion generally occurs after infection. Viral antigen may be detected by FA test on kidney, lung, or lymph node.[266] Virus neutralization and enzyme-linked immunosorbent assay are used to detect antibodies in fetal thoracic fluid, which indicate prenatal exposure to the virus but do not necessarily incriminate BVDV as the cause of abortion. Maternal titers are seldom of diagnostic value because a rise in titer generally occurs before abortion.[5]

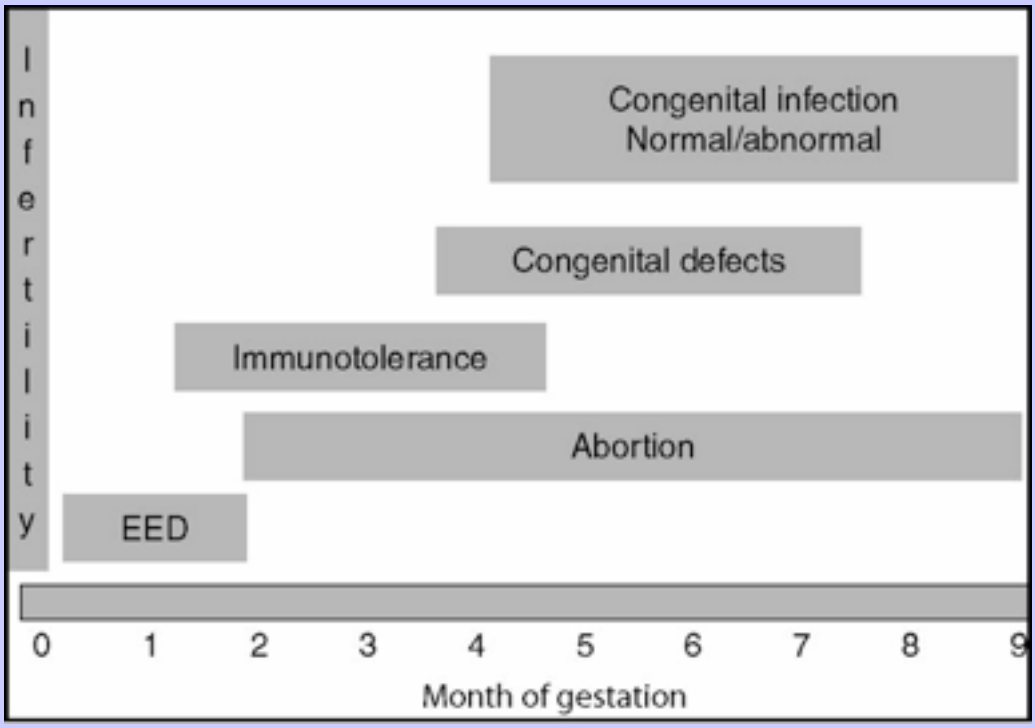
43.45.2.2.2.3

Pathophysiology

BVDV may be shed in most body secretions. The effects of exposure to BVDV vary greatly depending on the gestational time during which exposure occurred (Fig. 43-11). In seronegative cows, exposure to BVDV at the time of breeding prevents conception.[268] Placental attachment at approximately 35 days' gestation seemingly must precede fetal infection. During the first 4 months of gestation, infection usually causes fetal death and abortion.[166] Fetuses that survive infection with noncytopathic strains between 18 and 125 days' gestation will be persistently infected (PI), are typically seronegative at birth, and subsequently shed BVDV continuously.[265] They may develop mucosal disease later in life from superinfection with cytopathic BVD virus.[269,270] Fetuses infected at between 100 and 150 days' gestation, considered congenitally infected (CI), are at risk for the development of dysplastic lesions including teratologic defects in the brain, skin, or bronchioles. Fetuses infected after 150 days usually recover without dysplastic lesions.[263] Recent evidence, however, suggests that those fetuses born with

neutralizing titers to BVDV are more likely to develop a serious illness within the first 10 months of life and less likely to conceive as heifers than those calves born without neutralizing titers to BVDV.[271,272]

Fig. 43-11 Potential clinical reproductive outcomes after infection with bovine virus diarrhea virus. *EED*, Early embryonic death.[265]



43.45.2.2.2.4 Epidemiology

Most cattle have serum antibodies to the virus. The abortion rate may approach 25% with new infection of a susceptible herd.[5]

43.45.2.2.2.5 Control

BVDV is not fully controlled with vaccination. Herd health plans must focus on elimination of PI animals and prevention of new PI animals being introduced into the herd.

43.45.2.2.3 Leptospirosis

Leptospirosis is a spectrum of diseases caused by multiple serovars of *Leptospira interrogans. Leptospira*, Hardjo is the major serovar associated with bovine leptospiral abortion, although isolations of *Leptospira*, Pomona*, Leptospira*, Canicola, *Leptospira*, Icterohemorrhagiae, *Leptospira*, Grippotyphosa, and *Leptospira*, Szwajizak have also been reported.[5,266] Two serologically indistinguishable but genetically distinct types of serovar Hardjo have been identified: *L. interrogans*, serovar Hardjo (type hardjo-prajitno)

and *Leptospira borgpetersenii*, serovar Hardjo (type hardjo-bovis). Serovar Hardjo type hardjo-bovis is cosmopolitan in cattle populations, whereas type hardjo-prajitno is isolated primarily from cattle in the United Kingdom.[265]

43.45.2.2.3.1

History and Clinical Signs

In cattle, *Leptospira*, Hardjo is associated with infertility, early embryonic death, abortions from 4 months' gestation to term, and birth of weak calves. Abortion rate is usually less than 10% but may approach 50% in some areas.[273] *Leptospira*, Pomona abortion usually occurs in the last 3 months of gestation, with an abortion rate as high as 50%.[5] Clinical signs of leptospirosis in the cow may include icterus, hemoglobinuria, anemia, fever, and mastitis that is characterized by a flaccid udder and thick ropy secretions from all four quarters, but usually cows abort without clinical illness.[266] Dead or weak calves may be delivered at term.[273] Abortions caused by serovar Hardjo tend to occur sporadically rather than in storms (as may be seen with serovars Pomona or Grippotyphosa).

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43.45.2.2.3.2

Laboratory Diagnosis

The aborted fetus is usually autolyzed, icteric, and edematous. Histologically, renal tubular necrosis is accompanied by lymphocytic interstitial nephritis, pneumonia, and placentitis.[5,266]

Leptospires are rapidly destroyed by autolysis or freezing. Isolation from fetal liver, kidney, or brain is possible but slow and impractical. Leptospires may be isolated or demonstrated by darkfield microscopy, FA staining, or histologic techniques in fetal or placental tissues or in the urine of the aborting dam within approximately 2 weeks after abortion.[5,266]

Diagnosis is usually based on serology. A few infected fetuses develop microagglutination titers of 1:10 or more. It is difficult to distinguish among vaccinated, acutely infected, and recovered animals, but titers to *Leptospira*, Pomona greater than 1:12,800 in the dam suggest leptospiral abortion. Maternal titer usually has peaked by the time of abortion. Single titers of 1:800 or more in unvaccinated animals, seroconversion, or fourfold changes in titers in paired sera indicate leptospirosis in the herd. Titers to *Leptospira*, Hardjo are often less than 1:100 in affected cows and seldom exceed 1:1600.[266]

43.45.2.2.3.3

Pathophysiology

Hematogenously spread leptospires colonize the gravid uterus up to 142 days after infection. Abortion occurs 1 to 6 weeks after acute disease with *Leptospira*, Pomona infection and 1 to 3 months with *Leptospira*, Hardjo.[5] *Leptospira*, Hardjo remains in the oviducts of infected cows up to 22 days after calving.[273]

43.45.2.2.3.4

Epidemiology

Leptospira, organisms are ubiquitous and an important cause of abortion in all cattle-producing regions. *Leptospira*, organisms persist in the genital tract and kidneys. The organisms localized in the kidneys of infected animals are shed in the urine and serve as a source of infection for other animals. The organisms localized in the female reproductive tract are responsible for abortions. Aborted tissues are

infectious to other animals and humans and should be handled with caution.[274] Vaccination may be useful in endemic areas.

43.45.2.2.3.5

Treatment and Control

In abortion outbreaks, pregnant cows can be vaccinated with killed bacterin and treated with oxytetracycline (antibiotic treatment can be limited to sick cows in dairy herds).[275] Aborting cows should be isolated and treated with streptomycin if they are not destined for slaughter. Aborted fetuses and placentas should be removed from the premises.[276] Preventing exposure to swine, rodents, and contaminated water lessens the opportunities for infection.[5,202] *Leptospira*, Pomona usually has no permanent effect on fertility, but infection with *Leptospira*, Hardjo has been associated with persistent herd infection and recurring abortions.[5]

Herd vaccination is recommended at 6-month intervals or more frequently in areas with heavy exposure to leptospires. Vaccination programs are aimed at reducing urinary shedding of leptospires and decreasing fetal loss. However, a commercial pentavalent leptospiral vaccine (serovar *Leptospira*, Hardjo type hardjo-prajitno is used for the *Leptospira*, Hardjo component of U.S. Department of Agriculture [USDA]—licensed leptospiral vaccines) did not prevent renal colonization, urinary shedding, or fetal infection after conjunctival instillation of cows with serovar *Leptospira*, Hardjo type hardjo-bovis (the only type of *Leptospira*, Hardjo isolated from cattle in the United States).[277]

43.45.2.2.4

Epizootic Bovine Abortion (Foothill Abortion)

Epizootic bovine abortion (EBA) or foothill abortion is a syndrome of late abortions in cattle in the foothills bordering the central valley of California.[278] Once thought to be caused by *C. psittaci*, studies have demonstrated that EBA differs from chlamydial abortion.[278] Currently a spirochete-like agent isolated from abortuses and from the tick vector of EBA is under investigation as the causative agent.[279–281]

43.45.2.2.4.1

History and Clinical Signs

Late abortion or delivery of weak calves occurs in affected herds. Many fetuses in the sixth to seventh month of gestation may be aborted, especially from heifers without premunition immunity from natural exposure to the causative agent. Older native cows show no clinical signs of infection.

43.45.2.2.4.2

Laboratory Diagnosis

A 3-month period is required for full development of pathologic changes in the fetus. Superficial cervical lymph nodes are enlarged up to 16 g, the spleen is enlarged up to 250 g, the thymus is slightly smaller than normal, and the liver may be enlarged and nodular.[266,278,280] Histologically there is loss of thymic cortical lymphocytes; remaining lymphocytes are enlarged and poorly differentiated. Follicular hyperplasia, histiocytosis, vasculitis, necrosis, and pyogranulomas occur in lymph nodes and spleen. Lymphohistiocytic proliferation may also occur around vessels in the liver, lung, and meninges.[266]

EBA has been diagnosed mainly by pathologic examination of the fetus. Recent studies have demonstrated high levels of IgG (3 mg/mL or more) in fetal blood.[266,278] A spirochete-like agent can be demonstrated in the plasma of aborted fetuses but also may occur in plasma of normal fetuses.[279] Currently no serologic test for EBA exists because the cause is uncertain.

43.45.2.2.4.3

Pathophysiology

Infection is transmitted by the soft-shell tick *Ornithodoros coriaceus*.,[280,281] The disease also can be transmitted with fresh or frozen fetal tissue.[278] Transformation and proliferation of fetal lymphocytes and macrophages occur by 50 days but are not severe enough for diagnosis until 100 days after maternal exposure to the tick vector. IgG and IgM are deposited in vascular lesions, but increase in fetal serum immunoglobulin is not detectable until at least 80 days after tick exposure.[278,281] Repeated superinfection may be necessary to result in fetal death.[280] Because at least 90 days are required for development of fetal lesions, infection after 6 months' gestation is not likely to result in abortion.[5,266]

43.45.2.2.4.4

Epidemiology

EBA is limited to the range of the tick vector in the foothills bordering the central valley of California.[278] Of the annual calf loss in California, 5% to 10% is attributed to EBA.[281] The prevalence of infection by the spirochete is far greater than the prevalence of abortion.[280] Abortion occurs 3 to 4 months after exposure to ticks but almost always late in gestation, regardless of the time of tick exposure.[282] Older native cows from enzootic areas usually do not abort, and introduced cows and heifers generally abort only once.[278] The abortion rate may be 30% to 80% in susceptible animals.[266,282]

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43.45.2.2.4.5

Treatment and Control

Chlortetracycline therapy (2 to 5 g/day in the feed) reduces the rate of abortion.[281] Currently no vaccine exists for EBA, but abortions can be controlled by exposing heifers to the tick vector before breeding or by changing from spring to fall calving,[5] which takes advantage of limiting exposure to the last trimester of gestation in some management systems. Therefore exposure of susceptible pregnant cattle to the tick only after the sixth month of pregnancy is a practical solution for ranchers using summer foothill pastures and fall calving. The tick lives in ground duff (e.g., leaves) and is not found on cattle that graze in irrigated pastures and most other areas outside of brushy foothills.

43.45.2.2.5

Brucella abortus, Abortion

B. abortus, infection (Bang's disease) causes abortion in cattle and, less commonly, in sheep and goats. Horses may be infected with *B. abortus*, which has been associated with fistulous withers, but usually experience no infertility, abortion, or other clinical evidence of infection. Bovine infections are caused by eight biovars of *B. abortus*, three of which (biovars 1, 2, and 4) are recognized in the United States.[5]

43.45.2.2.5.1

History and Clinical Signs

Abortion is the chief clinical sign of bovine brucellosis and usually occurs after the fifth month of gestation. Lameness, mastitis, epididymitis, and/or orchitis may be present in infected herds.[283]

43.45.2.2.5.2

Laboratory Diagnosis

Autolysis frequently obscures gross lesions in the fetus, but fibrinous serositis may be apparent, and abomasal content may be discolored and flocculent. Placentitis is a consistent finding. Cotyledons are necrotic; the intercotyledonary placenta is thickened and opaque with accumulation of odorless, flocculent, yellow-brown exudate between maternal and fetal membranes. Histologically there is suppurative placentitis (and endometritis in the dam). Suppurative bronchopneumonia and lymphoreticular hyperplasia are frequent histologic findings in the fetus.

Diagnosis depends on culture of *B. abortus*, from fetal lung, abomasum, or placenta or from maternal uterine or mammary secretions. Organisms and *Brucella*, antigen can be detected in fetal tissues by avidin-biotin-peroxidase complex immunostaining.[284]

No serologic test is 100% accurate, but a positive card test or titer of 1:100 or more on plate or tube agglutination suggests brucellosis. False-negative serologic reactions occur in approximately 15% of infected cows, particularly just before or after parturition. False-positive reactions are a problem in cows vaccinated with strain 19. Supplemental tests such as the Rivanol test, complement fixation, and mercaptoethanol sensitivity of agglutination are used in suspect cases. Dairy herds are surveyed by the *Brucella*, ring test on milk.[5] In goats, tube agglutination titers of 1:25 or more indicate infection.[283]

43.45.2.2.5.3

Pathophysiology

Initial replication of *B. abortus*, occurs in regional lymph nodes. Bacteremia is followed by colonization of supramammary lymph nodes, the mammary gland, and the gravid uterus. Uterine infection occurs during the second trimester.[5,285] In the placenta the bacteria appear first in phagosomes of erythrophagocytic trophoblasts. Replication occurs in the rough endoplasmic reticulum of chorioallantoic trophoblasts.[285] Preferential replication in chorioallantoic trophoblasts has been attributed to their erythritol content; however, the placentas of several laboratory rodents that lack detectable erythritol still support *B. abortus*, replication.[286] The organism also occurs in fetal placental endothelial cells and capillary lumina, where it is associated with vasculitis and destruction of chorionic villi. Placental inflammation spreads along the allantochorion to involve additional cotyledons with resultant chorioallantoic ulceration, necrosis of trophoblasts, and ulcerative endometritis. Fetal death results from placental disruption and endotoxemia.[5,285] The fetus is frequently retained 1 to 3 days in utero. Numerous bacteria are expelled from the genital tract at parturition, but shedding usually stops by 3 weeks after abortion.[5]

43.45.2.2.5.4

Epidemiology

Infection with *B. abortus*, occurs naturally by ingestion. Contaminated materials are infectious for humans and should be handled with caution. Infection is not easily transmitted between cattle separated by fences or roads.[287] Most calves infected at birth clear the infection, but persistent congenital infection has been documented.[288,289]

Bovine brucellosis has been nearly eradicated in the United States by test and slaughter of seropositive cattle and vaccination. However, a reservoir remains in bison and elk, especially in the greater Yellowstone area.

43.45.2.2.5.5

Treatment and Control

Treatment of brucellosis is usually not effective. Combination therapy with long-acting oxytetracycline and streptomycin has been shown to reduce shedding in most cows and potentially eliminate infection in some,[290] but because of the eradication program used in many countries, infected cows are rarely treated. In the United States, infected individuals are destroyed, and exposed herdmates are quarantined to the herd until slaughter or the herd is recertified as brucellosis-free (United States Department of Agriculture, 2003).

In the past, strain 19 vaccine was used as part of the eradication program. However, vaccinated and field strain—infected cattle could not be differentiated. A newer vaccine for *B. abortus*, vaccine strain RB51, was developed to overcome the serologic problems associated with the strain 19 vaccine.[291] Animals vaccinated with RB51 lack antibodies to the O-polysaccharide chain and can thus be distinguished from field-infected cattle. Strain RB51 is also less abortifacient for cattle than strain 19, although vaccination of pregnant heifers may result in abortion and subsequent zoonotic exposure if obstetric assistance is necessary (Centers for Disease Control, Morbidity and Mortality Weekly Report, March 13, 1998), and so the vaccine is to be administered only to young heifers before pregnancy.[261,290a,291]

43.45.2.2.6

Campylobacter fetus, subspecies *venerealis*, Abortion

C. fetus, subsp. *venerealis*, is the main cause of bovine campylobacteriosis (vibriosis).[5] The organism is an obligate parasite of the bovine genital tract and is not known to cause disease in other species.[266]

43.45.2.2.6.1

History and Clinical Signs

Infection with *C. fetus*, subsp. *venerealis*, mainly causes temporary infertility or early embryonic death, but sporadic abortions from the fourth to eighth months of gestation are possible.[266] The usual history includes a high percentage of cows exposed for the first time returning to estrus or found nonpregnant after the breeding season, and cows calving late because they returned to estrus one or more times.

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43.45.2.2.6.2

Laboratory Diagnosis

Autolysis is usually minimal, and the lungs of the term fetus may be partially inflated. Dehydration, fibrinous serositis, and necrotizing placentitis may be apparent grossly. Histologically, bronchopneumonia and hepatitis may also be evident. Diagnosis is based on demonstration or isolation of the organism. By darkfield microscopy the bacterium appears as a curved rod with darting corkscrew motility.[266] Cows that abort may have serum antibody titers; however, they may not be diagnostic because they are not specific for *C. fetus*, subsp. *venerealis*., Culture from placenta or fetal abomasal contents requires at least 72 hours. The vaginal mucus agglutination test is used to survey herds for infection.[5] Alternatively the penis and preputial mucosa of infected bulls may be swabbed and cultured, although culture is difficult because the organism is slow-growing and often overwhelmed by saprophytes.

43.45.2.2.6.3

Pathophysiology

Within a week of vaginal infection the organism is established in the uterus, causing mucopurulent endometritis, which persists 3 to 4 months. Intrauterine infection either prevents conception or causes embryonic death, and infected heifers typically return to estrus by 40 days. Less commonly, abortions occur at up to 8 months' gestation.[5,266]

43.45.2.2.6.4

Epidemiology

C. fetus, subsp. *venerealis*, is ubiquitous. Venereal transmission from infected bulls to virgin heifers approaches 100%. Cows with previous exposure to infected bulls develop immunity and therefore are less likely to experience infertility than heifers. The abortion rate seldom exceeds 10%.[266]

43.45.2.2.6.5

Treatment and Control

Infected cows usually recover spontaneously within 5 months and resist reinfection. Recovery is hastened by intrauterine infusions of streptomycin and penicillin. Infertility may be permanent if endometritis or salpingitis is severe.[5] Heifers should be vaccinated with a killed bacterin before breeding. Most vaccines are administered 1 month before breeding and require a booster vaccination 2 weeks later.[*,†] Higher than normal doses of vaccine may be needed to clear the infection from bulls. Cows and bulls must be vaccinated annually. Exclusive use of *C. fetus*, subsp. *venerealis*,—negative semen via AI controls the disease by preventing transmission.

* Vibrin, SmithKline Beecham Animal Health, Exton, PA.

† Trivib-5L, Fort Dodge Labs, Fort Dodge, IA.

43.45.2.2.7

Haemophilus somnus, Abortion

H. somnus, has been associated with vulvitis, vaginitis, endometritis, weak calf syndrome, stillbirths, and occasional abortion in cattle.

43.45.2.2.7.1

Laboratory Diagnosis

Aborted fetuses have been free of gross lesions. Necrotizing placentitis is associated with fibrinoid necrosis of placental arteries.[207] Diagnosis is based on recovery of large numbers of the organisms in relatively pure culture from placenta or fetus, histologic evidence of placentitis, and lack of other apparent causes.

Interpretation of maternal titers to *H. somnus*, is difficult, and it is best to take paired serum samples. Titers between 1:256 and 1:512 in nonvaccinated herds may be the result of early active or chronic infection. Titers between 1:1040 and 1:4096 indicate recent active infection. A fourfold change in titer in paired sera is the best indicator of active infection.

43.45.2.2.7.2

Pathophysiology

Although *H. somnus*, can be isolated from the genital tract of clinically normal cows,[194] the rate of isolation is higher in cows with endometritis or cervicitis.[207,292] Experimentally, *H. somnus*, can adhere to zona pellucida—intact embryos and cause degeneration.[293] Vaginitis can be induced by inoculation with *H. somnus*,[294] and abortion has been induced by intraamniotic, intravenous, or intrabronchial challenge with the organism.[295] Cervical infusion with the organism has resulted in colonization of the chorioallantois and placentitis, but calves were born alive without culturable *H. somnus*.,[296,297]

43.45.2.2.7.3

Treatment and Control

Antibiotic treatment and vaccination anecdotally increase fertility in herds affected with *H. somnus*,—induced vulvovaginitis.[207]

43.45.2.2.8

Listeria monocytogenes, Abortion

Listeriosis is caused by *L. monocytogenes*., Listerial abortions are of importance mainly in ruminants.

43.45.2.2.8.1

History and Clinical Signs

Bovine abortions usually occur in the last 2 months of gestation.[266] Infected ewes and does typically abort in the last month.[5,298] Fever, depression, RFMs, or endometritis may occur,[5,266,299] but often the dam shows no clinical signs of infection.

43.45.2.2.8.2

Laboratory Diagnosis

In less severely autolyzed fetuses, fibrinous polyserositis may be apparent. Most aborted fetuses have gray-white hepatic foci up to 2 mm in diameter. Similar foci may be visible in cotyledons; exudation occurs between cotyledons. Abomasal erosions have been reported in aborted lambs.[266] Histologically, suppurative placentitis and endometritis are consistent findings.

Listeria, is readily cultured from abortuses without cold enrichment. Serovars 1 and 4b are commonly isolated from bovine fetuses; serovars 4b and 5 are the usual ovine isolates.[266] *Listeria*, appears in impression smears as gram-positive pleomorphic coccobacilli.[266]

43.45.2.2.8.3

Pathophysiology

Listerial abortion can be induced experimentally in cattle 6 to 8 days after infection and in sheep 3 to 11 days after infection. Fetuses die from placentitis and septicemia and are often retained in utero several days before expulsion.[266]

43.45.2.2.8.4

Epidemiology

Listerial abortion is usually sporadic, and incidence seldom exceeds 15%.[266] Infection is most common in the winter and has been associated with feeding of silage. The elevated pH of spoiled silage enhances multiplication of the organism. Aborted tissues are infectious for humans and should be handled with care.

43.45.2.2.8.5

Treatment and Control

The effect on fertility is usually transient, and aborting animals tend to resist reinfection. Tetracycline may be used in remaining pregnant animals in the herd.[5] Aborting animals should be segregated, and fetuses and placentas should be removed from the premises. The feeding of spoiled silage should be avoided.

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43.45.2.2.9

Mycoplasma, Abortion

Mycoplasmal isolations from the bovine genital tract have been mainly *M. bovigenitalium*, and *Mycoplasma bovis. M. bovis*, is probably the more important cause of abortion.[299] *Mycoplasma mycoides*, subsp. *mycoides*, (see *Mycoplasma*, Polyarthritis) and *Mycoplasma agalactiae*, have been associated with caprine abortions.[5]

43.45.2.2.9.1

History and Clinical Signs

M. bovigenitalium, is associated with granular vulvovaginitis and less commonly with endometritis, especially in heifers. Infertility is more common than abortion. *M. bovis*, causes mastitis and abortion.[299] In goats, mycoplasmal infection is associated with septicemia, arthritis, pneumonia, mastitis, and abortion.[5]

43.45.2.2.9.2

Laboratory Diagnosis

Placentitis and fetal pneumonia have been associated with bovine mycoplasmal abortion.[299] Isolation of *Mycoplasma*, from the genital tract, milk, placenta, or fetus indicates infection. However,

mycoplasmosis should not be considered the cause of abortion unless placentitis or fetal inflammation is present and other more likely causes of abortion have been eliminated.

43.45.2.2.9.3 Pathophysiology

M. bovigenitalium, can be isolated from the vagina of as many as 12% of clinically normal cows, but *M. bovis*, is isolated from fewer than 1%. Vulvitis can be induced by inoculation with mucosal scarification with *M. bovigenitalium;*, therefore venereal transmission may be the natural route of infection.[5,299] Experimental inoculation with *M. bovis*, induces abortion with placentitis and fetal pneumonia.[299,300] *M. bovigenitalium*, is rarely isolated from abortuses or normal fetuses.[5]

43.45.2.2.9.4 Epidemiology

Mycoplasma, species are ubiquitous, but mycoplasmal abortions are not commonly documented.

43.45.2.2.9.5 Treatment and Control

Tetracycline or tylosin is the recommended antibiotic for mycoplasmal granular vulvovaginitis in heifers.[299]

43.45.2.2.10 *Salmonella*, Abortion

A variety of *Salmonella*, serotypes have been isolated from aborted fetuses of cattle, sheep, goats, and horses. A complete discussion of salmonellosis is presented elsewhere. Infection is acquired by ingestion of contaminated feed or water. Maternal septicemia is followed by localization of salmonellae in tissues, including the pregnant uterus, where placentitis and fetal septicemia occur. Salmonellosis accompanied by endotoxemia causes early pregnancy loss without colonization of the uterus, because the infection and endotoxemia cause endogenous prostaglandin release. Endogenous $PGF_{2\alpha}$ initiates luteolysis and abortion in the first trimester (<100 days for cattle), as is the case with exogenous administration of PGF products.

43.45.2.2.10.1 History and Clinical Signs

The animal may show systemic signs before abortion. Abortion may occur at any stage of gestation and is characterized by placental necrosis, edema, and hemorrhage. RFMs and fetal autolysis may occur. Abortion may be accompanied by diarrhea, fever, or vaginal discharge, particularly in the ewe, but often infection is not clinically apparent in the dam.[266,301,302] Fetuses also may be lost as a result of stillbirth or perinatal septicemia.

43.45.2.2.10.2 Laboratory Diagnosis

The fetus is frequently autolyzed. Placentitis is usually present. Diagnosis is based on isolation of the organism and evidence of placentitis or inflammation of fetal tissues. FA techniques can identify the bacteria in impression smears or sections of placenta or fetal tissue.[266] The dam can be tested

serologically for evidence of recent active infection,[301] but at present many diagnostic laboratories do not perform *Salmonella*, serology.

43.45.2.2.10.3

Pathophysiology

Infected adult animals are often short-term carriers and shed salmonellae in the feces or milk. True long-term asymptomatic carriers occur mainly with the host-adapted serotypes: *Salmonella*, Dublin in cattle, *Salmonella*, Abortus ovis in sheep, and *S. abortivoequina*, (or *Salmonella*, Abortus equi) in horses. Salmonellosis caused by *Salmonella*, Abortus equi has been eradicated in the United States. Occasionally, long-term carriers of other serotypes are seen; these are usually intestinal carriers and fecal shedders. Infection usually occurs by ingestion. There is no evidence of venereal transmission.[301] Maternal septicemia is followed by localization of the organism in a variety of tissues, including the pregnant uterus. The bacteria multiply in and cause necrosis of connective tissues of the cotyledon.[301] The incubation period between infection and abortion varies from approximately 1 week to 1 month.[5,302] Fetal death results from placentitis and fetal septicemia.[266,303] In most cases, maternal shedding of the organism in cattle ceases by 5 weeks after calving.[301]

In a second mechanism of *Salmonella*,-induced abortion, *Salmonella*, septicemia causes endotoxemia and release of endogenous PGF, which causes luteolysis and abortion. In this case the fetus and placenta are culture negative for salmonellae.

43.45.2.2.10.4

Epidemiology

Bovine abortion resulting from salmonellosis is caused mainly by *Salmonella*, Dublin and *Salmonella*, Typhimurium. Abortion is sporadic and most common in the summer and fall.[301]

Ovine abortion is associated with *Salmonella*, Typhimurium*, S.*, Dublin, *Salmonella*, Arizona, and *Salmonella*, Abortus ovis. *Salmonella*, Abortus ovis (which infects only sheep) is enzootic in parts of England and Europe but is not reported from the United States.[5,266] Young ewes in late gestation are most susceptible, and the abortion rate may approach 50%,[5,302] but usually only one or two ewes in a flock abort.[266]

43.45.2.2.10.5

Treatment and Control

Metritis is a rare complication of salmonellosis that can be fatal.[266] Usually there is no lasting effect on fertility, but animals infected with host-adapted serotypes may become carriers and should be cultured and tested serologically and culled if positive. Salmonellosis can be controlled by hygiene and by avoiding the introduction of carrier animals. Aborting animals should be isolated; the fetus, placenta, and contaminated material should be removed from the premises. *Salmonella*, species are infectious for humans; therefore aborted tissues should be handled with caution.

43.45.2.2.11

Ureaplasma, Abortion

Ureaplasma, is a small bacterium without cell walls; it differs from *Mycoplasma*, in its ability to hydrolyze urea. *U. diversum*, has been associated with granular vulvitis and abortion in cattle.

43.45.2.2.11.1

History and Clinical Signs

Granular vulvitis appears as reddish nodules in the vulvar mucosa, with mucopurulent discharge in the early stages. The discharge is usually more copious and protracted than with IPV induced by herpesvirus.[5,299] Affected cows are not systemically ill.[266] The organism has been recovered from embryo flushing media and can adhere to the zona pellucida, resisting removal by washing. It is believed to be responsible for an 18% reduction in pregnancy rate in embryo recipients when the transfer medium contains the organism.

43.45.2.2.11.2

Laboratory Diagnosis

Gross lesions include thickening of placental membranes with foci of hemorrhage and fibrinous exudate. Gross lesions are seldom apparent in the fetus. Microscopically the placenta is fibrotic, with heavy mononuclear cell infiltration, multifocal necrosis, fibrin deposition, and mineralization. Cuffs of lymphocytes surround fetal intrapulmonary airways.[266] Diagnosis is based on isolation of the organism from genital mucosa, placenta, or fetal stomach or lung and the presence of genital or fetal inflammation.

43.45.2.2.11.3

Pathophysiology

Ureaplasma, can be isolated from the genital tract of normal cows and from normal fetuses.[304] Vulvitis has been induced by inoculation of virgin heifers with *U. diversum*.,[304] Uterine involvement is considered rare but may cause conception failure, early embryonic death, or abortion. Abortion presumably results from placentitis.[5] Intraamniotic inoculation of *U. diversum*, caused placentitis, abortion, and fetal alveolitis in two of four experimental cows.[304] One cow delivered a weak calf at term. Experimental infection in ewes did not decrease fertility.[305]

43.45.2.2.11.4

Epidemiology

Bovine infection is common, but documented abortions caused by *Ureaplasma*, are rare.[299] Infertility is more common in heifers than in cows.

43.45.2.2.11.5

Treatment and Control

Nonirritating tetracyclines by intrauterine infusion are recommended for treatment. Products may not be approved for intrauterine use.[5] Uterine contamination can be avoided by use of the double-rod technique of AI.[5]

43.45.2.3

MISCELLANEOUS BACTERIAL ABORTIONS

In addition to the aforementioned bacteria, other bacteria occasionally produce maternal septicemia. Many of these bacteria are ubiquitous, frequently contaminate aborted fetuses and placentas, and should not be considered the cause of abortion unless (1) they are isolated from the placenta and fetus in large numbers and

relatively pure culture, (2) placentitis or fetal inflammation is evident, and (3) other more likely causes of abortion have been eliminated.[266]

In cows, most bacterial infections of the uterus result from septicemia. Miscellaneous bacterial causes of infertility and abortion include *A. pyogenes, E. coli, Bacillus*, species, *Pasteurella*, species, *Staphylococcus*, species, *Streptococcus*, species, *F. necrophorum*, and *Bacteroides melaninogenicus*.,[266]

A. pyogenes, with or without accompanying anaerobes has been associated with pyometra and abortion in cattle.[188,266,306] Abortions are sporadic and may occur at any stage of gestation. Clinical signs are seldom apparent in the cow. The fetus is commonly autolyzed, and placentitis is typical. Polyserositis may be evident. In fetuses aborted in the first half of gestation, 1-mm yellow foci (bacterial colonies) may be grossly apparent in the lung.[266]

In the ewe or doe, miscellaneous bacterial causes of abortion include Staphylococcus aureus, Streptococcus species, Pasteurella species, E. coli, Yersinia pseudotuberculosis, Francisella tularensis, Histophilus ovis, Bacillus species, *A. pyogenes*, and Corynebacterium species.[266,307–310]

A spirillum-like organism has been documented as a cause of ovine abortion, fetal mummification, stillbirth, and birth of weak lambs. Abortion generally occurs in the last 2 weeks of gestation. Placentitis is consistently present; many fetuses also have fibrinous peritonitis and focal hepatic necrosis that resembles that of campylobacteriosis.[311] Abortion can be reproduced experimentally by inoculation of pregnant ewes.[312] Diagnosis is based on pathologic lesions and identification of the spindloid flagellated organism by darkfield microscopy of fetal abomasal content or liver or by anaerobic culture on selective medium.[311,313]

43.45.2.3.1

Tritrichomonas foetus

Trichomoniasis is a venereal infection of cattle caused by the flagellated protozoan *T. foetus*., [5,189,266,314,315]

43.45.2.3.1.1

History and Clinical Signs

Infertility characterized by a high percentage of cows returning to estrus or found nonpregnant after the breeding season and cows calving late plus occasional pyometras and abortions are the most common clinical signs of trichomoniasis. Pyometra in postcoital heifers or cows suggests that trichomoniasis may be the cause. Abortions generally occur in the first half of gestation at a rate of 5% to 30%.[314] The placenta may be expelled or retained.[5,266]

43.45.2.3.1.2

Laboratory Diagnosis

Diagnosis in the female is made by identifying or culturing trichomonads from cervicovaginal mucus (approximately 76% sensitivity), uterine exudate, placental fluids, or fetal abomasal contents. [5,189,266,314,315] Preputial smegma collected from bulls by using a plastic pipette run against the mucosa can also be cultured for trichomonads (sensitivity 80% to 90%). Diamond's medium (or modified Pastridge medium) is recommended for cultures from cows, bulls, or aborted fetuses.[315] Samples should be transported at ambient temperature, kept out of sunlight, not refrigerated, and delivered promptly to the diagnostic laboratory. The organisms are identified microscopically by their size (10 μm×15 μm),

the presence of three anterior flagellae and an undulating membrane, and a characteristic jerky, rolling motion.[266]

There are no specific gross lesions in aborted fetuses. However, placentitis is a consistent microscopic lesion, and trichomonads can frequently be recognized in the placental stroma in histologic sections. Organisms may also be observed in the fetal lung in association with pyogranulomatous bronchopneumonia.[316]

43.45.2.3.1.3

Pathophysiology

Trichomoniasis is transmitted venereally from infected bulls to cows or vice versa. The organisms colonize the vagina, cervix, uterus, and oviducts; yet they do not generally interfere with conception. Embryonic death frequently occurs within the first 2 months of infection,[5] followed by a 2- to 6-month period of immunity to reinfection.[189] Clearance of infection in cows commonly occurs within 95 days; infection rarely persists as long as 6 months.[314] However, infection in bulls over 4 years of age is permanent and the main source of carryover from one breeding season to the next in beef cattle.[189]

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43.45.2.3.1.4

Treatment and Control

Systemic treatment of infected animals with imidazole compounds (ipronidazole, dimetridazole) is effective, but these compounds are prohibited in food animals in the United States.[242,317,318] Infected cows should be either culled or given at least 3 months' sexual rest. The use of AI with semen from *T. foetus*,—negative bulls controls the disease once infected natural service bulls have been removed from the herd. In natural breeding situations, vaccination, use of young virgin bulls, and testing and elimination of positive bulls older than 3 years of age will allow herd owners to gain control over the incidence of trichomoniasis.

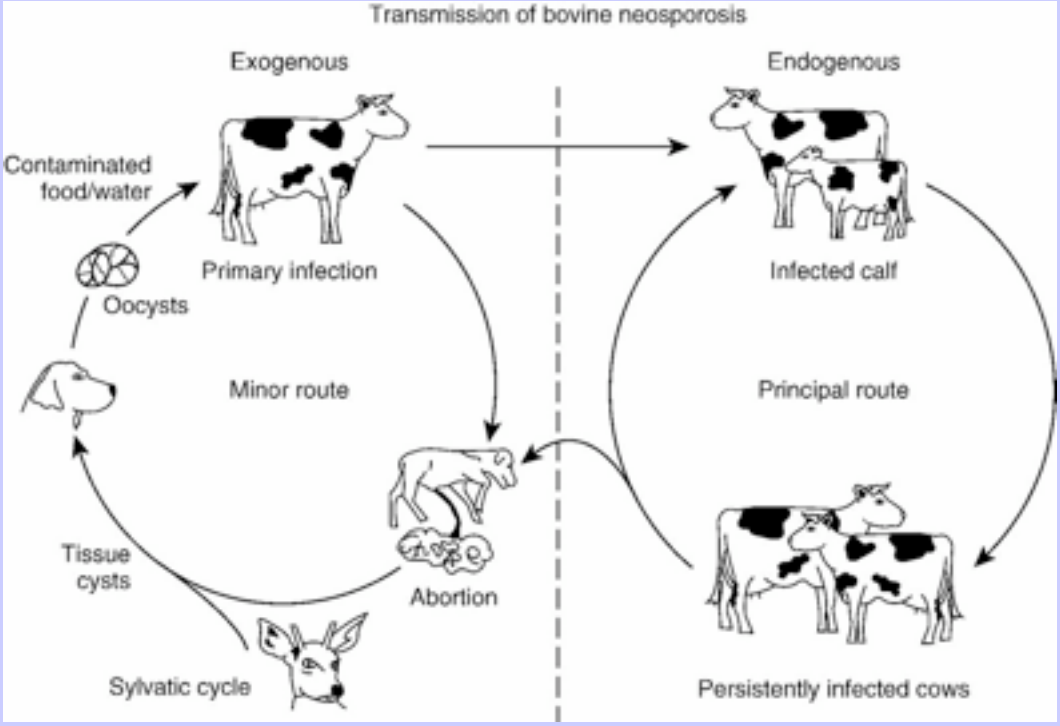
43.45.2.3.2

Neospora caninum, Abortion

Abortion in cattle caused by *N. caninum*, is relatively common and of economic importance especially in dairy cattle. Congenital infection with limb paresis or dysfunction at birth as a result of encephalomyelitis may also occur. Canids are the definitive hosts and shed oocysts in their feces after ingestion of infected tissues from intermediate hosts (Fig. 43-12). Both the domestic dog and the coyote have been shown to transmit the oocysts in their feces.[319,320,321] Along with cattle, deer have been shown to serve as intermediate hosts.[321] The role of birds and wild rodents as intermediate hosts is suspected but has not yet been definitively demonstrated.[321] Aborted, infected fetal tissues ingested by canids will also result in massive shedding of oocysts in feces.[322] Transmission may be vertical (dam to fetus in utero) or via point-source horizontal transmission (ingestion of feed contaminated with feces containing oocysts).[323,324] Horizontal transmission from cow to cow does not occur. Bovine fetal lesions are distinctive and may include nonsuppurative encephalitis with foci of necrosis and gliosis, nonsuppurative myositis, hepatitis, and, most consistently, myocarditis.[261] Most abortions occur in the early second trimester, but they may occur throughout gestation. Diagnosis is based on characteristic lesions in aborted fetuses, and seroepidemiologic study of an equal number of aborting and nonaborting herdmate cows if the proportion of seropositives is statistically higher in those that have aborted.[325] Finding one aborting cow to be

seropositive does not confirm *N. caninum*, as the cause, and cows that abort once because of *N. caninum*, are not protected from future abortion caused by this organism. A vaccine based on whole killed tachyzoites (Neoguard1, Intervet, Millsboro, Del.) is available for *N. caninum*.

Fig. 43-12 Transmission of bovine neosporosis. Oocysts are produced by the canine definitive host, and their subsequent ingestion by a susceptible pregnant cow leads to infection of the fetus (exogenous transplacental transmission). Liveborn infected heifer calves would be expected to remain infected into adulthood, when they, in turn, may pass infection to their fetuses (endogenous transplacental transmission). Spread of *N. caninum*, in this second way is the principal route whereby the parasite is propagated in a herd.



43.45.2.3.3

Sarcocystis, Abortion

Sarcocystosis may cause abortion in cattle, sheep, and goats. Cattle are infected by *Sarcocystis cruzi*, sheep by *Sarcocystis ovicanis*, and goats by *Sarcocystis capracanis*.,

43.45.2.3.3.1

History and Clinical Signs

Most cattle are infected with *Sarcocystis*, but do not show clinical signs of infection; however, massive or repeated infections may elicit depression, anorexia, weight loss, lameness, hair loss, emaciation, or death. Abortions occur in late gestation, usually in severely affected animals.[266,326,327]

43.45.2.3.3.2

Laboratory Diagnosis

There are no specific gross lesions in the aborted fetus. Histologically protozoa may be observed in villi and small arteries of the cotyledon or (more likely) the caruncle but are seldom seen in the bovine, ovine, or caprine fetus. Parasites are more likely to be observed in the fetal brain than in other tissues.[326] Nonsuppurative inflammation may occur in the placenta or, less commonly, in fetal tissues, particularly the brain, heart, lung, liver, or kidney.[266,326,327]

FA demonstration of numerous developing protozoa in the cotyledon or caruncle is considered diagnostic. Caruncles are reported to be atrophied.[326] The protozoa can also be isolated by feeding aborted tissues to canids and recovering coccidian sporocysts from their feces.[266]

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43.45.2.3.3.3

Pathophysiology

The pathogenesis of abortion in sarcocystosis is unclear. Generally, numerous spores are required to induce abortion experimentally. Fetal invasion by *Sarcocystis*, is rare, and abortion may result from maternal fever, anemia, or placental insufficiency.[326] Pregnant does apparently have diminished immunity to *Sarcocystis*, because low doses of *S. capracanis*, result in fetal death without maternal illness if given in early pregnancy.[328]

43.45.2.3.3.4

Epidemiology

Ruminants are infected by consumption of canid feces that contain oocysts. *Sarcocystis*, occurs in the skeletal and cardiac muscle of most cows without associated lesions or clinical evidence of illness.

43.45.2.3.3.5

Control

Effective therapeutic regimens for clinically ill animals have not been developed. For the lifecycle of *Sarcocystis*, to be broken, feeds should be kept free of dog or cat feces. These carnivores should not be allowed to eat aborted fetuses, placentas, or other ruminant carcasses.

43.45.2.4

Fungal Abortions

43.45.2.4.1

Mycotic Diseases That Cause Abortion

Fungal causes of bovine abortion include *Aspergillus, Absidia, Mucor, Rhizopus, Candida*, and *Mortierella*.,[266,329,330] Mycotic abortion is uncommon in sheep and goats.[266]

43.45.2.4.1.1

History and Clinical Signs

Mycotic abortions usually occur in the latter half of gestation (often near term) and seldom are associated with prodromal or postabortion clinical signs in the dam.

43.45.2.4.1.2

Laboratory Diagnosis

The most consistent lesion is placentitis with necrosis and thickening of fetal membranes. In ruminants, both cotyledons and the intercotyledonary placenta are affected. Histologically, necrotizing inflammation of the chorionic villi is associated with vasculitis and thrombosis.[266] Gross lesions may not be apparent in the fetus, but granulomatous bronchopneumonia is frequently observed histologically.[266,330–332] In bovine aspergillosis the fetus is often near term with minimum autolysis and partially inflated lungs. Emaciation and dehydration with multifocal dry, scaly skin lesions occur in approximately 25% of affected fetuses.[266] With other fungi the aborted fetus is often autolyzed, placentitis may be more severe, and skin lesions, if present, tend to be moister than those of aspergillosis.[266] The placenta is characteristically thickened and leathery. The fetus may be emaciated, and granulomatous bronchopneumonia has been observed.[331] The fungus can be isolated from the fetus and placenta or demonstrated on histologic sections with immunostaining.

43.45.2.4.1.3

Pathophysiology

The route of fungal infection in the bovine uterus is thought to be hematogenous.[11]

43.45.2.4.1.4

Epidemiology

Mycotic abortion generally affects only one or two animals in a herd and is more common in the winter.[266] Fungi cause 3% to 10% of bovine abortions.[333,334] *Aspergillus*, accounts for up to 80% of bovine mycotic abortions; Mucorales account for an additional 10% to 15%.[5] *Mortierella*, is a common abortifacient in Australia and New Zealand and has been associated with feeding of grass silage,[330,334] but *Mortierella*, abortion is rare in the United States.

43.45.2.4.1.5

Control

The only means of control of mycotic abortion is reduction of exposure to fungal agents.

43.45.2.4.2 DOES AND EWES

43.45.2.4.2.1 INFECTIOUS CAUSES

43.45.2.4.2.1.1 Bluetongue Abortion

Bluetongue is an orbivirus infection that can result in embryonic death, abortion, and fetal anomalies in sheep, cattle, or other ruminants. Twenty-four serotypes of bluetongue virus have been recognized; five of these (serotypes 2, 10, 11, 13, and 17) occur in the United States (see Chapter 32 for complete discussion and Chapter 35 for nervous system anomalies).[335]

43.45.3 Border Disease (Hairy Shaker Disease)

Border disease or hairy shaker disease is an ovine pestivirus infection that causes embryonic and fetal death; stillbirths; dysplasia of the central nervous system, skeleton, and fleece; and birth of weak lambs with low viability.

43.45.4 *Coxiella burnetii*, (Q Fever)

Coxiella burnetii, a rickettsia, is the causative agent of Q fever, which can cause abortions in sheep and goats. Most infections are completely asymptomatic, and the disease is of more importance as a zoonosis than as a cause of ovine or caprine abortion.

43.45.4.1 History and Clinical Signs

Late abortions or delivery of weak lambs may occur in an affected flock over a period of 2 to 4 weeks.[5,302]

43.45.4.2 Laboratory Diagnosis

There are no specific gross lesions in the fetus, but the placenta is thickened with white, chalky plaques and red-brown exudate, especially in intercotyledonary areas. Histologically cotyledonary and intercotyledonary necrosis is accompanied by heavy neutrophil infiltration.[5,336] Diagnosis of Q fever abortion should be based on the presence of characteristic placental lesions with large numbers of rickettsiae and a rising maternal titer. Rickettsieae can be identified in placental impression smears stained with modified Koster's stain, Stamp's modified Ziehl-Neelsen stain, or Gimenez stain as pleomorphic acid-fast coccoid or filamentous organisms in trophoblasts or extracellularly. Complement fixation titers greater than 1:8 in the dam are considered diagnostic. Enzyme-linked immunosorbent assay is rapid and sensitive but requires species-specific peroxidase conjugate for each host species. Laboratory results must be interpreted carefully because *C. burnetii*, also can be isolated from the placenta of normal animals.[5] In one survey of California dairy goats, 24% were seropositive by microagglutination.[337]

43.45.4.3 Pathophysiology

C. burnetii, infection can be transmitted by ixodid or argasid ticks or by ingestion of infected material. The organism replicates in trophoblasts and is often of low pathogenicity in sheep and goats but can result in placentitis with late abortion and shedding of large numbers of rickettsiae.[5]

43.45.4.4 Epidemiology

Q fever is reported in many countries, including the United States and Canada. Abortions typically occur over a 2- to 4-week period and may affect 5% to 50% of the flock.[5] The organism also is infectious for other animals, including humans. Pregnant women should not handle Q fever—infected animals or tissues.

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43.45.4.5 Treatment and Control

Aborting does and ewes should be segregated, and abortuses and placentas removed from the premises to prevent oral transmission. Pregnant animals can be treated with tetracycline to reduce the chances of abortion. A carrier state may develop, but abortions do not usually occur in subsequent pregnancies in sheep; they may be more likely to recur in goats.[338] Inactivated vaccines (not commercially available) lessen the chances of rickettsial abortion in sheep and reduce but do not eliminate rickettsial shedding at parturition.[336]

43.45.5 *Campylobacter fetus*, subspecies *fetus*, Abortion

C. fetus, subsp. *fetus*, is one agent of ovine campylobacteriosis (vibriosis) that causes abortion in sheep and sporadic abortion in cattle and goats.[5,266,302]

43.45.5.1 History and Clinical Signs

Infection of ewes causes abortion in the last 6 weeks of pregnancy, stillbirths, and birth of premature lambs. Infected ewes may have fever, diarrhea, depression, and vaginal discharge several days before parturition.[302] In cattle the infection is not associated with infertility (unlike infection with *C. fetus*, subsp. *venerealis*), but sporadic abortions can occur from the fourth to eighth months of gestation.[266]

43.45.5.2 Laboratory Diagnosis

Campylobacter, causes placentitis with cotyledonary necrosis and intercotyledonary edema. The fetus is edematous and may have fibrinous polyserositis. Foci of necrosis up to 2 cm in diameter occur in the liver of approximately 40% of aborted ovine fetuses and, although not pathognomonic, suggest campylobacteriosis.[5,266] Histologic changes include suppurative necrotizing placentitis and fetal bronchopneumonia.[266] Diagnosis is based on culture (which usually requires less than 48 hours)[5] or on microscopic demonstration of the organism.[5]

43.45.5.3 Pathophysiology

C. fetus, subsp. *fetus*, is transmitted by ingestion. The organism localizes in the gallbladder but may invade the pregnant uterus, where it replicates in chorioallantoic trophoblasts. The incubation period in the ewe varies from 7 to 25 days.[5] In the cow, dissemination of the organism to the placenta is less common.[266] In either species, localization in the placenta causes placentitis and fetal bacteremia.[266] Metritis, fetal retention, and maternal peritonitis may occur in the ewe.[5]

43.45.5.4 Epidemiology

Infection with *C. fetus*, subsp. *fetus*, is important in sheep in the United Kingdom, the United States, and New Zealand.[5] Fetal infection is most common during the last 2 months of gestation. Outbreaks of abortion tend to occur in 4- to 5-year cycles.[5] Infection is highly contagious in confined ewes, and the abortion rate may approach 70% but is more commonly approximately 25%.[5,266,302]

43.45.5.5 Treatment and Control

Abortion outbreaks can be treated with daily intramuscular injections of procaine penicillin G (22,000 IU/kg) and dihydrostreptomycin (11 to 22 mg/kg) or with oxytetracycline in the feed (75 mg/head/day).[5] Metritis is rarely fatal in the ewe. Generally, affected ewes abort only once and therefore they may be retained as breeding stock.[266] Ovine campylobacteriosis can be controlled by the use of a killed adjuvanted bacterin at breeding and 60 to 90 days later.[5]

43.45.6 *Campylobacter jejuni*, Abortion

Campylobacter jejuni, is the other agent of ovine *Campylobacter (Vibrio)*, abortion. *C. jejuni*, is an enteric pathogen that causes enteritis and diarrhea in many species. Only in sheep is placental and fetal infection common. This organism has been associated occasionally with abortion in cattle and goats.[5,11,266,339,340]

43.45.6.1 History and Clinical Signs

Ovine infection with *C. jejuni*, is clinically indistinguishable from that with *C. fetus*, subsp. *fetus*.,

43.45.6.2 Laboratory Diagnosis

Aborted fetuses are autolyzed and frequently lack specific gross lesions. Cotyledons are mottled yellow to tan, but the intercotyledonary membranes are grossly normal. Histologically necrosis occurs in chorionic villi with arteriolitis and numerous leukocytes in the lamina propria. Purulent bronchopneumonia is a common histologic finding in the fetus.[341]

C. jejuni, can be distinguished from other *Campylobacter*, species by growth at 42° C (107.3° F), resistance to cephalothin, inhibition by nalidixic acid, and the presence of heat-labile glycoprotein surface antigen 1, which does not occur in *C. fetus*, subsp. *venerealis*, or *C. fetus*, subsp. *fetus*., Placenta or fetal tissues should

be cultured on *Campylobacter*, agar with incorporated cefoperazone, vancomycin, and amphotericin B (CVA medium) at 42° C (107.3° F).[340,341]

43.45.6.3 Pathophysiology

Intravenous inoculation of pregnant ewes with *C. jejuni*, at 114 and 123 days of pregnancy consistently induced abortion 7 to 12 days later in one study.[341]

43.45.6.4 Epidemiology and Control

C. jejuni, is ubiquitous. Certain strains have been associated with an abortion rate as high as 80%, but usually fewer than 20% of the animals in the flock abort.[341] Aborted tissue is infectious for humans and should be handled with caution. Treatment and control of ovine infection with *C. jejuni*, are similar to those for *C. fetus*, subsp. *fetus*.,

43.45.7 *Brucella melitensis*, Abortion

Brucella melitensis, causes abortion in goats and sheep and less commonly in cattle.[5] Infection is associated with late abortion, stillbirth, or birth of weak kids or lambs.[5,283] Necropsy findings include severe placentitis and fetal serositis.[5,302] The disease is diagnosed by culture or demonstration of the organism in tissue or by maternal serology (complement fixation test).[5] Animals are infected by ingestion, and, after bacteremia, replication occurs in chorioallantoic trophoblasts.[5,285] Infection with *B. melitensis*, is important in Mediterranean countries and in Central and South America but is rare in the United States.[283,302] Suspected cases should be reported to state and federal authorities. Human infection with *B. melitensis*, can be very severe.

43.45.8 *Brucella ovis*, Abortion

Brucella ovis, infects only sheep. Epididymitis in rams is the most common manifestation of infection. Ewes seldom show clinical evidence of infection; late abortions, stillbirths, and delivery of weak lambs are rare.[5,266] 1467
Fetal and placental lesions resemble those induced by *B. abortus*., Diagnosis is based on culture or on 1468
demonstration of the organism in tissue. Serology (complement fixation) can identify infected animals. However, not all ewes showing a rise in complement fixation titer at parturition deliver infected lambs. In addition, ewes can maintain elevated titers for months or years after exposure to *B. ovis*., Therefore *B. ovis*, abortion should not be diagnosed on the basis of complement fixation testing alone.[266]

Infection is thought to occur by the conjunctival route.[302] The bacterium has low virulence for the ewe but may replicate in chorioallantoic trophoblasts, resulting in placentitis and fetal bacteremia.[285] *B. ovis*, infection has been reported from Europe, Africa, Australia, New Zealand, and the western United States.

43.45.9 *Chlamydia psittaci*, Abortion (Enzootic Abortion of Ewes)

C. psittaci, is a major cause of abortion in sheep and goats.[5,266] Ovine chlamydial abortion is called *enzootic abortion of ewes. Chlamydia*, may cause abortion in cattle[266] but is not the cause of epizootic bovine (foothill) abortion.

43.45.9.1 History and Clinical Signs

Chlamydiosis is best characterized in sheep and goats. Abortions or stillbirths with placentitis usually occur in the fourth to fifth months of gestation. The dam seldom shows signs of illness but may have serosanguineous vaginal discharge several days before and after parturition.[5] Other animals in the flock may be affected by arthritis or pneumonia.[342]

43.45.9.2 Laboratory Diagnosis

Placentitis is the most consistent necropsy finding in chlamydial abortion. Necrosis occurs in cotyledons; the intercotyledonary placenta is thickened with accumulation of red exudate.[266,342] The fetus has no specific gross lesions.[266,342] Histologically, necrotizing placentitis is accompanied by nonsuppurative vasculitis. Nonsuppurative meningoencephalitis, necrotizing hepatitis, and proliferation of mononuclear cells in spleen and lymph nodes are other histologic findings that may occur in the fetus.[266,343]

Diagnosis of chlamydial abortion should be based on identification of the organism and the presence of typical placental lesions. Chlamydiae appear in placental impression smears stained with Giemsa, Gimenez, or modified Ziehl-Neelsen stains as 200-nm dark red spheric bodies in the cytoplasm of trophoblasts.[5,266] The organism can be positively identified by FA tests on cytologic preparations, cryostat sections of placenta or other fetal tissues, or cultures. *Chlamydia*, grows in chick embryos in 1 to 6 weeks, but cell culture using mouse L cells requires only 2 to 10 days.[266]

Abortion or delivery of chlamydial-infected fetuses induces a rise in serum titer that peaks in 2 to 3 weeks.[266] Paired sera should be collected at abortion and 3 weeks later. Maternal titers greater than 1:32 generally indicate recent active infection.[344] Complement fixation is the standard serologic test for the dam; indirect immunofluorescence and enzyme-linked immunosorbent assay are also used.[345] Double immunodiffusion can be performed on fetal fluids.[266]

43.45.9.3 Pathophysiology

Chlamydiae reside in the intestinal tract and are also shed from the genital tract of infected animals before and after parturition. Ingestion is the main form of transmission.[5,346] In sheep and goats, abortion occurs 4 to 8 weeks after experimental infection,[342] but the fetus is not susceptible until the last third of gestation.[5]

High maternal antibody titers do not prevent abortion or stillbirth, but experimental work suggests that cell-mediated immunity is protective.[347] Infection with small numbers of *Chlamydia*, organisms seldom

stimulates adequate cell-mediated immunity and consequently may be more likely to cause abortion than infection with numerous organisms.[5]

43.45.9.4 Epidemiology

Chlamydial abortion has been reported from most major sheep- or goat-producing countries. *C. psittaci*, also may infect other animals, including human beings. Pregnant women should not handle infected animals or tissues. The abortion rate in sheep is usually approximately 5%[266] but may be up to 30% or more in goats.[5,342] Although abortions usually occur 1 to 2 months after infection in sheep, the incubation period in goats may be as short as 2 weeks.[344]

43.45.9.5 Treatment and Control

Aborting does or ewes should be segregated, and abortuses and placentas should be removed from the premises to avoid oral transmission. Oxytetracycline therapy (80 to 450 mg/head every day in feed or water, or long-acting oxytetracycline injected subcutaneously at a dose of 20 mg/kg twice weekly until the last month of gestation)[5] reduces the number of abortions and stillbirths in sheep[347] and goats, particularly if instituted in the first half of pregnancy.[5] However, short-term treatment does not eradicate infection or prevent chlamydial shedding at parturition and should be reserved for abortion outbreaks.[348] Most ewes develop cell-mediated immunity, which eliminates the organism from the genital tract by 3 months after lambing and protects against abortion for approximately 3 years.[5,348] Does are more likely than ewes to have placental retention and metritis after abortion.[346] Killed vaccines* can be used in enzootic areas 4 to 6 weeks before breeding but are not 100% effective. Experimentally avirulent live vaccines have been used with success.

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43.45.10 Toxoplasmosis Abortion

Toxoplasma gondii, is a ubiquitous protozoan that is a major abortifacient in sheep and goats but only rarely causes abortion in cattle or horses.

43.45.10.1 History and Clinical Signs

Infection does not cause clinical illness in the adult but may result in embryonic death, fetal death and abortion, stillbirth, or birth of weak, nonviable lambs or kids.

43.45.10.2 Laboratory Diagnosis

The most characteristic gross lesion of toxoplasmosis is the presence of white, chalky foci of necrosis and calcification up to 2 mm in diameter in cotyledons.[349–351] The intercotyledonary areas of the placenta are grossly normal. Specific gross lesions are not observed in the aborted fetus, but histologically most have nonsuppurative encephalomyelitis[350] and many also have pneumonia, myocarditis, or hepatitis. Tachyzoites may be found in placenta or other fetal tissues but are not numerous.[351,352] The tachyzoites are oval, 2 to 4 by 4 to 8 mm, with a central nucleus and appear larger in impression smears than in paraffin sections. Several

serologic tests, including the modified agglutination test, indirect FA test, Sabin Feldman dye test, indirect hemagglutination test, and enzyme-linked immunosorbent assay, reliably detect toxoplasmosis in pleural or amniotic fluid or presuckling serum from nondecomposed fetuses.[266,353,354] The modified agglutination test is commercially available, safer, and more sensitive than the dye test. Fetal antibodies to *T. gondii*, can be detected 35 days after infection.[349] Absence of fetal antibody does not always preclude a diagnosis of toxoplasmosis.[266] High maternal titers are not diagnostic of toxoplasmal abortion, but lack of titer eliminates toxoplasmosis as the cause for abortion.[349] The peroxidase-antiperoxidase method for detecting *Toxoplasma*, antigen in fetal tissues or placenta is reliable even in autolyzed fetuses. Fetal heart, lung, brain, spinal cord, skeletal muscle, and placenta are the preferred specimens for the peroxidase-antiperoxidase method and should not be held in formalin more than 2 days before paraffin embedding.[352] *T. gondii*, can be isolated by intraperitoneal inoculation of placental or fetal tissue suspensions into mice.[266]

43.45.10.3 Pathophysiology

Placental infection occurs approximately 14 days after ingestion of oocysts.[352] Infection acquired before 50 days' gestation may result in embryonic death and resorption. Infection between 60 and 100 days' gestation usually causes fetal death or birth of weak lambs. Infection during the last month of gestation often has no apparent effect on the fetus.[349] In experimental infection of ewes between 6 and 14 weeks of pregnancy, abortions occurred 1 to 2 months after inoculation.[354] In natural infections, most abortions occur 1 month before parturition.[349]

43.45.10.4 Epidemiology

Toxoplasmosis is a major cause of ovine abortion in many sheep-raising countries, including the United States.[350,351,355] Sheep are infected by ingestion of oocysts from feed or grass contaminated with cat feces. Most ewes are infected by 4 years of age.[356] Aborted tissues may be infectious for humans and should be handled with caution.

43.45.10.5 Control

Infected ewes or does seldom abort from toxoplasmosis in subsequent pregnancies.[350] The prevalence of abortion can be reduced by avoiding contamination of feedstuffs with feline feces. Cats should not be allowed to eat placentas or carcasses that may contain tachyzoites or tissue cysts. In endemic areas, exposing replacement ewes to aborting ewes may provide immunity before breeding age.[5]

43.45.11 *Mycoplasma*, Abortion

Treatment of *Mycoplasma*, infection in goats is usually not recommended because treated animals may remain carriers. The infection is eliminated from the herd by testing milk and slaughtering infected animals.[300]

43.45.12 Leptosirosis

Serovar *Leptospira*, Pomona is the major ovine isolate,[266] but *Leptospira*, Bratislava and *Leptospira*, Hardjo have also been isolated from sheep.[266] *Leptospira*, Grippotyphosa is the major caprine isolate.[5] Leptospiral abortion is less common in sheep and goats than in cattle.

43.45.12.1 CAMELIDS

The incidence of abortion in llamas and alpacas is low. Infectious causes in North America include leptospirosis, toxoplasmosis, chlamydiosis, and other nonspecific uterine infections.[191] Bovine virus diarrhea is considered an emerging disease in alpaca herds and may be responsible for some of the early pregnancy losses and abortions in some herds. Diagnostic workup for abortion in camelids is similar to that described in this chapter for other species.

43.46 MALE REPRODUCTIVE DISORDERS

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43.46.1 INFERTILITY CAUSED BY DISEASES OF THE PENIS AND PREPUCE

43.46.1.1 PENILE INJURY

43.46.1.1.1 STALLION

43.46.1.1.1.1 Definition and Etiology

If the penis is injured while erect, it may swell rapidly and massively from vascular rupture and hemorrhage. Hemorrhage usually originates from the superficial penile vessels in the plexus external to the tunica albuginea.[357] The stallion may be kicked during mating, or hematomas may follow breeding a mare with a tightly sutured vulva or may be induced if the mare moves suddenly during mating.[358,359] Injuries can also occur during semen collection if proper techniques are not employed.

43.46.1.1.1.2 Clinical Signs and Differential Diagnoses

Cutaneous abrasions, lacerations, and visible hemorrhage may be present. Paraphimosis occurs when enlargement is sufficient to prevent retraction of the penis through the preputial ring.[357] Edema may extend to the scrotum and interfere with thermoregulation of the testes.[360] Venous thrombosis, lymphatic occlusion, excoriation, and swelling accompany chronic inflammation.[357] Hemorrhage from

the corpus cavernosum penis (CCP) is uncommon. Rupture of the surrounding tunica albuginea, when healed, may develop fibrous adhesions that lead to penile deviation during erection.

43.46.1.1.1.3 Treatment and Prognosis

Immediate treatment is directed toward reducing edema and inflammation and controlling infection. Treatment is similar to that described for paraphimosis in a later section. Sexual rest is indicated until the lesions have healed.[361] If treatment is initiated early and paraphimosis does not occur, the prognosis for recovery is good.[357,359]

43.46.1.1.2 BULL

43.46.1.1.2.1 Definition and Etiology

The penis of bulls is susceptible to injury during mating. The vigorous thrust that accompanies copulation predisposes the penis and prepuce to excoriations, lacerations, and bruising. Rupture of the tunica albuginea (penile hematoma or "broken penis") occurs if the penis is misdirected during copulation.[362] Penile hematomas most commonly occur in young, sexually aggressive bulls. Injuries occur when these bulls attempt to breed heifers or cows that are not receptive, when females falter or collapse under the weight of the bull, or when the bull slips because of poor footing.[358] During copulatory thrusting in which the penis is bent, the tunica albuginea ruptures on the dorsal or dorsolateral surface of the penis opposite the attachment of the retractor penis muscle. Presumably, CCP pressure rapidly increases as the functionally closed system is compressed during bending to rupture the tunica albuginea. Experiments with fresh postmortem specimens indicated that a CCP pressure of 1180 to 1720 psi was required to rupture the tunica albuginea. Tearing virtually always occurred at the site described in naturally occurring cases. Mean peak CCP pressure recorded during normal coitus (275 psi) occurs when cavernous spaces fill with a relatively small volume of blood, perhaps as little as 110 mL.[360] Blood escapes from the CCP into the surrounding tissue.[357] The size of penile hematomas may be related to the number of repeated trials made by the bull before cessation of attempts at mating. Larger hematomas restrict full retraction of the penis and result in prolapse of the prepuce from the sheath. Secondary preputial injury is common.[357]

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43.46.1.1.2.2 Clinical Signs and Differential Diagnoses

Diagnosis of penile hematoma is made based on the presence of a swelling immediately cranial to the scrotum. Initially it is soft, fluctuant, and painful, and becomes firm as clot organization and fibrin formation progress.[358] The main differential diagnosis is extensive preputial laceration. If a distance of more than two handbreadths is present between the scrotum and the enlargement, the swelling is more likely to be a preputial laceration. Other differential diagnoses include rupture of the urethra, abdominal hernia, and chronic, fibrous adhesions. Dysuria usually does not occur in conjunction with penile hematoma. Other signs of urethral rupture or blockage, such as extensive preputial cellulitis and "water belly," elevated blood levels of urea nitrogen and creatinine, and tissue necrosis do not occur. Abscess formation of penile hematomas sometimes occurs. A soft, fluxuant center is characteristic of an abscess. Occasionally, differentiation between blood clot and abscess may be difficult. An aseptic tap can be

done to determine the character of the fluid, but the risk of inducing an abscess in a sterile hematoma is great and a tap should be used only as a last diagnostic resort or just before surgery.

If penile hematoma has been present for longer than 2 weeks, fibrous adhesions may form that prevent penile extension. Adhesions are frequent sequelae of abscesses, and have also been reported to occur secondary to infiltration of local anesthetics to block the dorsal nerves of the penis.[358] Another sequela is the development of venous shunts that communicate between the CCP and either the peripenile vasculature or the corpus spongiosum penis (CSP).[357,363] Such vascular shunts result in rapid drainage of blood from the CCP and impotence caused by failure to achieve or maintain full erection. If the dorsal nerves of the penis are damaged, sensation of the distal penis is lost or deficient and results in failure of the bull to successfully seek out the female's vagina and/or ejaculate. Organization of the portion of the blood clot (thrombosis) within the body of the CCP may result in functional blockage of engorgement of the more distal cavernous spaces, preventing full erection.

43.46.1.1.2.3

Treatment and Prognosis

Treatment of penile hematomas should be aimed not only at restoring the bull to usefulness, but also at preventing recurrence. Approximately 50% of bulls with hematomas that are treated conservatively (i.e., nonsurgically) are reported to return successfully to breeding.[357] Some theriogenologists feel that small hematomas (less than football size) do not require surgery.[364] However, Auburn University faculty report that surgical intervention is required to optimize chances of full recovery. Surgical correction has the advantages of (1) removing the blood clot before extensive fibrous adhesions develop, (2) permitting removal of blood clot from within the body of the CCP itself, thereby reducing the chance of blockage of cavernous filling, and (3) suturing the tunica albuginea, which should reduce the chance of recurrence of the condition after return to service and the likelihood of development of vascular shunts that will prevent complete filling of the CCP. Surgical intervention is not recommended before coagulation of the extravasated blood. Once significant fibrin formation is present, the prognosis for successful correction is greatly reduced and should be attempted only in valuable bulls.[357]

Additional recommendations before electing surgical intervention include extending the penis manually. Cases in which the penis can be extended from 6 to 8 inches or more beyond the sheath orifice, and in which penile sensation remains, carry a better prognosis.[365] If engorgement of the distal penis does not occur after careful stimulation with the electroejaculator, blockage of the CCP should be suspected and reduces the prognosis. Finally, cases with abscesses are poor risks because severe restrictive adhesions usually develop.[357]

Regardless of whether surgical or conservative intervention is selected for a penile hematoma, the bull should be treated with high levels of systemic antibiotics in an attempt to prevent abscess formation. Penicillin is a good choice because abscesses are usually caused by *A. pyogenes*., Postsurgical complications are much the same as those that may occur without surgery, but these adverse consequences are reported to occur less frequently after surgery. Bulls should not be returned to service for 2 to 3 months after treatment.[357,358]

43.46.1.1.3 RAM AND BUCK

Adhesions of the penis and prepuce caused by trauma are uncommon in adult small ruminants. The penis does not separate from the prepuce until puberty and cannot be extended before this time (4 to 5 months of age in bucks).[366] Most traumatic lesions of the penis or prepuce in sheep and Angora goats are from shearing injuries.[264] Blockage of the urethral process by calculi can cause necrosis and sloughing of tissue that may extend into the glans penis.[367] Fighting among horned animals may result in injury to the external genitalia, including the penis. In dairy goats the intersex condition can result in congenital malformation of the penis and prepuce (hypospadias).[368]

43.46.1.2 PHIMOSIS AND INJURY TO THE PREPUCE

43.46.1.2.1 STALLION

43.46.1.2.1.1 Definition and Etiology

Stenosis of the preputial orifice prevents extension of the penis. The defect is likely to be a sequela to an injury that results in cicatrix formation, but may rarely be congenital.[357,358] Tumors (such as melanoma or SCC) or *Habronema*, granulomas may encroach on the preputial cavity, thereby preventing penile extension.[369]

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43.46.1.2.1.2 Clinical Signs and Differential Diagnoses

Acute posthitis often accompanies injuries to the prepuce or infections such as equine coital exanthema and dourine.[357,358] Edema is common with acute posthitis, particularly after trauma. Gravitational effects typically worsen the preputial edema, which may induce prolapse of the external prepuce, trapping the penis in the swollen internal prepuce with a constricting preputial ring.[357] Cicatricial scar formation may follow, narrowing the diameter of the preputial orifice. Transpreputial ultrasound examination may be of benefit in differentiating tumors or abscesses from inflammatory edema or hemorrhage. Containment of the penis within the prepuce causes preputial urine accumulation, worsening balanoposthitis and secondary bacterial infection. The extended chronic inflammation leads to cicatrix formation with phimosis.[370]

43.46.1.2.1.3 Treatment and Prognosis

Preputial edema can be relieved by administration of diuretics and exercise. Application of crushed ice in plastic bags or preputial immersion in cold water may reduce inflammatory edema if performed soon after injury. Subsequently, emollient antibiotic preparations and hydrotherapy can be used to massage injured tissues and reduce edema. Systemic antibiotics and nonsteroidal antiinflammatory drugs are indicated to control secondary infection and inflammation. Sexual rest is indicated until the lesions have healed.[361]

A biopsy can be procured from encroaching tumors to identify cell types and improve prognostic capability.[361] Cicatricial scars can sometimes be successfully removed surgically. Once inflammation and infection are resolved with local or systemic antibiotic and antiinflammatory drug treatment, incision of the ventral aspect of the preputial orifice (preputiotomy) may be necessary to enlarge the opening sufficiently to permit penile extension.[371] Large tumors or granulomas of the prepuce can sometimes be successfully removed surgically if sufficient elastic and membranous tissue remain to permit normal penile extension and retraction.[361] The prognosis for return to breeding soundness, however, is guarded when surgery must be performed. Postsurgical adhesions may develop that result in continued phimosis or penile deviation. In cases of habronemiasis, treatment with systemic insecticides or ivermectin may be indicated to kill remaining parasitic larvae.[369] Congenital abnormalities can seldom be corrected surgically.

43.46.1.2.2

BULL

43.46.1.2.2.1

Definition and Etiology

Trauma to the prepuce involving the elastic lamellar layers may prevent the required flexibility of the prepuce to permit penile extension. Breed predisposition to preputial injuries corresponds to genetic differences in pendulousness of the sheath and development of the muscles responsible for retraction of the prepuce. The polled gene is linked to weak or failed development of the preputial muscles, leading to habitual preputial eversion, which predisposes to injury. Brahman-blooded cattle have the added predisposition of a loose, pendulant sheath. With their tendency to partially evert the preputial membrane through the sheath orifice, they are at greater risk for damaging the prepuce accidentally than those breeds of cattle in which the sheath is held in close apposition to the abdominal wall.[357,358,372]

Inability of the bull to extend the penis most commonly follows injury to the penis and prepuce that culminates in strictures or adhesions that restrict normal penile movement.[357,358,373–376] Other causes of phimosis include congenital anomalies such as a short penis, a short retractor penis muscle, and developmental abnormalities of the reproductive tract such as occur in pseudohermaphrodites.[358,374]

43.46.1.2.2.2

Clinical Signs and Differential Diagnoses

The more common preputial injuries are contusions, abrasions, lacerations, and frostbite. When the injured prepuce can be retracted, the injury may not be suspected unless hemorrhage is noted from the sheath or the bull is observed having difficulty during breeding. Although minor injuries may spontaneously resolve, more extensive injuries commonly progress to abscess formation and fibrous stricture formation.[357,364,375,376] Extension and examination of the penis may result in further injury if the case is complicated by phimosis. In such cases an attempt to extend the penis to facilitate examination is contraindicated because forcibly stretching the prepuce will extend the laceration and spread infection to uncontaminated areas.[357]

43.46.1.2.2.3

Treatment and Prognosis

Treatment of preputial injuries in the bull may be either medical or surgical. With few exceptions, such as fresh avulsive lacerations in the fornix area, surgical intervention carries a better prognosis when medical treatment is first carried out to control inflammation and infection.[375] The healing leaves more normal tissue to be identified and salvaged during surgery. In cases in which the injured prepuce is retracted into the preputial cavity, digital or speculum examination can be done in an attempt to locate lesions and determine the extent and depth of tissue involvement. Systemic administration of antibiotic is necessary to reduce the incidence of abscess formation preoperatively, and antibiotic should be administered through the surgical and postsurgical periods if surgery is elected. When the injured prepuce remains prolapsed in presented bulls, the first consideration is to attempt to return the prepuce to the preputial cavity.[357,375] The exposed epithelial covering of the prepuce is easily injured and becomes quite edematous and friable because of its pendent location. Hydrotherapy for 20 to 30 minutes may be helpful in cleansing the exposed prepuce and reducing edema. After the prepuce is gently cleansed and the degree of patency of the lumen is determined, a protective emollient preparation is used to massage edematous swelling upward out of the prolapse.[375] Massage for 15 to 30 minutes may be required to reduce swelling sufficiently to permit the prepuce to be returned to the preputial cavity. If the prolapsed prepuce can be returned to the sheath, a retention technique should be used to prevent reprolapse. With the prepuce in place, a tube can be inserted just beyond the swollen internal portion of the prepuce to avoid urine retention. The tube is taped in place at the external preputial orifice. Tape should not extend past the proximal end of the tube, or urine retention and migration into peripreputial tissue will occur. If this technique will not retain the prepuce, a purse-string suture in the skin of the sheath orifice can be used.[357] It should be tight enough to retain the prepuce but leave sufficient space for urine to pass freely. To avoid suture abscesses and stricture formation, the sheath should be clipped and prepared aseptically for suture placement, and sutures should be removed as soon as swelling and inflammation subside. If the prolapsed prepuce cannot be returned to the preputial cavity, the prognosis for correction without surgery is guarded. After cleansing as described previously, a portion of stockinette is coated in ointment and is applied over the prepuce. A diaper constructed from heavy canvas or burlap with straps and centrally located perforations for urine drainage is applied under the prepuce and tied up over the back to hold the prepuce gently next to the abdominal wall to decrease gravitational edema. It is changed daily until infection and swelling are controlled and the prepuce is either returned to the sheath or surgery is performed. Alternatively, the prolapsed portion of the prepuce can be wrapped in medicated gauze followed by application of a gentle but firm pressure wrap around a section of tubing. The pressure wrap is left in place temporarily to reduce edema, at which time the wrap is removed and the prepuce replaced into the sheath.[375]

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Once sufficient healing has occurred the necessity for surgery is determined by extending the penis.[357] Adhesions most commonly take the form of encircling cicatricial strictures that must be removed surgically. Guidelines suggested for predicting successful outcome of surgery include the following:

- A minimum of 5 cm of normal prepuce should be present on either side of the surgical site, or proper unfolding may not be possible after surgery
- Free prepuce remaining after surgery should be at least twice the length of the free portion of the penis, or the prepuce may be too short to permit full penile extension.

Presurgical and postsurgical considerations, and surgical techniques used to correct phimosis, are described by Walker and Vaughan.[357]

Congenital anomalies contributing to phimosis are diagnosed based on physical examination of the entire reproductive tract. Abnormal karyotypes may be helpful in determining causes. If the penis cannot be extended with the techniques described and if evidence of injury or adhesions is not present, congenitally short penis or retractor penis muscles should be suspected.[358] Accompanying history may provide information that the bull could copulate when young, but as he aged his abdomen progressively enlarged, causing the penis to be relatively of insufficient length to effect copulation.[358]

43.46.1.2.3 RAM AND BUCK

Phimosis is uncommon in small ruminants. It may be congenital, or acquired as a result of adhesions or preputial scarring associated with trauma or balanoposthitis. This condition is diagnosed during the physical examination and/or by observing the animal during the breeding process. If phimosis results from acute inflammation of the prepuce (posthitis), it may resolve when the preputial swelling reduces. However, the prognosis is guarded until scarring can be evaluated. Phimosis may also be congenital in small ruminants.[367]

43.46.1.3 PARAPHIMOSIS

43.46.1.3.1 STALLION

43.46.1.3.1.1 Definition and Etiology

When injury of the penis and the laminae of the prepuce is attended by hemorrhage and edema, paraphimosis (the inability to retract the penis into the prepuce) is likely to occur.[357] Prolonged penile prolapse, caused by debility or paralysis after the use of some tranquilizers, usually culminates in extensive penile trauma.[377,378] Protracted priapism (persistent erection) can lead to penile trauma and complications similar to those of penile prolapse.[379] Penile paralysis and priapism are distinctly different conditions. Penile paralysis develops secondary to insufficient tone of the retractor penis muscles.[380] Motor innervation of the retractor penis muscles in stallions is believed to be solely supplied by α-adrenergic fibers. When α-adrenergic blocking drugs such as phenothiazine-derivative tranquilizers are administered, paralysis of these muscles can cause penile prolapse.[381] The prolapsed penis is flaccid and cannot be maintained in the retracted position.[357,380] Priapism is a persistent erection without sexual arousal and is initially unassociated with penile paralysis. It develops from engorgement of the CCP with blood, and although the horse may not achieve a full erection, its penis is not flaccid.[382,383] When the penis fails to detumesce, CO_2 tension in the CCP increases, resulting in increased blood viscosity and subsequent venous occlusion where collecting veins join the cavernous spaces. Edematous swelling of corporeal trabeculae further reduces venous outflow, thus increasing the likelihood of irreversible venous occlusion, fibrosis of the cavernous trabeculae, and arteriolar occlusion. Disruption of the arteriovenous supply and fibrosis of the CCP prevent subsequent erections.[361,384]

43.46.1.3.1.2

Clinical Signs and Differential Diagnoses

Penile paralysis has been reported in exhausted or debilitated horses, in horses with myelitis or spinal injury, and in horses with severe injury to the penis.[357,377] Traumatic inflammatory edema often results in severe swelling of preputial membranes that prevents retraction of the penis into the prepuce. The inability to retract the penis results in further gravitationally induced edema, and as the problem worsens, edematous fluid eventually oozes through the increasingly fragile penile and preputial integument. Cellulitis develops and the integument becomes thickened, inelastic, desiccated, necrotic, and irreversibly damaged.[357,361] In cases of long-standing priapism, the distal end of the penis becomes cool to the touch, and the clot may become palpable in the body of the CCP as fibrin organization occurs. The organized clot may be visible on ultrasound examination.[379]

43.46.1.3.1.3

Treatment and Prognosis

Prognosis for recovery becomes guarded to grave the more chronic the paraphimosis becomes. Principles of treatment are similar to those described for the bull. To maintain the penis within the prepuce, a temporary purse-string suture of heavy Vetafil can be placed near the preputial orifice. Alternatively, a padded plastic bottle from which the bottom has been removed can be used to support penile hematomas.[385] After the injured penis is dressed, the bottle is placed over it and pushed back into the sheath. The bottle is held in place with straps running over the lumbar area and on either side of the scrotum up over the tail head. Voiding of urine occurs through the bottle. The apparatus should be cleaned and replaced twice daily until the penis can be retained in the retracted position. If the penis cannot be returned into the prepuce, an external support for the prolapse should be applied. Prolonged penile prolapse may result in excess gravitational pull that damages smooth muscle cells, the retractor penis muscle, and the pudendal nerves[357,380]; such sequelae decrease the prognosis for recovery and return to a successful breeding career. Chronic, refractory penile prolapse results in severe balanoposthitis that may require circumcision or penile amputation. Surgical penile retraction (the Bolz technique) is described by Walker and Vaughan.[357]

Medical treatment of horses with priapism has generally been unsuccessful.[361,382] In cases of drug-induced priapism seen within 2 to 4 hours of occurrence, slow intravenous injection of 8 mg of benzotropine mesylate may cause detumescence and penile retraction to occur.[386] If the animal is not seen immediately, treatment is the same as for traumatic paraphimosis. Rapid detumescence can be induced by injecting 10 mg of phenylephrine into the CCP, even in long-standing cases. However, the detumescence may be only transient. Flushing the CCP with heparinized lactated Ringer's solution through 12-gauge needles to remove sludged blood has been recommended for horses with priapism of 12 to 24 hours' duration that have not responded to medical treatment.[361] If a blood clot forms in the CCP, the prognosis is poor and amputation may be necessary. Some stallions, if severe nerve damage does not occur, may regain the ability to breed and ejaculate when assisted with placement of the penis into either the vagina of the mare or an artificial vagina. When the stallion does not regain the ability to completely retract the penis into the sheath, continued penile trauma is likely to result in damage to the sensory nerves to the glans penis. Such horses may achieve an erection but may have difficulty both in seeking the mare's vulva for intromission and in ejaculating. Ultrasonography of the CCP to detect cavernosal fibrosis may be useful in assessing prognosis for recovery from priapism. Prognosis for

recovery is good once penile retraction occurs, but breeding should not be permitted until healing is complete.

43.46.1.3.2 BULL

43.46.1.3.2.1 Definition and Etiology

Paraphimosis is less common than phimosis in the bull. The conditions have some common causes, but for paraphimosis the causes also include penile tumors, parasitic invasion, traumatic or spinal disease affecting innervation of structures responsible for penile retraction, inadvertently severed retractor penis muscles, and physical trapping of the penis by a constricted prepuce after injury. Penile paralysis and paraphimosis sometimes occur as a result of spinal injury or disease, and in rabies cases as well.[357,358,373–376,387]

43.46.1.3.2.2 Clinical Signs and Differential Diagnoses

Persistent exposure of the penis results in congestion, inflammation, and necrosis of the penile integument.[358,373,374]

43.46.1.3.2.3 Treatment and Prognosis

Management of the prepuce has been discussed. Exposed portions of the penis should be frequently cleansed and protected by a bandage soaked in oily antibiotic preparations. The prolapsed penis should be supported close to the abdomen to reduce edema. The penis should be returned to the sheath as soon as possible and mechanically restrained if necessary. If the ability to retract the penis does not return in a few days, prognosis for recovery is poor.[357]

43.46.1.3.3 RAM AND BUCK

Paraphimosis is uncommon in small ruminants. The diagnosis is obvious, although the cause may not be. Treatment involves the same principles as in the bull. Prognosis is guarded and correlates with the degree of injury and necrosis at the time the condition is discovered.

43.47 URETHRAL INJURY AND URETHRITIS

43.47.1 STALLION

43.47.1.1 Clinical Signs and Differential Diagnoses

Traumatic injuries to the urethral process are usually obvious and are characterized by hemorrhage. *Habronema*, granulomas are firm and friable. Ulcers of the urethral process often become secondarily invaded with bacteria such as *Pseudomonas*, species. Parasitic lesions tend to regress during winter, but if untreated they may mineralize and result in recurrence of hemospermia during the following breeding season.[388]

Bacterial urethritis may be associated with hemospermia.[389] Lesions can occur throughout the urethra, including the pelvic urethra in the area of the ejaculatory ducts. Diagnosis is based on demonstration of the lesions by fiberoptic examination.[361] Ultrasonography and fractionation of the ejaculate may be helpful in eliminating involvement of the accessory sex glands.[390]

Urethral inflammation and lacerations may result in fibrous strictures.[389] Strictures are often painful and may separate and bleed during urination and ejaculation. Bacteriologic culture of the urethra, urine, and semen; fiberoptic examination; and histologic examination of biopsies of lesions are helpful in making a diagnosis.[5] Strictures in the distal urethra may be identified by contrast radiography of the extended penile urethra.[357,389]

Clinical signs of uroliths include dribbling of urine with chronic cystitis, dysuria and stranguria, occasional hematuria, recurrent colic, and a stilted, painful gait in the hindquarters. Penile protrusion is frequent or constant in cases of chronic, involuntary escape of urine.[357] Diagnosis is by urinalysis, revealing the characteristic crystals, red and white blood cells, and bacteria. Urethral calculi typically restrict the passage of urethral catheters. Bladder calculi may be palpated per rectum or visualized by ultrasonography.[357,388]

43.47.1.2

Treatment and Prognosis

Treatment of urethral injuries involves first removing inciting factors such as a tight stallion ring. Sexual rest is indicated while palliative therapy is given. The ability to void urine should also be established. Systemic treatment with antibiotics that are eliminated in the urine may be useful as a prophylactic measure or in cases in which secondary bacterial invasion has occurred. More severe cases of urethritis may be treated locally either by infusion of oily antibiotic preparations through sterile, rubber urethral catheters passed to the area of the seminal colliculus of the pelvic urethra, or alternatively by insertion of soluble suppositories through a perineal urethrostomy. After resolution of the urethritis, the urethrostomy is allowed to heal by granulation.[389] Lacerations of the proximal urethra that result in hemospermia can be treated by perineal incision into the corpus spongiosum urethra (CSU) or by perineal corpus spongiotomy in which the CSP is incised but the incision is not extended into the urethra. These surgeries are believed to prevent stretching of the urethra when engorgement of the corpus spongiosum occurs during urination or erection. Repeated stretching is thought to prevent urethral lacerations from healing.[391]

Inflammation of the urethral process may respond to local antibiotic salves. Treatment of parasitic granulomas with ivermectin speeds resolution of these cases.[369,392,393] Larger, nonresolving granulomas with mineralization may require surgical removal.[394] The skin of the urethral process should be rolled inward when sutured to the mucous membrane to prevent eversion that predisposes it to reinjury after healing. Remaining hemorrhagic or ulcerative lesions are lightly cauterized with silver nitrate.[388] More proximally located nonresolving urethral strictures, prolapsed subepithelial vessels, or ulcers can be removed surgically. Leave as much normal urethral mucosa as possible to avoid postsurgical stricture formation.[389]

Calculi lodged within the lumen of the pelvic urethra can be removed via perineal urethrostomy. Treatment for urethral calculi is described in the discussion of diseases of the urinary system, Chapter 34.

43.47.2 BULL

43.47.2.1 Definition and Etiology

Urolithiasis is the primary problem affecting the urinary system that may interfere with normal function of the reproductive tract of the bull.[395] It is of less importance in bulls than in steers but occasionally occurs and may result in hematuria or urethral obstruction.[357,358] Urolithiasis is thoroughly discussed in Chapter 34.

43.48 BALANOPOSTHITIS

In the stallion, inflammation of the glans penis (balanitis) and prepuce (posthitis) often occur together (balanoposthitis). Traumatic injury resulting in inflammation of the penis and prepuce has been discussed. Balanoposthitis may also be caused by dourine, EHV-3 infection (see Equine Coital Exanthema), miscellaneous bacteria, and parasites.[359,373,374,396,397]

43.49 EQUINE COITAL EXANTHEMA

Equine coital exanthema is caused by EHV-3.[398] The occurrence of neutralizing antibodies to EHV-3 primarily in horses of breeding age suggests that spread of this infection may be primarily by genital contact.[399] Typically an inapparently infected mare transmits the virus to a stallion at the time of breeding. The stallion then transmits the infection to other susceptible mares before developing clinical signs of the disease. Clinical signs in the stallion are sometimes more severe than those observed in the mare and may include systemic manifestations such as dullness, anorexia, and fever.[399] Vesicles up to 1.5 cm in diameter develop first on the penis and then on the prepuce 2 to 5 days later. The vesicles progress to circumscribed pustules with raised borders and depressed centers, which slough and ulcerate.[393,400] Scabs are seldom noted on penile lesions because they are rubbed off by extension and retraction of the penis during breeding.[400] Some affected stallions may refuse to breed mares, whereas others breed willingly, even while extensive penile lesions are present. Healing occurs in a few weeks, often leaving depigmented spots.[400]

Some immunity to the virus is acquired after infection, because reinfection without recurrence of clinically apparent disease is common. It is probable that the virus remains in the genitalia in a latent form.[373] Recurrent coital exanthema usually occurs in aged broodmares but may also occur in stallions.[400] In stallions, recurrence within the same breeding season is uncommon. The relationship between viral recrudescence and recurrent coital exanthema in the equine is unknown but may mimic that in human genital herpes infections.

Diagnosis usually can be made on the basis of the characteristic clinical signs. During the acute stage the virus can be isolated from swabs or scrapings taken from the edge of erosions. Inclusions in lesion specimens can be confirmed by using an electron microscope to visualize typical herpesvirus particles in fluid or tissue samples. Probably the most sensitive, specific, and accurate tool for the detection of EHV-3 is the PCR assay. Demonstration of antibody titers in serum may be useful in establishing time of exposure to the virus.[401]

Infection with EHV-3 is self-limiting.[373] Local treatment with antibiotic ointments will not speed healing but may minimize secondary bacterial infection and soreness.[400] Care should be taken to avoid iatrogenic transmission of

the infection (e.g., through contamination of sleeves, water, and examination or insemination equipment) to susceptible animals. Attending veterinarians may choose to refrain from breeding affected stallions until the lesions heal. One method that may be helpful in circumventing transmission of the infection while still breeding the stallion is to collect semen in an open-ended artificial vagina as soon as lesions are no longer painful. Collecting the semen as it directly exits the urethra reduces the chance of viral contamination from the penile and preputial lesions. It is imperative, however, to adhere to any breed registry restriction regarding artificial breeding.[361]

43.50 BACTERIAL INFECTIONS

43.50.1 STALLION

The external genitals of stallions harbor potentially pathogenic bacteria, fungi, and yeasts, yet balanoposthitis caused by bacterial agents is uncommon.[402–404] These organisms are usually considered to be surface contaminants, and the stallion is a lesionless carrier in most instances in which venereal transmission occurs.[378] Sperm motility, however, may sometimes be adversely affected by bacteria and their products in semen.[403] Offensive odors may occasionally be associated with heavy colonization of the penis and sheath with *Pseudomonas*, species or *Proteus*, species.[358] Documentation of a bacterial infection is dependent on serial isolation of a pathogen, preferably in large numbers and relatively pure culture.[404] A single isolation of *T. equigenitalis*, is considered diagnostic for CEM.[378] Samples for bacteriologic culture should be retrieved from the fossa glandis, free portion of the penile body, and folds of the external prepuce before washing of the genitals of a stallion presented to an estrual mare.[404]

If there is evidence of horizontal transmission of *Pseudomonas*, or *Klebsiella*, to mares, or if longevity of sperm is reduced in association with these organisms, the preferred method of management is to breed mares artificially with semen mixed with an antibiotic-containing semen extender.[405] Antibiotic selection is based on trials comparing extended semen with and without antibiotic. Extenders containing antibiotics that control the offending bacteria and permit maintenance of sperm motility are then used to breed mares.[406] Bacteria are usually not recovered after 5 to 30 minutes of incubation at room temperature.[403,405,406] Penicillin G (1000 to 1500 U/mL), streptomycin sulfate (1000 to 1500 mcg/mL), polymyxin B (100 to 1000 U/mL), reagent grade gentamicin sulfate (100 to 1000 mcg/mL), amikacin sulfate (100 to 1000 mcg/mL), or ticarcillin (100 to 1000 mcg/mL) is usually the most suitable antibiotic.[361] Gentamicin sulfate and amikacin sulfate should be buffered with 8.4% sodium bicarbonate solution to adjust pH to approximately neutral before they are mixed with semen extender. A suitable volume of extender can be infused into a mare's uterus immediately before cover when natural service is necessary.[405]

Colonization of the external genitals with *P. aeruginosa*, and *K. pneumoniae*, can be treated by thoroughly washing the penis and prepuce, including the fossa glandis and diverticulum, daily with an iodine-based surgical scrub. The genitals are then rinsed with copious quantities of tap water with dilute disinfectants added (10 mL of concentrated HCl per gallon of water for *Pseudomonas*, colonization, or 40 mL of 5.25% sodium hypochlorite bleach per gallon of water for *Klebsiella*, colonization).[407] Drying of the penis can be followed by generous application of 1% silver sulfadiazine cream. The procedure is repeated daily for 1 to 2 weeks and followed by serial cultures to determine if treatment was successful.[408] The clinician should be cognizant that

recolonization with these organisms may occur and that routine scrubbing and disinfection may predispose to infection of the genitals with potential pathogens by displacing commensal organisms.[402]

43.50.2 BULL

Balanoposthitis in the bull is caused by traumatic injury and infections. Whereas injury of the prepuce is more common, penile inflammation often accompanies the traumatic posthitis. A multitude of potentially pathogenic organisms inhabit the prepuce, and injuries predispose to infection particularly when deeper tissues are exposed. Pain and preputial discharge may be evident. Because of the presence of the many organisms in the preputial cavity, culture to identify a specific offending organism is likely to be misleading. When injury results in infection of the penis and prepuce, sexual rest in conjunction with local antibiotic treatment is indicated. Treatment should be performed as previously outlined for the penis and prepuce until inflammation is corrected.

Balanoposthitis unassociated with trauma has been associated with infections resulting from IBR-IPV, by tuberculosis, and by screwworm infestation.[358,373,374,409] Acute lesions associated with IBR-IPV infections are numerous small pustules that progress to ulcers and erosions in a few days. Purulent preputial discharge is present, and lesions may become confluent. The prepuce and penis may become quite inflamed and swollen. Healing is commonly spontaneous and rapid, beginning in 1 week and usually complete in 2 weeks. Severe cases may take longer to resolve.[409] Virus is shed from the prepuce for 2 weeks or longer, during which time venereal spread is possible. Sexual rest for 6 to 8 weeks has been recommended to prevent spread and to avoid abrasions that may aggravate inflammation.[358] Enlargement of the lymphoid follicles may be present, along with a seromucoid exudate for several weeks. Histologic changes include the transient appearance of eosinophilic intranuclear inclusions in degenerating epithelial cells.[373] Infusion of the preputial cavity daily may be of benefit in treatment, particularly in more severe cases. Vaccination with attenuated intranasal products has been reported as a method to prevent viral shedding into semen in bulls from AI studs.[358,410] The vaccine has been infused into the prepuce experimentally and did not result in viral shedding in the semen. Because persistence of herpesvirus in body tissues is a common occurrence, recurrence of viral shedding in semen after apparent recovery may be possible. Tuberculosis of the penis and sheath apparently has not been reported in the United States for some time. It is characterized by enlarged, granulomatous lesions on the glans penis, prepuce, and sigmoid flexure that are prone to hemorrhage. Penile lymph glands may abscess.[358]

43.51 Ram and Buck

Balanoposthitis (also called *pizzle rot, sheath rot*, and *ulcerative posthitis)*, commonly affects the penis and prepuce of intact and castrated male small ruminants.[367,368,411,412] The disease is discussed in Chapter 34.

43.52 PERSISTENT PENILE FRENULUM AND PENILE DEVIATIONS

43.52.1 BULL

43.52.1.1 Definition and Etiology

Phallocampsis, or deviation of the erect penis, is a relatively common condition in the bull. The most common cause of penile deviation is persistent penile frenulum.[358] Other types of penile deviations include spiral, ventral, and S-curved deviations.[357] Less commonly, preputial or penile injury may result in scar tissue formation that subsequently leads to deviation of the erect penis.[357]

When the penile frenulum persists, it remains connected to the ventral surface of the tip of the penis and the prepuce and causes the penis to bend ventrally during erection by preventing complete extension.[413] Copulatory ability is interfered with except in some of the Zebu-influenced breeds that are endowed with a plentiful prepuce.[357] Diagnosis is based on physical examination of the extended penis.

Because spiraling of the penis is thought to be a normal physiologic event that occurs in the vagina during ejaculation,[414] care should be taken in making this diagnosis. Bulls affected with penile deviations often have a history of no problems in mating cows for some time, occasionally for several breeding seasons. If such bulls have been closely observed, it may have been noted that the condition did not occur on every mating attempt, but the frequency of occurrence gradually increased until bulls might require numerous mounts to successfully intromit and breed a cow in estrus.[358] Penile deviations occur at full erection when the CCP is maximally distended with blood. Caution should be exercised in diagnosing this condition during erection stimulated by electroejaculation. Such erections are not considered to be entirely physiologic and frequently result in penile deviations in bulls that have no deviations under natural mating conditions. The spiral deviations that occur with use of the electroejaculator may be a result of tension exerted by the retractor penis muscles.[357] Diagnosis is best based on observing occurrence of the deviation frequently in natural mating situations.

The ventral or rainbow deviation of the penis is less common than the spiral deviation and is a result of the apical ligament being too thin to support the engorged, stretched distal end of the erect penis.[357] The ventral curvature may be quite pronounced, preventing affected bulls from directing and inserting the penis into the vagina of the female.

The least common of the spontaneous penile deviations is the S-shaped curvature. It primarily occurs in older bulls with an apical ligament that is short in relation to an excessively long penis.[254] Penile deviations that result from adhesions that developed from penile or preputial injury are diagnosed based on physical examination.

43.52.1.2 Treatment and Prognosis

Persistent penile frenulum is easily corrected by severing the persistent band. Owners of affected bulls should be advised of the probable genetic basis and therefore the undesirability of retaining such bulls for breeding.[357] Treatment of spiral and ventral deviations is surgical.[357]

43.53 TUMORS OF THE PENIS AND PREPUCE

43.53.1 STALLION

43.53.1.1 Clinical Signs and Differential Diagnoses

The most common neoplasm of stallion genitalia is SCC. Generally, it is of low malignancy.[357,415] The tumor usually involves the glans penis but may also involve the shaft of the penis and prepuce and produce a fetid discharge.[373,374] Large tumors may ulcerate and bleed, resulting in hemospermia. Carcinomas may resemble *Habronema*, granulomas, which are more common and are diagnosed by histologic examination of affected tissue.[358,361] Carcinomas are usually well differentiated and surrounded by eosinophils. Necrosis and calcification may occur, but parasite larvae are usually not present[373] unless secondary habronemiasis has occurred from flies feeding on the ulcerated tissue. Carcinomas may extend into the CCP or may metastasize to the inguinal lymph nodes or other abdominal or thoracic organs.[373] The superficial inguinal lymph nodes lie midway between the prepuce and external inguinal ring; secondary tumors in this region often grow rapidly and develop necrotic centers with purulent sinuses that must be differentiated from bastard strangles.[357]

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Tumors encountered much less frequently include melanoma, papilloma, angioma, lymphosarcoma, and sarcoid. Melanoma is a common equine tumor, especially of grey horses,[369] and occasionally involves the penis and prepuce[357,359,416] (see Chapter 40). Genital papillomas are rare in stallions but may occur on the glans or shaft of the penis. The lesions appear as multiple proliferative cutaneous growths and may become friable and result in hemorrhage during erection and ejaculation.[361] The lesions are generally thought to be caused by a papilloma virus,[417,418] and papilloma virus antigens have been found in cutaneous and genital papillomas.[418] Angiomas and lymphosarcomas have occasionally been reported on the genitals of stallions.[359] Sarcoids may involve the skin of the prepuce or scrotum[357,416] (see Chapter 40).

43.53.1.2 Treatment and Prognosis

When SCCs are relatively small and noninvasively attached to the skin, neoplasms may be successfully treated by cryosurgery or hyperthermia.[419] Hyperthermic treatment (50° C for 1 to 2 minutes) appears to be most successful for SCC when lesions are small (less than approximately 2 cm). If the tumor is extensive but superficial, cryosurgery may be attempted after the tumor is debulked and hemorrhage controlled. The remaining base of the tumor is then frozen and thawed twice; healing occurs as necrotic tissue is sloughed. Successful treatment of small lesions has been reported with topical application of 5-fluorouracil.[420] If removal of tumors is unsuccessful or if neoplasia is extensive, penile amputation may be necessary.[357,421] If superficial inguinal lymph nodes are involved, euthanasia may be required.[357]

In contrast to nongenital squamous papillomas, genital forms generally are quite refractory to treatment.[361] Surgical removal and autogenous vaccine administration have been tried to treat fibropapilloma of the penis of two stallions but did not effect a cure.[388]

43.53.2 BULL

43.53.2.1 Definition and Etiology

Fibropapilloma is the only tumor that frequently invades the bovine penis or prepuce.[373,374] The tumor may be single or multiple and usually affects young bulls. The cause is thought to be a papilloma virus antigenically similar to the virus that causes cutaneous papillomatosis in cattle.[422] Frequent mounting among young bulls is thought to result in damage to epithelial surfaces of the penis and prepuce that serves as a route of entry for the virus.[357,358]

43.53.2.2 Clinical Signs

Small papillomas may be discovered during routine breeding soundness evaluations, but many become larger before they are discovered. Large fibropapillomas may prevent withdrawal of the penis into the preputial cavity. Fibropapillomas are pedunculated and attached at a narrow base in early cases. The surface becomes cauliflower-like and friable; hemorrhage is easily induced.

43.53.2.3 Treatment and Prognosis

Many fibropapillomas regress spontaneously within a few months. Regression may be more likely in bulls approaching 2 years of age and usually occurs within 4 months of the appearance on the penis.[422,423] Several vaccines, including autogenous preparations, have been used for treatment, but vaccines may be more successful for prophylaxis.[358] Frequently, surgical removal is indicated, but the fibropapillomas may recur. If only superficial attachment is present, surgical removal is easily accomplished. Catheterization of the distal urethra before surgery is helpful in identifying its location to avoid injury. If attachment has become extensive and sessile, amputation of a portion of the distal penis may be necessary.[357] Housing of young replacement bulls in individual pens, if possible, is recommended as a method to reduce the incidence of penile fibropapillomas.

43.54 PARASITIC INFESTATIONS OF THE PENIS AND PREPUCE IN STALLIONS

43.54.1 Definition and Etiology

Habronema muscae, Habronema microstoma, and *Draschia megastoma*, larvae commonly invade the urethral process, glans penis, and preputial ring of stallions.[357,369] Other terms for this condition are *genital bursatti*, and *summer sores*.,[373]

43.54.2 Clinical Signs

Shallow irritations progress to irregular 1- to 3-cm granulomatous growths that may involve the entire circumference of the urethral process.[358] Lesions are friable and bleed when manipulated. Stretching of the infected urethral process during penile engorgement and ejaculation may result in hemospermia.[361] Pruritus

associated with the lesions may be intense. Frequent micturition and dysuria may resemble urine spraying that accompanies accumulation of smegma in the urethral diverticulum ("bean"). Lesions subside during the colder months in northern areas but usually reappear and increase in size during subsequent warm weather.[358] Diagnosis is made by seeing yellowish granules (calcified larvae) in the lesion and by microscopic identification of larvae.[369]

43.54.3 Treatment and Prognosis

See Chapter 40 for treatment and prognosis information.

43.55 HEMOSPERMIA

Hemospermia, refers to contamination of ejaculates with blood. Stallions with overt hemorrhage into ejaculates are subfertile. Erythrocytes rather than serum have been implicated for the marked depression of fertility, although the precise factor(s) involved are not known.[389] A small amount of sanguineous contamination is compatible with fertility, especially if the semen is quickly diluted with a suitable extender before insemination. A disproportionate number of leukocytes to erythrocytes suggests infection of the internal genital organs. Specific causes of hemospermia include lacerations of the penis, cutaneous habronemiasis, urethritis, urethral lacerations, and infection or inflammation of the accessory genital glands,[361] which are discussed elsewhere in this chapter.

43.56 UROSPERMIA (URINATION DURING EJACULATION)

43.56.1 Definition and Etiology

Urospermia is an uncommon but perplexing disorder of breeding stallions. Affected stallions generally exhibit normal libido and mating ability, but semen becomes contaminated with urine during the ejaculatory process. The problem may be incessant or unpredictably intermittent; urination can occur at any time or continuously during ejaculation. The amount of urine ranges up to 250 mL or more.[361] 1476 1477

The underlying cause(s) of urospermia is speculative. Closure of the bladder sphincter and seminal emission are controlled by the α-adrenergic sympathetic nervous system, and a disturbance in this pathway might contribute to urospermia.[424] Similarly, neuropathies that result in bladder paralysis (e.g., cauda equina neuritis or nerve damage secondary to EHV-3 infection or sorghum or Sudan grass poisoning) can create urinary incontinence that permits voiding during ejaculation. Most stallions with urospermia do not exhibit signs of a neurologic deficit.[361]

43.56.2 Clinical Signs and Differential Diagnoses

Gross contamination of ejaculated semen with urine is easily detected by its color and odor. Contamination with significant quantities of urine adversely affects sperm motility and fertilizing capacity. Elevated concentrations (relative to serum levels) of urea nitrogen or creatinine in semen document presence of urine in the ejaculate.[361,425]

43.56.3 Treatment and Prognosis

Treatment options for urospermia vary, can be arduous, and are often unrewarding. Delay of semen collection (or breeding) until immediately after the stallion has voided urine may be a helpful management policy. Urination can be stimulated by administration of a diuretic drug (e.g., furosemide). Stallions may also void urine when provided access to feces of another stallion. Some stallions can be trained to urinate on command. Alternatively, the bladder can be catheterized to aid evacuation of urine before breeding, but urethritis or cystitis may result from routine use of this procedure. Fractionation of ejaculates using an open-ended artificial vagina can be used alone or in combination with any of the above measures. When an open-ended artificial vagina is used, only the first three jets of the ejaculate are collected. These jets contain a majority of the spermatozoa in the ejaculate, and urination may not occur until the end of the ejaculatory process.[426] Dilution of urine-contaminated semen in extender can restore sperm motility. Semen may be centrifuged after initial dilution, and the sperm pellet resuspended in extender before insemination[361]; however, centrifugation to remove urine may not provide a significant advantage over dilution in extender.[426]

Pharmacologic agents such as bethanechol chloride or flavoxate hydrochloride have been used in an attempt to correct urospermia but usually without success.[361] α-Sympathomimetic drugs have sometimes been used successfully to prevent retrograde ejaculation in men, but their use has not been critically studied in stallions.[427] Oral administration of imipramine (100 to 500 mg twice daily) has reportedly been useful for controlling urospermia in stallions, presumably by enhancing contractility of the bladder neck during emission.[424]

43.57 INFERTILITY CAUSED BY DISEASES OF THE SCROTUM AND TESTES

43.57.1 SCROTAL INJURY, HYDROCELE, AND HEMATOCELE

43.57.1.1 Definition and Etiology

Trauma to the scrotum can result in excoriation, lacerations, hemorrhage, and edema.[358,373] Systemic diseases such as hepatic disease and EIA may result in scrotal edema.[358,378] Suppurative inflammation may develop as an extension of scrotal injury.[358] Adhesions often develop between the visceral and parietal tunics when inflammation, infection, or hemorrhage occurs.[374] Adhesions are usually thin fibrous strands that become thickened over time. In such cases the testis and its tunics are not freely movable within the scrotum.[373]

Hydrocele is an accumulation of serous fluid within the vaginal tunic.[374] Ascites, anasarca, or local lymphedema may contribute to hydrocele because the vaginal tunic communicates with the peritoneal cavity.[373] Accumulation of a significant volume of fluid around the testis may cause thermal degeneration and a decline in seminal quality.[428]

Hematocele occurs when trauma to the scrotum results in accumulation of blood within the testicular tunics.[374] Scrotal damage initially accompanies hematocele. Thermal degeneration of the testes follows, and a thick fibrous capsule encompasses the testis after the blood clot organizes.[429]

43.57.1.2

Clinical Signs and Differential Diagnoses

Diagnosis of scrotal injury, hydrocele, and hematocele is made by physical and ultrasonic examination of the scrotum. Testes remain freely movable within the scrotum if hydrocele is present. Ultrasonographic examination reveals variable amounts of anechoic fluid surrounding the testes and epididymides, which are easy to visualize because of their echoic nature against the fluid background. With hematocele, evidence of trauma is often present, with thickening of the scrotal skin. Blood surrounding the testis and epididymides becomes progressively more echogenic over time as the clot organizes.[361,430] Extensive edema of the scrotal fascia next to the tunica dartos may be difficult to differentiate ultrasonographically from hematocele. Abdominal paracentesis is helpful in eliminating ascites or peritonitis as a cause of hydrocele. Palpation per rectum of stallions and bulls may occasionally reveal that the internal inguinal rings are enlarged, readily permitting fluid transfer into the vaginal cavity.

An aseptic tap is useful to identify the character of this fluid and must be performed with care not to contaminate or penetrate the testis or its visceral vaginal tunic.[429] A modified transudate of low cellularity is typical of fluid drained from a hydrocele.[431] Fluid usually returns after drainage unless the initiating cause is corrected.[361]

43.57.1.3

Treatment and Prognosis

Acute scrotal injury is treated with cold water or ice application to reduce edema (see earlier discussion on penile and preputial injuries). Lacerations and abrasions should be treated with topical antibiotic ointments. Systemic antiinflammatory drugs and antibiotics may reduce swelling, control infection, and prevent abscess formation.[361,429]

Scrotal thickening usually results in elevation of testicular temperature, causing degeneration and atrophy similar to that seen with experimental scrotal insulation.[432,433] Semen quality quickly deteriorates, and a rapid reduction in numbers and motility of spermatozoa occurs with a concurrent increase in morphologic abnormalities of spermatozoa.[358,373,434] If swelling and edema resolve and adhesions do not develop among the testes, tunics, and scrotum, spermatozoa may gradually reappear in the ejaculate by 1 to 2 months after injury, but 4 to 5 months may be required for testes to return to normal size and sperm production.[360] One or both testes may remain atrophic and become firm because of fibrosis and loss of tubules. If only one testis is atrophied, the normal testis may eventually hypertrophy.

If hemorrhage occurs within the scrotum or testicular tunics, the prognosis for return of testicular function is poor. In unilateral cases, surgical removal of the clot and affected testis may minimize damage and speed recovery of the remaining testis.[435,436] Hydrocele is managed by correcting the underlying cause of fluid accumulation such as peritonitis or ascites.[429] Exercise may aid in control of fluid accumulation in some horses. Some stallions and bulls with persistent minor fluid accumulations within the tunics may continue to produce sufficient normal spermatozoa.[358] Permanent testicular degeneration may result in cases with extensive fluid accumulation that are unresponsive to therapy. If the condition is unilateral, removal of the affected testis may permit the animal to remain in service.[431] Because hydrocele and associated impairment of spermatogenesis may be transient (2 to 6 months),[428] caution should be exercised in recommending castration or culling of affected animals until demonstration that the disorder is long-standing.

43.58 SCROTAL DERMATITIS AND ABSCESS

The scrotal skin is delicate and vulnerable to dermatitis. Causes include nonspecific environmental contaminants, bacteria, fungi, parasites, and frostbite.* Scrotal abscesses are not uncommon in small ruminants and are due to shearing injuries and penetrating wounds.[367] Treatment is directed toward removing the affected testis. Bulls affected by frostbite should be provided a warm and dry environment.[437] Systemic and local antibiotics may be indicated. Abscesses should be drained. Thermal degeneration of the testes may follow dermatitis and may be temporary or permanent.[358] Semen quality should be evaluated at periodic intervals after skin lesions have resolved to gauge prognosis for improvement and return to fertility.

* References 367, 369, 373, 374, 434, 437.

43.59 TESTICULAR APLASIA AND HYPOPLASIA

43.59.1 Definition and Etiology

Complete absence (aplasia) of one or both testes is rare and usually occurs in conjunction with anomalous development of other organs.[358,438] Testicular hypoplasia may be unilateral or bilateral and affects both scrotal and abdominal testes.[374] Testicular hypoplasia is thought to result from failure of germ cells to multiply in the gonad.[258] Causes of testicular hypoplasia may include transplacental infections and intoxications, zinc deficiency, hormonal insufficiency, impaired testicular descent, abnormal karyotype, and vascular disturbances.† Exogenous administration of hormones to prepubertal males can result in testicular hypoplasia. Testicular size of adult stallions is reduced after prolonged administration of exogenous steroids.[440–442] Scrotal circumference is diminished in bulls implanted with zeranol.[443]

† References 368, 373, 374, 434, 439.

43.59.2 Clinical Signs and Differential Diagnoses

Hypoplastic testes are usually smaller than normal, but they occasionally are normal in size.[373] The scrotal circumference of beef bulls should be at least 32 cm at 12 months of age.[444–446] Stallions 3 years of age should have a scrotal width greater than 8 cm.[378,447] Yearling rams with a scrotal circumference of less than 30 cm and mature rams with a scrotal circumference of less than 32 cm are not recommended for breeding.[448] The texture of affected testes varies from normal to soft in mild or moderate hypoplasia. Severely affected small testes are firm because of the relatively increased amount of stromal connective tissue.[374]

Depending on the number of seminiferous tubules affected, ejaculates from males with testicular hypoplasia may be azoospermic or may contain a low concentration of spermatozoa with numerous morphologic defects.[358] Round spermatogenic cells may also appear in ejaculates, along with giant and medusa cells.[374]

43.59.3 Treatment and Prognosis

No successful treatment is available for severe hypoplasia. The useful breeding life of males with testicular hypoplasia may be shortened because affected bulls are thought to be predisposed to early testicular

degeneration.[444] Because of the value of some individuals, particularly stallions, owners may elect to breed males with small testes. Effective management of such stallions is based on breeding a book of mares limited by the number of normal, motile spermatozoa present in ejaculates.

43.60 CRYPTORCHIDISM

43.60.1 Definition and Etiology

Incomplete or abnormal testicular descent is thought to be a genetic abnormality.[358,368,374] The inheritance pattern in horses is thought to be dominant,[449] although studies of offspring of some cryptorchid stallions suggest that inheritance of the condition may be multifactorial.[450] The relative risk for equine cryptorchism also appears to be influenced by breed.[451] Other modes of inheritance have been suggested from studies of offspring of cryptorchid rams, bucks, and bulls. These include a recessive gene with incomplete penetrance in Angora goats,[452] a dominant gene with variable expressivity in Hereford cattle,[453] and either an autosomal recessive gene or a dominant gene with incomplete penetrance in inbred sheep.[454]

Testes originate near the kidney and migrate to the superficial inguinal rings before descending into the scrotum; the epididymis precedes the testis in descent. Retained testes are located at some point along the path of migration.[373] Ectopic testes not associated with cryptorchidism may be found under the skin of the ventral caudal abdomen or elsewhere in bulls.[357,374]

43.60.2 Clinical Signs and Differential Diagnoses

The majority of cases of cryptorchidism in stallions are unilateral.[455] Although testicular descent can occur in horses up to 2 years of age, the testes are normally descended at birth in large animals.[456] Testes are readily palpated in the scrotum of colts at 30 days of age.[358,359] Spermatogenesis is inhibited in the abdominal testis because of the elevated temperature within the abdomen. The interstitial cells remain active and secrete testosterone,[359,373,374] enabling even bilateral cryptorchids to maintain libido and copulatory activity. The descended testis may be hypertrophic[373]; unilateral cryptorchids are fertile but are not considered sound breeders.[358,457]

Deep palpation of the superficial inguinal rings may reveal the testis in the canal (“high flankers”). If the testis is not located in the inguinal canal, transrectal palpation or ultrasonography can be performed in stallions and bulls in an attempt to locate a testis or to detect the vas or epididymis entering the superficial inguinal ring, thereby providing evidence of descent into the inguinal canal.[458]

43.60.3 Clinical Pathology

Equine cryptorchids have high basal concentrations of testosterone (usually >100 pg/mL) and respond to hCG administration (10,000 to 12,000 IU IV) with a significant elevation of circulating testosterone within 30 to 60 minutes if testicular tissue is present. Geldings and “false rigs” (geldings with malelike behavior) have low basal concentrations of testosterone (<40 pg/mL) and do not respond to hCG stimulation. Stallion testes contain a high concentration of conjugated estrogens, and a single measurement of high plasma conjugated estrogens

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(>400 ng/mL) is reported to be almost as reliable in diagnosing cryptorchidism as hCG stimulation.[459,460] In some ruminants, measurement of testosterone concentrations before and after administration of hCG has also proved helpful in identifying cryptorchidism.[461]

43.60.4 Treatment and Prognosis

Stimulation of testicular descent with repeated injections of GnRH, sometimes combined with hCG or acupuncture, has been attempted, but the success has not been critically evaluated. Surgical removal of the abdominal and scrotal testes is indicated.[357] Surgical placement of the retained testis into the scrotum is not considered an ethical procedure.

43.61 TESTICULAR DEGENERATION

43.61.1 Definition and Etiology

Testicular degeneration is an acquired condition with multiple causes.[462] Infections or traumatic orchitis may progress to permanent degeneration. Degeneration may be associated with thermal factors after elevation of body temperature by systemic infections; prolonged increase or decrease in ambient temperature; scrotal insulation from edema, dermatitis, scrotal hernias, or hemorrhage; or abnormal conformation resulting in an incompetent heat exchange system.* Degeneration results when testicular vasculature becomes occluded in torsion of the spermatic cord.[466] Obstruction of the proximal epididymis and malformation of the efferent tubules results in degeneration caused by pressure within the seminiferous tubules.[434] Various chemicals and ionizing radiation are capable of inducing testicular degeneration.[373] Administration of steroid hormones may induce testicular degeneration by inhibiting secretion of gonadotropins.[428,467,468] Gradual degeneration also occurs with increasing age.[469]

* References 359, 373, 432, 434, 437, 463–465, 478.

43.61.2 Clinical Signs and Differential Diagnoses

Diagnosis of testicular degeneration is based on physical examination and semen evaluation. Testes are typically thought to be small, but they may be normal size. Semen examination reveals a low concentration of spermatozoa, a decreased number of spermatozoa in the ejaculate, and a high percentage of spermatozoa with morphologic defects, sometimes with premature (round) germ cells.[357] Without a history of normal testis size and function before atrophy, differentiation from testicular hypoplasia is usually not possible.[374,378] Discrepancies between testicular size (measured by scrotal width in stallions and scrotal circumference in ruminants) and daily sperm output may indicate testicular degeneration.[443,446,470,471]

43.61.3 Clinical Pathology

The measurement of plasma hormone concentrations may be helpful in establishing a diagnosis of testicular degeneration in large animals. However, the relationship between the concentrations of various hormones and the parameters of testicular function appears to be quite variable. Measurements of hormone concentrations in subfertile stallions have demonstrated that serum gonadotropins can be abnormally low or high.[472] Hormonal

criteria for confirming testicular degeneration in stallions typically include low concentrations of testosterone, with concurrent low LH concentrations in early cases of degeneration, or with high FSH and low estradiol concentrations in cases of chronic (or irreversible) testicular degeneration.[360] Less is known concerning hormone concentrations in other large animal species with testicular dysfunction. In one study, plasma testosterone concentrations were lower in young beef bulls with testicular degeneration than in a similar group of normospermic bulls; however, patterns of secretion and plasma concentrations of LH and FSH were not significantly different between the two groups.[446] Scrotal insulation of rams resulted in an increase in plasma FSH concentrations and a decrease in plasma testosterone concentrations within 1 to 4 weeks.[473]

Testicular biopsy can confirm degeneration.[474] Excision of an amount of tissue sufficient for evaluation often results in hemorrhage, pressure degeneration, and necrosis.[358] Therefore testicular biopsy is usually undertaken only as a final recourse. However, testicular biopsy in the stallion appears to be a relatively safe procedure.[475]

43.61.4 Treatment and Prognosis

Once testicular degeneration has occurred, treatment is usually of no benefit.[358] However, any factors that might contribute to testicular degeneration (such as febrile conditions or systemic illness) should be corrected. Treatment of injuries of the scrotum and its contents was described earlier in this chapter.

Recent findings regarding variations in serum hormone concentrations in subfertile stallions have stimulated an interest in gonadotropin replacement therapy, including the use of GnRH. Although the hypothalamic-pituitary-testicular (HPT) axis of the stallion is remarkably refractory to GnRH-induced downregulation compared with other domestic species,[476] few controlled studies have evaluated the effectiveness of GnRH therapy. In one study, pulsatile or constant administration of GnRH for 20 weeks did not promote testicular growth or alter spermatozoa output in reproductively sound or unsound stallions.[477]

In some cases, degeneration is temporary, and improved semen quality is evident after 2 to 5 months. The prognosis for an animal recovering its fertility and the economic losses the client will sustain from treatment and decreased production must be considered when deciding whether treatment of testicular degeneration is warranted.

43.62 ORCHITIS

43.62.1 Definition and Etiology

Orchitis is most commonly caused by infection or trauma. Bacterial infections may develop hematogenously, or occasionally by retrograde movement from infected accessory sex glands.[374] Extension of infection to the testes from periorchitis or epididymitis also occurs.[434] Testicular enlargement is due to edema that accompanies the inflammatory reaction. Contusion and inflammation of the testes occur in racing stallions, particularly standardbreds.[359] *S. zooepidemicus*, is commonly isolated from infectious orchitis in stallions.[360] In bulls, infectious orchitis is caused by *B. abortus, M. tuberculosis, A. pyogenes, Nocardia farcinica*, bovine herpesvirus 3 (IBR-IPV), and other miscellaneous organisms.[358,373,374,434] Epididymoorchitis in rams may be associated with *B. ovis*, or *Actinobacillus seminis*, and *Actinobacillus*,-like organisms.[368]

43.62.2 Clinical Signs and Differential Diagnoses

Acutely orchitic testes are hot, swollen, and painful. The swollen testis is turgid because of restriction by the tunica albuginea. Edema of the testicular parenchyma, and concurrent presence of periorchitis or epididymitis, may be detectable by ultrasound examination. Increased testicular temperature, congestion, and interference with circulation lead to ischemia and infarction. Abscesses sometimes develop, occasionally culminating in purulent liquefaction of testicular parenchyma. Testicular atrophy and fibrosis follow as the condition becomes chronic.[373,374]

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Acutely affected animals may refuse to mate. Ejaculates may contain numerous white blood cells. Variable mineralization of seminiferous tubules can occur as a chronic change. Decreased sperm motility and increased sperm morphologic abnormalities are evident. Standardbreds affected by acute orchitis may switch from a trot to a pace, whereas thoroughbreds may suddenly develop a hopping gait.[358]

43.62.3 Treatment and Prognosis

Treatment consists of scrotal cryotherapy and systemic administration of antiinflammatory drugs. Bacterial orchitis is treated with antibiotics chosen by semen culture and in vitro sensitivity. Antibiotic therapy should continue for 1 to 2 weeks beyond resolution of testicular swelling and pain.[361] Testicular atrophy and sterility are common sequelae to orchitis.[359] Changes in the testes, including precise measurements of in situ testis size, are followed by sequential ultrasound examinations or caliper measurements. Serial semen analyses over a period of several months allow the clinician to monitor response to treatment and return of testes to normal production of spermatozoa.

43.62.4 Prevention and Control

Support devices may aid in preventing recurrence of traumatic orchitis in racehorses. With *Brucella*, or *Actinobacillus*, orchitis in sheep, the presence of subclinical carriers in the flock must be considered.[411]

43.63 TESTICULAR NEOPLASIA

43.63.1 Definition and Etiology

Primary testicular tumors are uncommon in large animals but may be slightly more frequent in older bulls than in stallions or rams. Testicular tumors originate from the interstitial (Leydig) cells, Sertoli cells, and the germinal epithelium. Testicular teratomas and lipomas of the testicular surface and lymphosarcoma also occur.[*] Although the incidence of testicular tumors is relatively greater in retained than in scrotal testes in dogs, this predisposition has not been confirmed in large animals, perhaps because most are castrated at an early age before the time of usual onset of testicular neoplasia. Retained testes in the horse, however, are thought to be more prone to neoplasia. Teratomas in particular are found more commonly in cryptorchid than in scrotal testes, probably because they are embryonal in origin and their size prevents migration of the testis into the scrotum.[373,374]

Seminomas are the most common primary testicular tumor in the descended testes of adult stallions, with the majority occurring in stallions over 10 years of age.[373,374,481] Seminomas are not hormonally active and are usually benign but may be malignant and invade inguinal and abdominal tissues.[361,482] Seminomas are rare and benign in bulls and are rarely seen in aged rams, where they are occasionally highly malignant.[373] The tumor arises from the germinal epithelium and occurs in retained and scrotal testes; these tumors grow very rapidly.[358,373]

Interstitial (Leydig) cell tumors have been reported in stallions and bulls[434] and can have a negative impact on semen quality and fertility.[483,484] Most do not produce androgenic hormones.[373] They may be single or multiple in one or both testes and are commonly 1 to 2 cm in diameter.[373]

Sertoli cell tumors are reported in horses, cattle, and sheep, but they are rare. Although metastasis is uncommon, extension of neoplastic tissue into the testicular vein and lymphatics can result in hydrocele.[373] Because of the importance of Sertoli cells in spermatogenesis, these tumors are likely to exert an adverse effect on semen quality and fertility. Tumors in newborn or young calves may be a result of impaired embryogenesis.[373,380]

Teratomas are usually benign tumors commonly found in cryptorchid testes of horses.[478,485] They are rare in other large domestic species. The tumors are often cystic and vary in diameter from 10 to 25 cm or more. Structures present in teratomas arise from all three embryonic layers and include hair, nervous tissue, salivary glands, adipose tissue, cartilage, and bone.[373,374]

* References 373, 374, 415, 434, 478–480.

43.63.2 Clinical Signs and Differential Diagnoses

Neoplastic testes are often larger than normal, with an affected scrotal testis often twice the size of the unaffected testis, especially in cases of seminoma. Abdominally located testicular tumors can be quite large. Neoplastic testes, particularly seminomas, are typically irregular and firm. Swelling may extend into the spermatic cord, and pain may be present that interferes with breeding or is evident on palpation. Ultrasonographically, testicular tumors tend to appear as discrete, well-circumscribed hypoechoic areas within the usually homogenous testicular parenchyma.[361,430] However, seminomas may involve so much of the testis at the time of diagnosis that differentiation between neoplastic and normal tissue can be difficult.

Swelling of the affected testis may interfere with thermoregulation of the contralateral testis, resulting in decreased sperm production. Semen examination, however, may reveal seminal parameters to be within normal limits, and fertility may be acceptable. A significant amount of normal testicular parenchyma may remain covering the tumor, and living spermatozoa may or may not be present in the epididymis on the same side.[358,373,374,486]

43.63.3 Treatment and Prognosis

Testicular tumors should be surgically removed. Although metastasis is uncommon, early identification and removal of unilateral tumors prevents spread to other tissues. If semen quality is satisfactory in seasonal breeders, removal may be delayed until the breeding season is completed to avoid the transient decrease in

semen quality associated with postsurgical swelling. If neoplasia is bilateral, surgical removal may be delayed until semen quality deteriorates sufficiently to negate the use of the animal for breeding.[361]

43.64 INFERTILITY CAUSED BY DISEASES OF THE SPERMATIC CORD

43.64.1 TORSION OF THE SPERMATIC CORD

43.64.1.1 Definition and Etiology

Torsion of the spermatic cord occurs more commonly in stallions than in other large animals because of the horizontal position of the testes within the scrotum. Torsions may be transient or permanent and typically are of 180 to 360 degrees, but rotations may be greater.[381] Abnormal elongation of the caudal ligament of the epididymis (scrotal ligament), the proper ligament of the testis, or an excessively long mesorchium may encourage spermatic cord torsion.[466,487]

43.64.1.2 Clinical Signs and Differential Diagnoses

Torsion of the spermatic cord occurs in degrees that vary from those producing no pain or abnormality of semen to those involving vascular obstruction and acute colic.[359] Torsion is often a transient condition that does not interfere with testicular function or cause pain.[457] In those cases the testis is usually rotated 180 degrees or less. If torsion is of sufficient degree to result in vascular compromise, acute pain results.[358,359,487,488] Diagnosis of torsion of the spermatic cord is aided when displacement of the tail of the epididymis and scrotal ligament is evident on palpation. The head of the epididymis is normally located craniodorsal to the testis and the tail lies caudally, where it is attached to the testis by the proper ligament. The tail of the epididymis is most readily palpable, and its location is helpful in determining the degree of rotation. Torsions of 360 degrees or greater generally cause clinical signs that must be differentiated from strangulation of herniated contents into the scrotum. The primary method used to differentiate between the two conditions is palpation per rectum of the superficial inguinal ring to identify if herniation is present.[361]

Clinical signs of vascular impairment with spermatic cord torsion include abdominal discomfort, elevated heart and respiratory rates, unilateral swelling and edema of the scrotum, and increased testicular temperature.[361] Affected testes are painful and quickly become soft and friable.[358,359,487,488]

43.64.1.3 Treatment and Prognosis

Manual correction of spermatic cord torsion is sometimes possible, but recurrence is likely. To attempt manual correction, the horse is sedated and the testis is rotated in the direction opposite the torsion. Both hands are used to reposition the scrotum as the testis and its tunics are rotated.[359] Surgical correction is indicated if manual correction is not possible.[361] Nonsteroidal antiinflammatory drugs and analgesics may be administered to control pain.

The rapidity with which correction must occur is unknown; human testes may be salvageable if torsion is corrected within 6 hours. If hemorrhage or necrosis of the testis is evident, removal is indicated because the

contralateral testis may become permanently damaged. The mechanism of the damage is probably immunologic, resulting from antibodies to spermatozoa liberated as a result of ischemia.[489]

43.64.2 VARICOCELE

43.64.2.1 Definition and Etiology

Varicoceles are abnormally distended and tortuous veins of the pampiniform plexus.[411,465] Varicoceles are most often recognized in rams, in which dilations in vessels may reach 15 cm and discourage movement and libido.[454] The incidence of varicoceles increases significantly with age, reaching approximately 2% in rams 3 years of age and older.[438] Varicoceles have been reported infrequently in stallions.[361]

Varicoceles may result from insufficiency of veins draining the testis or a deficiency of the fascia and connective tissue surrounding those veins that allows backflow and stasis of blood in the vessels.[373] Infertility associated with varicocele is thought to result from disturbance of the local thermoregulatory mechanism, causing increased testicular temperature and subsequent disturbance in spermatogenesis.[361] Concomitant atrophy of the testis is common in rams.[438] Bilateral varicoceles and atrophied testes have been reported in the ram.[490]

43.64.2.2 Clinical Signs and Differential Diagnoses

Diagnosis of varicocele is made by palpating the dilated tortuous veins (“bag of worms”) within the spermatic cord.[358,411] Confirmation of the varicocele has been accomplished by ultrasonographic examination in stallions. Large echolucent areas in the venous plexus of the spermatic cord, sometimes with concurrent distention of the central vein of the testis, are described as the identifying features.[430] The ultrasonographic appearance of a suspected varicocele can be compared with the structures of an uninvolved contralateral testis and spermatic cord or those of an unaffected animal.

Thombosis of the varicocele can occur.[358,373] The large, organizing laminated thrombi can be mistaken as *Corynebacterium pseudotuberculosis*, abscesses in the scrotal fascia of rams.[373] Varicoceles might also be mistaken for sperm granulomas of the caput epididymis. Unless thrombosis has occurred, varicoceles are typically fluxuant and soft and fail to elicit pain when palpated.

43.64.2.3 Treatment and Prognosis

Surgical removal of varicocele has improved semen quality and fertility of some human patients but has not been reported in large animals. Thrombosis of a varicocele necessitates unilateral castration, with transection of the spermatic cord proximal to the thrombus.[357] Castration is also recommended for rams because of potential heritability risks.[454]

43.65 INFERTILITY CAUSED BY DISEASES OF THE EPIDIDYMIS AND ACCESSORY SEX GLANDS

43.65.1 EPIDIDYMITIS

43.65.1.1 Definition and Etiology

Epididymitis is caused by infection or trauma and may occur separately but is commonly secondary to orchitis or infection of the accessory sex glands.[373,374,491] The tail of the epididymis is commonly involved, but the head and body may be affected. *S. zooepidemicus*, is commonly isolated from equine epididymitis, although a number of other miscellaneous organisms, including *Proteus mirabilis*, have been incriminated.[358,492] In bulls, *B. abortus, A. seminis, A. pyogenes*, and other miscellaneous organisms cause epididymitis.[373,374,491] In mature rams the disease is commonly associated with *B. ovis*, whereas in ram lambs organisms from the *Actinobacillus, Haemophilus, Histophilus*, and *Corynebacterium*, groups are prevalent.[411,493] Routes of infection have been postulated to be hematogenous, venereal, or ascending from genitourinary passages, similar to routes of infection proposed for orchitis.[358,373] All routes of infection are likely to occur to some degree, depending on the pathogen and species involved. In an interesting study performed in yearling rams, conjunctival inoculation of *B. ovis*, culminated primarily in localized infections of the reproductive tract, which tended to first result in lesions of the distal tail of the epididymis.[494] Injuries, such as penetrating wounds, may also result in epididymitis.

43.65.1.2 Clinical Signs and Differential Diagnoses

Diagnosis of epididymitis is based on detection of clinical signs that include pain when irregular swellings of the epididymis are palpated, changes in shape and texture of the organ, adhesions between the epididymis and scrotal tunics, and enlargement of the tail of the epididymis.[358,361,411] The course of epididymitis varies from acute swelling and edema to chronic abscesses, periorchitis, and fibrosis.[373,374] Granulomas may develop if sperm escape into surrounding tissue.[438,491,495] In rams, epididymal lesions may be palpable along the entire length. Abnormal sperm morphology (especially detached heads) and leukocytes in the ejaculate may be seen before lesions are palpable.[496]

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Animals affected with the *Actinobacillus, Histophilus*, and *Haemophilus*, groups of organisms may acquire an epididymoorchitis syndrome.[411,497] Affected rams are usually less than 1 year of age. They may be subclinical carriers or acutely ill with pyrexia, depression, pain as evidenced by an arched back, and unilateral or bilateral swelling and tenderness of the scrotal contents. If these animals recover from the acute phase, the disease may become chronic and is characterized by an enlarged, firm, and often irregular epididymis; palpable adhesions of portions of the epididymis to the testis and vaginal tunics; atrophic testes; abscess formation; and draining fistulas to the scrotal surface. Ultrasonographic examination of the epididymis may reveal dilated ducts, fluid accumulation around the tail of the epididymis, and cystic areas within the epididymis that contain purulent material.[361,430]

43.65.1.3 Clinical Pathology

Inflammatory cells may be present along with abnormal sperm in the ejaculate of affected animals. Seminal leukocytes correlate positively with epididymitis lesions and correlate negatively with seminal quality.[496] Bacteriologic culture of the semen may aid in identifying infectious causes. Serologic tests for *B. ovis*, and *H. ovis*, are available and are helpful in determining exposure to the organisms.[411,497]

43.65.1.4 Treatment and Prognosis

Infectious causes of epididymitis are treated with systemic antibiotics selected by in vitro sensitivity. The ability of the antibiotic to gain access to the epididymis must also be considered. Treatment should continue for 1 to 2 weeks after inflammatory cells disappear from the semen. In unilateral cases, removal of the testis, epididymis, and spermatic cord on the affected side may salvage some valuable animals for breeding. If unilateral castration is elected, sequential postcastration examinations are indicated to ensure infection has not spread to remaining reproductive organs.[361]

Treatment of ram epididymitis is usually not recommended but might be attempted in valuable animals with minimal clinical signs. Oxytetracycline 10 mg/kg and dihydrostreptomycin 25 mg/kg IM twice daily for 7 days has been reported to resolve shedding of *B. ovis*.,[498]

In cases of moderate or severe bilateral epididymitis, the prognosis for recovery is poor. Obstructions and granulomas usually develop, resulting in sterility.[438] Testicular atrophy is a common sequela to epididymitis.

43.66 SEMINAL VESICULITIS (VESICULAR ADENITIS)

43.66.1 Definition and Etiology

Inflammation of the vesicular glands is uncommon in stallions but more likely in bulls.[373,374,499–501] Bacterial infections including *B. abortus*, and *P. aeruginosa*, are incriminated in stallions.[359,390,502–504] Various organisms have been isolated from cases of seminal vesiculitis in bulls including *A. pyogenes, B. abortus, M. tuberculosis*, mycoplasmas, ureaplasmas, *C. psittaci*, and *H. somnus*.,[358,373,374,499,505]

Vesiculitis may affect bulls of all ages but is most common in young growing bulls fed high-energy rations and housed together.[499] The prevalence may reach 20% to 30% in small groups of yearling bulls in close confinement.[501] The role of viral pathogens in outbreaks of the disease is not defined. Infections may arise by either ascending or descending routes from other areas of the urogenital tract, or hematogenously. Frequent homosexual activity among young bulls, high nutrition, and fast growth rates may be involved in spread of the infection.[358]

43.66.2 Clinical Signs and Differential Diagnoses

The seminal vesicles of affected stallions may be of normal size or enlarged and painful when palpated per rectum.[502,503] Stallions may refuse to cover or may be unable to ejaculate.[359] Semen contains numerous

neutrophils and blood, and fertility of infected semen is reduced.[390] Bacterial pathogens are readily recovered from semen of affected stallions.[361] However, special culturing techniques are necessary to pinpoint the seminal vesicles as the site of internal genital infection (see under Clinical Pathology).[404]

Bulls affected with vesiculitis may exhibit few clinical signs other than deterioration of semen quality. In severe cases pelvic inflammation and peritonitis result in pain reflected by reluctance to move, stiff gait, tense abdomen, and refusal to mate.[358] Other reproductive organs, particularly the ampullae, testes, and epididymides, may be inflamed.[499] The vesicular glands may not be significantly increased in size during the acute phase. If inflammation becomes chronic, the glands usually enlarge, eventually losing their lobularity and becoming fibrotic.[358,373] Abscesses are often associated with *A. pyogenes*, and may rupture into the rectum or urinary bladder.[358,374] Tubercular vesicular adenitis results in marked enlargement of the glands with caseous nodule formation. *B. abortus*, causes suppuration, necrosis, and calcification of the glands.[373] Purulent exudate is present in the ejaculate, sometimes as thick clots. Neutrophils may become less evident in semen as the condition becomes chronic. Poor sperm motility, increased morphologic defects, and an elevated pH are characteristics of semen from bulls with vesiculitis.[358]

Fertility of mildly affected bulls may remain satisfactory. More extensive involvement in which semen quality is markedly affected results in subfertility or infertility.[501] Semen from bulls with vesiculitis freezes poorly, and antibiotics used in extenders usually do not control the high numbers of bacteria present.[501]

43.66.3 Clinical Pathology

Bacterial pathogens can be recovered from the semen of affected stallions. However, without other evidence of infection of the accessory sex glands, recovery of pathogens from the semen should be interpreted with caution because the bacteria could originate from another location. Repeated samples for culture should be obtained from the sheath, penis, fossa glandis, preejaculatory fluid, urethra (before and after ejaculation), and seminal vesicle effluent manually expressed through a sterile urethral catheter positioned at the colliculus seminalis. Prostatic fluids can be collected through a catheter by massage per rectum. The first jet of a fractionated ejaculate includes the secretions of the ampullae.[404] Alternatively, a suitable fiberoptic endoscope can be passed in the urethra to the level of the seminal colliculus and into the seminal vesicles. Purulent material may then be aspirated for culture.[361]

Vesicular secretions from bulls can be collected by extension and disinfection of the penis followed by irrigation of the distal urethra with sterile saline. A sterile catheter is then passed 30 cm into the urethra, and the accessory sex glands are massaged to stimulate their secretion. Fluid is collected into sterile containers.[506]

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43.66.4 Treatment and Prognosis

Accessory sex gland infections are treated with antibiotics selected by culture and in vitro sensitivity. Antibiotics are administered for 2 to 4 weeks, but treatment failures may occur.[390] Negligible amounts of certain antibiotics may diffuse across mucosal cell borders into the seminal plasma.[507] Properties of antimicrobials suitable for parenteral treatment of accessory sex gland infections include high lipid solubility, a favorable pKa, and low protein binding. The antimicrobial should have a pH that is basic relative to the accessory gland fluid into which penetration is desired.[508] Vesicular and prostatic fluid have a pH of 7.3 to 7.5,

whereas bulbourethral gland secretion has a pH of 8 to 8.2.[404,447] Antimicrobials that may prove suitable for treatment include the basic macrolides such as erythromycin, which is fat soluble and has a high pKa, and trimethoprim, which also has a high pKa and a high percentage of nonionized molecules in plasma, favoring diffusion across the lipid membrane of epithelial cells.[508] Because of its antimicrobial spectrum and tissue diffusion characteristics, enrofloxacin has been found to be very effective for systemic treatment of seminal vesiculitis in stallions. Treatment of stallions by lavage and instillation of antimicrobials directly into the seminal vesicles via a flexible videoendoscope can be accomplished by skilled operators. Removal of the affected gland has been performed in stallions and bulls.[502,509,510] A technique used with fair success in stallions with localized vesicular adenitis is repeated irrigation through a catheter guided into the vesicles by endoscopy. Antibiotics are instilled into the vesicular gland lumen after each irrigation.[361]

The prognosis for correction of seminal vesiculitis is only fair to poor. Animals with mild cases may recover spontaneously in 2 to 3 months. In chronic cases glands that do not abscess become fibrotic and destroyed even though purulent material does not persist in the ejaculate.[358] In stallions with vesicular adenitis, immediate filtration of the ejaculate in order to remove cellular debris and mixing of semen in an appropriate antibiotic-containing extender to control bacterial growth may maintain sperm motility and fertility.[406]

43.67 BLOCKAGE OF THE EFFERENT DUCTS (SPERM STASIS)

Blockage of the efferent ducts between the testes and penile urethra sometimes occurs in stallions. If the condition is bilateral, azospermia results in spite of apparent ejaculation. The ampullae are frequently tense, and enlargement may be demonstrated by ultrasonography.[511–513] Massage of the ampullae per rectum followed by prolonged sexual stimulation and semen collection may result in ejaculation of a semen sample with a high concentration of spermatozoa, often present as “strings” or “plugs.”[511] Large numbers of detached sperm heads, often in clumps, are commonly observed. Collection of semen on a regular schedule may aid in preventing recurrence once the blockage is relieved. Empirical treatment by blockade of β-receptors and stimulation of α-receptors has been successful in some stallions that fail to ejaculate.[514]

Sperm granulomas caused by accumulation of spermatozoa in blind efferent ducts are a common cause of infertility in the buck.[368] Granulomas have also been identified in the stallion,[515] and particularly in rams with sperm extravasation as a result of chronic epididymitis.[373,374]

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44 Chapter 44 Critical Care and Fluid Therapy for Horses

K. Gary Magdesian

44.1 EQUINE FLUID PHYSIOLOGY

C. Langdon Fielding

Physiologic fluid compartments consist of total body water (TBW), extracellular fluid volume (ECFV), and intracellular fluid volume (ICFV). TBW is the most clearly defined compartment because it represents the total amount of water comprising an individual. Values for TBW in adult horses have been reported to range from 0.623 to 0.677 L/kg.[1–4] Values in foals are believed to be larger than in adult animals. In human neonates, TBW values up to 0.784 L/kg have been measured.[5] Acute changes in TBW in clinical patients can be detected with serial body weight measurements, but this becomes less accurate over long periods of time.

ECFV represents the component of TBW that is not contained within the cells. This includes plasma volume, interstitial volume, and transcellular compartments (gastrointestinal tract, joint fluid, cerebrospinal fluid [CSF], body cavities, and so on). The ECFV has been measured using a number of techniques in horses; reported values in adult horses range from 0.214 ± 0.01 to 0.253 ± 0.01 L/kg.[1,6] Estimations of ECFV in foals are significantly larger, including 0.400 L/kg in newborn foals and 0.290 L/kg in foals 24 weeks of age.[7] Plasma volume has been determined to be 0.050 L/kg in healthy adult horses and 0.090 in foals at 2 days of age.[7]

ICFV is the volume of fluid contained within cells. It has been estimated as the difference between TBW and ECFV. Bioimpedance technology has also been used to estimate the volume of intracellular space in horses, whereas standard indicator dilution techniques cannot be easily applied to the ICFV.[1,2] Reported values for ICFV in adult horses range between 0.356 ± 0.01 and 0.458 ± 0.06 L/kg.[1,2]

Rapid changes in fluid balance and compartment volumes can occur during disease states, especially critical illness. The next section discusses the physiologic relationships between these fluid volumes.

44.1.1 Plasma and Interstitial Balance

Although both are components of the ECFV, the plasma volume is separated from the interstitial space by blood vessel walls, with constant flow of fluid and proteins into the interstitial space. The plasma and interstitial volume therefore are in constant flux, and a single equation (the Starling hypothesis) describes the flow between these two spaces:

$$\text{Net capillary filtration} = K_f([P_{cap} - P_{if}] - \sigma[\pi_P - \pi_{if}])$$

where K_f is the capillary filtration coefficient, being dependent on capillary surface area and hydraulic conductivity. The other five terms in the equation represent the primary determinants of fluid balance between plasma and the interstitium:

1. π_{cap} is the colloid osmotic pressure (COP) within the capillary (capillary oncotic pressure).

COP is determined by the concentration of plasma proteins, primarily albumin, and their ability to attract ions. Normal COP in adult horses is approximately 20 mm Hg (19 to 26 mm Hg) and in neonatal foals is 18.8 ± 1.9 (15 to 22.6) mm Hg.[8,9] Hypoproteinemia with resultant decreased oncotic pressure can occur during a variety of diseases in horses but is most often a result of loss or decreased production. Losses most commonly occur through the diseased gastrointestinal tract in large animal species (protein-losing enteropathies); losses also may occur secondary to glomerular diseases or large accumulations of protein-rich effusions within body cavities or the interstitial space. Decreased production of protein (specifically albumin) occurs in response to systemic inflammation because albumin is a negative acute-phase protein.[10] Hypoproteinemia also occurs uncommonly because of liver disease.[11] Improvement of plasma COP is one of two primary means of manipulating Starling forces for fluid balance during treatment of clinical cases.

2 π_{if} is the COP within the interstitium.

Interstitial COP is more difficult to measure than plasma COP, but estimates of this number include 12 to 15 mm Hg in other species under experimental conditions.[12] Changes in total plasma protein concentration are likely to also affect the interstitial protein concentration and therefore alter both oncotic pressure components in Starling's equation. This may explain why some horses with significant hypoproteinemia do not show clinical signs of interstitial fluid accumulation (i.e., edema). That is to say, the gradient between capillary and interstitial oncotic pressure is only minimally affected when both have decreased proportionally, especially with time. It has been speculated that acute changes in plasma total protein concentration, however, may lead to edema formation more often than chronic hypoproteinemia; this is because of a relatively larger decrease in plasma protein concentration as compared with that in the interstitium with acute disease. Conversely, administration of hyperoncotic intravenous fluids (fluids with a COP >20 cm H_2O) can potentially shift the balance of oncotic pressure back to the vascular space by raising plasma COP. However, the colloid molecules from these fluids must remain within the vascular space to have this effect, which may be negated by significant alterations in capillary permeability.

3 P_{cap} is the hydrostatic pressure within the capillary

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Vascular hydrostatic pressure represents the pressure of plasma within the vessels pushing out toward the 1488 interstitium. A number of factors influence this pressure, including blood volume, vascular tone, and central venous pressure (CVP). This outward pressure on the vessel walls serves as the driving pressure for the continuous flux of fluid and protein out of the vessels into the interstitium. Pathologic increases in hydrostatic pressure can be caused by right-sided heart failure or other obstructive processes, such as venous thromboses, which can lead to edema formation. Pulmonary capillary hydrostatic pressure increases with left-sided heart failure and significant pulmonary vasoconstriction.

Administration of intravenous fluids can also increase capillary hydrostatic pressure; this is the second means by which therapeutic intervention can affect fluid balance between plasma and interstitial spaces in clinical patients (the first was altering plasma oncotic pressure). Fluid losses resulting from diuretic administration and acute blood loss are examples of decreased capillary hydrostatic pressure.

4 P_{if} is the hydrostatic pressure within the interstitium.

The hydrostatic pressure of the interstitium varies in different tissues but often has been overlooked as a significant contributor to fluid balance between the vascular and interstitial spaces. Newer understanding of interstitial fluid balance has recently been reviewed.[12] This information suggests that degeneration of the interstitial collagen network may cause a decrease in interstitial hydrostatic pressure, resulting in a shift of fluid into the interstitium. Inflammatory cytokines have been implicated as a cause for these changes in interstitial hydrostatic pressure. Severe burn injury can also result in marked negative pressures within the interstitium, causing a draw of fluid into the interstitial space and subsequent edema formation. In the future there may be therapeutic options to manipulate interstitial hydrostatic pressure and alter fluid balance, but currently there are no practical measures to do so.

5 σ is the capillary reflection coefficient for proteins.

Changes in capillary permeability can dramatically increase the flux of fluid and protein from the intravascular space into the interstitium. If this increase in flow cannot be balanced by a corresponding increase in lymphatic return, edema results. Increased vascular permeability has been regarded as a major mechanism of edema formation; however, it may be only one component of the significant fluid shift that results from a systemic inflammatory response syndrome (SIRS). Adult horses and neonatal foals may have significant differences in interstitial composition and vascular permeability. It has also been proposed that foals have an increased capillary filtration coefficient as compared with adults.[13] These hypotheses may explain the propensity of neonatal foals to form edema relatively easily in response to overzealous fluid administration. Because of this increased risk, careful monitoring and serial assessment of the balance between plasma volume and the interstitium is warranted when treating neonatal foals with fluid therapy.

44.1.2 Extracellular to Intracellular Fluid Volume Relationship

There are three main determinants of net movement of fluid between the ECFV and ICFV:

1 Tonicity of the ECFV

The tonicity (or effective osmolality) of the ECFV is estimated by the following equation[14]:

$$\text{Effective extracellular fluid osmolality} = (2 \times \text{Na}) + \frac{\text{Glucose}}{18}$$

Under normal circumstances, sodium and chloride are the primary determinants of ECFV tonicity; the equation doubles the sodium concentration rather than including the concentration of specific anions, some of which may not be easily measured. It should be noted that BUN is not included in the tonicity formula, because BUN is an ineffective osmole.

Other effective osmoles can be added to the ECFV, thereby increasing tonicity and inducing a shift of water from the ICFV to the ECFV. The tonicity of the ECFV is primarily regulated by vasopressin (ADH). Administration of fluids with a tonicity greater than or less than ECFV tonicity is a means to manipulate the balance of fluid between the ECFV and ICFV. This explains why hypertonic saline causes a shift of water from the ICFV to the ECFV. Recent mathematic models have been used to predict the influence of tonicity on the absolute volumes of these fluid compartments.[15] Similarly, fluid loss that has a tonicity different from the ECFV will also alter the ratio of fluid between the ECFV and the ICFV.

2 Tonicity of the ICFV

The tonicity of the ICFV is primarily determined by the intracellular concentration of potassium and its related anions. The tonicity of the ICFV and ECFV are the same at any given time point, a homeostatic mechanism meant as a safeguard to prevent acute changes in cell volume. Any imbalance in tonicity between the two fluid spaces will result in a rapid shift of fluid in order to maintain osmolar equality. The tonicity of the ICFV can be altered over time by the cells in response to changes in ECFV tonicity; an example of such a response is the production of idiogenic osmoles during hypernatremia.[16] Significant changes to ICFV tonicity during disease (resulting from damaged cell membranes) can result in accumulation of intracellular potassium, calcium, or cellular debris.

3 Cellular membrane permeability

Cell membranes are selectively permeable to water and ions. Changes in this permeability usually do not cause large alterations in global fluid balance during healthy states. However, cell membrane damage during disease states can result in significant fluid shifts. In fact, a shift of fluid from the ECFV to the ICFV is an indicator of cellular membrane damage.

44.1.3 Effects of Fluid Physiology on Clinical Fluid Therapy

Specific disease states dictate individualized fluid plans. However, with intravenous therapy the administered fluid enters the vascular space. From there, the characteristics of the administered fluid will determine its movement from the vascular space into the interstitium and from the ECFV to the ICFV. Hyperoncotic or hypertonic fluids result in the greatest relative expansion of plasma volume, with a corresponding reduction in ICFV. Hypotonic fluids result in the smallest increase in ECFV but add volume to the ICFV owing to a decrease in the tonicity of the ECFV. Estimates of the volumes of the different fluid spaces (whether based on clinical or laboratory values) before and during fluid therapy will allow for evaluation of the physiologic response in the clinical setting. The standard and universal administration of isotonic and hypooncotic fluids (such as lactated Ringer's solution [LRS] or physiologic saline) to all patients regardless of disease condition ignores the available research and clinical insight to suggest otherwise.

44.2 GENERAL PRINCIPLES FOR FLUID THERAPY IN CRITICAL CARE

K. Gary Magdesian

Current guidelines for fluid therapy in human critical care emphasize the “fluid challenge” method, believed to be more effective and safer than traditional estimates of percent dehydration.[17] The author's (KGM) protocol of fluid administration in horses follows this same algorithm. Considerations for the fluid challenge technique incorporate four primary decision phases: (1) type of fluid, (2) rate and volume, (3) goals or endpoints of fluid therapy, and (4) safety limits to fluid therapy.

1 Types of fluids include crystalloids (isotonic, hypotonic, and hypertonic) and natural and synthetic colloids. There is much controversy and no consensus as to whether crystalloids or colloids are more effective or advantageous in human critical care.[17] Currently the advantages of both fluids are capitalized on by using them together in the treatment of hypovolemia. The reader is referred to the section on fluid therapy for horses with gastrointestinal disease for further information regarding specific fluid types. Table 44-1 lists the composition of several commercially available crystalloids that are used in equine practice.

2 The rate of fluid therapy for replacement is based on the "fluid challenge" principles, whereby a 30-minute bolus of 10 to 20 mL of isotonic crystalloid per kilogram is administered with subsequent reassessment of perfusion parameters.[17] Alternatively, or in addition, hypertonic saline (7% to 7.5%) can be administered at a rate of 4 to 5 mL/kg. Colloids, because of their limited distribution in the central compartment, are bolused at slower rates than isotonic crystalloids, such as 3 to 5 mL/kg for hetastarch. Up to 10 mL of hetastarch per kilogram may be administered, being limited by development of dose-dependent coagulopathies. If after reassessment of the perfusion parameters it is deemed necessary to provide additional resuscitative fluids, then another similar bolus is given. This is repeated until signs of hypoperfusion resolve (endpoints are achieved) or safety limits are reached, at which point inotrope and/or vasopressor therapy is indicated.

Table 44-1 Composition of Commercial Replacement and Maintenance Fluids

Crystalloid	Sodium (mEq/L)	Potassium	Chloride	Calcium	Magnesium	Osmolarity (mOsm/L)	Organic Salt
REPLACEMENT							
Lactated Ringer's solution	130	4	109	3	0	272–273	28 lactate
Saline (0.9%)	154	0	154	0	0	308	0
Ringer's solution	147–148	4	156	4.5	0	310	0
Plasma-Lyte 148	140	5	98	0	3	294	27 acetate 23 gluconate
Normosol-R	140	5	98	0	3	294	27 acetate 23 gluconate
MAINTENANCE							
Plasma-Lyte 56	40	13	40	0	3	111	16
Normosol-M	40	13	40	0	3	110	16
0.45% NaCl + 2.5% dextrose	77	0	77	0	0	280	0
5% dextrose	0	0	0	0	0	252–253	0

3 The goals or endpoints of fluid therapy include both replacement and maintenance of fluid balance. *Replacement* refers to the replenishment of fluid deficits, primarily referring to those in the extracellular fluid compartment. *Maintenance fluid therapy* refers to the provision of maintenance fluid requirements to account for metabolism, insensible losses, growth, and ongoing losses. In general terms, *replacement* refers to replenishment of circulating volume and secondarily of interstitial fluid deficits; *maintenance* refers to

provision of fluids after hypovolemia and dehydration have been corrected. Maintenance fluid therapy maintains both circulating volume and hydration status, including that of the intracellular compartment.

The goals of replacement fluid therapy include rapid correction of hypovolemia by reversal of the signs of shock, including seven perfusion parameters: tachycardia (except in some neonatal foals), pale mucous membranes, prolonged capillary refill time, cold extremities, poor pulse quality, depressed mentation, and, in horses, reduced jugular fill. Urine production is another positive sign indicating correction of fluid deficits. Dehydration is corrected more slowly and is marked by reduced skin turgor (increased skin tent), dry mucous membranes, and dry corneal surface (reduced tear production).

Additional goals of volume replacement include correction of hypotension, tachycardia, oliguria, and blood lactate.[17] A decrease in urine specific gravity (in the absence of renal failure), an increase in arterial blood pressure and CVP, and improvement in venous oxygen saturation are specific endpoints. The goals of maintenance fluid therapy are different; they are to maintain a normal degree of hydration by providing for ongoing losses, including insensible losses (respiratory, cutaneous evaporative losses) and any abnormal ongoing losses such as diarrhea. Maintenance fluid rates for horses vary with ambient temperature, use, diet, and metabolic status. In general, a reasonable starting point for maintenance fluid requirements includes 2 to 3 mL/kg/hr for adult horses and 4 to 6 mL/kg/hr for neonatal foals.[18,19]

4 The safety limits to fluid therapy are indicators of intravascular volume overload, including supranormal CVP, a decrease in arterial oxygen saturation (or Pa_{O_2}), and clinical indicators of volume overload and overhydration. Once maximal CVP is achieved (10 to 12 cm H_2O in neonatal foals and 15 cm H_2O in adult horses), replacement fluid therapy must stop; if continued, edema will form as systemic and capillary hydrostatic pressures increase in response to test boluses. A decrease in oxygen saturation in arterial blood in a horse receiving fluid boluses may be consistent with development of pulmonary edema; this may precede development of tachypnea or frank edema. Although no published reports address fluid overload in clinical equine patients, one experimental study evaluating hyperhydration before moderate-intensity exercise in horses suggested the development of arterial hypoxemia during exercise.[20] These animals were administered oral fluids equivalent to 6% of body weight (approximately 26 L of isotonic fluid by nasogastric tube). Hyperhydration resulted in arterial hypoxemia, suspected to be cause by pulmonary edema associated with hyperhydration, during moderate-intensity exercise.[20] Clinical indicators serving as limits to fluid therapy include visible subcutaneous edema and tachypnea; with optimal monitoring, fluid therapy will not be allowed to continue to this point. Another endpoint or limitation to fluid therapy is a lack of further improvement in perfusion parameters despite repeated fluid boluses. If safety limits are reached before the goals of fluid therapy are achieved, the next step is to turn to inotrope and vasopressor therapy.

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The reader is referred to the section entitled Fluid Therapy for Horses with Gastrointestinal Diseases for side effects of fluid therapy and principles of oral fluid therapy.

44.3 CRITICAL CARE AND FLUID THERAPY MONITORING TECHNIQUES

K. Gary Magdesian

Monitoring tools provide for advanced critical care in the large animal intensive care unit. Several of these tools are pertinent to fluid therapy and provide guidance, endpoints, and safety limits. Many of these allow for direct

monitoring of fluid during administration of therapy, whereas others provide indirect information through hemodynamic data. Both of these are important to overall case management of the critically ill equine patient.

44.3.1 Central Venous Pressure

CVP is the pressure within the vena cava; the term most commonly refers to that within the cranial vena cava. It is determined by blood volume as well as venous tone and cardiac contractility. With serial measurements CVP provides a limit to the administered volume of fluid. Normal CVP is approximately 2 to 12 cm H_2O in foals and 5 to 15 cm H_2O in adults.[21–24] Subnormal to negative CVP values signify hypovolemia; however, normal values do not necessarily imply euvolemia. This is because CVP is affected by compensatory responses such as venoconstriction.

CVP is easily measured in neonatal foals through the use of 20-cm central venous catheters, such as long-term single- to triple-lumen polyurethane catheters. Measurements can be obtained in adult horses with the use of 55-cm commercial CVP catheters. CVP can also be measured by passing a smaller gauge polyurethane catheter or polyethylene tubing through a 14-gauge, 5¼-inch standard intravenous catheter. CVP can be measured with a disposable water manometer (for spot readings) or using a pressure transducer for continuous waveforms. Interpretation of CVP waveforms requires knowledge of component waves and descents, including the a, c, and v waves and x and y descents. The a wave represents atrial contraction. The mean of the a wave is the appropriate point at which to measure CVP (at expiration). The c wave is associated with tricuspid valve closure and a bulging of the valve into the right atrium, and the v wave is caused by atrial filling from venous return. The x descent occurs after the a wave and represents the fall in pressure associated with atrial relaxation. The y descent occurs after the v wave, representing a drop in CVP caused by ventricular relaxation and reopening of the atrioventricular valves.

High CVP readings also occur with pericardial tamponade, pleural effusion, or pneumothorax, as well as false increases from catheter occlusion and air within the lines. For accurate and consistent serial results a zero reference point should be selected and used for each measurement. The top of the sternal manubrium is a good reference point for the level of the pressure transducer or water manometer. The pressure transducer or water manometer can be taped to a fluid pole, providing a fixed zero point for repeated measurements in standing horses.

It should be noted that adequacy of intravascular volume cannot be guided by any one CVP level. Precision and reliability are limited by variable zero reference points, the effects of afterload and ventricular compliance, and alterations in intrathoracic pressure.[17] There is no linear relationship between intravascular volume and filling pressures, and CVP should be regarded as only an indirect estimate of volume. Serial measurements and trends over time are more useful than single numbers. The way CVP can be used on a clinical level for monitoring fluid therapy is as follows: if the patient responds to fluid boluses without increases or with only minor increases (2 to 3 cm H_2O) in CVP, then it is appropriate to continue infusions until signs of hypoperfusion are reversed.[17] Additional guidelines used in human patients are as follows: if the CVP increases to 3 to 7 cm H_2O (2 to 5 mm Hg), the infusion should be paused and perfusion reevaluated after a 10-minute wait. If the change in CVP was an increase ≥7 cm H_2O (>5 mm Hg) after the fluid bolus, the infusion is stopped.[17]

44.3.2 Arterial Blood Pressure

Arterial blood pressure measurements provide some insight into perfusion status, particularly when used in conjunction with clinical signs and labwork, such as blood lactate. It can be measured either directly through the use of arterial catheters or indirectly with a blood pressure cuff on the tail head. Arterial lines can be placed in the great metatarsal artery of recumbent foals and the transverse facial artery in standing adult animals for direct measurements. Indirect measurements are best performed with oscillometric blood pressure monitors that provide systolic, diastolic, and mean arterial pressure (MAP). Cuffs are provided by the manufacturer and vary in width and length with size of the patient.

Arterial blood pressure in healthy neonatal foals is highly variable and depends on breed, gestational age, and size of foal. In general, normal mean arterial blood pressure (direct) is 84.4 ± 3.7 mm Hg at 1 day of age and up to 101.3 ± 4.4 mm Hg at 14 days of age.[22] Indirect blood pressure readings in thoroughbred foals has been reported as 144 ± 15, 74 ± 9, and 95 ± 13 mm Hg for systolic, diastolic, and mean pressures, respectively.[25] Direct blood pressure has been reported for adult horses: 126 to 168 (systolic)/85 to 116 (diastolic) with a range for the mean arterial pressure of 110 to 133 mm Hg.[26–29] Indirect blood pressure in adult horses is 111.8 ± 13.3 mm Hg for systolic pressure and 67.7 ± 13.8 mm Hg for diastolic pressure.[30]

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Blood pressure values should not be regarded as the sole criteria for intervention. Rather, they should be used in conjunction with perfusion parameters, blood lactate concentration, and urine output in deciding whether there is need for further fluid administration or inotrope and vasopressor support.

44.3.3 Blood or Plasma Lactate

Blood or plasma lactate concentrations are very useful in monitoring fluid support as well as perfusion and metabolic status. Increased blood lactate may be a result of hypoperfusion and reduced oxygen delivery (hypovolemia, hypotension, anemia, hypoxemia, heart failure). Other considerations for hyperlactatemia should include SIRS, sepsis, catecholamine surges, liver or renal failure, thiamine deficiency, alkalosis, hyperglycemia, exercise, seizure activity, and the action of drugs such as salicylates and theophylline.[31–34] SIRS may increase circulating lactate concentrations independent of perfusion status; inflammatory mediators and cytokines activate pyruvate dehydrogenase kinase, an inactivator of pyruvate dehydrogenase, resulting in reduced activity of the citric acid cycle. Normal lactate concentrations in horses are <2 mmol/L, with most horses having levels <1 mmol/L.[35–37] Neonatal foals have decremental values after birth, with reported concentrations of 4.9 ± 1.02, 2.25 ± 0.6, and 0.89 mmol/L at birth, 12 hours of age, and 24 hours of age, respectively.[37–39] In a study I performed, foals had values of 2.3 ± 0.9, 1.2 ± 0.3, 1.1 ± 0.3 at 0 to 2, 24, and 48 hours of age, respectively, compared with 0.6 ± 0.2 mmol/L in adult horses.[40]

44.3.4 Cardiac Output

Advanced monitoring in equine critical care includes cardiac output measurement. A number of methods of cardiac output monitoring have bee described in horses, including the Fick principle, indicator dilution methods (such as lithium dilution), Doppler and volumetric echocardiography, pulse contour analysis, and partial carbon dioxide rebreathing. The most practical of these include lithium dilution and echocardiographic techniques.[41–46]

Lithium dilution precludes the need for placement of cardiac catheters. A small bolus of lithium chloride is injected into a peripheral vein or the cranial vena cava (via central line). Arterial blood is sampled using an arterial catheter at a constant rate and passes through a lithium electrode to generate a lithium concentration-time curve. Cardiac output is calculated from the area under the curve for lithium over time. Advantages of lithium dilution include only moderate invasiveness, good accuracy, and requirements for only small volumes of injectate. Disadvantages include the need for continuous arterial blood and limitations on repetitive measurements owing to lithium accumulation.[44–46]

Noninvasive cardiac output measurements can be made using the Bullet method through volumetric echocardiography.[43] Giguere and colleagues reported that the Bullet method provided an accurate estimate of cardiac output in anesthetized foals.[43] Cardiac output is calculated using heart rate and stroke volume (SV) as follows:

$$SV = \left(\frac{5}{6} \times LVAd \times LVLd\right) - \left(\frac{5}{6} \times LVAs \times LVLs\right)$$

where LVAd = left ventricular area in diastole (short axis view); LVLd = left ventricular length in diastole (long axis view); LVAs = left ventricular area in systole (short axis view); and LVLs = left ventricular length in systole (long axis view).

Cardiac output in healthy adult horses (400 to 500 kg) is 32 to 40 L/min.[41] Normal cardiac index, which is cardiac output expressed per unit of body weight, is 72 to 88 mL/kg/min. In the neonatal foal cardiac output has been reported to be 7.1 ± 0.4 L/min (cardiac index = 155.3 ± 8.1 mL/kg/min) in 2-hour-old foals.[22] At 24 hours of age cardiac output was determined to be 9.0 ± 0.5 L/min (cardiac index = 197.3 ± 12.0 mL/kg/min). This increased to 15.7 ± 1.5 L/min (cardiac index = 222.1 ± 21.6 mL/kg/min) at 14 days of age.[22] A general guideline for normal cardiac index is 100 to 300 mL/kg/min.[43]

44.3.5 Blood Glucose

Blood glucose concentration has been the focus of much study in human critical care in recent years. A number of studies have demonstrated improved survival and reduced complications with tight glucose control using intensive insulin therapy in critically ill humans.[47,48] Maintenance of euglycemia (80 to 110 mg/dL) resulted in reduced mortality in surgical intensive care unit patients as compared with hyperglycemia (180 to 200 mg/dL). Hyperglycemia may be associated with detrimental effects in pediatric intensive care patients as well.[49] How these findings relate to critically ill horses is unknown, but prevention of hyperglycemia is likely warranted and its effects in the equine intensive care unit require further study.

44.3.6 Monitoring Urine Analytes

Urine indices are useful for monitoring responses to fluid therapy. Successful production of urine output is a primary goal of fluid therapy, and measurement of urine production allows determination of "fluid balance" (input – output). Another important means of assessing the response to fluid loading is measurement of urine specific gravity and/or osmolarity. In the absence of renal failure, progressively dilute urine is a positive response to fluid administration. Urinalysis should be performed, and fractional excretion of electrolytes, particularly sodium, provides information regarding tubular function and can aid in differentiation

of prerenal from renal azotemia. Normal fractional excretion is <1% in adult horses and 0.31 ± 0.18% in neonatal foals.[50–53]

44.4 FLUID THERAPY FOR SPECIFIC DISEASES AND DISORDERS

44.4.1 Fluid Therapy for Liver Dysfunction and Failure (Box 44-1)

K. Gary Magdesian

Acute liver disease may result in hypovolemia owing to lack of water intake, third space losses into the gut and peritoneal cavity, and possibly pooling of blood in the portal circulation. Portal hypertension may result in gut edema with subsequent fluid loss. Considerations of fluid therapy in cases with hepatic dysfunction include reduced metabolic capacity as well as compromised synthetic ability of the liver. Because lactate clearance primarily occurs in the liver, fluids containing lactate should be avoided. Isotonic replacement fluids, such as Normosol-R (Abbott Laboratories, North Chicago, Ill.) and Plasma-Lyte 148 (Baxter Healthcare Corporation, Deerfield, Ill.), and acetated Ringer's are preferred over LRS. One millimole of acetate yields 1 mmol of bicarbonate during metabolism and is therefore alkalinizing.[54] These balanced, polyionic fluids are optimal as compared with physiologic saline because of the propensity of the latter to produce a mild, strong ion (hyperchloremic) acidosis, and many horses with liver dysfunction have a propensity toward acidemia.[55]

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44.4.1.1 Box 44-1 Fluid Considerations for Liver Failure

1. A combination of balanced, polyionic crystalloids and colloids is optimal.
2. Acetated fluids, rather than lactate Ringer's solution, should be used.
3. Colloids, particularly plasma, can be very beneficial if hypoalbuminemia is present and to minimize third space accumulation of fluids.
4. Potassium supplementation (20 to 80 mEq/L) may aid in reducing hyperammonemia.
5. Dextrose supplementation (1 to 2 mg/kg/min) should be provided for energy support.

Provision of dextrose, even in the face of normoglycemia, should be considered unless enteral nutrition is adequate. The addition of dextrose to fluids will minimize gluconeogenesis demands on the liver, as well as catabolism of endogenous tissues with subsequent increases in nitrogen turnover (and increased ammoniagenesis). Risk of hypoglycemia from liver dysfunction is also minimized, as patients may have insufficient liver and muscle glycogen reserves and impaired hepatic gluconeogenesis to maintain normal blood glucose concentrations. A dextrose supplementation rate for adult horses is 1 to 2 mg/kg/min. This equates to 3% to 6% dextrose in fluids if 1 L of crystalloid per hour is administered to a 500-kg horse. The addition of B vitamins can be helpful for anorectic horses because they are required cofactors for oxidative metabolism. Horses that remain anorectic for longer than 24 to 72 hours should be considered candidates for parenteral nutrition.

Horses with liver dysfunction should be monitored closely for hyperammonemia as a marker of hepatic encephalopathy. Fluids can be tailored to minimize the risks of hyperammonemia. Provision of potassium provides for an electrolyte draw of hydrogen atoms from intracellular stores, thereby lowering pH and promoting ionization of ammonia to its less diffusible form, ammonium ion, which is not able to cross the

blood-brain barrier.[56] Hypokalemia also promotes metabolic alkalosis and may compound hepatoencephalopathy owing to increased urinary losses of hydrogen ion (H^+) and increased tubular absorption of ammonia. For similar reasons, sodium bicarbonate should be used judiciously and with caution in horses with a propensity toward hepatic encephalopathy. Increases in the pH of plasma will result in conversion of ammonium ion to ammonia; this facilitates the brain uptake of ammonia with subsequent intracerebral trapping of ammonium.

The rate of fluid administration for horses with liver dysfunction will vary with the volume and hydration status of the individual. In general, rates should exceed maintenance requirements to account for hypoperfusion and produce diuresis of ammonium and other toxins such as conjugated (direct) bilirubin that would otherwise have been metabolized or eliminated by the liver. Volume of fluid administration should be monitored closely in horses with ascites or portal hypertension resulting from severe liver disease because of the propensity of these patients for third space fluid accumulation. Other considerations for horses with liver disease include hypoalbuminemia, hyponatremia, hypokalemia, coagulopathies, and hyperlactatemia. Monitoring CVP will aid in preventing rises in hydrostatic pressure that would contribute to transudates or ascites.

Fluid support should be modified in horses with preexisting ascites or edema to reduce the administered sodium load. Commercially available solutions with restricted sodium concentrations (maintenance crystalloids), such as Plasma-Lyte 56 or Normosol-M, can be used in foals. Because of their availability in only small volumes (1-L bags), combinations of isotonic crystalloids and sterile water or 5% dextrose in water can be used as maintenance fluids in larger patients. If sterile water is selected, it should be allowed to mix with the isotonic fluid before entering the patient; administered alone, water could cause osmotic hemolysis. Another option in such horses is to restrict the volume of crystalloid administered through concurrent administration with colloids. Colloids expand the intravascular volume, limit the requirement for crystalloids, and may reduce the propensity of edema formation by raising oncotic pressure.

Colloids are indicated in horses with significant hypoalbuminemia (<1.5 g/dL). Hetastarch can be used at a dose of 10 mL/kg/day unless coagulopathies are present. Liver failure may result in decreased production of clotting factors or antithrombin and can initiate disseminated intravascular coagulation (DIC). Because hetastarch can induce decreased activity of von Willebrand's factor and factor VIII, as well as interfere with platelet function, it is contraindicated in horses with bleeding tendencies (after consumption of factors).[57] Plasma is an alternative colloid that has additional benefits for horses with hepatic failure. Coagulopathies associated with liver disease can be addressed through provision of exogenous antithrombin and clotting factors in plasma products. Plasma should probably not be administered to horses with serum hepatitis (Theiler's disease), as this disease is poorly understood and associated with prior administration of equine-origin biologics. Replacement of albumin is beneficial not only for oncotic pressure support but also for drug and toxin binding and as an endogenous buffer. If hypoalbuminemia is a result of hepatic dysfunction, and not urinary or gastrointestinal losses, colloids will have a longer retention time in the circulation.

44.4.2

Fluid Therapy for Diarrhea and Colitis (Box 44-2)

K. Gary Magdesian

Horses with acute colitis are often presented in a state of severe SIRS with endotoxemia, hypovolemia, and malperfusion of tissues. Fluid therapy is the cornerstone of hemodynamic and therapeutic support for these horses. Not only is circulating volume an indication for fluids, but acid-base and electrolyte derangements also warrant their use in these cases. Specifically, horses with colitis often exhibit hypovolemia, both organic and

inorganic acidoses, and hyponatremia. Organic acidosis primarily is a result of hyperlactatemia, whereas inorganic acidosis is often a result of relative hyperchloremia (or hyponatremia).

44.4.2.1

Box 44-2 Fluid Considerations for Horses with Diarrhea or Colitis

1 A combination of crystalloids and colloids has many benefits in horses with colitis.

2 Colloids are indicated when concurrent hypoproteinemia and hypovolemia are present.

3 Potassium, calcium, and magnesium should be supplemented as necessary.

4 Hypertonic saline has several potential benefits for horses with acute colitis, including volume expansion, immunomodulation, antiinflammatory effects, antiedema effects, and positive inotropic effects.

Because of the poor sensitivity of physical examination in detecting hypovolemia, estimates of percent dehydration and water deficit are not very accurate.[17] A more objective means of providing fluids is through the "fluid challenge method" described in the previous sections.[17] In this protocol a bolus dose of 10 to 20 mL of isotonic crystalloid per kilogram is administered, with subsequent reassessment of perfusion parameters. Perfusion parameters consist of mentation, peripheral pulse quality, heart rate, mucous membrane color, capillary refill time, and extremity temperature. Lactate, arterial blood pressure, and central venous oxygen saturation are perfusion monitoring tools that should be evaluated serially in patients undergoing fluid administration and can provide endpoints to fluid therapy. Urine output is another clinical indicator of improvement in perfusion in response to fluid loading. Fluid challenge should continue as repeat boluses until perfusion parameters normalize or plateau in terms of improvement. No further improvement of perfusion parameters in response to boluses of fluids suggests that inotrope or vasopressor support may be required and that further fluid therapy will not be of aid. A safety limit to fluid loading includes measurement of a high CVP value.

Crystalloid fluid choices for horses with colitis include replacement fluids, such as Normosol-R, LRS, and Plasma-Lyte 148. Normosol-R and Plasma-Lyte 148 are slightly advantageous over LRS from the stand point of providing a wider strong ion difference (sodium-chloride difference). In contrast, LRS has a chloride concentration greater than that of equine plasma (109 vs. approximately 100 mEq/L) and can compound an inorganic acidosis. Physiologic saline (0.9%) is even greater in its chloride concentration and produces a mild strong ion acidosis on administration of large volumes.[55]

Colloids are an important adjunct to crystalloid therapy, particularly for horses with hypoproteinemia such as those with acute colitis. In human critical care medicine there is no consensus as to whether crystalloids or colloids provide more successful fluid resuscitation.[17] A combination of both is likely optimal.[17] Colloids are particularly important for horses with hypoproteinemia, such as those with colitis. Concurrent hypovolemia and hypoproteinemia warrant administration of colloids in the resuscitative period, because the use of crystalloids alone could result in dilutional hypoproteinemia.[57]

Hypertonic saline (7% to 7.5%) is a rapid plasma volume expander that can be used in the early volume replacement period. Hypertonic saline increases plasma volume by three to four times the volume administered. In comparison, crystalloids increase plasma volume by only 0.25 to 0.33 mL for each milliliter administered. Hypertonic saline has additional advantages beyond volume expansion, particularly for the horse with endotoxemia. These include immunomodulatory, antiinflammatory, antiedema (particularly of the endothelium

and erythrocytes), and inotropic effects.[58–60] Microvasculature effects enhance microcirculatory perfusion, which is often disturbed during sepsis and endotoxemia. Reduction of endothelial and erythrocyte edema, two processes that contribute to multiple organ dysfunction during sepsis, results in reduced vascular resistance and blood viscosity.[59,60] The hypertonicity created by hypertonic saline evokes vasodilation, which also contributes to microperfusion when coupled with an increase in cardiac output caused by contractility-enhancing effects of hypertonic saline. The antiinflammatory and immunomodulatory effects include antiapoptosis, free-radical scavenging properties, inhibition of leukoactivation, and prevention of immunosuppression after sepsis.[58–60] In an experimental model of hemorrhagic shock in horses, hypertonic saline resulted in improved cardiac output, stroke volume, cardiac contractility and blood pressure as compared with isotonic saline.[61] Hypertonic saline has demonstrated attenuation of cardiovascular derangements in equine endotoxemia models as compared with isotonic saline.[62]

The dose for hypertonic saline is 4 mL/kg, and it should be followed with isotonic crystalloids or water to replace the "borrowed" water from the intracellular space. Hypertonic saline is generally safe but should be avoided in horses with uncontrolled hemorrhage when hypotensive resuscitation is indicated. In addition, horses with marked sodium derangements should not be administered hypertonic saline.

44.4.3 Fluid Therapy for Sepsis (Peritonitis, Pleuritis, Pneumonia, Internal Abscess) (Box 44-3)

K. Gary Magdesian

The optimal fluid for resuscitation of patients with sepsis is unknown.[63–65] Despite this controversy, a rational approach to fluid therapy in patients with sepsis is to optimize hemodynamics (increase blood pressure and urine output) while attempting to limit edema formation.[17,63,66] There is no evidence to support the use of either colloids or crystalloids over the other. Metaanalysis of clinical studies comparing crystalloids and colloids in human patient populations showed no outcome difference.[64–68] Regardless of the lack of consensus recommendations for fluid choices, fluid therapy is a keystone in the management of severe sepsis and septic shock. This is because septic shock is associated with both absolute and relative hypovolemia. Relative hypovolemia is the result of vasodilation and peripheral blood pooling in the face of cytokinemia. Volume repletion allows for increases in cardiac output and subsequently in systemic oxygen delivery.[67]

Fluid therapy in horses with sepsis is similar to that recommended for horses with acute enterocolitis; both conditions are examples of a state of SIRS. In fact, enterocolitis can be thought of as a form of sepsis. Sepsis incites a host of hemodynamic derangements that challenge fluid therapy. It causes myriad microperfusion abnormalities; these include hypovolemia, myocardial depression, vascular permeability derangements, vasodilation, DIC, and cellular changes resulting in abnormal membrane potential and membrane pump or channel function.[69] These pathophysiologic processes must be considered when a fluid plan for horses with sepsis is designed.

Sepsis is defined as concurrent SIRS and documented or suspected infection.[70] Many equine cases fall into this category, including horses with peritonitis, pneumonia, pleuritis, enterocolitis, meningitis, and metritis. Sepsis and SIRS are states of cytokine milieu, in which cytokines and inflammatory mediators predominate. Aside from antimicrobials, the fundamental therapy is hemodynamic support, consisting of fluid and vasopressor therapy.

44.4.3.1

Box 44-3 Fluid Considerations for Horses with Sepsis

1 A combination of crystalloids and colloids may have advantages in patients with sepsis.

2 The presence of concurrent hypoproteinemia and hypovolemia may be an indication for initial resuscitation with colloids.

3 Fluid challenge, consisting of 10- to 20-mL/kg boluses, is a safe and effective means of determining volume to be administered.

4 Monitoring of fluid therapy increases safety, especially in those prone to edema. Monitoring should consist of measurement of central venous pressure, arterial blood pressure, and urine output.

5 Metabolic acidosis is very common among patients with sepsis.

Initial fluid resuscitation is centered on isotonic (or near isotonic) replacement type fluids, colloids and hypertonic saline. Horses with sepsis often are presented with negative fluid balance resulting from both hypovolemia and dehydration. Fluid choices are the same as for horses with enterocolitis, and a combination of crystalloids and colloids may have advantages in sepsis.[17] Such a combination would address both blood volume and interstitial deficits, with colloids expanding the vascular space and crystalloids addressing both fluid spaces. Hypertonic saline may have some additional advantages for sepsis, including immunomodulatory, antiinflammatory, antiedema, vascular, and inotropic effects.[58–60] A dose of 2 to 4 mL of hypertonic saline per kilogram may be added to the combination of crystalloids and colloids.

Colloids are intriguing fluids for horses with sepsis. Colloids may attenuate capillary leak associated with sepsis and SIRS.[71] The exact physiology behind this colloid effect is not exactly worked out; however, theories include reduction in endotoxin-induced leukocyte-endothelial cell interactions.[72] Interactions with endothelial glycocalyx are also hypothesized in the ability of both synthetic colloids and albumin to reduce capillary leakiness.[73] Hetastarch exhibits antiinflammatory properties by reducing neutrophil adhesion and accumulation in tissues.[74] In addition, hetastarch has been suggested to be beneficial for tempering DIC in that it exerts dose-dependent effects on coagulation.[57] Hetastarch lowers concentrations of von Willebrand's factor and factor VIII:C and reduces platelet aggregability, which may aid during hypercoagulable states such as DIC.[57,75–79] Both of these properties warrant further investigation in horses with sepsis because vascular derangements and coagulopathies are quite common. It should be kept in mind, however, that bleeding may be potentiated by the administration of hetastarch to the hemorrhaging patient.[80] In a trial comparing concentrated albumin with crystalloids in human patients, there was a trend toward improved survival with albumin in patients with sepsis.[81] Concentrated equine albumin is not currently available; however, one study showed that a human albumin product could be used safely in horses.[82]

Care should be taken to avoid overexpansion of the extracellular fluid compartment with excessive fluid administration. Horses with sepsis have a predilection for edema because of the presence of concurrent hypoalbuminemia and increased vascular permeability. Therefore careful monitoring of fluid balance is warranted. *Fluid balance* refers to input and output of fluids, and it can be monitored with urinary collection systems. CVP is also useful in monitoring for safety limits in this group of patients; maximal normal CVP (10 cm H_2O in foals; 15 cm H_2O in adults) should not be exceeded. Serial ultrasonography and arterial blood gas

analysis can be used to detect pulmonary edema from relative or absolute fluid overload, before the development of gross signs (froth, crackles, tachypnea) of edema.

Because of thrombotic risks associated with sepsis-induced coagulopathies, these patients should be instrumented with minimally thrombogenic catheters, such as long-term polyurethane catheters. Attention to asepsis and cleanliness are paramount.

In human critical care "early goal-directed therapy" has been advocated by some clinical trials.[83] These studies have used goal-oriented therapeutic adjustments of preload, afterload, and contractility to achieve a balance between oxygen delivery and demand. Endpoints have included normalization of central venous oxygen saturation, blood lactate, CVP, and MAP. The therapy consisted of crystalloids and colloids for correction of CVP, vasopressors and vasodilators for MAP, and dobutamine and red cell transfusions for central venous oxygen saturation. Patients receiving this early goal-directed therapy received a greater volume of fluids early (first 6 hours of treatment) and less later, as compared with patients in the conventional group. The treatment group had a lower mortality rate and less severe organ dysfunction, highlighting the importance of early identification of patients with insidious or occult malperfusion, consisting of patients with global hypoxia yet stable vital signs.[83] There has been considerable debate over what the optimal fluid choices are for human patients with sepsis: crystalloids or colloids. The ideal fluid for volume replacement remains equivocal because concrete evidence implicating one over the other is lacking.[64,84] A current philosophy is to recognize the advantages of both fluids, with concurrent or sequential administration of both. Because crystalloids distribute approximately 75% of administered volume to the interstitium, they allow for greater interstitial expansion compared with colloids. This property is advantageous when dehydration is also present, but a disadvantage when edema is a risk. In fact, crystalloid administration further dilutes total protein and albumin concentrations, thereby lowering COP and predisposing to edema. Colloids, on the other hand, are restricted to the intravascular space and are particularly indicated in hypovolemic shock; they replace intravascular losses more rapidly than do crystalloids.[85] Colloids are associated with a plasma volume expansion between 100% and 200% of the infused volume.[86–88] In humans and anesthetized horses with colic, cardiac output is better maintained with lower volumes of fluid administration when colloids are used rather than crystalloids.[89]

Marked alterations of the reflection coefficient, as are associated with severe capillary leak and acute respiratory distress syndrome (ARDS), warrant careful consideration and monitoring of patient status when colloids are administered; because of a theoretic potential for extravascular leakage of colloids with marked endothelial alterations, patients with ARDS should be monitored closely for clinical deterioration. Despite these theoretic concerns, a new form of hydroxyethyl starch (130/0.4) has demonstrated protective effects in a model of acute lung injury (ALI).[90] The numbers after the colloid in the preceding sentence refer to the average molecular weight and degree of substitution of starch molecules with a hydroxyethyl group, respectively. This hydroxyethyl starch resulted in the best oxygenation and a reduced inflammatory response as compared with a modified gelatin colloid or Ringer's acetate crystalloid in a rabbit model of ALI.[90] Standard hetastarch has an average molecular weight of 450 kDa and a degree of substitution of 0.7; the newer hydroxyethyl starch (Voluven; 130/0.4) has been modified to have more complete renal elimination and less tissue storage than the standard product, with fewer side effects such as coagulopathies. The use of different colloids in patients with ARDS needs further study. Except for situations that may call into question the use of colloids, the concurrent use of crystalloids and colloids obviates the need for large volumes of crystalloids; this approach minimizes the risk of interstitial edema and may restore blood volume more rapidly than crystalloids alone. A "blending" of crystalloids and colloids should therefore be considered for patients with sepsis whenever colloids are not contraindicated.

Tight glucose control has been one of the very few therapeutic modalities to affect outcome in patients with sepsis. Through the use of intensive insulin infusions, glucose is regulated in the range of 80 to 110 mg/dL as compared with traditional approaches that allow for slight hyperglycemia. This direction has led to a reduction in mortality, organ failure, and septic complications in human patients.[91] Whether this approach will have similar results in horses remains to be seen. The author (KGM) uses regular insulin as a continuous rate infusion (CRI) at a rate of 0.01 to 0.1 IU/kg/hr.

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44.4.4

Fluid Therapy for Renal Failure (Box 44-4)

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K. Gary Magdesian

Fluid therapy is the major component of therapy of renal failure in horses, regardless of cause. Hemodialysis has been reported in horses; however, it is not widely available, further highlighting the importance of fluid diuresis. Peritoneal dialysis is an option to complement fluid therapy, particularly if unresponsive anuria is present.[92,93] Development of a fluid plan for horses with renal failure begins with classification of the disease into polyuric, anuric, or oliguric renal failure. Polyuria and anuria are self-explanatory; oliguric renal failure in this section refers to a normally hydrated animal with concurrent azotemia and urine production <0.5 mL/kg/hr.

For both oliguric or anuric and polyuric renal failure, there are two primary considerations when beginning fluid therapy: fluid type and rate. The total amount of fluid administered is usually determined by the response to treatment and does not necessarily need to be identified at initiation of therapy.

44.4.4.1

POLYURIC RENAL FAILURE

The goal of fluid therapy in these patients is to induce diuresis, with removal of uremic toxins and maintenance of fluid, acid-base, and electrolyte balance.[94,95] The degree of renal failure that is reversible is often unknown at the onset; this is evaluated over time, particularly with response to fluid therapy. It should be noted that azotemia may not improve for up to 72 hours after initiation of fluid therapy when acute renal failure is severe. A lack of initial improvement in plasma creatinine or BUN during the first day or two of therapy should not necessarily prompt a poor prognosis or discontinuation of therapy.

44.4.4.1.1

Box 44-4 Fluid Considerations for Horses with Acute Renal Failure

1 Horses with acute renal failure can be either polyuric or oliguric or anuric.

2 Polyuric horses should be treated with isotonic crystalloids with the goal of diuresis. A rate of administration equal to 1.5 to 2 times a maintenance rate (3.75 to 5 mL/kg/hr) is a reasonable starting point, but input should match output. Balanced, polyionic commercial electrolyte solutions, such as Normosol-R or lactated Ringer's solution, can be used in most cases.

3 Physiologic (0.9%) saline is mildly acidifying because of hyperchloremia. Its effects on potassium balance in plasma are controversial. Hyperkalemia, commonly found in renal failure patients, can be treated with sodium bicarbonate, dextrose, calcium, and insulin when it does not respond to fluid diuresis.

4 Anuric or oliguric horses should be treated promptly. Adequacy of circulating volume and blood pressure must be ensured initially. If fluid loading with isotonic replacement crystalloids does not correct the lack of urine production, then furosemide, mannitol, and dopamine can be tried.

5 Failure to produce urine after these measures warrants hemodialysis or peritoneal dialysis.

The rate of fluid administration should facilitate diuresis.[95] A rate of two to three times maintenance fluid rate (4 to 6 mL/kg/hr, where maintenance rate is 2 to 3 mL/kg/hr) is a reasonable starting point; however, there is a paucity of literature to recommend evidence-based rates of fluid administration for treatment of acute renal failure or other disorders. Similar fluid rates have been suggested in small animal patients with renal failure.[95] It is unknown whether increases in the fluid rate beyond this point are beneficial. Certainly, if urine output is greater than this rate, it should be matched with fluid input. Measurement of CVP has become more practical in equine patients and can be used to ensure that fluid administration is not excessive.[96,97] Reference ranges of <15 cm H_2O have been reported for adult horses; values exceeding 20 cm H_2O indicate a need to decrease the rate of fluid administration to avoid development of edema.[97]

A balanced isotonic crystalloid is suitable for diuresis while preventing significant electrolyte alterations.[95] Horses should be allowed free access to water whenever possible while intravenous fluids are administered. This allows for some degree of self-regulation of water balance and can provide free water for renal excretion of the large sodium load provided by isotonic crystalloids.

Hyperkalemia is a relatively common feature of acute renal failure.[98,99] This is often corrected when renal perfusion is optimized and diuresis is instituted. When hyperkalemia is present, anuria should be ruled out. Cardiac dysrhythmias can develop during hyperkalemia; potassium free fluids (0.9% saline or isotonic sodium bicarbonate) should be administered to patients with dangerous hyperkalemia (>6 mmol/L), along with calcium, dextrose, and possibly insulin.

LRS has the benefit of containing a minor amount of free water (osmolarity 273 mOsm/L) and slightly less sodium than other fluids (130 mEq/L). A potential disadvantage, however, is that it contains more chloride (109 mEq/L) than equine plasma. Horses with renal insufficiency may be unable to excrete excess chloride provided by LRS diuresis. Mild hyperchloremia may result, causing a minor strong ion acidosis. LRS also contains potassium (4 mEq/L), which is a consideration in the hyperkalemic patient. However, studies in human renal transplant patients failed to demonstrate development of hyperkalemia as a result of LRS administration.[100]

Isotonic saline (0.9%) solution has an even higher chloride content (154 mEq/L) than LRS. In fact, neither the sodium nor the chloride concentration in this fluid is similar to those of equine plasma. Isotonic saline solution has been shown to cause hyperchloremia and a mild acidosis during prolonged administration; for these reasons it is not the ideal fluid for long-term management of acute renal failure.[101,102] Saline does not contain potassium and therefore may be warranted in horses with hyperkalemia. However, creation of a metabolic acidosis because of hyperchloremia may also pose a risk for hyperkalemia by causing an extracellular shift of potassium; this shift occurs as a result of acute changes in blood hydrogen concentration, which occur in association with hyperchloremic metabolic acidosis.[100] The effects of saline on potassium balance in horses warrant further study. Metabolic alkalosis, caused by hypochloremia or relative hypernatremia, is an indication for saline administration.

Normosol-R (Abbott Laboratories, North Chicago, Ill.) and Plasma-Lyte 148 (Baxter Healthcare Corporation, Deerfield, Ill.) have a sodium and chloride concentration most similar to equine plasma among the commercial isotonic or nearly isotonic fluids and are excellent fluids for diuresis of acute renal failure cases. It should be noted that these contain the highest potassium concentration (5 mEq/L) of all of the commercial fluids described; however, this potassium content is unlikely to contribute to clinically significant hyperkalemia in polyuric animals because of urinary excretion of excessive potassium (possible exceptions: uroperitoneum, anuria).

Isotonic sodium bicarbonate solution can be made by mixing sterile water and sodium bicarbonate to create a solution with a sodium concentration of 150 mmol/L. Isotonic sodium bicarbonate does not contain potassium or chloride and can be modified to contain an increased amount of free water as needed by lowering the sodium concentration. It exerts an alkalinizing effect by increasing strong cation (Na^+) concentrations without a corresponding increase in strong anions (i.e., strong ion alkalosis).

Blending of fluids with different compositions is also an option in order to correct or maintain electrolyte and free water balance. Over time, horses often develop a plasma electrolyte profile similar to that of the administered fluid, especially when large volumes are administered for prolonged periods; therefore combining or changing fluids may be necessary if derangements develop. It is also clear that monitoring of electrolytes (one to four times per day) is particularly important in renal patients.

44.4.4.2 ANURIC OR OLIGURIC RENAL FAILURE

Anuria and oliguria should be considered emergency medical conditions; the longer the duration of little to no urine production, the lower the chances of correcting it. Urine output in healthy horses is approximately 1 mL/kg/hr, but this may decrease by 80% (to 0.2 mL/kg/hr) in horses deprived of water.[103,104] In humans without significant fluid deficits, a urine flow <0.5 mL/kg/hr is one criterion used to define acute renal *injury,* whereas acute renal *failure* is associated with a urine flow <0.3 mL/kg/hr.[105] Oliguric renal failure should be suspected in azotemic horses with urine production <0.5 mL/kg/hr despite the administration of intravenous fluids. Once anuria or oliguria is suspected, a methodic approach to fluid administration and monitoring should be instituted immediately because of the associated high mortality rate. A delay in instituting treatment makes reversal of anuria less likely.

44.4.4.2.1 Treatment of Anuria or Oliguria

1. Obtain baseline laboratory and hemodynamic parameters. These should include serum or plasma electrolyte levels, total plasma protein and blood lactate concentrations, packed cell volume, and clinical perfusion parameters. When possible, CVP, arterial blood pressure, and central venous oxygen tension should be measured as well.

2. If CVP is not already significantly increased and there are no clinical signs of fluid overload (increased respiratory rate, peripheral edema, and so on), a fluid challenge should be initiated using 20 mL of an isotonic crystalloid per kilogram. CVP, clinical pathology, urine output, and physical examination status should be reevaluated for improvement after completion of the bolus.

3 If urine output has not significantly increased, additional fluid challenges should be given and the patient reevaluated until urine production begins or until CVP limitations are reached. A CVP value >15 to 20 cm H_2O (>10 to 12 cm H_2O in foals) signifies an endpoint to fluid administration.

4 Arterial blood pressure should be monitored. If hypotension is present despite fluid loading, inotrope and vasopressor therapy should be considered. Dobutamine can be used as an inotrope (5 to 10 mcg/kg/min). Norepinephrine, a vasopressor, can be used if dobutamine does not correct hypotension (0.01 to 0.1 mcg/kg/min). (The reader is referred to the section on inotrope and pressor therapy under Fluid Therapy for Horses with Gastrointestinal Disease.)

5 Once urine flow has increased, fluids should be continued as described previously for polyuria; careful monitoring of CVP and fluid balance (measurement of serial body weight and urine output) should be done.

6 If urine flow does not begin over the next 30 to 60 minutes with fluid challenge, furosemide should be started with an initial bolus of 0.12 mg/kg intravenously (IV) followed by a CRI of 0.12 mg/kg/hr.[106] If CRIs are not possible, a bolus dose of 1 mg/kg IV can be administered instead.

7 If urine production does not begin within 30 to 60 minutes of instituting furosemide therapy, a dose of mannitol should be administered (0.25 to 0.5 g/kg bolus as a 20% solution). If there is still no urine produced after an additional 30 minutes, another dose of mannitol can be administered; a total dose of 1 g/kg should not be exceeded in the anuric patient to prevent hypervolemia and edema formation.

8 If urine output has not improved after furosemide and mannitol, the prognosis is grave without peritoneal dialysis or hemodialysis. Treatment with low-dose dopamine has been controversial in human medicine, and several large studies have failed to demonstrate a benefit.[107,108] In fact, furosemide, mannitol, and dopamine may increase urine flow but have not been shown to unequivocally improve outcome in humans with acute renal failure.[109] When dialysis is not an option for horses with anuric renal failure, dopamine can be tried in an attempt to produce urine flow (2 to 3 mcg/kg/min); its proposed action is through increasing renal perfusion with renal afferent arteriolar vasodilation.[110] Without urine flow, there is no opportunity to provide the patient with time to heal if the acute renal injury is reversible. If dopamine is successful at reversing anuria, this time can be provided.

Hyperkalemia and metabolic acid-base disorders are common in horses with anuric or oliguric renal failure.[98] As noted earlier, hyperkalemia can be associated with life-threatening dysrhythmias. Rapid initiation of diuresis and administration of sodium bicarbonate, dextrose, and insulin are therapeutic interventions for hyperkalemia. If dysrhythmias are present, calcium should be administered to raise membrane threshold potential thereby reducing the likelihood of abnormal rhythms.

As mentioned previously, hemodialysis has been reported infrequently in horses.[92] More recently, peritoneal dialysis has been described as a cost-effective and practical approach for horses with acute renal failure.[93] These are therapeutic options in horses that do not respond to conventional fluid therapy and medical treatments of anuria described earlier.

44.4.5 Fluid Therapy for Horses with Vasculitis

K. Gary Magdesian

Horses with vasculitis present a unique challenge to fluid therapy in that they have increased vascular permeability and are therefore at increased risk for developing edema. Examples of such patients that may require restoration of fluid volume include horses with purpura hemorrhagica, type I hypersensitivity reactions (such as anaphylaxis or anaphylactoid reactions), and *Anaplasma phagocytophila* infections. Often horses with systemic vasculitis have edema, particularly in the distal limbs and ventrum, in the face of concurrent hypovolemia.

Correction of hypovolemia in these horses is challenging, as increasing the extracellular fluid compartment with crystalloid fluids may compound edema and lose efficiency in terms of blood volume expansion. Such cases may benefit from colloid administration. Depending on the degree of vasculitis and the molecular weight of the colloid, a portion of the administered colloid may also extravasate into the interstitium or third space area, compounding edema. Therefore horses receiving colloid fluids should be monitored for progression of their overall status, including increasing edema in response to fluid administration. 1496 1497

Colloids with a molecular weight of 100 to 300 kDa and those with narrower ranges, such as pentastarch (average molecular weight of 268 kDa) and the newer (third-generation) hydroxyethyl starches (molecular weight of 130), may have reduced extravasation compared with those with smaller molecular weights and wider molecular weight ranges. Colloids with this size molecule may reduce endothelial-leukocyte responses and are thought to interact with the endothelial glycocalyx in reducing capillary leakiness.[72,73] However, these are not yet available in the United States. Commercial hetastarch is heterogeneous in terms of particle size (range, 15 to 3400 kDa), and those molecules below 100 kDa could extravasate more readily.

The total amount of colloid administered needs to be considered, as doses above 10 mL/kg/day of hetastarch lead to coagulopathies.[57] The safe total cumulative dose of hetastarch over time (over days) is unknown. Plasma can be administered instead; however, albumin is relatively small (68 kDa), and much of it can redistribute extravascularly because of the altered reflection coefficient.

44.4.6 Fluid Therapy for Horses with Hypoproteinemia

K. Gary Magdesian

Similar to horses with systemic vasculitis, those with hypoproteinemia are at increased risk for edema formation with fluid therapy, making them among the most challenging to manage. The presence of concurrent hypovolemia and hypoproteinemia is a potential indication for colloids rather than crystalloids. Administration of crystalloids alone may result in compounding of the hypoproteinemia through hemodilution.[111] With altered Starling's forces, crystalloids distribute to the extracellular fluid to a relative greater extent than they would otherwise, because of a lack of plasma oncotic force for retention. Currently available colloids include hetastarch, dextrans, plasma, and concentrated human albumin.[112] Because of the increased potential for side effects associated with dextrans, there is no clear indication to use them over hetastarch. Side effects of dextrans reported in horses include muscle fasciculations, swaying of the hindquarters, tachycardia, and collapse in 8 of 64 horses.[113]

Numerous commercial equine plasma products are also currently available. Many include antibodies to salmonella, endotoxin, and clostridial organisms; these are unlabelled claims and are largely unstudied in terms of efficacy. Other advantages of plasma, especially for the hypoproteinemic horse, include provision of albumin, antithrombin, and additional clotting factors. Because albumin has multiple functions, including as a carrier protein (drugs, toxins) and physiologic buffer, plasma cannot be entirely replaced with synthetic colloids. Concentrated albumin has been used in neonatal foals, but its use in adult horses may be limited by cost.[112] The potential side effects of human plasma products in horses are largely unknown and require further study.

In one study evaluating the response of hypoproteinemic horses with gastrointestinal disease to hetastarch, it was determined that the oncotic benefit lasted 24 hours; in contrast, hetastarch raised the oncotic pressure of healthy horses for up to 5 days.[57,111] Nevertheless, even a short-term benefit in oncotic pressure may be preferable to the dilutional effects of crystalloids.

44.4.7

Fluid Therapy for Hemorrhagic Shock (Box 44-5)

K. Gary Magdesian

With the exception of prompt hemorrhage control, the key component to early trauma care is adequate fluid resuscitation. Traditionally, replacement with isotonic crystalloids of three times the volume of shed blood has been the approach in human trauma patients. Up to eight times the blood loss volume has been administered in severe shock states.

Despite its importance, high-volume resuscitation is not innocuous; ARDS has been described in patients that received massive crystalloid resuscitation after trauma.[114] Severe trauma patients enter a phase of SIRS, with some patients developing multiple organ failure and others entering a compensatory antiinflammatory response syndrome (CARS). This latter syndrome causes immune suppression and increased susceptibility to infections. Both commercial LRS, which is a racemic mixture of L- and D-lactate, and artificial colloids, namely dextrans and some hydroxyethyl starches, have proinflammatory effects.[115] It appears that the D-lactate (nonmammalian form) is largely responsible for the inflammatory reaction to LRS, because removing it from the solution eliminates this effect.[116] These fluids, both artificial crystalloids and colloids, can also cause neutrophil activation and upregulation of adhesion molecules.[117] There is currently an L-isomer form of LRS available commercially (Baxter Healthcare Corp., Deerfield, IL). Hypertonic saline, on the other hand, has been shown to be immunomodulatory and causes suppression of neutrophil oxidative burst activity and neutrophil-endothelial adhesions.[118–121] Hypertonic saline counteracts the inflammatory effects of dextrans when used in combination.[122] Therefore hypertonic saline has potential advantages for early fluid resuscitation of patients with significant blood loss, after the source of hemorrhage has been controlled. This should be followed with isotonic crystalloids, perhaps acetate-containing fluids, such as Normosol-R, or physiologic saline rather than racemic lactate. Plasma similarly does not result in inflammatory cell activation. If hetastarch is used, hemorrhage must be controlled before its administration because of its rapid volume expansion as well as dose-dependent induction of coagulopathies.[57,75–79]

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44.4.7.1

Box 44-5 Fluid Considerations for Horses with Acute Hemorrhage

1 For horses with controlled hemorrhage, a combination ofhypertonic saline, colloids, and acetated isotonic crystalloids or physiologic saline can be used.

2 Because of experimental evidence of proinflammatory effects of racemic lactated Ringer's solution (LRS) in severe trauma, use of this solution should be questioned in cases of severe trauma until further studies are available.

3 Hypertonic saline exhibits antiinflammatory effects and may have benefits for horses with severe trauma, especially when LRS or synthetic colloids are used for resuscitation.

4 For controlled hemorrhage, a volume three to four times the estimated blood loss should be administered in isotonic crystalloids.

5 For uncontrolled hemorrhage, hypotensive resuscitation should be employed; small volumes of fluids are administered to maintain organ perfusion and a mean arterial pressure of 60 mm Hg until the hemorrhage can be controlled.

Aggressive fluid resuscitation in the face of uncontrolled hemorrhage cannot be justified. Such fluid protocols can exacerbate bleeding as a result of increases in blood pressure, disruption of clots, and hemodilution of clotting factors. Instead, a protocol of hypotensive resuscitation should be followed when bleeding cannot be stopped directly.[123] With hypotensive resuscitation, low volumes of crystalloids or whole blood should be administered to maintain organ vitality without normalizing pressures. A goal of maintaining a MAP of 60 mm Hg will still allow end organ perfusion while allowing for hemostasis.

44.4.8

Fluid Therapy in Acute Neurologic Injury (Box 44-6)

Darien J. Feary

The approach to fluid therapy in horses and ruminants with acute brain or spinal cord injury is aimed at maintaining oxygen delivery and energy supply to meet the metabolic demands of the neuronal tissue, and fluid therapy is a fundamental part of preventing or minimizing secondary neuronal injury, ischemia, and irreversible damage.

The primary goals of fluid therapy for both brain and spinal cord injury follow similar principles and include prevention and/or prompt recognition and treatment of hypovolemia and hypotension, intracranial hypertension (or cerebral edema), and glucose and electrolyte abnormalities.

Although both brain and spinal cord injuries are potentially life-threatening in large animals, acute brain injury is likely to be the most influenced, either negatively or positively, by the particular fluid therapy plan that is instituted. This is mainly because the cranial vault is a closed space, composed of brain (approximately 80%), blood (approximately 10%) and CSF (approximately 10%). An increase in one component has to result in a compensatory decrease in another. The presence of the blood-brain barrier, intact or not, is another important factor in the selection of the most appropriate fluid for management of acute brain injury.

The most important consideration in the management of cerebral injury is the maintenance of cerebral blood flow (CBF), which is often reduced postinjury. The major determinant of CBF is cerebral perfusion pressure

(CPP), which is the difference between MAP and intracranial pressure (ICP) as defined by the following equation: CPP = MAP – ICP. In the normal brain, cerebral autoregulation maintains a relatively constant CBF despite wide variations in perfusion pressure, within the range of 50 to 150 mm Hg (in humans). In the injured brain autoregulation may be impaired, often with concurrent traumatic shock and hypotension, and CBF becomes directly dependant on CPP. Therefore it becomes critical to prevent hypotension by maintaining MAP >80 mm Hg and to avoid increases in ICP that result from cerebral edema or hemorrhage. ICP is not routinely measured in large animal patients, limiting its use in guiding fluid therapy. However, neurologic signs suggestive of elevated ICP (such as obtunded mentation, mydriasis) indicate the need for specific treatment to reduce ICP, with frequent reassessment of neurologic status being important in determining response to treatment.

44.4.8.1

Box 44-6 Fluid Guidelines for Horses with Acute Neurologic Injury

1 The clinical outcome of large animal patients with brain and spinal cord injury may be improved by the prompt recognition and treatment of systemic and central nervous system hypoperfusion.

2 Isotonic crystalloid solutions appear to be the most appropriate fluids for resuscitation in acute neurologic injury, followed by careful administration of hyperosmolar therapy with mannitol or hypertonic saline if evidence of cerebral edema is present.

3 Diligent monitoring of clinical and laboratory measures of perfusion, osmolarity, and electrolyte concentrations is important for optimizing patient care and the likelihood of recovery in these patients.

Fluid management in large animal patients with acute neurologic injury is essentially based on the principles and guidelines established in human medicine from extensive laboratory and clinical studies. The ideal fluid for these human patients remains controversial and is a topic of ongoing research. When presented with a large animal patient with central nervous system injury, the clinician should formulate a fluid therapy plan tailored to the individual animal, based on findings of thorough physical and neurologic examinations and assessment of laboratory data. I suggest the following goal-directed approach:

- Goal 1—Treat hypovolemia and hypotension with adequate fluid replacement therapy to attain a normovolemic and normotensive state.
- Goal 2—Treat signs of cerebral edema or intracranial hypertension with hyperosmolar therapy.
- Goal 3—Use fluid additives to normalize glucose and electrolyte values, and provide thiamine supplementation.

44.4.8.2

REPLACEMENT FLUID THERAPY FOR NEUROLOGIC TRAUMA CASES

Although fluid restriction historically has been advocated for patients with traumatic brain injury (TBI) under the premise that intravenous fluids increase cerebral edema formation, this practice is no longer recommended, in humans or horses, for two main reasons. First, inadequate data support the theory that fluid restriction decreases cerebral edema formation, and second, systemic hypotension has been associated with increased mortality and poor neurologic outcome in human patients with TBI.[124–126]

Therefore prompt restoration of adequate intravascular volume with the goal of achieving and maintaining euvolemia and normal blood pressure should be the primary goal of fluid management in patients with neurologic injury. This is best achieved and controlled via the intravenous route in injured horses. Overhydration should be avoided, particularly in neonates, which are more susceptible to volume overload than adult horses.

Selection of the appropriate fluid for replacement therapy requires an understanding of the role of the blood-brain barrier. Because of its unique properties, the development of cerebral edema is fundamentally different from edema formation in other organs or tissues.[127] Briefly, the normal blood-brain barrier functions as a semipermeable membrane, separating the brain from the intravascular space. In the normal animal the blood-brain barrier is impermeable to large molecules (plasma proteins) but is only minimally permeable to most ions. It is freely permeable to water, however. The tonicity of the intravascular fluid, determined by its sodium concentration, influences the movement of free water across the blood-brain barrier by creating an osmotic pressure gradient between the brain interstitium and the intravascular space. In TBI the blood-brain barrier may be damaged, often producing heterogeneous regions of varying degrees of blood-brain barrier integrity and permeability. Unfortunately, demonstrating and predicting the extent of such injury in clinical patients is very difficult; the clinician often likely has to assume the presence of normal brain and functional blood-brain barrier regions for certain principles of fluid management, such as osmotherapy, to be effective.[128]

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Hypotonic crystalloids, such as 5% dextrose in water or 0.45% saline solutions, are contraindicated in TBI patients. They lower plasma osmolarity and result in excess free water diffusion into the brain, with subsequent cerebral edema formation. Hypotonic fluids should be avoided for rapid volume replacement in patients with brain injury.

Isotonic crystalloids, such as 0.9% saline, LRS, and Normosol-R, create a minimal to no osmotic gradient across the blood-brain barrier, are readily available and inexpensive, and are therefore the current fluids of choice for replacement and maintenance therapy in brain and spinal cord injury patients.

Hypertonic crystalloids, such as 7.5% saline, create an osmotic gradient across the blood-brain barrier in favor of free water movement out of the brain, thereby reducing ICP. Hypertonic fluids are indicated *only after adequate provision of intravascular fluid volume* in horses with signs of elevated ICP or deteriorating neurologic status and are discussed in more detail in the following section on hyperosmolar therapy.

Colloids, such as plasma, human albumin, and the synthetic agents hetastarch, pentastarch and dextran, exert variable oncotic pressures and are very effective for intravascular volume expansion and maintenance. The use of colloid solutions in neurologic injury is debatable, mainly because the major determinant of fluid flux across the blood-brain barrier is plasma osmolarity, and because colloids contribute only a small number of particles in plasma, even large changes in plasma colloid oncotic pressure only minimally influence water movement across the normal blood-brain barrier. This is in contrast to the effectiveness of even small changes in plasma osmolarity.[129] In addition, the relatively higher cost of colloid solutions and the greater risk of development of hemostatic abnormalities and allergic reactions suggest little benefit of colloid solutions over crystalloids in cases of TBI. The exception is when they are used in combination with crystalloids for fluid volume expansion, provided hydrostatic pressures are not increased excessively as a result of the colloid infusion.[127]

44.4.8.3

HYPEROSMOLAR THERAPY IN BRAIN AND SPINAL CORD INJURY

If clinical evaluation of the equine patient with TBI suggests the patient has, or is at risk for developing, intracranial hypertension, then osmotherapy may be indicated. Clinical signs such as obtunded mentation, progressive mydriasis, or any deterioration of neurologic status may indicate increased intracranial hypertension. Hyperosmolar solutions exert their effect of reducing ICP by creating an osmotic gradient across the blood-brain barrier of at least a 10 mOsm/L. Studies in humans suggest that the goal of increasing plasma osmolarity without exceeding 320 mOsm/L is probably a safe and effective approach.[130] It is advisable to measure plasma osmolarity in large animal patients, at least before administration of hyperosmolar solutions, to avoid excessive increases in plasma osmotic pressure. Osmotherapy should be instituted only after restoration of adequate intravascular volume and blood pressure if CPP is to be optimized.

The two most commonly used and available hyperosmolar solutions for use in large animals are mannitol (20%) and hypertonic (3% to 7.5%) saline. Both agents have been shown to be effective in lowering ICP in human TBI patients, and although there has been recent renewed interest in hypertonic saline, studies comparing the effectiveness of the two agents have not yet demonstrated a consistent benefit of one solution over the other.

Mannitol (20%) is a six-carbon sugar with an osmolarity of 1098 mOsm/L. The recommended dose is a 0.25- to 1-g/kg intravenous bolus administered over 20 to 30 minutes, every 6 to 8 hours. The ICP-reducing effects of hyperosmolar solutions are believed to be biphasic in nature. After bolus dose administration, there is an initial plasma-expanding effect that reduces blood viscosity and hematocrit and improves rheologic properties of red blood cells, resulting in reduced ICP and improved CBF. After this immediate hemodynamic effect is a delayed osmotic diuretic effect resulting from the decreased reabsorption of sodium and water by the renal tubules, which also contributes to ICP reduction. Onset of effect of mannitol therapy is 15 to 30 minutes after bolus administration. Mannitol should not be administered as a continuous infusion for the purpose of treating cerebral edema, as it loses its plasma-expanding effects and increases the likelihood of development of side effects.[131]

The detrimental effects of mannitol are more likely to develop and become clinically significant with excessive or prolonged (>2 to 3 days) use. Side effects include hypovolemia and hypotension caused by excessive diuresis, electrolyte disturbances (hyponatremia, hypochloremia, hypokalemia, hypocalcemia), acute renal failure, and a rebound increase in ICP associated with reversal of the osmotic gradient, a phenomenon most likely explained by accumulation of the osmotic agent in brain tissue after movement across regions of damaged blood-brain barrier.[131] There is insufficient evidence to support the dogma that mannitol is contraindicated in the presence of intracranial hemorrhage.

Hypertonic (7.5%) saline has an osmolarity of 2400 mOsm/L and, similarly to mannitol, effectively reduces ICP primarily through an immediate hemodynamic effect, followed by a delayed osmotic effect. Hypertonic saline can be administered as an intravenous bolus dose (4 mL/kg) or as a CRI. Hypertonic saline may have addition beneficial effects over mannitol in TBI because of rapid augmentation of cardiac output, contractility, and MAP with administration of smaller volumes. In addition, hypertonic saline is theoretically less likely to cross the blood-brain barrier than mannitol because the reflection coefficient of NaCl is 1 (not permeable), compared with 0.9 for mannitol (more permeable). Additional benefits of hypertonic saline on

the injured brain include Na-related stabilization of cell membrane electrochemical gradients and modulation of the inflammatory response.[132]

Laboratory studies investigating the effect of hypertonic saline in resuscitation after spinal cord injury have also shown promising results, with increased spinal cord blood flow, downregulation of the inflammatory response, and attenuation of spinal cord injury.[133] Further clinical studies are needed.

Complications of hypertonic saline are uncommon and include hypernatremia and development of central pontine myelinolysis (theoretic, as it has not been reported to occur when used in cases of TBI).[130] Hypokalemia can occur because of kaliuresis in response to reabsorption of large amounts of Na in the distal tubule, as well as hyperchloremic acidosis, emphasizing the importance of regular assessment of hemodynamic and plasma electrolyte and acid-base status. Coagulopathy and bleeding complications can occur as a result of dilutional effects but are of more concern in the actively bleeding patient. Risk of hypovolemia and acute renal failure are not reported for hypertonic saline in TBI, although renal insufficiency is a relative contraindication to all hyperosmolar therapy. Rebound elevations in ICP can occur with withdrawal of therapy; therefore slow, gradual weaning of hypertonic saline infusions is recommended.[130]

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Osmotherapy is likely to be most effective if initiated early (after isotonic fluid replacement) and with duration determined by response to therapy, with close observation and monitoring to minimize development of side effects.

44.4.8.4 FLUID ADDITIVES IN NEUROLOGIC INJURY

44.4.8.4.1 Glucose

It has been widely recognized that hyperglycemia is a common occurrence in acute brain injury in humans.[134] Hyperglycemia is believed to worsen neuronal injury and is associated with increased mortality and neurologic outcomes after TBI.[134,135] Consequently, glucose supplementation during large-volume fluid replacement should be avoided, unless the patient is hypoglycemic.

It has not been determined whether hyperglycemia after TBI is a physiologic reflection of the response and severity of injury, or if it contributes to the progression of secondary brain injury. Nevertheless, in ischemic brain tissue aerobic metabolism is impaired and excess glucose leads to lactate accumulation and intracellular acidosis via anaerobic metabolism; this can contribute to a proinflammatory and prooxidant state, thereby potentially worsening neurologic injury and increasing cell death.[130] A beneficial effect of reducing blood glucose with insulin therapy in human patients with TBI has been suggested but has not been clinically proven at this time.[136]

It is prudent to avoid hypoglycemia as well as hyperglycemia in neurologic injury. The brain is dependant on a constant supply of glucose for aerobic energy production, and glucose use may be increased after TBI, thereby increasing energy demands. These factors should be considered in the monitoring and fluid therapy plan for any large animal with neurologic injury, particularly neonates, as they are more susceptible to hypoglycemia.

44.4.8.4.2

Thiamine

Thiamine (vitamin B_1) is a water-soluble B vitamin synthesized only by plants and microorganisms. Most animals have a nutritional requirement for this vitamin, although adult ruminants and horses normally can obtain adequate quantities produced by bacteria in the rumen or cecum.

Thiamine, in its active form (thiamine pyrophosphate), plays a very important role in glucose metabolism and energy production, where it functions as a required cofactor for certain enzymes (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, branched-chain ketoacid dehydrogenase, transketolase) involved in glycolysis, the citric acid cycle, and the pentose phosphate pathway. Thiamine is also important in nerve and muscle function, where it plays a role in neurotransmission and excitation.

Thiamine deficiency is known to be associated with neurologic disease in humans and in ruminants (polioencephalomalacia). Determination of thiamine status of an animal requires measurement of red blood cell transketolase activity; therefore measurement and documentation of thiamine deficiency in clinical cases is not routinely reported. Whether or not supplementation of thiamine in acute traumatic neurologic injury is indicated is not currently supported by published evidence. However, given the increased susceptibility of damaged neuronal tissue to inadequate energy production and supply, the practice of thiamine supplementation in neurologic injury in large animals appears justified. In addition, recent experimental investigation suggests a potential neuroprotective role of thiamine in reactive oxygen species—induced neuronal injury.[137] The author (DJF) has used a dose of 5 to 10 mg of thiamine per kilogram diluted in crystalloids.

Thiamine should be protected from light.

44.4.8.4.3

Electrolytes

Sodium disturbances can have serious consequences in brain injury and should be corrected promptly if they are acute (<24 hours' duration). Isotonic fluid administration is appropriate in the majority of cases. Glucose and mannitol cause translocation of water into the extracellular fluid, and excessive amounts can lead to a clinically significant reduction in sodium concentration, as can free water administration with hypotonic fluids. If hyponatremia (Na^+ <125 mEq/L) is believed to have been present for >24 hours, then slower correction (0.5 mEq/L/hr) is needed to avoid development of central pontine myelinolysis.

Calcium is essential in maintaining cell membrane potentials and promoting neurotransmitter release. Excessive intracellular calcium accumulation is also well recognized as one of the most important pathways of secondary neuronal damage. During conditions of cerebral or spinal cord ischemia, inadequate energy supply in the form of adenosine triphosphate (ATP) leads to widespread neuronal depolarization and alterations in ion channel permeability, ultimately resulting in excessive intracellular calcium concentrations and cell death.

Serum total and ionized calcium concentrations are measures of extracellular calcium, and so the goal of targeting intracellular calcium homeostasis is limited to maintaining normal extracellular fluid concentrations at this time. Because of the known toxic effects of excessive calcium in neuronal injury, a conservative approach to calcium supplementation may be justified in the acute fluid management of large animal patients. In order to prevent the detrimental effects of hypocalcemia, one approach may be to avoid

the addition of calcium to the intravenous fluids over the initial 24 to 48 hours unless the ionized calcium concentration is <1.0 mmol/L or clinical signs of hypocalcemia are present.

Magnesium is an important cofactor in many enzymatic reactions and for the regulation of sodium and potassium transport across cell membranes through activation of the Na-K ATPase pump. Magnesium is essential for central nervous system cellular energy metabolism, modulation of excitatory amino acid transmission, and calcium channel antagonism. After neurologic injury, disruptions in the blood-brain barrier may impair regulation of CSF magnesium concentrations, and hypomagnesemia is commonly recognized in human patients with brain injury.[138] Experimental and clinical evidence suggests that a depletion of CSF magnesium concentrations is associated with the risk of secondary neurologic injury.[130] Studies also suggest a neuroprotective effect of intravenous magnesium administration after traumatic brain injury,[139] although results of other studies are conflicting.[130] Currently the dose of intravenous magnesium needed to achieve adequate CSF concentrations for neuroprotective benefits is unknown.

In large animal patients it would seem important to monitor serum total and ionized magnesium concentrations to prevent and treat hypomagnesemia after neurologic injury. Selection of intravenous fluids containing magnesium, such as Normosol-R (Mg^{2+} = 5 mmol/L) may be beneficial.

Other electrolyte disturbances identified commonly in patients with neurologic injury include hypokalemia and hypophosphatemia. A combination of decreased dietary intake and increased renal loss as a result of diuretic therapy is a likely explanation. Because of the important role of potassium in establishing normal resting membrane potential and nerve conduction, among other functions, regular monitoring and intravenous fluid supplementation if serum potassium concentration decreases to <3.0 to 3.2 mEq/L is indicated in large animal patients with neurologic injury.

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Serum phosphate concentrations are not as routinely monitored as other electrolytes in large animal patients, and so deficiency is rarely reported. Clinical signs of hypophosphatemia usually do not manifest until serum concentrations fall below 1 mg/dL in humans and animals. It is important to recognize phosphate deficiency in patients with recent neurologic injury because it can cause or contribute to altered mental status, muscle weakness, seizures, respiratory insufficiency, and ventricular dysrhythmias. Because clinical manifestations of hypophosphatemia have not been reported in horses, it is difficult to make recommendations for supplementation. I have used a dose of 0.01 mmol/kg/hr of sodium phosphate when marked hypophosphatemia has been present in horses.

44.4.9

Fluid Therapy for Horses with Rhabdomyolysis (Box 44-7)

K. Gary Magdesian

Horses with severe rhabdomyolysis are at risk for renal failure from myoglobinuria and hypovolemia. In addition, they may develop marked electrolyte derangements from cell lysis, including hyponatremia, hypochloremia, hyperkalemia, and hyperphosphatemia.[140,141] In one study evaluating the electrolyte changes in horses with acute rhabdomyolysis, the most consistent abnormality was hypochloremia.[140] These changes have been reported in foals with rhabdomyolysis as a consequence of selenium deficiency with or without vitamin E deficiency, possibly combined with increased oxidant stress resulting from sepsis or hypoxia and reperfusion injury after parturition.[141] Three of four foals developed cardiac arrhythmias characterized by spiked T wave and decreased P wave amplitude on electrocardiographic analysis. Destruction of the major intracellular fluid compartment through extensive myonecrosis, combined with myoglobinuric renal insufficiency, produces

major fluid shifts and electrolyte derangements. In this report foals with hyperkalemia caused y rhabdomyolysis were effectively treated with mineralocorticoids, loop diuretics, and ion exchange resins to enhance elimination of potassium. Intravenous calcium, glucose, insulin, and sodium bicarbonate were also administered to help redistribute potassium back to the intracellular fluid.[141]

Metabolic acidosis is not common in horses with acute rhabdomyolysis, and alkalosis associated with hypochloremia may be more of a concern.[140] Therefore the use of sodium bicarbonate may not be indicated in the treatment of all such patients. In fact, fluids with relatively higher chloride concentration as compared with horse plasma may be optimal when hypochloremia is present. These include LRS (chloride, 109 mEq/L) and 0.9% saline (chloride, 154 mEq/L). If LRS is used, attention should be paid to serum potassium concentrations, because LRS contains potassium chloride in the amount of 4 mEq/L (see Table 44-1). LRS might be preferable over acetate-containing fluids such as Normosol-R or Plasma-Lyte 148 because the liver is the primary organ of lactate metabolism, whereas the muscle tissue plays a larger role in metabolism of acetate. In addition, the chloride concentration of these acetated fluids is lower than that of LRS. Lactate in LRS does not preclude its use in hyperlactatemic horses with muscle disorders, because hepatic metabolism of lactate occurs rapidly once plasma volume is expanded. In addition, lactate is not necessarily markedly elevated in horses with rhabdomyolysis.[142]

44.4.9.1

Box 44-7 Fluid Considerations for Horses with Rhabdomyolysis

1 Horses with acute myopathies often exhibit hypochloremia and may have concurrent hyponatremia, hyperkalemia, and hyperphosphatemia, especially when the rhabdomyolysis is severe.

2 Because metabolic acidosis is not a common finding, the indiscriminate use of sodium bicarbonate should be avoided.

3 Lactated Ringer's solution and 0.9% sodium chloride are fluids with a physiologic basis for use with rhabdomyolysis.

4 Horses with acute myopathies should be administered fluids at a rate greater than maintenance requirements in order to provide for diuresis of myoglobin.

Hereditary causes of rhabdomyolysis in horses include polysaccharide storage myopathy, glycogen branching enzyme deficiency, and recurrent exertional rhabdomyolysis (RER).[143–145] Because an alteration in muscle cell calcium regulation is a primary feature in the pathophysiology of RER, calcium supplementation of fluids administered to affected horses should be avoided.[146] Serum potassium concentrations should be monitored frequently in horses with rhabdomyolysis, because of risks associated with hyperkalemia.

Because horses with acute rhabdomyolysis are at risk for renal failure, rates of fluid administration should exceed maintenance requirements. Affected horses are usually hypovolemic and dehydrated, and in severe cases horses are myoglobinuric. Myoglobin is nephrotoxic directly, as well as indirectly causing renal arteriolar vasoconstriction and hypoperfusion. Rates of fluid administration vary with individual fluid balance and renal function, but 1.5 to 2 times maintenance requirement is a reasonable starting point. The rate can be adjusted based on the rate of creatine kinase (CK) decline and resolution of myoglobinuria.

44.4.10

Fluid Therapy for Hyperkalemic Periodic Paralysis (Box 44-8)

K. Gary Magdesian

Hyperkalemic periodic paralysis (HYPP) is caused by a genetic defect in the sodium channel on the sarcolemma, resulting in intermittent signs of sweating, muscle fasciculations, stridor, and weakness.[147] Stressors such as anorexia, anesthesia, concurrent illness, trailering, and cold environmental temperatures can precipitate hyperkalemia and onset of clinical signs. Fluid therapy for horses with hyperkalemia should be low or free of potassium. Physiologic (0.9%) saline and isotonic sodium bicarbonate (1.3%) are options. Of note is that these two fluid types have potential effects on acid-base physiology, with saline producing a mild strong ion acidosis and sodium bicarbonate a metabolic alkalosis. Another option for horses without acid-base disturbances is to combine commercial balanced polyionic fluids, such as LRS or Normosol-R, with one of these fluids. This would dilute the potassium administered from the LRS or Normosol and would minimize the effects of saline or sodium bicarbonate on acid-base balance.

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44.4.10.1

Box 44-8 Fluid Guidelines for an Acute Hyperkalemic Periodic Paralysis Episode

1. 4 to 20 mL of 0.9% saline per kilogram, depending on severity and duration
2. 2.5% to 5% dextrose
3. 1 mEq of sodium bicarbonate per kilogram
4. 0.2 to 0.5 mEq of calcium per kilogram (0.2 to 0.5 mL of 23% calcium gluconate per kilogram)
5. For refractory cases—insulin can be added to dextrose supplementation (regular insulin, 0.01 to 0.1 unit/kg/hr)

Fluid therapy for horses experiencing stressors such as forced withholding of feed before surgery or off feed because of concurrent illness should be administered fluids with dextrose and/or calcium supplementation prophylactically at a maintenance rate. These additives may minimize the development of hyperkalemia and subsequent HYPP episodes. Calcium does not decrease serum potassium concentrations but rather protects the heart from its adverse effects by raising threshold potential. Horses experiencing an active episode of hyperkalemia or showing clinical signs of HYPP should be administered 0.9% saline, sodium bicarbonate (1 mEq/kg empirically), dextrose (2.5% to 5% for provision of 0.5 to 2 mg of dextrose per kilogram per minute), and calcium (0.2 to 0.5 mEq of 23% calcium gluconate per kilogram). Calcium and sodium bicarbonate should not be administered concurrently in the same fluid administration set because of a potential for precipitation. LRS also contains calcium, and therefore sodium bicarbonate should not be added directly to it. Administration of two 5-L bags of saline with 2.5% to 5% dextrose, with one bag containing calcium (250 mL of 23% calcium gluconate total) and the other containing sodium bicarbonate (1 mEq/kg) given sequentially, is a reasonable approach to treating an acute episode. Some horses may not require this volume of crystalloid and can be treated with less; if less volume is desired, 4 to 6 mL of saline per kilogram can be administered. Dextrose, calcium, and sodium bicarbonate can be added to 1-L bags; the sodium bicarbonate and calcium must be kept separate. In this case 5% dextrose, 0.2 mL of 23% calcium gluconate per kilogram, and 0.5 to 1 mEq of sodium bicarbonate can be used.[148]

Long-term management of horses with HYPP consists of a low-potassium diet, regular exercise, attempts to minimize stressors, and medications such as acetazolamide and phenytoin.[149] Horses undergoing chronic acetazolamide therapy could theoretically develop hyperchloremia and a tendency toward metabolic acidosis because of the effects of long-term inhibition of carbonic anhydrase. Administration of large volumes of 0.9% saline can compound hyperchloremia[62]; to minimize acidemia, it can be coadministered with isotonic sodium bicarbonate or other alkalinizing crystalloid when such horses require long-term fluid therapy devoid of or low in potassium. Phenytoin can mask the clinical signs of HYPP, even when hyperkalemia is present; it must be emphasized that phenytoin should not be the sole prophylactic medication in these horses, because hyperkalemia may be left unchecked.[149]

44.4.11 ## Fluid Therapy for Competitive Endurance Horses

C. Langdon Fielding

Endurance horses are disqualified from rides for a variety of metabolic or lameness problems. Veterinarians are responsible for the emergency treatment of horses with metabolic derangements, but there is a paucity of research available for guidance. Fluid therapy is an essential component of the therapeutic management of critically ill endurance horses.

44.4.11.1 ### GENERAL APPROACH TO FLUID MANAGEMENT OF ENDURANCE HORSES

Endurance horses experience significant fluid losses during competition; even horses successfully completing rides lose approximately 5% of body weight in water.[150,151] Horses presented for treatment of metabolic problems often exhibit clinical signs of hypoperfusion. In evaluating sick endurance horses the seven clinical perfusion parameters should be evaluated:

1 Mentation

2 Heart rate

3 Pulse quality

4 Mucous membrane color

5 Capillary refill time

6 Extremity temperature

7 Jugular fill

Urine production, when apparent, can be used as an additional perfusion parameter. In the absence of polyuric renal failure, urine output signifies renal perfusion, which is one means of assessing organ perfusion. Horses with altered mentation, persistent tachycardia (>60 bpm), poor peripheral pulse quality, pale mucous membranes, capillary refill time >2 seconds, cool extremities, or lack of urine production should be considered candidates for fluid therapy.

The rapid administration of large volumes of crystalloids is the basis of treatment at many ride events. Volume loading increases preload, thereby enhancing stroke volume, cardiac output, and subsequent oxygen

delivery. One suggested protocol for fluid resuscitation of hypovolemic endurance horses is the fluid challenge method described earlier; this consists of a bolus dose of 20 mL of isotonic crystalloid per kilogram (10 L for an average, 500-kg horse) followed by reassessment of the seven perfusion parameters. If the parameters have not improved in response to the initial bolus, then another 20-mL/kg bolus should be administered and followed by clinical reassessment. Approximately 1 hour is required to administer a 10-L bolus through a 14-gauge intravenous catheter and standard administration set; multiple catheters or those with large bores (10 gauge) can be used for more rapid administration. Affected horses may require up to 40 to 60 L of crystalloids to address hypovolemia.

Several types of intravenous crystalloids are available for administration to endurance horses. LRS and Normosol-R are balanced polyionic crystalloids commonly administered to treat hypovolemia in these horses. Specific electrolyte abnormalities may dictate the use of isotonic saline (when hypochloremic alkalosis is present) or fluid additives (potassium chloride or calcium gluconate when hypokalemia or hypocalcemia is identified, respectively). The electrolyte and serum biochemistry profiles of endurance horses that fail to finish a race are not necessarily markedly abnormal and allow the use of commercial fluids such as LRS.[151] Electrolyte monitoring identified hypokalemia as a common derangement in a small group of horses treated for metabolic disorders during a 100-mile endurance ride.(Fielding CL, unpublished data from the Western States 100-mile endurance ride, 2005 and 2006).

Calcium supplementation is common during fluid therapy of pulled endurance horses. However, results of studies examining the concentration of total and ionized serum calcium in horses during endurance rides have been equivocal as to calcium status.[150–152] If calcium is used, it can be added to fluids through the use of calcium gluconate (1 mL of 23% calcium gluconate per kilogram at a rate of 50 mL of crystalloid per liter). Calcium supplementation is required in horses with synchronous diaphragmatic flutter and should be administered until clinical signs resolve.[153] Excessive use of calcium in endurance horses may not be warranted, as it plays a role in cell death and apoptosis, particularly with reperfusion injury; supplementation of calcium in humans with rhabdomyolysis is controversial.[154]

Endurance horses with prolonged ileus or anorexia may benefit from dextrose supplementation of fluids. A dose of 1 mg of dextrose per kilogram per minute is well tolerated by adult horses and is equivalent to 3% dextrose in fluids administered at a rate of 1 L/hr for a 500-kg horse. Ideally, blood glucose concentrations should be monitored in horses administered dextrose to avoid hyperglycemia. 1502 1503

Medications commonly used in the treatment of endurance horses with metabolic derangements may affect fluid balance and should be considered in horses receiving fluid therapy. Sedatives and tranquilizers such as α_2-agonists (xylazine, detomidine, romifidine) and phenothiazines (acepromazine) have deleterious effects on cardiac output and/or blood pressure.[155,156] Drugs such as dimethyl sulfoxide (DMSO) and α_2-agonist sedatives also affect urine output and can therefore alter fluid balance.[157,158]

The following metabolic conditions are common metabolic disorders of endurance horses.

44.4.11.2

EXERTIONAL MYOPATHY

Intravenous fluid therapy is the most important feature of treatment for rhabdomyolysis. The reader is referred to the section on fluid therapy in rhabdomyolysis elsewhere in this chapter. Fluids should be administered in 10-L (20-mL/kg) boluses until urine output is achieved and the urine is grossly clear. Low doses of flunixin meglumine (0.5 mg/kg IV) are indicated for inflammation once hypovolemia is resolved

and diuresis is achieved. Adequate fluid resuscitation is indicated before release of affected horses because exertional rhabdomyolysis has been associated with severe renal failure in both humans and horses.[159,160] Horses with myopathies should be monitored closely and reevaluated within 48 hours for azotemia and progress of increased muscle enzymes.

44.4.11.3 FAILURE TO RECOVERY

Horses that are pulled from ride events because of persistent tachycardia warrant close monitoring. Such horses often require treatment at a later time. The seven clinical perfusion parameters should be evaluated thoroughly, and any animal with equivocal circulatory or hydration status should be reevaluated frequently to make sure that it is improving through voluntary eating and drinking, rather than deteriorating further. Those with clear hypovolemia or failure to improve with rest should be administered intravenous fluids as described earlier.

44.4.11.4 SYNCHRONOUS DIAPHRAGMATIC FLUTTER (THUMPS)

Synchronous diaphragmatic flutter is typically associated with hypocalcemia, and concurrent metabolic alkalosis, hypochloremia, and hypokalemia are often also present and have been implicated in its development.[161] Many affected horses are otherwise stable hemodynamically and meet all the criteria for adequacy of perfusion. Despite these findings, horses with thumps often require treatment with intravenous fluids supplemented with calcium for resolution of hypocalcemia and clinical signs. Calcium gluconate can be added to 5-L bags of crystalloid (0.5 mL of 23% calcium gluconate per kilogram per 5-L bag), and fluids with dilute calcium can be administered as a bolus. Adverse effects of rapid calcium administration include bradycardia and warrant slow administration. Many mildly affected horses would likely resolve synchronous diaphragmatic flutter with oral electrolytes and/or the consumption of feed (particularly alfalfa).

44.4.12 Fluid Therapy for Burn (Thermal) Injury (Box 44-9)

K. Gary Magdesian

Horses with severe burn injuries develop hypovolemic shock and require large volumes of balanced electrolyte replacement fluids.[162] Hypertonic saline and colloids may also be used but should be followed with isotonic crystalloids. In humans with burn injuries the guidelines for rate of administration of isotonic fluids is 2 to 4 mL/kg for each percentage of surface area burned (Parkland formula).[163] Recently a retrospective study found that significantly larger volumes of fluid (5.58 mL/kg per percent total body surface area affected) were administered to patients during the first 24 hours of hospitalization than was predicted by the Parkland formula.[164] If smoke inhalation has occurred, then the affected horse is at risk for pulmonary edema. In this case, fluid deficits should be corrected but not exceeded. Administration of excess crystalloids or high rates of fluids after resolution of hypovolemic shock will result in edema, which is detrimental to healing of burned tissues and potentially smoke-injured lungs. Once hydration is adequate, fluid therapy should be discontinued or administered at a rate necessary only to maintain hydration status. If maintenance rates of fluids are required, patients with severe burns may require more sodium than provided for by commercial maintenance fluids owing to the tremendous sodium losses through wounds.[165] In these cases, isotonic to slightly hypertonic (1.8%) crystalloids may be required.[166] Excess free water should be avoided in these patients, as it can promote intracellular tissue edema.[166]

44.4.12.1

Box 44-9 Fluid Guidelines for Burn Injury Patients

1 Hypertonic saline can be used in the resuscitative phase of burn patients but should be followed with isotonic crystalloids.

2 Colloids can be used in conjunction with or in place of hypertonic saline during fluid resuscitation.

3 Isotonic to slightly hypertonic (1.8%) crystalloids are often necessary because of tremendous sodium losses through burn wounds.

4 Plasma is an important component of fluid therapy in the severely burned patient because of the potential for protein loss.

5 Administration of excessive volumes of fluids should be avoided because edema is a common complication of burn injuries.

An important component of fluid therapy of the thermal injury patient is the administration of plasma. Significant amounts of plasma proteins are lost through cutaneous burns.[165] In addition, burn patients are at risk for coagulopathies, although this has been reported to be rare.[167] Plasma transfusions are an effective source of albumin, as well as antithrombin III for coagulopathies. Horses with significant burns can require large volumes of plasma in the first 2 to 3 days. CRI of plasma can be provided for as long as required when ongoing losses are present.

44.4.13

Fluid Therapy for Acute Respiratory Distress Syndrome (Box 44-10)

K. Gary Magdesian

ARDS presents a therapeutic challenge; because of altered Starling's forces (increased vascular permeability), affected horses and foals often have significant pulmonary edema, with protein-rich fluid.[168] Pulmonary capillary hydrostatic pressure becomes the main determinant of edema in these patients owing to the increased permeability of pulmonary capillaries.[169] Despite this propensity toward edema formation, horses and foals with ARDS should not be allowed to develop dehydration. Maintenance of normal blood volume and hydration status is critical to tissue oxygenation, including the diseased pulmonary tissue. The goal in therapy of ARDS patients is to reduce extravascular lung water while still maintaining hemodynamic stability and perfusion. In a human clinical trial, conservative fluid management in patients with ALI improved lung function and shortened duration of mechanical ventilation and intensive care as compared with patients managed with a liberal fluid strategy, although there was no difference in mortality.[170] The conservative management did not increase nonpulmonary-organ failures.[170] It should be noted that the patients in this study were volume replete and relatively stable hemodynamically. Conservative fluid therapy therefore applies to the postresuscitation phase of these patients, when administration in excess of physiologic needs can be detrimental.

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44.4.13.1

Box 44-10 Fluid Guidelines for Acute Respiratory Distress Syndrome

1 The ideal initial resuscitative fluid choice for acute respiratory distress syndrome (ARDS) patients is unknown, but crystalloids should probably be used rather than colloids because of the risk for

compounding pulmonary edema as colloids leak into lungs. The exception would be the hypoproteinemic patient, in which plasma should be used to correct albumin deficits.

2 Hypovolemia and dehydration should be corrected, but excessive fluid volume should be avoided to minimize worsening of edema. A conservative long-term fluid plan is warranted.

3 Fluid balance in patients with ARDS should be assessed frequently; central venous pressure is a useful means of monitoring fluid balance to prevent large increases in capillary hydrostatic pressure.

Large swings in pulmonary vascular pressures should be avoided to minimize increases in pulmonary hydrostatic pressure. To avoid these wide fluctuations, intravenous fluids should be provided as a continuous infusion rather than as intermittent boluses.[171] The ideal type of fluid for volume replacement at the time of initial therapy of ARDS patients is unknown; however, colloids should be used judiciously owing to the theoretic risk of potentiating pulmonary edema through extravasation of colloids across the leaky pulmonary vasculature. This concern warrants further study; one study demonstrated no increase in net increase of transmicrovascular flux of radiolabelled colloids when COP was raised with albumin administration.[172] Isotonic crystalloids, administered at a modest rate and only to effect in normoproteinemic patients, and replacement of plasma proteins in hypoproteinemic patients are probably the safest fluid guidelines for these patients with the current level of understanding.

Patients with ALI or ARDS should be monitored closely for hypoproteinemia. Correction of hypoproteinemia in human patients with ALI benefits from concurrent administration of albumin.[173] Hypoproteinemic patients receiving both furosemide (as a CRI) and albumin had improved oxygenation, increased net fluid loss, and better maintenance of hemodynamic stability compared with those receiving only furosemide.[173] In addition, 50% of patients in the treatment group achieved resolution of the ALI or respiratory distress syndrome, compared with only 11% of controls. Consideration should be given to correction of hypoproteinemia in foals and horses with ARDS or ALI. An additional benefit of albumin is its antioxidant properties. Albumin also can reduce microvascular permeability and endothelial cell apoptosis.[174–176]

Monitoring of fluid therapy in these patients is especially important in order to avoid marked increases in pulmonary hydrostatic pressure. This can be accomplished through measurement of pulmonary capillary wedge pressure; however, this requires placement of an intracardiac catheter. Alternatively, CVP can be measured directly. This is easily performed through central lines, those placed in the cranial vena cava. In a study comparing the use of pulmonary artery catheters with that of central venous catheters in guiding treatment of ALI in humans, it was found that pulmonary catheter—guided therapy did not improve survival or organ function and was associated with more complications than central venous catheter—guided therapy.[177] The predominant catheter-related complication was development of arrhythmia. It was concluded that pulmonary catheters should not be routinely used for the management of ALI.[177]

44.4.14 Fluid Therapy for Horses with Metabolic Acidosis (Box 44-11)

K. Gary Magdesian

Both organic and inorganic acidoses are found in horses with critical illness. A common cause of organic acidosis in horses is lactate (lactic acidosis). Hyperlactatemia occurs with hypovolemia, sepsis, and SIRSs such as endotoxemia, marked hypoxemia, heart failure, cytopathic hypoxia, and liver failure.[31–34] Volume resuscitation can be performed with a combination of crystalloids and colloids, and possibly hypertonic saline.

Acetated crystalloids (such as Normosol-R or Plasma-Lyte 148) do not contain lactate; however, even LRS will correct hyperlactatemia when it is caused by hypoperfusion. Hepatic perfusion will clear the lactate previously accumulated. The exception is liver failure, where fluids devoid of lactate should be administered. Other less common causes of organic (high anion gap) acidosis include ethylene glycol and salicylate toxicity and uremic acidosis. The treatment of lactic acidosis is correction of the underlying pathogenesis. If the cause is hypoperfusion, reversal of that state should be the goal of therapy; this is accomplished through restoring blood volume, cardiac output, and finally systemic vascular resistance through the administration of fluids, dobutamine, and vasopressors, respectively. Sodium bicarbonate is therefore not a part of the routine treatment of lactic acidosis. Its use in lactic acidosis is in fact controversial.[178,179] In a canine model of lactic acidosis, the administration of sodium bicarbonate actually caused a decrease in pH and bicarbonate concentration and an increase in lactate.[180] Similarly, in a model of endotoxemia in ponies, administration of sodium bicarbonate actually increased blood lactate concentration.[181] Despite these controversies with sodium bicarbonate and lactic acidosis, when the pH of the patient's blood is below 7.2, administration of sodium bicarbonate is justified to prevent the detrimental effects of severe acidemia, even when the acidosis is a result of lactate. Severe acidosis can lead to life-threatening cardiovascular complications such as impaired contractility, sensitization to ventricular arrhythmias, and impaired responses to pressors.[182] Small doses of sodium bicarbonate should be administered slowly to increase the pH to 7.2, at which point increasing perfusion should be the goal.

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44.4.14.1

Box 44-11 Fluid Guidelines for Metabolic Acidosis

1 The two primary forms of metabolic acidosis in horses are organic, most often resulting from hyperlactatemia, and inorganic, often resulting from relative or absolute hyperchloremia.

2 Treatment of hyperlactatemia consists of addressing the underlying cause. In many cases, lactic acidosis is caused by hypovolemia.

3 Commercial acetated fluids, such as Normosol-R or Plasma-Lyte 148, are good fluid choices for hypovolemia, although volume rather than type of fluid is the most important component of treatment.

4 The use of sodium bicarbonate is controversial in lactic acidosis and may be contraindicated.

5 Sodium bicarbonate is the treatment of choice for inorganic acidosis.

6 Sodium bicarbonate can be administered as a fluid in the form of an isotonic solution.

Inorganic acidoses occur because of strong ion acidosis associated with electrolyte derangements. In horses these commonly result from hyperchloremia or hyponatremia, both of which decrease the strong ion difference. Common diseases associated with these metabolic abnormalities include enteritis, colitis, renal failure, and renal tubular acidosis (RTA). In these cases the acidosis is often caused by renal or gastrointestinal dysfunction of electrolyte homeostasis, and perfusion may be normal (i.e., normal lactate). Chronic administration of carbonic anhydrase inhibitors, such as acetazolamide, is another cause of hyperchloremia. The fluid of choice for patients with hyperchloremic metabolic acidosis is one containing only strong cations without strong ions. Because sodium bicarbonate contains only strong cations (sodium), it is an ideal choice for patients with normal anion gap (hyperchloremic) acidosis. Sodium bicarbonate should be administered slowly to allow time for distribution and evaluation of its effects. As a fluid choice, rather than as a supplement, isotonic (1.3%) sodium bicarbonate can be used; this formulation contains 150 mEq each of sodium and bicarbonate ion per liter. Potential side effects of sodium bicarbonate therapy include hypernatremia, hypokalemia, ionized

hypocalcemia, vasodilation, metabolic alkalosis (if in excess), and an increased affinity of hemoglobin for oxygen (left shift of the oxygen dissociation curve).[181]

44.4.15 Fluid Therapy for Heart Failure (Box 44-12)

K. Gary Magdesian

The cardiac patient represents a unique challenge to fluid therapy. Volume expansion poses significant risk to the horse with heart failure by raising venous pressures and potentiating sodium retention. Administration of sodium-containing fluids can lead to or compound edema and body cavity effusions. Despite these risks, patients with heart failure sometimes require fluid therapy, such as when they develop anorexia, renal failure, or diarrhea. Monitoring of CVP should be performed in these patients to aid in prevention of edema. Initial fluid therapy should consist of conservative rates, with frequent reassessment of the effects of fluids on the patient. Continuous, slow administration of fluids, rather than boluses, should be employed to avoid rapid swings in CVP. Any rise in CVP should be avoided in horses with heart failure.

44.4.15.1 Box 44-12 Fluid Guidelines for Heart Failure

1 Horses with heart failure are intolerant of significant changes in central venous pressure.

2 Fluid boluses should be avoided, and fluids should be administered at a slow, continuous rate.

3 Consideration of the amount of sodium administered should be a priority.

4 Conservative fluid rates are warranted.

5 Concurrent and careful use of diuretics may be indicated.

The choice of fluid depends largely on concerns over sodium retention in the heart failure patient. Fluids with lower sodium content may be preferable, such as maintenance fluids (0.45% NaCl/2.5% dextrose, Plasma-Lyte 56, or combinations of replacement fluids mixed with sterile water).[183] As soon as the patient is able to drink water the intravenous fluids should be discontinued.

Because of sodium retention in heart failure, these horses are often treated with diuretics such as furosemide, which aid in minimizing edema formation.[183] A fine balance between fluid therapy and diuretics is required.

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45 Chapter 45 Principles of Antimicrobial Therapy

Consulting Editors

Gordon W. Brumbaugh

45.1 PRINCIPLES OF ANTIMICROBIAL THERAPY

Gordon W. Brumbaugh

"Rational therapeutics" is the scientific account of the management and care of a patient for the purpose of combating a disease or a disorder based on knowledge of the disease and the action of the remedies used. It requires clinical judgment, overall medical knowledge, information about a specific patient,[1] selection of the proper drug, and the formulation of a dosage regimen appropriate to the patient after appraisal of potential benefits and risks of that therapy.[2] That process is not simplified by the vast number of antimicrobial drugs available. It is therefore essential that basic principles be applied so that antimicrobial drugs may be appropriately selected and used in patients. The purpose of this chapter is to explain general principles of rational antimicrobial therapy (Box 45-1) rather than to discuss individualized treatment of specific infectious conditions. Guidelines for prudent use of antimicrobial drugs have been published by several professional associations and organizations. Guidelines are by nature inherently dynamic and can be general or very specific, but in either case they should follow a principled approach.[3]

The ultimate expectation of an antimicrobial drug is to inflict an insult on an infectious organism that is sufficient to kill the organism or to render it susceptible to lethal effects of natural host defenses or the microenvironment around it, without adversely affecting the patient.[4,5] To accomplish this goal, antimicrobial drugs must be selectively toxic to the infectious organism.[6,7] Different structures, biochemical activity, virulence factors, mechanisms of resistance, generation times, and nutritional requirements of infectious organisms (i.e., bacteria, viruses, fungi, and parasites) form the mechanistic basis for selective toxicity of antimicrobial drugs. No individual drug is sufficient to meet all therapeutic needs. It is irrational to treat a viral infection with antibacterial drugs or a bacterial infection with antiparasitic drugs. However, principles of selection and use of antimicrobial drugs are similar regardless of the infectious agent.

45.2 PRINCIPLE 1: CONSIDER THE PATIENT

The patient occupies the paramount position with regard to treatment and recovery from infection. Although the organism is the target of the drug's action, it is the *patient* with an infection that receives the drug. Before the patient can be considered adequately recovered, infectious agents must be controlled and removed from the site of infection, debris must be removed from the site, and the damaged tissue must be repaired or replaced.[8] Inactivation of microbes is the *only* role played by antimicrobial drugs; the patient must participate in that aspect and perform the others. Most infections are prevented by efficient nonspecific host defense mechanisms.[9] When infections occur, many patients recover without treatment because of nonspecific and specific host defense mechanisms. Ideally, if the host's defenses are functional and a pathogen's virulence can be weakened by antimicrobial drugs, the host should be able to kill and remove the microbe.

Many host-related factors must be considered during the formulation of a therapeutic plan.[10,11] The animal's age, sex, breed, use, residence, contacts with other animals, travel, diet, exposure to inclement weather, vaccination status, and medical experiences may influence natural defenses in the animal and prevalence of certain infections. Prevalence of an infectious disease may vary with year, susceptible population, and geography. Medical history of the herd may also be of value because virulence of some infectious agents may change after "passage" through several animals.

Clinical signs must be interpreted carefully because identification of the agent is frequently not possible on the basis of clinical signs alone.[10] Clinical manifestations of infection result from direct effects of microbial pathogens, their toxins, or the inflammatory response elicited in the host. Similar clinical signs may be caused by different microbial agents, and one species of microbe may produce a variety of clinical signs.[12] Signs of noninfectious conditions can mimic those of infectious conditions.

Inadequacies in host defense mechanisms are as important as the organism's virulence in determining whether infection will result from contact with an infectious agent and whether recovery will result if infection develops.[9] This is exemplified by infections associated with combined immunodeficiency syndrome or failure of passive transfer. It is irrational to expect antimicrobial drugs to resolve those conditions because the primary problem is not an "antimicrobial deficiency." Reasonable attempts should be made to assess weaknesses in a host's defenses that may contribute to the disease. Natural defenses of note include skin, mucous membranes, mucociliary escalator activity, cough reflex, transit time through the gastrointestinal tract, blood supply at portals of entry of infectious agents, humoral and cellular immunity, and resident microflora.[13] It is not possible to assess many of these objectively in most clinical situations. The attending veterinarian must have astute clinical acumen to subjectively evaluate contributory factors. Attempts should be made to replenish temporarily inadequate host defenses. If the host's defensive response contributes to clinical signs (e.g., if inflammatory edema compromises breathing), the response should be modified to enhance convalescence.

Antimicrobial drugs can alter the response of the host's immune system or the stimulatory antigen.[14] The outcome of complex interactions among antimicrobial drugs, bacteria, and phagocytic cells depends on the organism, the drug, its concentration, and the duration and timing of exposure to the phagocyte and microbe.[15] Antimicrobial therapy of proven efficacy should not be withheld from a patient to potentially enhance that animal's immunity. Effects of antimicrobial drugs on chemotaxis, phagocytosis, metabolism of neutrophils, and the complement system are demonstrable in vitro but have inconclusive or insignificant clinical importance.[14] Inhibitory effects of chloramphenicol or rifampin on cellular and humoral immunity have been studied most extensively, but their immunomodulatory effects are not sufficient to warrant restricting their clinical use. Clinical consequences of effects of antimicrobial drugs on immunity are limited but should be conservatively considered. For example, florfenicol did not interfere with responses of cattle vaccinated against bovine herpesvirus type 1.[16] Tilmicosin had neutrophilic antiinflammatory activity in cattle that were experimentally infected with *Mannheimia (Pasteurella) hemolytica*.[17] Some antimicrobial drugs accumulate in phagocytes, but increased bactericidal activity is not equally correlated to the degree of that accumulation; likewise, no relationship has been demonstrated to clinical response.[18,19]

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45.2.1

Box 45-1 Principles of Antimicrobial Therapy

1 Consider the patient.

2 Document the infection.

3 Determine microbial susceptibility in vitro.

4 Use an appropriate dosage regimen.

5 Monitor results of treatment.

6 Investigate causes of therapeutic failure.

7 Restrict concomitant use of antimicrobial drugs.

8 Appropriately attend adverse reactions to drugs.

45.2.2 Special Considerations

45.2.2.1 MATURATIONAL STATUS

An animal's responses to pharmacologic agents are significantly influenced by the age or maturity of the animal.[10,20,21] Physiologic differences that alter disposition of drugs in vivo are primarily responsible for that. Pharmacologic effects of xenobiotics (chemicals that are foreign to the biologic system) administered to brood animals before conception, during gestation, or at parturition or to neonates are not universally predictable. Drugs may distribute into gonads at sufficient concentrations to adversely affect gametogenesis. Drugs in luminal fluids of the oviducts or uterus may be teratogenic. Distribution of drugs into the placenta and fetus is affected by factors such as placental circulation, placental maturation, placental and fetal biotransformation of drugs, and fetal circulation. Among these variables, species-related differences may occur. Therefore drugs should be administered conservatively to brood animals, pregnant animals, and neonates and with adequate explanation of pertinent facts to the client. Potentiated sulfonamides administered to gestating mares for treatment of equine protozoal myelitis were shown by Fenger and colleagues to be associated with increased incidence of anemia, fever, anorexia, depression, and abortion.[22] Stallions treated with potentiated sulfonamides and another diaminopyrimidine (pyrimethamine) were shown to develop signs of neuromuscular weakness and ejaculatory dysfunction.[23] It is not clear how each of these signs could be attributed to these drugs. Indirect effects such as folate deficiency may account for some of the adverse signs that have been observed. Some adverse findings with one species should be interpreted with care when dealing with another species. Anemia is a good example. An aspirate or biopsy of bone marrow is necessary to adequately evaluate anemia in horses, whereas peripheral blood may be sufficient with other species.

Biotransformation of drugs in neonates can be altered by administration of medication to the gestating dam. Phenylbutazone administered to gestating mares during the final days of gestation resulted in substantial amounts of phenylbutazone and of oxyphenylbutazone in plasma of their foals.[24] Although phenylbutazone is not an antimicrobial drug and results of similar studies with antimicrobial drugs are not known to us, this example serves to emphasize the importance of considering peripheral effects of medication administered to gestating animals.

Fluoroquinolones are known to cause cartilaginous arthropathies in weight-bearing joints of young animals of several species. The horse may be unique in that adult horses have also developed the same syndrome,

which was inconsistently related to dose and duration of treatment with enrofloxacin.[25,26] Tissues peripheral to plasma contained higher concentrations of fluoroquinolones than did plasma; therefore accumulation from repeated dosage regimens should be considered when developing those regimens.[25,27–29] Although arthropathic syndrome has now been recognized and acknowledged as a risk associated with use of fluoroquinolones, nothing is known about the healing and recovery of joints that are injured. Therefore the overall assessment of risks of treatment with those drugs remains speculative; anecdotal reports suggest that the injured cartilage may repair and not carry prolonged clinical consequences, but that needs to be confirmed.

45.2.2.2

LACTATION

There are at least three aspects to consider regarding distribution of drugs into milk: the lactating animal, the suckling animal, and the milk-consuming public. Distribution of drugs into milk is influenced by the same factors that influence distribution of drugs into other tissues.[10,21,30] Some antimicrobial drugs are concentrated in milk, others equilibrate between milk and circulating blood, and still others reach insignificant concentrations in milk (Table 45-1).[31–39] A ratio greater than 1 indicates accumulation of the drug in milk relative to plasma. Results often vary with pH of milk. Concentrations of tetracycline may be high as a result of chelation with calcium but remain bioinactive.

Therapeutic implications of the distribution of drugs into milk are clear, but inflammation of the mammary gland may alter distribution of drugs. Mastitic milk may resemble an exudate rather than “milk,” thus providing a different microenvironment from that of milk. Nearly all drugs administered to a lactating animal will be detectable in her milk and can thereby expose the suckling animal. However, the total amount of most drugs received by the suckling animal via milk does not pose significant concerns.[20]

Antimicrobial drugs in milk may render that milk unsuitable for use as food.[30] Subtherapeutic concentrations of drugs in milk may cause no adverse effect, may cause the milk to be condemned as adulterated, may interfere with production of cheese or other dairy products, or may induce reactions in an allergic person who consumes the milk. For these reasons, compliance with and adherence to withdrawal times should be considered seriously.

45.2.2.3

WITHDRAWAL TIMES

Withdrawal times are intended to allow adequate time for elimination of the drug from the animal to reduce the risk of violative residues of drugs inadvertently entering the food supply. Withdrawal times are established for drugs that are licensed for use in animals intended for use as food, and the withdrawal time applies only when the drug is used according to the approved labeling.[13] Because of this, it is important 1507
before treatment is initiated to discuss the patient's condition with the client, to determine if the animal 1508
(regardless of species) is intended for use as food, and to ascertain if extralabel use of the drug is needed. Without such a discussion the client cannot make a wise decision regarding the risks and benefits of therapy, and precautions to prevent adulteration of food may be inadvertently omitted.

Table 45-1 Ratio of the Concentration of Drug in Ultrafiltrate of Milk to That in Plasma After Systemic Administration of the Drug[31–39]

Drug	Ratio (Range) (Milk: Plasma)	Reference
Ampicillin	0.24–0.30	28
Benzyl penicillin	0.13–0.26	28
Cephaloridine	0.24–0.28	28
Erythromycin	6.00–7.30	29
Gentamicin	0.20–0.50	30
Kanamycin	0.60–0.80	30
Lincomycin	2.50–6.25	31
Spectinomycin	0.37–1.12	32
Sulfacetamide	0.08–0.11	33
Sulfadiazine	0.16–0.19	33
Sulfadimethoxine	0.13–0.24	34
Sulfadimidine	0.59–0.62	33
Sulfanilamide	0.97–1.04	33
Sulfathiazole	0.37	33
Tetracycline	1.22–1.91	35
Trimethoprim	3.00–4.90	36
Tylosin	1.00–5.35	32

Withdrawal times are not established for drugs that are used in an extralabel manner; therefore the most conservative time should be allowed when drugs are used in a manner inconsistent with their labeling.[40,41] Aids to determine useful withdrawal times include screening tests for drugs in milk* or urine.† Results may not match those of methods used by regulatory agencies assigned the task of detection of residues, and those agencies may test different tissues.

* IDEXX Laboratories, Westbrook, Maine.

† DSM Food Specialties, The Netherlands.

45.2.2.4

EXTRALABEL USE OF DRUGS

Veterinarians often encounter infectious conditions for which the drug of choice is not approved by the U.S. Food and Drug Administration's Center for Veterinary Medicine (FDA-CVM).[13] In these situations the veterinarian is not exempt from professional and ethical obligations. Treatment must be based on experience, established practices, and scientifically substantiated facts. Drugs that are used in any manner other than that described on the drug's labeling (e.g., the treatment of diseases, with doses, routes of administration, duration of treatment, or species not specified on the approved labeling) are said to be used in an *extralabel* manner.

The Animal Medicinal Drug Use Clarification Act (AMDUCA)[40] of 1994 amended the Federal Food, Drug, and Cosmetic Act so that a particular use or intended use of a drug shall not be deemed unsafe if such use or intended use is (1) by or on the lawful written or oral order of a licensed veterinarian within the context of a veterinarian-client-patient relationship, and (2) in compliance with regulations promulgated by the Secretary of the U.S. Department of Health and Human Services. In short, the amended act contains statutory allowance of extralabel use of drugs, and regulatory authority is retained by the FDA-CVM. For veterinarians to discharge their professional duties within the public trust and in an ethical manner, a professional approach to extralabel use of drugs is necessary. Some guidelines include the following:

- A valid licensed veterinarian—client-patient relationship
- A medical diagnosis
- A situation in which approved use of a drug has proven ineffective in animals being treated or for which no available drug is specifically labeled (as is often encountered with some species)
- Carefully maintained identity of treated animals
- Observation of extended withdrawal times calculated by the attending veterinarian[42]
- Acceptable labeling of the prescribed drug[13,42–44]

Regulations specify contents of acceptable labeling. Consultation with a representative of the FDA-CVM is advised before treatment is initiated when particularly perplexing therapeutic problems exist and no alternatives to extralabel use of drugs are apparent.

45.2.2.5

HERD TREATMENT

Each member of a herd may have the same disorder, but one animal cannot receive treatment that is intended for another (there are no surrogate patients), and treatment of an animal that does not need it is wasted treatment. Treatment must be implemented for each affected animal in the herd. The method of treatment must be practical and efficacious, or compliance by the client will be difficult. Unfortunately, requests by some owners and veterinarians for “herd treatment” are really requests to treat each animal identically and easily rather than according to its individual needs. Each animal may indeed require the same treatment, and treating all animals in question may be acceptable, but each animal deserves a reasonable assessment of its condition before treatment is instituted. Metaphylactic or therapeutic medication of all animals has benefits and risks, but the cost must be offset by savings in areas such as labor of handling of the animals, reduced needs for therapeutic medication, or improved production.[45,46]

45.2.2.6

COST OF THERAPY

The cost of appropriate therapy is an important consideration for the client. The client (or his or her financial advisor) is the only one who can decide whether the value of treatment is “worth” the “cost.” The cost of medical care is not static, and the veterinarian should keep the client informed of the financial commitment associated with treatment. Naturally, cost-effective therapy should be sought. This is not to say that the least expensive therapy is the best therapy or that ineffective drugs should be used just because they are inexpensive. Similarly, expensive drugs are not “better” just because they cost more. Clients require adequate information to make financial and medical decisions regarding their animals.

45.3 PRINCIPLE 2: DOCUMENT THE INFECTION

Antimicrobial therapy is predicated on the premise that the disease is caused by an infectious agent and that the patient will be unable to effectively eliminate the infection without antimicrobial treatment.[1,4] The primary purpose of documentation of infection is to help the veterinarian determine the necessity of this treatment. Clinical experience and diagnostic and interpretive skills are particularly important. Use of antimicrobial drugs for relatively trivial infections exerts selective pressure for resistant organisms.[5] Contamination or colonization by microorganisms (i.e., contamination of the surface of granulation tissue) does not necessarily constitute infection and is not always a sufficient reason for antimicrobial treatment. Inoculum size, microbial virulence, concurrent infection, site of infection, and resident flora contribute to the significance of infection. Death resulting from some bacterial diseases such as botulism (except toxicoinfectious botulism), enteric colibacillosis, or enterocolitis caused by salmonellae is not directly caused by vegetative bacterial invasion, so antimicrobial drugs are a secondary component of treatment. Without evidence of involvement of a susceptible causative agent(s), use of an antimicrobial drug is irrational and exposes the patient to unnecessary risks.[1] The more information that can be discerned about the infecting agent, the more reasonable will be the treatment.[1,11]

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Sequential steps necessary to document an infection are as follows[1,47]:

- Development of reasonable suspicion of infection based on the patient's clinical signs and the veterinarian's knowledge of the pathophysiologic and microbiologic characteristics of the condition
- Careful procurement and submission of a representative sample of material from the lesion
- Initial detection of organisms by microscopic examination of a stained smear of the sampled material
- Demonstration and identification of the infectious agent in vitro, on the basis of its morphologic, immunologic, or biochemical characteristics
- Serologic evidence of antibodies produced against a particular infectious antigen
- Interpretation of the results of all diagnostic procedures

There are nonspecific and specific methods of documenting infection.[10] Nonspecific methods include medical history, clinical signs, hematologic changes, and characteristics of lesions. The drug(s) used for initial therapy will most often be selected on the basis of the veterinarian's clinical judgment and medical knowledge, as well as on nonspecific indications of infection.[2,11,47] This is not a trial-and-error approach.[48] Potential for a particular infectious cause, most probable causative agent, status of the patient's natural defense mechanisms, and site of infection must be considered when interpreting clinical signs.[49] “Response to treatment” is an inconsistent means of revealing the cause of infection. Although nonspecific methods are the weakest form of documentation, that information, coupled with astute clinical judgment, is often successfully used in practice. For example, a young horse with fever, nasal discharge, and submandibular lymphadenitis can be assumed (with a relatively high degree of certainty) to have strangles, and penicillin could be chosen for therapy. However, the possibilities for misdiagnosis are numerous in this and many other disease conditions, and specific methods of documenting infection should be used. An aspirate obtained from involved lymph nodes of the patient in the example may reveal chains of gram-positive cocci, and *Streptococcus zooepidemicus* may be isolated. The immediate treatment may not change, but the management of the rest of the animals in the herd would differ greatly from that indicated for strangles.

Different organisms may be susceptible to and successfully treated with one antimicrobial drug, making treatment choice easy. However, a specific causative diagnosis may be of considerable relevance for the development of herd-health programs.

Antimicrobial therapy cannot be consistently successful if formulated on the basis of nonspecific diagnostic methods and historical probabilities alone.[10] Treatment formulated in that manner may cause more harm than good by interfering with the pursuit of a specific diagnosis, by allowing the development of superinfection, or by inducing reactions to the drugs.

Specific diagnostic methods should be attempted before initial treatment is instituted. Specific methods of documenting infection require proper collection and submission of appropriate samples, reliable laboratory procedures, and accurate interpretation of results. Because laboratory facilities and personnel can work only with materials submitted to them, the veterinarian must properly collect and submit appropriate samples to the laboratory and interpret results relative to the condition of the individual patient. Procurement of tissues or bodily fluids for cytologic, histologic, or microbiologic evaluation remains the cornerstone of accurate documentation of a specific infection.[10] Inadequate or improper sampling and improper submission of samples to the diagnostic laboratory are the most frequent and often unrecognized reasons for failure of documentation of causative agents of infectious diseases. The sample must be representative of the site of infection and may be bodily fluid (blood, peritoneal fluid, pleural fluid, percutaneous transtracheal aspirate, material draining from a site of infection) or tissue (biopsy, scraping, curettage, aspirate). Collection and submission procedures differ for aerobic and anaerobic bacteria, mycoplasma, protoplasts, viruses, and parasites. Special media or particular constraints of time and temperature must often be observed to transport fastidious organisms. Because each laboratory may use different techniques, it is wise to contact laboratory personnel in advance to learn preferred collection and submission equipment and procedures. The veterinarian and laboratory personnel can assist each other in reducing inappropriate collection and submission practices.

The choice of site to be sampled is critical. Isolates from draining tracts are unreliable and should be evaluated in the context of other related information.[50] Organisms isolated from wounds are of questionable significance unless they are present in pure culture or are clearly predominant. In these instances susceptibility testing is probably warranted. Any microorganism isolated from bodily fluids that are normally sterile (blood, cerebrospinal fluid (CSF), pleural fluid, or synovial fluid) in the presence of clinical evidence of infection should be evaluated for its antimicrobial susceptibility in vitro. If dissemination of infection is suspected, isolation of the agent from samples obtained from sites distant from the primary site of infection will strengthen confidence in the diagnosis.[10] Cultures of blood samples should be performed if dissemination is suspected because of systemic signs or if no primary site of infection is apparent. It is important to properly prepare the site of venipuncture so that the sample does not become contaminated. Results of cultures may be difficult to interpret if such details are ignored. The type of sample to be submitted (biopsy, feces, fluid, aspirate, blood) is selected on the basis of the disease. Recommended sites and materials to be sampled are presented in discussions of specific diseases elsewhere in this text.

If the patient has received antimicrobial drugs, the collection procedure should be delayed until the drugs are adequately eliminated from the animal's body so that residual drugs will not interfere with bacterial growth. Because approximately 99% of a drug will be eliminated from the body within seven half-lives of disappearance, an appropriate delay between treatment and sampling can be estimated if pharmacokinetics of the drug are known. However, the delay calculated by this method may not be appropriate for severely ill patients. A fairly reliable rule of thumb is to wait 18 to 36 hours after the last dose of a drug. If a repository form of the drug is used, a longer delay is indicated. If the patient's condition does not permit a delay, the probability of isolating organisms

from bodily fluids can be increased if samples are passed through a device designed to remove antimicrobial drugs from the sample.* Directions for use of such a device should be closely followed. If samples are obtained for culture at the time of a necropsy, the treatment history may be important for interpretation of results of subsequent antibiograms.

Evaluation of stained smears of samples remains the most rapid and useful method of early recognition of some infectious agents.[1,10] A direct smear should be made from a part of the sample, stained, and evaluated microscopically for bacteria and to characterize the cytologic response. Gram stain for bacteria, Wright stain for cytologic examination, acid-fast stain for mycobacteria, methylene blue and potassium hydroxide preparations for fungi, India-ink preparations for cryptococci, darkfield microscopic examination for spirochetes, fresh wet mounts for motile organisms (trichomonads), phase-contrast microscopy, immunofluorescence, and electron microscopy are methods of identification of infectious agents and inflammatory cells by direct examination. Techniques of DNA typing and polymerase chain reaction (PCR) are finding their place as modern diagnostic procedures for identifying some organisms.

Knowledge of morphologic and staining characteristics of bacteria is important to predict the identity of the microorganisms observed in the smear (Box 45-2).[1] Gram or Wright stain will demonstrate the presence of most microorganisms. If only one stain is used, Wright stain* is preferred because its cytologic staining is superior to that of Gram stain. Characteristics of the microorganisms (fungal, bacillary, or coccoid bacteria), the nature of the inflammatory cells, and suspicions of which microorganism(s) might be present at the site of infection are especially beneficial for deciding initial treatment. With this information, treatment can be rationally initiated at least 24 hours before results of cultures are known and within minutes of the time that diagnostic samples are obtained. Although the list of those organisms is shrinking, some microorganisms respond predictably to certain antimicrobial drugs. Other organisms respond unpredictably because of genetically related resistance, which may arise by mutation, induction, or acquisition of a plasmid. If gram-negative bacilli are seen in samples, at least one member of the unpredictable class of microorganisms should be suspected. If one or more unpredictable species are present, isolation and antimicrobial susceptibility procedures must be performed.

45.3.1 Box 45-2 Morphologic Description of Microorganisms[1]

45.3.1.1 RODS (BACILLI)

45.3.1.1.1 Enteric Organisms

Pasteurella

Actinobacillus

Bordetella

Pseudomonas

45.3.1.2 Anaerobes

*Corynebacterium**

Haemophilus

45.3.1.3 Cocci

Staphylococci

Streptococci

Anaerobes

45.3.1.4 Branching Filaments

Nocardia

Actinomyces

Dermatophilus

Sporothrix

Fungi

* Corynebacteria characteristically are pleomorphic; they align in V shapes after division and often appear as “Chinese letters.”

Serologic methods of diagnosing infections may be beneficial.[10] However, because most patients have recovered from infections by the time a convalescent sample is obtained, serologic diagnoses may not be available in time to influence treatment. However, serologic data may be beneficial for the development of preventive strategies. The class of immunoglobulin and the timing of its production are determined by the previous antigenic experience of the host. High concentrations of specific immunoglobulin M (IgM) are useful in diagnosing certain viral infections and toxoplasmosis. Acute and convalescent sera demonstrating a fourfold rise in the concentration of a specific IgG indicate the presence of infection. Samples of serum should be obtained at an interval of 2 to 3 weeks to permit an adequate time lapse for the formation of significant amounts of IgG. Although the presence of IgG in a single serum sample, regardless of concentration, indicates exposure to the agent, it is of little assistance in diagnosing a current infection. There is no consensus about what constitutes adequately protective concentrations

of immunoglobulins. Because serologic response is used to diagnose some conditions, is the presence of immunoglobulins an indication of infection, protection, vaccination, or passive transfer?

Documentation of infection entails more than merely listing isolated microorganisms on a laboratory report. The veterinarian must decide if the isolated organisms could be responsible for the condition in the animal, if they are commensal, resident flora, or if they are merely contaminants resulting from improper sampling technique. For example, *Escherichia coli* isolated from a sample of feces from a calf does not indicate that the calf's diarrhea was caused by that organism. However, if that isolate was shown to possess the K99 pilus antigen and the ability to produce enterotoxin and if the signalment and clinical signs are compatible with coliform enteritis, the veterinarian can establish a cause-effect relationship from the bacterial presence.

* BBL Septi-Chek, Becton Dickinson and Co., Microbiologic Systems, Cockeysville, MD.
* Diff-Quik Differential Staining Set, American Scientific Products, Mc-Gaw Park, IL.

45.4 PRINCIPLE 3: DETERMINE MICROBIAL SUSCEPTIBILITY IN VITRO

Quantitative assays of a microbe's susceptibility to antimicrobial drugs in vitro are necessary for patients with severe or complicated infectious processes and for those with infections caused by organisms with unpredictable susceptibility patterns.[1,10,51,52] It is important to remember when formulating a therapeutic strategy that "the bug denotes the drug."[4] A microbe is considered sensitive to a drug if the concentration of the drug that inhibits growth of the organism in the testing system in vitro can be achieved in vivo after administration of the drug by methods customarily used in clinical situations. Two commonly used quantitative assays of susceptibility are broth dilution and disc diffusion tests.[6,10,50–54] Reliability and reproducibility of these procedures depend on the organism examined, standardization of the inoculum, medium used, conditions of incubation, and concentrations of the drug. The development and promotion of performance standards, as well as interpretive criteria, for in vitro antimicrobial susceptibility testing of bacteria isolated from animals is the mission of the Subcommittee on Veterinary Antimicrobial Susceptibility Testing of the Clinical and Laboratory Standards Institute (CLSI).* Results of these procedures can be coupled with knowledge of the clinical pharmacology of potentially useful drugs and of pathophysiologic changes in the patient to design an individualized dosage regimen for the patient.

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Broth dilution procedures involve inoculation of a known number of organisms into tubes or wells holding a volume of broth that contains specific concentrations of antimicrobial drugs. These inoculated tubes or wells are incubated under standardized microenvironmental conditions. The lowest concentration of antimicrobial drug that inhibits visible bacterial growth is defined as the minimum inhibitory concentration (MIC) of that drug for that organism. The lowest concentration of antimicrobial drug that prevents bacterial growth, when an aliquot of the inoculated broth that contains no visible growth is subcultured onto drug-free agar or into broth, is the minimum bactericidal concentration (MBC). Therefore the MIC is a measure of the bacteriostatic concentration of the drug, and the MBC is a measure of the bactericidal concentration of the drug. Drugs that are by some conventions classified as bactericidal have an MBC within one or two twofold dilutions of the MIC. The adjectives *bacteriostatic* and *bactericidal* should be used to describe concentrations of drugs rather than to classify drugs. The disk diffusion susceptibility test involves application of antimicrobial drug-impregnated paper disks onto inoculated agar plates. The antimicrobial drug diffuses from the disk into the agar, and a progressively decreasing gradient of concentrations of the drug is developed centrifugally around the disk. If the drug is active against the organism, a growth-free zone will surround the disk. The size of the growth-free zone can be correlated with the MIC determined by dilution assays. Because multiple factors affect diffusion of drugs in the medium, the size of the growth-free zone induced by one drug cannot be equated to a zone of the same size induced by another drug.

The microdilution method provides information that may be more clinically relevant than that offered by the agar dilution method for determining therapy for bacterial infections of animals. The quantitative endpoint of susceptibility can be correlated with concentrations of the drug in bodily fluids or tissues. As a result, a more informed choice of treatment can be made than is usually possible when using agar dilution methods.

Standards for susceptibility in vitro do not necessarily apply to activity against pathogens that can be found within phagocytes in the patient. Results of intracellular antimicrobial activity were not predictable based on data from standard susceptibility procedures and have generated additional questions about the wisdom of generalizing susceptibility information in vitro or as predictable of clinical response.[18,19]

Laboratory reports of susceptibility of microorganisms to antimicrobial drugs provide only part of the information needed to formulate appropriate therapeutic actions. Interpretation and application of that information remain the responsibility of the veterinarian. It is reasonable to assume that if the same conditions are present at the site of infection as in vitro, the results obtained in vitro could also be expected in vivo. However, standardized microenvironmental conditions of a system in vitro are seldom present in the patient, and those conditions in the patient are usually unknown to the attending veterinarian. Temperature, humidity, partial pressures of oxygen and carbon dioxide, pH, osmotic pressure, presence of debris from damaged tissue, inactivating substances, and nutritional substrates at the site of infection are as important to therapeutic success as is the concentration of the drug. Limitations of susceptibility procedures and difficulties encountered with interpretation and application of results are eclipsed by the benefit provided. During recent years the clinical relevance of categorizing organisms as “susceptible,” “intermediate,” or “resistant” has been questioned. Although it is generally agreed that patients with “susceptible” organisms should respond successfully to those antimicrobials, classification of organisms as “intermediate” or “resistant” is not necessarily associated with clinical failure. Retrospective and prospective studies, as well as studies with models—computerized and laboratory animal—have been undertaken to resolve the dilemma, but accurate predictors of clinical outcome remain elusive.[55] Niederman states that the clinical relevance of resistance is overemphasized.[3] Other investigators emphasize that the outcome of microbe, antimicrobial, and host defenses is dependent on time and concentration of medication to which the microbe is exposed, regardless of medication evaluated.[18] Those times and concentrations may be clinically relevant but beyond those used by standard procedures in vitro. Several reports demonstrate that being a member of a subpopulation of patients, categorized by disease, organism, and concurrent health issues, has significant influence on final clinical outcome.[3,56,57] Metlay conveys concerns that changing treatment patterns based on perceptions of clinical relevance of resistance rather than on scientific evidence severely limits the ability to continue to monitor effectiveness of available treatments; yet clinical effectiveness continues to be the primary factor driving selection of antimicrobial medication.

Although the previously mentioned evidence germinated in human medicine to form the basis for development of treatment protocols, similar data for veterinary patients are severely lacking.

* Clinical and Laboratory Standards Institute (CLSI), Wayne, PA.

45.5 PRINCIPLE 4: USE AN APPROPRIATE DOSAGE REGIMEN

In most instances there are insignificant differences in clinical response after bactericidal or bacteriostatic therapeutic protocols.[53,58] Bacterial meningitis, endocarditis, and gram-negative bacillary infections in neutropenic human patients are conditions in which bactericidal concentrations of active drugs at the site of infection were correlated with improved response. Confirmatory data with animal patients are lacking, but extrapolation may be acceptable when similar causative organisms are present. Because of complex interactions

among microbes, subtherapeutic concentrations of drugs, postantimicrobial effects, host defenses, and microenvironment at the site of infection, dogmatic statements about the requirement for bactericidal protocols should be avoided.

The drug selected for treatment must reach the site of infection, at an adequate concentration of the active form(s), for a sufficient time that its selectively toxic effect can be inflicted on the infectious agent. Astute application of clinical judgment and knowledge of pathophysiology and clinical pharmacology are important for the development of an appropriate dosage regimen so that therapeutic success may be expected.

A dosage regimen has six components: formulation of the drug to be used, dose of drug to be administered, route of administration, site of administration, dosing interval, and duration of treatment.[10,59] When the appropriate drug has been selected, dose, route, site, and interval of administration can be formulated using pharmacokinetic values of the drug in the targeted species. The drug's bioavailability, its distribution to the site of infection, the duration of therapeutic concentrations at the site of infection, and its clearance from the body must be considered. The following are affected by drug- and host-related factors: solubility of the drug and its formulation in water and lipids, formation of a concentration gradient, blood flow at the site of absorption and at the site of infection, ionization of the drug, binding of the drug to proteins, biotransformation of the drug, chemical characteristics of the drug, presence of an inflammatory response, and microenvironment at the site of infection.

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Postantimicrobial effects of some drugs may be significant. These effects can be considered with pharmacokinetic values and mathematically factored into the calculation of a dosage regimen.[60] Few patients have conditions that require detailed mathematic calculation of a dosage regimen. Patients that may require such attention are those with compromised function of organs involved with biotransformation or elimination (primarily liver or kidneys), those that need treatment with drugs that are potentially toxic, and those that receive two or more drugs that interact in a potentially dangerous manner or that alter biotransformation or elimination of themselves or other drugs. Diligent monitoring of the high-risk patient for evidence of insult or toxic damage to organs is recommended (e.g., routine urinalysis, blood urea nitrogen, creatinine, sorbitol dehydrogenase).

The ability of an antimicrobial drug to distribute to an infected site depends on circulating concentrations of the drug, molecular size, binding of the drug to proteins in plasma and in tissue, water and lipid solubility of the drug, ionization of the drug, inflammation, active transport mechanisms, affinity for the particular tissue, and rate of elimination.[10,18,53,61] Increased blood flow and capillary permeability associated with inflammation at the site of infection allow passage of drugs into areas that might otherwise be inaccessible. The blood-brain barrier poses such a barrier to drug passage. Distribution of penicillins and cephalosporins into CSF and other tissues is inversely proportional to the degree of plasma protein binding of the drug and directly varies with the degree of inflammation present. Aminoglycosides enter the CSF poorly, regardless of the presence of inflammation. However, no drug completely equilibrates across the blood-brain barrier; therefore high systemic concentrations of drugs are necessary to achieve adequate concentrations in the CSF, unless the intrathecal route of administration is used.

For reasons and by mechanisms that aren't totally understood, some drugs, particularly macrolides, concentrate in tissues and remain in those tissues for expended periods.[3,19,55,57] Those characteristics are at risk of being misinterpreted because specific contributions to clinical outcome are not clear. Also, the time course of those drugs in plasma, as described by classical pharmacokinetic methods and as used typically for pharmacokinetic and pharmacodynamic (PK/PD) modeling, do not adequately apply to the time course in the target tissue. Therefore for macrolides, typical PK/PD modeling does not adequately serve as a predictor of clinical outcome.

Drugs may be concentrated along routes of elimination and used advantageously to treat infections along those routes. However, when usual pathways of excretion are impaired, therapeutic success may fall, and drug-induced toxicity becomes more likely. Drugs that concentrate in urine can be used to treat urinary tract infections, even though concentrations of those drugs in blood may be ineffective against infection elsewhere (e.g., benzathine penicillin G or ampicillin trihydrate in the horse). This illustrates the necessity for relating the susceptibility of the organism to the concentration of drug at the site of infection. Penicillins, cephalosporins, trimethoprim-sulfonamide, and other drugs that attain high concentrations in urine may be effective against organisms that are otherwise considered resistant. Similarly, drugs that are eliminated by the biliary route may be used to treat biliary or hepatic infections. Drugs that undergo significant biliary elimination or reach beneficial concentrations in the liver include erythromycin, chloramphenicol, tylosin, and tetracyclines.

Duration of treatment varies with the disease and individual patient.[3] Activity of the host's defenses and ability of the organism to resist those defenses, mechanism(s) by which the organism develops resistance to the drug, location of the infection, and primary activity of the drug influence decisions about the duration of therapy. If antimicrobial drugs are truly necessary for the patient, one dose of the drug(s) is seldom sufficient unless the product is designed for prolonged exposure of the pathogen to adequate concentrations. Usually, treatment continues beyond resolution of the patient's clinical condition. Duration of treatment remains a judgment call of the attending veterinarian.

Microenvironmental conditions at the site of infection must be compatible with the selected drug. Supernate of fluid from abscesses is acidic, hyperosmotic, and hyperionic, with relatively low concentrations of sodium and chloride and high concentrations of potassium and phosphate.[62] Relative to the respective concentrations in serum, concentrations of calcium are lower, those of magnesium are higher, and those of albumin and protein are lower in abscesses. Regarding drugs with intracellular sites of action, only that part of the drug that is nonionized, unbound to proteins or other constituents, and escapes inactivation by enzymes or competitive compounds crosses the bacterial plasma membrane to reach the site of action to be therapeutically active. Penicillins and cephalosporins inhibit synthesis of the bacterial cell wall, but death of bacteria occurs when the bacteria rupture as a result of the relatively hyperosmolar interior of the bacteria. If the extracellular microenvironment is isosmolar relative to the interior of the organism, a cell-wall variant (protoplast or spheroplast) may form and continue to survive.[6,63]

Aminoglycosides are ineffective in an anaerobic microenvironment because the oxygen-dependent transport system that is necessary for intracellular uptake of the drug by susceptible bacteria is nonfunctional in an anaerobic environment.[6,53,62] Drugs that are extensively bound to proteins in plasma are also extensively bound to proteins in pus.[62] In addition to binding to proteins, aminoglycosides and polymyxins bind to constituents in sediment of pus from human patients. Binding of gentamicin is reversible and does not inactivate the drug. The antimicrobial activity of gentamicin may be inhibited as much as 16- to 32-fold by the acidic pH, high ionic content, and osmolality of pus. Activity of microbial β-lactamase at the site of polymicrobial, anaerobic infection can be sufficient to reduce the concentration of effective β-lactam antimicrobial drugs. Debris from tissue may provide adequate substrates for bacteria to circumvent effects of trimethoprim or sulfonamides.[6,64]

Size and purity of the inoculum also influence antimicrobial activity. A certain number of molecules of aminoglycosides is needed to kill a single bacterium; therefore antimicrobial activity is influenced by the amount of active drug relative to the size of the inoculum.[53] Many infections are polymicrobic, and antimicrobial activity at the site of infection is influenced by complex interactions among microbes, the host, and antimicrobial drugs that are not influential in susceptibility test systems in vitro.[62]

The effect of most antimicrobial drugs is best when the pathogen is actively growing and dividing, because at that time the organism is most susceptible.[6] When infections mature, bacterial growth rates are reduced, and bacterial population density increases.[53] Mature infections caused by gram-positive cocci respond poorly to delayed treatment. Effects of delayed treatment against *Bacteroides fragilis* have been demonstrated with metronidazole, clindamycin, cefoxitin, and moxalactam. Metronidazole was the least affected by delay. A group of β-lactam antimicrobial drugs, the penems, have good activity against slowly growing bacteria.[65] They have been used in animal patients, but their applicability in veterinary medicine will be better defined by results of well-designed studies.

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A drug formulation administered to animals of different species or to different animals of the same species may have different pharmacokinetic characteristics. Pharmacokinetic characteristics may be altered by disease and can vary from animal to animal. Pharmacokinetic studies are usually performed with healthy animals; pharmacokinetics of drugs in diseased animals may be substantially different. Pharmacokinetic values are used to describe the time course of a drug in the body and to predict what will occur if the drug is administered to another animal. If predicted values do not accurately describe the time course in diseased animals, those predicted values are not acceptable, and data from appropriately designed studies with diseased animals should supersede previous data. A calf with hypovolemic shock associated with gram-negative bacteremia and endotoxemia may have inadequate peripheral perfusion with subsequent inadequate absorption of drugs administered intramuscularly. Because of individual variation, this principle can be remembered as "the horse directs the course"[4] or "the cow dictates how."

A good example of this is found in the combination of trimethoprim and sulfadiazine. The pharmacokinetics of both drugs are relatively similar in both horses and cows. However, in cattle the time course and circulating concentrations of each drug differ significantly.[66–68] Absorption of trimethoprim appears to be the limiting factor affecting circulating concentrations of that drug when it is administered extravascularly. However, this should not be considered as an overall impediment to the efficacy of this combination of drugs. Efficacy has been demonstrated experimentally against salmonellosis in calves[68]; its efficacy against urinary tract infections cannot be adequately judged by circulating concentrations of these drugs.

45.6 PRINCIPLE 5: MONITOR RESULTS OF THERAPY

It is surprising to note that optimal therapy (drug, dose, route, dosing interval, duration, and ancillary treatment) against pulmonary infections in people is not inflexible or established.[3,57,58] The same is probably true for infections in animals. It is extremely difficult to determine the minimally effective dosage regimen of a drug; therefore the veterinarian must monitor, by appropriate means, results of treatment.

Without monitoring the therapeutic response, the veterinarian is unable to assess success or failure of treatment. Assessment should continue throughout the treatment period.[3,10] Nonspecific and specific methods used to document infection can also be used to monitor therapeutic response. Intervals at which these procedures should be performed depend on the type, severity, and site of the infection. Clinical signs, morbidity, mortality, hematologic changes, radiologic signs, microbial reduction, and monitored concentrations of drugs are useful in assessing success of therapy; but each has inherent limitations and none is clearly superior.[3,56,57] Measurement of concentrations of some antimicrobial drugs in serum or plasma is an aid to assessing adequacy of the dosage regimen and reducing risks of toxicity.[50] Therapeutic drug monitoring is most applicable when patients are receiving aminoglycosides, have impaired function of organs of elimination or biotransformation of the drugs, or

receive more than one drug, which may result in adverse interactions.[50,69] Therapeutic success against bacterial endocarditis is more likely when the patient's serum (with drug) will inhibit bacterial growth in a 1:8 or higher dilution and will kill the organisms in a 1:4 or higher dilution.[50,52] Critical concentrations of antimicrobial drug in serum for other infections have not been established but are generally targeted at concentrations that are severalfold higher than the MIC.

Studies are needed that evaluate the relationship between circulating concentrations of the drug and response to therapy. As with documentation of infection, interpretation of these data is important. Fever, other signs of inflammation, and even hematologic abnormalities can result from the therapy (drug-induced fever, leukocytosis) and nonspecific factors and may not be caused by infection.[10,70] Monitoring is the only means of determining clinical applicability of results of susceptibility tests in vitro and efficacy of the treatment used. Disparity between results in vitro and those in vivo is not uncommon.[3,52,53,56,57,64]

45.7

PRINCIPLE 6: INVESTIGATE CAUSES OF THERAPEUTIC FAILURE

Failure of treatment can result from any of several factors (Box 45-3). When response to treatment is not as expected, the cause should be sought, and the problem should be corrected. Potential for therapeutic failure can be decreased by applying principles outlined in this chapter, by considering the status of the host's defenses, by initiating appropriate treatment before the condition becomes irreversible, and by providing appropriate adjunctive therapy with drugs or by lavage, drainage, or removal of foreign bodies from the site of infection. Conditions caused by bacteria will not respond to antiparasitic drugs; those caused by viruses, helminths, or fungi will not respond to antibacterial drugs; those caused by helminths will not respond to antifungal drugs. These examples serve to demonstrate inappropriate choice of drug, but equally inappropriate is the use of drugs to which the organisms are resistant, that are ineffective in the microenvironment, or that do not distribute to sites of infection. Occasionally an infection that does not respond may be overcome by changing the dose of drug being used, the formulation, the route of administration, or the administration interval or by prolonging the duration of treatment. 1513
Compliance with the selected dosage regimen is necessary before therapeutic success can be expected. Studies 1514
have revealed that inadequate compliance is commonly encountered.[3,57,71] Disease can alter host-related factors such as function of organs, perfusion, or inflammatory response, which affect absorption, distribution, biotransformation, and/or elimination of the drug. Because antimicrobial drugs act in concert with the host's defense mechanisms, any defect in these defenses can reduce the efficacy of antimicrobial drugs. A microenvironment that is inappropriate for activity of the drug, organisms that are resistant to the selected drug, or superinfection may also result in therapeutic failure. Interactions of drugs in vivo or in comixtures can alter pharmacokinetic variables of drugs or render them chemically ineffective. Direct toxicity of antimicrobial drugs can be detrimental to the patient, as well as cause therapeutic failure. If the patient's condition has advanced to a point of irreversibility, any amount of appropriate therapy may be ineffective. Therapeutic failure is too frequently blamed on an inactive or “bad” drug. This is probably the least common cause of therapeutic failure if dates of expiration and conditions of storage of the drug are properly observed and if the product is appropriately used as prescribed.

45.7.1

Box 45-3 Causes of Therapeutic Failure

Inappropriate diagnosis

Inappropriate drug

Inappropriate dosage regimen

Inappropriate absorption, distribution, biotransformation, or elimination of the drug

Impaired host's defense mechanisms

Inappropriate microenvironment

Development of resistance to the drug

Inadequate compliance with the dosage regimen

Superinfection

Interactions of drugs

Irreversible condition of the patient

Toxicity of the drug

Inactive drug

45.8

PRINCIPLE 7: RESTRICT CONCOMITANT USE OF ANTIMICROBIAL DRUGS

Fixed-drug combinations or concomitant use of two or more antimicrobial drugs is occasionally appropriate, as shown in Box 45-4.[10,52,53] However, in most instances one drug with a specific antimicrobial spectrum will provide adequate therapy and will reduce the potential of adverse effects in the patient or the potential for selection of resistant organisms. There are very few, if any, situations in which some fixed-drug combinations are superior to individual drugs. When used concomitantly against a specific organism or organisms, two or more antimicrobial drugs may be synergistic, additive, antagonistic, or indifferent in their effect. Selection of two or more antimicrobial drugs for concomitant use should not be undertaken without considering their cumulative effects and the legitimate need for concomitant use of drugs. Too frequently, antimicrobial drugs are combined or used concomitantly to provide “broad-spectrum coverage” because of the attending veterinarian's diagnostic insecurity or to replace diagnostic procedures. Concomitant use of antimicrobial drugs should be limited to the following: to provide synergy against infecting organisms, to prevent bacterial resistance to antimicrobial drugs, to extend the antimicrobial spectrum as part of the initial therapy against life-threatening conditions, or to treat mixed-bacterial infections. Concomitant use of antimicrobial drugs beyond these situations is not justified, unnecessarily exposes the patient to risks of adverse reactions to drugs, and increases pressure for development of resistance to drugs by the infecting organism or others.

45.8.1

Box 45-4 Concomitant Use of Antimicrobial Drugs

45.8.1.1

Potentially Beneficial

Penicillin + aminoglycoside

Cephalosporin + aminoglycoside

Erythromycin + rifampin

Lincomycin + spectinomycin*

Trimethoprim + sulfonamide

Penicillin + sulfonamide

Tetracycline + sulfonamide

Penicillin + clavulanic acid

45.8.1.2

Undesirable

Penicillin + tetracycline

Chloramphenicol + erythromycin

* Potentially lethal complications may develop in horses or sheep that receive lincomycin.

Synergy results when antimicrobial activity of two drugs in combination is greater than would be expected by the sum of the activity of the individual drugs. Synergy can result if the drugs act at different sites in the same metabolic pathway (e.g., trimethoprim + sulfonamide) or at different sites (e.g., 30S and 50S ribosomal subunits) in the organism. Activity of one drug may improve the entry of another drug into the organism (e.g., penicillin or cephalosporin + aminoglycoside) or prevent the degradation of another drug by the organism (e.g., amoxicillin + clavulanic acid). Synergistic combinations of antimicrobial drugs may be essential in some severe infections that are difficult to eradicate or infections in patients with temporarily impaired defense mechanisms. However, concomitant use of antimicrobial drugs is not necessary in routine treatment of most infections. Synergy does not imply that a “better” clinical response will result. Despite evidence of synergy between two drugs in vitro, convincing evidence that such synergistic combinations are superior to single drugs in vivo when treating defined infections is sadly lacking in veterinary medicine. Controlled, prospective clinical investigations designed to evaluate synergistic responses in vivo are desperately needed.

Antagonism has been demonstrated between penicillin and tetracycline.[10] In some instances, ampicillin and chloramphenicol have been antagonistic, whereas in other instances they have been therapeutically beneficial. Antimicrobial drugs that have the same or an anatomically proximate site of action (phenicols, macrolides, and lincosamides) should not be used concurrently because of antagonistic competition for those sites in bacteria.

If bacterial resistance to drugs occurs by mutation and with separate frequencies for two different antimicrobial drugs, the statistical probability that mutational resistance against both drugs will develop is inversely related to the product of the individual frequencies. Following this rationale, concomitant use of antimicrobial drugs has been most successfully applied in the treatment of infections caused by organisms in which resistance to single drugs develops rapidly. Resistance against multiple drugs that is encoded by plasmids should not be expected to follow this pattern. Data fail to support the popular belief that such a combination of drugs is necessary to avoid the development of resistance when there is evidence that resistance forms in face of this concomitant use. The popularity of combination treatments does not necessarily mean they are more efficacious than single-drug treatments.

It is justifiable and recommended to use more than one antimicrobial drug as initial treatment of life-threatening infections before results of bacterial cultures are known. This treatment should be based on the presumption that most, if not all, organisms that cause the infection will be susceptible to selected drugs and that withholding treatment will most likely result in death of the patient. Because such therapy is initiated before the causative agent and its susceptibility can be ascertained, it is imperative that all appropriate diagnostic samples be obtained before initiation of such treatment. It is important that historical or statistical data be taken into account when selecting the most probable causative agent(s). After the infectious agent and its susceptibility are known, treatment should be appropriately adjusted. Extended antimicrobial spectrum is too often abused as a substitute for collection of diagnostic data, because of the veterinarian's diagnostic insecurity or because of the client's insistence on treatment of the patient.

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45.9 PRINCIPLE 8: APPROPRIATELY ATTEND TO ADVERSE REACTIONS TO DRUGS

Adverse reactions to drugs can develop in patients as a result of drug-related or host-related factors.[10,70,72] Most can be classified as side effects of the drug, hypersensitivity to the drug or its metabolites, interactions of two or more drugs in vivo or incompatibilities in an admixture before administration, alterations of indigenous microflora by the drug, and direct toxic effects of the drug on the host's tissues or as idiosyncratic or idiopathic reactions that defy elucidation and classification.

Adverse effects are not always predictable and may not be side effects of the drug. Side effects of a drug are usually predictable because they result from the pharmacologic activity of the drug. For example, tetracycline may be selected primarily for its activity against a respiratory pathogen in a foal. Discolored dental enamel on permanent teeth may be an acceptable side effect, but altered intestinal microflora and fatal diarrhea are adverse effects.

All types of hypersensitivity reactions can occur in response to drugs. Clinical signs demonstrated by animals with hypersensitivity reactions to drugs are typical of those caused by other allergens. Because the molecular weight of most drugs is too small for the parent drug to serve as an allergen, polymers of the drug or its metabolites chemically combine with amino acids, polypeptides, or carbohydrates to form allergenic complexes. Polymers alone may be large enough to be allergenic. Figures regarding the frequency and type of hypersensitivity reactions in animal patients may not be representative because reports of such reactions are probably not complete. In the United States, adverse reactions to a drug in animal patients should be reported to the manufacturer of the product

and to the FDA-CVM. It is my opinion that the manufacturer should be the first to be contacted. Manufacturers are the primary resource for data related to their products and are usually equipped and staffed to respond to emergency clinical situations that may result from adverse reactions.

Table 45-2 Specific Drugs and Additives That Are Incompatible When Comixed Before Administration[72,73]

Drug	pH	General Comments	Incompatibilities
Aminophylline	8–9	Not stable if pH <8	Cephalothin Na, tetracyclines, polyionic fluid solutions, penicillin G, morphine sulfate, erythromycin gluceptate, methylprednisolone Na succinate, multiple vitamin solutions, thiamine
Ammonium chloride	4.5–6		Chlortetracycline, sulfadiazine, sulfisoxazole
Ampicillin sodium	8.5–10	Do not mix with other medication because of pH changes	
Calcium chloride	6–8.2		Cephalothin Na, chlorpheniramine, hydrocortisone or prednisolone phosphate, kanamycin sulfate, tetracyclines, sodium bicarbonate (concentration dependent)
Calcium disodium EDTA	6.5–8		Dextrose solutions, tetracyclines
Calcium gluconate	6–8.2		Cephalothin Na, tetracyclines, prednisolone phosphate, sodium bicarbonate, phenylbutazone, sulfonamides
Carbenicillin disodium	6–7		Tetracyclines, aminoglycosides
Cephalothin sodium	5.2	pH <4 or >7	
		Not advised; do not mix with other medication	
Cyanocobalamin (vitamin B_{12})	4–5.5		Alkaline solutions, ascorbic acid, vitamin B complex with C, vitamin K, warfarin
Dexamethasone phosphate	6.5–7		Chlorpromazine
Ergonovine maleate	2.7–3.5		Do not mix with other medications
Erythromycin lactobionate	6.5–7.5	Do not combine with mixtures having a final pH <5	Aminophylline, multiple vitamins, cephalothin Na, pentobarbital, sodium iodide, heparin Na, penicillin G, tetracyclines
Furosemide	8.8–9.3		Acid solutions
Gentamicin sulfate		Do not mix with other medications	

Heparin sodium	5–7.5		Sodium bicarbonate, multiple vitamins, tetracyclines, chlorpromazine or promazine, erythromycin lactobionate or gluceptate, gentamicin SO_4, hydrocortisone sodium succinate, methylprednisolone Na succinate, kanamycin SO_4, meperidine HCl, morphine SO_4, penicillin G (K^+), protamine
Hydrocortisone sodium succinate	7–8		Cephalothin Na, tetracyclines, heparin Na, kanamycin SO_4, multiple vitamins, pentobarbital Na, promazine, erythromycin, tylosin
Kanamycin sulfate	4.5		Cephalothin Na, dextrose, heparin Na, hydrocortisone Na succinate, penicillins, sulfadiazine
Levamisole			Neomycin, phenylbutazone, sulfonamides, tetracyclines
Lidocaine	6–7		Alkaline solutions
Magnesium sulfate	5.5–7		$NaHCO_3$, calcium-containing solutions, tetracyclines
Mannitol	4.5–7		Strongly acidic or alkaline solutions, whole blood, penicillin G
Methylprednisolone sodium succinate	7–8		Aminophylline, heparin Na, tetracyclines, vitamin B
Multiple vitamins			Aminophylline, cyanocobalamin, erythromycin lactobionate, heparin Na, hydrocortisone Na succinate, penicillin G, sodium bicarbonate, tetracyclines
Nitrofurantoin sodium	7.7–9.8		Calcium chloride, insulin, phenol, procaine
Oxytocin	2.5–4.5	Do not mix with other medications	
Penicillin G (K^+ or Na^+)	6–7	Significant inactivation if pH <5.5 or >8	Tetracyclines, acetylcysteine multiple vitamins, vitamin B with C, lincomycin, aminophylline, pentobarbital, thiopental, cephalothin Na, erythromycin, sodium bicarbonate, sulfonamides, heparin Na, gentamicin
Pentobarbital sodium	10–10.5		Acidic solutions, cephalothin Na, erythromycin, tetracyclines, sodium bicarbonate, succinylcholine chloride
Ringer's lactate solution	6–7.5		Epinephrine HCl, tetracyclines, sodium bicarbonate, sulfadiazine Na

Sodium bicarbonate	7–8		Calcium-containing solutions, magnesium sulfate, vitamin B with C, tetracyclines, penicillin G (Na or K), thiopental sodium, pentobarbital Na, streptomycin
Sodium iodide	7.5–9		Vitamin B with C
Succinylcholine chloride	3–4.5		Alkaline solutions, pentobarbital Na, thiopental Na
Sulfonamides	Basic		Acidic solutions, ammonium chloride, gentamicin SO_4, kanamycin SO_4, lincomycin HCl, methicillin, penicillin G, tetracyclines, vitamin B with C, calcium gluconate, dextrose, tylosin, procaine
Tetracyclines	1.8–2.8		Aminophylline, penicillins, magnesium or calcium salts, cephalothin Na, erythromycin, lactobionate, heparin Na, hydrocortisone Na succinate, methylprednisolone Na succinate, multiple vitamins, nitrofurantoin, novobiocin, polymyxin B, lactated Ringer's or Ringer's solution, sodium bicarbonate, sulfonamides, barbiturates
Thiamine (vitamin B_1)	3–4	Neutral or alkaline pH causes decomposition	Iron salts
Thiopental sodium	10–11		Acidic solutions, promazine HCl, sodium bicarbonate, succinylcholine Cl, atropine SO_4, penicillins, cephalosporins, tetracyclines, hydrocortisone Na succinate
Ticarcillin disodium	6–8		Aminoglycosides
Tylosin			Hydrocortisone, tetracycline, streptomycin, sulfonamides
Vitamin B complex	10–11		Alkaline solutions, cephalothin Na, cyanocobalamin, erythromycin lactobionate, hydrocortisone Na succinate, tetracyclines
Vitamin B complex with C	3–6.5		Aminophylline, cephalothin Na, erythromycin lactobionate

EDTA, Ethylenediaminetetraacetic acid.

Interactions of drugs in vivo and incompatibilities of drugs in admixtures are possible when more than one drug is used.[72,73] Some interactions and incompatibilities are well known, and references to these data should be available. Pharmacists have considerable reference material to consult, and their input is extremely valuable in these matters. Before drugs are mixed or administered concurrently, interactions and compatibilities should be determined (Table 45-2). In this context, polyionic fluids, vitamins, minerals, and other substances should all be considered as "drugs."

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Alterations in indigenous microflora can reduce the effectiveness of natural host defenses, allow superinfection, or alter normal function of some bodily systems. Fibrinonecrotic colitis in horses that receive clindamycin or lincomycin is an example. This problem is serious enough that the use of these drugs is contraindicated in horses. Tetracyclines (especially doxycycline), macrolides, or potentiated sulfonamides can also alter the intestinal bacterial flora and thereby may precipitate potentially lethal diarrhea.[74,75] These drugs may be drugs of choice for treatment of some patients, and the adverse effects considered in context while a strategy for treatment is formulated.

Toxic effects of antimicrobial drugs may not be predictable. Some drugs such as aminoglycosides or amphotericin B have predictable, dose-related toxicities. The ratio of toxic-to-therapeutic concentrations (therapeutic index) of drugs varies with the drug's properties and host-related factors that alter the patient's susceptibility to toxicity of the drug. If a drug with a low toxic-to-therapeutic ratio is chosen to treat an infection, its toxic and therapeutic effects should be closely monitored. If toxicity of a drug is predictable by its circulating concentrations, total amount of the drug administered, or duration of therapy, careful attention should be afforded these values. The greatest difficulty in predicting either efficacy or toxicity is knowing the minimum concentration of the drug that predictably causes each of these effects in the individual patient. Monitoring circulating concentrations of aminoglycosides is an essential aspect of therapy with these drugs because of their potential for causing toxicity and erratic pharmacokinetics in patients.[69,76] Amphotericin B is also predictably toxic, and careful monitoring of its effects is necessary. Toxicity of drugs that require biotransformation for activation or inactivation can be enhanced or reduced by alterations in biotransformation resulting from disease or concomitantly administered drugs. Chondrotoxic effects of fluoroquinolones in adult and young horses is supported by results of some investigations[25,26] and refuted by others.[27–29] Perhaps an equally important question to be answered while trying to resolve discussions of occurrence of that arthrotoxicity is how well the insulted articular cartilage heals. Just as with disease, drug-injured tissue may regenerate and regain healthy function resulting in indistinguishable effects at a later date.

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Frequently the true pathogenesis of an adverse effect is not known. It may not be clearly related to the drug or may not have been observed previously. Because drug-related reactions in animals are iatrogenic, reasonable suspicion that a reaction could be drug related should be maintained until proven otherwise. Observations and thoroughness of investigation by the attending clinician remain the best means of establishing the cause-effect relationship of drug-induced reactions. That diagnosis is often arrived at by a process of elimination of other potential causes.

45.10 PROPHYLACTIC OR METAPHYLACTIC USE OF ANTIMICROBIAL DRUGS

Gordon W. Brumbaugh

The medical definition of *prophylaxis* is the prevention of disease.[77] The word is derived from the Greek prefix, *pro,* which signifies before or in front of, and the word *phylaxis,* which means a guarding or protection from infection. Prophylactic use of antimicrobial drugs implies that the medication is administered before exposure to an infectious organism in order to prevent infection. The term *metaphylaxis* is also of Greek origin, with the prefix *meta* meaning after, beyond, or over. The prefix indicates change, transformation, exchange, after, or next. Metaphylactic use of antimicrobial drugs implies timely administration of the medication after exposure to an infectious organism, during the transformation or development of clinical signs of the disease, before clinical disease is apparent. In previous editions of this text, no distinction between prophylactic use and metaphylactic use of antimicrobial drugs was made. That has been corrected in this edition.

Despite apparently widespread administration of antimicrobial drugs to prevent disease, prophylactic use of antimicrobial drugs remains controversial and of unproven value in many instances.[77a] Far too frequently veterinarians and lay personnel use antimicrobial drugs prophylactically because of concern over diagnostic accuracy. Although indiscriminate use of antimicrobial drugs to prevent disease should be condemned, prophylaxis can be useful in certain circumstances.[78] Unfortunately these circumstances have not been well defined in veterinary medicine, partly because of difficulties in assessing response to microbial prophylaxis.[79] If a beneficial effect results from prophylactic use of drugs, the therapist is encouraged to repeat their administration when later presented with a similar situation. For example, antimicrobial drugs may be administered to horses with viral upper respiratory disease to prevent secondary bacterial pneumonia. If the horse does not develop pneumonia, it is assumed that the antimicrobial drug prevented bacterial pneumonia. Therefore the next horse that demonstrates signs of upper respiratory disease will receive antimicrobial drugs prophylactically. This is not sound reasoning, nor is it justification for prophylactic use of antimicrobial drugs. That horse may not have developed pneumonia if the antimicrobial drugs had been withheld. Seldom is a determination made about whether a result is "because of" or "in spite of" the prophylactic use of medication.

In some instances, antimicrobial drugs are used prophylactically with guidance by clinical impressions. Unfortunately, objective data to support such uses are not always available. Controlled, blinded, prospective clinical investigations are of paramount importance for obtaining that information.[79] Proper performance of such studies can be difficult. The multitude of factors involved with such studies (e.g., large numbers of patients, criteria for selection of patients, confirmatory diagnostic procedures, choice of "appropriate controls," variables to be evaluated, dosage regimens, and ancillary measures to be used) result in a complexity that discourages most veterinarians who initially desire to embark on such studies. An additional factor that complicates studies of the efficacy of antimicrobial drugs perioperatively is that historical incidences of infection may not be reliable controls because surgical techniques vary among surgeons and have changed because of advances in surgical materials and procedures. Therefore prophylactic use of antimicrobial drugs in many situations remains a matter of opinion, risk, and concern based on conditions pertaining to the individual patient rather than a matter of fact that is universally applicable. Consequently, recommendations for prophylactic use of antimicrobial drugs should not be dogmatic.

However, principles for prophylactic use of antimicrobial drugs in each situation are the same. Antimicrobial drugs are occasionally used in animals to prevent coccidiosis, clostridial infection of wounds, bacterial pneumonia, and bacterial infections after orthopedic or intraabdominal surgical procedures. Morbidity and mortality associated with coccidiosis was reduced in susceptible calves by preexposure administration of monensin.[80] The incidence of clostridial infections in untreated wounds is not accurately known. Specific immunity in the host, complicating factors, use of biologics, and ancillary procedures influence the incidence and severity of such infections. Because clostridial organisms produce severe and often lethal infections, the risk of fatal vegetative infection warrants the prophylactic use of antimicrobial drugs in high-risk patients. However, antimicrobial drugs should not be considered a substitute for active immunization provided by biologic products or for proper local treatment of the wound.

Antimicrobial drugs used prophylactically are perhaps used most to prevent or control bacterial pneumonia. It has been stated that viral respiratory diseases predispose the respiratory tract to secondary bacterial infections. Concerns that viral infections predispose the entire respiratory tract to bacterial infection are based on the fact that the former can destroy ciliated epithelium and inhibit mucociliary clearance mechanisms, reduce production of surfactant, promote virulence of bacteria, and inhibit phagocytic activity against some bacteria.[81–84] But the

efficacy of antibacterial mechanisms in preventing bacterial superinfections appears to depend on the bacteria and the virus(es) involved.

All viral pneumonias do not result in bacterial superinfections; conditions must be appropriate for that to occur.[82] One investigator proposed that the secondary bacterial infection of the upper respiratory tract was probably "beneficial in the total infection experience" of the young horse entering training or racing.[85] In spite of these data the true incidence and risk-related factors surrounding secondary bacterial infections are not known. Several controlled prospective studies have evaluated metaphylactic use of antimicrobial drugs against respiratory disease in cattle. Similar, but limited, studies performed with horses have shown that some transported horses may benefit from prophylactic use of antimicrobial drugs.[86]

Control of bovine respiratory disease complex (BRDC) with antimicrobial drugs in cattle at high risk for developing the disease has been studied intensely for several years.[87–98] Nevertheless, effects of metaphylactic use of antimicrobial drugs in BRDC and recommendations for such use are far from universal. Many factors contribute to the incidence of BRDC: vaccination history of the animals, environment, diet, duration of shipment, time of initial medication after arrival, number of calves per group, commingling of animals from different sites of origin, condition of the calves, method of administration of medication (by injection, in water, or in feed), duration of administration, and sequence of administration if more than one antimicrobial drug was used.

Many factors can complicate assessment of metaphylactic use of antimicrobial drugs against BRDC, but efficacy of control of BRDC can be evaluated by several variables that include morbidity, mortality, epidemiologic pattern of morbidity and mortality, days of treatment, amount of medical attention required (labor and medication), weight gain, relapses, and/or economic return.[87,89,91,93–96,99]

Metaphylactic use of antimicrobial drugs can be beneficial, but it is unrealistic to expect total elimination of disease. Control or management of a disease and its effects would be a more realistic expectation. The effect desired from prophylactic or metaphylactic use of drugs must be specifically understood. Reduced morbidity or mortality, reduced severity of clinical signs, reduced duration of therapy, improved growth rate, improved feed efficiency, and improved or maintained production may be benefits of metaphylactic use of antimicrobial drugs, but false confidence in prevention of disease should be avoided. Volatility of costs associated with production and the market probably influences profit more than does the cost of metaphylactic use of antimicrobial drugs.

Ambiguity of antimicrobial prophylaxis or metaphylaxis in equine medicine is supported in part by a review of reports of experimentally induced as well as naturally occurring equine rhinopneumonitis and equine influenza. Equine herpesvirus 1 produces viral bronchopneumonia[100] and interstitial pneumonia.[101] Serous to mucopurulent rhinitis was observed commonly and was similar with equine influenza.[81,85,100–106] Secondary bacterial infections were confined to the upper respiratory tract (i.e., rhinitis, lymphadenopathy) and did not include bacterial pneumonia.[99,102,104,105]

Perioperative use of antimicrobial drugs prophylactically is a common practice. In human patients, such use has proven to be of benefit in prosthetic cardiac valvular operations, gynecologic surgical procedures, and gastrointestinal operations.[79] The drugs were administered orally, systemically, or topically as indicated by the procedure. A study with 122 dogs and seven cats undergoing elective, clean surgical procedures revealed no significant difference in incidence of infection between a group that received ampicillin and a group that received a placebo.[107] Similar studies with horses are not known to the author at this time. Principles for prophylactic use of antimicrobial drugs perioperatively are similar to those outlined here. Principles for timely metaphylactic use of antimicrobial drugs have been proposed and are similar to those listed for prophylaxis.[87]

When antimicrobial drugs are used prophylactically, several principles should be followed.[77a–79,108–111]

1 The relative risk of infection must be sufficient to warrant the use of antimicrobial drugs prophylactically. Risks associated with the prophylactic medication must be less than risk of development of the disease and consequences of that disease. Risk of infection is related to virulence of the organism, amount of exposure (size of inoculum and duration), and the host's defense status. All these factors should be considered before antimicrobial drugs are used prophylactically. “Sufficient risk” is difficult to clarify because of numerous factors used to assess risk. Mortality or morbidity, severity of the disease, duration of the disease, or the effects of the disease on production or performance may be considered unacceptable in some situations if prophylaxis is not implemented. However, risks and costs of the prophylactic medication must also be considered. There are few epidemiologic data from which to accurately predict these risk factors; therefore they must be assessed on an individual basis. The primary potential advantage of prophylactic use of antimicrobial drugs is prevention of infection, but other advantages are also possible and include decreased morbidity and/or mortality, decreased duration of treatment if infection subsequently occurs, decreased severity of disease, shortened convalescence, improved or maintained production, and decreased cost of overall effects of disease. Potential disadvantages of prophylactic use of antimicrobial drugs include alteration of resident bacterial flora, development of resistant organisms, superinfection, delayed onset of infection, relaxed attention to diagnostic details, adverse reactions to the drug(s), and increased overall cost of therapy.

2 The organism(s) that is likely to cause infection and its antimicrobial susceptibility should be known or accurately predicted. Just as biologic products are used prophylactically to stimulate specific active or passive immunity, prophylactic use of antimicrobial drugs should be directed at a specific pathogen rather than at all possible organisms. It is difficult to anticipate all possible infectious organisms that are likely to be encountered, but agents that cause some diseases are reasonably predictable. It is preposterous to expect sterilization of the site of potential infection. The antimicrobial susceptibility of the pathogen should be consistently predictable on the basis of historical data. Clostridial and streptococcal organisms are not as predictably susceptible to penicillin as they were in years past. The susceptibility of gram-negative, aerobic organisms is not reliably predictable, and resistance develops frequently when these bacteria are continuously or intermittently exposed to antimicrobial drugs. Anaerobes are predictably susceptible to penicillin G, chloramphenicol, metronidazole, or lincosamides.[112] Lincosamides should not be used systemically in horses; chloramphenicol and metronidazole are prohibited in the United States for administration to animals that are used for human consumption. *B. fragilis* produces β-lactamase, rendering 1518
those organisms resistant to penicillins. Aminopenicillins and cephalosporins that are classified as greater 1519
than first-generation have less predictable activity against anaerobes than does penicillin G.[113]

3 For effective prophylaxis the drug must be administered and must distribute to the site of potential infection before contamination or the onset of infection and should at least reach inhibitory concentrations. For effective metaphylaxis, the drug should be administered after exposure to the organism, with sufficient time for the medication to act on those organisms before clinical signs develop. In those clinical situations a rational basis for use of antimicrobials is formed by the attending veterinarian, who is well acquainted with the production system, the profile of the animals, and the diseases present or likely to develop that threaten the health of the animal(s). After infection is established and clinical signs are apparent, the use of the antimicrobial drug becomes therapeutic, not prophylactic or metaphylactic. Therefore the time of exposure or contamination with a pathogen, incubation time of the pathogen, and distribution characteristics of the selected drug should be considered in order to administer an antimicrobial drug prophylactically or metaphylactically and in a timely manner.

4 As much as possible, drugs used prophylactically should not be those that would be used therapeutically if an infection develops. If infection develops during the prophylactic regimen, an alternative treatment must be formulated, because if the disease is not prevented by an appropriate dosage regimen with the drug, it will not be cured by the drug. If that infection is caused by induced resistance to the selected drug, therapy could be compromised if that drug is the therapeutic drug of choice. The population of resistant organisms poses risks of increased incidence of refractory infections in other animals as well.

5 The duration of antimicrobial prophylaxis should be as abbreviated as possible (e.g., 3 to 6 hours postoperatively). Generally, little benefit can be gained beyond 24 to 36 hours postoperatively. If exposure to infectious organisms is brief and host defenses are functional, prolonged administration of the drug is not necessary. However, there are a few indications for prolonged prophylactic therapy. If host defenses are temporarily deficient or if exposure is prolonged, administration may need to be extended. The duration of administration should be directed by the same factors that direct the duration of therapeutic use of drugs (i.e., activity of the host's defenses, ability of the organism to resist those defenses, mechanisms by which the organism develops resistance to the drug(s), location of the infection, and primary activity of the drug against the organism).

6 No drug can be used without risk of adverse reactions, but antimicrobial drugs used prophylactically should present minimal risk of adverse effects. Deleterious reactions may occur when drugs are administered. It is better to abstain from using drugs than to use them inappropriately.

7 Theoretically the selected dosage regimen should provide bactericidal rather than bacteriostatic concentrations of the drug at the site of infection. It would be desirable to kill the pathogen rather than to inhibit its growth; however, no data clearly show this is necessary in clinical situations.[56] Host defenses, subtherapeutic concentrations of the drug, and postantibiotic effects, as well as ancillary management, should be used to enhance the efficacy of drugs in vivo.

Decisions about prophylactic use of antimicrobial drugs are not easily made and are usually based on logic and analogous situations.[78] Classification of clinical circumstances and diseases of human patients has been proposed as an aid to such decisions for that species. That classification considers the risk of developing infection based on function of the patient's natural defenses, duration of exposure to pathogens, and potential for infection by either one or multiple organisms. Direct application of that classification system to animal patients may be difficult.

Assessment of some defense mechanisms in domestic animal patients is complicated and beyond routine use in many clinical situations. Some pathogens are noted for their ability to temporarily compromise the host's defenses, yet effects of others are unknown. Methods that are applicable (e.g., determination of concentrations of immunoglobulins, numbers and function of phagocytes and of lymphocytes) should be used when indicated and when appropriate medical management is determined. However, numbers of cells do not equate with function, and concentrations of immunoglobulins do not equate with specific activity. Animal patients must convalesce in an environment that is less hygienic than that of human patients. Animals are constantly exposed to many primary and opportunistic pathogens (bacteria, viruses, fungi, parasites) and intermittently exposed to individual pathogens that cause diseases of epizootic proportions. Therefore criteria for classification by risk of infection and indications for prophylactic use of antimicrobial drugs in animals need to be developed from epidemiologic studies of diseases of animals and controlled clinical investigations. At this time, that information is sadly lacking.

Except in specific instances with specific goals in mind, the use of antimicrobial agents to prevent infection has not been as valuable as the therapeutic use of antimicrobials. Prophylactic use of antimicrobial drugs must be

tailored to the specific needs of each individual patient, as determined by the attending veterinarian and tempered by application of the principles outlined here.

45.11 EXTRALABEL USE OF MEDICATIONS IN FOOD ANIMALS

Michael Payne

In 1994 the Animal Medicinal Drug Use Clarification Act (AMDUCA) was signed into law, amending the Food, Drug, and Cosmetic Act and legalizing most instances of extralabel use of drugs (ELUD) by veterinarians.[114] For food animal practitioners, with this privilege comes the weighty responsibility of protecting the health of consumers of animal products. Veterinarians must meet very specific conditions before they may legally use or prescribe drugs in an extralabel fashion. Extralabel drug uses include prescribing or administering a human or veterinary drug at a higher dose, frequency, or duration, by a different route of administration, in a different species, or for a different indication than as described on the product's label. ELUD is limited to cases in which the health of the animal is threatened or when suffering or death may result from a lack of treatment. ELUD may not be used to enhance production or for reproductive cycle manipulation in normal animals. ELUD may be considered in food-producing animals only when no approved drug is available that contains the same active ingredient in the required dose, form, and concentration or when the veterinarian finds that there is no approved drug that is clinically effective for the intended use. Extralabel drug use in or on animal feed is also expressly prohibited. Veterinarians' obligations regarding extralabel use are listed in Box 45-5. Veterinarians violating state or federal laws regulating the transport, sale, or use of drugs may face a variety of sanctions including warning letters, fines, temporary or permanent revocation of license, and incarceration.

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45.11.1 Box 45-5 Conditions Necessary for Extralabel Use of Drugs

1. Extralabel use of drugs (ELUD) is permitted only by or on the order of a veterinarian.
2. The veterinarian judges on-label treatments to be unavailable or ineffective.
3. ELUD uses only U.S. Food and Drug Administration (FDA)–approved animal and human drugs, not drugs imported from foreign countries or compounded from bulk sources.
4. A valid veterinarian-client-patient relationship (VCPR) exists in which the veterinarian:
   - oversees medical treatment decisions on the farm
   - is familiar with animal care through appropriate and timely visits
   - has sufficient knowledge to initiate a diagnosis
   - is available for follow-up care as needed
5. ELUD is for therapeutic or humane purposes only, not to increase production or manipulate reproductive cycles in normal animals.
6. ELUD applies only to administration to individual animals and in water, not in feed.
7. Animal identification and treatment records are sufficient to identify treated animals and their treatment history and are maintained for 2 years.

8 The veterinarian establishes an extended drug withdrawal period protective of human health supported by scientific evidence. ELUD resulting in violative or dangerous food residues is not permitted.

9 Drug labels list the name and address of the prescribing veterinarian, animals to be treated, and the drug name, disease indication, dose, frequency, duration, cautions, and withdrawal periods associated with treatment.

10 Certain extralabel uses specifically prohibited by the FDA are not used (Box 45-6).

45.12 DRUGS PROHIBITED FROM EXTRALABEL USE IN FOOD ANIMALS

Certain drugs may not be prescribed or used even under the auspices of AMDUCA.[115] Under statutory authority provided in AMDUCA, the FDA's Center for Veterinary Medicine (CVM) has prohibited approximately a dozen drugs or drug classes, making their extralabel use in food animals illegal. Other compounds not specifically listed in AMDUCA are prohibited by virtue of the fact that no approved animal or human products are commercially available. Lastly, extralabel use of treatments is also regulated by the Pasteurized Milk Ordinance (PMO). The extralabel use in food animals of the compounds listed in Box 45-6 represents one of the FDA's highest priorities for regulatory attention.

45.12.1 Diethylstilbestrol

From the 1940s to the 1970s U.S. physicians prescribed diethylstilbestrol (DES, a potent nonsteroidal synthetic estrogen) to pregnant women to prevent miscarriage and other reproductive diseases. In 1971 a link between in utero exposure to DES and a rare vaginal cancer (clear cell adenocarcinoma) was established. In the same year the FDA published an alert advising doctors against the use of DES during pregnancy. The U.S. Department of Agriculture (USDA) banned the use of DES in food animals in 1979.

45.12.1.1 Box 45-6 Drugs or Drug Classes Prohibited from Extralabel Use of Drugs*

Diethylstilbestrol (DES)

Chloramphenicol

Nitroimidazoles (including dimetridazole, metronidazole, and ipronidazole)

Sulfonamide (other than sulfadimethoxine) in adult dairy cattle†

Clenbuterol

Fluoroquinolones (e.g., enrofloxacin and danofloxacin)

Glycopeptides (e.g., vancomycin)

Nitrofurans (including nitrofurazone, furazolidone; topical use prohibited as well)

Phenylbutazone in adult dairy cattle*

Adamantidine and neuraminidase inhibitors in poultry

* Extralabel use of some drugs or drug classes (not specifically addressed in the Animal Medicinal Drug Use Clarification Act) are prohibited because these drugs are not available as approved animal or human products, by U.S. Food and Drug Administration (FDA) policy or in the Pasteurized Milk Ordinance (see text).

† Defined by FDA as dairy cattle (lactating or dry) older than 20 months of age.

45.12.2 Chloramphenicol

An estimated one in 10,000 to 50,000 people exposed to chloramphenicol will develop a non—dose-related aplastic anemia. Because of concerns that this idiosyncratic and frequently fatal complication could be triggered by residues, chloramphenicol use in food animals was prohibited in 1984. The prohibition extends to all formulations of chloramphenicol including ophthalmic ointments. Florfenicol, a synthetic member of the chloramphenicol family, lacks the p-NO2 group thought to be responsible for inducing the aplastic anemia. Florfenicol may be used extralabel in food-producing species.

45.12.3 Nitroimidazoles

Historically, dimetridazole and ipronidazole have been approved for the treatment of histomoniasis (infectious enterohepatitis, blackhead) in turkeys. Ipronidazole and the human drug metronidazole have been used off-label to eliminate the carrier state of trichomoniasis in bulls. Laboratory studies of members of this drug class demonstrated mutagenicity and carcinogenicity, leading to the prohibition of their use in food animals. Because there are no approved veterinary nitroimidazole labels, the use of any member of this drug class in food animals is illegal.

45.12.4 Sulfonamide in Adult Dairy Cattle

The observed carcinogenicity of sulfonamides in laboratory animals, coupled with frequent finding of sulfonamide residues in milk, led to the prohibition of extralabel use of these compounds in adult dairy cattle. The FDA defines a lactating cow as any dairy cow (milking or dry) older than 20 months of age. Only one sulfonamide has a label for dairy cattle, sulfadimethoxine (SDM). The use of any sulfonamide other than SDM in adult dairy cattle is illegal. In addition, extralabel use of SDM in lactating dairy cattle is prohibited. This would include use of a higher dose of SDM or using slow-release formulation SDM boluses.

45.12.5 Nitrofurans

In the past, nitrofurazone and furazolidone were approved for a variety of protozoal and bacterial infections in poultry and swine. Topical formulations (sprays and "puffer" products) have also historically been marketed for wounds and ocular infections in livestock ("pinkeye"). Based on laboratory evidence of carcinogenicity and the absence of a reliable detection method, the FDA withdrew approval for systemic animal nitrofuran products in 1991 and prohibited all extralabel treatment (including topical use) in 2002. Because nitrofurans have no approved food animal uses, the use of any member of this drug class in food animals is illegal.

45.12.6 Clenbuterol

Marketed in the United States as an equine bronchodilator, this synthetic sympathomimetic has been used illicitly to increase weight gain and lean body mass in food animals, particularly show animals. Because muscle depletion and fat redeposition commences after drug withdrawal, producers may be tempted to market animals with little or no withdrawal interval. Cooking temperature only minimally denatures the compound, and toxicity from residues has resulted in hundreds of emergency hospitalizations in European consumers.

45.12.7 Fluoroquinolones

Uncertainty exists related to the magnitude and significance of human pathogen resistance resulting from antibiotic use in animals. Fluoroquinolones are mainstay treatments of antibiotic-resistant *Salmonella* and anthrax infections in humans. Concern that fluoroquinolone use in food animals was promoting human pathogen resistance prompted CVM in 1997 to prohibit extralabel use of these compounds. Any deviation from a fluoroquinolone product label (altering species use, dosage, route of administration, or disease indication) is illegal. In the case of the approved beef cattle formulation of enrofloxacin and danofloxacin, this prohibition extends to use in all non—beef-production animals including lactating and nonlactating dairy cows, heifer replacements, bulls, and veal calves.

45.12.8 Glycopeptides

Vancomycin, the only glycopeptide antibiotic available in the United States, is often the therapy of last resort for methicillin-resistant *Staphylococcus aureus* (MRSA) infections in humans. Demonstration of vancomycin-resistant *Enterococcus* in the feces of poultry and swine fed the glycopeptide avoparcin led CVM in 1997 to prohibit extralabel use of glycopeptides in food animals.

45.12.9 Phenylbutazone in Adult Dairy Cattle

The use of phenylbutazone, a nonsteroidal antiinflammatory agent in humans, has been associated with a variety of adverse drug reactions including fatal blood dyscrasias. After USDA reports of a high incidence of phenylbutazone tissue residues in cull dairy cows, CVM prohibited its use in female dairy cattle older then 20 months of age. Antiinflammatory therapy for lactating dairy cattle is available as flunixin meglumine. Flunixin should be used only on-label (intravenously) because intramuscular or intravenous administration can greatly extend withdrawal times.[116]

45.12.10 Antiviral Drugs in Poultry

Concern exists that use of antiviral drugs in poultry could promote drug resistance in zoonotic pathogens, particularly avian influenza H5N1 (“bird flu”). These concerns led CVM in 2006 to prohibit extralabel use of two drug classes used in treating human influenza. Adamantidine and neuraminidase inhibitors may not be used in chickens, turkeys, and ducks.

45.12.11 Dipyrone

Aside from compounds specifically prohibited through AMDUCA, there are several compounds that CVM has reminded veterinarians cannot be legally obtained as finished animal or human products and therefore have no legal extralabel uses.

Dipyrone, used historically as an antipyretic and antiinflammatory, has been associated with teratogenicity and agranulocytosis in humans and cannot be used in food animals.

45.12.12 Estradiol Cypionate

Before 2003 estradiol cypionate (ECP, a synthetic estrogen) was commercially marketed as reproductive therapy in food animals. ECP had not undergone a formal approval process, however, and discretionary marketing was discontinued for lack of food safety and efficacy data. Use in or compounding of ECP for food animals remains illegal.

45.12.13 Hormone Implants in Veal Calves

Although growth-promoting hormone implants have been marketed for ruminating cattle, these products never underwent regulatory approval for nonruminating veal calves. Concern existed in CVM that nonruminating calves may eliminate the hormone contained in the implants differently then ruminants. In 2005 a new warning statement was added to the label of all growth-promoting hormone implants reminding producers and veterinarians that their use in veal calves is illegal.

45.12.14 Dimethyl Sulfoxide and Colloidal Silver

Besides AMDUCA, the Grade A PMO also directs how drugs will be used and stored on dairy farms. Dimethyl sulfoxide (DMSO) and colloidal silver may not be used in or on dairy animals and if found during a dairy inspection can result in “debits.”

45.13 TREATMENT OF COMPANION OR PACK ANIMALS WITH PROHIBITED SUBSTANCES

The prohibitions listed previously pertain to food-producing animals only and not companion species such as dogs and cats. Veterinarians occasionally treat companion animals belonging to a food-producing species (horses, llamas, pygmy goats, pot-bellied pigs). As long as these animals are never offered for slaughter, CVM does not normally consider these to be food animals. Practitioners who have used a prohibited substance in a companion or pack animal that subsequently enters the food supply are subject to enforcement actions under the Food Drug and

Cosmetic Act. In choosing to use a prohibited drug in a companion or pack animal, the practitioner is accepting a certain amount of liability because the ultimate fate of such treated animals is often beyond their control. Practitioners may choose to have owners sign an agreement (entered into the medical record) not to introduce the animal into the human chain.

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45.14 EXTRALABEL USE OF MEDICATED FEEDS IN MINOR SPECIES

AMDUCA also prohibits the extralabel use of medications in feed. Generated by concerns of antibiotic resistance, AMDUCA's Section 530.11 specifically prohibits the “extra-label use of an approved new animal drug or human drug in or on an animal feed.” As a matter of enforcement discretion, CVM generally has not objected to mixing a drug with an individual animal's feed, but extralabel mass medication in feed is prohibited “without limitation or exception.”

Veterinarians may, however, be called on to treat minor food animal species such as farmed exotic ruminants, fish, or game birds. CVM has found that for many of these species there exist very few approved drugs. In addition CVM recognizes that some minor food animal species (such as fish and game birds) cannot be practically medicated in any way other than through the use of medicated feeds. In such situations, a veterinarian may determine that extralabel use of medicated feeds (approved for use in other species) can prevent suffering and death in these minor species.

Although AMDUCA prohibits ELUD in feed, in the previously described circumstances CVM “ordinarily will not consider regulatory action” against the veterinarian or animal producer provided that certain criteria listed in Box 45-7 are met.[117] The CVM policy being implemented in these cases is akin to that of extralabel drug use by veterinarians before the 1994 passing of AMDUCA. The drug use is still illegal, but CVM will apply regulatory discretion relative to taking enforcement action.

45.14.1 Box 45-7 Conditions Necessary for Extralabel Use of Medicated Feed in Minor Species

1. Extralabel use of medicated feed is only for treatment of minor species, defined by exclusion as animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats.
2. Extralabel use of medicated feed is limited to farmed or confined minor species but not unconfined wildlife.
3. Extralabel use of medicated feed is limited to situations where the health of an animal is threatened and suffering or death may result from failure to treat.
4. There is no alternative therapeutic dosage form (besides feed) that can be practically used under legal extralabel use.
5. Only feeds formulated and labeled for use in a major species animal are used.
6. Extralabel use of medicated feed in aquaculture is limited to medicated feed products approved for use in aquatic species.

7 The medicated feed is used within 3 months of a veterinarian's written recommendation. Recommendations, feed labels, and invoices are kept for at least 1 year. Adverse reactions are reported to the U.S. Food and Drug Administration within 10 days.

8 All other Animal Medicinal Drug Use Clarification Act requirements are complied with, including a valid veterinarian-client-patient relationship, lack of label alternatives, treatment records, animal identification, and extended withdrawal times (see Box 45-6).

9 The medicated feed is used in accordance with federal, state, and local environmental regulations and approval. This is particularly important for aquaculture uses.

10 The producer has followed worker safety provisions in the approved product labeling.

A critical aspect of CVM's regulatory discretion in this practice is that labeled treatment alternatives are not available. The best resource to aid practitioners in determining what treatments are approved for minor food animal species is the Minor Species Drug Approval site (www.nrsp-7.org).

45.15 COMPOUNDING IN VETERINARY PRACTICE

Compounding is defined as a manipulation to produce a dosage form of a drug other than that provided for in the labeling, such as reconstitution. CVM recognizes the need for compounding within certain areas of veterinary practice, such as mixing or dilution. Because of the absence of safety, efficacy, and food safety data for compounded drugs, potential exists for adverse reactions in treated animals or consumers of their products. Under AMDUCA, it is legal for veterinarians (or pharmacists on the order of a veterinarian) to compound from U.S.-approved animal and human drugs if the conditions listed in Box 45-8 are met.[114,118]

45.16 ANTIDOTES FOR FOOD ANIMALS

For both regulatory and economic reasons, there are relatively few antidotes available to treat cases of toxicity in food-producing species. In most circumstances practitioners treating toxicity in food animals are compelled to use products in an extralabel manner or to compound antidotes from bulk sources.[119] From a regulatory standpoint veterinary antidotes can be placed in one of three categories, discussed in the following paragraphs.

45.16.1 Unapproved Commercially Marketed Veterinary Antidotes

CVM has applied regulatory discretion to allow commercial manufacture and marketing of several compounds that can be used as antidotes, even through they have never completed formal regulatory approval. These are atropine sulfate, epinephrine, and vitamin K.

45.16.2 Antidotes Labeled for Humans Only

There are additional human-label antidotes that can be used off-label under AMDUCA. These include pralidoxime chloride (2-PAM) and dimercaprol (British anti-lewisite or BAL).

45.16.2.1

Box 45-8 Requirements for Compounding in Veterinary Practice

1 No approved animal or human drug can be used in its available dosage form and concentration.

2 Only approved animal or human drugs are used in the compounding, specifically not foreign or bulk drugs.

3 Compounding is performed by a licensed pharmacist or veterinarian in compliance with state pharmacy laws.

4 Adequate procedures are in place to ensure the safety and effectiveness of the product.

5 Withdrawal times are set by the veterinarian and not the pharmacist.

6 The scale of the compounding operation is commensurate with the established practice needs.

7 All other Animal Medicinal Drug Use Clarification Act requirements are met (see Box 45-5).

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45.16.3

Antidotes Compounded from Bulk Drug

Several chemicals commonly recommended as food animal antidotes are available only through compounding from bulk drug. As described in the previous section, compounding veterinary medications from bulk drugs is illegal. However, analogous to its policy concerning ELUD in feed for minor species, CVM will not normally consider regulatory action against veterinarians compounding certain antidotes from bulk sources if certain conditions are met, essentially the same as those listed in Boxes 45-5 and 45-8. CVM has listed nine chemical antidotes against which the FDA and CVM would presently not ordinarily object. These include ammonium molybdate, ammonium, tetrathiomolybdate, ferric ferrocyanide, methylene blue, picrotoxin, pilocarpine, sodium nitrite, sodium thiosulfate, and tannic acid.[117,118] This list should not be construed as containing the only drugs for which the FDA would extend regulatory discretion for compounding, and inquiries about additional compounds can directed to the FDA/CVM, Division of Compliance, 301-827-1168. It is critical that veterinarians recognize that in toxicity cases withdrawal periods will need to be established not only for the antidotes but the toxicants as well. For this reason practitioners are advised to consult the Food Animal Residue Avoidance Databank (FARAD) when dealing with cases of toxicosis in food animals.

45.17

FOOD ANIMAL RESIDUE AVOIDANCE DATABANK SUPPORT FOR VETERINARIANS

Consistent regulatory requirements for ELUD (using approved drugs, feed, or compounding) are that approved, effective veterinary drugs are not available and that the attending veterinarian prescribe scientifically valid withdrawal periods before marketing of milk, meat, eggs, or other edible products. Commonly the most efficient way for a food animal practitioner to meet these requirements is to consult FARAD. Veterinarians, producers, students, or regulatory personnel may obtain free consultation with specialists by contacting 1-888-US-FARAD or accessing the FARAD website at www.farad.org. FARAD maintains a database of all food animal products approved in the United States and more then 9000 pharmacokinetic citations describing depletion of more then 2000 chemicals in various species. The FARAD website contains a database of approved food animal drugs searchable by drug, trade name, and species as well as downloadable copies of past published summary recommendations.

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46 Chapter 46 Biosecurity and Infection Control for Large Animal Practices

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Infection control, biosecurity, biocontainment, and biosafety are essential functions at all health care operations, including veterinary practices.* All veterinarians at some level recognize and act to prevent adverse outcomes in patients. However, as major outbreaks of nosocomial infections at veterinary hospitals have become more publicized[1–11] it has become increasingly apparent that coordinated infection control practices are a critical component of delivering high-quality care at veterinary facilities, especially those with large case loads and those that specialize in intensive care of patients. The standard of veterinary care is changing such that sporadic occurrences and outbreaks of nosocomial infections may no longer be interpreted as unavoidable accidents if coordinated measures are not routinely used to minimize their likelihood. Our understanding about infection control issues in veterinary medicine has also advanced significantly during the past decade. What may have passed as sufficient for infection control in veterinary practices 10 or 20 years ago may not be sufficient today. It is also important to realize the important part that infection control and biosecurity must play in ambulatory practices and on our clients' premises. Inherently, healthy animals with lower contagious disease risks represent a smaller proportion of hospital populations than they do among populations in their home environments. However, veterinarians are obviously called on to contact those animals most likely to be shedding contagious pathogens regardless of whether this is in hospitals or in the field. In addition, we are aware of several examples in which patients discharged from hospitals were the likely source of viral and bacterial infections in animals in their home environments. Therefore it is also true that the need to apply sound biosecurity and infection control practices extends well beyond the walls of veterinary hospitals. Although the discussions in this chapter are mostly framed in the context of hospital settings, the concepts and issues apply much more broadly to ambulatory practices and animals' home premises.

46.1 HOW MUCH IS ENOUGH? HOW MUCH IS TOO LITTLE?

Just as nobody can tell someone how much health insurance or how much fire insurance for a home is enough, it is not possible to define a correct or best level of risk aversion, and there are no absolute determinants of whether one specific biosecurity action is necessary or superfluous. Although it may not be possible to judge whether a veterinary practice is employing too much biosecurity, a more critical concern must be whether there is too little effort being expended in infection control. Exposures to contagious disease threats, nosocomial infections in patients, and zoonotic infections in care providers are all undeniable risks in every veterinary practice. Because veterinarians have an ethical and legal obligation to take reasonable protective actions to prevent their patients and employees from foreseeable harm associated with their actions (and inactions), it is therefore undeniably possible to not pay enough attention to infection control.

Recognition of these risks undoubtedly gives reason for pause, but a better motivation regarding infection control should be to provide the best veterinary care possible (within the scope of a veterinary practice's specialization). In order to create an environment in which patient care can be optimized, it is incumbent on veterinarians to actively manage the risk of nosocomial infections in their patients. Achieving excellence in patient care and helping clients are undoubtedly among the highest priorities for all veterinary practices. However, the occurrence of nosocomial infections in our patients is an ever-present hazard that interferes with our ability to deliver optimal patient care. *Good infection control practices are not the only feature defining excellence in veterinary care, but it is impossible to achieve excellent patient care without employing logical infection control procedures.* The

implications of suboptimal infection control practices may not always be readily apparent, but both sporadic infections and outbreaks can have a significant effect on patient morbidity, patient mortality, hospital economics, personnel health, personnel morale, and facility reputation. There are also potential liability implications for nosocomial infections that occur in the absence of a proper infection control program.

Although nosocomial infections are an undeniable hazard associated with caring for patients, and although it is possible to reduce the risk of infections through a variety of prevention strategies, it is important to note that not all nosocomial infections are preventable using practical and cost-effective control programs. For such programs to be most successful, it is important that over time administrators and personnel responsible for infection control programs strive to better understand and target prevention efforts at the preventable fraction of all nosocomial infections.

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* Throughout this chapter the terms *infection control* and *biosecurity* are used interchangeably to encompass all practices related to the prevention of introduction and spread of infectious diseases in populations of animals or their human caregivers. Some authors differentiate activities by using the term *biosecurity* to specifically refer to issues related to disease introduction and differentiate this from *biocontainment,* which may focus more on control of the spread of agents after introduction. In addition, the term *biosafety* is sometimes used to specifically relate to matters pertaining to human health.

46.2 PRINCIPLES OF INFECTION CONTROL

In general, all comprehensive infection control programs center on three major activities: decreasing the likelihood of exposing patients to infectious agents, maximizing participation of personnel in infection control activities, and optimizing the efficiency of infection control procedures and policies.

When initiating an infection control plan, it is important to take a global assessment of the contagious disease hazards in your practice, your level of risk aversion, and the resources that can be expended on infection control efforts. If a veterinary practice predominantly works in preventive health care under extensive field conditions, the contagious disease hazards may be less common and less severe than those encountered if a practice concentrates on intensive care of patients in a hospital. The specific disease hazards will also vary with the types of patients being managed (e.g., sick neonates vs. patients with acute gastrointestinal disorders vs. reproduction cases, equine vs. bovine vs. camelid, and so on). Risk aversion is a concept that relates to how much a person or business is unwilling to accept a negative event or allow it to occur. The inverse of risk aversion can be thought of as risk tolerance. The more risk averse a person is, the more it may be reasonable for him or her to initiate and maintain a rigorous infection control program. In contrast, a more risk-tolerant veterinarian may recognize the potential for contagious disease hazards in the practice but may not believe it is necessary to engage in extreme preventive strategies. The third component of this internal inventory is to assess the resources that will be available for infection control activities. The term *resources* in this context is intended to broadly encompass monetary resources, personnel time, and effort.

Keeping in mind this assessment of mindset and resources, the next step in developing an infection control program is to elaborate what the specific goals will be. For example, published goals for a biosecurity program might include protection of hospital personnel and clients from exposure to zoonotic disease agents, creating an environment in which patient care can be optimized by minimizing the risk of nosocomial infection, optimizing education of personnel and clients regarding important infectious disease hazards, and protecting the operational capabilities of the practice. Using a comprehensive, systematic process for evaluation of disease hazards and design of control systems will then allow design of a logical control system that triages efforts to optimize efficiency. One systematic approach that we have used successfully is Hazard Analysis and Critical Control Points

(HACCP) methodology.[12] After identification of the specific hazards (infections) are most likely to occur as well as when and where in the systems these events might occur or be prevented, the next step is to define specific control measures. As mentioned previously, all of these prevention efforts can be briefly summarized as being effective by decreasing the likelihood of exposing patients to infectious agents. In general, this is achieved either by optimizing hygiene in the environment, personnel, or patients or by decreasing direct and indirect contact among patients. To understand which control measures are of greatest importance and where efforts should be targeted, it is critical to consider the life-cycle and methods of transmission for the specific agents of concern. Among the questions that should be asked are the following: Is the agent most likely transmitted through direct contact, or are respiratory aerosols or contaminated surfaces and fomites also important sources of exposure? Is there a subclinical carrier state associated with agent shedding, or is shedding mostly restricted to clinically affected patients? Does the agent persist well in the environment, and can common disinfection procedures readily inactivate organisms?

Each potential infectious disease may be considered individually in this evaluation process, but it is useful to remember that control measures that are effective against one agent are usually effective against others, particularly if they share common routes of transmission or have common risk factors in patients. Design of infection control programs should focus on practical control plans for known problems, but it is important not to ignore the potential for newly recognized and reemerging diseases. Infectious diseases continue to emerge internationally, and many are of relevance to large animal veterinary medicine. The general strategy used in infection control protocols should be sufficiently rigorous to protect against most emerging issues, at least at a basic level. However, infection control programs should also be adequately fluid that they can be modified to address new issues.

Another critical aspect in the practice of infection control is effective targeting of disease prevention efforts. Taken to a hypothetical extreme, the most rigorous infection control methods would prescribe that *every* patient be handled in complete isolation, using barrier precautions verging on those used by “hazmat” personnel. Clearly this is not practical or needed in most situations, and yet in a few rare circumstances this level of precaution can be warranted. In many more situations, some lesser level of precaution is warranted beyond that used in casual encounters with animals in their environments. By their very nature, extra measures used to decrease infection risks inevitably inconvenience caregivers and clients in addition to increasing costs associated with care. In addition, these measures, particularly taken to the extreme, could affect patient care and result in a corresponding *increase* in morbidity. The challenge is to target prevention efforts to just those patients that warrant increased concern and to use the most appropriate, albeit inconvenient, methods for controlling risks to personnel and other patients.

Another side effect of the inconvenience created by infection control efforts is that people by their very nature gravitate to the most convenient methods for daily activities. The more personnel are inconvenienced by infection control efforts, the less likely they are to follow prescribed policies *unless* they understand and believe that procedures are needed and have value. Therefore a critical component of any effective infection control program is maximizing awareness of personnel and educating them about potential hazards and the value of established control measures. Presenting nightmarish worst-case scenarios without other objective information may be initially effective in getting people's attention, but continually using this approach as justification for infection control inevitably fails to truly motivate all or even most personnel. Establishing interactive communication regarding risks and concerns coupled with logical, objective, evidence-based presentations is clearly a better approach for convincing personnel of the need to fully participate in infection control efforts. However, this is also dependant on engaging sufficiently in surveillance and investigation so that useful objective information will be available regarding the significance of specific disease risks in a practice.

46.2.1 Informed Consent and Implications for Infection Control

The principle of informed consent, as it applies to veterinarians caring for animals, implies that owners have the right to be provided with adequate information before treatment so that they can make appropriate decisions for their animals and themselves.[13,14] As professionals with specialized training, veterinarians are expected to have knowledge about the health and care of animals that goes beyond that of someone without this training. One of the components that experts generally agree is part of the informed consent process is the disclosure of potential risks that may be associated with a veterinarian's management of a client's animals, particularly in situations in which there is greater than average risk for a particular adverse consequence.[15] It is reasonable and prudent for veterinarians to routinely disclose the potential for nosocomial infections as part of the informed consent process for all patients. This is especially true for patients with an enhanced risk of acquiring a nosocomial infection (e.g., because of required invasive procedures or because patients are immunocompromised). However, it is also true that if veterinarians know there is an increased risk of nosocomial infections at a facility, there is likely an ethical and legal obligation to disclose before admission how this risk pertains to new patients. In situations in which there is an increased risk of nosocomial infection (if not in all veterinary care situations), it is extremely prudent to document in writing the informed consent process with clients.

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46.2.2 Paying for Infection Control Activities

As mentioned previously, procedures used to decrease the risk of nosocomial infections inherently increase labor and material costs related to patient care. If infection control activities are an essential part of delivering veterinary care, then it should reasonably be expected that these costs will be passed on to clients, and it should not be expected that they will be paid for by veterinarians or hospitals. This includes the costs for additional care that is necessary to treat complications associated with nosocomial infections. This assumes that prudent and reasonable precautions have been employed in an effort to manage nosocomial disease risks for patients. In addition, if nosocomial infections are an expected risk related to care of any patient, then veterinarians and hospitals should develop plans for management of financial issues related to these risks. It is also important to differentiate consideration for how charges might be presented to the client from how costs for infection control activities are accounted for. These costs might be passed on to clients by directly accounting for each item, which is most reasonable when there are specific charges that can be attributed to a specific patient (e.g., increased costs related to care of a specific patient in isolation). However, this is less applicable to costs related to care and protection of more than one patient (e.g., costs related to cleaning and disinfection of the environment). In these cases it may make more sense to compensate for costs by aggregating expenses into a general fee category related to infection control (such as a daily biosecurity surcharge) or to include these costs in overhead costs that are covered by general admission or hospitalization fees. In special circumstances, such as when it is necessary to investigate or mitigate against suspected outbreaks of infections, it is useful to have a contingency fund that has been accrued and earmarked to pay for unforeseen expenses such as mass testing, additional labor related to cleaning and disinfection, and so on. Administrators should ensure that the possible need for these monies in case of infection control emergencies is considered and that fee schedules are sufficient to allow development of this type of reserve fund.

46.3 Environmental Hygiene

Much attention is paid to the possible role of the inanimate environment in hospital-associated infections of large animals. Contamination of the inanimate environment by microorganisms is inevitable and entirely expected, and

detection of microorganisms in a hospital environment does not, by itself, indicate anything of clinical relevance. Various factors are likely involved in the potential clinical relevance of contaminants, including the organism, numbers present, likelihood of contact with susceptible hosts, degree of susceptibility of potential hosts, environmental effects (temperature, ultraviolet exposure, humidity), and routine infection control protocols. Many microorganisms grow well on environmental surfaces, provided there is adequate moisture and organic debris, and may survive for very long periods of time. Even with relatively inhospitable conditions, many organisms persist for extended periods. If environmental pathogens are able to contact the appropriate body site of a susceptible individual in adequate numbers, disease could result. Environments where patients are housed or veterinary care is delivered can be expected to have greater numbers of environmental microorganisms than corresponding areas with less animal and human traffic.[16]

The relevance of environmental contamination is often difficult to determine. Even recovery of genetically indistinguishable organisms from the environment and from a patient does not confirm that exposure to an environmental reservoir was the source of infection, as it can be difficult to distinguish cause versus effect. Environmental contamination, however, is of concern for both direct transmission (e.g., oral inoculation from a reservoir of microorganisms in a stall) and indirect transmission (e.g., transmission of an organism from an environmental reservoir to the hands of a care provider and then to an animal). Measures should be used in all veterinary care environments to reduce the environmental pathogen load. This involves cleaning and disinfection of environmental sites.

46.3.1 Cleaning

Cleaning is defined as the removal of all visible debris.[17] It is arguably the most important step in decontamination of animal environments. Even the best disinfectants will be minimally effective when used in the presence of moderate volumes of dirt and organic debris such as feces and bedding material. Dirt and debris hamper disinfection by inactivating many chemicals, acting as a physical barrier between disinfectants and microorganisms, and providing a nutritional source for microorganisms. Not only does cleaning enhance efficacy of the disinfection process by providing optimal conditions for desired biochemical reactions, cleaning can actually remove a majority of microorganisms so that fewer need to be killed by disinfectants. Therefore removal of as much organic debris as possible is required for optimal disinfection. This involves manual labor consisting of removing all bedding and feces and scrubbing all surfaces to remove adherent debris and biofilms. Detergents should be used to loosen organic debris, emulsify fats, and decrease biofilm formation. The disinfectant to be used must be considered when choosing a detergent because there can be interaction between chemicals in detergents and disinfectants.

Because of the effort required to clean and scrub a stall, less labor-intensive methods are often sought. For example, cleaning with high-pressure (>120 psi) power washers is frequently employed in barns and hospitals. 1526
There are theoretic advantages that seemingly justify use of high-pressure washers, especially when they are 1527
designed to dispense high-temperature water and steam. However, whereas power washing is quite helpful in removing organic debris, infectious agents can easily be aerosolized and dispersed over wide areas if pressure washers are used indiscriminately. The true risk related to the use of high-pressure washers is unclear. However, the convenience of using high-pressure systems must obviously be balanced with more intensive manual cleaning methods in order to minimize untoward consequences. Using high-pressure systems on surfaces with large amounts of gross contamination should clearly be avoided.[18] In areas likely to be contaminated with important contagious pathogens (e.g., isolation facilities), it is logical to minimize use or at least use them only as a secondary cleaning process on surfaces that have been previously manually cleaned and disinfected.

46.3.2

Disinfection

Even with proper cleaning and selection of an appropriate disinfectant, disinfection errors can occur. It is critical that disinfectants be used at appropriate concentrations allowing for adequate contact time. It is also important to consider that microbial responses to disinfectant exposures are not uniform. There is tremendous variation in the ability of microorganisms to tolerate cleaning and disinfection. Most enveloped viruses are easy to eliminate, whereas protozoal oocysts, nonenveloped viruses, and bacterial spores may be difficult or impossible to kill.[19]

For disinfection to be effective, a few key factors must be considered: the presence of organic debris, disinfectant concentration, temperature, and contact time. Organic debris inactivates disinfectants to varying degrees, emphasizing the need for careful cleaning. Most disinfectants are available as concentrates and must be diluted before use. Excessively dilute disinfectant solutions may have little or no effect, whereas excessively concentrated solutions can be dangerous to use in addition to being wasteful of resources. Dilution of disinfectants is an important process and must be performed by measurement, not estimation. One solution that makes it easier to ensure that disinfectants are appropriately diluted is to use metered dispensing units that can be either wall mounted or attached to the end of a hose. For some disinfectants, different concentrations may be recommended for different situations. Test strips that can commonly be purchased from restaurant supply companies can also be used to verify appropriate dilution and activity disinfectant solutions. This is especially important when stock solutions are prepared for use over time. Cleaning staff must be informed of the importance of disinfectant dilution and trained in proper methods. Contact time is critical, particularly for certain disinfectants and difficult-to-kill microorganisms. If disinfectants are applied and immediately rinsed away, there is little chance that they can be effective. Most disinfectants require 10 to 30 minutes of contact time. Chemical reactions that produce disinfection are slowed in cold temperatures, which should be considered when determining the amount of contact time that is required. Disinfectants should never be combined because of the potential for inactivation and production of toxic gases.

Disinfection processes can be divided into three categories: high-level, intermediate, and low-level. High-level disinfection involves elimination of all viruses and vegetative bacteria but not all bacterial and fungal spores or protozoal oocysts. High-level disinfection is, in reality, difficult to attain and is uncommonly used. Intermediate disinfection involves eliminating all vegetative bacteria but not necessarily all viruses (especially nonenveloped viruses), spores, or oocysts. Low-level disinfection results in elimination of most but not all potentially pathogenic bacteria. Items requiring disinfection should be classified as to the level of disinfection required, examples of which are shown in Box 46-1.

46.3.2.1

Box 46-1 Examples of Items Requiring Different Levels of Disinfection

46.3.2.1.1

High level

Endotracheal tubes

Tonometer tips

Cystoscope

46.3.2.1.2

Intermediate Level

Dental equipment

Endoscopes

Thermometers used on multiple patients

Vaginal specula

46.3.2.1.3

Low level

Thermometers used on individual patients

Feeding instruments

Muzzles

Nasogastric tubes

Oral specula

Stethoscopes

46.3.3

Disinfectants

It is critical to be aware that all disinfectants do not have the same effectiveness. As with antimicrobial drugs, disinfectants have a spectrum of activity that can be highly variable among disinfectant classes (Table 46-1) Choosing the most appropriate disinfectant can be complex, involving a variety of factors including spectrum of activity, relative efficacy in the presence of organic debris, toxicity to animals and humans, potential damaging effects on certain surfaces, cost, and potential environmental effects. There is no standard disinfectant to be used in all situations in large animal facilities, although oxidizing agents such as accelerated stabilized hydrogen peroxide and peroxymonosulfate are increasing in popularity because of their broad spectrum of activity, acceptable performance in moderate amounts of organic material, relatively rapid action at room temperature, relative safety for personnel, and environmental friendliness. Other options may be appropriate in certain situations. When disinfectants with a narrower spectrum of activity are used as the primary disinfectant, protocols should be in place to use alternate products should certain situations be encountered that require a higher level of activity.

46.3.4 Effect of Surface Material on Cleaning and Disinfection

The material to be cleaned and disinfected can also have a tremendous impact on efficacy. Many surfaces found in large animal clinics and farms are not amenable to thorough cleaning and disinfection. These include unsealed wood surfaces, unsealed block, dirt flooring, and areas that are difficult to clean.

For stalls, solid walls with a sealed surface are optimal for disinfection. This may be difficult to achieve; however, there are certain procedures that can be performed to facilitate disinfection.[18] Cement block walls can be reasonably well sealed with at least two coats of good-quality enamel. Wood walls can be sealed using two or more coats of marine epoxy. Regular maintenance of stalls is required to seal defects that occur from kicks or chewing.

Table 46-1 Disinfectants Commonly Used in Veterinary Medicine*

Disinfectant	Activity in Organic Debris	Spectrum	Comments
Bleach (sodium hypochlorite)	Rapidly inactivated	Broad, including nonenveloped viruses and bacterial spores; no activity against *Cryptosporidium*	Used to disinfect clean environmental surfaces. Sporicidal activity is particularly useful. Efficacy decreases with increasing pH, decreasing temperature, and in the presence of ammonia and nitrogen. Varying concentrations can be used. 1:64 dilution of standard commercial bleach is most commonly used. Higher concentrations, up to 1:10, can be used but should be reserved for infrequent use in special situations. Inactivated by cationic soaps or detergents and sunlight. Chlorine gas can be produced when mixed with other chemicals. Bleaches fabrics and is corrosive to concrete.
Quaternary ammonium	Moderate	Variable; in general, effective against gram-negative bacteria and enveloped viruses, variably effective against gram-positive bacteria, limited activity against enveloped viruses, and no activity against bacterial spores or *Cryptosporidium*	There are differences between different types of quaternary ammonium compounds. Commonly used primary environmental disinfectant, although the spectrum is not necessarily optimal. In general, low toxicity. Inactivated by anionic detergents. Some residual activity after drying. Less effective in cold temperatures and low pH. Stable in storage.
Phenols	Very good	Relatively broad spectrum, with limited activity against nonenveloped viruses and no activity against bacterial spores or *Cryptosporidium*	Main advantage is better activity in organic debris. Can be irritating to skin and mucous membrane surfaces. Reportedly toxic to cats and pigs. Some residual activity after drying. Noncorrosive.

Peroxygen and accelerated hydrogen peroxide	Very good	Broad spectrum, including bacterial spores and nonenveloped viruses; some activity against *Cryptosporidium*	Excellent choice for routine environmental disinfection, footbaths, and environmental fogging. Rapid action makes them a good choice for footbaths. Low toxicity except at high concentrations. Environmentally friendly. Can be corrosive to plain steel, iron, copper, brass, bronze, vinyl, rubber, and concrete. More expensive than most other disinfectant options.
Alcohols	Rapidly inactivated	Moderate No activity against nonenveloped viruses, bacterial spores, and *Cryptosporidium*	Not appropriate for environmental disinfection. Can be used to disinfect certain medical and patient care items, but better options are available. Flammable. Minimally toxic. Fast acting.
Chlorhexidine	Rapidly inactivated	Moderate Limited activity against enveloped viruses No activity against nonenveloped viruses, bacterial spores, and *Cryptosporidium*	Not appropriate for environmental disinfection. Appropriately diluted solutions are suitable for use on tissues or on materials that contact skin or mucous membranes. Minimally toxic. Bactericidal activity on skin is more rapid than many other compounds, including iodophors. Residual effect on skin diminishes regrowth.
Povidone iodine	Rapidly inactivated	Moderate Limited activity against enveloped viruses No activity against nonenveloped viruses, bacterial spores, and *Cryptosporidium*	Not appropriate for environmental disinfection. Appropriately diluted solutions are suitable for use on tissues or on materials that contact skin or mucous membranes. Minimally toxic, but some people can become sensitized to skin contact. Appropriate dilution is important to maximize activity.

* It is critical to handle disinfectants and other chemicals using appropriate safety precautions. Refer to Material Safety Data Sheets (MSDSs) for each product to obtain recommendations regarding appropriate handling and personal protective equipment that is recommended.

The optimal floor surface, in terms of cleaning and disinfection, is a smooth, solid, completely sealed surface. However, surfaces meeting these criteria are not all amenable to animal housing, so a compromise may be required. Finding the right balance of floor cushion, traction, durability, ease of cleaning, and cost is difficult. Regardless, certain key factors should be considered. The floor should be completely sealed so that water (and pathogens) cannot seep underneath, as this creates an obvious environmental reservoir and prevents adequate contact with disinfectants. Damaged stall matting has been cited as the likely environmental reservoir associated with serious outbreaks of nosocomial disease.[10] If obtaining a seamless, water-impervious floor surface is not possible, floor coverings should be completely removable (e.g., rubber mats over sealed concrete floor) and must be removed regularly for disinfection. Remember that dirt, sand, and other organic materials cannot be disinfected and are therefore unsuitable for permanent flooring in hospital stalls or other veterinary care facilities. If sand is required for care of orthopedic patients, plans should be made to completely remove and discard this material between every patient.

46.3.5 Animal Contact Items

After use, all items in a patient's stall should be considered potentially contaminated with pathogens that the animal might be shedding. Therefore for patients suspected or known to have contagious diseases, every item in the stall should be treated as a source of infectious material and must be appropriately decontaminated or discarded. Many stall items may be difficult to disinfect, or it may not be possible to be confident in the ability to fully decontaminate them. If it is cost effective, disposal of these items is ideal. Otherwise, standard principles of cleaning and disinfection apply. It must be recognized that rough, damaged, and permeable surfaces may be very difficult to adequately disinfect. Particular attention should be paid to disinfection of surfaces that patients contact orally, such as feeders and water bowls, and surfaces likely to be contacted by hands of personnel. Appropriate decontamination of automatic water bowls can be problematic. Ideally, the water supply should be turned off, the bowl should be drained and cleaned, and disinfectant should be applied for an appropriate time before the bowl is rinsed and the water is turned back on. Nets used to hold hay have a high likelihood of contamination and are difficult to disinfect without use of gas or plasma sterilization techniques. Therefore their use should be avoided if possible.

Certain items may be at particular risk for contamination. For example, thermometers used on animals with salmonellosis are almost assuredly contaminated, and complete disinfection of digital thermometers is very difficult. It is reasonable to dedicate thermometers to individual patients and discard them when they are no longer required. An alternative is the use of disposable temperature strips, which are sometimes used in human medicine. These have not been specifically validated but are routinely used in some large animal hospitals.[20]

Twitches and muzzles have a high potential for contamination with pathogens such as *Streptococcus equi* and methicillin-resistant *Staphylococcus aureus* (MRSA). Rope used for twitches is extremely difficult to disinfect, apart from removing the rope for autoclaving. Chain twitches are easier to disinfect, but many find them less desirable to use. The ideal twitch material is easy to disinfect and atraumatic and provides good grip on the nose. It is debatable whether the ideal material is available at this time. Twitches should be routinely disinfected to the best of degree possible, considering the material. Consideration should be given to regularly changing or autoclaving rope used for twitches and routinely decontaminating twitches with the understanding that complete disinfection may not be possible. Twitches that are used on animals harboring nasal or upper respiratory tract pathogens should be considered contaminated and material discarded or disinfected.

Few areas show a greater difference in approach to infection control between human and veterinary medicine than the handling of needles after use. In human medicine, recapping of needles is strictly forbidden because of the potential for needlestick injuries and subsequent exposure to life-threatening blood-borne pathogens. In veterinary medicine, recapping of needles is very common, and needle-stick injuries are not perceived to be a significant health threat to veterinary personnel. Currently there are minimal risks to veterinary personnel in almost all situations regarding blood-borne transmission of infectious agents from large animals. However, infectious disease hazards clearly are continuing to emerge, and it is prudent to develop safe practices that minimize the potential for exposure to blood-borne pathogens that might be transmitted from domestic large animals.

46.4 HAND HYGIENE

Rigorous use of hand-hygiene procedures is one of the oldest recognized infection control measures and is perhaps the most important single infection control measure that can be performed. Unfortunately, extremely poor compliance with good use practices in human and veterinary hospitals as well as in the community negate much

of the benefit that can be realized. Centers for Disease Control and Prevention (CDC) guidelines suggest that health care workers in human hospitals should wash hands or use hand-sanitizing products before and after every contact with patients, as well as before eating, and after using the restroom. It is hard to argue that less stringent procedures are warranted in veterinary hospitals.

46.4.1

Box 46-2 Indications for Hand Hygiene in Medical Practice

- When hands are visibly dirty or contaminated with proteinaceous material, blood, or other body fluids
- Before direct contact with patients
- Before donning sterile gloves for invasive procedures (e.g., suturing wounds)
- Before inserting an indwelling urinary catheter, peripheral vascular catheter, or other invasive device that does not require a surgical procedure
- After contact with a patient's intact skin
- After contact with body fluids or excretions, mucous membranes, nonintact skin, and wound dressings
- After contact with an inanimate object in the immediate vicinity of a patient
- After removing gloves
- Before eating and after using a restroom

Adapted from Boyce JM, Pittet D: Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force, *Infect Control Hosp Epidemiol* 23(Suppl):S3, 2002.

Numerous indications for hand-hygiene procedures in health care settings have been identified as part of guidelines for human medicine (Box 46-2). As evidenced by this box, hand hygiene is needed frequently in a clinical situation, something that may be problematic in typical settings where veterinary care is provided to large animals. Maintaining optimal hand hygiene can be especially important for ambulatory clinicians and yet can also be particularly difficult to achieve because of logistic difficulties. A variety of options exist for decontaminating hands. The most common practices are hand washing and use of waterless hand-sanitizing solutions. Both are acceptable methods in most situations, and each has individual benefits and drawbacks.

46.4.2

Hand Washing

Washing with antibacterial soap has been the standard method of decontaminating hands of health care workers for over a century. However, the potential benefits of this practice generally are never realized because of failure to use appropriate methods or failure to wash hands at all.[21] Common errors in hand washing include inadequate duration of hand washing, failure to use soap, use of contaminated items to dry hands, and contamination of hands immediately after hand washing (e.g., through contact with contaminated faucets or door handles). An appropriate technique for hand washing is outlined in Box 46-3.

The importance of the type of soap used in hand washing is also often overlooked. Plain soaps, those without antibacterial agents, have minimal direct antibacterial activity. The main benefit of these is assistance with

removal of dirt and organic debris, although efficacy data are conflicting. The use of plain soap can slightly decrease bacterial numbers on hands, but studies in human medicine have failed to demonstrate effective removal of significant pathogens from the hands of hospital personnel.[22] Also, the routine use of plain soap can at times be associated with *increases* in numbers of bacteria carried on hands if use of these products, results in skin damage and irritation through drying.[23] Plain soaps are therefore not an optimal choice for routine use in medical settings, but use is certainly preferable to not washing hands in the absence of suitable alternatives (such as in field settings).

46.4.2.1

Box 46-3 A Recommended Technique for Hand Washing

- Wet hands first with water, then apply an appropriate amount of disinfectant soap (as recommended by the manufacturer).
- Vigorously rub hands together for *at least* 15 seconds, covering all surfaces of the hands and fingers. Make sure to scrub fingertips and clean under fingernails.
- Rinse hands with water and dry thoroughly with a disposable paper towel. Multiple-use towels of any type are not recommended.
- Use towel to turn off the faucet (and open doors when exiting a restroom).

Avoid using hot water, because repeated exposure to hot water may increase the risk of dermatitis. Adapted from Boyce JM, Pittet D: Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force

Infect Control Hosp Epidemiol 23(Suppl):S3, 2002.

Most soaps used in hospital settings contain biocides such as triclosan or chlorhexidine. Both of these can produce greater decreases in skin contamination compared with plain soap, and both compounds have antibacterial effects that persist after application,[21] although the duration of activity is shorter against gram-negative organisms (especially *Pseudomonas* species).[21] Iodine and iodophors have been used as skin disinfectants and have a broader antibacterial spectrum. However, both (particularly iodine) can be irritating to skin and are less commonly used for routine hand washing and skin disinfection in medical personnel. In addition, some people become sensitized to skin contact with these products.

Compliance with hand washing protocols is often poor for a variety of reasons. The time required is a major factor, particularly in situations where contact with a large number of patients is likely. Although hand washing requires less than a minute to complete, if it is indicated 100 times in a day, cumulatively this represents a significant amount of time committed to this activity. Lack of convenient access to proper hand-washing facilities is also frequently a problem. If access to sinks with running water, soap, and disposable towels is not convenient (i.e., not adjacent to where animal contacts occur), then it is less likely that hand-washing protocols will be rigorously followed. Regardless of the type of soap used, frequent hand washing can also lead to skin irritation,[21] which compounds compliance problems by making people reluctant to wash their hands and by making hand surfaces more amenable to colonization by bacteria.

Nail care and jewelry can also be significant impediments to achieving optimal levels of hand hygiene.[24] Colonization with higher bacterial numbers, colonization with bacterial pathogens, and outbreaks of infectious

disease have been reported in human hospitals in association with effects related to long fingernails and artificial nails.[25] Studies have shown that these hamper effective hand disinfection, and many health care facilities, particularly intensive care units, prohibit their staff from having long (≥¼ inch) or artificial nails. The role of these factors in risks to patients in veterinary settings is unclear, but some veterinary facilities have developed similar protocols and restrictions.

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46.4.3 Waterless Hand Sanitizers

An alternate approach designed to make hand hygiene easier and more accessible involves the use of waterless hand sanitizers. Most waterless hand sanitizers use varying concentrations of alcohol (isopropanol, ethanol, n-propanol, or a combination), whereas a few products contain alcohol plus biocides, or biocides alone. Alcohol products are most commonly available, with concentrations ranging from 60% to 95%. Most products are available as gels, but newer products are dispensed as foams, which may increase acceptability of products. Products with alcohol concentrations >95% are less effective because the presence of water is important for the bactericidal activity. Alcohols have excellent effect against gram-positive and gram-negative bacteria but not bacterial spores or protozoal oocysts.[21] Antiviral effects are variable, with less reliable effects against nonenveloped viruses. Alcohol-based products have been shown to have good effect on reduction of hand contamination of health care workers and have been shown to be more effective than standard hand washing.[26] Frequent contact with alcohol can lead to significant drying of skin, so most commercial products contain emollients, humectants, or similar skin-conditioning agents. Alcohol-impregnated towelettes are also commercially available but contain a small volume of alcohol and are no more effective for hand decontamination than washing with plain soap.[27]

One concern that is sometimes expressed about waterless hand sanitizers is their activity in the presence of organic debris. This is a particular concern in large animal practice, where the likelihood of gross contamination is high and access to hand-washing facilities is sometimes limited. However, a study of the efficacy of hand sanitizers on hand disinfection after performing physical examinations in horses reported that both alcohol and alcohol-chlorhexidine hand sanitizers were more effective for decreasing bacterial contamination than washing hands for 15 seconds with antibacterial soap.[28] This level of disinfection was noted even though the culture fluid collected off the hands was visibly dirty, indicating that there was a reasonable amount of gross contamination. Thus, waterless hand sanitizers are likely to be effective in normal large animal practice situations. When there is readily apparent contamination of the skin, however, debulking of the hands is probably required for optimal effect. It is important to remember that alcohol-containing products are flammable. Although very rare, fires have been associated with exposure to open flame. Common sense, and ensuring that hands are rubbed together until all the alcohol has evaporated, should greatly minimize any risks.

Although most available products contain alcohol alone, some commercial products contain alcohol plus other biocides such as chlorhexidine. Some of these products have sufficient efficacy such that they are widely used for presurgical hand disinfection. The main advantage of using this combination of products is the residual antibacterial effect that the chlorhexidine confers. Some users complain of a “sticky” feel to the skin, which is one of the reasons that this combination is less commonly used for routine situations.

One of the main advantages of waterless hand sanitizers is their portability. It is difficult to make water sources for hand washing portable or always accessible, but these products can be easily placed in ambulatory vehicles, can be carried by individual staff members, and can easily be placed throughout hospitals. Therefore there is a greater likelihood of obtaining compliance by facilitating access. Unfortunately, regardless of the types of products used, compliance with hand hygiene is often a major problem.[29,30] Infection control programs need to

address hand-hygiene compliance through a variety of means to increase use of this critical infection control tool.

46.4.4 Surgical Hand Antisepsis

Scrubbing of the hands and forearms with disinfectant solutions is a standard practice before surgery. Recommended techniques vary somewhat but typically involve a 5-minute scrub with antimicrobial soap. Some studies have reported acceptable hand disinfection with 2- or 3-minute scrubs.[31] Other studies have demonstrated that a two-step approach using a 1- to 2-minute surgical scrub followed by application of an alcohol-based hand sanitizer is as effective as a 5-minute surgical scrub.[32] One concern with repeated surgical scrubbing is the potential for skin irritation and subsequent increases in bacterial contamination. This has led to evaluation of brushless techniques, such as direct application of waterless hand sanitizers. It has been shown that brushless application of a preparation containing 1% chlorhexidine gluconate and 61% ethanol reduced hand bacterial counts more than did brush application of 4% chlorhexidine soap.[33]

There may be some concern about sole use of brushless techniques in situations where there may be moderate debris contamination, as could be encountered in veterinary applications. Various hybrid techniques have been recommended, including performing a hand wash or full surgical scrub at the beginning of the day, followed by application of a waterless hand sanitizer product as the sole hand antiseptic technique for subsequent procedures, or performing a brief hand wash before application of a waterless hand sanitizer. The main advantage of these may be elimination of alcohol-resistant bacterial spores.[34] One factor to consider, however, is that alcohol products may work better on dry hands, so hands should be allowed to thoroughly dry if hands are washed before application of an alcohol hand sanitizer.[34]

46.5 BARRIER PROTOCOLS AND PROTECTIVE ATTIRE

Barrier nursing techniques are an important infection control tool. The basic premise for their use is that placing some type of barrier between caregivers and patients prevents skin or clothing from being contaminated, and the contaminated outer barrier item can be discarded or left in the contaminated environment. Prevention of contamination of people's skin, regular clothing, personal items, and medical instruments can substantially reduce the risk of transmission of pathogens between animals, contamination of the general environment, and zoonotic transmission.

46.5.1 Use of Barrier Precautions

Basic barrier techniques should be used in all veterinary hospitals. Standardized, clean protective outerwear should be worn over hospital-dedicated attire for any patient contact, regardless of the anticipated nature of contact or the assumed infectious disease status of the patient. The need for other barrier items varies with circumstances and is often dictated by the type of disease syndrome being managed (e.g., diarrhea or gastrointestinal disease, respiratory disease, wound infection, fever of unknown origin) as opposed to as opposed to specifically documented infections or diseases (e.g., patients that are culture-positive for contagious pathogens). Other factors that might indicate a need for additional barriers include farm of origin (e.g., farms with endemic *S. equi equi* or rotavirus infections) or a patient that is considered to have an increased risk of infection (e.g., compromised neonates). Gloves, gowns, and overboots are the items most commonly used for additional barrier protection, but masks, caps, and eye protection may also be required at times. In some

facilities, overboots are not used in all areas, but personnel are required to wear footwear that can be readily disinfected, and disinfection of this footwear is required after exiting potentially contaminated areas.

46.5.2 Limitations of Barrier Precautions

The greatest limiting factors associated with use of barrier precautions in infection control are poor compliance and improper use. Written protocols should be developed that document practical use protocols for barrier precautions. These should specifically state when additional barriers are required; it is not possible to achieve consistent results if protocols are ambiguous or suggest too much discretionary interpretation. In addition, it is critical to educate personnel regarding the need for barrier nursing precautions and on proper application. It is also important to regularly monitor compliance with protocols.

46.5.3 Protective Outerwear

Standard protective outerwear for large animal veterinary personnel should include clean coveralls, lab coats, scrubs, or other dedicated clothing (hospital uniforms). Protective outerwear should be worn for every animal contact and should be changed regularly. This includes any time outerwear becomes visibly soiled or otherwise contaminated with body fluids perceived or known to be contaminated with potential pathogens (e.g., feces, blood, nasal exudates, urine, or uterine fluid). In addition, outerwear should be changed frequently (at least daily) because gross contamination does not need to be present for pathogen contamination to have occurred. Hospital personnel should change their hospital outerwear before leaving the building to decrease the risk of transfer of infectious agents from the hospital to the community. In order to facilitate this control measure, it is optimal from an infection control perspective for veterinary practices to provide laundry services or laundry facilities. Clothing that is potentially contaminated with biohazardous material should be handled appropriately so that personnel handling laundry are aware of the hazards and how to reduce risk of exposure.

46.5.4 Gloves

Gloves are an important component of barrier precautions if used properly. The CDC recommends glove use by health care workers to reduce the risk of transmission of infections from patients to personnel, to prevent health care workers' skin flora from being transmitted to patients, and to reduce transient contamination of the skin on the hands of personnel by microorganisms that can be transmitted from one patient to another.[35] The same concepts apply to veterinary medicine. In certain situations glove use has been shown to be an effective means of reducing pathogen transmission in human medicine.[36] However, incorrect use can negate these effects, or even be harmful. Common errors with glove use include failure to wear gloves when needed, not changing gloves after contact with infectious items, touching items (e.g., pagers, cell phones, pens, medical supplies) while wearing contaminated gloves, contamination of hands or clothing while removing gloves, and failure to wash hands after glove removal.[37] Although gloves are used to prevent contamination of hands, the potential for inadvertent contamination through microbreaks in the glove surface or contamination during glove removal necessitates use of hand washing or application of hand-sanitizing solutions in conjunction with their use.

There are no widely accepted standards in veterinary medicine for when gloves must be used, apart from the use of sterile gloves during surgical procedures. Examination gloves that are clean but not sterile are often used when handling wounds and infected body sites and during contact with animals known or suspected to be shedding contagious pathogens. Despite relatively widespread use of examination gloves in a variety of

circumstances in veterinary medicine, it is quite unusual for practices to have formal protocols regarding how and when they should be used.

46.5.5 Gowns

Whereas protective gowns have traditionally been used only during surgery, their use as a barrier garment when contacting high-risk patients is increasing in both human and veterinary medicine. The CDC has produced guidelines for human medicine stating that “gowns should be worn by personnel during the care of patients infected with epidemiologically important microorganisms to reduce the opportunity for transmission of pathogens from patients or items in their environment to other patients or environments.”[35] In general, gowns should be worn whenever direct or indirect with patients or their environment may result in contamination of caregivers' clothing or skin that facilitates transmission of pathogens.

The ideal barrier gown would cover all areas of the body that might become contaminated, would prevent penetration of liquids, would be of adequate strength to resist tearing and puncture under normal activities, would be comfortable to wear for long periods, would be available in appropriate sizes for all personnel, would be easy to put on and remove without contamination of regular attire, would be nonabrasive to skin, would be unlikely to startle patients, and would be of acceptable cost. Unfortunately, a product with all of these characteristics does not currently exist, and facilities must prioritize the relative importance of different gown properties. This is often difficult because neither the overall effectiveness of gowning nor the effectiveness of different gowns in veterinary situations has been adequately evaluated. The problem most likely to be encountered with barrier gowns in veterinary practice is poor resistance to liquids, especially under direct contact or pressure. In large animal practice, there is a greater likelihood of contact with relatively large volumes of fluids (e.g., with diarrheic animals) or direct contact with patient surfaces that would have moist secretions or excretions (e.g., animals with nasal discharge or large infected wounds). The types of anticipated activities may also affect the required size of gown. Gowns that do not completely cover the legs and feet may be useful in some circumstances but ineffective in situations with prolonged direct contact such as with assisted neonatal nursing.

In human medicine, there are conflicting data regarding the efficacy of gowning for prevention of hospital-associated infections.[38,39] Gowns may be more effective for reducing infection of personnel. It is possible that the most significant advantage in some situations is not the protective effect of gowns or other protective outerwear, but rather the raised awareness of the potentially infectious nature of the patient, which may in turn encourage concurrent application of other important infection control practices.

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46.5.6 Eye Protection

The use of protective eyewear, including goggles and face shields, is common in human medicine during procedures that generate aerosols or airborne droplets of blood, body fluids, and secretions.[40] Use of these items is mandated in some instances by health and safety regulations.[41] Despite the current low prevalence of blood-borne zoonotic pathogens in large animal species, it would be prudent to consider the use of some type of eye protection whenever generation of aerosols from liquids or secretions that might contain contagious pathogens is likely to occur. Situations in which eye protection should be seriously considered include examination of animals with suspected viral encephalitides.

46.5.7 Respiratory Protection

Masks and respirators are often used to reduce the risk of exposure to infectious agents by respiratory and oral routes, to reduce the risk of contamination of patient sites with organisms from personnel, and in some situations to prevent contamination of hands with nasal or oral microflora. Standard surgical masks may be effective against the spread of large particle droplets that are transmitted by close contact and travel only short distances (up to 3 feet) from infected patients.[42] However, the overall effectiveness of standard masks has come under debate, and some authors have questioned the overall effectiveness of surgical masks in hospital situations.[43]

Airborne transmission of zoonotic pathogens is commonly thought to be of minimal concern in most veterinary settings, and mask use is uncommon in veterinary hospitals apart from use during surgical procedures. The actual reduction in zoonotic disease risk that might be associated with the use of surgical masks during routine patient contact is unclear. However, increased awareness of risks of specific zoonotic disease risks, and infections in immunocompromised personnel and others with special disease risks, has prompted reconsideration of recommendations regarding personal protective equipment in some circumstances. For example, although airborne transmission is not considered an important route of exposure for MRSA, hospital personnel primarily become colonized in the nasal passages, and hand-to-nose contact is frequent. Therefore mask use prevents direct contact of hand and nose, thereby decreasing hand contamination or decreasing the risk of inoculation of the nose after contamination of the hands during animal contact. Masks capable of filtering nonoily particulate aerosols with 95% capability (N95 masks) are recommended in human medicine for dealing with airborne contagions such as the severe acute respiratory syndrome (SARS) coronavirus. Although there is currently little indication that these masks are routinely required in large animal practice, it may be reasonable for facilities to at least have a plan in place to implement N95 masks if required. A critical aspect of the use of N95 masks is fit-testing and training in their use, as improperly fitted or used masks may confer little or no benefit over surgical masks.

46.6 ANIMAL MOVEMENT AND HOUSING

Housing and movement can have a profound effect on the likelihood of exposure of patients to pathogens. Ideal facilities have no contact between inpatients and outpatients, allow for grouping and segregation of animals with different risks for contagious diseases, prevent direct contact between adjacent animals, reduce the potential for indirect exposures through contact with contaminated environments, and have adequate space so that there is time to properly disinfect all housing and handling environments between uses with different animals.

One major problem frequently encountered in large animal facilities, particularly older facilities, is that construction and design factors often hinder infection control activities. Infection control issues were not always given high priority during the design of many older facilities, so various problems are often encountered. These include patient traffic flow problems, requisite mixing of inpatients and outpatients, inability to segregate different cohorts in the population, heavy traffic around important areas (e.g., surgery, isolation), inadequate stall numbers, inadequate isolation facilities, poor ventilation, improper drainage, use of materials that are difficult to clean and disinfect, design issues that hinder adequate cleaning and disinfection, and so on. A variety of challenges is encountered when an optimal facility is designed. Many measures used to enhance infection control inherently are inconvenient, and designs that optimize infection control often have a significant impact on building costs and efficiency of use of the facility. It can be difficult to reconcile ease of operation with the level of infectious disease risk that is desired.

46.6.1 Outpatient Areas

In general, outpatients tend to have a lower contagious disease risk, in terms of both likelihood of shedding infectious agents and their susceptibility to infectious disease. However, “lower” risk does not mean “no” risk, and it is important to design holding areas that minimize contact with other animals while clinicians obtain histories and conduct initial examinations to more clearly categorize patients relative to their contagious disease risk. Ideally, outpatients should have little or no contact with inpatient animals and minimal contact with areas visited by inpatients. However, this is often not entirely possible. For example, it is often impractical to build completely separate areas for diagnostic imaging of inpatients and outpatients. However, the general principle of separation of inpatients from outpatients should be adhered to as much as possible.

Holding stalls in admission and outpatient examination areas may need to house a large number of animals every day. Therefore it is important that a sufficient number of stalls is available to allow appropriate cleaning between use, that there are established mechanisms to allow admitting clinicians to identify high-risk cases, and that this information is promptly conveyed to relevant personnel so extra precautions can be taken with that patient and the environment with which it has been in contact. Environmental precautions may range from routine cleaning and disinfection to restricting use pending high-level cleaning and disinfection, stall cultures, or patient cultures.

46.6.2 Inpatient Areas

Inpatients pose greater challenges than outpatients because they often have significant risk factors for infectious disease acquisition such as comorbidity, dietary changes, antimicrobial treatment, disruption of natural defense mechanisms, surgery, and placement of invasive devices. Compromised inpatients, particularly certain patient groups (e.g., those with gastrointestinal disease) may be more likely to shed infectious agents such as *Salmonella enterica*. Thus, infection control protocols should emphasize the need to reduce the risk of transmission of infectious agents from inpatients to other hospitalized animals and hospital personnel, and to minimize risks related to contamination of the hospital environment. A variety of methods can be used to manage this risk; these need to be balanced with levels of risk aversion and available resources to support infection control efforts.

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One method of reducing the risk of disease transmission among individuals and groups (e.g., between animals in different wards or those assigned to different services) is to assign animals to different cohorts and then create physical and procedural separation among the different groups. It is important to group animals based on known or suspected infectious disease status or infectious disease susceptibility, as well as to group and separate animals with different disease syndromes (e.g., respiratory disease or gastrointestinal disease). It is also logical to group and segregate animals that are managed by different clinical services in order to decrease the probability of transmitting infectious agents through indirect contact. As an example, because of the documented risk associated with *Salmonella* shedding among cattle from intensively managed populations, several large hospitals have found that it is very important to house and manage cattle separately from other large animal patients (especially horses). In general, managing inpatients as smaller cohorts helps contain transmission risk, thereby decreasing the likelihood of a widespread outbreak in the entire patient population. Creating smaller cohorts of patients with different risks for contagious disease also facilitates the use of varying levels of infection control precautions for different groups.

The design of some facilities does not allow for the separation of different cohorts in different buildings or wards. When physical separation of inpatient groups (excluding isolation cases) is impossible or impractical,

animals with different disease risks can still be managed differently in a common ward system. One approach is to designate areas within large wards for different cohorts. Another is to identify animals in different risk categories, applying different levels of infection control precautions, but to allow interspersing of animals from different risk categories in the same area. Physical separation within a ward can be enhanced by use of chain or rope barricades to identify and minimize access to patients with elevated contagious disease risk status. A key for successful infection control using this type of system is the absolute need for prominent identification of different groups, having defined protocols for each group, and maintaining effective communication about disease status of these patients. One system that has been employed is the use of color labels to indicate infection control status. For example, colored adhesive dots can be placed on stalls or stall cards of all patients; red dots might indicate animals with a known highly contagious disease, yellow dots might indicate that animals are suspected of having an infectious disease or may have increased risk of acquiring infectious disease, and green dots might indicate that animals are considered to have an average or low risk of carrying or acquiring contagious disease agents. This type of system is easy to apply and easy to understand. In addition, more prominent signs can be used to more clearly indicate to all personnel certain concerns (e.g., *Salmonella*, MRSA, rabies suspect). One consideration with these more specific labels, however, is whether visitors could obtain confidential and sometimes prejudicial information from visible notices.

46.6.3 Isolation of Highest-Risk Patients

The most rigorous control of contagious disease hazards requires that transmission potential be absolutely minimized for patients suspected or known to be infected with highly contagious pathogens or pathogens associated with highly consequential diseases. In general this means that these patients should have no direct or indirect contact with other animals or areas used in routine care of patients via personnel, fomites, aerosols, or other materials. It also means that human access to these patients and their care environment should be tightly controlled. In general, in order to achieve this level of isolation, these patients will require housing in a separate, specially designed unit.

Most isolation protocols in large animal medicine focus on a limited number of pathogens. Protocols for large animal facilities tend to focus heavily or solely on *S. enterica*. Whether these protocols are adequate or excessive for control of other pathogens is debatable, and a broader scope is likely required in many facilities. That said, protocols that reduce the risk of transmission of one agent generally reduce the transmission potential of other agents, particularly if there are similarities regarding transmission routes or risk factors for exposure and infection.

Large animal isolation protocols need to take into consideration a variety of issues, including indicators for isolation, cleaning and disinfection protocols, protocols regarding personnel movement and barrier precautions, protocols for patient contact and movement, manure disposal, and supply stocking. Defining methods for identifying animals that need to be isolated and establishing specific criteria for handling these animals is critical, and these methods must be properly communicated to all individuals associated with patient or facility care. Developing protocols for rapid identification of patients that represent a contagious disease hazard is critical to the success of any biosecurity program. The best isolation units are not effective if unoccupied. Specific disease and syndromic criteria for isolation should be developed to facilitate prompt isolation of appropriate individuals. Isolated animals should be physically separate from the rest of the hospital population at all times if at all possible. This means that isolation units should be designed so that animals will rarely if ever have to leave the unit except for those that need an emergency procedure such as surgery. Stocks, examination areas, and scales should be available. Ideally, there should be minimal contact of personnel with isolated animals and their stall environment. The ability to monitor patients in isolation using viewing windows

or by remote electronic means (e.g., web cameras, closed circuit video) facilitates the ability to deliver excellent patient care while minimizing risks associated with direct contact.

These units must be strictly managed with specific predetermined protocols in order to reliably manage the risk of transmission. Isolation protocols should be comprehensive and clearly documented in writing. Proper training of all staff, particularly lay staff who may have no background in infectious diseases and infection control, is critical. Standardized protocols for management of isolation units in human health care settings have been published by the CDC.[42] However, similarly standardized guidelines have not been established for veterinary medicine, and protocols used at veterinary facilities are highly variable as they are tailored to specific operations and different facility and logistic resources. It is logical for veterinary facilities to consider guidelines that have been developed at other veterinary facilities and in human health care settings when developing their own isolation protocols.

In some situations, housing of potentially infectious animals in an isolation unit is not possible because of patient care issues or limitations in isolation space. As a result, consideration needs to be given to management of higher-risk patients within the general hospital environment. This can be done in a few different ways, including grouping of general risk groups and application of intermediate isolation techniques to patients that are considered at higher risk for being infectious but that are not deemed candidates for housing in an isolation unit. In-hospital isolation protocols allow for an increased level of protection but are not a replacement for a proper isolation unit and should not be used solely for clinician convenience. Protocols should be developed regarding the handling of animals, the stall, and the area around the stall. Animals that are isolated in the hospital should not leave stalls unless they are being moved for required procedures. If movement is necessary, feet should be cleaned and disinfected using appropriately diluted chlorhexidine solutions. The potential for environmental contamination can be reduced by having a person follow the animal with a bucket to collect any feces that may be passed during transit. Traffic areas should be promptly cleaned and disinfected. Protective barrier clothing such as full waterproof coveralls or full-length waterproof gown, gloves, and dedicated footwear or boot covers should be worn for any contact with the patient or its environment. The area around the stall entrance should be considered potentially contaminated and disinfected routinely (at least three or four times per day). Disinfectant footbaths or footmats used at stall doors can reduce bacterial contamination of footwear.[44,45] Attention should be paid to the pattern of water drainage from the stall and in the area. If water runs from the stall to the breezeway or runs down the breezeway past the stall, then housing of potentially or known infectious animals in the stall may be inappropriate. Animals should not be allowed contact with neighboring animals. Barriers may be required if solid walls are not present on all sides. Specific protocols should be developed for cleaning in-hospital isolation stalls. These stalls should be cleaned last, personnel cleaning stalls must wear protective gear, and items used to clean the stall must be disinfected immediately after use.

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Isolation guidelines for human medicine target the prevention of five different types of transmission: contact transmission, droplet transmission, airborne transmission, common vehicle transmission, and vector-borne transmission.[42]

- Contact transmission is typically the most important mode of transmission and involves transmission of infectious agents to patients by caregivers or directly between patients. In large animal medicine, this could include situations such as transfer of MRSA from a colonized person to an animal under care, transmission of *S. equi* between horses by personnel, or direct transmission of viral respiratory pathogens between horses in adjacent stalls that can have nose-to-nose contact.

- Droplet transmission involves transmission of infectious agents in relatively large fluid droplets generated by coughing, snorting, or vocalizing. These large droplets do not remain suspended in the air for long periods, nor are they transmitted long distances; therefore special air handling is not required. An example of this is transmission of bacterial agents from a coughing horse to another horse stabled in relative proximity. An extrapolation to veterinary context might also include transmission of surface contaminants during environmental cleaning processes with water under high pressure.
- Airborne transmission involves agents that can be transmitted effectively in small particles (5 μm or smaller) that can remain suspended in air and travel greater distances. Special air handling is required to control this route of transmission. Equine influenza can be spread through a barn via the airborne route over extended distances.
- Common vehicle transmission involves infection caused by contact with contaminated items such as feed bins, muzzles, twitches, thermometers, and other medical equipment.
- Vector-borne transmission involves vectors such as mosquitoes, flies, and rodents. This may be of particular concern in some areas with reportable vector-borne diseases such as equine infectious anemia.

46.7 SURVEILLANCE

All comprehensive infection control programs should have a surveillance component, as the information collected serves as sensory input to guide ongoing efforts so that they are focused and efficient. Without surveillance information, infection control programs will be guided more by emotions and opinions than by data and evidence. Infection control programs will have much greater acceptance and utility if in the long term decisions are based on objective information about infection and disease occurrence at a specific hospital. Useful surveillance goals for infection control programs include developing a system to allow prompt identification of contagious disease threats, evaluating the effectiveness of infection control practices, measuring personnel compliance with infection control procedures, providing a basis for logical infection control decisions, and stimulating efficient and economical use of resources.

46.7.1 Surveillance Options and Strategies

Theoretically, an optimal surveillance system would allow real-time detection of every occurrence of nosocomial infection. However, pursuing this goal would be unrealistic for reasons of practicality and would be an inefficient use of resources. Although all nosocomial infections are important relative to patient well-being, some are more important than others. This is because the impact on patient health is much more significant for some diseases, and also because highly contagious diseases are more likely to affect a larger number of patients. Focusing surveillance on these high-impact nosocomial infections is logical, as a greater proportion of these occurrences are also likely to be preventable in comparison with more sporadic problems. Furthermore, experiences with infection control in human health care settings have shown that it is possible to be more efficient with infection control and just as effective if special high-risk or high-cost problems are targeted.

Determining which specific nosocomial infections were likely preventable is a difficult and potentially contentious task. Rather than focus on individual infections, infection control efforts in human hospitals have benefited by focusing on comparing rates of infection and estimating the proportion that might be preventable by referencing some accepted standard. During the past 30 years, human hospitals have made great efforts to characterize rates of nosocomial infection that can be expected even under the best of circumstances. By

estimating rates for these “nonpreventable” infections, it has then been possible to identify hospitals with higher than average rates for nosocomial infections. Because of the tremendous differences among hospitals and among patient populations, it has become standard to focus on more restricted, high-risk patient groups for which there is better comparability (e.g., neonatal or cardiac intensive care patients). It is also far more feasible to perform surveillance for nosocomial surveillance in these high-risk patient subgroups than it is in the larger general population, which has a much lower risk of nosocomial infection. Performing surveillance with standardized case definitions over time allows identification of specific risk factors, which could then be used to prospectively refine management of patients (e.g., a high-risk patient could be identified and be subjected to more aggressive control measures as a preventive strategy). Unfortunately, there is very limited information available regarding rates of nosocomial disease that can be found at individual hospitals, let alone estimation in multiple hospitals, which would be required in order to obtain interhospital comparisons that would be useful in identifying latent problems at specific facilities. Although making standardized comparisons among hospitals would require tremendous cooperative effort, individual facilities could make significant progress in identifying important changes in nosocomial infection rates if efforts were made to benchmark their nosocomial infection rates over time.

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When designing a formal surveillance effort to aid infection control programs, it is important to tailor efforts to a specific facility or practice. There is a wide variety of design possibilities for hospital surveillance systems, and the specific focus and methods should be carefully matched to the needs and resources of each establishment. Diseases that are the highest priority for surveillance must be specified, along with standardized case definitions that will be used to identify these cases. Efforts may target nosocomial disease related to specific procedures or organ system involvement, or just as commonly they may target specific infectious agents of interest. For example, systems might be established to look for surgical or intravenous catheter site infections, methods may target surveillance for respiratory tract infections, or efforts may specifically target detection of *Salmonella* or MRSA infections. It must also be determined whether clinical disease will be the outcome of interest or whether it is important to look for animals with subclinical infections. This will generally vary by disease and likely will be determined by the natural history or pathophysiology of the disease (e.g., Does shedding occur in the absence of clinical signs? Is there a chronic carrier state? What are the risk factors related to the likelihood of shedding?). Furthermore, if clinical disease is the outcome of interest, it is important to consider whether the case definition will include some type of confirmation of the cause or whether diagnoses will be more based on clinical signs and syndromic in nature (e.g., surgical site infections could be defined based on recovery of a bacterial agent in the presence of clinical disease, or they could be defined solely on the presence of a predetermined combination of clinical signs such as erythema and drainage). As discussed previously, another consideration is whether surveillance will target specific subgroups of the population or whether it will include all patients. The major benefit of targeted surveillance is that it decreases the cost and effort of data collection, but the tradeoff is the inability to detect potential problems in the patients that are not being monitored. However, increasing awareness about infection control methods for common or more important diseases generally has the effect of increasing awareness and compliance with control measures that relate to other potential nosocomial problems. It also must be determined whether surveillance will be active (i.e., patients with nosocomial problems will be actively sought out) or whether passive surveillance (i.e., reporting is voluntary) is acceptable and appropriate. In general, active surveillance will be used only in targeted subpopulations and only to look for more common and more important diseases, and syndromic surveillance should be more heavily relied on when the targeted population is larger or as a supplement to culture or etiologically based surveillance efforts.

Another important consideration is how data will be gathered for this effort. Significant personnel compliance is needed for active culture-based surveillance of large numbers of patients. Similarly, any type of chart review system for benchmarking expected rates of nosocomial disease requires a significant time commitment.

Surveillance efforts are greatly aided by the ability to use computer-based search mechanisms, and it is strongly recommended that any practice use electronic medical record systems to maximize the ability to perform surveillance. For example, something as simple as being able to monitor the number of febrile or leukopenic patients on a daily basis could be extremely powerful as an aid to infection control efforts. Even financial databases can be useful in surveillance efforts. For example, financial databases may be very useful for surveillance for benchmarking antimicrobial prescriptions or specific procedures, such as intravenous catheterization or surgeries.

Monitoring for bacterial contamination of the hospital environment has been a useful adjunct to patient monitoring in comprehensive biosecurity programs at veterinary hospitals.[20,46,47] In addition, in some situations, such as when attempting to control ongoing outbreaks, there is no substitute for culturing the hospital environment to detect important environmental reservoirs.[10,48] Use of electrostatic household wipes has been extremely useful for sampling to detect *S. enterica* in routine surveillance as well as in the face of outbreaks.

As an alternative to culturing environmental samples for one specific agent, it may be useful to enumerate total numbers of bacteria recovered from hospital surfaces using either swabs or contact plates (e.g., RODAC).[16,47] Contact plates are simple to use, require minimal investment of labor, and when used on regular basis can provide valuable information regarding cleanliness of hospital surfaces. Such data can be used as feedback for the cleaning personnel, for monitoring of quality of cleaning, or for pinpointing problem areas. It is important to remember that bacteria can be recovered from most surfaces, even in the cleanest of hospitals. Therefore, in order to be most meaningful, if quantitative environmental cultures are to be performed they should be repeated on a regular basis in order to establish meaningful baseline values for comparison.

The use of rapid and sensitive diagnostic tests is particularly important for the management of highly contagious diseases. Polymerase chain reaction (PCR) and antigen detection tests, which can be much more rapid than traditional culture systems for bacteria and viruses, have become more widely used for both patient and environmental surveillance efforts. However, these tests cannot fully replace culture-based assays, because analysis of microbes is essential to fully understand the epidemiologic implications of each recovery. For example, if on a single day three patients were found to be shedding *Salmonella* using PCR assay, it would not be possible to know whether these were unrelated events. In contrast, if shedding were detected using culture and the *Salmonella* isolates were then shown to be from different serogroups, this would make it unlikely that shedding was related to nosocomial exposures from a single source. In some situations it may be logical to use both rapid and culture-based assays to maximize both speed and ability to perform epidemiologic investigations. Availability of qualified laboratories, rapidity of testing, and costs will all have to be considered and balanced in these considerations.

46.7.2 Monitoring Personnel Compliance

Success of an infection control program is absolutely dependent on corporate participation that arises from a well-developed sense of responsibility among individuals. Actively engaging all personnel in biosecurity programs becomes increasingly difficult as organizations become larger and more complex. Unfortunately, the most cautious actions of a majority of personnel can be for naught if even one individual neglects to take appropriate precautions under just the right (wrong) circumstances. Although it is very important for administrators to engage in surveillance to detect systematic noncompliance with policies, it is just as important to empower all personnel and expect them to participate in monitoring for individual acts of noncompliance. Remembering that most noncompliance arises from a natural tendency for people to revert to the most convenient practices (which are not necessarily the most “safe” from the biosecurity perspective), it is

important to couple surveillance efforts with education so that all personnel fully understand why they are being inconvenienced. In addition, providing useful feedback and communication about issues that arise in the hospital will help to reinforce the need for compliance. For example, monitoring and reporting of bacterial shedding or environmental contamination detected as a part of surveillance programs can help to keep hospital personnel aware of the potential hazards of reduced biosecurity efforts.

46.7.3 Measurements Related to Health and Disease

Although outcomes for individual animals may be the most important bottom line for many clinicians, it is important to remember that infection control by its very nature often has a larger population-based perspective. Therefore, although diagnostic tests results have great relevance for an individual animal, a positive test result may not have great value for the entire population unless it is interpreted contextually. As such, it is critical to remember that some type of denominator information is needed in addition to numerators to provide relevance over time or for different subpopulations (e.g., numbers of all infections, numbers of animals tested). Some examples of relevant denominators include patient admission totals for a given period, patient-days of hospitalization, procedure events such as surgeries or catheter placements, and culture totals.

46.7.4 Developing a Comprehensive Surveillance Strategy

As mentioned, it is unrealistic to expect to detect all occurrences of nosocomial infection or all animals shedding agents of interest through any hospital surveillance system. Rather, veterinarians should work toward developing strategic surveillance programs that will allow reliable estimation of rates for important events if they occur with any significant frequency, as well as rapid detection of “unexpected” important events. It is likely that a mix of strategies described earlier will be used for the various agents and disease problems. For example, if *S. enterica* shedding occurs at some low-level yet regular frequency in a hospital (e.g., 3% of all hospitalized equine patients) and it is considered an important potential hazard for other patients, it is reasonable for an active surveillance program to be developed that allows detection of clinical and subclinical shedding of *Salmonella* as a patient management tool and also allows detection of important trends over time so that nosocomial outbreaks could be rapidly identified and stopped. In contrast, *Clostridium difficile* and *Clostridium perfringens* may not have been detected with any regularity in patients at a particular hospital or may be more difficult to actively monitor because of available testing methodologies, yet they may still be considered important because of their significance as pathogens and their potential for contagious spread. For these pathogens, it may be more reasonable to use a reliable passive surveillance strategy to call attention to patients when clinical signs or culture results indicate that these agents may be present. In addition, maintaining some level of surveillance for compliance with infection control procedures and policies is necessary to ensure that a biosecurity program is functioning properly.

46.8 EDUCATION AND AWARENESS

Education of all personnel regarding infectious disease hazards to themselves, patients, and veterinary practices is essential to the long-term success of any infection control program. Successful programs are critically dependant on all personnel knowing and following procedures and policies used for control of contagious disease transmission in a practice. Although this type of information can be acquired over time through personal experience, this is an inefficient and unreliable method for disseminating critical information.

46.8.1 Written Protocols

The first step to ensuring that necessary information is disseminated to all personnel is to document policies and protocols in writing. This effort is valuable for all veterinary practices but is especially critical in larger and more complex veterinary hospitals. This relatively simple step has many benefits. First, documenting procedures requires a thorough review, which by itself is beneficial. Second, documenting policies and protocols in writing imbues the infection control program with a sense of purpose and commitment. Third, documenting procedures helps to ensure consistency in application by all personnel as well as over time. As discussed, all infection control procedures are inherently inconvenient, and the natural tendency is for personnel to drift toward more convenient ways performing activities, which may not provide an adequate degree of protection against nosocomial infections. Fourth, documented policies demonstrate a degree of due diligence, which is useful from a legal liability standpoint relative to the occurrence of nosocomial or zoonotic infections.

Once these protocols have been documented, it is important to require their use as a reference and to make a specific effort to educate personnel about the policies and procedures. A written document serves no purpose if it is not used. Veterinarians and other personnel are busy people, and the immediacy of caring for patients and clients can easily overwhelm seemingly mundane tasks such as studying written protocols. A valuable aid in this process is to have some type of training program. This does not necessarily mean formal presentations; it is valuable to organize a meeting of all personnel for the sole purpose of discussing infection control issues. Although this seems logical, biosecurity training is not a universal occurrence even in teaching hospitals. In a survey of teaching hospitals from American Veterinary Medical Association (AVMA)–accredited institutions, only 15 of 37 responding institutions reported that they required that personnel (students, technical staff, veterinarians) participate in some type of formal training program regarding infection control and biosecurity, and only seven of these institutions provided more than a single training exposure.[49]

46.8.2 Training Programs

It is also important to consider the differences in training and experience among personnel. By their nature, infection control programs are dependant on adherence to important protocols by all personnel regardless of their position description. Nonveterinarians are invaluable members of most veterinary practice teams, and even personnel who might never touch patients but instead are employed as receptionists or for the single specific task of cleaning are absolutely critical for the success of infection control programs. Veterinarians sometimes underappreciate how their specialized training has provided them a broad appreciation for basic principles of contagious disease transmission and control. Without the experiences of a veterinary education, many personnel do not have the same basic understanding of contagious diseases. Simply telling people to follow certain rules leads to inevitable compliance problems. Although it is important for people to know what is expected of them, it is just as critical for them to know why these procedures are important. Without a thorough understanding of why inconvenient infection control practices are needed, they will inevitably be discarded over time as seemingly illogical. To help ensure uniformity of exposure among all personnel, some hospitals have developed training documents and require that new employees pass a written evaluation before they are permitted to begin work.

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Another important aspect of education and awareness is to instill a need to lead by example and to empower all personnel to hold anyone else in the practice accountable for his or her actions. The hierarchy in authority that is needed in the delivery of patient care (veterinarians at the top of the hierarchy, personnel without formal training at the bottom) can interfere with optimal infection control. A common non sequitur related to infection

control is that those with the most training can be the persons least likely to adhere to important policies. This is true both in human and veterinary medicine, as has been repeatedly shown relative to hand hygiene.[21] Physicians and residents have been shown in numerous studies conducted in a variety of settings to be significantly less likely than nurses to adhere to appropriate hand-hygiene protocols. Observations in the veterinary setting suggest that the same trends are true for hand hygiene, as well as for appropriate use of barrier nursing precautions. All people pick up cues for behavioral expectations from their surroundings. If personnel who clearly understand the importance of preventive measures such as hand washing (physicians and veterinarians) fail to routinely follow best infection control practices, there is little hope that trainees and laypersons will routinely trouble themselves to habitually use an important albeit inconvenient practice. Furthermore, it seems that the more respected the position a person holds in a practice, the more likely it is that individual acts of noncompliance will influence the actions of others. Students in teaching hospitals can watch classmates correctly follow infection control policies throughout the day and yet can be more influenced to be noncompliant by observing the single time that a senior clinician ignores a practice guideline.

One way to improve compliance and counter these influences is to use disseminated enforcement by actively encouraging all personnel to call attention to noncompliance. Once it has been determined which procedures are required for a particular situation and this has been documented, there is no reason that nontechnical staff should be any less capable than a veterinarian in determining whether a procedure has been correctly followed. It is important that this community enforcement be empowered by all in a spirit of friendly camaraderie and team building. Some hospitals have noted significant improvements in compliance using this method of enforcement and have even used competitions between “teams” with the incentive of agreeing that the loser must pay a reward to the other team (e.g., pizza lunch).

46.8.3 Zoonosis Awareness

One of the most important objectives for an infection control program is to protect personnel and clients from illness associated with zoonotic infections. This is another area in which veterinarians sometimes forget that not all personnel have an understanding of hazards or of how to take appropriate actions to protect themselves. Without this knowledge, personnel may take inappropriate risks or may overreact to perceived hazards in what is actually a low-risk situation. In addition to holding briefings or question-and-answer sessions, it is wise to provide a good resource text, written summaries, or URL addresses of reliable Internet resources so that personnel have tools available to help them research answers to their questions. Table 46-2 provides a brief summary of some zoonotic pathogens that might be transmitted from domestic large animals through occupational activities of veterinary personnel.

46.8.4 Personnel with Increased Risk of Infection

An important area for which there is not much published literature relates to risks for zoonotic infections in personnel who have an increased susceptibility to infectious diseases or those in whom the consequences of clinical infection may be particularly severe. Obviously there is an overall increase in risk of infection for immunocompromised personnel, but there is very little specific information about which disease risks might be of greatest importance to this population. In addition, it is essentially impossible to predict which agents are of little risk to people with a healthy immune system but may be of much greater risk to immunocompromised personnel. Individuals being treated orally with antimicrobial drugs are generally considered to have an increased risk for infections with enteropathogens, so it is prudent for personnel being treated with antimicrobial drugs to be especially attentive to protocols related to personal protection. Pregnant women have a special risk for infections that can result in fetal infections or abortion and should therefore employ practical

precautions that reduce the likelihood of infection. In general, paying strict attention to good hand-hygiene protocols, routine use of gloves to reduce the likelihood of contact exposures, regular use of protective outer garments or hospital dedicated-attire, and avoiding eating and drinking around animals or in their environments should help to reduce the likelihood of exposure to potential zoonotic pathogens.

46.9 INTERVENTION AND INVESTIGATION OF NOSOCOMIAL OUTBREAKS

An outbreak is defined as an increased occurrence of infections above the expected baseline (endemic) level. Outbreaks are an ever-present risk in all health care facilities, veterinary or otherwise, and outbreaks will occur despite rigorous infection control protocols. The general principles of outbreak management are to contain the outbreak and reduce the overall impact on individual animals and the facility. It is critical to note that despite the stigma that is often attached to outbreaks, an outbreak of disease does not necessarily indicate poor management or malpractice. By their very nature, most veterinary hospitals will always have higher risks for the occurrence of outbreaks of infectious disease. However, making no attempt to identify nosocomial infections, neglecting signs of a developing outbreak, or responding inappropriately to the spread of nosocomial infections could all be construed as poor management or even malpractice. There are numerous reasons why plans for a logical, aggressive, organized, and cooperative response should be developed. Consultation with internal and external experts in epidemiology, infectious diseases, microbiology, and infection control can be useful. It is unlikely that the person involved in coordinating the outbreak response will be an expert in all areas. Consulting others does not indicate a lack of ability on the part of the response team; rather it indicates a logical approach to a typically complex problem. It makes sense to consult with those who through interactions at multiple facilities have gained experience that cannot usually be obtained while concentrating on primary responsibilities as a clinician at a single institution. Ideally, these individuals are consulted early in the outbreak, and it may be prudent to develop contingency plans and contact consultants in anticipation of potential problems. The use of external consultants can be particularly useful because they can examine a situation and facility without the same degree of inherent bias that develops through experience and habit of regular daily practice in a facility.

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Table 46-2 Zoonotic Diseases of Domestic Large Animal Species That Are Transmissible through Occupational Exposures to Veterinary Personnel*

Agent or Disease	Susceptible Animal Species	Clinical Signs in Humans	Methods of Transmission to Humans	Personal Protection for Veterinary Personnel
***Bacillus anthracis* (anthrax)** Gram-positive, spore-forming, anaerobic bacterium	All species	There are three clinical forms of anthrax in humans: cutaneous, pulmonary, and gastrointestinal. Cutaneous infections manifest as skin papules and vesicles with associated cellulitis that evolve into a characteristic black eschar (scab). Pulmonary anthrax initially resembles upper respiratory infection and can evolve into severe respiratory compromise and death. The gastrointestinal form results in gastroenteritis with vomiting and dysentery.	Cutaneous transmission occurs through direct contact; respiratory transmission occurs through inhalation of bacteria or spores; gastrointestinal transmission results from eating undercooked contaminated meat.	Enhanced barrier precautions, including eye protection and a minimum of N95 respiratory protection, should be used when handling affected animals or working in their environments. Blood and secretions from anthrax suspects should not be allowed to contact skin. Necropsy should not be performed on animals that have died from anthrax.
Bordetella bronchiseptica Gram-negative bacterium	Pigs, dogs, cats, rabbits, horses	Disease is rare in humans and occurs almost exclusively in immunocompromised individuals, resulting in pneumonia and upper respiratory tract infections.	Respiratory infection through contact and droplet routes.	Immunocompromised individuals should avoid contact with mucous membranes and nasal discharges of susceptible animal species. Barrier precautions and adherence to good hand-hygiene protocols will reduce the risk of exposure.

Brucella melitensis, Brucella abortus, Brucella suis, and ***Brucella canis*** **(brucellosis)** Gram-negative bacterium	Cattle, sheep, goats, camelids, pigs, horses, dogs, and other species	Flulike illness, gastrointestinal signs occur frequently in adults but less often in children; irritability, insomnia, mental depression, and emotional instability sometimes develop. Recurrent fevers are the hallmark of chronic infections, in addition to fatigue, arthritis, and cardiac and other complications.	Contact, droplet, or aerosol exposure to infected fetuses, placenta and placental fluids, or infected tissues, contact with contaminated fomites. Ingestion of unpasteurized milk or milk products.	Avoid contact with fluid or tissues from abortions. Use of barrier precautions including gloves, protective eyewear, and a minimum of N95 respiratory protection are recommended when performing obstetric procedures or performing necropsies on high-risk animals.
Burkholderia mallei **(Glanders and Farcy)** Gram-negative bacterium	Horses and other equid species	Flulike symptoms, photophobia, lacrimation, diarrhea, septicemia, pneumonia, ulcerative and suppurative cellulitis, lymphadenopathy, splenic and hepatic abscesses.	Direct contact or droplet exposures to skin or mucous membranes; prolonged contact with infected animals is generally required for infection.	Enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols are warranted when working with infected animals.
Campylobacter jejuni and ***Campylobacter coli*** Spirochete bacterium	Cattle, sheep, goats, camelids, pigs, poultry, dogs, cats, other species	Disease varies from mild gastrointestinal distress that resolves within 24 hr to fulminating or relapsing colitis. Signs may include watery diarrhea, fever, nausea, vomiting, abdominal pain, headache, and muscle pain. Feces may contain frank blood. The acute symptoms usually diminish in 2-3 days and resolve in 7-10 days. Complications are rare but include Guillain-Barré syndrome, a disorder of the nervous system.	Fecal-oral transmission after contact with infected animals or their environments is a suspected but not well documented risk factor. Ingestion of contaminated water and food including undercooked poultry or meat, raw milk.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.

Clostridium difficile Gram-positive, spore-forming, anaerobic bacterium	Pigs, horses, cattle, dogs, cats, other species	Colitis leading to fever, abdominal cramps, diarrhea or dysentery, dehydration, and electrolyte imbalances. Rarely, severe colitis can lead to life-threatening complications such as megacolon, peritonitis, and colonic perforation.	Oral-fecal exposure through contact or droplet exposure to infected animals or their environments.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments; personnel should use respiratory protection when cleaning practices may produce droplet exposure. Avoid eating or drinking near animals or their environments.
Clostridium perfringens Gram-positive, spore-forming, anaerobic bacterium	All species	Wound infections can result in gas gangrene with accompanying fever, swelling, and erythema of affected area; systemic signs as disease progresses. Oral exposure is associated with abdominal cramps, diarrhea, and in rare cases necrotic enteritis and septicemia.	Wound contamination through contact or droplet exposure, ingestion of food contaminated with large numbers of bacteria, potentially oral-fecal exposure through contact or droplet exposure to infected animals or their environments.	Routine use of protective outer garments or dedicated attire when working with animals or their environments. Strict adherence to good hand-hygiene protocols and appropriate cleaning and management of wounds.

***Coxiella burnetii* (Q fever)** Gram-negative, spore-forming, intracellular bacterium	Primarily sheep, goats, cattle but also camelids, horses, dogs, cats, other species	Symptoms of Q fever include fever, chills, headache, fatigue, and chest pains. Pneumonia and hepatitis can occur in serious cases. In pregnant women infections can cause premature delivery, abortion, and infection of the placenta. In people with preexisting heart valve disease, endocarditis may occur.	Contact, droplet, or aerosol exposure to urine, feces, milk, and especially fetuses and placental tissues from infected animals. Respiratory exposure to contaminated dust, occasionally ingestion of unpasteurized milk or milk products.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Caution is warranted when handling tissues or fluids of infected animals or aborted fetuses. Consider use of eye protection when performing obstetric procedures on high risk-animals. Enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols are warranted when working with infected animals.
Cryptosporidium parvum (“**Crypto**”) Apicomplexan protozoal parasite	Ruminants, pigs, horses, poultry, dogs, cats, other species	Gastrointestinal disease, including signs of abdominal pain, nausea, anorexia, and profuse watery diarrheas. Severe infections can require hospitalization for fluid therapy and treatment of electrolyte imbalances. The disease is usually self-limiting but may be chronic and debilitating in immunocompromised individuals.	Oral-fecal transmission primarily through contact with infected animals or their environments but also through droplet exposures during cleaning.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments; personnel should use respiratory protection when cleaning practices may produce droplet exposure. Avoid eating or drinking near animals or their environments.
Dermatophilus congolensis Gram-negative, actinomycete bacterium	Cattle, sheep, goats, camelids, horses, rarely pigs, dogs, and cats, other species	Pustular desquamative dermatitis.	Direct contact with lesions on affected animals.	Use gloves when handling affected animals; strict adherence to good hand-hygiene protocols.

***Erysipelothrix rhusiopathiae* (erysipelas in pigs, erysipeloid in humans)** Gram-negative, facultative anaerobic bacterium	Pigs, other species	Characteristic cellulitis with raised red lesions and edema, intense pruritus. Skin infections can progress to involve other cutaneous sites and also rarely to systemic infections with flulike illness, septicemia, and arthritis.	Primarily via direct contact with infected animals, contamination of skin wounds. There are rare reports of transmission through ingestion of undercooked pork.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Gloves should be used when working with clinically affected animals. Avoid eating or drinking near animals or their environments.
Enterohemorrhagic*Escherichia coli*(e.g., *E. coli* serotypes O157:H7, O111, O26) Gram-negative bacterium	Cattle	Fever, enteritis, diarrhea or dysentery. In children under 5 and the elderly, infections can cause hemolytic uremic syndrome (hemolysis and kidney failure).	Oral-fecal transmission via contact or droplet exposure through exposure to cattle or their environments or through ingestion of contaminated water and food.	Strict adherence to good hand-hygiene protocols, routine use of protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.
***Francisella tularensis* (tularemia)** Gram-negative bacterium	Sheep, rabbits, cats, other species	Flulike illness, rashes, nausea, splenomegaly, papular or ulcerative lesions at site of cutaneous exposure, lymphadenopathy and ulcerative lymphadenitis, pleuropneumonia from inhalation or hematogenous spread; ingestion is associated with enteritis, stupor, and delirium.	Contact, droplet, or aerosol exposure to tissues or secretions of infected animals, ingestion of tissues from infected animals.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments is warranted when handling tissues or fluids of infected animals or aborted fetuses. Gloves, eye protection, and a minimum of N95 respiratory protection should be used when performing obstetric procedures on high-risk animals.

Foot-and-mouth disease virus Nonenveloped, single-stranded RNA virus	Cattle, sheep, goats, camelids, pigs, other species	Infection in humans is very rare; headache, fever, vesicular lesions on the hands or feet or in the mouth.	Contact, droplet, or aerosol exposure to infected animals.	When working with infected animals, enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols.
Giardia lamblia Flagellated protozoan parasite	Ruminants, pigs, poultry, dogs, cats, other species	Gastrointestinal disease, including signs of diarrhea, intestinal gas, stomach cramps, and nausea. A significant proportion of patients develop lactose intolerance while infected. The illness usually lasts 1 to 2 weeks, but chronic infections can last months to years.	Oral-fecal transmission through contact with infected animals or their environments or through ingestion of contaminated water or food.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.
Hendra virus Enveloped, single-stranded RNA virus	Horses, other species	Fever, lethargy, respiratory distress, neurologic signs including headache and disorientation.	Occupational contact with infected horses or their tissues.	Classified as a Biosafety Level 4 agent; contact with infected animals or their tissues should be avoided unless personnel are specifically trained to work with this agent.
Influenza virus (swine flu, avian flu) Enveloped, single-stranded RNA virus	Pigs, aquatic fowl Influenza viruses are generally host restricted.	Cross-species infection with influenza strains is extremely unusual under normal circumstances but has been rarely documented with swine and avian influenza viruses, resulting in fever, malaise, upper respiratory illness, pneumonia.	Close contact with infected pigs leading to respiratory exposure through contact, droplet, and aerosol routes.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. When working with infected animals, use enhanced barrier precautions, gloves, eye protection, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols.

Leptospira species ("**Lepto**") Spirochete bacterium	All mammals appear to be susceptible to at least one species of *Leptospira*.	Severity of illness varies greatly; signs include flulike illness with fever, chills, headache, and severe myalgia. Aseptic meningitis can occur, and 5%–10% of cases may be associated with multiple organ failure.	Skin or mucous membrane contact with urine or less commonly with blood and tissues of infected animals; ingestion in contaminated water or food.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. A minimum of N95 respiratory protection may be appropriate if droplet exposure to urine is likely. Avoid eating or drinking near animals or their environments.
Listeria monocytogenes Gram-positive bacterium	All species	Contact can result in papular lesions on hands and arms. Most commonly flulike illness and gastroenteritis. Less commonly infections can result in a mononucleosis-like syndrome (glandular listeriosis) or in fetal infection, abortion, stillbirth, neonatal septicemia, or meningoencephalitis. Meningoencephalitis is also noted in elderly and immunocompromised.	Immunosuppression greatly increases the risk of infection. Direct contact of skin or mucous membranes with infectious material, feces, or contaminated soil. Respiratory exposure to secretions from infected animals via droplet or aerosol routes. Oral-fecal exposures through contact, droplet or aerosols or ingestion of contaminated foods.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments, especially among immunocompromised people. Avoid eating or drinking near animals or their environments. Enhanced barrier precautions, gloves, eye protection, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols are warranted when performing obstetric procedures on high-risk animals or when handling aborted fetuses, or tissues and fluids of infected animals.

***Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium avium avium* (tuberculosis)** Acid-fast bacterium	All species	Signs depend on the organ system involvement. General signs of infections include anorexia, weight loss, fatigue, fever, chills. Signs of pulmonary infection include coughing and hemoptysis. Skin lesions are characterized by ulcers, papular lesions, and suppurative lesions. Signs of other organ involvement relate to the specific system.	Inhalation and oral exposure through respiratory droplet and aerosol transmission from infected animals, oral or cutaneous exposure through contact with infected tissues or contaminated surfaces, ingestion of raw or unpasteurized milk and milk products.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. A minimum of N95 respiratory protection may be appropriate if working with infected animals with clinical pulmonary disease or if performing necropsy.
Nipah virus Enveloped, single-stranded RNA virus	Pigs, other species	Fever, neurologic signs including drowsiness, headache, disorientation, and confusion, shortness of breath and coughing.	Occupational contact with infected pigs.	Classified as a Biosafety Level 4 agent; contact with infected animals or their tissues should be avoided unless personnel are specifically trained to work with this agent.
Parapox viruses (Orf virus, bovine papular stomatitis virus [BPSV]) Enveloped, double-stranded DNA viruses	Sheep and goats (Orf virus), cattle (BPSV)	Papular lesions at areas of contact (usually hands or arms). Lesions can be 1 cm in diameter, and surrounding tissues often become swollen and painful.	Contact with lesions on animals, scabs, or contaminated objects.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Gloves should be worn when examining mouths of animals suspected of being infected.

Rabies virus Enveloped, single-stranded RNA virus	All mammals	Encephalitis with accompanying behavioral and physical signs.	Bite injuries from infected carnivores, contact with infected animals, and contact with bats or their habitats are the most common methods of human exposure. Contact, droplet, and aerosol exposures to saliva and respiratory secretions of infected livestock are also thought to be possible methods of infection but are not well documented.	Complete isolation of animals suspected of infection, minimizing contact with personnel. When necessary to examine or manage suspect animals, use enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, eye protection, and strict adherence to good hand-hygiene protocols. Personnel that may be exposed to rabies should be vaccinated in accordance with Centers for Disease Control and Prevention (CDC) recommendations.[50]

Rift Valley fever virus Enveloped, single-stranded RNA virus	Cattle, sheep, goats, camelids, other species	Flu-like illness, photophobia, neck stiffness, and vomiting, which may progress in severe cases to one of three characteristic syndromes: eye disease, meningoencephalitis, or hemorrhagic fever. Retinal lesions are the prominent sign associated with eye disease.	Contact with blood, other body fluids, or tissues of infected animals. Accidental inoculation through sharps injuries or by inhalation of droplet or aerosols. People may also become infected by mosquitoes or possibly from ingestion of raw milk.	Extreme caution should be taken when working with animals during epidemics. An inactivated vaccine has been used experimentally to protect veterinary and laboratory personnel at high risk of exposure. Enhanced barrier precautions, gloves, eye protection, and a minimum of N95 respiratory protection are strongly recommended when working with high-risk animals or their tissues. Universal precautions should be taken when obtaining and processing specimens from patients. Samples should be handled only in laboratories by trained staff and processed in suitably equipped laboratories. Control of the mosquito vectors and use of personal protection is important.
Rhodococcus equi Gram-positive facultative intracellular bacterium	Horses; also found in feces of sheep and cattle	A problem with growing recognition, infections in immunocompromised people commonly lead to life-threatening chronic, progressive, granulomatous pneumonia. In contrast, infections are very rare in immunocompetent people and are typically less severe.	Regular contact with horses is a documented risk factor for infection, presumably through oral-fecal exposure via direct contact or droplets, although there is often no documented direct exposure to horses.	Immunocompromised people working with horses should adhere to good hand-hygiene protocols and routinely use protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.

Ringworm (*Microsporum* and *Trichophyton* species) Fungi	Cattle, horses, dogs, cats	Characteristic circular, well-circumscribed, red lesions that are pruritic. In immunocompetent people, infection is limited to the keratinized layers of the skin and hairs. However, in immunocompromised people, infections may extend to deep tissues or become systemic.	Direct contact with lesions on affected animals or with objects that have contacted affected areas.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Gloves should be worn whenever working with animals known to have dermatophytosis.
Salmonella enterica Gram-negative bacterium	All species	Flulike illness, gastroenteric disease, diarrhea or dysentery, septicemia.	Oral-fecal transmission through contact with infected animals, their environments, or contaminated items or through ingestion of contaminated water or food.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Enhanced barrier nursing precautions are needed when working with clinically affected animals. Avoid eating or drinking near animals or their environments.

***Staphylococcus aureus* (methicillin resistant *s. aureas* or MRSA)** Gram-positive bacterium	Horses, pigs, dogs, cats, other species	*Staphylococcus aureus* commonly colonizes the anterior nares and other sites without causing clinical signs. Infections most commonly involve skin and soft tissues, either as a primary infection or by infecting cuts or other skin injuries, including sites of intravenous injection or catheterization. Infections of the respiratory tract and urinary tract are also noted. The risk of infection may be increased in immunocompromised people. Skin infections most commonly result in swollen, painful, erythematous lesions that can often be purulent.	Direct contact with colonized or affected animals, droplet or aerosol exposure to discharge from infected sites.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with horses or pigs. Enhanced barrier nursing precautions and gloves should be required when working with animals known to be colonized or infected. Cuts and abrasions should be kept bandaged and disinfected regularly.
Vesicular stomatitis virus Enveloped, single-stranded RNA virus	Cattle, sheep, goats, camelids, pigs, horses, other species	Infections in humans are very rare but typically result in flulike symptoms. Less commonly, oral vesicles and cervical lymphadenopathy can be noted.	Mucosol exposure via direct, droplet, or aerosol exposures with clinically infected animals.	Enhanced barrier nursing precautions and gloves can be used when working with animals known to be colonized or infected. Eye protection and N95 respiratory protection may also be warranted when examining or treating lesions.

* This is not a complete list of all zoonotic diseases; less common diseases and those with vector-borne or solely foodborne routes of transmission are not included.

One of the most important factors in outbreak intervention is early recognition of potential problems. Ideally, infection control programs should be designed to allow early identification of related clusters of infection or disease either through laboratory testing, clinical disease reporting, or syndromic surveillance. When an infectious animal is exposed to a susceptible population, transmission may occur. First generation transmission—that is, transmission from the index case (directly or indirectly) to other animals—can be difficult to detect, particularly in situations when the index case is infectious before developing clinical disease. The most important control aspect related to the first generation of cases is prompt identification so that an outbreak can be recognized early enough to implement measures to reduce the risk of further transmission to a second generation of cases. Often outbreaks

are not identified or addressed until multiple generations of transmission have occurred, thereby increasing the overall morbidity and mortality and complicating the response.

General principles of outbreak response include identification of the infectious agent, identification of infectious animals, identification of animals that have likely been exposed, determination of the mode of transmission, and prevention of further transmission by means such as isolation, implementation of barrier precautions, active surveillance, environmental surveillance, increased environmental disinfection, restriction of animal and personnel movement, and under extreme conditions minimization of new exposures through restriction of admission of new patients.

Although useful, initial intervention measures do not require definitive identification of the causative agent. In the absence of a confirmed cause (e.g., diarrhea cluster of unknown cause), outbreak intervention can still be performed using general infection control practices combined with knowledge of appropriate response to the most likely causes. General principles such as isolation of infected or affected animals and their direct contacts, use of barrier precautions, close attention to personal hygiene, restriction of animal and human movement, regular examination of animals, and careful attention to cleaning and disinfection are important measures that are useful for most types of infectious disease outbreaks. Indeed, these measures alone will often constitute the full response after a causative agent is identified.

Identification of animals likely to be shedding the agent responsible for the outbreak is critical. Definitive confirmation is not required, and a syndromic response is often better. For example, in the midst of a *Salmonella* outbreak it is wise to consider all animals with diarrhea, depression, or fever as likely to be infected and shedding bacteria even if culture results have been negative. This will result in some misclassification, but erring on the side of being overly sensitive in identifying infectious animals is the more appropriate response when trying to halt the spread of disease. The main problem with this type of response is imposing excessive strain on available resources (e.g., isolation stalls, personnel time) because of excessive misclassification.

Identification of potentially exposed animals is also critical. Depending on the pathophysiology of disease, these animals may or may not require segregation or isolation. For some pathogens, clinical disease precedes development of the infectious state, so exposed animals can be monitored and isolated if required. For example, horses exposed to *S. equi* develop fever before shedding the organism,[51] so close monitoring of body temperature of exposed animals and prompt isolation of animals developing fever may be sufficient to prevent propagation of an outbreak. For many pathogens, screening of all potentially exposed animals can be useful. In particular, the use of rapid screening techniques that can provide a turnaround time of a few hours (e.g., antigen detection test for equine influenza, *S. equi* PCR) can be very useful. However, testing strategies should also include some use of culture so that whole organisms will be available to aid epidemiologic investigations. Widespread screening of hospitalized animals will often be required to determine the extent of the outbreak and facilitate removal of infectious animals from the population. Therefore, if screening is imposed as a response to suspected spread of nosocomial infections, it is essential that it not be an elective procedure. It is prudent for facilities to have previously considered how costs for diagnostic testing will be distributed in the event of suspected nosocomial infections. Surveillance for shedding of specific contagious agents at the time of admission can facilitate prevention of outbreaks as well as intervention responses. In situations where recently exposed animals do not necessarily develop consistent overt clinical signs or where rapid diagnostic testing is not available, it may be necessary to segregate all potentially exposed animals, either in an isolation unit or in the main hospital.

Determination of the likely mode(s) of transmission is also required for initiation of an effective response. This is usually relatively clear based on the identity of the known or suspected pathogen. However, in general, all agents of concern for nosocomial infection will spread through contact and common vehicle transmission, and therefore

controlling all methods of contact exposure to patients will be critical in response to suspected outbreaks. Although droplet transmission might be most important for respiratory agents, practicalities of cleaning hospital environments for large animals usually necessitate use of large volumes of water, which can also create hazards related to droplet transmission. Therefore the potential for droplet transmission should also be tightly controlled in response to suspected outbreaks. Generally, only highly contagious viral respiratory agents pose a hazard through airborne transmission. However, in situations in which routes of transmission are not clear, it is prudent to assume the worst and manage the outbreak as if the pathogen were highly transmissible by multiple routes until proven otherwise.

Prevention of further transmission is obviously one of the most important goals of outbreak response. A variety of factors need to be considered to achieve this. In addition to identification of infectious animals, measures need to be established to prevent direct and indirect contact of these animals with other animals and the general hospital environment. Isolation and the use of barrier precautions can achieve this. The response to implemented infection control measures should be closely monitored to determine their adequacy, with an understanding that there is an inherent lag time from implementation of measures to control of the outbreak that is proportional to the incubation period for infectious diseases.

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At times, partial or complete closure of the facility may be useful or necessary. Restricting new admissions decreases the number of newly susceptible individuals that might promote propagation of an outbreak. Furthermore, if new infections appear to be occurring despite implementation of best control efforts, it is important to consider whether it is prudent or ethical to continue admitting new patients. It is also critical to consider the tremendous burden that can be created by the need to deal with infection control measures and the possible effects on patient care. During outbreaks, stall space, particularly isolation space, may become limited, and decreasing the number of admissions facilitates depopulation of the facility for proper cleaning and disinfection. Clinical personnel are often overworked during outbreaks because of the number of ill animals, and excessive workload can contribute to breaches in protocols. There may be reluctance among some people to restrict hospital admissions because of potential negative impacts related to public relations and finances, but early, short-term closure of a facility to stem a small but developing outbreak is much better than a subsequent longer closure in response a larger outbreak with more affected animals. A key component of facility closure is proper communication to staff and the public, emphasizing the proactive approach that is being taken to protect patients and clients and to prevent a major problem from developing. Regardless of whether it is deemed necessary to restrict admission of new patients, as described previously, whenever outbreaks of nosocomial infections are suspected, it is critical to consider whether standard informed consent procedures suitably convey the risks associated with hospitalization to clients.

If environmental contamination is suspected of being widespread, complete depopulation of a ward or even the entire hospital may be necessary to allow for thorough cleaning and disinfection. The availability of multiple wards can facilitate this process, as individual problem wards can be closed and disinfected while the hospital remains functioning. Assuming sensitive culture or other antigen detection methods are available, postdisinfection environmental screening may be indicated for certain pathogens (e.g., *S. enterica*) before a facility is reopened.

Although vaccination is often perceived as being a cornerstone of infection control, the indications and limitations of vaccination must be considered. No vaccine will confer 100% protection, and vaccination should never be used as a replacement for good infection control practices. A more appropriate perspective is that vaccination is principally useful when more useful infection control methods have failed.

Requiring vaccination before hospital admission is an area that has received limited commentary in large animal practices. Although vaccination requirements are difficult to enforce in animals admitted for emergency procedures, it may be reasonable for facilities to consider encouraging or requiring vaccination against relevant

pathogens before admission for elective procedures. For example, requiring vaccination before admission for influenza in horses or bovine viral diarrhea virus in pregnant cattle or alpacas could decrease the risk of infection and transmission in hospitals. Problems that might be encountered with such an approach include the lack of relevant efficacy data for many vaccines, potential concerns regarding adverse effects with some vaccines, difficulty ensuring compliance, and competitive issues if all competing practices do not have the same standards.

Vaccination may be a useful intervention measure during some outbreaks, but efficacy in these situations has not been evaluated. It is important to remember that there are three possible outcomes associated with any intervention: it may help, it may have no effect, or it can be harmful. For vaccination during an outbreak to be helpful in control efforts, the vaccine must be given to susceptible animals before exposure, must initiate a protective response before natural exposure, and must not be harmful when administered to animals that are incubating disease. These criteria are often difficult or impossible to meet in the midst of an outbreak. The greatest potential use for vaccination during an outbreak is likely with the use of intranasal influenza vaccination, as this type of vaccine can provide a rapid and effective immune response and is not contraindicated in exposed animals.

46.10 INFECTION CONTROL ISSUES RELATED TO SPECIFIC PATHOGENS

Although all contagious diseases have the potential to be important hazards for the health of individual patients, there is more empiric evidence regarding the importance of some diseases. Furthermore, although safeguarding the health of veterinary personnel must be a priority for all veterinary practices, some zoonotic diseases have been shown to be of greater concern. Information is listed in the following sections regarding control of diseases of particular importance as nosocomial and zoonotic disease hazards.

46.10.1 Salmonella

S. enterica is the agent most commonly reported in association with nosocomial disease outbreaks and closure of large animal hospitals. In a recent survey of teaching hospitals from AVMA-accredited institutions, 31 of 38 responding institutions (82%) reported documenting outbreaks of nosocomial disease during the previous 5 years and 65% of institutions reported *S. enterica* as being associated with an outbreak (20 of 37).[49] Additionally, most of these institutions (17/20) had to restrict admissions to reduce patient risk or mitigate contamination, and 11 of these institutions closed at least part of their facilities completely. All species are susceptible to infection, but hospitalized cattle from intensively managed populations generally have the highest prevalence of shedding and camelids the lowest. The likelihood of shedding in patients while hospitalized is greatly influenced by the prevalence of infection in animals at home premises. A notable number of patients shed *Salmonella* without evidence of associated illness, but patients are significantly more likely to shed if they are systemically ill. This is especially true if animals show signs of gastrointestinal illness. Numbers of organisms shed per gram of feces are generally much greater in clinically affected animals. Animals known to be infected with *Salmonella* should be managed in isolation with strict barrier precautions and hand-hygiene protocols. Shedding tends to be more commonly detected in the summer and fall and may also be generally more common in warmer climates. Although nosocomial outbreaks are usually detected in association with the spread of clinical disease, subclinical infections can be more common than clinical infections during outbreaks. Zoonotic infections in veterinary personnel have been commonly detected in association with nosocomial outbreaks. There is apparent variability among strains with regard to virulence, infectivity, and ability to persist in the environment, and this strain variability may be a very important determining factor regarding nosocomial outbreaks of infection. Environmental contamination near infected patients is the rule rather than the exception, and active surveillance has shown that contamination can become disseminated to quite distant areas of the hospital from only a single infected patient. In one study 12% of 452 environmental samples collected over 10

weeks in a nonepidemic period using electrostatic household wipes were positive for *Salmonella*.[46] Experience has shown that environmental contamination is even greater during outbreaks. In nonepidemic situations there tends to be great variability in phenotypic markers (serogroup, serotype, and antimicrobial susceptibility) among isolates recovered from patients over time, which often makes it possible to differentiate isolates in epidemiologic investigations. In other situations, especially when certain strains are circulating actively in the region of a hospital, use of genetic analysis may be necessary in order to differentiate strains of *Salmonella* for purposes of epidemiologic investigations. Culture methods used in diagnostic laboratories are highly variable, which can significantly affect assay sensitivity. Veterinarians should seek out laboratories that are known to have optimized culture methods for use in diagnostic situations. PCR assays for *Salmonella* are available commercially at a number of laboratories. However, because of the importance of phenotypic and genotypic comparisons of isolates that are conducted as part of epidemiological investigations, PCR assays are not recommended for regular use in surveillance programs without parallel analysis using culture. Active surveillance programs are commonly used in large hospitals as a management tool to detect clinical and subclinical infections in large animal patients. In addition, environmental surveillance is sometimes used as an adjunct to detect environmental contamination. All common disinfectants are effective against *Salmonella* organisms under optimal conditions. However, its common association with fecal material, other organic matter, and dirt necessitates careful adherence to good cleaning (physical disruption of surface matter using detergents) and disinfection procedures in order to minimize the likelihood of environmental persistence. Mitigation in response to nosocomial outbreaks requires thorough decontamination of all environmental surfaces, which may be possible only after closure to new admissions, although disinfectant misting may be a useful alternative in some situations.[52]

46.10.2 Clostridium difficile

Although less commonly implicated with diarrheic disease than *S. enterica, C. difficile* is a potentially important nosocomial pathogen in horses. *C. difficile* should be considered as a differential diagnosis in horses with diarrhea and duodenitis-proximal jejunitis. Standard infection control methods used for salmonellosis should be adequate to control transmission of *C. difficile,* with the exception of disinfection. Because *C. difficile* is a spore-forming bacterium, disinfection can be difficult. Clostridial spores are highly resistant to environmental degradation, and most disinfectants that kill *Salmonella* are ineffective against bacterial spores, with the exception of bleach (hypochlorite solutions). Accelerated stabilized peroxide and peroxygen disinfectants may also be effective, although less information is currently available. An additional, albeit mostly unsubstantiated concern is the potential for zoonotic transmission of *C. difficile* from horses or cattle to humans. The strains of *C. difficile* isolated from animals are often indistinguishable from those that cause disease in people. Therefore, animals infected with *C. difficile* should be considered as potential sources of zoonotic infections in humans.

46.10.3 Cryptosporidium parvum

Animals of all ages in a variety of host species have been shown to shed *C. parvum* oocysts, but the shedding prevalence is much greater in young animals, and the primary infection control hazard involves shedding by diarrheic neonates, especially calves. This is because of the extraordinary numbers of oocysts shed by affected young animals, the small infectious dose, and the hardiness of organisms. Affected calves can shed more than 10^7 oocysts per gram of feces during peak shedding, whereas humans and other animals can be clinically infected with fewer than 100 oocysts, although there does appear to be some difference among individuals and also among strains. To further complicate control, oocysts are profoundly resistant to all disinfectants that can

be regularly used in hospitals. Research has shown there are different lineages of *C. parvum* that relate to host range; genotype 1 appears to infect only humans, whereas genotype 2 (sometimes called *bovine genotype*) infects a wide variety of other species, including domestic large animals and humans. Cryptosporidiosis is an important zoonotic disease hazard in veterinary personnel, and there are a number of documented outbreaks involving animal caretakers. *Cryptosporidium* is considered to be a relatively common nonviral cause of self-limiting diarrhea in immunocompetent persons, particularly children. Clinical disease can be severe and even life-threatening in immunocompromised persons. Diarrheic neonates can be easily and inexpensively screened using direct microscopic examination of fecal smears prepared with acid-fast stains. Regardless, it is very prudent to house diarrheic neonates in isolation and handle with strict barrier precautions and hand-hygiene protocols. Personnel cleaning these housing areas should avoid using high-pressure water, to minimize the risk of aerosol and droplet exposure. This is complicated by the resistance of coccidian parasites to disinfectants, which necessitates the reliance on vigorous scrubbing with soap and rinsing with copious amounts of water in decontamination efforts. The likelihood of inadvertent oral exposure while cleaning can be reduced by using face shields or N95 disposable masks along with gloves.

46.10.4 Equine Rotavirus

Although outbreaks of rotavirus are not uncommon on breeding farms, outbreaks in veterinary clinics are rare. Equine rotavirus is of most concern in facilities with a large neonatal caseload. Rotavirus may be shed in the feces of affected foals, clinically normal foals, and adult horses. Therefore prevention of exposure is difficult. However, it is likely that clinically affected foals are the most common source of infection, through direct contact or common vehicle exposure. As a result, isolation of affected animals and the use of barrier precautions are the most important infection control measures. With the exception of disinfectants, protocols directed at control of *S. enterica* should be adequate for rotavirus control. Little specific information is available regarding the relative effectiveness of different disinfectants on equine rotavirus. However, as a nonenveloped virus, equine rotavirus should be expected to be resistant to environmental degradation and many disinfectants commonly used in veterinary medicine. The use of phenolics has been recommended because of their better activity in the presence of organic debris. Oxidizing agents probably have similar effectiveness and may be preferable because they have a much lower potential for toxicity.

46.10.5 Bovine Viral Diarrhea Virus and Border Disease Virus

The closely related members of the genus Pestivirus are not commonly considered nosocomial disease hazards, but this may be more because of a lack of detection than a lack of occurrence. The main infection control hazard is related to exposure of susceptible pregnant cattle, sheep, goats, or camelids to persistently infected animals that continuously shed large amounts of virus. The long period between infection of pregnant females and the birth of affected offspring complicates the ability to make relevant observations about the frequency of nosocomial infections. Therefore it may be important to encourage or require vaccination of valuable pregnant cattle or alpacas before admission. In addition, animals known or suspected to be persistently infected should be managed in isolation with barrier precautions to minimize transmission. This includes neonates showing signs of congenital infection. Increased biosecurity precautions should also be used with animals from herds with a recent history of disease related to these viruses. Direct contact with persistently infected animals is an efficient method of transmission, but limited research shows that calves can be infected through contact with contaminated stalls and through droplet or aerosol exposure over a distance of at least 1.5 m.[53] Appropriate use of cleaning and disinfection methods should readily decontaminate the environment.

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46.10.6 Strangles *(Streptococcus equi equi)*

An important aspect of *S. equi* control is identification and management of subclinically infected animals. Syndromic guidelines for isolation on admission (e.g., isolation when patients are admitted from farms with recent a history of clinical *S. equi* infections, or isolation of horses with fever of unknown origin or unexplained nasal discharge) can help in managing potentially infectious horses so that they can be isolated pending the results of screening. The ubiquitous nature of *S. equi* and the possibility that essentially any hospitalized horse could be a subclinical carrier means that there is an ever-present, if low, likelihood of *S. equi* introduction into the hospital environment. Experience suggests that routine universal screening of horses admitted to veterinary hospitals is not necessary to control nosocomial *S. equi* infections. However, screening and isolation of horses from farms with endemic *S. equi* would be a reasonable control strategy. Standard infection control measures, including preventing direct contact of hospitalized animals, optimizing hand hygiene, and using appropriate cleaning and disinfection, should be useful for reducing the risk of *S. equi* transmission should a colonized horse be admitted. Vaccination in the face of an outbreak with vaccines that are currently available is not recommended because of a lack of proven efficacy and concerns regarding development of purpura hemorrhagica. There is also no evidence of a need to require vaccination of elective cases before hospital admission. *S. equi* is susceptible to all routinely used disinfectants, when used properly.

46.10.7 Equine Influenza

Influenza is one of the most contagious diseases affecting horses. Immunity is transient, and horses can be repeatedly affected during their lifetime. There is no carrier state, and maintenance in a population is dependant on transmission from one acutely infected horse to another. In horse populations aggregated at racetracks, shows, or other venues, attack rates can reach 15% to 30%.[54] The incubation period from exposure to onset of clinical signs is typically about 2 to 4 days, which commonly coincides with the onset of virus shedding. Horses are often febrile and obtunded at the onset of disease. Paroxysmal coughing is a classical sign of influenza infection that develops in some horses as disease progresses. Because of its contagious nature, identification of multiple acutely febrile horses can be an early indication that influenza virus is spreading in the population. Rapid identification and confirmation of animals shedding virus allow initiation of efforts to minimize contagious spread. Antigen detection assays are commercially available and very useful for rapid confirmatory testing (e.g., Directigen Flu A, BD Diagnostic Systems). However, these assays have limited sensitivity; virus shedding was detected in only approximately 30% of clinically affected horses during outbreaks using this assay, and so tests should be performed on multiple horses and interpreted in the aggregate for the population.[55] Negative test results for individual samples should be interpreted with caution because of the consequences associated with not using appropriate control measures during an outbreak of a highly contagious disease. PCR tests are available and may be more sensitive than antigen detection assays, but published validations of these assays are generally unavailable. Virus can be transmitted through aerosol, droplet, and contact transmission and can easily be transmitted over several feet in respiratory aerosols generated by coughing horses. Therefore horses confirmed to be infected should be managed in complete isolation with full barrier precautions, paying strict attention to hand-hygiene protocols. Influenza virus can survive on surfaces at most for a few days in a cool, moist environment. As an enveloped virus, influenza is susceptible to damage from extreme environmental conditions and is readily inactivated by all common disinfectants if they are properly applied. Although clinically affected animals are the most likely to shed large amounts of virus, in unaffected horses sampled during large outbreaks, seroconversion and virus shedding can be found in about 30% and 5% of the exposed populations, respectively.[54,55] Therefore it is prudent to increase infection control precautions for all

exposed but apparently unaffected horses in order to minimize risks of transmission. Early vaccination of all horses with intranasal vaccine may be of value in abbreviating the course of an epidemic. If new admissions are allowed when there is an elevated risk of influenza virus infection, horses should be required to have been recently vaccinated before admission (preferably a minimum of 2 weeks before admission) with vaccines having proven efficacy. Regardless of vaccination history, it is unwise to admit very young or immunocompromised horses when there is an increased risk of infection with influenza virus.

46.10.8 Equine Herpesviruses

Equine herpesvirus (EHV) types 1 to 5 are ubiquitous in horse populations and are highly contagious. EHV-1 and EHV-4 are the most widely recognized as important causes of outbreaks of disease in horses, and nosocomial transmission of both agents has been noted. EHV-4 infections are associated with contagious respiratory disease that principally affects horses under 3 years of age. EHV-1 infections are associated with respiratory disease, neurologic disease, acute to peracute pulmonary vasculitis, and abortion. Immunity is relatively short-lived, and infections are likely to occur throughout the life of horses. Many if not most of these infections are undetected or occur with only mild clinical signs. The most common clinical sequela of infection is mild respiratory disease during the first 2 years of life. Infrequently, EHV-1 infections can result in more severe complications such as abortions in pregnant mares or paralysis. All EHV-1 and EHV-4 infections originate in the respiratory tract, but epidemiologic evidence suggests that contact and droplet transmission between horses in relative proximity is much more common than aerosol transmission over greater distances. Fever is commonly the initial clinical sign exhibited by infected horses, and identification of multiple acutely 1548
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febrile patients can be an early indication of nosocomial spread of EHV in the population. Most horses can be shown to be latently infected with EHV-1 and EHV-4 by the time they reach adulthood, and subsequently any hospitalized horse might serve as a source of infection for other patients by recrudescing virus in response to stresses of disease, hospitalization, and transport. However, clinical experience suggests that nosocomial spread most commonly originates from clinically affected horses. Therefore, rapid identification of animals suspected of being infected, isolation of affected horses, and use of barrier precautions with appropriate hand-hygiene protocols are generally effective for minimizing the risk of nosocomial transmission. All horses exhibiting ascending weakness, paresis, or paralysis should be suspected of having EHV-1 infection and managed in isolation until they can be proven to have stopped shedding or another diagnosis is confirmed. Herpesviruses are enveloped viruses, and routine cleaning and disinfection procedures should be adequate for decontamination of surfaces, assuming appropriate protocols are followed. PCR testing of nasal secretions is the most useful assay for rapid confirmatory testing. Serial testing is useful for establishing that shedding has stopped. Without adjunctive testing, infected horses should be quarantined for a minimum of 28 days after cessation of disease. Using serial testing as a confirmatory adjunct, this quarantine period might be shortened to 14 days after cessation of disease. However, experimental infection studies have shown that shedding can be intermittent, and negative test results must be interpreted with caution.

EHV-3 is less commonly regarded as a nosocomial problem but has been noted to be spread through contact with contaminated materials during reproductive procedures as well as between horses during coitus. Therefore it is a notable hazard for practices that specialize in reproductive services. EHV-3 causes coital exanthema, a pustular disease affecting the vulva and vagina of mares and the penis and prepuce of stallions. Appropriate cleaning and disinfection of materials used in reproductive examinations, avoiding use of examination sleeves and gloves with multiple horses, and rigorous adherence to sound biosecurity precautions for breeding populations should control spread of EHV-3. The prevalence of latent EHV-3 infections is not well documented. Recently, evidence associating respiratory disease in young horses and EHV-2 or EHV-5 infection has been published,[56] but the significance of these agents in the occurrence of nosocomial disease is unknown.

46.10.9 Methicillin-Resistant *Staphylococcus aureus*

MRSA is emerging as an important veterinary and zoonotic pathogen. In large animals, MRSA infections have been most commonly identified in horses and pigs. Transmission of MRSA between these species and attending personnel can occur, and MRSA colonization and infection appear to be an emerging occupational risk associated with large animal veterinary practice. Transmission of MRSA is thought to mainly occur through direct or indirect contact between infected or colonized people or horses and hospitalized horses. Despite the potential for respiratory tract colonization, the potential for droplet and airborne transmission is minimal. The largest nosocomial infection problem related to this pathogen in large animals has been associated with the infection and colonization of equine patients. Infections are principally noted at surgical sites and wounds, whereas colonization predominantly occurs in the nasal passages, although gastrointestinal colonization has also been noted. If not identified by active surveillance, colonized horses can be silent yet prolific reservoirs for infection of humans and horses. Prevention of MRSA transmission requires careful attention to practices that prevent contact and common vehicle transmission, including use of good hand-hygiene practices, restriction of horse contacts and isolation of infected or colonized animals, and use of specific measures aimed at identifying carriers. All colonized or infected horses should be treated as infectious, housed in isolation, and handled with strict attention to contact barrier precautions. Screening by culture of nasal swabs collected at the time of admission can help control MRSA in areas where it is endemic in the community or the horse population. Screening of personnel may be required periodically if there is epidemiologic evidence of nosocomial transmission or zoonotic infections. Personnel screening can be a difficult and contentious area, so it is wise to develop screening guidelines in advance of an outbreak.[57] *S. aureus* is susceptible to most disinfectants, if used properly.

46.10.10 Coxiella burnetii

Coxiella burnetii is the causative agent associated with Q fever. Although most infections in humans are subclinical, personnel that contact livestock have a greater risk of infection, and disease can be severe and even fatal in a small portion of cases. It is also highly infectious, has a low infective dose, and can be transmitted through contact as well as by droplet and airborne routes. *C. burnetii* can be found in a variety of animal species, but zoonotic transmission is most commonly associated with periparturient ruminants (especially small ruminants). Serum antibody tests, antigen detection assays, and PCR assays can be used to identify infected animals, but the sensitivity of these assays has been questioned. Because of the potential significance of clinical infections in humans, all attending personnel should be appropriately aware of the zoonotic potential and risks associated with Q fever. The risk of serious clinical consequences should noted in particular by pregnant women and people with valvular heart disease or immunosuppression. Medical histories for individuals and flocks should be considered to determine if there is an indication that *C. burnetii* may be a greater than average risk. Biosecurity measures that could be used to minimize hazards to people with a high risk of clinical infection include isolating periparturient small ruminants, paying strict attention to hand-hygiene protocols, and using respiratory protection and barrier nursing precautions when handling potentially infected animals. Particular care should be taken during parturition and when handling aborted fetuses and newborn small ruminants. For animals known to infected, care should be used when cleaning and disinfecting stalls or other housing environments, and contaminated bedding and other materials should be handled with caution.

46.10.11 Antimicrobial Resistance and Drug Use

Although antimicrobials are undoubtedly required for proper management of a significant percentage of hospitalized large animals, it is reasonable to consider whether antimicrobial resistance and antimicrobial drug use affect the occurrence of or the ability to control nosocomial infections. The first relates to outbreaks of nosocomial infections with bacteria that are resistant to multiple antimicrobial drugs. These outbreaks are not extremely common but are a noted occurrence in human and veterinary hospitals and often occur in association with care in specific hospital units such as a critical care or surgery facility. Agents frequently identified in association with these outbreaks include enteric organisms such as *E. coli* and enterococci, skin commensals such as *S. aureus*, and *Pseudomonas* and other bacteria. Significant research into these organisms has identified 1549
specific strains and even specific genes that are commonly identified in association with agents responsible for 1550
these outbreaks (e.g., MRSA, vancomycin-resistant enterococci [VRE], bacteria with extended spectrum β-lactamase resistance). The role of antimicrobial use in specific patients or even in specific hospitals in promoting the occurrence of nosocomial outbreaks is not always conclusive. However, some experimental evidence does show that treatment with a specific antimicrobial drug is associated with an increased propensity for shedding of bacteria that are resistant to analogous drugs.[58] Therefore common use of a particular drug within a hospital could apply selective pressure that more generally promotes colonization with resistant bacteria,[59] or it could enable or promote the survival of specific bacterial strains capable of causing nosocomial epidemics (e.g., VRE and MRSA). These concerns are supported by specific documentation that antimicrobial drug exposure can be associated with increased likelihood of shedding of enteropathogens[60,61] and multidrug resistant pathogens.[62] In addition, antimicrobial drug exposure is a recognized risk factor for colitis in horses, which can be one of the most important infection control concerns in large animal facilities. Therefore efforts to reduce antimicrobial use and ensure logical (prudent) use can be beneficial to the individual patient and other hospitalized animals, in addition to addressing the more abstract concerns about emergence of antimicrobial resistance.[58] Surveillance aimed at benchmarking the use of antimicrobial drugs over time, or to monitor use for specific conditions or in specific circumstances (e.g., outside of regular hours), may be useful for guiding policy decisions, but it is not useful for identifying specific occurrences of “imprudent” use. Of greatest importance is education so that all individuals with prescribing power understand the issues and the reasons for careful antimicrobial use. Measures such as developing selection algorithms for patients with specific types of disease and restricting the use of certain drug classes (e.g., glycopeptides) have been used by some facilities and may decrease the likelihood of some occurrences of nosocomial infection.[59]

46.10.12 Management of Donor Animals

It is increasingly common to use animals owned by hospitals or veterinary personnel as donors for blood and ingesta (e.g., ruminal fluid) transfer to patients. Animals used for this purpose should be known to have a very low risk of contagious diseases, should be housed away from hospitalized patients, should be clinically healthy at the time of specimen recovery, and should be screened periodically for diseases that could be transmitted by use of transfer products. Diseases of concern that might be transferred by blood products from ruminants include bovine leukemia virus, bovine viral diarrhea virus and border disease virus, and anaplasmosis; similarly, horses should be screened for equine infectious anemia infection. Ingesta donors should be screened for Johne's disease *(Mycobacterium paratuberculosis avium)* and *S. enterica*.

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47 Chapter 47 Prevention, Detection, and Response to Foreign Animal Diseases

Pam Hullinger

Perhaps one of the most critical roles that private veterinary practitioners play on a daily basis is serving as the nation's front line of defense against exotic, transboundary, and foreign animal diseases (FADs)—the important transmissible livestock or poultry diseases that are believed absent from the United States, but that if introduced would cause significant adverse animal health, public health, or economic consequences to the nation. Although many of these disease threats are known, new or "emerging" diseases may also enter the United States and affect human or animal populations. The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) has primary responsibility for addressing foreign and emerging diseases of livestock, and it works closely with state animal health officials, private veterinary professionals, and the livestock industry to conduct surveillance and detect, control, eradicate, or mitigate the impacts of these diseases on the industry and the public. A list of the diseases successfully eradicated from the United States is in Box 47-1. The *Code of Federal Regulations* (CFR), Title 9, part 53[1] details the federal government's list of reportable diseases of livestock and poultry and its policies and procedures for the diagnosis, appraisal, euthanasia, and disinfection of livestock and poultry infected with these diseases. The list specifically includes foot-and-mouth disease (FMD), rinderpest, contagious pleuropneumonia, exotic Newcastle disease (END), highly pathogenic avian influenza (HPAI), and infectious salmon anemia and generically includes "any other communicable disease of livestock or poultry that in the opinion of the Secretary constitutes an emergency and threatens the livestock or poultry of the United States." In addition to the federal list, many states require the reporting of additional disease conditions beyond those specifically listed in the CFR. Additional diseases specified by states may include diseases of public health importance, such as equine encephalomyelitis, or other domestic diseases of regulatory importance or interest, such as bovine trichomoniasis. Licensed, practicing veterinarians are responsible for maintaining a familiarity with the federal reportable disease list as well as those of the states in which they practice. The reportable disease list for each state can be obtained through the state veterinarian's office. States may also have their own more specific policies and procedures for the diagnosis, appraisal, euthanasia, and disinfection of livestock and poultry infected with such reportable diseases. Box 47-2 lists some reportable diseases of horses.

The Office of International Epizootics (OIE)[2] is an international organization, representing more than 167 member countries, that seeks to provide leadership and guidelines to ensure transparency and solidarity in the management of the global animal disease situation. The OIE publishes health standards for international trade in animals and animal products as well as criteria for the validation and certification of diagnostic assays. Policies and procedures that the federal government implements to manage the intrusion of FADs into the United States are often aligned with the OIE health standards and guidelines to help ensure the most rapid and efficient recovery of U.S. trading status. Another equally important function of the OIE is to provide an early warning system to enable countries to have rapid situational awareness and to act quickly to protect themselves when outbreaks of OIE reportable diseases are confirmed in member countries. More than 130 animal diseases are reportable to the OIE. It is important to remember that some of the domestic diseases that are present in the United States, such as bluetongue, are reportable to the OIE and have implications on trade with countries free of those diseases.

To protect the long-term, overall health and viability of U.S. animal agriculture, any incursion of a FAD must be rapidly identified and controlled. In the United States, ideally control leads to the eradication of the disease and full return to the status present before the outbreak. These FAD eradication efforts present significant short-term costs to affected industries as well as the government and the public. In some cases the effects become long term, lasting for years, and some industries may never fully recover. Most FAD incursions have a significant economic cost associated with disease control and eradication efforts. The costs associated with FAD control include the direct

costs of disease control as well as the potential loss of foreign trade and the indirect costs to the affected industries that result from the implemented control measures, such as livestock movement restrictions. Direct costs to the government include personnel costs, indemnity costs (cost to buy diseased animals from producers for destruction), and the cost of necessary supplies and equipment for euthanasia, carcass management, and disinfection. In addition to these direct control costs, one of the most immediate consequences of a FAD occurrence in the United States would be the loss of export markets and disruption of normal business continuity in the United States. The indirect costs to the affected livestock sectors and other affected industries that would result from the disruption of the normal business continuity are likely to be the most significant economic costs. One example of such an indirect cost or loss associated with disease control may be the reduction or loss of income for a dairyman who is no longer able to ship his milk across state lines to his customary processor. For all FADs, early detection and rapid application of situational awareness to assess the extent of the outbreak and efficiently implement necessary controls to minimize further spread will minimize the overall impact of the outbreak on the affected producers, the affected industries, and the U.S. economy as a whole.

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Box 47-1 Years When Foreign Animal Diseases Were Eradicated from the United States

1892—Contagious bovine pleuropneumonia

1929—Foot-and-mouth disease

1929—Fowl plague

1934—Glanders

1942—Dourine

1943—Texas cattle fever

1959—Vesicular exanthema

1959—Screwworm (southeastern United States)

1966—Screwworm (southwestern United States)

1971—Venezuelan equine encephalitis

1973—Sheep scabies

1974—Exotic Newcastle disease

1978—Classical swine fever

1985—Highly pathogenic avian influenza

2003—Exotic Newcastle disease

2004—Highly pathogenic avian influenza

47.2

Box 47-2 Reportable Diseases of Horses*

African horse sickness

Contagious equine metritis

Dourine

Glanders *(Burkholderia mallei)*

Hendra virus

Japanese encephalitis

Piroplasmosis

Venezuelan equine encephalomyelitis

Vesicular stomatitis virus

* The list will vary by state.

The risk of a FAD incursion into the United States today is much greater than it was in the past. There are two main reasons for this. First, there has been a rapid expansion of international trade and travel, and in the ever-expanding climate of free trade, this can only be expected to continue. With a greater volume of people, animals, and animal products entering the United States on a daily basis, the opportunity for a FAD to be unintentionally introduced is greater. Second, in the wake of the World Trade Center bombing on September 11, 2001, there is heightened awareness and concern about the possibility of agroterrorism, or the deliberate introduction of a biologic agent targeting livestock for the purposes of causing economic damage and societal instability. Whether a FAD is

intentionally or unintentionally introduced, the detection of the first case as soon as possible is critical to minimizing the overall impact of the resulting outbreak.

Private veterinary professionals need to be familiar with the clinical signs associated with FADs, especially those that can be confused with signs of domestic diseases. When veterinary professionals are concerned about the possibility of a FAD, they need to know how to contact their federal or state animal health officials, who will consult with them on the history of the herd or flock, examine the affected animals, and take and submit necessary samples for testing at no expense to the producer or veterinarian. Testing will be prioritized by disease and level of concern. Both the producer and private veterinarian should be contacted with regular updates as test results become available. Hundreds of investigations such as this occur annually in the United States, and fortunately most lead to the determination that a FAD is not involved. It is the FAD that goes undetected or unreported for some time because of lack of vigilance that will cause major economic harm to the nation. Veterinary practitioners should not be concerned about reporting a suspected FAD and having it confirmed as a domestic disease problem, as it is important that the animal disease emergency response system be tested regularly to ensure that it is as efficient and effective as possible. Most important, the impact of a delay in detection of a true FAD could be catastrophic.

47.3 U.S. DEPARTMENT OF AGRICULTURE NATIONAL VETERINARY ACCREDITATION PROGRAM

The USDA established the veterinary accreditation program in 1907 to allow private practitioners to assist federal veterinarians in certifying animals for interstate and international movement and to assist in controlling animal diseases. The current mission of the National Veterinary Accreditation Program (NVAP) is to ensure the health of the nation's livestock and animal population and to protect the public health and well-being. NVAP's goal is to maintain the effective cooperation and use of private veterinary practitioners for regulatory work in a manner that is consistent with international trade requirements and safeguarding animal health. APHIS Veterinary Services (VS) administers NVAP. Participation in NVAP is voluntary and is not mandated by the federal government. A list of the requirements for a veterinarian wishing to become accredited by the USDA is shown in Box 47-3. Accredited veterinarians participating in NVAP must carry out their duties according to the Standards for Accredited Veterinarian Duties described in CFR Title 9, Part 161. Box 47-4 lists the standards for accredited veterinarians. USDA veterinary accreditation is specific to a given state, so one needs to contact the USDA APHIS VS office in the state in which he or she is practicing to ensure accreditation in that state. One requirement of USDA accreditation is the reporting of all suspected FADs to state or federal animal health officials for evaluation and testing if necessary. Box 47-5 lists some of the clinical signs that should alert a private veterinarian that a foreign animal disease should be considered.

Accredited veterinarians are the backbone of U.S. regulatory programs for livestock and poultry diseases. The responsibilities of an accredited veterinarian are extraordinary. In fact, the United States depends extensively on accredited veterinarians for many official functions (e.g., inspecting, testing, and certifying animals). Livestock producers who ship animals domestically or export animals internationally rely on the expertise of accredited veterinarians to help ensure that exported animals meet the requirements of the receiving location and will not introduce diseases into the receiving state or country. The accreditation program has served the animal industry well for many years and remains integral to its continued growth. There are currently more than 60,000 active accredited veterinarians in the national database, and these accredited veterinarians are instrumental in providing national capability to perform competent health certifications and to maintain extensive disease surveillance and monitoring. Today, more than 80% of all U.S. veterinarians are accredited and work cooperatively with federal and state animal health officials in NVAP.

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47.3.1

Box 47-3 U.S. Department of Agriculture Accreditation Requirements

Graduate from an AVMA-accredited school.

Attend an accreditation seminar.

Submit accreditation application to the appropriate U.S. Department of Agriculture (USDA) Veterinary Services (VS) office.

Be licensed and accredited in each state in which you plan to perform official work.

47.3.2

Box 47-4 Standards for Accredited Veterinarians (9 Code of Federal Regulations, 161.3)

Immediately report program diseases.

Know current regulations.

Perform activities according to regulations.

Accurately complete all forms.

Personally inspect all animals.

Properly identify reactors.

Maintain proper biosecurity.

Use regulated materials according to the regulations.

Maintain security of official tags, forms, and certificates.

47.3.3

Box 47-5 Clinical Signs or Observations That Indicate a Foreign Animal Disease Should Be Considered

Vesicles in oral cavity or around coronary bands

Central nervous system signs

Mucosal diseases

Hemorrhagic septicemias

Larvae in wounds

Unusual (ornate) ticks

High morbidity or mortality

Unusual or unexplained illness or symptoms

The accreditation process has changed dramatically over the years. In the 1980s and early 1990s veterinarians were required to pass a written examination, but currently accreditation requires only attendance at a seminar at which the responsibilities and requirements for accreditation are discussed. Attendance at such a seminar provides for lifetime accreditation as long as one does not practice in a new state. Concerns have been raised that this process does not enable private veterinarians, who are the first line of detection of FADs, to keep current on FADs and the world animal disease status. Many recent efforts have focused on enhancing private veterinarians' awareness of their important role in FAD surveillance. In addition, in June 2006 a notice was published in the *Federal Register* proposing changes to the existing NVAP program. These included the implementation of two different categories or levels of accreditation. These changes are being proposed to help ensure that all accredited veterinarians have the tools needed throughout their careers to meet the evolving challenges of FAD prevention and preparedness in the United States.

47.4 OVERVIEW OF A FOREIGN ANIMAL DISEASE INVESTIGATION AND RESPONSE

Protecting the nation's livestock and poultry industries from FADs involves four basic principles or phases of emergency management. They are prevention, preparedness, response, and recovery. To be effective these phases require support, cooperation, and communication among individuals, groups, and organizations at the local, state, regional, and national levels. Livestock and poultry owners; veterinarians in private clinical practice; industry groups; the federal, state, and local governments; state universities; veterinary diagnostic laboratories; and the public must all be included in emergency response preparation and planning. A response to a FAD outbreak would be carried out in accordance with the guidelines established by the National Response Plan (NRP) and using the National Incident Management System (NIMS) and the Incident command system (ICS). Veterinarians who are interested in participating in either animal disease or disaster emergency response efforts, either as temporary employees or as volunteers, need to be familiar with these systems before an event occurs, in order to effectively integrate into the response effort. There are both online and classroom-based training programs offered by federal, state, and local emergency response agencies. The Federal Emergency Management Agency (FEMA) offers several Web-based, self-paced courses.[3]

Although the details of the clinical signs and epidemiology of the FADs themselves are discussed in detail in other sections of this book, there are many additional references and resources available to practicing veterinarians to help them keep apprised of the clinical presentation and importance of these diseases as well as to whom to report suspected cases. Two excellent references for disease-specific information are *Foreign Animal Diseases: "The Gray Book,"* revised 1998,[4] available at http://www.vet.uga.edu/vpp/gray_book02/index.php, and the website of the Center for Food Security and Public Health of Iowa State University,[5] http://www.cfsph.iastate.edu.

47.5 ## PREVENTION AND PREPAREDNESS

Early recognition of a FAD can be difficult because many domestic diseases seen by veterinarians on a routine basis have clinical signs that are similar to those of a FAD (e.g., FMD) and because a FAD may have mild clinical signs that may allow it to spread undetected for some period of time (e.g., low pathogenic form of classical swine fever [CSF]). Examples of both domestic and foreign vesicular or ulcerative diseases which may be difficult to distinguish clinically in cattle are presented in Box 47-6. A similar list for small ruminants is provided in Box 47-7. The increased threat status and severe consequences of the introduction of a FAD into the United States require private veterinarians to be continually vigilant for unusual emerging animal health conditions. In order to be best prepared to identify these rare disease conditions, veterinary practitioners must understand how they may manifest and what clinical signs they may possess. Participation in continuing education programs aimed at increasing awareness of the clinical signs of FADs can facilitate the necessary awareness. Education and awareness should also be extended to producers and their employees who will likely be the first individuals to recognize a problem in the herd or flock with which they work on a daily basis.

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47.5.1 ### Box 47-6 Diseases of Cattle That Are Difficult to Clinically Distinguish and May Resemble Foot-and-Mouth Disease

Foot-and-mouth disease

Vesicular stomatitis

Rinderpest

Bovine viral diarrhea (BVD)

Malignant catarrhal fever

Bovine herpes mammillitis

Bovine papular stomatitis

Pseudocowpox

Infectious bovine rhinotracheitis

Note: Reportable diseases are highlighted in bold.

47.5.2

Box 47-7 Diseases of Small Ruminants That Are Difficult to Clinically Distinguish and May Resemble Foot-and-Mouth Disease

Foot-and-mouth disease

Vesicular stomatitis

Malignant catarrhal fever

Peste des petits ruminants

Bluetongue

Contagious ecthyma (ORF)

Epizootic hemorrhagic disease (EHD)

Note: Reportable diseases are highlighted in bold.

Another important component of the prevention of FAD incursions is the implementation by APHIS of policies and procedures related to the importation of animal species or products into the United States These rules vary by animal and product, as well as by country of origin. APHIS monitors the OIE reports of the world animal health status and continually updates the importation requirements accordingly. These requirements may dictate the quarantine and possible testing of specified animal species for specific periods of time before the animals are allowed to enter the United States. As of 2007 there were four import centers, located in New York, Miami, Los Angeles, and Honolulu, through which such animals could enter the country legally. Illegal importation of such animals and animal products via other channels poses a significant risk to U.S. agriculture. APHIS port veterinarians are responsible for the examination of the animals, their identification, and evaluation of health certificates and permits for accuracy at the importation stations. If the requirements are not met or the animals are found to be diseased, then the animals are refused entry. Once it has been determined that an animal is healthy, all the test results are negative, and all the requirements have been met, then the animal can be released to its owner and the state of destination is notified of the animal's movement into that state.

47.6

DETECTION

Although border controls and import procedures have historically been largely effective in keeping FADs out of the United States, there is always the possibility that a FAD could appear in this country by either unintentional or intentional means. The responsibility for rapidly detecting and effectively responding to incursions of FADs is

primarily that of APHIS in cooperation with livestock and poultry owners, veterinarians in private clinical practice, and state animal health officials. An additional challenge for early detection of FADs is that there are very few ongoing surveillance programs that routinely test for FADs in targeted, high-risk livestock populations or in conjunction with screening for clinically indistinguishable domestic diseases in state or regional animal diagnostic laboratories. Because many of the FADs can mimic domestic diseases, a FAD may not be properly identified for some time if the condition is believed to be a domestic disease problem and if it is investigated with that primary differential in mind without initiating testing for a FAD. Even a single day's delay in identifying a FAD can result in significantly greater disease spread owing to the large amount of livestock movement that occurs in the United States on a daily basis. Prompt reporting, investigation, and diagnosis can prevent a FAD from spreading, can reduce the overall economic cost of the event, and can reduce the likelihood that the disease may become endemic in a wildlife or arthropod reservoir.

The most likely person to initially suspect a FAD is the producer or private veterinarian called by the producer to investigate the unusual disease condition. It is critical that any time a FAD is suspected it is reported to state or federal animal health officials for expedited investigation and testing as necessary. The state animal health official, usually the state veterinarian, and federal veterinarians working for USDA APHIS VS routinely work to increase awareness of such conditions and reporting information among the state's private veterinarians and livestock producers. These activities require the support and assistance of state veterinary diagnostic laboratories, the Cooperative Extension Service of the USDA, state and federal meat and poultry inspection services, universities, animal scientists, market operators, and livestock and poultry producers and their private veterinarians.

For FAD outbreaks to be detected quickly, any suspicious signs of a FAD must be promptly reported to the state veterinarian, the USDA VS federal veterinarian, or both so that a FAD can be confirmed or ruled out. Private veterinarians are knowledgeable regarding the occurrence of various domestic animal diseases in their practice area and the history of such diseases on their clients' farms and ranches. This type of historical information and a herd's vaccination and animal movement history are critical to assessing the likelihood of a suspected FAD. Working with the herd veterinarian and the producer, the investigating state or federal, specially trained FAD diagnostician (FADD) will use the herd history and clinical investigation to assess the likelihood that the situation involves a FAD and to determine the appropriate sample(s) to collect, the method of sample delivery, and what precautions must be taken at the site while test results are pending. Specimens are submitted to the National Veterinary Services Laboratories (NVSL) in Ames, Iowa or to the Foreign Animal Disease Diagnostic Laboratory (FADDL) in Plum Island, New York to confirm the presence or absence of a FAD. On the basis of initial FAD investigation findings, often before the laboratory has completed testing of the samples, state and federal officials in the affected state may take action to quarantine affected animals or poultry at the site of the suspected case, increase surveillance in the area, and initiate steps to gather further information to assess the situation and characterize and control the outbreak if necessary.

One of the disadvantages of the current system is that there may be a 1- to 2-day delay in obtaining a diagnosis when an affected animal is located in a state distant to FADDL in New York. An additional disadvantage is that FADDL does not do routine testing for domestic diseases. Therefore, under the current system, domestic disease testing often cannot be initiated until the FAD is ruled out. This delay in domestic disease diagnosis may be a disincentive for a private veterinarian to involve a FADD in the process when his or her clinical judgment is that the likelihood of a FAD is low. One possible solution to this situation would be to allow select, trained, proficiency-tested state or regional veterinary diagnostic laboratories to run screening tests for FADs; positive results could then be confirmed at FADDL. This would allow domestic disease testing to occur in parallel with FAD surveillance. The USDA is currently working with the National Animal Health Laboratory Network (NAHLN) to proficiency-test and transition some of the screening tests for FADs to approved laboratories. At

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present only assays for CSF, HPAI, and END have been successfully transitioned to some of the NAHLN laboratories for use in national surveillance programs. Although there is a singleplex polymerase chain reaction (PCR)–based FMD assay slated for deployment to proficiency-tested NAHLN laboratories, it has not yet been deployed for routine use in any of the laboratories.

Other diagnostic tools that may be available in the near future include deeply multiplexed nucleic acid, antibody, or protein assays that could allow the simultaneous screening for many disease agents in one reaction for a reduced cost per agent. Although these types of assays are still undergoing development and validation in the veterinary community, similar assays are in use as part of the BioWatch program, which is a human biothreat agent surveillance system operated by the Centers for Disease Control and Prevention in Atlanta, Georgia. Once validated, such assays could become useful components of targeted surveillance programs in the United States.

47.7 RESPONSE, MANAGEMENT, AND CONTROL

A FAD response will be conducted according to the guidelines set forth in the NRP. This response plan incorporates best practices and procedures from various emergency management disciplines and integrates them into a unified structure that forms the basis of how the federal government coordinates with state, tribal, and local governments and the private sector during all incidents, including animal disease outbreaks. Under the NRP the USDA is the lead agency coordinating the protection of agriculture and natural resources. All national responses are conducted in accordance with NIMS, which established a national emergency response framework to allow local, state, tribal, and federal agencies to more efficiently and quickly work together in an emergency. The NIMS uses the ICS to organize the response. The ICS is designed to be expandable and to meet the needs associated with incidents of all sizes, to allow individuals from a variety of agencies to meld more efficiently into a common management structure, to be cost-effective by reducing duplication of effort, and to provide needed logistic, administrative, and operational staff. There are five main management functions in the ICS: incident command, operations, planning, logistics, and finance and administration. Most veterinarians work in the operations or planning sections during a FAD response. The operations section is where the bulk of the tactical field work is conducted, such as diagnosis, surveillance, and depopulation.

Once a FAD has been confirmed by the USDA, the notification and coordination process for all involved parties begins. This includes federal, state, international, local, industrial, and public stakeholders. Conference calls, electronic notification, and press conferences may be used to communicate key messages. In addition, if agroterrorism is suspected, the Federal Bureau of Investigation and the Department of Homeland Security will be involved in the response efforts. If a zoonotic disease is suspected, then the state and federal public health departments will also become involved. Federal officials will notify the OIE of the situation so that the international communities will be made aware of the change in the nation's animal health status. Throughout the response the goal will be to maintain accurate, timely communications regarding the status and progress of the eradication efforts.

When the diagnosis of the initial case is confirmed, there is still much information to be gathered to determine the true magnitude of the situation. The species affected, history of the diseased herd or flock (including recent animal movements), and stage of disease in the affected animals will provide valuable information regarding the likely extent of disease. Outbreaks can be large or small, simple or complex, and localized or widespread. Timely development of situational awareness will be critical for mobilizing the necessary resources to effectively respond to the situation.

Tactical measures or procedures employed to control an outbreak may include quarantine and/or animal movement restrictions; biosecurity; epidemiologic investigations; surveillance for disease in surrounding areas;

vaccination, euthanasia, or treatment of affected animals; carcass disposal; disinfection; vector control; and education campaigns. The exact approach to control will vary by disease, affected region, and extent of the outbreak. In many cases federal and state veterinarian resources will be sufficient to respond to and control the situation quickly. However, if the outbreak is large or widespread it may require the use of additional personnel resources.

When APHIS requires temporary personnel to assist with disease eradication, it uses the National Animal Health Emergency Response Corps (NAHERC), a roster of private veterinarians and animal health technicians, to assist with the control efforts. Private veterinarians may be enlisted to examine herds or flocks for clinical disease, vaccinate animals, collect laboratory samples, perform necropsies, collect epidemiologic data, and euthanize infected animals. During the United Kingdom's 2001 FMD epidemic, many private veterinarians found that their clients stopped using their routine services as a precaution to reduce the chances that their farms would become infected, and in other cases clients' farms were lost to disease control efforts. In many cases these veterinarians joined the FMD task force as Temporary Veterinary Inspectors (TVIs) working on behalf of the British government to assist in the control of the epidemic for some period of time. U.S. veterinarians interested in registering for NAHERC should contact their state USDA APHIS VS office or go to the NAHERC website for details.

47.8 RECOVERY

The goal of the recovery process is to return the nation to a status equal to or better than what existed before the FAD outbreak. Full recovery can be a long and arduous process. Recovery activities include payment for animals and materials destroyed for disease control purposes, successful cleanup and restocking of affected premises, renegotiation and reestablishment of international trading status, and government and industry's reassurance to the consumers and the public that the outbreak has been managed successfully. The OIE's international animal health code sets the standards that determine when a country will be classified as disease-free. The OIE standards, which must be satisfied before resumption of international trade, serve to reassure the international community that trading with a previously affected country is now safe.

The ultimate cost of an outbreak for a country, its producers, affected industries, and the public can be quite high. Many of the costs beyond those to the directly affected industries can be significant yet difficult to quantify.

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47.9 THE FUTURE OF FOREIGN ANIMAL DISEASE DETECTION AND RESPONSE

A comprehensive review of the national framework for addressing animal diseases was conducted by a committee assembled by the National Academies and published in 2005.[4] The committee's findings and recommendations support the compelling need for significant changes to create a new future for animal health in the United States. Some of the key findings included the need for new tools for detection, diagnosis, and risk analysis and the expansion of the NAHLN's capabilities for both routine and emergency diagnostics. The committee called for the colleges of veterinary medicine to lead an effort to develop a national animal health education plan to educate and train individuals from all sectors in disease prevention and early detection and to recruit veterinary students into careers in public health, food systems, biomedical research, diagnostic laboratory investigation, pathology, epidemiology, ecosystem health, and food-animal practice. As animal health has broad implications, ranging from the health of individual animals and the well-being of human communities to issues of global security and the adequacy of the global food supply, there is significant need to plan carefully for the future. The committee concluded that given the changing nature of the risks to animal health in this country, it is unlikely that the current philosophy on how to protect animal health will be adequate in the future.

Extraordinary changes including continued globalization will continue to present new threats to U.S. agriculture and necessitate the continued vigilance of the veterinary and agricultural communities. While state and federal governments are working to provide more targeted, active surveillance programs, private veterinary practitioners, who on a daily basis provide health care to the national herd, will remain the core of the nation's early warning system for FAD surveillance. Therefore their awareness of FADs and willingness to serve in the critical role of being part of the nation's early warning system for FADs will continue to be a cornerstone of national defense against the intrusion and the devastating impact of such diseases.

47.10 REFERENCES

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2. The World Organization for Animal Health: *Office of International Epizootics (OIE)* http://www.oie.int/eng/en_index.htm.

3. Emergency Management Institute: *FEMA Independent Study Program: IS-700 National Incident Management System (NIMS), an introduction* Available at http://www.training.fema.gov/emiWeb/IS/is700.asp.

4. *Foreign animal diseases: the gray book*. Available at: www.vet.uga.edu/vpp/gray_book02/index.php, . (Reference for foreign animal diseases organized by disease and including photos.).

5. Center for Food Security and Public Health; www.cfsph.iastate.edu, . (Information and PowerPoint resources for a wide variety of animal diseases, bioagroterrorism awareness education, and emerging and exotic diseases of animals.).

6. National Research Council of the National Academies: In *Animal health at the crossroads: preventing, detecting and diagnosing animal diseases*. 2005, National Academies Press, Washington.

47.11 OTHER VALUABLE FOREIGN ANIMAL DISEASE-RELATED WEB RESOURCES

Plum Island Animal Disease Center: http://www.ars.usda.gov/main/site_main.htm?modecode=19400000.

United States Department of Agriculture, Animal and Plant Health Inspection Service: *Keeping America free from foreign animal diseases*. Available at: http://www.aphis.usda.gov/vs/ep/fad_training/bibpage.htm, . (Slide show format for foreign animal disease information, including photos.).

National Biosecurity Resource Center for Animal Health Emergencies; http://www.biosecuritycenter.org, . (Includes a reference library and information on cleaning and disinfection, personal protective equipment, carcass disposal, and reportable diseases.).

Animal Health Australia, AUSVETPLAN; http://www.aahc.com.au/ausvetplan, . (The AUSVETPLAN is a series of technical response plans that describes the proposed Australian approach to an exotic disease incursion. The series contains disease-specific information, operational procedures [decontamination, etc.], and some wildlife-related information.).

48 Chapter 48 Use of Biologics in the Prevention of Infectious Diseases

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48.1 EQUINE VACCINATION AND INFECTIOUS DISEASE CONTROL

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48.2 GENERAL CONSIDERATIONS

Programs for controlling infectious diseases are important components of management practices directed toward maximizing the health, productivity, and performance of horses.[1] Infectious disease in an individual horse or an outbreak of infection in a group occurs when horses experience challenge with an infectious agent at a dose sufficient to overcome resistance acquired through previous natural exposure to the disease or through vaccination. For this reason, programs for controlling infectious diseases should have the following three goals:

1. To reduce exposure to infectious agents in the horses' environment
2. To minimize factors that diminish resistance
3. To enhance resistance through the use of vaccines (vaccination alone cannot be expected to prevent disease; management practices must reduce challenge with infectious pathogens)

The incidence of infectious disease in horse populations tends to rise with an increased number and stocking density of susceptible horses at a facility, with movement of horses on and off the facility, and with favorable external environmental and management influences. Other factors that influence the risk of acquiring infection and developing disease include the age, type, breed, gender, and use of the animals; geographic, climatic, and other environmental factors; facilities' layout and management practices; and history of exposure to or vaccination against individual diseases.

The conditions on breeding farms, in performance and show horse barns, and at racetracks are ideal for the introduction and transmission of infectious diseases, particularly those of the respiratory tract. On breeding farms, the introduction and commingling of horses of various ages and origins and the high proportion of young, susceptible horses and pregnant mares create a situation that poses special problems and demonstrates some important considerations in the practice of disease control. The risk of acquiring infection can be reduced by maintaining distinct groups by age and function. Resident mares and foals should be kept separate from weanlings, yearlings, horses in training, and visiting mares. Visiting mares and other horses entering the farm should have a negative Coggins test result for equine infectious anemia (EIA) and should be appropriately

vaccinated and dewormed before arrival. They should be received and maintained in barns and paddocks separate from the resident farm population. Preferably a specific group of caretakers should attend to incoming horses; and footbaths, separate equipment, and a clean change of coveralls and boots should be used.

New arrivals should be quarantined for 30 days and monitored for signs of contagious disease. The rectal temperature should be recorded at least once daily, and any prophylactic procedures not done before arrival should be performed. Foaling mares being sent to a distant breeding farm for breeding should be transported 6 to 8 weeks before foaling; this permits timely exposure to resident pathogens at the destination farm, which allows the mare's immune system to mount a response and concentrate antibodies in the colostrum to improve passive protection of the foal. Mares being shipped short distances for breeding can be transported during estrus and returned to the farm on the same day to reduce the risk of the foal acquiring infection.

Regardless of the type of equine facility, any horse that becomes ill with a possibly contagious disease should be isolated, preferably in an air space separate from the remainder of the herd, for at least 10 days beyond complete abatement of clinical signs. Separate equipment should be used, and if a separate group of caretakers is not available for these animals, workers should always complete their work with healthy horses before handling sick horses. Caretakers should wash their hands and boots thoroughly between horses and wear different outer clothing or coveralls. Stalls that have housed sick horses should be cleaned thoroughly, disinfected, allowed to dry, and left empty as long as possible. This approach is particularly important in dealing with organisms such as *Streptococcus equi* that can survive in a protected, moist environment for several weeks.[2]

In most equine enterprises, vaccination is important to the overall management program for controlling infectious diseases. No “standard” vaccination program can be recommended for all horses; each situation must be evaluated individually by weighing the risk of acquiring infection and the medical and economic consequences of infection against the cost and expected efficacy of the product or products being considered for inclusion in the program, and their potential for inducing adverse reactions. Cost should include expenses incurred and money lost during the time the horses are out of competition, labor and medication expenses if the animals develop clinical disease and require treatment, and the expenses in time, labor, and vaccines required for proper immunization. The client's expectations should be realistic, and the veterinarian should explain the following points carefully:

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- Vaccination minimizes the risk of infection but does not prevent disease in all circumstances.
- The primary series of vaccines and booster doses should be administered appropriately before likely exposure.
- Horses in a population are not all protected equally nor for an equal duration after vaccination.
- Whenever possible, all horses in a herd should be vaccinated on the same schedule; this simplifies record keeping, minimizes replication and transmission of infectious agents in the herd, and optimizes herd immunity by protecting those animals that responded poorly to vaccination.

A properly administered, licensed product should not be assumed to provide absolute, effective protection during any given field epidemic. Copies of the vaccination and health maintenance records should accompany each horse leaving the facility for sales, training, or breeding. Similarly, owners of equine facilities should establish prerequisites for vaccination of all horses entering the facility and request that copies of the vaccinal records accompany those horses.

Client expectations and the goals of disease control programs vary considerably. In performance horses, the goal generally is to minimize time spent out of training and thereby to maximize earning potential. In this case an

enforced period of rest owing to infectious disease has much more profound economic consequences than a similar recommendation for a barren broodmare or backyard horse. On the other hand, many owners of backyard horses diligently vaccinate against even low-risk diseases, despite the expense involved, to keep their horses healthy.

Only federally licensed vaccines should be used, and strict attention must be paid to the manufacturer's recommendations for storage, handling, and routes of administration to maximize the product's efficacy and safety. However, research or clinical experience may support alternate protocols for vaccination that will improve the vaccine's efficacy without increasing adverse effects. The length of time needed to induce a protective immune response should be considered in relation to expected exposure. For instance, when inactivated (killed) vaccines are administered by intramuscular injection, optimal protection generally is not achieved until 2 to 3 weeks after completion of the primary series or 1 or more weeks after administration of a booster dose. Inactivated vaccines administered intramuscularly (IM) generally induce a greater serologic response when an initial series of three doses is given rather than the two-dose series recommended by most vaccine manufacturers.

The primary role of authorities charged with licensing vaccines in North America traditionally has been to ensure the purity and safety of the vaccines, with less emphasis placed on documentation of efficacy.[3–5] Consequently, little published information was available in the past documenting the efficacy of most vaccines licensed in North America. Thankfully, the situation has improved substantially in recent years, to the extent that published efficacy data are available for almost all equine vaccines licensed in North America since 1999.[6–18] Field experience and some experimental evidence suggest that the efficacy of vaccines directed against different diseases varies considerably and that efficacy also varies among the vaccines from different manufacturers directed against the same disease.[8,19,20]

Vaccination is unlikely to confer protection more durable than that produced by recovery from natural disease, especially when the route of vaccination (usually intramuscular) is different from the route of natural infection; this is because vaccines frequently do not evoke the full array of protective immune responses induced by natural infection.[21,22] For example, the efficacy and durability of protection induced by parenteral vaccines against respiratory tract pathogens are frequently questioned.[4,5,22] In part this reflects the fact that parenterally administered vaccines generally are poor inducers of the local mucosal immune responses that are important for effective protection against infection of the respiratory tract.[4,21,22] In addition, immunity achieved after natural infection with some respiratory tract pathogens is short-lived.

48.2.1

Vaccination of Foals and Influence of Maternal Antibodies on Vaccine Responses

Maternally derived antibodies (MDAs) and perhaps other immune effectors such as lymphocytes that are concentrated in colostrum and are passively transferred to the foal play a crucial role in defense against pathogens encountered during the first few months of life while endogenous immune function continues to mature. Passive transfer of MDAs should therefore be exploited in immunization programs for foals by consistently administering booster doses of selected vaccines to mares 4 to 8 weeks before foaling and by ensuring that foals ingest adequate amounts of high-quality colostrum within 24 hours of birth. In addition to passively protecting the foal, MDAs may also exert a profound inhibitory effect on the active immune response of the foal to antigens, including those contained in vaccines. This phenomenon is known as *maternal antibody interference*.

Several studies reported during the 1990s brought this issue into focus by demonstrating that foals less than 6 months of age consistently failed to mount serologic responses to inactivated influenza vaccines.[23–29] Of potentially greater concern was the finding that a high proportion of foals vaccinated under the cover of MDAs not only failed to seroconvert in response to the recommended primary series of two or three doses of influenza vaccine, but many also failed to respond to multiple additional doses administered during the next year, suggesting induction of a potentially detrimental "immunotolerance-like" phenomenon.[26,27,30] Our studies confirmed an apparent lack of response of foals to multiple doses of inactivated influenza vaccines when the hemagglutination inhibition (HI) test was used to detect serologic responses, but responses were detected when the same samples were assayed using sensitive isotype-specific enzyme-linked immunosorbent assay (ELISA). Rather than representing true tolerance, it appears that MDAs may cause misdirection of the immune response away from the more important virus-neutralizing (VN) IgGa and IgGb subisotypes in favor of the less effective IgG(T) subisotype of IgG.[23] Subsequent studies in which titers of total rather than antigen-specific IgG subisotypes were determined documented that the age-related increase in concentrations of IgGb lagged significantly behind increases in concentrations of other isotypes and remained below adult levels beyond 6 months of age.[31]

Maternal antibody interference has now been documented to be a significant issue for many other antigens, including tetanus, eastern equine encephalomyelitis (EEE), western equine encephalomyelitis (WEE), and equine herpesvirus types 1 and 4 (EHV-1 and EHV-4), contained in vaccines administered to foals.[23,32–36] 1558
Even low levels of antibody, below those detectable by many routine serologic tests and below those thought to 1559
be protective, can completely block the serologic response to some vaccines, resulting in a potentially prolonged period of susceptibility before the foal is capable of responding appropriately to vaccines.[35] These findings also indicate that it is not typically feasible to test samples from foals serologically to predict whether they will respond to particular vaccines. We now recommend that primary immunization with most vaccines containing inactivated antigens should be delayed until foals are 6 months of age or older and that, with the exception of rabies vaccine, three doses of vaccine should be included in the primary series rather than the two doses routinely recommended by vaccine manufacturers. Typically, the third dose stimulates a serologic response of greater magnitude and durability than two doses and may also contribute to a higher "set point" for the response to subsequent booster doses.[23,35,37,38] In contrast to the results cited previously, maternal antibodies do not appear to exert a marked inhibitory effect on the response of foals to either the inactivated or recombinant live West Nile virus (WNV) vaccines (West Nile-Innovator, Fort Dodge; Recombitek, Merial), thereby permitting antibody-positive foals as young as 3 months of age to be immunized successfully.[37]

Study results should be interpreted with caution because only humoral responses are typically assessed and infectious challenge is not performed to confirm that lack of serologic response equates to lack of protection. Lack of a serologic response may correlate well with lack of protection for some diseases and some vaccines, whereas for others this may not be the case. In contrast, the presence of a serologic response may not correlate well with protection, as is frequently the case for respiratory tract pathogens. With the exception of the intranasally (IN) administered strangles and influenza vaccines (Pinnacle IN, Fort Dodge; Flu Avert IN, Intervet), the modified live virus EHV-1 vaccine (Rhinomune, Pfizer), the modified live virus EVA vaccine (Arvac, Fort Dodge), and the canarypox-vectored WNV and influenza vaccines (Recombitek, Merial), most commercially available vaccines are inactivated, adjuvanted, and administered by intramuscular injection (Table 48-1). Because inactivated vaccines administered by injection have limited potential to stimulate cellular and mucosal responses, serologic responses to these vaccines likely correlate well with their potential to induce protection. In turn, MDA interference with serologic responses to inactivated vaccines likely equates to failure to induce protection. In contrast, failure to detect a serologic response to a modified live, vectored, DNA, or

mucosally administered vaccine may not equate to lack of protection because vaccines of these types induce a broader array of systemic and local responses that may not be affected by MDAs.

Table 48-1 Types of Equine Vaccines Commercially Available

	Dead Vaccines		Live Vaccines		
Disease	Inactivated	Subunit	Modified Live	Recombinant	DNA Vaccine
Tetanus		X			
Western equine encephalitis	X				
Eastern equine encephalitis	X				
Equine Venezuela encephalitis	X				
West Nile virus	X			X, X (chimera)	X
Equine influenza	X		X	X	
Equine herpesvirus 1	X		X		
Equine herpesvirus 4	X				
Strangles		X	X		
Equine viral arteritis			X		
Rabies	X				
Potomac horse fever	X				
Botulism		X			
Equine protozoal myeloencephalitis	X				
Rotavirus	X				

If maternal antibody interference were not an issue, the approach to vaccination of foals would be greatly simplified because primary vaccination against all important diseases could be completed before MDAs had declined to nonprotective levels. In effect, the “window of susceptibility” would be eliminated. In reality, an attainable goal is to maximize the beneficial effects of MDAs while minimizing their negative impact on primary immunization. In order to best meet this goal, one or both of the following should be determined to be the primary focus:

1 To protect the foal and weanling against specific high-risk infectious diseases that affect this age group and have the potential to cause significant disease, either directly or by predisposing to other secondary infections

2 To initiate primary immunization to protect against disease later in life

Assessing risk takes into account both the likelihood that the foal will become infected as well as the risk of serious sequelae or death if the horse does become infected and develop disease. If the disease affects the foal

early in life, such as is the case with rotavirus (RV) infection, there is usually insufficient time to induce a protective immune response by actively immunizing the foal. Under these circumstances, the approach should be to maximize the degree of protection passively transferred from the dam via colostrum. Other diseases, such as rabies, affect horses of all ages, but the risk of acquiring infection is generally low.

48.2.2 Diseases of Moderate to High Risk to Young Foals but Low Risk to Adults

Diseases of moderate to high risk to young foals but low risk to adults include RV infection (on certain breeding farms in certain years) and, in geographic areas such as Kentucky and some other eastern states, type B botulism. For these diseases, the following approach is appropriate: 1559 1560

- Booster-vaccinate the dam before foaling to maximize uniformity of passive transfer.
- Ensure good passive transfer of maternal antibodies.
- Introduce management practices to reduce exposure to the infectious agent.
- Vaccinate the foal if risk continues beyond the first few months of life.

48.2.3 Diseases of Moderate to High Risk for Weanlings and Older Horses but Lower Risk to Young Foals Born to Vaccinated Mares

Diseases of moderate to high risk for weanlings and older horses but lower risk to young foals born to vaccinated mares include EHV-4, EHV-1, strangles, influenza, tetanus, EEE, and WNV infection. For these diseases, the following approach is appropriate:

- Vaccinate the dam before foaling to maximize uniformity of passive transfer.
- Ensure good passive transfer of maternal antibodies.
- Start foal vaccination after the risk of maternal antibody interference is no longer present in *most* foals. When several vaccine types are available for a particular disease, the vaccine that is least subject to MDA interference should be used. Introduce management practices to reduce exposure to the infectious agent while primary vaccination is being completed.
- If a two-dose primary series is recommended for adult horses, use three or more doses of vaccine in the primary series to improve the chances that foals that do not respond to earlier doses will respond to additional doses administered later.

48.2.4 Diseases of Low Risk to Foals

Diseases of low risk to foals in most circumstances include rabies, Potomac horse fever (PHF), WEE, and equine viral arteritis (EVA). For these diseases, the following approach is appropriate:

- Vaccinate the dam before foaling if the disease is a significant risk to adult horses and a vaccine shown to be safe for use in pregnant mares is available. If the available vaccines are not considered safe for use in pregnant mares, administer boosters before breeding.
- Ensure good passive transfer of maternal antibodies.

- Start foal vaccination after the risk of maternal antibody interference is no longer present in *any* foal (typically 9 months to 1 year of age).

48.2.5 Adverse Reactions to Vaccines

Although uncommon, the possibility always exists for adverse reactions (including anaphylaxis) associated with administration of a vaccine; therefore vaccines should be administered by or under the direct supervision of a veterinarian. Adverse reactions should be reported to the vaccine's manufacturer and to the U.S. Department of Agriculture (USDA) (1-800-752-6255) or the U.S. Pharmacopeia (USP) Veterinary Practitioners Reporting Program (forms may be obtained or reports submitted by calling the USP at 1-800-487-7776). Anaphylaxis constitutes a life-threatening emergency requiring prompt treatment with epinephrine (3 to 5 mL of a 1:1,000 dilution IM or 5 mL of a 1:10,000 dilution slowly intravenously [IV] for a 450-kg horse). Repeated doses of epinephrine can be administered at 15-minute intervals if necessary.

Local irritant tissue reactions occur more frequently, particularly when polyvalent combination vaccines and injectable strangles vaccines are used. These reactions usually are self-limiting, but resolution can be promoted by parenteral or oral administration of nonsteroidal antiinflammatory drugs (NSAIDs), topical application of warm compresses or the cutaneously absorbed NSAID diclofenac (Surpass, Idexx Pharmaceuticals, Greensboro, NC), and gentle exercise. Significant reactions in the neck muscles may make the horse reluctant to lower or raise its head; therefore feed and water buckets should be positioned accordingly. The occurrence of externally visible local reactions can be reduced by administration of the vaccine deep in the semimembranosus and semitendinosus muscles of the hind leg rather than in the neck and by allowing the horse to exercise after vaccination. In addition, horses that repeatedly react to polyvalent vaccines may benefit from administration of an NSAID before vaccination, from administration of the individual antigenic components separately in different sites, from use of a different brand of vaccine, from use of a vaccine that can be administered by a route other than IM, or from use of a vaccine that contains a different adjuvant or no adjuvant at all.

Some horses develop transient, self-limiting systemic signs that may include fever, anorexia, lethargy, colic, diarrhea, tachycardia, and congested mucous membranes after intramuscular administration of vaccines. The systemic signs are perhaps more common with certain vaccines but can be associated with any vaccine.[39,40] It is therefore inadvisable to give horses any injectable vaccine within 2 weeks before a show, performance event, sale, or domestic shipment or within 3 weeks before international shipment. It may also be beneficial to minimize environmental dust when vaccinating horses known to have allergic airway disease or hypersensitivity.[39]

If unacceptable reactions occur repeatedly, the need for continued annual or more frequent revaccination against individual antigens should be carefully reevaluated, taking into account risk of disease, balanced against the risk of an adverse reaction. Many of the horses that experience adverse reactions have received many doses of many vaccine antigens, repeated over many years. In this situation the vaccination protocol should be “pared down” so that only the most essential antigens are administered and the maximum possible interval between boosters is employed. For diseases such as rabies and tetanus for which resistance can reasonably be correlated with circulating antibody titer, one possible approach to define the maximum or optimal interval between booster doses would be to measure the antibody titer. Unfortunately, this approach is currently limited by paucity of laboratories that offer this type of testing on a routine basis, inexpensively, and with a short turnaround time. Introduction of commercially available ELISA testing for antibodies to the SeM protein of *S. equi* subsp. *equi* (Equine Biodiagnostics-Idexx, Lexington, Ky.) and neutralizing antibody testing for WNV (Cornell University, Colorado State University, the University of Florida, and the USDA Animal and Plant

Health Inspection Service [USDA/APHIS] National Veterinary Services Laboratory) in recent years has made it possible to refine vaccination protocols for these diseases in horses that experience adverse reactions to vaccination. In addition, testing for antibodies to other pathogens may be available through State Diagnostic Laboratories.

48.2.6 Safety of Vaccines in Broodmares

Consideration of vaccine safety in broodmares must take into account risks to the pregnancy and safety to the fetus. Potential adverse effects of vaccines on pregnancy are difficult to document, even when large numbers of mares are used, unless obvious problems occur. Because fetal organogenesis occurs early in gestation and this period is also characterized by substantial embryonic loss, even in normal mares, it is sound practice to avoid administering vaccines to mares during the first 60 days of gestation unless conditions of imminent risk prevail. Few vaccines carry specific label recommendations for use in pregnant mares, and few published data document the safety of equine vaccines during pregnancy. Of the available fully licensed vaccines, the two EHV-1 vaccines (Pneumabort-K+1b, Fort Dodge, and Prodigy, Intervet) marketed for use in pregnant mares as an aid to prevention of EHV-1 abortion, the vaccine marketed for prevention of type B botulism in foals (BotVax B, Neogen), and the Calvenza line of influenza and EHV vaccines (Boehringer Ingelhein, St. Joseph, Mo.) include directions for use in pregnant mares. In addition, the conditionally licensed vaccine for prevention of RV infection in foals (Equine Rotavirus Vaccine, Fort Dodge) is similarly labeled for use in pregnant mares. Although not specifically labeled for administration during pregnancy, widespread use in practice over many years has failed to document that any of the inactivated vaccines currently marketed for use in horses pose an unacceptable risk to pregnant mares. Therefore pregnant mares are routinely vaccinated with inactivated vaccines directed against tetanus, EEE, WEE, WNV, influenza, EHV-4, strangles, and, to a lesser extent, PHF, rabies, and VEE. Similarly, adverse impacts on pregnancy have not been documented for modified live intranasally administered strangles and influenza vaccines or the modified live parenterally administered EHV-1 vaccine (Rhinomune, Pfizer). In addition, safety of the recombinant WNV and influenza vaccines (Recombitek, Merial) should not be a significant concern because the modified live canarypox vector lacks the ability to infect mammalian cells. In contrast, modified live virus EVA and VEE vaccines and live anthrax spore vaccines should not be used in pregnant mares. Protection of mares against the potential abortigenic effects of EVA infection is therefore best accomplished by completing the primary immunization series before the mare enters the broodmare band and by administering subsequent boosters during the open period before rebreeding.[41]

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The practice of booster vaccinating mares against multiple diseases to maximize colostral transfer of antibodies to the foal, and the fact that mares in broodmare bands are generally middle aged or older, result in the typical broodmare receiving multiple doses of many vaccine antigens and adjuvants during her lifetime. In addition to stimulating high levels of antibody against a range of antigens for the benefit of the foal, this practice may also predispose these mares to a higher rate of local and systemic adverse reactions, an issue that not only warrants further investigation but may force horse owners and veterinarians to carefully consider strategies for revaccination.

48.3 AVAILABLE VACCINES AND THE CONCEPT OF CORE AND NONCORE VACCINES

Fully licensed vaccines are now available in North America as aids to the prevention of tetanus, viral encephalomyelitis (EEE, WEE, VEE), WNV infection, influenza, EHV-1 and EHV-4 infection, strangles, rabies, EVA, PHF, and type B botulism. In addition, conditionally licensed vaccines are available to immunize horses against RV infection and equine protozoal myeloencephalitis (EPM). Tetanus and viral encephalomyelitis caused

by EEE, WEE, and WNV pose a threat to horses in all geographic areas and are therefore considered to be core diseases against which all horses in North America should be vaccinated. In addition, the public health consequences of infection and the 100% mortality rate warrant inclusion of rabies as a core disease for horses residing in or being transported to those many areas of North America where rabies is endemic in the wildlife population. The abortigenic potential of EHV-1 warrants inclusion of this disease in the core for all pregnant broodmares. Although influenza is not routinely included as a core disease, vaccination against this highly contagious respiratory tract infection is strongly recommended for all horses that are likely to be colocated with horses from other facilities during transportation or at sales, shows, trail rides, races, or other events. The remaining diseases for which vaccines are available are considered "noncore." Indications for use of vaccines against these diseases will be discussed in relevant sections that follow later in this chapter. Tables 48-2 and 48-3 provide general guidelines for use of the most frequently indicated equine vaccines in foals, weanlings, yearlings, and adult horses under various management conditions and in various geographic locations. Table 48-4 presents manufacturer recommendations for use of single-component equine immunizing agents and other biologicals licensed for use in horses.

48.4 VACCINATION RECOMMENDATIONS FOR SPECIFIC DISEASES

48.4.1 Tetanus

All horses are at risk for developing tetanus, an often-fatal disease caused by a potent neurotoxin elaborated by the anaerobic, spore-forming bacterium *Clostridium tetani*. Infection of tissues typically occurs via puncture wounds (particularly those involving the foot or muscle), open lacerations, surgical incisions, exposed tissues such as the umbilicus of foals and reproductive tract of the postpartum mare (especially in the event of trauma or retained placenta). *C. tetani* is present in the intestinal tract and feces of horses, other animals, and human beings, and spores are abundant as well as ubiquitous in soil. Spores of *C. tetani* survive in the environment for many years, resulting in an ever-present risk of exposure of horses and people on equine facilities. Tetanus is expensive to treat and has a high mortality rate; therefore all horses should be actively immunized using tetanus toxoid as part of the core vaccination program. Active immunization reduces the need to administer tetanus antitoxin, the use of which is associated with risk of inducing potentially fatal serum hepatitis.

Protection against tetanus is mediated by circulating antibodies; toxin binding inhibition (ToBi) antibody titers of >0.2 IU/mL are considered to be protective in the horse.[38,42] The many available vaccines are formalin inactivated, adjuvanted toxoids that are inexpensive, safe, and potent antigens that induce an excellent serologic response and solid, long-lasting immunity when administered according to manufacturer recommendations. Primary immunization involves administration of two doses of toxoid at 3- to 6-week intervals. Titers of specific antibody increase to protective levels within 14 days after administration of the second dose in the primary series and, in adult horses, persist at detectable levels for 12 months or longer, depending on the adjuvant system used in the vaccine.[38,42–44] A recent study documented substantial differences between currently licensed combination tetanus-encephalomyelitis vaccines with regard to the magnitude of the vaccine-induced tetanus-specific IgGb and IgG(T) antibody responses.[20] The vaccine containing a Carbopol adjuvant induced substantially higher antibody titers than those containing either saponin or squaline combined with surfactants.[20] Revaccination once annually is recommended.

Table 48-2 Guidelines for Vaccination of Foals, Weanlings and Yearlings Against Core and Non-Core Diseases

Disease/Vaccine*†	Foals And Weanlings (<12 Months of Age) of Mares Vaccinated in the Prepartum Period Against the Disease Indicated	Foals And Weanlings (<12 Months of Age) of Mares Not Vaccinated in the Prepartum Period	Yearlings	Comments
CORE DISEASES				
Tetanus (toxoid)	3-dose series: First dose at 4–6 months of age Second dose 4–6 weeks after the first dose Third dose at 3–5 months after the second dose (e.g.,10–12 months of age)	3-dose series: First dose at 1–4 months of age Second dose 4–6 weeks after the first dose Third dose 3–5 months after the second dose	Annual	
Eastern and Western equine encephalomyelitis (EEE, WEE)	3-dose series: First dose at 4–6 months of age Second dose 4–6 weeks after the first dose Third dose at 10–12 months of age, prior to onset of next vector season. *Foals in the Southeastern USA*: The primary vaccination series should be initiated with an additional dose at 3 months of age due to early seasonal vector presence.	3-dose series: First dose at 3–4 months of age Second dose 4–6 weeks after the first dose Third dose 3–5 months after the second dose, prior to onset of next vector season. *Foals in the Southeastern USA*: The primary vaccination series should be initiated at 3 months of age or earlier due to early seasonal vector presence.	Annual in spring, prior to onset of vector season	Month of birth and geographic location influence the risk of exposure to insect vectors at specific foal ages; therefore, scheduling of the primary immunization series may be amended by administration of EEE/WEE vaccines to foals at an earlier age if vectors are present.

West Nile virus (WNV)	**Inactivated vaccine:** 3-dose series: First dose at 4–6 months of age Second dose 4–6 weeks after the first dose Third dose at 10–12 months of age, prior to the onset of the next vector season	**Inactivated vaccine:** 3-dose series: First dose at 3–4 months of age Second dose 4 weeks after the first dose Third dose at 10–12 months of age, prior to the onset of the next vector season	Annual in spring, prior to onset of vector season	Month of birth and geographic location influence the risk of exposure to insect vectors at specific foal ages; therefore, scheduling of the primary immunization series may be amended by administration of WNV vaccines to foals at an earlier age if vectors are present.
	Recombinant canarypox-vectored vaccine: 3-dose series: First dose at 4–6 months of age Second dose 4–6 weeks after the first dose Third dose at 10–12 months of age, prior to the onset of the next vector season	**Recombinant canarypox-vectored vaccine:** 3-dose series: First dose at 3–4 months of age Second dose 4–6 weeks after the first dose Third dose at 10–12 months of age, prior to the onset of the next vector season		
	Flavivirus chimera vaccine: 2-dose series: First dose at 5–6 months of age Second dose at 10–12 months of age, prior to the onset of the next vector season *Foals in the Southeastern USA:* The primary vaccination series should be initiated at 3 months of age due to early seasonal vector presence.	**Flavivirus chimera vaccine:** 2-dose series: First dose at 5–6 months of age Second dose at 10–12 months of age prior to the onset of the next vector season. *Foals in the Southeastern USA*: The primary vaccination series should be initiated at 3 months of age due to early seasonal vector presence.		There is no data for the use of the Flavivirus chimera product in foals <5 months of age. If administered to foals <5 months of age, the recommended schedule for primary vaccination should be completed by administration of a dose of vaccine at 5 months of age or older.

Rabies	3-dose series: First dose at 6 months of age Second dose 4–6 weeks after the first dose Third dose at 10–12 months of age	3-dose series: First dose at 3–4 months of age Second dose 4–6 weeks after the first dose Third dose at 10–12 months of age	Annual	
NON-CORE (RISK-BASED) VACCINES				
Anthrax	Not applicable because vaccination of pregnant mares is not recommended.	No age specific guidelines are available for this vaccine. Manufacturer's recommendation is for primary series of 2 doses administered subcutaneously (in the neck) at a 2–3 week interval.	Annual, spring	Anthrax vaccination is rarely indicated—only in focal endemic areas. Antimicrobial drugs must **not** be given concurrently with this vaccine. Caution should be used during storage, handling and administration of this live bacterial product. Consult a physician immediately should accidental human exposure (via mucous membranes, conjunctiva, or broken skin) occur.
Botulism (type B toxoid)	3-dose series: First dose at 2–3 months of age Second dose 4 weeks after the first dose Third dose 4 weeks after the second dose	3-dose series: First dose at 1–3 months of age Second dose 4 weeks after the first dose Third dose 4 weeks after the second dose	Annual	Limited information suggests that maternal antibody does not interfere with vaccination; therefore, foals at high risk may be vaccinated as early as 2 weeks of age.

Equine herpesvirus (EHV)	**Inactivated EHV-1, EHV-1/4, or modified live EHV-1 vaccine:** 3-dose series: First dose at 4–6 months of age Second dose 4–6 weeks after the first dose Third dose 3–4 months after the second dose Revaccinate at 6-month intervals	**Inactivated EHV-1, EHV-1/4, or modified live EHV-1 vaccine:** 3-dose series: First dose at 4–6 months of age Second dose 4–6 weeks after first dose Third dose 3–4 months after the second dose Revaccinate at 6-month intervals	Semiannual (6-month intervals)	
Equine influenza	Inactivated vaccine: 3-dose series: First dose at 6 months of age Second dose 3–4 weeks after the first dose Third dose at 10–12 months of age Revaccinate at 6-month intervals	Inactivated vaccine: 3-dose series: First dose at 6 months of age Second dose 3–4 weeks after the first dose Third dose at 10–12 months of age Revaccinate at 6-month intervals	Semiannual (6-month intervals)	An increased risk of disease may warrant vaccination of younger foals. Because potentially interfering maternal anti-influenza antibody is likely to be present, a complete primary vaccination should be given after 6 months of age.
	Modified live intranasal vaccine: 2-dose series administered intranasally: First dose at 6–7 months of age Second dose at 11–12 months of age Revaccinate at 6-month intervals	Modified live intranasal vaccine: 2-dose series administered intranasally: First dose at 6–7 months of age Second dose at 11–12 months of age Revaccinate at 6-month intervals	Annual	The modified live intranasal vaccine is licensed for administration to horses 11 months of age or older. If the vaccine is given before 11 months of age, a second dose should be administered at 11 months or older.
	Canarypox-vectored recombinant vaccine: 3-dose series: First dose at 5 months of age Second dose 5 weeks after the first dose Third dose at 10–12 months of age Revaccinate at 12-month intervals	Canarypox-vectored recombinant vaccine: 3-dose series: First dose at 5 months of age Second dose 5 weeks after the first dose Third dose at 10–12 months of age Revaccinate at 12-month intervals		

Equine viral arteritis (EVA)	*Colt (male) foals*: Single dose at 6–12 months of age (see comments)	*Colt (male) foals*: Single dose at 6–12 months of age (see comments)	Annual for colts intended for use as breeding stallions	*Prior to initial vaccination, colt (male) foals should undergo serologic testing* and be confirmed negative for antibodies to EAV. Testing should be performed shortly prior to, or preferably at, the time of vaccination. Maternally-derived anti-EAV colostral antibodies can persist in the foal for up to 6 months; therefore, testing and vaccination should **not** be performed prior to 6 months of age.
Potomac horse fever (PHF)	3-dose series: First dose at 5–6 months of age Second dose 3–4 weeks after the first dose Third dose at 10–12 months of age	3-dose series: First dose at 5–6 months of age Second dose 3–4 weeks after the first dose Third dose at 10–12 months of age	Semiannual to annual	If risk warrants, vaccine may be administered to younger foals, in which case subsequent doses should be administered at 4-week intervals until 6 months of age.
Rotovirus	Not recommended in foals	Not recommended in foals	NA	
Strangles	**Inactivated M-protein subunit vaccines:** 3-dose series: First dose at 4–6 months of age Second dose 4–6 weeks after the first dose Third dose 4–6 weeks after the second dose	**Inactivated M-protein subunit vaccines:** 3-dose series: First dose at 4–6 months of age Second dose 4–6 weeks after the first dose Third dose 4–6 weeks after the second dose	Semiannual	Vaccination is **not** recommended as a strategy in outbreak mitigation.

	Modified live intranasal vaccine: 3-dose series administered intranasally: First dose at 6–9 months of age Second dose 3–4 weeks after the first dose Third dose at 11–12 months of age	**Modified live intranasal vaccine:** 3-dose series administered intranasally: First dose at 6–9 months of age Second dose 3–4 weeks after the first dose Third dose at 11–12 months of age	If warranted by risk, the modified live vaccine (MLV) may be safely administered to foals as young as 6 weeks of age. However, vaccine efficacy in this age group has not been determined. If the MLV product is administered to foals less than 6 months of age, a third dose of vaccine should then be administered 2- 4 weeks prior to weaning.

Modified, with permission, from recommendations developed by the AAEP Infectious Disease Committee and posted on the AAEP website (aaep.org) in January 2008.

* Core vaccines protect against diseases that are endemic to a region, are virulent or highly contagious, pose a risk of severe or fatal disease, have potential public health significance, and/or are required by law. Core vaccines have clearly demonstrable efficacy, and have a sufficiently high level of patient benefit and low level of risk to justify their use in all equids in North America.

† Non-core (risk-based) vaccines are selected for use based on assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of non-core vaccines will vary between individuals, populations, and/or geographic regions.

Table 48-3 Guidelines for Vaccination of Adult Horses Against Core and Non-Core Diseases

Disease/Vaccine*†	Broodmares	Other Adult Horses (>1 Year of Age) Previously Vaccinated Against the Disease Indicated	Other Adult Horses (>1 Year of Age) *Not Previously Vaccinated* Against the Disease Indicated or Lacking a Vaccination History	Comments
CORE DISEASES				
Tetanus (toxoid)	*Previously vaccinated:* Annual, 4–6 weeks prepartum *Not previously vaccinated or vaccination history unknown:* 2-dose series: Second dose 4–6 weeks after the first dose Revaccinate 4–6 weeks prepartum	Annual	2-dose series: Second dose 4–6 weeks after the first dose	Booster at time of penetrating injury or surgery if last dose was administered more than 6 months previously
Eastern and Western equine encephalomyelitis (EEE, WEE)	*Previously vaccinated:* Annual, 4–6 weeks prepartum *Not previously vaccinated or vaccination history unknown:* 2-dose series: Second dose 4 weeks after the first dose Revaccinate 4–6 weeks prepartum	Annual in spring, prior to onset of vector season	2-dose series: Second dose 4 weeks after the first dose; revaccinate prior to onset of the next vector season.	Consider 6-month revaccination interval for horses residing in endemic areas with a? prolonged vector season or immunocompromised horses.

West Nile virus (WNV)	*Previously vaccinated:* Annual, 4–6 weeks prepartum *Not previously vaccinated or vaccination history unknown:* It is preferable to vaccinate naïve mares when open. In areas of high risk, initiate primary series as described for adult horses that have not previously been vaccinated.	Annual in spring, prior to onset of vector season	**Inactivated vaccine:** 2-dose series: Second dose: 4–6 weeks after the first dose; revaccinate prior to onset of the next vector season **Recombinant canarypox-vectored vaccine:** 2-dose series: Second dose: 4–6 weeks after the first dose; revaccinate prior to onset of the next vector season **Flavivirus chimera vaccine:** One dose; revaccinate prior to onset of the next vector season.	When using the inactivated or the recombinant product, consider a 6-?month revaccination interval for: Horses residing in endemic areas with a prolonged vector season. Juvenile horses (<5 years of age) Geriatric horses (>15 years of age) Immunocompromised horses For naïve horses being imported into an endemic area during the vector season, the?preferred approach is to complete the primary vaccination series prior to importation. If this approach is not feasible, protect them from being bitten by mosquitoes if possible, and vaccinate them with one of the vaccines (Flavivirus chimera or canarypox-vectored) that have the most rapid onset of immunity.
Rabies	Annual, prior to breeding OR 4–6 weeks prepartum	Annual	One dose; annual revaccination	Because booster vaccination induces persistently elevated levels of antirabies antibody, this vaccine may be given postfoaling, but prior to breeding, in order to reduce the number of vaccines given to mares prepartum.
NON-CORE (RISK-BASED) VACCINES				

Anthrax	Not recommended for use during gestation.	Annual	2-dose series: Second dose 3–4 weeks after the first?dose; annual revaccination.	Use only in endemic areas or in the face of an outbreak. Antimicrobial drugs must ***not*** be given concurrent with this vaccine. Administer subcutaneously in the neck. Use caution during storage, handling and administration. Consult a physician immediately if human exposure to anthrax vaccine occurs by accidental injection, ingestion, or otherwise through the conjunctiva or broken skin.
Botulism	*Previously vaccinated:* Annual, 4–6 weeks prepartum *Not previously vaccinated or vaccination history unknown:* 3-dose series: First dose during eighth month of gestation Second dose 4 weeks after the first dose Third dose 4 weeks after the second dose	Annual	3-dose series: Second dose 4 weeks after the first dose Third dose 4 weeks after the second dose	
Equine herpesvirus (EHV)	3-dose series with product labeled for prevention against EHV abortion. Administer during the fifth, seventh, and ninth months of gestation.	Annual (see comments)	3-dose series: Second dose: 4–6 weeks after the first dose Third dose: 4–6 weeks after the second dose	Consider 6-month revaccination interval for: Horses <5 years of age Horses on breeding farms in contact with pregnant mares Performance or show horses at high risk

Equine influenza	*Previously vaccinated:* **Inactivated vaccines:** Semiannual with one dose administered 4–6 weeks prepartum **Canarypox-vectored vaccine:** Semiannual with one dose administered 4–6 weeks prepartum *Not previously vaccinated or vaccination history unknown:* **Inactivated vaccine:** 3-dose series: Second dose 4–6 weeks after the first dose Third dose 4–6 weeks prepartum **Canarypox-vectored vaccine:** 2-dose series: Second dose 4–6 weeks after first dose but no later than 4 weeks prepartum	Semiannual for horses with ongoing risk of exposure Annual for horses at low risk for exposure	**Modified live intranasal vaccine:** One dose administered IN. Revaccinate semiannually to annually. **Inactivated vaccines:** 3-dose series: Second dose: 4–6 weeks after the first dose Third dose: 3–6 months after the second dose Revaccinate semiannually to annually. **Canarypox-vectored recombinant:** 2-dose series: Second dose 4–6 weeks after the first dose. Revaccinate semiannually.	The MLV intranasal vaccine can be used to protect pregnant mares against influenza, but its use for the prepartum booster is not recommended because it does not reliably stimulate high levels of circulating antibody.
Equine viral arteritis (EVA)	Not recommended unless risk of exposure is high	Annual *Stallions and teasers*: Vaccinate 3–4 weeks before the start of the breeding season *Mares:* Vaccinate when open	Single dose (see comments)	Prior to initial vaccination, intact males and any horses potentially intended for export should undergo serologic testing and be confirmed negative for antibodies to EAV. Samples for testing should be collected shortly prior to, or preferably at, the time of vaccination.

Potomac horse fever (PHF)	*Previously vaccinated:* Semiannual with one dose administered 4–6 weeks prepartum *Not previously vaccinated or vaccination history unknown:* 2-dose series: First dose 8–10 weeks prepartum Second dose 4–6 weeks prepartum	Semiannual to annual	2-dose series: Second dose: 3–4 weeks after the first?dose Revaccinate semiannually to annually.	A revaccination interval of 3–4 months may be considered in endemic areas when disease risk is high; however, strategic revaccination to maximize immunity prior to expected peak challenge in the summer and fall is the preferred approach.
Rotovirus	3-dose series: First dose at 8 months gestation Second dose 4 weeks after the first dose Third dose 4 weeks after the second dose	NA	NA	Check serum concentrations of immunoglobulins in the foal to verify adequate passive transfer
Strangles	*Previously vaccinated:* **Inactivated M-protein subunit vaccines:** Semiannual with one dose given 4–6 weeks prepartum *Not previously vaccinated or vaccination history unknown:* **Inactivated M-protein subunit vaccines:** 3-dose series: Second dose 2–4 weeks after the first dose Third dose 4–6 weeks prepartum	Semiannual to annual	**Inactivated M-protein subunit vaccines:** 2 to 3-dose series: Second dose 2–4 weeks after the first dose Third dose (when recommended by manufacturer) 2–4 weeks after the second dose Revaccinate semiannually. **Modified live intranasal vaccine:** 2-dose series administered IN: Second dose 3–4 weeks after the first dose Revaccinate semiannually to annually.	Vaccination is not recommended as a strategy in outbreak mitigation.

Modified, with permission, from recommendations developed by the AAEP Infectious Disease Committee and posted on the AAEP website (aaep.org) in January 2008.

* Core vaccines protect against diseases that are endemic to a region, are virulent or highly contagious, pose a risk of severe or fatal disease, have potential public health significance, and/or are required by law. Core vaccines have clearly demonstrable efficacy, and have a sufficiently high level of patient benefit and low level of risk to justify their use in all equids in North America.

† Non-core (risk-based) vaccines are selected for use based on assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of non-core vaccines will vary between individuals, populations, and/or geographic regions.

Table 48-4 Manufacturers' Recommendations for Use of Single Component Equine Immunizing Agents and Biologics

Disease	Etiologic Agent	Type of Product	Available Products	Manufacturer	Dose
Anthrax	*Bacillus anthracis*	Nonencapsulated live bacterial spores	Anthrax Spore Vaccine	Colorado Serum Co.	l mL
Botulism (shaker foal syndrome)	*Clostridium botulinum* type B toxin	Toxoid	BotVax-B	Neogen Corporation	2 mL
*Escherichia coli*septicemia	*E. coli*	*E. coli* antibody, equine origin	Equine Coli Endotox	Novartis (Food Animal)	10 mL
		*E. coli*antiserum, equine origin	E. Colicin-E	Agri Labs	10 mL
Endotoxemia	*Salmonella typhimurium*	Inactivated; bacterin toxoid	Endovac-Equi	Immvac	1 mL
	Endotoxin produced by gram-negative bacteria	*Salmonella typhimurium* antiserum, equine origin	Endoserum	Immvac	1.5 mL/kg (0.7 mL/lb)
Equine encephalomyelitis	Bivalent vaccines: WEE, EEE	Inactivated; chicken tissue culture origin	Encevac	Intervet	1 mL
		Inactivated; cell culture origin	Encephalomyelitis vaccine, eastern and western	Colorado Serum Co.; Professional Biological	1 mL
Equine viral arteritis	Equine arteritis virus	Modified live; equine cell line origin	Arvac	Fort Dodge Animal Health	1 mL
Equine influenza	Equine influenza A equine 2	Modified live (cold adapted)	FluAvert I.N.	Intervet	Entire contents of vial after reconstitution
		Recombinant, canarypox-vectored	Recombitek Equine Influenza Virus	Merial	2 mL
		Inactivated; canine kidney call line origin	Fluvac Innovator	Fort Dodge Animal Health	1 mL
		Inactivated; cell line origin	Flumune A2 KY98	Pfizer Animal Health	1 mL
		Inactivated; cell line origin	Calvenza-03 EIV	Boehringer Ingelheim	2 mL

Route	Age for Primary Series	Regimen for Primary Series	Regimen for Revaccination	Comments*
SC		Two doses 2–3 weeks apart	Annual	Vaccinate 4 weeks before possible exposure. Light to moderate swelling may occur at the injection site. Do not administer antibiotics within 1 week of vaccination.
IM		Three doses at least 4 weeks apart	Annual	In pregnant mares, administer booster 4 weeks before parturition. Protects only against botulism caused by *C. botulinum* type B.
PO	Within 12 hours of birth			Colostrum should be fed to each foal.
PO	Within 12 hours of birth			Colostrum should be fed to each foal.
IM	6 months or older	Two doses 2–3 weeks apart	Annual	Indicated for prevention of endotoxin-mediated disease caused by *S. typhimurium* and *E. coli*. Label includes multiple precautions—read thoroughly.
IV				When treating failure of passive transfer in foals, administer 500 mL to a 70-lb foal.
IM		Two doses 3–4 weeks apart	Annual or at any time epidemic conditions exist or are reported and exposure is imminent or likely.	Time primary series and boosters to precede mosquito season.
IM		Two doses 3 weeks apart		
IM	6 weeks or older	One dose	Annual	Prior authorization by a state veterinarian is recommended, and a permit may be necessary (regulations vary from state to state). Vaccinate stallions at least 3 weeks before breeding season. Vaccinate mares as maidens or while open at least 3 weeks before breeding. Pregnant mares should not be vaccinated during the last 2 months of gestation. Vaccinated horses may be ineligible for export because of seroconversion.

IN	11 months or older	One dose	Semiannual. Horses at high risk may benefit from revaccination every 3 months.	Contains Kentucky/91 (A_2) strain. Horses vaccinated before 11 months of age should be given a dose of vaccine at age 11 months. This vaccine is NOT intended for IM or SC administration.	
IM	5 months or older	Two doses, 5 weeks apart	Annual	Contains Kentucky/94 (A_2) and Newmarket/2/93 (A_2) strains.	
IM		Two doses 3–4 weeks apart	Annual	Contains Kentucky/97 (A_2) strain.	
IM		Two doses 2–3 weeks apart	Annual or whenever epizootic conditions exist and exposure is likely.	Contains Kentucky/98 (A_2) strain.	
IM for first two doses; IM or IN for subsequent doses	6 months or older	Two doses 3–4 weeks apart	Annual or prior to anticipated exposure	Contains Ohio/2003 (A_2), Newmarket 2/93 (A_2), and Kentucky/95 (A_2) strains. The first and second doses must be administered by the IM route; the third and subsequent booster doses may be administered by either IM or IV routes. Labeled for use in pregnant mares.	
Disease	**Etiologic Agent**	**Type of Product**	**Available Products**	**Manufacturer**	**Dose**
Rotaviral diarrhea	Rotavirus	Inactivated	Equine rotavirus vaccine	Fort Dodge Laboratories	1 mL
Equine monocytic ehrlichiosis(Potomac horse?fever)	*Neorickettria risticii*	Inactivated	PHF-Gard	Pfizer Animal Health	1 mL
		Inactivated	Equine Potomavac	Merial	1 mL
		Inactivated	PotomacGuard	Fort Dodge Animal?Health	1 mL
		Inactivated	Equovum PHF	Boehringer Ingelheim	1 mL
		Inactivated	Mystique	Intervet	1 mL
Rabies	Rabies virus	Inactivated; cell line origin	Imrab 3	Merial	2 mL
		Inactivated; cell line orign	Imrab Large Animal	Merial	2 mL
		Inactivated; cell line origin	Rabvac 3	Fort Dodge Animal Health	2 mL

		Inactivated; cell line origin	Rabvac 3TF	Fort Dodge Animal?Health	2 mL
Rhinopneumonitis	Equine herpesvirus type 1 (EHV-1)	Inactivated	Pneumabort-K+1b	Fort Dodge Laboratories	2 mL
		Inactivated; tissue culture origin	Prodigy	Intervet	2 mL
		Modified live; equine cell line orign	Rhinomune	Pfizer	1 mL
	EHV-1 and EHV-4	Inactivated bivalent;tissue culture origin	Prestige	Intervet	1 mL
		Inactivated bivalent	Equivac Innovator EHV-1/4	Fort Dodge Animal?Health	1 mL
Strangles	*Streptococcus equi* subsp. *equi*	Modified live	Pinnacle I.N.	Fort Dodge Animal?Health	2.5 mL
		Inactivated;bacterial M-?protein extract	Strepguard	Intervet	1 mL
		Inactivated;bacterial M-?protein extract	StrepVax II	Boehringer Ingelheim	1 mL
Route	Age for Primary Series	Regimen for Primary Series	Regimen for Revaccination	Comments*	
IM	Adult broodmares	Three doses, 4 weeks apart during the eighth, ninth, and tenth months of gestation.	Annually, three doses during the eighth, ninth, and tenth months of gestation.	Contains the G3 (H2) serotype of equine rotavirus. Product is conditionally licensed by the USDA, while additional efficacy and potency data are being developed, for vaccination of pregnant mares to promote passive transfer to foals of antibodies against equine rotavirus.	
IM	1 year or older	Two doses 2–3 weeks?apart	Annual		
IM	3 months or older	Two doses 3–4 weeks?apart	Annual		
IM		Two doses 3–4 weeks?apart	Annual		
IM	3 months or older	Two doses 3–4 weeks?apart	Annual		
IM	3 months or older	Two doses 3–4 weeks?apart	Annual, or when epidemic conditions exist or are reported and exposure is imminent.		

	IM or SC	3 months or older	One dose	Annual	Effectiveness of a single dose of rabies vaccine in the primary series for foals has recently been questioned (see text).
	IM	3 months or older	One dose	Annual	
	IM	3 months or older	One dose	Annual	
	IM	3 months or older	One dose	Annual	
	IM		Two doses 3–4 weeks?apart	*Pregnant mares for abortion prevention*: Repeat doses annually during fifth, seventh, and ninth months of gestation; *Young horses:* 6 months after primary series and annually thereafter	Vaccinate open and maiden mares at the same time as pregnant mares. For mares beyond the fifth month of gestation when vaccination is initiated, vaccinate on presentation and every 2 months thereafter until foaling.
	IM	6 months or older	Three doses 4–6 weeks?apart	*Pregnant mares for abortion prevention:* annually during the fifth, seventh, and ninth months of gestation. *Respiratory disease prevention:* Annually or at any time epidemic conditions exist or are reported and exposure is imminent.	Maiden and barren mares housed or pastured with pregnant mares should be vaccinated on the same schedule. Booster

IM	3 months or older	Two doses 3–4 weeks?apart	3-month intervals	Vaccine is approved for use in pregnant mares, but no label claim is made for prevention of EHV-1 abortion. Vaccinate pregnant mares after the second month of gestation. Foals vaccinated before 3 months of age should receive a 2-dose series after reaching 3 months of age.	
IM		Two doses 4–6 weeks apart	Annual or any time epidemic conditions exist or are reported and exposure is imminent.	Approved for use in pregnant mares, but no label claim is made for prevention of EHV-1 abortion.	
IM		Two doses 3–4 weeks?apart	Annual		
IN		Two doses at 2–3 week?intervals	Annual	For intranasal use only. Do not administer parenterally by injection.	
IM		Two doses 3–4 weeks?apart	Annual or before expected exposure	Foals vaccinated when less than 3 months of age should receive an additional dose at 6 months.	
IM	3 months or older	Three doses at 3-? week intervals	Annual or before expected exposure		

Disease	Etiologic Agent	Type of Product	Available Products	Manufacturer	Dose
Tetanus	*Clostridium tetani*	Inactivated; toxoid	Tetanus toxoid	Fort Dodge Animal Health	1 mL
			Super-Tet	Intervet	1 mL
			Tetguard	Boehringer Ingelheim	1 mL
			Tetanus toxoid—concentrated	Colorado Serum Co., Professional Biological	1 mL
			Tetanus toxoid-unconcentrated	Colorado Serum Co.	10 mL
		Antitoxin	Tetanus antitoxin	Fort Dodge Animal Health	1500 U
				Colorado Serum Co.; Professional Biological	1500 U
				Durvet	1500 U
			Antitox Tet	Novartis (Farm Animal)	1500 U
West Nile virus infection	West Nile virus (WNV)	Inactivated	West Nile-Innovator	Fort Dodge Animal Health	1 mL
		Canarypox-vectored recombinant	Recombitek West Nile Virus	Merial	1 mL
		Flavivirus Chimera (YF-17D)	PreveNile	Intervet	1 mL
		DNA	West Nile-Innovator DNA	Fort Dodge Animal Health	2 mL
Route	Age for Primary Series	Regimen for Primary Series	Regimen for Revaccination	Comments*	
IM		Two doses 4–8 weeks apart	Annual	For small horses use 0.5 mL.	
IM		Two doses 3–4 weeks apart	Annual		
IM or SC		Two doses 4 weeks apart	Annual or prior to anticipated exposure		
IM		At least two doses, 4 weeks apart	Annual		
IM or SC		Two doses 4 weeks apart	Annual		

IM, SC, IV, IP	NA	NA	NA	Administer upon exposure to unimmunized animals or those with an unknown vaccination status. Doses of up to 100,000 U have been used for treatment of tetanus. Fatal serum hepatitis has been seen after administration of tetanus antitoxin to horses.
IM or SC	NA	NA	NA	
IM or SC	NA	NA	NA	
IM or SC	NA	NA	NA	
IM		Two doses 3–6 weeks apart	Annual	
IM		Two doses 3–6 weeks apart	Annual	
IM	5 months or older	One dose	Annual	
IM		Two doses, 2–4 weeks apart	Duration of immunity (DOI) not established.	Product is licensed but not marketed as of January 2008.

Information on combination vaccines is available in *Compendium of Veterinary Products*, ed 9, Port Huron, Mich, 2006, North American Compendiums.

EEE, Eastern equine encephalomyelitis; *IM*, intramuscular; *IN*, intranasal; *IV*, intravenous; *NA*, not applicable; *PO*, oral; *SC*, subcutaneous; *VEE*, Venezuelan equine encephalomyelitis; *WEE*, western equine encephalomyelitis.

The addresses of the manufacturers mentioned in this table are listed below:

Boehringer Ingelheim Vetmedica, Inc. St. Joseph. MO.

Colorado Serum Co., Denver, CO.

Equi Laboratories. St. Joseph, MO.

Fort Dodge Animal Health, Fort Dodge, IA.

Grand Laboratories, Larchwood, IA.

IMMVAC, Inc. Columbia, MO.

Intervet, Shawnee, KS.

Merial, Iselin, NJ.

Neogen Biologics, Lexington, KY.

Novartis Animal Health US, Inc., Greensboro, NC.

Pfizer, Inc. Exton, PA.

Professional Biological Co., Denver, CO.

Schering-Plough, Kenilworth, NJ.

Information on combination vaccines is available in *Compendium of Veterinary Products*, ed 9, Port Huron, Mich, 2006, North American Compendiums.

Information on combination vaccines is available in *Compendium of Veterinary Products*, ed 9, Port Huron, Mich, 2006, North American Compendiums.

Note: The recommendations contained in this table were obtained from package inserts or from the *Compendium of Veterinary Products*, ed 9. In those instances in which research or extensive field experience indicate that increased efficacy can be achieved through use of alternative vaccination protocols, recommendations contained in Table 48-4 may differ from those in Tables 48-2 and 48-3.

* Avoid administering immediately before an athletic event or show, because transient, usually self-limiting febrile responses may occur after vaccination.

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No published challenge studies are available to document the speed of onset or duration of protection induced by tetanus toxoid preparations currently licensed in North America; conclusions regarding their efficacy are therefore based on the serologic response obtained in horses and laboratory animals and on field experience. However, a challenge study conducted in Europe more than 40 years ago found that horses were resistant to challenge 8 days after receiving a single injection of tetanus toxoid, before antibody could be detected in their serum.[45] A second study demonstrated that a series of three doses of tetanus toxoid induced protection lasting for at least 8 years, and perhaps for life, even when antibodies could no longer be detected.[42] In contrast, tetanus has been documented in vaccinated horses in North America,[46] although survival was strongly associated with previous vaccination. Thus it would not be prudent to recommend extension of the annual interval for revaccination with tetanus toxoid, pending publication of data documenting duration of immunity

(DOI). Vaccinated horses that sustain a wound or undergo surgery more than 6 months after receiving their previous tetanus booster should be revaccinated with tetanus toxoid immediately at the time of injury or surgery.

Annual revaccination of pregnant mares should be completed 4 to 8 weeks before foaling to protect the mare if she sustains foaling-induced trauma or retained placenta and to enhance concentrations of specific immunoglobulins in colostrum. Colostrum-derived antibodies significantly interfere with the immune response of foals vaccinated with tetanus toxoid until they are approximately 6 months of age.[23,44]

Primary vaccination of foals that have received appropriate transfer of colostral antibodies from a vaccinated mare should include three doses of tetanus toxoid beginning at age 6 months or older. The interval between the first two doses of vaccine should be approximately 4 weeks, and the interval between the second and third doses should be 8 to 16 weeks. The three-dose primary series is recommended for foals because a high proportion of foals fail to seroconvert in response to two doses of tetanus toxoid, regardless of whether maternal antibodies are detectable at administration of the first dose.[23,44] For foals born to nonimmune mares, this initial three-dose series can start at 1 to 4 months of age.

Tetanus antitoxin is produced by hyperimmunization of donor horses with tetanus toxoid. Administration of one vial of antitoxin (1500 IU) to unvaccinated horses induces immediate passive protection that lasts not more than 3 weeks.[44] More prolonged protection may be accomplished with higher doses. In addition to the use of high doses of tetanus antitoxin to treat tetanus, indications frequently cited include administration to newborn foals born to unvaccinated mares and to unvaccinated horses that sustain an injury. In these cases the concurrent administration of tetanus antitoxin and tetanus toxoid at different sites using separate syringes has been advocated, followed by administration of additional doses of toxoid at 4- to 6-week intervals to complete the primary series.[47] Because a small but significant number of horses experience serum sickness and fatal hepatic failure (serum hepatitis) several weeks after receiving tetanus antitoxin,[48,49] a preferred approach to the unvaccinated horse that sustains a puncture or deep laceration is to thoroughly clean and debride the wound, initiate active immunization by administering tetanus toxoid, and institute a course of antimicrobial treatment with penicillin or alternate antimicrobial that is active against *C. tetani*.

48.4.2 Equine Encephalomyelitis (Sleeping Sickness)

The equine encephalomyelitis viruses (EEE, WEE, and VEE) belong to the Alphavirus genus of the family Togaviridae. They are transmitted by mosquitoes, and infrequently by other bloodsucking insects, to horses from wild birds or rodents, which serve as natural reservoirs for these viruses. Risk of exposure and geographic distribution of the encephalomyelitis viruses vary by season and from year to year with changes in distribution of insect vectors and wildlife reservoirs. The distribution of EEE has historically been restricted to the eastern, southeastern, and some southern states with recent northward encroachment. WEE has caused minimal disease in horses in North America during the last two decades; however, the virus continues to be detected in mosquitoes and birds throughout the Western states. In the past, outbreaks of WEE have been recorded in the western and midwestern states, with sporadic cases in the Northeast and Southeast United States. Because EEE, WEE, or both are endemic in most areas of North America, vaccination against these diseases should be part of the core vaccination program for all horses. VEE is a reportable foreign animal disease. Epidemics of VEE occur when the virus undergoes genetic change and develops greater virulence for avian and mammalian hosts. These viral variants are able to multiply to high levels in the horse, and then the horse becomes a reservoir for infection in these outbreaks. VEE occurs in South and Central America but has not been diagnosed in the

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United States or Mexico for many years; therefore routine vaccination of horses in these regions against VEE is not recommended at this time, unless transportation to endemic areas is planned.

Available vaccines are formalin inactivated, adjuvanted, bivalent whole-virus products containing EEE and WEE (Encevac with Havlogen, Intervet; Encephaloid Innovator, Fort Dodge; Cephalovac EW, Boehringer Ingelheim), or trivalent products that also contain VEE (Cephalovac VEW, Boehringer Ingelheim). Veterinarians and horse owners often use combination products containing other antigens, such as tetanus, influenza, WNV, or EHV for primary or booster immunization of horses against encephalomyelitis viruses. Although correlates for protection against EEE, WEE, and VEE are not well established, circulating antibodies are assumed to be important because infection is acquired by vascular injection (mosquito bites) and current inactivated vaccines appear to have good efficacy.[50,51] A study evaluating the serologic response of horses to commercial encephalomyelitis-tetanus combination vaccines showed that the EEE neutralizing antibody responses to Encevac T (Intervet, Carbopol adjuvant) and Equiloid (Fort Dodge, squaline and surfactant adjuvant) were of greater magnitude and persistence than responses to Cephalovac EWT (Boehringer Ingelheim, saponin adjuvant).[20] However, no comparative randomized challenge studies have been performed using these vaccines to document whether differences in serologic responses equate to differences in efficacy. Early testing of bivalent (EEE/WEE) vaccines was performed by intracranial challenge with either EEE or WEE; the formalin inactivated preparations demonstrated 100% protection.

Primary immunization of unvaccinated adult horses is accomplished by administering two doses of inactivated vaccine 3 to 6 weeks apart. In areas where EEE is not a threat and mosquito vectors are active for less than 6 months of the year, annual revaccination in the spring, before the peak insect vector season, is recommended. In areas such as the Gulf States where EEE is endemic and mosquitoes are active virtually year-round, many veterinarians prefer to revaccinate horses semiannually to ensure more uniform protection throughout the year. Inactivated encephalomyelitis vaccines are considered to be safe for use during pregnancy; therefore booster vaccination of pregnant mares 4 to 8 weeks before foaling is routinely recommended to enhance colostral concentrations of specific immunoglobulins. Neutralizing antibodies to WEE and EEE are transferred passively to foals through colostrum and decline with an estimated half-life of 33 and 20 days, respectively. MDAs appear to confer protection and are detectable in the serum of many foals from vaccinated mares for at least 3 months and up to 7 months, depending on the postnursing titer.[34,52–54]

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Several studies have shown that MDAs exert a profound inhibitory effect on the ability of foals to mount serologic responses to inactivated bivalent WEE/EEE vaccines, which likely accounts for some of the reported cases of vaccine failure and resultant clinical EEE in vaccinated horses, particularly those less than 2 years of age.[30,34,35,52,53] Studies have shown that 3-month-old foals born to immune mares consistently failed to mount a serologic response to two doses of inactivated bivalent WEE/EEE vaccine and the majority had not responded even after administration of a third dose.[35,37] Whereas many 6-month-old foals failed to seroconvert after administration of two doses of vaccine, most responded after administration of a third dose.[35] Based on these data, inclusion of a third dose in the primary series, 8 to 16 weeks after administration of the second dose, is strongly recommended for primary immunization of foals and yearlings.

WEE has a lower mortality rate than EEE, and prevalence of WEE in many western states is sufficiently low that the risk of foals acquiring infection during their first year of life is also low. Therefore primary vaccination of foals of vaccinated mares in areas where mosquitoes die off in the winter and the risk of infection is low is best completed when foals are 5 to 6 months of age or older in order to minimize the potential for MDA interference. Because foals born in the late spring and summer months are still less than 6 months of age by the time the mosquito season comes to an end in many regions, primary vaccination of these foals can be delayed

until the spring of the yearling year. In contrast, EEE is a highly fatal disease that poses a significant risk to foals during their first year of life, particularly in the Gulf States, where competent vectors are present year-round.[30,53,55] Therefore most veterinarians in these regions recommend commencing primary vaccination of foals at 3 to 4 months of age using a three-dose primary series followed by a fourth dose before the onset of the next mosquito season and semiannual boosters thereafter, to maximize the chances of overcoming the inhibitory effects of MDAs and inducing protection.[53]

48.4.3 West Nile Virus

In the few years since WNV infection was first diagnosed in horses in the northeastern United States in 1999, it has spread across the entire North American continent and is now considered to be endemic in all mainland areas of North America and Mexico, where it has become an important consideration in the differential diagnosis of horses with signs of neurologic disease. As of June 2007 the disease had been confirmed in almost 25,000 horses in the United States, approximately 35% of which had died or been euthanized. Approximately 40% of horses that survive acute illness caused by WNV exhibit residual effects, such as gait and behavioral abnormalities, 6 months postdiagnosis.[56]

WNV, a member of the family Flaviviridae, is transmitted by mosquitoes and infrequently by other bloodsucking insects to horses, human beings, and a number of other mammals from avian hosts, which serve as natural reservoirs for these viruses. Horses and humans are considered to be “dead-end” hosts of the WNV and therefore do not contribute to the transmission cycle. The virus is not directly contagious from horse to horse or from horse to human. Similarly, indirect transmission via mosquitoes from infected horses is highly unlikely because horses do not experience a significant level of viremia.[57] Risk of infection and death appears to increase with increasing age; however, the disease has been confirmed in foals as young as 3 weeks of age. Although cases have been seen virtually year-round in the southeastern United States, the risk of acquiring infection is highest during those months in which mosquito activity peaks, typically July, August, September, and October in most areas of North America. WNV infection is a core disease against which all horses residing in the continental United States and Canada should be vaccinated.

As of June 2007, three fully licensed vaccines (West Nile—Innovator, Fort Dodge Animal Health; Recombitek, Merial; and PreveNile, Intervet) were marketed for use in horses in North America. West Nile—Innovator is an inactivated whole virus vaccine that contains a metabolizable oil adjuvant.[9] This vaccine is available as either a monovalent (single component) or as a multivalent vaccine containing other encephalitis virus antigens (EEE and WEE). Recombitek is a Carbopol-adjuvanted canarypox-vectored recombinant modified live vaccine,[11,12,17] and PreveNile is a nonadjuvanted chimeric yellow fever—vectored vaccine.[15,58] A fourth vaccine, a plasmid DNA vaccine with a metabolizable oil adjuvant (Fort Dodge Animal Health) was licensed in 2005 but had not been marketed as of June 2007.[13] All four vaccines have met USDA requirements for safety in tests, each involving more than 640 horses.

Needle and mosquito challenge models have shown that West Nile—Innovator, Recombitek, and the plasmid DNA vaccine all significantly reduce the magnitude of viremia in experimentally infected, vaccinated horses compared with unvaccinated control horses for as long as 12 months after primary vaccination with two doses of vaccine.[9,11,13,59] Although viremia was reliably induced in unvaccinated control horses in these challenge models, clinical disease was not. Therefore West Nile—Innovator and Recombitek are labeled as aids to the prevention of viremia caused by WNV infection. In contrast, an intrathecal challenge model that reliably induced severe clinical disease was used to test the efficacy of PreveNile in studies for licensure.[15,16] In this

model a single dose of PreveNile prevented clinical disease as well as viremia in 4- to 6-month-old horses challenged 1 year after vaccination; therefore PreveNile is labeled for protection against viremia and as an aid in the prevention of disease and encephalitis caused by WNV.[15,16] Subsequently, Recombitek was shown to induce a high level of clinical protection when tested using this rigorous intrathecal challenge model in a placebo-controlled study in which horses were challenged 14 days after completion of a two-dose vaccination series.[17] The comparative efficacy of West Nile—Innovator, Recombitek, and PreveNile has now been tested in a randomized, blinded, placebo-controlled intrathecal challenge study in which groups of five or six horses ≥6 months of age were challenged intrathecally 28 days after completion of the two-dose (West Nile—Innovator and Recombitek) or one-dose (PreveNile) primary vaccination series.[59] In this study, all six unvaccinated control horses developed grave neurologic signs postchallenge, whereas all vaccinated horses survived and none developed detectable viremia. Clinical disease was prevented in 100% of PreveNile-vaccinated horses, 80% of Recombitek-vaccinated horses, and 33% of Innovator-vaccinated horses. These findings support the results of field studies that provide clear evidence that, when used according to manufacturer recommendations, both West Nile—Innovator and Recombitek reduce the risk of disease and death after natural challenge, although clinical disease may not be fully prevented.[60–62]

Directions for primary immunization using West Nile—Innovator and Recombitek include administration of two doses of vaccine 3 to 6 weeks apart (consult the specific label). Optimal protection cannot be expected until 2 weeks after administration of the second dose, although Recombitek has been shown to induce significant protection as early as 26 days after administration of the first dose when tested in both the mosquito challenge and intrathecal challenge models.[12,17] Primary immunization with PreveNile requires one dose. A challenge study in yearlings showed that 83% (five of six) were protected when challenged intrathecally 10 days after vaccination with one dose, indicating that onset of immunity is rapid (Vaala W, personal communication, 2007). Rapid onset of immunity is an important feature when faced with the challenge of protecting naive horses that are being introduced into an endemic area, as is the case when horses from Europe and other nonendemic countries are imported into North America.

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Vaccine manufacturers recommend revaccination of previously vaccinated horses on an annual basis, or more frequently when local conditions are conducive to a prolonged period of potential exposure to infected mosquito vectors. Annual revaccination is best completed in the spring (late February through early April), before the onset of the insect vector season. In areas such as the southeastern states where the mosquito season is prolonged, revaccination twice annually, once in the spring and again in the late summer or early fall (late July through early September) has been advocated in the past to maximize protection, although the rationale for semiannual vaccination against WNV has not been tested in controlled studies.

None of the licensed vaccines currently marketed in the United States carry label recommendations for administration to pregnant mares; therefore it is recommended that mares be vaccinated before breeding whenever possible. It is well recognized, however, that pregnant mares are at risk for acquiring infection from infected mosquitoes. Consequently it has become accepted practice by many veterinarians to administer vaccines to pregnant mares on the reasonable assumption that the risk of adverse consequences of WNV infection far exceeds the reported adverse effects of use of vaccines in pregnant mares. Thousands of doses of West Nile—Innovator vaccine have been administered safely to pregnant mares, and a published study failed to document vaccine-associated adverse effects in a large population of pregnant mares.[63] Although the Recombitek vaccine is a live vectored vaccine, the canarypox vector is incapable of replication in mammals and does not induce a viremia that could infect a fetus. In addition, a canarypox-vectored influenza vaccine available in Europe is licensed for use in horses during pregnancy; therefore the vectored WNV vaccine is unlikely to be associated with an increased risk of adverse effects in pregnant mares. Similarly, data currently

under review by the USDA from studies involving a large number of pregnant mares suggest that PreveNile will likely also be shown to be safe for use in pregnant mares (Vaala W, personal communication, 2007). As with other vaccines, it is sound practice to avoid administering West Nile vaccines to mares during the first 60 days of gestation unless conditions of imminent risk prevail.

Booster vaccination of previously primed pregnant mares 4 to 8 weeks before foaling appears to induce a strong anamnestic serologic response that provides their foals with passive colostral protection lasting at least 3 to 4 months.[37] In contrast, a significant proportion of naive pregnant mares failed to seroconvert when the primary series of WNV—Innovator vaccine was administered during the second half of gestation, perhaps reflecting pregnancy-associated downregulation of Th2 responses.[37] This observation adds further justification to the recommendation that when inactivated West Nile—Innovator vaccine is used, the primary series is best completed before breeding. In a similar study, pregnancy did not appear to suppress the response of mares to primary immunization with Recombitek (Wilson WD and colleagues, unpublished observations, 2007).

In contrast to findings with many other vaccines in the foals of immune mares, MDAs do not block the response of foals as young as 3 months of age to vaccination with either the inactivated or the recombinant vaccine.[37] Although this finding is somewhat surprising for the inactivated vaccine, it might reasonably have been expected for the recombinant vaccine because the canarypox vector system accomplishes transfection of cells and expression of the major E-peptide and M-peptide antigens of WNV on the surface of antigen presenting cells (APCs) in association with major histocompatibility complex (MHC) class I and class II antigens. These peptide antigens are therefore not free in the tissues and circulation to be neutralized by MDAs.

Primary vaccination of foals from properly vaccinated mares can be started by administration of the first dose of either West Nile—Innovator or Recombitek as early as 3 to 4 months of age, followed by a second dose approximately 1 month later, then a third dose 8 to 16 weeks after the second dose. This third dose increases the likelihood that foals with high MDA levels, which may have attenuated the response to the first dose of vaccine, will become primed and protected. Even in foals that have no maternally derived WNV antibodies after nursing, the third dose of inactivated vaccine in the primary series induces significantly higher and more persistent levels of antibody than do two doses. A booster should be administered during the spring of the yearling year, after which the recommendations for vaccination of adult horses should be followed. Primary vaccination of foals from unvaccinated, unexposed mares should commence at 3 months of age or younger (as early as 1 month of age), depending on month of birth and seasonal level of activity of mosquito vectors in the area. The three-dose primary vaccination protocol previously outlined should be followed. Revaccination should be performed before the onset of the next mosquito season.

The influence of MDAs on the response of foals to PreveNile has not been established, but the product is labeled for administration of a single priming dose to foals 5 months of age or older. A second dose of vaccine should be administered before the onset of the next mosquito season. Considering the rapid onset of immunity induced by this vaccine, protection can likely be accomplished at a similar age to that induced when the primary series with the inactivated or canarypox-vectored vaccines is started at 3 to 4 months of age. Preliminary data suggest that the plasmid DNA WNV vaccine may also circumvent the potentially interfering effects of MDAs.[13]

Horses that have recovered from clinical WNV infection will likely be protected for the remainder of their lives and should not need to be revaccinated unless changes in their immune status, as might occur with prolonged corticosteroid administration, alter their susceptibility to infection.[64]

It is remarkable that in little more than 6 years after WNV disease was first encountered in the Americas, four vaccines with documented efficacy based on challenge studies have been licensed for the benefit of horses, including three that apply the most modern technologies available for either animals or humans at this point in time.

48.4.4 Rabies

Rabies is an infrequently encountered neurologic disease of equids resulting from inoculation of the rabies virus through the bite of infected (rabid) wildlife. Wildlife species that serve as the natural reservoirs for infection with this rhabdovirus differ among regions of North America but include raccoons, foxes, skunks, and bats. Horses most often sustain bites on the muzzle, face, or lower limbs. The rabies virus then migrates via nerves to the brain, where it initiates rapidly progressive encephalitis. Even though the incidence of rabies in horses is low, the disease is invariably fatal and has considerable public health significance. All horses kept in areas where rabies is endemic in the wildlife population are at risk and should be vaccinated as part of the core vaccination program. Therefore it is recommended that horses be vaccinated against rabies by, or under the direct supervision of, a veterinarian using one of the three inactivated, tissue culture—derived products currently licensed for use in horses (Rabvac 3, Fort Dodge; RM Imrab 3, Merial; and Rabguard TC, Pfizer). These vaccines are potent immunogens that induce strong serologic responses that peak within 28 days after intramuscular administration of a single dose.

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Although correlates for protection against infection with rabies virus in horses are not well defined, it is logical to assume that protection correlates with titers of circulating antibody. In humans, postvaccination antibody titers are used to predict protection. In dogs, however, postvaccination serologic test results were not found to be completely predictive of resistance to challenge exposure during tests performed with certain inactivated vaccines.[65] Challenge studies demonstrating efficacy are required for licensing of all rabies vaccines, including those labeled for use in equids in the United States; however, published results are not available. The challenge studies are conducted by the vaccine manufacturers as outlined in the Code of Federal Regulations (CFR) from the USDA. These studies indicate a DOI of 12 months, and a minimum of 80% of vaccinated animals must be resistant to severe challenge with rabies virus.

For primary immunization, label directions on inactivated rabies vaccines licensed for use in horses suggest administration of one dose to horses age 3 months or older followed by a second dose 1 year later. Thereafter, annual revaccination is recommended. Although none of the licensed vaccines carries a specific label approval for use in pregnant mares, it is important to acknowledge that only a limited number of equine vaccines are specifically licensed for use in pregnant mares, and veterinarians do administer inactivated rabies vaccines to pregnant mares. Alternatively, veterinarians may recommend that mares be vaccinated against rabies before breeding in order to reduce the number and type of vaccines given in the period before foaling. Because rabies antibodies persist in serum for a prolonged period, foals born to mares that are revaccinated while open acquire substantial titers of rabies antibody after ingesting colostrum.

Documentation of rabies in reportedly vaccinated horses, most of which were less than 2 years of age, has brought into question the efficacy of label recommendations for primary vaccination of foals against rabies.[66] Recent studies in our laboratory have shown that the serologic response of most 3-month-old foals from antibody-positive mares is completely blocked, even when a two-dose primary vaccination series is used. Although the response to the first dose of vaccine is typically blocked in 6-month-old foals from antibody-positive mares, these foals appear to seroconvert after administration of a second dose 4 weeks later. Primary vaccination of foals from vaccinated mares should therefore be delayed until they are 6 months of age or older

and should include 2 doses of inactivated vaccine administered approximately 4 weeks apart, followed by a third dose at 1 year of age. For foals from unvaccinated mares the primary vaccination series can be started according to manufacturers' recommendations as early as 3 months of age and may consist of only one dose, although a two-dose series will likely induce more durable immunity.

48.4.5 Equine Influenza

Infection of the respiratory tract of horses with the orthomyxovirus influenza A/equine/2 (H3N8), remains one of the most common causes of rapidly spreading outbreaks of respiratory disease, despite the widespread practice of frequently revaccinating horses with inactivated vaccines by intramuscular injection. The influenza A/equine/1 subtype (H7N7) has not been recognized as a cause of clinical disease for many years and is likely extinct in nature. Influenza is endemic in the equine populations of the United States and much of the world, with the notable exceptions of New Zealand and Iceland. Rapid national and international transportation of horses facilitates spread of the virus. Concentrating young horses at racetracks, training facilities, boarding stables, breeding farms, shows, or similar athletic events increases the risk of infection, as does a low serum concentration of specific antibody.[67] Older horses are generally less susceptible to infection but may become ill when partial protection is overwhelmed by exposure to horses excreting large amounts of virus. Explosive outbreaks occur at intervals of several years when the immunity of the equine population wanes and sufficient antigenic drift has occurred to generate a new viral strain. In contrast to herpesviruses, equine influenza virus is not maintained in asymptomatic carrier horses and does not circulate constantly, even within large groups of horses. Rather, the disease is introduced sporadically by a symptomatic or asymptomatic infected horse. This epidemiologic finding and the rapid elimination of the virus by the equine immune response suggest that infection can be avoided by preventing entry of the virus into an equine population (e.g., by quarantine of newly arriving horses for at least 14 days) and by appropriate vaccination.[68]

Equine influenza virus is highly contagious and spreads rapidly through groups of horses in aerosolized droplets dispersed by coughing. Contaminated buckets, grooming or feeding equipment, tack, and transport vehicles may serve as fomites because the virus can survive for hours on such objects. Severity of clinical signs of influenza, which include nasal discharge, fever, lethargy, anorexia, cough, and myalgia, depends on the degree of existing immunity and other factors. Infected horses shed virus for up to 10 days in their nasal secretions. Inactivated vaccines do not induce sterile immunity; therefore recently vaccinated horses can become infected, shed virus, and contribute to interepidemic persistence of infection within the equine population and propagation of infection during outbreaks.[19]

Immunity to the same (homologous) strain of H3N8 virus after natural infection persists for more than a year and involves both local and systemic humoral and cellular mechanisms These include induction of large amounts of virus-specific neutralizing IgG and secretory IgA antibody in nasal secretions, high levels of circulating IgG antibodies, and genetically restricted antigen-specific cytotoxic T lymphocytes (CTLs) that kill infected cells.[69–73] Memory CTLs can be detected in peripheral blood for at least 6 months after infection, and solid immunity persists even when circulating antibody titers have declined to low or undetectable levels.[70,71,74,75] Similarly, protection induced by the licensed modified live intranasal influenza vaccine (Flu-Avert IN, Intervet) is presumably mediated through induction of local immune responses in the respiratory tract, because this vaccine does not typically induce high levels of circulating antibody.[6,8] With the possible exception of ISCOM vaccines, inactivated vaccines administered by intramuscular injection have limited potential to induce CTL or nasal secretory IgA responses and induce only low levels of neutralizing antibody in nasal secretions.[69,75,76] The degree of protection induced by inactivated influenza vaccines is highly correlated

with postvaccination titers of circulating antibody, predominantly of the IgGa and IgGb subisotypes, as measured by HI or single radial hemolysis (SRH) tests.[67,77–80] SRH levels ≥100 mm^2 are considered to be at least partially protective; however, levels >140 mm^2 are required for successful prevention of disease.[79] The partial protection induced by inactivated vaccines is of limited duration (up to approximately 7 months, depending on the vaccine) and is manifested as a reduction in clinical signs and attenuation of viral shedding in horses exposed to infection.[68,69]

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The magnitude of the serologic response to inactivated influenza vaccines depends on many factors, the most important of which are the quality and quantity (mass) of the viral antigen and the choice of the adjuvant.[79,81,82] Carboxypolymer-based compounds (carbomer, Carbopol) and ISCOMs are contained in some of the most efficacious inactivated influenza vaccines, whereas some commonly used adjuvants such as alum have been associated with induction of unproductive immune responses.[69,81] History of previous vaccination or infection, interval since the last dose of vaccine, antibody titer at the time of vaccination, age, maternal antibody status, and relatedness of the vaccine strain to circulating field strains of influenza virus are other important determinants of efficacy, at least for inactivated influenza vaccines.[77,83,84] Antigenic drift of the A/equine/2 subtype has resulted from point mutations in the genes encoding the amino acid sequences of the hemagglutinin (H) and neuraminidase (N) glycoprotein antigens on the surface of the virus. The result is emergence of viral strains representing two antigenic lineages, American and Eurasian, of the H3N8 virus. Further antigenic drift within each lineage has generated variants that, as with the prototypic strain A/equine/2/Miami 63, are named according to the location and year in which they were first isolated. Antigenic drift, by generating antigenically heterologous viruses, reduces the degree and duration of protection conferred by previous infection or vaccination because of the specificity of immunoglobulins, and it allows horses with high titers to become infected and develop clinical signs of disease if the vaccine strain is not closely related to the drifted infectious field strain.[85] Although antigenic drift of equine influenza viruses is slower than that of human influenza viruses, it is recommended that inactivated equine influenza vaccines include viral antigens from isolates obtained within the most recent 5 years and, ideally, representatives of both the American and Eurasian lineages. An expert surveillance panel meets annually to recommend strains that should be included in influenza vaccines in subsequent years (www.equiflunet.org.uk). In order to comply with federal regulations for licensing and marketing of vaccines, any change of a vaccine, such as including the most recently isolated influenza virus, usually leads to costly and time-consuming evaluation of the revised product. Consequently, viral antigens contained in inactivated vaccines typically lag more than the recommended 5 years behind the antigenic drift of field viruses, resulting in suboptimal protection. Even though Flu-Avert IN contains only a 1991 H3N8 strain of North American lineage, it has been shown to be protective against challenge with Eurasian strains and recently isolated North American strains.

The short-lived immunity after vaccination with inactivated equine influenza vaccines was the impetus for past recommendations for frequent revaccination, at intervals as short as 2 months. However, too short an interval between revaccination may compromise efficacy because influenza vaccination in a horse with a high antibody titer inhibits development of an optimal anamnestic response.[86] An additional consideration that potentially limits the efficacy of influenza vaccines is the phenomenon termed “original antigenic sin,” whereby horses exposed to a drifted field A/equine/2 virus will mount an anamnestic immune response directed more strongly against the strain with which they were vaccinated initially than against the drifted field virus.[82]

A considerable amount of published efficacy data, based both on challenge studies and on field epidemiology studies, has been available for many years in Europe to support the use of influenza vaccines. In contrast, information regarding the efficacy of influenza vaccines marketed in North America has remained sparse until

recently. Furthermore, studies conducted in North America during the late 1990s showed that the inactivated influenza vaccines in use at the time failed to provide much benefit in terms of reducing the risk of infection and clinical disease during field outbreaks.[19,67] Serologic testing performed during these and other studies indicated that vaccine failure was caused by failure of the influenza vaccines in use at the time to induce protective antibody titers.[19,67,87]

Fortunately, vaccine manufacturers in North America have responded to the challenge of producing more efficacious equine influenza vaccines during the last few years by incorporating more relevant recent viral strains, by increasing antigenic mass of relevant strains, by eliminating the seemingly irrelevant H7N7 strain, by modifying adjuvant systems, and by introducing novel technologies. An important advance occurred in 1999 when Heska Corporation marketed an attenuated live, cold-adapted influenza vaccine (Flu-Avert IN, Intervet, Millsboro, Del.) for intranasal administration. This vaccine, which contains a Kentucky/1991 strain of North American lineage, was found to be highly efficacious in blinded, controlled challenge studies conducted 5 weeks, 6 months, and 1 year after administration of a single dose to naive horses.[8] Subsequently Flu-Avert IN was shown to cross-protect against European H3N8 strains, as well as against North American strains isolated during the late 1990s and early 2000s, and to induce a rapid onset of protection within 7 days of administration of a single dose to naive horses.[6,88] Although horses challenged 1 year after administration of a single dose showed a significant, but only partial, reduction in severity of clinical signs and virus shedding, a more marked reduction in clinical signs and viral shedding was found when the challenge was performed 6 months after vaccination.[8] Based on these results, revaccination at 6-month intervals is recommended. Field experience indicates that this regimen induces solid clinical protection after natural challenge. Currently Flu-Avert IN is licensed for use in nonpregnant horses 11 months of age or older, primarily because this was the youngest age of the horses used in the challenge studies for licensing. Horses may shed small amounts of vaccinal virus for several days after vaccination with Flu-Avert IN, but the amount of virus shed is so low that in-contact horses will not generally become infected or immunized with vaccinal virus shed by recently vaccinated horses, and the likelihood of reversion to virulence is extremely low.[7]

Recently updated inactivated influenza vaccines have demonstrated good efficacy in challenge studies. Inactivated influenza vaccines containing one or more relevant H3N8 strains are currently marketed by Boehringer Ingelheim (Calvenza EIV) and Fort Dodge Animal Health (Fluvac Innovator). These and other companies also market a large number of multicomponent combination vaccines that contain the same inactivated influenza antigens as are in their single-component products but also contain tetanus, WEE and EEE virus, EHV, or WNV antigens. Calvenza EIV is adjuvanted with Carbopol and is the only inactivated vaccine currently licensed in North America that contains antigens from H3N8 viruses of both the American and European lineages (Kentucky/95 and Newmarket/2/93).

The initial two doses of this vaccine are administered IM; subsequent doses may be administered IM or intranasally. It is proposed, but not proved, that administration of booster doses by the intranasal route may provide a stronger local mucosal immune response. This vaccine is licensed for use in horses older than 6 months of age, including pregnant mares. Fluvac Innovator contains a KY/97 H3N8 strain in a metabolizable oil (MetaStim) adjuvant.

In late 2006, Merial was granted a North American license to market an injectable canarypox-vectored recombinant equine influenza vaccine that has been used with success in Europe for several years. This vaccine, named Recombitek Equine Influenza Virus vaccine, has been shown to induce strong protection in challenge studies and shows great potential to have a positive impact on influenza prevention in North America.[14] The vaccine incorporates the HA gene from the Kentucky/94 and Newmarket/2/93 H3N8 strains into the same

vector delivery platform as the efficacious WNV virus vaccine (Recombitek) and contains a carbomer polymer adjuvant in the diluent.[14] Consequently, this vaccine invokes a broad array of humoral and cellular immune responses. Challenge studies document onset of protection as soon as 2 weeks after completion of a two-dose primary series and persistence of solid protection for at least 5 months. Administration of a booster dose at 5 months induced a strong anamnestic response that provided solid protection persisting for at least 12 months.[18] Preliminary evidence suggests that this canarypox-vectored influenza vaccine will be able to circumvent the inhibitory effect of maternal antibodies, an issue that significantly affects primary immunization of foals using inactivated influenza vaccines.[89] Recombitek Equine Influenza Virus vaccine is licensed for vaccination of healthy horses as young as 5 months of age.

48.5 VACCINATION PROTOCOLS FOR INFLUENZA

The following are options for primary vaccination of adult horses that have not previously been vaccinated:

- Flu-Avert—Administer a single dose intranasally. A second dose administered 3 months later may be beneficial, particularly for horses vaccinated at less than 11 months of age.
- Recombitek Equine Influenza Virus vaccine—Administer two doses, 5 weeks apart.
- Inactivated IM administered vaccines—Administer two doses, 3 to 6 weeks apart, according to label directions. Although not specifically recommended by some manufacturers, administration of a third dose of vaccine, 2 to 6 months after the second dose, is indicated because it significantly enhances the magnitude of the primary response and duration of persistence of antibodies at protective levels.

Routine revaccination at an interval of 6 months appears to be appropriate for the intramuscularly administered inactivated and intranasally administered modified live virus influenza vaccines currently marketed in North America. A revaccination interval of 12 months is recommended for the recombinant vaccine, although this recommendation has not yet been tested in the field setting in North America. These “routine” revaccination protocols should be customized, by adjusting timing of boosters or inclusion of an additional booster, to achieve maximum protection during periods when the risk of exposure is high. For example, strategic revaccination 1 month before being placed at high risk of exposure, such as at a show or sale, or being transferred to a training or boarding facility is justified to maximize protection.

Revaccination of pregnant mares 4 to 8 weeks before foaling with a vaccine that stimulates a robust serologic response is recommended. Although the intranasally administered Flu Avert IN vaccine induces good protection, it does not routinely stimulate high levels of circulating antibody, at least when used for primary immunization. An inactivated or canarypox-vectored recombinant injectable vaccine is therefore recommended at this time for prefoaling booster vaccination of pregnant mares.[37]

48.5.1 Vaccination of Foals

The antibody status of a mare at the time of foaling is the main determinant of the postnursing circulating antibody titer in her foal and therefore has a profound impact on the ability of the foal or weanling to respond to influenza vaccines administered during the first year of life. Foals born to seronegative, unvaccinated mares respond appropriately to influenza vaccines; therefore primary vaccination can commence at 3 months of age or younger if significant risk of exposure to influenza exists. In contrast, maternal antibodies have been shown to completely block the serologic response of foals to a primary immunization series composed of two or more

doses of inactivated influenza vaccines when the first dose is administered when the foal is younger than 6 months of age.[23–29,35] Interference from MDAs may persist until 9 months of age or beyond for foals with high antibody titers postnursing; therefore primary vaccination of foals from immune mares should be delayed as long as possible, and preventive measures should focus on preventing introduction of infected horses.* Studies in Newmarket, United Kingdom, have shown that influenza virus infection is rare in thoroughbred yearlings before they enter training, suggesting that the risk of influenza is low in horses younger than 1 year of age born to mares in herds that are well vaccinated.[84,91,92] Therefore there appears to be little justification to vaccinate young foals from vaccinated mares against influenza, as was recommended in the past.[54,93,94]

The intranasal modified live vaccine (Flu-Avert IN) is licensed for vaccination of horses 11 months of age or older. Whereas this vaccine has been shown to be safe in foals as young as 2 months of age,[95] published data regarding the potential for MDAs to interfere with the response are lacking. Unpublished observations suggest that MDA interferes with the response of foals aged 3 to 6 months, whereas foals with maternal antibody vaccinated at 7 months of age were protected against virulent challenge (Holland and Chambers, personal communication, 2000). Pending publication of well-controlled studies, it is recommended that if the first dose of Flu-Avert IN vaccine is administered before 11 months of age, a second dose should be administered at 11 months of age or older.[96] The European-licensed live canarypox-vectored recombinant influenza is labeled for use in pregnant mares and foals as young as 4 months of age.[75] The North American—licensed Recombitek Equine Influenza Virus vaccine has been shown to be safe in foals as young as 4 months, but the minimum age recommended for vaccination of foals from immunized dams is 5 months. Effective priming has been documented after administration of the first dose of the vectored vaccine to foals aged 10 to 20 weeks that had detectable MDAs at the time of vaccination.[89] If the foal experiences failure of passive transfer of maternal antibodies or if the mare is seronegative for influenza, vaccination can commence at 4 months of age but should include an additional dose in the primary series.

The decision whether to vaccinate in an outbreak is dependent on many factors, the most important of which are the age, vaccination status, and size of the population of horses at risk; the elapsed time since onset of the outbreak; the rapidity with which a diagnosis can be confirmed; the layout of the physical facilities; and availability of personnel. Rapid (same-day) diagnosis of influenza should be pursued during outbreaks of contagious respiratory disease and can be accomplished using the highly sensitive and specific polymerase chain reaction (PCR) test or antigen-capture ELISA. Outbreaks of influenza at racetracks and similar large facilities typically take 1 month or more to spread through the entire population; therefore sufficient time exists to enhance immune protection of many at-risk horses while implementing other management strategies to minimize disease spread.[88] It is prudent to booster vaccinate those horses that have been on a regular influenza vaccination program but have not been revaccinated within the previous 3 months. It is also important to induce protection as quickly as possible in horses that have not previously been vaccinated. Of the vaccines currently available, Flu-Avert IN induces protection most rapidly, within 7 days of administration of a single intranasal dose; therefore this is currently the product of choice for vaccination of naive horses and those of unknown vaccination status in the face of an outbreak.[88] There is no evidence to suggest that any adverse effects occur when Flu-Avert IN is administered to horses that are incubating infection, although vaccination of horses that are already clinically ill is not recommended. Preliminary evidence suggests onset of immunity within 14 days of administration of one dose of the canarypox-vectored vaccine; therefore use of this vaccine would likely also prove useful in controlling outbreaks.

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* References 25, 27–29, 35, 37, 90.

48.6 FUTURE INFLUENZA VACCINES

In addition to the modified canarypox-virus vector described earlier,[14] a recombinant modified vaccinia Ankara (rMVA) vector that delivers genetic material encoding for relevant HA antigens of an H3N8 influenza virus has been developed.[97,98] The rMVA system is designed to focus the CTL response on the recombinant antigen and was initially tested in a prime-boost strategy in which the priming dose consisted of a DNA plasmid encoding for expression of the HA antigen. The intent of this DNA prime-rMVA boost regimen was to invoke both cellular and humoral immune responses involved in protection.[97] A subsequent study showed that the rMVA system was capable of inducing virus-specific lymphoproliferative and interferon gamma (IFN-γ) mRNA responses; antigen-specific IgGa, IgGb, and IgA antibodies; and protection from challenge, both with and without a priming dose of the DNA vaccine.[98] These data indicate that vaccination of horses with rMVA alone, or as part of a prime-boost regimen, is an effective means of inducing protective immunity to influenza virus infection.[98] Considerable research has been performed to document the efficacy of the DNA vaccine used in the previously mentioned studies against equine influenza. However, the delivery system used (multiple sublingual, conjunctival, and subcutaneous injections delivered with a gene gun with the patient under general anesthesia) is impractical for use in the field.[98,99] Recent licensing of a naked plasmid DNA vaccine that can be conveniently administered to horses by intramuscular injection to prevent WNV infection clearly documents the potential for development of a DNA vaccine to prevent influenza in horses in the future.

48.6.1 Equine Herpesvirus (Rhinopneumonitis)

The respiratory tract is the primary route of infection for both EHV-1 and EHV-4, both of which cause respiratory tract disease that varies in severity from subclinical to severe and is characterized by fever, lethargy, anorexia, nasal discharge, and cough.[100] Seroepidemiologic studies indicate that the vast majority of foals become infected with EHV-1 and EHV-4 during the first few months of life, but the clinical disease syndromes resulting from these infections are not always well defined, perhaps reflecting the modulating effect of MDAs.[101–103] Recurrent or recrudescent clinically apparent infections are seen in weanlings, yearlings, and young horses entering training, especially when horses from different sources are comingled.[100,104] In contrast, surveillance studies involving racehorses document that seroconversion to both EHV-1 and EHV-4 occurs sporadically during the course of a racing season, but these seroconversions are often not clearly associated with outbreaks of respiratory disease that follow an epidemiologic pattern consistent with an infectious agent.[105,106] EHV-1 and EHV-4 are spread by direct and indirect (fomite) contact with nasal secretions, by aerosolized secretions from infected horses, and, in the case of EHV-1, by aborted fetuses, fetal fluids, and placentas associated with abortions. Management practices are therefore of primary importance for control of clinical disease caused by EHVs.

Viremia occurs frequently after infection with EHV-1, potentially leading to paralytic neurologic disease (myeloencephalopathy) secondary to vasculitis of the spinal cord and brain, abortion of virus-infected fetuses, or birth of infected nonviable foals. In contrast, manifestations of infection with EHV-4 (rhinopneumonitis) are generally confined to the respiratory tract because EHV-4 does not typically infect endothelial cells or produce a cell-associated viremia.[107] As with herpesvirus infections in other species, horses typically fail to clear primary infections with either EHV-1 or EHV-4, the result being that most horses in the population remain latently infected with both viruses.[100,103,108] Latently infected horses do not show clinical signs but may experience recrudescence of infection, with or without clinical signs, an increase in antibody titer, and shedding

of the virus when stressed. Consequently, many horses have detectable levels of virus-neutralizing (VN) antibody to both EHV-1 and EHV-4 in their serum.[101,108] These features of the epidemiology of herpesvirus infections seriously compromise efforts to control these diseases and explain why outbreaks of EHV-1 or EHV-4 can occur in closed populations of horses. Whereas most mature horses have developed some immunity to EHV-1 and EHV-4 through repeated natural exposure and do not typically show respiratory signs when they become reinfected, horses do not appear to become resistant to the abortigenic or neurologic forms of infection with EHV-1, even after repeated exposure.[109] In fact, mature horses previously exposed are more likely to develop the neurologic form of the disease than are juvenile horses.[110,111]

Correlates for protection against EHV-1 and EHV-4 infection have been investigated extensively but are not yet clearly defined. Infection with EHV-1 induces a strong humoral response, but protection from reinfection is short-lived and is not achieved until the horse has experienced multiple infections with homotypic virus.[100,107] No clear relationship exists between protection from EHV-1 infection and concentrations of circulating antibody induced by vaccination or infection, but the duration and amount of virus shedding from the nasopharynx is reduced in animals with high levels of circulating neutralizing antibody.[107] Mucosal immunity and cell-mediated responses likely play a role at least as important as circulating neutralizing antibodies in protection against EHV-1 infection,[112] because the presence of MHC class 1—restricted CTL precursors in peripheral blood is correlated with protection.[107] Because EHV-4 replication is largely confined to epithelial cells of the upper respiratory tract, it is likely that mucosal immunity is important in protection.[107] Whereas circulating antibodies alone do not prevent EHV-4 infection, high levels of vaccine-induced circulating VN antibody markedly reduce virus shedding and clinical signs after challenge infection.[107,113–115]

Various killed vaccines are available, including those licensed only for protection against respiratory disease; currently all contain a low antigen load, and two (Pneumabort-K+1b, Fort Dodge Animal Health, and Prodigy, Intervet) that are licensed for protection against both abortion and respiratory disease contain a high antigen load. Performance of the killed low—antigen-load respiratory vaccines is variable, with some vaccines outperforming others. Performance of the killed high—antigen-load abortion and respiratory vaccines is superior, resulting in higher antibody responses and some evidence of cellular responses to vaccination. This factor may provide good reason to choose the high—antigen-load abortion and respiratory vaccines when the slightly higher cost is not a decision factor. A single manufacturer provides a licensed modified live EHV-1 vaccine, which to date has not been compared directly with high—antigen-load respiratory and abortion vaccines. This modified live vaccine has been shown to offer superior clinical protection and reduce viral shedding in a comparison with a single killed low—antigen-load respiratory vaccine.[116] Vaccination with either EHV-1 or EHV-4 can provide partial protection against the heterologous virus, and vaccines containing EHV-1 may be superior in this regard.

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The principal indication for use of EHV vaccines is prevention of EHV-1—induced abortion in pregnant mares and reduction of signs and spread of respiratory tract disease (rhinopneumonitis) in foals, weanlings, yearlings, and young performance and show horses that are at high risk of exposure. Many horses do produce postvaccinal antibodies against EHV, but the presence of those antibodies does not ensure complete protection. Consistent vaccination appears to reduce the frequency and severity of herpesvirus-induced disease. Although convincing evidence is lacking, field experience suggests that, whereas the incidence of sporadic EHV-1—induced abortion in individual mares has not changed, the incidence of abortion storms caused by EHV-1 has declined significantly since the introduction and widespread use of EHV-1 vaccines in the United States.[108,109] Outbreaks of abortion and associated perinatal foal death, however, do continue to occur on occasion in herds of vaccinated mares.

Of the vaccines currently licensed for use in pregnant mares in North America, only inactivated monovalent EHV-1 vaccines (Pneumabort-K+1b, Fort Dodge Animal Health, and Prodigy, Intervet) containing abortigenic strains of EHV-1 carry a label claim for preventing abortion, whereas at least one bivalent EHV-1/4 vaccine is licensed for prevention of abortion in Europe (Duvaxyn EHV-1/4, Intervet). One of the vaccines available in North America, Pneumabort-K+1b, incorporates both the 1p and 1b subtypes of EHV-1 to reflect the documented increase in the proportion of EHV-1 abortions caused by the 1b subtype that occurred during the 1980s as compared with earlier years.[117] Pregnant mares should be vaccinated during the fifth, seventh, and ninth months of gestation. Many veterinarians also recommend a dose during the third month of gestation. Similarly, vaccination of mares with an inactivated EHV-1/EHV-4 vaccine at the time of breeding and again 4 to 6 weeks before foaling is commonly practiced to enhance concentrations of colostral immunoglobulin for transfer to the foal. However, no published reports document the effectiveness of this approach in raising titers of specific antibody in mares that have already been vaccinated against EHV-1 three times during the previous 5 months. Vaccination of barren mares and stallions with either a bivalent EHV-1/4 vaccine or a monovalent EHV-1 vaccine before the start of the breeding season, and thereafter at 6-month intervals, is recommended, with the goal of increasing herd immunity in an attempt to reduce viral shedding and challenge to pregnant mares on breeding farms.[108]

The modified live virus EHV-1 vaccine (Rhinomune, Pfizer) has been used as an aid to prevention of EHV-1 abortion by some practitioners for many years,[118] even though this vaccine is not currently labeled for this use. However, several recent developments have created a renewed interest in the potential for use of modified live virus vaccines for protecting horses against manifestations of EHV-1 and EHV-4 infection. Sequencing of the EHV-1 genome has made it possible to document the nature of the mutation encoding for attenuation, mediated through truncation of the gp2 glycoprotein, of the KyA strain.[119] Similar studies may soon yield information regarding the mutation underlying attenuation of the RAC-H strain from which Rhinomune was derived.

Because currently available inactivated vaccines do not block infection with EHV, the most we can hope for when using inactivated vaccines is reduction of severity of clinical signs and attenuation of virus shedding to help protect herdmates. Challenge studies in weanlings aged 5 to 8 months have clearly demonstrated the efficacy of an inactivated whole virus EHV-1/4 vaccine in reducing clinical manifestations and virus shedding induced by virulent EHV-1 challenge administered 2 weeks after completion of the two-dose primary series.[114] Efficacy was clearly correlated with vaccine-induced antibody levels at the time of challenge in this study.[114]

Specific antibodies against both EHV-1 and EHV-4 are passed in colostrum.[32,33,36,120,121] Field studies with EHV-1 modified live vaccines indicate that colostral antibodies exert a profound inhibitory effect on serologic responses to vaccination up to at least 5 months of age.[32,122,123] However, a cytotoxic cellular immune response to both EHV-1 and EHV-4 was induced in a substantial percentage of foals vaccinated with an EHV-1 modified live vaccine in the presence of maternal antibody, even though humoral responses were often absent.[124] It is uncertain whether these responses would provide protection against natural challenge. Recent studies with two different commercially available inactivated bivalent EHV-1/4 vaccines and one inactivated EHV-4/influenza vaccine showed that the majority of foals from EHV-vaccinated mares do not mount a detectable neutralizing antibody response to vaccines administered at 3 and 4 months of age, even when three doses are administered in the primary series.[33,35,36] An increased proportion of foals responded when vaccinated with a three-dose series starting at 5 or 6 months of age, but a substantial number still failed to seroconvert.[35,36] Some foals with low or undetectable levels of SN antibody at the time of vaccination failed to mount a serologic response, suggesting that low levels of antibody, below the lower limit of detection of the SN test based on

EHV-1 antigen, are capable of inhibiting the serologic response to inactivated EHV-1/4 vaccines.[36] The failure of a large proportion of foals less than 6 months of age to mount serologic responses to inactivated EHV-1/4 vaccines and the influence of antibody titer at the time of vaccination on failure to respond has been confirmed using sensitive gD and gG ELISAs in studies on commercial stud farms in Australia.[125] In parallel studies, these researchers concluded that mares were the source of infection for foals and that intensive use of inactivated EHV-1/4 vaccines on breeding farms in Australia had minimally affected the infection rate of young foals and weanlings with EHV-1 and EHV-4.[101,103,126]

Considering the uncertainty regarding the role of EHV-1 and EHV-4 as causes of clinically important respiratory disease, the lack of published data regarding the efficacy of available vaccines in preventing infection and establishment of latency, and results of a recent study documenting the poor serologic responses of naive horses to a number of killed low—antigen-load EHV respiratory vaccines currently marketed in North America,[20] there appears to be little rationale to support the common practice of frequent revaccination of foals, weanlings, yearlings, and young performance horses against EHV-1 and EHV-4.[5] Furthermore, an obvious dilemma in designing a vaccination strategy to prevent EHV-1 and EHV-4 infection in foals and weanlings is that if primary immunization is delayed until 6 months of age or older to reduce the likelihood of MDA interference, foals are likely to encounter field infection before the three-dose primary series can be completed. 1580
Thus it is unreasonable to expect a high degree of efficacy for vaccination programs designed to protect foals 1581
and weanlings against EHV infection using available vaccines. Despite these uncertainties, many practitioners elect to vaccinate against both EHV-1 and EHV-4. Under these circumstances, a reasonable compromise would be to start foal vaccination at 4 to 6 months of age using two doses of an inactivated bivalent vaccine or an EHV-1 modified live vaccine administered 3 to 4 weeks apart, followed by administration of a third dose 8 to 12 weeks later. Revaccination at 4- to 6-month intervals thereafter using either an inactivated bivalent vaccine or a modified live EHV-1 vaccine appears appropriate for yearlings and young performance or show horses that experience contact with other horses. Frequent vaccination of nonpregnant mature horses, except those on breeding farms, with EHV vaccines is generally not indicated.

Available vaccines make no labeled claim to prevent the myeloencephalopathic form of EHV-1 infection (EHM). However, recent outbreaks of EHM in populations of horses in several regions of North America have prompted many racing jurisdictions and managers of equine facilities and events to impose EHV-1 vaccination requirements for incoming and resident horses in the hope that EHV-1 infection and development of EHM can be prevented. The efficacy of this approach remains to be proven. In fact, frequent revaccination of mature horses to prevent the neurologic form of EHV-1 is not clearly justified in most circumstances because EHM is a relatively rare disease from a population standpoint and most mature horses have previously been infected with EHV-1 and are latent carriers. Currently available vaccines do not reliably block infection, development of viremia, or establishment of latency, and EHM has been observed in horses vaccinated against EHV-1 regularly at 3- to 5-month intervals with inactivated or modified live vaccines.[110,111,127,128] Furthermore, vaccination has been cited by some as a potential risk factor for development of neurologic EHV-1, although evidence to support this opinion is far from conclusive.[129]

The genetic basis underlying the apparent increased likelihood that some EHV-1 isolates will cause EHM has only recently been described and involves a single point mutation in the DNA polymerase *(DNApol)* gene.[130] This mutation results in the presence of either aspartic acid (D) or an asparagine (N) residue at position 752. More than 80% of EHV-1 isolates associated with EHM are of the D_{752} form, whereas less than 20% are of the N_{752} form.[130] Isolates of the D_{752} form have been designated “neuropathogenic strains” in recent publications, lay articles, and laboratory PCR result reports, whereas N_{752} isolates have been designated as “wild-type,”

"abortigenic," or "nonneuropathogenic." The latter terminology is unfortunate because both the D_{752} and the N_{752} isolates are capable of inducing all syndromes (i.e., respiratory disease, abortion, neonatal death, and EHM).

A challenge study performed almost 30 years ago to test the efficacy of Pneumabort K in preventing abortion and a recent study to test the efficacy of Rhinomune against challenge with a "neuropathogenic" strain of EHV-1 provided some evidence that these vaccines may have a place in control of outbreaks of EHM.[113,116] Of interest, the Army 183 EHV-1 strain used as the challenge virus in the Pneumabort K efficacy study has now been shown to carry the D_{752} mutation, as has the Findlay '03 strain used in the Rhinomune study. However, the low numbers of horses used in these studies, the failure of either vaccine to prevent infection or significantly reduce the level of viremia, the lack of statistical significance of results pertaining to prevention of neurologic signs, and the well-known difficulties encountered in accomplishing a consistent and reproducible challenge model for neurologic EHV-1 infection justify caution in interpretation. However, the significant reduction in viral shedding observed in vaccinated horses provides reasonable justification for booster vaccination of unexposed horses that are at risk for infection in order to reduce viral shedding in the event that they do become exposed to EHV-1. Through enhancement of herd immunity, it is hoped that the level of infectious virus circulating in the at-risk population will be reduced and that, in turn, the risk that individual horses in the population will develop disease will be reduced.[128] This approach also relies on the assumption that the immune system of most mature horses has already been "primed" by prior exposure to EHV-1 antigens through field infection or vaccination and can therefore be "boosted" within 7 to 10 days of administration of a single dose of vaccine. Although the validity of this approach has not been critically evaluated for the prevention of EHV-1 neurologic disease, its implementation seems rational when faced with one or more horses with confirmed clinical EHV-1 infection (any form) at a particular facility. Whereas booster vaccination of horses that are likely to have been exposed already is not recommended, it is rational to booster vaccinate unexposed horses, as well as those that must enter the premises, if they have not been vaccinated against EHV-1 during the previous 90 days. Use of the Rhinomune modified live vaccine or one of the inactivated EHV-1 vaccines known to stimulate high circulating titers of neutralizing antibody appears justified for this purpose. Horse owners must develop an understanding of the concept of boosting herd immunity to help protect the individual horse rather than focusing on the as yet unattainable expectation that the veterinarian can reliably protect an individual horse from developing potentially fatal EHM by administering one of the vaccines currently marketed as aids to prevention of clinical manifestations of EHV-1 infection. Ultimately, enforcement of strict biosecurity measures and hygiene practices is likely to be more effective than widespread vaccination in reducing the risk of acquiring infection.

48.7 FUTURE VACCINATION STRATEGIES TO PREVENT HERPESVIRUS INFECTION

In order for vaccination to be completely effective in blocking primary infection and establishing a lifelong carrier state with EHV-1 and EHV-4, future vaccination strategies should be directed at inducing a strong mucosal immune response in the upper respiratory tract during the first few weeks of life, at a time when high levels of maternal antibodies are present. Promising progress toward this goal was reported recently by Patel and colleagues,[131] who documented that intranasal administration of a single dose of temperature-sensitive modified live EHV-1 vaccine to maternal antibody—positive foals aged 1.4 to 3.5 months afforded partial but significant protection against febrile respiratory disease, viremia, and virus shedding after intranasal challenge with virulent EHV-1 performed 8 weeks after vaccination.[131] This vaccine has also been shown to provide significant protection against abortion in challenge studies, and because it is capable of preventing the development of viremia, shows potential to prevent EHM.[112,132] Recent studies with vaccinia and canarypox-vectored

recombinant vaccines and DNA vaccines have generated promising results, but more research will be needed to identify the immunodominant protective antigens of EHV-1 and their interaction with the equine immune system before these approaches will be applicable for use in the field.[133–136]

48.7.1 *Streptococcus equi* subsp. *equi* Infection (Strangles)

Strangles is a highly contagious disease caused by the bacterium *S. equi* subsp. *equi*. Strangles primarily affects young horses (weanlings and yearlings), although horses of any age can become infected if not protected by previous exposure to the organism or by vaccination. The organism is transmitted by direct contact with infected horses or subclinical carriers or indirectly by contact with water troughs, feed bunks, pastures, stalls, trailers, tack, or grooming equipment contaminated with nasal discharge or pus draining from lymph nodes of infected horses. The organism survives for several weeks in the environment, particularly in aquatic locations and when protected from exposure to sunlight and disinfectants, and can be a source of infection for new additions to the herd. Because *S. equi* is a clonal organism, there is minimal antigenic variation among different isolates, even though isolates vary in their pathogenicity.

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Most horses develop a solid immunity during recovery from strangles, which persists in over 75% of animals for 5 years or longer,[137] indicating that induction of durable protection through vaccination is biologically feasible if the protective antigens can be identified and presented in an appropriate manner.[138] Although the basis for acquired resistance to strangles is not completely understood, the finding that recovered horses rapidly clear intranasally inoculated *S. equi* despite not making circulating antibody to its surface proteins indicates that to be highly effective a strangles vaccine must stimulate local nasopharyngeal tonsillar immune clearance responses and that serum antibody is of lesser importance.[139] This conclusion is further supported by the finding that ponies with high levels of circulating antibody to multiple unique surface-exposed and secreted proteins after systemic vaccination remained susceptible to challenge with *S. equi*.[139] The cell wall M protein of *S. equi* (SeM) is recognized in the acquired immune response to *S. equi* infection, a response that involves both production of local antibodies in the nasopharynx and circulating opsonophagocytic antibodies.[140–142] The predominant opsonophagocytic antibodies are of the IgGb subisotype but also include IgGa and IgA, whereas IgGb and later mucosal IgA predominate in nasopharyngeal secretions.[140,143]

Strangles vaccines licensed for use and marketed in North America include two inactivated, adjuvanted M-protein cell wall extracts (Strepvax II, Boehringer Ingelheim, and Strepguard with Havlogen, Intervet, prepared by extraction with hot acid or mutanolysin plus detergent, respectively) and one attenuated live vaccine (Pinnacle IN, Fort Dodge) derived from an unencapsulated mutant of *S. equi* for intranasal administration.[144] Infection of horses with *S. equi* continues to cause troublesome outbreaks of strangles throughout North America, despite the availability and widespread use of these vaccines, indicating that their efficacy is suboptimal.[145] M-protein vaccines induce a good opsonophagocytic antibody response in serum but a minimal mucosal IgA response, which likely accounts for the incomplete protection observed when they are used in the field.[140,146] However, data do exist to document that vaccination using injectable SeM vaccines reduces the attack rate and severity of strangles in herds with endemic infection.[146–148] The live intranasal vaccine has been shown to induce a relevant mucosal immune response and partial or complete protection but may do so without inducing a strong serologic response.[145,149] Because vaccinal organisms in the intranasal vaccine must reach the inductive sites for immunity in the pharyngeal and lingual tonsils, accurate vaccine delivery is critical to vaccine efficacy.

Vaccination against *S. equi* is not routinely recommended for pleasure or performance horses kept in low-risk situations, but it is a consideration for horses that are resident on, or being transported to, premises such as breeding farms where strangles is a persistent endemic problem or where a high risk of exposure is anticipated. The bacterial modified live vaccine is generally preferred over inactivated injectable vaccines for primary vaccination of foals and weanlings and for routine use in older horses that are at high risk for infection. On breeding farms, efforts should be concentrated on preventing infection of foals and weanlings by booster-vaccinating broodmares 4 to 6 weeks before foaling to maximize colostral content of antibodies. Whereas the intranasal vaccine has been shown to be safe for use in mares at all stages of pregnancy and can be used in mares in the face of an outbreak, it does not reliably stimulate high levels of circulating antibody. For this reason, intramuscularly administered inactivated SeM products are preferred for prefoaling booster immunization of mares. Antibodies of the IgG and IgA class recognizing the SeM are passively transferred to the foal through colostrum and are also present in the milk of immune mares.[150] Antibodies of predominantly the IgGb isotype are absorbed from colostrum and redistribute to the nasopharyngeal mucosa.[143] These IgGb antibodies, along with the SeM-specific IgA antibodies that are present in milk and passively coat the pharyngeal mucosa of nursing foals, provide protection to most nursing foals up to the time of weaning.[142,143,150] Resistance of nursing foals to strangles during the first few months of life appears to be mediated by IgGb antibodies in nasal secretions and milk and not by IgA.[150] Serologic (ELISA) responses to M-protein vaccines are poor in foals, most likely owing to the inhibitory effect of maternal antibodies.

Whereas the intranasal modified live vaccine may be less susceptible than the inactivated extract vaccines to MDA interference, this issue has not been investigated, and the manufacturer does not recommend administration of this vaccine to horses less than 9 months of age. Considering that on farms where strangles is endemic foals often become infected around the time of weaning, at 4 to 8 months of age, it is difficult to protect them if vaccination is delayed until 9 months of age. Therefore a reasonable compromise on breeding farms where the risk of strangles infection is high and mares are on a regular vaccination program would be to begin primary vaccination of foals using the intranasal live vaccine as early as 4 months of age. The recommended two-dose primary series administered 2 to 3 weeks apart should be followed by a third dose 3 to 4 months later and boosters at 6- to 12-month intervals thereafter, depending on risk of infection. The intranasal vaccine has been administered to foals as young as 5 or 6 weeks of age during outbreaks. If a vaccine is used in this manner, a third dose of the vaccine should be administered 2 to 4 weeks before the foal is weaned to optimize protection during this high-risk period. Although there are few reports of adverse effects attributable to use of the intranasal strangles vaccine in young foals, the inability of foals to mount an adequate mucosal IgA response during the first month of life and the potential for interference by maternal antibodies suggest that foals are unlikely to fully benefit from intranasal strangles vaccine administered before 4 months of age. When an inactivated M-protein vaccine is used for primary vaccination of foals, it is recommended that the initial series begin at 4 to 6 months of age, using three doses administered at 3- to 6-week intervals, followed by semiannual boosters for as long as high-risk conditions prevail.

Strangles vaccines should be administered only to healthy, nonfebrile horses free of nasal discharge and should not be administered to those that are known to have had recent direct exposure to clinically ill animals.[138] However, outbreaks of strangles generally persist for several months to more than 1 year, particularly on breeding farms where each foal crop adds new susceptible animals to the population. Therefore strangles vaccines are frequently administered in the face of an outbreak as an adjunct to management practices designed to bring outbreaks under control, and it is not always possible to accurately determine the exposure status of each horse. Under these circumstances the likelihood of preventing strangles is greatest for horses that have not yet been exposed and can be kept isolated from infected horses until 2 weeks after the vaccination protocol can

be completed. Horses that have been vaccinated previously will generate a response more rapidly than will naive horses. Similarly, the intranasal modified live vaccine is preferred over inactivated vaccines for immunization of naive horses in an outbreak because it is likely to generate a protective immune response more rapidly.

Injectable strangles vaccines tend to cause local reactions at the site of injection more often than do other equine vaccines. Injection in the gluteal muscles is not recommended because gravitational drainage along fascial planes can prove troublesome in the event that an abscess develops at the injection site. In addition, purpura hemorrhagica, a serious and sometimes life-threatening systemic immune complex (Arthus-type) vasculitis manifested as edema with or without petechial hemorrhages on mucosal surfaces, has been observed with low frequency in the weeks after administration of strangles vaccines. Inactivated extract vaccines are implicated more often than the intranasal modified live vaccine, but all strangles vaccines have the potential to induce purpura. The antigen present in immune complexes is SeM, along with antibodies of the IgA class. Because a high serum IgG titer against *S. equi* appears to be associated with an increased risk of developing purpura, routine testing for specific IgG antibodies using a commercially available ELISA test has been recommended as a means of preventing vaccine-associated purpura.[145] Horses with titers of 1:1600 or greater in the SeM ELISA and those known to have had strangles during the previous year should not be vaccinated.[145]

The bacterial modified live vaccine for intranasal administration will cause injection site abscesses if inadvertently injected IM. To avoid inadvertent contamination of other vaccines, syringes, and needles, it is advisable and considered good practice to administer all parenteral vaccines before handling and administering the intranasal strangles modified live vaccine. Other reported adverse responses after administration of the intranasal modified live vaccine include nasal discharge, submandibular or retropharyngeal lymphadenopathy with or without abscessation, limb edema, internal abscesses (bastard strangles), and purpura hemorrhagica. The overall frequency of adverse events is low but appears to be higher than reported to the manufacturer (4.8 per 10,000 doses). On the other hand, the majority of reported adverse events, including the development of nasal discharge, lymph node abscesses, and purpura hemorrhagica, occur in horses on farms with endemic or epidemic strangles. Therefore it is often uncertain whether the adverse event was caused by the vaccine or by a wild strain of *S. equi*.

48.8 RECENT DEVELOPMENTS IN STRANGLES VACCINES

The nonspecifically attenuated Pinnacle strain of *S. equi* was produced by chemical mutagenesis to induce random mutations throughout the bacterial genome.[41,151] Because the point mutations responsible for attenuation have not been defined specifically, the potential exists for back mutation and reversion to full virulence.[151] In contrast, the live attenuated vaccine strain TW 928 contained in a strangles vaccine (Equilis StrepE, Intervet) recently licensed in Europe was stably attenuated by targeted deletion of the *aroA* gene.[152] This allowed development of a companion PCR test that has been used in molecular epidemiologic studies to determine whether strangles in vaccinated horses was caused by the vaccine or by wild-type strains.[153] Although this development proves that targeted gene deletion is a promising route for generating stable candidate mutants for inclusion in future vaccines, the high residual virulence, unconventional route of administration (submucosal in the upper lip), and short DOI induced by Equilis StrepE will limit its use.

The incomplete protection afforded by bacterins and SeM extracts administered parenterally or by attenuated live vaccines administered intranasally or submucosally, and the undesirable side effects associated with some of these products, have prompted research to investigate other potential vaccine antigens and vaccination strategies. Promising results have recently been achieved in challenge studies involving horses vaccinated intramuscularly

and intranasally with combinations of the recombinant antigens EAG (a protein that binds α_2-macroglobulin, albumin, and IgG), CNE (a collagen-binding protein), and SclC (a collagen-like protein).[154]

48.8.1 Equine Monocytic Ehrlichiosis (Potomac Horse Fever)

Equine monocytic ehrlichiosis, also known as *Potomac horse fever*, is caused by *Neorickettsia risticii* (formerly *Ehrlichia risticii*). Originally described in 1979 as a sporadic disease affecting horses residing in the northeastern United States near the Potomac River, the disease has since occurred in horses in 43 states in the United States, three provinces in Canada (Nova Scotia, Ontario, and Alberta), South America (Uruguay, Brazil), Europe (the Netherlands, France), and India. The disease does not appear to be directly contagious, and it now appears that accidental ingestion of aquatic insects harboring metacercariae infected with *N. risticii* is at least one mode of transmission.[155] PHF is seasonal, occurring between late spring and early fall in temperate areas, with most cases in July, August, and September at the onset of hot weather. The disease may affect individual horses sporadically or cause outbreaks involving multiple horses. Foals appear to be at low risk for the disease. If PHF has been confirmed on a farm or in a particular geographic area, it is likely that cases will occur in future years. Documentation of the involvement of operculate freshwater snails and aquatic insects such as caddisflies and mayflies in the life cycle of *N. risticii* has permitted formulation of focused control measures directed at minimizing exposure of horses to the habitats occupied by these species during the summer and fall months when disease risk is highest in endemic areas.[155] Risk reduction is best accomplished by denying horses access to river banks, creek beds, and irrigation ditches, as well as pastures that have recently been flooded or flood-irrigated.

Recovery after natural infection with *N. risticii* induces a strong antibody response and durable protection from reinfection lasting 20 months or longer. However, the presence of antibodies does not necessarily correlate with protection, and cell-mediated responses likely play a crucial role.[156] A β-propiolactone inactivated host cell—free *N. risticii* vaccine protects mice against homologous challenge.[157] Several inactivated PHF vaccines for intramuscular administration (Mystique, Intervet; Potomavac, Merial; PotomacGuard, Fort Dodge; PHF-Gard, Pfizer; and Equovum PHF, Boehringer Ingelheim) are licensed for use in horses with the label claim that they aid in prevention of PHF. Two of these are also available combined with a rabies vaccine. None carry a label claim for prevention of abortion. The high rate of serious complications and mortality associated with this disease has been considered adequate justification for vaccinating horses residing in or traveling to endemic areas. In a series of studies in which ponies were challenged IV with *N. risticii* approximately 4 weeks after completion of the two-dose primary vaccination series using a formalin-inactivated, aluminum hydroxide—adjuvanted vaccine (PHF-Vax, Schering-Plough), Ristic and colleagues (1988) reported that 78% of experimentally infected ponies were protected against all clinical manifestations of disease except fever, and 33% were protected against all signs, including fever.[158] A published noncontrolled field study involving the same vaccine documented induction of serologic responses in most vaccinated horses and a substantial reduction in disease prevalence, morbidity, and mortality compared with data collected in a previous year when horses were not vaccinated.[156,159]

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In contrast to the results of the studies cited above, an epidemiologic investigation involving a large number of horses failed to demonstrate any clinical or economic benefit from annual vaccination with currently available vaccines in New York State.[160,161] Failure of a substantial number of individual horses to mount an immune response to inactivated PHF vaccines, heterogeneity of *N. risticii* isolates, the presence of only one *N. risticii* strain in vaccines, and much more rapid waning of immunity after vaccination than after natural infection likely account for the observed failure of vaccines to provide protection against field infection.[156,162] Despite the lack

of documented efficacy of approved vaccines to prevent infection in the field setting, many practitioners who work in endemic areas believe that severity of disease is attenuated and mortality is reduced in vaccinated horses when vaccines are administered at 4- to 6- month intervals, with administration of one booster timed to precede the anticipated period of peak challenge.

If vaccination is elected, a primary series of two doses should be administered 3 to 4 weeks apart. Manufacturers recommend revaccination at 6- to 12-month intervals; however, some veterinarians encourage a revaccination interval of 4 months in order to achieve a reasonable likelihood of protection. Because the disease has a distinct seasonal pattern, revaccination in the late spring, approximately 1 month before the first cases are expected, followed by a second dose 4 months later appears to be a reasonable approach for strategic immunization to maximize the chances of protection during the period of peak challenge. Available vaccines are licensed for use in stallions and pregnant mares and can be administered to gestating mares 4 to 8 weeks before foaling to maximize passive transfer of specific antibodies to foals through colostrum. Whereas approximately 67% of foals from antibody-positive mares were antibody negative by 12 weeks of age, antibody was detectable in 33% of foals up to 5 months of age. On the basis of these findings, the low risk of clinical disease in young foals, and the apparent susceptibility to infection of two foals vaccinated earlier than 12 weeks of age, primary vaccination of foals from antibody-positive dams should begin with a two-dose primary series starting 5 months of age or older, followed by administration of one subsequent booster dose 8 to 12 weeks later.[159] However, the efficacy of this recommended regimen requires further study. If the primary series of two vaccinations is initiated before 5 months of age, additional doses should be administered at monthly intervals up to 5 months of age to ensure that an immunologic response is achieved. Vaccination of foals in endemic areas is further complicated by the distinct seasonal incidence of disease in July, August, and September, a time when most foals are aged between 2 and 6 months and may be subject to maternal antibody interference with vaccination.

48.8.2 Botulism

Botulism is a neuromuscular paralytic disorder caused by one of eight distinct neurotoxins (A, B, Ca, Cb, D, E, F, G) produced by *Clostridium botulinum*, a soil-borne, spore-forming, saprophytic, anaerobic, gram-positive bacterium.[163] Botulinum toxins are among the most potent biologic toxins known and act by blocking transmission of impulses at motor endplates, resulting in weakness progressing to paralysis, inability to swallow, and frequently death. Of the seven serogroups (A through G) of *C. botulinum*, types A, B, C, and D have been reported to cause disease in horses, with types B and C being responsible for most cases.[163] Three forms of botulism—toxicoinfectious botulism (shaker foal syndrome), forage poisoning, and wound botulism—have been observed in horses. Forage poisoning results from ingestion of preformed toxin produced by decaying plant material or animal carcasses present in feed, whereas “wound botulism” results from vegetation of spores of *C. botulinum* and subsequent production of toxin in contaminated wounds. Shaker foal syndrome results from toxin produced by vegetation of ingested spores in the intestinal tract. Currently toxicoinfection with *C. botulinum* type C is being investigated as a cause of equine grass sickness, a largely fatal, pasture-associated dysautonomia affecting horses mainly in Great Britain, continental Europe, and Australia, with reports of isolated cases in the United States. Almost all cases of shaker foal syndrome are caused by type B. Shaker foal syndrome is a significant problem in foals aged 2 weeks to 8 months in Kentucky and in the mid-Atlantic seaboard states and occurs sporadically in other areas.[164–166]

A toxoid vaccine (BotVax-B, Neogen Corporation, Tampa, Fla.) directed against *C. botulinum* type B is licensed for use in horses in the United States. Its primary indication is prevention of the shaker foal syndrome via colostral transfer of antibodies induced by vaccination of the mare. For primary vaccination, mares should

be vaccinated during gestation with a series of three doses administered 4 weeks apart, scheduled so that the last dose will be administered 4 to 6 weeks before foaling to enhance concentrations of specific immunoglobulin in colostrums (i.e., months 8, 9, and 10 of gestation). Subsequently, mares should be revaccinated annually with a single dose 4 to 6 weeks before foaling. A similar type B toxoid is available to protect foals in endemic areas in Australia.[167]

Passively derived colostral antibodies appear to protect most foals for 8 to 12 weeks, although foals from properly vaccinated dams can develop botulism.[165–167] Insufficient production of specific antibody by the dam in response to the vaccination, failure of passive transfer of specific immunity to botulinum toxin, overwhelming toxin production, and loss of passive immunity by the time exposure to the toxin occurs may be reasons for vaccine failure. The clinician should therefore be aware of the status of MDA transfer of each foal.

Maternal antibodies do not appear to interfere with the response of foals to primary immunization against botulism[168]; therefore a primary series of three doses of vaccine administered 4 weeks apart can be started when foals in endemic areas are 2 to 3 months of age or older. Other horses can be immunized using a primary series of three doses of vaccine administered at 4-week intervals, followed by annual revaccination. Currently there are no licensed vaccines available for preventing botulism caused by *C. botulinum* type C or other subtypes of toxins, and cross-protection between the B and C subtypes does not occur; therefore routine vaccination against *C. botulinum* type C is not currently practiced. A type C toxoid approved for use in mink was administered to horses under special license to protect them during an outbreak of forage poisoning caused by contaminated alfalfa cubes in southern California in 1989.

Horses and foals with clinical botulism may be treated with botulinum antitoxin administered IV. Antitoxin is not effective against toxin that has been translocated to motor endplates. Therefore clinical signs may progress for 12 to 24 hours after administration of the antitoxin or until all internalized toxin has attached to motor endplates. The dose of botulinum type B antitoxin recommended for treating a foal is 30,000 IU and for an adult is 70,000 IU. Foals of unvaccinated mares born in or being moved to endemic areas may benefit from transfusion with plasma from a vaccinated horse or from administration of *C. botulinum* type B antitoxin. The efficacy of these practices needs further study. Vaccination with type B toxoid as described previously is an alternative to passive immunization.

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48.8.3 Equine Viral Arteritis

EVA is a contagious disease of equids caused by equine arteritis virus (EAV), an RNA virus that is found in the horse populations of many countries. EAV is the prototype virus in the family Arteriviridae of the genus Arterivirus, order Nidovirales. Although all horse breeds appear to be equally susceptible to EAV, the prevalence of infection, as determined by seroconversion, is much higher in some breeds, notably standardbreds and warmbloods, than in others. Despite the high seroprevalence of infection in standardbreds, clinical disease is rarely observed in this breed, indicating that subclinical infection is common.[41,169] Conversely, thoroughbreds and most other breeds have a low seroprevalence of infection but are more likely to show fulminant clinical signs when they become infected. Most primary EAV infections are subclinical or asymptomatic. Clinical signs, if they occur, typically develop 3 to 7 days postinfection and vary in severity, both within and between outbreaks, but may include some or all of the following: fever; anorexia; depression; dependent edema involving the limbs, prepuce, scrotum, mammary glands, or ventrum; localized or generalized urticaria; supraorbital or periorbital edema; conjunctivitis; lacrimation; and serous or mucoid nasal discharge. EAV is of special concern because abortion is a frequent sequela to infection in the unprotected pregnant mare. In addition, EAV can cause life-threatening pneumonia or pneumoenteritis in young foals, and infection of the

postpubertal colt or stallion may establish a long-term carrier state.[41,170] Transmission most frequently occurs through direct or aerosol contact with virus-infective respiratory secretions, leading to widespread dissemination of the virus among susceptible horses in close proximity. Indirect transmission, although less significant, can occur through contact with virus-infected fomites. Venereal transmission from infected carrier stallions to mares via semen during natural breeding or artificial insemination with fresh, chilled, or frozen semen can play a significant role in introduction and spread of infection on or between breeding farms or other equine facilities. The virus can persist in the reproductive tract of stallions for many years and possibly result in lifelong infection.

Historically, large-scale outbreaks of EVA have been relatively infrequent. However, the number of confirmed occurrences appears to be increasing, likely as a result of increased global movement of horses, increased accessibility of carrier stallions, and increased use of shipped cooled or frozen virus-infected semen. Outbreaks can be associated with serious economic consequences, as clearly exemplified by the 2006 multistate outbreak in quarter horses that was propagated by widespread shipment of semen from the index cases, two inapparently infected carrier stallions in New Mexico. Because the carrier stallion is widely accepted as the natural reservoir of EAV and the source of diversity among naturally occurring strains of the virus, identification of these individuals through serologic testing, followed by PCR testing or virus isolation from semen, forms the cornerstone of eradication measures. Vaccination also constitutes an important means of controlling spread and minimizing the consequences of infection.

A modified live vaccine based on an attenuated strain of EVA virus was developed by researchers in Kentucky in 1969.[171] This vaccine (Arvac, Fort Dodge Animal Health, Fort Dodge, Iowa) was first used extensively in the field during the 1984 outbreak of EVA in Kentucky and proved to be safe and effective in bringing the outbreak under control.[41] Subsequently this vaccine was developed further and licensed for use in North America. Vaccination of stallions, nonpregnant mares, and prepubertal colts has been shown to be a safe and effective means of controlling EVA. Strategic use of the modified live vaccine has formed the cornerstone of a highly successful program to control EVA in the Kentucky thoroughbred breeding population for many years.[41]

The indications for vaccination against EVA are as follows:

- To protect stallions against infection and subsequent development of the carrier state.
- To immunize seronegative mares before they are bred with EAV-infective semen.
- To curtail outbreaks in nonbreeding populations. Vaccination in the face of an EVA outbreak in concentrated populations of performance horses at racetracks has been successful in controlling horizontal disease dissemination within 7 to 10 days.

Primary immunization with the modified live vaccine involves intramuscular administration of a single dose, with a booster administered annually thereafter. VN antibodies are induced within 5 to 8 days after modified live virus vaccination and persist for at least 2 years.[41,172] Revaccination induces high VN antibody titers that persist for several breeding seasons.[172] Although the current modified live vaccine is highly attenuated and has been shown to be safe and effective in stallions and nonpregnant mares, a small proportion of first-time—vaccinated horses develop mild febrile reactions and transient lymphopenia after vaccination with the modified live vaccine, and vaccine virus may be isolated sporadically from the nasopharynx and buffy coat for 7 days but occasionally up to 32 days after vaccination.[41,172–174] Vaccinated stallions do not shed vaccine virus in either semen or urine.[172]

Primary vaccination provides sustained clinical protection against EVA but does not prevent reinfection and subsequent limited replication and shedding of field strains of virus.[175] However, in vaccinates the frequency, duration, and amount of viral shedding via the respiratory tract are significantly less than observed with natural infection. Vaccinated mares may shed field virus transiently after being bred to carrier stallions; therefore isolation of these individuals for 21 days after breeding is recommended.[41]

Annual revaccination of breeding stallions 28 days before the start of breeding season is highly recommended as a means of preventing establishment of the carrier state.[41] Annual revaccination of mares being bred to carrier stallions should occur at least 21 days before breeding. The modified live vaccine is not recommended for use in pregnant mares, especially during the last 2 months of gestation, or in foals less than 6 weeks of age, except in emergency situations when there is a high risk of exposure. Apparent fetal infections with modified live vaccine after vaccination of pregnant mares have been documented, but only rarely.[172,176]

Foals born to seropositive mares become seropositive after ingesting colostrum. MDAs decay with a mean half-life of approximately 32 days, with the result that foals become seronegative between 2 and 7 months of age.[177,178] Maternal antibodies are unlikely to interfere with the response to vaccine administered at 7 months of age or older.[177] However, when foals less than 6 months of age are vaccinated during conditions of high risk, they should be revaccinated after 6 months of age. Establishment of the carrier state appears to depend on the high levels of androgens circulating in intact stallions and can be prevented by vaccinating colts, preferably before puberty, before they are used for breeding.[41] Vaccination of prepubertal colts at 6 to 12 months of age is therefore central to effective control of the spread of EAV infection and should be strongly encouraged in breeds such as standardbreds and warmbloods in which EVA is prevalent and on facilities on which risk of infection is high. Persistent infection has never been documented in a stallion that was properly vaccinated with the licensed modified live vaccine before exposure.[41]

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48.9 REGULATORY AND EXPORTATION CONSIDERATIONS WITH VACCINATION AGAINST EQUINE VIRAL ARTERITIS

In planning a vaccination program against EVA, it is important to consult with state and/or federal animal health officials to ensure that any such program is in compliance with the state's control program for EVA, if one exists. Because it is not possible to differentiate a vaccine-induced antibody response from that due to natural infection, it is strongly recommended that before vaccination all first-time male vaccinates be tested and confirmed negative for antibodies to EAV by a USDA-approved laboratory (www.aphis.usda.gov/cvbapps/Labs.jsp). Mares intended for export should be similarly tested. When there is uncertainty or concern over whether vaccination against EVA could prevent the export of a horse to a particular country, it is advisable to consult the federal area veterinarian (www.aphis.usda.gov/vs/area_offices.htm#CO) in charge in the state to determine the specific import requirements of that country. Several countries bar entry of any equid that is serologically positive for antibodies to EAV, regardless of vaccination history. Countries that do accept EVA vaccinated horses regardless of gender typically require stallions or colts to have a certified vaccination history and confirmation of prevaccination negative serologic status.

48.10 FUTURE DIRECTIONS

A killed-virus vaccine (Artervac, Fort Dodge Animal Health) is licensed for use in the United Kingdom, Ireland, France, Denmark, and Hungary, and a killed-virus vaccine is also used in Japan. As with the modified live vaccine

licensed in the United States, serologic responses to these inactivated vaccines cannot be distinguished from those resulting from natural infection. Development and marketing of a marker vaccine that not only affords protection but also allows vaccinated horses to be distinguished serologically from inapparently infected carriers would greatly facilitate control, and even eradication, of EAV from horse populations. Several "new generation" EAV vaccines that potentially meet these criteria have been developed in recent years. These include a modified live virus DIVA vaccine with a deletion in the GP5 ectodomain,[179,180] a DNA vaccine that incorporates open reading frames (ORFs) 2b, 5, and 7,[181,182] and a subunit EAV vaccine using recombinant replicon particles derived from a vaccine strain of VEE virus that includes genes encoding both major envelope proteins (GP5 and M) of EAV.[183,184]

48.10.1 Rotaviral Diarrhea

Equine RV, a nonenveloped RNA virus, is one of the most important causes of infectious diarrhea in foals during the first few weeks of life and often causes outbreaks involving the majority of the foal crop on individual farms.[185–187] Older foals and adult horses are more resistant to infection. Equine RV is transmitted via fecal-oral contamination and causes diarrhea by damaging the tips of villi in the small intestine, resulting in cellular destruction, maldigestion, malabsorption, and diarrhea. The genus Rotavirus is one of five genera of the family Reoviridae and is divided into seven serogroups (A through G) based on differences in the inner capsid protein, VP6.[187,188] All equine RV isolates to date are in group A, which is further subdivided using neutralizing antibodies to the VP4 and VP7 outer capsid proteins into P (protease-sensitive, VP4-positive) and G (glycoprotein, VP7-positive) serotypes, respectively.[188] Five P serotypes (P1, P6, P7, P12, and P18) and eight G serotypes (G1, G3, G5, G8, G10, G13, G14, and G16) have been identified and characterized in horses.[189–191] Most equine RV isolates from all parts of the world are, however, of the P12 and G3 serotype and include 2 subtypes (A and B).[192] A number of RV isolates remain untyped, so it is possible that other equine RV serotypes, and perhaps other serogroups, are active in the equine population.

An inactivated RV A vaccine (Equine Rotavirus Vaccine, Fort Dodge Animal Health, Fort Dodge, Iowa) containing the G3, P12 serotype (H2 strain) in a metabolizable oil-in-water emulsion is conditionally licensed in the United States and is indicated for administration to pregnant mares in endemic areas as an aid to prevention of diarrhea in their foals caused by infection with RVs of serogroup A. Foal vaccination is not indicated because there are no data to suggest that vaccination of the newborn foal with inactivated RV A vaccine has any benefit in preventing or reducing the severity of infection. Label recommendations call for a three-dose series of the vaccine to be administered to mares during each pregnancy at 8, 9, and 10 months of gestation. This protocol has been shown to induce significant increases in serum concentrations of neutralizing antibody in vaccinated mares and in the concentrations of antibodies of the IgG, but not IgA, subclass in the colostrum and milk of vaccinated mares.[193,194] It is essential that the newborn foal receive an adequate amount of good-quality colostrum so that it absorbs sufficient anti-RV antibodies. After nursing, the concentration of passively derived RV-specific antibody of the IgG subclass in the serum of foals up to 90 days of age from vaccinated mares is significantly higher than that measured in serum of foals born to unvaccinated mares.[193,194] A field study showed this vaccine to be safe when administered to pregnant mares and provided circumstantial evidence of at least partial efficacy. An approximately twofold higher incidence of rotaviral diarrhea was found in foals from unvaccinated mares compared with those from vaccinated mares, although this difference did not prove to be statistically significant.[193] Similarly, a controlled field study in Argentina in which an inactivated aluminum hydroxide—adjuvanted vaccine containing the SA11 (G3P2), H2 (G3P12), and Lincoln (G6P1) strains was administered to 100 mares at 60 days and again at 30 days before foaling demonstrated a substantial reduction in the incidence and severity of rotaviral disease in foals from vaccinated mares compared with foals

from unvaccinated mares.[195] As MDA titers wane at approximately 60 days of age, foals may develop rotaviral diarrhea. However, the severity of diarrhea is generally milder and of shorter duration than occurs in foals that become infected during the first 30 days of life.

Challenge studies involving two inactivated RV vaccines administered in a similar manner to pregnant mares in Japan showed that their foals were not completely protected against infection but had a substantial reduction in severity of clinical signs after challenge.[189] The major correlate for protection against rotaviral infection appears to be mucosal immunity, predominantly mucosal IgA, in the gastrointestinal tract. Studies of the immunoglobulin isotype responses of mares and of antibodies passively transferred to their foals after parenteral vaccination of their dams with inactivated RV vaccines indicate that this approach is unlikely to provide foals with intestinal mucosal protection in the form of IgA.[194] Consequently it is not surprising that current protocols do not provide complete protection. In addition, because the conditionally licensed vaccine available in the United States contains only the G3 serotype of the A serogroup, it cannot be expected to protect against infection with all field strains.

48.10.2 Equine Protozoal Myeloencephalitis

EPM is a multifocal neurologic disease caused by the apicomplexan parasites *Sarcocystis neurona* and, less often, *Neospora hughesi*. Serologic studies indicate that exposure to *S. neurona* occurs in most regions of North America, and in some areas seroprevalence exceeds 50%. Prevalence of clinically apparent neurologic disease caused by *S. neurona* and *N. hughesi* is much lower than the prevalence of antibodies, indicating that many horses become infected and mount an immune response that is effective in clearing infection before substantial damage occurs in the central nervous system. It is not known whether all seropositive horses have experienced neural infection or whether the immune response in these individuals is successful in clearing parasites before neural invasion occurs. The life-cycles of *S. neurona* and *N. hughesi* have not been determined definitively, although opossums are a definitive host for *S. neurona* and horses are likely dead-end hosts that inadvertently become involved in the life cycle.[196]

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There is widespread exposure of horses in North America to *S. neurona* and a high level of owner concern (in some cases hysteria) within the equine industry, leading to the perception that EPM is of high economic importance. This, coupled with inadequate diagnostic techniques for antemortem confirmation of EPM and the suboptimal effectiveness of current treatment and control protocols, led the USDA to grant a conditional vaccine license to Fort Dodge Laboratories in 2000. This vaccine is an inactivated whole-parasite *S. neurona* vaccine with a metabolizable oil adjuvant (EPM Vaccine, Fort Dodge Animal Health) that has met USDA requirements for quality assurance and purity in the manufacturing process. The criteria for safety were also met in a field study involving vaccination of more than 700 horses. The manufacturer met the requirement for documenting “a reasonable expectation of efficacy” by demonstrating seroconversion in vaccinated horses using a plaque reduction assay to measure neutralizing antibodies. Subsequent studies in which indirect fluorescent antibody testing (IFAT) and immunoblot (IB) tests were used to measure humoral responses, and intradermal skin testing and peripheral blood mononuclear cell proliferation assays were used to assess cell-mediated immunity (CMI), documented seroconversion and sensitization of CMI in a high proportion of vaccinated horses.[197,198]

Development of a clinically relevant experimental model for *S. neurona* infection has proven to be difficult; therefore the efficacy of this vaccine has not been determined in experimental challenge studies or in prospective controlled double-blind field studies. Because antibody to *S. neurona* is detectable in the cerebrospinal fluid (CSF) as well as blood of some horses postvaccination,[197] prospective field efficacy studies

will be difficult to complete because one of the criteria now used to confirm a diagnosis—the presence of antibodies detectable by IB testing or IFAT in CSF not contaminated with blood—will be rendered invalid in vaccinated horses. This vaccine has not gained widespread use, even though it may ultimately prove to be effective in preventing EPM. However, such use has inevitably generated controversy within the veterinary and scientific communities. In addition, one of the most useful aspects of currently available serologic tests, the finding of a negative IB test or IFAT result to rule out a diagnosis of EPM, will be invalidated in vaccinated horses. The vaccine manufacturer has indicated that a modified IB procedure currently being tested may be effective in differentiating vaccinated horses from those that have experienced natural exposure. It is hoped that answers to these questions and concerns will be revealed in the future.

48.10.3 Anthrax

Anthrax is a serious and rapidly fatal septicemic disease caused by proliferation and spread of the vegetative form of *Bacillus anthracis* in the body. *B. anthracis* is acquired through ingestion, inhalation, or skin penetration through contamination of wounds by soil-borne spores of the organism. Anthrax is encountered only in limited geographic areas where moist alkaline soils, particularly those with high organic content, favor survival, germination, and sporulation of the organism. Vaccination is indicated only for horses pastured in endemic areas.

The only vaccine currently licensed for vaccination of livestock, including horses, contains viable live Sterne's strain 34F2 nonencapsulated spores in saponin (Anthrax Spore Vaccine, Colorado Serum Company, Denver, Colo.). A primary series consisting of two doses of that vaccine should be administered subcutaneously 2 to 3 weeks apart followed by annual revaccination. Mild to moderate swelling at the injection site is common, and adverse systemic reactions may occur occasionally, particularly in young and miniature horses. Little objective information is available regarding use of this vaccine in horses, but clinical evidence suggests that it provides protection; however, vaccination of pregnant mares is not recommended.[199] Because the vaccine is a live bacterial product, appropriate caution should be used during storage, handling, and administration to prevent accidental inoculation of people and to maintain vaccine potency. Concurrent administration of antimicrobial drugs that are effective against *B. anthracis* is contraindicated if the vaccine is to function as intended.

48.11 OVINE AND CAPRINE VACCINATION PROGRAMS

Nancy East

Joan Dean Rowe

Several commercially available vaccines are labeled for sheep or goats. Some cattle vaccines are used off label in these ruminants, but little critical evaluation is available regarding the efficacy of this practice. The same general considerations presented for bovine vaccination programs apply to programs for sheep or goats. The vaccines available for sheep and goats are listed in Table 48-5. It is important to compare the cost of vaccination with projected losses from the disease, especially in commercial sheep operations, because of the low individual animal value and the high cost of vaccines. When considering the use of expensive vaccines, such as those for foot rot, the high labor cost associated with the disease must be taken into account in addition to the more obvious cost of the disease. Flock health records, regional diagnostic laboratories, local veterinarians, and county extension agents are good resources for obtaining information about disease prevalence in a particular area.

The subcutaneous route is the preferred route for sheep or goat vaccines. The preferred site is the neck or behind the elbow, away from superficial regional lymph nodes. In sheep, injections should not be given in the loin or

hindquarters because this area makes up three fourths of the prime carcass cuts. Subcutaneous injections over the ribs in goats often cause unsightly, persistent granulomas.

Compliance with a vaccination program is best achieved if the program is designed around the times when livestock normally are handled. The major problems and errors that occur in vaccination programs are (1) failure to provide adequate booster doses of clostridial vaccines, (2) inappropriate handling of modified live virus bluetongue vaccines, (3) vaccination of ewes in early gestation with modified live virus bluetongue vaccines, (4) use of contagious ecthyma vaccines on uninfected premises, and (5) failure to obtain diagnosis of causes of abortion.

All sheep and goats should be vaccinated against *Clostridium perfringens* types C and D and tetanus with one of the available commercial products. Some of the multiway clostridial vaccines are less expensive than the *C. perfringens* types C and D/tetanus toxoid combination and are used for this reason rather than because of any real need for protection from the other diseases. The available clostridial toxoids tend to vary both in efficacy and the extent of adverse reactions (especially vaccination site granulomas). There is some indication that *C. perfringens* toxoids may be less effective in goats than in sheep. Annual vaccination of pregnant ewes and does with a *C. perfringens* types C and D/tetanus toxoid combination approximately 4 weeks before parturition confers adult flock immunity and maximizes passive transfer of antibody to newborn lambs and kids. These antibodies protect up to 4 to 6 weeks of age, through the high-risk period for *C. perfringens* type C enterotoxemia and for tetanus from customary husbandry procedures (castration, tail docking, and disbudding). 1587 1588

Table 48-5 Vaccines and Antisera Available for Sheep and Goats[a]

Disease or Organism	Vaccine Product Name
Enzootic abortion of ewes (EAE, *Chlamydophila abortus*, formerly *Chlamydia psittaci*)	*C. psittaci* bacterin[b]
Vibriosis (*Campylobacter fetus* subsp. *fetus*, *Campylobacter jejuni*)	*C. fetus* bacterin[b]
Bluetongue	Modified live serotypes 10,[b,c] 11,[c] 17[c]
Foot rot	Footvax, *Bacteroides nodosus* bacterin[d]
	Volar, *Fusobacterium necrophorum* bacterin[e]
Clostridium tetani/*Clostridium perfringens* combination toxoids (many contain additional clostridia)	Bar Vac CD/T[f]
	C. perfringens types C and D, tetanus toxoid[b]
	Covexin 8[d]
	Vision CD-T[e]
	Caseous DT[b] (*C. perfringens* type D, tetanus toxoid, and *C. pseudotuberculosis*) Various other combinations and brands are available
Anthrax *(Bacillus anthracis)*	Anthrax spore vaccine[b] Various combinations and brands are available
Contagious ecthyma (sore mouth, orf) (live viral vaccine)	Ovine ecthyma vaccine[b]
Brucella ovis (ram epididymitis)	*B. ovis* (ram epididymitis) bacterin[b]
Caseous lymphadenitis *(Corynebacterium pseudotuberculosis)*	Case-Bac (*C. pseudotuberculosis* bacterin toxoid[b])
Tetanus antitoxin	Tetanus antitoxin[g]
C. perfringens antitoxin (A, B, C, D available)	*C. perfringens* types C and D antitoxin[b]
Rabies	Imrab, Imrab 3[h] Prorab-1[e] Rabdomun[d]

a Many additional vaccines manufactured for use in cattle can be used safely in sheep and goats when the need arises.

b Colorado Serum Co., Denver, CO.

c Poultry Health Laboratories, Davis, CA.

d Schering-Plough Animal Health Inc., Kansas City, KS.

e Intervet, Shawnee Mission, KS.

f Boehringer Ingelheim, St Joseph, MO.

g Widely available.

h Merial, Inc., Athens, GA. 30607.

Adverse reactions to combination clostridial, *Campylobacter*, and *Chlamydophila* vaccines are not unusual, especially when these vaccines are given at the same time as foot rot vaccine or vitamin E—selenium injections. Particularly in purebred flocks, owners should be taught the clinical signs and treatment of adverse reactions, which can occur 30 minutes to longer than 12 hours after vaccination. Adverse reactions include localized swelling, stiffness, pyrexia, anorexia, pulmonary edema and respiratory distress (foaming at the nose and mouth), laminitis, bloating and groaning, abortion (2 to 7 days after vaccination), and sudden death. Vaccination granulomas may persist.

Campylobacter species vaccination is recommended in sheep annually, whereas *Chlamydophila abortus* (formerly *Chlamydia psittaci*) vaccination is used in affected flocks or herds 2 to 4 weeks before the breeding season. *C. abortus* vaccine is of low efficacy when administered to pregnant ewes or does. Rams and bucks should receive annual boosters in affected herds.

The use of bacterins of *Leptospira interrogans* in sheep and goats is of questionable value under most circumstances. It is difficult to induce abortion in susceptible females with experimental infection. In endemic areas when sheep and cattle are grazed together or are adjacent and drink groundwater from streams or irrigation runoff, explosive outbreaks of leptospirosis in young growing lambs and occasional abortion storms in pregnant ewes have been described.

The cattle vaccines most commonly used in sheep are those directed against the respiratory disease complex; these vaccines are the intranasal infectious bovine rhinotracheitis (IBR) vaccine, the bovine respiratory syncytial virus (BRSV) vaccine, the killed or modified live virus *Pasteurella* vaccines, and the killed bovine virus diarrhea (BVD) vaccines. Justification of the use of these vaccines is based on current understanding of the possible potentiating and synergistic role of the cattle respiratory virus complex in ovine pneumonia and the prevalence of antibody to these viruses in the North American sheep population. Few well-controlled clinical trials using respiratory complex vaccines have been completed. Many respiratory problems can be best controlled by changes in management (see Chapter 31). Various vaccines for *Mannheimia haemolytica* pneumonia are marginally efficacious.

Table 48-6 shows a sheep vaccination schedule and flock management calendar for ewes and lambs in North America, and Table 48-7 shows a schedule and calendar for rams. Geographic differences in the distribution of endemic disease dictate which vaccine protocols are most economic and efficacious. Vaccines recommended for sheep include those that immunize against the following diseases or pathogens:

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- Foot rot
- *C. abortus* (enzootic abortion of ewes [EAE]; formerly *C. psittaci*)
- *Campylobacter* species (vibriosis)
- Bluetongue virus (endemic areas only)
- Contagious ecthyma (sore mouth; infected premises or outbreak only)
- *C. perfringens* types C and D
- *C. tetani* (tetanus)

- Other clostridial agents as needed

Table 48-6 Ewe and Lamb Vaccination Schedule and Flock Management Calendar for North America

Procedure	Prebreeding	Breeding	Tag or Shear	Lambing	Lamb Growth	Shearing	Weaning
Vaccination*	EAE (*Chlamydophila* species) *Vibrio (Campylobacter)* species	*Vibrio* booster	Vaccinate bagged ewes with clostridial caseous DT or eight-way clostridial and footrot vaccine	Footrot vaccination booster in yearling ewes	Clostridial vaccination (caseous DT) or eight-way vaccine for 6- to 10-week-old lambs		Vaccinate feeder lambs against clostridial agents
	Bluetongue						
Parasite control (see Chapter 49)	Deworm		Deworm if indicated	Soremouth vaccine for lambs on endemic premises	Give clostridial booster 4 weeks later; use caseous DT for replacement ewes		Vaccinate replacement ewes with caseous DT
Treatment	Vitamin E and selenium if needed		Vitamin E and selenium if needed		Coccidiostat in creep feed or salt to young lambs	Control external parasites	Deworm feeder lambs
					Deworm older lambs		
Reproduction	Condition score ewes, separate and flush; check udders, cull undesirables Check for lameness, treat as needed	30 to 60 days after breeding, check for pregnancy and cull open ewes Supplement pregnant ewes if thin	Separate ewes in late pregnancy, and supplement last 4 weeks of gestation	Dock lamb tails Castrate excess male lambs		Sell fat lambs	Identify and cull ewes: Thin Missing or loose teeth (incisors or molars) or molar points Chronic mastitis Dry ewes (no lamb) Poor mothers Chronic lameness

EAE, Enzootic abortion of ewes.

* See vaccine list, Table 48-5.

Table 48-7 Ram Vaccination Schedule and Flock Management Calendar for North America

Procedure	Prebreeding	Breeding	Tag/Shear	Lambing	Shearing	Weaning
Vaccination*	EAE Bluetongue		Foot rot vaccine	Foot rot vaccine booster	Clostridial vaccines or caseous DT vaccination	
Parasite control (see Chapter 49)	Deworm		Deworm		Deworm	
					External parasite control	
Treatment					Vitamin E and selenium if needed	
Reproduction	Breeding soundness examination, including: Epididymitis Lameness Condition score Conformation score Semen evaluation	Rotate rams Observe for poor libido and cull	Cull for epididymitis or chronic lameness		*Brucella ovis* ELISA, cull positives Palpate for epididymitis; cull those with lesions	Purchase new rams tested *B. ovis* ELISA—negative and with breeding soundness evaluated; scrotal circumference ≥32cm, and rams free of abscess
Other		Remove sick, lame, injured, or very thin rams	Check teeth, cull for loose or missing teeth or molar points	Cull rams not gaining weight	Condition score, separate, and bring to breeding condition	
			Put on good feed for 60 days		Check for lameness, treat or cull	

EAE, Enzootic abortion of ewes; *ELISA*, enzyme-linked immunosorbent assay.

* See vaccine list, Table 48-5.

Foot rot vaccine should be given 4 weeks before the wet season. *Brucella ovis* bacterin is not recommended to control ram epididymitis because vaccination interferes with ELISA testing and eradication programs. There are

approved rabies vaccines for sheep but not for goats (see Table 48-4). The use of these vaccines in goats is extralabel.

A dairy goat vaccination schedule and flock management calendar is shown in Table 48-8 for does and bucks in North America and in Table 48-9 for kids.

Vaccines recommended for goats include those that immunize against the following pathogens:

- *C. perfringens* types C and D
- *C. tetani* (tetanus)
- Contagious ecthyma (sore mouth) virus (only if premises are infected)
- *C. abortus* (EAE; formerly *C. psittaci*)
- Other clostridial agents as needed

Colostral protection against sore mouth is reported to be minimal.

Table 48-8 Dairy Goat (Does and Bucks) Vaccination Schedule and Herd Management Calendar for North America

Procedure	December-March	April-July	August-November
Vaccinations*	*Clostridium perfringens* types C and D	Booster of vaccines given previously	
	Tetanus and other clostridial diseases	*Chlamydophila* vaccine if needed	
Parasite control (see Chapter 49)	If access to pasture, deworm; may not be necessary if drylot only	Deworm if needed (access to pasture)	
Treatment	Vitamin E and selenium injection to does at drying off if in selenium-deficient area	Vitamin E and selenium if needed; vitamins A and D	
Mastitis control (see Chapter 36)	Culture milk from fresh does for bacteria and mycoplasma; treat or cull	Bulk tank mycoplasma culture; monitor milk quality; culture does with mastitis or increased CMT or SCC	Treat dry does as needed with intramammary antibiotics Monitor milk quality
Reproduction (see Chapter 43)	Pregnancy check before dry off; cull open does Institute photoperiod manipulation for dry yearling does and all bucks needed for out-of-season breeding	Institute out-of-season breeding using hormone therapy on lactating does‡ Pregnancy check 45 days after breeding Breed light-treated yearling does	Plan breeding adult does to spread out fresh dates and begin breeding to assigned bucks; maintain breeding records Examine short-cycling and repeat-breeder does; cull nonresponders; pregnancy check does
Other	Maintain first lactation yearling does in separate pen; milk first; feed for both growth and production	Cull low-producing does Prebreeding examination on bucks, cull abnormals, bring bucks to breeding condition by optimizing nutrition	Supplement bucks to maintain condition

CMT, California Mastitis Test; *ELISA*, enzyme-linked immunosorbent assay; *SCC*, somatic cell count.

* See vaccine list, Table 48-5.

† 22 hours/day for 8 weeks, usually January to February; start cycling 4 to 8 weeks after start of light; *dry* does only.

‡ CIDR-g, according to label instructions (Pfizer, DEC, NZ; assuming FDA approval). Give PMSG (equine chorionic gonadotropin; 500 IU needed in early spring, 250 U in May or June or later) 48 hours before pulling implant; then pull implant, and animals will cycle 12 to 72 hours later (maximum number in heat at 36 hours).

48.12 BOVINE VACCINES AND HERD VACCINATION PROGRAMS

Victor S. Cortese

With the increasing size of today's cattle operations and the extensive movement of cattle, disease exposure continues to occur at a high rate in cattle. These exposures often put pressure on the efficacy of the vaccines used and may give field experience as to how well they can protect cattle. The wide diversity in uses of cattle and management practices make a single vaccination protocol impossible for all of cattle production. Today it is even more important to scientifically choose a vaccine or design a vaccination program based on good information. When designing programs, variables such as the following must be considered.[200]

- The presence and degree of challenge of the particular diseases on the farm or ranch
- Management practices on the facility that support or hinder vaccination programs
- The times or ages at which the disease problems occur and if the diseases are associated with any stressors
- The immune system components necessary to afford protection against various diseases
- Some basic immunologic concepts
- The information available on products being considered and the source and quality of the information
- Required vaccines for a particular use of the animal (e.g., 4-H shows).

48.12.1 Challenge

The level of disease challenge and the degree of protection continually fluctuate. Because of biologic variability, the degree of protection is different in every vaccinated animal. The same is true of the level of exposure to a pathogen. Overwhelming challenge can override immunity and lead to disease even in well-vaccinated animals.[201]

Table 48-9 Dairy Kid Vaccination Schedule and Herd Management Calendar for North America

Procedure	December-March	April-July	August-November
Vaccination*	*Clostridium perfringens* types C and D	Booster clostridial or caseous DT vaccines given previously	Before breeding, *Chlamydia* vaccine (or use tetracycline in feed before and during breeding season)
	Tetanus or caseous DT		
	Other clostridial diseases		
Parasite control	Coccidiostat in kid starter feed at 2 weeks of age (Deccox recommended)	Continue coccidiostat Deworm if access to pasture	
Treatment	Vitamins A, D, E Vitamin E, selenium if needed	Vitamin E, selenium if needed	
Reproduction	Castrate excess males; pregnancy check kids		Pregnancy check kids Cull short-cycling and repeat-breeder kids
			Hold small females to breed using photoperiod manipulation (see Table 48-8)
Other	Isolate from does at birth, feed cow colostrum or heat-treated goat colostrum, followed by cow milk, milk replacer, or pasteurized goat milk to control mycoplasma and CAE Disbud kids Tattoo kids	Maintain isolation from adults Do not overcrowd Provide ration for maximum growth Keep male and female kids separate	Group kids by size and sex Start breeding kids over 29.3 kg

CAE, Caprine arthritis-encephalitis.

* See vaccine list, Table 48-5.

* Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

48.12.2 Timing of Disease

On many farms certain diseases occur at consistent times. The timing may give some insight into stresses that occur in the management of the cattle. Correcting these stresses can have a positive impact on vaccination and lessen animals' susceptibility to disease. This type of history also is helpful in determining the timing of vaccinations, a concept that often is underused in veterinary medicine. Knowing when a problem historically

has occurred allows vaccinations to be scheduled when they will induce maximum immune responses in preparation for expected challenges.

48.12.3

Assessing Vaccine Efficacy

The efficacy of a vaccine can be extremely difficult for the practitioner to assess. Traditionally, serologic data showing prevaccination and postvaccination titers have been equated with protection. For many diseases, however, the correlation is poor between the antibody measured and the protection generated by the vaccine in the animal.[202] Recently, cell-mediated immune function tests have been added to show a more complete stimulation of the immune response after vaccination.[203] Although these tests provide more information about the vaccine, they still do not answer the basic question of how well a vaccine really protects. This question can be answered only by well-designed challenge studies. There are many examples of well-designed studies involving both viral[204,205] and bacterial[206,207] agents. To assess a challenge study, the following information is needed:

1 The trial design, including animal characteristics

2 A statistical analysis of the results

3 Determination of whether the statistical differences are biologically important

4 The route of administration of the challenge

5 The characteristics of the challenge organism

6 Whether the challenge model is consistent with the desired protection (e.g., respiratory versus reproductive protection)

7 The method of clinical score assignment

8 The level of disease seen in the control unvaccinated cattle

9 Publication of the results in a peer-reviewed article

Unfortunately, the challenge model is not well established for many diseases. Field trials are even harder to assess but are valuable for judging the effectiveness (i.e., efficacy in a particular situation) and efficiency (i.e., cost-effectiveness) of a vaccine[208] (Boxes 48-1 and 48-2). Several good references on field trial analysis are available.[209,210] Recently the Center for Veterinary Biologics (CVB) began giving vaccines different labels depending on the strength of the efficacy data submitted to the Center in the licensing trials.

48.12.3.1

Box 48-1 Bovine Vaccines Seldom Needed on Most U.S. Ranches and Farms*

Anthrax vaccine

Clostridium septicum (malignant edema) bacterins

Leptospira grippotyphosa bacterins

Leptospira icterohaemorrhagiae bacterins

Leptospira canicola bacterins

Clostridium botulinum toxoids

Clostridium novyi bacterins

Rabies vaccine

Tetanus toxoids

Erysipelas bacterins

Clostridium sordellii (malignant edema) bacterins

* These vaccines also are not cost-effective.

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48.12.3.2

Box 48-2 Bovine Vaccines for Ranch- and Farm-Specific (Soil-Borne) Diseases

Blackleg bacterins

Clostridium haemolyticum (redwater) bacterins

Anthrax vaccine

Clostridium novyi (infectious necrotic hepatitis) bacterins

Table 48-10 Antigens Available in Currently Licensed* Cattle Vaccines

Antigen Type	Common Name of Disease or Vaccine	Pathogen
Virus	BRSV	Bovine respiratory syncytial virus
	Rednose	Bovine herpesvirus type 1, infectious bovine rhinotracheitis virus (IBRV)
	BVD-MD	Bovine virus diarrhea virus (types 1 and 2)—mucosal disease
	PI-3	Parainfluenza type 3 virus
	Rabies	*Lyssavirus* species
	Warts	Bovine papillomavirus, bovine rotavirus, bovine coronavirus
Bacteria	Anthrax	*Bacillus anthracis*
	Bangs	*Brucella abortus*
	Vibriosis	*Campylobacter fetus* subsp. *veneralis*
	Blackleg	*Clostridium chauvoei*
	Redwater disease (bacillary hemoglobinuria)	*Clostridium haemolyticum*
	Black disease	*Clostridium novyi*
	Enterotoxemia	*Clostridium perfringens* type C
	Haemophilus, TEME	*Histophilus somnus*
	Hemorrhagic bowel syndrome	*Clostridium perfringens* type A
	Overeating	*Clostridium perfringens* type D
	Malignant edema	*Clostridium septicum, Clostridium sordellii*
	Mycoplasma pneumonias and mastitis	*Mycoplasma bovis*
	Tetanus	*Clostridium tetani*
	Endotoxin vaccines	*J5 Escherichia coli* R mutant *Salmonella* vaccine
	Coliform scours	*Escherichia coli* K99 and non-K99
	Foot rot	*Fusobacterium necrophorum, Haemophilus somnus, Leptospira* Canicola, *Leptospira* Grippotyphosa, *Leptospira* Hardjo, *Leptospira* Icterohaemorrhagiae, *Leptospira* Pomona

	Pinkeye	*Moraxella bovis*
	Leptospirosis	*Leptospira borgpetersenii* serovar Hardjo-bovis *Leptospira interrogans* serovar Hardjo-bovis *Leptospira interrogans* serovar Canicola *Leptospira interrogans* serovar Icterohemorrhagiae *Leptospira interrogans* serovar Grippotyphosa *Leptospira* Pomona
	Johne's disease	*Mycobacterium paratuberculosis*
	Salmonella	*Salmonella* Dublin, *Salmonella* Typhimurium *Salmonella* siderophore vaccines
	Shipping fever	*Mannheimia haemolytica (Pasteurella haemolytica), Pasteurella multocida*
	Endotoxin vaccines	R *Salmonella*, J5 *Escherichia coli*
	"Staph" mastitis	*Staphylococcus aureus*
Rickettsiae and protozoa	Neosporosis	*Neospora* species (provisional license)
	"Trich"	*Tritrichomonas foetus*
	Anaplasmosis	*Anaplasma marginale*

Modified from *Compendium of veterinary products*, ed 5, 1999, Adrian J Bayley.

* Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

48.13 CATTLE VACCINES

Bovine vaccines tailored for use against eight viral diseases, more than 28 bacterial pathogens, two neorickettsial diseases (anaplasmosis and *Neospora* infection), and one protozoal disease (trichomoniasis) currently are marketed in the United States (Table 48-10). These vaccines have been designed to aid in the prevention of reproductive, respiratory, generalized septicemic, and toxic (endotoxic and exotoxic) diseases. The vaccines have demonstrated some degree of protection against the pathogen for which they were designed, but they may not have proved protective against all the various syndromes known to be caused by a specific infectious agent. The challenge models for each pathogen and the release requirements for each vaccine are monitored by the Veterinary Biologics division of USDA/APHIS and can be found in Book 9 of the CFR.

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During gestation the bovine reproductive system, with its multilayered placenta, leaves the fetus in a naive environment susceptible to infection. Abortions may occur as a result of infection of the placenta, inflammation of the ovary, death of the fetus, or disruption of the cervical plug. Reproductive disease therefore is the most difficult against which to achieve protection. Vaccination must minimize the amount or duration (or both) of the viremia or septicemia, or it must prevent the pathogen from moving through the cervix or crossing the placenta. Only a few of the currently licensed vaccines have proved protective against the reproductive forms of various diseases. Furthermore, the DOI afforded by the various vaccines has not been established for most currently licensed products.

Each manufacturer develops and produces cattle vaccines differently; consequently the composition of vaccines varies dramatically among the different manufacturers. Outlines of production are proprietary for each manufacturer, but some information can be found in technical and marketing materials. For example, some viral vaccines are grown on bovine-derived kidney cell lines, and others are grown on porcine-derived kidney cells. Some vaccines are grown only on calf serum, whereas others are grown on both calf and fetal calf serum. Differences in passages may be found as well. The variability is seen in the strain or strains chosen for the vaccine, the number of passages chosen in the growth, the growth medium, and the number of viral or bacterial particles in the vaccine.

The following three types of vaccines represent the basic technologies currently available in cattle viral and bacterial vaccines.[201,211–215]

1 Modified live (attenuated) vaccines contain living bacterial or viral organisms. These organisms usually are collected from a field disease case and then grown in abnormal host cells (viruses) or media (bacteria) to change or attenuate the pathogen. Each completion of growth through a replication is known as a *passage*, and the changed pathogen then is administered back to the animal to determine if it is still virulent. After several passages the pathogen begins to lose virulence factors because it cannot cause “disease” in the unnatural host cells. Once the pathogen can no longer cause “disease” in the target species, it is tested to see if it can confer protection. The final vaccine usually is passed a number of times beyond the passage where virulence disappears in order to reduce the risk of reversion to a virulent pathogen. These vaccines usually require good quality control to reduce the risk of a contaminant entering the vaccine.

2 Inactivated (killed) vaccines are easier to develop because virulence after growth is not a problem. The same pathogen is isolated from a disease outbreak. The pathogen is grown and then chemically or physically killed. The inactivation usually is achieved either by adding a chemical to the pathogen or by using ultraviolet rays. The major concern with inactivation is the potential loss of important epitopes. An adjuvant normally is added to inactivated vaccines to heighten the immune response. The vaccine is then tested for efficacy.

3 Genetically engineered vaccines have been altered genetically, usually through a mutation. This mutation may be induced by several different methods, but the resulting bacterium or virus has different properties that may alter virulence or growth characteristics. Most of these vaccines are modified live mutants (e.g., temperature-sensitive viral vaccines or streptomycin-dependent *Mannheimia* or *Pasteurella* vaccines), but inactivated marker vaccines are also genetically engineered. These vaccines have been engineered to delete a gene and cause an immune response deficient in antibodies to a certain epitope; this allows diagnostic methods to distinguish between vaccine and natural exposure responses (e.g., gene-deleted IBR vaccines).

Once its efficacy has been established, the vaccine is put through a series of experiments to determine the minimum dose required to achieve adequate protection, called the *minimum immunizing dose* (MID). The vaccine will contain more than the MID in order to obtain at least the MID at the expiration date found on the label. In effect, a vaccine's efficacy is determined not via the final product used by the veterinarian but via a reduced level of immunogens from the amount contained in the final vaccine.

48.13.1 Autogenous Vaccines

In addition to the vaccines licensed by the USDA, several companies will make autogenous vaccines for use by veterinarians and cattle owners. These vaccines do not fall under any particular USDA/APHIS guidelines and

usually are derived from cultures (e.g., viral or bacterial) isolated from specimens submitted by the particular farm. Such vaccines can be used only on that particular facility and cannot be sold for use on other farms. These vaccines are not tested for efficacy or safety, and the components found in the vaccines may vary from batch to batch; this adds some element of risk when they are used. Nevertheless, this type of vaccine may be an option to consider when federally licensed vaccines are not available for a specific farm problem.

48.13.2 Maternal Antibody Interference Revisited

It is an accepted belief that maternal antibodies can block immune responses from vaccination. This belief has been based on a procedure of vaccination followed by a titer evaluation in the vaccinates. Many studies have shown that vaccinated animals may not display increased antibody levels if high levels of maternal antibody to that antigen are present. However, recent studies have shown that both the formation of B cell memory responses and cell-mediated responses can be stimulated in spite of high maternal antibody for the same antigens.[216–218] Seropositive calves vaccinated at a young age with modified live bovine herpesvirus type 1 (BHV-1), parainfluenza type 3 (PI-3), and/or BRSV vaccines have shown higher antibody responses on revaccination than control calves vaccinated only at the second date. These young vaccinates typically do not show increased antibody responses after the first vaccination in the presence of high maternal antibody. Cell-mediated immune responses, as indicated by antigen-specific T cell blastogenesis, have been demonstrated in the face of high maternal antibody levels[219] when attenuated BRSV and BHV-1 vaccines were used. Similar responses have been reported in laboratory animals as well.[220,221] One study also demonstrated higher levels of protection at challenge if calves were vaccinated with a modified live BRSV vaccine.[218] It is clear from these studies that maternal antibody interference with vaccines is not as absolute as once thought. The animal's immune status, the specific antigen, and the presentation of that antigen should be considered when designing vaccination programs in which maternal antibody may be a factor.

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48.13.3 Impact of Stress

Stress affects the immune system of all cattle, as can a number of other factors. The release of corticosteroid that occurs during the birthing process has a dramatic impact on the newborn's immune system. Newborns also have a higher number of suppressor T cells than do adults.[2] These factors and others dramatically diminish systemic immune responses for the first week of life.[222] Other stressors should be avoided at vaccination time to maintain the integrity of the immune system. Procedures such as castration, dehorning, weaning, and movement need to be considered as stressors in cattle, and all have the potential to diminish immune system functioning temporarily.[223–225]

Systemic vaccinations should be avoided during high-stress times because of these diminished responses and because vaccination at such times may even have undesired effects.

48.13.4 Booster Importance

It is important to follow the label directions for administering vaccines. Many inactivated vaccines and some modified live BRSV vaccines require a booster before protection is complete. The first time an inactivated vaccine is administered, the primary response occurs. This response is not very strong, is fairly short-lived, and is predominantly composed of IgM antibodies (Fig. 48-1). The response seen after a booster vaccination is called the *secondary*, or *anamnestic, response*. This response is much stronger, is of longer duration, and is

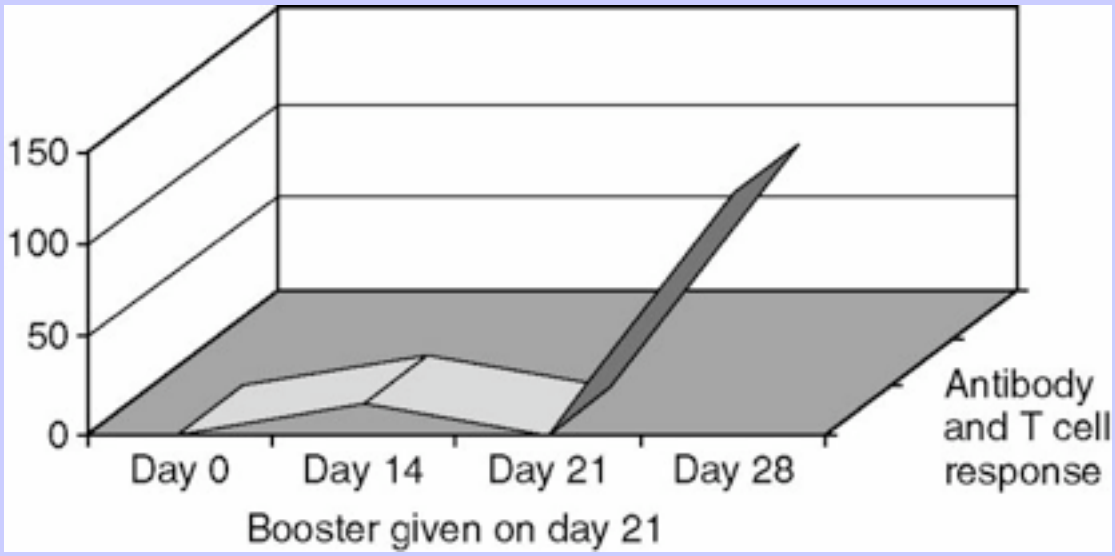
primarily composed of IgG antibodies.[201,210] If the booster is given too early, the anamnestic response does not occur, and if too much time elapses before the booster is given, it acts as an initial dose, not as a booster.

With most modified live virus vaccines (except for some BRSV vaccines), the primary vaccination also stimulates the secondary response without the need for a booster because the virus or bacterium is replicating in the animal.

48.13.5 Adverse Reactions

Adverse reactions are a risk with any vaccination. These reactions can be categorized as one of the following two primary types of hypersensitivity.[201,203,226–231]

Fig. 48-1 Anamnestic response seen after a booster dose is administered to vaccinates.



1 Type I, or immediate, hypersensitivity is mediated by IgE stimulation and the release of granules from basophils and mast cells. This reaction is seen within minutes of vaccination and often begins with shaking or sweating. Most of these animals respond to intravenous injection of epinephrine. Every vaccine occasionally can elicit an anaphylactic reaction. Cattle should always be kept under observation for at least 30 minutes after administration of a vaccine. Epinephrine should be administered at a dose of 1 mL of 1:1000 solution per 50 kg of body weight, preferably by intravenous injection, at the first sign of weakness, staggering, or dyspnea. With most vaccines anaphylactic reactions occur no more often than one case per 5000 to 10,000 doses administered. The rate of occurrence may be much higher after administration of *Salmonella, Escherichia coli*, and some *Moraxella bovis* bacterins, which may have high levels of endotoxin.

2 Type III, or immune complex, hypersensitivity is mediated by the attachment of an antibody-antigen complex to complement and the ensuing activation of the complement cascade. The resultant reaction may occur locally or systemically. The reaction may be delayed, as the complexes form and the cascade

begins, or subsequent, as products begin to exert their effects. The signs are similar to those of an immediate hypersensitivity reaction, and the treatment is administration of epinephrine.

One of the more common reactions seen in dairy cattle has been associated with the endotoxin and other bacterial components found in most gram-negative vaccines.[230–233] Currently, there are no requirements for monitoring or reporting the amount of endotoxin found in cattle vaccines, and the level of endotoxin may vary dramatically among vaccines and among serials of the same vaccine. Furthermore, the potency of endotoxin varies among different gram-negative bacteria. This type of reaction is seen primarily in Holsteins because of a genetic predisposition and may be seen after administration of any gram-negative bacterin. The signs vary depending on the farm's or the individual's sensitivity to gram-negative bacterial components. The number or potency of the gram-negative fractions in vaccinations administered simultaneously also are instrumental in causing these reactions. As a general rule, no more than two gram-negative vaccines should be administered to dairy cattle on the same day because of the possibility of adverse reactions, which may include anorexia and transient decreases in milk production, early embryonic death, abortion, and gram-negative bacterial shock (endotoxic shock), which requires treatment with flunixin or ketrofen, steroids, antihistamines, and fluids.

Site reactions are common sequelae to many vaccines. These granulomas usually are caused by overreaction to the adjuvants, but they may also be directly aimed at the antigen or antigens. This has been a major focus of beef quality programs and has generated a push to have all vaccines labeled and to have them administered subcutaneously to avoid damaging the muscle.

48.13.6 Read the Labels

The vaccine label is a wealth of information that is approved by the CVB. The CVB evaluates the supportive efficacy data supplied by the vaccine manufacture and decides whether the vaccine can be licensed or not. They also determine what type of efficacy claim can appear on the vaccine labels and in advertising. Included are dosage, route of administration, precautions, timing, indications, storage indication, withdrawal period, and shelf life. As found in Veterinary Services Memorandum 800.202, June 2002, the CVB also does some preliminary rating of vaccine efficacy by granting one of five protection statements. According to the memorandum, one of five levels of protection may be granted (in order of highest efficacy to lowest): Prevention of infection, Prevention of disease, Aid in the prevention of infection, Aid in disease control, Other miscellaneous claims. The label can be a good starting point for comparing vaccines.

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48.13.7 Summary

Designing a vaccination program requires a good history of the individual farm and a basic understanding of the immune system. Vaccines that should be considered for routine or optional use in various classes of pastured beef cattle, feedlot cattle, and dairy cattle are listed in Boxes 48-3 to 48-12. The vaccines chosen should be supported by good, solid efficacy studies (and by effectiveness and efficiency studies if possible) to ensure that the product can fulfill the needs of the farm or ranch (Table 48-11). Management decisions may be made that do not maximize the potential of the product chosen, and realistic expectations of all products should be well explained to the producer before the vaccines are administered. The owner should be involved in the vaccine decision-making process, and all information on the product should be shared.

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48.13.7.1

Box 48-3 Vaccines Recommended for Use in Adult Beef Cows

48.13.7.1.1

Vaccines Highly Recommended for All Herds

Infectious bovine rhinotracheitis (IBR) vaccines

Bovine virus diarrhea (BVD) vaccines

Leptospira borgpetersenii var Hardjo

Leptospira pomona bacterins

Campylobacteriosis bacterins*

48.13.7.1.2

Vaccines that may be Useful or Necessary in Specific Herds or Geographic Locations

Tritrichomonas foetus vaccine

Anaplasmosis vaccine (inactivated)

Rotavirus-coronavirus (calf scours) vaccine (inactivated)

Fusobacterium necrophorum (foot rot) bacterin

Escherichia coli bacterins

Clostridium haemolyticum (*Cl. novyi* type D, redwater) bacterins

Clostridium perfringens type C (enterotoxemia) toxoids

Anthrax vaccine

Clostridium novyi bacterins

* Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the “closed” status of the herd and by isolation from other potentially infected herds by distance, terrain, and/or “bull proof” perimeter fencing).

48.13.7.2

Box 48-4 Vaccines Recommended for Use in Adult Beef Bulls

48.13.7.2.1

Vaccines Highly Recommended for All Herds

Infectious bovine rhinotracheitis (IBR) vaccines

Bovine virus diarrhea (BVD) vaccines

Leptospira borgpetersenii serovar Hardjo

Campylobacteriosis bacterins*

48.13.7.2.2

Vaccines that may be Useful or Necessary in Specific Herds or Geographic Locations

Tritrichomonas foetus vaccine

Anaplasmosis vaccine (inactivated)

Leptospira pomona bacterins

Fusobacterium necrophorum (foot rot) bacterin

Clostridium haemolyticum (*Cl. novyi* type D, redwater) bacterins

Anthrax vaccine

Clostridium novyi bacterins

* Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the “closed” status of the her and by isolation from other potentially infected herds by distance, terrain, and/or “bull proof” perimeter fencing).

48.13.7.3

Box 48-5 Vaccines Recommended for Use in Beef Calves*

48.13.7.3.1

Highly Recommended Vaccines

Infectious bovine rhinotracheitis (IBR) vaccines

Bovine virus diarrhea (BVD) vaccines

Bovine respiratory syncytial virus (BRSV) vaccines

Parainfluenza type 3 (PI-3) vaccines

Leptospira borgpetersenii serovar Hardjo

Leptospira pomona bacterins

Brucellosis vaccine†

48.13.7.3.2

Vaccines that may be Useful or Necessary in Specific Herds or Geographic Locations

Blackleg bacterins

Moraxella bovis (pinkeye) bacterins

Histophilus somni (formerly *Hemophilus sommus*) bacterins

Anaplasmosis vaccine‡ (modified live)

Clostridium haemolyticum (*Cl. novyi* type D, redwater) bacterins

Anthrax vaccine

Fusobacterium necrophorum (foot rot) bacterin

Clostridium novyi bacterins

Mannheimia haemolytica vaccines (new)

* Under 12 months of age.

† Heifer replacements only.

‡ Heifer and bull replacements only.

48.13.7.4

Box 48-6 Vaccines Recommended for Use in Stocker Cattle

48.13.7.4.1

Highly Recommended Vaccines

Infectious bovine rhinotracheitis (IBR) vaccines

Bovine virus diarrhea (BVD) vaccines

Bovine respiratory syncytial virus (BRSV) vaccines

Parainfluenza type 3 (PI-3) vaccines

Mannheimia haemolytica vaccines (new)

Leptospira pomona bacterins

48.13.7.4.2

Vaccines that may be Useful or Necessary in Specific Herds or Geographic Locations

Blackleg bacterins

Histophilus somni (formerly *Hemophilus somnus*) bacterins

Moraxella bovis (pinkeye) bacterins

Clostridium haemolyticum (*Cl. novyi* type D, redwater) bacterins

Anthrax vaccine

Fusobacterium necrophorum (foot rot) bacterin

Clostridium novyi bacterins

48.13.7.5

Box 48-7 Vaccines Recommended for Use in Beef Replacement Heifers

48.13.7.5.1

Vaccines Highly Recommended for Use in All Herds

Infectious bovine rhinotracheitis (IBR) vaccines

Bovine virus diarrhea (BVD) vaccines

Leptospira borgpetersenii serovar Hardjo

Leptospira pomona bacterins

Campylobacteriosis bacterins*

48.13.7.5.2

Vaccines that may be Useful or Necessary in Specific Herds or Geographic Locations

Blackleg bacterins

Tritrichomonas foetus vaccine

Anaplasmosis vaccine (modified live)

Rotavirus-coronavirus vaccine (inactivated)

Escherichia coli bacterins

Fusobacterium necrophorum (foot rot) bacterin

Moraxella bovis (pinkeye) bacterins

Histophilus somni (formerly *Hemophilus somnus*) bacterins

Clostridium haemolyticum (*Cl. novyi* type D, redwater) bacterins

Clostridium perfringens type C toxoids

Anthrax vaccine

Clostridium novyi bacterins

* Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the "closed" status of the herd and by isolation from other potentially infected herds by distance, terrain, or "bull proof" perimeter fencing).

48.13.7.6

Box 48-8 Vaccines Recommended for Routine Administration to Cattle Entering Feedlots

48.13.7.6.1

Essential Vaccines

Infectious bovine rhinotracheitis (IBR) vaccine (modified live)

Bovine virus diarrhea (BVD) vaccine (modified live)

Bovine respiratory syncytial virus (BRSV)

48.13.7.6.2

Highly Recommended Vaccines

Mannheimia haemolytica vaccine*

Leptospira pomona bacterins

48.13.7.6.3

Vaccine that may be Needed in Some Groups of Cattle in a Feedlot

Clostridium haemolyticum (redwater) bacterins

48.13.7.6.4

Vaccines Necessary Only in Specific "Problem" Feedlots

Blackleg bacterins

Bovine respiratory syncytial virus (BRSV) vaccines

Fusobacterium necrophorum (foot rot) bacterin

* Some commercial modified live cytopathic virus BVD vaccines trigger severe fatal BVD in cattle that are chronically infected with noncytopathic strains of BVD virus and immunologically tolerant as a result of prenatal infection.

48.13.7.7 Box 48-9 Vaccines Recommended for Use in Adult Dairy Cows

48.13.7.7.1 Vaccines Highly Recommended for Use in All Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines

Bovine virus diarrhea (BVD) vaccines

Bovine respiratory syncytial virus (BRSV)

Leptospira borgpetersenii serovar hardjo

Leptospira pomona bacterins

48.13.7.7.2 Vaccine Highly Recommended for Cows in Specific Infected Herds

Core endotoxin vaccines

48.13.7.7.3 Vaccines Highly Recommended for Dairy Cows Grazing in Specific Endemic Areas

Clostridium haemolyticum bacterins

Anthrax vaccine

Clostridium novyi bacterins

48.13.7.7.4 Vaccines that may be Useful in Controlling Specific Disease Problems in Individual Dairy Herds

Escherichia coli (calf scours) bacterins

Rotavirus-coronavirus (calf scours) vaccine (inactivated)

Fusobacterium necrophorum (foot rot) bacterin

Clostridium septicum (malignant edema) bacterins

Clostridium sordellii (malignant edema) bacterins

48.13.7.8 Box 48-10 Vaccines Recommended for Use in Adult Dairy Bulls

48.13.7.8.1 Vaccines Highly Recommended for Bulls in All Commercial Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines

Bovine virus diarrhea (BVD) vaccines

Leptospira borgpetersenii serovar Hardjo

Campylobacteriosis bacterins*

48.13.7.8.2 Vaccines Highly Recommended for Bulls Grazing in Specific Endemic Areas

Anaplasmosis vaccine (inactivated)

Clostridium haemolyticum (*Cl. novyi* type D, redwater) bacterins

Anthrax vaccine

Clostridium novyi bacterins

48.13.7.8.3 Vaccines that may be Useful in Specific Herds or Geographic Locations

Leptospira pomona bacterins

Fusobacterium necrophorum (foot rot) bacterin

* Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the “closed” status of the herd and by isolation from other potentially infected herds by distance, terrain, or “bull proof” perimeter fencing).

The establishment of good baseline immunity of replacement heifers and the foundation vaccination program can have dramatic effects on the health and profitability of the herd; therefore such programs must be well planned.

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48.13.7.9

Box 48-11 Vaccines Recommended for Use in Dairy Calves*

48.13.7.9.1

Vaccines Highly Recommended for Calves in All Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines

Bovine virus diarrhea (BVD) vaccines

Bovine respiratory syncytial virus (BRSV) vaccines

Parainfluenza type 3 (PI-3) vaccines

Leptospira borgpetersenii serovar Hardjo

Leptospira pomona bacterins

Brucellosis vaccine

48.13.7.9.2

Vaccines Highly Recommended for Calves Grazing in Specific Endemic Areas

Blackleg bacterins

Clostridium haemolyticum bacterins

Anthrax vaccine

Clostridium novyi bacterins

48.13.7.9.3 Vaccine Highly Recommended for Calves in Herds with Adult Cows Grazing in Specific Endemic Areas

Anaplasmosis vaccine (modified live)

48.13.7.9.4 Vaccines that may be Useful in Controlling Specific Disease Problems in Individual Dairy Herds

Mannheimia haemolytica vaccines (new)

Histophilus somni (formerly *Hemophilus somnus*) bacterins

Moraxella bovis (pinkeye) bacterins

Fusobacterium necrophorum (foot rot) bacterin

* Up to 12 months of age.

48.13.7.10 Box 48-12 Vaccines Recommended for Use in Yearling Replacement Dairy Heifers

48.13.7.10.1 Vaccines Highly Recommended for Use in Heifers in All Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines

Bovine virus diarrhea (BVD) vaccines

Bovine respiratory syncytial virus (BRSV) vaccines

Leptospira borgpetersenii serovar Hardjo

Leptospira pomona bacterins

48.13.7.10.2 Vaccines Highly Recommended for Dairy Heifers Grazing in Specific Endemic Areas

Blackleg bacterins

Anaplasmosis vaccine (Anavac* or Anaplaz)

Clostridium haemolyticum (*Cl. novyi* type D, redwater) bacterins

Anthrax vaccine

Clostridium novyi bacterins

48.13.7.10.3 Vaccines that may be Useful for Controlling Specific Disease Problems in Individual Groups of Dairy Heifers

Fusobacterium necrophorum (foot rot) bacterin

Moraxella bovis (pinkeye) bacterins

48.13.7.10.4 Vaccines Administered to Springing Heifers that may be Useful for Controlling Specific Disease Problems in Specific Dairy Herds

Gram-negative core antigen (coliform mastitis) vaccines

Escherichia coli (calf scours) bacterins

Rotavirus-coronavirus (calf scours) vaccine (inactivated)

Clostridium septicum (malignant edema) bacterins

Clostridium sordellii (malignant edema) bacterins

* Anavac (BioLOGIC Laboratories, Davis, CA 95616) is the preferred vaccine for use in dairy herds in which the adult cows are grazing in an endemic area.

48.14 BOVINE RESPIRATORY DISEASE VACCINES

48.14.1 BOVINE HERPESVIRUS TYPE 1: INFECTIOUS BOVINE RHINOTRACHEITIS VIRUS

48.14.1.1 Bovine Herpesvirus 1 Vaccines

In 2005 more than 175 vaccines against BHV-1 were available in the United States for use in cattle.[234] Vaccination protocols for beef and dairy cattle in the United States routinely incorporate use of one or more vaccines against BHV-1. These vaccines are classified into five types: (1) modified live virus vaccines for parenteral administration (intramuscular and/or subcutaneous); (2) modified live virus, intranasally administered vaccines; (3) chemically altered, live virus, temperature-sensitive vaccine for parenteral use; (4) inactivated viral vaccines for parenteral use; and (5) a combination of parenteral modified live virus and inactivated viral vaccine. These vaccines may be single-component (monovalent) vaccines (e.g., BHV-1 alone) or may contain several immunogens, including various combinations of BVD virus (BVDV) types 1 and 2; bovine PI-3 virus, BRSV*, Leptospira* species, *Histophilus somni, M. hemolytica, Pasteurella multocida*, and/or *Campylobacter* species.[234] The characteristics of the BHV-1 vaccines are described in the following sections.

BHV-1 modified live virus parenteral vaccines induce both B cell (humoral) and T cell (cell-mediated) active immune responses after one dose of modified live virus vaccine.[235] Serum antibodies to BHV-1 along with BHV-1 specific CD^{4+}, CD^{8+}, and γδ T cells were detected after BHV-1 modified live virus vaccination.[235] Calves born to dams with circulating BHV-1 antib5odies may absorb the colostrally derived maternal antibodies to BHV-1 and other viruses.[236] The mean half-life of viral antibodies to BHV-1 in calves receiving maternal immunity was 21.2 days.[236] Potentially, calves receiving passive immunity to BHV-1 may have reduced response to BHV-1.[237] Calves seronegative to BHV-1 were given BHV-1 neutralizing antibody intramuscularly and subsequently given modified live vaccine BHV-1 intranassally. The passive BHV-1 immunity via BHV Ig reduced the efficacy of the modified live virus BHV-1.[237] The passively administered BHV-1 antibodies protected against viral shedding in viral challenged calves.[237]

Table 48-11 Recommendations for Use of Some Bovine Disease Vaccines

Characteristic	Pathogen								
	Anaplasma marginale[1]	*Anaplasma marginale*[2]	*Moraxella bovis*[3–11]	*Staphylococcus Species*[12]	*Bacillus anthracis*[13]	*Fusobacterium necrophorum*[14,15]	Papillomatous Digital Dermatitis[16,17]	Rabies Virus[18–20]	Bovine Papilloma Virus[21–25]
Passive antibodies protective			Yes	NA		NA	NA	Yes	Yes
Duration of colostral immunity (months)			4–6	NA		NA	NA	4–10	3
Type of vaccine	Modified live	Inactivated	Bacterin	Bacterin	Sterne nonencapsulated avirulent spore	Bacterin	Bacterin	Inactivated virus	Inactivated wart tissue extract
Immunizes in the presence of passive immunity	No		No	NA	7	NA	NA	No	—
Earliest recommended age for initial vaccination (months)	1 to 4[a]		1[a]-5	6	Any	6	12	3	Any[a]
Site of administration	IM	SC	IM[6,7] or SC	IM	SC	IM or SC	SC	IM	SC
Doses required for protection	1	2	1[b]-2[c]	2	1–2	2	3	1	2
Interval between priming and immunizing doses (weeks)	NA	3–4	3	2	2–3	3–4	3–4	NA	3–5
Interval from first dose to protection (days)	42	35	21[b]-42[c]	28	8	35			14–30
Duration of vaccinal immunity (months)	Lifelong	12	<9	5–6	12		<6	12	6
Recommended booster interval (months)	NA	12	12	5–6[d]	12[f]	12	4–6	12	6
Contraindications	Do not use in cattle over 2 years of age or in the last 4 months of pregnancy; do not administer tetracyclines	—	—	—	Avoid simultaneous administration of antimicrobials; do not use in sick animals	—	—	—	—
	Illness, anemia, abortion, death	Anaphylaxis	Anaphylaxis	Anaphylaxis	Mild illness, fever, decreased milk production	Anaphylaxis	Anaphylaxis	Anaphylaxis	Anaphylaxis
Side effects					production				
Withdrawal time (days before slaughter)	—	60	21, 60[6,7]	21[e]	42	21	28	21	21

?, Unknown; *IM*, intramuscular administration; *NA*, not applicable; *SC*, subcutaneous administration.

1 Anavac, BioLOGIC Laboratories, Davis, CA.

2	Anaplasmosis Vaccine, University Products LLC, Baton Rouge, LA.
3	I-Site, AgriLaboratories, St. Joseph, MO.
4	Maxi/Guard Pinkeye bacterin, Addison Biological Laboratory, Fayette, MO.
5	Ocu-Guard MB and Alpha-7 MB, Boehringer Ingelheim, St. Joseph, MO.
6	Piliguard Pinkeye-1 and Piliguard Pinkeye + 7, Schering-Plough Animal Health, Union, NJ.
7	Pinkeye Shield XT4, Novartis Animal Vaccines, Larchwood, IA.
8	20/20 Vision 7 with Spur and 20/20 with Spur, Intervet, Millsboro, DE.
9	TrustGard MB, Vedco, St. Joseph, MO.
10	Cattle Vac Pinkeye 4 and Piliguard Pinkeye-1, Durvet, Blue Springs, MO.
11	Pinkeye-3, Aspen, Kansas City, MO.
12	Lysigin, Boehringer Ingelheim Vetmedica, St. Joseph, MO.
13	Anthrax Spore Vaccine, Colorado Serum Co., Denver, CO.
14	Volar, Intervet, Millsboro DE 19966.
15	Fusogard, Novartis Animal Vaccines, Larchwood, IA.
16	*Serpens* species bacterin, Hygieia Biological Laboratories, Woodland, CA.
17	Trep Shield HW, Novartis Animal Vaccines, Larchwood, IA.
18	Defensor 3, Pfizer Animal Health, New York, NY.
19	Rabdomun, Schering-Plough Animal Health, Union, NJ.
20	Imrab 3 and Imrab Large Animal, Merial, Duluth, GA.
21	Papillomune, Biomune, Lenexa, KS.
22	Wart Shield, Novartis Animal Vacccine, Grand Laboratories, Larchwood, IA.
23	Wart vaccine, AgriLaboratories, St. Joseph, MO.
24	Wart vaccine, Colorado Serum Co., Denver, CO.
25	Wart Vac, Durvet, Blue Springs, MO.
a	Calves vaccinated before the age at which passive immunity no longer exists should be revaccinated on reaching that age.
b	Oil-adjuvant vaccines.
c	Aluminum hydroxide-adjuvant vaccines.
d	Give booster 3 to 6 weeks before calving.
e	No milk withdrawal required.
f	Booster can be given sooner in heavily contaminated areas.
g	May be given when exposure is imminent in endemic areas.

48.15 MODIFIED LIVE VIRUS PARENTERAL VACCINES

The modified live virus parenteral vaccines were the initial vaccines licensed for use in cattle for protection against BHV-1.[238] Vaccines are attenuated by multiple passages in cell culture and often retain their ability to replicate in a susceptible animal, possibly causing a viremia. Modified live virus parenteral vaccines are relatively

inexpensive, offer a convenient route of administration, and stimulate a rapid onset of immunity (i.e., within 3 days of administration).[239–241] In general, one dose given to a susceptible animal stimulates protective immunity, which varies in duration depending on the clinical form of the disease challenge. Calves receiving a combination modified live virus vaccine with BHV-1 were protected for at least 126 days after vaccination as measured by protection against infection[242] The modified live virus parenteral vaccines may cross the placenta and infect the fetus, causing abortion.[243] Almost all modified live virus BHV-1 parenteral vaccines are not approved for use in pregnant heifers or cows nor for nursing calves.[234] Recently two companies have received label claim approval for BHV-1 and BVDV modified live virus vaccine use in pregnant cows providing they vaccinated with that line of vaccines within 12 months of being vaccinated during pregnancy and to nursing calves provided their dams were vaccinated within 12 months.[234]

48.16 MODIFIED LIVE VIRUS INTRANASAL VACCINES

Modified live virus intranasal vaccines generally can be divided into two types, based on the attenuation process: (1) those modified by passage in a cell culture[244,245] and (2) those modified by treatment such that they become "temperature sensitive"[246] (i.e., they do not replicate at internal body temperature). Modified live virus intranasal vaccines stimulate protection in susceptible animals with only one dose, in contrast to the chemically altered modified live virus parenteral vaccines. The label directions for selected, but not all, modified live virus intranasal vaccines may indicate that they can be safely used in pregnant cattle.[234] These vaccines induce a rapid onset of protection (within 3 days of administration), possibly through IFN in the nasal secretions.[244] One benefit of modified live virus intranasal vaccines is that they stimulate immunity at the upper respiratory tract, the portal of entry of the virus. Another benefit is their potential to immunize calves that are already seropositive because of maternal (humoral) antibodies passively transferred through the colostrum.[247] Animals vaccinated with modified live virus intranasal vaccines may transiently shed virus in the nasal secretions and therefore might infect susceptible contact animals.[248]

48.17 CHEMICALLY ALTERED LIVE VIRUS VACCINES

The chemically altered BHV-1 vaccine strain was modified by nitrous acid treatment, which caused changes in the viral genome that resulted in a strain that is temperature sensitive, meaning that it has limited replication at internal body temperature.[249] Presumably, because of the limited viral replication, the vaccine requires two doses to stimulate immunity. Because it is temperature sensitive, the vaccine can be used in pregnant cattle.[234,249,250] In one study, heifers received two doses of the vaccine and were challenged with BHV-1 7 months later (at 6 months' gestation). These heifers showed a significant reduction in the number of abortions and stillbirths compared with controls.[250]

48.18 INACTIVATED VIRAL VACCINES

Inactivated viral vaccines are prepared by growing virus in cell cultures and then inactivating them with chemicals. An adjuvant is added to the inactivated strain to help stimulate an immune response. Inactivated BHV-1 vaccines require two doses (14 to 28 days apart) when used for the initial vaccination of susceptible cattle. Historically it has been thought that inactivated vaccines against viruses did not induce as long a DOI as the modified live virus vaccines, nor did they confer protection against mucosal infections. Controlled studies should be performed to determine the DOI induced by inactivated BHV-1 vaccines and modified live virus vaccines, both

for respiratory disease and for fetal infections. A disadvantage of inactivated vaccines is that the onset of protection may not be as rapid as with modified live virus parenteral or modified live virus intranasal vaccines. An advantage of the inactivated vaccines is that they can be used in pregnant cows and nursing calves.

48.18.1 Use of Vaccines to Prevent and Control Bovine Herpesvirus Type 1 Diseases

Many vaccines are available for preventing and controlling the different forms of BHV-1 disease, and each vaccine has certain characteristics that should be considered when designing a vaccination program. Each vaccine also has both benefits and limitations. Probably more important is the management of the cattle for which the vaccines are used.

48.19 PREGNANT ANIMALS OR ANIMALS NEARING BREEDING SEASON

The modified live virus parenteral vaccines may infect the fetus if pregnant susceptible heifers or cows are vaccinated. Abortions have been reported subsequent to vaccination with modified live virus parenteral vaccines.[243] The modified live virus vaccine virus may also result in corpus luteum infection or disease.[251,252] Experimental studies have indicated a reduced conception rate in susceptible cattle that received a modified live virus parenteral vaccine 3 to 4 days before or 14 days after breeding.[251,252] It has been reported that pregnant cattle raised in contact with calves recently vaccinated with modified live virus parenteral vaccines had a greater incidence of BHV-1 abortion than those that did not have contact with vaccinates.[253] Consequently, the labels of modified live virus parenteral vaccines have usually stated that the vaccine should not be used in calves nursing pregnant cows. Recent studies have shown that calves given a modified live virus parenteral vaccine did not shed virus in their nasal secretions, nor did contact animals become infected with the vaccine virus.[254–256] One company received label claim of prior vaccination for the modified live virus vaccine containing BHV-1 and BVDV for pregnant cows, provided the cows had received the same line of vaccines with the modified live virus BHV-1 and BVDV within 12 months of being vaccinated during pregnancy.[234] Likewise, that vaccine could be used in nursing calves if the cows had been previously vaccinated with that line of vaccines within 12 months of prior vaccination.[234] Another concern is that the modified live vaccine virus may recrudesce, with resulting shedding of virus in cattle either stressed or receiving corticosteroids.[257] Realistically, concern about transmission of BHV-1 to animals in contact with those receiving modified live virus parenteral vaccines would be negligible if the contact animals were properly immunized and immune to BHV-1.

Until the vaccine labels on most modified live virus parenteral vaccines are changed, modified live virus intranasal vaccines or the inactivated or chemically altered live virus vaccines usually are recommended for pregnant cattle or those near breeding. The one exception is the approved vaccine cited previously. Vaccine recommendations should be weighed using the benefits of vaccination as a guide and especially with the realization that properly vaccinated cattle are better protected when exposed to either field (virulent) or vaccine strains shed by vaccinated animals. 1601 1602

48.20 RAPID ONSET OF IMMUNITY

Cattle that are susceptible and likely to be exposed to BHV-1 should receive either a modified live virus parenteral vaccine or a modified live virus intranasal vaccine because both types induce immunity within 3 days of the initial dose. Rapid onset of immunity is desirable in such situations as stocker calf and feedlot operations, in which calves are transported long distances to pastures or feedlots, which stresses the animals and makes them more

susceptible to infection. Such calves also are exposed to infection with BHV-1 from contact cattle in the markets. The drawback to inactivated vaccines is that two doses are required to obtain good immunity.

48.21 DURATION OF IMMUNITY

Controlled studies on the DOI are limited. A degree of protection against challenge existed at 6 to 9 months after vaccination with a modified live virus intranasal vaccine or an inactivated vaccine.[258,259] A parenteral modified live virus BHV-1 vaccine provided protection up to 126 days after vaccination.[242] A second parental modified live virus BHV-1 vaccine provided protection against BHV-1—induced abortions for 12 months after vaccination.[234] Challenge studies for licensure usually are performed on calves within days of vaccination, at the time of peak immunity. Also, the challenge may be for only one form of disease, usually the respiratory type. Such challenges may detect only protection against a severe form of the respiratory disease. BHV-1 manifests itself in other forms, such as abortions, neonatal disease, genital disease (male and female), and conjunctivitis. Yet little or no data are available regarding the efficacy of vaccines against these other forms of disease. For example, in one case the genital form of BHV-1 disease (infectious pustular vulvovaginitis) occurred in heifers that had received a modified live virus parenteral vaccine 5 months earlier.[260] Given the lack of DOI studies for all BHV-1 vaccines individually and the cost of vaccines, breeding animals usually are vaccinated at least annually. In some feedyard situations the animals may be revaccinated during the feeding period. It is industry practice that feedlot cattle receive a monovalent BHV-1 modified live virus parenteral vaccine at reimplant time at approximately 100 days after arrival. There have been field reports of BHV-1 respiratory disease (IBR) in feedlot cattle a few months after entry or processing, at which time they received modified live virus vaccines containing BHV-1.

48.22 VACCINATION OF CALVES WITH MATERNAL ANTIBODY

The possibility exists that maternal BHV-1 antibodies acquired by the calf through ingestion and absorption of colostrum may interfere with vaccination. The level of these serum BHV-1 antibodies in the calf depend on the amount in the colostrum, the amount absorbed, and the half-life of the particular antibody; for BHV-1, it is 21.2 days.[236] Some calves receive no BHV-1 antibodies through the colostrum, or they may lose them within 1 month. Some calves, however, may have serum BHV-1 antibodies for up to 6 months after birth.[257]

Vaccination recommendations for neonatal calves include use of multiple doses of a modified live virus parenteral, an inactivated, or a chemically altered live virus vaccine or administration of a modified live virus intranasal vaccine. The maternal antibodies may block the parenterally administered modified live virus or inactivated vaccine. However, the modified live virus intranasal vaccine may induce BHV-1 antibody immunity.[247] Calves often are revaccinated at 6 to 8 months of age regardless of their prior vaccination history.

48.23 ADVANCES IN VACCINES

Molecular techniques of biotechnology have been applied to the study of vaccines and the response to vaccination (vaccinology). These advances are especially noted for herpesviruses, including BHV-1. In addition to conventional vaccines manufactured via propagation of modified live virus and inactivated BHV-1 strains, current and future technologies offer opportunities for other vaccines.[261,262] These include subunit vaccines with a portion of the virus, deletion mutants with specific viral genomic fragments deleted, live vectored strains, DNA vaccines using plasmids, and plant-based vaccines. Deletion mutant BHV-1 vaccines as marker vaccines with selected glycoprotein genes deleted along with diagnostic tests for the deleted genes permit identification of

vaccinates under control programs.[261] Recently, needle-free delivery of vaccines has been developed and implemented.[261] By high pressure gas delivery, vaccines may penetrate the skin and be administered intradermally, subcutaneously, or intramuscularly.[261] Such delivery is designed to minimize damage resulting from intramuscular injections. Two studies compared needle-free intramuscular injection of multivalent modified live virus vaccine containing BHV-1 with conventional subcutaneous injection via syringe in dairy calves and feedlot cattle. In both studies, antibody titers to BHV-1 were higher at day 21 postvaccination than after conventional needle injection.[263,264]

48.24 Vaccination Programs

The best possible vaccine provides protective immunity in the host against infection (viral replication) when challenged; protects the animal against all forms of disease, including multiple organ and systemic forms; and provides lifelong mucosal and systemic immunity. Ideally the vaccine recommendations would incorporate the results of field trials that are carefully designed to show the efficacy of the vaccine against a pathogen. Unfortunately little information is available, as can be seen by a review of the literature, for evaluating the field efficacy of the respiratory disease vaccines.[265] The summary of results was mixed for BHV-1 vaccines and for other respiratory viral and bacterial vaccines.

Veterinarians therefore must make recommendations based on (1) experimental studies of vaccination followed by challenge under controlled laboratory conditions apart from the field conditions of normal cattle management and (2) clinical experience with vaccines. Data from challenge studies often are under the control of universities, the federal government, or a biologic manufacturer and may not be published. Government licensure studies require efficacy and safety evaluations, but these studies may not be available in scientific publications for review by those making recommendations. For these reasons the veterinarian may not have access to all the data needed to make a good decision on vaccines.

The veterinarian's dilemma is confounded by other factors. First, licensure may be granted for vaccination efficacy that demonstrated protection against one form of disease, such as respiratory type. However, the virus may be just as important a pathogen of other organs, such as the developing fetus, as is the case with BHV-1. Second, information about the DOI induced by each commercially available BHV-1 viral vaccine is not available or is limited. Licensure studies may use challenge of vaccinated animals within 2 to 4 weeks of initial vaccination, yet cattle may be in feedyards (months) or breeding herds (years) after vaccination. Third, vaccines may induce a strong parenteral immunity, yet the surface mucosal defenses at the portal of entry may still be susceptible to infection even in presumably well-vaccinated animals. Thus it is entirely possible that natural infections could still occur in these vaccinated animals. Ecologically this point is reinforced, because viruses for which there are good immunization products are still circulating in cattle populations after years of vaccination.

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The veterinarian therefore must weigh both the benefits provided by vaccines and their limitations. This probably is best done by focusing on the real, economic effects of certain disease manifestations, including morbidity, mortality, and treatment and prevention costs. Historically this approach has been applied to two important forms of BHV-1 disease: the respiratory form, singularly or in combination with pneumonic bacterial diseases, and the fetal disease (abortions). As a result, most vaccine regimens focus on preventing respiratory disease in both young or adult animals and on protecting the pregnant breeding herd of cows and heifers against abortions. Another fact to be considered is that many vaccines may have multiple viral or bacterial components (or both), which may require multiple doses for an immunogen mixed with one that requires only one dose.

48.25 GUIDELINES

48.25.1 Calves

Calves may be vaccinated at weaning or 30 days before weaning. Calves vaccinated before 6 months of age should be revaccinated because the earlier vaccination may have been blocked by maternal antibodies. The modified live virus parenteral and intranasal vaccines require only one dose in susceptible calves, whereas the chemically altered live virus or inactivated vaccines require two doses. Although the labels for most modified live virus parenteral vaccines state that the vaccine should not be used if the calf is nursing a pregnant cow, the likelihood of infection of the pregnant cow may be minimal, especially if she is already immune. Yet as described earlier, modified live virus parenteral vaccines are available for use in pregnant cows and nursing calves.

48.25.2 Breeding Cows and Heifers

Yearling heifers (12 to 14 months of age) should be vaccinated at least 1 month before breeding. Any of the vaccines may be used, but if two doses are required, the second dose should be given at least 1 month before breeding.

Pregnant cows may be vaccinated with a vaccine that has a label description warranting such use; these include modified live virus intranasal vaccines, chemically altered live virus vaccines, inactivated vaccines, and approved modified live virus parenteral vaccines. Generally one dose is used, primarily because of management considerations. Administering booster doses of the BHV-1 vaccines may have two conflicting outcomes as a result of booster dose stimulation of an increase in colostral BHV-1 antibodies, which are transferred to the newborn calf in the colostrums: (1) it may be beneficial to the calf to have increased BHV-1 serum antibodies for protection against BHV-1 disease, or (2) the calf may have longer duration of BHV-1 antibodies, which may block BHV-1 immunization. There are no published multiyear DOI studies in vaccinated cattle challenged with virulent BHV-1. Because of the relatively low cost of BHV-1 vaccines and the need to vaccinate against other pathogens, many breeding cows are given a BHV-1 vaccine annually.

48.25.3 Stocker and Feeder Cattle

Cattle to be shipped to forage pasture after weaning (wheat pasture or native grass) or to feedyards should be vaccinated 2 to 3 weeks before shipment. However, management practices and marketing may permit vaccination only at initial collection point, market site, or stocker or feedlot delivery. All the major types of BHV-1 vaccines may be used, but those that require only one dose have two advantages: onset of immunity is rapid, and less handling is required (one dose versus two).

Cattle presented for purchase immediately before shipment, with no known vaccination history, pose a challenge. Presumably healthy cattle may be candidates for the one-dose modified live virus parenteral or modified live virus intranasal vaccines because these calves may benefit from rapid immunity. Cattle already infected with BHV-1 may not be protected by vaccination.

Cattle entering the feedyard usually receive either the modified live virus parenteral or modified live virus intranasal vaccine, particularly for the rapid onset of immunity. Cattle sometimes are revaccinated during the feeding period to ensure protection against BHV-1 disease later in the feedyard.

48.25.4 Breeding Services

Veterinarians should consult the breeding bull center for vaccination requirements of bulls, especially relating to export shipment and collection for artificial insemination. Modified live virus intranasal vaccines have been used in artificial insemination bulls because these vaccines are less likely to cause latent infections than modified live virus parenteral vaccines.[266,267] As mentioned previously, modified live virus parenteral vaccines cause latent infections that may recrudesce with stress or the administration of corticosteroids, which means the virus would be present in the semen.[257,267]

48.26 BOVINE VIRUS DIARRHEA VIRUS VACCINES

Victor S. Cortese

Our knowledge of the different vaccines' ability to protect against infection with BVDV is increasing rapidly. Currently, three kinds of BVDV vaccines are available: modified live virus vaccines, temperature-sensitive vaccines (available only in Europe), and inactivated virus vaccines (Table 48-12). Modified live virus BVDV vaccines have demonstrated advantages over the newer inactivated vaccines. Most of these advantages are common to all modified live virus vaccines[268,269]: (1) modified live virus vaccines are less expensive; (2) postvaccination anaphylactic reactions occur less often than after administration of some inactivated vaccines; (3) immunity is achieved more rapidly after administration of a single dose (within 7 to 10 days); (4) modified live virus vaccines produce much higher levels of serum neutralizing antibodies[270]; (5) immunity lasts longer[271–273]; and (6) modified live virus vaccines are effective against a broader spectrum of viral strains.[270]

On the other hand, modified live BVDV vaccines have certain disadvantages compared with inactivated BVDV vaccines; these disadvantages are that (1) some modified live virus vaccines can produce mild immunosuppression for brief periods after administration[272]; (2) some have been associated with what is usually a rather low incidence of a highly fatal disease syndrome, postvaccinal mucosal disease (MD)[273,274] (see later); and (3) until recently, modified live virus vaccines were not ordinarily recommended for routine use in pregnant cattle.

Studies have shown that the duration of cross-neutralizing antibodies stimulated by inactivated BVDV vaccines depends on the antigenic similarity between the vaccine strain and the wild type virus to which the cow is exposed.[275,276] If there are few common proteins, the ability to neutralize can be as short as 4 months; if there are many common antigenic sites, neutralization may last a year. Modified live BVDV vaccines stimulate cross-neutralizing antibodies that can still be detected 18 months after vaccination.[270] This longer duration was further demonstrated when a modified live BVDV vaccine received a USDA label describing a 1-year duration of immunity against the birth of both type 1 and type 2 persistently infected calves.[277]

Recent studies have demonstrated the ability of both modified live[278,279] and inactivated type 1 vaccines[280] to provide protection against type 2 BVDV strains, although the protection afforded by the modified live virus vaccine was more complete. USDA/APHIS has established a licensing protocol for BVDV vaccines to obtain a type 2 BVDV protection claim. Most of the vaccines licensed against both BVDV type 1 and type 2 contain BVDV type 1 and type 2 isolates (see Table 48-10). The question of current vaccines'ability to cross-protect against BVDV type 1b strains has been raised,[281] and further studies are needed to determine the level of protection afforded by current vaccine strains.

Table 48-12 Currently Licensed* Vaccines for Bovine Virus Diarrhea Virus

Product	Company	Type of Vaccine	BVDV†	BVD Type 1 Strain	BVD Type 2 Strain
Arsenal	Novartis	MLV	M	1b—GL760—nCP	
Bovi-Shield GOLD FP	Pfizer	MLV	M	1a—NADL—CP	2—53637—CP
Breed-Back FP	Boehringer	MLV	M	1a—Singer—CP	2—296—CP
CattleMaster	Pfizer	Hybrid (TS-IBR & PI-3, Killed BVD)	K	1a—5960—CP 1a—6309—nCP	
CattleMaster GOLD	Pfizer	Hybrid (TS-IBR & PI-3, Killed BVD)	K	1a—5960—CP	2—53637—CP
Elite	Boehringer	Killed	K	1a—Singer—CP	
Express	Boehringer	MLV	M	1a—Singer—CP	2—296—CP
Herdvac	Pfizer	MLV	M	1a—NADL—CP	
Jencine	Schering	MLV	M	1b—WRL—nCP	
Master Guard	Intervet/AgriLabs	Hybrid (Killed IBR, BVD)	K	1a—C24V—CP	2—125C—CP
PregGuard GOLD FP 10	Pfizer	MLV	M	1a—NADL—CP	2—53637—CP
Prism	Fort Dodge	Hybrid (Killed BVD)	K	1a—NADL—CP	2—5912—CP
Pyramid 4 Pyramid 8 Pyramid 9	Fort Dodge	MLV	M	1a—Singer—CP	
Pyramid 5, Pyramid 10	Fort Dodge	MLV	M	1a—Singer—CP	2—5912—CP
Reliant	Merial	Hybrid (Killed BRSV)	M	1a—NADL—CP	
Reliant Plus	Merial	Hybrid (Killed BRSV)	M*	1a—Singer—CP	
Respishield	Merial	Killed	K	1a—Singer—CP	
Resvac 4/ Somubac	Pfizer	MLV	M	1a—NADL—CP	
Surround	Novartis	Killed	K	1a—Singer—CP 1b—NY—NCP	
Titanium	AgriLabs	MLV	M	1a—C24V—CP	2—296—CP
Triangle+Type II BVD	Fort Dodge	Killed	K	1a—Singer—CP	2—5912—CP

Vira Shield 6	Novartis	Killed	K	1a—KY22—CP 1b—????—nCP	2—TN131—nCP
Vista	Intervet	MLV	M	1a—Singer—CP	2a—125A—CP

BVD, Bovine virus diarrhea; *BVDV*, bovine virus diarrhea virus; *CP*, cytopathic; *MLV*, modified live virus; *nCP*, non-cytopathic; *PI-3*, parainfluenza type 3; *TS-IBR*, cytopathic; USDA, U.S. Department of Agriculture.

* Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

† M, Modified live BVDV component(s); *K*, killed BVDV component(s).

48.27 VACCINATION AND MUCOSAL DISEASE

MD is seen when an animal that is persistently infected is exposed to another closely related cytopathic strain of BVDV. Also, theoretically a noncytopathic BVDV strain can mutate spontaneously into a cytopathic strain, resulting in MD without any subsequent exposure. High stress and immunodepression may be involved in this mutation.[282,283]

A major concern with the modified live virus vaccines is whether they can cause MD.[275,284,285] For MD to occur, the cytopathic strain in the modified live virus vaccine must be closely related to the noncytopathic strain in the persistently infected animal. With the degree of attenuation of modified live virus vaccines today, an animal must be nutritionally deficient or severely stressed, or both, to face an increased likelihood of developing MD from the vaccine. This suggests that a specific set of circumstances is required and that MD caused by vaccination, when it occurs, is rare.

48.28 BOVINE VIRUS DIARRHEA VIRUS VACCINES AND REPRODUCTIVE CONTROL

Control of BVDV centers on prevention of persistent infection and elimination of persistently infected cattle; this means that identifying and removing persistently infected animals and continued vaccination to prevent persistent infection are necessary for effective control. Persistent infections occur through in utero infection of the fetus (up to approximately 125 days' gestation) with a noncytopathic strain of BVDV.[270,282] The mechanism of transplacental transfer of BVDV is unknown; however, small amounts of virus in the dam's bloodstream appear to be sufficient to produce these immunotolerant cattle. Protection of the dam may or may not correlate with protection of the fetus from subsequent persistent infection if viremia of the dam occurs. To break the vicious cycle of in utero infection and persistent infection, it is essential that vaccination provide fetal protection.

Several studies have been performed to assess the ability of vaccines to protect the fetus against either natural or artificial challenge. The results of these studies showed that most inactivated vaccines failed to provide much fetal protection,[275,286–291] except for one experimental vaccine, which is reported to give a high level of fetal protection. With the experimental vaccine, the lack of virus isolation from offspring of vaccinated animals indicated good protection.[292] However, the challenge of controls resulted in only approximately a 50% rate of persistent infection. Recently, the new inactivated vaccine has demonstrated a high level of fetal protection and was given the appropriate label by the USDA (see Table 48-9). Other published reports demonstrated that modified live virus BVDV vaccines were more effective at protecting the fetus[293–295] and that inclusion of a type 2 vaccine broadened the strains against which the vaccine protects.[296] To date, vaccines licensed in the United States have not been required to provide fetal protection. However, label indications are now being granted by the

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USDA to vaccines that have demonstrated the ability to prevent the development of persistently infected calves. Several vaccines have achieved this label (see Table 48-9).

48.28.1 Bovine Virus Diarrhea Virus Vaccination Programs

Because BVDV infections can cause severe death loss and immunosuppression, all herds of cattle should be vaccinated against BVDV. Although it was once thought that BVDV vaccines would not immunize calves that were passively immune to BVDV,[297,298] recent studies have shown that immunization can occur with certain inactivated vaccines[299] and with modified live virus vaccines (when the passive antibody titer against BVDV is 1:64 or below).[278,300] When required, BVDV vaccines can be administered to young calves, with the possibility of gaining some degree of protection. In most calves the maternal antibodies against BVDV drop below the 1:64 level by 5 to 6 months of age. If an early BVDV problem does not exist, waiting to administer the first BVDV vaccine until at least 6 months of age increases the number of animals that respond to vaccination.

Among cows given modified live BVDV vaccines in the last trimester of pregnancy, 86% of the calves from seronegative cows[301] and some calves (0%[301] to 52%[302]) from seropositive dams were actively immune at birth. In addition, the calves' level of passive immunity to BVDV was enhanced, in that seronegative cows seroconverted, and serum antibody titers were boostered in 52% of the seropositive cows. The rate of occurrence of BVD in neonatal calves was reduced.[303] Administration of a modified live BVDV vaccine to seronegative cows after day 118 of gestation did not result in adverse effects.[303,304] However, vaccination with a modified live noncytopathic virus vaccine before day 118 resulted in fetal resorption, abortion, congenital defects, and the birth of undersized, weak, persistently infected calves.[305] Several authors have recommended vaccination of cows with a modified live BVDV vaccine during the last trimester of pregnancy.[283] Two modified live BVDV vaccines are now labeled for use in pregnant animals. However, the label directions must be adhered to in order to ensure the safety of these vaccination schedules.

It is important to consider the epidemiologic, nonresponse rate to any vaccine when designing a BVDV vaccination program. Therefore even though modified live BVDV vaccines do not require a booster dose, a second dose may be advised to stimulate protection in animals that did not respond to the initial vaccination. BVDV vaccination programs should include the following features:

1. A virus isolation and cull program should be instituted, along with a vaccination program that includes administration of at least one dose of a modified live BVDV vaccine to all replacement animals.
2. Vaccination with killed vaccines should be increased to two or three times a year, *or* a modified live BVDV vaccine should be given to open cows 3 weeks before breeding or turning in the bull.
3. The vaccines used should have been proved to stimulate protection against BVDV type 1 and type 2.

48.29 BOVINE RESPIRATORY SYNCYTIAL VIRUS VACCINES

John A. Ellis

BRSV is a prevalent paramyxovirus that can cause disease in cattle of all ages but that primarily affects calves in recurrent seasonal outbreaks.[306–308] Clinical disease is characterized by pyrexia, coughing, and tachypnea, which

can progress rapidly to severe expiratory dyspnea.[307,309] BRSV is also considered one of the viral agents that predisposes animals to secondary bacterial infections in the bovine respiratory disease (BRD) complex; however, secondary infections often are absent in fatal BRSV-associated respiratory disease.[310,311] As well, subclinical BRSV infection or mild respiratory disease resulting from BRSV infection in dairy cattle may have a negative impact on milk production.[312]

48.30 PARENTERAL VACCINES

Modified live virus and inactivated parenteral BRSV vaccines have been commercially available since the 1980s. Most of these vaccines are formulated in combination with other viral respiratory pathogens, including PI-3, BHV-1, and BVDV.[168] The efficacy of commercial modified live virus nonadjuvanted and adjuvanted combination BRSV vaccines in protecting calves from severe clinical disease subsequent to experimental infection with a virulent field isolate has been demonstrated.[313] Most vaccinated calves shed virus, but the peak virus titer was suppressed compared with unvaccinated controls. Viral clearance was coincident with the simultaneous appearance of mucosal antibody, cytotoxic T cells in the lungs, and anamnestic or primary serum antibody responses. In contrast, virus clearance in unvaccinated calves was coincident with the appearance of BRSV-specific cytotoxic cells before mucosal antibody was detected. Although administration of modified live virus BRSV vaccines by the intramuscular route to passively immune calves reportedly did not elicit mucosal memory IgA or serum antibody responses, or even prime for such responses,[308] T cell responses have been demonstrated after parenteral vaccination in passively immune calves.[314] Whether these responses correlate to a protective cell-mediated memory response when maternal antibodies decline has not been determined.

More recent investigations using the same challenge model in BRSV-seronegative calves have documented a similar efficacy of at least two combination inactivated vaccines containing BRSV formulated with different adjuvants.[315,316] Clinical protection was associated with serum concentrations of BRSV-specific IgG as determined by ELISA[315,316] and in one case[315] the presence of IFN-γ—secreting BRSV-specific $CD4^+$ T lymphocytes in the blood of vaccinated calves. There are conflicting data concerning the ability of commercial inactivated BRSV vaccines to override maternal antibodies and stimulate protective responses after parenteral immunization, which may be related to the vaccine formulation and adjuvant.[317,318]

Most experimental studies concerning the efficacy of commercial BRSV vaccines are consistent with previous field trials, demonstrating the safety and efficacy of parenterally administered vaccines.[319,320] In addition, one study suggested the usefulness of combination vaccines in reducing the impact of subclinical BRSV infections.[313]

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Protection against BRSV infection and disease is associated, at least in part, with an IgA response[306–308]; however, serum IgG acquired from either passive or active immunization can significantly reduce the severity of clinical respiratory disease that results from BRSV infection. Several studies have reported that the incidence and severity of disease in calves were inversely related to the maternal antibody titers.[308,321,322] In the case of herd immunity, passive antibodies were detectable in 50% of the calves for 3 months after birth and were present in some calves until 7 months of age.[323] Therefore administration of BRSV vaccines to cows in late gestation to booster colostral antibody titers is a rational strategy to deal with BRSV-induced respiratory disease in young calves (1 to 3 months of age) in problem herds, without having to be concerned about the immunizing potential of particular parenteral vaccines in young seropositive calves.

48.31 INTRANASAL VACCINES

Because BRSV is an endemic infection in most cow herds, most young calves will have BRSV-specific maternal antibodies, unless there is failure of passive transfer. As well, given the endemic nature of BRSV, it is likely that many calves are exposed to BRSV early in life and will contract BRSV-associated respiratory disease if their passive protection is poor or has waned. Considering the mixed results, to date, with parenteral administration of BRSV vaccines to young seropositive calves, the availability of a safe, effective intranasal modified live virus BRSV vaccine may represent the most effective means of immunizing young calves. In fact, it was demonstrated in the late 1980s that intranasal inoculation of tissue-culture—attenuated BRSV to passively immune calves primed for mucosal memory and an anamnestic IgA response subsequent to challenge.[324] More recent similar studies with culture-attenuated BRSV confirmed this phenomenon.[325] In addition, two recent studies suggest that currently available parenteral combination modified live virus vaccines can be efficacious if administered intranasally.[326,327] Single intranasal administration of these vaccines to young calves primed for protective responses to subsequent experimental challenge. In one of these studies,[326] results demonstrated that effective priming was achieved in BRSV-seropositive calves, confirming the previous observations with experimental single component BRSV vaccines.[322,323] Recently an intranasal BRSV vaccine was licensed in Europe and the United Kingdom.

48.32 ADVERSE REACTIONS TO BOVINE RESPIRATORY SYNCYTIAL VIRUS VACCINES

The major factor hampering the development of a vaccine for human respiratory syncytial virus (HRSV) is the dramatic HRSV vaccine failure in the 1960s, in which vaccination with a formalin-activated (FI), alum-adjuvanted HRSV predisposed children to more severe disease after subsequent HRSV infection.[328] Although this same disease-enhancing phenomenon has been demonstrated in some studies of experimental FI-BRSV vaccines in cattle,[329,330] it is unlikely that modern manufacturing practices would use formalin inactivation for BRSV or other viral vaccines. Nevertheless, there are documented cases of apparent enhancement of BRSV-associated respiratory disease in cattle that received either inactivated or modified live virus vaccine in the field, indicating that some commercial vaccine formulations may stimulate potentially pathogenic immune responses in some cattle.[329,330] The immunologic mechanisms responsible for vaccine-associated disease enhancement are not completely understood. The current hypothesis is that some BRSV vaccines, notably FI-BRSV, mainly prime Th2-like responses involving eosinophil influx into the lung and production of high concentrations of BRSV-specific IgE.[329,330] Several studies have consistently documented a disparity in the type of antibody responses induced in cattle by modified live virus and inactivated BRSV vaccines.[330–335] Parenterally administered modified live virus BRSV vaccines generally stimulate moderate to high concentrations of VN antibody in the serum, whereas inactivated vaccines stimulate high concentrations of partially neutralizing or nonneutralizing antibody. The data are conflicting concerning the prophylactic or disease-enhancing properties of these different types of vaccine-induced antibody responses.[329,333] Alternatively, as was suggested in the case of disease enhancement after parenteral administration of a combination modified live virus BRSV vaccine,[331] the timing between vaccination and infection could be a critical factor. This may be related to the stage of the immune response—specifically, a predominance of BRSV-specific IgM at the time of infection may somehow predispose to enhanced disease.

Currently there is little information about the duration of the protective response after vaccination; however, cattle can be experimentally reinfected by 35 days after initial infection with virulent BRSV even in the presence of

circulating antibody.[331] Nevertheless, as the epidemiology of BRSV-associated respiratory disease in the field indicates, disease caused by reinfection usually is less severe than that after the initial infection.[306–308] These observations indicate that most cattle do not develop an allergic (IgE) response to BRSV from naturally acquired infections, or to most BRSV vaccines, in the vast majority of cases.

48.33 PARAINFLUENZA TYPE 3 VIRUS VACCINES

John A. Ellis

Parainfluenza virus type 3 (PI-3V) is a ubiquitous paramyxovirus in cattle populations worldwide.[336,337] In uncomplicated experimental PI-3V infections, clinical signs of coughing, tachypnea, and fever have been observed from 4 to 12 days after infection.[336] Although respiratory disease has been experimentally reproduced in calves infected with PI-3V, seroconversion has been demonstrated after outbreaks of respiratory disease,[338] and PI-3V has been identified in the lesions of BRD complex at postmortem examination, the importance of this agent in the BRD complex remains controversial.[336] Generally PI-3V is viewed as a potentiating agent in mixed infections, predisposing the animal to bacterial pneumonia by altering bacterial clearance in the upper and lower airways and by infecting both respiratory epithelia and alveolar macrophages.[336]

Currently five types of PI-3V vaccines are available commercially: (1) modified live virus intramuscular vaccines; (2) modified live virus, temperature-sensitive, intramuscular vaccines; (3) modified live virus intranasal vaccines; (4) modified live virus, temperature-sensitive, intranasal vaccines; and (5) inactivated virus vaccines. All PI-3V vaccines available in North America are combined at least with a BHV-1 vaccine. Currently, a single-antigen, modified live virus PI-3V intranasal vaccine is available in Europe. The efficacy of this formulation recently was demonstrated in a severe challenge model.[339]

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Opinions are divided as to the relative importance of mucosal versus systemic immune responses in achieving protection from PI-3V—associated respiratory disease and, by extension, the comparative efficacy of intranasal and intramuscular vaccines. Some comparative studies[339,340] reported that intranasal vaccination resulted in better protection against experimental challenge; others[341] were unable to demonstrate any advantage to the use of one vaccine or route of administration over the other. A notable exception, however, was young calves with maternal antibodies, in which intranasal administration was thought to produce a more effective immune response. Passive antibodies may persist in calves until 8 months of age and may interfere with active immunization.[342] Consequently, calves vaccinated parenterally before 6 months of age should be revaccinated after reaching 8 or 9 months of age.[342]

Although not experimentally documented, as in the case of BRSV, it is likely that, given the similar biology of PI-3V infection, a mucosal (IgA) response is necessary to prevent PI-3V infection but that passively (maternal) or actively acquired serum IgG is likely to mediate significant sparing of clinical disease subsequent to infection. The cell-mediated (cytotoxic T cell) response in the clearance of PI-3V is a poorly documented but probably important effector mechanism stimulated by modified live virus vaccines, as is the case with BRSV.

There is debate about the overall utility and economic benefit of using PI-3V (and BRSV) vaccines in the field.[343,344] Much of the uncertainty undoubtedly is related to the difficulties involved in determining the relative importance of a particular agent in a multifactorial disease process such as BRD complex. Few studies[344,345] address the economic impact of subclinical paramyxovirus infections in cattle. No recent studies (in the last 5

years) directly address the economic impact of inclusion of PI-3V in combination vaccines. One large study[346] conducted under commercial feedlot conditions demonstrated an economic benefit to using a four-way combination modified live virus vaccine containing PI-3V together with BHV-1, BRSV, and BVDV versus a single component BHV-1 vaccine; however, it was not possible to determine which antigen(s) were responsible for disease sparing.

48.34 *MANNHEIMIA (PASTEURELLA) HAEMOLYTICA, PASTEURELLA MULTOCIDA*, AND *HISTOPHILUS SOMNI (HAEMOPHILUS SOMNUS)*

Anthony W. Confer

48.35 *MANNHEIMIA HAEMOLYTICA* VACCINES

M. haemolytica serotype 1 is the main species of bacteria responsible for the clinical signs and lesions of severe bovine fibrinous pleuropneumonia (shipping fever).[347,348] The bacterium is a gram-negative commensal in the bovine nasopharynx, and after stress or viral infections the bacterium proliferates and is inhaled into the lungs where it stimulates a series of pathologic events leading to acute, severe fibrinopurulent inflammation and necrosis. The bacterium was renamed *Mannheimia haemolytica* because of substantial genomic differences between it and other members of the *Pasteurella* genus; however, it is still often referred to in commercial vaccines by its previous name, *Pasteurella haemolytica*.[349] In this discussion the organism's current and correct scientific name, *M. haemolytica*, will be used.

48.35.1 Important *Mannheimia haemolytica* Immunogens

M. haemolytica has numerous potential immunogens. Those with the greatest potential for stimulating immunity include capsular polysaccharide, lipopolysaccharide (LPS), outer membrane proteins (OMPs), iron-regulated OMPs, a secreted leukotoxin (LKT), a serotype-specific antigen, and several other secreted enzymes including neuraminidase, a sialoglycoprotease, and a bovine IgG1 protease.[350,351] The central dogma of *M. haemolytica* vaccination is that immunity to the organism requires stimulation of antibodies that neutralize LKT and antibodies that bind to surface antigens allowing for complement-mediated killing and/or phagocytosis of the bacterium.[352] There is no agreement as to what are the most important surface antigens; OMPs and iron-regulated OMPs are the major candidates based on many in vitro and in vivo studies.[353–357] Capsular polysaccharide is theoretically an important surface antigen because it is the first surface molecule encountered by cellular and humoral components of the immune system, and its presence enhances *M. haemolytica* resistance to phagocytosis and complement-mediated killing.[358] However, antibody responses to *M. haemolytica* capsular polysaccharide do not always correlate with resistance, and vaccination with purified capsular polysaccharide failed to protect against challenge.[359,360] LPS is also a surface antigen; however, antibodies to *M. haemolytica* LPS failed to correlate with resistance to experimental challenge, and passive antibodies to *M. haemolytica* LPS were not protective in experimentally challenged calves.[361,362]

48.35.2 Commercial Vaccines

When a vaccination program for prevention of BRD is designed, four questions should be addressed:

- Should *M. haemolytica* vaccine be used?

- What type of *M. haemolytica* vaccine should be used?
- How many doses of *M. haemolytica* vaccine should be given?
- When should *M. haemolytica* vaccine be given?

The practicing veterinarian must answer these questions based on the cattle production situation; stocker, dairy, or feedlot management; interpretation of published literature; consultations with colleagues; and personal experience.

Numerous commercially available bovine biologics contain *M. haemolytica* antigens.[363] *M. haemolytica* vaccines are often in combination with viral vaccines, *H. somni* or *P. multocida* bacterins, and occasionally *Clostridium* species biologics. Despite the various licensed *M. haemolytica* biologics available, formulations of *M. haemolytica* vaccines fall into one of eight categories, seven of which are nonliving vaccines. These are described by their manufacturers as follows: (1) bacterin with aluminum hydroxide adjuvant; (2) bacterin with water-in-oil adjuvant; (3) outer membrane extract; (4) bacterin-toxoid (LKT toxoid); (5) toxoid—cell-associated antigen; (6) adjuvanted toxoid (culture supernatant); (7) autogenous (herd-specific) bacterins produced from isolates submitted by practicing veterinarians; and (8) live streptomycin-dependent mutant. The last vaccine is the only currently licensed live *M. haemolytica* biologic. In the past, several live *M. haemolytica* vaccines were commercially available, and those vaccines showed potential efficacy; however, untoward side effects such as severe local and systemic reactions often occurred after vaccination.

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48.35.3 Experimental Studies

Conventional formalin-inactivated, whole-cell, aluminum hydroxide—adsorbed *M. haemolytica* bacterins were the industry standard for many years; however, they stimulate low antibody titers to surface antigens, do not stimulate antibodies to LKT, and in experimental challenges or field trials were either ineffective in substantially enhancing resistance to pneumonic pasteurellosis or associated with increased disease and/or lesions.[364] In contrast, experimental studies with *M. haemolytica* bacterins in water-in-oil adjuvants, outer membrane extracts, and recombinant iron-regulated OMP vaccines significantly enhanced resistance against experimental challenge even though they did not stimulate antibodies to LKT, indicating that the adjuvant used is probably of importance in *M. haemolytica* immunity.[365–367] The other commercial *M. haemolytica* vaccines stimulate antibodies to LKT and to various surface antigens.[368,369]

Vaccine efficacy has been demonstrated primarily with experimental models of pneumonia using one of several challenge methods including direct *M. haemolytica* challenge via intratracheal, intrabronchial, or transthoracic routes or using a combination viral (usually BHV-1) and *M. haemolytica* challenge.[350] The majority of published reports of experimental vaccination and challenge studies have used experimental vaccines and not commercial ones. There are few published reports of efficacy of individual commercial vaccines against experimental *M. haemolytica* challenge. For example, in one experiment, cattle were vaccinated with a commercial bacterin toxoid and compared with unvaccinated controls after a transthoracic *M. haemolytica* challenge.[366] In a second experiment in the same manuscript, cattle were vaccinated with a commercial outer membrane extract vaccine and compared with control cattle after experimental challenge.[366] Both vaccines significantly enhanced resistance against experimental challenge. In recent years, several studies have demonstrated that although vaccination with commercial vaccines can enhance resistance against experimental *M. haemolytica* challenge, addition of one of several *M. haemolytica* recombinant proteins, including LKT,

sialoglycoprotease, or outer membrane lipoprotein, PlpE, enhanced efficacy of the commercial product.[353,354,369,370] Direct comparisons of two or more commercial *M. haemolytica* vaccines after experimental challenge have rarely been published. In one such comparison between a commercial *M. haemolytica* bacterin toxoid and the live streptomycin-dependent mutant vaccines, the bacterin toxoid elicited the greatest serologic responses and significantly reduced lung lesions after experimental challenge.[367] Calves receiving the live mutant vaccine had lesions that were not significantly lower than in control cattle. Demonstration of protection against experimental challenge, however, may not necessarily indicate that the vaccine will be efficacious against natural disease under field conditions.

48.35.4 Field Studies

The number of published field studies using commercial *M. haemolytica* vaccines is limited. I am unaware of any published studies using autogenous *M. haemolytica* bacterins. In both dairy and beef cattle, maternal antibodies to *M. haemolytica* and *P. multocida* decline to undetectable levels between 30 and 90 days of age.[369] Most calves subsequently spontaneously develop antibodies to these bacteria owing to natural exposure. There is substantial evidence that cattle entering a feedlot with preexisting serum antibody titers to *M. haemolytica* have less respiratory disease and fewer deaths than do those without serum antibodies.[371] Therefore vaccination of cattle before shipment so that they can develop appropriate immunity is ideal, and determination of the appropriate time to vaccinate cattle with an *M. haemolytica* vaccine becomes critical.[372–374] Manufacturers of *M. haemolytica* biologics usually recommend vaccination between 15 and 21 days before "weaning, shipping or exposure."[363] Although many of the currently available *M. haemolytica* biologics are licensed for only one injection, manufacturers recommend a booster if possible. However, administration of two doses of an *M. haemolytica* vaccine may not be practical for beef cattle. Shewen[375] demonstrated that one of the reasons that one dose of *M. haemolytica* vaccine often stimulates adequate antibody response is because most cattle carry *M. haemolytica* in their nasopharynx and have a primed immune system that can produce a rapid anamnestic response to vaccination.

To determine the best time to vaccinate before shipping cattle, several studies have looked at how rapidly various commercial *M. haemolytica* vaccines induce antibody response and how long after vaccination do detectable antibodies remain. Two studies followed antibody responses to LKT and surface antigens in beef calves vaccinated with various commercial *M. haemolytica* vaccines and found marked differences both in rapidity and persistence of antibodies.[354,376] With few exceptions, antibody responses reached their maximum 14 days after vaccination and had markedly waned by day 42. In another study, long-term antibody responses of cattle were followed after vaccination with three nonliving commercial *M. haemolytica* vaccines, a bacterin toxoid, outer membrane extract, and adjuvanted toxoid.[377] Serum antibody responses to *M. haemolytica* surface antigens (all tested vaccines) and LKT antigens (bacterin toxoid and adjuvanted toxoid only) were at a maximum 2 to 3 weeks after vaccination, but most antibody responses had returned to normal by 6 weeks after vaccination. Revaccination 140 days after the initial vaccination resulted in rapid anamnestic responses that were usually higher than the initial responses. These data support manufacturer recommendations and indicate that if cattle are to be vaccinated with one of these *M. haemolytica* vaccines before shipment, vaccines should be given within 2 to 3 weeks of shipment to maximize antibodies at the time of shipment stress. If vaccination was performed before that time, a booster should be given before shipment.

Vaccination of cattle against pneumonic pasteurellosis on arrival at the feedlot is somewhat controversial because it may not allow enough time for development of solid protection before the period of highest morbidity.[364] In addition, if cattle were vaccinated 2 to 3 weeks before shipment and had adequate antibody

responses, antibody titers may be adequate, and revaccination may not be cost-effective. However, the vaccination history is not always known for beef cattle, and vaccination on entry to the feedlot is often practiced.[372–374] Results in several field trials indicate that this practice can often afford some protection against shipping fever during the first 14 days in the feedlot.[373] Selective use of *M. haemolytica* vaccines has also been advocated. Some feedlots designate cattle as high risk or low risk for respiratory disease. Managers may be more willing to vaccinate low-risk cattle, because high-risk cattle are either sick on arrival or can develop disease soon after entry into the feedlot.[374] Therefore there would not be sufficient time for vaccination of high-risk cattle to stimulate immunity. However, low-risk cattle are less likely to develop disease soon after entry into the feedlot, and when they are vaccinated there is often adequate time for immunity to develop before a respiratory outbreak occurs.[374]

Perino and Hunsaker[378] reviewed 10 published studies of several commercial live and subunit *M. haemolytica* vaccines with respect to their efficacies in field studies of feedlot cattle. Their report confirms that vaccination of cattle with newer generation *M. haemolytica* vaccines does not consistently reduce morbidity or mortality or increase weight gains. Of those studies, five showed positive outcomes based on reduced morbidity, mortality, or increased weight gain, whereas five studies demonstrated no positive outcome. Three of those studies demonstrating positive outcomes involved the same *M. haemolytica* bacterin toxoid given at arrival in the feedlot; however, two clinical trials with the same vaccine showed no significant differences when given at arrival and/or 3 weeks before shipment. In several field studies in which a positive outcome was demonstrated using a new generation *M. haemolytica* vaccine, economic benefits ranged from approximately $10 to $34 per head. Morbidity and mortality rates have been reduced by approximately 30% to 45% and 84% to 100%, respectively.[379]

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48.35.5 Dairy and Veal Calves

Studies of *M. haemolytica* vaccinations in dairy and veal calves have been published less frequently than those in beef calves. In one study, dairy calves vaccinated at around 10 weeks of age with *M. haemolytica* toxoid failed to produce significant antibody responses to LKT or OMPs.[380] In another study, vaccination of Holstein calves with adjuvanted toxoid (culture supernatant) at 2 to 4 weeks of age resulted in 50% or less of the calves seroconverting to *M. haemolytica* surface antigens, and those antibodies were in the IgM class.[381] None of those vaccinates developed LKT neutralizing antibodies. Furthermore, many unvaccinated calves developed anti—*M. haemolytica* antibodies after 5 weeks of age, suggesting natural exposure to the organism. Low antibody responses in *M. haemolytica*—vaccinated young dairy calves probably indicate interference of vaccination by colostral antibodies.

With respect to protection afforded young calves by *M. haemolytica* vaccines, *M. haemolytica* toxoid— or live-mutant—vaccinated calves had incidences of respiratory disease similar to those of unvaccinated controls.[382,383] In another study, an *M. haemolytica* bacterin toxoid was found to be less effective than a commercial streptomycin-dependent mutant *M. haemolytica* and *P. multocida* vaccine in reducing respiratory disease in veal calves.[384] However, antibody responses to *M. haemolytica* and the causes of respiratory disease were not determined in the veal calf study. Failure of *M. haemolytica* vaccines to provide protection in dairy and veal calves could occur because *P. multocida* is usually the most common isolate from dairy calf pneumonia.

48.36 *PASTEURELLA MULTOCIDA* VACCINES

P. multocida, particularly serogroup A, serotype 3 isolates, is the second most common bacterium associated with pneumonia in beef cattle and the most common isolated from pneumonia in dairy calves.[347] Although *M. haemolytica* has traditionally been the major pathogenic bacterium associated with shipping fever, recent studies suggest that the incidence of *P. multocida* in this disease has increased in beef cattle.[348,372]

The pneumonia produced by *P. multocida* is less acute and severe than *M. haemolytica*—associated pneumonia. The antigenic makeup of nonliving *P. multocida* vaccines presently available are proprietary and are described in the *Compendium of Veterinary Products* as bacterial extracts, cell-associated antigens, soluble antigens, and/or bacterins. Conventional formalin-inactivated, whole-cell, aluminum hydroxide—adsorbed bacterins have been the industry standard and are not considered highly efficacious.[363] A commercial live streptomycin-dependent mutant *P. multocida* and *M. haemolytica* vaccine is available. Its efficacy is not well documented in the literature.

The immune mechanisms involved in resistance to *P. multocida* lung infections in cattle are poorly understood. There is more published work related to vaccines against *P. multocida* serogroups B and E, which cause hemorrhagic septicemia in cattle and water buffalo.[385] Recent studies suggest that *P. multocida* OMPs or iron-regulated OMPs could be important immunogens for protecting cattle against pneumonia, and vaccination of calves with outer membrane preparations substantially enhanced resistance against experimental challenge.[350,386,387] Although the *P. multocida* toxin, which is produced primarily by serogroup D isolates, is an important virulence factor and immunogen for *P. multocida* in atrophic rhinitis of swine, there is no evidence that this toxin is important in pneumonia of cattle, nor would it be beneficial to include the toxin in a vaccine for cattle.[350]

48.37 *HISTOPHILUS SOMNI (HAEMOPHILUS SOMNUS)* VACCINES

Haemophilus somnus' name was recently changed to *H. somni*, which we will use in this discussion. *H. somni* is the cause of thrombotic meningoencephalitis (TME), septicemia, and reproductive disorders in cattle. In addition, it is the third most common bacterial isolate from beef cattle pneumonia in most epidemiologic surveys.[347,348] Cases of *H. somni*—induced pneumonia are often associated with concurrent myocardial necrosis. Potential immunogens have been experimentally studied in *H. somni* and consist of lipooligosaccharide (LOS),[388] several OMPs—including a surface protein that binds the Fc receptor of bovine immunoglobulin and is associated with serum resistance of pathogenic strains[389]—and iron-regulated OMPs.[390] As with most gram-negative bacteria, *H. somni* LOS is a dominant antigen that stimulates an antibody response to the polysaccharide moiety after natural or experimental exposure. It is interesting to note that *H. somni* LOS has been demonstrated to exhibit phase variation in its epitopes (i.e., antigenic drift), thereby allowing the bacterium to escape the immune response.[388] Currently there is no evidence that those anti-LOS antibodies are protective.[391] Likewise, several OMPs and iron-regulated OMPs have been shown to be immunogenic in cattle. The major *H. somni* OMP is weakly immunogenic and shows strain antigenic variability.[392] Their role in stimulating immunity is not known.

Several approved *H. somni* biologics are available, often in combination with respiratory viruses and *Pasteurella* species. All of the currently licensed *H. somni* biologics are formalin-killed bacterins with aluminum hydroxide as an adjuvant. Efficacy of *H. somni* bacterins has been generally favorable in stimulating protection against experimental pneumonia, against intravenous and intracisternal *H. somni* challenge as a model of TME, and against natural TME.[354] Overall, vaccine-induced immunity has been best against experimental and natural TME.

[364,380,393] Using an experimental challenge model of *H. somni*—induced pneumonia, significant protection was afforded calves vaccinated twice with an *H. somni* bacterin.[394] Resistance correlated with a high serum antibody response to the bacterium. One study demonstrated a reduced risk for respiratory disease in cattle that had high antibodies titers to *H. somni* on arrival in a feedlot.[395] Therefore the potential exists for stimulating resistance to *H. somni*—associated pneumonia. In addition, commercial *H. somni* vaccines can stimulate IgE antibodies and thus potentially increase the risk for type I hypersensitivity.[396]

Under field conditions, commercial *H. somni* bacterins have had limited success in inducing protection against respiratory disease. Published reports have shown conflicting results. Perino and Hunsaker[378] reassessed the results of three published commercial *H. somni* bacterin field trials and reaffirmed that this is the case. In one trial *H. somni* vaccination resulted in a reduced treatment rate when vaccinations were given at arrival and 21 days later.[397] In another study, vaccination once with a commercial bacterin was associated with significantly more animals being treated for respiratory disease compared with unvaccinated cattle or those vaccinated twice at 21 day intervals.[398,399] In another study, vaccination with a commercial *H. somni* bacterin on arrival at the feedlot was associated with no significant differences between the number of animals treated for respiratory disease compared with unvaccinated controls.[400] In a recent study, partial reduction in feedlot respiratory disease was associated with vaccinating for *H. somni*, whereas a significant reduction in respiratory disease was associated with *H. somni* vaccine in combination with *M. haemolytica* or *M. haemolytica* vaccine alone.[401] Ribble and colleagues,[402] however, demonstrated reduced steer mortality after *H. somni* vaccination, but not heifer mortality.

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48.38 BOVINE REPRODUCTIVE DISEASE VACCINES

Victor S. Cortese

Carol A. Bolin

As explained earlier, cows have a multilayered placenta, which leaves the fetus susceptible to infection. Infection of the placenta, inflammation of the ovary, death of the fetus, or disruption of the cervical plug all may cause abortion. Reproductive disease therefore is the most difficult disorder against which to achieve protection. Vaccination must minimize the amount or duration (or both) of the viremia or septicemia, or it must prevent the pathogen from moving through the cervix or crossing the placenta.

The reproductive diseases and protection against them through vaccination are areas of active research. With current research a vaccination program can be designed to aid in the control of reproductive diseases. Unfortunately, there is little or no research on the efficacy of many vaccines currently used to prevent reproductive disease. Because the causes of reproductive failure are so numerous (infectious agents account for only a small percentage), vaccination to prevent infectious reproductive losses many not appear to be effective. This often is a result of the fact that diagnostic testing has not been attempted or has not determined the cause of reproductive inefficiencies. A vaccination program may be inappropriately instituted when the cause is not infectious, or the current program may unfairly be deemed ineffective. A *Neospora* vaccine against *Neospora*-induced reproductive disease in cattle has been granted a license. Little published information is available on this product. Although safety has been shown, the efficacy is questionable.

The use of viral vaccines to help prevent reproductive diseases was discussed earlier in the chapter.

48.39 *BRUCELLA ABORTUS* VACCINE

Brucella vaccination has best shown the effectiveness of vaccination in controlling a reproductive disease. The successful control or even eradication of *B. abortus* in many areas of North America is a testament to the ability of a program involving testing, culling, and vaccination to control a reproductive disease. Vaccination with either strain 19 or strain RB51 *Brucella* has proved to be effective; however, many herd owners have stopped vaccinating against this disease as states have been declared *Brucella* free.

Abortions caused by *B. abortus* usually are seen after 5 months of gestation. Retained placentae and subsequent metritis usually follow. The abortion is caused by severe placentitis. *Brucella* infections have also been associated with a decrease in conception rates and an increase in services per conception. A higher number of dead and weak calves has also been demonstrated in infected herds. Orchitis or seminal vesiculitis or both may characterize infections in bulls.

Only heifer calves can be vaccinated for brucellosis. Both of the two licensed *B. abortus* vaccines are modified live bacterins, and vaccination of bulls may lead to orchitis.[403] Legal use of the vaccines usually is confined to heifer calves 4 to 12 months of age, because vaccination of older animals with the strain 19 vaccine may lead to false-positive results on routine *Brucella* screening tests. Because the strain 19 vaccine may cause septicemia, clinical illness, and occasionally death,[404] sick, unhealthy, or stressed cattle should not be vaccinated. The RB51 strain vaccine is an O antigen—deficient mutant of *B. abortus* strain 2308. The RB51 vaccine has three primary advantages:

- Antibodies induced by this vaccine do not react with the serologic tests routinely done to diagnose *Brucella* infections.
- The vaccine can be used in adult cattle at a lower dosage under special circumstances and with the permission of the USDA.
- The vaccine tends to cause less postvaccination fever and stress than the traditional strain 19 vaccines.

The long-term immunity conferred by *Brucella* vaccination is the cell-mediated type.[405,406] Calfhood vaccination does not prevent a herd of cattle from becoming infected with *B. abortus*. However, it does largely prevent abortions and protects 65% to 75% of the cattle in the herd from infection while infected reactors are identified and slaughtered.[407] For these reasons, in addition to vaccination, a control program should include testing and culling of all animals that test positive.

48.40 *LEPTOSPIRA* BACTERINS

Leptospirosis occurs worldwide and is caused by infection with the spirochete *Leptospira*. The pathogenic leptospires were formerly classified as members of the species *L. interrogans;* the genus has recently been reorganized, and pathogenic leptospires are now identified in seven species of *Leptospira*.[408] As part of this reclassification the serovar names have remained the same, but some of the common leptospiral pathogens of cattle have different species names than before. The key changes for this discussion include the following: (1) *L. interrogans* serovar Grippotyphosa is now *L. kirschneri* serovar Grippotyphosa, and (2) the two types of serovar Hardjo have been formally split into two species; serovar Hardjo type hardjo-bovis (found in the United States

and much of the world) is now *L. borgpetersenii* serovar Hardjo, and the less common serovar Hardjo type hardjo-prajitno (found primarily in the United Kingdom) is now *L. interrogans* serovar Hardjo.

Although traditionally associated with abortions, infection with various serovars of *Leptospira* are associated with a variety of clinical signs including severe systemic disease most often in young animals, decreased milk production, birth of weak calves, and infertility. In addition, infected cattle are known to present a risk of zoonotic transmission of the infection to humans. Many different serovars of *Leptospira* have been shown to cause reproductive failure and abortions in cattle. Of these serovars, Hardjo, Pomona, and Grippotyphosa[409–412] are more common, with serovars Canicola, Icterohaemorrhagiae, and Bratislava occasionally implicated. The epidemiology of infection of cattle with these serovars differs, with cattle serving as the reservoir or maintenance host for serovar Hardjo and as an incidental host for the other serovars. In general, maintenance host infections are associated with a high prevalence of infection, a poor immune response, and long-term infection and shedding, whereas incidental host infections are characterized by low overall prevalence of infection with epidemics recognized, a vigorous immune response, and short-term infection and shedding. These differences in the epidemiology of leptospirosis caused by different serovars of *Leptospira* require different strategies for prevention.

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Leptospirosis can cause abortion storms in which a high number of cattle may abort within a short period. There may also be an increased number of stillbirths and births of premature and weak calves during these periods.[413] Although serovars Pomona and Grippotyphosa tend to cause abortions in the last trimester of pregnancy, serovar Hardjo can cause abortions at any stage of pregnancy. Abortions usually are caused by fetal infection and subsequent death of the fetus, although placentitis may also occur. Serovar Hardjo can also colonize the oviducts and uterus,[410,414,415] diminishing fertility. After an initial serovar Hardjo infection, cattle may remain infected and shed the spirochete for long periods,[416,417] whereas infection and shedding of the others serovars is relatively brief.

Current bacterins generally contain combinations of leptospiral serovars Pomona, Grippotyphosa, Canicola, Icterohaemorrhagiae, and either *L. interrogans* serovar Hardjo (hardjo-prajitno) or *L. borgpetersenii* serovar Hardjo (hardjo-bovis). At the time of this writing a monovalent *L. borgpetersenii* serovar Hardjo (hardjo-bovis) vaccine is also available. There has been considerable debate in recent years regarding the efficacy of leptospiral bacterins for cattle. The bacterins have label claims that indicate they are to be used as an “aid in the prevention of disease.” Therefore these bacterins should be expected to decrease the severity of clinical signs, including abortion, associated with such infection. In general, the evidence supports such claims for serovars for which cattle are an incidental host, that is, serovars Pomona, Grippotyphosa, Canicola, and Icterohaemorrhagiae. Protection mediated by these bacterins for these serovars is thought to occur because of induction of antibodies directed against the LPS on the surface of the *Leptospira*.[418] However, vaccination does not always prevent infection and leptospiruria caused by serovar Pomona.[419–421]

The efficacy of bacterins for prevention of infection, leptospiruria, and clinical signs associated with serovar Hardjo infection is significantly more controversial. The evidence that the efficacy of traditional serovar Hardjo vaccines is less that optimal includes induction of a relatively poor antibody response in vaccinated animals, the common presence of Hardjo infection in herds despite routine vaccination, and experimental trials that did not demonstrate protection afforded by these traditional vaccines for prevention of infection, colonization of the renal or genital tract, or transplacental infection on challenge with *Leptospira borgpetersenii* serovar Hardjo (hardjo-bovis).[422–424] In these studies, cattle were not protected from infection despite the induction of antibody directed against serovar Hardjo LPS. Further investigation and evaluation of other serovar Hardjo bacterins has led to a hypothesis that CMI may play a role in protective immunity against serovar Hardjo in cattle.[425–429] Newer

bacterins for serovar Hardjo have been introduced in monovalent and polyvalent formats, and there is evidence that these bacterins provide significant protection of cattle against infection, tissue colonization, shedding, and transplacental infection.[424,428–430] Other new bacterins for serovar Hardjo are also entering the marketplace, but as of this writing extensive data regarding the performance of these products are not available in the literature.

Some *Leptospira* bacterins are labeled as single initial dose products, but a booster dose is recommended approximately 1 month after the first dose.[418] *Leptospira* bacterins must be administered by intramuscular or subcutaneous injection. Although some manufacturers specify revaccination at 12-month intervals, this DOI has been questioned, and more frequent revaccination often is needed to control *Leptospira* abortions.[419,420,422] One of the newer serovar Hardjo bacterins has documented a 1-year DOI for this component, but this DOI has not been documented for other Hardjo vaccines or for the other serovars, making vaccination every 6 months a reasonable recommendation in many circumstances. Nevertheless, because leptospiral abortions are uncommon during the first half of pregnancy, it may be possible to use an annual vaccination schedule (serovar Hardjo excepted) in seasonally calving herds such as beef herds. Cattle in such herds can be vaccinated when they are 2 to 4 months pregnant, usually at the time that pregnancy is diagnosed, and protected through the balance of the pregnancy with a single annual dose.[419]

Prevention of leptospirosis caused by serovar Hardjo requires a somewhat different approach. Prebreeding vaccination of heifers that is effective in managing reproductive sequelae of other types of leptospirosis may be too late to prevent the consequences of serovar Hardjo infection. Heifers exposed very early in life may remain infected well into the time of breeding. Therefore efforts to control serovar Hardjo infection should be targeted at preventing the initial infection and is best done by vaccinating young stock well before the time when they are mixed with older animals. In addition, bulls can carry serovar Hardjo and transmit the infection quite readily during breeding.[431] Therefore bulls should be fully included in efforts to control serovar Hardjo infection by vaccination.

48.41 BOVINE GENITAL CAMPYLOBACTERIOSIS VACCINES

Originally classified as *Vibrio, Campylobacter fetus* subsp. *veneralis* causes a venereal infection of cattle. The bacteria are introduced during natural breeding by infected bulls or by artificial insemination (AI) with infected semen. Bulls usually are infected by breeding with infected cows, but contact with infected bedding may also be a cause. Older bulls (over 4 years of age) are more likely to be infected. After deposition in the vagina, the bacteria rapidly colonize the vagina and cervix, and in 25% of these cows the bacteria are found in the oviducts. The organism can persist for months after infection of these sites. It has been shown that fertility never returns to normal in some infected animals, and some animals may be permanently sterile because of the damage caused by salpingitis.

Vaccination with *Campylobacter* vaccines has been shown to be effective in protecting heifers even when vaginal cultures test positive for the bacteria.[432] It appears that the uterus is very resistant to the bacteria after vaccination. Studies have demonstrated improved breeding efficiency in vaccinated herds.[432] Vaccination of bulls with oil-adjuvant vaccines not only prevents infection of bulls for up to 1 year[433] but also aids in prevention of mechanical transfer of organisms during natural service.[434] Furthermore, vaccination with two doses has been shown to be effective at clearing infections from carrier bulls.[435,436]

48.41.1 Vaccination

Use of C. *fetus* bacterins is recommended in all breeding herds that use bulls, even if only on selected cows. In heifer herds using virgin bulls or in 100% AI-bred herds, vaccination against *Vibrio* organisms is not necessary. 1611 1612

Several different *C. fetus* vaccines are available, including oil-adjuvanted and aluminum hydroxide—adsorbed types. Oil-adjuvant *C. fetus* bacterins have proved to be more effective[437] and to provide longer lasting protection after a single dose.[438] Unfortunately, oil-adjuvant vaccines cause localized granuloma formation and fibrosis at the site of injection. This may cause visible blemishes, which may be objectionable in registered stock or show cattle. Administration no earlier than 4 months before the breeding season is preferred.[438] When aluminum hydroxide—adsorbed *C. fetus* bacterins are used, a priming dose should be administered at least 6 weeks before the immunizing (booster) dose, and the booster should be administered 10 days before the beginning of the breeding season.[437] After administration of an aluminum hydroxide—adsorbed bacterin, serum antibody concentrations peak rapidly and decline precipitously, falling to susceptible levels by 4 weeks after one dose or 11 weeks after two doses.[439] Some aluminum hydroxide—adsorbed bacterins do not require an initial booster.

Campylobacteriosis (vibriosis) is most effectively controlled when all breeding-age animals, including bulls, are included in the vaccination program.[434] Vibrin* is the only *C. fetus* bacterin available in the United States that has been evaluated in bulls.[432] Two 5-mL doses are administered to breeding bulls at 4-week intervals beginning 8 weeks before the start of the breeding season.[432] In subsequent years a single booster dose is administered 4 weeks before the start of the breeding season.[433] This dosage is 2½ times that recommended for vaccination of cows.

* Pfizer Animal Health, Exton, PA.

48.42 BOVINE TRICHOMONIASIS VACCINES

Bovine trichomoniasis is a venereal infection of cattle caused by the protozoal agent *Tritrichomonas foetus*. Early in the course of the disease, abortions with pyometra may be seen in 5% of infected cows. These abortions occur early in gestation.[440] However, infertility is the most common sign, with long interservice intervals.[441,442] Early embryonic death is followed by a period of conception failure. Some natural resistance develops after infection, but carrier cows may be an important component of the epidemiology of this disease. In rare cases a cow may be left sterile after an infection because of uterine destruction.[443]

The efficacy of *Tritrichomona*s vaccines is questionable,[444–446] but the vaccines do appear to reduce actual reproductive losses.[447] Heifers, cows, and breeding bulls should be vaccinated twice at 2- to 4-week intervals, the second dose given 4 weeks before the beginning of the breeding season.[448] Subcutaneous administration is recommended. In subsequent years a single annual booster vaccination should be given 4 weeks before the beginning of the breeding season.

In a problem herd, trichomoniasis vaccination must be coupled with other control measures, such as culturing, culling, and treatment to effectively control the disease.

48.43 NEONATAL CALF ENTERIC DISEASE VACCINES

Gerald E. Duhamel

Neonatal calf enteric diseases (NCEDs) can have a devastating impact on the profitability of beef cow-calf and dairy operations. In addition to mortality, medical, and labor costs, NCED can significantly reduce body weight of beef calves at weaning and performance of replacement dairy heifers.[449]

Several well-characterized infectious causes of NCED have been described.[450] Some of the more common infectious agents are group A RVs, coronavirus (CV), enterotoxigenic *E. coli*, salmonellae, and *Cryptosporidium* species.[451–457] Sporadic outbreaks of necrohemorrhagic enteritis affecting 3- to 10-day-old calves have been associated with infection with *C. perfringens* type C.[458] Other less well-characterized viruses (group B RV, calicivirus, torovirus, astrovirus), bacteria (enterotoxigenic *Bacteroides fragilis*, attaching-effacing enteropathogenic and enterohemorrhagic *E. coli*, *Enterococcus durans*), and protozoans *(Giardia duodenalis)* also have been associated with NCED.

Because of the continuous calving and constant introduction of replacement heifers on dairy farms and the continuous flow of susceptible calves on veal calf operations, infections caused by more than one agent should be suspected in these types of operations.[451–457,459–461] In addition to different infectious agents, mixed infections with different groups and serotypes or genotypes of viruses and bacteria also can occur. As a consequence, the severity, duration, and spread of clinical disease associated with complicated infections are usually greater than with a single agent, and control may be more challenging. When scours occurs in a herd that has been vaccinated against enteric diseases, possible contributing factors should be considered, including concurrent infection with pathogens not present in the vaccine (e.g., *Cryptosporidium* species, salmonellae, nongroup A RVs, other pathogens) and suboptimal management, including poor control of environmental contamination. Under these conditions, strategic improvement in husbandry practices might be sufficient to reduce the infectious threshold for NCED and obtain the full benefit of pathogen-specific vaccination. In any situation, thorough laboratory diagnostic investigation is essential in order to correctly identify the primary cause of NCED and any other possible contributing factors and to serve as a basis for appropriate control strategies for the present and future calf crops.

Management practices and risk factors associated with the development of NCED are sufficiently different between dairy and beef herds that control measures can be tailored according to the type of production. For example, in dairy herds, high turnover of older cows and continuous introduction of replacement heifers pose a higher risk for introducing new strains of enteric disease pathogens in a susceptible population than in closed beef herds. Similarly, the continuous calving and the proximity of susceptible calves on dairy farms create an ideal environment for recirculation of enteric disease agents back into the adult population. This in turn may increase and broaden herd immunity such that the efficacy of a vaccine in these herds might be enhanced, partly because of the booster effect vaccine can have on preexisting immunity. Beef cattle herds, in contrast, are generally relatively closed, and a susceptible calf population is present only for a relatively short period annually during the calving season. Introduction of new pathogens or new strains of enteric disease agents, particularly during the calving season, can have a devastating effect because of the potential for exposure of a high number of susceptible animals over a relatively short period of time. Conversely, after an outbreak, herd immunity might be more stable and the occurrence of NCED might be reduced during the following calving seasons.

Under both types of production systems, vaccination for NCED is rarely successful without reasonably good management programs and sanitation aimed at providing adequate intake of protective colostrum and minimizing environmental contamination. General herd health management steps that can affect the success of a vaccination program for NCED should include a calving cow-calf care plan aimed at minimizing exposure of newborn calves to infectious agents that can overwhelm innate or passively acquired immunity. This is accomplished by eliminating all potential means of NCED transmission and by reducing the load and duration of exposure to pathogens present in the calving environment by following eight simple recommendations: 1612 1613

1 Establish a sound biosecurity program, including purchase of replacement animals only from reputable sources and a complete ban on the introduction of foster calves, which pose a risk of introducing new NCED agents.

2 Provide adequate protein and energy feed, including proper concentrations of micronutrients (e.g., copper and selenium), and abundant clean drinking water throughout gestation and calving so that heifers and cows are within acceptable body condition score at calving and therefore produce an adequate volume of high-quality colostrum and milk, and calves are healthy and vigorous at birth, with a fully developed and functional immune system.[462]

3 Avoid crowding, and keep calving area and equipment clean, dry, and protected from elements, particularly winter wind. Separate feeding and bedding grounds should be available in the calving area. Similarly, to minimize infectious disease transmission, separate feeding and manure handling equipments should be used.

4 Limit the spread of infectious disease agents from younger, more susceptible, and potentially shedding pairs to the main herd by segregating first-calf heifer pairs from the mature cow herd during the calving season until the youngest calf is at least 4 weeks old. Also, because of potential problems associated with nursing in first-calf heifers, newborn calves in this group should be monitored closely for colostrum intake and early detection of failure of passive transfer (e.g., total serum protein concentration below 5 at 12 hours of age) so that rapid intervention can be implemented.[462–464] Because first-calf heifers are at a competitive disadvantage with mature cows, segregation of pregnant first-calf heifers also ensures free access to feed and water at all times.

5 Ensure that each calf ingest approximately 10% of its body weight in colostrum within the first 6 hours of birth, and if a calf is unable to nurse naturally or is at risk for failure of passive transfer of maternal immunity, then force-feed fresh or frozen colostrum from the calf dam's or from a mature cow in the same herd or from a neighboring herd.

6 Disinfect all equipment used for feeding colostrum and treating sick calves routinely; this includes such items as nipple bottles, esophageal probes, and balling guns.

7 Move cow-calf pairs away from the calving area as soon as possible after birth in dairy herds, whereas in beef herds, segregate calves by age by scheduled movement of dams that have not calved to new calving pastures—the so-called “Sandhills Calving System” (http://vetext.unl.edu/stories/200703050.shtml).

8 Quickly isolate scouring calves from healthy calves in dairy herds, or sick cow-calf pairs from healthy pairs in beef herds.[462]

Giving calves a healthy start maximizes their genetic production potential while reducing the costs and labor associated with treatment of sick animals.

48.44 ROTAVIRUS AND CORONAVIRUS VACCINES

RVs and CVs are ubiquitous in the cattle population; most adult cattle have VN serum antibodies.[465–469] RV infections are widespread in both dairy and beef cow-calf productions, whereas infection with CV most often occurs as sporadic outbreaks of severe diarrhea in beef cow-calf herds or chronic low-grade diarrhea in dairy and veal calf operations. In addition to causing NCED, CV has been associated with winter dysentery in adult cattle[470] and respiratory tract infections in calves[471] and as a contributing infectious cause of BRD complex in feedlot cattle.[472] Fecal shedding of RV and CV is common among adult cattle,[473–476] which provides an immediate source of virus challenge for naive newborn calves and allows persistence of these agents at the herd level.

Although only one type of CV is known to cause NCED,[477] different subtypes of CVs can be identified on the basis of minor genomic and antigenic differences.[477–481] On a herd basis, however, affected calves can display a range of clinical signs from enteric only to mixed enteric and respiratory signs. A recent molecular epidemiologic investigation based on comparative analyses of the gene encoding the S glycoprotein, a major structural protein of bovine CV, revealed (1) identical CV strains in different animals from the same herd and from paired nasal and fecal samples from the same animals, suggesting herd outbreaks are associated with a single strain circulating among susceptible cattle, (2) identical CV strains in affected cattle from different herds in the same region, suggesting transmission between herds, and (3) different CV strains in cattle affected during different outbreaks occurring over several years in the same herd, suggesting herd outbreaks are associated with the introduction of new strains in a recovered herd.[482]

Currently RVs are classified into at least seven distinct groups, A through G.[483] Although RVs that belong to groups A, B, and C have been found to naturally infect cattle,[476,483–487] group A RVs are by far the prevalent type.[485,487] Members of the group A RVs are further classified according to antigenic and genetic differences in their outer capsid proteins, G and P.[488–490] Because both of these proteins are involved in neutralization of infectivity in vitro and protection in vivo,[491–493] consideration of the G-P configuration of RVs is critical to development of an effective vaccination program for prevention of NCED.

Although a good correlation has been found between the antigenicity of the G proteins and their corresponding gene sequences, a similar relationship has not been found for the P proteins. Therefore 14 different G serotypes, which correspond to 14 G genotypes, have been identified among group A RVs, whereas 10 serotypes identified on the basis of the antigenicity of the P proteins have been assigned to 20 genotypes when compared on the basis of the nucleotide sequence of the P protein genes.[490] At least eight distinct G serotypes or genotypes (G1, G2, G3, G6, G8, G10, G11, and untypeable) are known to infect cattle in the United States[494,495]; G6 is the most widespread, and G8 and G10 account for lower percentages of infections.[469,495–500] Conversely, RVs with any of four P serotypes or genotypes—P6(1), P7(5), P8(11), and untypeable—are known to infect catte, with P7(5) being the prevalent type.[495,498,501]

The genome of RVs is composed of 11 gene segments that can be exchanged among RV isolates when animals are infected by more than one virus type at the same time.[489] Therefore mixed infections produce virus with a genetic makeup derived from either parental strain by a mechanism called *gene reassortment*. Because the G and

P proteins independently are involved in generation of specific VN antibodies, reassortment of these genes during mixed infections can generate new progeny viruses that can evade what once was a protective immune response, thus allowing persistence of RVs in susceptible populations.[500] Therefore the potential occurrence of RVs carrying any of 36 possible antigenic configurations (4 Ps × 8 Gs = 32 potential types) underscores the limitation of vaccination programs and also the importance of sound management practices designed to minimize exposure by limiting environmental contamination.

48.44.1 Vaccination Programs

Two approaches are widely used in an attempt to protect calves against RV and CV infection and diarrhea. The most common approach involves passive protection of the suckling neonate by transfer of high levels of specific VN colostral antibodies induced by parenteral vaccination of the pregnant dam.[467,502–510] The mechanism of passive protection with this approach is attributable to the continuing presence of an amount of specific VN antibodies in the intestinal lumen sufficient to neutralize infectious virus before infection of the intestinal villous enterocytes.[465,507,511–515] The continuous presence of VN antibodies in the gut lumen also may reduce the severity of the disease if infection has already developed. In addition, some of the VN colostral antibodies that are absorbed into the bloodstream are secreted onto mucous membranes and may provide local immunity later in life.[516] However, colostral transfer of immunity is less efficient in ruminants than in other species; high concentrations of maternal antibodies are present for less than 3 days postpartum, and these concentrations often fall below protective levels within 1 week of parturition.[*]

A delicate balance exists between passive protection afforded by lactogenic immunity and development of the calf's own innate and adaptive local immunity to RV and CV. Because most calves' level of resistance to the adverse clinical effects of RV and CV infection increases with age, disease caused by these agents can be controlled under certain circumstances by continuous hand-feeding of fresh, frozen, or fermented colostrum from vaccinated cows throughout the first 3 to 4 weeks of life.[†] The goal with this approach is to allow development of subclinical infection while the milk VN antibody concentration is partially protective.[504,515,521] Conversely, lactogenic immunity might interfere with development of adaptive immunity, or some calves might not be exposed to RV and CV infection until after milk antibody concentrations have fallen below protective levels, leaving the calf fully susceptible to infection.[502,504,522]

An RV and CV vaccine for parenteral administration to pregnant cows (Calf-Guard[a]) first became commercially available in 1979. This vaccine contained a single live attenuated G6:P6(1) strain of group A RV. However, because VN antibody concentrations in the colostrum and milk of vaccinated cows were low,[467,468,504,518] this product later was replaced by a formulation containing inactivated RV and CV (ScourGuard 3 [K][b]). In early 2000 an inactivated RV and CV vaccine (Scour Bos[d]), which contains three strains of group A RV, was licensed for use in pregnant cattle in the United States. More recently, in 2005 an inactivated RV and CV vaccine (Guardian[e]) containing two strains of group A RV and two strains of CV was licenced for subcutaneous administration in pregnant cattle in the United States. A significant advantage of the later vaccine for dairy cattle is the administration schedule, with the second booster dose administered before the dry period. In late 2006 the single G6 RV ScourGuard 3[K]/C[b] vaccine was upgraded to contain G6 and G10 strains of group A RV, and the window for administration of both formulations to pregnant cows was extended (ScourGuard 4[K]/C[c]).

Vaccination of pregnant cows with inactivated RV and CV vaccine can raise the level of VN antibodies in the colostrum.[467,502–511,523] Although there are reports of successful protection of calves against NCED by parenteral vaccination of pregnant cows with RV and CV,[*] negative results also have been reported.[531] Failures of this vaccination strategy generally are attributable to failure of passive transfer of colostral antibodies to the calves or overwhelming infectious virus challenge. An alternative explanation might be that the serotypic specificity of the passively transferred maternal antibodies may affect the efficacy of the RV vaccine.[532]

Information on protective immunity against infection of calves with group A RVs having the same or a different G-P serotype configurations as the vaccine strain is incomplete.[496,523,533–537] Although immunity to RV appears to be G-P serotype specific with some strains,[496,523,533,536] there is some indication that immunity directed against certain strains can neutralize in vitro[496,537] and protect challenge-exposed calves in vivo[496,536] against RV strains with different G-P configurations. Also, parenteral vaccination of seropositive cows with a single strain of RV can elicit serum VN antibodies to a broad spectrum of RV serotypes and genotypes, suggesting that this strategy may provide a means of enhancing passive protection against a range of potential RV serotype and genotype challenges.[524,534,535] However, a difference in the P protein between the vaccine RV and the infecting RV was suggested as the basis for failure of the inactivated monovalent RV and CV vaccine in beef cow-calf herds.[538,539]

Although antigenic and genotypic variation has been documented among bovine CV infections,[477–481] reduced protection of nursing calves after challenge with a strain of bovine CV different from the vaccine strain has not been demonstrated. Consequently, presence of more than one strain of bovine CV in certain vaccine might not be justified at this time.

Another approach for prevention of NCED caused by RV and CV involves oral vaccination of calves with a modified live virus vaccine (Calf-Guard[a]), which contains an attenuated G6:P6(1) strain of group A RV.[540–552] The mechanism of disease prevention with this vaccine is unknown, but interference with infection by virulent virus followed by development of secretory IgM and IgA and/or CMI in the intestinal mucosa have been proposed.[522,543] To achieve adequate protection, the manufacturers recommend that the vaccine be given immediately after birth, before the calf has nursed. This regimen might be applicable to calves whose dams have not been vaccinated. However, because the colostrum of most heifers and cows contains some level of VN antibodies arising from natural exposure,[‡] administration of colostrum should be delayed for several hours after vaccination to avoid inactivation of the vaccine virus. Under commercial conditions, it is nearly impossible to administer vaccine within minutes of birth or to effectively regulate the intake of colostrum in relation to the time of vaccination. Therefore infection before vaccination, neutralization of the vaccine virus by colostral antibodies, and overwhelming challenge with infectious virus shed by unvaccinated, diseased calves might explain a lack of efficacy of this approach.[505,545–548] This is evident from the data obtained in vaccine efficacy evaluation studies in which only a portion of the calves on a farm or a ranch were vaccinated in double-blind or odd-even—day vaccination trials.[517,549,550] When all calves were either vaccinated or not vaccinated in sequential comparisons, morbidity and mortality rates from NCED were significantly reduced by this vaccination strategy,[511,540–542,549,540] but the design and statistical validity of the latter kinds of trials have been questioned.[531,546]

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Although not recommended by the manufacturer, the oral attenuated vaccine has been administered to calves with unknown immune status that were raised as veal calves or replacements in heifer development operations.

[551] Under these circumstances, vaccination might provide active immunity and protection against potential virus challenge when calves from several different sources are commingled.

* References 502, 505, 508, 514, 515, 517.

† References 505, 509, 510, 514, 519, 520.

a Calf-Guard, Pfizer Animal Health, Exton, PA.

b ScourGuard 3(K), Pfizer Animal Health, Exton, PA.

d Scour Bos, Novartis Animal Health U.S., Inc., Larchwood, IA.

e Guardian, Shering-Plough Veterinary Corp., Summit, NJ.

c ScourGuard 4(K), Pfizer Animal Health, Exton, PA.

* References 503–505, 507, 509, 510, 520, 521, 523–530.

‡ References 465, 467–469, 502–510, 514, 518, 519, 523, 527, 529, 531, 535, 544.

48.45 ROTAVIRUS AND CORONAVIRUS VACCINATION PRODUCTS

48.45.1 SCOURGUARD 4(K)/C

ScourGuard 4(K)C[c] consists of inactivated bovine G6 and G10 strains of group A RV and a bovine CV strain combined with K99 *E. coli* bacterin and *C. perfringens* type C toxoid. Two doses of vaccine should be administered by intramuscular injection to pregnant cows and heifers 6 to 9 weeks precalving. A second dose should be given 3 to 6 weeks before the expected calving date to first-calf heifers and mature cows not previously vaccinated. A single annual booster dose should be administered 3 to 6 weeks before each subsequent calving.

c ScourGuard 4(K), Pfizer Animal Health, Exton, PA.

48.45.2 SCOURGUARD 3(K)/C

ScourGuard 3(K)/C[b] consists of inactivated bovine G6:P6(1) strain of group A RV and a bovine CV strain combined with K99 *E. coli* bacterin and *C. perfringens* type C toxoid. Two doses of vaccine should be administered by intramuscular injection to pregnant cows and heifers 6 to 9 weeks precalving. A second dose should be given 3 to 6 weeks before the expected calving date to first-calf heifers and mature cows not previously vaccinated. Cows that have not calved within 40 days after administration of the last vaccine dose should be revaccinated. A single annual booster dose should be administered 3 to 6 weeks before each subsequent calving.

b ScourGuard 3(K), Pfizer Animal Health, Exton, PA.

48.45.3 Scour Bos

Scour Bos[d] consists of inactivated bovine group A RV strains G6:P6(1), G8, and G10 and a CV strain combined with bacterins from four *E. coli* K99 serotypes and *C. perfringens* type C toxoid. The vaccine should be administered by deep intramuscular injection into the neck of pregnant cows and heifers up to 10 weeks before the expected calving date. A booster dose of Scour Bos RV and CV vaccine must be given

approximately 6 weeks later during the first year. Only one annual dose up to 10 weeks before calving is required thereafter.

d Scour Bos, Novartis Animal Health U.S., Inc., Larchwood, IA.

48.45.4 Guardian

Guardian[e] consists of inactivated bovine group A RV G6 and G10 strains together with "type 1" and "type 3" bovine CV strains combined with enriched K99 pili from *E. coli* and type C and D toxoids of *C. perfringens*. The vaccine should be administered by subcutaneous injection of pregnant cows and heifers up to 12 weeks before the expected calving date. A booster dose of vaccine must be given approximately 3 to 6 weeks later during the first year. Only one annual dose up to 5 to 7 weeks before calving is required thereafter.

e Guardian, Shering-Plough Veterinary Corp., Summit, NJ.

48.45.5 Calf-Guard

Calf-Guard[a] is a modified live bovine G6:P6(1) strain of group A RV and bovine CV recommended for oral vaccination of newborn calves. The vaccine should be administered immediately after birth, before the calf has nursed. As indicated earlier, interference by maternal antibodies may limit the efficacy of the vaccine.

a Calf-Guard, Pfizer Animal Health, Exton, PA.

48.46 BACTERIAL SCOURS VACCINES

Victor S. Cortese

Charles A. Hjerpe

48.47 ENTEROTOXIGENIC *ESCHERICHIA COLI* (CALF SCOURS) BACTERINS

Most cases of scours caused by *E. coli* occur within the first 72 hours of life. More than 90% of these cases are caused by *E. coli* containing the K99 pilus attachment fimbriae.[552–554] These strains also may have other fimbriae types, such as F41 and F1 (type 1).[552,555] Villous attachment and colonization by strains of enterotoxigenic *E. coli* having multiple fimbriae types appear to be effectively prevented by vaccination with bacterins that have only a single pilus antigen in common with challenge strains.[552,555] However, disease occasionally may be caused by non-K99 *E. coli*.[556] The attaching and effacing *E. coli* types, which may cause disease at 7 to 21 days of age, often do not produce K99 pilus and are not protected by current *E. coli* K99 bacterins.[557,558] This apparent lack of efficacy may be seen with other non-K99 *E. coli;* therefore typing of *E. coli* isolates from scours cases may be important in determining which vaccine to use.

Because *E. coli* scours occurs so early in life, the newborn calf does not have enough time to derive protection from vaccination. Therefore control of *E. coli* infection has been aimed at controlling calf exposure to the pathogens and vaccinating the cow to increase the colostral antibody levels against this pathogen (i.e., usually against the K99 pilus antigen).[554] Cows are vaccinated in late gestation to ensure high concentrations of anti-K99 colostral antibodies. When colostrum from vaccinated cows is fed to newborn calves, the antibodies act in the small intestine to block the pili from binding to specific receptor sites on the brush border of small intestinal

villous enterocytes.[552,559] *E. coli* bacteria that are prevented from attaching to the jejunal and ileal villi are carried into the large bowel by peristalsis. In this way, colonization of villi and production of enterotoxin are avoided. By the time they are 48 to 96 hours old, most calves are highly resistant to infection.[552,560] Thus feeding calves colostrum with a high concentration of antibodies against K99 antigen, even though restricted to the first day of life, often is sufficient to prevent the disease.[555] Passive circulating humoral antibodies, which are absorbed into the bloodstream from the calf's gut, are thought to play little or no role in immunity to neonatal enteric disease caused by enterotoxigenic *E. coli*.[552] In dairies these vaccines are only as good as the colostrum program that is in place.

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Nearly all strains of enterotoxigenic *E. coli* that have been isolated from neonatal calves have K99 pili.[561] Currently there is no evidence that bacterins with multiple pilus antigen types are more effective than those with only one pilus antigen type, as long as the vaccine and the challenge strains share a common pilus antigen.[552] However, vaccines with multiple pilus antigens are more likely to have at least one of the antigens found on the virulent challenge strain of *E. coli*.

Table 48-13 Currently Licensed* *Escherichia coli* Bacterin-Toxoids, *Salmonella* Bacterins, and Core Endotoxoid Vaccines

Antigens	Vaccine	Vaccination Regimen	Manufacturer
ESCHERICHIA COLI			
K99	Pili Shield	One dose 2 weeks before calving	Grand Laboratories (Larchwood, IA)
K99, K88, F41, 987P	Prosystem 3	*Year 1:*Two doses 5 weeks and 2 weeks before calving *Subsequent years:* One dose 2 weeks before calving	Intervet (Millsboro, DE)
K99	ScourGuard 3(K)	*Year 1:* Two doses 5 weeks and 2 weeks before calving *Subsequent years:* One dose 3 weeks before calving	Pfizer Animal Health (New York, NY)
K99, K88, F41, 987P	*E. coli* Bac	*Year 1:* Two doses 5 weeks and 2 weeks before calving	AgriLabs (St Joseph, MO)
?	Piliguard *E. coli*	One dose 2 weeks before calving One dose 3 weeks to 6 months before calving	Schering-Plough Animal Health (Union, NJ)
SALMONELLA			
Salmonella Typhimurium	PolyBac B Somnus	Two doses 2 weeks apart	Texas Vet Lab (San Angelo, TX)
	Bo-Bac 2X	Two doses 2 to 4 weeks apart	Boehringer Ingelheim (St. Joseph, MO)
Salmonella Dublin and *Salmonella* Typhimurium	Salmo-Shield TD	Two doses 2 to 4 weeks apart	Novartis, Grand Laboratories (Larchwood, IA)
	SDT-Guard	Two doses 2 to 4 weeks apart	Boehringer Ingelheim (St. Joseph, MO)
	Salmonella Dublin/ Typhimurium Bacterin	Two doses 2 to 3 weeks apart	Colorado Serum Company (Denver, CO)
Salmonella Dublin	Salmonella Dublin Modified live Entervene-d	Two doses 2 weeks apart; start at age 2 weeks or older	Fort Dodge Laboratories (Fort Dodge, IA)
SALMONELLA*SUBUNIT VACCINE*			

Siderophore *Salmonella* vaccine (conditional USDA license)	SRP	Two doses 2 to 4 weeks apart	Agrilabs (St. Joseph, MO) Intervet (Millsboro, DE)
CORE ANTIGENS			
Re *Salmonella* Typhimurium mutant (endotoxin core)	Endovac-Bovi	*Year 1:* Two doses 5 weeks and 2 weeks before calving *Subsequent years:* One dose 2 weeks before calving	Immvac (Columbia, MO)
J5 *E. coli* mutant endotoxin core	JVac	*Year 1:* Three doses 5 weeks and 2 weeks before calving *Subsequent years:* Two doses	Merial (Iselin, NJ)
	J-5	*Year 1:* Two doses 5 weeks and 2 weeks before calving *Subsequent years:* One does 2 weeks before calving	Pfizer Animal Health (New York, NY)
Siderophore *Salmonella* vaccine	SRP		Intervet (Millsboro, DE 19966)

* Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

48.47.1 *Escherichia coli* Vaccination Programs

The general recommendations for use of *E. coli* bacterins are summarized in Table 48-13. *E. coli* bacterins are offered as single-antigen vaccines and in combination with other antigens. Oil-adjuvant *E. coli* bacterins are administered by intramuscular injection in a single dose 2 weeks to 6 months before calving, and administration is repeated annually.[561] Non—oil-adjuvant *E. coli* bacterins are recommended for intramuscular or subcutaneous injection in two doses administered at a 2- to 4-week interval, with the second dose given 3 to 6 weeks before calving. In subsequent years a single booster dose should be administered 3 to 6 weeks before calving. *E. coli* bacterins do not protect calves that do not ingest sufficient amounts of colostrum sufficiently soon after birth. Also, because this protection is based on passive immunity, high challenge levels may overwhelm the finite amount of antibodies present.

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48.48 *SALMONELLA* VACCINES

Salmonella outbreaks can be caused by myriad *Salmonella* serotypes and strains (see Chapter 32). These bacteria may cause diarrhea or septicemia or both. Most outbreaks in cattle have historically involved either *Salmonella* Dublin or *Salmonella* Typhimurium; therefore all but one of the commercial *Salmonella* vaccines contain either *Salmonella* Typhimurium alone or *Salmonella* Typhimurium and *Salmonella* Dublin. More recently, *S.* Newport and other group C *Salmonella* have greatly increased in importance. All currently licensed products are formalin-inactivated, whole-cell, aluminum hydroxide—absorbed bacterins, except for a modified live *S.* Dublin vaccine,* and the newest vaccine against bovine *Salmonella*, the siderophore receptor vaccine.† The gram-negative core antigen vaccines may also provide some protection from morbidity and mortality associated with salmonellosis.

A modified live, genetically altered (via deletion) *S.* Dublin vaccine is marketed as Entervene-d for parenteral use in young calves. Research indicates that it is effective in calves 2 weeks of age and provides some cross-protection to challenge with virulent *S.* Typhimurium.[561a,561b] As with many gram-negative vaccines, adverse reactions to this vaccine have been reported. Anecdotal reports of effective oral use in calves younger than 2 weeks of age indicate that this route may help avoid some adverse reactions associated with injection of an endotoxin-containing product.

Killed *Salmonella* bacterins can produce measurable antibody responses to bacterial proteins in calves and mature cattle. However, calves vaccinated with a killed bacterin are not able to produce anti-LPS antibodies until 12 weeks of age,[562] and optimum responsiveness does not occur until 1 year of age.[563] Most controlled studies in which calves were vaccinated with a killed *Salmonella* bacterin and orally challenged reported lack of protection.[564–566] One small study that reported good protection after vaccination of 3- to 6-week-old calves with two doses of killed bacterin used intramuscular challenge.[567] Another study in 6-month-old cattle found that a single intradermal dose of heat-killed *Salmonella* Dublin protected against intravenous challenge.[568] Vaccination of cattle 3 months of age or older with two doses of killed *Salmonella* bacterins is likely to be useful for preventing salmonellosis. A newer *Salmonella* vaccine (SRP) using subunit technology has been conditionally licensed. Although little has been published on this vaccine, the clinical impression is that it has been successful in controlling disease caused by multiple different serotypes of *Salmonella* in some cases.

Vaccination of adult cows, with passive transfer of antibody to calves through colostrum, frequently is used in dairies to control calfhood salmonellosis. Controlled trials evaluating passive protection have produced mixed results, with some indicating lack of protection[566,569] and others demonstrating some protection in very young calves (5 days old).[570] Vaccination of dry cows may be useful for helping to control salmonellosis in calves younger than 3 weeks of age but is probably minimally effective for controlling salmonellosis in calves older than 3 or 4 weeks. Anecdotal reports exist of protection against salmonellosis from vaccinating young calves several times with a gram-negative core antigen vaccine (Endovac-Bovi*). Another gram-negative core antigen vaccine, a J5 *E. coli* bacterin (J Vac†, J-5‡), reduced the mortality rate from naturally occurring salmonellosis in dairy calves vaccinated at 3 and 17 days of age.[571]

* Entervene-d, Fort Dodge Animal Health, Fort Dodge, IA.

† Agrilabs Inc., SRP S. Newport vaccine, conditional USDA license.

* Endovac Bovi, Endovac, Inc.

† J Vac, Merial, Iselin, NJ.

‡ J-5, Bayer Animal Health, Shawnee Mission, KS.

48.49 GRAM-NEGATIVE, CORE ANTIGEN BACTERINS

All genera and species of gram-negative bacteria contain a common set of gram-negative core antigens, which are present in the deeper layers of the bacterial cell wall.[572] Endotoxin from gram-negative bacteria is thought to play an important role in the production of the clinical signs, biochemical and hematologic alterations, and pathologic lesions associated with a wide variety of bovine diseases caused by gram-negative bacteria,[572] including coliform mastitis (caused by *E. coli, Klebsiella* species, or *Enterobacter aerogenes*), *Pasteurella* bronchopneumonia and fibrinous pneumonia, and salmonellosis. Gram-negative core antigen vaccines are designed to reduce the severity

of clinical signs associated with gram-negative sepsis and endotoxemia. They offer breadth against all gram-negative infections.

48.49.1 General Considerations

Three gram-negative, core antigen, oil-adjuvant vaccines are currently marketed. Two use the J5 Rc-mutant strain of *E. coli*. This strain of *E. coli* lacks the serotype-specific O-chain surface antigens that ordinarily prevent deeper cell wall antigens from contacting the host immune system and stimulating production of antibodies against gram-negative core antigens.[572] The third vaccine uses an Re-mutant strain of *Salmonella* Typhimurium.

Theoretically, gram-negative core antigen vaccines would be expected to reduce the severity of disease manifestations but not the rate of occurrence of disease. In four different clinical trials, however, the incidence of clinical coliform mastitis in dairy cows was reduced by 69%, 72%, 80%, and 82%, respectively, by vaccination with a J5 *E. coli* vaccine.[573–575] These data are consistent with the hypothesis that antibodies induced against gram-negative core antigens assist in both the destruction and the removal of intact bacteria and in the neutralization of endotoxin. In the trial in which clinical coliform mastitis was reduced by 82%, however, vaccination did not reduce the incidence of subclinical intramammary coliform infections that were present at the time of calving.[575]

48.49.2 Vaccination Programs

Recommendations for use of these bacterins to prevent coliform mastitis and scours are summarized in Table 48-13. Cows should not receive any other vaccine containing gram-negative organisms (*Pasteurella, Salmonella, Brucella, Campylobacter [Vibrio], H. somnus, E. coli*, or *M. bovis* bacterins) within 5 days of vaccination with J5 bacterin.

A J5 *E. coli* bacterin also has successfully reduced morbidity and mortality in experimental *Salmonella* Typhimurium infections in calves.[576] However, because of the short half-life of passively acquired antibodies stimulated by gram-negative core antigen vaccines,[577] vaccination of dry cows is unlikely to be an effective control measure for salmonellosis in calves except when calves are exposed to and infected with salmonellosis in the first week or two after birth. Salmonellosis in dairy calves often occurs after 2 weeks of age. However, when vaccinated at 3 and 10 days of age with an oil-adjuvant J5 *E. coli* bacterin, calves do develop strong antibody responses by 17 days of age; this strong antibody response occurs even in the presence of passively acquired antibodies to gram-negative core antigens.[578] Consequently, a combined program in which both dry cows and neonatal calves are immunized against gram-negative core antigens appears to be a promising approach for reducing the severity of salmonellosis in neonatal dairy calves.

Table 48-14 General Considerations for Use of Clostridial Seven-Way and Eight-Way Bacterin-Toxoids*

	Coverage Designation*	
Protection, by Species	**Seven-Way**	**Eight-Way**
Clostridium chauvoei	x	x
Clostridium septicum	x	x
Clostridium novyi B	x	x
Clostridium sordellii	x	x
Clostridium perfringens type C	x	x
Clostridium perfringens type D	x	x
Clostridium perfringens type B†	x	x
Clostridium haemolyticum (*novyi* type D)		x
Dose (mL)	2–5	5
Recommended boosters	After 2–4 weeks for *C. sordellii* and *C. perfringens* C and D; after 5–6 months for *C. novyi* type B and *C. haemolyticum;* calves vaccinated initially at <3 months of age should be revaccinated at 4–6 months (or at weaning)	
Comments	No use <21 days preslaughter	

* Note that many combinations are available commercially, including some that also contain immunogens against nonclostridial diseases. Some of these combinations also include tetanus toxoid.

† No currently licensed product is produced by use of cultures of C. *perfringens* type B, but protection against type B infection is implied by the inclusion of toxoid prepared against type C (beta-toxin) and type D (epsilon-toxin) strains.

In a field study, vaccination of healthy dairy calves with an oil-adjuvant J5 *E. coli* bacterin at 3 and 17 days of age reduced the mortality rate from salmonellosis.[571] (In this study, the dams were not vaccinated.) In addition, the morbidity rate from undifferentiated respiratory disease was significantly reduced by 9%.[576] In a parallel study in poorly nourished calves, however, vaccination actually increased the cumulative 60-day mortality by 113%.[571] These kinds of vaccines may prove more effective for reducing the severity of *Pasteurella* infections of the lung when used in older calves.

48.50 CLOSTRIDIAL VACCINES

J. Glenn Songer

Clostridia produce acute and frequently fatal disease, with pathogenesis often mediated by toxic proteins.[579] Prevention is often based on immunoprophylactic amelioration of the effects of these molecules. However, the ready availability of inexpensive, efficacious bacterins, toxoids, and bacterin-toxoids has not eliminated clostridial infections. Accurate diagnosis remains an important component in management of clostridial diseases.[580,581]

Immunization against clostridial diseases can be complicated by the development of "site reactions," leading to trimming at slaughter.[582] These problems are exacerbated by the multivalent nature of many modern products and have stimulated the biologics industry to seek a new paradigm for preparation and delivery of immunoprophylactic products. Approaches have included concentration of the antigen into a smaller dose and use of alternate adjuvants; recombinant proteins, delivered by conventional means, by application of "slow-release" media, or by in vivo expression from attenuated bacterial delivery systems, will likely be a major focus of effort.

48.51 *CLOSTRIDIUM CHAUVOEI* (BLACKLEG) BACTERINS

Blackleg is not uncommon, in spite of the long-term availability of generally effective bacterins. Ingestion is probably the most common route of exposure in cattle, and dormant spores seeded to skeletal muscle germinate when muscle damage provides appropriate conditions. Affected animals have fever, anorexia, depression, and lameness, with extensive dry and emphysematous to edematous, hemorrhagic, and necrotic lesions. Diagnostically, it is important to distinguish between blackleg and malignant edema.

As with other histotoxic clostridial infections, vaccination against blackleg is universally advocated, especially in cattle under the age of 2 years. Dogma is that protection arises from the immune response to a heat-labile soluble antigen, but *C. chauvoei* produces alpha-toxin and several other toxic factors, which may be equally important targets.[583,584] Recommendations for immunization are summarized in Table 48-14.

48.52 *CLOSTRIDIUM SEPTICUM* (MALIGNANT EDEMA) BACTERINS

Wound infections caused by *C. septicum* (malignant edema)[585] usually follow direct contamination of a traumatic wound, including genital tract infections after mismanaged deliveries. Infection spreads along fascial planes, and lesions proceed from warm and pitting to crepitant and cold. Death commonly occurs in less than 24 hours. Braxy is a form of enteric infection that occurs not uncommonly in calves.[586] Diagnosis is often by use of a fluorescent antibody test.[587]

A single immunizing dose of *C. septicum* bacterin yields adequate protection, but annual booster vaccination is recommended in high-risk situations[588] (see Table 48-14). Vaccines elicit antibody responses to both somatic and toxin antigens, and recent findings suggest a central role for alpha-toxin.[589,590]

48.53 *CLOSTRIDIUM NOVYI* TYPES A AND B (BIGHEAD AND INFECTIOUS NECROTIC HEPATITIS) BACTERINS

48.53.1 *Clostridium haemolyticum* (*Clostridium novyi* type D) (Bacillary Hemoglobinuria) Bacterins

C. novyi toxigenic types A and B cause myonecrosis in humans (gas gangrene) and domestic animals (bighead of sheep) and infectious necrotic hepatitis (black disease of sheep and cattle).[591] The hallmark lesion is edema, likely resulting from vascular damage caused by alpha-toxin. Dormant spores are often found in Kupffer cells but germinate when liver injury provides appropriate conditions. Type C strains are nontoxigenic and therefore nonpathogenic.[592]

Clostridium haemolyticum (*C. novyi* type D) beta-toxin mediates the pathogenesis of redwater, usually in well-nourished animals at least 1 year of age. Liver damage caused by migrating flukes encourages germination of dormant spores in Kupffer cells. Dissemination of beta-toxin via the bloodstream results in intravascular hemolysis, hemorrhage, and hernoglobinuria,[593,594] and death ultimately results from anoxia. A vaccination program is essential for herds pastured in endemic areas. When light exposure to fluke metacercariae is expected, a single annual dose of bacterin should be administered to all cattle over the age of 6 months, before they are pastured in the spring. With heavy exposure to flukes, a booster dose should be administered in season. The prominent roles of alpha- and beta-toxins suggest that they may find use in second-generation immunoprophylactic products.

48.54 *CLOSTRIDIUM BOTULINUM* (BOTULISM) AND *CLOSTRIDIUM TETANI* (TETANUS) TOXOIDS

Botulism is caused by *C. botulinum* neurotoxins, which block acetylcholine release from cholinergic nerve endings.[595,596] Type C is most common in cattle in the United States. Direct contamination of feeds by the organism sometimes leads to intoxication, but it is more commonly associated with an animal carcass in the feed. Clinical signs include incoordination, flaccid paralysis, and difficulty in swallowing; respiratory paralysis eventually causes death.[597,598]

Toxoids of botulinum toxins can be employed for immunoprophylaxis, but vaccination is usually practiced only in populations at immediate risk, such as beef cattle grazed on phosphorus-deficient range land.[599] Feeding of poultry litter poses as similar problem, in that it may contain animal remains.

Spores of *C. tetani* originate in soil and are usually introduced traumatically to animal hosts, where they germinate and produce tetanus neurotoxin.[600] Tetanus can develop in dairy cows as a postparturient complication and in calves after castration by the elastrator method.[601] Toxin moves retrograde, binding to presynaptic axonal terminals and resulting in muscular tremor and increased stimulus response; continued motor neuron hyperactivity causes sustained tetanic spasms in the innervated muscles and then permanent rigidity. Death is due to respiratory failure.

Acquired resistance to tetanus is based on circulating antitoxin, and widespread vaccination with toxoid has dramatically lessened the impact of tetanus on animal production. Neonatal passive immunity is followed by

active immunization with toxoid after 2 to 3 months. Boosters are commonly recommended at 1- to 5-year intervals. Passive immunotherapy is directed toward neutralization of preformed toxin, although it is much more effective when used prophylactically than therapeutically. Universal vaccination is not usually recommended as a cost-effective means for control of tetanus.

Table 48-15 Diseases of Cattle Caused by *Clostridium perfringens*

C. perfringens Type	Diseases In Domestic Animals	Major Toxins
A	Myonecrosis, enterotoxemia, abomasitis, possible sudden death	Alpha
B	Neonatal hemorrhagic enteritis	Alpha, beta, epsilon
C	Neonatal hemorrhagic or necrotic enterotoxemia	Alpha, beta
D	Enterotoxemia	Alpha, epsilon
E	Enterotoxemia	Alpha, iota

48.55 *CLOSTRIDIUM PERFRINGENS* TOXOIDS

C. perfringens causes a wide variety of diseases in domestic animals, and those of greatest importance affect the gastrointestinal tract[602] (Table 48-15) (see Chapter 32). Type B infections are apparently extraordinarily rare in the United States, but it has been speculated that their pathogenesis can be explained by additive or synergistic effects of beta- and epsilon-toxins. Type C strains multiply rapidly in the gut of neonates, and in this relatively trypsin-free environment, beta-toxin produces local hemorrhage and necrosis, as well as systemic effects.[603] Type D strains fill intestinal niches opened by sudden dietary changes, and epsilon-toxin in circulation damages the central nervous system and other systems distant from the gut.[604] Type E causes hemorrhagic enteritis in calves, and its virulence is based apparently on the action of iota-toxin.[605]

The current enigma is type A infections. Although long accepted as causes of lamb enterotoxemia,[606] fowl necrotic enteritis, and enteritis in dogs and horses, they are increasingly recognized as causes of enteritis in piglets and calves. Little is known about the pathogenesis of type A enteric infections, but type A strains are commonly found in cases of tympany, abomasitis, and abomasal hemorrhage and ulceration in calves.[607,608]

Most agree that routine vaccination against type C enterotoxemia is required only in herds in which the disease has been documented. The usual practice is to vaccinate the dam, providing passive immunity via colostrum. Initial immunization should be followed by a booster after 3 to 4 weeks, with the second dose (and subsequent annual boosters) administered approximately 2 weeks before calving. Type D enterotoxemia occurs sufficiently infrequently in cattle that many believe vaccination to not be cost-effective. No commercial products are licensed in the United States for use against infections by strains of types A and E, and production of autogenous toxoids or bacterin-toxoids has become quite common; anecdotal evidence suggests remarkable efficacy in many cases. Similar products have been produced from strains of type E. These should be used with the awareness that, unlike beta- and epsilon-toxin concentrations in commercial products, alpha- and iota-toxin concentrations in autogenous toxoids may not be optimal.

48.56 *CLOSTRIDIUM SORDELLII* BACTERINS

C. sordellii is commonly found in feces of domestic animals, as well as in the soil, and is occasionally isolated from fatal myositis, liver disease, and sudden death in cattle. Edema in the subcutaneous tissues and along fascial planes of muscles and subendocardial hemorrhage are common signs. The organism produces numerous toxic or putatively toxic substances, foremost of which is a toxin that resembles toxins A and B of *Clostridium difficile*.[609] Immunization is achieved by administration of multiway bacterin-toxoids (see Table 48-13).

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48.57 MISCELLANEOUS BOVINE RICKETTSIAL, BACTERIAL, AND VIRAL DISEASE VACCINES

Derek A. Mosier

48.58 ANAPLASMOSIS

Anaplasmosis is a vector-borne or mechanically transmitted disease caused by the rickettsia *Anaplasma marginale*.[610] The disease occurs worldwide and is most prevalent in tropical and semitropical areas. Anaplasmosis is the only major tick-borne disease of cattle in North America, being enzootic in the southeastern and some midwestern and western states and sporadic in the northern states and Canada.[610–612] In enzootic areas with adequate numbers of arthropod vectors, most adult cattle become naturally immune through repeated exposure. Maternal antibodies protect calves until they also become subclinically infected and develop immunity. Disease is more severe in older cattle than in calves, and nonimmune older cattle are particularly at risk when they are moved into an endemic area.[610] Susceptibility to disease occurs when there is a lack of arthropod vectors to maintain natural infection and immunity or when a nonimmune adult is introduced into an enzootic area. In these situations or when vector or environmental conditions suggest an increased risk of disease, vaccination can be beneficial.

No widely marketed commercial vaccines against anaplasmosis were available as of 2006 in North America. A killed vaccine* is available in some states including Florida, Louisiana, Texas, Oklahoma, Arkansas, California, Oregon, Nevada, Tennessee, Mississippi, Indiana, Iowa, Illinois, and Kansas and in Puerto Rico. The vaccine employs the same *A. marginale* antigens and purification procedure that was used for the discontinued Plazvax† vaccine. The killed vaccine is not USDA licensed, but it is USDA approved for use as an experimental vaccine. The vaccine has reportedly been used successfully in cows at all stages of pregnancy without an episode of neonatal isoerythrolysis. In endemic areas the vaccine is recommended for use just before the onset of the vector season. Vaccine-induced immunity does not generally occur until 2 weeks after administration of the second dose of an initial series or 2 weeks after a booster dose in previously immunized cattle.[612] Vaccination does not prevent infection or clinical disease and does not eliminate *A. marginale* from a herd, but it does reduce the severity and incidence of disease.[610,611] Inactivated vaccines could be used in conjunction with oxytetracycline in the face of outbreaks to provide both temporary and more prolonged protection.[611]

A sheep-passaged, modified live vaccine‡ has been used in California and Latin America.[613] Because this vaccine causes mild clinical disease, it has limited use for vaccination of mature susceptible cattle.[610,613] If the vaccine is administered to cattle over 2 years of age, anemia, severe clinical disease, and death may occur, especially in bulls and heavily lactating cows.[613] The vaccine is recommended for use in healthy cattle between 1 month and 2 years

of age and is most commonly administered to 7- to 24-month-old cattle in herds in endemic areas. Concurrent use of certain antibiotics or other live or modified live virus vaccines is contraindicated.

A live vaccine* derived from *A. marginale* subsp. *centrale*, a less pathogenic species or subspecies of *A. marginale*, is used in some countries but not in North America.[614,615] This vaccine consists of standardized and frozen red blood cells from splenectomized cattle that were infected with *A. marginale* subsp. c*entrale*. The vaccine is recommended for use in 4- to 9-month-old cattle; older cattle have an increased risk of severe vaccine-induced disease. The vaccine produces mild disease but protects against subsequent severe disease caused by *A. marginale*. Immunity is considered long term, or possibly for life if subsequent natural exposure occurs to ensure the development of durable immunity.

Immunity to *A. marginale* is proposed to involve humoral responses to a variety of major surface proteins and enhanced macrophage phagocytosis and killing, both mediated by IFN-γ—producing $CD4^+$ T lymphocytes.[610,612,616–618] Inadequate protection from vaccines during field use can result from antigenic variability of the organism, geographic differences in the organism that result in a lack of cross-reactivity between *A. marginale* strains, and weak immune responses to protective *A. marginale* antigens.[610,615,617,618] Purified native, recombinant, and tick culture—derived *A. marginale* immunogens and DNA vaccines are being investigated for possible commercial use in the future.[615,617,619–622]

* Anaplasmosis Vaccine, University Products, LLC, Baton Rouge, LA.

† Plazvax, Schering-Plough Animal Health, Kenilworth, NJ.

‡ Anavac, BioLOGIC Laboratories, Davis, CA.

* Anaplasmosis vaccine, Onderstepoort Vaccines, Onderstepoort, South Africa.

48.59 INFECTIOUS BOVINE KERATOCONJUNCTIVITIS

The most common infectious agent associated with infectious bovine keratoconjunctivitis (IBK) is *M. bovis*.[623] Vaccination is most effective when done before fly season in herds with a history of problems. Certain breeds, such as Herefords and Hereford crosses, are particularly susceptible and may benefit from vaccination.[623] Commercial vaccines used to help prevent the disease consist of inactivated cultures of various strains of *M. bovis*.[624] Some products recommend two doses given 3 weeks apart for initial vaccination, beginning as early as 3 weeks of age to no earlier than 5 months of age. Other products recommend a single dose administered 3 to 6 weeks before the predicted onset of the disease season, with annual vaccination thereafter. *M. bovis* bacterins are also available in combination with seven-way clostridial bacterin-toxoids.[625] Although multivalent *M. bovis* bacterins can provide some protection in field use, efficacy varies depending on the *M. bovis* strains present in the bacterin and those responsible for disease.[623,626–630] Seven different disease-producing serogroups of *M. bovis* are recognized based on differences in pili, and there is variable cross-reactivity between serogroups.[624] Furthermore, pilin gene rearrangements and pilin-type switching can allow *M. bovis* to switch from expression of one type of pilus antigen to another, making it difficult to predict what serogroup(s) may be necessary for protection.[624,627,631] Therefore monovalent bacterins are generally ineffective in field use, and multivalent bacterins provide neither consistent nor reliable protection.[624,626,627,629] Vaccines must incorporate pili from all major serogroups or conserved, immunogenic portions of all serogroups to provide optimum protection.[624,627–630,632] Experimental recombinant vaccines containing cloned pili of various serogroups have demonstrated some promise for future vaccines.[624,626,628] Another immunogen considered important for protection is *M. bovis* hemolysin/cytolysin.

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[623,624] Experimental vaccines containing hemolysin/cytolysin preparations have shown some efficacy in experimental trials.[623,624,633,634] Other potential immunogens include iron-regulated OMPs, proteases, fibrinolysins, and phospholipases.[623,624] Vaccine-induced protection is correlated predominately with a suitable lacrimal (IgA) mucosal immune response and not with serum antibody levels to *M. bovis* antigens.[623,624] Therefore an antigen delivery system that enhances mucosal immunity is an important feature of an effective vaccine. The presence of other agents contributing to IBK (e.g., *Moraxella [Branhamella] ovis, Mycoplasma bovoculi*, or BHV-1) should also be considered when there is poor *M. bovis* vaccine efficacy.[635] Autogenous *M. bovis* vaccines have not been consistently effective against the disease.[623,636] Use of modified live virus vaccines for IBR is contraindicated in the presence of an outbreak of IBK because it may exacerbate the IBK.[623]

48.60 STAPHYLOCOCCAL MASTITIS

Staphylococcus aureus is considered one of the most important causative agents of bovine mastitis.[637] Vaccination against *S. aureus* may be beneficial in dairy herds that have an existing mastitis problem.[637,638] However, vaccination in well-managed dairy herds with a low level of staphylococcal mastitis may not provide much economic benefit.[638] Staphylococcal bacterins contain antigens from multiple strains or serotypes of *S. aureus*.[639,640] The recommended vaccination protocol is two doses given 2 weeks apart followed by revaccination at 6-month intervals. Vaccination can start at 6 months of age, and one of the semiannual doses should be given 3 to 4 weeks before calving. Vaccination with *S. aureus* bacterins does not generally eliminate disease but can substantially reduce clinical mastitis and the incidence of subclinical and chronic staphylococcal infection.[638,641–644] Vaccination may be more effective in heifers because of their initial lower basal immunity compared with older cows.[642] The benefits of immunity induced early in life include the abilities to clear the organism and to resist chronic infection on initial natural exposure.[645] Vaccination during the dry period may be more effective than vaccination during lactation.[637] In some but not all studies, vaccination has reduced somatic cell counts in milk.[642,643,645] Vaccination in combination with antimicrobial therapy has been successfully used to eliminate chronic staphylococcal mastitis.[646]

In considering the use of staphylococcal vaccines, the prevalence of various pathogens that can cause mastitis must be considered. For mastitis caused by *S. aureus*, differences between the *S. aureus* strains in vaccines and the strains specifically responsible for the disease may diminish the efficacy of the vaccine.[637,640,644] Experimental trials suggest that more effective vaccines may be derived by stimulating immune responses to combinations of *S. aureus* capsular polysaccharide.[647] A vaccine based on technologies used for human staphylococcal vaccines that incorporates capsular polysaccharide from the three *S. aureus* serotypes most commonly associated with mastitis stimulated immunologic parameters necessary for protection.[648] These studies may form the basis for more effective vaccines in the future.

In herds in which other pathogens are a major cause of mastitis, *S. aureus* vaccines may be of minimal benefit.[638,641] Other important causes of bovine mastitis include *Streptococcus* species (e.g., *Streptococcus uberis*, *Streptococcus dysgalactiae*, and *Streptococcus agalactiae*) and coliform bacteria (e.g., *E. coli*).[637,649] *Streptococcus agalactiae* vaccines generally are not protective, but other *Streptococcus* species are responsive to vaccination.[649] Experimental vaccines composed of bacterial proteins derived from *S. uberis* and *S. dysgalactiae* reduced somatic cell counts compared with controls after challenge.[650,651] *E. coli* J5 vaccines have also been used to successfully reduce the severity of mastitis (reviewed elsewhere in this section).

48.61 ANTHRAX

Anthrax is an acute, highly fatal disease caused by *B. anthracis*.[652] Vaccination has proven to be an effective means of controlling the disease in endemic areas and in the face of outbreaks.[653,654] Bovine anthrax vaccines are derived from the live toxigenic, nonencapsulated spore vaccine developed by Sterne and consist of spores suspended in a diluent containing saponin and glycerin.[655] Annual vaccination of livestock in areas of endemic anthrax is recommended 4 weeks before outbreaks are expected. A single dose generally provides adequate immunity, but a second dose given 2 to 4 weeks after the first is often recommended.[656] Cattle should not be vaccinated within 42 days of slaughter. Antibiotics should not be administered within 7 days of vaccination to avoid interference with in vivo growth of the vaccine organism. Vaccination in the face of an outbreak does not protect all cattle, but the spread of infection and the number of new cases generally declines within 10 days.[654,657] Localized subcutaneous edema commonly develops at the injection site within 24 hours; it may last for several days and is sometimes severe.[653] Since the intentional release of *B. anthracis* via the mail system in 2001, there has been increased interest in technologies for the development of an efficacious, long-acting human vaccine for anthrax.[653,658–662] Although some of these technologies could hold promise to reduce some of the localized side effects of the current bovine vaccine, it is unlikely that a new bovine vaccine will match the safety and efficacy of the Sterne strain vaccine in the foreseeable future. All anthrax outbreaks should be reported to local regulatory and public health officials, and appropriate guidelines for vaccination should be followed, including quarantine and vaccination of all susceptible livestock on affected and surrounding premises.

48.62 INTERDIGITAL NECROBACILLOSIS (FOOT ROT)

Interdigital necrobacillosis (foot rot) in cattle results from interdigital infection with *Fusobacterium necrophorum* with lesser contributions from *Prevotella (Bacterioides) melaninogenica* and sometimes *Dichelobacter (Bacterioides) nodosus* and other bacteria.[663–665] Commercial *F. necrophorum* bacterins to aid in the prevention of foot rot (and hepatic necrobacillosis) are available for use in cattle. Recommendations for initial vaccination are two doses given 3 to 4 weeks apart, followed by annual revaccination. Vaccination is also recommended when endemic conditions exist or when exposure is imminent. The efficacy of *F. necrophorum* vaccines is not clear, but some benefit has been demonstrated in experimental studies and field trials.[666,667] Vaccination is especially recommended in herds that have a high incidence of disease.[666] Protective immunity most closely correlates with the level of anti-LKT antibodies.[668,669] A leukotoxoid vaccine composed of cell-free supernatant from a high LKT—producing strain of *F. necrophorum* was effective in reducing experimental hepatic necrobacillosis[669] and presumably would have some benefit against interdigital *F. necrophorum* infection. An autogenous vaccine containing *D. nodosus* reduced the severity of interdigital dermatitis but not of necrobacillosis.[670]

48.63 PAPILLOMATOUS DIGITAL DERMATITIS (FOOTWARTS)

Papillomatous digital dermatitis, or footwarts, can be a serious problem in dairy cattle.[671,672] The disease is characterized by ulcerative to proliferative digital lesions that most often occur in replacement heifers and younger cows after introduction into a milking herd.[671–673] Risk is greatest in larger dairy breeds in herds of greater than 500 head. The cause of the disease is uncertain, but *Treponema* species—like spirochetes and flexible, gram-negative rods (*Serpens* species) have been incriminated.[673–676] Commercial bacterins are available for use as preventatives and/or aids to treatment and consist of killed cultures of *Serpens* species or *Treponema* species

organisms. The recommendations are for three doses administered subcutaneously at 3- to 4-week intervals, followed by revaccination every 4 to 6 months. Company field trials report reduced onset of new infections and sometimes more rapid resolution of existing infections in vaccinated cattle. Another study of clinically affected cattle in which vaccination was combined with treatment with topical lincomycin showed no significant improvement in vaccinated cows compared with unvaccinated ones.[677] The high recurrence rates of natural infection suggest that immunity to the disease is short-lived or weak.[673]

48.64 RABIES

Rabies is a highly fatal, zoonotic neurologic disease caused by a rhabdovirus.[678] Routine vaccination of cattle is not common in most situations. However, vaccination may be cost-effective in rural areas of Latin America, where vampire bats are important sylvatic vectors.[679,680] In endemic areas vaccination of valuable cattle or herds may be a reasonable precautionary measure.[678] This is particularly true in situations in which cattle are in frequent contact with human beings, in order to reduce the anxiety of animal workers and minimize the likelihood of human exposure. Currently licensed rabies vaccines for cattle contain inactivated, cell culture—derived virus.[681] The recommended regimen is initial vaccination at 3 months of age followed by annual vaccination thereafter. The duration of protective neutralizing antibody levels after initial vaccination can vary.[682] Therefore some experts have suggested that a second booster dose be given either 1 month after initial vaccination or at 6 months of age.[682,683] Subsequent annual revaccination induces strong anamnestic responses that persist for 1 year or longer.[682,683] In Latin America, modified live vaccines are sometimes used.[680] However, these do not stimulate the same level of immunity as do the inactivated virus vaccines. A Capripoxvirus vector expressing rabies virus glycoprotein has shown promise in providing long-term protection against rabies (and lumpy skin disease) and may be a cost-effective mechanism for rabies control in cattle in some developing countries.[684]

48.65 FIBROPAPILLOMAS (WARTS)

Fibropapillomas (warts) are manifested in a variety of forms and locations, each caused by a specific bovine papillomavirus (BPV).[685,686] Lesions associated with papillomaviruses can occur in the epidermis of the head, face, neck, and legs (BPV-1 and BPV-22), upper alimentary and urinary tracts (BPV-4), teats and udder (BPV-1, BPV-3, BPV-5, and BPV-6), and genital epithelium (BPV-1).[685–688] Immunity after infection or vaccination is virus type specific and is induced by viral structural proteins.[685,687–690] Therefore the efficacy of both autogenous and commercial vaccines depends on which viral antigens are incorporated into the vaccine and which virus type is responsible for the disease. Vaccines containing BPV-1 and BPV-2 are generally effective for prevention but not treatment of disease caused by the homologous virus.[687] Vaccines usually are ineffective for treatment or prevention of disease caused by BPV-3 and BPV-5.[687] Vaccination with recombinant capsid proteins of BPV-4 was effective in preventing papillomas after experimental challenge with BPV-4.[691] The interpretation of the response to vaccination against fibropapilloma can be complicated by spontaneous regression of some lesions.[685] Lesions associated with BPV-1 and BPV-2 usually spontaneously regress within 1 to 12 months, whereas lesions caused by BPV-3 and BPV-5 do not normally spontaneously regress.[687,692]

Commercial vaccines consist of inactivated, virus-laden tissue extracts derived from bovine papillomas.[693] The recommended regimen is an initial dose divided and given in at least two different sites, followed by a second dose in 3 to 5 weeks. Vaccination should continue for at least 1 year after elimination of disease from the herd. Autogenous vaccines can be made by homogenization and inactivation (0.3% formalin) of excised wart tissue,

followed by dilution of the homogenate in physiologic saline and filtration through gauze. Three 1- to 5-mL intradermal injections given at 1-week intervals are recommended. Vaccination is most commonly used with valuable animals destined for competitive shows or for overseas sale.[687] Vaccination can also be helpful as a preventive measure in herds with a high incidence of cutaneous fibropapillomas or to reduce the risk of penile fibropapillomas in groups of young bull calves.[685] Recombinant BPV proteins have shown promise in experimental studies and could form the basis for a vaccine that protects against all BPV types.[691,694] Vaccination with avian Newcastle disease virus vaccine has also enhanced clinical recovery from disease.[695]

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49 Chapter 49 Parasite Control Programs

Consulting Editors

Sherrill A. Fleming

The traditional approach to parasite control programs has focused on using the appropriate anthelmintic at appropriate intervals. Parasitic disease in domestic animals is assumed to be the result of not dosing the animals often enough with anthelmintics. Scant attention has been paid to the interaction of the parasite with the host and the environment because of the reliance on anthelmintics. These drugs have been placed directly into the hands of the producer, as the expertise of a veterinarian did not seem necessary in the control of parasites. However, reports of resistance to anthelmintics and emergence of new manifestations of parasitism are surfacing throughout the world. It has become increasingly apparent over the past 20 years that this approach to parasite control is no longer sustainable.

Secondary to the notion that parasitism is under control is the decrease in research to develop new anthelmintics. Currently there is little in pharmacologic development other than variations on the current anthelmintics. Research programs in parasitology of domestic animals are facing funding reductions as research priorities are shifted to other diseases. As producers and owners struggle to deal with the realities of anthelmintic resistance, veterinary medicine must reassess traditional approaches to parasite control programs. Veterinarians will need to reeducate themselves away from the traditional tools of deworming, anthelmintic rotation, and pasture rotation. Integrated management strategies incorporating selective use of anthelmintic agents, enhancement of host immunity to parasitic infection, and grazing and environmental management have become increasingly important in the design of sustainable parasite control programs.

The impact of parasitic infection varies widely with geographic area and management system. General guidelines may be suggested for parasitic control, but it is inadvisable to adhere to any rigid anthelmintic schedules or even management recommendations. The best parasite control programs are those designed with the goals of the producer in mind, as well as the costs and returns of treatment. Other factors that must be considered include the animal's environment, climatic variations, and geographic location. Although many producers and owners would like a “cookbook” approach to parasite control, these are rarely effective across the various management conditions. It is unfortunate that an epidemiologically and economically sound parasite control program designed for animals in one geographic area may be neither efficient nor effective in another location.

The most important concept in the design of sound parasite control programs is the interaction of the parasite with the host and the environment. An understanding of the life-cycle and epidemiology will suggest the most effective methods for parasite control. In this chapter parasite factors, host factors, and environmental factors affecting transmission and disease expression are discussed for each major class of parasites in each host species (horses, cattle, small ruminants). The methods of monitoring parasite infections and anthelmintic resistance are presented in detail. The classes of anthelmintics and their modes of action are discussed, and finally, coccidiosis in cattle and small ruminants is summarized at the end of the chapter.

49.1 EQUINE PARASITIC DISEASE

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From the perspective of parasite control, horses should be divided into two age groups: adults and young horses under the age of 18 months. Small strongyles are, epidemiologically speaking, the principal parasite of the adult horse.[1] The fecundity, rapid generation time, and emergence of anthelmintic resistance make control of small strongyles the primary focus of adult equine anthelmintic strategies. Parasite control in adult horses is also tailored to include tapeworms (*Anoplocephala* species), bots (*Gastrophilus* species), large strongyles (*Strongylus* species), and the equine pinworm *(Oxyuris equi)*. In addition to the parasites that affect older horses, horses under 18 months of age are susceptible to the equine roundworm, *Parascaris equorum*. Horses under 6 months of age are also sporadically affected by the equine threadworm *Strongyloides westeri*.

49.1.1 Small Strongyles

The small strongyles consist of more than 40 species of nematode parasites primarily of the genus *Cyathostoma*. Small strongyles have a direct and completely enteral life-cycle in which adults produce strongyle type eggs that are indistinguishable from those of large strongyles.[2,3] Eggs passed in the feces develop at a critical temperature range of 7.2° to 29.4° C (45° F to 85° F) to first-stage larvae (L_1), which hatch and undergo continued development on pasture, becoming second-stage larvae (L_2) then infective third-stage larvae (L_3). Transmission is almost totally limited to pasture, with little infection thought to originate from stalls or dry lots. The rate of development is directly proportional to the environmental temperature; development takes as little as 3 days to several weeks at lower temperatures. L_1 die quickly at higher temperatures, and freezing generally kills strongyle eggs. Resilience of the infective L_3 is dramatically different owing to retention of the L_2 cuticle, which protects from desiccation but also prevents continued feeding. Warm weather leads to rapid death of L_3 as energy stores are depleted by activity in the absence of intake. In contrast, at very low temperatures energy depletion does not occur, and L_3 remain viable in freezing conditions. Accordingly, L_3 disappear quickly in hot, dry climates but remain viable in the winter.

L_3 are ingested with herbage and exsheath in the small intestine, cecum, and ventral colon, where the majority enter a period of dormancy as early L_3 (EL_3) in the crypts and epithelial cells of the cecum and colon. Continued development through late L_3 to fourth-stage larvae (L_4) occurs within the cyst. Development to fifth-stage larvae (L_5), the sexually mature, egg-producing stage, occurs in the gastrointestinal (GI) lumen. At any given time EL_3 constitute the greatest proportion of cyathostomes.[4,5] Cyst formation within the wall of the large intestine conveys some degree of protection from the immune response and from anthelmintic therapy.[6] Practically speaking, limitations to drug diffusion may also be a factor in the generation of anthelmintic resistance for drugs with larvicidal activity. In contrast, anthelmintics that lack larvicidal activity should not be expected to exert resistance pressure in encysted forms. Therefore encysted stages remain effectively in refugia when nonlarvicidal anthelmintic therapies are used.

Encysted L_3 are an important clinical entity for several reasons. There is evidence that seasonal signals as well as signals from lumen-dwelling mature forms delay development of encysted larvae, creating an important reserve for reinfection of the lumen. When environmental conditions are not favorable to larval development, large numbers of EL_3 can remain dormant.[4,5] As seasonal conditions become favorable, large numbers of hypobiotic larvae are signaled to exit and complete their life-cycle.[7] In addition, lumen-dwelling adult small strongyles remain in balance with encysted forms such that anthelmintic killing of luminal parasites triggers a reemergence and repopulation of the lumen from the intramural reserve.[8] Studies of small strongyle—

parasitized ponies moved to a parasite-free environment indicate that the encysted stages can serve to reseed the lumen for at least 30 months of confinement under parasite-free conditions. Therefore it is obvious that under practical conditions of access to contaminated pastures, viable encysted larvae are present in the colon for years after ingestion, even in the absence of continued exposure. This would indicate that it is relatively difficult to "empty" horses of small strongyles.

Clinical syndromes associated with cyathostome infections have been extensively reviewed.[1] The larval challenge dose, age, prior cyathostome exposure, and immunity of the host interact to determine the clinical picture. Most infections are asymptomatic with little response to encysted larvae. Clinical signs result from larval penetration into or emergence from the large intestinal mucosa.[9] Despite an emphasis on diarrhea in most reports, weight loss is the primary clinical finding in horses with clinical cyathostomiasis. During an initial high-exposure infection, local irritation can result in decreased feed efficiency, anorexia, anemia, weight loss, and diarrhea as a result of local inflammatory reactions in the large intestine. Blood biochemistry and hematology may demonstrate neutrophilia, hypoalbuminemia, and hyperglobulinemia from 2 to 9 weeks after infection.[9–11] Prior exposure tends to hasten the onset of laboratory abnormalities.

Larval cyathostomiasis is a potentially fatal disease syndrome that results from a synchronous emergence of encysted larvae that disrupt the mucosal barrier of the cecum and ventral colon.[2,12] Fluid and protein transudation into the GI lumen and leakage of bacterial toxins into the vasculature are facilitated. All animals experience some degree of larval reemergence during winter or spring, but larval cyathostomiasis generally affects animals less than 6 years of age, when they have not yet acquired significant resistance to infection.[12–14] Classic clinical signs include colic, which may be severe, impaired GI motility, sudden-onset diarrhea, and weight loss. Weight loss, fever, and dependent edema have also been reported in the absence of diarrhea.[15] Some affected individuals may die acutely with few signs, whereas others may become emaciated and die over a period of 2 to 3 weeks.[2,12]

Signs consistent with larval cyathostomiasis have also been observed 7 to 10 days after administration of anthelmintics.[16] This is presumed to result from a synchronous reactivation of hypobiotic larvae that is triggered by removing adult parasites from the GI lumen.[8] It is conceivable that anthelmintic therapy during the period of seasonal cyathostome emergence superimposes signals for emergence on seasonal signals such that clinical disease is worse than either signal alone.

Cyathostome infection may also cause recurrent diarrhea in adult animals,[17] a severe weight loss syndrome with associated edema and pyrexia in young horses,[15] chronic weight loss leading to diarrhea,[18,19] cecocolic intussusception,[20,21] nonstrangulating infarction,[19,22] cecal tympany.[19]

Controlling small strongyle infection is the primary goal of anthelmintic therapy in adult horses. Anthelmintic resistance in small strongyles is a growing problem, and parasite control strategies must be tailored to minimize anthelmintic use and maximize the generation of natural immunity.

49.1.2 Large Strongyles

Three species of large strongyles—*Strongylus vulgaris, Strongylus edentatus*, and *Strongylus equinus*—parasitize the horse. All three species have similar preparasitic phases. However, the migratory route of *S. vulgaris* makes it, on a per-worm basis, the most pathogenic of the enteric parasites of the adult horse. Both the life-cycle of and pathology caused by *S. vulgaris* have been comprehensively reviewed.[70] Infective L_3 are

ingested from pasture. *S. vulgaris* L_3 penetrate the mucosa of the small intestine, molt to L_4 over 7 days, and then begin their arterial migration by penetrating the submucosal arteries. L_4 travel via the cecal and colic arteries (by 14 days postinfection), reaching the root of the cranial mesenteric artery and its main branches by day 21 after infection. Larvae mature over a period of 3 to 4 months, then return primarily to the cecum and colon via the arteries. After a short period of maturation within the wall of the cecum and colon, the young adult parasites are released into the lumen of the intestine, where they mature in another 6 to 8 weeks. The prepatent period is 6 to 7 months.

Pathology and accordingly clinical signs *of S. vulgaris* infection result from the extensive larval migrations through the mesenteric arterial system.[23–25] Larval migrations result in marked cellular infiltration and damage the endothelium of the arteries, leading to thrombus formation. The walls of all branches of the ileocecal colic artery are affected, and with chronicity the vessels become thickened and dilated with aneurysm formation. Disease results from thrombus showering of the bowel, leading to multifocal avascular necrosis in areas of the intestine that are supplied by the occluded arteries. Clinically affected horses show varying degrees of pain depending on the nature of the infarcts. Fever and serosanguineous peritoneal fluid with elevated protein and red and white blood cell counts are common.

The life-cycle of *S. equinus* was characterized by Slocombe.[26] *S. equinus* also invades the wall of the small intestine, cecum, and colon, causing formation of small cystic and hemorrhagic nodules where the organisms molt to L_4. Twelve to 14 days after infection larvae exit the nodules, traversing the peritoneal cavity to the liver by 19 to 20 days after infection. Larvae remain in the liver for at least 12 weeks and then return to the large intestine by traversing the abdominal cavity directly or passing through the pancreas and then the abdominal cavity. By 15 weeks postinfection mature L_5 penetrate the lumen of the large intestine to complete the sexual phase of their life-cycle. The prepatent period of *S. equinus* is approximately 9 months.

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S. edentatus L_3 invade the walls of the terminal small intestine, cecum, and right ventral colon, where they penetrate the vasculature and then migrate to the liver via the hepatic portal vein.[27–30] Larvae remain in the liver for approximately 40 days, during which time they molt to L_4.[28] Larvae then migrate via the hepatic ligament to the parietal peritoneum of the right flank and molt to immature adults between 13 and 15 weeks after infection.[27] *S. edentatus* organisms then return to the large intestine via the mesentery between 3 and 5 months after infection, migrating through the walls of the cecum and colon and causing the formation of parasitic nodules. Adults emerge into the large intestine to complete the sexual phase of their life-cycle. The prepatent period is generally acknowledged to be approximately 11 months, although some authors suggest it may be as short as 6 months.[29]

The pathology of *S. edentatus* and *S. equinus* is fairly restricted to hemorrhagic nodules and parasitic cysts of the large intestine.[26–28] Such lesions are generally regarded as not severe enough to account for recognizable signs of colic. However, these lesions are evidence of poor deworming and a reasonable indicator that other large and small strongyle burdens are likely. Larval migrations through the liver may produce nodules and formation of fibrous tissue but are not considered clinically significant.

Although large strongyle infections are sporadically identified, they have been virtually eliminated in most areas through the widespread use of macrocyclic lactones and larvicidal fenbendazole regimens (10 mg/kg sid × five treatments) that kill both adults and migrating larvae.[31] This reflects the protracted prepatent period (>5 months) of the large strongyles, coupled with limited survival of larvae in the environment. Simultaneous treatment of all horses on a premises with larvicidal anthelmintic regimens eradicates the parasite because

despite continued ingestion of infective larvae from the pasture, the larvae never reach sexual maturity to produce eggs that can recontaminate the pasture. Therefore, given a maximal survival of large strongyle larvae of 12 months on pasture, larvicidal anthelmintics administered at 5-month intervals will effectively eliminate large strongyles from a premises within 18 months.

49.1.3 Tapeworms

During the last two decades the equine tapeworm, *Anoplocephala perfoliata*, has risen from clinical obscurity to be recognized as a significant potentiating factor in certain types of abdominal pain. The tapeworm life-cycle is indirect, cycling through oribatid mites, which horses swallow while grazing. Oribatid mites feed on organic material in feces on pasture, ingesting tapeworm eggs. Eggs develop into infective cysticercoids within the mite over a 2- to 4-month period. Tapeworms are hermaphrodites in that each infective form, the cysticercoid, contains the sexual organs of the male and female. After ingestion of cysticercoids by the horse, eggs develop in saclike body segments, termed *proglottids*, within 6 to 10 weeks.[32] Proglottids then break away and pass in the manure. Detection of tapeworm eggs in manure is extremely insensitive for identification of tapeworm infestation, and this is thought to reflect an uneven distribution of the eggs within equine feces, associated with patchy distribution of the disintegrating proglottids.[33–35] Accordingly, serologic diagnostic methods have proven advantages for detection of tapeworm infection.[35]

Three species of tapeworms have been identified in North America.[36,37] *A. perfoliata*, the most commonly identified, inhabits the region of the ileocecal valve. *Anoplocephala mamilliana* is the smallest and *Anoplocephala magna* the largest of the tapeworms that inhabit the small intestine and stomach. Postmortem investigations in Kentucky have indicated that the prevalence of tapeworm infections exceeds 50% of the population.[38,39] Serologic evaluation of horses from 19 U.S. states representing 10 geographic regions chosen to encompass the entire United States indicated an overall prevalence of 54%, with a geographic distribution that was lower in the western United States, ranging from 1.3% in California to near 100% in Minnesota.[40] Lower prevalence of tapeworm seropositive status in young animals and stallions was attributed to reduced access to pasture in these individuals.

Tapeworms infect horses of all ages, although a peak in worm burden has been identified in animals between 6 months and 2 years of age and in animals over the age of 15 years.[41] Susceptibility to tapeworms appears to mimic susceptibility to small strongyles in that some horses develop immunity, others maintain small burdens, and a small percentage (10%) of horses maintain large tapeworm loads regardless of deworming.[36,39,42–47] *Anoplocephala* organisms cause severe inflammation, ulceration of the mucosa, edema, and scarring at their attachment sites, which can in some cases partially obstruct the lumen.[48–50] This inflammation, in coordination with large quantities of acetylcholine found within *A. perfoliata*, is believed to interfere with normal peristalsis. Tapeworm burden increases the risk of spasmodic colic eightfold, and the risk of ileocecal impaction twenty-eight-fold.[51–54] Tapeworms also increase the risk of ileocecal intussusception and cecal rupture.[55–58]

Effective recommendations for the control of equine tapeworms in the United States are compromised because epidemiologic studies have been confined to Kentucky and investigations of oribatid mites are lacking. Tapeworm infections occur year-round throughout the world.[39,47,59–62] However, investigations in Spain, Switzerland, Sweden, and Kentucky have identified significant seasonal increases in *A. perfoliata* infection from late summer through early spring.[30,59–61,63–65] Comprehensive examination of 372 horses from Spanish abattoirs also demonstrated that *A. magna* infections peaked in fall.[60] Of importance, gravid *A. perfoliata*

organisms were not evident in summer and displayed an increasing seasonal prevalence peaking in spring, suggesting that strategic use of cestodicidal drugs before spring may be especially effective in interrupting the life-cycle.

Praziquantel (1 mg/kg) and double to triple doses of pyrantel pamoate (13.2 to 19.8 mg/kg) are efficacious in eliminating tapeworms.[66,67] Limited evidence suggests that pyrantel tartrate (2.64 mg/kg) for 30 consecutive days is also efficacious.[68,69] In the United States praziquantel is available only in combination with moxidectin or ivermectin. Annual treatment with an efficacious product is recommended for horses beginning at weaning. Available epidemiologic findings suggest that annual treatments might be of greatest benefit in late fall to minimize burdens and prevent the development of gravid forms. However, on farms with a confirmed tapeworm burden, based on fecal counts, serologic evaluation of the herd, or a history of tapeworm-related colics, treatments two to three times per year may be justified, especially during the late summer through early spring.

49.1.4 Bots

Two primary species of bot larvae infect horses in North America.[39,66,70,71] *Gasterophilus nasalis* lays eggs in the intermandibular region, whereas *Gasterophilus intestinalis* eggs are found attached to the forelegs. By day 5, larvae hatch and migrate to the mouth in the case of *G. nasalis* or enter the mouth as the horse rubs and scratches the eggs with its muzzle and teeth in the case of *G. intestinalis*. First-stage *G. intestinalis* larvae embed deeply in the tongue and migrate to the interdental spaces of the upper molars, where they molt to L_2, whereas *G. nasalis* larvae reside in the interdental spaces. L_2 are swallowed and come to reside in species-dependent predilection sites, where they molt to L_3. *G. intestinalis* organisms attach to the nonglandular lining of stomach in the region of the margo plicatus, and *G. nasalis* organisms attach to the most proximal portions of the duodenum, where they remain for up to 12 months. In late spring, larvae pass in the feces, pupate to adult flies over 3 to 9 weeks, and begin laying eggs again until fall. Fly activity ceases with the onset of cold weather.

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Moderate *Gasterophilus* species infestations are asymptomatic.[71] Large larval burdens in the tongue can cause inflammation and perhaps difficulty swallowing.[63–65] However, this association is not well recognized. Heavy loads in the stomach may be associated with gastric ulceration, abscessation, and rarely stomach rupture and peritonitis.[75,76]

Gasterophilus infection is easily controlled through once-yearly administration of boticidal drugs, ivermectin, or moxidectin.[77,78] Highest numbers of larvae are found in the stomach from winter through early spring.[71] Accordingly, timing of treatment should be in late autumn or early winter. Daily grooming to remove bot eggs, which are yellow and easily visible, minimizes infection.

49.1.5 Pinworms

The parasitic phase of *O. equi*, the equine pinworm, begins with ingestion of an embryonated egg containing infective L_3. Larvae hatch in the small intestine and come to inhabit the mucosal crypts of the cecum and colon. Maturation to gravid adults includes a lengthy maturation phase that ranges from 139 to 156 days, creating a prepatent period that approximates 5 months. Gravid females lay their eggs in clumps in a yellowish-grey gelatinous material around the anus. After completing their egg laying, the females pass out of the anus and die.

The primary clinical sign of *O. equi* infection is intense pruritus of the tail head that is referable to drying and cracking of the egg masses in the region of the anus. Tail rubbing facilitates deposition of the eggs in the environment. In severe infections, mild colic can result from inflammation of the cecum and colonic mucosa.

Benzimidazoles (BZDs), pyrantel pamoate, pyrantel tartrate, and the macrocyclic lactones are all efficacious against pinworms. Owing to the prolonged prepatent period, treatment regimens tailored to control ascarid or small strongyle infections will control *O. equi* infections. Frequent cleansing of the perineum will also limit spread.

49.1.6 Roundworms

Infection with the equine roundworm, *P. equorum*, is limited to young horses owing to the development of acquired lifelong immunity by 18 to 24 months of age.[79] The high prevalence, size, fecundity, and persistence in the environment make *P. equorum* the most pathogenic parasite of the young horse. The life-cycle of *P. equorum* is direct, with a hepatotracheal migration and a prepatent period of 10 to 12 weeks.[80,81] Mature ascarids range in length from 1 to 14 inches, and the females are extremely prolific, producing hundreds of thousands of eggs per day.[80] These eggs are very sticky, enabling them to adhere to pasture and surfaces in the environment from which they are ingested. Ascarid eggs are also extremely resistant to chemicals and the environment, remaining viable for over 10 years and being capable of withstanding bleach, iodine, cresol, quaternary ammonium compounds, and steam cleaning.[82] Over a period of weeks eggs mature to an infective stage in the environment characterized by the presence of L_3, which is visible within the egg. After ingestion, larvae emerge from the eggs in the small intestine, penetrate the intestinal wall, and travel via blood or lymphatics to the liver. Larvae migrate within the liver for approximately a week; they molt to L_4 before being carried, via the vasculature, to the lungs. Larvae break into the alveoli, ascend the bronchial tree, are swallowed and then mature to L_5 and reproduce.

Clinical signs referable to adult ascarid infection include weight loss, stunted growth, rough hair coat, a pendulous pot-bellied appearance, lethargy, depression, and abdominal pain.[83–85] Migratory stages of the parasite are commonly associated with respiratory signs including fever, coughing, and nasal discharge, which may be partially responsive to antimicrobial therapy but recur when therapy is discontinued.[81,84] The most immediately life-threatening effect of ascarid infection is the ascarid impaction which is an obstructive mass of dead worms occurring shortly after deworming in the face of high ascarid burdens.[86] Affected animals display signs of severe abdominal pain referable to small intestinal obstruction.

High fecundity and egg resistance make elimination of *Parascaris* from an infected premises virtually impossible. Ascarid burdens in weanlings often reach several hundred, yielding fecal egg counts (FECs) in the millions of eggs per gram feces (epg).[80] Pasture is the primary route of exposure to ascarids, and accordingly clean pastures (see the discussion under Clean Pasture) should be prioritized for young animals and mares with foals. Young animals are also commonly exposed when they lick the infected stall environment. Despite the chemical and environmental resistance of ascarid eggs, efforts should be made to decrease the environmental load by frequently removing manure from stalls and pasture (before development of infective stages); feeding horses off the ground in feeders that can be cleaned; washing stall surfaces with detergent and phenol-based disinfectant (especially in stalls that have held foals and weanlings); and bathing the mare, including her udder, before foaling. Anthelmintic protocols tailored to the control of *Parascaris* will also adequately control most other intestinal parasites of the young horse with the exception of tapeworms.

49.1.7 Threadworms

S. westeri is a sporadic cause of diarrhea in foals before weaning. *S. westeri* is acquired primarily through lactogenic transmission, with infections being acquired during nursing in the first few days postpartum.[87] Less commonly infection can be acquired from a wet environment.[88] The life-cycle is completely enteral, with the parasite infecting the small intestine and producing eggs within 6 to 14 days of infection.[87–89] Sources have reported acquired immunity to be complete by 6 to 12 months of age.[88–90] *S. westeri* transmission is significantly reduced, although not eliminated, by treating the mare with ivermectin at foaling.[90] Foals can be treated empirically with either ivermectin or oxibendazole (15 mg/kg) within the first 2 weeks of life or based on positive fecal examination results.[90–92]

49.1.8 A New Paradigm for Equine Parasite Control

For at least two decades administration of anthelmintics has focused on the practice of "rotation" or deworming of all horses with drugs from different anthelmintic classes, each separated by a predictable interval. These regimens are not in the patients' best interest for several reasons. First, rotation does not slow the progression of resistance and in fact actually selects for resistance to all drugs in the rotation.[93–97] Rotational regimens also provide no venue to detect anthelmintic resistance, and, because an alternate class of dewormer is used sequentially, resistance may be masked by the regular substitution of efficacious products in the deworming schedule. Equally, the concept of "slow rotation," in which a single anthelmintic is applied for an entire year, is not prudent because of the high prevalence of resistance among small strongyles.[6] Slow rotation, without monitoring the effectiveness of the anthelmintic by assessing for a reduction in FECs, allows resistant parasites to propagate unchecked for a prolonged period. During this time, parasites that are sensitive to the anthelmintic are selectively killed, allowing the resistant parasites to dominate the population. Computer modeling has demonstrated that the most effective method of delaying resistance is the simultaneous use of two effective and chemically distinct anthelmintics.

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Investigations focused on anthelmintic resistance have identified a phenomenon of individual variability in parasite susceptibility in many species including the horse. Certain individuals that are "more susceptible" or *permissive* to strongyle infection maintain higher quantitative FECs then their herdmates, despite identical exposures, and account for the majority of pasture contamination.[98,99] Other individuals can be identified that limit the infection and pass few to no eggs in their feces. Calendar-driven deworming ultimately translates to anthelmintic overuse in animals whose immune response can limit the infection, whereas suboptimal parasite control may result when the same treatment regimen is applied to susceptible individuals. Anthelmintic overuse hastens development of anthelmintic resistance.[100,101] Therefore the time-honored principle of simultaneous anthelmintic treatment of all herdmates is being rewritten to be simultaneous reevaluation of all herdmates and treatment of horses with moderate and high strongyle *susceptibility* as documented by elevated FEC.

The last two decades of anthelmintic research have determined that preserving a population of parasites termed *refugia* or said to be *in refugia* is critical to controlling anthelmintic resistance. The most basic biologic meaning of refugia is an isolated population of once widespread species. Refugia should be viewed as "wild-type" parasites that have not been selected for anthelmintic resistance. Accordingly, the genetics of parasites in refugia are critical to preventing dominance of anthelmintic-resistant strains. Refugia are protected during anthelmintic treatment of the host only when they are on pasture and, in the case of nonlarvicidal anthelmintics, when they are encysted. Because refugia are anthelmintic sensitive, a central tenant to their preservation is

decreasing the frequency of anthelmintic use, especially when parasite numbers are low in the environment. Balancing a desire for decreased anthelmintic treatments with maintaining the health of the horse can be achieved only through the rational application of routine FECs to differentiate horses that need treatment from those that do not.[6]

49.1.9 Factors Influencing Parasite Control Strategies for Adult Horses

The primary goal of parasite control in adult horses is to minimize infective small strongyle larvae on pasture. A thorough understanding of three factors is critical to the proper timing and selection of anthelmintics. These factors are the load of infective larvae in the environment, the residual capacity of the anthelmintic agent, and the horse's ability to limit egg excretion via an effective immune response.

Climactic conditions of a geographic region directly affect the lifespan of infective larvae and accordingly the load of infective larvae in the environment. This is exploited when developing a parasite control strategy by timing anthelmintic administration for the times of peak fecal egg production.[102] Ultimately such strategic timing will minimize the number of anthelmintic treatments, which limits resistance by decreasing selection pressure. In contrast, anthelmintic treatment should be avoided when pasture refugia are diminished, because such treatments place the greatest selection pressure on the population.[103] Pasture refugia are at their lowest numbers when climactic conditions limit the survival of infective larvae on pasture.

In warm temperate and subtropical or tropical climates such as the southern United States, refugia are at their lowest during the summer because larvae cannot survive the extreme heat of the southern climate, providing a period of grazing in the summer that is relatively free of exposure to small strongyles.[103,104] In this region, peak fecal egg production occurs from autumn (September) through spring (April). It is important to recognize that infective larvae are present on pastures in the warm temperate, subtropical, and tropical regions of the southern United States throughout the winter months. In the northern cool temperate regions, refugia are at their lowest during the winter, whereas larval development is favored during spring, summer, and fall.[103,105] Northern winters (November through March) do not support hatching of eggs nor larval development, although L_3 that have already developed sufficiently to be competent for infection do persist during these months.[105] This is important to recognize because rested pastures in northern climates remain infective until early summer, when rising temperatures cause the demise of L_3. Despite the fact that infective larvae are present on pasture in northern climates during winter, management practices, in which the horses are stabled and their manure is removed, limit winter exposure to infective larvae. This reflects the requirement for a moist environment in order for strongyle larvae to develop to infective L_3, conditions that are not achieved in the stall. Furthermore, ammonia from a dirty, wet stall environment is toxic to nematode larvae.[106] Together these factors create a winter period in northern climates that is relatively free from exposure to infective strongyle larvae.

In addition to climactic factors, the residual ability of a given class of anthelmintics to suppress egg excretion must be considered. This characteristic of each anthelmintic is reflected in the egg reappearance period (ERP), which is the time after treatment that a horse's feces will remain negative for strongyle eggs. The ERP has generally been reported to be on the order of 8 weeks for ivermectin[107–110] versus 12 weeks for moxidectin.[109] However, shortening of the ERP for ivermectin to 6 weeks has been demonstrated on some farms, raising concerns regarding reduction in efficacy and emerging resistance to macrocyclic lactones.[97,110,112] For pyrantel the ERP is on the order of 4 to 6 weeks.[108,110,112] ERP after BZD administration is on the order of 4 weeks, but periods as short as 2 weeks have been reported.[112,113] Longer ERPs reflect the residual ability of an

anthelmintic to prevent emergence and sexual reproduction of encysted small strongyle larvae. The clinician must recognize that BZD resistance is widespread in small strongyle populations, making monitoring of FEC reduction with these products especially important.[6,114] From the standpoint of formulating an anthelmintic treatment regimen, the ERP is a useful interval for reevaluating FECs after anthelmintic therapy in order to determine if an individual horse requires subsequent anthelmintic therapy. Shortening of the ERP may also be an early indicator of reduction in anthelmintic efficiency.

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The ability of a horse's immune response to limit strongyle infections and egg production directly influences the intervals between anthelmintic administration. Strongyle resistance is reflected in an index termed the *Strongyle Contamination Potential* (SCP), which is defined as the FEC 4 weeks after the ERP of the previous anthelmintic. At this time residual anthelmintic effects are exhausted, and the ability to limit fecal egg production is reflective of the immunity of the host. SCP has been categorized as low (<150 epg), medium (150 to 500 epg), and high (>500 epg), corresponding to approximately 40%, 25%, and 35% of the population, respectively.[112] FECs at the beginning of the parasite season (September in the south, April in the north) are also reflective of the relative immunity of the individual to small strongyles, because infective larvae are in low numbers on pasture at these times. Accordingly, FECs at these times are proportional to the individual's tendency to “permit” the development and sexual reproduction of the few larvae that are ingested, or more significantly, hypobiotic strongyle larvae that are emerging to complete their life-cycle.

49.1.10 Parasite Control Strategy for Adult Horses

To be effective, parasite control strategies must be multifactorial and take into consideration the husbandry and dynamics of the premises or owner, ages of the patients, and epidemiology of the parasites. Anthelmintic resistance issues have highlighted the need to employ all measures that minimize pasture contamination. Strongyles develop from eggs to infective L_3 outside the host, and simply removing feces from the environment before eggs become infective has been shown to provide parasite control that is superior to that of anthelmintic administration.[115] Horses maintained in environments with fecal removal had lower FECs and grazing area was increased by 50% when compared with cohorts that were given anthelmintics. Pasture vacuuming and manual removal of feces from pasture may not always be feasible, and such measures have been dismissed in deworming schemes of the past. However, with anthelmintic resistance rising and with the need to minimize reliance on anthelmintics in order to protect refugia, the ability of manure removal to virtually eliminate anthelmintic use should cause responsible veterinarians to strongly encourage some degree of environmental management.

When targeted deworming is applied, the deworming season begins in September in warm temperate, subtropical, and tropical climates of the southern United States and in April in the cool temperate climates found in the northern regions of North America. Quantitative FECs are performed and reflect the small strongyle susceptibility of the individual horses because environmental loads are minimal at these times. Anthelmintic treatments are administered according to treatment thresholds, which range from 100 to 500 strongyle type epg (generally 150 to 200 epg). Evidence-based medicine indicates that these thresholds are efficacious in decreasing anthelmintic administration while preserving health.[97,99,111,116] Lowering the treatment threshold imposes greater selection pressure for resistance and serves to limit immunity to small strongyles. After the initial evaluation and treatment at the beginning of the parasite season, FECs are repeated at intervals according to the ERP, with subsequent anthelmintic treatments being administered to only those individuals whose FECs exceed the treatment threshold. Within this program, the fall deworming should be with a macrocyclic lactone and praziquantel combination to target *Gasterophilus* species and *Anoplocephala* species. The cost of repeated fecal examinations may be concerning initially to owners employing targeted

deworming. However, such regimens have been shown to be economically viable because they decrease anthelmintic use as much as 78%.[97] Repeated evaluations of FECs indicate that individuals exceeding the treatment threshold at the beginning of the parasite season (or 4 weeks after the ERP of the previous anthelmintic) are likely to maintain elevated FEC and require repeated deworming at intervals consistent with the ERP. Animals with FEC below the treatment threshold should have FECs monitored according to the appropriate ERP and be dewormed when the treatment threshold is reached.

It is proposed that horses whose FEC exceeds 500 after the ERP or in the beginning of the parasite season (i.e., those with high SCP) should be singled out for larvicidal anthelmintic therapy.[112] See Table 49-1. This reflects the fact that these animals are permissive to the infection, allowing both pasture-derived larvae and emerging encysted larvae to complete their life-cycle and produce eggs that contaminate the pasture. These horses are a reservoir for contaminating the environment, harboring large numbers of hypobiotic larvae that repopulate the GI lumen when adults are removed by deworming. Both moxidectin and "larvicidal dose" fenbendazole (10 mg/kg for 5 days) have larvicidal activity against encysted small strongyles, making these agents especially useful in managing individuals that are highly permissive to strongyle infections.[117–119] However, it is important to recognize that neither moxidectin nor larvicidal dose regimens of fenbendazole are 100% efficacious. A report of small strongyle resistance to larvicidal fenbendazole doses in Kentucky yearlings should prompt caution in the use of such protocols because they exert extreme resistance pressure.[120]

A cornerstone of every deworming program is to identify anthelmintic resistance. Anthelmintic resistance is of tremendous concern in small strongyles, in which resistance to all commonly used anthelmintics, with the exception of the macrocyclic lactones, has been identified.[6] Shortening of the ERP is an important indicator of anthelmintic resistance in the horse.[121] However, the gold standard for detecting resistance has been the FEC reduction test (FECRT). FEC reduction (FECR) is determined by comparing FEC before and 10 to 14 days after anthelmintic administration. The percentage of reduction is calculated using the following formula:

$$\frac{\text{Pretreatment EPG} - \text{Posttreatment EPG}}{\text{Pretreatment EPG}} \times 100$$

The FECRT has several problems. First, the action levels to identify anthelmintic resistance have not been determined for equine parasites, so values are extrapolated from other species. Second, the FECRT is relatively insensitive, meaning that when anthelmintic resistance is identifiable by FECRT, resistance genes are widely disseminated within the parasite population. At this time egg reductions in excess of 90% are considered evidence of BZD and tetrahydropyrimidine efficacy. Values of 80% to 90% raise suspicion of resistance, and FECRs less than 80% indicate that resistance is present. In the case of the macrocyclic lactones ivermectin and moxidectin, egg reductions less than 98% are cause for concern.[6,122]

The primary concern with new additions to the herd is their ability to introduce resistant strongyles to a previously sensitive population.[6] In this respect it is especially important that farms without anthelmintic resistance take precautions to prevent the introduction of resistant strongyles. FECRT should be performed in conjunction with the initial dewormings, and larvicidal treatment regimens should be selected to kill encysted parasites, which might bear resistance genes. Both moxidectin and larvicidal regimens of fenbendazole may be used. However, the widespread prevalence of BZD resistance in small strongyles must be considered because larvicidal doses of fenbendazole may be inferior to moxidectin to prevent the introduction of resistant worms in new additions. Accordingly, single-dose administration of a macrocyclic lactone has been advocated for new arrivals after fenbendazole larvicidal regimens to remove remaining luminal worms. New additions should be quarantined until appropriate response to anthelmintic therapy, as supported by a reduction in FECs, is

available to substantiate that resistant parasites will not be introduced to the herd. On the other hand, horses staying less than 6 weeks may be efficaciously treated with ivermectin because ivermectin resistance is extremely uncommon and the ERP for ivermectin is 6 to 8 weeks.

Table 49-1 Efficacy of Various Anthelmintics Against Strongyles in Horses

		Large Strongyles		Small Strongyles	
Drug	**Dose**	**Adults**	**Larvae**	**Luminal**	**Mucosal**
BENZIMIDAZOLES*					
Febantel	5–6 mg/kg	+	–	+	–
Fenbendazole	5 mg/kg	+	–	+	–
	7.5–10 mg/kg daily for 5 days	+	–	+	+
Mebendazole	6–10 mg/kg	+	–	+	–
Oxfendazole	10 mg/kg	+	–	+	–
Oxibendazole	10 mg/kg	+	–	+	–
	20 mg/kg daily for 5 days	+	+	+	+†
PYRANTEL					
Pyrantel pamoate or embonate	6.6 mg/kg	+	–	+	–
Pyrantel tartrate‡	2.65 mg/kg daily	+	+	+	+
AVERMECTINS AND MILBEMYCINS					
Ivermectin	0.2 mg/kg	+	+	+	–
Moxidectin	0.4 mg/kg	+	+	+	+/–¶
OTHER					
Piperazine	110–200 mg/kg	–	–	+	–
Dichlorvos	30–35 mg/kg	+	–	+	–

All doses are for oral administration.

+, Highly effective; +/–, moderately effective; –, ineffective.

* Ineffective against benzimidazole-resistant strongyles, except for larvicidal regimens.

† Efficacy against EL_3 unknown.

† Pyrantel tartrate continually kills all stages of luminal parasites; prophylactic; prevents infection by newly acquired infective larvae.

¶ Moderate to high efficacy against L_3/L_4; poor efficacy against EL_3.

49.1.10.1

PARASITE CONTROL STRATEGIES FOR YOUNG HORSES

S. westeri is the earliest maturing nematode of foals, passing eggs by 10 to 14 days, followed by small strongyle eggs which can be detected at 6 weeks.[3,87–89] However, by virtue of its prevalence, size, fecundity, and pathogenicity in young horses, management of *P. equorum* is the primary focus of deworming strategies for horses under 18 months of age. Unfortunately, studies to identify treatment thresholds based on FEC, expected ERPs, and FECRT thresholds to identify resistance are not available. Anthelmintic strategies for controlling *P. equorum* should be expected to change as such data become available. In the absence of these data, current recommendations focus on interval administration designed to prevent egg production, which is known to exert significant anthelmintic resistance pressure in nematodes. Accordingly, it is prudent to document the presence of *P. equorum* on a premises by examining the feces for characteristic eggs. Four- to 6-month-old foals have been shown to have the highest *P. equorum* FECs, making them excellent sentinels.[123] Parasite control programs in young horses on farms that lack *P. equorum* should focus on small strongyles.

Several published reports show poor reductions in ascarid FEC after both ivermectin and moxidectin, indicating macrocyclic lactone resistance.[110,123,124] Daily exposure to low doses of pyrantel tartrate and monthly deworming with ivermectin are being scrutinized for their role in perpetuating anthelmintic resistance in equine parasites.[6,122] Daily administration of pyrantel tartrate has been shown to interfere with the development of acquired immunity to small strongyles.[125] Although the effect of daily pyrantel administration on immunity to ascarids is not known, inhibition of invasion and migration that are characteristic of this therapy could also limit immunity to ascarids. This is especially concerning in horses that have been maintained on daily dewormer and then introduced to heavily contaminated premises. In such horses the lower innate immunity to the parasite could increase morbidity associated with infection.

Monthly deworming with ivermectin has been advocated to decrease lung pathology in young horses caused by ascarid migration. However, ascarid resistance to ivermectin raises concern regarding the selection pressures imposed by monthly ivermectin administration. Accordingly, practitioners should monitor vigilantly for evidence of anthelmintic resistance in young horses where repeated ineffective deworming could yield burdens capable of causing an ascarid impaction on subsequent deworming with an efficacious product. A link between emerging ivermectin resistance in *P. equorum* populations and surgical ascarid impactions has been postulated.[126] Resistance should be considered a possibility with any anthelmintic agent, particularly when a single drug is used repeatedly. Guidelines for FECRT identification of *P. equorum* resistance are not available. However, FECR for both BZDs and pyrantel have been shown to reach 100% in ivermectin-resistant *P. equorum* populations, suggesting that values previously described for small strongyles are reasonable choices.[124]

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BZDs, tetrahydropyrimidines (pyrantel pamoate and pyrantel tartrate), and the macrocyclic lactones (ivermectin and moxidectin) are generally considered efficacious against ascarids. Moxidectin products are not approved for use in foals under 6 months of age. Recognize that doses of BZDs required to effectively kill ascarids are double the doses recommended to kill parasites of adult horses. This highlights the need for accurate weights to ensure proper administration, which is a problem in young horses, in which body weight is often estimated. This problem can be alleviated by use of weight tapes.

Although the timing of the initial anthelmintic treatment is influenced by the environmental load of *P. equorum*, treatment on endemic farms should begin at 8 to 10 weeks of age, which is the minimal prepatent

period after initial exposure.[80,81,127] Recognize that in addition to ascarid control, ivermectin administration should be incorporated at 5-month intervals if large strongyles are present on the farm. One of these treatments should be an ivermectin and praziquantel combination in the fall to kill *Gasterophilus* and *Anoplocephala* species. Both BZDs and pyrantel pamoate have a slightly shorter duration of ascarid egg suppression than the macrocyclic lactones because they do not kill migrating ascarids. The treatment interval with these compounds is 56 days, which is the minimum time required for migrating larvae not killed by BZD or pyrantel treatment to reach the intestine and produce eggs. More frequent administration of BZD or pyrantel maximizes resistance pressure without altering egg production unless shortening of the ERP occurs.

Macrocyclic lactones (restricted to ivermectin administration in foals) and larvicidal fenbendazole regimens (10 mg/kg × 5 days) have the advantage of killing all ascarids in the intestine as well as migrating larvae outside of the intestine.[128–129] See Table 49-2. Therefore treatment intervals shorter than 56 days with larvicidal drugs are still efficacious in the control of ascarid infections but maximize resistance pressure. On farms with a high *P. equorum* burden, ivermectin may be administered as early as 45 days of age. Treatment intervals as short as 30 to 45 days with larvicidal drugs have been recommended by some practitioners on farms with high ascarid loads to minimize lung pathology. These recommendations should be critically evaluated in light of the resistance pressure imposed by the practice. Treatment intervals after administration of larvicidal agents should approximate 70 days because the foal is essentially cleared of all ascarids and begins the cycle of infection anew after treatment. Commonly the recommended ivermectin interval is shortened to 60 days for brevity in communication. Regardless, larvicidal drugs should be followed by retreatment before 70 days, and nonlarvicidal agents require retreatment in 56 days. Treatments are repeated until the horse develops solid acquired immunity as supported by negative ascarid fecal examinations, which generally occurs by 18 months of age. Failure to remain within these intervals risks egg contamination of the pasture that persists for years.

Ascarid eggs are extremely resilient, and infection occurs from both pasture and fomites in the stall environment. Emerging anthelmintic resistance in *P. equorum* highlights the need to institute management practices that prevent ingestion of parasite eggs. Clean pastures (see below) should be provided for young animals and mares with foals. Manure should be removed at least twice weekly from stalls and pasture, before infective larvae can develop. Horses should be fed off of the ground in feeders that can be cleaned. Although ascarid eggs already in the environment cannot be eliminated, washing stall surfaces, especially those that have held foals and weanlings, and bathing the mare including her udder before foaling help to minimize egg contamination.

Table 49-2 Anthelmintics Effective Against Ascarids in Horses

Drug	Dose	Efficacy	
		Adults	Larvae*
BENZIMIDAZOLES			
Fenbendazole	5 mg/kg	+/–	–
	10 mg/kg once	+	–
	10 mg/kg daily for 5 days	+	+
Mebendazole	8.8 mg/kg	+	–
Oxfendazole	10 mg/kg	+	–
Oxibendazole	10 mg/kg	+/–	–
PYRANTEL			
Pyrantel pamoate or embonate	6.6 mg/kg	+	
Pyrantel tartrate	2.65 mg/kg daily	+	+†
AVERMECTINS AND MILBEMYCINS			
Ivermectin	0.2 mg/kg	+	+
Moxidectin	0.4 mg/kg	+	+
OTHER			
Piperazine‡	110–200 mg/kg	+	–
Dichlorvos‡	20 mg/kg	+	–
Trichlorfon‡	40 mg/kg	+	–

All doses are for oral administration.

+, Highly effective; +/–, moderately effective; –, ineffective.

* Do not use in heavily parasitized foals.

† Pyrantel pamoate continuously kills all stages.

† Prophylactic; prevents infection by newly acquired infective larvae.

A word of caution: if high ascarid burdens are suspected based on a prior poor deworming history or high FECs, deworming with highly efficacious anthelmintics is contraindicated because of the risk of ascarid impaction. In such cases young horses should be initially dewormed with an anthelmintic of lower efficacy, such as fenbendazole at a dose of 5 mg/kg, followed in 1 to 2 weeks with proper doses of an anthelmintic known to be efficacious on the premises.

49.1.10.2 CLEAN PASTURE

Creating a pasture that is entirely devoid of parasites is impossible. However, as part of a comprehensive parasite control program the following measures will reduce the parasite burden on pasture.[130] Pastures that have been vacant for at least 2 months during the warm season, fields that have recently produced hay, and pastures grazed by alternate livestock species can be viewed as having a reduced parasite burden. Dragging and harrowing disperse parasite larvae, which is advantageous only in the summer and only if pastures can be left unoccupied for 2 weeks in the south or 4 weeks in the northern climates. Pastures should not be harrowed after October 1 in the United States because parasite larvae dispersed by harrowing will not undergo the climate extremes required to kill them. Similarly, manure should not be spread on pasture. Reducing the stocking density of a pasture will decrease parasite exposure because the horses are not forced to graze as close to their feces in order to meet their forage demands. Often, decreasing the number of horses on a pasture is not practical, but even in such cases useful pasture can be maximized and larval burdens minimized by removing feces from the pasture every few days. This interval exploits the nematode parasite's requirement for a period of development outside of the horse in order to become infective. Removal of feces before this maturation prevents infection.

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49.1.11 Less Common Equine Parasites

49.1.11.1 STOMACH WORMS

Four species of nematode parasites inhabit the equine stomach.[131–135] These are *Habronema muscae, Habronema microstoma, Draschia megastoma*, and *Trichostrongylus axei*. The first three are collectively termed *spiruroid* species in that they belong to the nematode superfamily Spiruroidea. *Habronema* and *Draschia* cycle through intermediate hosts, the flies *Musca domestica* and *Stomoxys calcitrans*. L_1 exit from embryonated eggs of infected horses during transit through the intestinal tract and are ingested by maggots in the environment. Larvae mature within the pupating fly; the life-cycle is completed within 2 weeks, and the adult flies emerge. L_3 migrate to the proboscis, and horses become infected when the flies are swallowed or the larvae are released on or around the muzzle, eyes, sheath, or open wound as the flies feed. The prepatent period for *D. megastoma* and *Habronema* species is approximately 2 months. Fourth-stage larvae and adults localize in the glandular stomach, predominantly in the region of the margo plicatus.

The most common pathology caused by spiruroid nematodes is a result of larvae that do not access the GI tract but are instead deposited in wounds or moist areas of the skin, where the parasite is therefore unable to complete its life-cycle.[136,137] During their migrations within the skin the larvae elicit tremendous eosinophilic responses characterized by the formation of eosinophilic granulomas. These granulomatous lesions, known as *cutaneous habronemiasis* or *summer sore*, consist of rapidly proliferating granulation tissue that is refractory to treatment and tremendously pruritic. Accordingly, lesions are generally ulcerated. Within the GI tract, *D. megastoma*, the most pathogenic of the species, causes submucosal eosinophilic granulomas near the margo plicatus that coalesce and later develop into large fibrous masses with purulent cystic cavities.[131] *Habronema* species stimulate the secretion of large amounts of thick tenacious mucus on the glandular part of the stomach, close to the margo plicatus, with adult worms embedded in the mucus.

The prevalence of spiruroid nematodes in horses has not been examined in the United States since 1985 to 1986, when a tremendous decline in prevalence was identified and attributed to the introduction of

ivermectin in the United States in 1983.[133] Before ivermectin's introduction *D. megastoma* was the most prevalent of the spiruroid nematodes with a regional prevalence ranging from 24% to 60%.[134,135,138,139] However, after ivermectin introduction *D. megastoma* prevalence rapidly declined to less than 5% of the population of horses examined in Kentucky.[133] At this time spiruroid parasite infections are sporadic because of widespread use of avermectins.

Collectively the stomach parasites are controlled with the administration of macrocyclic lactones.[131] Spiruroid transmission wanes in the cold, when the intermediate host is no longer active. Therapy in the fall, which also coincides with the timing for treatment of bots, will interrupt the life-cycle. Elimination of spiruroid parasites from granulomatous summer sore lesions is more challenging owing to limited diffusion of the anthelmintic into the fibrous capsule of the lesions.[136] Accordingly, topical preparations consisting of organophosphates (OPs) and corticosteroids are commonly used in association with oral avermectin administration. Repeated treatments are commonly required.

Equine infection with the stomach worm *T. axei* is generally associated with shared grazing between horses and ruminants. *T. axei* also infects pigs. The life-cycle of *T. axei* closely resembles that of the strongyles. Exposure begins in the spring when infective *T. axei* L_3 that survive winter are ingested during grazing. Pasture contamination wanes during the summer. L_3 develop into adults in the lumen of the mucosal crypts or deeply in the mucosa of the stomach. The prepatent period is approximately 3 weeks. Light infections with *T. axei* are generally asymptomatic, but heavy infections lead to a hyperplastic reaction of the glandular tissue, predominantly in the fundus, and production of abundant mucus.[132] Raised plaques enlarge, reaching several centimeters in diameter, and become eroded in the center as the disease progresses, appearing as reddened ulcers surrounded by hypertrophied gastric mucosa. In large numbers *T. axei* can trigger a severe watery diarrhea.

The epidemiology of *T. axei* transmission mimics that of strongyles in that infective L_3 die off during hot, dry weather, effectively eliminating transmission during the summer months, but larvae that reach pasture in late summer can be infective or overwinter to infect in the spring. Accordingly, *T. axei* infections can be controlled by several methods depending on the husbandry of the farm. Infected horses can be treated with macrocyclic anthelmintics before their introduction to pastures that have not been grazed by ruminants or just before they are introduced to ruminant-grazed pastures after the summer drop in L_3 pasture contamination. Horses that cannot be removed from infected pasture will require frequent deworming to minimize pasture infection during the spring, fall, and winter, as the prepatent period for *T. axei* is 3 weeks.

49.1.11.2 ## LUNGWORMS

See the discussion of lungworm infection in large animals.

49.1.11.2.1 ### ONCHOCERCA CERVICALIS

Unlike the previously discussed parasites that inhabit the GI tract, *Onchocerca cervicalis* is a filarid nematode whose adult organisms are found woven within the nuchal ligament.[140] This predilection site, which has little blood supply, makes it impossible to eliminate the adult parasite.[141] Microfilariae resulting from sexual reproduction tend to congregate in certain regions of the body including the ventral midline and face where they are ingested when *Culicoides* feed in these regions.[142] From this intermediate host,

microfilariae complete their life-cycle when they are transferred to another horse. *O. cervicalis* microfilariae cause pruritus, which may be severe in certain individuals and mild in others.[141] Such pruritus does not appear to be as dependent on microfilarial burden as on the reactivity of the individual.

Onchocerca microfilariae are effectively eliminated by the macrocytic lactones.[143,144] Complete resolution of signs may require 30 days, and recurrence of signs after treatment is not uncommon. Recurrence has been attributed to death of the microfilariae. In the absence of regular administration of macrocytic lactones, recurrence of signs is predictable owing to continued microfilaria production by the adult parasite.

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49.2 GASTROINTESTINAL NEMATODE INFECTIONS IN CATTLE

LORA RICKARD BALLWEBER

Cattle are hosts to numerous species of nematodes.[145–147] Of these, nematodes in the genera *Ostertagia, Haemonchus, Trichostrongylus*, and *Cooperia* are most prevalent and usually are considered to be the most important of the nematode species. Mixed infections are the rule and even though some genera, such as *Nematodirus, Oesophagostomum*, and *Trichuris*, comprise a smaller portion of the total nematode population, their presence contributes to the overall assault on the animal's health and well-being. The various nematodes do differ somewhat with respect to their site of infection and pathologic effects, but their general life-cycle patterns are quite similar.

49.2.1 Life-Cycle

Adult female nematodes produce eggs that are passed out of the host with the feces. Under optimal conditions in the external environment, first-stage larvae (L_1) can develop and hatch from eggs within 24 hours. L_1 grow and develop to second-stage larvae (L_2), which in turn grow and develop into third-stage larvae (L_3). In general, the third stage is the infective larval stage. After ingestion, L_3 develop into fourth-stage larvae (L_4), which then develop into immature adults. Sexually mature adult nematodes develop within 2 to 4 weeks after ingestion of the L_3 unless arrested development occurs. The life-cycle of *Nematodirus* is the same except that development to infective L_3 occurs within the egg before hatching. For *Trichuris*, development to the infective L_1 occurs in the egg. However, rather than hatching in the external environment, L_1 hatch after ingestion of the eggs by the animal, and approximately 8 weeks are required before sexually mature adults are present.[147,148]

Climate and management of pastures and animals are among the numerous factors that influence the level and extent of parasitism. Although temperature is considered to be the driving force behind larval development, larval development can proceed only in the presence of adequate moisture. Larvae of all stages can be killed by extremely low temperatures, desiccation, and/or exposure to direct sunlight. Larval development and transmission tends to occur in predictable seasonal patterns based in part on regional climatic differences.[146,147,149] In the southern United States, infective L_3 persist longest when conditions are cool and wet (October to May) but die off quickly during the summer after rain-induced liberation from the fecal pat.[150,151] Nematodes acquired by grazing cattle during the summer months came from eggs recently deposited on pasture. In the northern United States, infective L_3 may be on pasture year-round. Significant numbers of *Cooperia* and *Nematodirus* may be acquired for at least 12 months after deposition of eggs on pasture, with acquisition of fewer numbers for up to 24 months. Acquisition of low levels of *Ostertagia* can occur for at least

14 months after deposition of eggs. In subtropical climates, seasonality may be much less marked, and pasture infectivity may follow the rainfall pattern. In arid climates, large numbers of larvae may be present on the pasture whenever local conditions permit lush grass growth.[147,152–154]

Not only can larvae survive on pasture, but some species can arrest development within the host. This usually occurs during the season when adverse environmental conditions would decrease larval survival in the external environment. Best known for this phenomenon is *Ostertagia ostertagi*. In northern temperate climates, pasture larval populations peak in the summer and early fall, and L_4 tend to overwinter in the host, resuming development in the spring. In warmer climates with hot, dry summers, the highest numbers of infective larvae may be found in the late spring to early summer, and L_4 tend to oversummer in the host, resuming development in the fall.[147,155,156]

49.2.2 Pathophysiology

Of all the cattle nematodes, *O. ostertagi* has long been considered to be the most pathogenic nematode in temperate regions. The pathophysiology of ostertagiasis centers around the development of larvae in the gastric glands of the abomasum. As the larvae develop within the glands, they cause gland hyperplasia and intense eosinophilic infiltration. Mucosal glandular cells lose their differentiation, and cell junctions are weakened. Albumin is lost into the lumen. Parietal cells cease to function, causing a decrease in HCl production. The change in pH stimulates overproduction of gastrin, which initiates cell proliferation and hyperplasia. Alkalinity also decreases the bactericidal activity of the abomasum, resulting in bacterial overflow from the rumen into the intestine. In addition a pH greater than 5 prevents the conversion of pepsinogen to pepsin. As a result, pepsinogen is released into the blood through permeable cell junctions. Hyperplasia and loss of cell differentiation become widespread and create the typical “Moroccan leather” appearance of the abomasum. In experimental models, *Ostertagia* infection in calves is associated with elevated peripheral eosinophil counts and decreased lymphocyte counts. Emergence of the larvae may complete the destruction of the glands. If the infection is severe, the proliferated cells and abomasal mucosa may slough, producing a diphtheritic membrane.[149,157]

49.2.3 Populations at Risk

Although exposure to some GI nematodes (GINs) readily induces immune responses that limit future populations of nematodes within the gut, cattle remain susceptible to *O. ostertagi* for many months. Protective immunity is usually not evident without prolonged exposure and may not occur until the animals are 2 years of age or older.[149] Consequently, clinical type I ostertagiasis occurs primarily in young cattle (up to approximately 18 months of age) during their first grazing season, with type II disease present in older animals (2 to 4 years of age). After their initial exposure and induction of immunity, adult cattle rarely show signs of nematode infection or require anthelmintic treatment. Although mature cattle ingest infective larvae, fewer larvae establish infections, so parasite burdens and the magnitude of fecal egg shedding generally are decreased. Most preventive and treatment strategies therefore are directed at young grazing stock, primarily beef calves and dairy replacement heifers.

49.2.4 Clinical Manifestations

In young animals, GINs may simply cause poor growth and ill thrift, or they may cause serious clinical illness and even death. Inappetence, a common feature of parasitic gastroenteritis, can result in reduced weight gain, growth, and onset of puberty.

The synchronous development and maturation of inhibited larval *O. ostertagi* can result in severe clinical disease, called *type II ostertagiasis*. Usually seen in cattle 2 to 4 years of age, it occurs months after ingestion of infective larvae. Anorexia, ill thrift, and hypoproteinemia are consistent signs. The animals may also show fever, diarrhea, anemia, and submandibular edema. The prognosis for recovery is guarded owing to the widespread destruction of abomasal glands. Conversely, type I ostertagiasis results from the rapid acquisition of large numbers of larvae that complete development to the adult stage within the usual 3-week time frame. The primary physiologic change is appetite suppression, which accounts for the reduction in weight gains in calves during their first grazing season. Although the underlying mechanism for the two types is the same, the seasonal occurrence of each type varies in accordance with the epidemiologic patterns of the area.[145,146,158]

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Compounding the effects of *O. ostertagi* is the presence of other GINs. Larval and adult *Haemonchus* organisms are blood feeders, producing anemia. *T. axei* produces local and systemic changes similar to those produced by *O. ostertagi*, resulting in similar clinical signs. Infection with *Oesophagostomum radiatum* produces structural and functional changes including anemia, hypoproteinemia, diarrhea, anorexia, and weight loss.[146,159]

49.2.5 Control of Gastrointestinal Nematodes

49.2.5.1 ANTHELMINTICS

Adult *Ostertagia* and other GINs are susceptible to most of the commonly used anthelmintics. Drugs and doses are listed in Table 49-3. Drug withdrawal times must be considered when selecting anthelmintics for beef cattle and lactating dairy cows, and the manufacturers' recommendations followed. Eprinomectin and moxidectin, in topical formulations, have no withdrawal period for either meat or milk.

Table 49-3 Efficacy of Various Anthelmintics Against Gastrointestinal Nematodes in Ruminants

Drug	Dose (mg/kg)* Sheep†	Cattle	Adults	Hypobiotic Larvae
BENZIMIDAZOLES				
Albendazole	5–7.5	7.5–10	+	+
Febantel	5	7.5–10	+	+/–
Fenbendazole	5	7.5–10	+	+/–
Mebendazole	15–20		+	+/–
Netobimin	7.5	7.5	+	+
Oxfendazole	5	7.5	+	+
Oxibendazole	15	15	+	+/–
Ricobendazole	5		+	–
LEVAMISOLE AND MORANTEL				
Levamisole	5–7.55	5–7.5‡	+	+/–
Morantel	5–12.5	10	+	–
Pyrantel	25	12.5	+	–
AVERMECTINS AND MILBEMYCINS				
Ivermectin	0.2	0.2§	+	+
Doramectin	0.2	0.2§	+	+
Eprinomectin		0.5‖	+	+
Moxidectin	0.2	0.2§	+	+
OTHER DRUGS				
Closantel	5–10		+¶	–
Nitroxynil	10		+¶	–

+, Highly effective; +/–, moderately effective or effective according to some authors; –, ineffective.

* All doses are for oral administration unless otherwise indicated. †Goats must be given higher doses for equal efficacy. ‡10 mg/kg for topical administration.

§ 0.2 mg/kg for oral, subcutaneous, or intramuscular administration; 0.5 mg/kg topically ("pour-on").

‖ Available only for topical administration at 0.5 mg/kg; not recommended for sheep.

¶ Effective against *Haemonchus contortus* only.*Note:* Administration of some of these products may constitute extralabel use in sheep and goats; follow manufacturers' guidelines for meat and milk withdrawal in cattle.

The newer macrocyclic lactones are particularly effective against both adult and larval stages of the various GINs in cattle, including inhibited L_4.[160–162] In addition, their residual effect helps minimize pasture infectivity during the grazing season (see later).[163–166] Intraruminal sustained-release devices (SRDs) containing a BZD, levamisole, morantel, or ivermectin can also be highly effective at limiting both clinical disease and pasture infectivity.[167–171] Use of highly efficacious drugs or SRDs can attenuate the immune response to GINs during the first grazing season in calves. However, in most cases immunity is sufficient to prevent clinical disease during the following grazing season, and weight gains by the end of the second season are similar to those of immune animals.[168,169,171]

Although the macrocyclic lactones are all highly effective, some differences between products in both efficacy and duration of effect are apparent. Doramectin, eprinomectin, and moxidectin are more effective and/or have a longer residual effect than ivermectin against *Ostertagia* and *Cooperia*.[172–178] Doramectin, eprinomectin, and moxidectin have a residual effect against *Ostertagia* for approximately 5 weeks, whereas ivermectin is effective for only 2 to 3 weeks.[165,178] As the prepatent period for *Ostertagia* is approximately 3 weeks, the treatment intervals in most management situations are 8 weeks for doramectin, eprinomectin, and moxidectin and 5 to 6 weeks for ivermectin. Duration of effect also varies somewhat with the parasite and the level of infection. Persistence of effect against *Cooperia* appears to be 1 to 2 weeks shorter than for *Ostertagia*, regardless of the product used.[164,165,178–180] The residual effect may be shortened by a week or so at high infection levels.[178,179]

Historically, anthelmintic resistance by GINs has been far less of a problem in cattle than in sheep or goats. However, this situation appears to be changing. Reports of anthelmintic-resistant nematodes of cattle are on the increase in the United States and elsewhere around the world.[149,181–187] Resistance has been reported in the most frequently used anthelmintic classes including the BZDs, macrocyclic lactones, and imidazothiazoles. Species of *Cooperia* are most commonly associated with these reports, although resistant species of *Ostertagia* and *Haemonchus* have also been documented.

49.2.5.1.1

Treatment Intervals

The choice of drug and treatment interval should be made on the basis of an individual herd or farm, as part of an overall control program. Factors to consider include the geographic location, time of year, and grazing management. Grazing management is discussed elsewhere.[188] There are several options for preventing clinical disease and maximizing gains in first-season grazing calves using strategic anthelmintic treatments:

- Two treatments with an avermectin or moxidectin early in the grazing season. The first treatment can be given either at turnout or weaning or 3 weeks into the grazing period. Depending on the product used, the second dose is given 6 weeks (ivermectin) or 8 weeks (doramectin, eprinomectin, moxidectin) later. This strategy can prevent clinical disease, keep FECs low, and increase weight gains during the first grazing season.[189,190] An alternative when using ivermectin in situations in which pasture infectivity is high is to treat calves at 3, 8, and 13 weeks after turnout or weaning.[191]

- Use of an intraruminal SRD, where available, at turnout or weaning. This strategy may be most cost-effective on farms where pasture infectivity is high.

- Treatment during peak pasture infectivity (e.g., summer and early autumn in temperate climates). Treatment interval depends on the product being used: every 3 weeks for nonivermectin drugs, every 5 weeks for ivermectin. For example, ivermectin can be given at 10, 15, and 20 weeks after turnout or weaning. This strategy prevents clinical disease in the majority of calves while allowing some level of infection, which stimulates an immune response in first-season calves. However, treatment at the start of the grazing season has been shown to result in better weight gains than tactical treatments given during the grazing season.[167]

- "Dose and move" strategy. This strategy consists of treating calves with a single dose of anthelmintic, then moving them to a clean pasture just before the anticipated peak in pasture infectivity (e.g., early to mid summer in temperate climates). This strategy minimizes the number of anthelmintic treatments during the grazing season. However, it is effective only on farms where a clean pasture is available. Furthermore, any residual nematodes left behind will likely possess resistant genes; therefore contamination of the clean pasture will be with resistant nematodes. This must be taken into account when planning for the future use of the pasture (see later).

Integrating effective pasture management can reduce the number of anthelmintic treatments necessary[192]; however, there currently is no realistic alternative to the continued use of available compounds. Therefore it is imperative that the efficacy of these compounds be maintained for as long as possible. Recommendations designed to promote this in cattle include the following: (1) do not treat second-year and adult cattle to maintain a population of unexposed nematodes (refugia) on the farm; (2) do not graze first-year calves on the same pasture each year (avoids exposure to larvae produced from resistant nematodes); and (3) do not use the same family of anthelmintic year after year in calves.[184]

The use of complimentary classes of drugs may be necessary in the situation where a producer is not satisfied with the response to treatment. The combination of a macrocyclic lactone with a BZD or levamisole has been shown to be effective against all important nematodes, including anthelmintic-resistant forms. Similar combinations may also be used in feedlots to help provide maximal productivity and enhance response to vaccination programs. However, care must be exercised when using this recommendation because heavy, indiscriminate use of anthelmintics is a strong selector for resistant genotypes and will hasten the development and spread of drug-resistant parasite populations.[149]

49.2.5.1.2

Adult Cattle

The cattle most at risk for clinical disease and production losses are beef calves and dairy replacement heifers in their first season at pasture. Strategic treatment early in the grazing season is effective in most management situations. Development of immunity should protect the animals during their second and subsequent grazing seasons. Treatment of adult cattle generally is unnecessary, unless immunity is inadequate or pasture infectivity is high. Anthelmintic treatment is most likely to be warranted in first-calf heifers and newly acquired cows that may not have been pastured as heifers. In some situations it may be beneficial to treat beef cows after spring calving.

49.2.5.2 EVALUATION OF ANTHELMINTIC PROGRAMS

Because of the importance of arrested larvae in the pathophysiology of ostertagiasis, FECs can be misleading. The parasite does the most damage to the host as it enters the gastric gland and as it leaves; however, the infection is unlikely to be patent during these periods. Consequently, animals with from type I or type II ostertagiasis may have low FECs. Therefore FECs are most useful as a tool to evaluate pasture contamination and the success of control programs. Detection of anthelmintic resistance currently depends on the FECRT. Unfortunately, this will only detect clinical resistance, which usually occurs only when the frequency of resistant alleles in the population reaches 25%.[196] Consequently, this test generally does not detect the presence of resistant nematodes within a population until clinical resistance occurs—that is, a less than expected response to the treatment is noticed. The FECRT estimates anthelmintic efficacy by comparing pretreatment and posttreatment FECs. Fecal samples are collected immediately before treatment and then 10 to 14 days later; for cattle, waiting the full 14 days before collection of the second sample is currently recommended.[149]

49.2.6 Clinical Management

49.2.6.1 DIAGNOSIS

The most reliable method of diagnosis is necropsy. The “Moroccan leather” abomasal lesion is pathognomonic for *Ostertagia*. It may be difficult to identify parasites with a casual macroscopic examination because both larvae in gastric glands and adult worms are small and easily overlooked. Histologic section and abomasal wall digestion techniques can be used to identify the presence of larvae. Antemortem, the history and clinical signs are most useful in suggesting a diagnosis of ostertagiasis. FECs are not specific for the disease.

49.2.6.2 TREATMENT

Animals should be treated with an avermectin or moxidectin and moved to a less contaminated environment at the first indication of clinical signs. History of the animals, time of year, and clinical judgment will determine whether all animals in the group should be treated. Animals with type I ostertagiasis can be expected to respond well; however, the prognosis for animals with type II ostertagiasis is less encouraging. Even though the larvae may be killed, the damage to the abomasal mucosa may limit complete recovery. Animals with profound hypoproteinemia and dehydration respond poorly compared with those showing only mild diarrhea and slight hypoalbuminemia. Severely affected animals may need treatment with fluids, plasma transfusions, and supportive therapy to survive. Recovered animals often fail to thrive.

49.3 GASTROINTESTINAL NEMATODE INFECTIONS IN SHEEP AND GOATS

Sherrill A. Fleming

GIN infections in sheep and goats are responsible for severe clinical syndromes and profound production losses. Young animals, periparturient ewes and does, and animals on substandard planes of nutrition are most susceptible to outbreaks of parasitic disease. The GIN of small ruminants includes *Haemonchus contortus, Teladorsagia circumcincta, Trichostrongylus axei, Nematodirus* species, and *Cooperia* species.[197] The proportions of each of

these nematodes in small ruminant populations vary according to geographic location. *H. contortus* usually is the most significant pathogen in wet, temperate climates. *T. circumcincta* may be the predominant infection in northern or arid climates. *H. contortus* and *T. circumcincta* represent the majority of parasite burdens seen in small ruminants, with *H. contortus* being present in highest numbers. Anthelmintic resistance is present in all these parasites, but the prevalence is highest for *H. contortus*, making it the most economically important GIN of sheep and goats.[195]

The problem of anthelmintic resistance in GIN of small ruminants has been reported in South Africa, Australia, 1634
New Zealand, Malaysia, Spain, France, Denmark, the United Kingdom, Brazil, and the United States.[196,197] In the 1635
United States, resistance to all classes of anthelmintics has been documented.[197,198] Recently resistance to two and three classes of anthelmintics was found on 14 of 15 farms and 6 of 18 farms, respectively, in a survey of 18 goat flocks in Georgia and South Carolina.[199] In 2005, the first report of total anthelmintic failure was made on a meat goat farm in Arkansas.[200] It is no longer acceptable to plan parasite control programs based solely on the use of anthelmintics. Veterinarians and producers must customize programs to control exposure to infection and reduce the use of anthelmintics. A thorough knowledge of the biology of GINs is necessary to plan effective control programs.

49.3.1 Life-Cycle[201,202]

The life-cycle of GINs is direct and consists of a host phase and a free-living phase. Worms mate in the host, and females lay eggs that pass in the feces. Eggs hatch and develop to infective larvae while remaining in the fecal mass. Infective larvae then move from the fecal mass onto the surrounding forage, where they can be consumed during grazing, thus completing the cycle. The time from ingestion of infective larvae to egg-laying adults, the prepatent period, is approximately 3 weeks. The time for development from egg to infective larvae can be as short as 4 to 10 days (especially during the summer months); therefore transmission (reinfection) and continual pasture contamination can be rapid. During the colder months, however, development is delayed, and organisms may take up to a month or two to reach the infective larvae stage; therefore pasture contamination and reinfection are minimized. The infective larvae have a protective sheath that makes them relatively resistant to adverse environmental conditions; they can therefore survive for months, thus extending transmission potential. As long as the temperature and moisture conditions remain favorable, development and survival continue; conditions that are too hot, too cold, and/or too dry threaten parasite survival.

49.3.2 Epizootiology[201,202]

The life-cycle of GINs has four phases.

49.3.2.1 PHASE 1—SYMBIOTIC OR PARASITIC PHASE

Phase 1 is the interaction between host and parasite. During this phase the parasite has to develop and survive in the host. After ingestion, infective larvae lose their protective sheath and invade the mucosa of the abomasum, small intestine, or large intestine depending on the GIN species involved. While in the mucosa larvae develop to the next larval stage and then return to the surface of the gut mucosa, where they become adult worms. The major host defense mechanism is immunity. When an infectious agent enters the body, the immune system reacts to mobilize various components (antibodies, killer cells, and so on) to inhibit or kill the invaders. These components act on larval stages in the mucosa and the adults in the lumen. How strong the immune response is depends on the age of the host, nutritional status, and concurrent stressors. The

immune system matures with age; therefore young animals are relatively more susceptible to infection and become more resistant with age. As a result, young animals usually harbor the highest GIN populations and experience the most severe consequences. Adult animals have developed stronger immunity and harbor lower infection levels. Under poor nutrition and/or stressful conditions, the immune system is compromised and cannot respond adequately. Therefore regardless of the age of the animal, the effects of infection will be worse. The prepatent period of most worms is approximately 3 weeks, but this period can be extended for worms that have the capability to enter a period of delayed development called *hypobiosis*. This occurs during the season of the year when the environmental conditions are unfavorable for development and survival of the free-living larval stages. Depending on the worm, this happens during either summer or winter.

49.3.2.2

PHASE 2—CONTAMINATION PHASE

Phase 2 results from eggs passed in the feces. The magnitude of this phase is affected by stocking rate, age of the animals, season of the year, and hypobiosis. The higher the stocking rate, the more feces are deposited on the grazing area, and therefore more eggs, and the lower the stocking rate, the lower the number of eggs deposited. More eggs are also passed from young versus older animals. Most worms have a definite seasonality, so during their “season,” more eggs are produced and passed. Of particular note is a phenomenon called the *periparturient rise* (PPR) in FEC. This occurs at or around parturition and extends through most of the lactation period. Because parturition and lactation are stressful conditions, the dam's immune system is compromised. This allows the existing female worms to increase the number of eggs deposited in the feces. If a worm species undergoes hypobiosis, the development time to the adult stage is extended. This will result in fewer adult worms over time and fewer eggs deposited in feces. However, when these hypobiotic larvae resume development, massive numbers become mature adults over a short period of time, and resultant egg production and deposition in the feces can be very high.

49.3.2.3

PHASE 3—FREE-LIVING PHASE

Phase 3 involves larval development and survival, which depend on prevailing environmental and nutritional conditions. Initially, development and survival from egg to first-stage, then to second-stage, and finally to third-stage (infective) larvae occur within the fecal mass. The first- and second-stage larvae are unprotected and require oxygen and energy (feeding on nutrients and microorganisms) to grow. The infective larvae are enclosed in a protective sheath and do not feed. Temperatures conducive to normal development and survival are 65° F to 85° F. With lower or higher temperatures, development and survival are reduced. Moisture is also crucial for development and survival. Because the initial development and survival occur within the fecal mass, moisture is usually adequate to allow development to the infective stage; however, if the fecal mass dries out quickly owing to high temperatures and/or physical disruption of the fecal mass, the first- and second-stage larvae are susceptible to desiccation and will die. Generally, infective larvae can survive very low temperatures, but sustained temperatures above 95° F are usually lethal. When infective larvae migrate out of the fecal mass, they are relatively resistant to environmental conditions encountered, because of their protective sheath. Temperature is usually the only factor that may adversely affect infective larvae. Again, sustained temperatures above 95° F can be lethal. The moisture conditions at ground level under forage cover usually are adequate for infective larvae to move around and survive. Because they do not feed, length of survival depends on how fast they use energy reserves. The hotter it is, the faster they move and use energy stores, and the shorter their survival time. Eventually, infective larvae move up and down the forage when there is a moisture medium (e.g., advancing and receding dew). Rain also provides a moisture medium for larval movement on forage. For the most part, infective larvae do not move much past 30 to 50 cm from the

fecal mass or 5 to 6 cm up the forage. Therefore the lower the animals graze and the closer to the fecal mass, the greater the consumption of infective larvae, and the higher they graze, the lower their exposure to larvae.

49.3.2.4 PHASE 4—INFECTION PHASE

Phase 4 occurs when available infective larvae are consumed during grazing. This phase is affected again by stocking rate in two ways. If the same (phase 2) animals remain on the same pasture, the stocking rate determines how many eggs initially contaminated the pasture and consequently how many infective larvae will be available to consume. If the initial contaminating animals are removed and replaced by new animals, the new stocking rate will determine the level of exposure of each animal to infective larvae during grazing—that is, the higher the stocking rate, the more chance of exposure, and the lower the stocking rate, the less chance of exposure. It is well known that grazing animals usually do not graze close to fecal masses, so the greater the distance between masses, the less the exposure. Eventually fecal masses disintegrate, forage grows well with the fertilization, and animals will graze over areas where exposure can be high. Natural sources of water, such as streams, ponds, or lakes, provide moisture along the banks where forage can grow readily. When animals congregate to drink and consume the attractive forage, defecation in these areas usually leads to increased contamination and eventually more infective larvae. Essentially a high stocking rate has been artificially created in a relatively small area. The same can be said for areas where supplements, especially hay, are fed if conditions are right for development and survival of the free-living stages. Once infective larvae are consumed, phase 1 is repeated.

49.3.3 Pathophysiology of Gastrointestinal Nematode Parasites

The damage done by *H. contortus* is the result of the blood sucking by L_4 and adult parasites. The pathogenesis of ostertagiasis in sheep is similar to that described in cattle and is a result of destruction of abomasal mucosa. *T. axei* causes abomasitis, whereas *Trichostrongylus colubriformis* penetrates beneath the intestinal mucosa and causes blood loss and enteritis.

49.3.4 Clinical Signs of Gastrointestinal Nematode Parasites

Most animals acquire mixed infections of nematodes. Clinical signs may therefore reflect the effects of more than one species of parasite. There appears to be some synergism between *O. circumcincta* and *T. colubriformis*, which makes the effect of the combined infection more severe than that of either alone. Although mixed infections with GINs are assumed, the actual population of parasites in small ruminants will vary depending on the geographic location. In general, the majority of clinical illnesses result from *H. contortus* infections. Most parasitic infections in small ruminants are associated with altered gut function, anorexia, ill thrift, weight loss, and hypoproteinemia. Diarrhea is a variable sign. Animals may die suddenly without overt clinical signs or may exhibit chronic wasting. Clinical signs of *H. contortus* infection can vary from peracute to chronic and result from decreased nutrient use and anemia or hypoproteinemia. The most common signs are failure to thrive, weight loss, and decreased appetite. Weakness, bottle jaw, pale mucous membranes, poor capillary refill time, and possibly diarrhea develop with more severe or long-term infections. After sudden exposure to large numbers of infective larvae, animals can die acutely, even before the infection is patent. Other diseases such as pneumonia and heat stress may result secondarily.

49.3.5 Anemic Crisis and Patient Management

The anemia created by *H. contortus* is due to blood consumed by the parasite and usually is chronic. Parasitized patients presented with lethargy and weight loss often have hematocrits <10%, yet many are still capable of rising and walking. Addressing the anemia by blood transfusion must be weighed carefully against stress to the patient caused by restraint, jugular catheterization, and blood administration as well as by the hemolysis of these same cells several days later. Obviously, in life-threatening circumstances (the patient that is unable to stand), administration of whole blood can be critical. In the noncrisis situation (patient rising and/or eating) treatment with an effective anthelmintic should eliminate the parasite and halt blood loss. Because *H. contortus* consumes blood, the affected animal actually loses substrates essential to erythrocyte production (iron, cobalt, copper). Providing supplemental iron and B-complex vitamins should speed reversal of the anemia. Assuming blood loss has been halted, a 1- to 1.5-point rise in the hematocrit per day is expected when the bone marrow is maximally stimulated. In most parasitized patients a rise of one half this value is a more realistic expectation.[203]

If blood is to be given, it is essential to be certain that the donor has a normal packed cell volume. An animal in the same environment may be as anemic as the patient, but the individual may be more capable of dealing with the anemia. In lambs weighing less than 45 kg, 1 unit of whole blood (approximately 450 mL) is often sufficient to survive a crisis, provided *H. contortus* has been controlled.

49.3.6 Populations at Risk

Young animals are most susceptible to infection and clinical manifestations of disease. Lambs and kids may become heavily infected with parasites and shed large numbers of nematode eggs. In sheep, some degree of immunity develops as the animal approaches 1 year of age. Adult animals typically have complete immunity against *Nematodirus* and variable resistance to *Trichostrongylus* species. Some immunity to *Haemonchus* and *Ostertagia* species develops with age; compared with lambs or kids, adults are more resistant to infection with these species. However, even mature animals may succumb to parasitic infection when malnourished or challenged with heavily contaminated pasture. A PPR in fecal egg production is seen in ewes and does.

Goats are more susceptible to GIN infections than are sheep. The difference lies in part in the host's immunologic responses to nematode antigens. Goats prefer to browse on brush and trees, and they graze grass only when forced to by management. Under natural conditions, goats would have a low level of exposure to infective larvae, and this might explain their lower level of natural immunity compared with sheep.[204,205]

49.3.7 Refugia

Biologically, *refugia* refers to isolated populations of once widespread animal or plant, or in this case parasite, species. Most parasitologists now consider levels of refugia as the single most important factor contributing to selection for anthelmintic-resistant parasites.[206,207] Worms in refugia provide a pool of genes susceptible to anthelmintics, thus diluting the frequency of resistant genes. For many years parasitologists and veterinarians have recommended that all animals should be treated with an anthelmintic at the same time. However, this strategy has proven problematic, and a selective approach is now recommended. Only those animals in danger of severe parasitism should actually receive medication. This selective approach is highly compatible with host-parasite dynamics, as 20% to 30% of animals harbor approximately 80% of the parasites.[208] Animals with low

worm burdens are an important source of refugia, are not in danger of the negative effects of parasitism, and should not be treated.

49.3.8 Management of Gastrointestinal Nematodes in Small Ruminants

The traditional approaches of deworming often, rotating classes of anthelmintics, and moving to clean pastures have allowed anthelmintic resistance to all classes of drugs to develop and the resistant parasites to disseminate over a wide area. It is obvious that drastic changes in the management of GINs in sheep and goats are long overdue.

49.3.8.1 FAMACHA OR SMART DRENCHING METHOD.[209]

In order to maintain adequate levels of refugia, it is necessary to leave a portion of the herd or flock untreated. FAMACHA is a selective approach that targets the portion of the herd or flock with high worm burdens, including those animals that are poorly resilient to worm infections.[210] This approach will successfully control parasites in the entire group while significantly reducing drug costs and delaying the development of anthelmintic resistance. The use of this system is not without risks, as individuals are not routinely treated with anthelmintics. Failure to observe animals closely for clinical signs may result in the death of some individuals. It is necessary to know which anthelmintics are effective before beginning this system. The differences among farms in overall quality of management, stocking rates, breeds of animals, preexisting levels and spectrum of anthelmintic resistance, presence of nematode species other than *H. contortus*, and production targets need to be considered while FAMACHA is implemented on individual farms.

FAMACHA is a novel system developed in South Africa for identifying sheep that are anemic; the system has been extended to use in goats.[211] In this method the ocular mucous membranes of sheep and goats are categorized by comparison with a laminated color chart bearing pictures of sheep conjunctivae classified into five categories ranging from red (A/1; normal) to practically white (E/5; severe anemia). Because anemia is the primary pathologic effect of infection with *H. contortus*, this system can be an effective tool for identifying animals that require treatment (but only for *H. contortus*). FAMACHA has been tested extensively and validated in both sheep and goats in South Africa and in the southern United States.[212,213] In all studies the number of false-negative results was very low, suggesting that when FAMACHA is used according to recommended guidelines, death from anemia would be rare.

Based on the results of recent studies in the United States and numerous studies performed in South Africa, guidelines for using FAMACHA have been developed, and it is suggested that these guidelines be read in their entirety before FAMACHA is practiced.[209] It is recommended that treatment be withheld until animals score 4 or 5 as long as animals are in good body condition and good overall general health, animals are examined frequently (e.g., every 2 weeks), and good husbandry is used to identify animals in need of treatment (e.g., unthrifty, anorexic, lagging behind, bottle jaw) between FAMACHA examinations. When this approach is used, the number of anthelmintic treatments administered will be reduced greatly, resulting in significantly diminished selection pressure for resistance and therefore a reduction in drug costs. Owing to the increased handling of animals, labor costs will be increased. *Only adult animals should be managed with this system*. Lambs and kids have comparatively small blood volumes, poor immunity, and poor resilience and can progress rapidly from moderate to severe anemia. This precaution should be extended also to ewes and does during the periparturient and early lactation period, because these animals have decreased immunity

to GINs.[209,214–216] These and other animals that may be stressed by disease or in poor body condition should always be treated if scored as 3. Alternatively, in the northern parts of the country where *H. contortus* is an important problem but resistance prevalence is much lower, it may be reasonable to be more liberal when making treatment decisions (e.g., treat all animals with scores of 3, 4, and 5). Many more treatments are given when all animals with scores of 3 and higher are dewormed, but a significant number of animals will remain untreated to supply refugia. These refugia combined with a relatively short transmission and treatment period are likely to produce a very slow evolution of resistance, but the more intensive treatment protocols will improve animal productivity.

On farms where low to moderate levels of resistance to one or more drugs have been diagnosed (60% to 95% reduction in FEC), a useful strategy to help gain the full benefits of both treatment and resistance prevention could be to use these “less-effective” drugs either singly or in combination on all animals scored as 3. Using drugs that are less effective in this group is unlikely to lead to clinical problems because the few 3 scores that are moderately anemic and in need of treatment should receive a sufficient reprieve from infection until the next FAMACHA examination, and the majority of the animals with scores of 3 that are not anemic do not need to be treated. This strategy will help preserve the efficacy of the drugs that are still fully effective by saving them for only the animals in the 4 and 5 categories and also will help to decrease egg contamination of pastures.

Training of producers is critical in the use of this method. It is the responsibility of veterinarians and other animal health professionals to ensure that standards of training are maintained. When FAMACHA is used, it is extremely important that efficacy of anthelmintics is known because animals are not treated until they become anemic. Treating anemic animals with a drug that has moderate to poor efficacy owing to worm resistance may result in animal deaths. Other important precautions for using FAMACHA include but are not limited to the following: (1) the card is an aid in the control of *Haemonchus* species only; (2) the system should be used by producers only where technical assistance is available from a veterinarian or other animal health professional; (3) other management-based worm control practices must be maintained; (4) smart drenching principles should be used; (5) paleness or reddening of the conjunctivae may have other causes; (6) animals should always be scored with the help of the chart, not from memory; (7) animals are examined at least every 2 to 3 weeks at the beginning of the expected period of *Haemonchus* species challenge in climates where a seasonal incidence of infection occurs, and during critical periods weekly examinations may be needed; (8) the card is protected from light when not in use and replaced after 1 year of use.[197,217]

Maintaining treatment records that are included with the FAMACHA kits gives the owner the ability to rate the genetic merits of individuals on the premises. Host resistance to infection with *H. contortus* measured on the basis of FEC and packed cell volume (PCV) is a moderately heritable trait, and it has been demonstrated that the same animals tend to exhibit the highest FEC and lowest PCV on each occasion they are measured.[218–220] Of importance, data from recent investigations examining the heritability of resistance and resilience of merino sheep to infection with *H. contortus* indicate a high heritability for the clinical estimates of FAMACHA scores.[212] Removing the most susceptible animals from the breeding pool each year will have the long-term effect of improving the overall innate genetic resistance and/or resilience of the herd or flock to *H. contortus*.

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49.3.8.2

GRAZING STRATEGIES

The goal of pasture management is to provide safe pastures for grazing by reducing the exposure of susceptible hosts to infective larvae.[224,225] A safe pasture is one that has had no sheep or goats grazed on it

for 6 months during cool and cold weather or 3 months during hot, dry weather. Weaning sheep and goats at 2 months of age and rotating them through pastures ahead of the adults while forage is longer will minimize the exposure of susceptible animals to infective larvae. Pastures should be subdivided into smaller lots to allow longer rest periods between grazings. Pastures that are overgrown provide a good environment for larval survival, as ultraviolet light and dry conditions are effective in killing larvae. Keeping pastures clipped will assist in weed and parasite control. Short-duration grazing carries pasture rotation to a level that maximizes forage production and harvesting by controlled animal grazing. It is management intensive but can be effective in controlling parasite burdens. Tilling and reseeding a heavily contaminated pasture will convert it to a safe pasture and gives an opportunity to improve the forage quality. Taking a cutting of hay from a pasture assists in reduction of infective larvae, but one report indicates GINs and tapeworms developing in "worm-free" lambs after they were fed hay from heavily infected pastures. During the most dangerous part of the grazing season it may be necessary to drylot the flock and feed hay and grain from elevated feeders.

Stocking rate is an important consideration in parasite control, as it affects the exposure to infective larvae and the contamination of the pasture. It is impossible to make a general recommendation on stocking rate, as this will vary according to the type of pasture, the time of year, the current weather conditions, and the type of animal being grazed. Rules of thumb are that five to seven goats or five sheep are the equivalent of one cow and suggest five to seven goats per acre. Goats prefer to browse brush and trees, whereas sheep prefer to graze near the ground. Pasture management must include monitoring the condition of herbage to ensure that overgrazing does not occur and to maintain a productive pasture.

In the early spring or at the onset of the rainy season, reduced pasture contamination is the most important aspect of control. The ewe or doe in the periparturient relaxation of resistance, even if she has the genetic capacity for resistance, will be a source of eggs for the environment. Strategic deworming to remove arrested or recently emerged larvae before they contaminate the pasture will have a great impact on pasture contamination. Treatment 2 weeks after a rain that removes recently acquired worms before they can begin passing eggs will also decrease pasture contamination. Providing sufficient dietary protein is vital during the periparturient period and during rapid growth so that animals will tolerate the worm burden better as their immunity is strengthened.[223–225] A strong link between nutrition and parasitism has been illustrated between protein intake and resistance to GIN infection. The most dramatic has been the abolishment of the periparturient egg rise in lambing ewes by providing protein at 130% of requirements. Immunity is closely related to protein repletion. GINs increase the demand for amino acids by the sheep. Lambs will voluntarily select a higher protein diet when infected with GINs compared with uninfected lambs. There is conflicting documentation that sheep will decrease feed intake when initially infected with GINs. Some authors hypothesize that the decrease in intake may be caused by stimulation of the immune system or that the host is becoming selective in its diet.

Pastures may be used for hay cropping and grazed during the last half of the grazing season to effectively reduce GIN challenge. When plants high in condensed tannins are grazed, there is evidence that the incoming larvae are adversely affected by condensed tannins, which also provide bypass protein for the host.[226–228] There is growing evidence in work from New Zealand and Europe that grazing or feeding of plants containing condensed tannins can reduce FEC, larval development in feces, and adult worm numbers in the abomasum and small intestine. Preliminary tests with sericea lespedeza *(Lespedeza cuneata)*, a perennial warm-season legume, have shown positive effects of reduced FECs in grazing goats, and in sheep and goats in confinement when the forage was fed as hay. In addition, an effect on reducing worm burden has also been reported. Similar results have been observed using quebracho extract for small intestinal worms but not abomasal worms. In addition to its potential use in controlling worms, sericea lespedeza is a useful crop for

limited resource producers in the southern United States. It is adapted to hot climatic conditions and drought and acidic, infertile soils unsuitable for crop production or growth of high-input forages, such as alfalfa. It can be overseeded on existing pasture or grown in pure stands for grazing or hay. In addition to hay, sericea lespedeza is being evaluated in the form of meal, pellets, and cubes to be fed as a supplement to grazing animals or as a deworming method under temporary short-term confinement. The physical structure of some plants may challenge larvae to ascend vegetation or may provide protection from adverse pasture conditions. If animals are allowed to browse, their chances of acquiring larvae diminish as the distance from the ground increases. Most infective larvae are found within 2 inches (50 mm) of the soil surface.

Alternate grazing or co-grazing with other species of livestock may harvest *Haemonchus* larvae from the pasture. Small ruminants can graze after cattle and this is considered to be a safe pasture, assuming adequate parasite control in the cattle. For the most part, each livestock species harbors its own parasite fauna, with the exception of overlap between sheep and goats. Only *T. axei*, a minor abomasal worm, is found in all livestock species. In general, the *Haemonchus* organisms in sheep and goats do not do well in cattle, and vice versa. However, some populations of *H. contortus* may thrive in calves. If practical, cattle and small ruminants can be grazed together where each consumes the parasites of the other, which reduces available infective larvae for the preferred host species.

Anthelmintic administration should be coordinated with the weather. During hot, dry weather, there will be little or no exposure to infective larvae. As soon as there is significant rainfall (½ to 1 inch) larvae exposure goes up exponentially, as previously inactive larvae become active and new larvae are hatched. The producers should be trained to plan deworming within 3 weeks of significant rain after a dry spell. Similar strategies can be used during cool weather. Once ambient temperatures drop below 50° F, the flock can be dewormed and no further treatments are necessary until temperatures become favorable to larval development and activity.

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49.3.8.3

ALTERNATIVE THERAPIES

1 Copper oxide wire particles (COWPs) have been marketed for years as a supplement for livestock being managed in copper-deficient areas.[229] COWPs come in adult cattle, calf, and ewe boluses (25, 12.5, and 4 g, respectively). Only the cattle boluses are available in the United States. Owing to potential toxicity in sheep, only one dose per year is recommended. It is also well known that copper has some anthelmintic activity against abomasal worms but not other GI worms. That makes COWPs a very narrow-spectrum product. However, in view of anthelmintic resistance in *H. contortus*, recent work has revisited the possibility of using COWPs to specifically target *H. contortus*. Such work has shown that as little as 1 g or less and 2 g may remove substantial numbers of *H. contortus* organisms in lambs and ewes, respectively. Similar work in goats has not been tested adequately to establish what is needed, but similar doses may be appropriate. As mentioned, copper has to be used cautiously in sheep because toxicity can develop as a result of liver accumulation. Toxicity may not be an issue in goats, as they have been reported as not being as sensitive to excess copper intake. Therefore higher doses and/or more treatments during haemonchosis season may be useful in goats.

2 Other nutritional considerations include phosphorus, cobalt, and molybdenum. Supplementation with phosphorus has been shown to prevent worm establishment. Cobalt deficiency has also been associated with reduced immunity to GIN. The addition of molybdenum at 6 to 10 mg/day to the diet decreased worm burdens in lambs. This effect was not attributable to the expected copper deficiency. Molybdenum may have a role in increasing jejunal mast cells and blood eosinophil numbers.

3 The use of nematode-trapping fungi included in feed or supplements has demonstrated potential for biologic control of the free-living stages of GIN parasites under experimental and natural conditions.[230–232] These fungi naturally inhabit soil throughout the world where they feed on a variety of free-living soil nematodes. These fungi capture nematodes by producing sticky traps on their growing hyphae. Of the various fungi tested, *Duddingtonia flagrans* possesses the greatest potential for survival in the GI tract of ruminants. After passing through the GI tract, spores geminate and looped hyphae trap the developing larval stages in the fecal environment. This technology has been applied successfully under field conditions and is an environmentally safe biologic approach for control of worms under sustainable, forage-based feeding systems. The major drawback is that the fungal spores must be fed daily. Daily feeding that ensures that all animals consume an equivalent amount of feed is necessary. For adequate control of larvae during the transmission season, spores must be fed for a minimum of 60 days. This can be expensive and time-consuming. A bolus prototype is being developed and would allow a single administration; spores would then be slowly released over a 60-day period. This product is not available in the United States at this time.

4 Vaccines have been explored for management of the negative consequences of parasitism.[233–235] Successful vaccines have been developed for lungworms in cattle and tapeworms in sheep. The most promising vaccine for small ruminant worms has been what is called a “hidden gut” antigen and specifically targets *H. contortus*. This antigen is derived from the gut of the worm, and when the antigen is administered to the animal, antibodies are produced. When the worm ingests blood during feeding, it also ingests these antibodies. The antibodies then attack the target gut cells of the worm and disrupt the worm's ability to process the nutrients necessary to maintain proper growth and maintenance, thereby killing the worms. This vaccine has been tested successfully in sheep under experimental conditions but has had limited success under field conditions. Vaccines for other worms that do not feed on blood have focused on using antigens found in worm secretory and excretory products. Protection has been quite variable, and marketing of such products has not been pursued.

5 Genetic improvement in resistance to nematode infection is most likely based on inheritance of genes that play a primary role in expression of host immunity.[236–238] Based on survival-of-the-fittest management conditions, several breeds around the globe are known to be relatively resistant to infection. Such breeds include Scottish Blackface, Red Maasai, Romanov, St. Croix, Barbados Blackbelly, and the Gulf Coast Native. Katahdin sheep have been considered as being more parasite resistant, but studies to document this are few and not conclusive. Using such breeds exclusively or in cross-breeding programs would certainly lead to improved resistance to worm infection, but some level of production might be sacrificed. Selection of more resistant stock can be accelerated by identifying sires that produce relatively resistant offspring. Computer programs have been used in New Zealand and Australia to rank sire genetics, but change takes up to 8 to 10 years. Heritabilities for FEC, a common measurement for assessing parasite burden, range from 0.22 to 0.40, which is high. Therefore selection for resistance using a measurement such as FEC has been moderately successful.

49.3.8.4

ANTHELMINTIC USE

Discussion of anthelmintics has deliberately been left until the end of this section because drugs cannot be considered the most important aspect of a parasite control program. Guidelines for drug doses are contained in Table 49-3. At this time, only oral administration of anthelmintics is recommended in small ruminants. In

general, goats require 1.5 to 2 times the doses of sheep, with the exception of levamisole, owing to more rapid GI transit times. It is critical that producers accurately assess weights of individual animals and determine the dose appropriately. If an approximate dose is going to be used in all animals, that dose should be for the lightest animal in the group.

The challenge of anthelmintic resistance is life-threatening in small ruminants. There is no point in repeatedly deworming with expensive drugs if the drugs are no longer effective. See the following section on monitoring parasite control programs for information on detecting anthelmintic resistance. On farms where low to moderate levels of resistance to one or more drugs have been diagnosed (60% to 95% reduction in FEC), a useful strategy to help gain the full benefits of both treatment and resistance prevention could be to use these "less-effective" drugs either singly or in combination. Drugs in the BZD family may be effective if multiple-day administration regimens are used.

49.4 LUNGWORM INFECTION IN LARGE ANIMALS

LORA RICKARD BALLWEBER

Lungworms traditionally are those nematode parasites that reside in the lung as adults. In ruminant and equine species, most clinical cases of lungworm involves the genus *Dictyocaulus*. Species of *Dictyocaulus* tend to be host specific with *Dictyocaulus viviparus, Dictyocaulus arnfieldi*, and *Dictyocaulus filaria* found in the bronchi of cattle, equids (horses, ponies, donkeys), and small ruminants, respectively. Sheep and goats may also be infected with *Protostrongylus rufescens* and *Muellerius capillaris*.[239] This section focuses on *Dictyocaulus* infection, with a brief discussion of other lungworm parasites found in small ruminants.

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Because verminous pneumonia requires specific treatment, it is important to distinguish it from diseases caused by other infectious agents. Often the role of lungworm in the cause of respiratory disease may be obscured by a parasite-induced hypersensitivity response or by superimposed secondary bacterial infections.

49.4.1 Life-Cycle

The life-cycle of *D. viviparus* is direct, with no intermediate host involved. Adults produce embryonated eggs that hatch shortly after oviposition. L_1 are passed in the feces, where they develop to L_2 and L_3 within a week under optimal environmental conditions. After the infective L_3 are ingested, they migrate through the wall of the intestine to the mesenteric lymph nodes and through lymphatics into the bloodstream and finally arrive, as L_4, in the lung as early as 7 days after ingestion. Larvae may then develop to sexually mature adult worms or they may arrest development as late L_4 or immature adults. Arrested development can prolong the normal prepatent period from 3 to 4 weeks to approximately 5 months.[239]

Most problems with cattle lungworms in North America occur in areas of moist climates where larvae on pasture are protected from desiccation and larval migration away from the fecal pat onto herbage is facilitated. Under favorable conditions, infective L_3 can survive on pasture for approximately 11 months.[240,241] These larvae plus the larvae produced from carrier animals harboring small numbers of adults or adults developing from arrested larvae can result in high levels of contamination on spring pastures. In subtropical climates, larvae are virtually absent during the hot summers; larval contamination of the pasture peaks in the autumn as a result of carrier animals.[242]

The life-cycle of *D. filaria* is similar to that of *D. viviparus* including the ability of the larvae to arrest development. The prepatent period is approximately 26 days, with peak larval output occurring 39 to 57 days postinfection. As with *D. viviparus, D. filaria* is more prevalent in moist climates and larvae can survive on pasture throughout the winter. Spring pastures contaminated with overwintering larvae and larvae produced from adults developing from arrested larvae in carrier animals are sources of infection for susceptible lambs or kids.[239,243–245]

The life-cycle of *D. arnfieldi* is similar to that of other species of *Dictyocaulus* except that, in addition to L_1, larvated eggs may be passed with the feces. The prepatent period is 2 months.[246]

Unlike species of *Dictyocaulus, M. capillaris* and *P. rufescens* have indirect life-cycles that involve intermediate molluscan hosts. Adults, occurring in the parenchyma *(M. capillaris)* or small bronchioles *(P. rufescens)*, produce eggs that develop and hatch. L_1 are passed with the feces; once on pasture, larvae invade the foot of a susceptible species of snail or slug and develop to infective L_3. Sheep and goats become infected when inadvertently ingesting the mollusk while grazing. The larvae penetrate the intestine and migrate to the lung in much the same manner as *Dictyocaulus*. Early L_4, developing L_4, and adult *M. capillaris* become embedded within a fibrous nodule within the parenchyma. *Protostrongylus* larvae mature in the alveoli and enter the bronchioles as adults. The prepatent period is 5 to 6 weeks, although arrested development may prolong the prepatent period of *M. capillaris*.[239,243–247]

49.4.2 Pathophysiology

Although infections with few worms may be inapparent, *D. viviparus* often results in parasitic pneumonia and bronchitis. The disease process is divided into four phases: penetration, prepatent, patent, and postpatent. In the penetration phase (days 1 to 7), no clinical sign or significant respiratory pathology occurs as the larvae migrate to the lungs. During the prepatent phase (days 7 to 25), clinical signs and lesions become evident. An eosinophilic infiltrate blocks bronchioles; excess mucous production and alveolar collapse occurs. The patent phase (days 25 to 55) is associated with egg-laying adults in the bronchi and trachea. Bronchial and tracheal epithelial damage occurs, air passages are blocked by exudate, and consolidation of lobules results from aspiration of eggs and L_1 into bronchioles and alveoli. Bronchitis, tracheitis and pneumonia follow. During the postpatent phase (after day approximately day 50), surviving animals recover and adult worms die off. Peribronchial fibrosis and epithelialization of alveoli may remain. Secondary bacterial infections resulting from weakened pulmonary defenses may also occur.[239]

Goats tend to be more susceptible to infection with *D. filaria* and more severely affected than sheep, although individual susceptibility to infections does occur. Heavy infections in both species produce bronchitis, pulmonary edema, atelectasis, and emphysema, although death is uncommon.[239,243,244] As with *D. viviparus*, secondary bacterial infections can occur.

In donkeys, whether *D. arnfieldi* causes pathologic lesions on its own is controversial because of the presence of other pathologic agents; however, in healthy infected individuals, pathologic changes include discrete circular areas of overinflation surrounding affected bronchi. Histologically these areas contain a small bronchus packed with nematodes. The small airways are often occluded with exudate. Small amounts of mucus surround adult worms in the main bronchi with little cellular reaction. L_1 are surrounded by an intense mucopurulent reaction. In addition to these types of lesions in horses, many immature nematodes are present in smaller

bronchi, accompanied by bronchial epithelial hyperplasia with large amounts of mucus and pus. Many areas of alveolar hemorrhage and edema are also present.[246]

Although morbidity with *M. capillaris* may be high in most flocks, massive infections with *M. capillaris* or *P. rufescens* are not common. Pathologic changes caused by *P. rufescens* are similar to chronic, low-grade *Dictyocaulus* infection. Heavy infections with *M. capillaris* infection in goats can result in interstitial pneumonia, bronchopneumonia, or fibrinous pleuritis. In sheep and goats, distinct subpleural nodules containing adults and L_1 are common. Secondary bacterial infections can also occur.[239,248–251]

49.4.3 Populations at Risk

Clinical disease occurs most frequently in pastured calves, lambs, and kids in the first year of life. The disease is also reported in housed cattle, related either to heavily contaminated bedding material or to synchronous maturation of large numbers of hypobiotic larvae. Clinical lungworm infestation is more of a problem in cattle than in sheep, possibly because lambs are treated for GINs more frequently than are calves under most management systems.

Immunity to lungworm infection occurs after first exposure and can develop before the end of the first grazing season. However, it is variable in both degree and duration. In cattle, exposed animals may be immune for 7 to 12 months after infection. In subsequent infections most larvae are either killed before reaching the lung or are inhibited from maturing into adults. Usually the immunity developed during the first grazing season is boosted by exposure in subsequent years and prevents manifestations of disease. However, without reexposure to infective larvae, immunity wanes and disease can occur in adult cattle.[239]

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Occasionally, outbreaks of acute lungworm disease are seen in adult cattle on pasture whose immunity is overwhelmed by exposure to very large numbers of larvae. This condition is called the *reinfection syndrome*. Although most ingested larvae are killed or fail to mature, some reach the lung and incite an acute, immune-mediated reaction.

Both sheep and goats develop a strong immunity to *D. filaria;* disease is more common in young animals. As with cattle, continued immunity in sheep depends on reexposure.[239,252]

Individual horse susceptibility to infection with *D. arnfieldi* is evident. Infections can occur during any time in the life of the horse. Donkeys apparently do not develop an immunity to infection, with larval excretion increasing with age.[246,253]

Although immunity to *M. capillaris* appears to be incomplete (adult nematodes can live for up to 4.5 years), responses to subsequent exposures do limit the numbers of adults that develop and the numbers of larvae shed in the feces. However, reexposure may be cumulative, resulting in older animals harboring larger numbers of worms.[239]

49.4.4 Clinical Manifestations

Clinical disease (“husk”) caused by lungworm infection in cattle can occur within 1 or 2 weeks of the introduction of susceptible animals to contaminated pasture. However, clinical disease most often occurs 2 to 4 months into the grazing season. Affected animals develop either an acute or a subacute form of the disease, depending on the number of larvae ingested and the animal's level of immunity. With acute verminous

pneumonia in calves, dyspnea and cough are prominent signs. Auscultation of the lungs initially reveals vesicular murmurs and bronchial tones that progress to moist rales as fluid accumulates. The animal may expectorate froth. Occasionally, emphysema occurs and crackling noises are heard on auscultation. Fever may be as high as 40.5° C (105° F). Mortality rates are high, and animals may die before a patent infection has been established.[239] The similarity between this presentation and that of bacterial pneumonia or shipping fever should be noted.

The subacute or chronic manifestation of disease is more common. In all species the primary signs are coughing, dyspnea, and loss of condition. The animals show elevated respiratory rates but initially are afebrile. Bronchial irritation caused by adult worms and fluid accumulations produces paroxysmal coughing. Animals with the subacute form of lungworm disease are susceptible to bacterial pneumonia. In fact, the subacute form is easily confused with enzootic pneumonia in calves. Signs of reinfection syndrome in adult cattle include severe cough, tachypnea, harsh respiratory sounds, and, for dairy cattle, a sudden drop in milk production approximately 2 weeks after exposure to heavily contaminated pastures.[239]

In horses, lungworm infection typically causes a syndrome similar to chronic obstructive pulmonary disease, although asymptomatic infections may also occur. Clinical signs include persistent coughing, nasal discharge, and respiratory distress; death is uncommon. Donkeys, the source of infection in most cases of lungworm disease in horses, tend to remain asymptomatic, although harsh lung sounds may be auscultated.[246,253]

Infections with *M. capillaris* are generally asymptomatic; however, impaired pulmonary gas exchange, reduced weights and breeding performance, and increased mortality have been reported.[248,249,254]

49.4.5 Control of Lungworm Infection

Management strategies designed to decrease exposure to infective larvae are most effective in preventing dictyocaulosis. Young animals should not be overstocked or allowed to graze in moist, low-lying pastures. It is often helpful to rotate pastures so that successive calf crops do not graze the same area. Young stock should not be grazed with older, clinically immune animals that may serve as a source of infective larvae. Horses should not be grazed with donkeys. If they are, then donkeys should be monitored for L_1 and treated to reduce larval output and pasture contamination. Limiting contact with intermediate hosts and provision of mollusk-free housing will decrease infections with parasites that require these intermediate hosts.

49.4.5.1 ANTHELMINTICS

Several anthelmintics are effective against lungworm. Drugs for the treatment and control of lungworm are presented in Table 49-4.[239,246] The avermectins and milbemycins are particularly effective against both adult and larval stages and have prolonged residual activity that prevents appearance of larvae in the feces for at least 60 days.[255,262] Strategic use of these products, such as treatment at turnout and again 8 weeks later, can substantially reduce pasture infectivity with lungworm larvae. Concerns that such highly efficacious anthelmintics would prevent induction of immunity in first-season grazing animals appear to be largely unfounded, with the possible exception of sustained-release intraruminal devices (see later). The immune response may be attenuated, but exposed animals still develop some degree of immunity to lungworm infection despite prophylactic treatment with these drugs.[256,257,263–265]

Young, susceptible stock may be given a prophylactic treatment in mid-spring or early summer to prevent or limit clinical disease. Housed animals, in particular 1- to 2-year-olds with subclinical but potentially patent infections, should be treated before being turned out to pasture in the spring. All early clinical cases should be treated in an effort to limit disease severity and decrease pasture contamination.

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Table 49-4 Drugs Used to Control Lungworm

Drug	Dose
AVERMECTINS AND MILBEMYCINS	
Ivermectin, abamectin, doramectin, eprinomectin, moxidectin	0.2 mg/kg PO, SC, IM*; 0.5 mg/kg topically ("pour-on"); intraruminal sustained-release device (ivermectin)
OTHERS	
Albendazole	5 mg/kg PO (O, C); 7.5–10 mg/kg PO (B)
Fenbendazole	5 mg/kg PO (O, C); 5–10 mg/kg PO (B); 30 mg/kg PO (E); intraruminal sustained-release device (B)
Mebendazole	15–20 mg/kg PO (O, C)
Netobimin	7.5 mg/kg PO (B, O, C)
Oxfendazole	4.5–7.5 mg/kg PO (B, O, C)
Levamisole	7.5–10 mg/kg PO, SC; 10 mg/kg topically ("pour-on") (B, O, C)
Diethylcarbamazine	22 mg/kg IM daily for 3 days or 44 mg/kg IM once (B)

B, Bovine; *C*, caprine; *E*, equine; *IM*, intramuscularly; *O*, ovine; *PO*, by mouth; *SC*, subcutaneously.

* Route depends on the product and species; follow manufacturers' recommendations.

Intraruminal SRDs containing ivermectin, levamisole, or a BZD can prevent clinical disease for several weeks or months during the grazing season.[265–271] However, some studies have shown that these devices impaired the development of immunity in treated calves.[265,269] SRDs may interfere with development of natural immunity by killing ingested larvae before they can penetrate the intestine and thus stimulate an immune response. However, other studies using these devices have shown that treated calves can develop immunity during the grazing season.[272]

49.4.5.2

VACCINES

An effective vaccine has been developed against *D. viviparus* in cattle and is available in the United Kingdom and parts of western Europe. Two doses of irradiated larvae are administered by mouth 4 weeks apart. The larvae migrate to mesenteric lymph nodes and provoke an immune response but die before they reach the lung. Management considerations associated with the use of the vaccine include the following: (1) calves must be at least 2 months old; (2) vaccinated calves should not be placed on pasture for at least 2 weeks after the second dose; (3) vaccinated calves must not be exposed to heavily infected pastures, nor

should they be mixed with animals showing signs of lungworm disease or with unvaccinated calves; (4) immunity is not long-lasting, so animals must continue to be exposed to low levels of infective larvae to maintain immunity; and (5) the vaccine has a short shelf-life and it is relatively expensive. Farms with contaminated grazing areas and a history of lungworm disease benefit most from vaccination, and it is best used in young nursing calves before exposure to pasture.[273]

49.4.6 Evaluation of Preventive Programs

The efficacy of preventive programs is best assessed by evaluating the number of susceptible animals that demonstrate signs of infection. Because total eradication of the parasite is difficult and low numbers of parasites produce minimum problems, a useful goal is the control of clinical signs such as cough and loss of condition. Fecal larval counts are an unreliable means of evaluating the severity of lungworm infection in an individual animal.

49.4.7 Clinical Management

49.4.7.1 DIAGNOSIS

As with many parasitic diseases, lungworm is often diagnosed on the basis of farm history, seasonal prevalence, clinical presentation, and response to treatment.[239,246,253] Verminous pneumonia may mimic respiratory diseases caused by other agents that require specific treatment. Although definitive diagnosis is difficult, it is important.

To document the presence of lungworm infection, it is necessary to demonstrate larvae, adult worms, or eggs. In cattle and small ruminants, the presence of L_1 in fresh feces indicates lungworm infection.[239] In horses, L_1 may be present in feces; however, patent infections in horses do not always occur, and antemortem diagnosis may best be achieved by examining donkeys co-grazing with the horses.[246,253] The Baermann technique is the technique of choice to detect L_1 in the feces. However, in acute outbreaks animals may succumb before infections are patent. Transtracheal wash may demonstrate a large number of eosinophils, which is supportive of verminous pneumonia; eggs or larvae are occasionally seen with patent infections. This procedure can also help rule out bacterial pneumonia. Finding of nematodes at postmortem examination is definitive. At necropsy, adult *Dictyocaulus* organisms are usually apparent in the bronchi or bronchioles, whereas adult *P. rufescens* organisms tend to be in the bronchioles and adult *M. capillaris* organisms are found in subpleural nodules on the dorsal aspect of the diaphragmatic lobes. Nematodes and the eggs may also be found in histologic section of the lung.

49.4.7.2 TREATMENT

In subacute or chronic forms of the disease, removal of the adult parasites with anthelmintics may result in recovery. However, if the infection is heavy and lung damage is severe, anthelmintic treatment is unlikely to result in complete recovery. In some animals, anthelmintic treatment worsens the signs, and some heavily infected animals die. In severely affected individuals, antihistamines and antibiotics should be included in the therapeutic regimen.

49.5 EVALUATION OF PARASITE CONTROL PROGRAMS

SHERRILL A. FLEMING

The efficacy of a given parasite control program should not be assumed; it should be assessed on a regular basis. The routine performance of quantitative tests for parasite burdens allows veterinarians to identify the development of anthelmintic resistance. Although fecal floatation is useful in identifying the presence of parasites, the use of the McMaster technique allows an estimation of the numbers of parasites. Both procedures are relatively simple and can easily be performed in the practice setting. Other specialized laboratory procedures are also discussed. Once resistance has been documented it is important to identify the species involved through larval identification.

49.5.1 FEC and FEC Reduction Tests [274–276] (Box 49-1)

Determining numbers of nematode eggs in feces is the simplest and least invasive way to evaluate a parasite control program. Fecal examination may be of limited value in an individual animal because animals dying of parasitic infection may have no eggs in the feces, whereas animals with high FECs may be clinically normal. Nevertheless, FECs can provide information on the level of infection present in an individual animal, particularly when egg counts are repeated over the course of 2 to 3 weeks. Herd average FECs are more useful and provide an accurate reflection of the degree of environmental contamination and rate of infection. Pretreatment and posttreatment FECs can also be used to establish the efficacy of an anthelmintic in a particular group of animals. A quantitative McMaster or Stolley technique, rather than simple flotation, is crucial for accurate monitoring.

It is suggested that guidelines published by the World Association for the Advancement of Veterinary Parasitology (WAAVP) be used to perform and evaluate data from an FECRT test, applying practical modifications to fit the situation on the farm.[276] Briefly, groups of 15 animals that have not been treated within the past 8 weeks are randomly allocated to treatment groups, and FECs are performed using a modified McMaster technique 10 to 14 days after treatment. An untreated control group must be included. If fewer than 12 to 15 animals per group are available, then treatment groups should be balanced by performing a pretreatment FEC. Animals are then stratified by FEC from highest to lowest, blocked by number of treatment groups, and then within each block are randomly assigned to treatment. Alternatively, where *Haemonchus* is the primary parasite, animals may be scored using the FAMACHA method as they come through the chute, blocked by FAMACHA score, and then randomly assigned to treatment within blocks. This approach is a bit more complicated but will result in groups that are balanced, which will result in a more accurate test. Calculations are performed using the following formula:

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$$\text{FECR } \% = 100\left(1 - \frac{Xt}{Xc}\right)$$

where Xt and Xc are the arithmetic mean number of eggs per gram (epg) in the treated (t) and untreated control (c) groups, respectively. Software is available for free that performs all calculations and gives data interpretation.[277] If the RESO calculator is used, the assignment of resistance status is based both on percent reduction and the 95% confidence intervals. If the RESO calculator is not used, the following guidelines can be applied: reductions of greater than 95% indicate sensitivity, reductions of 90% to 95% indicate low or suspected resistance, and reductions of <90% indicates resistance. FECRT yields reliable data only if FECs are sufficiently high to properly measure a reduction from treatment. If the control group's mean FECs are below

150 epg, then objective assessment of resistance will not be reliable. Group mean FECs of less than 150 epg can be common in adult sheep; therefore when FECRT is performed on a sheep farm it is preferable to use weaned lambs if available. With goats, low FECs are usually not a problem.

49.5.1.1

Box 49-1 Modified McMaster Technique (Fecal Egg Count)

This is one method for performing a McMaster fecal egg count. Similar protocols are used routinely in many laboratories, so you may see a slightly different procedure recommended elsewhere. The important point is to use the same procedure each time.

The first step is to collect freshly passed feces uncontaminated by soil or bedding. The best way is to wear a rubber glove and extract feces directly from the rectum. Alternatively, feces can be picked up off the ground if done soon after deposition. The collection container should be labeled with the identification of the animal and the date of collection. Fresh samples work best, but accurate results can be obtained if the sample is refrigerated during the interim. If samples are not refrigerated, the eggs will hatch within 12 to 24 hours. Once hatched, eggs cannot be counted.

49.5.1.1.1

MATERIALS

Compound microscope

Scale

Saturated sodium chloride (table salt)

50-mL centrifuge tube, with screw cap and marked with milliliter increments

Pipette (1-mL syringe or eye dropper works well)

McMaster egg counting slide*

Paper towels

A fresh fecal sample, refrigerated until tested

49.5.1.1.2

PROCEDURE

1 Weigh out 2 g of feces into a 50-mL centrifuge tube and fill to 30-mL line with salt solution. It is recommended to purchase a small scale and weigh feces, but if you do not have a scale you can still get a close estimation by putting 28 mL of salt solution into a 50-mL centrifuge tube first and then adding feces until a volume of 30 mL is achieved.

2 Pour off approximately 25 mL of the salt solution into another small container, keeping feces in the tube (use tongue depressor).

3 Soak feces for a few minutes and mix (soft feces) or break up (fecal pellets) with tongue depressor.

4 Add back approximately one half of the salt solution and mix well, breaking up any remaining feces as well as possible.

5 Add back the remaining salt solution and screw the cap back onto the tube.

6 Shake tube vigorously for approximately 1 minute to disrupt any remaining feces as much as possible.

7 Set tube aside for a few minutes to let bubbles dissipate.

8 Wet McMaster chamber with water and dry top and bottom on paper towels.

9 Rock (do not shake) tube several times to thoroughly mix solution without causing large air bubbles to form.

10 Immediately pipette (using 1-mL syringe or eye dropper) a sample of the suspension and fill both sides of counting chamber. Work quickly. If it takes more than a few seconds to load the first chamber, then mix fecal solution again and refill pipette before loading the second chamber.

11 Let stand for 1 to 2 minutes to allow eggs to float.

12 Count all eggs inside of grid areas (>½ of eggs inside grid) using low power (10×) objective. Focus on the top layer, which contains very small air bubbles (small black circles; if numerous large air bubbles are visible, remove the fluid and refill).

13 Count only trichostrongyle and strongyle eggs (oval shaped, approximately 80 to 90 microns long). Do not count *Strongyloides* species (oval, approximately 50 microns long), tapeworm eggs (triangular or D-shaped), or coccidia (various sizes). Note the presence of other species, but count only the trichostrongyle and strongyle eggs.

14 Once filled, the chambers can sit for no longer than 60 minutes before counting without causing problems. After 60 minutes, drying and crystal formation may begin.

15 Total egg count (both chambers) × 50 = epg (eggs per gram).

49.5.1.1.3

NOTES

This is a dilution technique, and theoretically this ratio of feces to flotation solution will not detect infections with less than 50 eggs per gram of feces (one egg seen on slide), so it is not very accurate for samples with low numbers of eggs. On a practical level this is not important, because from a clinical standpoint slight differences in results when egg counts are low do not matter.

Fairly soon after counting is complete, thoroughly rinse out the McMaster chamber with warm running water. Doing so will keep the chamber clean and ready it to be used again. If fecal solution dries in the chamber do not soak in soapy water for long periods, as this will cause the chamber to become cloudy. If

the chamber gets dirty, soak for only a few minutes in water containing dish soap and then rinse completely with tap water.

* Chalex Corporation, Issaquah, WA, chalexcorp@att.net; www.vetslides.com

49.5.2 Larval Identification

Ideally, if there is <90% egg count reduction, the eggs should be hatched and the larvae species identified. In the majority of cases these will be *H. contortus*, but other species, especially *Trichostrongylus* species, readily develop resistance as well. One can sometimes be fooled into an improper interpretation of egg count reduction results if mixed species are present and only one is resistant. 1643 1644

49.5.3 Egg Hatch Assays and Larval Development Tests[276]

Eggs from feces are incubated with concentrations of the anthelmintic to be tested, and the eggs hatched. A dose-response curve is generated (DrenchRite test from Horizon Technology).[275] The advantage of this test is that a single fecal sample can be tested for all available classes of anthelmintics simultaneously. The cost of this test has recently increased and may discourage owners from pursuing this diagnostic. However, when compared with the cost of using anthelmintics that are ineffective, it is easy to justify the use of this test. It is important to read instructions for submitting this test and scheduling a testing date before the samples are collected.

49.5.4 Larval Culture

Larval cultures can be used to distinguish between large and small strongyles in horses and to identify the various nematode species in ruminants. Most parasitology laboratories can perform this examination. It requires submission of 200 to 400 g of fresh feces. Pooled samples from several herd members are often used.

49.5.5 Pasture Larval Counts

Counts of parasitic larvae on herbage are useful to indicate the level of exposure experienced by the grazing animal. This examination is somewhat tedious but can be performed by many university laboratories. A 2-kg sample of forage is gathered for submission to the laboratory. The grass is sampled by walking a V pattern across the acreage and stopping every three paces to sample grass. The samples are subsequently washed and passed through screening to isolate and identify larvae.

49.5.6 Necropsy Evaluation

The nature and magnitude of parasitic infections can be established by necropsy examination. Gross examination and an estimate of adult worm population in the gut lumen are often sufficient. Many worms detach from the mucosa as the carcass cools; however, the damage done by the parasites can be seen on gross or histologic examination. Occasionally it is necessary to use digestion techniques or histologic examination to document the presence of hypobiotic larvae.

49.6 ANTHELMINTIC USE

CHRISTINE A. UHLINGER

Anthelmintic drugs are administered to treat, control, and prevent parasitic infections and to minimize the economic losses associated with parasitic infection. Anthelmintics are also used for the treatment of an individual animal exhibiting clinical signs of parasitic disease.

49.6.1 Drug Action

To use an anthelmintic properly, it is necessary to consider its mode of action, spectrum of activity, and duration of effect. Efficacy for a given drug may be defined as its ability to kill adult or larval parasites, suppress parasitic egg production, or promote the expulsion of worms from the GI tract.

Because of the emergence of drug-resistant strains of nematodes, it is difficult to predict how a particular drug will perform in a specific animal or herd. Package inserts should be regarded as guidelines rather than gospel. It is prudent to run periodic pretreatment and posttreatment fecal examinations to assess the performance of commonly used drugs on a given farm. Readers should refer to the sections on horses, cattle, and small ruminants for more specific recommendations.

49.7 ANTHELMINTIC DRUGS

49.7.1 Avermectins and Milbemycins

The avermectins and milbemycins are macrocyclic lactones. They act by increasing the permeability of parasite cell membranes to chloride ions, which results in nonspastic paralysis and death of the parasite. These drugs may also act by potentiating presynaptic release of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, although this theory has been challenged.

These products have a high level and broad spectrum of activity against adult and larval nematodes. They are also effective against various ectoparasites such as mites, lice, ticks, bots, and cattle grubs; however, they are ineffective against flukes and tapeworms. These drugs suppress nematode egg production for longer than other anthelmintics. Because of its long duration of effect, moxidectin suppresses fecal egg counts and protects against reinfection for longer than ivermectin. Concern has been expressed about the environmental impact of these long-acting anthelmintics in grazing animals.

Several products have been developed for use in animals. The avermectins include ivermectin, abamectin, doramectin, and eprinomectin. The milbemycins include nemadectin and moxidectin. Oral (drench, sustained-release intraruminal device), topical (“pour-on”), and injectable formulations are available, depending on the drug. Ivermectin is safe to use during pregnancy, but currently it is not approved for use in lactating dairy animals or females of breeding age. Similarly, doramectin and moxidectin are not approved for use in female dairy cattle of breeding age. Eprinomectin is unique in that it has no withholding period for milk or meat, so there are no restrictions on its use in cattle. At labeled doses, moxidectin is a safe drug; however, accidental overdosage has caused neurologic signs in foals and miniature horses.

49.7.2 Benzimidazoles

BZDs comprise a large class of anthelmintics that interfere with parasitic carbohydrate metabolism by inhibiting the enzyme fumarate reductase. Many BZDs have been developed and marketed. They include

albendazole, fenbendazole, mebendazole, oxfendazole, oxibendazole, parbendazole, ricobendazole, thiabendazole, triclabendazole, and the probenzimidazole drugs febantel and netobimin.

BZDs are widely used in horses and ruminants. In general they exhibit a high degree of safety and a broad spectrum of activity against GINs and lungworms. Some members of this class (e.g., albendazole) are also active against liver flukes and certain cestodes in ruminants. Albendazole and netobimin can cause teratogenicity and embryo toxicity in sheep when given during early pregnancy. Fenbendazole, oxfendazole, and oxibendazole are considered to be safe for use in pregnant animals.

Resistance to BZDs has been documented in certain equine, ovine, and caprine parasites. In general a strain of parasite resistant to one BZD drug quickly develops resistance to other BZDs or pro-BZDs, a phenomenon known as *side resistance*. 1644 1645

49.7.3 Levamisole

Levamisole acts by causing neuromuscular depolarization and paralysis of the parasite. It has been widely used in ruminants to treat GIN and lungworm infections. However, levamisole resistance has become a problem in many areas.

The dose of levamisole should be calculated carefully because toxic doses are only one to two times therapeutic doses. Signs of toxicity may mimic those of OP toxicity, including muscle fasciculations around the lips and eyelids, hypersalivation, spastic movements, depression, and diarrhea. In ruminants, muzzle foam may develop after oral administration of the drug but usually disappears within a few hours after administration. In horses, transitory excitement has been seen after treatment. Levamisole is not recommended for use as an anthelmintic in horses. Concurrent administration of morantel, pyrantel, diethylcarbamazine, or OPs could enhance the toxic effects of levamisole.

49.7.4 Morantel and Pyrantel

The tetrahydropyrimidines morantel and pyrantel are cholinergic agonists that exert their anthelmintic effect by depolarizing neuromuscular junctions and causing irreversible paralysis of susceptible parasites. Morantel is slower in its onset of action but much more potent than pyrantel. These products are effective against many species of adult nematodes but do not appear to be active against larval stages. Pyrantel is also effective against tapeworms in horses when given at twice the recommended dose. The margin of safety is relatively wide, and there is no contraindication to use with other cholinergic drugs. However, it is recommended that morantel and pyrantel not be used concurrently and that neither be given with levamisole. Piperazine antagonizes the effects of morantel and pyrantel, so it should not be used with either of these drugs. Resistance to morantel and pyrantel has been documented in strains of *H. contortus* and in some cyathostomes (equine small strongyles).

49.7.5 Organophosphates

OPs block neurotransmission by inhibiting acetylcholinesterase. Various formulations of OP drugs are available for treating GI nematodiasis. Commonly used OPs include haloxon, coumaphos, trichlorfon, and dichlorvos. Toxicity occurs with these products in a dose-related manner, so dosages should be calculated with care. In addition, the potential danger to humans administering these products should not be overlooked. Atropine is recommended in cases of overdose in livestock.

49.7.6 Phenothiazine

The mode of action of phenothiazine (PTH) has not been clarified; it is thought to interfere with anaerobic metabolism of nematodes. The various formulations of PTH differ in purity and particle size. The purified product (99% PTH) with small particle size (2 μm) is the most effective.

Although PTH is effective against a wide spectrum of GINs, resistant strains of parasites have emerged in several species. The drug is synergistic with piperazine; combinations of these drugs have effective activity against PTH-resistant nematodes. PTH used in combination with piperazine can be administered at a much lower dose.

PTH toxicity has been reported. Toxic reactions include corneal inflammation, abortion, ataxia, hemolytic anemia, photosensitization, and nephrotoxicity. The drug should not be administered to debilitated or anemic animals or to animals in the last month of pregnancy.

49.7.7 Piperazine

Piperazine salts block neuromuscular transmission, resulting in paralysis of susceptible GINs. The worms are then passively removed from the GI tract by intestinal peristalsis. Piperazines have low toxicity and are safe in young or pregnant animals. However, their spectrum of activity is limited, in practical terms, to ascarids. Piperazine must be used with caution in horses heavily infested with ascarids because the paralyzed ascarids can cause an impaction that may culminate in bowel rupture. Diethylcarbamazine is a piperazine derivative that has been used to control lungworm infection in sheep and cattle.

49.7.8 Praziquantel

Praziquantel is a cesticidal drug that causes spastic paralysis, decreased glucose uptake, and disruption of the tapeworm's tegument. Although not approved for this use, praziquantel is effective for treating tapeworm infestation in horses. It has also been used to control various cestodes in small ruminants.

49.8 COCCIDIOSIS IN FOOD ANIMALS

LORA RICKARD BALLWEBER

Coccidiosis causes serious economic losses in a variety of food animal species. Regular infections with a mixture of species generally occur throughout the life of the animal. Infections tend to be asymptomatic and self-limiting unless management or other factors allow the abnormal concentration of oocysts in the environment or when host defenses are compromised. Kids are especially susceptible to coccidiosis and may develop chronic diarrhea as a consequence. In many production operations, coccidiosis is an annual event.

49.8.1 Life-Cycle

Coccidiosis in ruminants is caused by intracellular parasites of the genus *Eimeria*. Essentially all of the species of *Eimeria* occurring in ruminants are rigidly host-specific. The life-cycle is complex, involving both sexual and asexual phases within the same host. Single-cell oocysts are passed in the feces and subsequently sporulate in the external environment to become infective. The sporulated oocysts are ingested by the host with

contaminated food or water. Digestive enzymes activate the sporozoites within the oocysts, which excyst in the intestine and enter intestinal cells. The asexual phase of development, in which two or more cycles of merogony occurs, is then initiated. Asexual fission results in the production of merozoites. As the meronts mature, they rupture, releasing the merozoites, which enter other cells and repeat the cycle or progress to the sexual phase of development (gamegony). In this phase, merozoites enter new cells and produce macrogametes and microgametes. Microgametes are released by cell rupture and fertilize a macrogamete to form a zygote. A cyst wall then forms around the zygote, resulting in the next generation of oocysts. Once again the host cell ruptures, releasing oocysts into the lumen of the intestine, where they are then passed with the feces. The prepatent period is approximately 2 to 3 weeks and varies with the particular species of *Eimeria*.[278,279]

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49.8.2 Pathophysiology

Most intestinal *Eimeria* organisms develop in the epithelial cells of the lamina propria, although a few exceptions (e.g., *Eimeria bovis*) do exist. As a result of the developmental cycle, particularly the sexual phase, infected host cells are destroyed. However, the degree of damage depends on the species of *Eimeria* involved, the number of oocysts ingested, and various host factors including age, physical condition, genetic susceptibility, and immunity from previous exposure.[278,279] If the number of oocysts ingested is low, nonimmune healthy animals may tolerate infection and show no signs of disease. Intestinal cells are destroyed, but because they normally are replaced at a rapid rate the damage done to the gut is minimal. However, if nonimmune animals are exposed to many oocysts, widespread rupture and exfoliation of intestinal cells alters gut function; causes loss of blood, fluid, albumin, and electrolytes into the gut; and allows secondary bacterial invasion. Sections of sloughed intestinal mucosa and fibrin casts may be seen in the feces, and the feces may be blood tinged.

Neurologic signs have been reported during coccidiosis outbreaks caused by *Eimeria zuernii* in calves and weaned beef cattle.[279,280] The pathophysiology of this manifestation has not been definitively established, and conflicting theories have been proposed, including copper imbalance, plasma electrolyte imbalances, a labile neurotoxin, and a combination of stressors in which coccidia are only one factor.[279,281–283]

49.8.3 Populations at Risk

Infections with mixtures of pathogenic and nonpathogenic species of *Eimeria* occur regularly throughout the life of mature animals; hence they provide the source of oocyst contamination leading to infections in young animals. After an initial period of infection the host acquires species-specific immunity. The degree of immunity acquired depends on the quantity of oocysts ingested and is boosted by continuous exposure to oocysts. It is possible that when exposed to few or moderate numbers of oocysts, a nonprotective immune response may occur; however, initial exposure is generally sufficient and animals are usually protected against clinical disease on reexposure to the same species.[278,279] Clinical coccidiosis is therefore primarily a disease of young, nonimmune animals crowded together in areas such as feedlots, small pastures, shady creek bottoms during hot summer weather, or areas near feed or water tanks or salt licks. Under these conditions the environment is highly contaminated with oocysts from the immune animals, which pose a significant threat to other young, immunologically naive animals in the same areas. Stress, such as from shipping, weaning, dietary changes, and/or adverse weather (e.g., blizzards), appears to facilitate outbreaks.[278,279] Corticosteroid treatment or concurrent illness can also precipitate a peracute form of coccidiosis.

Although outbreaks have been reported in range animals, coccidiosis is chiefly a disease of confinement. Clinical disease usually occurs in cattle less than 1 year of age. In dairy cattle, coccidiosis is most common in calves when they are taken from hutches into group calf pens or mini—free-stall barns. In beef cattle the disease is most prevalent in feedlot calves. In sheep, disease is usually limited to lambs less than 6 months old. Coccidiosis is most common in intensively reared lambs, although suckling lambs on pasture in constant use at high stocking rates are also at risk. Young kids appear particularly susceptible to coccidiosis, with clinical disease especially prevalent 2 to 3 weeks after weaning.[284] Previously exposed animals may show clinical signs under conditions of stress and heavy infections. Occasionally, adult animals develop coccidiosis when moved into a new herd and exposed to different species of the parasite to which they are not yet immune.

49.8.4 Clinical Manifestations

The destruction of epithelial cells and subsequent loss of blood, albumin, fluid, and electrolytes typically cause a profuse, sometimes bloody, catarrhalic diarrhea. Dehydration may occur, but most animals continue to drink water and can meet their fluid requirements. Despite the blood loss, anemia is not usually apparent. Typical of infections in dairy cattle, light infections tend to cause watery feces, poor condition, and reduced weight gain. Severe infections cause projectile, bloody diarrhea with mucus, rectal tenesmus, inappetence, dehydration, and weight loss. Clinical signs last approximately 1 week. In lambs, clinical signs are similar to those of cattle except blood and tenesmus do not usually occur. In kids, clinical signs include pasty, watery diarrhea and dehydration.[284] Sudden death can occur in both lambs and kids, but the case fatality rate is usually low in most outbreaks. After recovery from the disease the gut does not return to normal function for several weeks, and appetite may be suppressed concurrently, leading to poor growth and/or stunting. Animals that develop “nervous” coccidiosis may exhibit muscle tremors, hyperesthesia, convulsions, nystagmus, and blindness. The mortality rate is high.

49.8.4.1 Control of Coccidiosis

The spread of coccidiosis depends on the prevalence of oocysts in the environment. The level of infection is directly related to the level of fecal contamination. Houses and pens used for sequential groups of young animals often become highly contaminated and serve as the source of infection for subsequent groups. Therefore minimizing exposure of susceptible animals to infective oocysts depends on management techniques that focus on either sanitation to avoid the buildup of fecal contamination or the elimination of environmental conditions conducive to oocyst survival or both. Decreased stocking rates, proper manure disposal, and elevated feed bunks will help reduce contamination and exposure to oocysts. Sunlight, low humidity, and treatment with formaldehyde, ammonia, or methylbromide will kill oocysts. Reduction of average temperatures in barns to 15° C and of humidity to a maximum of 80% has significantly decreased clinical coccidiosis in some areas.[278] Prophylactic use of coccidiostats is inevitable if conditions of animal husbandry cannot or do not improve.

49.8.4.1.1 DRUGS

The various drugs that have been used to prevent or treat coccidiosis in ruminants are listed in Table 49-5.[285–290] These drugs are most often administered in the feed or water. Therapeutic anticoccidials are used in acute outbreaks; however, the gamonts are the main target of these drugs. Because the life-cycle of the parasite is essentially complete and most of the intestinal damage is done by the time anticoccidial

therapy is administered, it is of limited value. In acute outbreaks, scouring calves should be removed from the group. Supportive therapy, including electrolytes, glucose, and antidiarrheals, may help improve survival.[278,284]

To prevent losses from coccidiosis, it is best to treat exposed animals prophylactically or metaphylactically rather than therapeutically. Often outbreaks of coccidiosis can be predicted based on farm history. Administration of coccidiostats during this time does not completely prevent infections; rather, they prevent clinical infections without interfering with the production of protective immunity. Drugs in this category tend to target merogony, preventing multiplication and subsequent mucosal damage.[278,279]

Table 49-5 Drugs Used for Treatment and Prevention of Coccidiosis in Ruminants

Drug	Treatment*	Prevention*
Amprolium	10 mg/kg bwt for 5 days (B)	5 mg/kg bwt for 21 days (B)
	25–40 mg/kg bwt for 5 days (O, C)	50 mg/kg bwt for 21 days (O)
	65 mg/kg bwt once	
Decoquinate		0.5 mg/kg bwt for 28–30 days
Diclazuril		1 mg/kg bwt once; a second dose can be given 14 days later
Lasalocid		1 mg/kg bwt continuously (B)
		25–100 mg/kg feed, continuously
		80 mg/kg milk replacer (neonatal calves)
		Free choice in salt at 0.75% total salt mixture
Monensin	2 mg/kg bwt for 20 days (O)	1 mg/kg bwt for 28 days
		10–20 ppm in feed, continuously
		16–33 g/ton of feed, continuously
		Intraruminal controlled-release device (weaned beef calves)
Nitrofurazone 10	15 mg/kg bwt for 5–7 days	33 mg/kg bwt for 14 days
	In feed at 0.04% or in water at 0.0133% for 7 days	In feed at 0.04% for 21 days
Salinomycin		10 ppm in feed (O)
Sulfadimethoxine		50 mg/kg bwt for 5 days (O)
Sulfamethazine	110 mg/kg bwt for 5 days	35 mg/kg bwt for 15 days (B)
	140 mg/kg bwt for 3 days	25 mg/kg bwt for 7 days (O)
	140 mg/kg bwt once, then 70 mg/kg bwt for 5–7 days	55 g/ton of feed (C)
Sulfaquinoxaline	10–20 mg/kg bwt for 5–7 days	
Toltrazuril	20 mg/kg bwt	20 mg/kg bwt once, 10 days after turnout onto pasture

B, Bovine; *bwt*, body weight; *C*, caprine; *O*, ovine.

* Oral administration; dose or regimen may vary among references.*Note*: Coccidiostats used in poultry feeds may be toxic to ruminants.

49.8.4.1.2 OTHER STRATEGIES FOR MINIMIZING CLINICAL INFECTIONS

Use of growth implants containing estradiol and progesterone can attenuate the effects of high oocyst challenge in dairy calves.[291] Attempts at developing a conventional vaccine against coccidiosis have been disappointing. Peptide or recombinant vaccines may prove to be efficacious in the future.[292] Immunization with a "trickle dose" of oocysts 2 weeks before turnout onto infected pasture may attenuate the effects of natural challenge in calves.[293] Oocysts can survive the hay-making process, so pastures known to be infected with coccidian oocysts should not be used to make hay for susceptible animals.[294]

49.8.5 Evaluation of Preventive Programs

Oocysts can be found using standard flotation techniques.[284] However, the presence or absence of oocysts does not necessarily correlate with the presence of disease. In any given herd or group a baseline level of oocyst shedding is normal. Because immunity is incomplete, many immune animals shed oocysts. On the other hand, nonimmune animals with low-level infections may shed oocysts but have no clinical signs or need for treatment. Furthermore, because intestinal damage occurs during the prepatent period, animals with clinical coccidiosis may not yet be shedding oocysts. This variation complicates both evaluation of preventive measures and the diagnosis of coccidiosis in clinically affected animals. The presence of oocysts in healthy or sick animals does not necessarily indicate the need for anticoccidial treatment.

Nevertheless, microscopic examination of diarrheic or bloody feces from young animals still remains the most direct and cost-effective method of diagnosis.[278,279] Examination of fecal samples from several animals is needed to obtain a true estimate of the presence of coccidia within a group. Because pathogenicity of the various species of *Eimeria* varies considerably and the clinical picture is not specific, it is imperative that species identifications be determined.[277] This information is then combined with a good history and thorough knowledge of the herd management on the farm in question to guide interpretation of clinical observations and diagnostics.

Herds that require preventive strategies have a history of prior disease and a large proportion of herd members shedding high numbers of oocysts. Efficacy is evaluated on the basis of a decreased prevalence of clinically ill animals.

49.8.6 Clinical Management

49.8.6.1 DIAGNOSIS

Definitive diagnosis may be made at necropsy. Antemortem, young, diarrheic animals passing large numbers of oocysts are not difficult to diagnose. However, as discussed earlier, making a diagnosis on the basis of oocyst counts alone can be misleading.

49.8.6.2 TREATMENT

Drugs used in the treatment of coccidiosis are listed in Table 49-5. Supportive therapy, when indicated, is primarily directed at replacing fluid losses and supporting the animal until the gut epithelium regenerates.

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50 Chapter 50 Nutrition of the Sick Animal

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The influence of nutrition on the recuperation of veterinary patients is often overlooked, although the effects of nutritional status on recuperative ability are well known. Many patients are in a state of protein calorie malnutrition when first presented to the clinician. Early intervention with supplemental calories, protein, and other essential nutrients provides the patient with the dietary resources needed to optimize immune function, promote wound healing, and improve the recovery of the animal.

Multiple research studies have demonstrated that the immune response of an animal is directly related to the nutritional state of the animal.[1–4] A deficiency of calories, protein, minerals, or vitamins alters the production of inflammatory cytokines, adversely affects leukocyte function, and decreases host resistance to bacterial infections.[1,2] Clinical studies in hospitalized horses have demonstrated an improved recovery after gastrointestinal surgery in patients supplemented with intravenous nutrition.[5]

Different forms of diet therapy may be employed, depending on the clinical condition of the animal and the ability of the animal to tolerate different types of supplemental nutrition. Large animal patients that have a functional gastrointestinal tract and can tolerate placement of a nasogastric (NG) or esophageal feeding tube are candidates for treatment with liquid enteral nutrition. Glucose can be added to a patient's intravenous fluids to provide an energy source. Parenteral nutrition (PN) is ideal for animals that have gastrointestinal ileus, that have an obstructive lesion in the gastrointestinal tract, or that are recumbent.

50.1 ASSESSMENT OF NUTRITIONAL STATUS

Before initiation of dietary therapy, the large animal patient must be examined to determine its nutritional needs. Animals may be anorectic owing to systemic disease, or they may be dysphagic owing to a mechanical (foreign body, abscess, poor dentition) or neurologic (botulism, tetanus, viral encephalitis) disease. Assessment of the nutritional status of the patient should include a measurement of the body weight (BW) and body condition score (BCS) of the animal. BW measurements should be taken at the time that the large animal patient is presented to the clinician and as frequently as possible during hospitalization. If a scale is not available, estimations of BW can be made with a weight tape or by using length and girth measurements (see Chapter 9). When a scale or weight tape cannot be used, the animal's BCS should be used to evaluate the nutritional status of the patient. The BCS system enables the clinician to subjectively assess the endogenous protein and lipid stores in a large animal patient. A list of BCS descriptions for different species is provided in Chapter 9. Changes in weight or BCS are often easily overlooked in day-to-day observations of the patient if a concerted effort is not made to detect them. Palpation of the animal (ribs, dorsal vertebral processes) is necessary in sheep with a heavy fleece, camelids with long fiber, and horses with a thick winter hair coat. Animals with a low BCS (1 to 3 of 9; 1 to 1.5 of 5) have minimal protein and lipid stores and are at greater risk for developing protein calorie malnutrition after a period of anorexia. Large animal patients with a high BCS (7 to 9 of 9; 3.5 to 5 of 5) that are anorectic may have an increased risk for developing complications (hyperlipemia, hepatic lipidosis) from abnormal lipid metabolism. A clinician should initiate dietary therapy in a large animal patient that loses 3% to 5% of its initial BW or whose BCS diminishes by ≥1 grade.

Biochemical tests provide another method to evaluate the nutritional status of the large animal patient. Endogenous protein catabolism is a normal physiologic response to anorexia in animals. To date, few biochemical tests are available to assess protein malnutrition in large animals. Although anemia and hypoproteinemia (hypoalbuminemia) are occasionally seen in cases of malnutrition, they are not specific and frequently are associated with another primary disease process such as parasitism or protein-losing enteropathy. Severe protein malnutrition can result in abnormally low serum urea nitrogen (SUN) concentrations in horses and ruminants. Liver disease also decreases the formation of urea nitrogen and must be ruled out when evaluating the animal. Protein malnutrition can result in an increase in the urinary excretion of 3-methylhistidine, a myofibril amino acid that is not metabolized. Measurement of this metabolite in the future may be a useful tool to monitor protein catabolism in large animal patients.

Underfed horses develop a mild hyperbilirubinemia (unconjugated) that, although not directly related to nutritional status, is readily reversed when food intake resumes.[6,7] Animals that are in negative energy balance also use endogenous lipid as an energy source. Serum nonesterified fatty acids (NEFAs) and/or triglycerides are expected to rise in these animals. Once nutritional support or refeeding is initiated, these lipid metabolites usually decrease. Pathogenic elevations in serum triglyceride (>500 mg/dL) develop in some equine patients that are anorectic and that have a high daily energy requirement (lactation, pregnancy), insulin resistance (Cushing's syndrome), or renal failure and in predisposed breeds (miniature horses, ponies). Ketone bodies have a glucose-sparing effect in the body and are normally produced from fatty acids and amino acids in animals that are in negative energy balance. Ketonuria develops after the excess production of ketones and can be used to indirectly monitor the severity of caloric malnutrition in ruminants. Hypoglycemia is a common complication in large animal neonates that are malnourished but is an uncommon finding in adults. Both adult and neonatal large animals may develop glucose intolerance and hyperglycemia during periods of systemic illness and may require 1648
treatment with a diet that will not exacerbate the hyperglycemia. Electrolyte and mineral derangements including 1649
hypocalcemia, hypomagnesemia, hyponatremia, hypochloremia, hypophosphatemia, and hypokalemia may develop in inappetent systemically ill large animals or during the refeeding process.[8,9]

50.2 NUTRIENT REQUIREMENTS OF LARGE ANIMALS DURING CLINICAL ILLNESS

Although it is generally accepted that sick animals have increased nutritional requirements, these requirements have not been quantified for specific disease conditions. The current trend in critical care nutrition is to provide adequate calories to meet the resting energy requirements of the hospitalized patient and sufficient protein to meet the maintenance requirements. These values can be calculated based on the animal's BW (see Chapter 9) or determined by reference to National Research Council (NRC) tables.[10] For adult horses, the resting digestible energy (DE) requirement is calculated as DE_{rest} (Mcal) = 0.975 + 0.021 BW(kg), and maintenance crude protein (CP) requirement is calculated as CP (g) = 1.26 BW(kg).[10] For a 450-kg horse, these would equate to a 10.4-Mcal resting energy requirement and a 567-g crude protein requirement. For foals and calves, resting energy requirement is approximated as DE (Mcal) = 0.07 BW(kg) and digestible protein as DP (g) = 3.5 BW(kg), which would equate to 3.50 Mcal (3500 kcal) and 175 g of protein for a 50-kg neonate. These values represent starting points for formulating dietary therapy, and adjustment based on clinical response or specific medical conditions may be necessary.

Vitamin and mineral requirements, also available from NRC tables, can usually be met if an enteral diet is formulated with commercial complete feed pellets or pelleted hay. Parenteral solutions can be supplemented with vitamins and minerals. Although B vitamin deficiencies do not occur naturally in horses and cattle,

supplementation is probably beneficial in large animals with gastrointestinal diseases that result in the disruption of the normal tract flora that produce B vitamins.

50.3 ORAL SUPPLEMENTATION

The animal's feed intake should be monitored during treatment. If the animal is losing condition despite consuming all feed offered, more or higher-quality feed should be provided. If the animal's appetite is poor, the patient should be offered a variety of highly palatable feeds including fresh grass, dried forages, and complete commercial feed pellets. Although sweet feeds are palatable, their use should be limited to a top dressing of other feeds. Ruminants in particular may consume small quantities of fresh feed if it is offered frequently, whereas if the same quantity is offered in one feeding, it may be ignored after a few bites. Many dairy cows can be coaxed into eating hay if it is placed in the back of the pharynx by the clinician, and oropharyngeal stimulation may result in increased voluntary feed consumption. Fresh silage and dried brewer's grain frequently appeal to the hypophagic cow. Many sick horses and ruminants benefit from grazing if grass is available.

A hospital feeding chart can be created to facilitate monitoring of the feed consumed by a hospitalized patient. Use of an inexpensive farm scale is the most accurate way to measure the amount of feed offered to a patient. Feed that is not consumed within a few hours should be weighed and discarded to prevent the accumulation of stale, and possibly fermented malodorous feed. If the animal does not voluntarily consume enough feed to meet its resting energy requirements or its maintenance protein requirements, or if the animal loses weight or condition, dietary therapy with a liquid diet by intragastric administration should be considered. Dysphagic animals can be managed with a liquid diet that can be fed through a tube as the sole source of nutrition.

50.4 LIQUID DIETS FOR HORSES

50.4.1 Adult Horses

Assisted enteral feeding (AEF) with a liquid diet should be used in horses that require nutritional support to maintain their energy and protein intake during a short period (2 to 14 days) of partial or complete anorexia. Horses that are good candidates for AEF do not have gastrointestinal ileus or gastric reflux and are able to tolerate an indwelling NG tube, repeated intubation, or an esophagostomy tube. Horses fed using AEF should be standing. Diet choice will depend on product availability and on the nutrient requirements of the equine patient. Energy, protein, vitamin, and mineral requirements should be calculated for each equine patient to ensure that the appropriate concentration of nutrients is administered. Enteral diets may be administered to provide partial or complete nutrient supplementation to an adult horse.

Liquid diets may be classified into three categories: (1) complete feed blender diets consisting of liquefied or finely ground whole food suspended in water; (2) composition diets containing highly digestible whole protein (usually casein or soy), fats, and carbohydrate; and (3) commercially available liquid enteral diets sold for human use. When commercial liquid enteral diets are chosen, the source of carbohydrate should be examined, and only diets that contain a limited amount of sucrose should be used for horses.

Vital HN* and Osmolyte HN* are human liquid enteral diets that have been administered to adult horses.[11,12] Ross Laboratories produces a variety of human liquid enteral products, including formulations that contain oat and soy fiber. A partial list of formulas that can be administered to adult horses is provided in Table 50-1. All human formulations are designed for administration through a small-diameter tube and are an option for horses that can tolerate only an 18 Fr feeding tube (Mila NG18100).† Most products contain approximately 1 kcal/mL

and 4.1 to 4.2 g of protein per 100 kcal. Almost 10.5 L of a human enteral product would be required to meet the stall resting energy requirement of 10.4 Mcal for a 450-kg horse, at an approximate cost of $120/day. The protein content (approximately 440 g) in 10.5 L of Osmolyte or Vital HN will not meet the requirement of 567 g of protein for a 450-kg horse, and supplemental protein (casein, lactalbumin, whey, soy) may need to be added to each formulation to ensure adequate protein intake. The nutrient composition of a human formulation should be evaluated to ensure that the horse is receiving the most appropriate product. Diets that contain a high (>15%) proportion of calories as fat are contraindicated in horses with hyperlipemia and hepatic lipidosis. The soluble carbohydrates included in a human enteral formulation may not be tolerated by horses that have a compromised gastrointestinal tract or by horses with hyperglycemia. Any commercial human product should be fed starting at approximately 25% of the final maintenance requirement, with the volume gradually increased over 4 to 7 days to the target quantity.

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Table 50-1 Human Liquid Enteral Products*

Product	Caloric Density (kcal/mL)	% Calories Protein	% Calories Fat	% Calories Carbohydrate	Carbohydrate Source
Osmolyte	1.06	14.0	29.0	57.0	Corn maltodextrin
Osmolite 1.2 Cal	1.20	18.5	29.0	52.5	Corn maltodextrin
Vital HN	1.00	16.7	9.5	73.8	Corn maltodextrin, sucrose
Promote	1.00	25.0	23.0	52.0	Corn maltodextrin, sucrose
Promote with Fiber	1.00	25.0	25.0	50.0	Corn maltodextrin, sucrose, oat fiber, soy fiber
Jevity 1.5 Cal	1.50	17.0	29.4	53.6	Corn maltodextrin, fructooligosaccharides, soy fiber, oat fiber

* Ross Nutrition, Abbott Laboratories, North Chicago, IL.

Table 50-2 Equine Feeds Suitable for Use in a Liquid Enteral Diet

Feed	Digestible Energy (kcal/kg)	Crude Protein (%)	Crude Fat (%)	Crude Fiber (%)
1. Equine Senior* (Purina Mills)	2695	14.0	4.0	13.0
2. Senior* (Seminole)	3124	14.0	7.0	16.0
3. Senior* (TDI)	3146	13.0	4.0	14.0
4. Senior* (LMF)	2341	14.0	4.0	20.0
5. Senior* (Triple Crown)	3401	14.0	10.0	17.0
6. Alfalfa pellets†	2156	16.7	2.3	21.5
7. Timothy hay pellets†	1760	8.5	2.4	31.5
8. Oat hay pellets†	1760	8.6	2.2	29.1

* As fed, manufacturer analysis.

† As fed, estimated values.

Although they may be inconvenient, complete feed blender diets have the advantage of being inexpensive ($5 to $10/day), and the ingredients are usually available. Most products contain 14% to 25% crude fiber (dry matter [DM]) and vary in energy density from 2.6 to 3.1 Mcal/kg of diet. A list of commercial feeds that can be fed as a liquid enteral diet is provided in Table 50-2. From 3.4 to 6.0 kg of diet per day is required to meet the resting energy requirements of a 450-kg horse. In some equine patients, protein supplementation may be required. Some patients may also benefit from vitamin and mineral supplementation. This type of a diet may be prepared either by grinding one quarter to one third of the daily requirement of dry pellets in a blender and suspending the blended product in water, or by soaking the pellets in water before blending to create a slurry. The total amount of water that is added to the preparation should be recorded and added to the daily fluid administration log for the patient. The preparation should be fed three to six times daily to horses that require complete feeding or once or twice daily if only partial supplementation is required. Hay pellets or alfalfa meal can be blended into a liquid enteral diet; however, the nutrient content and quality of pelleted forages is often more variable than those of commercial feeds.

An ingredient-based composition diet can be designed using structural carbohydrate and protein ingredients that are available in the local region. One such diet (Table 50-3) composed primarily of dehydrated cottage cheese, dextrose, and alfalfa meal requires considerable preparation by the clinician.[13] Corn, canola, or soy oil (113 to 227 mL) can be added as an energy source. Diets with high concentrations of oil and dextrose should be avoided. Structural carbohydrate should comprise 50% to 75% of the diet DM. The approximate cost for complete supplementation with the homemade equine diet is $30 to $40 per day for a 450-kg horse. As indicated in Table 50-3, the homemade diet is introduced gradually over a period of 7 days.

The consistency of any formulation can be adjusted by blending the ingredients with water to ensure that the formulation can be delivered through the NG tube that has been selected for administration. Larger diameter

NG tubes (>0.65 cm inner diameter) must be used when fiber is included in the diet. The diet should be tested using the NG tube before the tube is placed in the animal to ensure that the tube will not be clogged with the feed. The total volume of enteral diet should be divided into at least three feedings per day and should be administered slowly enough to ensure that feed does not reflux around the NG tube. No more than 6 to 8 L of total volume should be administered at one time. This volume must be appropriately lowered when treating a pony or miniature horse. Before feeding, the amount of residual fluid in the stomach should be checked. Horses with ≤2 L can be fed the meal, but if the volume of gastric fluid is >2 L, the feeding should be delayed for 2 hours. Horses with persistent gastric reflux should not be fed enterally, and instead the clinician should consider treatment with PN. After the horse has been fed, the tube should be flushed with at least 500 mL of water before the tube is capped. Excessive distention of the stomach must be avoided. If the NG tube will remain in place between feedings, a muzzle may be used to prevent the horse from removing the tube. During treatment, horses should be offered palatable feeds to encourage a transition to voluntary food consumption. The equine patient can gradually be weaned from AEF once it is consuming 75% of its DE_{rest} on a daily basis.

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Table 50-3 Suggested Feeding Regimen for a Liquid Diet for a 450-kg Adult Horse[11]*

	Day						
Ingredient	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Water (L)	21	21	21	21	21	21	21
Dextrose (g)	300	400	500	600	800	800	900
Dehydrated cottage cheese (g)†	300	450	600	750	900	900	900
Alfalfa meal (g)	2000	2000	2000	2000	2000	2000	2000
Electrolyte mix (g)‡	230	230	230	230	230	230	230

* Ration divided into three equal feedings daily.

† May substitute edible acid casein—90 mesh, American Casein Company, Burlington, NJ.

† Electrolyte mix ingredients: NaCl, 10 g; $NaHCO_3$, 15 g; KCl, 75 g; K_2HPO4, 60 g; $CaCl_22H_2O$, 45 g; MgO, 25 g.

All liquid enteral diets may result in a mild, self-limiting diarrhea when fed as the sole source of nutrition, possibly because of lack of dietary fiber or because of fermentation of the highly soluble ingredients in the large colon.[11,13,14] This may be ameliorated by addition of a fiber source such as alfalfa meal.

* Ross Products Division, Abbott Laboratories, Columbus, OH.

† Mila International, Florence, KY.

50.4.2 Foals

Mare's milk is the ideal supplemental feed for orphan or critically ill foals. Neonatal foals with normal gastrointestinal tract motility can initially be fed a volume sufficient to meet 10% of BW (100 mL/kg BW) each day. The volume should be incrementally increased until the foal is consuming 20% of its BW (200 mL/kg/day). Neonatal foals should be offered milk every 2 hours as long as the feedings are tolerated and should be encouraged to nurse from their dams once they develop a strong suckle reflex. A small-diameter NG feeding tube can be used for milk supplementation until the foal can nurse voluntarily. Foals have minimal endogenous energy stores and require supplemental nutrients within 6 to 12 hours of losing the ability to nurse. Any foal that cannot tolerate enteral feedings should be placed on PN to ensure that its dietary requirements are met.

Orphan foals can be fed 20% of their BW per day using a commercial foal milk replacer (Mare's Match*, Mare's Milk Plus†, Foal Lac‡) if a nurse mare or mare's milk is not available. If a foal milk replacer is not available, goat's milk can be fed as a short-term substitute but is not recommended for long-term use because the nutrient profile is different from that of mare's milk. Because indigestion occurs relatively commonly when using milk substitutes in foals, dietary changes should be instituted gradually over a period of 1 to 2 days at a minimum. If indigestion occurs, both the frequency and volume of feeding should be decreased until the indigestion resolves. Foals that are 2 weeks of age or older can be fed every 4 to 8 hours, with a decreased frequency of feeding as the foal ages. Orphan foals should be fed from a pan or bucket because it forces the foal to actively ingest and swallow the milk and decreases behavioral complications that can develop when an orphan foal is bottle-fed. If a foal will be bottle-fed, the nipple should be checked to ensure that milk does not freely flow from the nipple. Improper use of a bottle can result in aspiration pneumonia if the foal does not have a normal swallow response.

* Land O' Lakes, Arden Hills, MN.

† Buckeye Nutrition, Dalton, OH.

‡ Pet Ag, Hampshire, IL.

50.5 LIQUID DIETS FOR RUMINANTS

In most cases the most practical and least expensive way to force-feed ruminants is the blender-type or slurry diet. Hypophagic adult cattle may be force-fed a suspension of alfalfa meal and dried brewer's grain (3 to 5 kg each in 20 L of water) two or three times daily. If a ruminal fistula is necessary (e.g., tetanus), the diet may be directed into the rumen. Presumably similar preparations would be suitable for sheep and goats, although published reports are scarce. Administration of ruminal liquor obtained from a healthy donor cow provides a good source of microflora as well as volatile fatty acids as an energy source in hypophagic cows.[15]

50.6 INTRAVENOUS FEEDING

50.6.1 Intravenous Dextrose

The simplest and least expensive form of intravenous feeding is the supplementation of intravenous crystalloid fluids with dextrose. This represents a short-term solution for boosting caloric intake when a rapid return to normal feed consumption is anticipated. Dextrose can be added to make a final solution with a concentration that ranges from 2.5% to 10%. If the fluids are infused at a rate to meet maintenance fluid requirements (2.2

mL/kg/hr), the patient's renal threshold of glucose (10 mmol/L or 180 mg/dL for adult horses; 12 mmol/L or 216 mg/dL for foals) will usually not be exceeded. The energy provided may be calculated based on 3.4 kcal/g of dextrose. A 450-kg horse treated with fluids supplemented with 2.5% dextrose and infused at a maintenance rate of 1 L/hr (24 L/day) will receive 2040 kcal from the dextrose (close to 20% of the patient's DE_{rest}). Although protein is not provided with the dextrose therapy, the supplemental energy will blunt the catabolism of endogenous lipid and protein stores. Dextrose-supplemented fluids can be administered as the sole source of nutrition for 24 to 48 hours. If a patient consumes <75% of its maintenance protein requirement and/or <75% of its resting energy requirement, supplemental nutrition should be administered. Patients that have complications with glucose regulation may be able to tolerate therapy with a 2.5% solution of dextrose, but if complications with glucose regulation persist, alternative methods of nutritional supplementation should be initiated. 1651

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50.6.2 Parenteral Nutrition

Intravenous feeding or PN is a means of providing nutritional support to animals that do not have a functional digestive tract or animals that cannot tolerate placement of an NG tube. Because of the greater expense (approximately $80/day for foals and $450/day for adult horses), the need for special infusion supplies, and the risk of complications when compared with enteral feeding, PN should be reserved for cases in which bowel rest is necessary. Possible indications for PN include neonatal diarrhea in cases in which oral feeding exacerbates the diarrhea, postoperative feeding after gastrointestinal surgery, nonsurgical intestinal obstruction or ileus (proximal jejunitis, botulism), dietary supplementation in a laterally recumbent patient, gastrointestinal intolerance in premature neonates, and hypoxic ischemic gastrointestinal syndrome. Because enteral nutrition provides nutrients directly to the enterocytes and promotes both intestinal barrier function and immune system function, a small volume of a liquid enteral diet should be administered whenever possible in a patient receiving PN.

PN formulations are composed of dextrose and lipids as an energy source, and amino acids as a protein and nitrogen source. Compatible vitamin and mineral supplements can be added to the PN formulation. A variety of PN mixtures can be designed to meet the nutritional requirements of a clinically ill large animal patient. Sufficient calories in the PN solution must be provided in the form of carbohydrates and lipids to promote the incorporation of amino acids into protein instead of the catabolism of amino acids for energy. The ideal calorie-to-nitrogen ratio for adult horses is extrapolated from data calculated for critically ill humans, in whom the ideal ratio is 120:1 to 150:1 for healthy individuals, and 80:1 to 90:1 for acutely ill humans.[16] (Glucose provides 3.4 kcal/g, amino acids provide 4 kcal/g, and lipids provide 11 kcal/g; amino acids include 0.16 g of nitrogen per gram.) Animals with systemic inflammatory diseases or severe protein loss and large animal patients recovering from major surgery will probably benefit from a therapeutic enteral or parenteral diet that has a calorie-to-nitrogen ratio that is between 80 and 100, as long as protein supplementation is not contraindicated in the patient. Although PN solutions can be formulated with dextrose alone as the energy source, addition of lipids provides many advantages. Because of the larger size of the molecule and higher energy density on a per-gram basis, replacement of dextrose with lipid lowers the PN osmolarity and/or infusion volume required to meet the energy needs of the patient and reduces the hyperglycemic effect of PN administration. The lipid content of the PN solution is usually targeted as approximately 50% but no more than 80% of the nonprotein calories in the formulation. Animals with hypertriglyceridemia (>500 mg/dL) or hepatic lipidosis that require PN should be treated with a formulation that is restricted in lipid, or that is lipid-free, whereas the concentration of dextrose or the PN administration rate should be restricted in animals with hyperglycemia. If long-term administration (>5 days) is expected, calcium (200 mg/kg/day), phosphorous (110 mg/kg/day), and other micronutrient supplementation of the PN solution should be considered. Commercial multiple vitamin (e.g., MVI-12*) and

trace mineral (e.g., Multitrace5[†]) supplements are available for addition to the PN mixture but may add as much as $20/day to the cost of the formulation.

All parenteral solutions must be mixed aseptically. A laminar flow hood should be used to prepare the formulation, but if this equipment is not available, the solution can be mixed in a clean room with low traffic such as a surgical instrument preparation room. Alternate options for PN compounding include human hospitals, human parenteral compounding companies, and the commercial compounding pharmacy CAPS (Central Admixture Pharmacy Services, http://www.capspharmacy.com). The formulation can be made in a 2- or 3-L all-in-one infusion bag (Vitalmix[‡]), in a sterile glass container, or in a sterilized carboy. Single-use infusion containers are preferred. Guidelines for PN compounding are listed in Box 50-1.

50.6.2.1

Box 50-1 Instructions for Compounding a Parenteral Nutrition Solution

1. Compound the solution in a laminar flow hood, if available. Use a clean room in the hospital if a laminar flow hood is not available.
2. Clean the preparation area well, using alcohol as a final preparation on the counter.
3. Wear a gown, mask, and sterile gloves when compounding the parenteral nutrition (PN) solution.
4. Wipe off all injection sites and infusion ports with alcohol before connecting the infusion lines.
5. Use a new transfer set for each PN ingredient.
6. Add the dextrose and amino acid solution to the compounding bag or container.
7. Add the lipid solution *after* the dextrose and amino acid solutions have been mixed together.
8. Gently swirl the solution to mix the ingredients.
9. Add any vitamin or mineral supplements to the solution *after* the macronutrients (dextrose, amino acid, lipid) have been added.
    a. Ensure that there are no incompatibilities with the supplemental additives.
10. The PN formulation can be stored in the refrigerator for 24 hours, followed by 24 hours of storage at room temperature. Shield the solution from sunlight.

Parenteral solutions should be administered through a dedicated line in a large-diameter or central vessel (jugular, vena cava) to reduce complications from phlebitis but can be administered in a peripheral vein (lateral thoracic, cephalic) if the osmolarity of the solution is <900 mOsm/L. A multilumen polyurethane catheter[§] is ideal for PN infusion because one port can be reserved exclusively for PN infusion while the other port(s) can be used for blood sampling and medication or fluid infusion. In many settings, when this is not feasible, dual infusion ports can be added to a single-lumen Arrow catheter. Patient medications may not be compatible with the PN solutions and should be given through a separate line, or the PN line flushed with saline before and after administration. Correction of electrolyte abnormalities in separate crystalloid supplemental fluids is best because rapid adjustments in the electrolyte supplements can be made without discarding an expensive PN solution.

The PN solution should first be administered at 25% to 33% of the total infusion rate, and if the patient tolerates the PN the rate should be gradually increased over 12 to 36 hours. A fluid administration pump facilitates a constant rate of infusion. During PN therapy the patient should be monitored for hyperglycemia, hypertriglyceridemia, and serum electrolyte abnormalities. Hyperglycemia and hypertriglyceridemia should be managed first by reducing the rate of infusion and then by lowering the concentration of dextrose or lipid in the PN solution. If hyperglycemia is persistent, treatment with subcutaneous Ultralente insulin (0.2 to 0.3 IU/kg, q12-24h) or regular insulin as a continuous rate infusion (0.005 to 0.01 U/kg/hr) may improve glucose use and permit increased caloric intake without further hyperglycemia. Similarly, heparin (40 IU/kg q12h) may be administered if hyperlipemia persists. At the conclusion of therapy, PN should be gradually discontinued over 18 to 36 hours.

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Fig. 50-1 Parenteral nutrition worksheet for adult horses.

Parenteral Nutrition Worksheet for Adult Horses

PATIENT INFORMATION

1. Initial body weight (BW) (kg) _____kg
2. Stall resting energy requirement: DE_{rest} (kcal/day) = 975 + 21 (BW in kg) _____kcal
3. Maintenance energy requirement: DE_{maint} (kcal/day) = 33.3 (BW in kg) _____kcal
4. Protein requirements: Crude protein (g/day) = 1.26 (BW in kg) _____g
5. Fluid requirements for maintenance: 60 mL/kg/day _____mL

PARENTERAL NUTRITION FORMULATION

6. Total kcal required per day (estimate between **2** and **3** calculated above) _____kcal
7. Calculate volume of 10% amino acids required to meet protein requirement (from 4)
   Protein (g) × 1 mL/0.1 g of protein for a 10% amino acid solution* _____mL
8. Calorie contribution from 10% amino acid solution (from **7**)
   4 kcal/g protein × grams of protein in solution _____kcal
9. Total kcal required/day (from **6**) – total kcal provided by amino acids (from **8**) _____kcal
   The caloric contribution from protein can be omitted from the following calculations, if desired.
10. Determine amount of lipid required to meet 20% to 70% of the remaining energy requirements; 10% lipid solution contains 1 kcal/mL, 20% lipid solution contains 2 kcal/mL
Example: If providing 50% of remaining energy requirements with 10% lipid:
(kcal [from 9] × 0.5) × 1 mL/1 kcal (substitute 0.5 mL/1 kcal if using 20% lipid) _____mL

11. Calculate remaining energy requirements to be provided by 50% dextrose _____

Example

Providing 50% of calories with dextrose: (kcal [from **9**] × 0.5) × 1 mL/1.7 kcal _____mL
12. Add 1 to 2 mL of B vitamin complex per liter _____mL
13. Add up to 5 mL of trace minerals per day _____mL
14. Determine the total volume of the PN solution **(7 + 10 + 11 + 12 + 13)** _____mL
15. Determine the rate of PN infusion for a 24 hour period: mL (from **14**)/24 mL/hr _____
16. Calculate the calorie:nitrogen ratio for the PN solution _____
    Total kcal from PN solution (from **6**)/(total g of protein/6.25) _____
17. Calculate osmolarity of the solution

10% Amino acid	_____ mL (from **7**) × 0.840 mOsm/mL =	_____mOsm
10% Lipid	_____ mL (from 10) × 0.276 mOsm/m =	_____mOsm
50% Dextrose	_____ mL (from 11) × 2.550 mOsm/m =	_____mOsm
	+ _____Total mL	+ _____Total mOsm

PN solution mOsm/L = Total mOsm/Total mL × 1000 mL/L _____mOsm/L

*An 8.5% amino acid solution with electrolytes contains 0.085 g of protein per milliliter and 1.045 to 1.444 mOsm/mL.

* AstraZeneca, Westborough, MA.

† American Regent, Shirley, NY.

‡ Churchill Medical Systems, Horsham, PA.

§ Arrow International, Reading, PA.

50.7 PARENTERAL NUTRITION IN HORSES

50.7.1 Adult Horses

The stall resting digestible energy (DE_{rest}) and maintenance protein requirements, calculated as shown earlier, should be used as guidelines when formulating a PN solution for an adult horse. Although the exact energy requirements during a clinical illness have not been determined for the equine species, provision of enough nutrients to meet the stall resting requirements should provide the adult horse with sufficient energy to blunt the catabolic effect of anorexia and illness. Horses with a limited medical budget can be managed with a PN solution that provides a portion of the DE_{rest} energy.

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The preferred way to formulate a PN solution is first to meet the calculated protein requirements of the horse with the amino acid solution and then to meet the remaining energy requirements with a combination of dextrose and lipid calories. A formula with approximately 50% of nonprotein calories as lipid and 50% as dextrose is recommended. The final composition of the solution can be altered to manage patients with hyperglycemia or hypertriglyceridemia. An example of a worksheet used to facilitate calculations for PN formulation for an adult horse is shown in Fig. 50-1. Alternatively, the clinician can calculate the daily requirements of dextrose, amino acids, and lipids on a dose per BW basis. The formula listed in Table 50-4 provides 2.8, 1.3, and 0.8 g of dextrose, amino acids, and lipids, respectively, per kilogram per day, providing the resting stall DE and maintenance protein requirements with a calorie:nitrogen ratio of 108:1, with 48% of nonprotein calories as lipid and an osmolarity of 1026 mOsm/L. Approximate cost is $450/day not including administration sets. If the clinician is willing to forgo the benefits of lipid inclusion, the lipid component in Table 50-5 can be replaced with an additional 2.8 g/kg/day of dextrose, at a savings of nearly $200/day.

A commercial amino acid and dextrose admixture (Clinimix, 5% Aminosyn II, 25% dextrose *) is a convenient alternative that does not require special preparation. However, because these products do not contain lipids, the osmolarity (1539 mOsm/L) is higher than that of the PN solution in Table 50-5. The increased cost of these products may be partially offset by the savings in sterile mixing containers and time costs of PN preparation.

* Hospira, Lake Forest, IL 60045.

50.7.2 Foals

The nutrient density of PN solutions for foals is higher than that for adult horses. The PN formula in Table 50-5 is designed to provide 10, 3.5, and 2 g of glucose, amino acid, and dextrose, respectively, per kilogram per day. This formula will provide 70 kcal/kg/day at a calorie:nitrogen ratio of 125:1 and an osmolarity of 1139 mOsm/L, with 40% of the nonprotein calories as lipid. Once the full flow rate is achieved, additional caloric density can be achieved by increasing the proportion of lipid emulsion, and if fluid volume restriction is required, 20% or 30% lipid emulsion can be used instead of 10%. Further increases in caloric intake require increased flow rates.

Table 50-4 Parenteral Nutrition Formulation for Adult Horses

Ingredient	Dosage Rate	Volume per Day (450-kg horse)
50% Dextrose	2.8 g/kg/day	2500 mL
10% Amino acids*	1.3 g/kg/day	6000 mL
10% Lipid†	0.8 g/kg/day	3500 mL
Begin administration at 0.3 mL/kg/hr and gradually increase to target of 1.1 mL/kg/hr (12 L/day for a 450-kg horse).		

* Available as Aminosyn II, Hospira, Lake Forest, IL; or Travasol, Baxter Healthcare (Clintec), Deerfield, IL.

† Available as Liposyn II, Abbott Laboratories, N. Chicago, IL; or Intralipid, Baxter Healthcare, Deerfield, IL.

Table 50-5 Parenteral Nutrition Formulation for Foals

Ingredient	Dosage Rate	Volume per Day (50-kg Foal)
50% Dextrose	10 g/kg/day	1000 mL
10% Amino acids	3.5 g/kg/day	1750 mL
10% Lipid	2 g/kg/day	1000 mL
Begin administration at 0.7 mL/kg/hr and gradually increase to target of 3.1 mL/kg/hr (3750 mL/day for a 50-kg foal).		

50.8 PARENTERAL NUTRITION IN RUMINANTS

Because of cost, use of PN is usually limited to calves, and little information exists on the use of PN in the adult bovine or the ovine and caprine species. The most common indication for the use of PN in calves is diarrhea, particularly in chronic cases accompanied by weight loss.[17] In such cases, if sufficient milk is fed to meet the calf's nutritional needs, the diarrhea is exacerbated, and PN allows the quantity of milk to be reduced without compromising the nutritional status of the patient. The PN regimen provided for foals in Table 50-5 would also be suitable for calves. However, because amino acids and lipids are the most expensive components of PN, a modified formula based on a 10:2:1 glucose:amino acid:lipid ratio has been used with success.[17] For a 50-kg calf, this would result in administration of 1 L of 50% dextrose, 1 L of 10% amino acids, and 500 mL of 10% lipids daily, at an approximate cost of $60 per day. Eliminating the lipid emulsion from the formula is an acceptable alternative that will reduce the cost approximately 15%. A multiple B vitamin product may be added to the formula (approximately 1 mL of supplement per liter of PN), but trace minerals are not usually necessary for the short-term administration that is most common in calves.

Catheter-related complications are rare in calves, and a central venous catheter, although preferred, is not required. I (RWS) have had success with 16-gauge, 3¼-inch, Teflon-coated, over-the-needle catheters available from several distributors. These are placed in the jugular vein, sutured or glued to the overlying skin, and left in place for up to 10 days if no signs of phlebitis or sepsis occur.

50.9 SPECIAL DIETS

Numerous diseases require specific alterations in the therapeutic ration because of metabolic disturbances that accompany these conditions. Recommendations are discussed in the individual chapters dealing with these diseases and include alterations in dietary protein for hepatic disease and restrictions in the protein and calcium content of the diet for horses with chronic renal failure. A nutritionist can develop therapeutic enteral and parenteral formulations to meet the unique nutritional requirements of individual patients.

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51 Chapter 51 Genetic Disorders

Angela M. Hughes

51.1 INHERITED DISEASES

Inherited diseases and congenital defects are structural or functional abnormalities that may or may not be obvious at birth. There are a wide range of possible defects, from a single structural change (e.g., leg length) to the involvement of multiple organs or systems (e.g., storage diseases, chromosomal abnormalities), depending on the type and extent of toxic exposure during gestation or genetic mutation. It is important to identify animals with genetic or congenital disorders because of the economic and emotional impact on clients, but many disorders can be difficult to recognize and trace, particularly if they lead to embryonic or fetal death, abortion, dysmaturity, premature birth, or full-term stillbirth.

It is important to remember that not all congenital defects are genetic in origin and making the distinction between conditions caused by an environmental factor and a genetic cause will help clients make appropriate changes to prevent the disorder in the future. To determine the cause of a disorder, it is vital that each case be thoroughly examined. Each case should be subjected to a full, careful description of the disorder, including a complete necropsy. The environment and management conditions should be investigated for potential causative agents, and all available genetic information for the affected animal(s) and unaffected herdmates should be collected, including gender, birth date, and breed. Environmental teratogens affecting large animals include toxic plants, drugs, viruses, and physical agents (e.g., hyperthermia, irradiation). Although it may be difficult to identify inciting teratogens, analysis of affected herds will reveal patterns that follow seasonal or management changes or stressful events.

This chapter focuses on the essential genetic information that veterinarians require to inform their clients about genetic diseases and how to find information on diseases and traits with a genetic component.

51.2 GENETIC INFORMATION

The basic blueprint for life in most organisms, the genetic material, is deoxyribonucleic acid (DNA). DNA is composed of two strands of bases: adenine (A), thymine (T), guanine (G), and cytosine (C). These bases align to form complementary base pairings such that A always pairs with T and G always pairs with C. These strands can be completely separated and replicated in preparation for cellular division. Alternatively, these strands can be partially separated, transcribed into ribonucleic acid (RNA), and translated into functional proteins.

The DNA sequence of a mammalian genome is divided into autosomes and a pair of sex chromosomes, X and Y. Each chromosome contains a variety of genes as well as “filler” DNA that does not code for proteins, but may determine where and to what degree each gene is expressed. Genes on each chromosome code for the various structural and enzymatic proteins required for life. One set of chromosomes, and thus one set of genes, is inherited from each parent. As a result, a mammal generally has two copies, or “alleles,” of any given gene. Simple traits or diseases involving these genes can be inherited in dominant or recessive patterns and involve the autosomes, or sex chromosomes. Unfortunately, not all traits or inherited diseases are simple; many involve multiple genes and interactions between genes and the environment, which can make it difficult to diagnose and understand a complex disease or trait.

51.2.1 Recessive Inheritance

Traits or diseases with a recessive mode of inheritance require two affected copies, or alleles, of the gene to express that trait or disease. These conditions can be *autosomal,* involving genes on the autosomes, or *sex-linked,* caused by genes on either the X or Y chromosome. Generally, autosomal recessive traits or diseases are caused by mutations that render a protein unable to perform its original function. When an animal inherits the affected allele from both parents, it is *homozygous* for the gene and is unable to make functional copies of that specific protein. *Heterozygous* individuals inherit only one copy of the affected allele, and they have a "backup" copy of the normal or wild-type allele to provide the functional protein. These heterozygous individuals are carriers of the trait or disease allele and can produce affected offspring if bred to another heterozygous or homozygous affected individual.

The hallmarks of autosomal recessive traits include that all offspring of two affected parents are affected and approximately equal numbers of males and females are affected. Unaffected carrier parents can produce affected offspring, and thus the trait or disease can skip generations. Additionally, mating an affected individual to a noncarrier (homozygous normal) produces all offspring that appear normal but carry the affected allele. Breeding two carrier individuals results in approximately 25% normal, 50% carrier, and 25% affected offspring.

An example of an autosomal recessive trait is spider lamb syndrome, or hereditary chondrodysplasia. Lambs affected with this syndrome display several skeletal abnormalities, including disproportionately long "spider" legs, curvature of the spine, facial deformities, rib and sternum deformities, lack of body fat, and muscular atrophy. The causative mutation is a single base-pair substitution, from a T to an A, altering a highly conserved amino acid in the fibroblast growth factor receptor 3 (FGFR-3) gene, which prevents the receptor from functioning to limit endochondral ossification and thus bone growth.[1]

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51.2.2 Dominant Inheritance

Traits or diseases with a dominant mode of inheritance only require one affected allele to express the trait or disease, also known as the affected *phenotype,* and there is no distinguishable difference in the affected phenotype of a heterozygote and homozygote. Again, the genes that are responsible for these traits or diseases can be on the autosomes or sex chromosomes. Dominant traits or diseases may be caused by mutations that enable the mutant protein to have an altered function or structure. Alternatively, a single, functional copy of a gene may not be enough to achieve normal levels of function ("haploinsufficient"), resulting in the need for two normal copies of the gene to achieve a normal phenotype.

The main feature of an autosomal dominant trait or disorder is that affected individuals must have at least one affected parent (unless it is a new mutation), and thus the disorder does not skip generations. There is no gender bias with an autosomal dominant trait, and approximately half the offspring of a heterozygous affected individual will be affected.

An example of an autosomal dominant disease is myotonia in goats. When startled or making sudden, forceful movements, these goats can develop severe, acute muscle stiffness causing immobility and sometimes falling over, resulting in descriptions such as "fainting," "nervous," "stiff-legged," or "epileptic" goats. A single nucleotide change was identified that substituted a proline for a conserved alanine residue in a chloride channel in the muscle fibers. This alteration in the chloride channel causes a diminished channel-open probability at voltages near the resting membrane potential of skeletal muscle, resulting in decreased chloride conductance

and a significantly decreased electrical threshold for firing action potentials. Ultimately, this altered chloride channel allows conduction of repetitive impulses that result in sustained muscle fiber contraction and stiffness.[2]

51.2.3 Co-dominant Inheritance

The co-dominant (or semidominant) pattern of inheritance is distinguished by the fact that homozygotes can be differentiated from heterozygotes based on clinical features. A well-known example of a co-dominant disease is hyperkalemic periodic paralysis (HYPP) in quarter horses. In HYPP the voltage-gated sodium channels in the muscle fibers have a mutation that increases sodium permeability across the skeletal muscle cell membrane, resulting in increased muscle mass, but also drooling, prolapse of the nictitating membrane ("third eyelid"), respiratory stridor, and weakness. Homozygous HYPP horses experience more frequent and severe clinical signs of disease than heterozygous horses.[3] Thus, it is important to counsel breeders to avoid producing homozygous affected horses by not mating two heterozygous horses, because 25% of their offspring would be expected to be homozygous affected, and 50% of the offspring would be heterozygotes. Breeding a heterozygous horse to an unaffected horse will also result in approximately 50% of the offspring being heterozygous and no possibility of producing a homozygous affected foal.

51.2.4 Sex-Linked Traits

Sex-linked traits and diseases involve genes located on either the X or the Y chromosome. Males are particularly susceptible to these conditions because they have only one each of the X and Y chromosomes. Thus, if they have a mutant allele for one of the genes on either of these chromosomes, they will express the affected phenotype because they do not have a "backup" copy. They have only one copy of the X and Y chromosomes, so they are *hemizygous*. Females generally are less likely to demonstrate sex-linked recessive traits or diseases because they have two copies of the X chromosome. However, because of random X inactivation in each cell during fetal development, some females may express an affected phenotype. To achieve this, the X inactivation must be skewed such that the unaffected chromosome is inactivated more often than the X chromosome carrying the affected allele. In rare cases in which the inactivation is significantly skewed, females may be mildly to severely affected, depending on the level of expression for the affected chromosome.

Key characteristics of X-linked recessive traits are that the trait appears with much greater frequency in males than females, half the sons of carrier females will be affected, and half the daughters of carrier females will also be carriers. Hemophilia A, characterized by a strong tendency to bleed resulting from mutations in the clotting factor VIII gene on the X chromosome, is an example of an X-linked recessive disorder.

X-linked dominant traits are characterized by the following: affected offspring must have at least one affected parent, the disorder does not skip generations, and an affected male mated to normal females will transmit the mutation to all his daughters but not to his sons.

There are very few Y-linked diseases recognized in any mammalian species because of the small number of genes on the Y chromosome. Additionally, the majority of the genes contained on the Y chromosome are involved in male fertility; thus mutations in these genes generally render the animal sterile, resulting in no transmission of the mutations to future generations.

51.2.5 Polygenic Traits

In addition to the single-gene traits and diseases, numerous conditions are the result of two or more genes and may also involve genetic and environmental interactions. Some of these polygenic traits are economically important, such as milk quality and yield in dairy cows. For milk quality, a large number of genes may be contributing a small portion to the overall milk production of an animal.[4] Teasing out the details of a complex polygenic system is difficult; however, research is ongoing to identify the exact genes involved and the role each gene plays for many economically important traits and diseases.

51.2.6 Penetrance and Expressivity

For many simple traits, there is an obvious difference between the two phenotypes that can be translated to the alleles involved, or *genotype,* with 100% certainty. A good example of this is albinism, which is considered to be 100% penetrant, with *penetrance* defined as the percentage of individuals with a given genotype who actually show the phenotype associated with that genotype. Influences such as modifying genes or environmental interactions can alter the expression of certain genes such that the exact genotype is not expressed in the outward phenotype. Alternatively, the function of a gene may be subtle, making it difficult to measure distinctions adequately between genotypes. Genotypes that may not be expressed in every individual are considered to be “incompletely penetrant.”

Another measure of genetic expression is the concept of *expressivity*. Modifier genes and environmental influences can affect the degree to which a genotype is expressed. For example, “variable expressivity” may be involved in pigment intensity when two individuals have the same genotype at the gene responsible for red pigmentation, but one has clearly darker red hairs than the other.

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Incomplete penetrance and variable expressivity can greatly complicate analysis of genetic traits and diseases. These factors can also make breeding decisions more difficult because it may not be possible to classify an animal's genotype based solely on a phenotype. In these more ambiguous cases, genetic testing will play a vital role in the unequivocal determination of genotypes, allowing appropriate and informed breeding decisions.

51.3 POSITIVE AND NEGATIVE SELECTION

Breeders can improve their breeding stock by selecting for or against specific traits and diseases. These processes are known as *positive* and *negative* selection, respectively. A breeder may choose to breed an animal because it has desirable genes or qualities (positive selection). Alternatively, they may choose not to breed an animal that has been shown, either through genetic or breeding tests, to carry an undesirable trait or disease (negative selection). Ultimately, both scenarios will achieve the goal of improved breeding stock.

51.4 CHROMOSOMAL ABNORMALITIES

Occasionally, problems arise during mitosis, meiosis, or fertilization, resulting in chromosomal, or *karyotype,* abnormalities. Many karyotypic abnormalities have been identified in all large animal species, but not every chromosomal abnormality has been associated with an overt disease phenotype.[5,6] Some examples of common chromosomal abnormalities include the absence of an X chromosome, called XO Turner's syndrome, which results in female infertility. An additional X chromosome in XXY Klinefelter's syndrome causes underdeveloped males with underdeveloped male sexual behavior. In addition to abnormal numbers of sex chromosomes, two

chromosomes can unite into a single chromosome, called a “Robertsonian translocation,” leading to reduced reproductive capacity in some species and early embryonic death in cattle. Because of possible chromosomal abnormalities, several countries have instituted mandatory kayotyping of some breeding cattle. Additionally, clinicians should consider karyotyping any animal that presents for reduced fertility or has multiple abnormalities.

51.5 BREEDING SCHEMES: TEST MATINGS

As a result of numerous advances in the field of genetics, the genetic causes of many diseases and traits are known and can be tested before using an animal in a breeding program. Additionally, more DNA-based tests are expected as research continues. However, clients may be interested in testing for a disease or trait that does not have a known genetic cause. For these situations, sires can be tested using breeding trials, as described in Table 51-1. For example, if a sire is bred to carrier females for a disease of concern, he would have to produce 10 normal offspring to ascertain that he is not a carrier with 95% confidence, 16 normal offspring to have 99% confidence, and 24 normal offspring to have 99.9% confidence that he is not a carrier for the disease of concern.

The time required to complete test matings can be significantly shortened using superovulated affected females, insemination, and embryo transfer (two per recipient) followed by early cesarean section at 60 days and examination of the offspring for the genetic defect(s) of concern.

51.6 OBTAINING GENETIC INFORMATION

Because of the ever-increasing wealth of genetic information, the most complete and current information can be found using online resources. It is recommended that clinicians use websites produced by reputable institutions to obtain the most accurate and referenced information available (Box 51-1).

Table 51-1 Test Mating Schemes to Examine Males for Genetic Traits or Diseases at Various Confidence Levels

Females Used for Test Matings	Offspring Needed to Reach Probability Level of		
	0.05	0.01	0.001
Affected*	5	7	10
Normal carriers*	10	16	24
Sire's daughters†	22	35	52

* Tests for only one trait.

† Tests for all undesirable recessive traits.

51.6.1 Box 51-1 Recommended Websites for Large Animal Genetics

OMIA—Online Mendelian Inheritance in Animals: horse, cow, sheep, goat, pig

http://omia.angis.org.au/

MIS—Mendelian Inheritance in Sheep

http://www.angis.org.au/Databases/BIRX/mis/

Veterinary Genetics Laboratory at the University of California, Davis: horse

http://www.vgl.ucdavis.edu/service/horse/index.html

http://www.vgl.ucdavis.edu/research/equine/

Alternatively, clinicians are encouraged to contact the Veterinary Genetics services available at many veterinary schools if they are unable to locate the information they require.

51.7 RECOMMENDATIONS FOR BREEDING PROGRAMS

When a genetic disease has been identified, it is recommended that parentage be verified by DNA analysis and the extended pedigree be confirmed. Additionally, a pathologist should make appropriate examinations of tissues for an accurate diagnosis, and a certified statement detailing the condition should be written by a veterinarian or other third-party witness. The final decision with regard to the status of a particular animal should be withheld until all reasonable doubt has been removed; for bulls, this is usually at least two thoroughly documented cases or a positive genetic test, if available. The artificial insemination (AI) organization and breed registry should be informed of the status of each animal because disease information is important in future breeding decisions. Many AI organizations list any undesirable recessive alleles in their advertising, and some also remove carrier animals from service.

Depending on the value of the animal in question, a breeder may choose to remove the animal from the breeding program at the first sign of a potential genetic problem. In these cases, documentation of the abnormal conditions should still be conducted for completeness and for comparison with other cases that may be found in the future.

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52 Chapter 52 Genetic Tests for Large Animals

Danika Bannasch

Genetic testing based on deoxyribonucleic acid (DNA) involves the analysis of an animal's DNA to determine the individual's genotype for an inherited disorder, trait, or anonymous marker. Genetic testing can be used for positive or negative selection in a population, depending on whether it is being used to identify a disease (negative) or a trait (positive). Genetic testing can also be used for permanent individual identification and parentage determination. Many breed registries require parentage verification to ensure the accuracy of their pedigrees.

Using genetic testing results for selection requires an understanding of the mode of inheritance of the disease or trait. Most often, a genetic test will be performed for a recessive disorder to determine if an animal is a carrier. Carriers are asymptomatic but have the potential to produce diseased progeny. Because they have no outward manifestation of disease, a genetic test is extremely valuable for managing their breeding appropriately. Carrier animals can be bred to noncarriers if needed to retain valuable characteristics while not producing diseased offspring. In the case of positive selection for a trait of interest, carrier animals may have higher breeding values because they can produce a trait if bred to other carriers or to animals with the trait. Genetic tests may also be used for dominant disorders if the disease/trait has a late age of onset or if it is inherited in a co-dominant manner. DNA testing for traits that are controlled by more than one locus (polygenic) may also be used for selection for economically important traits. In these cases, one particular genotype may confer a slight advantage over another and therefore, in a large population, can have a significant effect on production.

Box 52-1 defines key genetic terms; see also Chapter 51.

52.1 INDIVIDUAL IDENTIFICATION AND PARENTAGE TESTING

Researchers use genetic markers distributed along all the chromosomes as tools to identify regions associated with diseases or traits. The markers are composed of small nucleotide repeats and are called *microsatellite* markers or *short tandem repeats* (STRs). These markers have a feature that makes them extremely useful to geneticists; the markers have been chosen to be “polymorphic” (show differences) between individuals. In other words, individual animals will have different lengths of the nucleotide repeats for each of these markers. The high level of polymorphism of this type of marker makes them useful for “mapping” (identifying the chromosomal location of diseases and traits.

The microsatellite markers are assayed by polymerase chain reaction (PCR) amplification using fluorescent-labeled primers. Primers are short (~20 base pairs), single-strand lengths of DNA that are complementary to a specific region of the genome. PCR is the amplification of a section of DNA contained between two primers designed to complement the unique sequence flanking the STR. The PCR products are then resolved by electrophoresis based on their length. Figure 52-1 shows a single microsatellite marker in three different animals. This marker is polymorphic and would be a useful marker for individual identification or parentage. Because the markers show differences between individuals, a collection of these markers can be used as a form of identification of an animal. High statistical significance can be obtained with as few as 10 markers, depending on the species and breed. The DNA type of an animal will not change over its lifetime and can therefore be used as a form of permanent identification.

Many purebred registries require parentage verification for registration purposes. To accomplish parentage verification, a DNA sample must be available from both parents as well as the offspring. DNA samples are taken

in the form of hair, blood, or buccal swabs (depending on the species and registry) and submitted at the time registration is requested. Each animal inherits one copy of each marker from its sire and one copy from its dam, so the markers can also be used to verify parentage. The most useful marker has a high polymorphism rate because that type of marker will be most likely to show differences not only between the sire and the dam, but also between the two copies (alleles) of the marker. A set of polymorphic markers (~10 to 20) is used to verify parentage to ensure a high probability that the parentage is correct. Table 52-1 shows the allele sizes for a set of markers in a parentage case. For marker *A* the offspring inherited a 122 and a 126 allele. The 122 came from its dam, so the 126 came from the sire. Because sire 1 does not have a 126 allele, it has been excluded. In this example, sire 1 is excluded as the sire of the offspring, and sire 2 is verified on the basis of the results for all three markers.

52.1.1

Box 52-1 Definitions of Genetic Terms

Allele One of the variant forms of a gene at a particular locus, or location, on a chromosome.

Base pairs Two bases that form a "rung of the DNA ladder." A DNA nucleotide is made of a molecule of sugar, a molecule of phosphoric acid, and a molecule called a "base." The bases are the "letters" that spell out the genetic code. In DNA the code letters are A, T, G, and C, which stand for the chemicals adenine, thymine, guanine, and cytosine, respectively.

Genotype Genetic makeup, either at a single locus or at all loci.

Linked Association of genes and markers that lie near each other on a chromosome; linked genes and markers tend to be inherited together.

Locus Place on a chromosome where a specific gene is located; a type of "address" for the gene.

Marker Segment of DNA with an identifiable physical location on a chromosome, the inheritance of which can be followed. A marker can be a gene or some section of DNA with no known function. Also known as a *genetic marker*.

Microsatellite Repetitive stretches of short sequences of DNA used as genetic markers to track inheritance in families.

Phenotype Observable traits or characteristics of an animal (e.g., coat color, weight, presence or absence of a disease).

Recombination Genetic transmission process by which the combinations of alleles observed at different loci in two parental individuals become shuffled in offspring individuals.

Splicing Ribonucleic acid (RNA) splicing removes introns and joins exons in a primary transcript.

Fig. 52-1 Microsatellite markers are visualized after polymerase chain reaction (PCR) by running the fluorescent-labeled PCR product (*shown in black*) through capillary electrophoresis, which separates the products based on size relative to an internal size standard (*shown in gray*). Each panel (**A, B,** and **C**) shows the results for a different animal. Size (base pairs of DNA) is resolved along the *x* axis, and the *y* axis shows the fluorescence intensity.

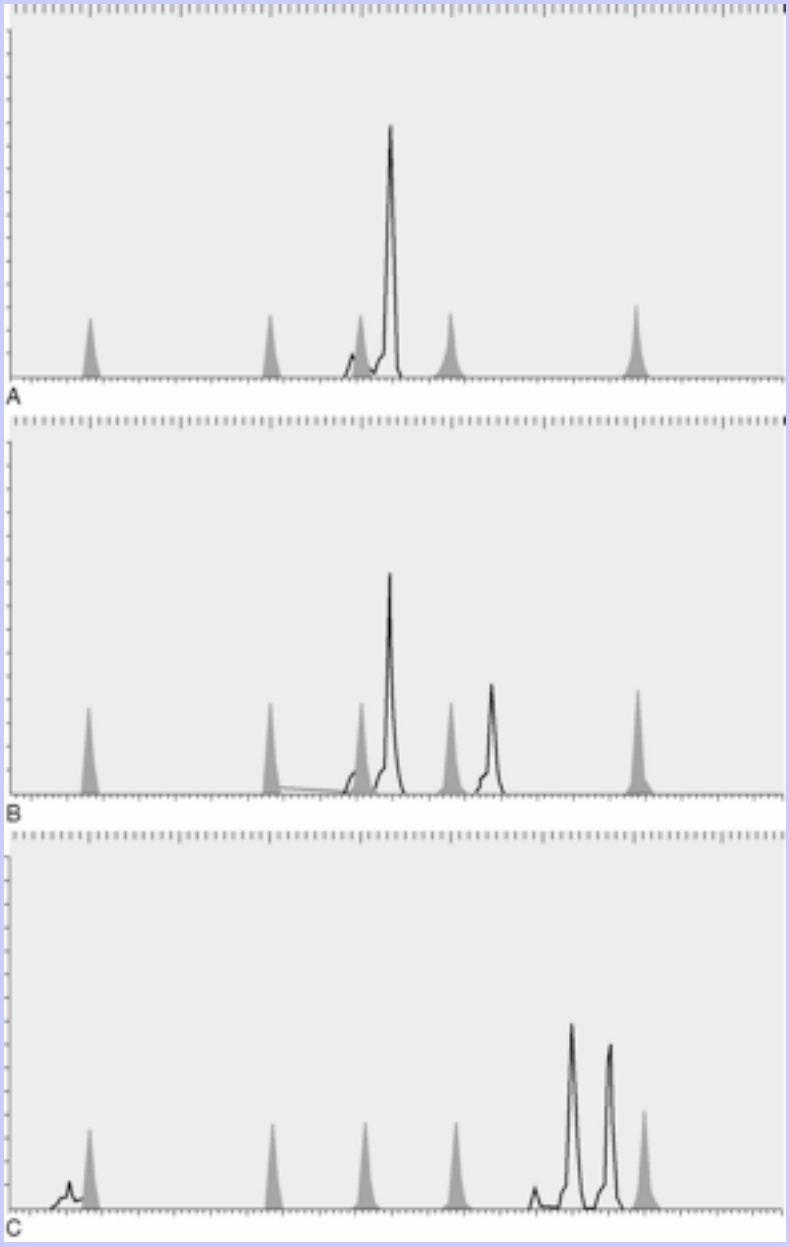

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Table 52-1 Parentage Verification Using Microsatellite Markers

	Allele Sizes for Four Markers			
Individuals	**A**	**B**	**C**	**D**
Dam	122/124	110	131/133	80/82
Offspring	122/126	110/112	133	82/86
Sire 1	128	112/114	131	84
Sire 2	126	112/114	131	86/90

52.2 DISEASE TESTING

Clinicians can use DNA testing in disease diagnosis or to determine an animal's potential for producing diseased progeny. Generally, disease diagnosis is based on clinical signs and other diagnostic tests, but occasionally DNA testing is used, in particular for later-onset diseases or diseases for which diagnosis by traditional methods is difficult or invasive. To offer a genetic test, the gene responsible must be known. Ideally, the actual mutation that causes the disease has been identified. Rather than knowing the exact gene or mutation, only a region of a chromosome may have been implicated in a particular disease. DNA tests can be divided into two categories: mutation tests and linked-marker or haplotype tests. *Mutation* tests are based on an actual mutation that causes disease, whereas the *linked-marker* or *haplotype* test is based on the region of the chromosome that is known to cause disease, but not necessarily the actual mutation. Usually, haplotype tests are offered instead of a mutation test because the mutation has not yet been identified.

Mutations that cause disease appear in many different forms. A change of a single base pair from one base to another can cause a disease either by changing an amino acid (“missense” mutation), truncating the amino acid chain (“nonsense” mutation), or altering expression or proper splicing. For example, missense mutations have been shown to cause lethal white foal syndrome in the American Paint horse.[1–3] Insertions or deletions of a single base pair (bp) can cause mutations in the coding sequence by altering the translational frame, which ultimately causes protein truncation. An 11-bp deletion in the myostatin gene causes a frameshift mutation and protein truncation in Belgian blue and Peidmontese cattle with the double-muscle phenotype.[4–6] Large deletions or insertions that remove hundreds and thousands of base pairs can also cause disease. For example, the polled intersexuality mutation in goats is caused by an 11.7-kilobase deletion that removes a regulatory element that controls the expression of two genes.[7] This endless array of possible changes in the DNA that result in disease makes each individual DNA-based genetic test different.

The basis for DNA testing is PCR. Primers can be designed specifically to amplify either the disease-causing allele or the normal allele. Alternatively, the PCR product can be digested with a restriction enzyme that cleaves the DNA at a particular sequence of bases. A restriction enzyme is chosen that shows a different cleavage pattern between the mutant and the normal version of the PCR product. Direct sequencing of a section of DNA can also be used to determine the animal's genotype. Many different methods are available to assay changes in DNA that lead to disease. Each company that offers a test may choose a different type of assay for the same mutation.

If the exact mutation that causes the disease has not been discovered, a linked-marker test can be used. A “linked marker” is a microsatellite marker similar to those previously described for individual identification and parentage analysis. The marker is “linked” along the chromosome to the disease gene. It can be used as a proxy for the actual mutation; the associated error rate can be decreased by using a set of markers that flank the gene causing the disease. When a set of markers is used, the test is called a “haplotype” test. Because the test does not directly test for the mutation, an error is still possible. Figure 52-2 shows a pedigree that is segregating a disease allele and a marker. In panel *A* the disease allele is in linkage phase with the marker allele 132. In this family the 132 allele is correlated to the disease locus. Panel *B* shows a family in which the linkage phase is different. In this family the sire has a 138 allele associated with the disease allele. Therefore, his affected son would be called a “carrier” and one of his daughters that is a carrier would be called “normal” based on this linked marker. Linked markers can be used in families with affected individuals to test for the presence or absence of the disease allele in other family members. The problem arises when a linked-marker test is used to test individual animals. The linkage phase is assumed based on research done in one family, but may not be true for every animal in the breed.

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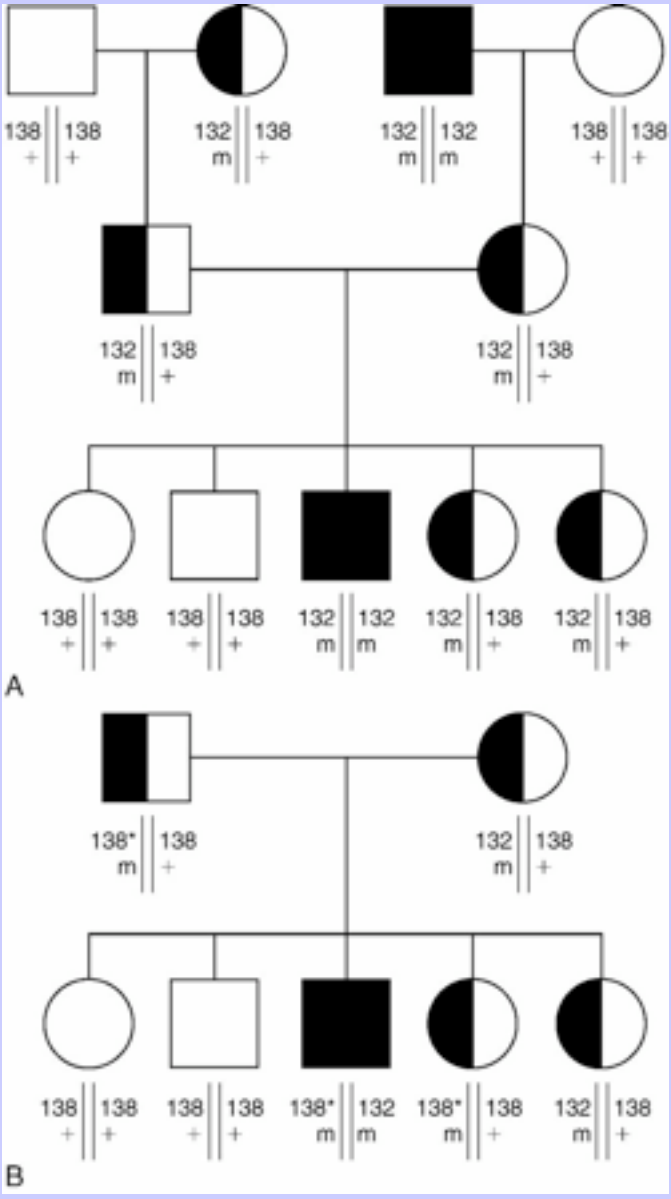
Fig. 52-2 In this pedigree, *squares* are males and *circles* are females. *Filled symbols* represent affected individuals, *half-filled symbols* represent carriers, and *open symbols* represent normal animals. The allele sizes for a marker linked to the disease locus are given below each symbol. For clarity, the genotype at the disease locus is also written below each symbol as *m* for the mutant allele and + for the normal allele. Panels **A** and **B** are two different families. The *asterisk* marks the allele in different linkage phase in family *B*.



There are limits to all genetic testing. In mutation tests the specific mutation being assayed is the only factor being evaluated. An animal may have a different mutation in that gene or a mutation in a different gene that causes the same phenotype (phenocopy). It is therefore correct to state that an animal has been “DNA tested negative” for this specific mutation rather than “DNA tested clear” of the disease. Linked-marker tests have these same sources of error, as well as additional sources. Recombination events between the markers and the disease gene can lead to false-positive and false-negative results. The use of multiple markers that flank the gene of interest (haplotype test) can increase the probability that a recombination event will be identified. If one is identified, the laboratory will know that the test is not valid in this individual. The second source of error with either a linked-marker or a haplotype test occurs when there is an ancestral recombination event that changes the linkage phase of the alleles. The result is that the laboratory would interpret an animal's genotype at the disease locus incorrectly, based on the linked markers.

Table 52-2 Genetic Tests for Horses

Disease/Trait	Breed	Mode of Inheritance	Reference(s)
Glycogen branching enzyme deficiency	American quarter horse American Paint horse	Recessive	9
Hyperkalemic periodic paralysis	American quarter horse American Paint horse Appaloosa	Co-dominant	10
Junctional EB	Belgian daft	Recessive	11
Herlitz junctional EB	French draft horses	Recessive	12
Lethal white foal syndrome	American Paint horse Pinto, American miniature	Co-dominant	1–3
Severe combined immunodeficiency	Arabian	Recessive	13
Chestnut	All	Recessive	14
Black/bay	All	Recessive	15
Tobiano	Many	Dominant	16
Sabino	Many	Co-dominant	17
Cream dilution	Many	Co-dominant	18

EB, Epidermolysis bullosa.

Table 52-3 Genetic Tests for Cattle

Disease/Trait	Mode of Inheritance	Reference(s)
Bovine leukocyte adhesion deficiency (BLAD)	Recessive	19
Growth hormone receptor (milk yield and composition)	Polygenic	20
Calpastatin (meat tenderness)	Polygenic	21, 22
μ-Calpain (meat tenderness)	Polygenic	23, 24
Citrullinemia	Recessive	25
Complex vertebral malformation (CVM)	Recessive	26
DGAT1 (milk yield and composition)	Polygenic	27
Deficiency of uridine monophosphate synthase (DUMPS)	Recessive	28
Leptin (marbling and milk production)	Polygenic	29, 30
Myostatin	Recessive	4–6
Polled	Dominant	31
Pompe's disease	Recessive	32
Red/black coat color	Recessive	33
Thyroglobulin (marbling)	Polygenic	34

No association or committee evaluates quality control of DNA tests that are available in animals. Most tests are published in the scientific literature not as tests but as articles describing the discovery of the mutation. Because some cases involve patent issues, some tests are offered before publication. Much of the research done to identify the mutations involved in the tests is performed at universities and funded by granting agencies that have both financial and intellectual interest in patenting the tests. Companies then license the rights to offer the tests. Because the companies that have a license for each test can change, company names are not listed in this chapter. Rather, searching on the Internet for the test name will give veterinarians access to the companies offering the tests. Tables 52-2, 52-3, and 52-4 list available genetic tests for horses, cattle, and sheep and goats, respectively. Only tests published in peer-reviewed journals are listed. Additional tests available in cattle for various forms of the milk proteins also are not listed in Table 52-3. The breeds of cattle are not listed because rapid changes in testing mean that tests are always being validated for new breeds. It is therefore recommended that a search be performed for the availability of a test for a particular breed each time the need arises.

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Table 52-4 Genetic Tests for Sheep and Goats

Disease/Trait	Breed	Mode of Inheritance	Reference(s)
Mucopolysaccharidosis IIID	Nubian	Recessive	35
Scrapie resistance	Various	Polygenic	36–38
Spider lamb syndrome	Suffolk	Co-dominant	39
Increased fertility	Various	Overdominant	40–43
Callipyge	American Dorset	Polar overdominant	44

The diseases or traits that are tested can be divided into two categories: those that have straightforward Mendelian inheritance patterns (recessive, dominant, and sex-linked) and those that are more complicated because many genes are involved with conferring the phenotype (polygenic). *Quantitative trait loci* (QTL) are the genes that contribute to a polygenic disease. In cattle a vast number of QTL have been placed in specific regions of chromosome for quantitative traits such as dairy form, milk production, and fertility.[8] Selection for these traits can be done with DNA testing (see Table 52-3). Because so many different QTL exist, however, selection can be challenging, and trade-offs need to be made.

Genetic testing relies on advances made in the field of genomics. Veterinarians and owners are fortunate that both cattle and horses were chosen as economically important species for whole-genome sequencing. A Hereford bull and a thoroughbred mare have both been sequenced, and studies describing the results should be available soon. The number of disease-based or trait-based tests available in the future will increase as the information in the genome sequence is translated.

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53 Chapter 53 Immunologic Disorders

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53.1 EQUINE IMMUNODEFICIENCY DISEASES

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JILL R. JOHNSON

The environment in whichdomestic animals live with regard to exposure to pathogens is challenging and often life threatening. Complex defense mechanisms have developed to protect the host from outside challenges, particularly the pathogenic effects of microorganisms. It is important to understand that diseases, particularly infectious diseases, can result from failure of the host's normal defense mechanisms, as well as from overwhelming challenge from the outside. When animals are plagued by repeated or chronic infections, the clinician should always determine whether host factors are involved.

The analysis of immunodeficiency diseases depends on an understanding of the normal immune response. The development of protective immunity is a result of the orchestration of numerous cell types and soluble serum factors (Fig. 53-1). Both *innate* (nonspecific) and *adaptive* (specific) mechanisms play a role.

Two major populations of lymphocytes are involved in immune responses, T cells and B cells. Classically, T cells are associated with cell-mediated immune responses that protect against fungal, protozoal, intracellular bacterial, and many viral infections. B cells are associated with humoral immunity. T cells originate from stem cells, which probably develop in the fetal liver. These cells must undergo a maturation process in the thymus before becoming fully functional. T cells comprise about 70% to 80% of peripheral blood lymphocytes and populate the periarteriolar regions of the spleen and the paracortical regions of lymph nodes. As with T cells, B cells originate from stem cells in the fetal liver. The site of B-cell maturation varies with species and includes several different organs, such as the bursa of Fabricius in birds and the bone marrow and certain Peyer's patches in mammals. Of peripheral blood lymphocytes, 15% to 30% are B cells. B cells populate germinal centers of spleen and lymph nodes.[1,2]

T lymphocytes are important in regulating the immune response, and both humoral and cellular immune responses depend on input from T cells. Initially characterized as either helper T (Th) cells or cytotoxic/suppressor T (Tc) cells based on their primary function, T cells have subsequently been differentiated on the basis of cell surface antigens, with Th cells expressing the CD4 antigen and Tc cells expressing CD8.[3,4] Further work has shown that the function of these cells is complex, and that the pattern of cytokine expression is important in regulation of the immune response. Based on their cytokine expression, $CD4^+$ cells have been further subdivided into distinct subsets, Th1 and Th2 cells (Fig. 53-2). Although there is some species variation, Th1 cells generally produce interferon-γ and interleukin-2 (IL-2) and are involved primarily in the generation of cell-mediated immune responses, whereas Th2 cells produce IL-4, IL-5, and IL-13 and are involved in humoral responses. In mice, either

protection from disease or development of lesions can be associated with the particular type of Th cell response, and the clinical relevance of this is currently being investigated in a number of equine diseases.

The second major class of lymphocytes is B lymphocytes, which produce immunoglobulins and are the precursors of plasma cells. Several classes of immunoglobulins are produced by B cells. There is some variation among species, but the major classes are IgG (IgG1 and IgG2), IgM, IgA, IgE, and in horses, IgG(T). Immunoglobulins provide a defense against extracellular bacterial and certain viral infections.

The innate immune system, which is nonspecific in nature, includes natural killer cells, phagocytic cells, neutrophils, eosinophils, basophils, and nonimmunoglobulin serum and cellular factors such as complement and interferon. These components play a distinct role in host defenses and work with T and B cells to produce an effective protective response.

A deficiency of functional T cells, B cells, nonspecific components, or any combination predisposes animals to infections that may result in death. Immune deficiencies can be classified according to (1) the site of defect in the host defense system and (2) whether the mechanism is primary or secondary.[1,5–7] In a *primary* disorder there is an inherent abnormality in the immune system that has a proven or suspected genetic basis, whereas in a *secondary* disorder the host's initially normal ability to respond immunologically is altered. Some factors that can produce secondary immunodeficiencies include irradiation, neoplasia, toxicities, malnutrition, and certain microbial infections.[1,6,7] Physiologic stress, such as that caused by pregnancy, lactation, and exercise, can also induce transient immunosuppression.[6,8] Both primary and secondary immunodeficiencies can affect various components of the immune system, and by careful dissection of the immune response, the site of the defect can often be identified.

General clinical features associated with immunodeficiencies include the following[1,5–7]:

- Onset of infections during the first 6 weeks of life.
- Repeated infections that respond poorly to standard therapy.
- Increased susceptibility to organisms with low pathogenicity.
- Infection with organisms rarely observed in immunocompetent individuals.
- Systemic illness after administration of attenuated live vaccines.

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- Failure to respond to vaccination.
- Persistent marked abnormalities in leukocyte numbers.

Fig. 53-1 Ontogeny of the immune response. Failures at any site in the maturation process can result in manifestation of immune deficiencies.

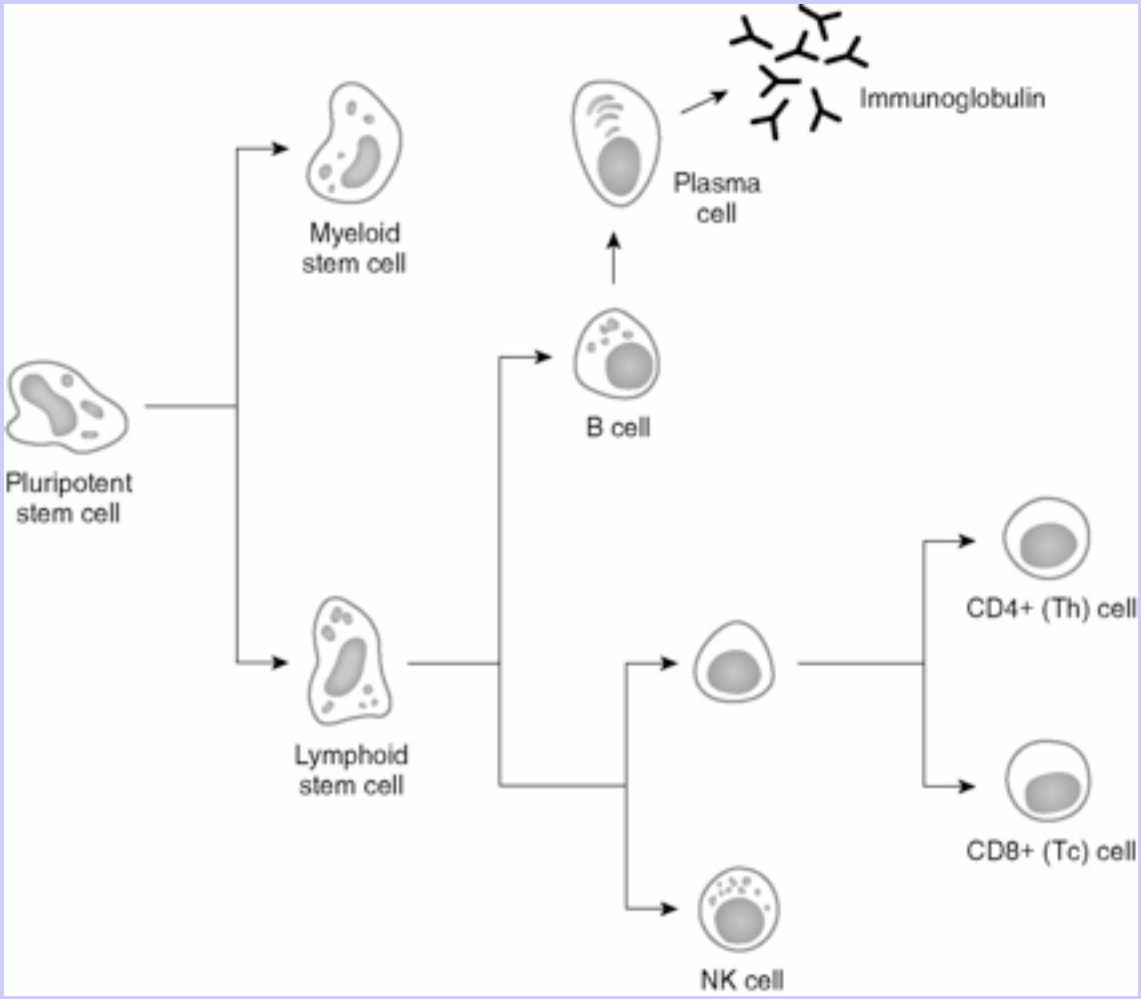
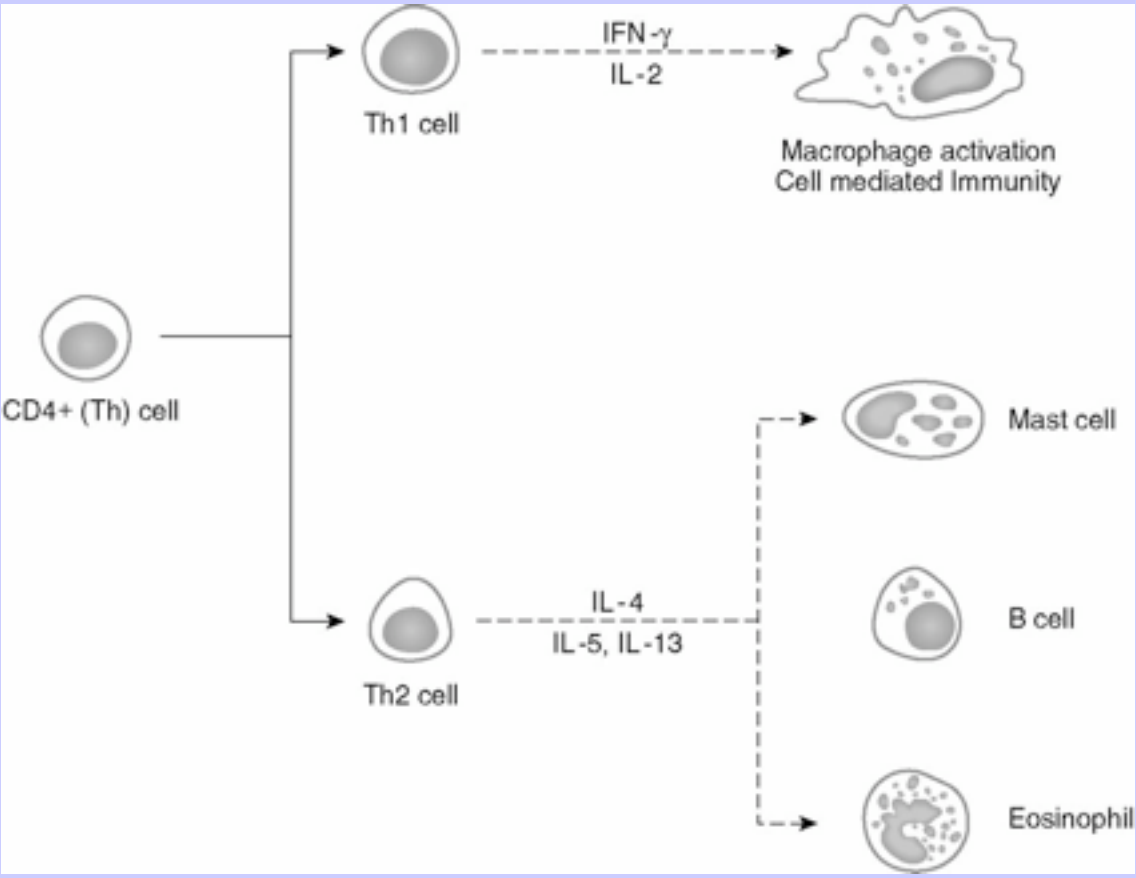


Fig. 53-2 $CD4^+$ T cells can be subdivided into Th1 and Th2 on the basis of their cytokine profiles. Preliminary data suggest that the pathogenesis of certain diseases is associated with the particular type of Th response.



Laboratory or special in vivo testing is necessary to confirm the presence of an immunodeficiency. Such testing is also important in differentiating the various immunodeficiency syndromes because clinically the presenting signs are nonspecific. In general, tests to evaluate the immune system either quantify the component or measure the functional capacity.

The enumeration of lymphocytes, and in some cases, specific lymphocyte types, can be useful in the diagnosis of immunodeficiencies. Currently, specific subsets of lymphocytes are most often identified using antibodies to cell surface markers and flow cytometry.[3,4,9] In normal horses, about 20% of circulating lymphocytes are B cells, and about 62% are $CD4^+$ T cells and 18% $CD8^+$ T cells.[9,10] B cells can also be enumerated in blood and lymphoid tissue using fluorescent-labeled antibody to detect surface immunoglobulin and erythrocyte-antigen-complement rosetting techniques to detect complement receptors. Erythrocyte rosetting assays and fluoresceinated peanut agglutinin surface labeling tests have been used to enumerate T cells in peripheral blood and lymphoid tissue. 1666 1667

The primary clinical tests of B-cell function are quantitation of immunoglobulins and measurement of specific antibody responses. Numerous methods are available to quantitate or semiquantitate immunoglobulin levels.

Semiquantitative tests are useful for some conditions, such as failure of passive transfer (FPT) after colostrum ingestion; however, they do not provide information on specific immunoglobulin classes. Some tests are species specific, whereas others can be used to detect immunoglobulins of several species. Precipitation of immunoglobulins with specific salt concentrations tends not to be species specific, although the tests may work better in some species than others. These tests include zinc sulfate and sodium sulfite precipitation and glutaraldehyde coagulation (see p. 1679).[11,12] Commercial tests based on these principles are available.* Serum electrophoresis can also be used in all species to quantitate γ-globulins, which are primarily immunoglobulins. Several species-specific tests based on antigen-antibody reactions that use latex bead agglutination† or enzyme immunoassay† as the marker systems are also commercially available. These tests are semiquantitative and are primarily marketed for detection of FPT after colostrum ingestion.

Radial immunodiffusion (RID) quantitates immunoglobulins of specific classes using a precipitation reaction between antigen and antibody directed against one species-specific, class-specific immunoglobulin to be quantitated. This is an accurate method for quantitating specific classes of immunoglobulin such as IgG and IgM. RID kits are commercially available for some immunoglobulin classes for domestic animals.§ These tests require incubation for 18 to 24 hours, which is their greatest drawback for clinical use. Test reagents are prepared for use in a single species; however, some cross-reactivity does exist among species. Test reagents designed for use in another species (e.g., human) have been shown to be useful[13]; however, they must be standardized and calibrated for the species in which they are to be used.

Production of antibody in response to immunization with specific antigens is another way B-cell function can be evaluated, although functioning T cells are also required for this response. The only requirement to assess antibody production is an in vitro test to detect specific antibody. Serologic measurement of antibody titers before and after vaccination with commercially available vaccines is one approach. Killed infectious bovine rhinotracheitis (IBR) and bovine viral diarrhea (BVD) vaccines in cattle and influenza or rhinopneumonitis vaccines in horses are readily available, and responses are easily tested. Another approach is to look for the presence of naturally occurring antibodies that are produced without immunization (e.g., antibodies that cross-react with sheep red blood cells in horses), although the assays for these antibodies may not be readily available. Other foreign “nonvaccine” antigens can also be used if an assay is available for the detection of antibody.

One clinical in vivo test of T-cell function is intradermal skin testing with the plant lectin, phytohemagglutinin (PHA), which identifies delayed-type hypersensitivity (DTH) responses. PHA is capable of eliciting a DTH response without requirement of prior sensitization, which is required with some other antigens, such as dinitrochlorobenzene. To perform this test, the thickness of a skin fold is measured before injection. A 50-μg dose of PHA* in 0.5 ml of phosphate-buffered saline (PBS) is injected intradermally, and the same volume of PBS is injected at a control site at least 10 cm (4 inches) away from the site. Twenty-four hours later the skin thickness is measured. A 1-mm to 3-mm increase in skin thickness at the test site should normally occur. An increase of 0.6 mm or less indicates a defect in cell-mediated immunity.[14]

Other tests for B- and T-cell function are available primarily on a research basis. In vitro lymphocyte blastogenesis with pokeweed mitogen requires both B- and T-cell function for normal responses, whereas lipopolysaccharide requires predominantly a B-cell response. Blastogenesis with PHA and concanavalin A assess primarily T-cell function.

A variety of assays for phagocytosis and killing by neutrophils and macrophages have been developed.[15–17] Recently, flow cytometric analyses of phagocytic function have been described, as well as methods for the quantitation of complement, interferon, and various lymphokines. However, these procedures are currently available only in selected research facilities.

From a practical standpoint, only a limited number of tests are available, and most are crude indicators of immune response and therefore detect only severe deviations from normal. Nevertheless, a number of immunodeficiency syndromes have been characterized in domestic animals. As methods improve, so will veterinarians' ability to define immune disorders more precisely.

* Equi-Z, Bova-S, and Llama-S, VMRD, Inc., Pullman, WA; Gamma-Check, Plasvacc USA, Templeton, CA.

† Foalchek, Centaur, Inc., Overland Park, KS.

‡ SNAP-Foal IgG, IDEXX Laboratories, Inc., Westbrook, ME.

§ VMRD, Inc., Pullman, WA; PlasVacc, Templeton, CA; Bethyl Laboratories, Montgomery, TX.

* PHA-P, Sigma Chemical Co., St. Louis, MO.

53.2 FAILURE OF PASSIVE TRANSFER

53.2.1 Definition and Etiology

Normal foals are immunocompetent at birth (i.e., they are capable of mounting an immune response). However, they are immunologically naive in that they have had no exposure to foreign antigens and have therefore not yet mounted any type of protective immune response or accumulated significant levels of immunoglobulins. Although foals are capable of producing antibody, they are essentially devoid of immunoglobulin at birth, with the exception of small amounts of IgM normally produced in utero. Because they are “starting from scratch,” foals are indeed more susceptible to infectious agents during the early neonatal period. Foals begin producing immunoglobulins immediately on exposure to antigens after birth, and immunoglobulins produced by the foal are detectable within 1 to 2 weeks of life and reach significant levels by 2 months.

Under normal circumstances, temporary protection against infection for the first 1 to 2 months is provided to the foal in the form of passively transferred antibody (Fig. 53-3). Because of the diffuse epitheliochorial nature of the equine placenta, no transplacental transfer of immunoglobulins occurs in horses. Instead, ingestion and absorption of immunoglobulin-rich colostrum are the sole means of passive transfer in foals. In a properly functioning system, maternal antibodies wane as levels of autologous antibodies increase, and thus the neonate is never left totally unprotected (Fig. 53-4).

Failure of the foal to ingest or absorb sufficient quantities of colostrum, primarily as defined by absorption of IgG, is termed *failure of passive transfer* (FPT). *Complete* FPT is defined as a foal with a serum IgG concentration of less than 400 mg/dL at 24 hours of age. *Partial* FPT is defined as a foal with a serum IgG concentration of 400 to 800 mg/dL at 24 hours of age. The reported incidence of complete or partial FPT in foals varies from 3% to 37.8%.[18–25]

Fig. 53-3 The duration of protection provided by maternal immunoglobulins varies with the class of immunoglobulin and the quantity ingested during the first 24 hours of life.

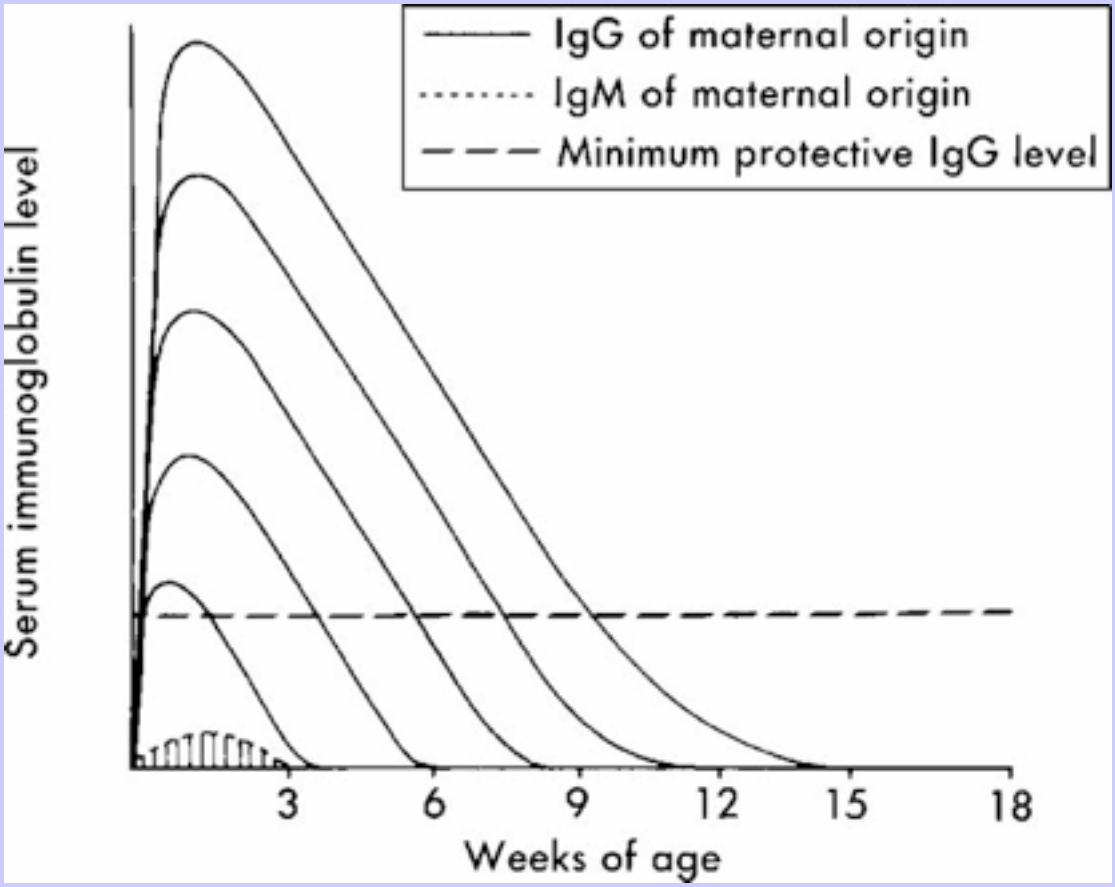
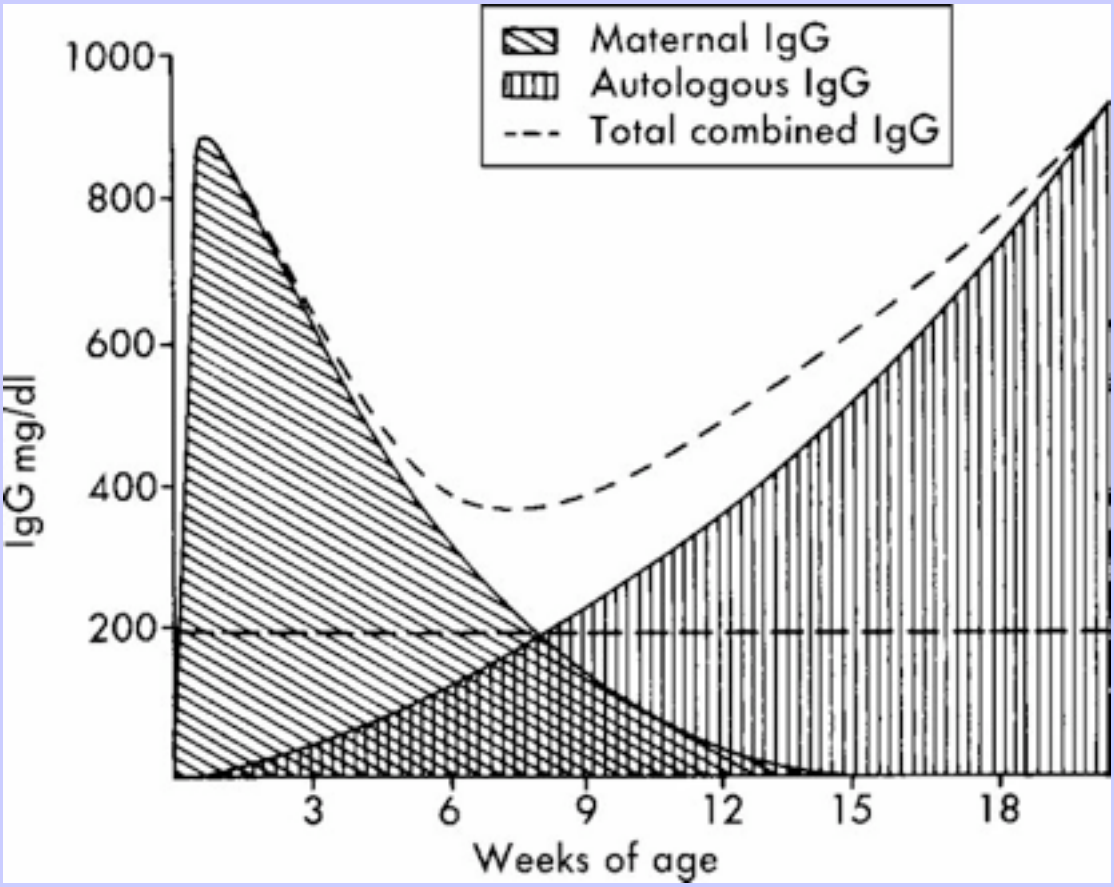


Fig. 53-4 Maternal immunoglobulin wanes, whereas the production of autologous immunoglobulin increases during the first several months of life. The combined total amount of immunoglobulin ideally remains above the level considered minimum for maintenance of good health.



Immunoglobulins are not produced locally in the mammary gland, but rather are selectively concentrated from the mare's sera into colostrum in response to hormonal changes that occur in the last 2 weeks of pregnancy. Most immunoglobulin in equine colostrum is IgG or IgG(T), with smaller quantities of IgM and IgA. At birth the neonate has specialized enterocytes in the gastrointestinal (GI) tract that are able to absorb large molecules such as immunoglobulins intact by pinocytosis. Absorbed proteins pass through the intercellular spaces and lacteals into the systemic circulation via the lymph. The window of gut absorptive capacity for immunoglobulins is narrow, lasting from birth until about 18 to 24 hours. Maximal absorptive efficiency occurs immediately after birth, declining to only 22% efficiency at 3 hours after birth and less than 1% by 20 hours.[26,27] The decline in immunoglobulin absorption is accompanied by transient proteinuria that peaks at 6 to 12 hours of age and declines by 24 to 36 hours of age. This proteinuria most likely reflects absorption and excretion of low—molecular-weight milk proteins.[28]

Diminished immunoglobulin absorption over the first 12-24 hours of life is the result of shedding of specialized enterocytes capable of pinocytosis and replacement by more mature cells that are incapable of absorbing immunoglobulins.[26,27,29] It has been hypothesized that delayed ingestion of macromolecules may prolong the duration of intestinal permeability to immunoglobulins. In one study, however, the type of fluid administered to foals before the ingestion of colostrum did not influence subsequent IgG absorption, suggesting that the process of gut closure is not mediated by a finite capacity for the uptake of macromolecules.[30]

The half-life for maternal antibodies in the foal's circulation varies between 20 and 30 days.[31–33] Concentrations decline as a result of normal protein catabolism, gradual dilution in an increasing plasma volume as the foal grows, and transfer of functional antibody into the GI tract. Most maternal antibodies are present in only negligible concentrations by 6 months of age, although antibodies to some infectious agents have been detected for up to 12 months after birth. As passive antibody concentrations decline, autogenous antibody production begins. There is a nadir in serum immunoglobulin concentrations in colostrum-fed foals at approximately 1 to 2 months of age, followed by gradually increasing concentrations until adult levels are reached at 5 to 10 months.[2,34] Serum immunoglobulin concentrations are similar in colostrum-fed and colostrum-deprived foals by 3 to 4 months of age.

In addition to antibody, other colostral factors may be important for optimal immune protection of foals. For example, colostrum influences cell-mediated immunity and activates granulocytes. Colostrum contains many constituents of innate immunity and immunomodulating agents, such as complement, cytokines, and trace elements, that have a local protective effect in the neonatal digestive tract.[35,36]

In foals, FPT may occur because of ingestion of poor-quality colostrum with a low immunoglobulin content, failure to ingest a sufficient quantity of colostrum, or failure to absorb colostral immunoglobulins from the GI tract.[29,37] Colostrum may have an insufficient quantity of immunoglobulin because of prelactation (lactation before parturition), premature foaling, a defect in the mare's ability to concentrate immunoglobulin in the colostrum, ingestion of endophyte-contaminated fescue grass or hay, or other factors. Mares most likely to produce colostrum with low immunoglobulin content are those older than 15 years of age, those that foal early in the year, and standardbred mares.

Foals that are orphaned or rejected at birth, too weak to stand, or unable or lack the desire to suckle are unlikely to ingest sufficient colostrum to prevent FPT. Malabsorption is occasionally incriminated as a cause of FPT in foals that are observed to suckle adequate quantities of good-quality colostrum. This most often happens in premature or dysmature foals, possibly as a result of immature GI function, but may also occur in otherwise healthy and vigorous full-term foals.[38] Glucocorticoids enhance the maturation of small-intestinal epithelial cells and thus their loss of absorptive capacity, leading to speculation that endogenous corticosteroids released secondary to stress at parturition may impair immunoglobulin absorption in foals.[39,40] However, administration of adrenocorticotropic hormone (ACTH) failed to affect absorption in experimental foals, and stress has not been a consistent historic finding in foals with FPT caused by presumptive impaired immunoglobulin absorption.[22,41]

53.2.2 Clinical Signs and Differential Diagnoses

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The association between FPT and infection has been investigated in numerous studies.[18–20,24,25] Although the results have varied somewhat, FPT is generally considered a risk factor for infectious disease. By itself, FPT

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produces no clinical signs of disease and cannot be detected by physical examination. Clinical presentations that strongly suggest an underlying problem with FPT include onset of bacterial infections within the first 2 weeks of life, particularly septicemia, septic arthritis, pneumonia, and enteritis. Other immunodeficiencies or simply exposure to potent pathogens cannot be ruled out solely on the basis of the time of onset; however, even with other forms of immunodeficiency, clinical signs of infection usually do not show up for several weeks if passive transfer is adequate.

53.2.3 Clinical Pathology

FPT is diagnosed by the demonstration of low serum concentrations of IgG in the foal as early as 6 to 12 hours after birth and probably for as long as several weeks after birth (Table 53-1). The level of IgG considered adequate for protection against infectious disease is poorly defined and probably varies considerably with the environment. A serum IgG concentration greater than 800 mg/dL is considered adequate for most foals. However, levels of 400 mg/dL may be sufficient in healthy foals housed in clean environments. In contrast, an IgG concentration of 400 to 800 mg/dL in a foal at high risk for sepsis because of its environment or other factors indicates the need for treatment. Importantly, these figures only address *total* immunoglobulin content and not specific antibody titers, which also play a critical role in determining resistance to particular pathogens.

In healthy foals that nurse within 2 hours of birth, serum IgG concentrations become detectable at approximately 6 hours of age and peak at approximately 18 hours. Routine determination of serum IgG concentrations in apparently healthy foals is usually recommended at 18 to 24 hours of age. Foals considered to be at high risk for FPT and sepsis may be assessed as early as 6 to 12 hours of age.[35,42]

Methods available for IgG quantitation include single radial immunodiffusion, zinc sulfate turbidity, latex agglutination, glutaraldehyde coagulation, turbidometric immunoassay, and enzyme immunoassay.[11,35,43–47] Single radial immunodiffusion is considered the most quantitatively accurate diagnostic test of those widely available to practitioners. However, this test is more expensive than some other screening tests, and results are not available for at least 24 hours, making it impractical when a critically ill foal needs rapid diagnosis and treatment. Total serum protein is not a reliable indicator of FPT in foals (unlike calves) because of the wide variation in total serum protein in cases of adequate transfer.

Table 53-1 Normal Serum Immunoglobulin Concentrations (mg/dL) in Horses

Age	Breed	IgG	IgG(T)	IgM
Newborn, presuckle	Arabian	1-10	ND	5-15
1-20 days	Arabian	814 ±583	142 ±88	28 ±11
21-40 days	Arabian	480 ±293	126 ±41	30 ±10
41-60 days	Arabian	264 ±193	96 ±33	42 ±12
61-80 days	Arabian	252 ±128	75 ±17	36 ±12
81-140 days	Arabian	248 ±92	162 ±126	39 ±15
3-5 months	Mixed	380 ±188	211 ±148	61 ±22
10-15 months	Arabian/thoroughbred	790	728	48
Adult	Shetland	1334 ±350	821 ±301	120 ±13

From Riggs MW: Evaluation of foals for immune deficiency disorders, *Vet Clin North Am Equine Pract* 3:515, 1987.*ND,* Not determined.

No consistent changes in the hemogram and biochemical panel are seen in foals with FPT; however, a range of abnormalities related to secondary infection (e.g., neutrophilia, neutropenia), hyperfibrinogenemia, and hypoglycemia may be present. The presence and severity of these changes depend on the organisms and systems involved.

53.2.4 Necropsy Findings

No specific necropsy findings are indicative of FPT. Necropsy findings reflect the site and severity of secondary infectious problems that have developed. Lymphoid tissue is normally developed, unless secondary infections have caused lymphoid necrosis or atrophy.

53.2.5 Treatment and Prognosis

Treatment of FPT depends on the degree of FPT, the environment in which the foal is exposed, the foal's age at diagnosis, and the presence of secondary infectious problems. Treatment is aimed at minimizing exposure to pathogens, supplying immunoglobulins, and managing secondary infections, if present.

If FPT can be anticipated within hours of birth because of premature lactation, low—specific gravity colostrum, or a weak or orphaned foal, treatment can include the provision of an alternative source of colostrum or antibody orally. Foals with complete colostrum deprivation require approximately 1.5 g IgG/kg body weight to achieve a peak serum IgG concentration of more than 800 mg/dL. In a 45-kg foal, administration of 1 to 3 L of colostrum with a specific gravity greater than 1.060, divided into multiple hourly feedings over the first 6 to 8 hours of life, is desirable. Mares that donate colostrum for feeding should be healthy, checked for blood type, negative for anti—red blood cell (RBC) alloantibodies (especially anti-A and anti-Q) and appropriately vaccinated during the last 4 to 6 weeks of gestation.

If equine donor colostrum is not available, bovine colostrum, a commercial colostrum substitute, or equine plasma may be administered orally to the foal.[48–55] Because bovine colostrum is often more readily available than equine colostrum, it may be substituted in emergency situations when equine colostrum is not available. Bovine colostrum is relatively well absorbed in the foal, but bovine immunoglobulins have a much shorter half-life in foals and do not contain antibodies specifically directed against equine pathogens. It is certainly better than no colostrum and, on the basis of a small experimental study, may be used without creating adverse reactions.[48–50] Approximately 2 to 4 L should be administered orally; many foals develop transient mild diarrhea.

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Lyophilized equine IgG* is available as an equine colostral substitute. A minimum of 50 to 70 g of IgG is recommended for treatment of the average 45-kg foal that receives no colostrum, but in one study this dose failed to increase serum IgG concentration to over 450 mg/dL in colostrum-deprived foals.[55] A concentrated equine serum product† is also available for use in foals with FPT.[56] Again, however, in one study it failed to increase serum IgG concentrations in colostrum-deprived foals to adequate levels, probably because of the relatively low total IgG dose administered.[51] If the product contains 25 to 30 g of IgG per 300-mL bottle, approximately three bottles may be required to increase the serum IgG concentration of a 45-kg colostrum-deprived foal to greater than 400 mg/dL.[51]

If no other sources of immunoglobulin are available for a foal, oral administration of equine plasma or serum may be considered. This is an expensive source of oral immunoglobulin, however, and approximately 2 to 4 L are required to treat a colostrum-deprived 45-kg foal.

If the foal is over 6 hours old, the absorption of colostral antibody is significantly decreased, although a locally protective effect of the colostrum may still be present in the intestinal tract. If the foal is over 12 hours old, it is unlikely that sufficient colostrum will be absorbed; therefore, immunoglobulin levels should be rechecked at 24 hours and intravenous (IV) plasma transfusion given, if indicated by persistently low serum immunoglobulin levels.

Some animals with FPT, particularly partial FPT, do well without treatment if they are systemically healthy, are not heavily exposed to pathogens, and have no preexisting infections. FPT itself is not necessarily fatal. If plasma transfusions are not administered, owners should be made aware of the risks, and these foals should be maintained in an environment with minimal exposure to potential pathogens. Foals with other risk factors for septicemia (e.g., prematurity, dysmaturity, placentitis) should receive IV plasma transfusions if they have blood IgG concentrations of less than 800 mg/dL at 12 to 24 hours of age.

If the decision is made to supplement plasma parenterally, equine plasma for transfusions is commercially available† or can be collected and processed locally. Commercial sources are convenient, save time, have been screened for anti-RBC antibody, are free of diseases such as equine infectious anemia, and originate from animals with known immunoglobulin levels. The major disadvantage is that plasma may not contain antibody specific for the pathogens from the particular environment to which the foal is exposed.

Use of a local donor is desirable in that it presumably has antibody specific to the environmental pathogens to which the foal has been exposed. If a local donor is to be selected, several criteria should be met. First, the horse should be healthy, and results of agar gel immunodiffusion for equine infectious anemia should be negative. Second, no anti-RBC antibody should be detectable in the horse's serum. The donor's plasma should be screened for lysins and agglutinins by a blood-typing laboratory against a panel of cells representing all known blood groups. If plasma evaluated in this way is not available, the presence of anti-RBC antibody in

donor plasma can be crudely evaluated with a minor crossmatch for agglutination using donor plasma and recipient blood cells. Lytic antibodies require an external source of complement for activity in vitro and may not be detected using this test.

Ideally, a third criterion is selection of a horse that is negative for blood group factors Aa and Qa. Even though there are dozens of blood group factors, Aa and Qa have been associated with the great majority of cases of neonatal isoerythrolysis (NI).[57–59] If plasma is collected and separated by sedimentation, it is inevitable that some RBC contamination be present. If Aa-positive (Aa+) RBCs are given to an animal that is Aa negative (Aa −), or if Qa+ RBCs are given to an animal that is Qa−, the recipients could become sensitized to these antigens. This sensitization would probably not have any immediate consequences for the recipient foal, because the foal's cells would not be affected by the antibodies, but it has potentially sensitized any Aa− and Qa− females for production of an NI foal later (see p. 1685). To avoid these potential complications, the ideal donor should be Aa− and Qa− and possess no anti-RBC antibody in its serum. It is desirable to have identified this type of donor to avoid the need for immediate crossmatching in every case of plasma transfusion.

The volume of plasma needed to correct the measured IgG deficit in a foal can theoretically be calculated on the basis of the blood volume of the foal and the concentration of IgG in the foal's serum and in the donor plasma; however, these calculations do not reliably predict the actual levels of IgG achieved after transfusion.[35,60] A 20-mL volume of plasma per kilogram of body weight administered intravenously routinely only raises serum IgG levels 200 to 300 mg/dL, and often two to three times this amount is needed to bring serum IgG levels into the range considered minimum for protection (e.g., 400 to 800 mg/dL).[35,61] If the foal is already clinically ill, additional plasma will often be required to raise IgG levels an equivalent amount.[35,44] In a newborn foal (estimated 50 kg) with complete FPT, between 2 and 4 L of plasma is frequently needed.

Plasma should be administered through an IV catheter placed aseptically in one jugular vein. Frozen plasma is thawed and warmed slowly to room temperature in a warm water bath. Microwave thawing or thawing with very high temperatures is not recommended because this may denature important plasma proteins. An appropriate in-line blood filter should be used for IV administration of any blood product to remove fibrin clumps and other debris. Initial infusion rates should be slow (0.5 mL/kg over 10 to 20 minutes) to monitor for adverse reactions. Muscle fasciculations, piloerection, increased heart or respiratory rate, fever, respiratory distress, abdominal pain, blanching of mucous membranes, and collapse are indicative of transfusion reactions. In the absence of these or other adverse effects, the remainder of the transfusion may be administered at rates up to 40 mL/kg/hr. Slower infusion rates are recommended for foals that are systemically ill. If other IV fluid therapy is being administered concurrently, slower infusion rates are also indicated to diminish the likelihood of inadvertent fluid overload.

Serum IgG concentrations in the foal should be rechecked 12 to 24 hours after plasma transfusion to confirm that the desired increase has been achieved. The delay from transfusion to IgG assessment is necessary to allow for distribution of immunoglobulin into extravascular spaces. Healthy foals transfused with plasma at 1 day of age experienced a 30% decrease in serum IgG concentrations by 7 days of age.[62] This decline might be even more dramatic in septic foals with increased vascular permeability, increased catabolism, and increased demand for utilization in immune responses.

Although several equine serum-derived products are marketed for IV administration in the treatment of foals with FPT, these products have been associated with significant adverse reactions in some foals. Administration of high-quality equine plasma is preferred for treatment of foals with FPT.

* Lyphomune, BIOQUAL, Inc., Rockville, MD.

† Seramune, Sera, Inc., Shawnee Mission, KS.

‡ Foalimmune, HiGamm-Equi, Lake Immunogenics, Inc., Onatrio, NY; Endoserum, Immvac, Inc., Columbia, MO; Equi-Plas, Polymune, Plasvacc USA, Inc., Templeton, CA; Sera, Inc., Shawnee Misson, KS.

53.2.6

Prevention and Control

Evaluation of colostral immunoglobulin content has proved to be valuable in predicting the occurrence of FPT and assessing the neonate's risk for FPT.[35,63] Colostrum with high immunoglobulin concentration tends to be sticky, yellow, and thick, but these subjective criteria are unreliable in assessing colostral quality. The quantity of immunoglobulin in colostrum may be more accurately estimated by single radial immunodiffusion (RID), refractometry, glutaraldehyde coagulation, or specific gravity.[62] Because 18 hours are required to read the results of RID, it is more practical in a field situation to assess specific gravity with a refractometer, glutaraldehyde coagulation test or colostrometer. Sugar refractometry using a hand-held Brix 0-50% sugar refractometer is a simple and cost-efficient stall-side screening test for assessing colostral quality.[64,65] A Brix reading of 20% to 30% correlates with adequate colostral quality; a reading greater than 30% indicates good-quality colostrum.[66] A commercial kit based on glutaraldehyde coagulation of immunoglobulins* is available for screening of colostral quality. Using a colostrometer,† colostral specific gravity should be a minimum of 1.060, corresponding to an IgG concentration of greater than 3000 mg/dL; levels of 6000 mg/dL or higher are desirable. Approximately 75% of foals that ingest colostrum with a specific gravity less than 1.060 will have serum IgG concentrations under 400 mg/dL; when colostral specific gravity is greater than 1.060, foals usually attain serum IgG concentrations above 500 mg/dL.[63]

Some of the causes of FPT can be alleviated or recognized for early intervention by careful management. These include identification of mares that drip colostrum before parturition, attendance at foaling to ensure that foals suckle within several hours of birth or are supplemented artificially with colostrum, and screening of high-risk foals with doubtful nursing histories. Routine screening of foals at 18 to 24 hours of age allows early identification of FPT and potentially allows for therapy before the onset of infections. Although signs of septicemia secondary to FPT are often first observed on day 3 to 4 of life, a bacteremia may already be present at 24 hours of age or earlier.[66,67]

A colostrum bank can be established by collecting small amounts of colostrum from lactating mares (e.g., 200 to 250 mL) within the first 3 to 6 hours after foaling. This is only about 10% of the total colostrum produced by the average mare in the first 20 hours after parturition and therefore does not adversely affect the foal suckling the donor mare. Although the volumes are quite variable, mares produce about 300 mL of colostrum per hour and about 5 L during the first 18 hours. Colostrum can be stored frozen for at least 1 year at standard freezer temperatures, approximately −20° C (−4° F). Although frozen immunoglobulins are stable for much longer, the overall quality of the colostrum may deteriorate. Ideally, banked colostrum should be screened for the presence of anti-RBC antibodies as advised for plasma. Colostrum typically has low titers of agglutinins, which are probably not of significance unless present a dilutions of 1/8 or greater.

* Gamma-Check-C, Veterinary Dynamics, San Luis Obispo, CA.

† Equine Colostrometer, Lane Manufacturing Company, Denver, CO.

53.3 SEVERE COMBINED IMMUNODEFICIENCY

53.3.1 Definition and Etiology

Severe combined immunodeficiency (SCID) is a lethal, inherited condition in which both T-cell and B-cell function is absent.[68] Affected foals have a stem cell defect that prevents maturation of T and B cells, resulting in a complete inability to produce antigen-specific immune responses. The condition primarily affects Arabians and part Arabians, although sporadic cases have been described in other breeds.[68,69] In horses of Arabian breeding, the condition is transmitted as an autosomal recessive trait.[70] Carriers of the gene are asymptomatic but can now be detected by genetic testing.[71]

53.3.2 Clinical Signs and Differential Diagnoses

Foals that are homozygous for the defective SCID gene are clinically affected. These foals generally appear physically normal at birth, but the absence of both specific humoral and cellular immune responses renders them susceptible to infections once colostral protection wanes.[68] Affected foals typically develop infectious diseases between birth and 2 months of age and die before 5 months of age. The age of onset of infectious disease depends to some degree on the adequacy of passive transfer and the environmental challenge by organisms. The infections in affected animals are nonspecific and are caused by a variety of bacterial, viral, parasitic, and fungal agents, some of which rarely affect animals that are not immunocompromised.[68,72,73] Many body systems may be involved, but pneumonia is a particularly common feature. *Pneumocystis carinii* pneumonia and adenoviral pneumonia are found often in SCID foals and rarely in other foals.

53.3.3 Clinical Pathology

A consistent finding on the hemogram is an absolute lymphopenia, which is consistently less than 1000 lymphocytes/μL and often much lower. The total white blood cell (WBC) count may be low, normal, or elevated, depending on the neutrophilic response; thus it is imperative that the absolute number of lymphocytes be determined. Infected and other compromised foals, as well as some normal foals, have low lymphocyte counts during the first few days of life; therefore, the clinician should establish persistent lymphopenia before considering a diagnosis of SCID.[68,74]

Foals affected with SCID are unable to produce immunoglobulins. Therefore, levels of autologous serum immunoglobulin for age are abnormally low. However, quantitative immunoglobulin tests do not distinguish between autologously produced and maternal-origin immunoglobulin. Thus the degree of colostral transfer and the age of the foal must be considered when interpreting the serum immunoglobulin values (see Table 53-1). Some IgM is normally produced in utero by the foal, and some IgM should be present in presuckle serum.[75] Although not pathognomonic, the absence of IgM in presuckle serum is a feature of SCID. The presence of colostral antibody of maternal origin may mask low levels of autologous IgG and IgM, particularly early in life. The levels of maternal IgM in colostrum are lower than IgG, and the half-life of IgM is shorter (Table 53-2). Most maternal IgM received from colostrum is metabolized by about 3 weeks of age, whereas the age at which maternal IgG is gone is much more variable and may actually be months, depending on the original amount absorbed. The absence of serum IgM after 3 weeks of age is not pathognomonic but is consistent with SCID.

Foals affected with SCID do not respond to intradermal phytohemagglutinin (see p. 1667) by increasing skin thickness as do normal foals, nor do they respond to DTH stimulators, such as dinitrochlorobenzene.[76] In vitro tests such as blastogenesis are depressed with all mitogens.[77,78]

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The definitive diagnosis of SCID in foals of Arabian breeding is based on demonstrating that the foal is homozygous for the defective SCID gene.[71,79] Blood or cheek swabs may be submitted to VetGen for DNA testing to determine if a horse is clear, heterozygous, or homozygous for the gene defect. Before the advent of genetic testing, the criteria required to confirm a diagnosis of SCID included (1) persistent lymphopenia (<1000/μL), (2) absence of serum IgM in presuckle samples or samples collected after 3 weeks of age, and (3) thymic hypoplasia and characteristic histopathologic changes in lymphoid tissue.[80,81]

Table 53-2 Approximate Half-Life (in Days) of Immunoglobulin Classes in Large Animals

Species	IgG	IgM	IgA	IgG(T)
Equine	11.5-23	4-5	NA	20
Bovine	G1: 17 G2: 22	2.8	4.8	—
Sheep	G1: 14.5 G2: 10.6	1.8	4.1	—
Goat	G1: 13.2-17.2	NA	NA	—

From Perryman L: Personal communication, 1988.

NA, Not available.

53.3.4 Pathophysiology

Foals with SCID lack activity of the enzyme DNA-dependent protein kinase (DNA-PK) resulting from a mutation in the gene encoding the catalytic subunit.[79,82,83] The mutation results in a five—base-pair deletion in the gene on equine chromosome 9. Without functional DNA-PK, lymphocyte precursors are unable to complete gene rearrangement events that lead to the expression of antigen-specific receptors on lymphocyte surfaces. As a result, there is an absence of mature, functional T and B lymphocytes. Interferon-γ (EqIFN-γ), which is produced by lymphocytes, is deficient.[84]

Neutrophils, monocytes, and natural killer (NK) cells appear to be fully functional.[85,86] Complement levels are normal.[78] Although these nonspecific protective mechanisms appear to be intact, the absence of both cell-mediated and antibody-mediated immunity leaves the foal vulnerable to even innocuous infectious agents.

53.3.5 Epidemiology

SCID has been reported in Arabians in the United States, Canada, Australia, and Great Britain.[68,87,88] It is believed that the trait originated in a horse in Great Britain and was subsequently imported into the United States. The distribution of this disease provides a significant example of the *founder effect* in population genetics.

The prevalence of SCID at one time was estimated to be 2% to 3% of Arabian foals born in the United States. From this, it was predicted that the numbers of SCID carriers at that time could be as high as 25% of the U.S. Arabian horse population. A 1998 study of 250 randomly selected Arabian horses in the United States found the frequency of SCID gene carriers to be 8.4%.[88] Based on this finding, it was predicted that 0.18% of Arabian foals would be affected with SCID, assuming a random breeding population.

53.3.6 Necropsy Findings

It is imperative to evaluate lymphoid tissues grossly and histologically in cases of suspected immunodeficiencies. In SCID the thymus is small and has a fatty appearance on gross examination.[80] It is frequently difficult to locate, and mediastinal tissue often must be collected "blindly" for subsequent histologic evaluation and identification of thymic remnants. Histologically, the thymus is largely replaced with adipose tissue, with only islands of lymphoid cells and partially formed Hassall's corpuscles present. The gross appearance of spleen and lymph nodes may not be dramatically abnormal; however, they have very abnormal microscopic appearances, including absence of germinal centers and periarteriolar lymphocytic sheaths in the spleen, as well as absence of germinal centers with scarcity of lymphocytes in other areas of lymph nodes.

Bronchopneumonia is a common finding in SCID. Infectious lesions in other systems are also frequently found, including colitis and hepatitis.

53.3.7 Treatment and Prognosis

Affected foals invariably die by about 5 months of age, despite intensive conventional therapy (e.g., antimicrobials, plasma, isolation).

There is no practical method of curing affected foals at this time. Successful bone marrow transplants have been performed between histocompatible full siblings in a research setting, but this option remains impractical.[89]

53.3.8 Prevention and Control

Production of an affected foal identifies both sire and dam as carriers of the SCID gene.[70] Mating of two carriers of an autosomal recessive trait such as SCID is expected to result in one in four foals affected with SCID, one in four completely normal and not a carrier, and two in four asymptomatic carriers of the SCID trait. Mating of a carrier and a normal (noncarrier) does not produce any affected foals, but half the offspring would be expected to be carriers.

The disease can be controlled in horses of Arabian breeding by avoiding the production of affected foals, which has been simplified now that carriers can be identified by genetic testing. Mares and stallions intended for breeding should be tested to determine whether they are free or heterozygous for the defective SCID gene. Under no circumstances should two heterozygotes be mated to each other. If an owner decides to continue breeding a heterozygote, the breeding partner should be confirmed homozygous normal. All foals from such matings should be tested to determine if they are clear of or heterozygous for the defective gene (50/50 probability). Homozygous normal foals may be selected for future breeding purposes, whereas heterozygous foals should be managed for nonreproductive pursuits.

53.4 SELECTIVE IgM DEFICIENCY

53.4.1 Definition and Etiology

Selective IgM deficiency is an immunologic disorder characterized by absent or decreased serum IgM levels with normal or elevated levels of other immunoglobulin classes. Three presentations of the disorder have been described in horses.[90–93] The most common involves foals that have severe infectious pneumonia, arthritis, or enteritis, resulting in death before 10 months of age. The second involves foals with a history of repeated episodes of infections that respond to antimicrobial therapy but that recur when treatment is stopped. These foals tend to do poorly and are stunted, although they may survive for 1 to 2 years. The third involves older horses that are usually 2 to 5 years of age at initial diagnosis. These horses do not necessarily have problems with recurrent infections, but about half ultimately have lymphosarcoma.[94]

It is not known whether the IgM deficiencies reported in foals are primary or secondary. The levels of IgM present before the onset of infections have not been measured. The occurrence of multiple cases within groups of related horses suggests a genetic basis. However, breeding trials have been inconclusive to date with regard to the heritability of this condition. In humans, both primary and secondary selective IgM deficiencies are known. Secondary cases are often associated with neoplasia, immunologic diseases such as Wiskott-Aldrich syndrome, and gluten-sensitive enteropathies.

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53.4.2 Clinical Signs and Differential Diagnoses

Foals with selective IgM deficiency tend to have frequent *Klebsiella* infections of the respiratory tract, although enteritis and septic arthritis may also be complicating infections. The age of onset of clinical signs may be slightly later than in foals with SCID and certainly later than in foals with FPT.

Older horses with IgM deficiency should be carefully evaluated for lymphoid neoplasia, including palpation of peripheral and internal lymph nodes. Weight loss, depression, and other nonspecific signs frequently accompany lymphosarcoma (see Chapter 37).

53.4.3 Clinical Pathology

The only significant immunologic abnormality is a low or absent serum IgM. IgM levels are more than 2 standard deviations below the age-specific mean IgM level (see Table 53-1). Other classes of immunoglobulin are generally within normal limits or elevated for age. It is advisable to document that IgM levels are persistently depressed rather than to base a diagnosis on a single sample, because IgM levels may sporadically decrease in seriously ill foals but return to normal with recovery. Lymphocyte counts and other in vitro immunologic tests are generally normal, and these features serve to differentiate selective IgM deficiency from other immunodeficiency conditions. In one horse with selective IgM deficiency, however, lymphocytes failed to respond to the B-cell mitogen lipopolysaccharide (LPS), whereas response to the T-cell mitogens concanavalin A (ConA) and phytohemagglutinin (PHA) was normal.[93] The hemogram and biochemical profile may reflect infection or inflammation, depending on the underlying infectious process (e.g., neutrophilia, hyperfibrinogenemia, anemia) and the organ system involved, but no diagnostically specific changes occur.

53.4.4 Pathophysiology

Whether IgM is low because of decreased production, hypercatabolism, or loss is not known. In one case with lymphosarcoma, suppressor activity was identified in the neoplastic cells, suggesting that the low IgM may be a result of suppression of B-cell function by neoplastic cells. Selective IgM deficiency has been most frequently reported in Arabians and quarter horses, although it affects other breeds as well.

53.4.5 Necropsy Findings

Lymphoid tissue in affected foals is grossly and histologically normal. Pneumonia is usually present and is frequently caused by *Klebsiella* infection. Other findings reflect secondary infections.

53.4.6 Treatment and Prognosis

Selective IgM deficiency has an unfavorable prognosis. Most horses eventually succumb to infection despite appropriate antimicrobial therapy. Plasma therapy may provide short-term benefit, but only small amounts of IgM are contained in transfused whole plasma, and the half-life of transfused IgM is probably quite short. No concentrated IgM preparations are commercially available for parenteral use. Relief, at best, can be considered only temporary. However, the outcome of these cases seems less certain than with SCID foals, and a rare case recovers. If persistently low IgM levels can be documented, a poor to grave prognosis can be expected.

53.4.7 Prevention and Control

Because some cases of selective IgM deficiency might be hereditary, it may be advisable to avoid repeating the mating that produced the affected foal. However, no firm recommendations can be made.

53.5 TRANSIENT HYPOGAMMAGLOBULINEMIA

53.5.1 Definition and Etiology

Transient hypogammaglobulinemia is a rare disorder characterized by the delayed onset of immunoglobulin synthesis by the neonate.[5,95] Foals normally begin to produce significant amounts of immunoglobulins at birth, when they are first exposed to environmental antigens (see Fig. 53-4). Assuming adequate passive transfer, maternal antibody fills the void from birth until the foal has produced sufficient autologous antibody for protection (e.g., first 1 to 2 months). In transient hypogammaglobulinemia the onset of autologous production is delayed for unknown reasons and may not begin for as long as 3 months. As maternal immunoglobulins wane, for a time the production of autologous antibody is insufficient to be protective, making the foal highly susceptible to infections.

The disorder has been described in an Arabian and a thoroughbred foal, but the low number of reported cases may not accurately reflect the prevalence. To make a diagnosis, serial samples are required to document decreasing maternal immunoglobulin and subsequent increasing autologous immunoglobulin. Many cases probably occur that are not followed this closely.

53.5.2 Clinical Signs and Differential Diagnoses

As with other immunodeficiency disorders, recurrent episodes of bacterial and viral infections are characteristic of transient hypogammaglobulinemia.

53.5.3 Clinical Pathology

The cardinal feature is low immunoglobulin levels.[5,23,95] At approximately 2 to 4 months of age, the concentrations of all classes of immunoglobulin, particularly IgG and IgG(T), are substantially below the means when age-matched. At this stage, maternal antibody will have waned, but the foal should have produced significant quantities of autologous antibody, regardless of whether passive transfer occurred. Affected foals have normal cell-mediated responses in vitro and in vivo and appear to be able to respond to immunization with some antigens. Normal numbers of B cells are present in blood and lymph nodes.

Differentiation between FPT and transient hypogammaglobulinemia is based on the age of the patient at evaluation. Transient hypogammaglobulinemia must be differentiated from agammaglobulinemia. Both disorders have normal lymphocyte counts and responses to PHA skin testing and show waning levels of maternal IgG and IgG(T) if followed serially. However, transient hypogammaglobulinemia cases usually have low but detectable levels of IgM and IgA, whereas agammaglobulinemia cases usually have no detectable levels. Differentiation between the two may require serial sampling to show that immunoglobulin production does ultimately increase in the patient with transient hypogammaglobulinemia.

53.5.4 Necropsy Findings

No specific gross or microscopic lymphoid changes have been associated with transient hypogammaglobulinemia. Necropsy findings reflect the secondary infectious processes that have affected the foal.

53.5.5 Treatment and Prognosis

The goal of therapy is to minimize infections until the foal's immune system begins to function properly. Treatment should include antimicrobial therapy and plasma transfusions. Bacterial infections may be manageable with antibiotics alone, but the effects of viral infections may be more difficult to manage and may be helped by plasma transfusions.

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53.6 AGAMMAGLOBULINEMIA

53.6.1 Definition and Etiology

Agammaglobulinemia is a rare primary immunodeficiency disorder of horses. It is characterized by complete B-cell dysfunction with an intact cell-mediated response. This condition has been observed only in males, suggesting the possibility of an X-linked disorder. It has been described in thoroughbreds, quarter horses, and standardbreds.[23,96–98] Agammaglobulinemia in a young boy was the first immunodeficiency disorder described in any species, and in human patients it is now known to be inherited as an X-linked trait.[99]

Horses with agammaglobulinemia illustrate the significant contribution of T and B lymphocytes to the maintenance of good health. Horses with defects in both B-cell and T-cell functions (e.g., SCID) seldom survive to 5 months of age, whereas the cases with a pure B-cell defect such as agammaglobulinemia have survived between 1 and 2 years. Recently, agammaglobulinemia with a lack of circulating B cells was diagnosed in a Pinto gelding that did not exhibit recurrent pyogenic infections until 3 years of age. Although it could not be established whether the immunodeficiency was primary or secondary, an underlying disease process was not identified.*

* VetGen, Ann Arbor, MI; 800-4-VetGen; www.vetgen.com.

53.6.2 Clinical Signs and Differential Diagnoses

No outward physical signs suggest agammaglobulinemia other than the opportunistic infections that develop. Frequently, recurrent infections of the respiratory tract or joints with extracellular bacteria have been reported. Dermatitis, enteritis, and laminitis have also been associated with this disease.

53.6.3 Clinical Pathology

Total peripheral blood lymphocyte counts are within the normal range. However, there is a lack of circulating B cells with normal numbers of T cells. Neutrophil counts may be normal, low, or high, depending on the response to infection. No specific changes are noted in the biochemical profile. Serum levels of IgM, IgA, IgG(T), and IgG are persistently low or absent. Depending on the age at evaluation, maternal antibody may be present, but its decline is evident if sampled serially. The continued presence of low levels of immunoglobulin in these foals may be explained by the prolonged catabolism of antibody or by some residual B-cell activity, as in human patients with sex-linked agammaglobulinemia.[23,96–99]

Specific antibody responses are depressed, both for antigens to which horses naturally tend to produce antibodies, such as sheep RBCs, and for antigens administered by planned immunization, such as vaccines. Cell-mediated tests are essentially normal, including blastogenesis and DTH skin testing. Total hemolytic complement activity is also normal.

53.6.4 Pathophysiology

The molecular basis of agammaglobulinemia in horses is unknown, but a defect at the stem cell level that blocks early B-cell differentiation is suspected because all classes of immunoglobulin are affected. In human patients a mutation in BTK, a gene encoding tyrosine kinase, accounts for the disease. Assessment of the BTK gene in horses may help in understanding this disorder.

53.6.5 Necropsy Findings

Gross lymphoid changes in lymph nodes, spleen, and thymus have been observed. Lymph nodes are small. The thymus may be small and difficult to locate. Lymphoid tissue taken from the mediastinal region where the thymus should be found lacks the defined lobular structure of normal thymus. The spleen grossly may be small and contracted. Microscopically, lymph nodes are devoid of germinal centers and follicles. The spleen has no germinal centers, periarteriolar lymphocytic sheaths, or plasma cells.

The thymus does not show recognizable epithelial structure and lacks defined nodules.[23,98] Why cell-mediated functions are normal while the architecture of the thymus is so abnormal remains unexplained.

53.6.6 Treatment and Prognosis

In the absence of production of autologous antibody, affected horses respond poorly to infections over the long term. Antimicrobial therapy and administration of plasma may temporarily control infections; however, the long-term prognosis is poor.

53.7 FELL PONY SYNDROME: ANEMIA, IMMUNODEFICIENCY, AND PERIPHERAL GANGLIONOPATHY

53.7.1 Definition and Etiology

A congenital fatal syndrome characterized primarily by severe anemia and immunodeficiency has been identified in Fell Pony foals.[100] In addition, peripheral ganglionopathy has been reported in some cases. Both genders are affected. The exact nature of the defect is as yet unknown, but an intrinsic genetic disorder transmitted by a single autosomal recessive gene is suspected.[101] The Fell Pony is considered an endangered breed by the Rare Breeds Survival Trust, with an estimated 5000 animals worldwide. Originally described in Fell Ponies in the United Kingdom, Fell Pony syndrome has also been found in the Netherlands and North America.[100–102]

53.7.2 Clinical Signs

Affected Fell Pony foals typically develop signs of decreased suckling, diarrhea, cough, and chewing motions beginning at 2 to 3 weeks of age.[100–102] The foals progressively lose condition and develop pale mucous membranes. The condition is generally fatal by 4 to 12 weeks of age. Opportunistic infections such as cryptosporidial enteritis, adenoviral pancreatitis, and adenoviral bronchopneumonia are frequently observed in affected foals and suggest an underlying immunodeficiency.

53.7.3 Clinical Pathology

Foals develop severe normocytic to macrocytic anemia associated with small numbers of erythroid precursor cells in the bone marrow.[100–102] Myeloid/erythroid ratios in the bone marrow have ranged from 21:1 to 62:1. Although total circulating lymphocyte counts are variable, lymphopenia is described in some cases. Numbers of both $CD4^+$ and $CD8^+$ T lymphocytes are normal, but numbers of B cells are decreased.[103,104] Consistent with this B-cell lymphopenia, serum immunoglobulin concentrations are often decreased once concentrations of maternal antibodies have declined.[102–104] Because maternally derived concentrations of IgM and IgA generally do not persist as long as IgG, concentrations of these antibodies are more likely to reflect production by the foal. The responses of lymphocytes to in vitro stimulation with mitogens have been variable.[105]

At this time, no definitive test is available for the diagnosis of Fell Pony syndrome, and diagnosis is based on the signalment, history, clinical signs, and laboratory findings, including anemia, B-cell lymphopenia, and low concentrations of IgM after 4 weeks of age. 1674 1675

53.7.4 Pathophysiology

The precise nature of the immune defect is unknown, and thus far the characteristics identified do not conform to any known immunodeficiencies in other species. In addition to the decrease in circulating B cells, immunohistochemical staining reveals decreased B cells in the bone marrow, lymph nodes, and primary follicles of the spleen. Although analyses of cellular immunity and phagocytic activity have not revealed any consistent abnormalities, the severity of disease has led to speculation that multiple arms of the immune system are affected. The anemia is associated with severe erythroid hypoplasia of the bone marrow.

53.7.5 Necropsy Findings

The absence of secondary lymphoid follicles and lack of plasma cells on histologic examination is characteristic of the condition. There is also marked erythroid hypoplasia in the bone marrow. In some cases, peripheral ganglionopathy is seen, characterized by neuronal chromatolysis and nuclear pyknosis of the trigeminal, cranial mesenteric, or dorsal root ganglia. Other common necropsy findings include abnormalities associated with infections characteristic of immunodeficiency, particularly infections with *Cryptosporidium parvum* and adenoviral infections of the pancreas and bronchial tree.

53.7.6 Treatment and Prognosis

Affected foals respond poorly to treatment for infections and anemia.[100–102] They generally die by 12 weeks of age.

53.8 COMMON VARIABLE IMMUNODEFICIENCY

53.8.1 Definition and Etiology

Common variable immunodeficiency (CVID), a heterologous syndrome of immunodeficiency, has been described in four horses.[106,107] It has also been suspected in additional horses with varying immunologic deficits.[108–110] CVID was initially defined in human patients, and although the syndrome is highly variable, recurrent bacterial infections and hypogammaglobulinemia are common characteristics.[111,112] CVID has also been reported in miniature dachshunds with *Pneumocystis carinii* pneumonia.[113]

53.8.2 Clinical Findings

Information on CVID in horses is limited because of the small number of cases. The syndrome has been identified in various breeds and both genders and is characterized by a late onset, with horses ranging in age from 6 to 14 years.[106,107] In human patients the disorder affects both men and women and can develop at any age, although the onset is most frequently seen during the second or third decade of life.[111,112]

Recurrent bacterial infection is common in CVID. Three horses with CVID diagnosed with presumptive bacterial meningitis were successfully managed medically with antibiotic therapy without immunoglobulin replacement therapy.[107] Another horse with CVID presented with infection of the guttural pouch and cholangiohepatitis and was ultimately euthanized because of deterioration in the horse's condition.[106] The clinical spectrum of CVID in human patients is broad, and as expected, clinical disease is more severe in patients with more marked immunologic abnormalities.[111,112]

53.8.3 Immunologic Findings

Common features of CVID in affected people include recurrent bacterial infections and agammaglobulinemia or hypogammaglobulinemia, particularly involving IgM and IgG.[111,112] The humoral response to vaccination is generally impaired. B-cell maturation may be arrested at various stages, and B-cell numbers may be normal or decreased. T-cell abnormalities may also be present. As in human patients, immunologic abnormalities identified in affected horses include hypogammaglobulinemia and failure to respond to immunization.[106,107] The type and severity of the hypogammaglobulinemia vary; IgM deficiency is common. Affected horses have an abnormal lymphocyte distribution characterized primarily by B-cell lymphopenia. The lymphocyte response to mitogens varies but generally is decreased. Phagocytosis, oxidative burst activity, and serum opsonization capacity were normal in three horses tested.

The variable immunologic abnormalities associated with CVID make it difficult to define cases, and it has been suggested that additional cases of recurrent bacterial infections and immune abnormalities may represent variations of CVID. An adult Paso Fino mare with proliferative interstitial pneumonia and *Pneumocystis carinii* infection was found to have a complete lack of IgM, low concentrations of IgG, and decreased numbers of immune cells expressing major histocompatibility complex (MHC) class II cell surface antigens.[108] In another case, a 3-year-old quarter horse with chronic diarrhea and bacterial pneumonia was diagnosed with an acquired B-lymphocyte deficiency associated with deficiencies in serum IgG, IgA, and IgM and a concurrent decrease in T-cell function.[109] Additional cases with hypogammaglobulinemia and other immunologic abnormalities may fit the description of CVID.[93,110,114]

53.9 UNCLASSIFIED AND SECONDARY IMMUNODEFICIENCIES

Many equine patients with evidence of immunologic defects cannot be placed in a currently recognized immunodeficiency category. These animals form a diverse group that may seem to have little in common except the propensity to develop infections. Attempts to further classify these cases have been hampered by the lack of specific, practical tests that precisely define the immunologic defect. As newer testing methods are developed, this group will eventually be defined. Numerous immunodeficiency syndromes are described in humans, the counterparts of which can be reasonably assumed to exist in horses. As previously discussed, some of the previously unclassified immunodeficiencies characterized primarily by hypogammaglobulinemia are now suspected to be a form of CVID.[93,107–110,114] Also, a $CD4^+$ and $CD8^+$ T-lymphocytopenia has been described in a filly with *Pneumocystis carinii* pneumonia.[115]

Numerous endogenous and exogenous factors can cause secondary immunodeficiency or suppression.[7] These include malnutrition, specific nutrient deficiencies or excesses, microbial and parasitic agents, corticosteroids and other hormones or drugs, and neoplasia. In addition, factors such as age and pregnancy can influence the immune system. Stress, such as that associated with exercise or transport, may also have immunomodulatory effects. To

complicate the issue, many of these factors can induce either suppression or stimulation under appropriate circumstances; thus their presence alone is not adequate to confirm immune compromise. In general, the effects of these factors on the immune system can be assessed by the same tests used to classify primary immunodeficiencies. Distinguishing the role of these factors from more subtle types of primary immunodeficiency is difficult.

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53.9.1 Adult Acquired Immunodeficiency

A 7-year-old Appaloosa gelding with no history of prior illness became lethargic, anorexic, and dyspneic.[114] *Rhodococcus equi* septicemia was diagnosed on the basis of blood cultures. Immunologic evaluation of the patient revealed lymphopenia, low IgM and IgA concentrations, marginally low IgG concentrations, low *R. equi* antibody titer, negligible response to lymphocyte stimulation, histologic depletion of the lymphoid tissue, and failure to respond to antigenic stimulation. Marked thrombocytopenia was also present. These abnormalities suggested suppression of both humoral and cell-mediated arms of the immune system. The age of the horse, absence of previous history of illness, and histopathologic findings suggestive of atrophy of lymphoid tissue indicated the immunodeficiency was acquired. No underlying cause was identified for the immunodeficiency; specifically, no neoplasms were identified at necropsy, and there was no history of exposure to immunosuppressive toxins. This may represent CVID.

53.9.2 Infectious Disease

Secondary immune suppression can result from a variety of infectious or inflammatory diseases. Many viral, fungal, and bacterial infections transiently suppress specific and nonspecific immune responses, predisposing to secondary bacterial infections.[116] Severe endotoxemia or septicemia may suppress neutrophil numbers and bactericidal function.

53.9.3 Perinatal Equine Herpesvirus Type 1 Infection

Infection of the fetus with equine herpesvirus type 1 (EHV-1, rhinopneumonitis) late in gestation has been associated with postnatal development of interstitial pneumonia, lymphopenia, marked necrosis and atrophy of the thymus and splenic lymphoid tissue, and increased susceptibility to bacterial infections.[117] Affected foals may be either weak or normal at birth. Despite apparently adequate passive transfer of maternal antibody, affected foals contract a variety of infectious bacterial diseases, including colibacillosis, streptococcal septicemia, salmonellosis, and Tyzzer's disease. EHV-1 is isolated from nasal passages of about 30% of the cases. The spleen and thymus are grossly small at necropsy. Bilateral adrenocortical hyperplasia is noted in most foals. Histologically, splenic periarteriolar lymphocytic sheaths are depleted of lymphocytes, and no lymphoid follicles are detectable. Thymic alterations vary from extreme diminutions of thymocyte numbers to complete necrosis of thymic lymphocytes with disappearance of Hassall's corpuscles and disruption of the epithelial matrix. Lymph nodes also show lymphoid necrosis.

An immunodeficiency secondary to the marked lymphoid damage induced by the virus is credited with allowing secondary bacterial infections to become established. Immunization of broodmares against EHV-1 would seem to be the most appropriate approach to prevention.

53.9.4 Immunodeficiency Associated with Oral Candidiasis and Bacterial Septicemia

53.9.4.1 Definition and Etiology

A group of foals with laboratory or histologic evidence of immunodeficiency that did not fit into any recognized category of primary immunodeficiency have been described with oral candidiasis and bacterial septicemia.[118] The foals shared no consistent pattern of in vitro immunologic abnormalities, but all had the clinical features of oral candidiasis and bacterial septicemia. This syndrome has some similarities to mucocutaneous candidiasis in people, which has been associated with several different subtle T-cell defects. Not all human cases are thought to result from a single immunodeficiency disorder. Candidiasis does not occur in the presence of B-cell defects alone, or in the absence of T-cell defects.

53.9.4.2 Clinical Signs

Most affected foals with oral candidiasis were about 4 months of age at onset, although several were less than 2 weeks old.[118] Oral lesions ranged from discrete, focal, white, plaquelike lesions on the margins of the tongue to a generalized, thick, white, pseudomembranous coating covering the tongue and gingival mucosa. Most foals exhibited bruxism, ptyalism, fever, and depression. Other significant clinical problems included pneumonia, septic arthritis, and diarrhea. This syndrome should be distinguished from the glossitis caused by *Candida* infection seen in inappetent or debilitated neonatal foals, which is fairly common and generally resolves with amelioration of the primary disease.[119]

53.9.4.3 Clinical Pathology

Serum IgG and IgM levels were variable, but most of the older foals also had low or marginal IgG or IgM for their age.[118] The younger foals all had FPT and low IgG levels. Some horses showed a transient lymphopenia, but lymphocyte counts were generally within normal limits. Almost all cases had other abnormalities, including depressed blastogenesis, suggesting a cellular defect distinct from previously described immunodeficiency cases that involved only immunoglobulin production.

53.9.4.4 Necropsy Findings

Thymic tissue was difficult to locate grossly at necropsy.[118] Mediastinal tissue collected in the thymic region was confirmed to be thymus microscopically in only one of six cases. Histologically splenic lymphoid depletion was present. Evidence of disseminated bacterial infections included pulmonary abscesses, enteritis, septic arthritis, and focal hepatitis. *Candida* species were identified in tissues histologically or with culture in all cases. A variety of bacterial organisms were associated with the septicemias and secondary infections. Organisms usually considered minor pathogens, such as *Acinetobacter* and adenovirus, were identified in some cases.

53.9.4.5 Treatment and Prognosis

Affected foals did not respond to extensive parenteral antibiotic, topical antimycotic, or plasma transfusion therapy. Because antibiotic administration can predispose animals to secondary candidiasis, the role that

antibiotic therapy may have played in the development of the oral lesions was considered. In light of the high frequency of antibiotic use in foals in the general population and the uncommon occurrence of oral candidiasis, additional factors such as an underlying immune defect are deemed likely. Whatever the cause, the prognosis for foals with oral candidiasis and associated bacterial septicemia is guarded to poor.

53.9.5 Neoplasia

Neoplastic disease can impair cell-mediated and humoral immune responses as a result of an abnormal bone marrow environment, altered patterns of cytokine production or release, or impaired proliferative responses (anergy). In horses, immunodeficiency has most often been described in association with lymphosarcoma or plasma cell myeloma.

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53.9.5.1 LYMPHOSARCOMA

Immunodeficiency has been identified in some cases of equine lymphosarcoma. The immunologic abnormality most often described is a decrease in the concentrations of serum immunoglobulins, especially IgM.[94,120–123] In addition, decreased lymphocyte blastogenesis in response to mitogens has been reported. Some horses with lymphosarcoma have been diagnosed with concurrent bacterial infections, which may be related to immunosuppression.[122,123] A horse with myelomonocytic leukemia was found to have pulmonary aspergillosis.[124]

53.9.5.2 PLASMA CELL MYELOMA

Plasma cell myelomas have been diagnosed in horses of several breeds.[125] Although reports of the condition are limited, there appears to be no gender predilection. Horses have ranged in age from 3 months to 22 years (median, 11 years) at diagnosis. Common clinical signs include weight loss, anorexia, fever, pneumonia, and limb edema. As a malignancy of plasma cells or lymphocytoid plasma cells, plasma cell myelomas typically produce large quantities of a homogenous immunoglobulin or immunoglobulin fragment, resulting in a monoclonal gammopathy. In both equine and human cases of myeloma, the predominant serum globulins are generally subclasses of IgG.[125,126] Hyperglobulinemia is a characteristic but not invariable finding. Monoclonal gammopathies in the horse have also been reported with lymphoma and benign disorders.[127,128] Both equine and human patients with plasma cell myelomas have an increased susceptibility to bacterial infections, probably as a result of a secondary immunodeficiency.[125,126,129] The concentrations of normal polyclonal immunoglobulins are generally decreased in myeloma patients as a result of several mechanisms, including decreased synthesis and accelerated catabolism of antibody and suppressed clonal expansion of B cells.[125,126,129] Decreased numbers of neutrophils, which may also be dysfunctional, and defective complement activation may also contribute to the impaired immune function.

53.9.5.2.1 Corticosteroid-Induced Immunosuppression

Increased concentrations of corticosteroids can result in varying degrees of immunosuppression. The increase in corticosteroids may be associated with stress or disease, most often pituitary pars intermedia dysfunction. In addition, corticosteroid treatment is the most common iatrogenic cause of immunosuppression. Increased concentrations of corticosteroids may exacerbate preexisting infectious diseases or decrease resistance to environmental pathogens.[130,131]

Corticosteroids have a number of effects on the immune system, many of which are dose dependent. They may suppress macrophage phagocytic function by impairing the killing of ingested microorganisms, decreasing secretion of monokines, and inhibiting antigen processing and presentation. Corticosteroids suppress cell-mediated immunity through induction of a T-cell lymphopenia, suppression of proliferation in response to mitogen stimulation, altered cytokine production, and decreased antigen presentation. Humoral immunity may be affected through impaired T-cell responses, enhanced catabolism of immunoglobulins, and decreased antigen presentation.[132,133]

53.9.5.2.2

Exercise

Exercise can clearly act as a stressor that may significantly alter the immune response.[134,135] However, defining the precise effects of exercise on the equine immune system and susceptibility to disease has been difficult because of the complexity of the immune system, host factors (e.g., age, level of fitness), and the variable nature of exercise.[134–136] In general, it appears that exercise may have both positive and negative effects on the immune response.[134–140] Suppressive effects, such as a decline in the ratio of $CD4^+$ to $CD8^+$ T cells, decreased lymphoproliferative responses, and suppression of the innate immune system, have been associated with strenuous high-intensity exercise, prolonged exhaustive exercise, or overtraining. In contrast, moderate exercise tends to have beneficial effects on the host defense mechanisms.

Data in horses directly linking exercise-induced immunosuppression and increased susceptibility to infectious disease are limited. However, the potential immunosuppressive effects of exercise need to be recognized. In one study, unconditioned ponies vaccinated with a killed influenza vaccine and subjected to 5 days of strenuous exercise had an increased susceptibility to clinical influenza after challenge exposure compared with rested ponies.[141] However, ponies with exercise-induced immunosuppression responded to the administration of an intranasal modified-live equine influenza vaccine and were protected from challenge.[142] In a study of influenza infection in trained horses, moderate exercise led to increased signs of clinical disease, but the duration of disease was unaffected.[143]

53.9.5.2.3

Age

Age has been shown to affect immune function in multiple species. The increased vulnerability of foals to respiratory tract infections, especially with specific pathogens such as *Rhodococcus equi,* is thought to reflect an innate immunodeficiency.[144] Although foals are immunocompetent at birth, it is likely that their immune responses differ from those of adults.[144–146] Recently it has been shown that newborn foals have a diminished ability to express the interferon-gamma (IFN-γ) gene and produce IFN-γ protein.[146] This ability increases steadily, reaching adult levels with the first year of life. These findings suggest that foals have an inherent inability to mount a Th1 immune response, which may contribute to their susceptibility to intracellular pathogens.

Aging may also be associated with a relative immunodeficiency. Data in horses are limited, but older horses have been shown to have lower proliferative responses to mitogens and antibody titers than younger horses.[136–147] However, older horses were more resistant to exercise-induced immune suppression than younger horses. The high prevalence of pituitary pars intermedia dysfunction in older horses is thought to be a risk factor for infectious disease, possibly because of elevated steroid concentrations.

53.10 RUMINANT IMMUNODEFICIENCY DISEASES

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53.11 FAILURE OF PASSIVE TRANSFER

53.11.1 Definition and Etiology

At birth, ruminants leave the sterile uterus and are exposed to an environment laden with pathogens. Although capable of mounting a measurable immune response at birth or even earlier, neonates are best characterized as being "immunonaive." A neonate's ability to mount a protective immune response is hindered by the immaturity of the immune system and the delay between initiation of response and effective protection. Unless adequate maternal immunologic assistance is provided, neonates have an increased likelihood of succumbing to infectious diseases such as septicemia, diarrhea, enteritis, omphalitis, arthritis, and respiratory conditions.

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Neonatal ruminants are protected against disease from infectious agents through passive transfer of maternal immunity by consumption of colostrum. The concept of failure of passive transfer (FPT) has largely been used to describe a neonate that does not absorb adequate levels of immunoglobulin. Immunoglobulins are a significant component of colostrum and have been the most studied constituent of colostrum. However, colostrum is a complex fluid that, in addition to immunoglobulins, contains high numbers of immune cells, immunoactive substances such as cytokines, and nutritional elements.[148]

Successful passive transfer of immunity can be defined as the timely ingestion and absorption of an adequate mass of colostral immunoglobulins (primarily IgG1 in calves), and possibly other colostral components as well. Successful passive transfer has been quantitatively defined as calves that have attained greater than 10 mg/mL serum IgG1 by 48 hours of age.[149] The levels of serum immunoglobulins defining successful passive transfer are simply guidelines derived from statistical analysis of large populations. Numerous factors interact with the level of passively acquired immunoglobulin to determine the occurrence of disease, including management, environment, hygiene, infection pressure, virulence of infectious organisms, and antibody specificity. Although neonates with FPT are at increased risk for disease, having low serum immunoglobulin does not necessarily guarantee disease if the neonate resides in a clean environment or does not interact with highly virulent organisms. Alternatively, neonates with adequate passive transfer can readily develop disease if exposed to an environment with a high pathogen load or highly virulent organisms.

53.11.2 Mechanism of Passive Transfer

Two distinct processes must occur for adequate passive transfer of maternal immunoglobulins through colostrum. The first process, *colostrogenesis,* is the transport of immunoglobulin from maternal serum into colostrum during the last 4 to 6 weeks of gestation and is largely controlled by lactogenic hormones.[150–152] Studies in cattle have demonstrated that the mechanism of immunoglobulin transfer involves an active, IgG1-specific, receptor-mediated process.[153]

The second process involves the transport of colostral IgG1 from the gut lumen into the neonate's system. This process is not selective for specific immunoglobulin isotypes and does not appear to differentiate between most macromolecules. Specific receptors for immunoglobulins are absent in the calf's gut; rather, transport occurs through nonselective pinocytosis. Absorption is initiated by the presence of macromolecules but declines over the first 24 hours of life[154]; absorption is finite and decreases regardless of macromolecules being present.[155,156] The absorptive process also appears to be saturable; efficiency of immunoglobulin absorption decreases with increasing immunoglobulin concentration in the colostrum being fed.[157] Presumably, because all macromolecules compete for the same absorptive process, the mass of immunoglobulin absorbed by the calf would be inversely proportional to the concentration of nonimmunoglobulin macromolecules present in the gut lumen.

53.11.3 Epidemiology

The percentage in calves with FPT at 24 hours of age varies from 15% to 68%.[158] Similar findings have been recorded in other neonatal ruminants. In one report comparing FPT in beef calves and diary calves, rates of 5% and 39% were reported, respectively.[159] Several interrelated factors account for the varying incidence of FPT, including the formation of colostrum with an adequate immunoglobulin concentration, ingestion of an adequate mass of immunoglobulin, and absorption of immunoglobulin in a timely manner.

53.11.4 Formation of Colostrum with Adequate IgG1 Concentration

The mass of immunoglobulin presented to the neonate for absorption depends on the colostral immunoglobulin concentration and volume of colostrum available. The volume of colostrum produced by the cow is usually not a limiting factor.[160] However, colostrums have varying immunoglobulin concentration; IgG1 concentration in beef cow colostrum is two to three times greater than that of dairy cow colostrum.[161–164] Significant differences exist not only among different breeds but also among cattle within a specific breed.[165] Lactation number also influences IgG1 concentration in colostrum, although this variation is less than between cows or breeds.

Colostrum with low immunoglobulin concentration, resulting in ingestion of an inadequate mass of immunoglobulin, is a primary cause of FPT in dairy calves.[161] In contrast, FPT in beef calves is unlikely to result from low colostral IgG1 concentration.

53.11.5 Ingestion of Adequate Mass of IgG1

Depending on the environment and pathogen load to which they are exposed, calves must ingest an adequate mass of IgG1 to obtain protective immunity. Although the actual mass of immunoglobulin needed for protection depends on many factors, studies suggest that for a 45-kg calf to attain a serum IgG1 concentration greater than 10 mg/mL, it must consume approximately 100 g of IgG1 in the first hours of life.[166] Consumption of 100 g colostral IgG1 ultimately depends on colostral volume and IgG1 concentration. A calf provided colostrum with 35 mg/mL IgG1 would need to consume approximately 3 L in the first 12 to 24 hours, whereas a calf provided colostrum with 100 mg/mL IgG1 must consume only 1 L. An accepted recommendation for attaining adequate passive transfer in diary calves is to administer 4 L of colostrum in the first 12 hours of life.[166]

Concentration of colostral immunoglobulin is rarely a significant factor leading to FPT in beef calves. Instead, factors such as mismothering, poor udder conformation, and environmental stresses are more significant in preventing beef calves from ingesting the colostrum. Other factors that may affect passive transfer in beef calves have been reviewed.[167] There is little evidence to suggest a direct effect on passive transfer when beef cows are fed protein- or energy-restricted diets. Dystocia does not appear to affect passive transfer of immunoglobulins as long as the calf receives an appropriate mass of immunoglobulin in a timely manner.

Young age of the dam is a risk factor for FPT, likely because of lower colostral immunoglobulin concentration in heifer colostrum (beef and dairy) and poorer mothering ability.

53.11.6 Timely Absorption of IgG1 by Gut

Cessation of absorption of colostral immunoglobulins (closure) occurs at approximately 24 hours of age.[154,168] If colostrum is completely withheld, closure will still occur by 30 hours of age.[155,156] Closure is minimally affected by stresses such as dystocia or cold environmental temperatures, although extremely high environmental temperature has been associated with reduced immunoglobulin absorption in calves.[154,169] In a study comparing three different feeding methods of colostrum to dairy calves, FPT was more prevalent with sucking than artificial feeding methods, presumably because of inadequate colostrum volumes ingested by calves.[166] That is, dairy calves consuming relatively low IgG1 concentration colostrum did not consume adequate volumes of colostrum to obtain 100 g of IgG1 in a timely manner. When artificial feeding methods are used, inadequate immunoglobulin concentration in the colostrum is the most important factor resulting in FPT, even when calves are fed in a timely manner.

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53.11.7 Mothering

Mothering has been associated with increased efficiency of absorption of colostral immunoglobulins. This may simply be a result of the dam's presence or may be related to the effect of the neonate physically suckling the dam.[154]

53.11.8 Clinical Signs and Laboratory Findings

Although not diagnosed by physical examination, FPT is typically suspected based on physical findings. Young ruminants devoid of passive immunity are highly susceptible to bacterial septicemia.[158,170] Clinical signs of bacteremia include central nervous system (CNS) depression, weakness, injected scleral vessels, rapid or labored respiration, diarrhea, and anorexia. Fever may or may not be present. Septic arthritis, meningitis, and panophthalmitis frequently develop in many neonates with FPT that survive the initial challenge of bacteremia. Diarrhea can also result from a number of dietary and infectious agents in neonatal ruminants with normal serum immunoglobulin levels.[171] Historical information of clinical disease may lead to a high degree of suspicion that FPT is present.

There are no consistent changes in the hemogram or biochemical panel of a neonatal ruminant with FPT. Abnormal laboratory findings usually reflect secondary processes involving sepsis, stress, or starvation. Laboratory evaluation is necessary to assess the degree of passive transfer.

53.11.9 Measurement of Passive Transfer

Several methods are available to measure passive transfer of immunity either directly or indirectly. The greatest degree of accuracy is obtained if the tests are performed during the first week of life, and most tests are optimized when serum samples are collected between 24 and 48 hours of age. After this period, neonates begin to synthesize significant amounts of immunoglobulins, although a tentative decision can still be made as to the degree of passive transfer that occurred after birth. Any question about the status of passive transfer in a newborn should trigger laboratory evaluation of the animal so that corrective measures can be undertaken.

Single radial immunodiffusion (RID) quantitatively measures serum IgG1 and is considered the standard in cattle. The semiquantitative methods for estimating passive transfer (zinc sulfate turbidity, sodium sulfite precipitation, glutaraldehyde coagulation, total serum solids) are based on the fact that IgG1 normally accounts for the majority of passively transferred proteins in colostrum. Measurement of serum γ-glutamyltransferase (GGT) is based on the findings that mammary secretory alveolar epithelial cells can secrete large amounts of GGT during colostrogenesis and that GGT is readily absorbed by the neonate before gut closure.

53.11.10 Single Radial Immunodiffusion

Quantification of each immunoglobulin class that is transferred can be determined using specific, commercially available antisera. Forty-eight-hour serum concentrations of less than 1000, 80, and 22 mg/dL for IgG, IgM, and IgA, respectively, are consistent with FPT.[160]

53.11.11 Zinc Sulfate Turbidity

Specific concentrations of zinc sulfate precipitate immunoglobulins.[149,172] Historically, a defined volume of serum (0.1 mL) is added to zinc sulfate solution (6 mL) containing 208 mg of $ZnSO_4 \cdot 7H_2O$ per liter, and the solution is allowed to incubate at room temperature for 1 hour. The turbidity of the solution is then evaluated visually or with spectrophotometric methods.[149] A decrease in or an absence of turbidity (precipitation) indicates failure of immunoglobulin absorption.

A study by Tyler et al.[173] suggests that the zinc sulfate test using a 208-mg/L solution has an inappropriately high endpoint, with a specificity of only 0.52. The poor predictive value of this method results in a significant misclassification of calves with adequate passive transfer as having FPT. A follow-up study suggests that higher zinc sulfate concentrations in the test solution provide a more accurate assessment of passive transfer. As zinc sulfate concentrations are increased from 200 to 400 mg/L, sensitivity decreases from 100 to 82.6, and specificity increases from 25.5 to 90.6, respectively. The concentration of zinc sulfate test solution chosen therefore depends on the goal of the test. Choosing a test solution with higher sensitivity (e.g., 250 mg/L zinc sulfate) is likely warranted when testing individual calves with high economic value. In herd-monitoring programs, however, the choice of a test solution with higher specificity (e.g., 350 to 400 mg/L zinc sulfate) will maximize the proportion of calves correctly classified.

53.11.12 Sodium Sulfite Precipitation

This test is similar to the zinc sulfate turbidity test and is also a precipitation test for immunoglobulins, primarily IgG1, with the results recorded visually.[174] The reagents are commercially available.* Historically,

three concentrations of $Na_2SO_3^-$ anhydrous (14%, 16%, and 18%) are used in the test. Serum (0.1 mL) is added to each concentration of sodium sulfite (1.9 mL), and these are allowed to incubate for 1 hour. Turbidity in only the 18% sample indicates transfer of less than 500 mg/dL immunoglobulin, turbidity in both the 16% and the 18% sample indicates 500 to 1500 mg/dL of transfer, and turbidity in all samples indicates greater than 1500 mg/dL transfer.

Similar to the zinc sulfate turbidity assay, the endpoint for the sodium sulfite precipitation assay is likely set too high.[173] The preferred test endpoint appears to be a 1+ test result. A 1+ result equates to observing turbidity in the 18% test solution, with no turbidity in either the 16% or the 14% test solution. Tyler et al.[173] demonstrated the lowest serum IgG1 concentration (measured by RID) observed in calves with a 1+ test result was 645 mg/dL (range, 645 to 2450 mg/dL), indicating at least partial successful passive transfer of immunoglobulin. Therefore, it is recommended that the sodium sulfite test be used as a single-dilution assay procedure whereby calves with 1+ test results (precipitation in only the 18% test solution) are classified as having “adequate” passive transfer.

* Bova-S, VMRD, Pullman, WA; ICN Immunobiologicals, Lisle, IL; Bethyl Laboratories, Montgomery, TX.

53.11.13 Glutaraldehyde Coagulation Test

This test is based on 10% glutaraldehyde reagent coagulating serum immunoglobulins in concentrations greater than 600 mg/dL. When performed on serum, the glutaraldehyde coagulation test is an accurate predictor of passive transfer status.[175–178] However, if whole blood is used in a similar assay, the sensitivity and specificity of the assay are deemed to be inadequate for routine diagnostic use.[179]

53.11.14 Refractometer (Total Serum Solids)

Quantification of total serum solids as an indicator of passive transfer of immunity assumes that the increase in serum proteins over that of presuckle newborn ruminants is caused by the absorption of immunoglobulin.[180] In the absence of dehydration, serum protein concentration greater than 5.0 g/dL has historically been associated with successful passive transfer, and values less than 4.5 g/dL are consistent with FPT. Values between 4.5 and 5 g/dL are deemed questionable. 1679 1680

In a study of 242 calves, use of a 5.0-g/dL threshold resulted in a highly specific (0.96) but insensitive (0.59) test, whereas a 5.5-g/dL threshold resulted in a highly sensitive (0.94) but relatively nonspecific (0.76) test.[173] The choice of threshold (5.0 or 5.5 g/dL) depends on the prevalence of passive transfer in the herd being tested and the costs associated with false-positive and false-negative results. Using regression analysis to predict serum IgG1 concentration as a function of serum protein concentrations (with a goal of 10 mg/mL IgG1), the optimal threshold value for serum concentration is calculated to be 5.2 g/dL.[173]

53.11.15 γ-Glutamyltransferase

GGT is present in colostrum at levels about 300 times higher than that normally found in serum. GGT is absorbed by the calf during the period of immunoglobulin absorption, and calf serum levels can be used as an indication of immunoglobulin absorption. Levels of GGT are maximal in the calf on the first or second day after birth.[181,182] Parish et al.[183] used a regression formula to set age-adjusted thresholds for serum GGT

activity in order to define passive transfer status in dairy calves.[183] Using serum IgG1 concentration of 10 mg/mL as an acceptable goal for passive transfer of immunoglobulins, calves at 1 day, 4 days, and 7 days of age should have serum GGT activities greater than 200, 100, and 75 IU/L, respectively. Calves in the first 2 weeks of life with serum GGT levels less than 50 IU/L can be classified as having FPT.

53.11.16 Prevention

The intake and absorption of adequate amounts of quality colostrum are key to the survivability of young ruminants. Documented natural sucking or force-feeding of colostrum in the first 6 hours of life helps to ensure adequate transfer. It is generally thought that a neonate should consume between 6% and 10% of its body weight as colostrum in the first 24 hours of life. Most calves consume approximately 2 L (40 to 50 mL/kg) of colostrum at the first feeding. In force-feeding practices, 2 L typically has been advocated as the proper amount for initial intake. However, the variance in colostrum quality suggests that a greater volume should be fed at the initial feeding.[154] As stated earlier, to attain adequate passive transfer in dairy calves, the current recommendation is to administer approximately 4 L of colostrum in the first 12 hours of life.[166] In herds or flocks where neonatal disease is a problem, levels of passive transfer should be determined, and force-feeding of all newborn animals should be instituted to ensure adequate transfer.

Whole-colostrum specific gravity can be reasonably measured with a colostrometer.[184] A specific gravity less than 1.050 is associated with colostrum that has low immunoglobulin concentration. This device can eliminate 50% of the low-immunoglobulin colostrums and predict high immunoglobulin concentrations.[154] At colostrum temperatures other than 20° C (68° F), less accuracy is achieved.[185] Colostrum should contain greater than 6000 mg/dL total immunoglobulin. To ensure that all neonates receive adequate amounts of colostrum, producers should be encouraged to maintain a bank of frozen colostrum. Colostrum from first milkings is preferred because immunoglobulin concentrations decrease with successive milkings.

Immunoglobulins are generally unaltered by freezing, and only small amounts are inactivated by thawing. Thawing frozen colostrum in warm water is quickly accomplished for individual calf feeding. Microwave ovens have been used to thaw frozen colostrum without adverse effects.[186]

Pooling or mixing colostrum from several cows is a common practice to ensure adequate immunoglobulin concentrations. This practice is advocated to circumvent the problem of low-concentration colostrum from being fed. However, calves that receive pooled colostrum acquire substantially lower serum immunoglobulin levels than calves fed equivalent volumes of homologous colostrum from their own dam.[160] This appears to relate to the fact that colostrums used in pooling frequently come from cows with high volumes of colostrum that tend to have lower immunoglobulin levels.[187]

Many commercially available colostrum substitutes can be used either to supplement available colostrum or to provide a source of immunoglobulins for calves when colostrum is not available. It is important to note the amount of immunoglobulin present in these products and administer enough product to ensure passive transfer. With some products, it may not be possible or practical to administer enough colostrum substitute to obtain 100 g IgG1. Furthermore, the antibody specificity of the immunoglobulins present in these products may be unknown.

Bovine colostrum is frequently used to supplement or replace homologous sources of colostrum in nonbovine ruminants. Neonatal lambs and kids are frequently supplemented in this way.[188,189] The immunoglobulins are

absorbed at rates similar to homologous colostrum. The half-life of bovine IgG1 in lambs is approximately 14 days,[189] which is similar to the 13.7 days reported for ovine IgG1 in lambs[190] (see Table 53-2). Occasionally, anemia has been reported in lambs and kids fed bovine colostrums as a result of immune complex attachment to erythrocytes, causing their removal from circulation.[191–193] The effectiveness of bovine or caprine colostrum in other species is unknown, but the practice appears to be widespread and has been used in a wild animal park successfully hand-raising neonatal exotic ruminants.

53.11.17 Treatment

FPT in an otherwise normal neonate can be treated with plasma administered at 20 to 40 mL/kg intravenously (or intraperitoneally if IV administration is not possible or practical). Whole blood can also be used, although the dose should be increased to account for the presence of RBCs. Similar approaches are indicated in animals with clinical disease, but the results are often less rewarding. Continued oral colostrum supplementation of neonates with FPT beyond the period of closure may also provide some local immune protection in the gut.[160] Some clinicians have advised oral supplementation with plasma after gut closure, but this practice is questionable in light of the cost of obtaining plasma, and plasma contains only about 15 mg/mL IgG1, significantly less than average colostrum.

53.12 LETHAL TRAIT A46

Lethal trait A46 is a primary immunodeficiency that is found in black, pied Danish cattle of Friesian descent.[194] It is an autosomal recessive trait in which the calves appear normal at birth but develop skin disease at 2 to 8 weeks of age. Skin lesions are characterized by exanthema, alopecia, and hyperparakeratosis, with initial lesions occurring around the head, neck, and flexor surfaces of the legs and later involving the entire animal. Death within 4 months is often associated with bronchopneumonia and diarrhea. These animals do respond normally to humoral antigens but show deficits in cellular immunity. At necropsy the calves show marked lymphoid regression involving the thymus, spleen, lymph nodes, and gut-associated lymphoid tissues in the thymic-dependent regions. The condition is responsive to oral zinc oxide therapy, which suggests an underlying problem in zinc metabolism. Daily oral dosages of up to 1 g zinc oxide have been used to establish normal function.[194] The primary immunologic defect is found in T lymphocytes. Because of a defect in a recessive gene, these animals apparently have an unusually high metabolic requirement for zinc ions to sustain normal T-lymphocyte development and function.

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53.13 SELECTIVE IgG2 DEFICIENCY

A primary IgG2 deficiency has been described in the red Danish milk breed of cattle involving a primary, partial to complete deficit in IgG2.[195,196] These animals appear to be more susceptible to gangrenous mastitis and pyogenic infections such as bronchopneumonia, peritonitis, and abomasoenteritis.[197] A transient IgG2 deficiency has also been reported in neonatal lambs.[196] Lambs that ingested colostrum had delayed onset of IgG2 synthesis until 5 to 6 weeks of age, with no adverse consequences.

53.14 CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome is an inherited disorder that affects neutrophil and monocyte function in Hereford cattle, mink, cats, mice, killer whales, and humans.[198,199] Clinically, these patients are recognized by partial

albinism that affects the skin and eyes, coagulation difficulties, and an increased susceptibility to bacterial infections. Large cytoplasmic granules are seen within neutrophils. The increased susceptibility to pyogenic infections is related to decreased neutrophil killing of ingested organisms caused by a defect in hexose monophosphate shunt activity and defective degranulation.

53.15 BOVINE LEUKOCYTE ADHESION DEFICIENCY

Bovine leukocyte adhesion deficiency (BLAD) is an autosomal recessive disorder of Holstein calves characterized clinically by chronic bacterial infections and premature death.[200–202] Leukocytes of affected calves lack surface glycoproteins, termed β-2 integrins. A mutation of the gene encoding bovine CD18 causes this disorder. The gene defect is termed the D128G allele mutation.

Heterozygous carriers are clinically normal; however bulls and cows with this mutation may produce homozygous calves that manifest the deficiency. All calves with BLAD can be traced to a single male ancestor that must be present in both the sire and dam pedigree. In the United States, approximately 14% of sires and almost 6% of Holstein calves are affected with BLAD.

Homozygous calves have chronic, recurrent bacterial infections. Consistent clinical findings include fever, bronchopneumonia, stomatitis, gingivitis, recurrent or chronic diarrhea, peripheral lymphadenopathy, vasculitis, and dermatitis.[203,204] Calves appear normal at birth, but clinical signs are often present within the first few weeks of life. Affected calves usually die within the first year of life. Those surviving past 1 year of age have persistent ill-thrift. Hematologic abnormalities include mature neutrophilia (>40,000/μL) without significant left shifts, lymphocytosis, and monocytosis. Abnormal serum biochemical findings include hypoalbuminemia; hyperglobulinemia; and low serum creatinine, urea nitrogen, and glucose concentrations.

Diagnostic tests are available to detect heterozygous carriers and identify homozygous affected calves. Information regarding testing is available from the Holstein Association of America, Brattleboro, VT.

53.16 VIRAL- AND BACTERIAL-INDUCED IMMUNODEFICIENCY

Decreased function of B and T lymphocytes has been associated with bovine viral diarrhea (BVD) infection in calves developing chronic BVD syndrome.[205] Depression of cellular, but not humoral, immunity is seen in cattle infected with Johne's disease (*Mycobacterium avium* subsp. *paratuberculosis*), with failure to develop or delayed-type hypersensitivity (DTH) reactions in vivo and in vitro.[206] It is associated with a humoral-suppressive factor.

53.17 COMBINED IMMUNODEFICIENCY

Genetic failure of development of both T and B cell lines results in a severely compromised, immunodeficient animal. As passively acquired maternal antibody wanes, infections tend to develop. One possible case of combined immunodeficiency was reported in a 6-week-old Angus calf that had an absence of serum IgM, low serum IgG, absolute lymphopenia, and an absence of lymphoid tissue at necropsy. The calf died of bronchopneumonia and disseminated fungal infection.[207]

53.18 PREGNANCY-ASSOCIATED IMMUNODEFICIENCY

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The areas of immunology pertaining to pregnancy, fetal survival, and postpartum periods have continued to expand over the past decade.[208,209] Additional input from the fields of epidemiology and evidence-based medicine has increased our understanding of the delicate balance that occurs at the maternal-fetal interface.[210] In its broadest context, the immune system of the pregnant animal becomes compromised as the fetus matures.[211] Although transitory, this immunodeficient state also apparently extends into the postpartum period for up to 4 weeks.[212]

53.18.1 Mechanisms

The cellular mechanisms responsible for the immunosuppression during pregnancy and postpartum involve (1) a shift of T-helper (Th) cells from a Th1 to a Th2 response and (2) a decrease in neutrophil functions.[213,214] The T-cell populations are affected by progesterone, prostaglandin $F_{2\alpha}$, and α-fetoprotein.[211] The Th1 cells are important effectors of the cell-mediated immune (CMI) response and interact with T-cytotoxic (Tc) cells. Tc cells are the main defense against foreign antigens, which include viral, intracellular bacterial, and protozoal pathogens. With the onset of pregnancy, the hormonal factors cause macrophages to release predominantly Th2-stimulating cytokines, which contribute to the overall dominance of humoral immunity during pregnancy and immediately postpartum. This phenomenon of the Th-cell populations is referred to as the "Th1-Th2 shift of pregnancy" and is generally regarded as a contributing factor to maternal tolerance of the fetus by suppressing the antifetal CMI response.[209]

The second key cell population affected during pregnancy and postpartum is the neutrophil.[212] The point of maximum immunosuppression occurs when glucocorticoid levels are acutely elevated in the periparturient cow.[215] Neutrophil dysfunction, as well as the effects on the Th-cell population, is considered temporary during this period. Nonetheless, with impaired neutrophil response, the animal is then vulnerable to increased bacterial infections because of compromised bactericidal functions.[212]

53.18.2 Outcome

This temporary immunodeficiency allows for fetal survival but may also result in an increased susceptibility to exterior environmental infection with viruses, bacteria, and fungi. Intracellular infections, such as with viruses and protozoans, which may have been acquired early during postnatal development, may become exacerbated during pregnancy because of the suppressive effects on the Th1 cells.[211] This results in a decreased CMI response. The CMI effector cells (Tc cells) function normally to control virtually all the viral infections, such as infectious bovine rhinotracheitis virus and BVD virus.[211,216] Intracellular bacterial infections, such as *Brucella abortus,* become more pathogenic during pregnancy. In addition to the effects on T-cell functions, macrophage function is also compromised, allowing for opportunistic bacteria and *Chlamydiophila* species (usually confined to external mucosal surfaces) to become systemic. Concurrent with the immunosuppression that accompanies pregnancy, there is an increased shedding of infectious microorganisms[211] (Figure 53-5). This is considered to be an extension of impaired Tc-cell function. Although the pregnant animal may appear clinically normal, her altered immune response results in an increased shedding of gastrointestinal (GI) viruses such as coronavirus and rotavirus[211,217] and bacteria (*Mycobacterium avium* subsp. *paratuberculosis, Escherichia coli*), usually during the periparturient period.[218,219] This increased shedding of infectious microorganisms is an

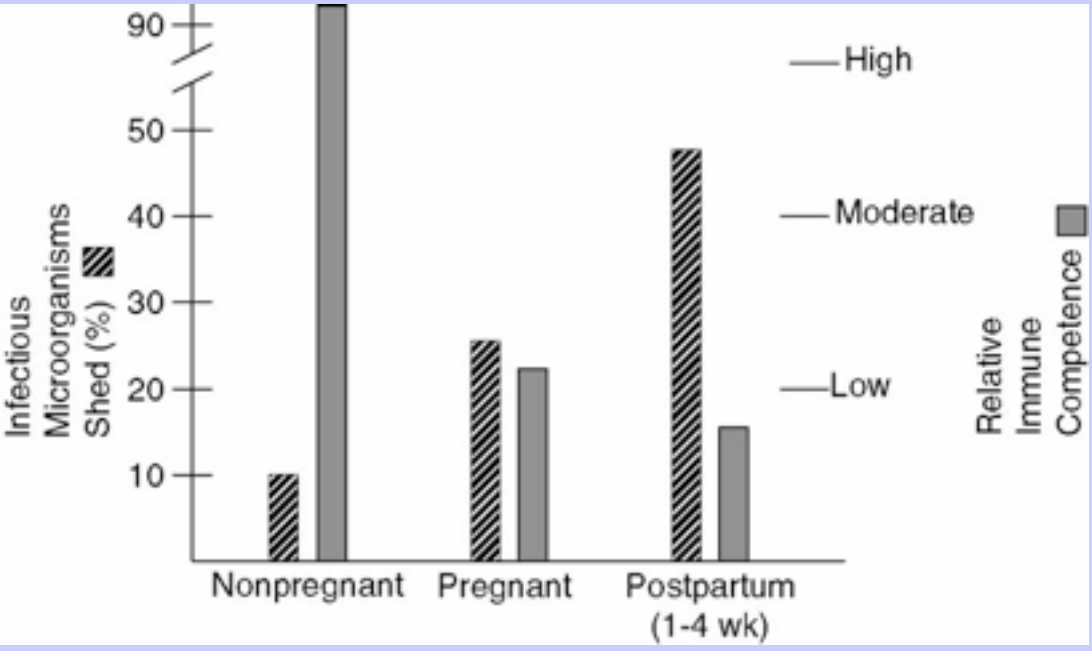
important factor in the management of animals through this period. The suppression of neutrophil functions during later stages of pregnancy and immediately postpartum are the subject of active investigation.[215,220]

The reduced neutrophil function and its association with periparturient immune suppression are significant problems, especially for the transition dairy cow.[215] This immunosuppression is directly associated with increased postpartum metritis and increased susceptibility to mastitis. As noted with the immunosuppression during pregnancy, this periparturient stage can be aggravated by both preexisting infections (e.g., bovine herpesvirus type 4)[221] and environmental bacterial pathogens (e.g., *Staphylococcus aureus, Klebsiella* species).[222]

53.18.3 Management

Although the immunosuppressive periods during pregnancy and up to 4 weeks postpartum are well recognized, current understanding of the cellular processes is still somewhat rudimentary. However, clinicians and owners can proceed with control measures that accomplish two primary goals: maximize reproductive performance and ensure successful neonatal survival.[210,223,224] Over the years, we have emphasized the importance of effective vaccination programs before breeding, clean birthing areas, and good hygiene for the lactating animal.[210,222] These measures, in conjunction with good colostral management, allow owners to compensate for the temporary immunosuppressive states encountered during and immediately after pregnancy.

Fig. 53-5 Proposed relationships among shedding of infectious microorganisms during periods of nonpregnant, pregnant, postpartum, and relative immune competence. Modified from Evermann JF: Immunology of bovine pregnancy: vulnerability to infectious disease, *Bovine Proc* 26:101, 1994.



53.19 DISEASES CAUSED BY ALLOGENEIC INCOMPATIBILITIES

JILL JOHNSON

STEVEN M. PARISH

The surfaces of cells are covered with molecular structures, the presence or absence of which is determined by genes. Some of these molecules have limited heterogeneity within a species, and all members of the species share identical forms (monomorphic). In other cases a spectrum of minor structural variations or polymorphisms of a particular molecule occur within the population, so that some members of the species will have one form of the molecule, whereas others will have another. If the structural variations are such that the immune system of one individual can recognize the differences in the molecules from another individual, these are known as *alloantigens*. Antibodies produced against these antigens are *alloantibodies*. Examples of alloantigens include red blood cell (RBC, erythrocyte) antigens and lymphocyte antigens.

In nature, because few situations arise in which tissues are exchanged, there are relatively few naturally occurring diseases that involve allogeneic incompatibilities. Neonatal isoerythrolysis (NI) and neonatal alloimmune thrombocytopenia (NAIT) are two examples of such naturally occurring diseases. Blood transfusion reactions and organ transplant rejection are examples of iatrogenic diseases associated with allogeneic incompatibilities.

The same alloantibodies that mediate disease are also useful in vitro as reagents to detect the presence of alloantigens and serve as the basis for blood typing.

53.20 BLOOD TYPING AND DNA PROFILING

The blood type of an individual is actually a composite list of genetic markers that have been detected in the individual's blood. Several types of genetic markers have been used in blood typing, including RBC alloantigens, electrophoretic markers, and lymphocyte alloantigens. Polymorphisms of the DNA itself have emerged as useful genetic markers and have essentially replaced other genetic tests for parentage verification.

53.20.1 Red Blood Cell Antigens

Seven independent RBC groups or systems have been internationally defined in horses under the auspices of the International Society for Animal Genetics[225–228] (Tables 53-3 and 53-4). These systems are named A, C, D, K, P, Q, and U. Additional systems are recognized by individual laboratories. Each system corresponds to a particular gene for which two or more alleles exist. Some blood groups are relatively simple and contain only two alleles, whereas other systems may have over two dozen different alleles.

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The blood group genes produce surface molecules that contain antigenic sites known as *factors*. More than 30 different factors have been identified. Each factor is associated with only one system, although the same factor may be associated with more than one allele within the system. The factors are named with an uppercase letter to denote the system and a lowercase letter to designate the factor within that system. Groups of factors that are produced by a single allele are called *phenogroups*.

Table 53-3 Domestic Animal Blood Groups

Species	Blood Group. Systems
Equine	A, C, D, K, P, Q, U
Bovine	A, B, C, F, J,* L, M, R′, S, T, Z
Ovine	A, B, C, D, M, R,* X
Caprine	A, B, C, M, J*

From Suzuki: Personal communication, 1990.

* Soluble antigens.

Table 53-4 Blood Group Systems, Factors, and Alleles of the Horse Recognized by the International Society for Animal Genetics

System	Factors	Recognized Alleles
A	a,* b,† c, d, e, f, g	Aa, Aadf, Aadg, Aabdf, Aabdg, Ab, Abc, Abce, Abe, Ac, Ace, Ae, A–
C	a	Ca, C–
D	a, b,† c,† d, e, f, g,† h, i, k, l, m, n, o, p, q, r	Dadl, Dadlnr, Dadlr, Dbcmq, Dcefgmq, Dcegimnq, Dcfgkm, Dcfmqr, Dcgm, Dcdmp, Dcgmq, Dcgmqr, Ddeklqr, Delno, Ddeloq, Ddelq, Ddfkir, Ddghmp, Ddghmq, Ddghmqr, Ddki, Ddlnq, Ddlnqr, Ddlqr, Ddno, Dq, (D–)
K	a	Ka, K–
P	a,† b, c, d	Pa, Pac, Pacd, Pad, Pb, Pbd, Pd, P–
Q	a,* b, c†	Qa, Qab, Qabc, Qac, Qb, Qbc, Qc, Q–
U	a†	Ua, U–

From Cothran G: Personal communication.

* Most common factors involved in neonatal isoerythrolysis (NI).

† Previously reported to cause NI in at least one case.

The presence of RBC antigens is detected primarily by either agglutination or complement-mediated lysis of test cells by antibodies directed against specific erythrocyte alloantigens. Antigens in some systems are detected with antiglobulin tests.

Eleven blood groups have been identified in cattle[229] (Table 53-5); groups B and J have the greatest clinical relevance. The B group is a very complex system, with more than 60 different antigens.[230] This complexity has been used to advantage for individual animal identification and parentage studies in the past, but it makes it difficult to match donor and recipient blood for transfusions.

The J antigen is a lipid that is found in body fluid and that is adsorbed to erythrocytes; thus it is not a true erythrocyte antigen. Newborn calves do not have this antigen but usually acquire it during the first 6 months of life. After acquiring it, some groups of cattle have high amounts of J antigen both in the serum and adsorbed to erythrocytes, whereas other groups have very small amounts found only on RBCs. These latter groups, often referred to as J-negative, may actually have anti-J antibodies and develop transfusion reactions when transfused with blood from J-positive donors.[225]

Table 53-5 Blood Group Factors of Cattle Recognized by the International Society for Animal Genetics

System	Factors
AA*	A1, A2, H, Z, a
F*	F, V
J	J, j
L	L, l
M	M, m
Z	Z, z
R″	R′, S′
B†	B, G1, G2, G3, I1, I2, K, O1, O3, OX, Pl, P2, Q, T, Y2, A′, B′, D′, E1′, E2′, E3′, G′, I1′ (I′), I2′, Jl′, J2′, K′, O′, P1′, P2′, Q′, Y′, A″, B″, G″, I″
C	C1, C2, R1, R2, W, X, X2, L′, E1, C′, C″, X′, Fl, F6, F10, Fl5
S	S1, S2, U, H′, U′, S″, U″
T	—

* Cases of neonatal isoerythrolysis associated with production of anti—red blood cell antibodies against factors in response to anaplasmosis and *Babesia* vaccines.

† Additional factors are recognized by individual laboratories.

Seven blood groups have been identified in sheep (see Table 53-3). The B system is analogous to the B system in cattle and is extremely polymorphic, with more than 52 different alleles. The R system is similar to the J system in cattle in that the antigens are soluble and are passively adsorbed to erythrocytes.[229] The M-L system is involved in the genetically determined RBC potassium polymorphism found in sheep.[231]

Blood groups of goats appear to be very similar to those of sheep, and many of the reagents used for typing sheep blood have been used to type goats' blood. Reagents used to detect antigens of the J system of cattle have been used to detect differences in a similar system in goats.[232]

The biologic function of red blood cell antigens is not known for any system in any species with the exception of the M–L blood group system in sheep, which is involved in active potassium transport across red blood cell membranes.

53.20.2 Electrophoretic Markers

Many plasma and intracellular proteins have polymorphic forms. These variants have subtle biochemical differences, which for the most part do not alter the major characteristics of the molecules, but which can be detected using electrophoretic methods. Technically, these are not alloantigens because the differences are not detected immunologically. The various forms of the molecules are detected on the basis of their different rates of migration in electrophoresis. The specific form(s) of any particular protein that an individual possesses are determined genetically, and those used in blood typing are usually expressed co-dominantly. Currently, no diseases are clearly associated with the presence or absence of particular alleles of polymorphic proteins; however, they are useful genetic markers for identification and parentage studies and were typically included in the blood type[227,232–234] (Table 53-6). Electrophoretic markers were used extensively in horses because RBC antigens did not provide the same degree of discrimination among individuals in this species as they do, for example, in cattle. The current application is limited to legacy parentage verification when parental DNA is not available for testing.

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Table 53-6 Examples of Polymorphic Proteins Used in Blood Typing

Protein	System	Source
A1B glycoprotein	AlB	Serum
Albumin	ALB	Serum
Transferrin	TF	Serum
Carboxylesterase	ES	Serum
Vitamin D–binding protein	GC	Serum
Protease inhibitor	PI	Serum
Peptidase A	PEPA	Serum
Plasminogen	PLG	Serum
Glucose phosphate isomerase	GPI	Red cells
6-Phosphogluconate dehydrogenase	PGD	Red cells
Phosphoglucomutase	PGM	Red cells
Catalase	CAT	Red cells
Carbonic anhydrase	CA	Red cells
Acid phosphatase	AP	Red cells
Hemoglobin-a	HBA	Red cells
NADH diaphorase	DIA	Red cells

53.20.3 Lymphocyte Antigens

Three systems of equine lymphocyte alloantigens have been described: ELA, ELY 1, and ELY 2.[235–239] ELA is the major histocompatibility complex (MHC) of the horse. ELA is a complex system that includes several

genes, each of which is polymorphic (e.g., has many different alleles). Because the MHC regulates the interactions of many cells in the immune response, disease susceptibility or resistance could be associated with ELA. An association between a particular ELA allele and equine sarcoid has been described.[240,241] ELY 1 and ELY 2 have limited polymorphism and appear to be two allele systems.

The MHC of cattle is called BoLA, for bovine lymphocyte antigen. In sheep the MHC is called OLA, for ovine lymphocyte antigen, and is also known as SH-LA. In goats the comparable system is GLA.[242]

53.21 DNA POLYMORPHISMS

A variety of approaches have been developed for detecting genetic variation using DNA. Certainly, DNA sequencing is the most sensitive approach; however, this remains too costly for routine testing outside of research laboratories. Other approaches have been developed to detect DNA variants. Genetic variation of DNA can be detected among individuals on the basis of differences in length for a section of DNA or even for differences in base composition at specific sites. DNA length variants are usually referred to as minisatellite or microsatellite markers. *Minisatellite* DNA markers are based on sequences, often 15 to 100 bases long, that may be repeated hundreds of times on a chromosome. The number of repetitions can vary dramatically between individuals and can be readily detectable in Southern blot assays. These tests were originally referred to as “DNA fingerprinting.” Although powerful, these tests are costly and time-consuming.

More recently, another type of DNA length variant has been discovered. *Microsatellite* DNA markers are short repetitions of nucleotides, usually ranging from one to nine bases long, which may be repeated 15 to 40 times. As with minisatellites, the number of repetitions may vary between chromosomes. The development of the polymerase chain reaction (PCR) has opened the door to easy, inexpensive detection of microsatellite and other types of markers. PCR is a method for amplifying short (<3000 bases) pieces of DNA, allowing a particular gene to be easily studied. The amplification products can be separated by electrophoresis and length variants readily detected. More than 100,000 of these markers are thought to exist in each species. These markers form an important core for development of genetic maps in diverse species. The markers currently form the basis for most parentage analysis.

Variation recognizable as a change in a single base of DNA is more subtle but can be detected through a variety of techniques. DNA sequence variation is often detectable using *restriction enzymes,* which are isolated from bacteria and will cleave DNA when the sequence is specific for the enzyme. For example, the method to detect the gene defect causing hyperkalemic periodic paralysis (HYPP) in horses is based on PCR amplification of the gene and then detection of sequence differences that occur between the normal and mutant gene using restriction enzyme digestion of the DNA. Other approaches to identifying DNA sequence differences include single-strand conformational polymorphism (SSCP), allele-specific PCR amplification, and ligase chain reaction.

Testing based on DNA has essentially replaced blood typing for purposes of parentage analysis. Furthermore, DNA-based techniques are also being used to develop gene maps for many species of domestic animals. These gene maps can be used to identify genes that play a role in performance, production, and disease.

53.22 BLOOD-TYPING AND DNA-GENOTYPING APPLICATIONS

To determine an animal's blood type or DNA genotype, a battery of tests are run on the blood or tissue to check for the presence or absence of each recognized allele in each of several genetic systems. Each system is controlled by a separate autosomal gene. These genes are inherited independently of one another.[228,239] Most genetic

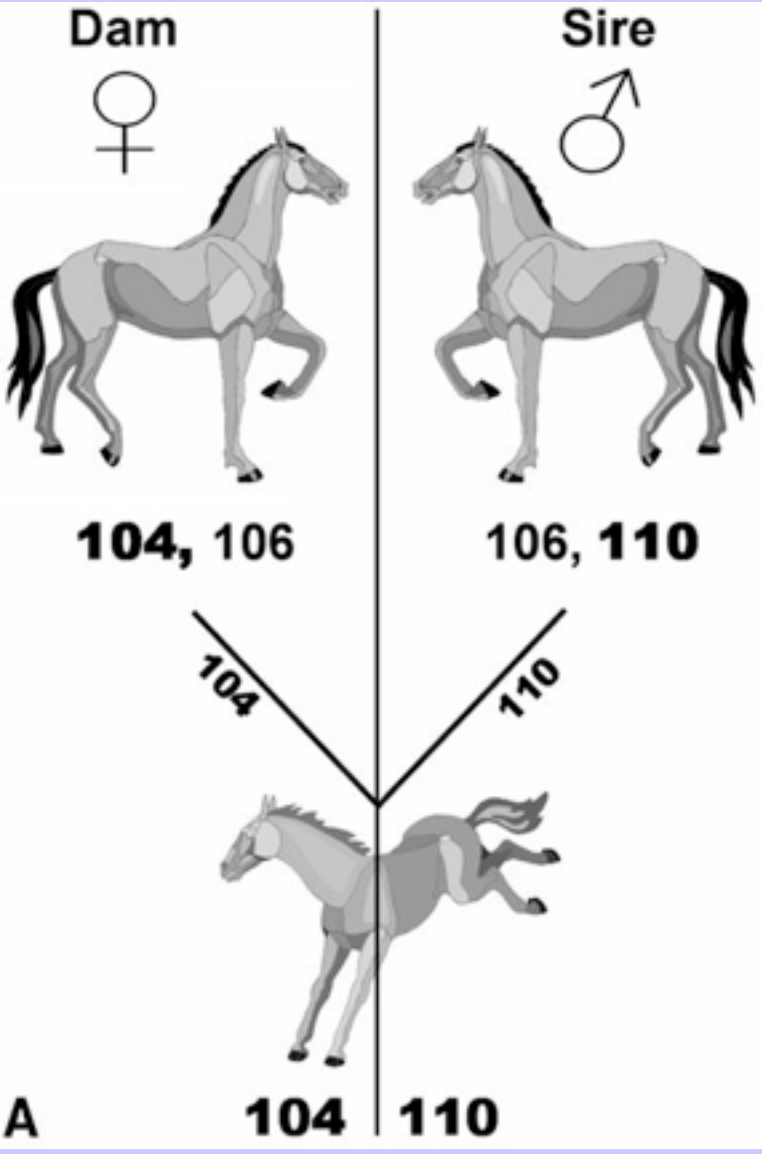
markers used in blood typing are expressed co-dominantly, which means that the alleles on both chromosomes are expressed. This often allows determination of *genotype* (the actual genes present) from the *phenotype* (the antigens actually detected). Some systems have *null alleles* (with no detectable products) that do not directly allow inference of genotype (e.g., C, K, and U blood group systems in horses). An individual can have only two of the possible different alleles for any given gene (one on each chromosome of a pair).

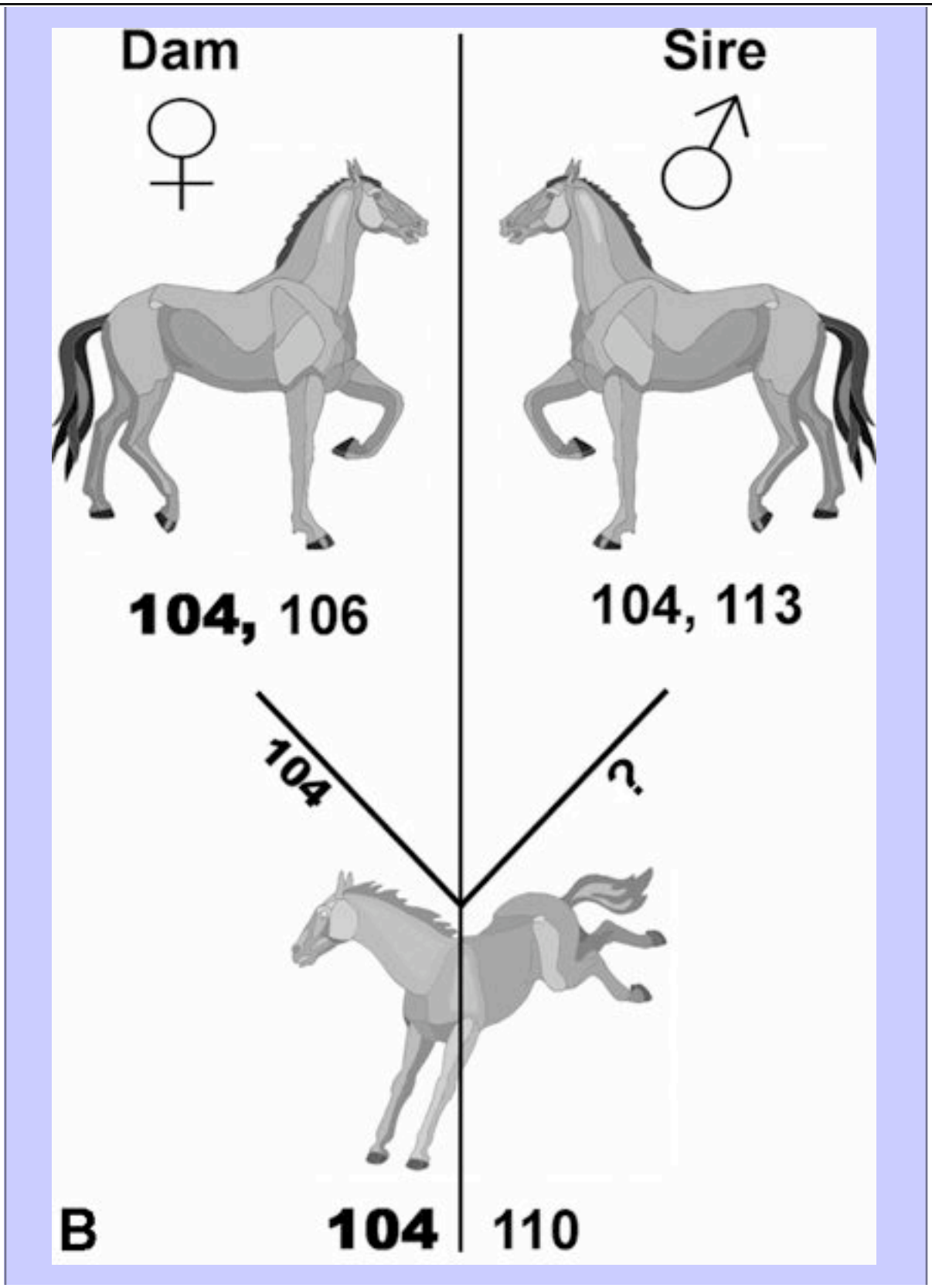
Blood typing based on RBC antigens and electrophoretic markers has been used for animal identification and pedigree analysis, but currently, RBC typing is used primarily for prediction of potential for NI and crossmatching for blood transfusion.

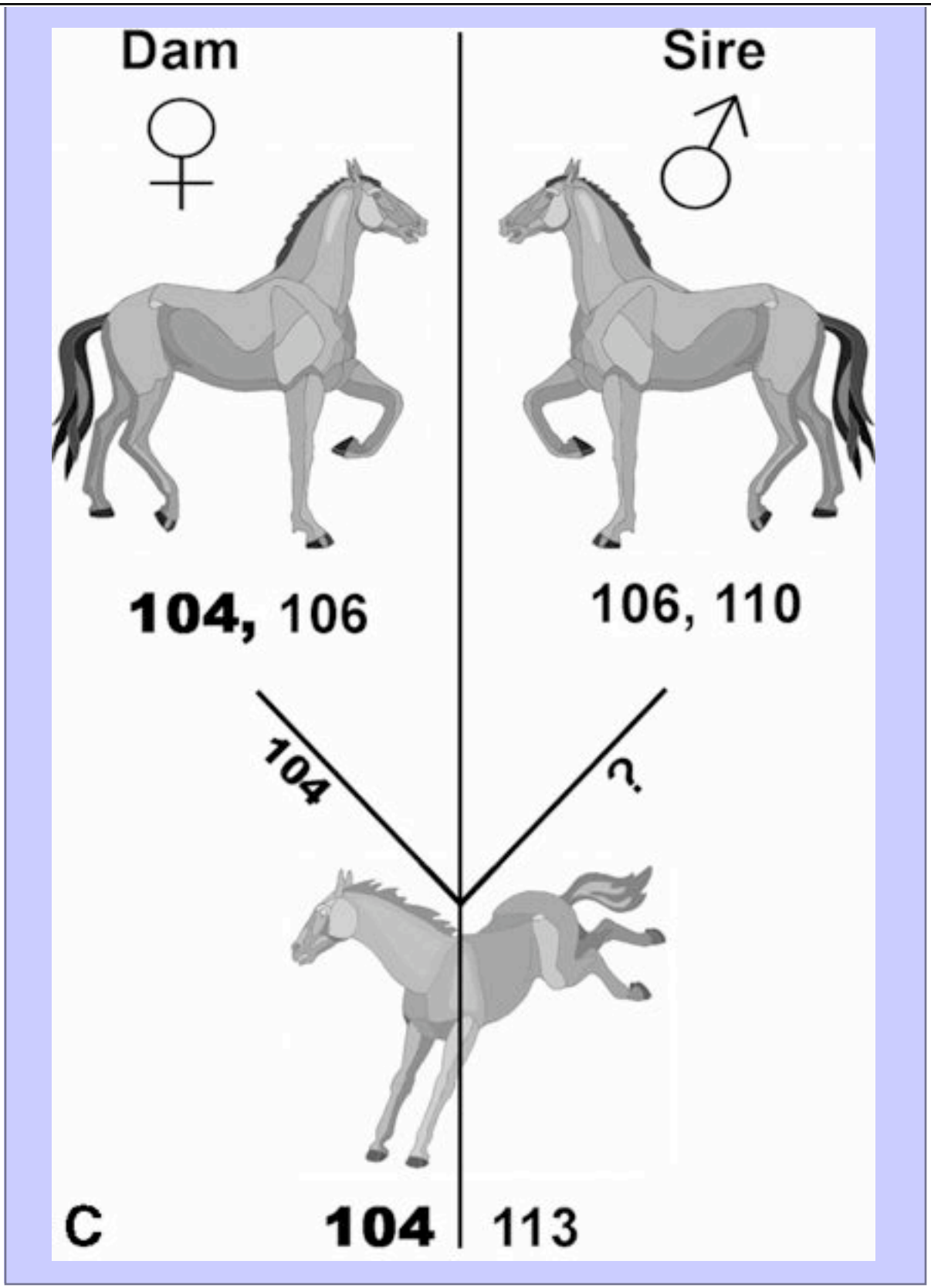
The use of genetic markers for parentage verification is based on exclusion (i.e., markers are tested until a discrepancy is found). If no discrepancy is observed after a statistically acceptable amount of testing, the probability of a match is determined.

Because genetic testing is a composite mosaic of a large number of different, largely independent genetic markers, the odds of two individuals sharing exactly the same pattern of markers, whether RBC antigens, electrophoretic markers, or DNA polymorphisms, is remote. Thus, once an animal's genetic type is on record, it can be a powerful identifier of an individual animal. In this sense it is an unalterable form of identification that is present from birth to death.

Fig. 53-6 **A,** The sire of this foal cannot be excluded as the sire of the foal based on the results for DNA marker VHL20. **B,** The sire of this foal is excluded by a type I exclusion. The foal possesses an allele for the DNA marker VHL20 not present on either parent. Assuming that the dam of the foal is known to be correct and therefore would have contributed the 104 allele to the foal, the sire must be incorrectly stated. **C,** The sire of this foal is excluded by both type I and type II exclusion. The foal possesses an allele not present on either parent and also does not possess either allele expressed by the putative sire.




Dam
Sire
104, 106
104, 113
104
?
B
104
110


Dam
Sire
104, 106
106, 110
104
?
C
104
113

Because the presence or absence of markers is genetically determined and because the markers contributed by both parents are expressed in a co-dominant fashion (unless "blank" alleles exist), these markers can be used to support or refute parentage claims. Blood typing and DNA profiling cannot prove that one horse is the parent of another; however, in certain cases it can exclude with certainty a stated parent as the true parent. Two types of parentage exclusions can occur, type I and type II[243] (Fig. 53-6). With type I the foal possesses a dominant or co-dominant marker that is not present in either parent. This means that at least one of the stated parents is incorrect. If one parent (usually the dam) is known with certainty on the basis of circumstances other than genetic type, the error lies with the other stated parent. With type II exclusions, the foal does not possess either of the dominant or co-dominant markers of a stated parent. Because a foal must inherit one of the two markers expressed by each parent, exclusion can be made if neither of the two markers present on the stated parent is detected in the foal. In parentage cases, each genetic system is evaluated for type I and type II exclusions. A parent can be excluded on the basis of an inconsistency in even one system. For this reason, the more systems used, the better genetic typing becomes as a tool for solution of parentage disputes. The calculated effectiveness of blood typing for detecting incorrect paternity using 20 internationally defined systems in horses is as high as 96%.[227,233,244] With DNA genotyping, effectiveness is as high as 99.998%.[245–247]

Box 53-1 lists laboratories in North America that provide DNA genotyping.

53.23 NEONATAL ISOERYTHROLYSIS

53.23.1 Equine

53.23.1.1 Definition and Etiology

Neonatal isoerythrolysis (NI) is a condition characterized by the destruction of RBCs in the circulation of a foal by alloantibodies of maternal origin absorbed from colostrum.[226,248,249]

Production of alloantibodies can be stimulated in mares several ways, including transfusion, exposure to blood from the foal during parturition, or as a result of placental pathology during gestation. Incompatibilities of at least some blood groups between the dam and foal are the rule rather than the exception, and yet the incidence of sensitization of the dam and occurrence of NI is relatively low. In thoroughbreds the prevalence is about 1% and in standardbreds about 2%.[250] The prevalence in mules (donkey sire, horse dam) has been reported to be as high as 10%.[226] Most blood groups are not strongly antigenic under the conditions of exposure through previous parturition or placental leakage. Several blood group factors, however, are particularly immunogenic, and antibodies against these antigens have been reported to cause almost all cases of NI. These include factor Aa in the A system and factor Qa in the Q system. In mules a unique donkey RBC antigen named *donkey factor* has been associated with NI.[251] Antibodies to these antigens develop after the exposure of the mare to RBCs and are not naturally occurring antibodies. In humans the absence of certain RBC antigens results in the production of natural antibodies against that antigen, presumably because of exposure to cross-reacting antigens in the diet. This does not occur in horses (with a few exceptions) and has not been associated with NI. Ca-negative (Ca–) horses frequently make anti-Ca antibody of low titer without known RBC exposure. However, anti-Ca antibody is generally not associated with NI, and mares with anti-Ca antibody actually appear less likely to develop certain antibodies responsible for NI.

53.23.1.1.1

Box 53-1 Laboratories in North America Providing DNA Genotyping Services

Equine Parentage Testing and Research Laboratory

University of Kentucky

Department of Veterinary Science

Lexington, KY 40546

(606) 257-3022

www.ca.uky.edu/gluck

(Horses)

Shelterwood Laboratory

DNA Diagnostics, Inc.

P.O. Box 455, 626 Bear Drive

Timpson, TX 75975

(936) 254-2228

www.dnadiagnostics.com

(Horses)

Maxxam Equitest

335 Laird Road, Unit 4

Guelph, Ontario N 1 H 6J3 Canada

(519) 836 2400

www.maxxam.ca

(Horses)

MMI Genomics

1756 Picasso Avenue

Davis, CA 95618

(800) 311-8808 ext. 3016

www.metamorphixinc.com

(Cattle)

GenMARK

3591 Anderson St., Suite 104

Madison, WI 53704

(877) 766-3446

www.genmarkag.com

(Cattle, sheep, swine)

Bovigen

250 Plauche St.

Harahan, LA 70123

(504) 733-8182

www.bovigen.com

(Cattle)

For NI to occur, several conditions must be present (Figs. 53-7 and 53-8). First, the dam must be negative for the antigen in question. Because most cases of NI in horses are associated with either anti-Aa or anti-Qa antibodies, mares that are Aa− or Qa− or both are considered at risk. All horses appear to lack donkey factor; thus all mule pregnancies are considered at risk. Second, the mare must become sensitized and produce antibody to the offending antigen. Sensitization can result from exposure during a previous pregnancy, blood transfusion, or transplacental contamination with fetal RBCs earlier in the current pregnancy (rare). Third, the foal from the current pregnancy must have inherited from its sire the antigen(s) to which the mare has been sensitized. When these conditions are met, there is a significant potential that maternal antibody directed against the foal's RBC antigens will appear in the colostrum and, if subsequently ingested and absorbed by the foal, could cause loss of RBCs. The higher the anti-RBC titer is at foaling, the higher the risk. The highest titers are likely to be produced in a previously sensitized mare that is reexposed to the same RBC antigens shortly before parturition.

Fig. 53-7 Entrance of RBCs of paternal antigen type into maternal circulation stimulates the production of alloantibody in the mare's serum.

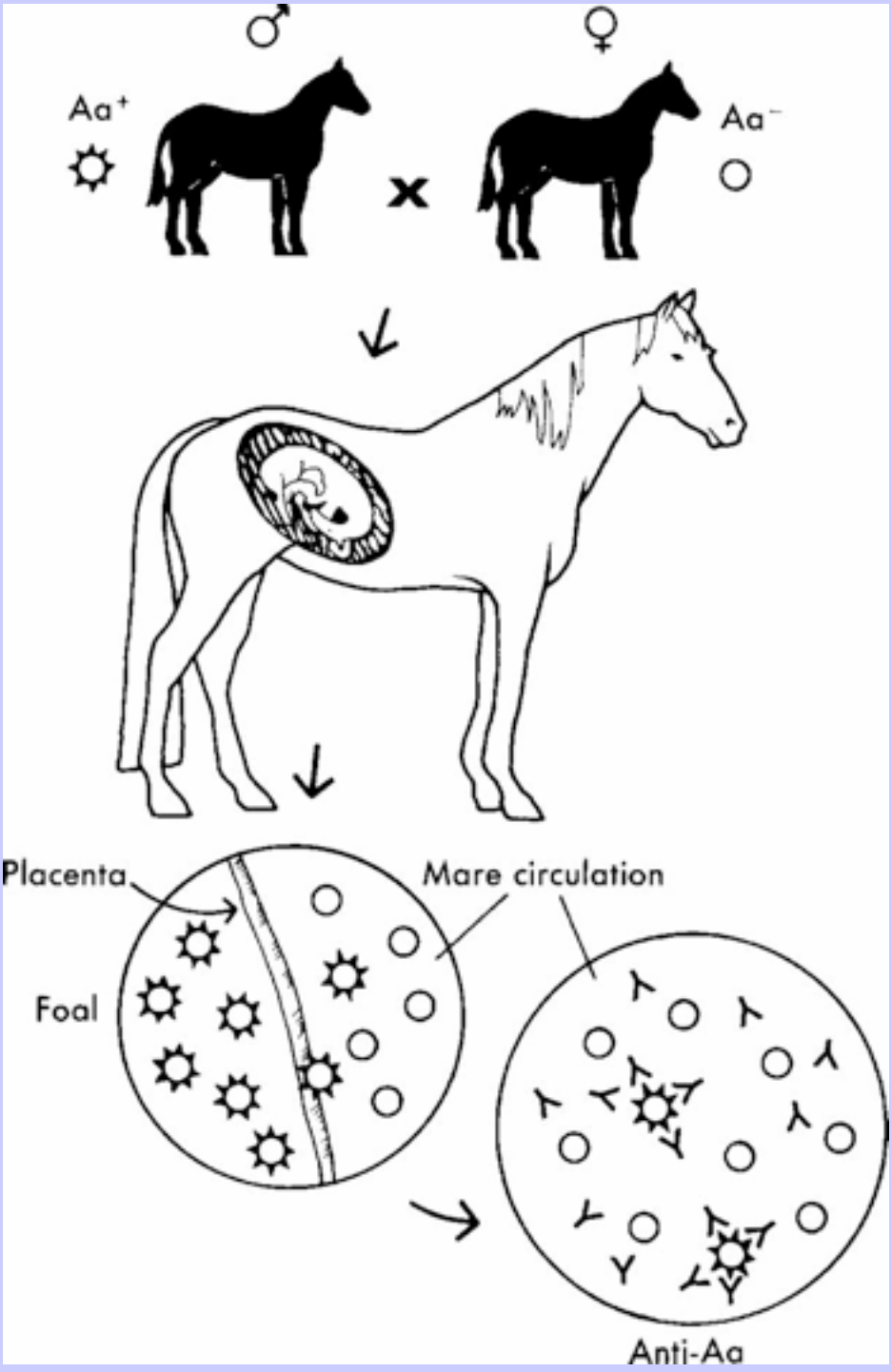
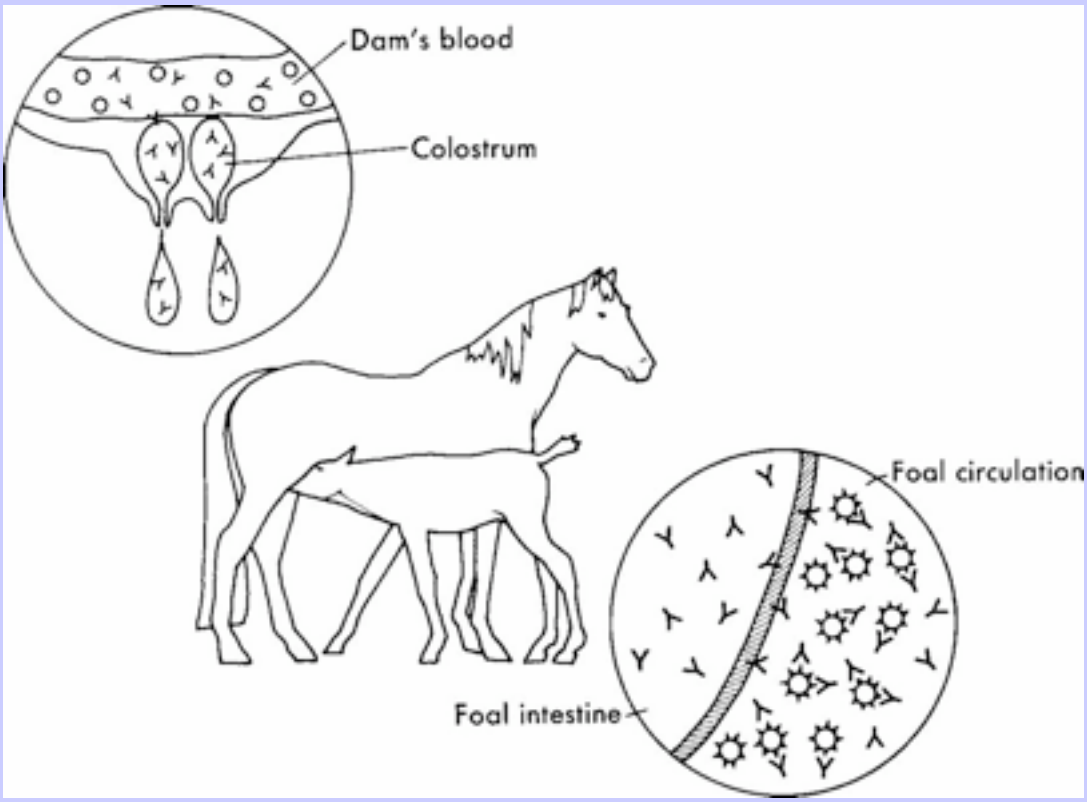


Fig. 53-8 Alloantibody in the mare's serum is concentrated in colostrum at the end of gestation. Through passive transfer, the foal absorbs immunoglobulins, including these alloantibodies. The antibodies attach to RBCs and cause either their premature removal from circulation or intravascular lysis.



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53.23.1.2 Clinical Signs and Differential Diagnoses

Foals are born healthy and usually begin to develop signs of NI at 24 to 36 hours of age, after suckling. Progressive lethargy and weakness are early signs. In acute cases, mucous membranes show initial pallor that is followed by icterus. In severe cases, hemoglobinemia and hemoglobinuria may be pronounced. In peracute cases, death may precede the development of icterus. Breathing becomes rapid and shallow, followed by labored breathing as the disease progresses. The foals may yawn repeatedly. Heart rate is elevated. Seizure-like activity may occur as the anemia becomes more severe.

53.23.1.3 Clinical Pathology

Affected foals are anemic. All indicators of RBC concentration (packed cell volume [PCV], hemoglobin, RBC count) show significant decreases. PCV values often decline to between 10% and 20%, and values as low as 5% have been observed. Hemoglobinemia and hemoglobinuria may be present. Bilirubin (mainly

unconjugated) levels will be increased as a result of accelerated RBC destruction. Total bilirubin levels may be close to 20 mg/dL in severe cases. Affected foals, especially mule foals, may also be thrombocytopenic.[228]

Demonstration of significant amounts of antibody in the colostrum (or serum from the mare) that are directed against the RBC antigens expressed by the foal provides a definitive diagnosis of NI. These antibodies are most often demonstrated by lytic and agglutinating tests. Lytic tests are believed to be more reliable indicators of the presence of offending antibody.[252] The presence of antibodies attached to the foal's RBCs can also be demonstrated with a direct antiglobulin test (Coombs' test). The presence of antibodies in the mare's serum that attach to RBCs can be demonstrated with an indirect antiglobulin test.[226]

53.23.1.4 Pathophysiology

In mares sensitized to RBC antigens, most often Aa or Qa, alloantibodies are concentrated in the colostrum late in gestation. These antibodies are passed to the foal through passive transfer. If the foal's RBCs carry the antigen that the antibody recognizes, the cells become antibody coated. Subsequently, they are removed prematurely by the reticuloendothelial system or lysed intravascularly by complement. A distinction has been made between antibodies that are lysins as opposed to agglutinins; however, this distinction is based on in vitro testing and may be somewhat artificial. Under appropriate laboratory conditions, offending antibodies may exhibit both abilities.[250] However, with conventional agglutination tests, some alloantibodies capable of producing NI may go undetected.[234]

53.23.1.5 Epidemiology

The percentages of mares at risk for sensitization against the common offending antigens (Aa and Qa) vary among breeds, depending on the frequency in the population of each gene involved (Table 53-7). Increased numbers of mares at risk in a breed does not necessarily translate into higher numbers of NI cases. A corresponding number of stallions lack the factors in question and are therefore unable to sire foals with the offending antigen.[249] Virtually all mule pregnancies are incompatible with regard to donkey factor.[251]

Although more common in multiparous mares, NI can occur with the first pregnancy.

53.23.1.6 Necropsy Findings

Pale tissues with or without icterus and splenomegaly are characteristic necropsy findings in foals dying of NI. Lesions associated with RBC destruction and anemia, such as nephrosis and centrilobular hepatic necrosis, may also be present.

Table 53-7 Estimated Percentage of Mares in Selected Breeds "At Risk" for Producing Foal with Neonatal Isoerythrolysis*

Breed	At Risk for Aa	At Risk for Qa
Thoroughbred	2%	16%
Standardbred, pacer	22%	†
Standardbred, trotter	3%	†
Saddlebred	25%	88%
Quarter horse	25%	68%
Arabian	3%	72%

Data from Bailey E, Conboy HS, McCarthy PF: Neonatal isoerythrolysis of foals: an update on testing, *Proc Am Assoc Equine Pract* 33:341, 1987.

* Based on the lack of all alleles, including factors Aa or Qa.

† All mares lack factor Qa and are technically "at risk," but all stallions in this breed also lack the factor.

53.23.1.7

Treatment and Prognosis

In most cases, by the time NI is recognized clinically (e.g., when the foal is about 24 hours of age), the bulk of colostral antibody will have been depleted from the mare's milk, and the absorptive ability of the foal's gut will have diminished. Withholding milk at this point is of questionable benefit.

Stress should be minimized and exercise restricted. Affected foals have decreased exercise tolerance and can collapse and die if forced to follow their dams. Generalized supportive care should be administered as indicated by clinical parameters. Intravenous fluids are frequently indicated to promote diuresis to minimize the effects of the large hemoglobin load presented to the kidneys. Acid-base balance should be monitored and corrected if indicated.

If the anemia becomes severe (e.g., PCV of 10% to 15%), transfusions that provide RBCs should be considered. Unless the PCV drops below this level, transfusion may not be necessary if rest is enforced. The object of transfusion is to provide the affected foal with RBCs that will not be destroyed by the maternal alloantibodies that were absorbed from colostrum. The foal is immunologically naive and will not have autologous alloantibody directed against any RBCs that would have an immediate effect on transfused RBCs. Thus the key is to select an RBC donor whose cells will not be destroyed by the maternal antibody derived from colostrum. Crossmatching, with particular attention to the reaction of mare sera, colostrum, and foal sera (all contain the same antibody), with the donor RBCs, is important for selecting a cell that will not be destroyed by the maternal antibody.

Washed RBCs from the dam are obviously the perfect choice in terms of cells that will not react with the alloantibodies present in the foal. However, to avoid administering additional harmful antibody to the foal, the mare's sera (containing antibody against the foal's cells) must be removed by washing before administration. Up to 6 to 8 L of blood can be collected from the mare and anticoagulated with acid-citrate-dextrose (ACD) or sodium citrate (3.8% Na citrate solution; 1 part Na citrate/9 parts blood), although 3 to 4

L usually provides sufficient RBCs. The preparation of large volumes of washed cells is aided by a large-volume centrifuge, but the procedure can be accomplished by serial sedimentations. Anticoagulated blood from the mare is allowed to settle for 1 to 2 hours. The plasma is aseptically drawn off; a similar or greater volume of sterile isotonic saline (0.9% Na citrate) is added to the RBCs and mixed; and the RBCs are again allowed to settle. The saline is then drawn off and discarded. At this point, the RBCs can be resuspended in an equal volume of isotonic saline for administration, or the washing procedure can be repeated. The sedimentation method is less desirable than centrifugation because it is slower and does not remove as much of the offending antibody. The aim is to dilute any harmful antibody to insignificant levels.

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If the dam's RBCs cannot be used, alternative donors can be selected. The donor should lack the antigen to which the alloantibody is directed. Because it is generally not possible to blood-type donors on short notice, a previously identified horse that has been determined by blood typing to be Aa–, Qa–, and free of alloantibody is a good choice for donor, based on most cases of NI being associated with these two antigens. The odds of randomly selecting a donor that lacks the offending type (e.g., Aa–, Qa–, or both) and would therefore be a suitable donor vary significantly with the breed and would mirror the percentage of the population of mares at risk. For example, the odds of finding an Aa– thoroughbred to serve as an RBC donor would be about 1 in 50 (2%), whereas in quarter horses the odds would be about one in four (25%) (see Table 53-7). The sire of the foal is not the donor of choice. He shares the same RBC antigens as the foal, and his cells would react with the maternal alloantibody present, adding more of a load to the foal's reticuloendothelial system as the cells are destroyed.

With mules the same considerations in the use of washed cells would be necessary if the dam's cells were used. However, because the offending antibody is generally directed against a unique donkey antigen, RBCs from any horse apparently would be satisfactory. Horses do not appear to make naturally occurring antibodies against donkey factor; therefore, in most cases it is not necessary to wash the cells from horses that would not be likely to have been immunized by pregnancy against donkey factor.

Transfusing RBCs that will not react with maternal alloantibody means introducing an obviously incompatible cell into the foal, a cell that will probably not survive long in the circulation. Such transfusions should be considered temporary stopgap measures. Transfused cells may also sensitize the foal to future transfusions, causing reactions (perhaps not within hours or a few days, but potentially within a week). This must be considered when weighing the potential good versus potential harm of such transfusions.

From 1 to 4 L of washed RBCs or whole blood is usually adequate to produce clinical improvement, although some cases may require repeated transfusion if the anemia progresses. Exchange transfusions can be done whereby blood is administered through one jugular vein and withdrawn simultaneously from the opposite jugular vein and discarded, allowing administration of large volumes of blood without overloading the vascular system. There is no good evidence to suggest that this is more effective than simply providing a source of RBCs that are unaffected by the maternal antibody.

Limited transfusion studies in adult horses have suggested that transfused RBCs do not survive long in circulation (e.g., 2 to 4 days), whereas in foals, cells survived slightly longer (e.g., 4 to 6 days).[253,254] PCVs in foals with NI usually increase after transfusion and then gradually decline. This decline is probably not a concern if it is gradual, because the PCV of the foal generally levels off as the offending maternal antibody is metabolized. However, even short-term survival of cells may be of benefit in severely affected foals and may allow them to survive until the titer of maternal anti-RBC immunoglobulin has declined in the circulation.

The prognosis varies, depending on the quantity of antibody ingested, the rapidity of onset of signs, and the degree of anemia. Foals with peracute NI may die before the problem is recognized, with no chance for

administration of therapy. Foals that develop the condition more slowly may respond to supportive care or transfusion if the PCV continues to fall.

53.23.1.8

Prevention and Control

Several strategies are available for prevention of NI.[255,256] First, identify broodmares at risk for development of NI by testing them for the presence of Aa and Qa. Mares negative for either antigen, which means they could potentially make antibodies against them, should be considered at risk. One subsequent strategy would be to breed at-risk mares to Aa/Qa-negative stallions, thus eliminating the possibility of the foal inheriting the offending antigens. However, in breeds in which a relatively small part of the population is negative for these antigens, identifying a stallion that is negative for these antigens and suitable on the basis of other criteria may be difficult. The percentage of at-risk females based on the presence or absence of Aa or Qa is somewhat balanced by the numbers of males able to transmit the offending antigen. For example, all standardbred mares would be considered at risk based on the absence of Qa; however, because the antigen Qa is not present in the standardbred population, no stallions have the Qa antigen to pass on to foals.

In the circumstance of an unknown or incompatible matings, sera from at-risk mares should be screened for the presence of anti-RBC antibodies within 30 days before foaling. This can be done by submitting a serum sample and an anticoagulated sample to a screening laboratory. A panel of 10 to 12 different RBCs selected to represent all major blood groups is adequate to screen for anti-RBC antibody in the absence of blood from the sire. If results of serum testing are equivocal (e.g., low but positive titer, especially if there is anti-Aa or anti-Qa activity), the test should be repeated closer to the time of parturition because the levels of offending antibody can rise very quickly late in gestation.

If anti-RBC antibody is detected in the mare before parturition, the colostrum should be checked for reactivity against the foal's RBCs before allowing the foal to ingest colostrum. An alternative source of colostrum should be provided to the foal. Most field screening tests of colostrum have not proved to be satisfactory for practical use; however, the jaundiced foal agglutination (JFA) test described in Box 53-2 has been shown to correlate well with the standard hemolytic assay, and it may detect antibody that does not react on the standard agglutination tests.[257,258]

Horses negative for Ca frequently make anti-Ca antibody; however, this antibody is not known to produce adverse effects in the foal. It has clouded the issue of field screening tests for NI because it causes positive reactions in most screening tests at low dilutions. Because these tests do not differentiate between antibody to Aa, Qa, Ca, or any other blood group, anti-Ca. antibody, when present in low dilutions, is responsible for many false-positive reactions. This antibody actually appears to play a protective role in the prevention of sensitization of mares to NI through a mechanism of antibody-mediated immune suppression. Aa−/Qa− mares that are also Ca− (and thus often produce anti-Ca antibody) become sensitized to Aa and Qa at a significantly lower rate than mares that are Ca+.[259] This is attributed to anti-Ca antibody being produced by Ca− mares. The anti-Ca antibody may more rapidly remove potentially sensitizing cells from the circulation before they stimulate production of antibody against Aa or Qa.

Other antigens infrequently have been associated with NI in foals. These include factors Db, Dc, Dg, Ua, Pa, Qc, and Ab.[226,228,260–263] Two other factors, R and S, have been described to be associated with NI, but they are not detected by routine hemolytic or agglutinating methods and are only detected using an antiglobulin test (direct Coombs' test).[248] Because of the difficulty in testing for these antigens, there has never been sufficient agreement between laboratories to allow international designation. These antigens may not be

detected using the JFA screening test.[249] Estimates are that 1 in 2000 pregnancies may result in sensitization against some other antigen besides Aa or Qa. Because these cases occur so infrequently, it is not practical to consider mares without these antigens to be at risk for NI. A blood type evaluation of mares with a history of production of foals with NI should be done to identify the offending antibody/antigen.

53.23.1.8.1

Box 53-2 Jaundiced Foal Agglutination (JFA) Test

53.23.1.8.1.1

MATERIALS

1. Centrifuge capable of spinning 300 to 600 × gravity
2. Test tube rack
3. Test tubes: 13 × 100–mm disposable or blood collection tubes
4. Pasture pipettes and rubber bulbs or other pipette system to deliver 1-mL volumes
5. Isotonic (0.9%) saline at room temperature
6. Serum or colostrum from the mare; RBCs from mare and foal, preferable in EDTA anticoagulant

53.23.1.8.1.2

METHODS

1. Collect colostrum from the mare.
2. Collect an EDTA-anticoagulated blood sample from the foal before nursing.
3. Set up six tubes and add 1 mL of saline to each tube. Label the tubes Control, 1:2, 1:4, 1:8, 1:16, and 1:32.
4. Make serial dilutions of the colostrum at 1:2, 1:4, 1:8, 1:16, and 1:32 in five of the tubes. Add 1 mL of colostrum (or serum) to the tube labeled 1:2 and mix. Then take 1 mL from that tube and add it to the second tube labeled 1:4 and mix. Take 1 mL from that tube and add it to the third tube labeled 1:8, and so on, until all five dilution tubes have been filled. Discard 1 mL from the last tube labeled 1:32.
5. Add 1 drop of the foal's whole blood to each of the six tubes and mix.
6. Centrifuge the tubes for 2 to 3 minutes at a medium speed (300 to 500 × gravity).
7. Invert each tube, pouring out the liquid contents; observe the status of the button of RBCs at the bottom of the tube. *Complete* agglutination causes the cells to remain tightly packed in the button; *strong* agglutination causes the cells to remain in large dumps; for *weaker* agglutination the cells are in smaller dumps as they run down the side of the tube. When there is *no* agglutination, the cells easily flow down the side of the tube. This should be the case in the control tube. If the cells in the control tube are clumped, they may be autoagglutinating, and the results will have questionable validity.

If there is a positive reaction with the foal's cells, the test should be run with the dam's own RBCs to ensure that the conditions of the test and the viscosity of the colostrum are not causing the agglutination.

Positive reactions at 1:16 or greater are considered significant. At levels of 1:16 or greater, this test correlates well with the standard hemolytic assay. At dilutions of less than 1:16, the correlation is not as good, and more false-positive results will be recorded. Also, other factors (e.g., viscosity of colostrum) make less diluted samples more difficult to read.

Data from Bailey E, Conboy HS, McCarthy PF: Neonatal isoerythrolysis of foals: an update on testing, *Proc Am Assoc Equine Pract* 33:341, 1987; and Blackmer JM, Costa LRR, Koch C: The jaundiced foal agglutination test, *Vet Tech* 23:577, 2002.

53.23.1.8.2

Box 53-3 Laboratories in North America Providing Equine Neonatal Isoerythrolysis (NI) Testing*

Shelterwood Laboratory

DNA Diagnostics, Inc.

P.O. Box 455, 626 Bear Drive

Timpson, TX 75975

(936) 254-2228

www.dnadiagnostics.com

Hematology Laboratory

University of California, Davis

Veterinary Medical Teaching Hospital

Clinical Pathology, Room 1012

1 Garrod Drive

Davis, Ca 95616

(530) 752-1303

www.vmth.ucdavis.edu

Equine Parentage Testing and Research Laboratory

101 Dimock Animal Pathology Building

University of Kentucky

Lexington, KY 40546-0076

(859) 257-1165

www.ca.uky.edu/gluck/

Rood and Riddle Equine Hospital

2150 Georgetown Road

Lexington, KY 40511

(859) 233-0331

www.roodandriddle.com

Hagyard Laboratory

4250 Iron Works Road

Lexington, KY 40511

(859) 259-3685

hdmlab@hagyard.com

www.hagyard.com

* Serum or colostrum from the suspect mare is needed to screen for the presence of alloantibody. Acid-citrate-dextrose (ACD)–anticoagulated blood is generally preferred in screening for RBC antigens.

Box 53-3 lists laboratories providing NI screening tests (e.g., Aa, Qa, and Ca typing and screening of sera for alloantibody). Routine agglutinating crossmatch tests using mare serum or colostrum and foal or sire cells can be performed by most veterinary or human hematology laboratories.

53.23.2 Ruminants

Neonatal isoerythrolysis is not a naturally occurring disease in cattle, sheep, or goats. Its occurrence in cattle has been associated with administration of vaccines derived from blood, such as certain anaplasmosis and babesiosis vaccines.[226] When used on breeding females, these vaccines may sensitize the dam to certain blood groups, most often in the A and F systems. Under chance circumstances, if the blood types of the sire and offspring reflect these systems and the dam has produced alloantibodies, an isoimmune hemolytic crisis may appear in the calf associated with successful passive transfer. Hemolytic crises are rare in sheep and are even difficult to induce experimentally.[226]

53.24 EQUINE NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

53.24.1 Definition and Etiology

Neonatal alloimmune thrombocytopenia (NAIT) is a condition characterized by the destruction of platelets in the circulation of a foal by alloantibodies of maternal origin absorbed from colostrum.[264] The syndrome has been observed in horse and mule foals.[251,264,265] The prevalence of NAIT is not known. Some foals may be asymptomatic, and the condition may be self-limiting as alloantibody is metabolized.

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53.24.2 Clinical Signs and Differential Diagnoses

Few clinical signs may appear unless foals are traumatized. Affected foals may have prolonged bleeding from venipuncture sites. Petechial hemorrhages may not be present. Other conditions often associated with thrombocytopenia in neonates include sepsis, disseminated intravascular coagulation, equine infectious anemia, drug-induced thrombocytopenias, and angiopathies. The challenge is to determine whether the thrombocytopenia is primarily caused by allogeneic antibodies or secondary to some other disease process. For differential diagnoses of thrombocytopenia in neonatal foals, see Chapter 19.

53.24.3 Clinical Pathology

Profound thrombocytopenia in the absence of other hematologic changes typifies uncomplicated NAIT. Evidence of successful passive transfer is present based on quantification of serum IgG. Affected foals are thrombocytopenic. Thrombocyte counts less than 10,000/μL have been observed. Prolonged bleeding from

venipuncture sites and petechiae may be present.[264] Demonstration of significant amounts of antibody in the colostrum (or serum from the mare) that are directed against platelet antigens expressed by the foal provides a definitive diagnosis of NAIT. However, assays for equine platelet-bindable and platelet-associated immunoglobulins are not routinely available.

53.24.4 Pathophysiology

The pathophysiology is believed to mirror that of neonatal isoerythrolysis. In mares sensitized to platelet antigens, alloantibodies are concentrated in the colostrum late in gestation. These antibodies are passed to the foal through passive transfer. If the foal's platelets carry the antigen that the antibody recognizes, the platelets become antibody coated. Subsequently, they are removed prematurely by the reticuloendothelial system. Platelet antigens have not been characterized in horses; however, platelet-associated antibodies have been demonstrated in affected foals. Circulating antibody is removed by attachment to platelets and rapid clearance by the reticuloendothelial system.

53.24.5 Treatment and Prognosis

Circulating antibody is removed relatively quickly, and treatment may not be necessary. Platelet-rich plasma may be indicated in cases of serve thrombocytopenia accompanied by clinical signs of bleeding problems. As offending antibody is removed, however, the problem will tend to be self-limiting.

53.24.6 Prevention and Control

Currently, there are no screening tests to predict NAIT. After production of an affected foal by a mare, it would be prudent to provide an alternate source of colostrum to foals born in subsequent pregnancies.

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54 Chapter 54 Disorders Caused by Toxicants

Consulting Editors

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Toxicology cases are not the most common clinical presentation to the veterinarian, but they challenge the clinician because large numbers of animals may be involved, emotions run high, litigation is frequently suggested, and publicity can be intense. This chapter provides tools to approach these potentially complex cases with confidence. After a general discussion of diagnosis and treatment of poisoning in livestock, common toxicoses caused by plants and other natural toxins, metals, inorganic compounds, and organic-synthetic compounds are discussed. Each section contains general comments about a group of poisons, followed by information on specific, commonly recognized toxicants. Each discussion begins with identification of the toxicant, its sources, likely targets, and hazardous situations, then describes the mechanism of toxicosis, signs and lesions, clinical pathology, diagnostic parameters, and approaches to management and prevention, including residue avoidance.

54.1 DIAGNOSIS OF POISONING

When toxicosis is suspected, possible sources of the toxicant should be identified and exposure to those sources rapidly eliminated. Diagnosis of poisoning rarely results from a single piece of evidence; rather, historical, clinical, pathologic, and analytical findings all need to be considered.

The investigation begins with tracing of animals, feedstuffs (especially lots and batches), and events that occurred up to the onset of signs to identify likely etiologies. Environmental conditions to check include water sources, surrounding industry or elements, plants, animals, human contact, and availability of these items to the animals. Samples of possible toxic sources should be obtained, labeled, and held for later testing.

Feed (constituents and as-fed) samples should not be pooled among lots or storage bins. Composite samples that are representative of an entire lot should be obtained within each lot. Hay and forage are also sampled in a representative manner and should be examined for weeds. As-fed materials can be tested for many toxicants, and then constituents are tested for any toxicant that is identified to track the original source. Weeds that are abundant in pasture or hay are identified (Table 54-1). Diagnosis of plant toxicity is aided by finding evidence of consumption of a plant from the animal or grazed pasture.

Water and environmental samples should be obtained. Water is sampled at the trough, in transport containers, and at the source. Samples of algal blooms are mixed in 10% neutral-buffered formalin for identification, and with a second 2-liter sample of fresh, thick bloom for toxin identification.

Clinical toxicoses may be *acute* (signs often appear in many animals at once; see causes of sudden death, Chapter 14), *chronic* (e.g., poor weight gain in cattle that graze locoweed), or *absent* (e.g., food animal residues, antibiotics in milk, organochlorines in fat). Signs may be *specific* (bradycardia from cardiac glycosides) or *vague* (diarrhea caused by many syndromes). Samples of blood, serum, urine, body fluids, and ingesta should be obtained for clinical pathologic and toxicologic analyses (see Table 54-1).

Complete necropsies should be performed on dead animals. The urine should be sampled first, after obtaining samples that might become contaminated during the examination. Appropriate tissues should be fixed for histologic examination. Separate samples of tissue are frozen fresh for toxicologic analyses (see Table 54-1). The

ingesta is completely examined for foreign objects and plants and then sampled in representative fashion for chemical analyses.

Pathologic lesions may range from none (residues or biochemical toxicants) to severe. Lesions may be very specific (e.g., nigropallidal encephalomalacia from yellow star thistle poisoning) or nonspecific (e.g., gastroenteritis from infectious, metabolic, and toxicologic causes). Some poisonings can be grouped by the type of lesion produced. For example, white snakeroot *(Eupatorium rugosum),* selenium deficiency, cobalt toxicosis, and monensin toxicosis all can cause white streaking in an animal's heart.

Chemical analysis can be useful as part of the diagnostic puzzle but rarely stands alone. Unless a specific toxicant is suspected, samples are kept frozen or cool (whole blood and some dry feeds) until clinicopathologic, pathologic, microbiologic, and histologic findings are known. Those tests help the diagnostician select the most useful toxicology tests. Environmental samples also must be available for testing because many toxicants, including plants, monensin, other antibiotics, and most mycotoxins, may not be detectable in animal samples.

Another diagnostic tool that may be useful is bioassay. One type of bioassay is assessment of the response of animals to therapy (e.g., animals with carbamate insecticide poisoning respond to atropine therapy). A second type is measurement of a relevant biomarker of toxicant exposure in an animal sample (e.g., cholinesterase assay to indicate exposure to an organophosphorus insecticide). A third type of bioassay, important for new toxicants, is administration of the suspected toxic material (or an extract) to target animals or laboratory animals to determine if a source is toxic.

Analytical results are interpreted in light of the history, epidemiology, signs, and pathology. A poison is determined by the dose received and the animal's response to that compound. The animal's response to a compound is affected by species, age, gender, environment, feed, medication, and other diseases. Species differences stem from varying habits (e.g., foraging), absorption (ruminants, horses, and swine have different digestive systems), and pathways for drug metabolism. Very young and old animals will respond differently to toxicants than typical adults. Neonatal animals tend to absorb chemicals more readily than adults (e.g., lead), are at risk from compounds in milk (white snakeroot), have poorly developed blood-brain barriers (penicillin or ivermectin toxicity), and are inefficient metabolizers of xenobiotics in the liver for up to 30 days after birth (long sleeping times caused by barbiturates). Elderly animals can have deficient liver metabolism, renal function, and immune competency.

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Table 54-1 Sampling Guide for Analytical Toxicology

Sample	Amount	Commonly Requested Tests
Whole blood	5-10 mL (EDTA)	Lead, arsenic, mercury, molybdenum, manganese, selenium, cholinesterase, anticoagulants, cyanide, some insecticides
Serum	5-10 mL (from clot)	Copper, zinc, iron, magnesium, calcium, sodium, potassium, drugs, nitrates, ammonia, alkaloids, tannins, vitamins A and E
Urine	50-100 mL	Drugs, heavy metals, plant alkaloids, tannins, cantharidin, fluoride
Milk	30 mL	Organochlorine insecticides, PCBs, antibiotics
Ingesta	1 kg	Heavy metals, plants, oleander, alkaloids, tannins, insecticides, drugs, nitrates, cyanide, ammonia, other pesticides, cantharidin, avitrol
Liver	300 g	Heavy metals, insecticides, anticoagulant rodenticides, some plant toxins, some drugs, vitamins A and E
Kidney	300 g	Heavy metals, calcium, some plant toxins
Brain	Half of brain	Sodium, organochlorine insecticides, cholinesterase
Fat	100 g	Organochlorine insecticides, PCBs
Ocular fluid	One eye	Nitrate, ammonia, potassium, magnesium
Feeds	1-kg composite	Pesticides, heavy metals, salts, feed additives, antibiotics, ionophores, mycotoxins, growth promoters, nitrates, sulfate, chlorates, cyanide, plant toxins (gossypol, alkaloids, tannins), plants (send weeds for identification), vitamins A, D, E, and K
Plants	Entire plant, press and dry, or freeze	Identification, alkaloids, tannins, glycosides
Water	1 L in preserving jar	Pesticides, heavy metals, salts, nitrate, sulfate, blue-green algae
Environmental	Source material	Variety of organic, inorganic, and natural toxicants

EDTA, Ethylenediamine tetraacetic acid; *PCBs,* polychlorinated biphenyls.

54.2 TREATMENT OF POISONING

Once poisoning is suspected, the first objective is to minimize exposure of all animals in the herd to a suspected toxicant. Strategies include removal of suspected sources, provision of alternative feeds, changing water sources, and moving the animals.

Once life support (airway, circulation) has been accomplished, animals are decontaminated. Decontamination includes washing or bathing dermally exposed animals. Animals exposed to oral toxicants can be given activated

charcoal, with or without a cathartic, to adsorb most organic toxicants. Some treatments can alter absorption of metals (e.g., sodium sulfate to block lead, molybdate for copper) or some organics (changing pH slows ammonia absorption). Nonspecific gastrointestinal damage, such as from nonsteroidal antiinflammatory drugs (NSAIDs), benefit from administration of demulcents (kaolin). Excretion of some organic acidic drugs or toxicants may be enhanced by making the urine more alkaline (ion trapping).

After decontamination, attention centers on maintenance of vital systems (fluid, electrolytes, and acid-base correction), and therapy depends on treating for specific signs (e.g., correction of arrhythmias from oleander) and administration of specific antidotes. Table 54-2 lists common therapies specific for poisoning.

54.3 PLANTS AND OTHER NATURAL TOXICANTS

FRANCIS D. GALEY

54.4 TOXIC PLANTS

Plant toxicity causes both direct and indirect losses to the livestock industry. Direct losses (deaths) cost producers approximately $340 million in 1989.[1] More recent estimates suggest annual losses may range 2% to 3% annually.[2] Indirect losses, not included in that estimate, are likely to be much higher. Estimates of losses in individual animals from locoweed *(Oxytropis, Astragalus)* in New Mexico ranged from $75 to $282 per head, depending on severity of poisoning, using production and management costs from the mid-1999s.[3] In addition to direct losses, indirect losses can result from reduced weight gains, decreased reproductive performance, poor production, fencing and management expenses, and effects on land values.

Plants toxic to herbivores may be in forages (hay, silage), grain (seeds), pastures, and water (blue-green algae). Diagnosis of plant poisoning uses an approach similar to that described in the introduction, except that few chemical assays are available for plant toxins. Thus, diagnosis of a plant poisoning relies heavily on identification of the plant in feed, pasture, or ingesta, along with appropriate clinical and pathologic findings. The presence of a poisonous plant in the environment is insufficient diagnostic evidence of plant poisoning without evidence of consumption by the animal (signs of grazing or presence of the plant or its toxin in ingesta).

Many toxic plants are not palatable and are avoided by livestock unless grazing is forced by other circumstances. Conditions favorable to ingestion of toxic plants include overgrazing, drought, use of some herbicides, and masking the plants in hay, silage, or grain. Environmental and harvesting conditions that can alter toxin levels in plants include soil type and content, herbicide use,[4] overwatering, drought, fertilizer application, and sunlight.[5] 1692
Conditions related to plant toxicity vary, however, depending on all the listed factors. Although overgrazing and 1693
intensive management may increase risk of poisoning from many plants, others such as the larkspurs (*Delphinium* species) are present in pristine conditions.[6,7] Usually, poisoning occurs when the toxic plants become more palatable than native forages, or when mismanagement has resulted in animals being forced to ingest less desirable forages.

Table 54-2 Common Therapeutic Agents for Poisoning

Agent	Action
Activated charcoal	Adsorbs most organic toxicants
Sodium sulfate	Cathartic with charcoal; binds lead; avoid if dehydrated or diarrhea
Magnesium sulfate	Cathartic; binds lead; avoid if dehydrated, diarrhea, or depression
Sorbitol	Cathartic
Atropine	Anticholinergic (extremely dangerous in horse)
2-PAM	Reverses organophosphorus binding
Methylene blue	Treatment for methemoglobinemia
Sodium nitrite	Used with sodium thiosulfate for cyanide poisoning
Sodium thiosulfate	Treatment for cyanide poisoning
Calcium EDTA	Chelation therapy for lead
D-Penicillamine	Chelation therapy for lead, copper
Dimercaprol (BAL)	Chelation therapy for arsenic, lead
DMSA	Chelation therapy for metals (awaiting approval)
Ammonium tetrathiomolybdate	Treatment for copper toxicosis
Barbiturates	Treatment for convulsants
Diazepam	Treatment for convulsants
Sodium bicarbonate	Ion trapping for acids, treatment for acidosis
Calcium, magnesium, fluids	Treatment for hypocalcemia, hypomagnesemia
Saline, lactated Ringer's, dextrose	Treatment for fluid and electrolyte deficits
Doxapram	Respiratory stimulant
DMSO, mannitol, corticosteroids	Treatments for cerebral edema
Mineral oil	Gastrointestinal evacuation
DSS	Treatment for gastrointestinal impactions
Emergency drugs	Drugs for cardiac and respiratory emergencies (e.g., epinephrine, lidocaine, oxygen)
Emergency equipment	Instruments needed to administer drugs, treat respiratory insufficiency (e.g., endotracheal tubes, tracheostomy sets), jars/ packages/tubes for analytical samples

2-PAM, 2-Pyridine aldoxime methiodide (pralidoxime); *EDTA,* ethylenediamine tetraacetic acid; *BAL,* British antilewisite; *DMSO,* dimethyl sulfoxide; *DMSA,* dimercaptosuccinic acid; *DSS,* dioctyl sodium sulfosuccinate.

To identify a plant, it should be sampled in its entirety: flower, seed, pod, leaves, and roots. For shipping, the plant should be dried in a newspaper under some heavy books. Plants or leaves found in ingesta should be separated

from the ingesta and shipped frozen for identification. In an emergency a plant can be pressed on a high-quality office copier, and the copy can be faxed to a diagnostic toxicologist for identification. Although chemistry analysis for most plant toxins in biologic specimens is not routinely available, recent developmental activity is making that option more available. Tests are currently available for toxins such as cyanide, nitrate, gallotannins, selected alkaloids, and some glycosides (e.g., cardiac glycosides).[5,8–11]

With a few well-documented exceptions, such as nitrate and cyanide, specific antidotes are rarely available for plant toxins (many have not been characterized). Thus, the primary goals when treating plant poisoning include providing supportive care and eliminating exposure of animals to the suspected feed, plant, or pasture. Curtailing exposure can entail switching feed sources, moving animals, fencing, mowing, and providing supplemental feed. Adsorbents such as activated charcoal may be administered to minimize absorption of organic compounds, including many plant toxins.[12]

Prevention is the most effective cure for plant toxicosis. With a few exceptions, such as larkspur, which is palatable and grows in pristine pastures,[13] many toxic plants are unpalatable and grow on overgrazed and disturbed soils. Therefore, plant toxicosis often can be prevented by feeding adequate amounts of feed that is free of toxic plants, managing grazing areas,[14] controlling weeds, and using proper harvest techniques for feeds. Some management schemes use selective spraying of herbicides or biologic control agents to help manage the problem.[15] Conditioned aversion of animals to ingestion of some plants has also been explored using lithium chloride to create persistent aversions to selected plants.[16,17] Averting lactating cattle to plants using lithium chloride apparently does not result in averting calves to milk contaminated with low levels of the agent.[18] In some cases, animals that are less susceptible to a given plant toxicity might be used to graze infested rangeland.[19] Timing of grazing can be altered to impact toxicity to a variety of plants, such as lupines, locoweeds, and ponderosa pine.[20]

Some plant toxins may cause potentially hazardous or otherwise noxious residues in milk and meat. For example, tremetone from white snakeroot, selenium, and several alkaloids may be passed in milk.[21,22] Thus, care should be taken when providing advice about the disposition of animals exposed to plant toxicants, especially about the disposition of milk from lactating animals.

Because a discussion of all toxic plants is beyond the scope of this chapter, this section discusses general aspects of plant toxicology as well as unique aspects of poisoning resulting from select, common classes of poisonous plants. It is assumed that the plants covered here have been identified. Plants can be identified using many resources, including various local agricultural extension agents or bulletins, textbooks,[23] diagnostic laboratories, veterinary schools, herbaria, Internet, and other botany sources. Specific statements about geographic location of plants are not made, because modern feed and seed transport have blurred the distinction between regions of the United States in which certain plants may be found.

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54.4.1 Alkaloids

Alkaloids are compounds that have nitrogen, usually in a heterocyclic ring, and are usually basic chemicals. Alkaloids are the largest class of secondary plant compounds, present in up to 30% of herbaceous species in North America.[24] Alkaloids are often quite bitter, and many are toxic.[25]

54.4.1.1

LOCOWEED

Astragalus spp.: Locoweeds

Oxytropis: Crazyweed

Swainsona: Darling pea

The locoweeds, *Astragalus* and *Oxytropis* species, are found from the Rocky Mountains and Texas to California. Plants of both genera are perennial, herbaceous legumes with opposite, pinnately compound leaves. Flowers are purple to white racemes.[25] Seeds are borne in pods. Various species of *Astragalus* have different toxic chemicals and effects. Some species are nontoxic, whereas others have excessive selenium concentrations, 3-nitrocompounds, or swainsonine (the locoweed toxin, also found in *Swainsona*).[26–28] Swainsonine (locoweed) inhibits cellular α-mannosidases, leading to abnormal glycoprotein metabolism.[29,30]

Locoweed is unpalatable to livestock and is initially ingested when other feed is lacking (during the winter and spring).[31] In addition, evidence suggests that cattle may learn to ingest locoweed from one another.[32] Once ingestion is initiated, however, animals apparently acquire a taste for the plant.[31] Locoweed remains toxic when dry,[33] and it affects all classes of livestock. Locoweed ingestion (up to 90% of body weight of plant material) causes gradual onset of signs related to the production, metabolic, central nervous, reproductive, and cardiovascular systems.[31,33–38] Affected animals become emaciated, lethargic, dull, and ataxic, with an impaired sense of direction.[33,37] Animals are nervous despite the depression and, especially horses, may react violently to stimulation. Horses do not seem to recover from the tendency to react uncharacteristically to stimuli. Reproductive consequences of "locoism" include abortion, prolonged estrus, altered breeding behavior, decreased libido, inhibition of normal spermatogenesis, weak and docile newborns, and deformed limbs with flexed tendons and joint laxity.[34,37,38,40,41] Locoweed ingestion predisposes calves to development of right-sided congestive heart failure at high altitudes ("high mountain disease").[35,36]

Sheep fed locoweed had clinical pathologic evidence of liver and renal (mild) damage, with increased serum concentrations of alkaline phosphatase (ALP), aspartate transaminase (AST), and blood urea nitrogen (BUN).[39,42] The major postmortem finding in locoweed intoxication is emaciation. Microscopically, locoweed (and swainsonine) causes widespread neurovisceral cytoplasmic vacuolation in animals and the fetus (if present).[43–45] The brain, liver, and kidney are the major affected organs. The vacuoles contain mannose-rich compounds.[46] Diagnosis of locoweed toxicosis is based on evidence of plant consumption, clinical signs, and lesions. No chemistry test is available for locoism. New tests are under development to stain tissues for mannose accumulation[46] and measure α-mannosidase activity in serum to indicate exposure to locoweed.[47]

No antidote is available for locoweed poisoning. Exposure to the plant should be stopped and proper nutrition provided. Recovery from emaciation frequently occurs, but horses that have developed locoism cannot be trusted. Proper grazing management of rangeland, including using range when other, more

palatable plants are present, is a recommended strategy to minimize losses caused by the plant.[48] Milk from animals exposed to locoweed can be toxic, suggesting that swainsonine is passed in milk.[49] Clearance studies suggest that poisoned animals should be given approximately 28 days to clear swainsonine because of an estimated half-life in livestock of 60 hours.[47,50]

54.4.1.2 PYRROLIZIDINE ALKALOIDS

Senecio spp.: Tansy ragwort *(S. jacobea)* and groundsels

Crotalaria spp.: Rattlebox

Cynoglossum officinale: Houndstongue

Amsinckia intermedia: Fiddleneck

Heliotropium spp.: Heliotrope

Echium plantagineum: Patterson's curse, Salvation Jane

Losses from pyrrolizidine alkaloids occur throughout the United States, resulting from ingestion of various species (spp.) of plants from the families of Compositae (*Senecio* spp.), Leguminosae (*Crotalaria* spp.), and Boraginaceae (*Cynoglossum* and *A. intermedia*).[51] *S. jacobea* is found in the northwestern United States, *S. vulgaris* (common groundsel) can be found throughout the western United States, *Crotalaria* is present in the Midwest, *Cynoglossum* is primarily in the Rocky Mountain region, and *Amsinckia* is in California. Toxin concentrations are highest in seeds, flowers, and leaves and are lower in stems. The most toxic pyrrolizidine alkaloids are diester rings with a 1,2 double bond and a branched ester group.[51] The compounds are bioactivated in the liver to reactive pyrroles and *trans*-4-hydroxy-2-hexenal.[52,53] The reactive metabolites bind cell molecules and cross-link deoxyribonucleic acid (DNA), leading to necrosis, alteration of cell division, or carcinogenicity.[52] The carcinogenicity of these compounds, which is a result of both genotoxic and promoting properties, is a reason for food safety concerns related to the pyrrolizidine alkaloids.[54,55]

Plants with pyrrolizidine alkaloids are unpalatable. Most poisonings occur when animals are forced to graze the plant, or when the plant is masked in hay (*Senecio* spp. and *A. intermedia*) or grains (*Crotalaria* spp.; a major contaminant before the availability of herbicides for weed control).[51] Toxicity is retained in dry hay and grains. All classes of livestock are affected. Small ruminants such as sheep are more resistant to the alkaloids than are cattle and horses. For example, ingestion of as little as 5% of their body weight of tansy ragwort *(S. jacobea)* in hay may be lethal to a cow or horse. Conversely, more than 100% of their body weight in plant material is needed to cause pyrrolizidine alkaloid poisoning in sheep and goats.[52] The resistance of sheep to the alkaloids likely results from differences in liver biotransformation patterns.[51] For example, sheep tend to have lower rates of hepatic production of toxic pyrroles plus higher levels of glutathione conjugation of toxic metabolites.[56] Interestingly, ingestion of pyrrolizidine alkaloids will enhance the toxicity of copper in sheep.[57] Although cattle and horses tend to have similar sensitivity to *Senecio*

species, it is apparent that cattle tend to resist the hepatotoxic effects of *Amsinckia* at levels in hay that would be hazardous to horses (although *Amsinckia* may still cause nitrate toxicity in the cattle instead).

Animals with pyrrolizidine alkaloid toxicosis are usually presented with signs and lesions compatible with liver failure (see Chapter 33 for a complete description of signs and lesions).[51,52,58] In addition to liver effects, pulmonary disease also has been reported for *Crotalaria* poisoning.[51] Signs may be delayed for months after ingestion of the plant, appearing after the liver damage has had an opportunity to become chronic.[59] Emaciation and hepatoencephalopathy often occur, leading to common names for the disease, such as “walking disease,” “walkabout,” and “hard liver disease.” 1694 1695

Diagnosis of pyrrolizidine alkaloid toxicosis depends on a history of exposure to the plants, clinical and pathologic evidence of liver failure, and classic histologic lesions.[60–62] Antemortem diagnosis, in the absence of an appropriate history, can be difficult because of the nonspecific nature of signs and the potential for delayed and progressive effects. Diagnosis in these cases benefits from histologic examination of a surgical liver biopsy. Recent studies suggest that a chemistry test for sulfur-bound pyrrolic metabolites of pyrrolizidine alkaloids in unfixed liver tissue may be useful, but is not yet available for diagnostic use.[63,64]

Treatment for pyrrolizidine alkaloid toxicosis centers on treating the liver failure and eliminating additional exposure to the plant. Although not preventive, evidence suggests that ingestion of sulfur-containing amino acids in high levels can influence pyrrolizidine alkaloid toxicity through maintenance of hepatic glutathione levels.[65] Note that sheep may be fed added molybdenum to delay accumulation of copper on a chronic basis.[51] Prognosis in advanced cases is poor. Very low levels of pyrrolizidine alkaloids are transferred into the milk, but attempts to transfer toxicity in the milk have not resulted in clinical or pathologic evidence of toxicosis.[52,66]

54.4.1.3

LARKSPUR ALKALOIDS

Delphinium spp.: Tall and low larkspurs

Aconitum spp.: Monkshood

Larkspur *(Delphinium)* and monkshood *(Aconitum)* have alternating, palmately divided leaves, which in larkspur may cluster at the base. Racemous flowers have a variety of colors, depending on species, and are characterized by a lower spur (larkspur) or an upper hood (monkshood).[67] Loss of cattle from larkspur is economically important in the western United States. Unlike many toxic plants that prefer disturbed soil, larkspur is found in undisturbed mountain ranges.[68] Larkspur species are divided into low and tall varieties based on height (low, <76 cm; tall, >76 cm) and elevations (tall larkspurs are found in high mountain altitudes).[68] Larkspurs contain a variety of complex, diterpenoid alkaloids, such as methyllycaconitine and deltaline.[69,70] The larkspur alkaloids cause skeletal muscle paralysis by blocking nicotinic, acetylcholine receptors at the neuromuscular junction and in the brain.[69,71,72]

Larkspurs are hazardous because they are palatable and appear early in the spring.[68,73] Although dried plants may be toxic, the diterpenoids are highest and most hazardous in the early-spring leaf growth, after flowering racemes are elongated.[72,74,75] During that period, cattle will tend to ingest more larkspur during or just after

a summer storm.[72] All animals may be poisoned by larkspur. Cattle are most sensitive to the plant (17 g/kg of body weight of early plant growth may be lethal), whereas sheep are four times less sensitive.[76] Calves are often affected when they graze with "nurse" cows on the edges of meadows (likely area for larkspur growth) while dams graze steep hillsides. Clinically, larkspur poisoning results in stiffness and weakness, abdominal pain, collapse (often with forelegs first), and death from aspiration of regurgitated ingesta or respiratory paralysis within 3 to 8 hours after exposure.[69,73,74,76,77] Death may be sudden (see Chapter 14). Recovery may occur in sublethal cases within 1 to 2 days.[74]

Postmortem, animals with larkspur poisoning bloat rapidly.[74] Clinicopathologic findings are nonspecific. Diagnosis of larkspur toxicosis depends on a history of sudden death with rapid bloating on rangeland in early spring, evidence of consumption of the plant, and a lack of other diagnostic findings. Chemistry testing is not routinely available for larkspur alkaloids, although testing of urine or serum for the alkaloids may be viable.[78]

Treatment for larkspur poisoning centers on control by pregrazing with sheep (less sensitive), delay of grazing until alkaloid levels drop to less than 3 mg/g in leaves (after seed shatter),[79] spraying larkspur with nonspecific herbicides such as tebuthiuron,[80] and attempts to develop in the animals an aversion to grazing the plant.[74,81] Recently, the ability of the larkspur mirid (*Hoplomachus affiguratus* Uhler) to control larkspur has been suggested as a biocontrol measure.[82]

54.4.1.4

NICOTINIC-ACTING ALKALOIDS

Nicotiana glauca: Tree tobacco; *N. tabacum:* Tobacco (pyridine alkaloid; e.g., nicotine)

Lupinus spp.: Lupines (quinolizidine alkaloids; e.g., anagyrine, sparteine)

Cytisus scoparus: Scottish broom; *Laburnum anagyroides:* Golden chain; *Thermopsis montana:* Mountain thermopsis (quinolizidine alkaloids)

Lobelia spp.: Indian tobaccos (pyridine alkaloids similar to nicotine)

Conium maculatum: Poison hemlock (piperadine alkaloids; e.g., coniine)

The lupines and thermopsis are found in climax and grassy habitats, whereas poison hemlock and the tree tobacco plants are found in disturbed soils. This group has three classes of nicotinic toxins: pyridine alkaloids, quinolizidine alkaloids, and piperadine alkaloids. Nicotinic alkaloids cause toxicity by ganglionic stimulation, followed by blockade and paralysis.[83,84] The teratogenic effects of lupines, tree tobacco, and poison hemlock may result from paralysis of the fetus during the period of joint formation (days 40 to 70 of gestation for cattle; days 30 to 60 for swine and sheep).[85–89] Thermopsis causes myonecrosis by an unknown mechanism.[90,91]

The plants are often bitter and are ingested when they are hidden in hay or forage or when animals are forced to do so by drought or hunger. Some lupines may be toxic when incorporated into feed as a supplement,

although the toxin and mechanisms remain to be defined.[92] The plants are toxic when dry except for *Conium,* which has quite volatile toxins that dissipate with time when plants are dry (fresh hay may be toxic).[84,93] All classes of livestock are affected by the plants, although species variations occur.[83,84,94,95] For example, acute toxicosis is more common in sheep. Conversely, teratogenesis is more likely in cattle.[91] Despite the lower likelihood of acute toxicity, it does occur. For example, deaths occurred in yearling Holstein dairy cattle pastured on lupine (personal observation). Cattle were more sensitive to the acute effects of coniine (poison hemlock) than were horses or sheep.[95] Acute toxicosis from nicotinic alkaloids is characterized by ataxia, weakness, tremors, initial stimulation of the central nervous system (CNS) followed by lethargy, increased salivation, respiratory distress, bloating, and death from respiratory paralysis.[83,84,96,97] Teratogenic signs include cleft palate (earlier in the susceptible period) and if exposed during joint development, classic arthrogryposis ("crooked calf syndrome") involving the joints of the legs and spine.[85–89,95,98] Acute *T. montana* toxicosis in cattle leads to tremors, a stilted gait, and recumbency, followed by respiratory paralysis and death. The animal may be found dead (see Chapter 14).[90]

Clinicopathologic changes are nonspecific for most of the nicotinic plants. *Thermopsis* may result in elevations of creatine kinase (CK) and AST, suggesting skeletal muscle damage.[90] Other than bloat and pulmonary edema, acute nicotinic alkaloid toxicosis results in few specific lesions.[93,96] The congenital malformations are usually obvious on postmortem examination. *Thermopsis* toxicosis is characterized by degeneration and necrosis of skeletal muscles.[90,91]

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Diagnosis of acute nicotinic alkaloid toxicosis depends on identification of the plant and appropriate signs. Additionally, reliable chemical assays have been developed to detect some of the alkaloids in urine and serum of exposed animals, including those of poison hemlock, tree tobacco, and some lupines.[93,96,99] Diagnosis of the source of crooked calf syndrome requires historical review of plants that may have been grazed during the susceptible period of gestation.

Treatment of acute toxicosis is nonspecific. Exposure should be eliminated. Animals in poor body condition may have higher circulating levels of lupine alkaloids at a given dose, suggesting that disposition of the alkaloids is affected by nutritional condition.[100] Many of the potentially teratogenic alkaloids of these plants, including some from poison hemlock and *Lupinus,* are passed into milk and muscle tissue.[101,102]

54.4.1.5

STEROIDAL ALKALOIDS

Zigadenus spp.: Deathcamas

Veratrum californicum and *V. viride:* False hellebore, also skunk cabbage

Solanum spp.: Nightshades; *Lycopersicon* spp.: Tomatoes

Deathcamas is a slender, perennial herb (up to 50 cm tall) with grasslike basal leaves that grows from an onionlike bulb and has yellow-white flowers.[103] False hellabore has short, hairy, stout stems with broad, prominently veined leaves.[104] *Solanum* species range from annual herbs to woody plants. They have four to five lobed, white to purple flowers.[105] The fruit is a berry. The leaves often have two small leaflets at the

base or incorporated as small lobes. Deathcamas and *Veratrum* species, both of which are Liliaceae, are found in moist meadows at upper elevations. *Solanum* species are found throughout the United States. Deathcamas (alkaloid is zygacine) and false hellabore contain steroidal alkaloids that cause cardiovascular hypotension.[103] *Veratrum* alkaloids include the teratogens jervine and cyclopamine.[106] Solanaceous plants such as the nightshades, tomatoes, and potatoes have steroidal alkaloids linked to sugars (glycosides).[107] Those *Solanum* alkaloids may inhibit cholinesterase, cause gastrointestinal (GI) irritation, and induce constipation. Some solanaceous plants accumulate nitrate (tomato vines)[108] or have other toxic factors such as vitamin D, which causes calcinosis (*Solanum malacoxylon,* found in South America and Hawaii).

The steroidal alkaloids are toxic to all classes of livestock. Sheep are most frequently poisoned by *Veratrum* and *Zigadenus*.[103,109] *Zigadenus* is most hazardous in the early spring because it is among the first plants present.[103] *Veratrum* is teratogenic when grazed by ewes around days 14 and 30 of gestation.[110,111] The alkaloids resist drying.[107] Ingestion of as little as 0.6% of body weight of deathcamas can cause ataxia, stiffness, tremors, increased salivation, vomition, and prostration. Death may occur within 1½ to 8 hours of exposure[103] (see Chapter 14). *Solanum* species vary in toxicity and effect, causing GI irritation, ileus (in horses), lethargy, increased salivation, dyspnea, tremors, paralysis, diarrhea or constipation, and death.[103,105,107] Pregnant ewes grazing *Veratrum* during day 14 of gestation produce lambs with craniofacial deformities, including cyclopia, microphthalmia, and cleft palate.[109,110] Gestation may be prolonged in affected ewes.[103] Limb and bone shortening in the metacarpal and metatarsal joints can occur in lambs when ewes ingest the plant around day 30 of gestation.[111]

Clinical and pathologic findings are nonspecific, except for the teratogenesis from *Veratrum*. Severe intoxication from *Solanum* species may lead to congestion of major internal organs.[107] Diagnosis involves accumulated signs with evidence of consumption of the plant. Chemistry testing is not routinely available.

Treatment for poisoning centers on prevention. Deathcamas and false hellabore should be avoided in early spring. The highly variable toxicity of the solanaceous plants makes recommendations about prevention difficult, although feeding large volumes of the plants is ill-advised.

54.4.1.6

TROPANE ALKALOIDS

Datura stramonium, D. metaloides: Jimsonweeds

Atropa belladonna: Belladonna

Datura and *Atropa* are also solanaceous plants. Jimsonweeds prefer disturbed soils such as barnyards.[112] The plants contain the tropane alkaloids, atropine and scopolamine, which block acetylcholine at muscarinic nerve synapses. Although *Datura* is bitter and unpalatable, herbicide application or overgrazing may encourage consumption. Grain contaminated with *Datura* seeds is toxic.[112] *Datura* toxicity results in GI atony, anorexia, rapid heart and respiratory rates, mydriasis, thirst, diarrhea, excess urination, disturbed vision, and delerium.[113–115] Death is uncommon, perhaps because gut atony and anorexia may limit plant intake.[112] However, gut atony can be fatal in some species, including the horse.[113,114] Exposure to trace amounts of *Datura* species, such as in the bedding or feed, may result in urinary residues of tropane alkaloids

in the horse's urine.[113] Lesions are nonspecific. Tropane alkaloids can be identified in urine, ingesta, and plant material.

54.4.1.7

YEW

Taxus cuspidata: Japanese yew

Taxus baccata: English yew

Yews are evergreen shrubs and small trees with flattened needles. The plants are found throughout the United States in hedges and yards.[116] Yews contain alkaloids called *taxines,* which depress myocardial conduction by blocking sodium movement through membranes.[117] Some yews also contains antimitotic, diterpenoid taxols, which are of medical interest as anticancer agents.[118]

Yew is extremely toxic; less than 0.1% of body weight of dried leaves may kill a horse.[119] Toxicity is retained in dry plants. All species are sensitive to yew toxicity. As with oleander, yew poisoning often results from accidental ingestion of hedge clippings.[116,120] Clinical toxicosis is usually manifested by collapse and sudden death (Chapter 14) related to heart failure, occasionally preceded by tremors and weakness.[116,119–121]

Lesions are uncommon, although focal, nonsuppurative myocarditis is possible.[120] Diagnosis of yew toxicosis requires a history of exposure to yew clippings and sudden death. Finding of leaf parts in the ingesta is diagnostic. The investigator may be confused by needles from *Pinus* and the coastal redwood *(Sequoia sempervirins)*. Alkaloids have been suggested by mass spectral chemistry in samples from poisoned animals.[122]

54.4.1.8

TRYPTAMINE ALKALOIDS

Phalaris spp.: Canary grass

Phalaris species are pasture grasses. Under poorly defined conditions, *Phalaris* accumulates indole and β-carboline alkaloids.[123,124] Those alkaloids block serotonin in the CNS and may inhibit monoamine oxidases. 1696
[124,125] Cattle and sheep are affected, although sheep are more likely to be poisoned by *Phalaris*.[126] The 1697
alkaloids are bitter, resulting in lowered weight gains if present at levels exceeding 0.2% of plant weight.[124]

Clinically, two syndromes can result from canary grass toxicity. Sudden death with cardiac failure is one possible result of poisoning.[124,126] Chronic lower-level exposures may lead to a staggers syndrome with ataxia, a hopping gait, tremors, excitability, head nodding, convulsions, and eventually paddling and death in sheep and horses.[124,127–129] Onset of signs may be delayed up to 40 days after ending exposure to canary grass.[130] (See later discussion and Chapter 35 for grass staggers.)

Postmortem examination of sheep with the staggers syndrome reveals characteristic gray to bluish discoloration of the brainstem.[130,131] The kidney and liver also may be pigmented. Pigment in the cytoplasm of the nerves apparently destroys those cells.[131] Clinical signs of sudden death or staggers in sheep that have

previously grazed canary grass pasture, along with characteristic discoloration of brain tissue, are used for diagnosis. Treatment of clinically affected animals has not been rewarding; however, supplementation with cobalt may help prevent toxicosis.[132]

54.4.2 Glycosides

Glycosides are ethers that link a sugar to a toxin, called *aglycone*. Either the glycoside or the aglycone alone may be toxic. Most work is based on the properties of the aglycone. Absorption of the aglycone is often enhanced by microbial activity causing release of the aglycone from the sugar.[133] The aglycone is frequently released by damage to plant tissue. As with alkaloids, glycosides are often bitter.[134]

54.4.2.1 CARDIAC GLYCOSIDES (CARDENOLIDES, GRAYANOTOXINS)

Nerium oleander: Oleander; *Thevetia peruviana:* Yellow oleander

Digitalis purpurea: Foxglove

Rhododendron spp.: Azaleas

Kalmia spp.: Laurels

Convallaria spp.: Lily-of-the-valley

Pieris japonica: Japanese pieris

Asclepias spp.: Milkweeds

Apocynum spp.: Dogbanes

Bufo marinus: Bufo toads

Many families of plants contain cardiotoxic glycosides. Many of the plants, including azaleas, oleander, and Japanese pieris, are evergreen shrubs and small trees.[135] In addition to plants, cardiac glycosides may be found in animals such as the bufo toad. The toxic cardiac glycosides, including various cardenolides and bufadenolides, are steroid-like in structure and have a lactone ring.[136] Common cardiac glycosides include digitoxin and digoxin from foxgloves, oleandrin (aglycone = oleandrigenin) from oleander, and grayanotoxins from rhododendron. Cardiac glycosides block cellular sodium-potassium adenosine triphosphatase (ATPase), leading to sodium accumulation in excitable cells such as nervous tissue and myocardium.[136–138] Grayanotoxins block fast sodium inactivation in excitable tissues by binding to sodium channels.[139] Increased cardiac contraction and altered heart rhythms result from myocardial effects. The plants also are potent GI irritants.

Cardiac glycosides are found in most parts of the toxic plants.[140] Although plants are bitter, dried leaves (oleander) and flowers are readily ingested by all classes of livestock, causing toxicosis.[10,140,141] Discarded lawn clippings that contain oleander leaves are a common source of livestock poisoning. Some of the plants are extremely toxic, and toxic effects are cumulative. For example, 0.005% to 0.015% of body weight of oleander (equivalent to a handful of leaves) can be lethal in sheep and cattle, and one leaf may kill a human.[125,142] Azaleas may be toxic when livestock ingest 0.2% to 0.6% of body weight of plant material.[142] Clinical signs of toxicosis reflect GI irritation and damage to the heart. The onset of toxicosis may be delayed by several hours after ingestion. Although death may be sudden (see Chapter 14), it usually occurs within 36 hours after ingestion but may take up to 14 days.[143] Signs include abdominal pain, nausea, weakness, anorexia, muscle tremors, rumen atony, increased salivation, bradycardia (or tachycardia later in the syndrome), heart block, and ventricular arrhythmias (including a gallop rhythm for oleander in cattle).[126,141–147]

Animals with acute cardiac glycoside toxicosis may have hypertension, hypoxemia, acidemia, hemoconcentration, hyperkalemia, hyperchloremia, and elevations of serum creatinine and glucose.[126] Electrocardiogram (ECG) alterations include widening of the QRS complex, ST segment depression, enlarged P waves, and a variety of ventricular arrhythmias. Lesions associated with cardiac glycoside toxicosis are nonspecific and include hemorrhagic gastroenteritis and pale mottling of the heart with congestion, hemorrhage, and histologic evidence of myocardial degeneration and necrosis.[125,126,143,144]

Diagnosis of cardiac glycoside toxicosis depends on identification of the plant and evidence of its consumption. Two-dimensional thin-layer chromatography (TLC) and liquid chromatography/mass spectrometry (LC/MS) methods have been developed for assay of oleander in ingesta and body fluids from affected animals.[10,145,146] LC/MS can be used to assess grayanotoxin exposure in urine and feces of affected animals.[147] A serum radioimmunoassay (RIA) can be used to assess exposure to *Digitalis;* this test may cross-react with oleander glycosides for some diagnostic utility.[148]

Treatment of cardiac glycoside toxicosis begins with elimination of exposure to the plant and decontamination using cholestyramine resins or activated charcoal (repeated applications suggested).[127] Fluids with calcium and potassium should be avoided (unless hyperkalemia is absent). Atropine may be useful if bradycardia or heart block is present (use care in horses; it may cause gut stasis). β-Adrenergic blocking agents and antiarrhythmic drugs can be used for cardiac dysrhythmias; otherwise, β-blockers should be avoided.[126,127] Use of anticardiac glycoside Fab antibodies is an experimental treatment for digitalis and oleander toxicoses.[148–150] Stress should be avoided in animals exposed to cardiac glycosides. Prevention of cardiac glycoside toxicosis includes keeping hedge clippings away from animals and avoidance of plants when in full flower. *Digitalis* glycosides are widely distributed in the body, including in milk and fetal fluids, and the primary elimination pathway is urinary.[126] Evidence of oleandrin was identified in the milk of poisoned cows using two-dimensional TLC in the author's laboratory. No oleandrin was found at 5 days after exposure in milk from that dairy.

54.4.2.2

PHOTOSENSITIZING SAPONINS

Tribulus terrestris: Puncture vine

Panicum coloratum: Kleingrass

Brachiaria decumbens: Signalgrass

Nolina texana: Sachuista

Agave spp.: Agave

Narthecium ossifragum: Narthecium

These grasses and weeds may contain toxic levels of hepatotoxic, steroidal sapogenins such as disogenin.[151–154] Sapogenins are metabolized in animals to glucuronide conjugates of epismilagenin, which crystallize in bile, leading to biliary blockage, cholangitis, and secondary photosensitization (Chapter 40).[153–155] 1697 1698

Plants are most hazardous when grazed during stages of early, rapid growth when sapogenin levels are highest.[155] Feed refusal can occur because the plants can be bitter. Mature plants are often grazed without incident. All herbivores may be affected. Signs of toxicity involve liver damage with anorexia, weight loss, icterus, hepatoencephalopathy, and secondary photosensitization.[151,152,156–160]

Serum chemistry alterations reflect liver damage.[157,158] Postmortem, affected animals are icteric and have evidence of necrosis and sloughing of skin.[159] Lesions in the liver include bridging and fibrosing hepatocyte necrosis, cholangitis, and occlusion of small bile ducts. Bile ducts may have birefringent crystals, probably related to sapogenin accumulation.[151,153,158,159] (See Chapter 40 for skin lesions.) Lesions also may be present in the kidneys, heart, and adrenals. *Narthecium,* as with other lilies, may cause chronic renal failure in ruminants, most likely from a furanone, not a saponin.[161] Animals should be removed from offending pastures (at least until the grass matures).

54.4.2.3

CYANOGENIC GLYCOSIDES

Linum spp.: Flax

Prunus spp.: Cherries, chokecherries, apricots, peaches

Sorghum spp.: Sorghum, Sudan grass

Triglochin spp.: Arrow grass

Trifolium repens: White clover

Zea mays: Corn

Many others; see references.

Many grasses, weeds, and cherry bushes contain cyanogenic glycosides. Damage to the plant causes contact between β-glycosidases and the glycosides, releasing free cyanide. Cyanide blocks a variety of metalloenzymes, most notably the terminal oxidase (cytochrome-*c* oxidase) of oxidative transport.[162,163] The tight affinity of cyanide for ferric (Fe^{3+}) iron in the cytochrome prevents electron transfer. Sorghums also can cause peripheral neurologic deficits in laboratory animals and horses (from nitriles or cyanide).[163,164]

Many of the listed plants may be grazed safely; however, cyanide is released when plants are damaged from maceration, drought, frost, wilting, and stunting.[162] Toxicity wanes with drying. All animals are sensitive to cyanide toxicosis. Cyanide toxicosis is very rapid in onset, often resulting in sudden death (see Chapter 14). Clinical signs include dyspnea, excitement, tremors, increased salivation, gasping, clonic convulsions, and death.[162,163] Chronic exposure to cyanide in rats can cause paralysis, and cattle, horses, and sheep grazing *Sorghum* species have developed ataxia, urinary incontinence, and cystitis.[163–166]

Blood from animals with cyanide toxicosis is cherry red because hemoglobin cannot release oxygen to tissue. Nonspecific postmortem findings include cardiac hemorrhage associated with acute death. Chronic exposure to cyanide may lead to patchy encephalomalacia and damage to the spinal cord, along with secondary thickening and necrosis in the bladder associated with cystitis.[163,164] Diagnosis of cyanide toxicosis is supported by analytical evidence of cyanide in forage and samples from affected animals. Cyanide levels in excess of 200 ppm in plant material and 1 ppm in liver or blood are significant.[162] Samples for cyanide analysis should be frozen immediately and held frozen until analyzed.

Treatment of cyanide toxicosis is based on removal of the cyanide from affected cytochrome *c*. Judicious use of sodium nitrite (16 mg/kg intravenously [IV], to form a small amount of methemoglobin, Fe^{3+}) can help pull cyanide away from the enzymes. Additional use of sodium thiosulfate (30 to 40 mg/kg IV) will provide substrate for the natural rhodanese enzyme that forms thiocyanate, which is readily excreted in the urine.[162,167]

54.4.2.4

NITROTOXINS

Astragalus spp.: Milk vetches (*A. miser:* Timber milk vetch; *A. emoryanus:* Emory milk vetch)

Coronalia varia: Crown vetch

Indigofera spicata: Indigo

Some common milk vetches in North America contain glucosides of 3-nitropropanol (NPOH) and 3-nitropropanoic acid (NPA).[26,168,169] Miserotoxin is a common glucoside of NPOH. The glucosides are relatively nontoxic until hydrolyzed in the rumen to toxic nitrocompounds and nitrite, which is also toxic.[170–

[172] NPOH is oxidized to the more toxic NPA in the liver.[170,171] Nevertheless, NPOH may appear more toxic than NPA in ruminants because the NPOH is more thoroughly absorbed from the rumen. Nitrocompound toxicity is distinct from nitrite poisoning (see Nitrates). Less than 33% methemoglobin is usually formed after exposure to nitrocompounds, so nitrite alone does not explain acute nitrocompound toxicity.[171] NPA is a powerful inhibitor of succinate dehydrogenase in the Krebs cycle, impairing cellular energy production in the nervous system.[173]

All livestock can be poisoned by nitrocompounds, but cattle and sheep are most at risk. Acute or chronic toxicosis may develop, depending on the amount ingested. Acute nitro-plant toxicosis has a rapid onset of ataxia, distress, dyspnea, cyanosis, weakness, collapse, and death within 4 to 12 hours.[172] Sheep may be found suddenly dead (see Chapter 14). Chronic nitro-plant toxicosis results in respiratory distress, weakness (especially in the pelvic limbs), knuckling of fetlocks, goose stepping, and knocking together of hindfeet when walking ("cracker heels").[172] Increased salivation, constipation, and diarrhea have all been reported. Animals may linger for months, but severely affected individuals seldom recover. Affected cattle may die suddenly if forced to move quickly.

Animals exposed to nitro-containing plants can have up to 33% methemoglobin.[172] Although not lethal at this level, methemoglobin probably contributes to respiratory distress. Lesions of nitrocompound toxicosis include pulmonary edema with fibrosis (in longer-standing cases) and nonspecific cerebral hemorrhages. Histologic alterations in nervous tissue include wallerian degeneration of the spinal cord and peripheral (sciatic) nerves, with variable changes reported in the cerebellum.[172] Other neuronal lesions may include white matter vacuolation, glial edema, and bilateral changes of the thalamus and cerebellum.[171]

Treatment of nitrocompound poisoning centers on prevention. Cattle native to pastures containing timber milkvetch *(Astragalus miser)* are somewhat tolerant to the plant through rumen microflora adaptation, which may be enhanced by protein supplementation.[174]

54.4.2.5

BRACKEN FERN

Pteridium aquilinum: Bracken fern (toxic glycoside + thiaminase)

Cheilanthes humilis: Rock fern (toxic glycosides)

Equisetum arvense: Horsetail (no known glycoside, does have thiaminase)

Bracken is a perennial fern (up to 2 m high) that arises from a black rhizome and is found in disturbed or cleared uplands. The fronds are coarse, triangular, entire at the apex, and lobed toward the stalk. Bracken fern 1698
contains a variety of glycosides, including ptaquiloside (up to 1%), which will alkylate DNA, leading to 1699
carcinogenicity and bone marrow suppression in ruminants and laboratory animals.[175–179] Bracken also contains thiaminase activity, which predominates in monogastric animals (horses).[175,178]

Grazing of fresh, young fronds when other forage is not yet available early in the grazing season is hazardous for cattle and horses, although plowed rhizomes and hay (20% bracken for 1 month in horses) also may be toxic.[175,180] Signs appear suddenly after animals have grazed approximately their body weight in plant

material over several months. Horses develop characteristic thiamine deficiency, with weight loss, ataxia, lethargy, and a braced stance with an arched back, tremors, recumbency (with violent attempts to rise), and death within days to weeks after onset of signs.[180] Cattle with bracken or ptaquiloside toxicosis develop widespread hemorrhages and hematuria ("enzootic hematuria") resulting from severe bone marrow depression and cancer in the bladder and other organs.[175,178–185] Reduced fertility may occur in chronic cases.

Cattle with bracken toxicosis have a normocytic, normochromic anemia, lymphocytosis, and neutropenia.[186] Severe thrombocytopenia and hemorrhage are also reported, associated with progressive bone marrow failure.[175,178] Urine from affected animals is hemorrhagic, with high levels of calcium and protein.[181,186] Lesions in cattle with bracken toxicosis include the hemorrhages, bone marrow hypoplasia, and a variety of tumors in bladders, including hemangiomas, hemangiosarcomas, transitional cell carcinomas, papillomas, fibromas, and adenomas.[180,181] Other cancers may involve hematopoietic tissues and the GI tract.[183] Horses with bracken toxicosis have low levels of thiamine.

In addition to prevention, horses that have not reached a terminal state may respond to large doses of parenteral thiamine. No specific treatment is currently recommended for ruminants with bracken poisoning. In terms of safety of food animal products, indirect evidence suggests that bracken ingestion by milking cows may be linked to stomach cancer in people who have chronically ingested that milk.[187,188]

54.4.2.6

PHYTOESTROGENS

Medicago sativa: Alfalfa

Trifolium subterraneum: Subterranean clover; *T. pratense:* Red clover

Hyperestrogenism caused by feeds and forages (including clover and alfalfa hays) has been reported in cattle, sheep, and swine. A variety of glycosides in those forages interact with estrogen receptors.[189,190] Commonly recognized estrogens include coumestrol, formononetin, biochanin A, daidzein, genistein, equol, and many others.[190,191]

Estrogenic compounds vary in potency. Coumestrol from alfalfa and isoflavones from clovers have the most estrogenic activity, followed by genistein, daidzein, biochanin A, and formononetin.[192] Biochanin A and formononetin are not potent in the laboratory, but ruminants metabolize them to the more estrogenic forms of genistein and daidzein, respectively.[190,192] Signs of hyperestrogenism from forages include infertility, hyperestrogenism, and antiestrogenism. Hyperestrogenism includes nymphomania, cystic ovaries, swollen genitalia, and in males development of female characteristics. Antiestrogenic signs include gonadal hypoplasia and anestrus.[189,190] Diagnosis of forage-induced hyperestrogenism is facilitated by demonstration of estrogens in forages and samples of plasma or urine.[193–195] Consumption of highly estrogenic forage types should be limited in breeding animals.

54.4.2.7

OTHER TOXIC GLYCOSIDES

Melilotus alba; M. offinalis: White and yellow sweet clovers

The sweet clover forages produce the glycoside melilotoside, which contains coumarin. *Penicillium* species in moldy hay can dimerize the aglycone to dicumarol, which inhibits vitamin K epoxide reductase, leading to failure of vitamin K–dependent clotting factors. Dicumarol can be assayed in feed and animal-related samples. Concentrations of dicumarol in hay as low as 10 ppm may be hazardous to cattle. Moldy sweet clover poisoning in cattle results in widespread, vitamin K–responsive hemorrhage, which is especially hazardous during late-term pregnancy (hemorrhagic abortions).[196,197]

Xanthium spp.: Cocklebur and spiny clotburs (carboxy-atractyloside)

Ingestion of young sprouts, burrs, or adult plant in hay of cocklebur can cause massive centrilobular liver necrosis in swine and cattle. Signs of toxicosis include depression, dyspnea, weakness, convulsions with opisthotonos, and death. Severe hypoglycemia may be observed by the clinician.[198–201]

Ammi majus: Bishop's weed

Cymopterus watsonii: Spring parsley

Thamnosa spp.: Dutchman's breeches (furanocoumarins)

Cooperia pedunculata: (unidentified phototoxin), Cooperia

Furanocoumarins such as psoralens are primary photosensitizing agents that lead to severe blistering of light-skinned areas of exposed livestock ingesting the plants and poultry exposed to seeds from Bishop's weed (see Chapter 40).[196,202]

Cestrum diurnum: Day-blooming jessamine

Solanum malacoxylon

Trisetum flavescens: (calcinogenic glycosides)

These plants contain glycosides of vitamin D (1,25-dihydroxycholecalciferol). Ingestion of the plants causes weight loss, lameness, stiffness, abnormal posturing, and clinicopathologic increases in serum calcium and phosphate in cattle and horses. Lesions include widespread calcification of tissues, including the cardiovascular system, tendons, lungs, and kidney. The vitamin D activity may cross the placenta to affect a developing fetus.[203–206]

Medicago spp.: Alfalfa

Saponaria spp.: Soapwort, cow cockle

Gutierrezia sarothrae: Broom snakeweed

Sesbania vesicaria: Bladderpod (enterotoxic saponins)

Plant saponins are bitter, foaming, detergent-like glycosides found in a variety of important forage crops and weeds. Midsummer alfalfa cuttings tend to have the highest saponin contents. Saponin toxicosis is characterized by gastroenteritis with diarrhea, poor weight gain, and ill-thrift in cattle. Broom snakeweed has an abortifacient factor with an effect similar to that in *Pinus*.[207]

Aesculus spp.: Buckeye or horse chestnut

Horse chestnuts are trees with characteristic palmate leaves and a one- to three-seeded, leathery fruit capsule (large seeds with a scar give the tree its name, buckeye). Young growth, sprouts, and seeds contain toxic levels of the glycoside aesculin. Aesculin causes ataxia, twitching, and excitability or sluggishness in livestock. The alcoholic extract from *Aesculus hippocastanum* causes incoordination.

Ranunculus spp.: Buttercups

Ceratocephalus testiculatus: Bur buttercup

Ranunculin is enzymatically converted to the toxic protoanemonin, a potent GI irritant that occurs in bur buttercup, and it becomes nontoxic when the plant is crushed or dried. Thus, bur buttercup in hay is not a hazard. However, grazing of this bitter plant by cattle and sheep, which occurs when animals are forced to do so, results in watery diarrhea, weakness, and dyspnea. Death may occur in severe cases (nonspecific edema and hemorrhage with fluid in the large cavities).[208–210]

1699

1700

Brassica spp.: Turnips, mustards, cabbages

These plants have a variety of glucosinolates and isothiocyanates that cause GI irritation and, for some chemicals, goitrogenic effects in adults as well as neonates.

Cycas spp.: Cycads

Macrozamia spp.: Cycads (azoxyglycosides)

Cycads are palmlike plants found in tropical and subtropical climates. They contain a variety of glycosides, including the hepatogastrointestinal toxin (and carcinogen) cycasin, which is metabolized to the highly toxic methylazoxymethanol, and the neurotoxic amino acid β-methylamino-L-alanine. Ruminants with hepato-GI

toxicosis from effects of the cycasin develop depression, anorexia, and weight loss. Necropsy findings reveal a cirrhotic liver, ascites, and hemorrhagic gastroenteritis. Ruminants with the neurologic syndrome develop "Zamia staggers," characterized by weight loss, swaying, weakness, ataxia, and hindlimb ataxia. Postmortem lesions include demyelination and axonal degeneration of the brain, spinal cord, and dorsal root ganglia. In addition, recent research suggests that cycad toxins may also harm pancreatic β-cells, contributing to development of diabetes mellitus.[211–214]

54.4.3 Alcohols and Acids

54.4.3.1 GOSSYPOL

Gossypium spp.: Cottonseed

Gossypol is a yellow, polyphenolic pigment found in glands of cottonseed *(Gossypium)*. It is present in free (toxic) and bound (to protein, perhaps to the epsilon amino of lysine; not directly toxic) forms.[215,216] Both whole cottonseed and cottonseed meal can be toxic. Extraction of cottonseed using steam and heat will bind gossypol, whereas solvent extraction may leave high levels of free (toxic) pigment. Gossypol binds to cell constituents such as lysine and phospholipids, binds iron, may cause hypokalemia through kidney damage, inhibits a range of dehydrogenases, and uncouples phosphorylation.[215–218] Gossypol also adversely affects male reproduction through a variety of mechanisms, including inhibition of lactate dehydrogenase (LDH) in testicular Leydig cells and inhibition of acrosomal plasminogen activator in the sperm.[218] Cottonseed meal has limitations in protein quality, poor iron availability, and low concentrations of vitamin A.

All species can be poisoned by gossypol. Mature ruminants are more resistant to its effects (probably a result of ruminal degradation) than monogastric animals.[215–222] The toxicity of free gossypol depends on the quality of the ration and the amount of stress on the animals. For example, although swine may develop toxicity at free gossypol levels in excess of 0.01% in the total ration,[216,220–223] supplementation of rations with iron and high-quality (lysine) protein will raise the tolerated level to 0.02% to 0.04%.[216] Although adult ruminants tolerate more than 0.1% to 0.2% of free gossypol in the total ration, some animals may be poisoned at the lower levels if stressed or on a poor ration.[215,219,220] Adult bulls may develop infertility at these levels. Young adult cattle, under conditions of stress and marginal rations, may be sensitive to as little as 0.05% free gossypol in the total ration (perhaps from binding of protein as well as direct toxicity).[215]

Gossypol effects are cumulative. Low levels of gossypol, if in a ration limited in iron or protein, may cause ill-thrift and poor weight gains in swine, baby calves, and young adult cattle (<1 year of age). Acute gossypol toxicosis results in dyspnea, violent labored respirations ("thumping" in swine), weakness, and death (see Chapter 14).[215,216,220,221,223] Signs may appear suddenly after stress, making gossypol toxicosis resemble acute shipping fever.[215] Adult ruminants may have decreased milk production, anorexia, dyspnea, weakness, gastroenteritis, decreased humoral immune response, and reproductive failure (impaired spermatogenesis in bulls).[215,219,224,225] Although the level in feed required to cause clinical reproductive failure in cows is not yet known, laboratory evidence suggests that high levels of gossypol may also impair reproductive performance in females.[226] However, these findings must be balanced with the benefits to lactation and milk quality from feeding a moderate level of cottonseed to dairy cows. Lesions of acute gossypol toxicosis

include large amounts of yellow proteinaceous fluid in all body cavities, myocardial degeneration and necrosis (pale streaks in the heart), and liver necrosis (centrilobular pattern).

Analysis of feed for free and bound gossypol levels will support a diagnosis of gossypol poisoning. Sperm morphology is adversely affected in bulls, with high levels of proximal droplets observed.[227] In addition, modern high-performance liquid chromatography (HPLC) methods can detect gossypol in some animal-related samples.

There is no specific treatment for acute gossypol toxicosis. Some evidence suggests that feeding of vitamin E may help control some gossypol effects in young animals, although vitamin E will not prevent toxicosis.[228] The total ration for monogastric animals and swine should contain no more than 0.01% of total gossypol.[215,216,221,223] Slightly higher levels may be fed successfully to swine if dietary protein and iron are adequate.[215,216,229] Cattle that are less than 1 year of age should have adequate nutrition and minimal stress if being fed more than 0.05% to 0.1% of free gossypol. Adult ruminant cattle should have less than 0.1% to 0.2% of free gossypol in the total ration (avoid cottonseed products in bulls). Lactating dairy cattle should be fed no more than 6 to 8 lb (2.7 to 3.6 kg) of cottonseed per day.[219,220] Infertility in bulls will take 1 to 2 months on feed that has no gossypol to recover.[227]

54.4.3.2

TANNINS

Quercus spp.: Oak

Oaks are trees and brushes that have characteristic multilobed leaves and bear acorns in the autumn. Oaks are common in the United States, especially in Texas and California (60 species in North America).[230] They contain variable amounts of toxic, complex, and hydrolyzable tannins.[231–233] The hydrolyzable tannins are astringents and apparently bind the proteins in plasma and organs, which causes coagulation and necrosis.[234] *Acorn calf syndrome,* a deformity in calves of cows eating oak, may have a nutritional mechanism and is completely different from the syndrome discussed here.[235]

The hazard of oak toxicity parallels the tannin content of plant material.[236] Plants tend to have the highest tannin content in the spring during the budding stage, and acorns may have high tannin levels in the fall.[231] All livestock may be poisoned by oak tannins. Signs generally appear after 3 days of initial ingestion of the oak. Losses from oak result from gastroenteritis, renal failure, liver damage, death, and deformities of calves.[230,234,235,237] Clinical effects in cattle include rumen atony, anorexia, constipation with black feces, lethargy, icterus, hematuria, dehydration, and evidence of renal failure.[230,234] (See Chapter 32 for further discussion of oak toxicosis.)

54.4.3.3

SOLUBLE OXALATES

Halogeton glomeratus: Halogeton or barilla

Sarcobatus vermiculatus: Greasewood

Rumex crispus: Curly dock

Setaria sphacelata: Setaria

Rheum: Rhubarb

Oxalis: Sorrel or soursob

Kochia scoparia: Fireweed, summer cypress (also nitrate, secondary photosensitizing agent, and sulfate)

Many oxalate-bearing plants grow in disturbed or arid soils.[238] Soluble oxalate in acidic plants such as *Oxalis* is present as the potassium salt. Sodium salts of oxalate are present in plants such as halogeton that grow at more neutral pH levels.[239] Proposed mechanisms of acute poisoning from soluble oxalates include hypocalcemia, GI irritation, and inhibition of respiratory enzymes. Subacutely, oxalate is deposited as insoluble, birefringent crystals in kidneys, leading to renal failure. Chronic oxalate poisoning resulting from *Setaria* may lead to calcium deficiency with relative hyperphosphatemia.[239,240] Insoluble calcium salts of oxalate are present in plants such as *Dieffenbachia* and *Philodendron* species. Those insoluble calcium oxalates are not absorbed, but they do act as potent local membrane irritants.

Oxalate-bearing plants are bitter and not ingested unless grazing is forced. All species are poisoned by oxalate, although historically sheep have been the most frequent victims.[239] Rumen flora adapt to oxalate in forage if animals are gradually acclimated to oxalate over 4 days.[241] Poisoning occurs when hungry animals that are unaccustomed to oxalate ingest the plants in large quantities.[236–240,242] Soluble oxalate toxicosis results in labored breathing, ataxia, rumen stasis and bloat, depression, weakness, coma, and death.[239,241] Horses chronically grazing setaria develop “bighead,” which is associated with a low calcium/phosphorus ratio.

Soluble oxalate—related changes in serum parameters reflect hypocalcemia or uremia. Postmortem lesions include hemorrhage and edema of the rumen wall and kidneys. Refractile crystals are found in the kidneys and rumen wall. Renal tubular necrosis and rumenitis are the major lesions, along with the presence of crystals.[239,240,242] Analytical tests are available for oxalate in plant and animal-related samples.

Treatment of oxalate toxicosis is for gastroenteritis, shock, and renal failure. Gradual acclimation of ruminants to forages containing soluble oxalates and providing adequate levels of clean water may help prevent clinical disease.

54.4.3.4 WHITE SNAKEROOT

Eupatorium rugosum: White snakeroot

Haplopappus wrightii: Desert haplopappus; perhaps also *H. heterophyllus* and *H. acradenius*

White snakeroot is a perennial that grows in clumps from clusters of snakelike roots in shady, wooded areas in the midwestern United States. The leaves are opposite and have three characteristic veins on the underside.[243] The plant tends to remain green when other plants have dried. The toxin of white snakeroot has not been identified but is extractable with a ketone and sterol-rich fraction, called collectively *tremetol*.[243] The toxins may require microsomal activation in animals.[244]

White snakeroot (fresh or dried) is hazardous to all species studied, although lactating animals are resistant because of rapid excretion of the toxins in milk.[243,245–248] The hazard to grazing animals is highest when other forages have dried during the winter season or conditions force overgrazing. Feeding of 1% and 2% of body weight of the plant to horses resulted in toxicity after 1 to 2 weeks.[245] White snakeroot toxicosis causes cardiac and skeletal muscle damage along with ketosis.[243] Clinical signs include weight loss, tremors and stiffness, ataxia, depression, cardiac arrhythmias (especially ST segment depression), recumbency, and death (within hours of recumbency).[243,245,247–249] Sudden death is possible (see Chapter 14).

Clinicopathologic alterations include ketosis (many have breath smelling of acetone) and increased serum activities of CK, LDH, ALP, and AST.[243,245–247] Lesions of white snakeroot toxicosis include pale streaking in the heart with multifocal myocardial degeneration, necrosis, and mineralization.[245] Skeletal muscle necrosis also may occur, especially with the *Haplopappus* species. The liver may have centrilobular degeneration and necrosis. Diagnostically, white snakeroot poisoning should be differentiated from selenium deficiency and ionophore toxicosis. Treatment for white snakeroot toxicosis is supportive. Milk from exposed animals is hazardous and should not be fed or consumed.

54.4.3.5

OTHER TOXIC ALCOHOLS AND ACIDS

Agropyron desertorum: Crested wheatgrass; many rapidly growing forages (plant acids such as transaconitic acid)

Lush, early growth of many forages, including crested wheatgrass, can contain acid compounds that sequester magnesium. Ingestion of the plants during this lush stage can lead to hypomagnesemia in cattle, including tetany (see Chapter 41).[250]

Pinus ponderosa: Ponderosa pine

Pinus radiata: Monterey pine

Juniperus communis: Juniper

Ingestion of pine needles by pregnant cows during late gestation causes abortions or birth of weak calves, with digestive upset and lethargy in cows. The abortions are characterized by retained placentas and metritis. Many cows may die from effects of metritis. The toxins in ponderosa pine include isocupressic acid esters along with a unique class of vasoactive lipids. The major lesion of pine needle abortion is necrosis in the placental trophoblast region, perhaps also resulting from reduced uterine blood flow.[251–258]

Cicuta spp.: Water hemlock

Asclepias fasicularis: Whorled milkweed

A. labriformis: Labriform milkweed

A. subverticillata: Narrow-leaved milkweeds

Water hemlock and some of the more toxic narrow-leafed milkweeds contain convulsant resins. Most of the toxicity of water hemlock lies in the resins of the chambered root. Ingestion of less than 0.2% to 0.5% of an animal's body weight of either plant may be lethal. Signs of toxicosis (in all species) may appear within 15 minutes of ingestion and include nervousness, excessive salivation, weakness, tremors, violent convulsions, and death. Postmortem lesions include skeletal muscle and myocardial necrosis, perhaps associated with seizures. Administration of sodium pentobarbital at the onset of signs can result in recovery.[259–262]

Hypericum perforatum: St. John's wort (hypericin)

Fagopyrum esculentum: Buckwheat (fagopyrin)

The toxins of St. John's wort (a weed of disturbed areas) and buckwheat (an off-season cover crop used for forage) are primary photosensitizing toxins (see Chapter 40).[263]

Tetradymia spp.: Horsebrush (tetradymol; requires *Artemisia nova* or *A. tridentata:* Black or big sages to induce toxicosis)

Ingestion of horsebrush by sheep, plus black sage (contains a sesquiterpene lactone), at levels of 1% of body weight, can cause hepatogenous photosensitization (see Chapter 40). The tetradymols are bioactivated in the liver to toxic substances that, among other mechanisms, uncouple oxidative phosphorylation.[264,265]

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54.4.4 Miscellaneous Toxic Plants

54.4.4.1 NITRATES

Sorghum spp.: Sorghum, Sudan grass

Avena spp.: Oat

Amaranthus spp.: Pigweed

Beta spp.: Beets

Solanum spp.: Nightshades

Zea mays: Corn

Various fertilizers, water runoff

Toxic levels of nitrate and nitrite are found in forage, water, and many fertilizers. Sources in water include biologic runoff, industrial effluents (nitrite in water from ponds near oil wells), and fertilizer. Nitrate is reduced to nitrite in the rumen. Nitrite converts hemoglobin (Fe^{2+}) to methemoglobin (Fe^{3+}), which does not bind or transport oxygen, leading to hypoxia.[266]

Although many of the listed forages are widely used for animals, environmental conditions such as drought, plant stress, rapid growth spurts, some herbicide uses, low light, and fertilization can lead to nitrate accumulation.[267] All animals are sensitive to nitrite. Ruminants are 10 times more sensitive to nitrate than monogastric animals because the rumen reduces nitrate to nitrite.[266,268] Forage containing a nitrate concentration of 1% (dry weight) may be lethal in cattle not acclimated to it.[266] Acute toxicosis can result from nitrate in water at levels over 0.12%.[266] Levels exceeding 0.5% in forage and 400 ppm in water may be hazardous to pregnant cattle.[266] Clinical nitrate toxicosis appears within 4 hours of exposure. Signs include polypnea, dyspnea, weakness, tremors, intolerance to exercise, and terminal convulsions; death is possible within hours (see Chapter 14).[266,268] Mildly affected cattle may recover spontaneously. Abortion may occur in mild, or apparently nonclinical, cases in cattle within 5 days of exposure (half-life of nitrite in fetus is greater than three times that of adults).[268,269] Hypoxic stress in the fetus may aggravate other causes of abortion.

Cattle with nitrate poisoning will have chocolate-brown blood (>30% methemoglobin). Postmortem findings are nonspecific. A diagnosis of nitrate toxicosis is supported by finding greater than 45 ppm of nitrate in ocular fluid or serum, along with identification of a toxic level of nitrate in forage or water.

Clinical cases respond well to administration of methylene blue (5 to 15 mL of a 1% solution) by intravenous injection.[266] Prevention of nitrate toxicosis requires proper harvest of forage and gradual acclimation of ruminants to potential high-nitrate—type forages.

54.4.4.2

SELENIUM (INDICATORS LISTED)

Stanleya pinnata: Prince's plume

Astragalus bisulcatus: Two-grooved milk vetch

Xylorrhiza spp.: Woody asters

Most common forages under conditions favorable to passive assimilation of selenium

The listed plants are called “selenium indicator plants” because of their requirement for high selenium levels in soil for growth.[26,270] Although these plants are not palatable because of a garlicky odor, they indicate the presence of selenium. In the presence of arid, alkaline soil, selenium also may be accumulated in toxic levels in a variety of common forage plants and consumable weeds (alfalfa, *Asteraceae, Castilleja, Atriplex*). Selenium, an essential element (see Chapter 40), can cause both peracute toxicosis from oversupplementation in feed or injection[270–273] or chronic toxicosis at lower levels.[26,270,274] The mechanism of acute selenium toxicity is unknown but may involve direct effects of organoselenium compounds on cell energy production.[274] The mechanism of chronic selenium poisoning is related to its replacing or interacting with sulfur in structural amino acids needed for cross-linking (cysteine or methionine).[270,274]

All species may be affected by selenium toxicosis. Acute toxicosis is caused by oversupplementation of feeds containing selenium, ingestion of indicator plants (10,000 ppm of selenium), or injection of excessive selenium (0.4 mg/kg of body weight was lethal to lambs). Signs include weakness, dyspnea, bloating, abdominal pain with diarrhea, paresis in some species, and shock and death from respiratory failure.[272–276] Animals, especially horses, with chronic alkali disease from selenium in forage (5 to 50 ppm dry weight in forage is toxic) develop ill-thrift, anemia, stiffness, lameness, loss of mane and tail, and deformation and sloughing of hooves.[26,270,274] Cattle with chronic selenosis may also develop hoof lesions, develop immune incompetence, and if pregnant, may give birth to nonviable calves.[277,278] Neurologic diseases often reported, such as “blind staggers,” are probably not caused by selenosis and may have resulted from ingestion of related locoweeds.[277]

Lesions of selenium toxicosis vary based on dose and duration of disease. Peracute toxicosis leads to widespread organ congestion, cardiac damage, and severe pulmonary edema.[272–274] Chronic selenosis results in articular erosions and deformed, sloughed hooves in horses with loss of longer mane and tail hair.[26,271,274] Selenium in feed should not exceed 1 to 2 ppm dry weight. Selenium in whole blood should range between 0.08 and 1.0 ppm and, in liver, from 0.25 to 1.0 ppm for most normal animals. After exposure to excessive selenium is terminated, tissue levels may return to normal well before clinical signs dissipate, leading to a false-negative finding (hair testing may be beneficial to diagnose chronic selenosis).

No specific treatment is recommended for chronic selenosis. Reportedly, feeding of proteins that are high in sulfur-containing amino acids may be beneficial.[270] Food animals poisoned with selenium may require at least 60 days to clear the excess selenium.[279]

54.4.4.3

SULFUR-CONTAINING PLANTS

Brassica rapus: Turnip

Kochia scoparia: Fireweed, summer cypress (also nitrate, secondary photosensitization)

Certain plants, feed mixes, and water can contain high levels of sulfur. In general, the total amount of sulfur intake for a ruminant should contain no more than 0.4% of sulfur overall. High levels of sulfur as sulfate may contribute to copper deficiency (see Chapter 32) and can cause polioencephalomalacia in ruminants, as can other forms of sulfur.

In the ruminant and perhaps the horse, ingestion of excess sulfur in water, feed, or from grazing plants such as turnips that can accumulate sulfur, intestinal microbes (rumen or large bowel) may produce excess sulfide. The excess sulfides can cause polioencephalomalacia as they are rapidly absorbed. Clinical signs of polioencephalomalacia include characteristic CNS disease with blindness (see Chapter 35).

Diagnosis of sulfur toxicosis requires testing of all potential sources of sulfur, including feed, pasture, and water, in addition to finding of signs and lesions characteristic for polioencephalomalacia. The differential diagnosis for sulfur toxicosis includes other causes of polio, salt toxicity, water deprivation, lead poisoning, and other infectious causes of neurologic disease in cattle.[280]

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54.4.4.4

PNEUMOTOXIC PLANTS

Perilla frutescens: Perilla mint (perilla ketone)

Rapidly growing forages accumulate tryptophan.

Ipomoea batatas: Moldy sweet potato (4-ipomeanol)

Phaseolus vulgaris: Moldy green beans

Lush forage ("foggage") and possibly feeds that are high in tryptophan, toxic plants (seed and flowering stage of perilla mint), moldy sweet potatoes (infected with *Fusarium solani* mold), and moldy green beans *(Fusarium semitectum)* can cause interstitial pneumonia in animals (see Chapter 31).[281–286] The toxins include the listed pneumotoxic ketones and 3-methyl indole, a rumen metabolite of excessive tryptophan.[284,287,288] Despite some diversity of structure, the toxins are metabolized by the mixed-function oxidases in pulmonary type I pneumocytes and nonciliated bronchiolar epithelial cells (Clara) to highly cytotoxic free radicals, leading to damage to local alveolar and, perhaps most important, endothelial cells.[281–293] These oxidant pneumotoxins also deplete cellular antioxidation factors such as glutathione in the liver and lung.[289]

Ruminants, especially cattle, are at risk of developing 3-methyl indole toxicosis when moved suddenly from dry feed to a lush pasture.[284] Unexplained isolated incidents of interstitial pneumonia also occur in feedlot cattle (perhaps from a change in flora or feed tryptophan). Feeding of moldy sweet potatoes or moldy green beans is also hazardous.[281–283] Perilla mint has pneumotoxic ketones in highest concentrations during the flowering and seed stages.[285] Toxicity is retained in dry plant material.[285] Clinical effects of these penumotoxins include sudden onset of increased respiration, severe dyspnea with an expiratory grunt, frothing at the mouth with the head down, and open-mouth breathing.[284,285] Animals may be found dead (see Chapter 14).

Affected cattle have wet, heavy lungs with variable amounts of emphysema. Histologically, the lungs have severe interstitial edema. Ultrastructural studies reveal degeneration and necrosis of type I pneumocytes, endothelial cells, and Clara cells, with proliferation of type II pneumocytes in longer-standing cases.[281,282,284,290–295] Perhaps a result of differential bioactivation rates, the major lesion in the horse is

bronchiolitis (not alveolitis).[296] The extremely short half-life of 3-methyl indole (14 minutes)[288] in cattle has hindered development of diagnostic tests. Specific treatment for toxic interstitial pneumonia is not available.

54.4.4.5 OTHER NOTABLE TOXIC PLANTS

Allium spp.: Onions, garlic, chives

Brassica spp.: Kale, beets, rape, cabbage, turnips (hemolytic disulfides)

Acer rubrum: Red maple (unidentified hemolytic toxin)

The onions and brassica plants contain *S*-methylcysteine sulfoxide, which is metabolized to dimethyl disulfide, which attacks red blood cell (RBC) membranes. Onions and Brassicaceae are toxic to a variety of species, whereas red maple poisoning is reported in horses. Signs in poisoned animals include lethargy, anorexia, dyspnea, coffee-colored urine, icterus, hypoxic abortion, and shock. Death results from respiratory failure secondary to anemia. Affected animals have hemolytic anemia with hemoglobinuria, Heinz bodies, and increased levels of AST, sorbitol dehydrogenase, plasma protein, and bilirubin. Postmortem findings may include icterus, brownish discoloration of blood, centrilobular hepatic degeneration, and hemoglobinemic nephrosis. Note that ruminants such as sheep may adapt to an onion diet because the rumen appears to quickly develop a population of sulfide-reducing bacteria to decrease the hemolytic forms of sulfur.[297–304]

Amaranthus retroflexus: Pigweed (renal toxin)

In addition to the potential to cause high levels of nitrate when in hay, redroot pigweed also can be toxic to kidneys when grazed fresh in the field. Cattle and swine have developed signs of renal failure, including weakness, tremors, ataxia, recumbency, and death after grazing the plant for 5 to 10 days. Serum potassium, BUN, and creatinine concentrations are increased. Lesions include marked perirenal edema (may be bloody), straw-colored fluid in body cavities, and pale kidneys with histologic evidence of degeneration and necrosis of both proximal and distal tubules. Tubules have proteinaceous, cellular casts.[305–307]

Cassia (Senna) occidentalis, C. obtusifolia, C. roemeriana: Senna

These annual shrubs of the southeastern United States contain an unknown myotoxin(s) in all plant parts, but the seeds are most hazardous. Signs of toxicosis may occur in all livestock grazing the plant and include anorexia, ataxia, weakness, intense decrease in weight gain, and recumbency. Clinicopathologic abnormalities may include increased serum levels of CK and AST and myoglobinuria. Postmortem findings include degeneration and necrosis of skeletal and cardiac muscle. Goats and cattle given *Cassia roemeriana* may also have hepatocellular damage.[308–313]

Centaurea solstialis: Yellow star thistle

C. repens: Russian knapweed

These plants contain sesquiterpene lactones such as the cytotoxic repen, along with aspartic and glutamic acids, all of which are potent neurotoxins. Prolonged ingestion of large amounts (>1.8 kg/100 kg body weight daily) of these plants by horses may result in neurotoxicity. The principal sign of toxicity is dysphagia, characterized by dystonia of the lips and tongue. Lethargy and aimless walking are also reported. Lesions include characteristic foci of necrosis in the globus pallidus and substantia nigra (bilateral) of the brain (nigropallidal encephalomalacia). Yellow star thistle is an aggressively growing plant that is difficult to control. Biologic measures, including introduction of rust and insects, have been considered as control measures. Prevention includes providing adequate alternative feeds.[314–317]

Helenium spp.: Sneezeweed

Hymenoxys richardsonii: Bitter rubberweed (sesquiterpene lactones)

These weeds of the Rocky Mountains and southwestern United States are unpalatable but may be ingested by sheep or goats in the winter when other forage is limited. Sesquiterpene lactones bind with sulfhydry groups (cysteine), leading to an extreme irritant effect on the nose, eyes, and GI tract. Affected animals develop severe gastroenteritis (sneezeweed toxicosis is called “spewing sickness” because of vomiting), often with secondary aspiration pneumonia. Affected animals may have increases in serum γ-glutamyltransferase (GGT), AST, creatinine, and BUN. Postmortem lesions include gastroenteritis, congestion of liver and kidney, and aspiration pneumonia. Administration of thiol groups (cysteine, protein, methionine) and antioxidants are protective.[318–322]

Juglans nigra: Black walnut

Horses exposed to fresh black walnut (as little as 5% in shavings used as bedding; possibly also plant) can cause a transient drop in leukocytes, limb edema, and laminitis. The toxin of black walnut is unknown but is not the naphthoquinone juglone, as originally thought. An unknown quinone is suspected. Treatment is removal of offending shavings and traditional therapy for acute laminitis in horses. Rotation of the third phalanx is possible in severe cases.[323–325]

Berteroa incana: Hoary alyssum

Toxicosis with hoary alyssum, a potential weed contaminant of alfalfa hay, is characterized by fever, limb edema, and laminitis in horses.[326] The toxin is unknown.

Karwinskia humboldtiana: Coyotillo

Rhamnus spp.: Buckthorn (neuromuscular toxins)

Coyotillo is a woody shrub from the southwestern United States that may cause toxicosis in cattle, sheep, goats, hogs, and fowl when other forages are scarce. Ingestion of small amounts of the fruit and seeds leads to weakness, incoordination, and eventually paralysis. The onset of signs is delayed for days to weeks after exposure. Lesions include segmental demyelination (wallerian degeneration) of nerve axons. Ingestion of the green parts of the plant may lead to wasting, weakness, and death. Lesions associated with the extraneural

syndrome of coyotillo poisoning include necrosis of the myocardium, liver, and kidney, and pulmonary hemorrhage.[327–329]

Hypochoeris spp.: Flatweed or smooth catsear

Lathyrus spp.: Pea

Ingestion by horses of plants such as flatweed, especially in conditions of overgrazing, is suspected as causing outbreaks of Australian stringhalt. *Stringhalt* is a distal axonopathy characterized in horses by an unusual gait with hyperflexed hock during movement, reluctance to back up, and in some reports a high incidence of roaring. The etiology is unknown for flatweed. *Lathyrus* neurotoxicity is well described (neurotoxic amino acid derivatives, β-*N*-oxalylamino-L-alanine).[330–333]

Persea americana: Avocado (persin)

Plant matter from avocado trees (primarily the Guatemalan varieties, from most reports) has caused aseptic mastitis, myocardial necrosis, and skeletal muscle lesions with edema. Aseptic mastitis with epithelial necrosis in the mammary gland has been reported in cattle, horses, and goats (an ischemic myotoxin, persin is toxic to the mammary gland). Myocardial necrosis (with widespread edema, including the brisket) has been reported for goats, sheep, horses, and avians including rattites (sudden death with fluid accumulation in avians). Horses develop edema of the lips, tongue, mouth, and neck, along with lethargy and colic. Serum factors increased with avocado toxicosis include CK, AST, and LDH.[334–341]

Ricinus communis: Castor bean

Robinia pseudoacacia: Black locust

Abrus precatorius: Rosary pea (the lectins: ricin, robin, and abrin)

The lectins in the listed plants are glycoprotein dimers, joined by a disulfide bond in ricin and abrin. Seeds, cakes, and foliage are poisonous, but not the oil. A portion of the dimer, the haptomer, binds the cell, allowing the other half to enter and block protein synthesis. All classes of livestock are sensitive to the compounds. Ricin and abrin are among the most potent toxins described. Clinical toxicosis reflects primary damage to the GI tract and includes violent gastroenteritis followed by weakness and death from shock and depression of cardiac function. Other poisonous lectins, although less acutely toxic, are found in legume seeds from a variety of unextracted beans. Those factors interfere with intestinal absorption, inhibit growth, and can inhibit the immune system.[342,343]

Vicia villosa: Hairy vetch

Cattle and horses grazing hairy vetch when it is green may develop a systemic granulomatous disease. Dried seeds may cause convulsions (apparently unrelated to the immunotoxic syndrome discussed here) in cattle. Prior sensitization may be required for development of clinical signs of systemic granulomatous disease in animals exposed to green vetch. Initially, animals are presented for listlessness and welts on the skin, with

alopecia and peeling of skin around the nares. Horses may have lymphadenomegaly and dependent edema. Affected animals may develop wasting, diarrhea, and clinicopathologic changes of lymphocytosis and hyperproteinemia. Mortality may be high in affected animals. Postmortem, skin is thickened with scaling and alopecia. Other organs that may be pale or may have gross abnormalities include the heart, kidneys, adrenals, and lymphoid tissues. Microscopically, the skin and other organs, including the liver, have cellular infiltrations of monocytes, lymphocytes, plasma cells, eosinophils, and often, multinucleated giant cells. The mechanism of hairy vetch toxicosis is not known but may involve an immunotoxic lectin.[344–348]

Setaria lutescens: Yellow bristlegrass

Other foxtails (mechanical trauma)

Yellow bristlegrass contains sharp, miniature barbs below the seed heads that can cause mucosal trauma, including oral ulcers, in animals ingesting contaminated hay. Horses and young cattle are most frequently affected.

Xanthoparmelia: Lichen

Ingestion of large amounts of lichen growing in the desert during winter has caused paralysis in sheep and Rocky Mountain elk. The paralysis resembles a lower motor neuron failure, but the mechanism of toxicity has not yet been determined. The toxin is not well characterized, although usnic acid has been implicated as causing part of the syndrome.[349]

54.4.4.6

BLUE-GREEN ALGAE (FRESHWATER)

Microcystis aeruginosa: (microcystin, a hepatotoxic cyclic peptide)

Nodularia spumigena: (nodularin, a hepatotoxic cyclic peptide)

Anabena flos-aquae: (anatoxin-a, a depolarizing neurotoxin; anatoxin-a[s], a cholinesterase inhibitor)

Aphanizomenon flos-aquae: (saxitoxin, neosaxitoxin, blockers of neural transmission)

Potentially toxic blue-green algae (cyanobacteria) may form on stagnant bodies of water under conditions of heat, eutrophication (high nitrogen and nutrients), low flow rates, oxidative stress, and a concentrating wind.[350–352] The cyclic peptide hepatotoxins cause dissociation of the cytoskeleton of the liver through inhibition of protein phosphatase and induction of apoptosis, leading to disintegration of that organ.[353–355] Anatoxin-a is a bicyclic, secondary amine that causes depolarization of nicotinic receptors, leading to muscle and respiratory paralysis.[351,356] Anatoxin-a(s) is a naturally occurring organophosphorus-like compound that inhibits peripheral cholinesterase.[351,357] Saxitoxin and neosaxitoxin cause paralysis by blocking neural sodium transport.[351] A variety of cyanophytes cause skin and GI irritation.

All species are sensitive to the listed algae, which, if ingested in sufficient quantities, may cause sudden death (see Chapter 14). Animals exposed to high doses of the cyclic peptide hepatotoxins may die within 1 hour of exposure from hypovolemia and shock secondary to blood loss into the disintegrated liver and embolism of hepatocytes into the lung.[350,351,353,354] Lower doses lead to characteristic signs of liver failure. Exposure to a toxic dose of anatoxin-a leads to tremor, collapse, exaggerated breathing efforts, convulsions, and death within minutes.[351,356] The paralysis is persistent and not responsive to assisted ventilation.[356] Anatoxin-a(s) also can kill in minutes after exposure. Characteristic signs of cholinesterase inhibition in the periphery include diarrhea, tremors, hypersalivation, dyspnea, paresis, opisthotonos, cyanosis, convulsions, and death.[351,357]

Animals with hepatotoxic blue-green algae toxicosis may have elevations in liver-associated serum factors including AST, GGT, ALP, and bilirubin, as well as creatinine, BUN, and LDH. Hepatotoxic lesions include enlarged, red- to blue-colored livers with gallbladder edema. Histologic alterations include severe centrilobular hepatocellular dissociation, degeneration, and necrosis. Only a rim of hepatocytes around the periportal triads may remain.[350,351,353,354] Hepatocyte emboli may be found in the lung.[354] Mild renal tubular degeneration may occur. Animals with anatoxin-a(s) toxicosis will have depression of peripheral cholinesterase, although brain cholinesterase may be normal.[351] Otherwise, pathologic changes in animals with neurotoxicosis reflect hypoxemia and are nonspecific.

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If blue-green algae toxicosis is suspected, samples of ingesta and bloom can be mixed with 10% neutral-buffered formalin for visual identification. Samples should be accompanied by at least 2 L of fresh bloom material (refrigerated) for demonstration of the toxin or toxicity. Liquid chromatography of bloom material or ingesta may be useful to help diagnose poisoning from the *Microcystis* toxins.[358]

Treatment for blue-green algae poisoning is supportive. Artificial ventilation is required for anatoxin-a toxicosis. Exposed animals might benefit from oral adsorbents such as activated charcoal.[350] Exposure of cattle to *Microcystis* toxins does not appear to cause a food safety risk when tested in liver and blood plasma.[359]

54.5 MYCOTOXINS

A mycotoxicosis is a disease caused by a toxin elaborated by a fungus, unlike a mycosis, which is a disease caused by fungal growth (not its toxins). Mycotoxins may be endomycotoxins (mushrooms, not discussed here) or exomycotoxins (this discussion). Mycotoxins are of worldwide veterinary and public health concern. Diseases caused by mycotoxins include acute and chronic poisoning, immunosuppression, loss of production, carcinogenicity, and teratogenicity.

Many genera and species of fungi are toxigenic. A given mycotoxin may be elaborated by more than one fungal species. Some species of fungi may produce more than one toxin. Conversely, a given fungus may not always be toxic (many are ubiquitous), so finding the fungus alone is rarely diagnostic; diagnosis requires chemical identification of the toxins. Colonization and toxin elaboration may occur in the field or in storage. Basic requirements for colonization include substrate with sufficient nutrients (why fruits and seeds are often infested), moisture content in feed greater than 14%, relative humidity over 70%, appropriate temperature (varies with species of fungus), and oxygen. Damage to fruits and plants favors colonization as well. Basic requirements for toxin elaboration may vary from those needed for colonization.

Mycotoxins are found in a variety of matrices, including cereal grains, other crop feeds such as beans, and grass and forage. Mycotoxins cause billions of dollars of losses worldwide from crop losses, animal and human sickness, reduced production, and costs of control measures. Although many toxins have been identified, many more, as yet unidentified, toxins may still exist. For example, moldy hay has been implicated as a cause of many problems, including GI disturbances, liver disease, and photosensitization, but many of those toxins have not been identified. Little testing is possible for mycotoxins in animal samples. Therefore, testing is best performed on suspected source feed. The sampling technique is critical because toxin levels will vary greatly within a lot of feed; samples should be representative of the lot and frozen for storage. Importantly, feed contaminated with mycotoxins may not be visibly moldy. Some mycotoxins are discussed earlier with plants (moldy sweet potatoes and moldy sweet clover hay). Other important mycotoxins of livestock are discussed here.[360–363]

54.5.1 Aflatoxins

Many fungal species can produce aflatoxins, including *Aspergillus flavus* (*A* + *fla* + toxin), *Aspergillus parasiticus,* and various species of *Penicillium, Rhizopus, Mucor,* and *Streptomyces*. Colonization and toxin production can occur in grains such as corn, cottonseed, and peanuts in all phases from growth through harvest. Aflatoxins are produced in soybeans and other small grains, mainly during storage. Aflatoxin production is encouraged when warm, moist ambient conditions are combined with crop damage (drought or storm). Although many aflatoxins exist, the major toxins of concern include aflatoxins B_1, B_2, G_1, G_2 (B or G = fluorescence color), and the major marker metabolite in milk and meat, aflatoxin M_1.[361,363] After bioactivation in the liver, aflatoxins act by binding of biologic molecules such as essential enzymes, blockage of ribonucleic acid (RNA) polymerase and ribosomal translocase (inhibiting protein synthesis), and formation of DNA adducts.[363,364]

Aflatoxin can cause oncogenesis, chronic toxicity, or acute signs, depending on the species and age of animal and the dose and duration of aflatoxin exposure. All animals may be affected by aflatoxins (birds and trout are more sensitive than mammals, possibly because of increased activation of aflatoxin B_1 in the liver and deficient detoxification mechanisms).[365] Among mammals, young swine and pregnant sows are most sensitive to aflatoxins, followed by calves (0.2 ppm in feed for 16 weeks caused mild liver damage), horses (0.4 to 0.6 ppm), fat pigs, mature cattle (0.66 ppm in feed caused mild liver damage after 20 weeks), and sheep.[361,366] Levels over 1 ppm may cause severe organ damage and acute deaths in livestock. As little as 0.15 ppm of aflatoxin in the feed may lead to actionable residues of aflatoxin M_1 in meat and milk (action level is 0.0005 ppm in meat and milk and 0.02 ppm for interstate transport of grains).[363,367] Aflatoxin in the diet of trout at 0.001 ppm is carcinogenic.[363]

Signs of peracute toxicosis include hemorrhage, bloody diarrhea, and rapid death.[363] Lesions of acute toxicosis include hemorrhages and prolonged prothrombin time (PT). Subacute toxicosis may lead to hepatic failure with icterus, anorexia, ataxia, reproductive failure (abortion), weakness and tremors, slowed rumen motility, coma, and death.[361,363,366,368–373] Impairment of immune function may also occur due to moderate levels of aflatoxin.[363,372] Animals with aflatoxicosis-induced liver failure may have anemia, ascites, pallor, elevated liver-associated enzymes (ALP, AST, total bilirubin), and decreased albumin levels. Lesions include a pale-yellow liver with centrilobular to portal fatty degeneration and necrosis (species dependent) along with biliary hyperplasia.[361,363,366,368–371] Chronic toxicity is associated with decreased growth rates, decreased feed efficiency, rough hair coats, ill-thrift, increased incidence of disease, and liver damage (fibrosis with

regenerative nodules). Carcinogenesis may occur at low levels. Spermatogenesis may also be disrupted in animals exposed to aflatoxins.[374] Experimental studies also suggest that aflatoxins may be present in grain dust in levels that may be bioactivated by pulmonary cytochromes to carcinogenic compounds.[375] Testing of feed and liver for aflatoxin will support a diagnosis.

Aflatoxin B_1 is one of the most potent known carcinogens.[361,363] Aflatoxins are distributed to tissues and milk of food animals, leading to a significant residue concern (aflatoxin M_1 is the marker residue).[373,376] The highest concentrations of aflatoxin are in liver. Aflatoxin is cleared from the liver over 7 days of withdrawal, during which aflatoxin-free feed is provided.[376] Dairy cows can "decontaminate" aflatoxin to below the 0.0005-ppm action level in milk (United States; may be as much as 10 times lower for some trading partners, such as the European Union [EU]) if the maximum level of aflatoxin in feed is below 0.1 ppm (up to 300:1 dilution in the cow).[363]

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Beyond providing aflatoxin-free feed and therapy for liver failure, treatment for aflatoxicosis centers on prevention. Feed has been ammoniated to prevent colonization and growth of fungi and to detoxify the aflatoxin. In emergencies, farmers may dilute feeds to nontoxic levels (risky).[361] Moderate levels of aflatoxins may be fed in combination with hydrated sodium calcium aluminosilicates (clay binders) to prevent aflatoxin absorption, toxicosis, and contamination in milk and meat.[377–380] Clays should be carefully selected to avoid health risks from untested clays.[380] However, experimental studies suggest that a common clay binder can be fed to laboratory animals without toxicity at levels of up to 2% of the diet.[381]

54.5.2 Trichothecenes

The trichothecene mycotoxins are tetracyclic sesquiterpenoid toxins produced in grains (e.g., corn), and some forages, by at least six genera of fungi, the most important of which include various *Fusarium, Myrothecium, Stachybotrys atra,* and *Trichothecium roseum*. Growth of these fungi and toxin production is favored by undulating, cool temperatures.[382,383] Trichothecenes may be present in combination with zearalenone. Toxins of major agricultural concern in the United States (in order of importance) include deoxynivalenol (DON or "vomitoxin"), T-2 toxin, stachybotryotoxin (can be in forage), and diacetoxyscirpenol (DAS).[361,382] The trichothecenes are potent inhibitors of protein synthesis, blocking initiation, elongation, and termination of ribosomal translation.[382] That mechanism leads to an effect that has been called *radiomimetic,* in which all rapidly dividing cells of the body are attacked, leading to severe gastroenteritis, skin necrosis, immune impairment, and initiation of shock.[361,382,384]

All species of animals are sensitive to the trichothecenes. The effects of trichothecene mycotoxins depend on the toxin present, its concentration, and species exposed; dairy cows and other ruminants are much less sensitive than monogastric animals. Toxicity in field cases may be greater than that reported for experimental toxicity studies, probably because related trichothecenes are often present in the field along with the toxin being assayed. For example, 10 ppm of pure DON is needed to cause feed refusal in swine experimentally, whereas 0.5 ppm in field-contaminated grain may lead to feed refusal.[382,383,385]

Dose-dependent signs of trichothecene toxicity include feed refusal, reduced weight gains, severe gastroenteritis with vomition and diarrhea, coagulopathy and shock, skin necrosis (from direct contact), decreased reproductive performance, and immunosuppression.[361,382,383,385–387] Clinicopathologic alterations for severe trichothecene toxicosis primarily reflect shock or hemorrhagic gastroenteritis and include decreases

in hematocrit, hemoglobin, leukocytes, and serum factors of glucose, calcium, and phosphate.[387,388] Bilirubin may be increased secondary to feed refusal.[387] Transiently increased liver-associated serum factors include AST, LDH, and bromosulphalein (BSP) clearance. DON, the most common trichothecene in field cases, usually causes feed refusal, increased incidence of disease, and associated weight loss.[385–388] Other trichothecenes are likely to cause more severe, acute signs of hemorrhagic gastroenteritis, shock, and death. Diagnosis of trichothecene mycotoxicosis is facilitated by finding the toxin in feed.

Toxicosis from DON is treated by providing mycotoxin-free feed. In addition to nonspecific therapy for signs, animals with acute trichothecene toxicosis with gastroenteritis benefit from administration of oral adsorbents such as activated charcoal, along with fluid and steroid therapy for the acute shock.[389] Broad-spectrum antibiotic therapy is indicated to minimize complications of skin lesions and gastroenteritis.[361] The trichothecenes are rapidly metabolized and would not be expected to be a residue hazard 12 to 24 hours postexposure.[386,390,391]

54.5.3 Fumonisins

Fumonisins are hepatotoxic, neurotoxic, and carcinogenic mycotoxins produced by *Fusarium moniliforme*. These toxins are responsible for the disease known as “moldy corn poisoning” of horses, or equine leukoencephalomalacia.[392,393] *F. moniliforme* is ubiquitous in the environment, so testing feed for the mold is not diagnostic. Fumonisins (A and B series; fumonisin B_1 most common) act in part by interfering with sphingolipid biosynthesis through inhibition of ceramide synthetase, among other mechanisms, by blocking protein synthesis and by causing apoptosis and oxidative damage in target tissues.[394–396] Neural tube defects may be caused by fumonisins through blockade of folic acid transport.[397] Fumonisins may predispose animals to infectious diseases, such as enhancing colonization of pathogenic *Escherichia coli* in the gut.[398] Sphingolipids are critical for cell growth, differentiation, and transformation and are present in brain and liver tissues at high levels.

Fumonisins are produced mainly on corn, especially screenings. Although other species can be affected, horses and swine are most sensitive to fumonisin's effects. Ruminants and poultry are resistant.[399,400] Fumonisin B_1 at levels of 10 ppm or greater may lead to toxicosis in horses (>40 ppm for swine). Clinical signs in horses appear suddenly after 7 to 90 days of ingesting toxic corn or screenings and may include depression, confusion, ataxia, sweating, apparent blindness, head pressing, recumbency, convulsions, and death within 5 days of onset of signs.[392,393,401,402] Morbidity is generally low, but mortality rates in affected animals are high.

Clinicopathologic changes include transient increases in serum enzymes associated with liver damage. The pathognomonic lesion of fumonisin toxicosis in horses is *leukoencephalomalacia,* characterized by liquefactive necrosis of white matter of the brain, leaving fluid-filled cavities (often grossly visible).[392,402] Acutely affected horses may have centrilobular hepatic necrosis, which may be present with or without the brain lesion.[392,402] Some monogastric species may develop pulmonary edema.[403,404] Diagnosis of fumonisin toxicosis is aided by finding 10 ppm or more of fumonisin in a corn-based concentrate or screened feed. Elevation of the sphinganine/sphingosine ratio in the urine is a very sensitive indicator of exposure to fumonisins. Assay for sphingolipids in urine may provide a marker for fumonisin exposure.[405]

Avoiding corn in the diet of horses, or at least eliminating corn screenings from the equine diet, will help prevent fumonisin toxicosis. Not much information is available regarding fumonisin as a food-animal residue.

The compound is of concern, however, because it is a potent hepatocarcinogen.[406] From a food safety standpoint, fumonisin is not apparently present in milk from exposed cows in appreciable quantities, possibly because of the low relative absorption of the compound by the rumen.[407] Although fumonisin B_1 parent compound has a relatively short half-life in most studies (18 minutes), some evidence in swine suggests that accumulation may occur in kidney and liver tissue.[407] Studies in swine suggest that fumonisins have little toxicologically significant carryover in tissues.[408]

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54.5.4 Grassland Staggers

Staggers in livestock is caused by ingestion of forages that contain tremorgenic mycotoxins. Forages causing staggers include perennial ryegrass *(Lolium perenne)* infested with *Neotyphodium* (formerly *Acremonium*) *lolia* in leaf-sheathes, ergotized dallisgrass (*Paspalum dilatatum;* seed fungus is *Claviceps paspali*), Bermuda grass (*Cynodon dactylon;* mold unknown), *Phalaris* species (discussed earlier), moldy walnuts (*Juglans* spp.; walnut mold is *Penicillium* spp.), and although not a forage, *Aspergillus* species in grain.[361,409–412] The toxins are alkaloidal, indole-based paxallines and include lolitrems (perennial ryegrass), paspalitrems (dallisgrass), tryptamine alkaloids *(Phalaris),* penitrems (moldy walnuts), and aflatrems *(Aspergillus).*[361,409–413] The mechanism of action of these toxins is incompletely understood but may involve enhanced release of excitatory amino acid neurotransmitters.[414] In addition, annual grasses infested with a nematode that is subsequently infected by the bacterium *Clavibacter toxicus* may also be toxic from production of corynetoxins. Corynetoxins are glycolipids with structures and effects similar to tunicamycin compounds. Affected grasses include annual ryegrass (*Lolium* spp.), blowgrass (*Agrostis* spp.), and *Polypogon,* especially in moist stubble and floodplains (sometimes called “floodplain staggers”).[415]

The toxicity of tremorgenic forages depends on grazing habits and climate. Perennial ryegrass tends to be most hazardous late in the grazing season, when grass is grazed low to the ground (lolitrems are found in lower leaf sheaths, so are more of a hazard for sheep).[409,416,417] Dallisgrass is hazardous when ergotized seed heads are grazed (more of a hazard for cattle).[412] All species exposed to the staggers toxins may be affected. Dried perennial ryegrass and ryegrass seeds may retain toxicity.[417,418]

Signs of staggers appear within 7 days of initial grazing (within hours for penitrems in walnut).[361,409] Animals appear normal at rest or may have a fine tremor in the ear and head. When stimulated, affected animals have a characteristic stiff, spastic gait, followed by spasms and tetanic seizures (opisthotonos occurs in severe cases).[361,409,416,419] Recovery from an episode may be rapid for perennial ryegrass, dallisgrass, and Bermuda grass staggers if animals are not stressed. Losses occur, however, from misadventure (e.g., injuries, drowning, becoming trapped during seizure episodes).[409] Seizure episodes dissipate within 2 weeks after animals are removed from the toxic forage. Annual ryegrass toxicity cases appear after floods or on grazing pastures with large amounts of stubble from the previous year. CNS signs include ataxia, convulsions, and other signs consistent with grassland staggers. Death often occurs within 24 hours.[415]

Lesions of staggers are minimal, although degeneration of cerebellar Purkinje cells has been reported for longer-standing, severe cases of perennial ryegrass staggers.[420,421] Postmortem, lesions from annual grass staggers from corynetoxins include a fatty liver and cerebellar degeneration.[415] Diagnosis of staggers syndromes is helped by ruling out other tremorgenic syndromes, identification of the fungus (e.g., for perennial

ryegrass), and identification of the toxin in the plant (lolitrem B in perennial ryegrass).[409] If forages are not available for analysis, bioassay using an extract of the forage in the laboratory can be diagnostic.[409,422]

Alternate forage should be provided for affected animals until new pasture growth is available. Some managers move animals away from the toxic pasture during the sensitive periods. Affected animals are placed in areas where misadventure can be minimized. Mowing the seed heads is suggested to minimize effects of ergotized dallisgrass.

54.5.5 Fescue Toxicosis

Fescue toxicosis is common throughout the United States. Tall fescue grass *(Festuca arundinacea)* infested by *Neotyphodium* (formerly *Acremonium*) *coenophialum* and strains of perennial ryegrass *(Lolium perenne)* infested by *Neotyphodium (Acremonium) lolia* (also produces staggers toxins) produce ergot-type alkaloids such as ergovaline and pyrrolizidine-type alkaloids (loline).[423–425] The ergot alkaloids act by interacting with dopaminergic neurotransmission and blocking prolactin.[426,427] The presence of endophyte may also be associated with lower copper levels in the fescue grass, contributing to copper deficiency in areas with marginal copper in forages.[428]

Toxicity of tall fescue depends on the ambient weather and reproductive stage of exposed animals.[424] During warm conditions, cattle, sheep, and horses develop "summer syndrome," characterized by increased rectal temperatures, lethargy, ill-thrift, failure to gain weight, and intolerance to ambient heat.[429–431] The breeds of cattle (*Bos indicus* vs. *Bos taurus*) are apparently alike in their sensitivity to ergot alkaloids from fescue.[432] This summer syndrome may partly result from alterations of hormonal (plasma cortisol, triiodothyronine [T_3]) and vascular control of body temperature.[433,434] During cool conditions, cattle may develop typical ergot-type lesions of dry gangrene in the distal extremities.[435–437] The most devastating aspect of tall fescue toxicosis may be reproductive failure, characterized by agalactia, prolonged gestation, weak offspring, stillbirths, and thickened placentas (horses and cattle).[424,438,439] Ruminants of both genders may also have decreased fertility.[440–442]

Lesions of fescue toxicosis are nonspecific. Serum prolactin, progesterone, and dopamine concentrations are decreased in exposed animals.[426,427] Postmortem, fat necrosis with foci of hard nodules in the omental region may be present in animals with summer syndrome, and ergotlike gangrene is present in distal extremities of animals with "fescue foot."[424] Diagnosis of tall fescue toxicosis is helped by demonstration of the endophyte or toxins in grass.

Pregnant animals should be removed from tall fescue pastures by 30 to 60 days before parturition. Some farms have successfully used herbicides to kill the tall fescue, planted an annual crop the next year, and then followed by planting of endophyte-free tall fescue, which is now available.[424] Current work suggests that infesting fescue grass with nonergot alkaloid—producing endophyte may maintain the fescue while eliminating the negative impact of alkaloid exposure.[443,444] Experimental vaccination and treatments with dopamine antagonists such as dromperidone are being investigated to treat fescue toxicity.[445,446]

54.5.6 Other Mycotoxins

54.5.6.1 ERGOT

Classic ergot results from parasitism of developing grass or grain flowers by *Claviceps purpurea,* leading to formation of a dark sclerotium on the seed heads. Several wild grasses and grains such as rye, triticale, wheat, oats, sorghum, and barley may be affected. Affected grains contain a series of alkaloids, including ergotamine, ergonovine, and ergotaxine (also found in fescue; see earlier). Ergotism in livestock may cause ataxia, convulsions, lameness, dyspnea, diarrhea, dry gangrene of the extremities similar to fescue foot, abortion, neonatal mortality, reduced lactation (ergot alkaloids have been used medicinally for uterotropic effects), poor weight gains, lowered production, and lowered feed intake.[447,448]

54.5.6.2 ZEARALENONE

Zearalenone is an estrogenic mycotoxin produced in corn and other grains by various *Fusarium* species (especially *F. roseum*) under similar warm and cold climatic cycles as for trichothecenes (zearalenone is often found with DON; see earlier). Prepubertal swine and dairy cows are the most sensitive animals to zearalenone. Corn contaminated with zearalenone may cause toxicosis at levels as low as 1 ppm, a level well below the toxicity of pure toxin, suggesting the presence of other estrogenic metabolites in field samples. Zearalenone can be metabolized to the more toxic zearalenol. Species-specific sensitivity to the mycotoxin is related to differential metabolism of the zearalenone to zearalenol and to differential detoxification rates in liver. Zearalenone causes chronic hyperestrogenism, with vulvar swelling, prolapsed rectum, enlarged mammary glands, reduced fertility, and feminization of swine and cattle. Although zearalenone may be distributed to milk and meat, medically significant residues would not be expected in products from animals exposed to grain with natural zearalenone contamination.[449–451]

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54.5.6.3 SLAFRAMINE

Slaframine is an indolizidine alkaloid mycotoxin produced by black batch mold *(Rhizoctonia leguminicola)* contamination in moldy red clover forage (including hay, *Trifolium repens*). Slaframine causes increased salivation, diarrhea, and bloat in affected cattle and horses.[452,453]

54.5.6.4 OCHRATOXIN

Ochratoxin is an isocoumarin derivative of phenylalanine. Feeding of more than 0.2 to 4.0 ppm in grain to livestock can cause nephropathy. Monogastric animals such as swine and horses are more sensitive than ruminants, although young ruminants may be susceptible to levels of ochratoxin above 2 to 40 ppm in the grain. Liver damage, enteritis, reduced growth rates, and abortion also have been reported. Citrinin, another nephrotoxic mycotoxin, might be found along with ochratoxin in a contaminated grain sample.[449]

54.6 ZOOTOXINS

A variety of lizards, insects, arachnids, ticks, and bees may cause toxicosis in animals.[454] The incidence of such envenomations (bites) and poisonings (ingestion of toxic animals or insects) is generally rare and requires

symptomatic treatment and removal of the toxic source. Two more common toxic and venomous syndromes of livestock are discussed here.

54.7 VENOMOUS SNAKES

Crotalus spp.: Rattlesnakes

Sistrurus spp.: Pygmy rattlesnakes

Agkistrodon spp.: Copperhead; *A. piscivorus:* Cottonmouth

Micrurus spp.: Coral snakes

The pit vipers *Crotalus* (rattlesnakes) and *Agkistrodon* are responsible for most of the reported envenomations of animals in North America. A pit organ and large, hollow fangs through which venom is passed into the victim characterize pit vipers. Envenomation by Elapidae or the coral snakes is possible in North America, but rarely reported. Coral snakes chew their venom into the victim. Crotalid venom largely consists of toxic proteins (>90% protein).[454] The toxins include proteolytic and phospholipase enzymes, coagulation and hemorrhagic toxins (affecting clotting cascade), myotoxins, and in the Mojave rattlesnake a potent paralytic neurotoxin.[455,456] Coral snakes produce neurotoxins. The effects of pit viper envenomation include anaphylactoid reactions with hemolysis and shock in systemically affected animals, with extensive local edema and necrosis near the bite from the proteolytic and myotoxic proteins (local effects are more common in large livestock).[457]

Livestock are usually bitten in the extremities and muzzle by snakes. The severity of effects depends on the size of the snake (larger snake = larger possible envenomation), size of the victim (smaller animal = more severe effects), severity of the strike (one or two punctures, amount of venom injected), and location of the bite (central vs. extremities).[454,458] Systemic effects vary depending on the crotalid species. For example, Eastern diamondback rattlesnakes may cause more hemolytic effects, the Mojave rattlesnake may be more neurotoxic, and the Western diamondback may cause more cardiovascular shock and local effects. Systemic signs include weakness, syncope, and hypotension. Mojave rattlesnake envenomations may result in respiratory distress and other signs of neurologic paralysis. Large livestock are more at risk from the local than the systemic effects of rattlesnakes. Signs in the bite region include pitting edema and pain within 20 minutes. Edema progresses rapidly and may involve an entire limb within hours. The skin may have ecchymoses and can become quite turgid. Untreated, local necrosis and effects may not peak until 4 days after envenomation.[457]

Common clinicopathologic abnormalities in animals with systemic envenomation include reduction of erythrocyte numbers (hemolysis), hypofibrinogenemia, echinocytosis, and thrombocytopenia. The presence of echinocytosis may aid in diagnosis of snakebite.[459] Clotting parameters are prolonged. Serum enzyme alterations reflect local tissue and muscle damage, especially high CK concentrations. The urine may contain protein, glucose, and blood.[454] Pathologic alterations in large animals include local tissue damage. Severe insect/bee stings, trauma, abscessation, and in the horse, purpura hemorrhagica, should be ruled out in the diagnosis of a snakebite.[454]

Initial treatment of snakebite in horses and large animals bitten near the nose requires maintenance of airway patency. A hose or tube can be placed in a nostril if treatment is initiated promptly. Otherwise, tracheostomy may

be indicated. Snakebites are optimal environments for a variety of infectious organisms, requiring treatment with broad-spectrum antibiotics. However, for systemically affected human patients, the use of prophylactic antibiotic therapy for snakebite is becoming controversial.[460] Horses especially should be given tetanus prophylaxis. Antiinflammatory treatment should be initiated using a nonsteroidal antiinflammatory drug (NSAID) such as phenylbutazone. Local wound care and debridement should be performed. Corticosteroids and fluid therapy are rarely indicated in large animals unless systemic shock develops (unlikely). Expense, marginal efficacy at the local site, and side effects argue against antivenin use in the horse. Systemic treatment of crotalid-induced neurotoxicity has been accomplished in human medicine using a polyspecific Fab antibody.[461] Antihistamine therapy is controversial and is not recommended for horses.

54.8 BLISTER BEETLE

Epicauta spp.: Blister beetles

Alfalfa and other blooming hays may attract blister beetles. Blister beetles can contain 0.1% to 12% cantharidin (dry weight).[462] *Cantharidin* is a potent vesicant toxin that causes necrosis of all mucous membranes that it contacts.

Although blister beetles may be found throughout the United States, conditions favoring swarming and toxicity in livestock hay occur in the midwestern United States. Cases have been reported in the region bounded by Florida to Arizona and north to Colorado, Minnesota, and Illinois.[462] Beetles tend to swarm when alfalfa (or nearby weeds) is in bloom and when conditions favor increases in the grasshopper population.[463] Harvest techniques that use a windrower type of machine that cuts, crimps or conditions, and piles hay (unlike classic practices that mow hay, then rake it without crimping) will trap the beetles in the hay, leading to possible toxicity.[462,463] The beetles retain toxicity in dried hay; 4 to 6 g of dried beetles, or about 100 beetles, may be fatal.[462–465] All classes of herbivorous livestock may be affected, although most cases have been reported for horses. Animals with blister beetle toxicosis develop colic, gastroenteritis, nonspecific neurologic signs, increased urination, cystitis, shock, and death. Shock and death alone may be reported in severely poisoned horses.

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Clinicopathologic alterations reflect dehydration, shock, and renal damage. Hemoconcentration occurs despite decreased levels of protein, calcium, and magnesium in the serum.[462,464] The serum has increased levels of CK, BUN, and creatinine. Renal damage is also reflected by decreases in urine specific gravity despite dehydration and shock. Hypocalcemia and hypomagnesemia are also likely to occur.[466] Postmortem lesions include hemorrhagic gastroenteritis (including oral); pale, moist, swollen kidneys; and hemorrhagic damage to the urinary tract. In some cases that involve sudden death, lesions may be absent. Histologic alterations include inflammation and hemorrhage with ulceration of the GI tract, bladder mucosa, ureters, and renal pelvis.[462,464] Direct myocardial necrosis may occur in severe cases.[464]

Diagnosis of cantharidin toxicosis is facilitated by identification of beetles in hay or ingesta and chemical analysis for cantharidin in beetles, ingesta, blood, and urine (urine may have from 0.0005 to 2.0 ppm of cantharidin).[462,466]

Blister beetle toxicosis can be prevented through proper harvest of hay by avoiding times when beetles swarm, managing flowering weeds, controlling grasshoppers, avoiding full bloom during cutting, and if possible, avoiding use of crimpers and conditioning equipment during hazardous times.[463] Insecticides should be avoided when hay is in full bloom (bees essential for alfalfa crops may be harmed). Livestock with blister beetle toxicosis should

have toxic hay removed from the diet (destroy hay; the toxin does not dissipate with time) and treated aggressively for shock and renal failure (fluid replacement).[462,464]

54.9 METALS AND OTHER INORGANIC COMPOUNDS

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54.10 ARSENIC

Trace levels of arsenic are present in tissues of most animals because arsenic is naturally found in plants and soil.[467,468] However, arsenic toxicosis can be caused by either inorganic or organic forms. In general, inorganic arsenic compounds are more toxic[469] and more likely to cause toxicosis than the organic arsenic compounds.[467]

Inorganic arsenic can exist in trivalent (commercial) or pentavalent (natural) forms. The trivalent arsenic compounds (arsenite) are more soluble and thus 5 to 10 times more toxic than pentavalent forms of arsenic (arsenate).[467,469,470] Inorganic arsenic compounds are used as rodenticides, insecticides, and herbicides.[469,471] Arsenic pentoxide is a preservative used in salt-treated or pressure-treated wood. However, toxicosis from ingestion of arsenic-treated wood has been reported only when the wood had been burned first, allowing the arsenic to become bioavailable.[468]

Organic arsenic compounds can be either aliphatic or aromatic. *Aliphatic* arsenic compounds are used as herbicides and tonics. *Aromatic* organic arsenic chemicals are trivalent or pentavalent. The trivalent form is used as a treatment for heartworms in dogs. The pentavalent forms (phenylarsonic compounds) are used as feed additives for poultry and swine.[469]

The different types of arsenic have varying mechanisms of action. The phenylarsonic feed additives have an unknown mechanism that causes degeneration of myelin sheaths and axons in monogastric animals. The inorganic and the aliphatic organic compounds directly irritate the gastrointestinal (GI) tract, resulting in necrotic lesions.[469] Arsenic also acts directly on capillaries, resulting in transudation of plasma and decreased blood volume. The subsequent shock that develops is believed to be responsible for sudden death.[467,469]

Trivalent inorganic and aliphatic organic arsenic chemicals react with sulfhydryl groups.[469,470] Two enzyme complexes of the citric acid cycle contain lipoic acid, which has two sulfhydryl groups and thus is sensitive to these forms of arsenic. Pyruvate dehydrogenase complex is inhibited, preventing formation of acetyl coenzyme A (CoA) from pyruvate. Also, α-ketoglutarate is inhibited, thus preventing formation of succinyl-CoA. The liver, kidney, gut, and heart are the organs most susceptible to this metabolic disorder. Arsenic also inhibits the amino acids that contain sulfur and results in fatty infiltration of the liver.[469]

Pentavalent inorganic arsenicals affect a different metabolic pathway. Normally, in the glycolytic pathway, an inorganic phosphate is added to glyceraldehyde 3-phosphate, which is converted to 1,3-diphosphoglycerate. Arsenate can replace the phosphate, resulting in production of 1-arseno-3-phosphoglycerate. This new intermediate can be used in the glycolytic pathway; however, the adenosine triphosphate (ATP) that would be produced during formation of 3-phosphoglycerate is lost. Therefore, arsenate uncouples oxidative phosphorylation.[469]

Clinical signs and lesions are similar except for the phenylarsonic compounds used as feed additives, which cause peripheral nerve degeneration in monogastric animals. All the other arsenic compounds can cause peracute, acute, or subacute conditions. Peracute toxicosis results in cardiovascular collapse and usually presents as sudden death.[467,469,470] Acute toxicosis is seen 3 to 12 hours after ingestion. The most prominent clinical sign of acute and subacute cases is diarrhea, which frequently is hemorrhagic. Other clinical signs include anorexia, dehydration, weakness, colic, and agalactia.[467,469–471] The most consistent necropsy lesions are in the GI tract and may be hemorrhagic, edematous, or eroded. The lesions may be confined to one region of, or spread throughout, the GI tract.[467–472] In ruminants, the abomasum is often the most severely affected area. The gut lumens are sometimes filled with necrotic material from the sloughed lining of the GI tract. Other lesions include pulmonary edema and hemorrhage of the cardiac serosa and peritoneum.[467,469,470] Histopathologic examination may reveal multifocal necrosis of the liver and the proximal tubules of the kidney.[472] Peracute cases often have no abnormal gross findings.

Diagnosis of acute arsenic toxicosis is generally made by finding elevated levels of arsenic in the liver, kidney, and GI contents.[469,472] In cases of peracute death, the tissues may have normal levels of arsenic, but the GI contents will have toxic levels. In animals with chronic toxicosis, arsenic deposition in hair begins 2 weeks after exposure. Arsenic levels in hair can be used as a retrospective diagnostic tool.[470] Chronic arsenic toxicosis is rare because arsenic is rapidly excreted in the urine.[470,471] Urine and whole blood are the best samples to collect from live animals suspected of having acute arsenic toxicosis.

Treatment is dictated by the type and severity of clinical signs. Dimercaprol, also known as BAL (British antilewisite), can be used as a specific antidote if the toxicosis is caused by a trivalent inorganic or an aliphatic organic arsenic. Dimercaprol contains two sulfhydryl groups and can bind to arsenic, forming a chelate that is eliminated by the kidney.[469] Galey[473] recommends a loading dose of 4 to 5 mg/kg intramuscularly (IM) followed by 2 to 3 mg/kg every 4 hours for 24 hours, then 1 mg/kg every 4 hours for the next 2 days. Stair et al.[474] recommend a more rigorous protocol of 3 mg/kg IM every 4 hours for the first 2 days, every 6 hours on the third day, and every 12 hours for another 10 days. Dimercaprol has the side effect of potentially inhibiting enzymes that contain metallic coenzymes needed for cellular respiration.[469] Adverse clinical signs associated with dimercaprol include hypertension, tremors, convulsions, and coma.[469]

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Lipoic acid reportedly is a superior chelating agent to dimercaprol when administered to calves in a 20% solution at 50 mg/kg IM (two or three injection sites) every 8 hours.[474] Sodium thiosulfate has been reported as a safe chelator in large animals at 30 to 40 mg/kg IV or 60 to 80 mg/kg orally (PO) two or three times daily for 3 to 4 days.[469] Newer chelators for humans and small animals, including 2,3-dimercaptosuccinic acid (DMSA, succimer), have the benefit of chelating toxic metals such as arsenic, lead, and mercury while sparing iron, magnesium, and calcium.[474] However, DMSA is likely cost-prohibitive for most large animals. D-Penicillamine is an effective arsenic chelator in humans, but also may be too expensive in livestock.[469] Ethylenediamine tetraacetic acid (EDTA) is not effective for arsenic toxicosis because this chelator removes only extracellular arsenic, not the intracellular arsenic causing the clinical signs.[468]

54.11 COPPER

Copper toxicosis can be acute or chronic. Acute toxicosis results from soluble copper salts. Acute copper toxicosis has been reported in adult and juvenile cattle that were given injections of copper disodium edetate as a treatment for copper deficiency.[475–477]

Chronic copper toxicosis can be categorized as simple, hepatogenous, or phytogenous. *Simple* chronic toxicosis is caused by ingestion of excessive copper relative to the levels of molybdenum or sulfate in the diet. Molybdenum and sulfate can bind to dietary copper and decrease its accumulation in the liver.[478] Copper accumulates in the liver when the dietary copper/molybdenum ratio is greater than 10:1 for sheep.[478] Many different sources of excess copper have been reported. Sheep are often poisoned when fed rations intended for cattle or horses,[479] and llamas have developed copper toxicosis when fed cattle feed.[480] Cattle develop copper toxicosis when supplemented with excessive copper[481] in their diets or when fields are contaminated with copper from industrial pollution, as with copper smelting units.[482,483] Cattle have become poisoned when fed litter from chickens that had been fed copper sulfate,[484] and sheep have developed toxicosis after grazing pastures fertilized with manure from swine that were fed copper sulfate.[487] Excessive copper in calf milk replacers has been the source of toxicosis in both calves[486,487] and goat kids.[488]

Hepatogenous copper toxicosis occurs when plant toxins damage the hepatic parenchyma, causing the liver to have an increased avidity for copper. The plants most often associated with hepatogenous copper toxicosis are *Senecio* species and *Heliotropium europaeum*.[478] *Phytogenous* copper toxicosis occurs when animals graze plants with elevated copper/molybdenum ratios for prolonged periods. In general, mature pastures have higher levels of molybdenum than young, rapidly growing plants.[478] Subterranean clover *(Trifolium subterraneum)* is especially noted for causing this type of chronic toxicosis.[478]

Copper is absorbed in the intestine, bound to proteins, and transported to the liver. Copper binds with ceruloplasmin, a metalloprotein, in the liver. Copper accumulates in hepatic lysosomes over several weeks to months during chronic copper poisoning.[478,485,486] During this accumulation phase, necrosis of hepatic parenchymal cells and swelling of Kupffer's cells occur.[478] This phase is followed by a sudden release of copper into the bloodstream from the liver, either spontaneously or after some type of stress to the animal.[478,484,485] This acute hemolytic phase includes an increase in erythrocyte fragility and a decrease in blood glutathione, followed by hemoglobin oxidation and methemoglobin formation.[478,486] The resulting intravascular hemolysis leads to anemia and hemoglobinuric nephrosis.[486]

The first noticeable clinical signs of chronic copper toxicosis are usually depression, anorexia, and weakness, which often have a sudden onset. Feces may be watery, dark, or blood tinged, especially in cattle. Evidence of a hemolytic crisis is apparent. Animals have anemia, methemoglobinemia, and hemoglobinuria. Mucous membranes are icteric or muddy brown.[478,481,484,489] Cattle that develop copper toxicosis after injection with copper disodium edetate have dyspnea, head pressing, ataxia, and circling rather than the hemolytic crisis that occurs with chronic copper toxicosis.[475,477]

Gross necropsy lesions are found in the liver, kidneys, and spleen. The liver is yellow and friable and may be larger or smaller than normal. The kidneys are dark red or blue-black. The spleen may be enlarged and congested.

Histopathologic changes in the liver include centrilobular necrosis, pigment-laden Kupffer's cells, hepatic fibrosis, and bile duct hyperplasia.[478,479,484,485] Granules in the liver will stain positive with rhodamine or rubeanic acid, two histochemical stains that are specific for copper. The degree of staining, however, does not always correlate well with the severity of lesions or with the amount of copper in the liver.[486]

Diagnosis of chronic copper toxicosis is made by measuring copper levels in serum, liver, and kidney.[485,486] Copper levels in serum are not elevated until just before or during the hemolytic crises.[478] Animals with toxic levels of copper in their livers can have normal or even deficient levels of copper in their serum. Therefore, measuring serum copper levels is not a reliable method of monitoring animals for excessive copper in the liver.[481]

If an animal is suspected to have died from chronic copper toxicosis, copper levels should be measured in both fresh liver and kidney, because after the liver has released its copper load into the bloodstream, liver copper levels may fall into a nontoxic range. In these cases the kidney copper levels will be in a toxic range, so the diagnosis will not be missed. The diagnosis should correlate with histopathologic lesions in formalin-fixed liver and kidney.[486] Unlike chronic copper toxicosis, acute toxicosis from copper disodium edetate does not necessarily result in elevated copper levels in liver or kidney.[475]

Treatment is often unsuccessful once an animal develops the acute hemolytic crisis. Ammonium molybdate (50 to 500 mg PO once daily) and sodium thiosulfate (300 to 1000 mg PO once daily) for 3 weeks has been used for many years as a treatment.[478,485] The liver copper levels begin to decrease within 4 days of beginning this therapy.[485]

A newer treatment is ammonium tetrathiomolybdate, 1.7 mg/kg IV or 3.4 mg/kg subcutaneously (SC) on alternate days for three treatments).[478,490] Either route of administration significantly decreases liver copper levels within 6 days. Thiomolybdates decrease copper absorption and increase copper removal from the liver.[478] This change is accompanied by an increase of copper in the blood, bile, feces, and urine.[478] Most of this copper is insoluble in trichloroacetic acid, indicating that it is bound with tetrathiomolybdate and albumin in an inert complex.[490] Interestingly, one report indicated that when xylazine is given with tetrathiomolybdate, the amount of copper excreted in the urine doubles compared with giving tetrathiomolybdate alone.[491]

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D-Penicillamine (26 mg/kg PO twice daily for 6 days) results in a 10- to 20-fold increase in urinary copper excretion in sheep.[478,492] This drug does not seem to increase fecal copper concentration.[492] Unfortunately, this treatment is often cost prohibitive for many livestock.[478,485]

Trientine is a cuprureticagent used to treat humans. One study reported clinical improvement in sheep given this drug at 0.5 mg PO four times daily.[478] Another study, however, demonstrated no increase in copper excretion in urine when the dosage was 26 mg/kg PO twice daily for 6 days.[492]

54.12 FLUORIDE

Most cases of fluorosis are caused by animal exposure to industrial emissions. Fluorosis has also occurred after volcanic eruptions, when gaseous fluoride is fixed by foliage.[493,494] Horses and sheep tolerate higher levels of fluoride than cattle.[495] Lesions are similar in all species.[495]

Fluoride primarily affects, and is incorporated by, developing and mineralizing teeth and bones.[495,496] The main clinical signs are weight loss and lameness, especially of the forelimbs. Palpation of the long bones results in intense pain.[493] Radiographs of animals with osteofluorosis reveal sclerosis, porosis, periosteal hyperostosis, endosteal hyperostosis, and osteophytosis.[496]

Characteristic lesions occur on incisors, premolars, and molars. Dental hypoplasia, dysplasia, and yellow to brown discoloration of the enamel are common. The enamel is eroded or pitted and may have a chalky appearance.[496] The molars may become so abraded and painful that animals have difficulty with mastication and drinking cold water.[495] Dental abrasion is reduced if nonaffected teeth are adjacent to affected teeth.[496]

Gross pathology lesions include abnormal bone formation on the periosteum and thickening of the cortex. The first lesions appear on the ribs, mandible, metatarsus, and metacarpus. Histologic findings include abnormal bone remodeling, abnormal mineralization, coarse collagenous fibers, and increased osteoid.[496]

Only small amounts of fluoride pass the placental barrier. Therefore, teratogenic lesions or congenital malformations have not been observed in offspring of horses, sheep, or cattle with fluorosis.[496]

Fluoride has an intense, dose-dependent osteogenic action, and osteofluorosis is associated with increased bone alkaline phosphatase (ALP) activities.[493,496] Urine, serum, and bone will have elevated levels of fluoride.[494,496] These findings, in conjunction with clinical signs, radiography, and lesions, are used to make a diagnosis.

Fluoride toxicosis has no antidote.[496] Animals should be removed from the source of the excess fluoride and given supportive care. Feeds that are easily masticated should be fed to reduce further abrasion of the teeth.[495] Affected animals will not completely recover.[496]

54.13 IODINE

Iodine is used to prevent infectious diseases and as a treatment for foot rot. Sources of iodine include potassium iodide, sodium iodide, kelp, and ethylenediamine dihydroiodide (EDDI). Oversupplementation can result in toxicosis.

Clinical signs include a nonproductive cough, lacrimation, serous nasal discharge, scaly hair coats, and hyperthermia. Other clinical signs include decreased milk production, decreased rate of gain, and decreased feed conversion. Young animals seem to be more susceptible. Adults may not develop toxicosis unless stress, disease, or other nutritional imbalances also are present.[497] Excess supplementation in mares has been associated with goiter in foals.

Serum biochemical changes are inconclusive for iodine toxicosis. A diagnosis can be confirmed only with serum or milk analysis. Nonlactating cows have higher serum iodine concentrations than lactating cows because the iodine is eliminated in milk. Iodine levels in milk are directly related to the levels of iodine in the diet.[497] Iodine-based teat dips can elevate milk iodine levels.

Treatment is restricted to removal of the dietary source of iodine. Clinical signs associated with the respiratory tract disappear 1 to 4 weeks after the iodine source is removed.[497]

54.14 IRON

Hemochromatosis can be classified as either primary (idiopathic) or secondary. Primary hemochromatosis is an inherited defect resulting in iron deposition in the liver caused by increased iron absorption.[498,499] This discussion is limited to iron toxicosis associated with excess oral or parenteral iron supplementation.

Most cases of iron overload have occurred in neonatal foals that were given ferrous fumarate orally before 3 days of age.[500,501] Adult horses, however, have developed iron toxicosis after oral supplementation with ferrous fumarate or ferrous sulfate.[501] Iron toxicosis has been reported in calves injected with a combination of ferrous gluconate and ferric ammonium citrate.[502] Young bulls injected with ferric ammonium citrate also developed iron toxicosis.[503]

Normally, the small intestine absorbs about 3% to 10% of dietary iron and stores the iron as ferritin in the mucosal cells. The iron is transferred to the plasma according to the body's needs. Excess iron is stored in the liver as ferritin and hemosiderin because the body has limited ability to eliminate iron.[498,500] Foals are born with a high serum iron level and have higher iron absorption than adults. Therefore, foals less than 3 days of age are more susceptible than adults to iron toxicosis.[504]

Clinical signs in neonatal foals include depression, icterus, head pressing, and disorientation.[501] Adult horses develop anorexia, icterus, and sometimes petechial hemorrhages.[500] Calves with iron toxicosis have trembling, vocalizing, bruxism, colic, and convulsions.[502]

If clinicopathologic findings are abnormal, they will be related to cholestatic liver failure. Animals often have elevated levels of γ-glutamyltransferase (GGT), ALP, bile acids, and unconjugated bilirubin. Coagulopathies are demonstrated by abnormal coagulation profiles, thrombocytopenia, and elevated fibrinogen and fructose diphosphate (FDP).[500,501]

Grossly, the liver lesions are variable. Most livers are friable and swollen or shrunken. In general the liver is discolored, pale tan or mottled red-brown. Microscopic lesions include periportal bile ductule proliferation, periportal necrosis, lobular necrosis, and fibrosis. Hemorrhages may be present in the gastric mucosa, intestines, and urinary bladder.[501–504]

Diagnosis of iron toxicosis usually is based on the presence of appropriate clinical signs and a history of recent iron supplementation. Serum levels of free (unbound) iron may or may not be elevated. Liver iron concentrations range from normal to several thousand parts per million. Interpreting iron levels in liver can be complicated because iron may be elevated above normal if the animal had hemolysis or if blood congestion occurred within the liver.

Treatment of iron toxicosis is usually limited to supportive care. Repeated phlebotomy or chelation therapy with deferoxamine is used to treat iron overload in humans and small animals.[498,500] The success rate of these treatments in large animals has not been well documented.

54.15 LEAD

Lead toxicosis is discussed in Chapter 35.

54.16 MERCURY

Mercury toxicosis has been associated with ingestion of seed treated with organic mercurial fungicides.[505–507] Topical application or ingestion of inorganic mercurials, used as counterirritants (blistering agents), also can result in toxicosis.[505,507,508] If the blistering agents are used concurrently with dimethyl sulfoxide (DMSO), the absorption of the mercury is enhanced and is more likely to cause toxicosis.[508]

Mercuric ions form covalent bonds with sulfhydryl groups and form mercaptides.[507] The kidney is the primary target organ, but mercury also localizes in the GI mucosa. Mercury is excreted by the kidneys, partly by exfoliation of renal tubular epithelium.[508] Metallothionein, a metal-binding protein, is synthesized within 48 hours of exposure to mercury. Metallothionein initially may protect the kidney by sequestering mercury; however, as the sequestered mercury is slowly released from the tubular epithelium, renal damage continues.[505,508]

Acute signs of mercury toxicosis are caused by the corrosive effect of mercury on mucous membranes. Ulceration of the mouth, esophagus, and rest of the GI tract may be followed by diarrhea and anorexia. If the animal survives, acute toxic nephrosis occurs. Anorexia, gastroenteritis, weight loss, nephritis, and alopecia have been reported in animals exposed to chronic, low doses of mercury.[507]

Clinical pathology testing may reveal elevated creatinine and blood urea nitrogen (BUN), as well as proteinuria, glucosuria, and isosthenuria, depending on the acuteness of the disease. Necropsy findings include an ulcerated and edematous GI tract, with possible intraluminal hemorrhage. The kidneys may be pale and swollen.[505,508]

Diagnosis of mercury toxicosis is made from history, clinical presentation, and mercury levels within the animal. Mercury concentrations can be measured in liver, kidney, brain, whole blood, and urine. Tissue samples and urine may be frozen after collection.

Chelation therapy can be done using BAL or sodium thiosulfate as for arsenic toxicosis. Remaining topical mercurials should be washed from the animal. Supportive care is necessary for the gastroenteritis and kidney failure. Oliguria indicates a poor prognosis.[505,508]

54.17 MOLYBDENUM

Excess dietary molybdenum (copper deficiency) is discussed in Chapter 32.

54.18 SELENIUM

See Toxic Plants.

54.19 SODIUM

Sodium (salt) toxicosis is discussed in Chapter 35.

54.20 SULFATE

Excess dietary sulfate is discussed with copper deficiency in Chapter 32 and with polioencephalomalacia in Chapter 35.

54.21 ZINC

Excess dietary zinc is discussed with osteochondrosis in Chapter 38.

54.22 TOXICOLOGY OF ORGANIC COMPOUNDS

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54.23 INSECTICIDES

54.23.1 Anticholinesterase Insecticides

The anticholinesterase insecticides include the organophosphates and the carbamates. Many organophosphate insecticides are used for insect control in crops. Several organophosphates also have been approved for use as insecticides or anthelmintics in domestic animals. Carbamate insecticides are used primarily for crops and other plants. Livestock are usually exposed to these insecticides as a result of drift, accidental ingestion, or improper treatment by owners.[509]

The mechanism of action of these insecticides is to bind with and inhibit acetylcholinesterase (AChE). As a result, acetylcholine (ACh) accumulates at nerve junctions, and repetitive firing of parasympathetic nerves occurs. Because carbamates bind with ACh on a reversible basis, inhibition of AChE is temporary.[509,510] Therefore, carbamates have a shorter duration of action than organophosphate insecticides, which bind irreversibly with AChE.[509]

Clinical signs are predominantly described by the acronym *SLUD: s*alivation, *l*acrimation, *u*rination, and *d*efecation. In addition, the animals may have miosis, diarrhea, muscle tremors, seizures, dyspnea, or bloating.[509] Death can occur within minutes, depending on the toxicity of the specific compound and the amount of toxicant ingested.[511] At postmortem examination, lesions may be minor or absent, depending on the acuteness of death. Pulmonary edema is a frequent finding, because death usually results from increased pulmonary secretions, bronchial constriction, and respiratory paralysis.[510]

Measuring the cholinesterase activity in brain, retina, or whole blood can be used to make a presumptive diagnosis of toxicosis.[512–514] Some laboratories use serum rather than whole blood, depending on the testing method used; therefore it is best to check with the laboratory before submission. Whole blood can reliably be used for cholinesterase evaluation for up to 1 week after collection if the sample is refrigerated.[515] Half the brain should be submitted for homogenization because cholinesterase activity varies among regions of the brain.[512] Cholinesterase activity in whole blood or brain that is less than 50% of normal for the species being tested indicates excessive exposure to a cholinesterase inhibitor. Cholinesterase activities less than 25% of normal indicates toxicosis, as long as appropriate clinical signs are present.[513]

An insecticide screen should be performed on GI contents or the liver to identify the insecticide chemical that is involved. These samples should be stored in glass or metal, such as foil, and frozen as soon as possible after collection. If the sample is stored in plastic, the insecticide may leech from the sample into the plastic.

Because carbamates rapidly dissociate from AChE, a diagnosis is often difficult to make based on cholinesterase activity in brain or blood. The activities can be normal or near normal even though the animal has toxicosis.[509,510] Because carbamates hydrolyze rapidly, parent compounds may be difficult to detect in ingesta and especially in tissue.[509,510] Therefore, when carbamate toxicosis is suspected, multiple samples should be collected and tested as soon as possible.

Treatment for organophosphate toxicosis includes supportive care, activated charcoal, atropine, and oximes. Activated charcoal (1 to 2 lb [0.45 to 0.90 kg] PO for 500-kg animal) should be given even if the route of exposure is not oral, because these insecticides can act systemically even when given topically. If the route of exposure is dermal, the animal should be washed with soap and water to decrease absorption through the skin.[513] Atropine competitively inhibits ACh at muscarinic nerve receptors. Therefore, muscarinic effects, but not nicotinic effects, are reduced. Atropine should be given at a dose of 0.10 to 0.25 mg/kg. One fourth of the initial dose is given by IV injection and the rest SC or IM. The dose can be repeated if the clinical signs reappear.[513] GI motility should be monitored carefully because atropine can cause ileus, especially in horses. Oximes such as 2-pyridine aldoxime methiodide (2-PAM) can be used as a treatment to release the bond between AChE and an organophosphate. However, oximes are of little benefit after the AChE-organophosphate bond undergoes "aging," meaning that the bond cannot be broken. The amount and time of "aging" that occurs vary among the different organophosphate compounds.[513,516] Recommended doses for 2-PAM are 20 mg/kg IV twice daily[517] or 10 to 15 mg/kg SC.[518]

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Treatment of carbamate toxicosis is restricted to atropine, activated charcoal, and supportive care. Oximes such as 2-PAM are contraindicated with carbamate toxicosis because the carbamates bind reversibly, and thus oximes are not needed to release the carbamate from the AChE.[509]

Most anticholinesterase compounds are rapidly metabolized and excreted.[519] Therefore these insecticides do not persist in tissues, and tissue levels are usually low. Animals that survive the toxicosis, however, should be analyzed for residues before consumption.[520] Animals that have died from anticholinesterase insecticide toxicosis have been prohibited from being rendered.[519]

Chlorpyrifos is a chlorinated organophosphorus insecticide used for lice and fly control in cattle. It is applied as a pour-on caudal to the shoulders. This product causes a delayed toxicosis that occurs primarily in bulls and some exotic breeds of cattle. Toxicosis is associated with the testosterone levels in the animal.[521] Larger and older bulls are affected more severely. The manufacturer recommends not treating bulls over 8 months old with chlorpyrifos.[517] Clinical signs do not occur until at least 2 to 7 days after exposure and include depression, weakness, muscle fasciculations, anorexia, rumen stasis, and rumen distention.[517,518,521] The clinical signs typically seen with acute organophosphate toxicosis are usually not present with chlorpyrifos toxicosis.

Animals with chlorpyrifos toxicosis will have depressed cholinesterase activities in brain and blood. After topical application, chlorpyrifos will undergo systemic distribution and may be detected in blood, rumen contents, fat, and hair for weeks. Animals with chlorpyrifos toxicosis should be washed with detergent and water as soon as possible.[517,518,521] Oral treatment with activated charcoal reduces the signs of toxicosis by

adsorption of the chlorpyrifos. The manufacturer recommends atropine as an antidote.[517] Because most cases involve ruminal stasis and few muscarinic signs, however, atropine may be contraindicated. [517,518] Severity of the rumen stasis often requires removal of rumen contents by a large-bore stomach tube or rumenotomy.[518] Pralidoxime (2-PAM) has decreased clinical signs in some animals when given within 4 days of insecticide exposure.[517,518]

Haloxon is an anthelmintic and toxicosis was reported in the 1970s in sheep that had a familial absence of a plasma A-esterase.[522] This enzyme rapidly hydrolyzes haloxon.[522] Clinical signs occur 5 to 90 days after exposure and predominantly include hindlimb ataxia or paresis.[523] Gross lesions are not evident on necropsy. Microscopically, the white matter of the spinal cord was vacuolated, with swollen axons and increased glial cells.[523] Cholinesterase activity can be decreased.[522]

Haloxon also has been associated with bilateral laryngeal paralysis in Arabian and part-Arabian foals.[524] The foals were 23 to 35 days old and had been treated with haloxon every 2 weeks since 2 days of age. The clinical signs were noticeable only when the foals exercised or were stressed. Rhinolaryngoscopy revealed no abductor movement of the arytenoid cartilages.[524] Active wallerian degeneration and loss of nerve fibers were seen in the recurrent laryngeal nerves.[524] Tracheotomy relieved the dyspnea, and in foals that survived, function of the right arytenoid cartilage returned before the left.[524]

54.23.2 Organochlorine Insecticides

Chlorinated hydrocarbons are used to control insects and other pests. Examples include DDT, aldrin, heptachlor, and lindane. Although use of several of these products has been banned or restricted, toxicosis in domestic animals still occurs, either from improper use or from exposure to discarded products.[525]

The mechanism of actions of organochlorines is not completely understood and seems to vary among compounds. Interference with the kinetics of nerve sodium channels and inhibition of γ-aminobutyric acid (GABA) binding are two proposed mechanisms.

Initial clinical signs may include apprehension, hypersensitivity, and a belligerent attitude. Fasciculations of the face and cervical muscles are followed by spasms of the eyelids, forequarters, and finally hindquarters.[525] Ataxia, hypersalivation, and diarrhea also have been reported.[526] Intermittent convulsions are the major manifestation in most cases.[520] Significant gross lesions usually are not found at necropsy.[527]

Organochlorines accumulate in fatty tissues. Therefore, diagnostic testing should be performed on samples such as brain, fat, milk, and liver.[525] The compounds also may be found in whole blood and GI contents. Collected samples should be put in glass or metal containers[525] and frozen, with the exception of blood, which should be refrigerated. As with other insecticides, plastic containers should be avoided if possible.

Treatment is mostly symptomatic because no antidote for organochlorine toxicosis exists.[525] The animal should be washed with water and detergent if the exposure was dermal.[525] Activated charcoal is beneficial if given immediately after oral exposure.[525,526] Convulsing animals require treatment with sedatives and muscle relaxants.

Organochlorine residues persist in fat and are excreted in the milk of lactating animals.[520] Some of these compounds cross the placental barrier and concentrate in fetal fat.[528] Several strategies have been tried to reduce residues as quickly as possible to minimize economic loss. Treatment with compounds such as phenobarbital and butylated hydroxyanisole (BHA) to promote metabolism, cholestyramine to increase excretion, or thyroprotein to increase elimination has not been very successful in livestock.[528]

At this time, the only successful method of reducing organochlorine residues in livestock is by fat mobilization and removal. One method of accomplishing fat mobilization is by feeding a calorie-restricted diet.[526] As the animal loses weight, the fat and organochlorine are mobilized and removed from the body. After removal of the fat, the animal should be fed a high-calorie diet that is free of organochlorine compounds to regain its body fat and decrease the whole-body concentration of the compound. As the body fat decreases, concentration of organochlorine may increase in other tissues as the chemical is mobilized.[525] If the diet is too restrictive, the organochlorine mobilization may occur too rapidly, and the animal may develop acute toxicosis.[526] The fastest method of reducing organochlorine residues is through milk secretion.[528] Residue elimination is fastest during early lactation. Unfortunately, residue reduction may not be economically feasible because of extra costs of feed, labor, and loss of saleable milk.

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54.24 HERBICIDES

54.24.1 Arsenics

See Metals and Other Inorganic Compounds.

54.24.2 Paraquat

Paraquat is in the class of bipyridyl herbicides, which act as dessicants by altering enzyme systems and reducing photosynthesis.[529] Most concerns about this product occur when it is sprayed on foliage that will later be used for animal consumption or when it accidentally drifts from a sprayed field onto animals or their pasture. Paraquat quickly becomes irreversibly inactivated once it comes into contact with soil.[529,530] It is a concern only when the animal ingests a concentrated form of the herbicide or grazes a field that is still wet from paraquat application.

Paraquat is concentrated against a gradient within type I alveolar pneumocytes. The herbicide accepts electrons to form free radicals.[529,530] This reaction is catalyzed by nicotinamide adenine dinucleotide phosphate (NADP), reduced from cytochrome P450 reductase (NADPH).[529] The result is destruction of cell membranes and subsequent cell death.

Acute signs generally occur 1 to 3 days after ingestion and involve anorexia, depression, and diarrhea. Several days later the animal develops respiratory distress, dyspnea, and pneumomediastinum. Death may be delayed until several weeks after ingestion. Gross and histopathologic lesions primarily consist of progressive lung fibrosis, but may include renal and liver damage.[529,530]

Treatment should include fuller's earth or bentonite given orally as soon as possible after exposure and certainly within 24 hours of ingestion.[529,530] These products inactivate the paraquat on contact and thus are more

effective than activated charcoal. Oxygen therapy reportedly worsens the lung damage.[531] Regardless of therapy, the prognosis is poor because of the progressive fibrosis of the lungs.

54.24.3 Chlorophenoxy Acids

Chlorophenoxy acid herbicides includes the compounds 2,4-D; 2,4,5-T; and silvex. These herbicides are plant growth regulators, so the mechanism of action is to alter the metabolism of the plant. Therefore they are relatively nontoxic to mammals unless ingested in a concentrated form.[529,530] Indirect toxicosis may occur, however, because of the altered metabolism of the sprayed plants. Toxic plants that are normally untouched by grazing animals may become more palatable and result in plant toxicosis after application of some herbicides. In addition, the altered plant metabolism may cause some plants to accumulate higher levels of nitrate or cyanide or increase the level of their inherent toxins.[530] Animals should be removed from treated pastures for at least 7 days after application to reduce the occurrence of plant toxicosis.[530]

Clinical signs of chlorophenoxy acid toxicosis include depression, anorexia, abdominal pain, and diarrhea.[529] Weakness is especially profound in the hindlimbs. Gross findings include epicardial hemorrhage and hydropericardium. The liver is swollen and friable. The kidneys may be congested.[532]

Clorophenoxy acid herbicides are quickly absorbed from the GI tract, but dermal absorption is minimal.[533] Treatment consists of activated charcoal and supportive care. The major route of elimination is the urine.[533] Neither parent compounds nor metabolites have been found in the milk from orally dosed cattle.[533]

54.24.4 Triazines

Triazine herbicides inhibit photosynthesis by blocking electron transport.[534] Products in this group of herbicides include atrazine, simazine, and propazine. Livestock should be held from pastures treated with simazine for 30 days and off hay for 60 days.[530]

Sheep have been reported to exhibit signs of generalized muscle tremors, which progressed to mild tetany and collapse of the hindlegs. Other sheep developed a short, prancing gait.[535] Cattle have been reported to develop diarrhea after 12 hours, followed by salivation, ataxia, and stiffness.[536] Gross lesions include myocardial degeneration, subcutaneous hemorrhages, and liver congestion. Histopathologic examination demonstrated focal degenerative myocardiopathy and mild nonsuppurative encephalitis.[535,536] Rumen papillae are edematous and the reticulum, rumen, and omasum may contain black pigment.[536]

Triazine herbicides have no antidote, but treatment with activated charcoal once daily for 4 consecutive days after exposure has reportedly decreased lesions and death loss.[536]

54.25 RODENTICIDES AND OTHER PESTICIDES

54.25.1 Anticoagulant Rodenticides

Toxicosis can result from anticoagulant rodenticides when animals ingest baits made with anticoagulants. These products are often incorporated into grains or pellets that are palatable to livestock. Toxicosis also has been

reported in horses that have been overdosed with warfarin, which has been used as a treatment for navicular disease and jugular phlebitis.[537,538]

First-generation compounds such as warfarin were developed originally, but rodents developed a resistance to these over time. The second-generation compounds, such as brodifacoum and bromadiolone, were created for rats that had developed a resistance to the first-generation compounds.[539–541] In general, the second-generation compounds are more toxic and have longer half-lives.

All anticoagulant rodenticides function by interfering with vitamin K–epoxide reductase, the enzyme that converts inactive vitamin K to its active form. This interference results in a depletion of active vitamin K and subsequently the vitamin K–dependent clotting factors (II, VII, IX, and X). Factor IX is in the intrinsic coagulation pathway, factor VII is in the extrinsic pathway, and factors II and X are in the common pathway. Therefore, all three pathways are affected.[539,540]

Clinical signs may not be noticed until 3 to 5 days after ingestion. Affected animals may exhibit melena, epistaxis, hematuria, or excessive bleeding from a wound or injection site.[540] Often the hemorrhaging occurs in body cavities, and the animal may show nondescript clinical signs such as depression, weakness, pallor, colic, dyspnea, or fever, depending on the location and extent of hemorrhage.[539,540] Sometimes the onset is acute, and the animal dies suddenly from extensive hemorrhage and shock.[539] Gross and histopathologic lesions primarily consist of unexplained hemorrhage, which may be generalized or localized.

Warfarin is almost completely absorbed from the GI tract of horses and has a biologic half-life of 13.3 hours, similar to that in other species.[538] Warfarin is mostly bound to plasma protein, and only the unbound drug is toxic. Therefore, concomitant use of other protein-bound drugs, such as phenylbutazone, can increase the risk of warfarin-induced hemorrhage.[537,542]

Diagnosis of anticoagulant toxicosis is based on history, clinical signs, clinical pathology, and response to treatment. The degree of anemia resulting from hemorrhage varies with the time since ingestion of the toxicant and severity of disease. A coagulation panel will reveal prolongation of prothrombin time (PT), partial thromboplastin time (PTT), and activated coagulation time (ACT).[540,543] The fibrinogen, fibrinogen degradation products, and platelet count are not directly affected by the anticoagulants.

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Determining which anticoagulant rodenticide was ingested is difficult in the live animal. Levels are often too low in blood to be detected. Postmortem detection is most promising in the liver. Although GI contents can be tested, the chemical is often completely absorbed before clinical signs appear or death occurs.

Vitamin K_1 is the treatment for all the anticoagulant rodenticides. The duration of treatment, however, depends on the specific compound because the half-life varies considerably. Warfarin has the shortest half-life of the anticoagulants (13.3 hours in the horse).[538] The half-lives of the other compounds have not been determined in the horse, but diphacinone has a half-life of 15 to 20 days in humans. Therefore, warfarin toxicosis may require treatment for only a few days, whereas toxicosis from the other compounds may have to be treated for several weeks. Vitamin K_1 treatment for an adult horse has been recommended at a dose of 300 to 500 mg SC every 4 to 6 hours.[537] The PT should return to normal within 24 hours. To monitor duration of treatment after the animal has stabilized, vitamin K should be discontinued for 48 hours and the PT retested.[539] Intravenous injection of vitamin K has been associated with anaphylactoid reactions, and intramuscular injection can

aggravate hemorrhage. Oral treatment is advocated for small animals but may be cost-prohibitive for large animals. Vitamin K_3 is less expensive but not as effective and will cause renal disease in horses.

Clotting factor synthesis requires 6 to 12 hours; therefore animals may need to be transfused with whole blood if anemic, or with fresh plasma if the anemia is not severe enough to warrant blood transfusion.[539] Once the packed cell volume (PCV) begins to decrease, it can continue to decrease at a rapid pace, so it should be monitored regularly. Activated charcoal can be given orally to decrease absorption of rodenticides.

54.25.2 Strychnine

Strychnine is used for mammals such as rats, gophers, moles, squirrels, and coyotes. Strychnine is sold as a powder, as pellets, or as treated seeds that are usually dyed bright green or red. Strychnine poisoning was reported in four horses that had eaten milo treated with it. Use of strychnine is restricted in some states to professionals or registered individuals; however, toxicosis in domestic animals still occurs.[544]

Strychnine competitively blocks glycine, the transmitter for inhibitory cells (Renshaw cells) of the spinal cord. This lack of inhibition results in rigidity and tetanic convulsions. Clinical signs include sweating, incoordination, recumbency, and tonic clonic seizures that are inducible by loud sounds, touch, or bright light. Signs appear 10 minutes to 2 hours after ingestion. Gross and histopathologic lesions are limited to those attributable to self-induced trauma.[544]

Diagnosis of strychnine toxicosis is based on clinical signs and detection of the toxicant in urine or serum. Urine is a good diagnostic sample because strychnine is absorbed from the GI tract and excreted in the urine. Stomach contents, liver, kidney, and urine should be collected postmortem and analyzed for strychnine.[544]

A lethal dose of strychnine can be eliminated in 24 to 48 hours. Because strychnine is an alkaloid, it becomes ionized in the acid of the stomach and is not absorbed until it reaches the intestine. Activated charcoal is a good treatment to prevent further absorption of the toxicant. Seizures should be treated with anticonvulsants and rigidity with muscle relaxants. Animals should be protected from excessive light and sound to reduce the incidence of convulsions.

54.25.3 Zinc Phosphide

Zinc phosphide is used to control mice, ground squirrels, rats, and moles. Zinc phosphide is a dark-gray powder that is mixed with grains such as bran, wheat, and oats. Therefore it is palatable to most livestock. The lethal dose for most animals is 20 to 40 mg/kg of body weight.[545]

Zinc phosphide produces phosphine gas under acidic conditions. Therefore, toxicosis occurs when the rodenticide comes into contact with an acidic stomach. Gastric acidity is an important factor in phosphine gas production. Ruminants should be more resistant because the rumen has a higher pH than a monogastric stomach. Studies show a higher survival rate in dogs that are dosed with zinc phosphide on an empty stomach rather than dosed after a meal when the stomach has a lower pH.[545]

Zinc phosphide affects the CNS, and clinical signs are similar to those caused by other toxicants, such as strychnine or the anticholinesterase insecticides.[545] Gross and histopathologic lesions are not specific, although the GI and pulmonary systems may be red and irritated. Thus, diagnosis is difficult without chemical analysis.

Diagnosis of zinc phosphide toxicosis is based on detecting phosphine gas in the stomach contents. Because the gas dissipates rapidly in air, the collected sample of stomach contents should be placed in an airtight container and frozen immediately.[545]

Treatment is mostly supportive care following activated charcoal therapy. Food should be withheld until the zinc phosphide has been emptied from the stomach. It may be helpful to add an antacid to the activated charcoal therapy to reduce the amount of phosphine gas produced.

54.25.4 Metaldehyde

Metaldehyde is a tasteless ingredient used in slug and snail baits and as a solid fuel for some camp stoves.[546] Baits may be liquid or dry, but most are dry pellets of metaldehyde mixed with soybeans, rice, oats, sorghum, or apples.[546,547] Some baits also contain other toxicants, such as arsenate or insecticides, which can cause concurrent disease. Toxicosis occurs mostly in coastal and low-lying areas where there is a high incidence of snails or slugs.[547]

The mechanism of metaldehyde toxicosis is unknown.[546] It may increase excitatory neurotransmitters or decrease inhibitory neurotransmitters.[546,547]

Clinical signs can occur immediately or can be delayed for up to 3 hours after ingestion. Affected animals will have convulsions, which may be continuous or intermittent. The animal may have muscle tremors and anxiety and may be hyperesthetic between convulsions. The seizures are not necessarily evoked by external stimuli. Elevated body temperature, up to 43° C (110° F), is a common finding and is probably caused by the excessive muscle activity. Other findings include tachycardia, defective vision, hyperpnea, hypersalivation, ataxia, cyanosis, acidosis, diarrhea, and dehydration. Death usually results from respiratory failure and occurs 4 to 24 hours after ingestion. Gross and histopathologic findings include petechiae and ecchymoses of various organs and subcutaneous edema.[548–550]

A diagnosis is based on testing for metaldehyde in GI contents or serum.[551] Milk samples taken within 24 hours from two affected cows tested negative for metaldehyde.[552] No antidote is available.[552,553] Administration of oral activated charcoal may prevent further absorption from the GI tract. If the animal is convulsing, tranquilizers should be used to control seizures. Tranquilizers should be allowed to wear off periodically and the convulsive condition reevaluated. Horses have been treated successfully with tranquilizers and mineral oil.[554]

54.26 INDUSTRIAL TOXICANTS

54.26.1 Petroleum

Animals can become exposed to petroleum hydrocarbons during crude oil spills, pipeline breaks, or careless disposal of automobile or tractor oil. Most cases of petroleum toxicosis occur when the animal's water supply is contaminated.[555]

Clinical signs vary but usually include anorexia, depression, GI stasis, bloat, and diarrhea or constipation. Oil may be seen in the feces within days after ingestion. The most common cause of death is aspiration pneumonia

after regurgitation of the hydrocarbons. The petroleum product may be seen around the muzzle of the animal. Oil may be found in the GI tract or the lungs at postmortem examination.

Diagnosis of petroleum toxicosis can be made based on history, clinical findings, and detection of hydrocarbons in tissues. The product may be visible on the animal as well as in the GI contents and lungs. A quick method of checking for oil is to place the GI contents or lung in warm water; the oil should float to the top of the water. Samples also can be checked under a black light because many petroleum products will fluoresce yellow or yellow-green. Liver, kidney, lung, and GI contents can be analyzed for hydrocarbons and matched with available source material.[555] Collecting suspect source material is especially important because these toxicoses may become legal cases.

The primary aim of treatment is to prevent aspiration pneumonia, which is best achieved by performing a rumenotomy and removing the contaminated ingesta. If surgery is not feasible, activated charcoal should be administered. The charcoal should be followed with a cathartic to enhance removal of the oil. Supportive care is needed for the GI stasis and diarrhea or constipation. Vegetable oil (500 to 1000 mL) may increase the viscosity of the ingested petroleum within the rumen and reduce the occurrence of aspiration pneumonia. The prognosis is generally good unless the animal aspirates or severely bloats.[555] Some petroleum products may contain heavy metals such as lead, and a concurrent metal toxicosis can occur.

54.26.2 Ethylene Glycol

The most common cause of ethylene glycol toxicosis is ingestion of antifreeze. Although cats and dogs are the species most often affected because of their proximity to available sources, ethylene glycol toxicosis has occurred in cattle and goats.[556] Some new brands of antifreeze contain propylene glycol rather than ethylene glycol. Although much less toxic than ethylene glycol, propylene glycol can still cause toxicosis.

Ethylene glycol is metabolized in the liver to several metabolic intermediates, especially glycolic acid. This reaction is catalyzed by alcohol dehydrogenase. Glycolic acid results in metabolic acidosis and hyperosmolality in the animal. This metabolite can be excreted or further metabolized into oxalic acid, which combines with ionic calcium and causes hypocalcemia and calcium oxalate formation, especially in kidneys. Ruminants may be more resistant to ethylene glycol toxicosis than monogastrics because the rumen microorganisms can metabolize some ethylene glycol before it is absorbed.[556,557]

Toxicosis results in an initial inebriation, followed by metabolic acidosis and renal damage.[557] Clinical signs in ruminants include ataxia, depression, hypersalivation, and absence of a menace response. These signs progressed to recumbency and clonic-tonic seizures in a pygmy goat.[556] Clinical pathology reveals azotemia, metabolic acidosis, and hyperosmolality. Postmortem findings include swollen kidneys and pulmonary edema. Dilated capsular spaces and birefringent crystals are found in renal tubules on histologic examination. These crystals may be arranged in sheaves or rosettes and are typical of oxalate crystals.[556]

Rumen or stomach contents can be analyzed for ethylene glycol. It is absorbed within 48 hours after ingestion by monogastrics; however, ethylene glycol has been detected in the rumen contents of a goat 4 days after clinical signs began.[5] Urine, serum, and ocular fluid can also be analyzed for glycolic acid.

The classic treatment for ethylene glycol toxicosis is 20% ethanol given at 5 ml/kg at 4- to 8-hour intervals. The ethanol binds with the alcohol dehydrogenase so that it is not available to convert ethylene glycol to glycolic acid. This treatment is effective, however, only if initiated within a few hours of ingestion. The effectiveness of

ethanol in treating livestock has not been addressed in the literature. Because the ethylene glycol appears to remain in the rumen for several days, treatment with activated charcoal may be beneficial even after the appearance of clinical signs.[556]

54.26.3 Chlorinated Naphthalene

Chlorinated naphthalene has been used in wood preservatives, asphalt roofing, insulating waxes, sealing compounds, and in condensers. Most toxicoses in cattle, however, have been from ingesting lubricating grease used on farm machinery or feed-pelleting machines. Chlorinated naphthalene is no longer used in lubricants, but toxicosis still occurs when animals have access to dumps and salvage yards. The toxic forms are tetra-, penta-, hexa-, hepta-, and octachloronaphthalenes, with the hexa and hepta forms being the most toxic.[558]

Chlorinated naphthalene interferes with the conversion of carotene to vitamin A. Serum vitamin A levels decrease significantly a few days after exposure and remain decreased for at least 4 weeks.[558]

Initial clinical signs include weight loss, anorexia, and depression. Excessive salivation and lacrimation occur because of the formation of papular stomatitis and keratinization of the meibomian glands. Several weeks later, nonpruritic thickening and fissuring of the skin occur. Hyperkeratosis involves the withers, neck, head, trunk, and medial thighs; but usually does not involve the lower legs. Diarrhea may occur late in the disease. Postmortem findings include epithelial hyperplasia or metaplasia of the gallbladder, bile ducts, salivary glands, pancreas, and genital tract.[558]

Diagnosis is based on clinical signs and a low vitamin A level. Suspected source material can be analyzed for chlorinated naphthalene. Treatment with vitamin A may minimize some clinical signs, but treatment of this toxicosis is usually unsuccessful, especially after the appearance of skin lesions.[558]

54.26.4 Pentachlorophenol

Pentachlorophenol (PCP) is used primarily as a wood preservative. Residues have been found in cattle exposed to wood troughs, silos, barns, and fences treated with PCP. Horses have developed toxicosis when bedded on wood shavings that contain PCP.[559–561]

The primary mechanism of action is uncoupling of oxidative phosphorylation.[559,561] PCP is quickly absorbed from the GI tract and excreted in the urine. It is stored mainly in the liver and kidney and acts as a mild hepatotoxin.[510] The half-life in cattle is 1.5 days.[559]

Acute clinical signs in cattle include weight loss, depression, anorexia, intense thirst, and decreased milk production.[559,560] Chronic signs in cattle are dyspnea, hyperkeratosis, liver damage, and increased abortion rate.[559] Horses have anorexia, dependent edema, weight loss, and alopecia. The skin has cracks and fissures that exude serum. Clinical pathology reveals hepatic changes, anemia, and thrombocytopenia. Horses also may develop colic or recurrent hoof problems.[561]

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Liver, kidney, and serum can be analyzed for PCP. Because of the rapid rate of excretion, serum PCP concentrations may be useful only during acute toxicosis.[561] No antidote exists, and treatment is usually unsuccessful. Residues may be a concern, especially from dioxin-related contaminants in the “penta”-treated wood.

54.26.5 Phosphatic Fertilizers

Phosphatic fertilizers selectively promote legume instead of grass growth. Therefore these are popular fertilizers for maintaining subterranean clover pastures. The major components of phosphatic or superphosphate fertilizers are calcium pyrophosphate, calcium orthophosphate, calcium sulfate, and sodium fluoride. Toxicosis is believed to be a result of the phosphate and fluoride. It usually occurs after a short pasture has been top-dressed recently.[562] The fertilizer is not usually palatable, except to ravenous animals.

Sheep have developed ataxia, bruxism, depression, and diarrhea. Animals will be hypocalcemic, probably because of renal failure. Hyperphosphatemia does not occur until oliguria develops and the animal is near death. Gross lesions include hyperemic GI mucosa, pulmonary edema, and bloody intestinal contents. Histopathologic examination reveals acute proximal renal tubular necrosis.[562]

Diagnosis is based on history, clinical signs, and lesions. Treatment is limited to supportive care, which is generally successful if the disease is diagnosed early.[562]

54.26.6 Boron Fertilizer

Sodium borate is mildly toxic, and clinical signs may not be seen in ruminants until they consume a near-lethal dose. Toxicosis usually occurs only if animals eat concentrated fertilizer.[563] The mechanism of action is unknown, but boron may have a stimulatory effect on serotonergic and dopaminergic neurons.[564]

Reported clinical signs in cattle include weakness, depression, muscle fasciculations, seizures, and a spastic gait. Most animals develop diarrhea and become dehydrated. Gross and microscopic lesions are not seen.[563] Goats that were given a sublethal dose of boron developed anorexia and depression. Seizure-like activity consisted mostly of ear flicking and chomping motions; however, tremors, stargazing, head jerking, and extensor rigidity also were noted.[564]

Liver, kidneys, and rumen contents can be analyzed for boron content.[563] Treatment is limited to supportive care.

54.27 THERAPEUTIC AGENTS

54.27.1 Vitamin K_3

Vitamin K_3 is the synthetic vitamin menadione sodium bisulfite. It has been used as a treatment for anticoagulant rodenticide toxicosis, sweet clover (dicumarol) toxicosis, and exercise-induced pulmonary hemorrhage. Its popularity stemmed from being much less expensive than vitamin K_1. Studies demonstrate, however, that vitamin K_3 is not an effective treatment for sweet clover disease in cattle.[565] Furthermore, case reports indicate that vitamin K_3 is toxic to horses, even when used at the manufacturer's recommended dose.[566–568]

The mechanism for the toxicosis is unknown. Within 4 to 48 hours of administration of vitamin K_3, horses become depressed, anorexic, and weak. They may develop muscle stiffness, laminitis, or colic.[566] The horses develop renal failure as evidenced by increased BUN and creatinine concentrations. Proteinuria, hematuria, and low specific gravity are found on urinalysis. Serum electrolyte levels are consistent with renal tubular disease: hyponatremia, hypochloremia, and hyperkalemia. Some patients develop hypercalcemia.[568] Grossly, the kidneys are enlarged.[566] Microscopically, the kidneys have nephrosis with tubular dilation, epithelial degeneration, and necrosis.[568] Diagnosis is based on history, clinical signs, and lesions. Treatment should include diuresis and maintenance of serum electrolyte concentrations.[567]

54.27.2 Propylene Glycol

Propylene glycol is used as a vehicle for drugs with poor water solubility, for treatment of bovine ketosis, and in some new antifreeze products.[569] Toxicosis has been reported when cows are overdosed or when horses are accidentally dosed with propylene glycol.[569,570]

The median toxic dose of propylene glycol in cattle is 2.6 g/kg body weight.[570] Ataxia develops in 2 to 4 hours and resolves by 24 hours after dosing. The cattle also become depressed and temporarily recumbent. Serum and cerebrospinal fluid osmolality increase.[570]

A horse mistakenly given propylene glycol rather than mineral oil developed ataxia and depression in 10 to 15 minutes. The horse also developed pain, excessive salivation, and sweating, but these signs disappeared within 5 minutes. The animal developed rapid, shallow breathing and cyanosis and died of respiratory distress the next day.[569] Gross lesions were not seen. Histopathologic findings included myocardial perivascular edema, pulmonary edema, scattered hepatocyte necrosis, and peracute renal infarcts.[569]

Serum and urine can be analyzed to determine the presence of propylene glycol.[569,570] Propylene glycol causes lactic acidosis in humans, which is treated with sodium bicarbonate. This treatment was unsuccessfully used in the horse described here[569]; if acidosis occurs, however, sodium bicarbonate may be beneficial if the disease is treated early.

54.27.3 Isopropyl Alcohol

Isopropyl alcohol is used as a topical antibacterial agent. When ingested, it is quickly absorbed from the GI tract and metabolized into acetone by the liver through alcohol dehydrogenase. The majority of the acetone is excreted by the kidney and to a lesser extent by the lungs.[571]

Toxicosis in a horse was reported when 2 L of alcohol was mistaken for mineral oil and administered by nasogastric tube. Initially the horse was depressed and reluctant to move before collapsing and becoming semicomatose. A menace response was not detected, and pupillary light reflexes were slow. Treatment consisted of repeated gastric lavage with 2-L aliquots of warm water, followed by activated charcoal and intravenous fluids. Activated charcoal was repeated the following day, and the horse recovered from the incident. However, the odor of acetone could be detected on the horse's breath for about 4 days, and acetone was detectable in the horse's serum during this time.[571]

54.27.4 Phenothiazine

This anthelmintic combined with piperazine and carbon disulfide has been used for horses in the past.[572,573] Phenothiazine currently is being manufactured for horses in combination with piperazine and trichlorfon. 1717
Phenothiazine also has been used in mineral blocks and protein supplements for ruminants.[574] Phenothiazine is 1718
toxic to both horses and ruminants but causes different diseases.

54.27.4.1 RUMINANTS

Phenothiazine causes primary photosensitization in ruminants. The rumen converts phenothiazine to a phototoxin, phenothiazine sulfoxide. This toxic metabolite can be converted by the liver to a nontoxic metabolite, leukophenothiazine; if the liver is overwhelmed, however, toxicosis can occur. Most cases occur in debilitated or young animals that do not have a fully functional liver.[574]

Clinical signs begin as erythema and edema combined with varying degrees of pruritus, photophobia, and pain. Vesicles and bullae form and progress to oozing, necrosis, and ulceration of the skin. These lesions are usually confined to areas that have white pigmentation or have little hair and are exposed to sunlight. The tail, ears, teats, feet, or ventral surface of the tongue may slough. The skin of black cattle does not usually slough, but these animals can develop epiphora, corneal edema, and blindness because the phototoxin is also secreted in tears and aqueous humor.[574,575]

Diagnosis is based on the history of phenothiazine consumption and the skin lesions. A skin biopsy may be helpful but usually is not necessary because the lesions are uniquely confined to lightly pigmented skin.

No antidote exists for phenothiazine toxicosis, and treatment is limited to supportive care. Antibiotics may be needed to treat secondary bacterial infections of the skin. Antiinflammatory drugs may be indicated for pain. When prescribing drugs for ruminants with photosensitization, those that can compromise the liver should be avoided. Affected animals should be housed and fed in areas out of direct sunlight to prevent further damage to the skin.

54.27.4.2 HORSES

Phenothiazine acts as an oxidant to produce hemolytic anemia in horses. Heinz bodies (precipitated denatured hemoglobin) damage the red blood cell membrane, which results primarily in intravascular hemolysis. Toxicosis has been noted primarily in horses that are in poor condition before exposure to the phenothiazine.[576] Primary clinical signs include anorexia, depression, weakness, icterus, anemia, and hemoglobinuria.[572,573] Colic, diarrhea, fever, and dependent edema are less frequently reported clinical signs.[576] Clinical pathology reveals anemia and elevated indirect bilirubin levels.[576]

Diagnosis is based on a history of exposure to phenothiazine and ruling out other causes of hemolytic anemia in the horse. Treatment is basically supportive. A blood transfusion may be necessary if the anemia reaches a critical level.[576]

54.28 FEED ADDITIVES

54.28.1 Urea and Nonprotein Nitrogen

Nonprotein nitrogen (NPN) products are converted by ruminal microorganisms to ammonia, which is used to form amino acids. Therefore, ruminants can use the nitrogen from NPN for part of their diet rather than the more expensive natural proteins. Urea is the best known source of NPN, and it is also the most toxic.[577]

Toxicosis can result from overexposure or loss of acclimation to NPN. Too much NPN may be fed to animals because of a miscalculation or by contamination. Urea toxicosis has been reported in cattle that drank from a water source that was contaminated with urea fertilizer.[578] Ruminants acclimate to NPN in their diets through the ruminal microorganisms. Animals that have been acclimated to a certain level of NPN in their diets and then go without NPN for more than 1 day can develop toxicosis. Ruminants quickly lose their adaptation to NPN, and toxicosis can occur when urea consumption resumes, even if NPN is fed at the same level as previously.

Ammonia that is not used by the ruminal microorganisms is absorbed from the rumen and detoxified by the liver back into urea for excretion. Toxicosis occurs when the microorganisms and the liver are overwhelmed by the level of ammonia.[577–579] As the ammonia level increases in the rumen, the ruminal pH increases and creates a shift from charged ammonium ions to uncharged ammonia. The uncharged ammonia is absorbed readily across the rumen wall and increases the ammonia level in the blood.[577]

Clinical signs begin 30 minutes to 4 hours after ingestion of NPN and include weakness, dyspnea, salivation, bruxism, bloat, and convulsions. Because death can occur in a few hours, some animals may be found dead with no clinical signs observed. The rumen pH will be greater than 8.0 with NPN toxicosis. Rumen pH can decrease with time after death, so the pH should be determined on a recently dead animal.[577,579]

Diagnosis can be made by analyzing rumen contents, whole blood, or an eye for ammonia. Because ammonia is volatile, the samples should be frozen immediately after collection. Feed material and rumen contents can be analyzed for urea. Urea concentration in the rumen may not be indicative of the amount that was eaten because the microorganisms continue to convert urea to ammonia even after the animal has died. Therefore, a diagnosis should not be based solely on the urea level in the rumen, but in conjunction with the ammonia levels in the animal.

Treatment focuses on decreasing the amount of ammonia absorbed from the rumen. Adult cattle should be given 20 to 30 L of cold water orally to reduce the microorganisms' ability to convert urea to ammonia. These animals also should receive 2 to 6 L of 5% acetic acid (vinegar) to decrease the pH in the rumen so that ammonia absorption is minimized.[577] Rumenotomies can be used to remove the excess NPN source.

To prevent toxicosis, NPN in feed should not exceed 40% of the total nitrogen requirement, and the animals should be acclimated slowly to NPN. Urea should not be fed at a concentration higher than 3% of the grain ration or 1% of the total ration.[577]

54.28.2 Ammoniated Feed

Molasses, hay, and silage can be treated with aqueous or anhydrous ammonia to increase the dietary quality for ruminants. Under certain conditions, these ammoniated feeds can cause “bovine bonkers,” a disease characterized by hyperexcitability. Treatment conditions that predispose to the occurrence of the toxicosis are ammoniating feedstuffs with more than 20% moisture, treating feedstuffs that contain ample soluble sugars, overapplying the ammonia, or treating the forage during high ambient temperatures. High-quality hays, such as wheat, Sudan, alfalfa, orchardgrass, Bermuda grass, fescue, and sorghum, contain high levels of soluble sugars and are more often incriminated in toxicosis than are low-quality hays such as corn stalks, corn silage, and most small grain straws.[577]

The mechanism of bovine bonkers is not completely understood. Pyrazines and imidazoles are the primary byproducts formed during ammoniation. The two major imidazoles that are formed, 2-methylimidazole (2-me-I) and 4-methylimidazole (4-me-I), cause convulsions in mice, with 4-me-I being more potent. Administration of 4-me-I has experimentally reproduced the disease in a nursing cow without affecting the calf.[577] Nursing calves in field cases have developed the disease,[580,581] even though the dams did not. However, when orally dosed with 4-me-I, cows developed the disease but the calves did not, despite the imidazole being detected in the milk and colostrum.[582] Therefore, more work is needed regarding the mechanism of this disease.

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The most striking clinical sign is hyperexcitability, which can occur spontaneously or can be induced by excitement. Animals will suddenly stampede and run in circles or in a straight line while they collide with other animals or with buildings and fences. Other clinical signs include ear twitching, mydriasis, trembling, salivation, increased urination, increased defecation, and bellowing. Gross lesions are not significant other than bruising and broken bones that are self-inflicted.[577,580,583]

Diagnosis is based on clinical signs and a history of feeding ammoniated feed. Treatment is limited to sedation of animals.[581] Thiamine also has been used as a treatment, with variable results.[577] It is often not possible to approach an affected animal to treat it without endangering the handler. Most animals recover spontaneously once the ammoniated feed source is removed.

Prevention of ammoniated toxicosis focuses on properly treating the feed. Only poor-quality roughages with low levels of soluble sugars should be ammoniated. The amount of ammonia used should not exceed 3% of the dry weight of the forage. Ammoniate only during cool weather so that the processing temperature of the forage is less than 70° C (158° F).[577,580]

54.28.3 Ionophores

Ionophore antibiotics are used as coccidiostats and feed additives for poultry and cattle. Ionophores alter the rumen so that a higher level of propionic acid is produced for improved feed efficiency. They also are used to prevent rumen acidosis and emphysema in cattle.[584–588] Toxicosis can result from calculation or mixing errors or from use in inappropriate species. Cattle and sheep have been poisoned by ingesting litter from poultry that had been treated with an ionophore.[589]

Ionophores form lipid-soluble complexes with cations to facilitate transport of the cations across lipid membranes. The monovalent ionophores are monensin, salinomycin, and narasin. Monensin preferentially

complexes with sodium ions, whereas salinomycin and narasin preferentially bind with potassium ions. Lasalocid is a divalent ionophore that binds with divalent cations, such as calcium and magnesium ions.[585,587]

Horses are the most sensitive species to the ionophore antibiotics.[586,590] The recommended dose of monensin for cattle can be lethal to a horse. Acute clinical signs in horses include colic, anorexia, weakness, and ataxia.[586] Creatinine phosphokinase (CPK) significantly increases within 24 hours; AST and serum ALP activities are increased to a lesser degree.[586] Unconjugated serum bilirubin will be slightly but consistently increased. Erythrocyte fragility increases.[590] Serum enzymes can be used diagnostically but are poor prognostic indicators.[591] If the animal dies peracutely, significant gross lesions may not be present. Acutely affected horses develop degeneration and necrosis of the cardiac muscle and to a lesser degree the skeletal muscles.[587]

If horses survive the acute episode of toxicosis, they often experience delayed toxicosis because of permanent damage to the heart. These animals have marked cardiac myopathy and fibrosis.[588] The most noticeable clinical sign is exercise intolerance, and affected animals may collapse and die during exercise, making them hazardous to use as riding horses.

Whereas the heart is the most affected organ in horses, ionophores damage the cardiac and skeletal muscles more equally in ruminants.[587] Clinical signs in feedlot cattle include anorexia, pica, diarrhea, hindlimb ataxia, and dyspnea. These animals have postmortem lesions of hydrothorax, ascites, and pulmonary edema besides hemorrhages and necrosis of the cardiac and skeletal muscles.[592] Signs of weakness, increased respiratory rate, nasal discharge, and reddened noses have been reported in dairy calves. Postmortem examination revealed pulmonary edema accompanied by pleural and peritoneal effusions. The hearts had myocardial necrosis.[585] Sheep reportedly develop depression, anorexia, diarrhea, and stiffness. CPK and AST activities are increased. Necrosis of the heart and diaphragm has been reported.[584]

Diagnosis relies on finding appropriate clinical signs and lesions. Currently, analysis for ionophores in tissue or serum is not reliable; however, the feed source can be analyzed for ionophores.[587]

Antidotes for ionophores are not available.[586,587] Mineral oil or activated charcoal may decrease further absorption of the toxicant. Large volumes of intravenous fluids are needed to treat dehydration and shock.[586] Serum electrolyte levels should be monitored frequently and fluid electrolytes adjusted accordingly.

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